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Azides: Their Preparation and Synthetic Uses

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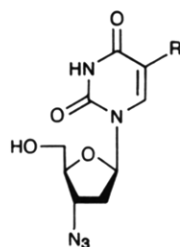
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I. Introduction

The chemistry of azides and nitrenes has attracted the attention of chemists since the discovery of phenyl azide by Griess over 100 years ago¹ and the first proposal of nitrenes as reaction intermediates by Tiemann in 1891.² However, after other important contributions, especially by Curtius and Bertho, interest waned until about 1950, when reviews by Smith (acyl azides)³ and Boyer (aryl and alkyl azides)⁴ stimulated further work, much of which is described in major reviews by Kirmse (1959),⁵ Horner and Christmann (1963),⁶ Abramovitch and Davis (1964),⁷ and L'abbé (1969).⁸ A comprehensive treatment of the literature up to 1969 is contained in two books. One, edited by Lwowski, deals with nitrenes⁹ and the other, on azides, is edited by Patai.¹⁰ Work on azides and nitrenes that appeared between 1969 and 1982 has been reviewed in another book¹¹ and in the supplement to Patai's book.¹² A list of reviews that have appeared since 1970 on azides and related topics is given in Table 1. An ideal supplement to the present review is the excellent short treatment of azide chemistry by Smith.¹³

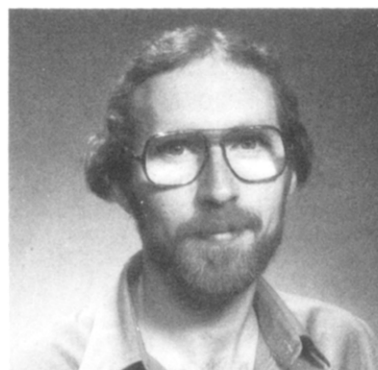
The aim here is to present applications of azides in synthesis, and it is hoped that this will reflect the current rapid increase in interest in the area. Our emphasis has been the recent literature (1983 to June 1986 inclusive) but important linking references and some mechanistic discussion are provided. In so doing, we are aware that scant recognition is given to the discoverers of the key reactions of azide and nitrene chemistry. Therefore we dedicate this review to that select band whose discoveries have made the synthetic



AZT, R = Me
CS-85, R = Et



Eric Scriven was born in Pembrokeshire, Wales, in 1941. He graduated (Grad. R.I.C.) at the University of Salford (1965) after part-time study while working for BISRA and ESSO. He obtained his M.Sc. (1967) from the University of Guelph (with M. J. Nye) and Ph.D. (1969) from the University of East Anglia (with A. R. Kartzky). After postdoctoral years at the University of Alabama (with R. A. Abramovitch) and University College London (with J. H. Ridd), he returned to the University of Salford. He was a faculty member until he joined Reilly Tar & Chemical Corp. in 1979. He is an adjunct professor at Purdue University School of Science in Indianapolis (since 1983), and he has been a visiting professor at the University of Florida (1983) and the University of Benin, Nigeria (1975–1976). His current research interests include synthetic and mechanistic aspects of azide and nitrene chemistry, heterocyclic chemistry, and the applications of polymers in organic synthesis. He is currently coeditor (with K. Turnbull) of *Annual Reports in Organic Synthesis*.



Kenneth Turnbull was born in Edinburgh, Scotland, in 1951. He received his B.Sc., and Ph.D. (1976, with P. N. Preston) degrees from Heriot-Watt University, Edinburgh. After 2 years as a postdoctoral research associate at the University of Toronto (with I. W. J. Still), he joined the chemistry faculty at Grinnell College, Iowa. Since 1980 he has been at Wright State University, where he is presently an Associate Professor. His research interests include synthetic aspects of azide chemistry, heterocyclic synthesis (mainly mesionic), and the preparation of compounds containing N=S or S=S functionalities. He is currently coeditor (with E. F. V. Scriven) of *Annual Reports in Organic Synthesis*.

work discussed herein possible. Many of their names appear in the first paragraph.

Of topical interest, azidonucleosides (viz., AZT (3'-azido-3'-deoxythymidine) and CS-85) have received international attention for the treatment of AIDS (acquired immune deficiency syndrome) and ARC (AIDS-related complex).¹⁴

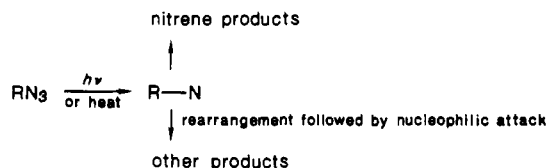
It should be noted that while most azides can be handled without incident, some members of this class are explosive. Accordingly, prudent practice should be scrupulously adhered to in the laboratory.

The most common types of reaction that will be encountered in the following sections are outlined in general form below. These are classified according to the number of nitrogen atoms from the starting azide that end up in the final product and they are subdivided

vided by reaction type. The mechanisms given are illustrative rather than precise; for more detail the reader should consult the references quoted.

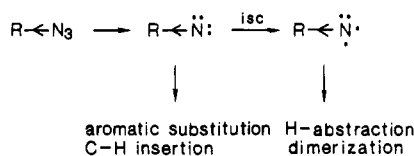
A. One Azide Nitrogen Retained in the Final Product

1. Unimolecular Decomposition by Light or Heat

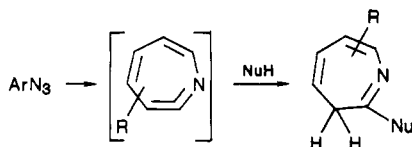


a. Nitrene-Derived Products (Section VI.A.3,5)

The more electron-attracting is R, the more electrophilic will be the singlet nitrene, so promoting its reactions relative to those of the triplet nitrene. The latter are not usually as synthetically useful.

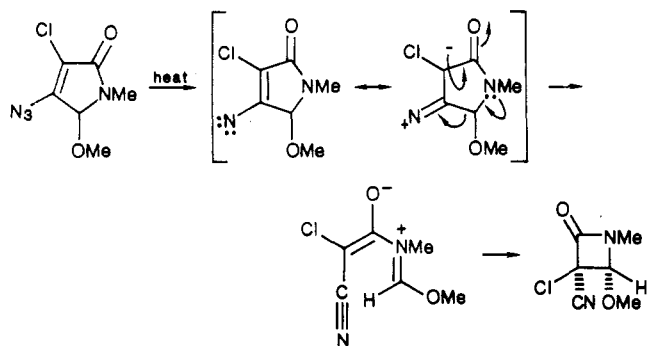


b. Rearrangement Followed by Nucleophilic Attack (Section VI.C.6)

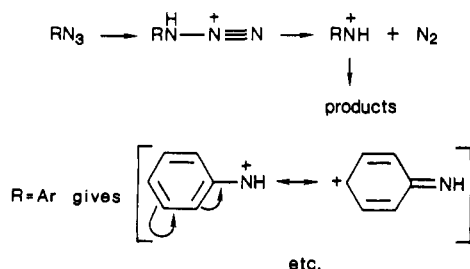


c. Zwitterazido Cleavage

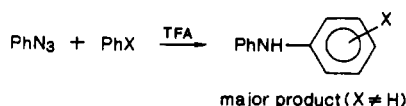
Applications of this reaction are not described herein since a review by Moore has just appeared.¹⁵



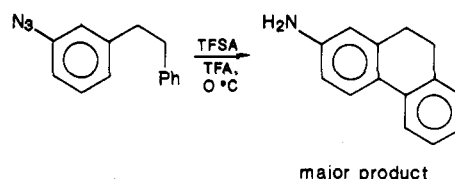
2. Acid-Catalyzed Decomposition (Sections IV.A. and VI.A.3)



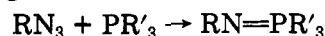
Arylnitrenium ions may react at N- or C- thus:



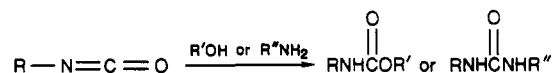
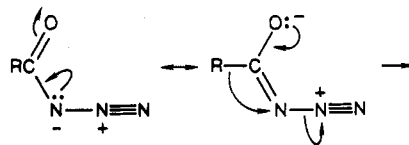
However



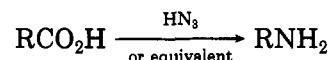
3. Staudinger Reaction (Sections III.F and VI.A.7)



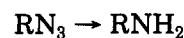
4. Curtius Rearrangement (Sections III.D, VI.A.4, and VI.C.4)



5. Schmidt Rearrangement (Sections III.E and VI.C.1)

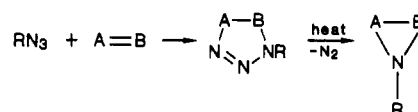


6. Reduction (Sections III.A,B,C and V.C)

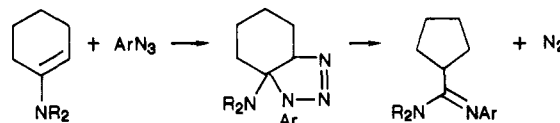


B. One, Two, or Three Nitrogens Retained in Final Product

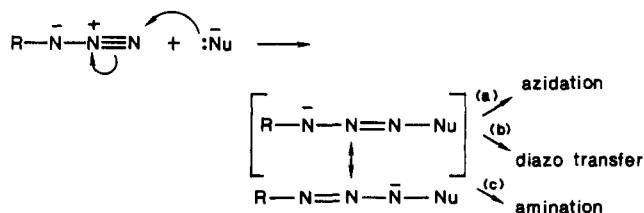
1. Cycloadditions (Sections IV.B,C and VI.B)



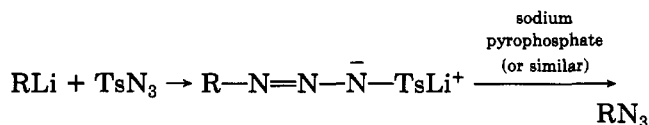
The above sequence offers a general synthetic approach to triazolines and related heterocycles; loss of nitrogen gives aziridines (see section VI.B). When A-B is part of a ring system, a Favorskii-like ring contraction can take place.



2. Nucleophilic Attack at the Azide Terminus



a. Azidation (Section II.J)



b. Diazo Transfer (Section III.I)

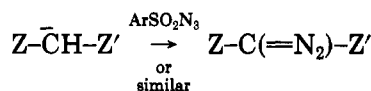
TABLE 1. Azide Reviews

| topic | ref |
|--|--|
| 1,2,3-triazoles | Gilchrist, T. L.; Gymer, G. E. <i>Adv. Heterocycl. Chem.</i> 1974 , <i>16</i> , 33 |
| acyl azides | Lwowski, W. Ref 11, p 205 |
| acylnitrene cyclizations | Edwards, O. E. Ref 9, p 225 |
| alkyl azides | Kyba, E. P. Ref 11, p 2 |
| alkylnitrenes | Lewis, F. D.; Saunders, W. H. Ref 9, p 47 |
| aminonitrenes | Lemal, D. M. Ref 9, p 345 |
| aminonitrenes in organic synthesis | Chow, T. J. <i>Hua Hsueh</i> 1984 , <i>42</i> , 139 |
| analysis of azides for assay | Kramer, H. In <i>Energetic Materials</i> ; Fair, H. D., Walker, R. F., Eds.; Plenum: New York, 1977; Vol. 2, p 55 |
| aryl and heteroaryl azides | Smith, P. A. S. Ref 11, p 95 |
| aryl- and heteroarylnitrenes in heterocyclic synthesis | Suschitzky, H. <i>Lect. Heterocycl. Chem.</i> 1980 , <i>5</i> , 1 |
| aryl azide photoaffinity labels in biochemistry | Staros, J. V. <i>Trends Biochem. Sci (Pers. Ed.)</i> 1980 , <i>5</i> , 320 |
| aryl azide pyrolysis | Dyall, L. K. In <i>Chemistry of Halides, Pseudohalides, and Azides</i> ; Patai, S., Ed.; Wiley: Chichester, 1983; Vol. 1, p 287 |
| aryl azides | Scriven, E. F. V. In <i>Reactive Intermediates</i> , Abramovitch, R. A., Ed.; Plenum: New York, 1982; Vol. 2, p 1 |
| arylnitrenes | Smith, P. A. S. Ref 9, p 99 |
| arylnitrenes in synthesis | Iddon, B. I.; Meth-Cohn, O.; Scriven, E. F. V.; Suschitzky, H.; Gallagher, P. T. <i>Ang. Chem., Int. Ed. Engl.</i> 1979 , <i>18</i> , 900 |
| azide derivatives of carbohydrates | Mester, L.; El Khadem, H. S. In <i>Carbohydrates: Chemistry and Biochemistry</i> , 2nd ed.; Pigman, W. W., Horton, D. Eds.; Academic: New York, Vol. 1B, p 929 |
| azide derivatives of cyclodextrins | Croft, A. P.; Bartsch, R. A. <i>Tetrahedron</i> 1983 , <i>39</i> , 1417 |
| azide derivatives of oligosaccharides | Paulsen, H. <i>Angew. Chem., Int. Ed. Engl.</i> 1982 , <i>21</i> , 155 |
| azide-containing photoresist materials | El'tsov, A. V.; Yurre, T. A. <i>Zh. Prikl. Khim.</i> 1979 , <i>52</i> , 365 |
| azides as synthetic starting materials | Sheradsky, T. Ref 10, p 331 |
| azides attached to elements other than carbon | Atkinson, R. S. Ref 11, p 247 |
| azides containing two different metal atoms | Krischner, H. <i>Monatsh. Chem.</i> 1985 , <i>116</i> , 189 |
| azides in organometallic chemistry | Cenini, S.; La Monica, G. <i>Inorg. Chim. Acta</i> 1976 , <i>18</i> , 279 |
| azidocumulenes | L'abbé, G. <i>Bull. Soc. Chem. Belg.</i> 1984 , <i>93</i> , 579 |
| azidoquinones | Moore, H. W. <i>Chem. Soc. Rev.</i> 1974 , <i>3</i> , 415 |
| azidotrimethylsilane | Groutas, W. C.; Felker, D. <i>Synthesis</i> 1980 , 861 |
| azirines | Anderson, D. J.; Hassner, A. H. <i>Synthesis</i> 1975 , 483. Hassner, A. H. <i>Heterocycles</i> 1980 , <i>14</i> , 1517. Padwa, A.; Carlsen, P. H. J. In <i>Reactive Intermediates</i> ; Abramovitch, R. A., Ed.; Plenum: New York, 1982; Vol. 2, p 55 |
| azo transfer | Regitz, M. In <i>The Chemistry of the Diazonium and Diazo Groups</i> ; Patai, S., Ed.; Wiley: London, 1978; p 751. Regitz, M.; Maas, G. <i>Diazo Compounds: Properties and Synthesis</i> ; Academic: Orlando, 1986 |
| behavior of arylnitrenes in the gas phase | Wentrup, C. In <i>Reactive Intermediates</i> ; Abramovitch, R. A., Ed.; Plenum: New York, 1980; Vol. 1, Chapter 4 |
| carbonylnitrenes | Lwowski, W. Ref 9, p 185 |
| characterization and determination of organic azides | Gurst, J. E. Ref 10, p 191 |
| conjugated ketones | Moore, H. W.; Decker, O. H. W. <i>Chem. Rev.</i> 1986 , <i>86</i> , 821 |
| Curtius rearrangement | Reichen, W. <i>Chem. Rev.</i> 1978 , <i>78</i> , 569 |
| cyanonitrene | Anastassiou, A. G.; Marsh, F. D. Ref 9, p 305 |
| cycloadditions | Lwowski, W. In <i>1,3-Dipolar Cycloaddition Chemistry</i> ; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 559 |
| decomposition of organic azides | Abramovitch, R. A.; Kyba, E. P. Ref 10, p 221 |
| deoxygenation of aromatic nitro compounds | Cadogan, J. I. G. In <i>Organophosphorus Reagents in Organic Synthesis</i> ; Cadogan, J. I. G., Ed.; Academic: London, 1979; p 269 |
| deoxygenations of nitro and nitroso groups | Boyer, J. H. Ref 9, p 163 |
| derivatives of hydrazine and related compounds | Atkinson, R. S. In <i>Comprehensive Organic Chemistry</i> ; Sutherland, I. O., Ed.; Pergamon: Oxford, 1979; Vol. 2, p 256 |
| diazo transfer | Regitz, M. In <i>Methods of Preparative Organic Chemistry</i> ; Foerst, W., Ed.; Academic: New York, 1971; Vol. IV |
| directing and activating effects of organic azides | Biffin, M. E. C.; Miller, J.; Paul, D. B. Ref 10, p 203 |
| ESR of azides | Wasserman, E. <i>Prog. Phys. Org. Chem.</i> 1971 , <i>8</i> , 319 |
| electronic structure and spectroscopy of nitrenes | Berry, R. S. Ref 9, p 13 |
| electrochemistry | Iverson, P. E. In <i>Encyclopedia of Electrochemistry of the Elements</i> ; Bard, A. J., Lund, H., Eds.; Marcel Dekker: New York, 1979; Vol. 13, p 209 |
| electronic spectroscopy of azides | McGlynn, S. P.; Rabalais, J. W.; McDonald, J. R.; Scherr, V. M. <i>Chem. Rev.</i> 1971 , <i>71</i> , 73 |
| gas-phase and matrix studies | Wentrup, C. Ref 11, p 395 |
| general | Abramovitch, R. A. <i>Chem. Soc. Spec. Publ.</i> 1970 , <i>24</i> , 323 |
| general and theoretical aspects | Trienin, A. Ref 10, p 1 |
| halogen azides | Dehnicke, K. <i>Adv. Inorg. Chem. Radiochem.</i> 1983 , <i>26</i> , 169 |
| handling, storability, and destruction of azides | Pollock, B. D.; Fisco, W. J.; Kramer, H.; Forsyth, A. C. In <i>Energetic Materials</i> ; Fair, H. D., Walker, R. F., Eds.; Plenum: New York, 1977; Vol. 2, p 73 |
| heterocycles via nitrenes | Meth-Cohn, O. <i>Heterocycles</i> 1980 , <i>14</i> , 1497 |
| heterocyclic synthesis | Kametani, T.; Ebetino, E. F.; Yamanaka, T.; Nyu, K. <i>Heterocycles</i> 1974 , <i>2</i> , 209 |
| (i) synthesis of five-membered rings with one heteroatom | Semenov, V. P.; Studenikov, A. N.; Potekhin, A. A. <i>Chem. Heterocycl. Comp.</i> 1979 , <i>15</i> , 467 |
| (ii) synthesis of heterocycles | Semenov, V. P.; Studenikov, A. N.; Potekhin, A. A. <i>Chem. Heterocycl. Comp.</i> 1978 , <i>14</i> , 233 |
| indoxazenes and anthranils | Smalley, R. K. <i>Adv. Heterocycl. Chem.</i> 1981 , <i>29</i> , 2 |
| industrial applications | Breslow, D. S. Ref 11, p 491 |
| introduction of the azido group | Biffin, M. E. C.; Miller, J.; Paul, D. B. Ref 10, p 57 |
| iodo azides | Dehnicke, K. <i>Angew. Chem., Int. Ed. Engl.</i> 1979 , <i>18</i> , 507 |

TABLE 1 (Continued)

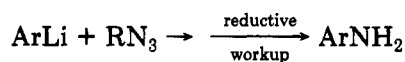
| topic | ref |
|--|---|
| lead tetraacetate oxidations | Aylward, J. B. <i>Q. Rev. Chem. Soc.</i> 1971 , <i>25</i> , 420 |
| main group element azides | Bertrand, G.; Majoral, J. P.; Baccaredo, A. <i>Acc. Chem. Res.</i> 1986 , <i>19</i> , 17 |
| <i>N</i> -nitrenes | Sakai, K.; Tanaka, A.; Koga, G.; Anselme, J. P. <i>Nippon Kagaku Zasshi</i> 1971 , <i>92</i> , 1065 |
| nitrene-induced aromatic rearrangements | Cadogan, J. I. G. <i>Acc. Chem. Res.</i> 1972 , <i>5</i> , 303 |
| nitrenes | Abramovitch, R. A. In <i>Organic Reaction Intermediates</i> ; McManus, S., Ed.; Academic: New York, 1973; p 127. Ioffe, B. V.; Semenov, V. P.; Ogloblin, K. A. <i>Zh. Vses. Khim. Ova</i> 1974 , <i>19</i> , 314. Jones, W. H. <i>Rearrangements in the Ground and Excited States</i> ; de Mayo, P., Ed.; Academic: New York, 1980. |
| | Lwowski, W. In <i>Reactive Intermediates</i> ; Jones, M., Moss, R. A., Ed.; Wiley: New York: 1978, Vol. 1, p 197; 1981, Vol. 2, p 315; 1985, Vol. 3, p 305 |
| | <i>Organic Reaction Mechanisms</i> ; Wiley: London, 1965 et seq. |
| nitrenes (annual survey) | Wentrup, C. <i>Adv. Heterocycl. Chem.</i> 1981 , <i>28</i> , 231 |
| nitrenes in heterocyclic chemistry | Semenov, V. P.; Studenikov, A. N.; Potekhin, A. A. <i>Sourem. Probl. Org. Khim.</i> 1982 , <i>7</i> , 97 |
| nitrenes in synthesis of six- and seven-membered nitrogen heterocycles | Abramovitch, R. A.; Jeyaraman, R. Ref 11, p 297. Gassman, P. G. <i>Acc. Chem. Res.</i> 1970 , <i>3</i> , 26. Lansbury, P. T. Ref 9, p 405 |
| nitrenium ions | Zbiral, E. <i>Synthesis</i> 1972 , 285 |
| organic syntheses using lead(IV) acetate azides | Meienhofer, J. In <i>Peptides</i> ; Gross, E., Meienhofer, J. Eds., Academic: New York, 1979; p 197 |
| peptide synthesis | Gilyarov, V. A. <i>Usp. Khim.</i> 1982 , <i>51</i> , 1579 |
| phosphorus acid azides | Cremlyn, R. J. W.; Wakeford, D. H. <i>Top. Phosphorus Chem.</i> 1976 , <i>8</i> , 1 |
| phosphorus azides | Knowles, J. R. <i>Acc. Chem. Res.</i> 1972 , <i>5</i> , 155. Lwowski, W. <i>Ann. N.Y. Acad. Sci.</i> 1980 , <i>346</i> , 491. Rilling, H. C. <i>Methods Enzymol.</i> 1985 , <i>110</i> (Part A), 125 |
| photoaffinity labeling | Bayley, H.; Staros, J. V. Ref 11, p 434 |
| photoaffinity labeling and related techniques | Chapman, O. L. <i>Pure Appl. Chem.</i> 1979 , <i>51</i> , 331 |
| photochemistry of azides in argon | Reiser, A.; Wagner, H. M. Ref 10, p 441 |
| photochemistry of the azido group | Bayley, H. <i>Photogenerated Reagents in Biochemistry and Molecular Biology</i> ; North-Holland/Elsevier: Amsterdam, 1983 |
| photogenerated reagents in biochemistry and molecular biology | Platz, M. S. Ref 11, p 359 |
| physical and spectrometric methods | Imoto, M.; Nakaya, T. <i>J. Macromol. Sci., Rev. Macromol. Chem.</i> 1972 , <i>7</i> , 1 |
| polymerization by nitrenes | Brown, R. F. C. <i>Pyrolytic Methods in Organic Chemistry</i> ; Academic: New York, 1980; Chapter 5 |
| pyrolytic methods | Peach, J. M.; Bailey, A. S. In <i>Studies in Organic Chemistry</i> ; Elsevier: Amsterdam, 1979; Vol. 3, p 56 |
| reactions of azides with indoles | Richardson, A. C. <i>Methods Carbohydr. Chem.</i> 1972 , <i>6</i> , 218 |
| reduction of azido sugars | Nishiyama, K. <i>Yuki Gosei Kagaku Kyokaiishi</i> 1985 , <i>43</i> , 176 |
| silyl azides | Abramovitch, R. A.; Sutherland, R. G. <i>Fortsch. Chem. Forsch.</i> 1970 , <i>16</i> , 1 |
| sulfonyl azides | Breslow, D. S. Ref 9, p 245 |
| sulfonylnitrenes | Richter, T. A. In <i>Energetic Materials</i> ; Fair, H. D., Walker, R. F., Eds.; Plenum: New York, 1977; Vol. 1, p 15 |
| synthesis and chemical properties of inorganic azides | Smalley, R. K.; Suschitzky, H. <i>Chem. Ind. (London)</i> 1970 , 1338 |
| synthetic aspects | Koldobski, G. I.; Ostrovskii, V. A.; Popavskii, V. S. <i>Chem. Heterocycl. Comp.</i> 1982 , <i>965</i> |
| tetrazoles | Duer, H.; Kober, H. <i>Top. Curr. Chem.</i> 1976 , <i>66</i> , 89 |
| triplet states of azides | Wentrup, C. <i>Top. Curr. Chem.</i> 1976 , <i>62</i> , 1973 |
| vapor-phase pyrolysis of aryl azides | Fowler, F. W. <i>Adv. Heterocycl. Chem.</i> 1971 , <i>13</i> , 45. Hassner, A. Ref 11, p 35. L'abbé, G. <i>Angew. Chem., Int. Ed. Engl.</i> 1975 , <i>14</i> , 775. L'abbé, G. <i>Newer Synthetic Methods</i> 1979 , <i>5</i> , 1. L'abbé, G.; Hassner, A. <i>Angew. Chem., Int. Ed. Engl.</i> 1971 , <i>10</i> , 98. Smolinsky, G.; Pride, C. A. Ref 10, p 555 |
| vinyl azides | Moore, H. W.; Goldish, D. M. <i>The Chemistry of Halides, Pseudohalides, and Azides</i> ; Patai, S., Ed.; Wiley: Chichester, 1983; Vol. 1, p 361 |
| vinyl, aryl, and acyl azides | Moore, H. W. <i>Acc. Chem. Res.</i> 1979 , <i>12</i> , 125 |
| zwittazido cleavage | |

An exhaustive review of this topic has just appeared.¹⁶



Z, Z' = COR, NO₂, CN, SO₂R, etc.

c. Amination (Section III.G)



R = vinyl, Ts, PhSCH₂, (PhO)₂P(O), TMSCH₂

II. Preparations

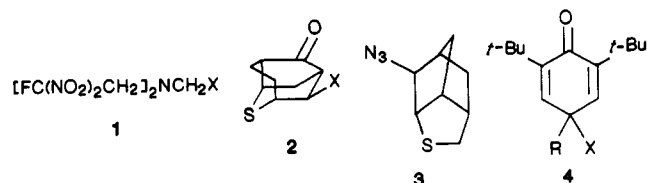
A. From Halides

1. By Displacement at Saturated Sites

The most commonly applied route, especially to alkyl azides, is halide displacement by azide ion or a con-

generic species. The reaction has been routinely used for the preparation of acyl azides (usually as intermediates for the Curtius reaction; see Section III.D) from the corresponding acyl chlorides and NaN₃¹⁷⁻²² or HN₃/pyridine.²³ The former approach has been improved by utilization of a phase-transfer catalyst (PT-C).²⁴ The same products are available from aryl chlorides with Me₃SiN₃/ZnI₂.²⁵ Mixed anhydrides have also been used to advantage (see section VI.A.4).

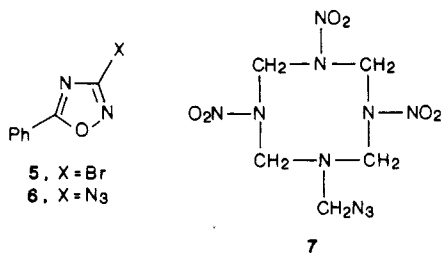
Similarly, (azidomethyl)bis(fluorodinitroethyl)amine (1, X = N₃) was prepared from its bromo congener (1,



X = Br) by treatment with sodium azide at 0 °C under

an inert atmosphere,²⁶ the azidoadamantane analogue (2, X = N₃) was obtained from 2 (X = Cl or OH) with NaN₃/57% sulfuric acid²⁷ (the chlorine in the equatorial position, as shown, was more reactive than that in the axial), azidothiabrendane (3) was isolated in quantitative yield from treatment of the bromo precursor with NaN₃/EtOH at 90 °C,²⁸ and the tertiary azides (4, X = N₃; R = Me, *t*-Bu) resulted from azide ion displacement of the corresponding bromo compounds (4, X = Br; R = Me, *t*-Bu).²⁹ In the latter, other dienones either did not react or gave only tar under the same conditions. Additionally, the reaction gave an 85% yield of the azido product in DMF at room temperature for 24 h but did not proceed in tetrahydrofuran or diethyl ether. Tertiary alkyl azides (as well as allyl or benzyl azides) have also been prepared by the action of NaN₃/ZnCl₂ on the appropriate halide.³⁰

With alkali metal azides (mainly sodium azide) it is usually helpful to use a polar solvent (typically DMF or DMSO, although acetone or even alcohols have found some use) to provide some homogeneity. In this regard, the increased solubility of lithium azide in such solvents can enhance the reaction rate or, in some cases, allow reaction where none occurred with sodium azide. Thus, the rate of reaction of azide ion with poly(vinyl chloride) was increased by the use of lithium azide in DMF or acetone.³¹ Additionally, the azidooxadiazole 6 could be prepared from the bromide 5 only by treatment with lithium azide in DMF or potassium azide and 18-crown-6.³² Attempted displacement with sodium azide/DMF, lithium azide/methanol, or tetrabutylammonium azide/acetonitrile led to a quantitative recovery of 5.



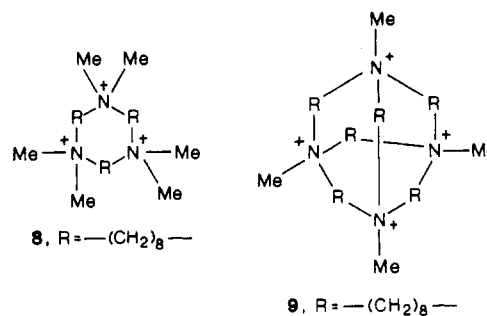
While good results can generally be obtained when DMF or DMSO is used, the difficulties associated with azide isolation from such solvents as well as the desire for homogeneity have stimulated considerable interest in alternatives.

One such is the utilization of organic azides, e.g., MeCON₃ and Me₃SiN₃, as the azide source. Both are soluble in organic solvents and permit azide synthesis under nonbasic conditions. The former has been used in a novel synthesis of the trinitro azide 7 from its bromo congener in 79% yield.³³ The acetyl azide is generated in situ and used at 10–15 °C to avoid decomposition into methyl isocyanate. A previous attempt to prepare 7 by treatment of the corresponding acetate with NaN₃ was unsuccessful.³⁴ The generality of this process has not been assessed but it would appear that activated halides are necessary. Trimethylsilyl azide also reacts with activated halides (benzyl chloride and benzyl bromides, allyl bromides, chloroacetonitrile, and ethyl chloroacetate) in hexamethylphosphoramide at 60 °C to give the azido compounds in good to excellent yield under homogeneous, neutral, nonaqueous conditions.³⁵ Olah and co-workers³⁶ have

shown that both secondary and tertiary cyclic azides can be prepared in 48–92% yield from the chlorides or bromides by using trimethylsilyl azide in the presence of stannic chloride.

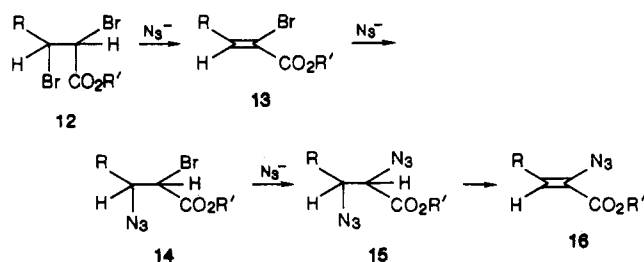
Another widely used approach is the addition of a phase-transfer catalyst, permitting use of solvents such as benzene. Thus, as previously mentioned, 6 could be prepared from 5 by using potassium azide and 18-crown-6,³² and numerous alkyl azides were synthesized from the corresponding bromides by heating under reflux in benzene in the presence of 5–10 mol % of tetrabutylammonium bromide.³⁷ The crude azides were reduced in situ by the Staudinger process (see section III.A.4). It was claimed³⁷ that better yields of the azides were obtained with an anhydrous solid-liquid PTC system (i.e., with solid sodium azide suspended in benzene) than from the reported^{38,39} liquid-liquid cases. The rates of nucleophilic substitution by N₃⁻ (as the hexadecyltributylphosphonium salt) in a series of *n*-octyl halides (and sulfonates) have been measured in different solvents (MeOH, DMSO, PhCl, cyclohexane). For the halo derivatives, the highest rates were in DMSO (cyclohexane for the mesylates), and in all solvents used the nucleofugacity scale was I > Br > Cl (their positions relative to mesylate and tosylate differed depending on the solvent).⁴⁰ While not a synthetic study, per se, the results obtained allow selection of an appropriate solvent and leaving group for a particular synthetic goal.

Along similar lines, the S_NAr reaction of azide ion with 1-halogeno-2,4-dinitrobenzenes is subject to significant catalysis by micelles of cetyltrimethylammonium bromide.^{41,42} It is claimed that the rate of these reactions can be further enhanced by the use of macrocyclic quaternary ammonium salts (cf. 8 and 9).^{43,44} Apparently, the azide ion is incorporated into the cavity of the cationic host prior to the rate-limiting step.



An interesting modification of this process has been developed recently.⁴⁵ Thus, graft polymerization of acryloyl onium salts (A-C_n⁻⁺XR₃, n = 2, 6, 10; X = N, P; R = Me, Bu) onto a large, porous ultrathin nylon-2,12 capsule membrane provides phase-transfer catalysts that accelerate reactions between benzyl bromide in the inner organic phase (chloroform) and water-soluble azide ion in the outer phase. It is claimed⁴⁵ that there is no observable induction period for the reaction, in contrast to many other insoluble polymer-supported PTC wherein swelling of the resin occurs.⁴⁶ The reaction rate is affected by azide ion concentration and the length and hydrophobicity of the onium salt side chain. Hassner has shown⁴⁷ that essentially quantitative azidation of activated and nonactivated alkyl halides can be achieved at room temperature with a polymeric

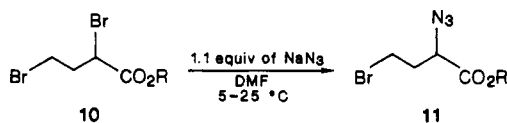
SCHEME 1



quaternary ammonium azide.

A useful addition for activated primary halides is ultrasound-promoted azidation in aqueous solution.⁴⁸ Reaction time is short (1–4 h), conditions are relatively mild (60 °C), isolation is straightforward, and yields are good to excellent. However, the reaction is apparently limited to propargyl-, allyl-, or cyanomethyl-activated species since 1-bromopropane under the same conditions gave only a 20% conversion to propyl azide.

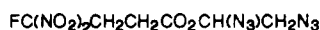
Treatment of dibromo ester 10 (R = Me) with a slight excess of sodium azide in DMF at 5 °C gives monoazide 11 (R = Me) in high yield and about 15% of the diazido



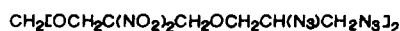
species.⁴⁹ The trimethylsilyl analogue 11 (R = Me₃SiCH₂CH₂) has been similarly prepared.⁵⁰ Presumably, steric factors favoring displacement at the primary site are countered by the electron-withdrawing effect of the ester function.

The related dibromo esters 12 (R = H, Me, Et, cyclohexyl; R' = Me, Et) react with 3 equiv of sodium azide to yield (*Z*)-2-azido-2-alkenoates (16) in good yield. The mechanism outlined in Scheme 1 has been proposed on the basis of model studies.⁵¹ Thus 12 (R = H, R' = Et) gave diazido ester 15 (R = H, R' = Et) in quantitative yield on treatment with 3 equiv of sodium azide at 20 °C in DMF, whereas 12 (R = Me, R' = Et) gave only 13 (R = Me, R' = Et). A similar product, 13 (R = H, R' = Et), was obtained from the reaction of 12 (R = H, R' = Et) with 1 equiv of sodium azide in DMF at 25 °C.⁵¹ Eliminative azidation has also been observed⁵² in the treatment of a 1,2-dibromobenzazepine derivative with sodium azide at room temperature.

1,2-Diazides containing other energetic groups (cf. 17 and 18) can be prepared from the corresponding dibromo compounds by overnight treatment with sodium azide.²⁶ Propargylic diazides 19 and 20 are similarly obtained.⁵³ The latter are extremely explosive and



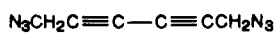
17



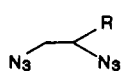
18



19



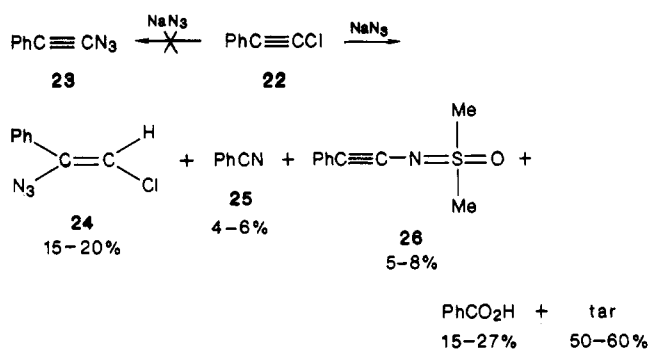
20



21

must be stored at low temperature; they survive several weeks at –25 °C. The results of a recent study con-

SCHEME 2

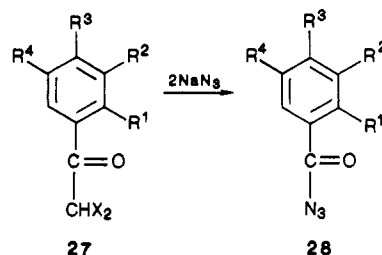


cerning the stability of functionalized vicinal diazides (cf. 21) in the presence of mild base suggest that unsaturated functional groups (–M type, e.g., R = COMe, CN, and CPh) destabilize the diazide.⁵⁴

2. With Rearrangement

In an attempt to prepare the elusive azidophenylethyne (23), chlorophenylethyne (22) was allowed to react with sodium azide in DMSO for 3 days at 25 °C.⁵⁵ Not unexpectedly,⁵⁶ the desired compound was not obtained (see Scheme 2) but one of the products (viz., 26) was rationalized as arising from decomposition of 23 to the nitrene and subsequent reaction with DMSO. The isolation of 24 suggests that attack at C-2 is a major competing process, as it is in other nucleophilic reactions with halogenoarylethyne.⁵⁷

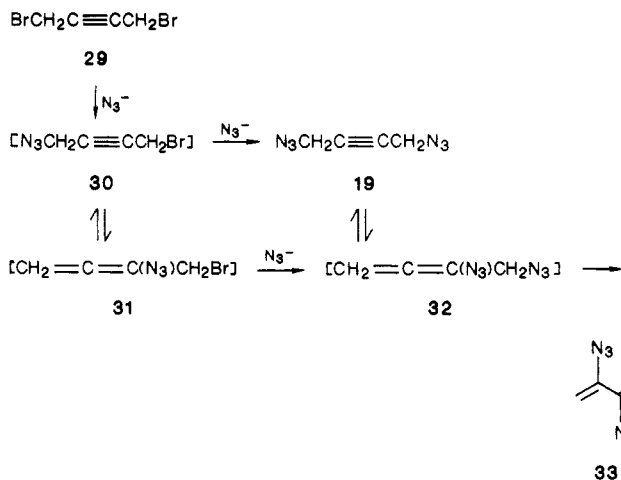
The ω,ω-dibromoacetophenone derivatives 27 (X = Br) react with 2 equiv of sodium azide to form the aroyl azides 28.⁵⁸ The process is apparently not merely displacement of dibromomethane anion but is rationalized as involving rearrangement of the initially formed diazide 27 (X = N₃) and subsequent extrusion of HCN and N₂.



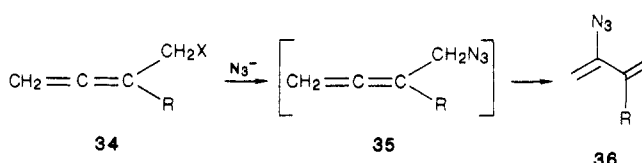
R¹ = H, NO₂, NHCOMe; R² = H, NO₂, Cl
R³ = H, halogen, NO₂, OMe, Ph, SO₂Me, NHCOMe; R⁴ = H, Br

As previously noted the propargylic diazide 19 can be isolated and stored at low temperature. However, warming solutions of 19 in benzene, chloroform, or aqueous acetone to 40–70 °C gives 2,3-diazido-1,3-butadiene (33).⁵⁹ This is the first example of direction of an azido group to a vinyl position by allyl rearrangement. Previously, only allyl rearrangements to allyl positions were known in propene and butene systems.⁶⁰ Diazide 33 could also be prepared directly from 29 (1 equiv) by heating (50 °C) with sodium azide (4 equiv) in ethanol/water. The series of reactions and equilibria shown in Scheme 3 has been postulated to explain these results. The rate of formation of 33 from 19 and thermodynamic data suggest a nonionic process involving sequential migration of the two azide groups in 19. Although none of the postulated intermediates

SCHEME 3

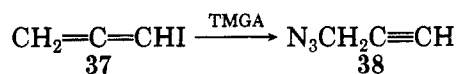


SCHEME 4

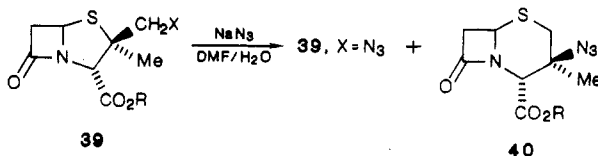


(30–32) to 33 could be isolated, the likelihood of their existence was strengthened by the isolation of 2-azido-1,3-butadiene (36, R = H) from the reaction of 4-bromo-1,2-butadiene (34, X = Br, R = H) with sodium azide in aqueous methanol for 5 days (Scheme 4). Compound 36 (R = H) could be more conveniently prepared from 34 (X = Br, R = H) and tetramethylguanidinium azide in sulfolane (1.5 h, 55–60 °C).⁵⁹ The postulated intermediate, viz., 35 (R = H), could not be isolated in the present study; however, in a closely related examination of the reaction of 34 (X = Cl, R = Me) and sodium azide, it was found that if the reaction was prematurely terminated, then 34 (X = Cl, R = Me), 36 (R = Me), and 35 (R = Me) were obtained.⁶¹ Better yields of 35 (R = Me) resulted from treatment of 34 (X = Cl, R = Me) with hexadecylphosphonium azide.

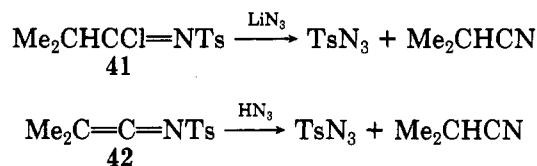
Tetramethylguanidinium azide (TMGA) in sulfolane also reacts with iodoallene (37) to give 3-azido-1-propyne (38).⁵³



Treatment of the halopenams 39 (X = Br, Cl) with sodium azide in DMF/water at 25 °C gave both azidopenam (39, X = N₃) (60–65%) and azidocepham (40) (35–40%).⁶²

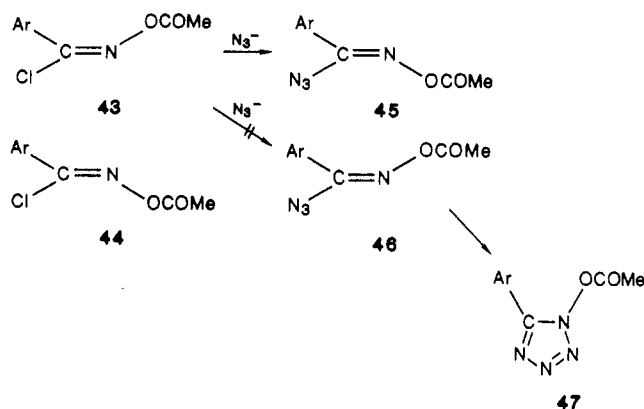


Eliminative azidation to form tosyl azide and isobutyronitrile occurs on treatment of the *N*-tosylimidoyl chloride 41 with lithium azide or the *N*-tosylketenimine 42 with hydrazoic acid.⁶³

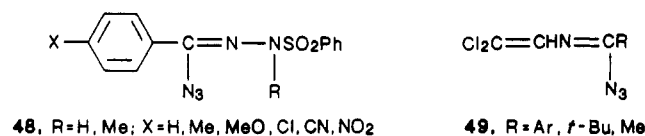


3. By Displacement at Unsaturated Sites

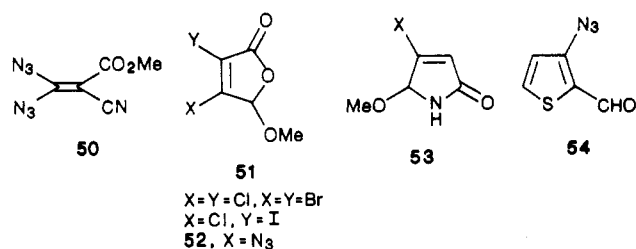
Both *E* and *Z* *O*-acyl imidoyl chlorides (43 and 44, respectively) react stereospecifically with sodium azide in acetone/water (1:1) at 25 °C to give quantitative formation of the *Z* azide (45).⁶⁴ No *E* azide (46) or tetrazole (47) (to which 46 should cyclize;⁶⁵ see section VI.B.4) was present in the reaction mixtures. The results have been rationalized mechanistically.



Hydrazonoyl azides (48)⁶⁶ and the unstable 1-azido-2-aza-1,3-butadiene derivatives (49)⁶⁷ have been prepared in standard fashion by the action of sodium azide on the corresponding chlorides.

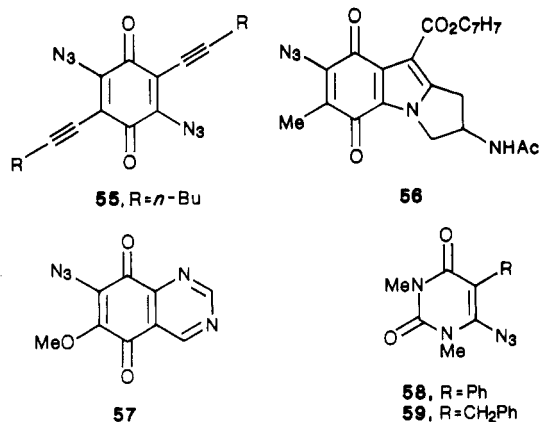


Methyl 3,3-dichloro-2-cyanoacrylate and sodium azide in acetone/water at –15 °C react in a few seconds to form diazide 50.⁶⁸ The 4-azido-2-furanones 52⁶⁹ are

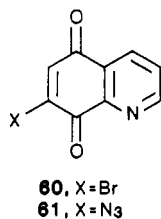


formed by Michael addition of sodium azide on the furanones 51 in methanol. The halide α to the carbonyl function remains intact. Bromopyrroline 53 (X = Br) reacts analogously to form 53 (X = N₃) in 85% yield.⁷⁰ No reaction occurred in THF. The yield (from the bromo species) of 3-azidothiophene-2-carbaldehyde (54) was increased from 45%⁷¹ to 75%⁷² by use of NaN₃ in HMPA rather than in DMSO.

Azidoquinones 55,⁷³ 56,⁷⁴ and 57⁷⁵ are similarly prepared from the corresponding halides. However, due to its instability, 57 was not isolated but used in situ for further transformations. The azidouracil derivatives 58 and 59 were likewise obtained.⁷⁶

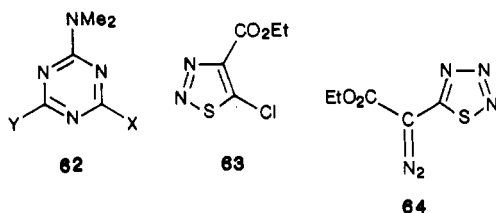


Recently, Boger and co-workers⁷⁷ studied azide attack on 7-bromoquinoline-5,8-quinone (60) as a model for the



preparation of the AB ring system in lavendamycin. Thus, treatment of 60 with sodium azide gave 7-azidoquinoline-5,8-quinone (61) in 91% yield. Interestingly, with excess reagent (1.5 equiv) 7-amino-6-azidoquinoline-5,8-quinone was the major product. Similar results had been observed previously with 2-bromo-1,4-naphthoquinone.⁷⁸

Displacement of activated heterocyclic halides is also possible (cf. 62 (X = Y = Cl) → 62 (X = Y = N₃) and 62 (X = NMe₂, Y = Cl) → 62 (X = NMe₂, Y = N₃),⁷⁹ although on occasion rearrangements occur. Thus, 4-carbethoxy-5-chloro-1,2,3-thiadiazole (63) gave diazo compound 64 in 77% yield on treatment with sodium azide in acetone/water at 0 °C. The corresponding azide was postulated as an intermediate.⁸⁰



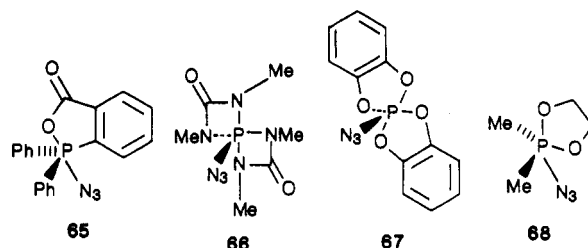
4. By Displacement at Atoms Other than Carbon

Various heteroazido species are commonly encountered: inter alia, halogen azides (see section II.G), tosyl azide (see section II.J)⁸¹ and other sulfonyl azides,^{82,83} diphenyl phosphorazidate,⁸⁴ and trimethylsilyl azide,⁸⁵ all of which can be made from the action of NaN₃ on the appropriate halide. The last two of these (viz., (PhO)₂P(O)N₃ and Me₃SiN₃) are now commercially available.⁸⁶

The *gem*-diazido-⁸⁷ and triazidosilanes⁸⁸ Me₂Si(N₃)₂ and PhSi(N₃)₃ have been prepared for photolysis and thermolysis studies.^{89,90}

Azidophosphoranes 65–67 were synthesized by the action of trimethylsilyl azide on the chlorophosphoranes.⁹¹ Previous to these preparations only one azidophosphorane (viz., 68) had been reported.⁹²

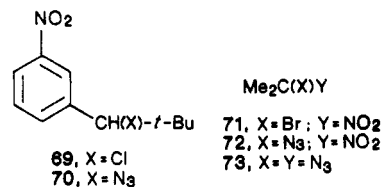
Bis(diisopropylamino)phosphinyl azide is derived from the chloride in the same manner.⁹³



Similarly, aryl-⁹⁴ alkyl-⁹⁵ and heteroalkylazido-boranes⁹⁶ (R₂BN₃) and diazidoboranes⁹⁶ have been prepared. Dibutyltin and dibenzyltin chlorides react with sodium azide to give the dialkyltin azides.⁹⁷ For kinetic studies, solutions of benzenesulfonyl azide (PhSON₃) were prepared at –20 °C from benzenesulfonyl chloride and sodium azide in 1,2-dimethoxyethane or acetonitrile,⁹⁸ an improvement on the literature method.⁹⁹

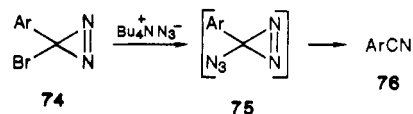
5. Via S_{RN}1 Reactions

Chloro compound 69 undergoes an S_{RN}1 reaction with sodium azide to provide the corresponding azide 70.¹⁰⁰ Similarly, an S_{RN}1 mechanism has been implicated in the preparation of the α-nitro azide 72 from the corresponding bromo compound 71.¹⁰¹ Interestingly, with excess azide ion, 72 reacts further to give the diazido species 73.

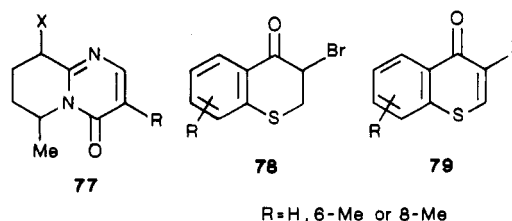


6. Thwarted Attempts

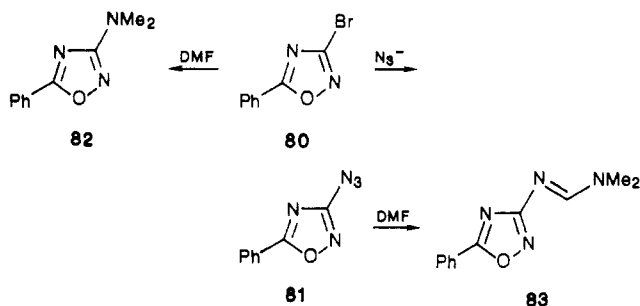
The reaction of arylbromodiazirines 74 with tetra-butylammonium azide gave the corresponding nitriles 76, presumably via azide 75 intermediacy.^{102,103}



Attempted azidation of the bromo compounds 77 (X = Br; R = CONH₂, CN) with sodium azide in acetone at 25 °C gave moderate yields (42% and 55%, respectively) of the amino congeners 77 (X = NH₂; R as above).¹⁰⁴ Presumably the azide is initially formed and cleavage occurs via neighboring group participation by a pyrimidine ring nitrogen. The aminothiochromone 79 (X = NH₂) resulted from azide treatment of 78 in MeOH/H₂O.¹⁰⁵ Interestingly, in DMF/H₂O, elimination to form 79 (X = H) occurred.

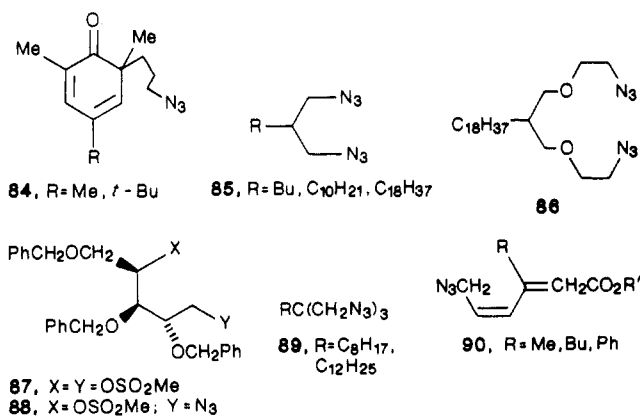


Treatment of 3-bromo-5-phenyl-1,2,4-oxadiazole (80) with sodium azide in DMF at 130 °C gave 3-(dimethylamino)-5-phenyl-1,2,4-oxadiazole (82) (39%) and 3-(((dimethylamino)methylene)amino)-5-phenyl-1,2,4-oxadiazole (83) (34%).¹⁰⁶ The azide 81 was formed at lower temperature and was shown to be a precursor of 83.



B. From Sulfonates and Acetates

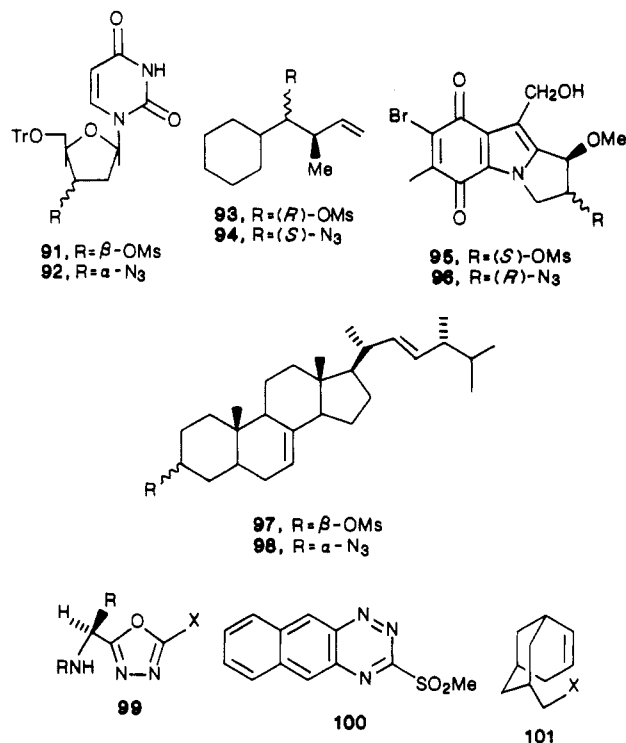
The displacement of sulfonates by azide ion, or congeneric species, is another important route to organic azides, especially alkyl examples. Overall, the process can be used as an indirect conversion of an alcohol to an azide (see section II.E for direct conversion). The most commonly employed sulfonate leaving group is the methanesulfonate (mesyl) moiety. Choice of conditions for displacement by azide ion is dictated by the same factors as described for halide leaving groups (see section II.A). Thus, in DMF, the azido compounds 84,¹⁰⁷ 85,¹⁰⁸ and 86¹⁰⁸ are prepared in good yield by the action



of NaN₃ on the mesylates (also PhSO₂ for 85). Selective displacement of a primary mesylate in the presence of a secondary mesylate can be effected in the same manner (cf. 87 → 88).¹⁰⁹ Similarly, triazide 89 is obtained by using NaN₃/Bu₄NCl in HMPA.¹⁰⁸ For the long-chain azides 85, 86, and 89, the nucleophilic substitutions leading to their formation required polar, aprotic solvents rather than ethylene glycol (as previously described for shorter chain analogues¹¹⁰). The 6-azidohexa-2,4-dienoates 90 were also prepared from the corresponding mesylates.¹¹¹

The S_N2 nature of the substitution (i.e., inversion of configuration) is apparent from a number of examples: inter alia, 91 → 92,¹¹² 93 → 94,¹¹³ 95 → 96,⁷⁴ and 97 → 98.¹¹⁴

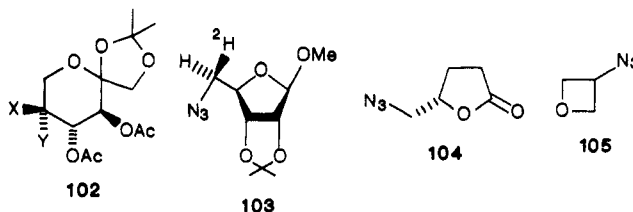
Displacement can be extended to activated aromatic systems; thus, oxadiazole 99 (X = N₃) results from treatment of 99 (X = SO₂Me) with NaN₃ in EtOH.¹¹⁵



A similar attempt with 100 gave a tetrazole derivative (see section VI.B.4) presumably derived from the initially formed azido compound.¹¹⁶

Tosyl groups can also be displaced, although not always efficiently, as evidenced by the attempts to prepare 101 (X = N₃) from the tosylate 101 (X = OTs).¹¹⁷ Thus, with sodium azide in dipolar aprotic solvents a low yield of the azido species was obtained, presumably because of competing π-route cyclization to adamantan-2-ol. With a 9-fold excess of sodium azide in DMSO at 90 °C for 5 days, a mixture of the required azide (34%) and adamantan-2-ol (65%) resulted. A 15-fold excess of sodium azide in DMF in the presence of 15-crown-5 at room temperature for 4.5 days gave 101 (X = N₃) (21%) and adamantan-2-ol (12%). Various other reaction conditions were employed, with no improvement in results.

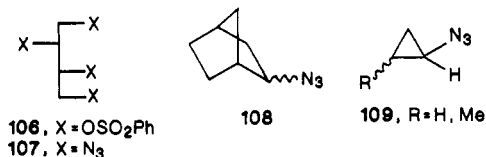
In contrast, tosylate 102 (X = OTs, Y = H) gave the azido compound 102 (X = H, Y = N₃) in 74% yield by treatment with lithium azide in DMF.¹¹⁸ Similarly, high yields (95% and 87%, respectively) of the azido sugar 103 and lactone 104 were obtained with sodium azide in DMF at 100 °C¹¹⁹ and reflux,¹²⁰ respectively.



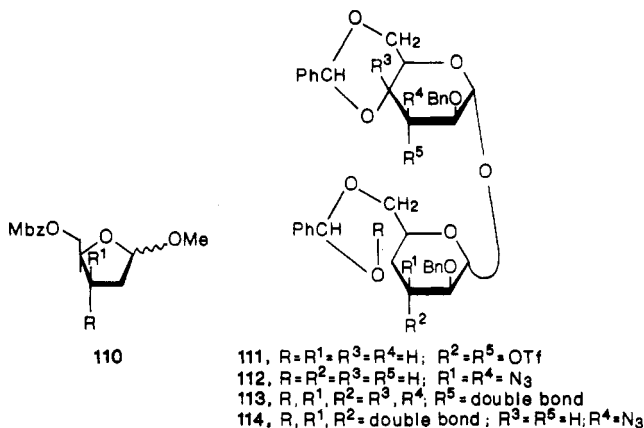
Reaction of 3-(tosyloxy)oxetane with liquid ammonia gave only a low yield of the corresponding amino compound, and hence a two-step process via 105 was instead employed (see section III.A).¹²¹ A 50% yield of 105 was obtained with KN₃ at 87 °C in HMPA and a 28% yield in refluxing acetonitrile in the presence of 18-crown-6. However, using NaN₃ and the tosylate in tetraethylene glycol (or higher homologues) at 120–130 °C and 7–10

mmHg gave an 86% yield of 105. The explosive azide distilled from the reaction mixture but was handled safely by collection in dichloromethane and use in solution.

The benzenesulfonate leaving group has been little utilized. One interesting example, however, is the conversion of 106 to the tetraazide 107 en route to the corresponding tetraamine.¹²² Likewise, there are very



few reports concerning displacement of 4-bromobenzenesulfonate (brosyl) groups by azide ion. In part, this may be due to the known incidence of competitive S_NAr bromine substitution.^{123,124} However, despite this difficulty, excellent yields of 2-norbornyl azides (108) were obtained by S_N2 displacement of the appropriate brosylates with tributylhexadecylphosphonium azide in toluene.¹²³ The same reagent also effects S_N2 displacement of cyclopropyl trifluoromethanesulfonates to give the cyclopropyl azides 109 and allylic azides as minor products.¹²⁵ The percentage of the product mixture comprising the cyclic azide decreased with growing steric hindrance. The use of the trifluoromethanesulfonyl (triflyl) group can sometimes be advantageous in that conversion occurs under very mild conditions; e.g., 110 (R = N₃, R¹ = H) was prepared



from the triflate 110 (R = H, R¹ = OTf) by treatment with LiN₃ in ethanol at room temperature for 40 min.¹²⁶ Competing elimination can be a problem, however; treatment of the ditriflate 111 with lithium azide under a variety of conditions gave a mixture of the required diazide 112 and the mono- and dialkenes 113 and 114.¹²⁷

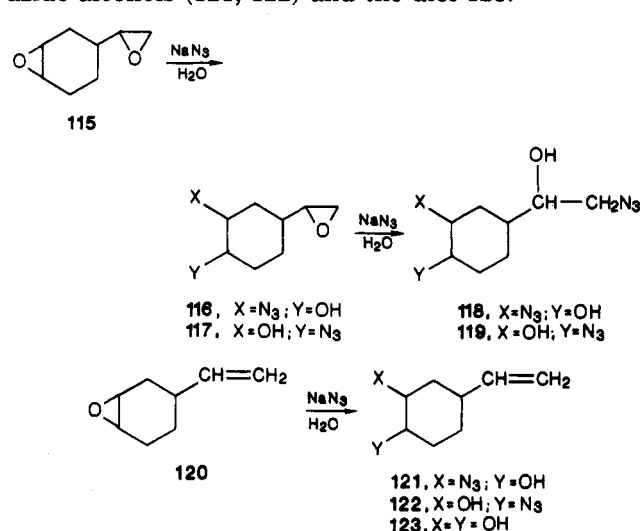
The first report of palladium-catalyzed azidation of allylic acetates appeared recently.¹²⁸ The conversion was effected under mild conditions (room temperature) and in good yield (66–88%) with sodium azide and a catalytic amount of Pd(Ph₃)₄ in THF/water. The process can be used as a "one-pot" amine preparation by in situ azide reduction (triphenylphosphine/NaOH) (see section III.A).

C. From Epoxides

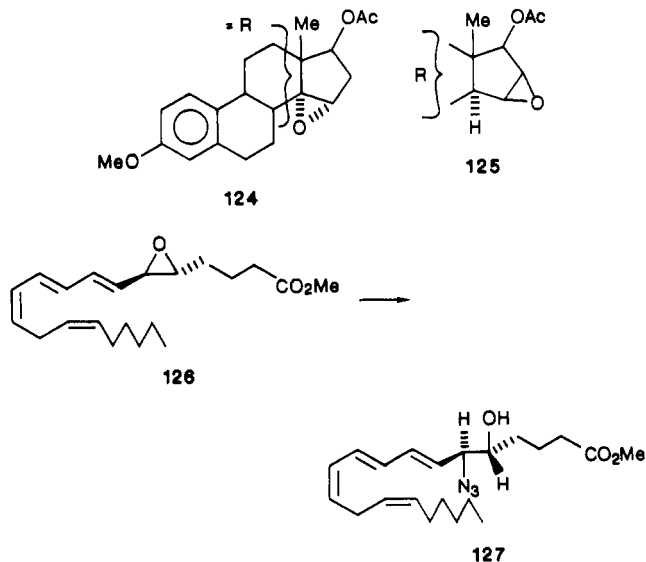
Azidation of epoxides often proves advantageous in that the azido alcohol normally formed is difunctional

(see section III.C for further transformations). Several other examples of this process are reported in section V.

Reaction of the diepoxide 115 with sodium azide gave a mixture of azides (116, 117) derived only from ring epoxide cleavage. Further treatment of the mixture (116, 117) with NaN₃ gave the expected diazides (118, 119).¹²⁹ Similar treatment of 120 gave a mixture of the azido alcohols (121, 122) and the diol 123.¹²⁹

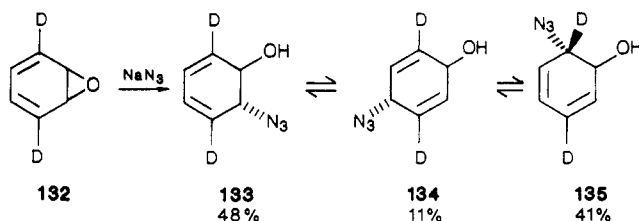
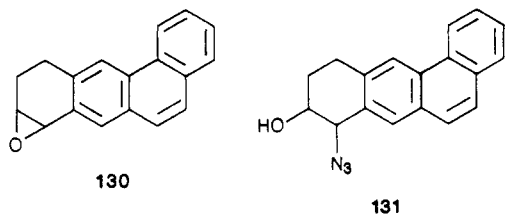
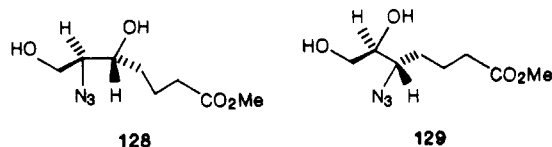


The reaction has been extended to the steroidal epoxides (124, 125) to give the 15- and 16-azido steroidal alcohols, respectively.¹³⁰ Additionally, in an attempt to transform the epoxide to an aziridine using Blum's two-step procedure ((1) NaN₃, (2) Ph₃P)¹³¹ (see section III.C), the epoxy ester 126 was transformed to azido alcohol 127 in >90% yield by treatment with sodium azide in MeOH/NEt₃ for 3 h at room temperature. The subsequent cyclization was unsuccessful.¹³²

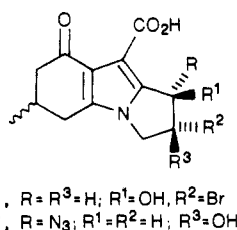


The mixture of azido alcohols (128, 129) was similarly prepared.¹³² Regioselective addition was also observed for the reaction of various polycyclic aromatic hydrocarbon epoxides (cf. 130 → 131) with sodium azide in acetone. Depending on reaction conditions the other azido alcohol was formed in 0–20% yield.¹³³

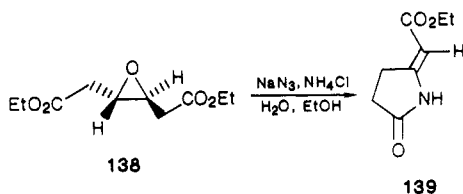
The deuteriated cyclohexadienyl epoxide 132 reacts with NaN₃ in water to give a mixture of three azido alcohols (133–135), postulated as arising from initial



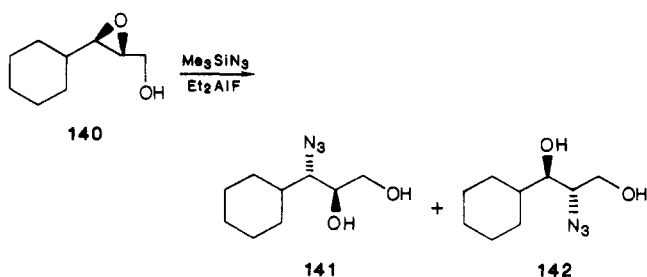
1,2-addition followed by [3,3]-sigmatropic rearrangement.¹³⁴ An intermediate epoxide is probably involved in the regio- and stereospecific conversion of 136 to 137.⁷⁴ Interestingly, the oxirane 138 gives a 67% yield



of a mixture of *E* and *Z* isomers of 139 on refluxing with NaN₃ and NH₄Cl in 60% EtOH for 18 h¹³⁵ (for similar transformations, see section III.C).



Greater control of regio- and stereoselectivity is often possible with Me₃SiN₃ (TMSA) and a Lewis acid catalyst. Thus, cyclohexene oxide and propylene oxide react slowly at room temperature with trimethylsilyl azide in the presence of a variety of Ti or V catalysts to give the anti and primary azido alcohols, respectively.¹³⁶ Similarly, the 2,3-epoxy alcohol 140 gives the azido diols (141, 142) (98:2) in 85% yield by treatment with TMSA and Et₂AlF in dichloromethane at room temperature. Other Lewis acids led to decomposi-

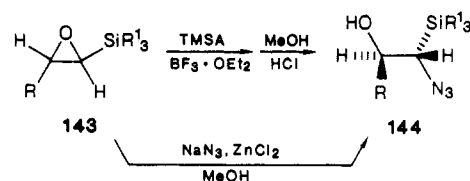


tion.¹³⁷ Similar regioselectivity was observed with other 2,3-epoxy alcohols using TMSA and a stoichiometric quantity of Ti(O-*i*-Pr)₄,^{138,139} TMSA and a catalytic quantity of Ti(O-*i*-Pr)₄,¹³⁶ and TMSA and ZnCl₂.¹⁴⁰ These methods apparently circumvent the steric difficulties encountered in the conventional method with azide ion. Thus, conventional azidation of 140 reportedly provides a (1.7–2):1 ratio of 141:142.¹⁴¹ More recently, a 13-compound study of the regioselectivity of ring opening with ammonium azide in analogues of 140 has been reported.¹⁴²

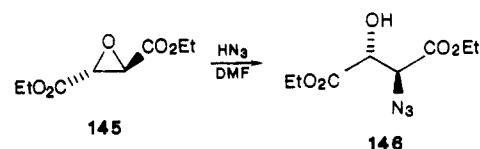
By comparison with sodium azide supported on alumina or silica, or the sodium azide/ammonium chloride system, sodium azide impregnated on a calcium cation exchanged Y-type zeolite (CaY) induced C-3 opening of 140 (and two analogues) with much greater selectivity to form predominantly 141 (or congeners).¹⁴³

Ti(O-*i*-Pr)₄ also catalyzes the regioselective ring opening of monofunctional epoxides with trimethylsilyl azide.¹⁴⁴ The primary azido species is formed with remarkable regioselectivity (92:8 → 100:0).

The boron trifluoride diethyl etherate catalyzed reaction of 1,2-epoxysilanes 143 (R = H, 1-hydroxy-1-cyclohexyl; R¹ = Me, Et) with TMSA followed by brief treatment with a trace amount of HCl in methanol afforded (1-azido-2-hydroxyalkyl)silanes 144 in 74–86% yield.¹⁴⁵ Direct conversion of 143 (R = alkyl, R¹ = Me, Et) to 144 could be effected in lower yield by prolonged treatment with sodium azide/zinc chloride in methanol.



On occasion hydrazoic acid itself has been utilized for the oxirane ring opening. Thus, epoxysuccinate 145 was converted to azido alcohol 146 in 97% yield by treat-

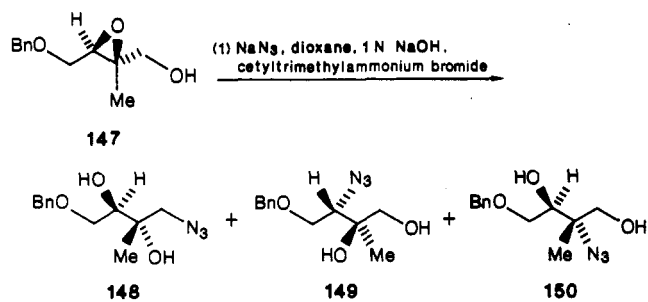


ment with HN₃ in DMF.¹⁴⁶ The hydrazoic acid was generated in situ from TMSA and methanol in DMF.¹⁴⁷ Other azide ion oxirane cleavage methods did not satisfactorily effect the transformation, and DMF appears to be essential. Regioselective ring opening by HN₃/Et₃Al has also been reported.¹⁴⁸

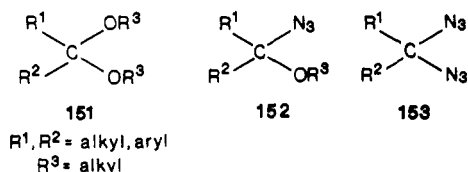
Under Payne rearrangement conditions epoxy alcohol 147 reacts with excess sodium azide to give azido diol 148 in 52% yield.¹⁴⁹ The use of a phase-transfer catalyst is essential and it appears that the PTC facilitates the Payne rearrangement. Support for this premise comes from the fact that two minor products (149, 150) formed in the catalyzed reaction become major components in the noncatalyzed process.

D. From Ketals

Ketals (cf. 151) can be converted to the corresponding α -alkoxy azides (152) or diazides (153) by treatment with trimethylsilyl azide (1 or 2 equiv, respectively) and



tin(IV) chloride.¹⁵⁰ With 2 equiv of trimethylsilyl azide,

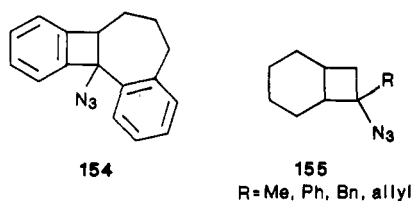


diphenyl ketal 151 ($\text{R}^1 = \text{R}^2 = \text{Ph}$) is converted to a tetrazole, presumably via diazide (153) intermediacy.¹⁵⁰ Similar results were obtained with the α -hydroxy analogues 151 ($\text{R}^1 = \text{CH}_2\text{OH}$; $\text{R}^2 = 4\text{-MeOC}_6\text{H}_4$, $4\text{-MeC}_6\text{H}_4$; $\text{R}^3 = \text{Me}$). The necessity for activating substituents is manifest since 151 ($\text{R}^1 = \text{CH}_2\text{OH}$; $\text{R}^2 = \text{Ph}$, $4\text{-ClC}_6\text{H}_4$; $\text{R}^3 = \text{Me}$) gave monoazido silyl ether 152 ($\text{R}^1 = \text{CH}_2\text{OSiMe}_3$).¹⁵¹ For a similar transformation to a tetrazole, see section VI.B.4.

E. From Alcohols

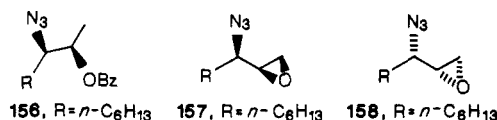
Azides can be prepared from alcohols in a two-step process involving conversion to a sulfonate and subsequent azide ion displacement (see section II.B). Direct conversions will be enumerated here.

Tertiary alcohols can be converted directly to azides (cf. 154 and 155) by using hydrazoic acid and boron trifluoride as catalyst.¹⁵²⁻¹⁵⁴ Other Lewis acids can be



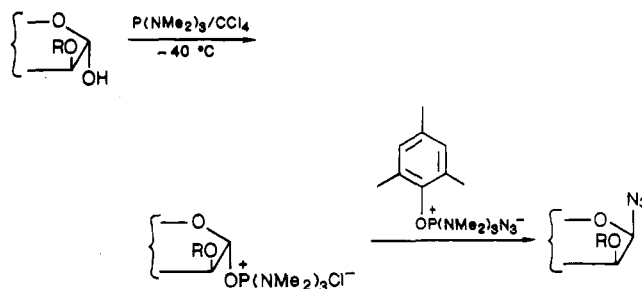
utilized and recently it was shown that $\text{HN}_3/\text{TiCl}_4$ smoothly converts benzylic, allylic, or tertiary alcohols to the corresponding azides in good yield.¹⁵⁵ Primary alcohols are unaffected and stereochemistry is not maintained, indicative of a carbocation intermediate.

The modified Mitsunobu reaction¹⁵⁶ (Ph_3P , DEAD, HN_3 , benzene, 2 h, 20 °C) converts alcohols to azides with inversion of configuration. Thus, azido benzoate 156 and epoxides 157 and 158 were prepared from the appropriate alcohols.¹⁵⁷

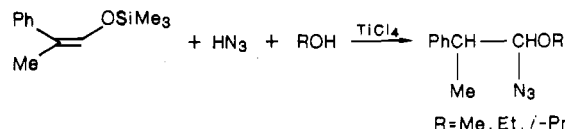


In some cases apparent rearrangement occurs; e.g., the secondary alcohol 6 β -hydroxypregnane (159) reacts with BF_3/HN_3 to give the 5-azido analogue 161, pre-

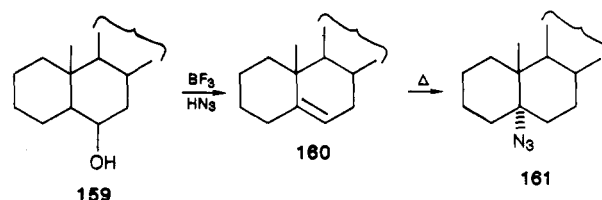
SCHEME 5



SCHEME 6



sumably via HN_3 addition to a Δ^5 -pregnene (160) intermediate.¹⁵⁸



Activation of the alcohol function by formation of a phosphonium salt has also been reported. Thus, protected sugars with a free anomeric OH can be directly converted to the glycosyl azides (with inversion of configuration) under extremely mild conditions as shown in Scheme 5.¹⁵⁹

F. From Carboxylic Acids

The preparation of acyl azides from acyl halides has been previously described (see section II.A). Similar two-step procedures (from the carboxylic acid) have been developed by using the reaction of a mixed anhydride with sodium azide.^{23,160}

One-pot reactions are potentially more useful, however, since one synthetic step is excised. A few such transformations have been reported. Thus, carboxylic acids react with O,O -diphenylphosphoryl azide to give the corresponding acyl azides.¹⁶¹ More recently, N,N -dimethyl(chlorosulfonyl)methaniminium chloride ($\text{Me}_2^+\text{N}=\text{CHOS}(\text{O})\text{ClCl}^-$; from thionyl chloride and DMF) was used as an activating reagent for the reaction of carboxylic acids with NaN_3 .¹⁶² For the four examples studied, yields were good to excellent (75–96%) and the conditions employed were mild (15–20 h, room temperature). Similar activation has been achieved with phenyl dichlorophosphate.¹⁶³ With the latter the conditions were also mild and outstanding yields were obtained (85–100%).

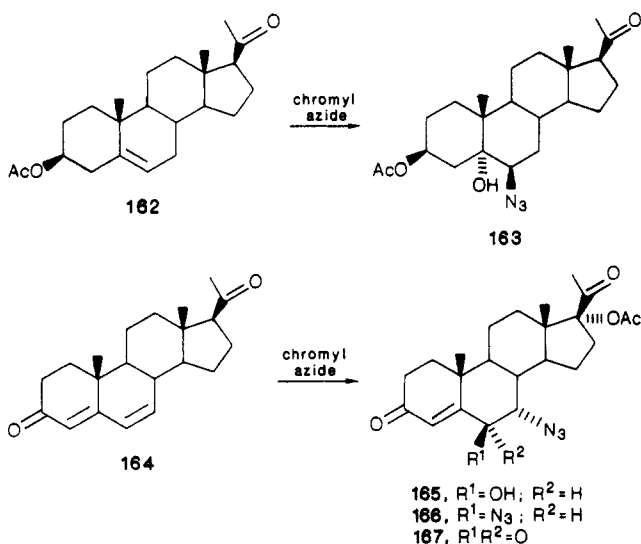
G. From Alkenes

In an extensive study of the reactions of hydrazoic acid with alkenes, Hassner¹⁵⁵ has shown that enol ethers and silyl enol ethers react to give azido ethers in good yield. A similar process occurs with trifluoroacetic acid catalysis.¹⁶⁴ Interestingly, TiCl_4 -catalyzed hydrazoic acid addition to silyl enol ethers in the presence of

primary and secondary alcohols gave products derived from ether exchange (Scheme 6).

Olefins bearing a phenyl or two geminal alkyl substituents require the presence of a Lewis acid (best with TiCl_4); mono- or 1,2-dialkyl olefins do not react. These data, in conjunction with the regioselectivity of the addition, are suggestive of a carbocation intermediate. This premise is further supported by the isolation of a mixture of 5 α - and 5 β -azidocholestanes from 5-cholestene. Previously, hydrazoic acid had been shown to add readily only in the case of cyclopropene¹⁶⁵ or in Michael additions to unsaturated carbonyl compounds.¹⁶⁶ A recent example of the latter has been reported.¹⁶⁷ Attempts to add HN_3 to diarylethylene in the presence of sulfuric acid led to considerable decomposition due to Schmidt rearrangement^{166c} (see section III.E).

Pregnenolone acetate (162) reacts with chromyl azide (formed in situ from chromium trioxide and sodium azide¹⁶⁸) to provide the azidohydrin 163. However, the situation with 164 was more complex. Three products (165–167) were formed, the major of which was the unexpected azidohydrin 165.¹⁶⁹ Similar results were



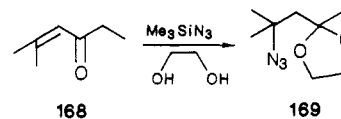
obtained with some other steroidal dienones.

Diazido species (cf. 166) were the major products when steroidal 4,6-diene-3-ones were reacted with lead tetraacetate and trimethylsilyl azide.¹⁷⁰ The mechanism was presumed to involve an initial conjugate nucleophilic attack by azide ion and subsequent electrophilic azide addition. Vicinal diazides have also been prepared from alkenes by using Fe(III) ¹⁷¹ and Pb(IV) ^{172,173} reagents. The latter converted 1,3-dienes to 1,4-diazides.¹⁷⁴ Recently, modifications of this approach have been reported.^{175,176} Thus, 1,2-diazides were the major products from treatment of alkenes with $\text{NaN}_3/\text{Mn}^{\text{III}}(\text{OAc})_3$; $\text{Mn}^{\text{III}}\text{N}_3$ species are presumably formed in situ.¹⁷⁵ The mechanism apparently involves ligand transfer to generate a β -azidoalkyl radical which subsequently reacts with a second $\text{Mn}^{\text{III}}\text{N}_3$ species. Similarly, vicinal diazides were formed in 34–85% yield under mild conditions by reaction of the corresponding alkene with PhIO and sodium azide.¹⁷⁶

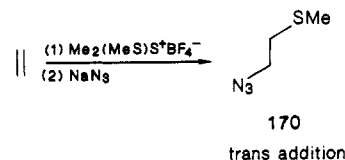
The lead tetraacetate/trimethylsilyl azide system has been previously utilized for the introduction of "positive" azide to a large variety of olefins and acetylenes;¹⁷⁷ with isolated trisubstituted steroidal olefins,

allylic azides¹⁷⁸ or *seco* keto nitriles¹⁷⁹ are formed, depending upon temperature. In contrast, isolated di-substituted olefins provide α -azido ketones.¹⁸⁰ Trialkylboranes (prepared from alkenes) react with lead(IV) acetate azide (formed in situ from LTA and TMSA at -25°C) in a "one-pot" process to form the corresponding alkyl azides.¹⁸¹

Interestingly, reaction of mesityl oxide 168 with trimethylsilyl azide and ethylene glycol in the presence of SiCl_4 (1%) leads to the azido ketal 169.¹⁸²

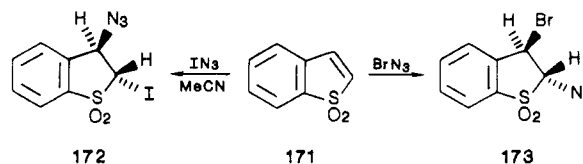


Nucleophilic attack by azide ion or congeneric species on nonconjugated alkenes can be facilitated by dimethyl(methylthio)sulfonium tetrafluoroborate.¹⁸³ The products (cf. 170) result from *trans* addition, and, in general, the greater the nucleophilicity of the azido species, the greater the amount of anti-Markovnikov product and vice versa. Olefin substitution also greatly affects orientation; monosubstitution favors anti-Markovnikov addition, and trisubstitution, Markovnikov addition. Control either way is possible with 1,1-disubstituted olefins, the nucleophilicity of the azido species being the deciding factor.



Halogen azides react with alkenes to form the corresponding halo azides, and the utility of this process has been reviewed.¹⁸⁴ It has been stated that iodine azide usually adds to olefins via a three-membered iodonium ion intermediate¹⁸⁵ whereas bromine azide can add either in an ionic or a free radical fashion, the latter being favored by nonpolar solvents.¹⁸⁶

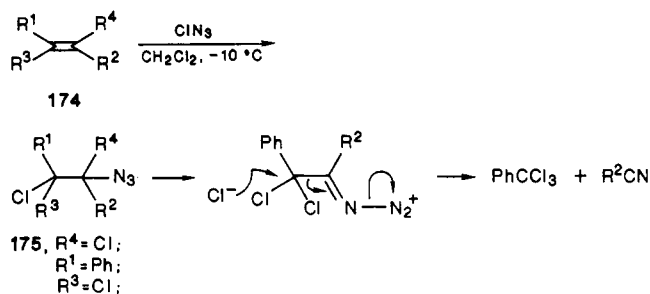
Tamura and co-workers have examined the reactions of iodine azide with indoles^{187–189} and benzo[*b*]furan.¹⁸⁷ Extension to benzo[*b*]thiophene 1,1-dioxide (171) gave intriguing results. Treatment of 171 with IN_3 provided the 3-azido species 172 whereas with BrN_3 the 2-azido product 173 was obtained.¹⁹⁰ The formation of 172 presumably involves azide attack on an iodonium intermediate; a similar mechanism has been proposed for open-chain vinyl sulfones.¹⁹¹



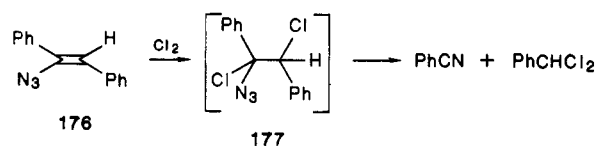
In contrast, it was suggested¹⁹⁰ that the reaction with bromine azide involves attack of N_3^\cdot radical on the double bond and subsequent Br^\cdot attack at the benzylic position. A mixture of azide-containing products was obtained from benzo[*b*]thiophene and iodine azide but their unstable nature precluded their characterization.¹⁹⁰

The α,α -dichloro azide 175 ($\text{R}^1 = \text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{Cl}$, $\text{R}^4 = \text{H}$) had been prepared by addition of chlorine

SCHEME 7



SCHEME 8

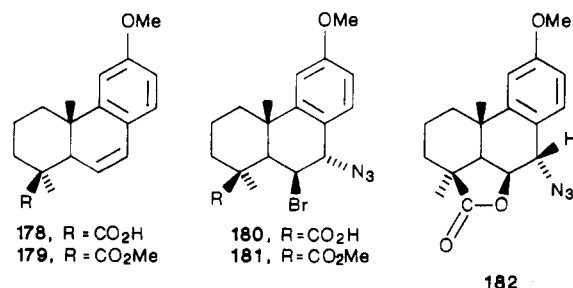


azide to the vinyl chloride 174 (R¹ = R² = Ph, R³ = Cl, R⁴ = H).¹⁹² However, an attempt to synthesize the analogous trichloro azides 175 (R¹ = Ph, R² = H or Ph, R³ = R⁴ = Cl) from the dichloroalkenes 174 (R¹ = Ph, R² = H or Ph, R³ = R⁴ = Cl) led to the formation of α,α,α -trichlorotoluene and the appropriate nitrile.¹⁹³ A plausible mechanism is shown in Scheme 7.

Support for the instability of α -chloro azides was provided by the observation that azidostilbene (176) reacted with chlorine to give PhCN and PhCHCl₂; the expected addition product (177) could not be isolated¹⁹³ (Scheme 8).

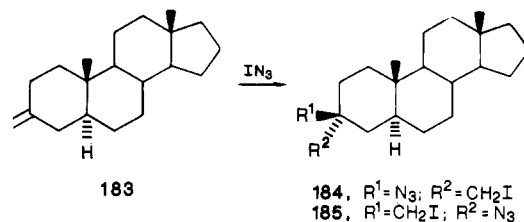
A recent reinvestigation of the regiochemistry of addition of iodine azide to 1-arylcyclohexenes has shown that the products obtained in 77–89% yield are 2-azido-1-iodo-1-arylcyclohexanes¹⁹⁴ and not 1-azido-2-iodo-1-arylcyclohexanes as previously reported.¹⁹⁵

A considerable body of data has been amassed regarding the addition of halogen azides to unsaturated steroids and related species. Thus, addition of bromine azide to the unsaturated acid 178 or its methyl ester 179 gave unexpected 6 β -bromo-7 α -azido species 180 and 181, respectively. Treatment of 180 with methanol/pyridine under reflux gave 182 in 77% yield, presumably via neighboring group participation by the azido group.¹⁹⁶

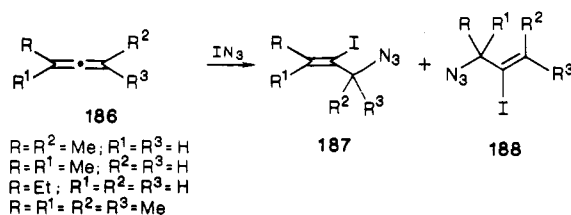


The addition of iodine azide to 3-methylene-5 α -androstane (183) in the presence of oxygen is regioselective but not stereoselective; iodomethyl-containing products 184 and 185 are formed.¹⁹⁷ The overall yield (up to 98%) and the relative amounts of 184 and 185 depend on the choice of solvent and mode of generation of iodine azide. The β -azido compound 184 is always the major component and is the sole product from treatment of 183 with *N*-iodosuccinimide/HN₃. Under a nitrogen atmosphere, products containing an azido-

methyl group are obtained, suggestive of a radical mechanism.

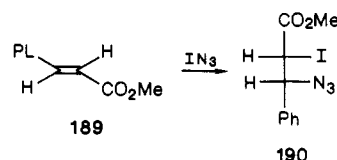


Alkyl-substituted allenes (186) react with iodine azide regioselectively to give allyl rather than vinyl azides.¹⁹⁸ It appears that the primary product is the allyl azide derived from azide attack at the most substituted site (i.e., 187). However, depending on the allene structure and the reaction temperature, substantial amounts of the [3,3]-rearrangement product (188) can also be formed.¹⁹⁸



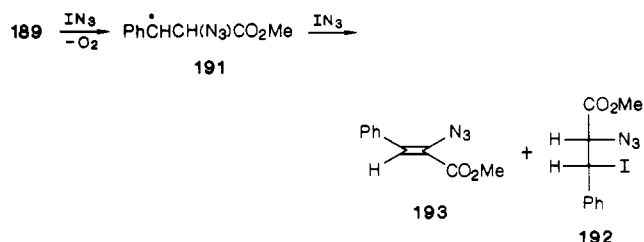
Similarly, norborn-2-ene reacts with IN₃ in the presence of oxygen to give products derived from an ionic process and in the absence of oxygen to give products derived from a radical addition.¹⁹⁹

The reaction of α,β -unsaturated esters and ketones with iodine azide was examined by Hassner and co-workers.²⁰⁰ Due to the regio- and stereoselectivity thus encountered, they proposed a mechanism comparable to that for the addition to alkenes. Thus, methyl *trans*-cinnamate (189) gave a 43% yield of the erythro adduct (190). The same reaction was later shown²⁰¹ to provide a crude yield of 79%. With thallium(I) azide-iodine a mixture of products (not including 190) was obtained.

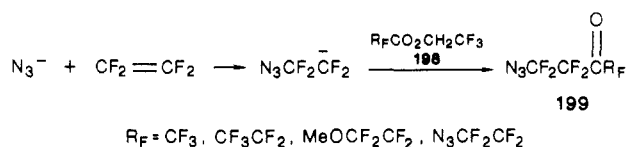


As before, under nitrogen, a regioisomer of 190 (viz., 192) was obtained in 21% yield. Additionally, methyl (*Z*)-2-azido-3-phenylpropenoate (193) (16%) was isolated. Presumably, under nitrogen, azido radical attack occurs to form the more stable radical 191, which on reaction with more IN₃ would afford 192 (Scheme 9). Vinyl azide 193 was shown not to arise from 192, but it is possible that it was formed from 190 via a diazide

SCHEME 9

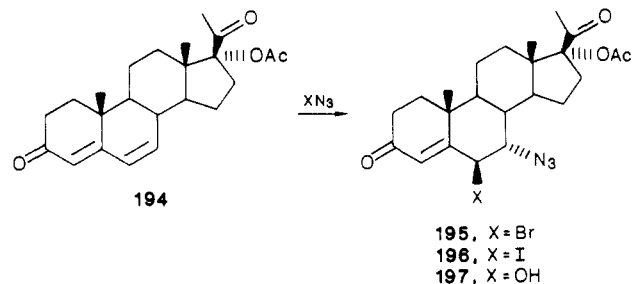


SCHEME 10



intermediate or by loss of a hydrogen atom from 191.

Another mechanism is indicated for the reaction of conjugated steroidal enone 194 with halogen azides.²⁰² Thus, 194 combines with bromine azide or iodine azide to give the corresponding 7 α -azido-6 β -halogeno 4-en-3-ones 195 or 196, respectively. The latter could be

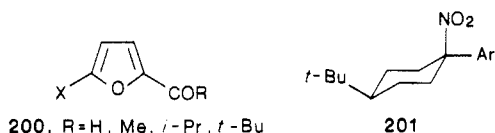


isolated but was unstable and easily hydrolyzed to 197. The regio- and stereochemistry can be explained in terms of initial conjugate addition of azide ion from the less hindered α -face followed by attack of the intermediate azido dienol on positive halogen. Similar results were obtained with other conjugated steroidal enones.

Nucleophilic addition of azide ion to tetrafluoroethylene followed by fluoro ester (cf. 198) trapping of the generated fluoro carbanions has been utilized as a versatile, one-step synthesis of functionalized fluoro ketones (cf. 199) (Scheme 10).²⁰³ The latter are formed in 39–88% yield.

H. From Nitro Compounds or Nitrates

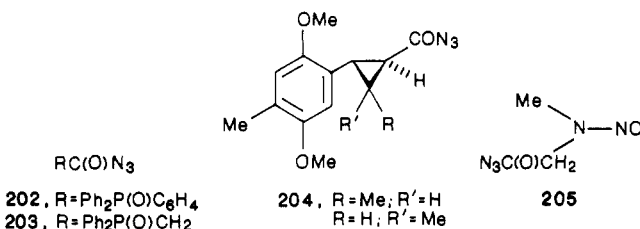
Activated nitro groups can be displaced by azide ion. Thus, the 2-acyl-5-nitrofurans (200, X = NO₂) react with NaN₃ in DMSO to give the corresponding unstable azido compounds (200, X = N₃).²⁰⁴ Displacement of the nitro group in the cyclohexane derivative 201 gives a mixture of C-1 azido epimers via an S_{RN}1 mechanism.²⁰⁵ The preparation of azide polymers by reaction of poly(vinyl nitrate) with sodium or lithium azide has been examined.³¹



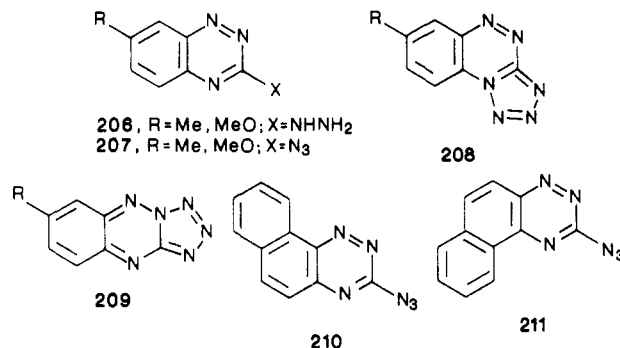
I. From Amines or Hydrazines

Nitrosation of hydrazines is a standard route to azides²⁰⁶ and in this regard, nitrous acid,^{207,208} nitrosyl chloride,²⁰⁹ and organic nitrites²¹⁰ have been previously employed. Recently, aryl, carbonyl, and sulfonyl hydrazines were reacted with N₂O₄ at low temperature to give the corresponding azides in excellent yield (84–95%).²¹¹ Nitrous acid is by far the most common reagent and has been recently utilized for the preparation of phosphinoacyl azides (cf. 202 and 203),²¹² cyclopropylacyl azides (204),²¹³ long-chain alkoxyacyl azides,¹⁸ and the *N*-nitrosoacyl azide 205.²¹⁴ A new

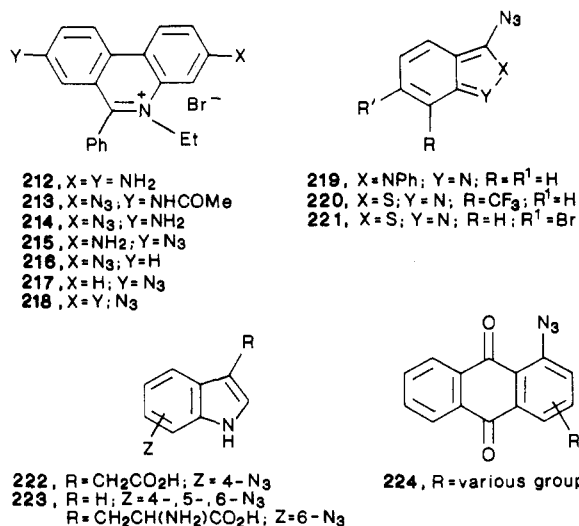
approach is the use of clay-supported ferric nitrate (clayfen);²¹⁵ conditions are mild and yields are good to excellent.



In line with previous studies it was shown that azides (cf. 207) were not the principal products from treatment of 3-hydrazinobenzo-*as*-triazines containing electron donors at the 7-position (e.g., Me, MeO) (cf. 206) with nitrous acid; instead cyclization to an angular tetrazole (208) (with 7-Me) or linear tetrazole (209) (with 7-MeO) occurred.²¹⁶ In contrast, the unstable azidonaphtho-*as*-triazines 210 and 211 could be isolated in crude form; both cyclized on standing or attempted recrystallization, respectively¹¹⁶ (see section VI.B.4).

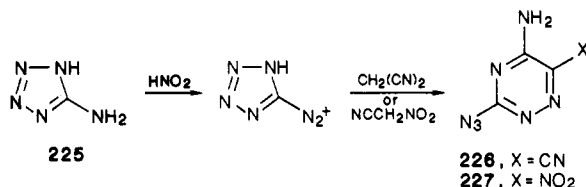


Diazotization of amines (aromatic and heteroaromatic) and subsequent treatment with sodium azide have been routinely employed for azide synthesis.²⁰⁶ Recently, this approach has been used for the preparation of photoaffinity-labeling analogues of both substance P, and undecapeptide neurotransmitter,²¹⁷ and the β -adrenergic antagonist carazolol.²¹⁸ A variety of heteroaromatic azides has been thus prepared, including ethidium bromide (212) analogues 213–218,²¹⁹ unstable azidoindazole 219, azido-2,1-benzisothiazoles 220 and 221,²²⁰ and azidoindoles 222 and 223.^{221,222} The azido-anthraquinone analogues 224²²³ are similarly obtained.



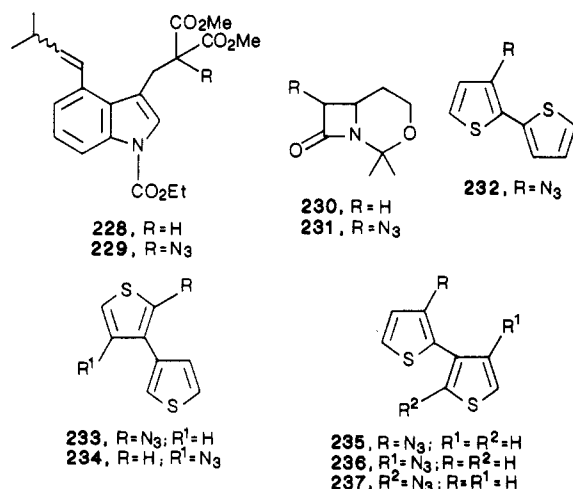
The yields of the azidoindoles **223** (from their amino congeners) were drastically improved by the simple expedient of substituting aqueous 80% acetic acid for the dilute HCl or H₂SO₄ commonly employed in such diazotizations.

Interestingly, diazotization of aminotetrazole (**225**) and subsequent treatment with malononitrile or nitroacetonitrile gave the azidotriazines **226** and **227**, respectively.²²⁴



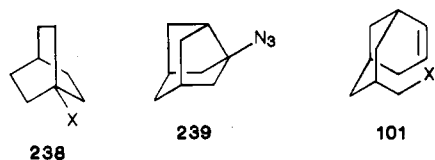
J. By Azide Transfer

The 3,4-disubstituted azido indole **229** was prepared in 62% yield by deprotonation of the malonate derivative **228** with sodium hydride and subsequent reaction with tosyl azide.^{225,226} A similar process was used to



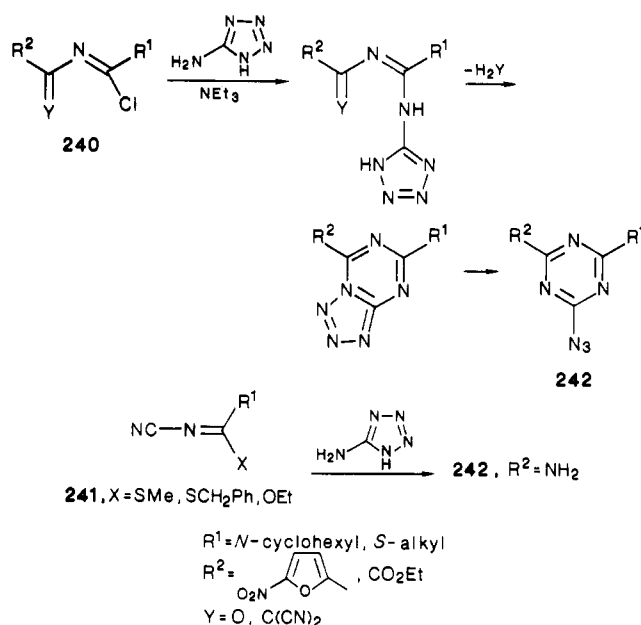
yield the azido β-lactam **231** (69% from **230**, LDA as base).²²⁷ Metal-halogen exchange followed by treatment with tosyl azide and subsequent low-temperature fragmentation of the resultant triazenyllithium salts with sodium pyrophosphate gave the bithienyl azides **232–237** from the corresponding bromo compounds.²²⁸ The 3-azido derivatives **232** and **234–236** were obtained in good yield and were quite stable, but the 2-azido species **233** and **237**, obtained in 30–40% yield, were somewhat unstable at room temperature. Accordingly, the sodium pyrophosphate induced fragmentation of the triazene salts of the latter to the azides **233** and **237** was conducted at considerably lower temperature (–70 °C) than that employed for the preparation of the 3-azido analogues (5 °C).²²⁸

1-Azidobicyclo[2.2.2]octane (**238**, X = N₃) was prepared in 83% yield from the corresponding amine (**238**, X = NH₂) by reaction with sodium hydride and then tosyl azide²²⁹ using Quast and Eckert's procedure.²³⁰



3-Azidonoradamantane (**239**) was similarly prepared in

SCHEME 11

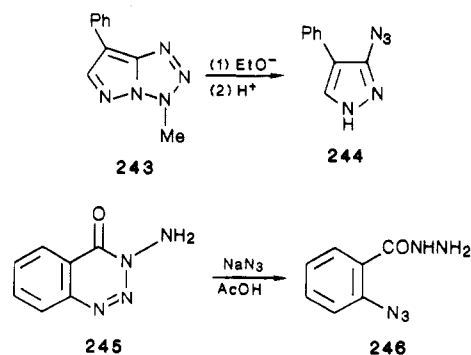


92% yield.²²⁹ With a 1.6-fold excess of *n*-butyllithium and a 1.3-fold excess of tosyl azide, amine **101** (X = NH₂) was converted to the corresponding azide in only 28% yield.¹¹⁷ Using a large excess of sodium hydride (Quast and Eckert's procedure²³⁰) increased the yield to 87%. 9-Triptycyl azides have been prepared similarly.²³¹ Since this review was prepared, Evans⁷³⁸ has developed an efficient, stereoselective electrophilic azidation of basic enolates.

K. By Fragmentation of Heterocycles

As described previously (see section II.I) tetrazoles can result from diazotization of heterocyclic hydrazines, presumably via azide intermediacy. The reverse process (viz., tetrazole → azide) can sometimes be realized (cf. Scheme 11).²³²

The demethylated azidopyrazole **244** was prepared in 77% yield by treatment of the pyrazolotetrazole **243** with 3 equiv of sodium ethoxide in ethanol under reflux for 60 h.²³³ Treatment of 3-amino-1,2,3-benzotriazin-4(3*H*)-one (**245**) with sodium azide in acetic acid gave an excellent yield of the hitherto unknown *o*-azido-benzohydrazide (**246**).²³⁴



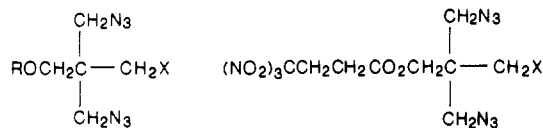
L. From Preformed Azides

One of the most exciting aspects of recent azide chemistry has been the extent to which it is possible to modify other functional groups without affecting the azide moiety. Much of the work in this area has been

developed by carbohydrate chemists (see section V). The reader is cautioned that owing to the explosive nature of some azides such transformations should be attempted on a small scale with appropriate safety precautions, especially where the generality of the process has not been assessed.

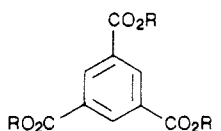
1. Alcohols and Derivatives

Various alcohol modifications have been performed in the presence of the azido group. Thus, the di- and triazides **247** and **248**, respectively, react with nitric acid



247, X = ONO₂; R = H
248, X = N₃; R = H
249, X = R = ONO₂
250, X = N₃; R = ONO₂

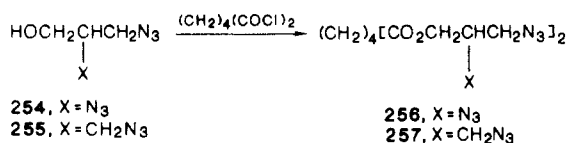
251, X = ONO₂
252, X = N₃



253, R = CH₂C(CH₂N₃)₃

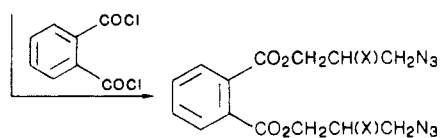
to give the corresponding di- and mononitrates **249** and **250**, respectively.²³⁵ The utility of **247** and **248** for the preparation of energetic esters has also been explored. Thus, both reacted with 4,4,4-trinitrobutyryl chloride to form the corresponding triester esters **251** and **252**, respectively. Additionally, triester **253** was obtained from **248** and 1,3,5-benzenetricarboxylic acid chloride.²³⁵

Similar results were obtained by reaction of diazido alcohols **254** and **255** with adipoyl chloride or phthaloyl chloride; the resultant tetraazides **256**–**259**, respectively, were thermally stable and relatively insensitive to impact.²³⁶



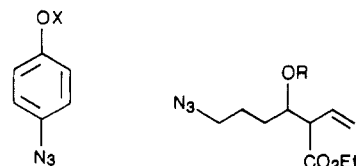
254, X = N₃
255, X = CH₂N₃

256, X = N₃
257, X = CH₂N₃



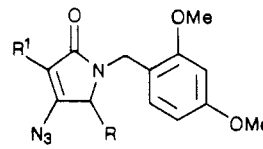
258, X = N₃
259, X = CH₂N₃

4-Azidophenyl methacrylate (**261**) was prepared in an analogous fashion by treatment of 4-azidophenol (**260**) with methacrylic acid chloride.²¹⁹ Copolymerization of **261** with styrene and ((*tert*-butoxycarbonyl)-amino)ethyl methacrylate was examined. Acetylation can also be performed in the presence of the azido group; acetates **264**²³⁷ and **265**²³⁸ were prepared in high yield from the corresponding alcohols **262** and **263**. The ester **266** was similarly synthesized from **263** (prepared from the lactone and 2,4-dimethoxybenzylamine) and 4-nitrobenzoyl chloride in 94% yield.²³⁸ Acid-catalyzed reaction of **263** with ethanethiol gave the dithioether **267** in 50% yield.²³⁸ Displacement from alkyl halides can also occur. Thus, azido alcohol **254** reacts with [FC(NO₂)₂CH₂]₂NCH₂Br to give the corresponding



260, X = H
261, X = COC(Me)=CH₂

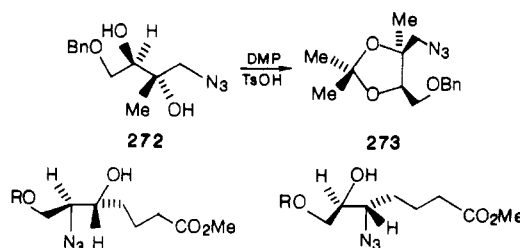
262, R = H
264, R = Ac



263, R = OH; R¹ = Cl
265, R = OAc; R¹ = Cl
266, R = 4-NO₂C₆H₄CO₂; R¹ = Cl
267, R = R¹ = EtS

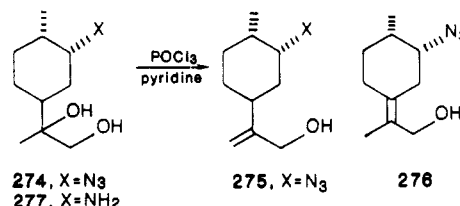
ether,¹⁹ and a carbamate results from treatment of HOCH(CH₂N₃)₂ with (NO₂)₃CCH₂CH₂NCO.¹⁹

Silylation of a primary alcohol in the presence of a secondary alcohol (and the azide moiety) was effected by allowing the inseparable, isomeric mixture (**268**, **269**) to react with *tert*-butyldiphenylsilyl chloride in DMAP/Et₃N; a separable 7:1 mixture of **270** and **271**, respectively, resulted.¹³¹



268, **269**, R = H
270, **271**, R = *t*-BDPSi

An acetone diol (**273**) was obtained by protection of diol **272** with DMP and a catalytic amount of *p*-toluenesulfonic acid.²³⁹ Dehydration of the diol **274** with POCl₃/pyridine occurred to form the less substituted double bond (as in **275**); none of **276** was observed.²⁴⁰ Only resinous material resulted when the same transformation was attempted with the amino diol **277**;²⁴⁰ the utility of the azido group as a masked amine (see section III.A) is thus manifest.

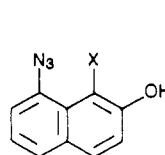


274, X = N₃
277, X = NH₂

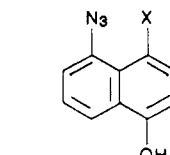
275, X = N₃

276

In a reaction not directly involving the OH group, azidonaphthols (cf. **278** and **279**) couple with aryldiazonium chlorides to provide the corresponding azo products **280** and **281**, respectively.²⁴¹

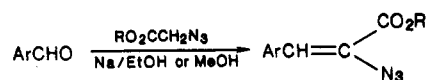


278, X = H
280, X = ArN=N



279, X = H
281, X = N=NC₆H₄Me-4

SCHEME 12

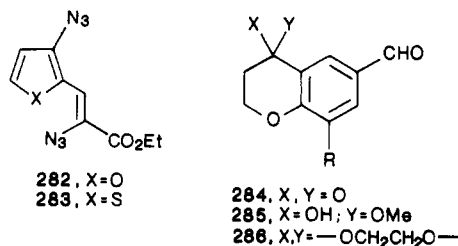


2. Carbonyl Compounds

(a) Carboxylic Acids and Derivatives. One of the most widely employed transformations with azido carboxylates is the preparation of vinyl azides by base-induced condensation with aryl or heteroaryl aldehydes (Scheme 12).^{71,72,242-246}

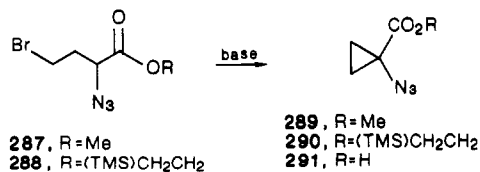
The method has been recently utilized for the preparation of azido acrylate precursors to indoles,^{242a,243,244a,b} isoquinolines,²⁴² thienopyrroles,²⁴⁵ azaannulenes,²⁴⁶ and related heterocycles^{242a,243} (see section VI). The interesting diazido furan **282** and thiophene **283** derivatives (precursors to furo- and thienopyridazines and (from **283** only) an isothiazole) have been prepared similarly.^{71,72}

In general, product stereochemistry about the double bond is not known but is assumed to be *Z*.^{242a} Various other bases (inter alia, Na_2CO_3 , KOH, or NaOH under phase-transfer conditions) gave unsatisfactory results, as did an attempt at acid-catalyzed condensation using TiCl_4 . Extension to azidoacetonitrile and azidonitromethane was also unsuccessful. Condensation of ethyl azidoacetate with formylchromanones (cf. **284**) did not occur; the hemiacetals **285** were instead obtained.^{244a} Protection of the keto group as the dioxolane (**286**) permitted efficient condensation.^{244a}



However, yields for the condensation are generally good²⁴²⁻²⁴⁶ and it has been reported^{242a} that the best results accrue from reaction temperatures between -10 and -15 °C using 4 equiv of ethyl azidoacetate.

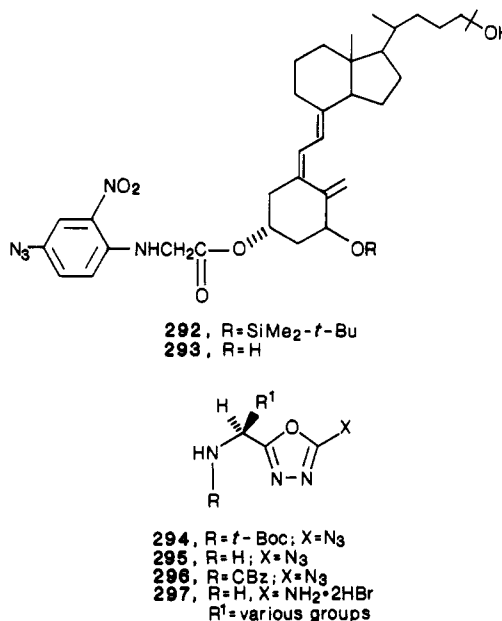
The acidity of hydrogens α to the ester function has also been utilized in the preparation of cyclopropyl azido carboxylates. Thus, treatment of the bromo azido ester **287** with potassium carbonate/NMP at 20 °C for



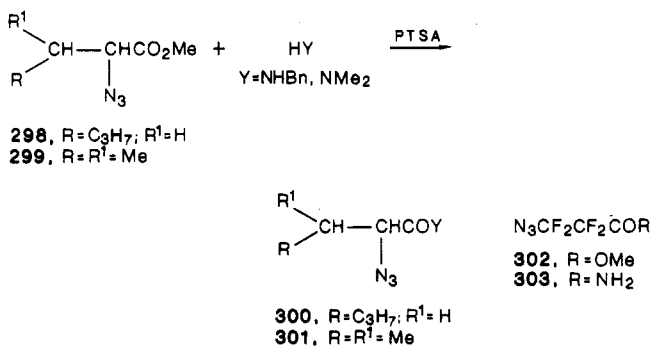
64 h gave a modest yield of the azidocyclopropane **289**.⁴⁹ A modification of the procedure using the (trimethylsilyl)ethyl ester **288** and DBU/DMF provided **290**.⁵⁰ The latter could be converted to the parent carboxylic acid **291** by deprotection with tetrabutylammonium fluoride.⁵⁰ Base-catalyzed hydrolysis of analogues of **289** to the corresponding carboxylic acids under mild con-

ditions has also been reported.^{246a} Deprotection of the *tert*-butyldimethylsilyl ether **292** to the corresponding alcohol **293** has been accomplished by using 5% HF.²⁴⁷

Removal of the Boc group in **294** with trifluoroacetic acid gave the crystalline amino acid derivatives **295**.¹¹⁵ Attempted deprotection of **296** with HBr/acetic acid led to simultaneous azide reduction to give **297**¹¹⁵ (see section III.A).

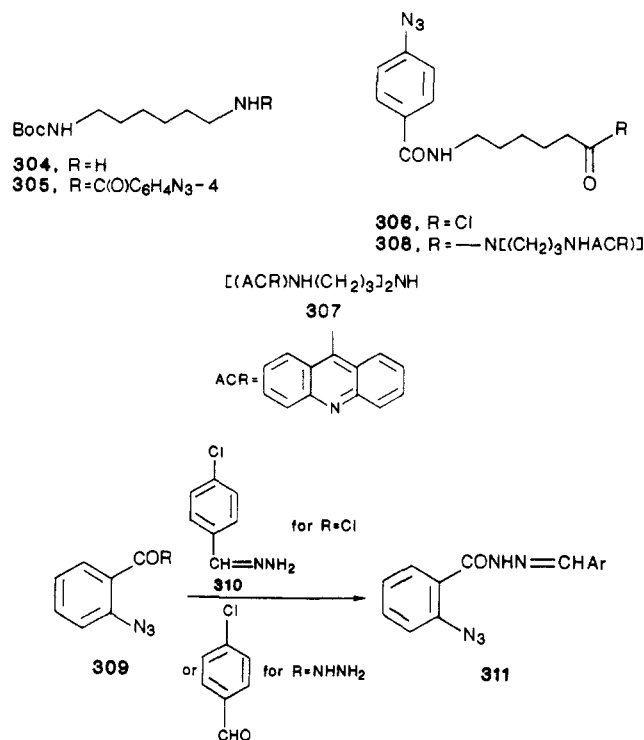


Nucleophilic attack at the ester function has been reported.²⁴⁸ Thus, azido esters **298** and **299** react with benzylamine and dimethylamine in the presence of a catalytic amount of *p*-toluenesulfonic acid to give azido amides **300** and **301**, respectively,²⁴⁸ and fluoro azide **302**



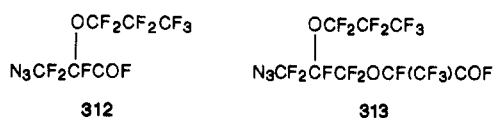
was converted to amide **303** in 84% yield by treatment with ammonia.²⁴⁹ More commonly, the carboxylic acid has been activated toward nucleophilic attack by conversion to the acid chloride or by use of activating agents such as dicyclohexylcarbodiimide (DCC) or trifluoroacetic anhydride. Thus, 4-azidobenzoyl chloride reacts with primary amine **304** to form amido species **305**.²⁵⁰ The Boc group in the latter could be removed subsequently with HCl.²⁵⁰ Diamide **308** was similarly prepared from **306** and **307**.²⁵⁰

2-Azidobenzoyl chloride (**309**, R = Cl) combines with hydrazine to provide benzylidene derivative **311**, which can also be prepared from 2-azidobenzohydrazide (**309**, R = NHHN₂).²³⁴ Attempts to synthesize the latter by treatment of methyl *o*-azidobenzoate (**309**, R = OMe) with hydrazine hydrate²⁵¹ or hydrolysis of **311**²⁵² were unsuccessful.

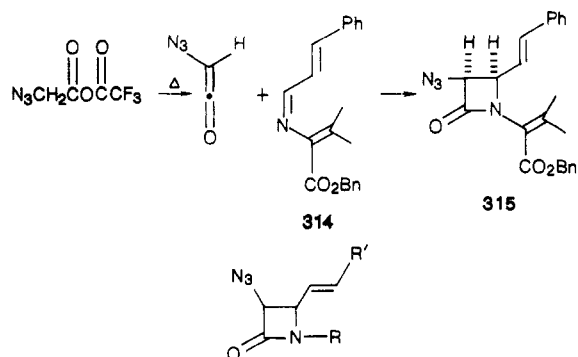


(Azidodinitrophenyl)glycine derivative **292** results from the reaction of the corresponding 3β -alcohol with *N*-(4-azido-2-nitrophenyl)glycine and DCC in the presence of DMAP.²⁴⁷

Recently, acid fluoride **312** was prepared from the carboxylic acid and sulfur tetrafluoride.²⁴⁹ Reaction of the analogous acid fluoride **313** with methanol gave the corresponding ester.²⁴⁹



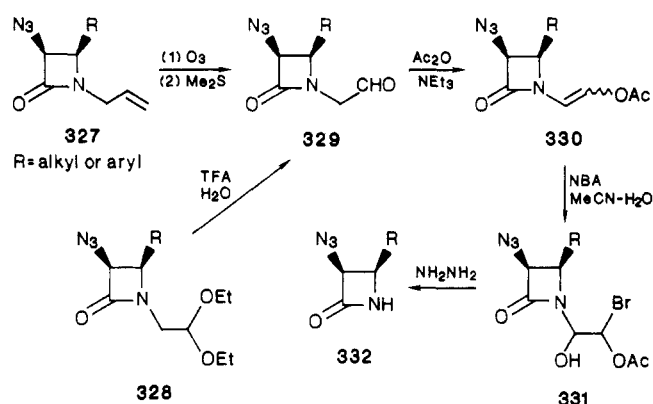
Similar approaches have been utilized for the preparation of β -lactams from azido carboxylic acid derivatives and imines. Thus, the mixed anhydride formed from azidoacetic acid and trifluoroacetic anhydride added to the imine **314** in the presence of triethylamine



- 316**, R = 4-MeOC₆H₄; R¹ = Ph
317, R = H; R¹ = Ph
318, R = 2,4-(MeO)₂C₆H₃CH₂; R¹ = Ph
319, R = 4-MeOCH₂OC₆H₄; R¹ = CH₂CH(OEt)₂
320, R = 4-HOC₆H₄; R¹ = CH₂CH(OEt)₂
321, R = 4-MeOCH₂OC₆H₄; R¹ = Ph
322, R = CH₃CH(OH)CHCO₂R²; R¹ = Ph; R² = PNB
323, R = CH₃CH(OH)CHCO₂R²; R¹ = Ph; R² = Me
324, R = CH₃CH(OH)CHCO₂R²; R¹ = Ph; R² = Bn
325, R = HOCH₂CHCO₂Me; R¹ = Ph
326, R = CH₃C(OH)=CCO₂R²; R¹ = Ph; R² = as above

to provide the azetidion-2-one **315**.²⁵³ An analogous

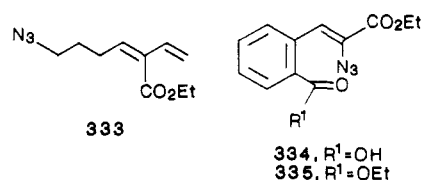
SCHEME 13



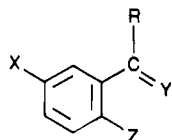
transformation occurs with the imine derived from *p*-anisidine and cinnamaldehyde; **316** is formed in 60% yield.²⁵⁴ There have been several reports of imines from *p*-anisidine reacting with acid chlorides or anhydrides of azidoacetic acid to give azetidionones, usually with a high degree of *cis* stereoselectivity.^{255,256} Dearylation of **316** to **317** with ceric ammonium nitrate (CAN) occurred in 68% yield under mild conditions.²⁵⁴ The yield of **317** was substantially better than that from potassium persulfate mediated debenzoylation of **318** (<25%).²⁵⁴ The dearylation of azidoazetidionones (cf. **319**) with CAN (after treatment of **319** with HCl, MeOH, and CH(OMe)₃) had been previously reported²⁵⁷ and the intermediacy of a phenol (cf. **320**) has been suggested.²⁵⁴ However, it is apparently not necessary to cleave the methoxymethyl ether prior to oxidation since **317** results in 69% yield from treatment of **321** with CAN.²⁵⁸ Deprotection of other side chains has also provided **317**. Thus, oxidation of the *cis*- β -lactams **322**–**325** (prepared from azidoacetyl chloride and the appropriate imines) with Jones reagent gave the β -keto esters **326** and/or **317** depending on how much oxidant was utilized.²⁵⁹ Similar *N*-substituted β -lactams (cf. **332**) have been prepared by deprotection of *N*-allyl (cf. **327**) or diethyl acetal (cf. **328**) species²⁶⁰ in excellent overall yields (Scheme 13).

The azidoacetyl chloride/imine cyclization process has also been applied recently to the preparation of azidoazetidionones bearing a ((methoxycarbonyl)diethylphosphono)methyl group²⁶¹ and for proof of imine structure by the preparation of identifiable bicyclic β -lactams.²⁶²

Other manipulations with azido carboxylic acid derivatives have included conversion of **262** to diene **333** (96% yield, 5 min, 0 °C) by the action of DBU in DME²³⁷ and esterification of **334** with ethanol/HCl to give **335**.^{242b}



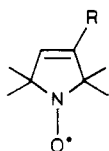
(b) Ketones and Aldehydes. 2-Azidoacetophenone oxime (**337**) was prepared in 45% yield by treatment of 2-azidoacetophenone (**336**) with hydroxylamine.²⁶³ This oxime (**337**) had been previously reported²⁶⁴ as arising from the reaction of *o*-chloroacetophenone oxime (**338**) with sodium azide. However, the reported melting



- 336, X = H; Y = O; Z = N₃; R = Me
 337, X = H; Y = NOH; Z = N₃; R = Me
 338, X = H; Y = NOH; Z = Cl; R = Me
 339, X = Cl; Y = O; Z = N₃; R = Ph
 340, X = Cl; Y = NOH; Z = N₃; R = Ph

point was different from that obtained by Boulton,²⁶³ and repetition of the procedure apparently did not provide any azide-containing material.²⁶³ It is thus reasonable to conclude that the current synthesis has afforded authentic material. 2-Azido-5-chlorobenzophenone (339) can also be converted to the oxime (340) by reaction with hydroxylamine.^{263,265}

In a reaction analogous to that performed with azido esters (see section II.L.2a), nitroxide spin labels 341–343 condense (base catalyzed) with *p*-azidobenzaldehyde or *p*-azidoacetophenone to give difunctional spin labels 344–346 in moderate to good yield.²⁶⁶

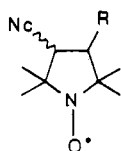


341; R = COMe

343; R = CHO

344; R = COCH=CHC₆H₄N₃-4

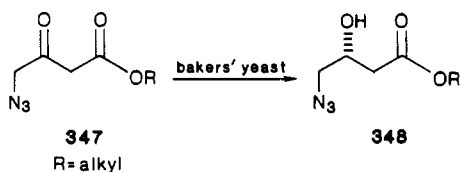
346; R = CH=CHCOC₆H₄N₃-4



342; R = COMe

345; R = COCH=CHC₆H₄N₃-4

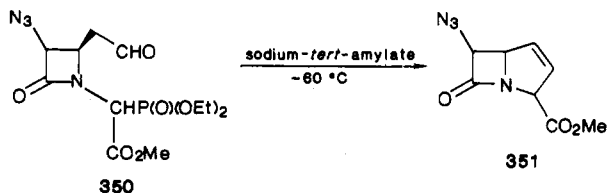
Bakers' yeast mediated reduction of alkyl 4-azido-3-oxobutyrate (347) (prepared by azide displacement from the 4-bromo compounds) gave the corresponding alcohols (348) in 70–80% isolated yield. The ee values for 348 were determined by ¹H NMR on the *O*-acetyl derivatives in the presence of a chiral europium shift reagent and ranged from 0.8 to approximately 1.0.²⁶⁷



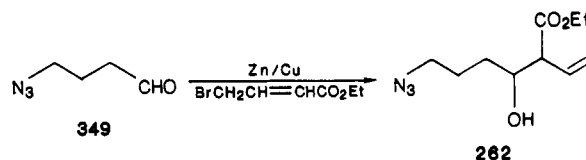
Azido alcohol 262 can be prepared from aldehyde 349 by the vinylogous Reformatsky reaction²⁶⁸ (Scheme 14).²³⁷

The same alcohol has also been prepared in 91% yield from 349 by the action of CH₃CH=CHCOOEt/LDA.²⁶⁹ Subsequent dehydration was effected in high yield.

Azidocarbapenem 351 was obtained in low yield (ca. 1%) from 350 via intramolecular Wittig–Horner reaction.²⁶¹ The low yield was ascribed to the instability of the 6-azido-1-carbapen-2-em nucleus.²⁶¹

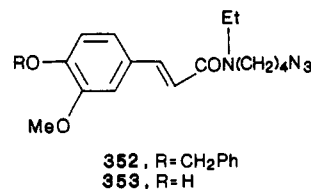


SCHEME 14

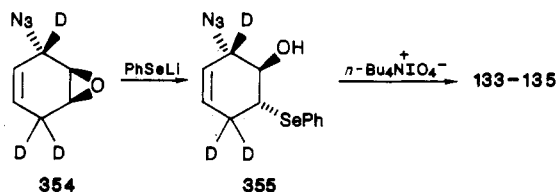


3. Ethers, Epoxides, and Related Species

Debenzylation of 352 with trifluoroacetic acid afforded the corresponding phenol (353).²⁷⁰

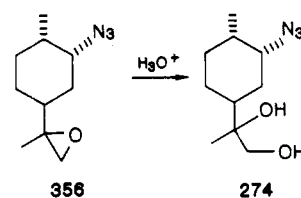


Reaction of epoxide 354 with PhSeLi in THF at room temperature gave a 53% yield of 355. Subsequent

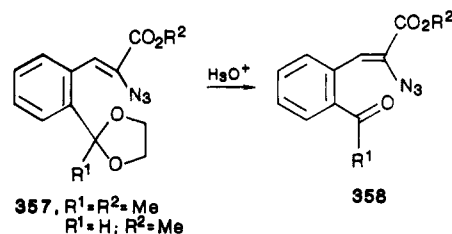


oxidation of the latter with tetrabutylammonium periodate and selenoxide elimination (6 h at room temperature) gave the same mixture of dienols, in essentially the same product ratios, as from addition of N₃⁻ to the parent epoxide (cf. 132 → 133–135, section II. C).¹³⁴

Acid hydrolysis of epoxide 356 gave diol 274 in reasonable yield.²⁴⁰



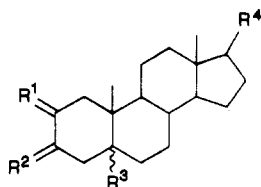
Hydrolysis of the dioxolane ring in 357 to yield 358 also occurred under acidic conditions.^{242b}



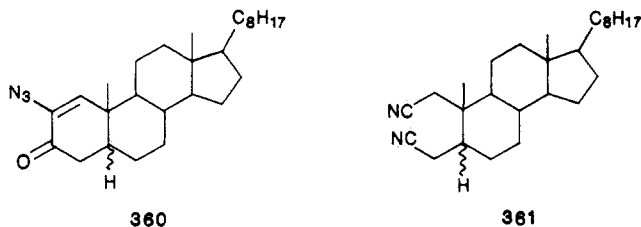
4. Oximes

Steroidal azido oxime 359 can be converted to α,β -unsaturated ketone 360 in modest yield by the action of PPA at 120 °C or P₂O₅ in refluxing benzene.²⁷¹ In the latter case the ring-cleaved dicyano compound 361 is the major product.²⁷¹ In contrast, the side-chain α -azido oximes 362 and 363 reacted with POCl₃ at 70 °C to give the nitriles 364 and 365 (20% and 32%,

respectively) and the Beckmann fragmentation products **366** and **367** (45% and 47%, respectively).²⁷¹

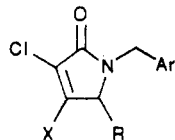


- 359**, R¹ = α -N₃; R² = (*E*)-NOH; R³ = H; R⁴ = C₈H₁₇
362, R¹ = H₂; R² = β -OAc; R³ = α -H; R⁴ = C(=NOH)CH₂N₃
363, R¹ = H₂; R² = β -OAc; R³ = Δ^5 ; R⁴ = C(=NOH)CH₂N₃
364, R¹ = H₂; R² = β -OAc; R³ = α -H; R⁴ = CN
365, R¹ = H₂; R² = β -OAc; R³ = Δ^5 ; R⁴ = CN
366, R¹ = H₂; R² = β -OAc; R³ = α -H; R⁴ = NHCOCH₂N₃
367, R¹ = H₂; R² = β -OAc; R³ = Δ^5 ; R⁴ = NHCOCH₂N₃



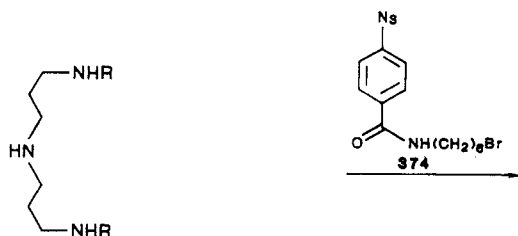
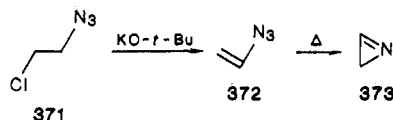
5. Halides

The 4-nitrobenzoate **266** was converted to the dichloro species **368** by treatment with dry HCl. The latter was not isolated but was reacted directly with benzenethiol to give **369** in 84% yield. The azido compound **369** could also be prepared from **370** by halide displacement with azide ion.²⁸⁸

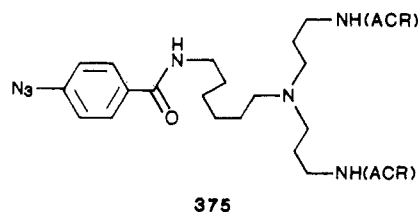


- 266**, R = OPNB; X = N₃
368, R = Cl; X = N₃
369, R = SPh; X = N₃
370, R = SPh; X = Cl

Halide elimination (to form an alkene) in the presence of the azido functionality has been reported for **371**. Thus, treatment of **371** with potassium *tert*-bu-



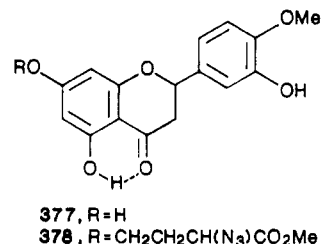
- 307**, R = ACR (9-phenoxyacridinyl)
376, R = *t*-Boc



toxide at 80 °C and 0.1 Torr gave vinyl azide **372**, which was transformed to Δ^1 -azirine (**373**) at 400 °C and 0.1 Torr. The whole process, including preparation of the chloro azide **371**, could be performed as a gas-solid phase multistep sequence by means of flash vacuum pyrolysis.²⁷²

The secondary amine **307** displaces the bromine from **374** to yield **375**. The latter, one of a series of potential photoaffinity-labeling reagents, could also be prepared by reaction of **376** with **374** followed by HCl deprotection and subsequent reaction with 9-phenoxyacridine.²⁵⁰

Alkylation of hesperetin (**377**) with bromo compound **11** occurred under basic conditions (potassium carbonate) only at the 7-hydroxy group. The yield of the alkylation product (**378**) was unusually dependent on



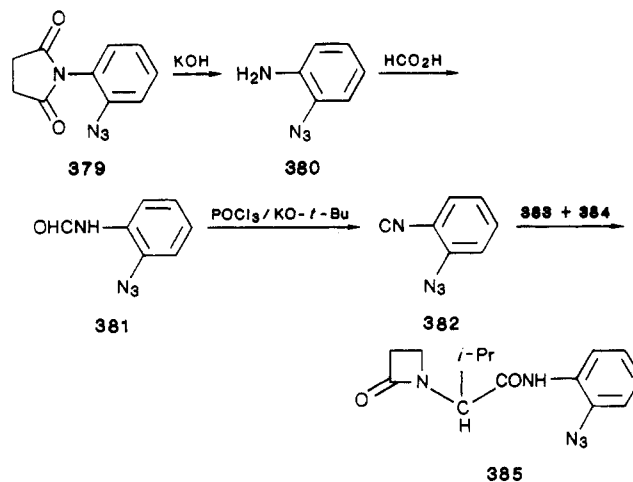
the time and temperature of the reaction, apparently due to its reversion to **377** after extended periods. A careful study of the effects of base, solvent, temperature, and time upon the reaction led to optimization of the process (85% yield) using potassium carbonate in *N*-methylpyrrolidone (solvent) and ICH₂CH₂CH(N₃)CO₂Me at 35 °C. A similar reaction occurred with 4-hydroxyacetophenone.⁴⁹

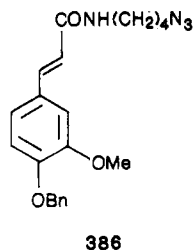
6. Amines and Derivatives

2-Azidoaniline (**380**) (prepared by KOH desuccinylation of **379**) can be converted to the β -lactam-containing azido species **385** via *N*-formylation (to **381**), dehydration of the latter with POCl₃/potassium *tert*-butoxide (to **382**), and subsequent condensation of **382** with β -alanine (**383**) and isobutyraldehyde (**384**) in methanol (Scheme 15).²⁷³

Alkylation of amines (in the presence of the azido group) has been reported. Thus, *N*-alkylation of **386** with EtBr/NaOH occurs under phase-transfer conditions to yield **352**.²⁷⁰ Many similar processes have been described.

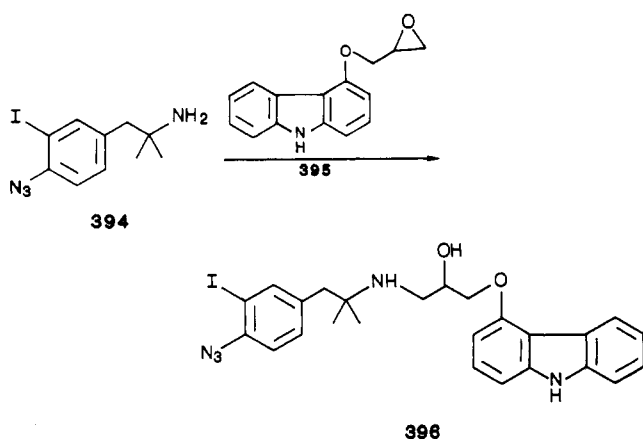
SCHEME 15



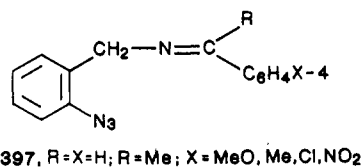


The synthesis of the potential bisintercalating photoaffinity-labeling reagent **393** was achieved in three steps from the thiourea **387** (Scheme 16).²⁵⁰ Attempted preparation of the key intermediate **392** by reaction of the carbodiimide **389** with **390** did not succeed. It was surmised that the addition of amines to carbodiimides to give guanidines was limited to carbodiimides containing at least one phenyl group.²⁵⁰

The β -adrenergic photoaffinity ligand **396** was prepared in low yield from amino azide **394** and epoxide **395** (7 days at 65 °C).²¹⁸

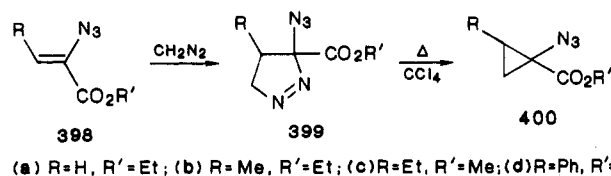


Condensation of *o*-azidobenzylamine with benzaldehyde or substituted acetophenones in refluxing benzene or toluene gives the imines **397** in moderate to good yield.²⁷⁴



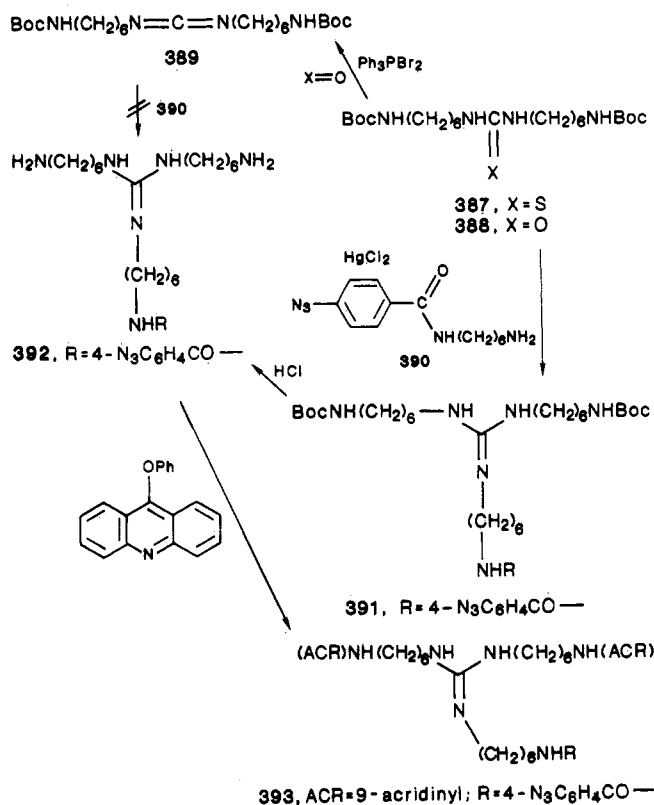
7. Alkenes and Alkynes

Vinyl azido esters **398a-d** react with excess diazomethane in ether at room temperature to give the corresponding pyrazoline derivatives **399a-d** in >90% yield (except for **398d** \rightarrow **399d**; 48%). Thermolysis of

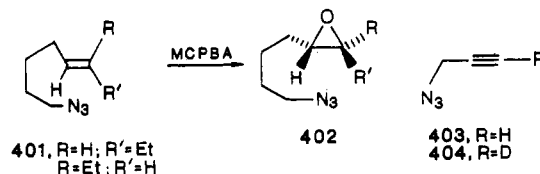


399a-d in carbon tetrachloride at 80 °C gave moderate to good yields of 1-azidocyclopropanecarboxylate derivatives **400a-d**.^{246a} The latter (**400**) could be hydrolyzed to carboxylic acids (see section II.L.2a) and subsequently hydrogenated to biologically important 1-aminocyclopropanecarboxylic acids (see section III.A).

SCHEME 16



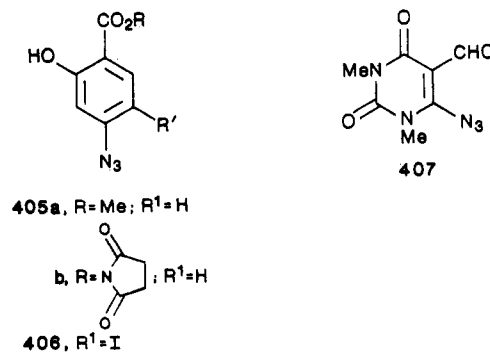
Epoxidation of **401** to give **402** occurs in high yield (>80%) under mild conditions (MCPBA, CH₂Cl₂, 0 °C).²⁷⁵



Deuteriated alkyne **404** was prepared from its hydrogen analogue (**403**) by treatment with potassium deuterioxide in D₂O at 0–10 °C under ultrasonic irradiation. After 1 h, 77% deuteration had occurred. After three repetitions, the degree of deuteration increased to over 99%.⁵³

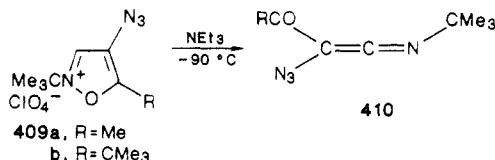
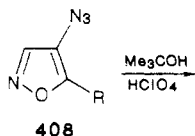
8. Aryl and Heteroaryl Derivatives

Iodination of the azidophenols **405a,b** with Chloramine T/sodium iodide in DMF or acetonitrile gave iodo compounds **406a,b** in 88% and 42% yield, respectively, under mild conditions (1 h at 25 °C). The



latter were of interest as radioiodinated, cleavable, bi-

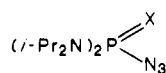
functional cross-linking reagents.²⁷⁶ Formylation of 6-azido-1,3-dimethyluracil provided 5-formyl derivative **407**, a useful precursor to fused pyrimidines.⁷⁶ Quaternization of **408a,b** with *tert*-butyl alcohol and perchloric acid at 0 °C gave isoxazolium perchlorates **409a,b** in 17% and 50% yield, respectively. The low



yields were reportedly due to extensive azide decomposition during this procedure.²⁷⁷ Interestingly, treatment of the perchlorates **409a,b** with triethylamine at -90 °C in an IR cell provided evidence for their conversion to azidoketenimines **410a,b**. Decomposition of the latter occurred at -60 °C; the ketenimine group apparently disappeared faster than the azide moiety.²⁷⁷

9. Phosphorus Compounds

Bis(diisopropylamino)phosphine azide (**411**) is converted to the oxide (**412**) with ozone (DMSO or H₂O₂ had no effect), to the sulfide (**413**) with sulfur, and to the iminophosphine (**415**) (via the spectroscopically



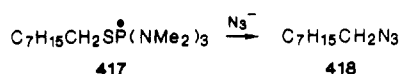
411-416, respectively, X = lone pair, O, S, NN=NPh, NPh, NSiMe₃

characterized adduct **414**) with phenyl azide.⁹³ The silylated iminophosphine **416**, formed from a photochemically induced reaction of **411** and trimethylsilyl azide, was postulated as arising from a [2 + 3] cycloaddition followed by ring opening of the resulting phosphatetrazole.⁹³

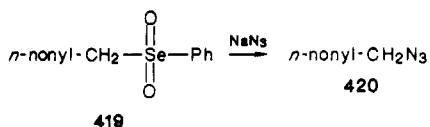
M. Other Preparations

A number of methods for azide synthesis have been developed that do not fall into the sections thus far described.

Thus, the thiaphosphonium salt **417** could be converted to the corresponding azide **418** in 79% yield.²⁷⁸

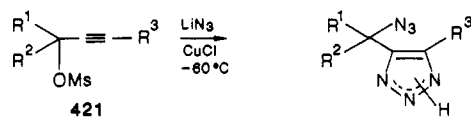


Decyl phenyl selenone (**419**) reacted with sodium azide in DME/water at 20 °C to form decyl azide (**420**) in 93% yield.²⁷⁹ Facile displacement with other nucleophiles was also observed.



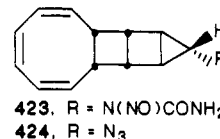
Attempted azide substitution of the propargyl sulfonates **421** gave azido triazoles **422** in low yield (4-24%)

rather than the anticipated allenyl azides.²⁸⁰

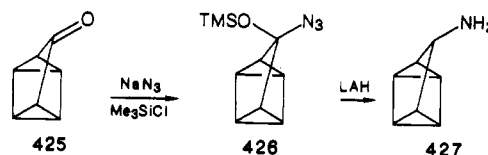


422, R¹ = *t*-Bu, Ph; *m*-NO₂C₆H₄
R² = H, Ph; R³ = *t*-Bu, Ph

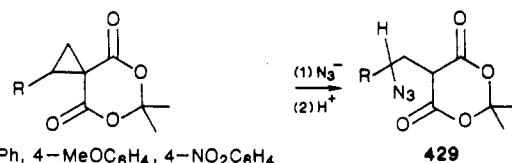
The unusual tetracyclic azide **424** was prepared in low yield (14%) from the *N*-nitrosourea **423** and lithium azide in methanol.²⁸¹ The same reaction was used for other tetracyclic azides.²⁸²



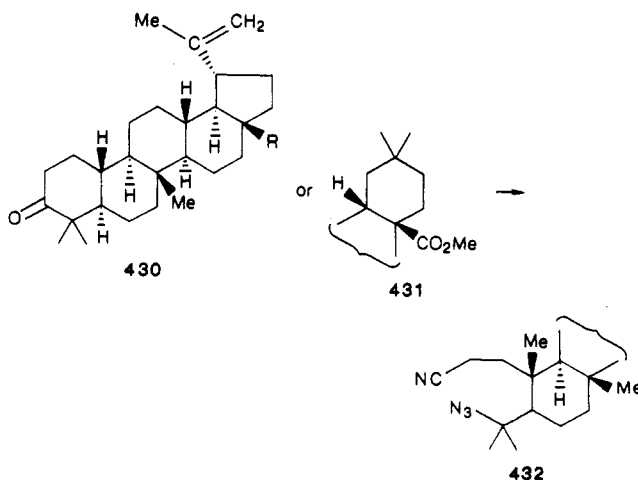
The quadricyclanone **425** was converted to the azido silyl ether **426** by treatment with sodium azide and trimethylsilyl chloride.²⁸³ Subsequent reduction with lithium aluminum hydride (LAH) gave **427**.



Ring opening of the spirocyclopropane derivatives **428** with azide ion occurs at the soft cyclopropane C-1 position to give azidoalkyl derivatives **429**.²⁸⁴ With harder nucleophiles (e.g., ⁻OR) attack instead occurs at a carbonyl carbon.

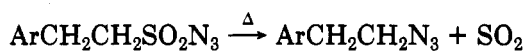


Ring opening was also observed in the reactions of 3-oxopentacyclic triterpenes **430** (R = Me, COOMe) and **431** with excess HN₃·BF₃ etherate to give the cyano azido secopentacyclic triterpenes **432**.²⁸⁵



Thermolysis of some arylalkylsulfonyl azides gave the corresponding arylalkyl azides, generally in low yield (Scheme 17).⁸³

SCHEME 17



In a series of papers, Desbene and co-workers have studied the reactions of azide ion with pyrylium and thiopyrylium species.^{286,287} Azidopyrans (and congeners) resulted only when the pyrylium ring was hindered; otherwise charge-transfer complexes were obtained. Extension to oxazinium²⁸⁸ and chromylum²⁸⁹ species and their subsequent conversions to β -tetrazolo-*trans*-benzal acetophenones and benz[*f*]oxazepins, respectively, has been reported (see section VI.C.1).

III. Reactions

A. Reduction to Amines

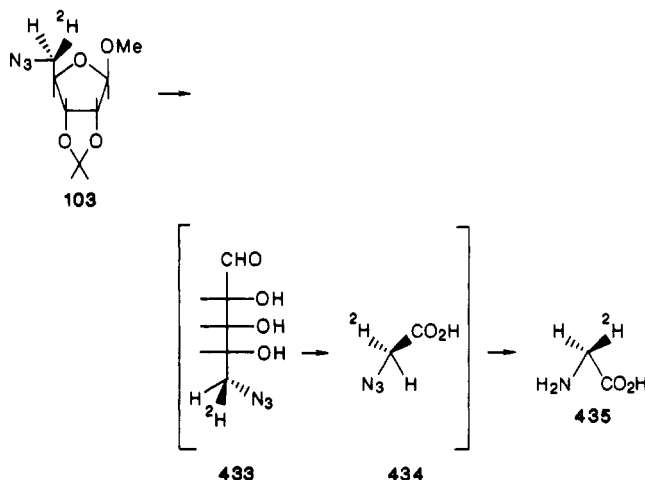
Reduction of the azide moiety to an amine constitutes a synthetically important process, and, since many azides can be prepared with regio- and stereocontrol (see section II), subsequent reduction permits a controlled introduction of the amine function. The reaction is of wide applicability and has been effected with a variety of reagents, including LiAlH_4 ,²⁹⁰ NaBH_4 ,²⁹¹ catalytic hydrogenation,²⁹² Ph_3P ,^{292d,293} H_2S ,²⁹⁴ dithiol/ NEt_3 ,²⁹⁵ $\text{Na}_2\text{S}/\text{NEt}_3$,²⁹⁶ diborane,²⁹⁷ Cr(II) ,²⁹⁸ V(II) ,²⁹⁹ Ti(III) ,³⁰⁰ Mo(III) ,³⁰¹ Bu_3SnH ,³⁰² Zn/HCl ,^{298a} and HBr/AcOH .^{291b} Applications of some of these and others have been described.³⁰³ More recent examples of these and other reagents are included in Table 2.

1. By Hydrogenation

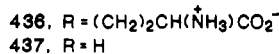
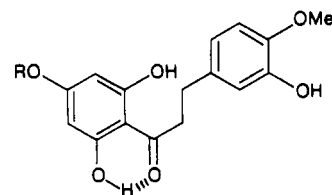
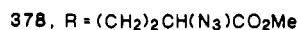
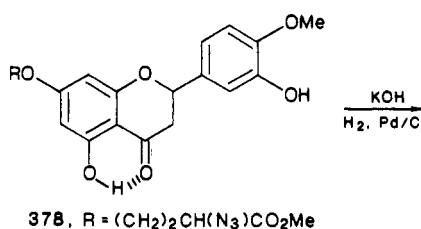
Hydrogenation methods have been very commonly applied to the reduction of azides (entries 1–13). The yields are generally excellent provided that no other reducible groups are present. In this regard some selectivity is possible; e.g., the azido function can be reduced without affecting the *O*-benzyl group (entries 6, 12, and 13) (the latter is removable under more forcing hydrogenation conditions). Additionally, as shown in Table 2, azide reduction without concomitant reduction of alcohol, ester, carboxylic acid, amine, amide, ketal, sugar, β -lactam, heterocyclic, or some ketone functionalities is possible.

Interestingly, Lindlar's catalyst proved to be the most effective method for reduction of 1,2-diazidodecane (entry 5). Although a 44% yield of the corresponding 1,2-diacetamide was obtained by hydrogenation with Pd/C in acetic acid/acetic anhydride, a variety of other approaches, including the use of sodium borohydride, Pd/C/H_2 , propanedithiol, diborane, LiAlH_4 , and $\text{Na/NH}_3/\text{MeOH}$,³⁰⁵ failed to completely reduce the diazide without polymer formation. Successful reduction of 1,2-diazides to the diamines using Adam's catalyst had been previously reported.³⁰⁶

Conversion of the azidoribofuranoside 103 to (*S*)-[2-²H]₂glycine (435) (in overall 60% yield) was effected by initial treatment with 5 N $\text{H}_2\text{SO}_4/\text{AcOH}$ to give 433 followed by room-temperature permanganate oxidation (to give 434) and catalytic reduction (10% $\text{Pd/C}/\text{AcOH}$) of the latter (entry 9).¹¹⁹ In order to minimize epimerization and loss of deuterium, compounds 433 and 434 were not isolated. Overall, this preparation provided an unequivocal confirmation of the absolute configuration of chiral glycine.



Dissolution of 378 in 10% KOH at room temperature or above followed by low-pressure hydrogenation gave the ring-opened amino acid 436 as major product, contaminated with other products, including 437. However, at ice bath temperature, nearly quantitative conversion to 436 occurred⁴⁹ (entry 11).



Catalytic transfer hydrogenation, largely introduced by Braude,³⁰⁹ involves the use of a hydrogen donor, usually cyclohexene,³¹⁰ in place of hydrogen gas. However, when this process has been used, reduction of alkyl azides has given variable results. In contrast, the recent use of ammonium formate as the hydrogen donor has permitted clean reduction of azides to amines (entry 13).³⁰⁸ The yields were excellent though generally slightly poorer than for the corresponding reductions with hydrogen gas (entry 12).³⁰⁸ However, the greater safety of the procedure is manifest.

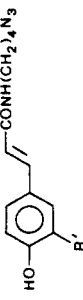
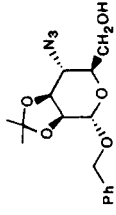
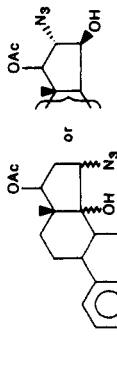
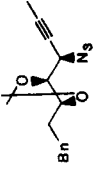
Reduction of some 15-azido steroids (prepared in situ) with hydrazine/Raney nickel gave the corresponding amines, which were isolated as the acetamido derivatives by treatment with pyridine/ Ac_2O (entry 14).¹³⁰ Overall, the process was used to convert steroidal 14,15-epoxides to 14-hydroxy-15-acetamido species in reasonable yields without isolation of the intermediates.

2. By Lithium Aluminum Hydride

Lithium aluminum hydride (LAH) effectively reduces azido species to the corresponding amines (entries 15–22). The reagent has been widely employed for examples where its lack of selectivity is unimportant.

Concomitant azide and epoxide reduction with LAH converted the epoxy azides 157 and 158 to the amino

TABLE 2. Reduction of Azides to Amines

| entry | RN_3 | reductant | conditions ^a | % yield | ref |
|-------|---|--------------------------------|-----------------------------------|---|-----|
| 1 | 348, R = H | H_2/PtO_2 | AcOH | | 267 |
| 2 | 108 | H_2/PtO_2 | toluene | 97.8 exo (from presumed exo azide) | 123 |
| 3 | $NaO_2CCH(N_3)CH_2CH_2N(Me)Ad$ (Ad = adamantyl) | H_2/PtO_2 | EtOH/MeOH, rt, 690 kPa, 3 days | 97.4 endo (from presumed endo azide) | 304 |
| 4 |  | $H_2/Lindlar$ | EtOH, rt, 2 h | 95-97 | 270 |
| 5 | (R' = H, MeO) $C_8H_{17}CH(N_3)CH_2N_3$ | $H_2/Lindlar$ | | 73 (other methods, including Pd/C/ H_2 , unsuccessful) | 175 |
| 6 |  | H_2/Pd black | MeOH, 4 h | quantitative | 307 |
| 7 | threo- or erythro-107 | $H_2/Pd/C$ | EtOH | >80 | 122 |
| 8 | 3'-azido-2',3'-dideoxycytidine or 3'-azido-2',3'-dideoxyuridine | $H_2/Pd/C$ | EtOH, 1.5 h, rt | 46-65 | 112 |
| 9 | 103 | $H_2/Pd/C$ | AcOH | >60 (2 steps) | 119 |
| 10 | 385 | $H_2/Pd/C$ | MeOH, 1 h, 20 °C | 90 | 273 |
| 11 | 378 | $H_2/Pd/C$ | 10% KOH, 0 °C | nearly quantitative (product 436) | 49 |
| 12 | alkyl azide (alkyl = hexyl, $HOCH_2C(Me)(Pr)CH_2CH_2$, 2-octyl, $H(C_7H_{14}O)_m$, $PhCH_2(C_2H_4O)_n$ [n = 3-6]) | $H_2/Pd/C$ | MeOH, rt, 10-15 h | 88-94 | 308 |
| 13 | same as above | $HCO_2NH_4/Pd/C$ | MeOH | 74-93 (lower yields than entry 12, but avoids use of H_2 gas) | 308 |
| 14 |  | hydrazine hydrate/ Raney Ni | EtOH, 5 min, reflux | 32-68 (as acetamido derivative) | 130 |
| 15 | 157, 158, R = n-C ₆ H ₁₃ | LAH | | | 157 |
| 16 | 98 | LAH | THF, reflux, 6 h | quantitative | 114 |
| 17 | 121 + 122 | LAH | | | 129 |
| 18 |  | LAH | ether, 0 °C | 76 (after N-Boc protection) | 311 |
| 19 | 94, R = (R)- or (S)-N ₃ | LAH | | | 113 |

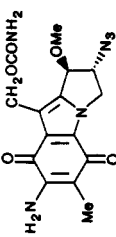
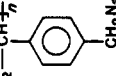
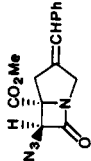
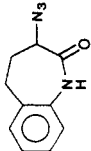
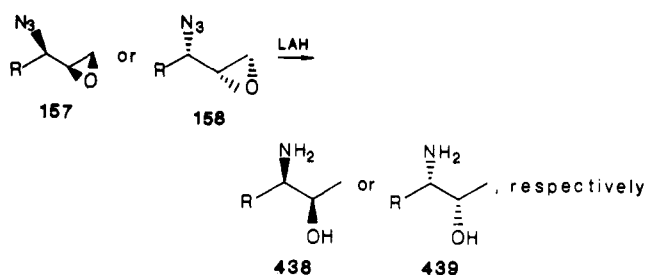
| | | | | | |
|----|---|--|--|--|---|
| 20 | 3, exo or endo | LAH | ether, 30–55 °C, 4.5 h (endo → endo amine only; exo → 4:1 exo:endo amine) | 32 | 28 |
| 21 | 274, 275 | LAH | ether, 30 °C, 3 h | 70–80 | 240 |
| 22 | 85, 89 | LAH | THF, 60 °C, overnight | 67–77 | 108 |
| 23 | alkyl, aryl, arylsulfonyl | NaBH ₄ | H ₂ O, toluene, PTC 1–6 h, rt, Ar or ArSO ₂ 16 h, 30 °C, alkyl (can be used as a one-pot halide to amine conversion) | 79–92 | 38 |
| 24 |  | 1. Ph ₃ P 2. pyridine, aq NH ₃ | rt, 36 h | ~30 (as <i>N</i> -acetyl) | 74 |
| 25 | 105 | 1. Ph ₃ P 2. NH ₃ | 1. CH ₂ Cl ₂ , 0 °C to rt, 4 h 2. MeOH, 40 h, 0–5 °C | 96 (more consistent yields than with H ₂ /Pd/C) | 121 |
| 26 | $-fCH_2-CH_2-$  | 1. Ph ₃ P 2. NaOH | 60 °C, MeOH | 50 | Cohen, H. L. <i>J. Polym. Sci.,</i> <i>Polym. Chem. Ed.</i> 1985, 23, 1671 |
| 27 | 440 + 441, X = N ₃ | 1. Ph ₃ P 2. H ₂ O/HCl | 1. pentane, 20 h, rt 2. 1 h, rt | 125 | |
| 28 | 442, 443 | Ph ₃ P | H ₂ O, THF, rt, 18 h | 275 | |
| 29 | alkyl, cycloalkyl, 4-nitrophenyl | Ph ₃ P/H ₂ O | rt, 6 h (longer for hindered) | 80–85 62–95 (thioether, alkene, ester, nitro, epoxide, ketal, alkyne all unaffected) | 293c, 315 |
| 30 | 2,4,6-(NO ₂) ₃ -3,5-Cl ₂ phenyl | 1. Ph ₃ P 2. CF ₃ CO ₂ H, MeOH | | 316 | |
| 31 | alkyl, aralkyl, alkenyl | 1. (EtO) ₃ P 2. HCl | rt | 0–80 (low yields with steric hindrance) [alkyne, alkene, ester unaffected] | 37 |
| 32 | 322 | H ₂ S/NEt ₃ | CH ₂ Cl ₂ , 0 °C, 1.5 h | 68.5 (isolated as the phenoxyacetamido derivative) | 259 |
| 33 |  | H ₂ S/NEt ₃ | CH ₂ Cl ₂ , 0 °C | 75 (isolated as the phenoxyacetamido derivative) | 262 |
| 34 | 56 | Na ₂ S ₂ O ₄ | 90–100 °C, 7 h | 33 | 74 |
| 35 | 448 | Na ₂ S ₂ O ₄ | | 60 (as Boc derivative 451) [benzyl ether also cleaved] | 318 |
| 36 | 273 | Na/NH ₃ | 25% aqueous solution, 40–50 °C, 3–5 h proton donor solvents, rt | 82 (ester in 454 converted to amide) ~25 | 239 320 322 |
| 37 | 452–454 | Me ₂ NH, Et ₃ N, or MeNH ₂ | | | |
| 38 | 2-nitro-3-azidopyridine | NaOH, RONA, KCN, or NaSC ₆ H ₄ Me-4 | | | |

TABLE 2 (Continued)

| entry | RN_3 | reductant | conditions ^a | % yield | ref |
|-------|--|--|---|---|-----|
| 39 | aryl, <i>n</i> -hexyl or benzoyl | $\text{KHfFe}(\text{CO})_4$ | CO , EtOH , rt, 12 h (benzoyl azide \rightarrow ethyl phenyl carbamate at rt and benzamide at -40°C) | 70-100 (aryl halide, methoxy unaffected) | 323 |
| 40 |  | $\text{NaH}_2\text{PO}_2/\text{Pd}/\text{C}$ | rt \rightarrow $50-65^\circ\text{C}$ (ketone, alkene, <i>N</i> -oxide, <i>O</i> -benzyl, aryl chloride, benzyl chloride, epoxide all potentially reducible) $\text{EtOH}/\text{Et}_2\text{O}$, rt, 15 min | 73 (ester, cyclic ketone, amide, alkyl chloride, nitrile unaffected) | 324 |
| 41 | aryl, benzylic, <i>n</i> -butyl, cyclohexyl, Ph_3C , ArCO , ArSO_2 | NaTeH | | 55-100 (alkene, alkyne, carbonyl, carboxyl, amide, ester, nitrile, haloaryl, haloalkyl, sulfone unaffected) | 325 |
| 42 | aryl | $\text{HSCH}_2\text{CO}_2\text{H}/\text{NEt}_3$ | EtOH , $50-60^\circ\text{C}$ | 89-100 (nitro, methoxy, chloro unaffected) | 326 |
| 43 | MeN_3 , $\text{HOCH}_2\text{CH}_2\text{N}_3$ | $(n\text{-Bu})_3[\text{Mo}_2\text{Fe}_8(\text{SPh})_8]$ | MeOH , THF or H_2O , resp | almost quantitative with careful addition of H^+ donors | 327 |
| 44 | $\text{PhCH}=\text{C}(\text{N}_3)\text{CO}_2\text{Me}$ | Hg/Pt or graphite cathodes + electrons | | reasonable yields of a mixture of <i>N</i> -acylated enamines | 328 |
| 45 | α -azidostyrene | Hg electrode + electrons, Ac_2O | | mix of aniline (67) and diphenylurea (23) | 329 |
| 46 | PhN_3 | $\text{Fe}_2(\text{CO})_9$ | $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 50°C | 26-70 (chloro and nitro unaffected) | 331 |
| 47 | ArN_3 | RhCl_3/CO | 150°C , 20 kg cm^{-2} , 4 h | 13-86 (nitro, methoxy unaffected) | 332 |
| 48 | ArN_3 | P_2I_4 | C_6H_6 , reflux, several hours | 13-86 (nitro, methoxy unaffected) | 333 |
| 49 | aryl or alkyl N_3 | SnCl_2 | MeOH , rt, 0.25-1 h | 85-98 | 334 |

^art = room temperature.

alcohols **438** and **439**, respectively¹⁵⁷ (entry 15). The



latter could also be prepared by catalytic hydrogenation ($\text{H}_2/\text{Pd}/\text{C}$) of the corresponding azido alcohols.¹⁵⁷ Long-chain alkyldiamines and -triamines were prepared by LAH reduction of the appropriate diazides (cf. **85** and **86**) and triazides (cf. **89**).¹⁰⁸

3. By Sodium Borohydride

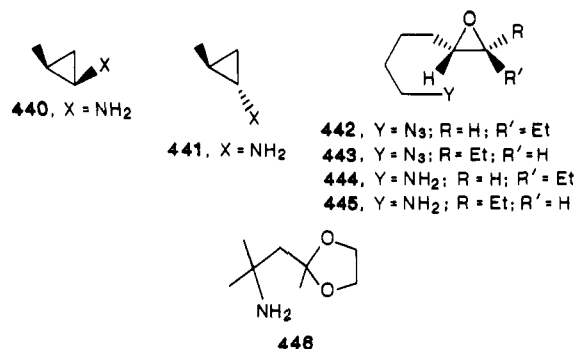
Sodium borohydride does not usually convert azides to amines in good yield in homogeneous systems,^{291b} except in the case of arylsulfonyl azides.³¹² However, it has been shown recently that under phase-transfer conditions efficient reduction of aryl, arylsulfonyl, and alkyl azides can be effected³⁸ (entry 23). The process could be extended to permit "one-pot" conversion of halides or methanesulfonates to pure primary amines in overall yields comparable to those for the conversion of azides to amines alone. The susceptibility of other functional groups to this approach has not been assessed and in this regard it is interesting that treatment of *tert*-butyl 2-azido-2-phenylacetate with NaBH_4 under phase-transfer conditions gave a 72% yield of phenylglycine.³⁸

4. Via the Staudinger Reaction

One of the mildest and most selective routes to convert azides to amines involves reaction of the former with triphenylphosphine to form the corresponding iminophosphorane and subsequent hydrolysis (see Scheme 18). The first step has become known as the



SCHEME 18
 Staudinger reaction after its discoverer.³¹³ The same author reported that conversion of the iminophosphorane to the amine could be effected with ammonium hydroxide.³¹³ This method has been modified to a "one-pot" process by Letsinger and co-workers,^{292d} and recent variants on the latter have allowed preparation of a mitosene⁷⁴ (entry 24) and 3-aminooxetane (**105**)¹²¹ (entry 25). More commonly, conversion of the iminophosphorane to the amine has been effected by hydrolysis rather than ammonolysis. Thus, poly(vinylbenzylamine hydrochloride) was prepared from the azide via NaOH (MeOH , 60 °C) hydrolysis of the isolated phosphine imine (entry 26) and subsequent treatment with hydrochloric acid. Again this procedure can be performed without isolation of the intermediate iminophosphorane and, as such, has been used to prepare the mixture of cyclopropylamines **440** and **441**¹²⁵ (entry 27). Indeed, the triphenylphosphine and water can be present together, providing a convenient, mild, one-step azide to amine conversion. Thus, the epoxy azides **442** and **443** react with triphenylphosphine (1 equiv) in THF in the presence of water (1.2 equiv) at



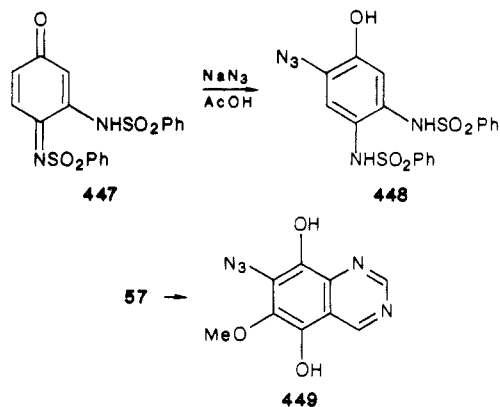
room temperature for 18 h to give the corresponding amines **444** and **445** in 80% and 85% yield, respectively²⁷⁵ (entry 28). A seven-compound study of the generality of the process has been reported^{293c} (entry 29). In general, clean conversion to the intermediate could be effected in 1 or 2 h at room temperature in dry THF. Addition of 1.2–1.5 equiv of water and further incubation at room temperature for 3–4 h gave good yields (80–91%) of the amines. Similar results were obtained when all reagents were premixed, except for in the case of the hindered amine **446**, where the two-step approach (72 h, toluene reflux; 24 h THF reflux) alone was successful. The reaction succeeds in the presence of a variety of functional groups (see entry 29) under very mild conditions and would hence appear to be the method of choice. Apparently, it is possible to selectively reduce an azide attached to a primary site in the presence of more hindered azides. A more comprehensive study has appeared recently.³¹⁵ In one reported case³¹⁶ the intermediate phosphazine was cleaved with trifluoroacetic acid/methanol (entry 30).

Phosphites have found limited use as phosphine congeners in the Staudinger type process. However, recently the reduction with trialkyl phosphites was declared the best available method for the azide to amine transformation.³⁷ This conclusion was based on the facility of the process (greater phosphine reactivity and easy deprotection) and the economic advantage accruing from use of the less expensive trialkyl phosphites. Thus, primary and secondary alkyl bromides can be converted to the primary amines in a one-pot procedure involving (a) azidation using solid-liquid PTC, (b) Staudinger reaction of the crude azide with triethyl phosphite, and (c) two-step deprotection using HCl gas in ether³⁷ (entry 31). The procedure reportedly offers a viable alternative to the Gabriel synthesis, especially in cases where nucleophilic displacement is accompanied by extensive elimination and/or when drastic deprotection conditions should be avoided.

5. By Other Established Methods

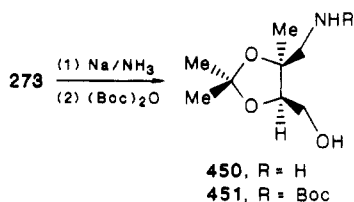
(a) Hydrogen Sulfide/Triethylamine. Recent uses of $\text{H}_2\text{S}/\text{NEt}_3$ for azide to amine conversion have been limited and mainly in the β -lactam^{259,262} (entries 32 and 33) and carbohydrate fields.³¹⁷ The mildness of the procedure is apparent but, in the light of the simplicity of the triphenylphosphine approach, will probably continue to receive scant attention.

(b) Sodium Dithionite. Reduction of azidoquinone **56** with sodium dithionite gave the corresponding amine in 33% yield⁷⁴ (entry 34). Azidophenol **448** (prepared from **447** by treatment with sodium azide/ AcOH) reacted with sodium dithionite to give the amine, which



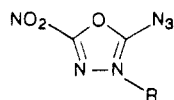
was further transformed in situ³¹⁸ (entry 35). Attempted reduction of the unstable azidoquinone **57** with excess sodium dithionite gave the unstable azido-hydroquinol **449** and not the expected amino congener.⁷⁵ The aminoquinone (analogous to **57**) could be prepared from **449** using Watanabe's method.³¹⁹

(c) Sodium/Ammonia. Acetonide **273** was reduced with Na/NH_3 to amino alcohol **450**, which was treated directly with $(\text{Boc})_2\text{O}$ in aqueous NaOH to give the N-protected alcohol **451**²³⁹ (entry 36).



6. By Nucleophiles

1-R-3-Nitro-5-azido-1,2,4-triazoles **452**–**454** were reduced to the corresponding amines in good yield by the action of methylamine, dimethylamine, or triethylamine (entry 37). The less basic ammonia and ethylenimine



- 452**, R = Me
453, R = $\text{CH}_2\text{CO}_2\text{H}$
454, R = $\text{CH}_2\text{CO}_2\text{Me}$ ($\text{CH}_2\text{CONHR}'$ in product)

did not effect reduction. Unlike the 3,5-dinitro congeners no nitro (or azido) displacement occurred and 1-R-3-azido-5-R-1,2,4-triazoles did not react.³²⁰ This unusual transformation had been previously observed in the pyridine series.³²¹ More recently, 2-nitro-3-azidopyridine was reportedly reduced to the amine in 25% yield by NaOH , RONa , KCN , or NaSC_6H_4 -4-Me in proton-donor solvents³²² (entry 38). Additionally, with the first two reagents, concomitant reduction and 6-substitution occurred. In contrast, with the stronger nucleophile, NaSC_6H_4 -4-Me, azide substitution took place and the reaction with KCN also provided a product derived from cyanide addition to the azido group.³²²

As previously described (section II.A), on occasion reduction to the amine occurs on attempted azidation of the halide precursor (cf. from **77** and **78**).^{104,105}

7. By New Methods

Various new reagents for the azide to amine conversion have been developed recently (entries 39–49).

Thus, tetracarbonylhydridoferrate ($\text{HFe}(\text{CO})_4^-$) reacts with aryl and hexyl azides in ethanol at room temperature under an atmosphere of carbon monoxide to give good yields (70–100%) of the primary amines. Interestingly, under the same conditions benzoyl azide gave ethylphenyl carbamate; the amide was formed quantitatively at -40°C ³²³ (entry 39). Sodium hypophosphite has been employed recently for the transfer hydrogenation of a number of functionalities, including an alkyl azide. The process may be of limited utility because of the range of other groups reduced³²⁴ (entry 40). A reagent of more general applicability is sodium hydrogen telluride (prepared from tellurium and sodium borohydride), which reduces aryl, benzyl, alkyl, acyl, and sulfonyl azides in good to excellent yield under mild conditions³²⁵ (entry 41). For aryl azides, mercaptoacetic acid appears to be a very efficient reductant³²⁶ (entry 42).

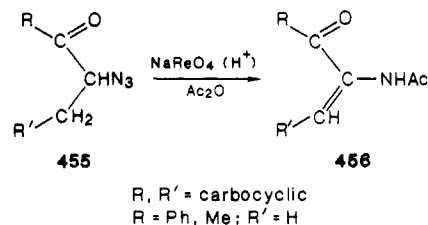
Multielectron reduction of methyl azide and 2-hydroxyethyl azide using a $(n\text{-Bu}_4\text{N})_3[\text{Mo}_2\text{Fe}_6\text{S}_8(\text{SPh})_9]$ -modified glassy carbon electrode provided the appropriate amine plus hydrazine and ammonia (depending on concentration)³²⁷ (entry 43). The method probably offers little synthetic scope at present. In the same vein, cathodic reduction of α -azidocinnamic ester³²⁸ and nonterminal vinyl azides³²⁹ has been examined. In the former, an excellent yield of α -aminocinnamic ester can be realized by careful addition of proton donors. N-Acylated species result from reduction in the presence of electrophiles (entries 44 and 45). Further work in this area has been reported recently.³³⁰

Azidobenzene was converted to a mixture of aniline (67%) and *N,N*-diphenylurea (23%) by treatment with $\text{Fe}_2(\text{CO})_9$ in acetonitrile/water at 50°C ³³¹ (entry 46). Azidoarenes were also converted to the aminoarenes in 26–70% yield by carbon monoxide and water in the presence of a RhCl_3 catalyst³³² (entry 47) and in 13–86% yield by P_2I_4 ³³³ (entry 48). With the latter, aryl and sulfonyl azides reacted sluggishly.

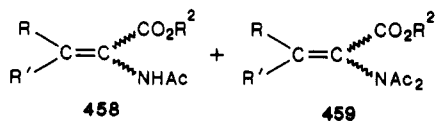
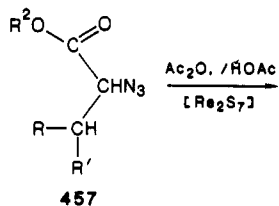
Both aryl and alkyl azides are reduced to the corresponding amines in excellent yield (85–98%) using stannous chloride in methanol³³⁴ (entry 49).

B. Other Reductions

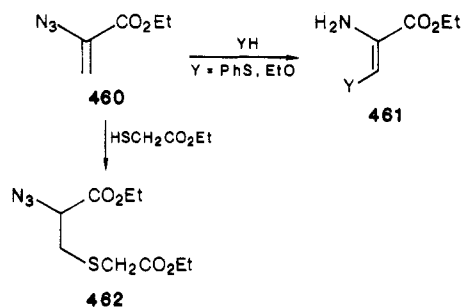
Cyclic and acyclic 2-azido ketones **455** eliminate nitrogen in the presence of catalytic amounts of perrhenate. When the reaction is conducted in acetic



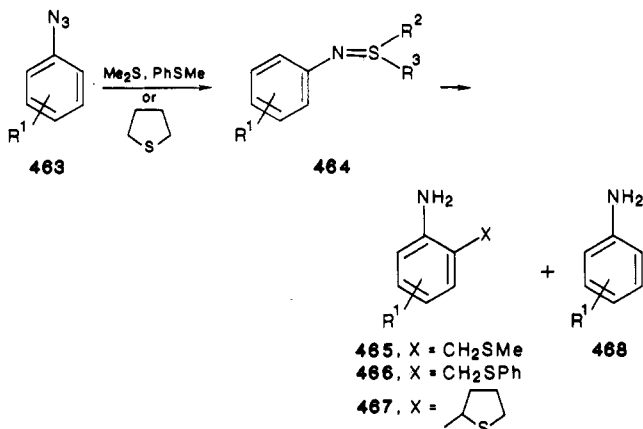
anhydride, containing small quantities of a mineral acid, if required, 2-(acetylamino)-2-alken-1-ones (**456**) are formed in good yield.³³⁵ Similarly, α -azido esters **457** react with acetic anhydride in the presence of catalytic amounts of rhenium heptasulfide (and hydrochloric acid if necessary) to give good yields of the mono- and diacetylated esters **458** and **459**. If water is added before workup or a smaller $\text{Ac}_2\text{O}/\text{AcOH}$ ratio is employed, monoacetylated ester **458** is the sole product.³³⁶



Treatment of ethyl 2-azidopropenoate (**460**) with thiophenol or with lithium ethoxide or sodium ethoxide gave (*Z*)-2-amino-3-(phenylthio)propenoate (**461**, Y = PhS) or (*Z*)-2-amino-3-ethoxypropenoate (**461**, Y = EtO), respectively, in reasonable yield.³³⁷ In contrast, ethyl mercaptoacetate reacted with **460** to give the expected Michael adduct (**462**) without concomitant azide reduction.

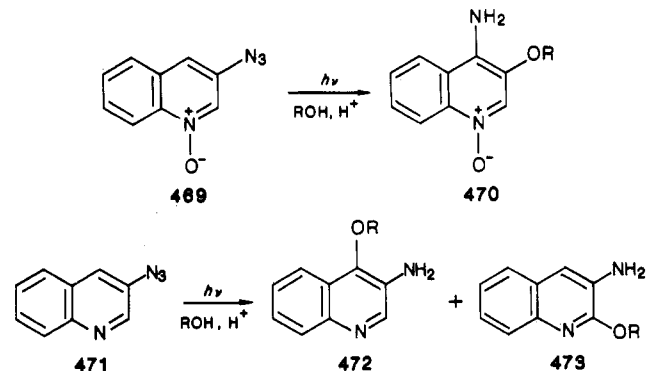


Aryl azides react with carbon monoxide at atmospheric pressure in the presence of a rhodium catalyst to give aryl isocyanates, which form urethanes with alcohols.³³⁸ Substituted aryl azides (cf. **463**) generally



decompose in the presence of dimethyl sulfide, thioanisole, or tetrahydrothiophene to give 2-substituted anilines **465**–**467**, respectively, in modest yields.³³⁹ Unsubstituted anilines **468** were also formed in variable yield. The mechanism apparently involves Sommelet-Hauser type rearrangement of intermediate *N*-aryl sulfimides **464**, with Sommelet-Hauser products **465** and **466** being favored by electron-withdrawing groups. 2-Substituted arylamino compounds (and/or ring-expansion products) can also be prepared by photolysis of aryl azides in the presence of nucleophiles.³⁴⁰ More recently, Tsuchiya and co-workers have extensively examined similar reactions of pyridyl, quinolyl, and isoquinolyl azides under acidic conditions;³⁴¹ in some cases reactions involving a nitrenium ion intermediate

also occur. Thus, 3-azidoquinoline *N*-oxide (**469**), upon irradiation in alcohols containing sulfuric acid, gave **470**, whereas under the same conditions 3-quinolyl azide (**471**) afforded 4-alkoxy- (**472**) and 2-alkoxy-3-aminoquinoline (**473**) via the nitrenium ion.³⁴²

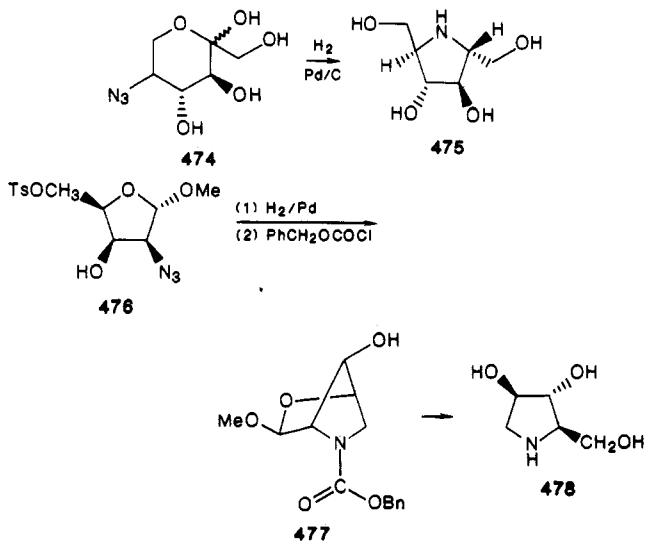


The same workers have examined the effects of reaction conditions upon the course of such reactions.³⁴³ With hydrohalogenic acids, α -halogeno amino compounds are formed (also via the nitrenium ion); lower yields result from thermolysis. Both photolysis and thermolysis of these azide types in alkanethiols afforded α -alkylthio amines, apparently via radical intermediates. More recently, this latter study has been extended to 3-, 4-, and 8-quinolyl azides and 4-isoquinolyl azide.³⁴⁴

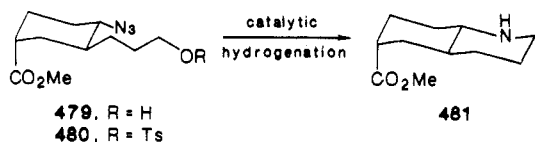
C. Reductive Cyclizations

On occasion, reduction of the azide function in the presence of displaceable functionalities (commonly hydroxyl groups) in the same molecule gives nitrogen heterocycles.

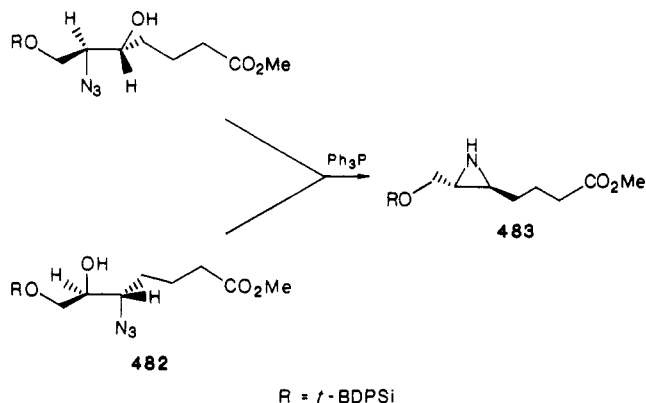
Thus, catalytic hydrogenation of 5-azido-5-deoxy-D-fructose (**474**) over 10% Pd/C gave pyrrolidine **475** in quantitative yield.¹¹⁸ Similarly, reduction of **476** with H₂/Pd black in ethanol containing sodium acetate at 50 °C, followed by treatment with PhCH₂OCOC/NaHCO₃, provided the bicyclic amine **477** in 36% yield. The latter could be further transformed to **478**.¹⁰⁹ Aziridine rings can be prepared in an analogous fashion.



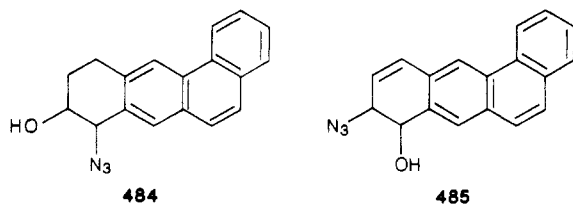
Azido alcohol **479** could not be cyclized to **481** using a variety of one-step procedures. However, conversion to tosylate **480** and catalytic hydrogenation did afford **481**.³⁴⁵



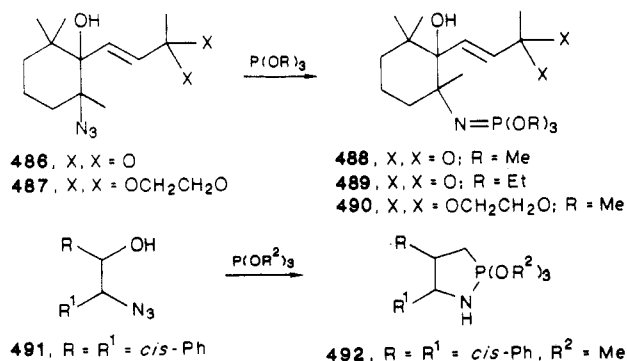
Cyclization of azido alcohols 482 to aziridine 483 (>80%) took place when either was heated in THF at 60–65 °C with triphenylphosphine.¹³² Under the pre-



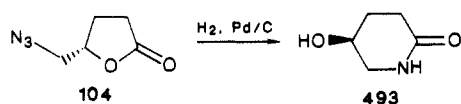
viously reported conditions (viz., triphenylphosphine in ether at reflux¹³¹) no cyclization occurred (see section II.A). The process was extended to the preparation of the aza analogue of LTA₄.¹³² Aziridines also result¹³³ from treatment of 484 and 485 with tri-*n*-butylphosphine³⁴⁶ or trimethyl phosphite.³⁴⁷ Similar results were obtained with a chrysene analogue.¹³³



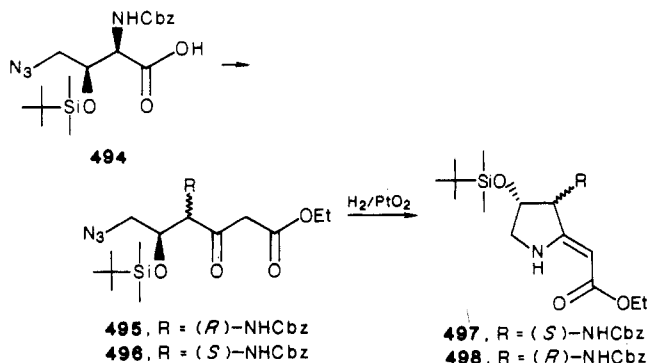
Azido alcohols 486 and 487 react with trialkyl phosphites to give the expected iminophosphoranes 488–490 (see section III.F) but, interestingly, azido alcohol 491 provided oxazaphospholidine 492 under the same conditions.³⁴⁸ For further examples see section VI.A.7.



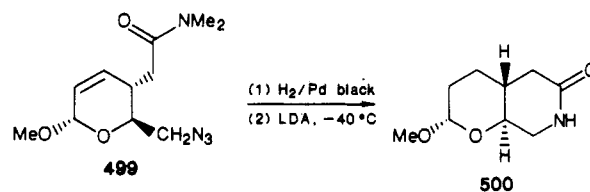
Reductive cyclization can also occur with azido carbonyl species. Thus, hydrogenation (H₂/Pd/C) of azido lactone 104 provides (*S*)-5-hydroxy-2-piperidinone (493) in 67% yield.¹²⁰



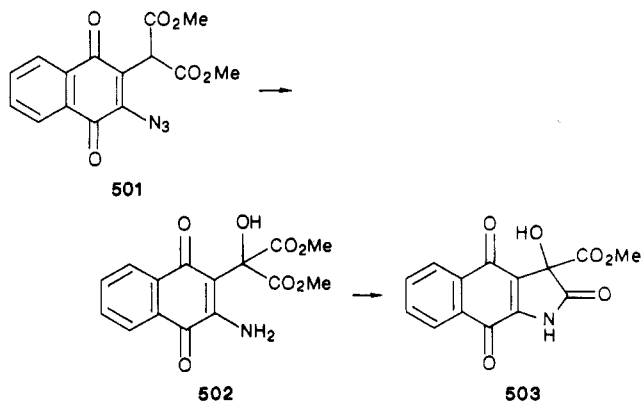
Homologation of 494 with the magnesium salt of ethyl hydrogen malonate gave the β-keto ester 495 (and its anti diastereomer (496)) in an 88% crude yield. Using H₂/PtO₂, the mixture was reduced and cyclized to 497 and 498 in 57% overall yield from 494.³⁴⁹



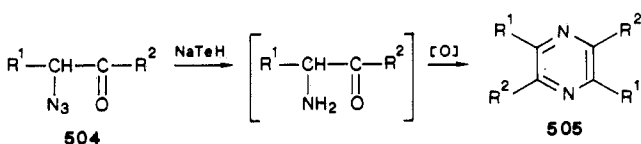
Hydrogenation of azido amide 499 in the presence of palladium black in ethanol reduced both the double bond and the azide to an amine, which was cyclized (68%) to lactam 500 with LDA.³⁵⁰



Refluxing an aqueous THF solution of azidoquinone 501 for 1.5 h results in the formation of aminoquinone 502 in 79% yield. However, extension of the reflux time to 5 h gives ring-closed indoloquinone 503 in 74% yield.³⁵¹

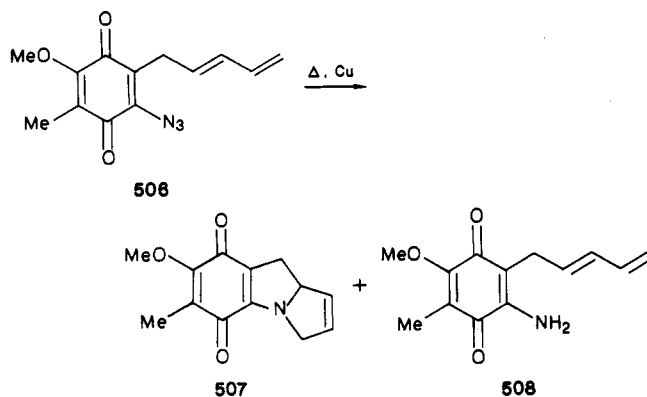


Treatment of α-azido ketones 504 with sodium hydrotelluride at room temperature gives pyrazines 505 in 40–98% yield.³⁵² The process is not of general



applicability, however, since some primary azido ketones give complicated reaction mixtures. Pyrazines have been prepared previously from α-azido ketones by reduction with hydrogen over catalyst³⁵³ or triphenylphosphine³⁵⁴ and from ketones and iodine azide.³⁵⁵

Pyrolytic decomposition of azidoquinone **506** under reflux in benzene for 4 h in the presence of copper powder gave the reductive cyclization product **507** in 53% yield and the aminoquinone **508** in 35% yield.³⁶⁶ Two other azidoquinones reacted similarly.



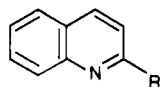
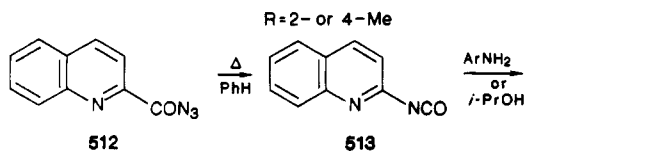
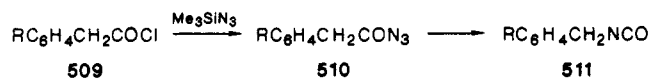
D. Curtius Reaction

The Curtius reaction is a general process involving the conversion of acyl azides (see section II.A) to isocyanates.^{3,10} The yields of the latter are generally good since the process can be conducted readily in the absence of water. If desired, the reaction can be performed in the presence of water or alcohol, whereupon amines, carbamates, or ureas result. For Curtius reactions involving heterocyclic species, see section VI.A.4.

1. Thermal

Typically, the Curtius process can be carried out by thermolysis in an inert solvent and subsequent isolation of the isocyanate or trapping of the latter by reaction with a nucleophilic species.

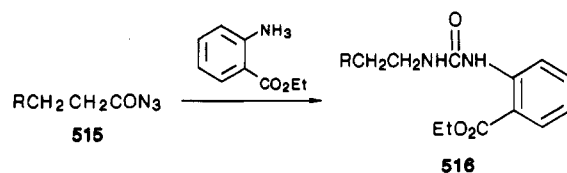
Recently, isocyanates **511** were prepared from the corresponding acyl chlorides **509** by treatment with trimethylsilyl azide and rearrangement of the intermediate acyl azides **510**.³⁵⁷ Thermolysis of quinoline



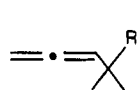
- 514 a.** R = NHCONHPh
b. R = NHCONHC₆H₄OMe-4
c. R = NHCONHC₆H₄Cl-4
d. R = NHCO₂-i-Pr

acyl azide **512** in benzene gave isocyanate **513**, which could be converted to urea derivatives **514a-c** with arylamines or to carbamate **514d** with isopropyl alcohol.³⁵⁸ Similarly, urea derivatives **515a-c** were prepared by thermolysis of acyl azides **515a-c** (obtained from the carboxylic acids with ethyl chloroformate followed by NaN₃) in the presence of ethyl anthranilate.³⁵⁹

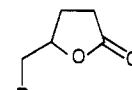
Most current utilizations of the Curtius rearrangement have involved isocyanates only as intermediates. Thus, allenic isocyanate **518**, formed from thermolysis



- a. R = 3,4-(MeO)₂C₆H₃-; b. 2-thienyl; c. 3-thienyl



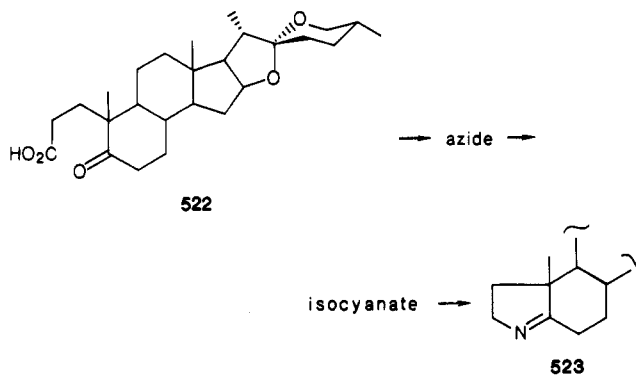
- 517.** R = CON₃
518. R = NCO
519. R = NH₂



- 520.** R = CO₂H
521a. R = *t*-BuO₂CNH
b. R = 4-MeOC₆H₄CH₂O₂CNH

in benzene (18 h) of **517** (in turn prepared from the carboxylic acid), could be hydrolyzed to amine **519** in 39% overall yield.²⁰ Similarly, some tetrazolymethyl isocyanates resulted from thermolysis of the acyl azides in toluene. Subsequent transformations to carbamates, amines, and ureas were reported.³⁶⁰ As part of a synthetic pathway leading to a GABA analogue, carboxy lactone **520** was converted to the carbamates **521** by Curtius rearrangement and trapping of the isocyanate with *tert*-butyl alcohol or 4-methoxybenzyl alcohol.³⁶¹

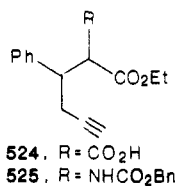
Without purification of the intermediates, keto acid **522** was converted to the acyl azide and thence to the corresponding isocyanate. The presence of these



species was monitored by their characteristic infrared absorptions and, in the latter case, by reaction with methanol to form the urethane. Hydrolysis of the isocyanate under acidic or basic conditions gave the ring-closed steroid **523**.³⁶² A better route for the conversion of carboxylic acids to amines, via the Curtius rearrangement, has been reported recently. Therein, carboxylic acids were converted to isocyanates either by the usual acid \rightarrow acid chloride \rightarrow acyl azide \rightarrow isocyanate sequence or by the more convenient one-pot procedure (using diphenylphosphoryl azide) developed by Shioiri, Ninomiya, and Yamada.³⁶³ Subsequent addition of (trimethylsilyl)ethanol gave carbamates, which then could be cleaved with tetrabutylammonium fluoride to provide amines in 68–85% yield (from the carboxylic acids).³⁶⁴ Previously, difficulties have often been encountered in the cleavage of other carbamates, especially where the R group contains sensitive functionalities. The present method appears to circumvent such problems.

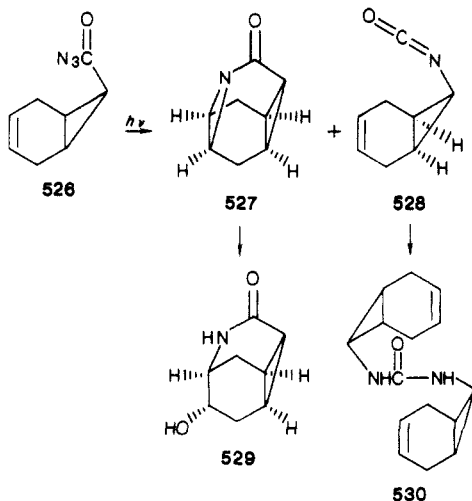
As mentioned above, direct transformation of carboxylic acids to isocyanates has been effected by using diphenylphosphoryl azide. The scope of this process has been explored by Shioiri and co-workers.³⁶⁵ Recent uses of this method include the preparation of benzyl

carbamate **525** from **524** (triethylamine/benzene, reflux 1.5 h followed by treatment with benzyl alcohol) in good yield (67%)³⁶⁶ and similar transformations (see section VI.A.4).



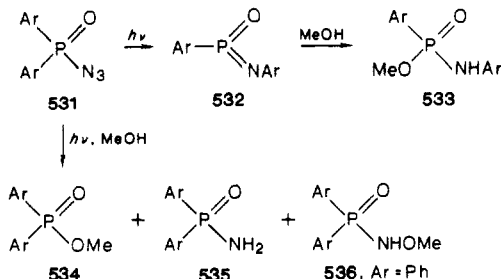
2. Photochemical

Photochemical Curtius rearrangements are often accompanied by products resulting from trapping of an intermediate nitrene. Thus, photolysis of **526** in pentane for 1 h at 0 °C gave **529** and **530**, presumably arising from **527** and **528**, respectively.³⁶⁷

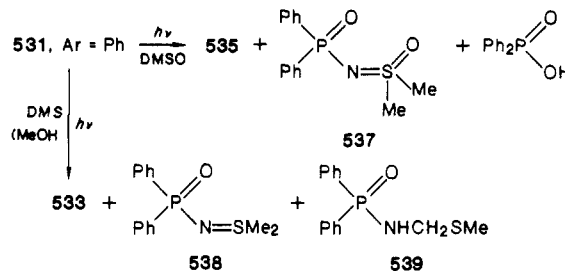


An excellent review of the photochemical (and thermal) rearrangements of heavier main group element (mainly B, Si, Ge, and P) azides has appeared recently.³⁶⁸ Accordingly, no attempt has been made to cover this topic comprehensively herein, and the reader is directed to the review for full details.

Diarylphosphinic azides (**531**)³⁶⁹ rearrange on photolysis in methanol to form metaphosphonimidates (**532**), which are trapped by the solvent³⁷⁰ to give methyl *N,P*-diarylphosphonamidates (**533**) in reasonable yield.³⁷¹ Methyl phosphinates (**534**), products of solvolytic azide displacement, and diarylphosphinic amides (**535**) are also formed.³⁷¹

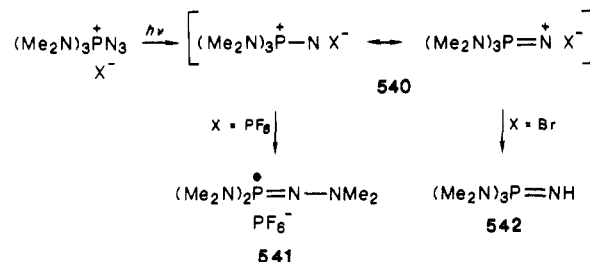


A careful study of the photolysis of diphenylphosphinic azide (**531** Ar = Ph) in methanol revealed that *N*-methoxy amide **536** was a minor product (ca. 2.5%). In an attempt to assess whether the Curtius rearrangement products **532** are formed via phosphinyl nitrenes (rather than directly from the azides), **531** (Ar



= Ph) was photolyzed in DMSO (a known nitrene trap³⁷²). The products presumed to arise from singlet and triplet nitrenes, viz., **535** and **537**, were obtained in low yield (4.7 and 2.8%, respectively) and the major product was diphenylphosphinic acid (Ph₂P(O)OH). The latter was apparently not derived from direct hydrolysis of the azide. The same product was formed in 98% yield from thermolysis of diphenylphosphinic azide in DMSO.³⁷³ Similar experiments conducted in the presence of dimethyl sulfide (DMS) (and methanol) provided sulfilimine **538** in addition to **533**.^{374,375} The role played by nitrenes in these transformations is still unclear.

Recently, the first example of a Curtius type rearrangement involving a charged atom was reported.³⁷⁶ Thus, irradiation of the azidophosphonium salt **540** (X = PF₆) at 254 nm for 15 h at room temperature gave the iminophosphonium salt **541**.³⁷⁷ In contrast, similar



irradiation of the bromide salt **540** (X = Br) afforded iminophosphorane **542** in 80% yield. These results were rationalized in terms of an intermediate phosphonium nitrene, with subsequent migration of a phosphorus substituent to nitrogen (when the anion is a poor nucleophile, e.g., PF₆⁻) or, with the good nucleophile Br⁻, direct attack at nitrogen followed by photolytic scission of the halogen–nitrogen bond.

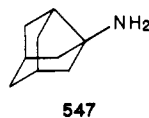
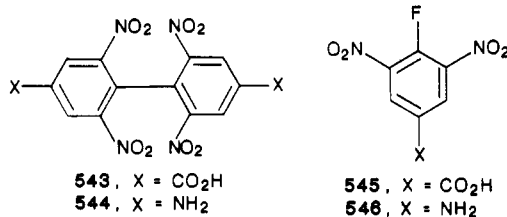
Recently, West and co-workers published their findings regarding the photolytic conversion of trimesitylazidosilane (Mes₃SiN₃) to the silanimine (Mes₂Si=NMe).³⁷⁸

E. Schmidt Reaction

The Schmidt reaction (viz., conversion of a carboxylic acid to an amine or a ketone to an amide by the action of hydrazoic acid or congeners) has been known for many years.¹⁰ Good results are generally obtained for aliphatic cases, but for aromatic examples the yields are variable. The main disadvantage of the procedure results from the use of more drastic conditions than for the closely related Hofmann or Curtius rearrangements. Consequently, the reaction is employed relatively infrequently for the acid to amine conversion, the Curtius (see section III.D) and Hofmann procedures being generally more facile. The Schmidt process is discussed only briefly in this section and the reader is directed

to the alicyclic (section IV.D) and heterocyclic (section VI.C.1) portions for further details.

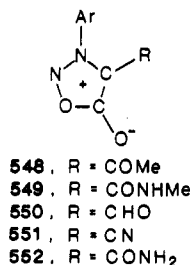
Recently, it was reported that diamino compound 544 could be obtained in excellent yield (93–100%) via a Schmidt reaction on the dicarboxylic acid 543.³⁷⁹ Ap-



parently, in this case, the process is superior to those previously employed, viz., a four-step Curtius rearrangement (<70% yield overall) and a three-step Hofmann reaction (<8–30% yield overall),³⁸⁰ and the hazard associated with hydrazoic acid (here generated from NaN₃ in fuming sulfuric acid at 80 °C) can be tempered somewhat by the addition of 1,2-dichloroethane. Similarly, 545 could be converted to 546 in 77% yield by using sodium azide in 20% oleum at 25 °C,³⁸¹ and 3-noradamantamine (547) is formed in 63% yield from the corresponding carboxylic acid.³⁸² The process has been extended to the formation of an acrylic acid–vinylamine copolymer by treatment of poly(acrylic acid) with sodium azide in sulfuric acid/chloroform.³⁸³ The conversion of carboxylic acid to amino groups was limited to about 50%.

The reaction between a ketone and hydrazoic acid is a method for insertion of NH between the carbonyl group and one substituent to yield an amide. Generally, dialkyl and cyclic ketones react faster than alkyl aryl ketones, which in turn transform more rapidly than diaryl ketones. There is usually a preference for aryl migration (when in competition with an alkyl group) except when the alkyl is bulky, although even on this latter point exceptions do exist.

Recently, selectivity has been observed in some cases. Thus, MeCOCHRCO-Gly-OEt (R = H, Bn, Me, Et, Pr, Bu) gave MeCONHCHRCO-Gly-OEt and MeCOCH₂CO-X-OH (X = Phe, Leu) afforded MeCONHCH₂CO-X-OH on treatment with HN₃/H₂SO₄.³⁸⁴ 3-Aryl-4-acetylsydnone (548, Ar = Ph, 4-Me-, 4-Br-, 4-MeO-, 4-EtO-C₆H₄) reacted to give only



Ar = Ph, 2- and 4-Me-, 4-EtO-, 4-MeO-, 4-BrC₆H₄

the corresponding *N*-methylcarboxamides 549 in reasonable yield (50–77%).³⁸⁵ The expected 4-acetamido congeners (derived from heteroaryl rather than methyl migration) were apparently not products of the reactions, in line with previous unsuccessful attempts to

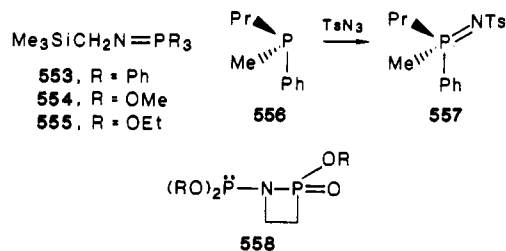
place electron-donating groups at the 4-position of the sydnone ring.

The Schmidt reaction has been applied infrequently to aldehydes; nitrile products usually result. Recently, nitrile 551 was shown to arise from 550 in 67–77% yield on treatment with sodium azide in dilute sulfuric acid. However, in concentrated sulfuric acid, carboxamides 552 were obtained in 47–74% yield.³⁸⁶ Aromatic aldehydes react with trimethylsilyl azide in the presence of zinc chloride to give the corresponding nitriles in 62–97% yield.³⁸⁷

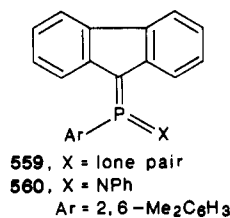
F. Staudinger Reaction

As previously mentioned (see section III.A.4), the Staudinger reaction has been employed as a means to convert azides to amines. Numerous analogous transformations have been reported and recent examples of these are described herein. Iminophosphoranes are valuable species since they undergo Wittig type reactions with, inter alia, aldehydes,³⁸⁸ ketones,³⁸⁹ ketenes,³⁹⁰ and other compounds containing polarizable oxygen or sulfur.³⁹¹ In addition, the reaction of iminophosphoranes with phthalic anhydride to form phthalimides in good yield has been reported.³⁹² For more details on “aza-Wittig” cyclizations, see section VI.A.7.

Reaction of azides (prepared by the action of “clayfen” on the hydrazines) with triphenylphosphine, triphenyl phosphite, or triethyl phosphite gives the corresponding iminophosphoranes, apparently via an intermediate phosphine–azide complex.³⁹³ In some cases the latter could be isolated. Recently, the Staudinger process has been extended to the preparation of the [(trimethylsilyl)methyl]iminophosphoranes (553–555)³⁹⁴ and reactions of azides with arsenic heterocycles,³⁹⁵ an anionic phosphorus(III) complex,³⁹⁶ and di- and triesters of phosphorous acid.³⁹⁷ Chiral phosphine 556 reacts with tosyl azide with retention of stereochemistry to form iminophosphorane 557.³⁹⁸ Tosyl azide has also been used to convert the *N*-phosphorylated 1,2-azophosphetidine 558 to the corresponding iminophosphorane.³⁹⁹

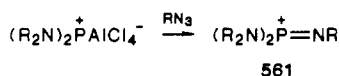


Interestingly, phosphalkene 559 reacted with phenyl azide to give iminomethylenephosphorane 560.⁴⁰⁰

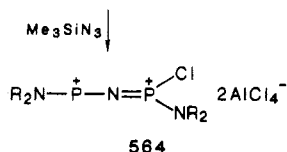
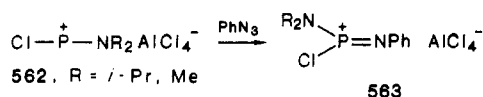


Even phosphorus cations can undergo the Staudinger reaction. Thus, azides were shown to react with bis-(dialkylamino)phosphenium species to give the corre-

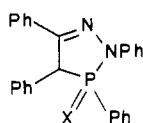
sponding bis(dialkylamino)iminophosphonium compounds (561).^{377,401} More recently, the process has been



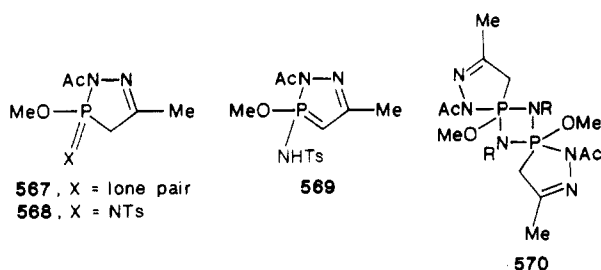
extended to the chlorophosphonium salts (562).⁴⁰² Reaction of 562 with phenyl azide gave the appropriate chloroiminophosphonium salts (563). Different results were obtained with trimethylsilyl azide, presumably since elimination of trimethylsilyl chloride is in competition with the Staudinger process. Thus, treatment of 562 with trimethylsilyl azide gave 564, the first examples of bisphosphocations. The latter are presumed to arise via intermediate phosphonium azides ($R_2N-P^+-N_3 AlCl_4^-$).



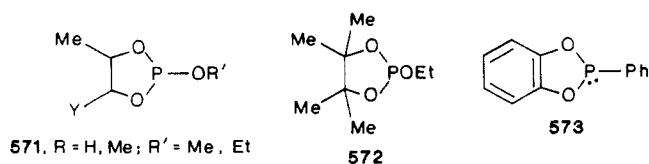
Heterocycles containing tricoordinated phosphorus usually form the pentacoordinated phosphorus imines on treatment with azides. Thus, the *cis*- or *trans*-2*H*-1,2,3-diazaphospholenes (565) gave the corresponding iminophosphoranes (566), with varying stereochemical results, on treatment with aryl azides.⁴⁰³



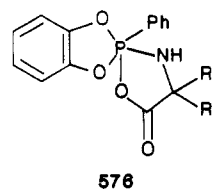
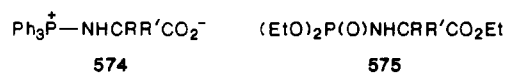
565. X = lone pair
566. X = NR (R = 4-ClC₆H₄, 4-NO₂C₆H₄, Ph, Ts)



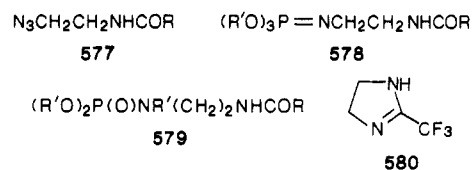
Similarly, reaction of 2-acetyl-3-methoxy-5-methyl-diazaphospholene (567) with tosyl azide gave imino product 568 in 81.5% yield.⁴⁰⁴ The latter is stable in the solid state but in dichloromethane forms the tautomer 569 and in ether affords the dimer 570. Similar dimers are also derived in 58–92% yield from the reaction of phenyl azide with the dioxaphospholanes 571.⁴⁰⁵ In contrast, with *p*-nitrophenyl or tosyl azide the expected iminodioxaphospholanes resulted in 62–87% yield. Normal Staudinger products were also formed from tetramethyldioxaphospholane 572 and phenyl, *p*-methoxyphenyl, or *p*-nitrophenyl azides.



Azido carboxylic acids and related species also have been subjected to the Staudinger process.⁴⁰⁶ In the latter, a systematic investigation of the imination of trivalent phosphorus compounds with aliphatic azides containing H atoms of different mobility (e.g., in carboxylic acids, amides, or amines) gave interesting results.⁴⁰⁶ Thus, treatment of azidoacetic acid derivatives with triphenylphosphine, triethyl phosphite, or 573 gave the betaines (574), amido phosphates (575), or cyclic phosphoranes (576), respectively. The latter two presumably arise from further transformations of betaines similar to 574 (see section VI.A.7).



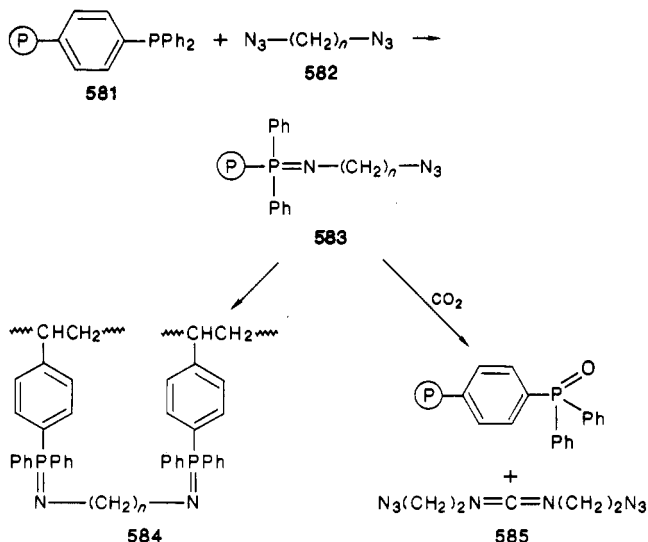
The key step of these transformations is certainly the transfer of the proton from the carboxylic acid to the imine nitrogen. In contrast, proton transfer does not occur from the amido group and an iminophosphorane results from treatment of 577 with $(Me_2N)_3P$. Trialkyl



phosphites react with 577 to give the corresponding iminophosphoranes (578), which are converted to amido phosphates (579) on vacuum distillation. Interestingly, the trifluoromethyl analogues 578 (R = CF₃) decompose to form both 579 (R = CF₃) and 2-(trifluoromethyl)-imidazoline (580). The triphenylphosphine analogues of 578 could also be converted to imidazolines by thermolysis.

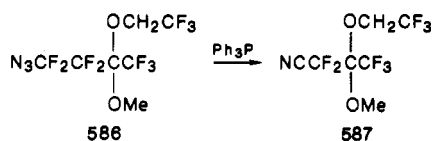
Polymeric phosphines can also be utilized in the Staudinger reaction. Thus, 581 combined with 1,2-diazidoethane (582, *n* = 2) to form the azidoiminophosphorane (583). With longer chain diazides the azide IR stretch in the products ranged from very weak (*n* = 4) to nonexistent (*n* = 6 and 10), apparently due to the formation of 584.⁴⁰⁷ When 583 was allowed to react with carbon dioxide the unusual diazido carbodiimide (585) was obtained.

Some useful one-pot azide conversions (via the Staudinger process) have been developed. Thus, heating a mixture of a carboxylic acid, aryl or alkyl azide, and triphenylphosphine in benzene, hexane, or toluene for 12–120 h gave the corresponding amide in good yield. ω -Azido acids gave insoluble zwitterionic products ($Ph_3P^+-NH(CH_2)_nCO_2^-$) and under these conditions cyclization was not observed. However, in refluxing pyridine $Ph_3P^+-NH(CH_2)_3CO_2^-$ did provide 2-pyrrolidone in 95% yield.⁴⁰⁸ More recently, a similar, but milder process was used for the preparation of small peptides. Therein, ethyl diphenylphosphinite (Ph_2POEt) proved to be the reagent of choice since on HCl workup its oxide is hydrolyzed to diphenylphosphinic acid, which can be extracted from the



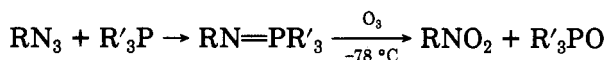
mixture (in contrast to Ph₃PO, which has to be separated by column chromatography⁴⁰⁸), and the iminophosphorane so derived reacts cleanly at room temperature with carboxylic acids.⁴⁰⁹

An iminophosphorane is presumably involved in the high-yield conversion of azide 586 to nitrile 587.²⁴⁹



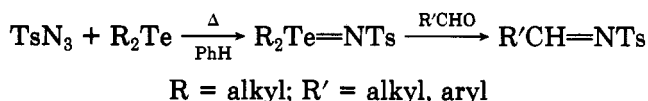
Corey and co-workers⁴¹⁰ have utilized iminophosphorane intermediacy in a recent conversion of alkyl azides to nitro compounds in moderate to good yield (Scheme 19).

SCHEME 19



A reaction analogous to the aza-Wittig process has been developed using dialkyl tellurides.⁴¹¹ Therein, heating tosyl azide and, e.g., diisobutyl telluride with an aldehyde in benzene for 15–20 h gives the corresponding *N*-tosyl imines in 28–82% yield (Scheme 20). The reaction is facilitated by the presence of copper powder and by the attachment of electron-donating groups to the aldehyde. The less basic aryl tellurides inhibit the process and ketones do not react under these conditions. The mechanism may involve a Staudinger-like reaction of the telluride with tosyl azide to form an intermediate tellurilimine.

SCHEME 20



G. Amination

As described in this review, azides can react with carbon nucleophiles to provide azido (see section II.J) or diazo compounds (see section III.I). Another pathway possible in certain cases is amination. While there is an overlap in concept with the following section (viz., section III.H), the importance of the amination process merits its inclusion as a separate section even when very

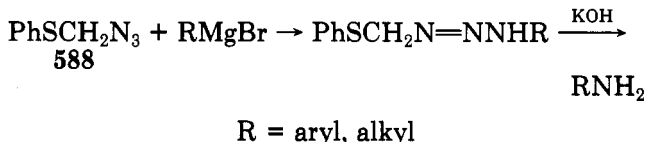
different mechanistic principles are involved.

1. By Reaction with Alkyl- or Aryllithium or Grignard Reagents

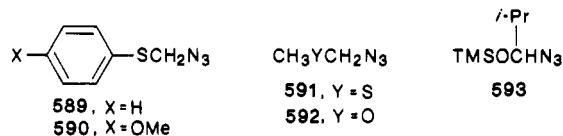
It has been well established that organic azides react with Grignard or organolithium reagents to give 1,3-disubstituted triazenes^{412a} which can be converted to amines by reductive workup.^{412b}

Trost and Pearson⁴¹³ have shown that azidomethyl phenyl sulfide (588) reacts with Grignard reagents to give triazene intermediates which can be hydrolyzed to the corresponding amines with KOH (Scheme 21). Recently, they further exemplified the utility of sulfur-activated azides for this process.⁴¹⁴

SCHEME 21



Therein, the efficacy of a series of heteroatom-substituted azides (589–593) for amine transfer was compared and it was clearly established that the order of reactivity was 589 ≈ 590 > 591 > 592 ≫ 593. The activating effect of sulfur compared to oxygen and of arylthio compared to alkylthio is thus manifest.

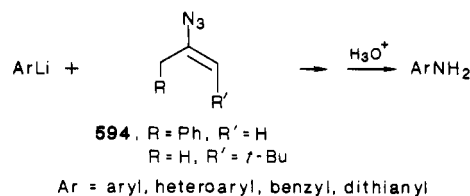


Low-temperature quenching of the intermediate triazene anion (from alkyl Grignards and 588 with acetic anhydride or aroyl chlorides followed by hydrolytic workup (tetrabutylammonium formate in DMF or KOH in DMSO) provides *N*-acylated or *N*-aroylated compounds in 64–98% yield.⁴¹⁴

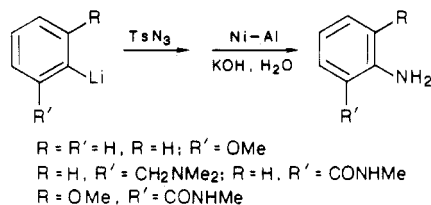
Complementary to this work is that of Hassner.⁴¹⁵ Whereas azidomethyl phenyl sulfide reacts more effectively with Grignard reagents than with organolithium species, the opposite is true with Hassner's vinyl azides (594). Thus, reaction of 594 with aromatic lithium reagents followed by dilute acid workup of the intermediate triazenes provides aromatic primary amines in fair to good yields (45–70%) (Scheme 22). Unlike with 588, the vinyl azides can be used to prepare heterocyclic amines. They are limited in scope, however, in that simple alkyl lithium species (e.g., MeLi, BuLi, and *t*-BuLi) react to give alkylated ketones rather than aminated products.⁴¹⁶

More recently, the readily available reagent tosyl azide has been shown to react with aromatic lithio compounds.⁴¹⁷ The initially formed triazenes can be reduced in situ with Ni–Al/KOH in an aqueous environment to yield aromatic amines in modest to good

SCHEME 22

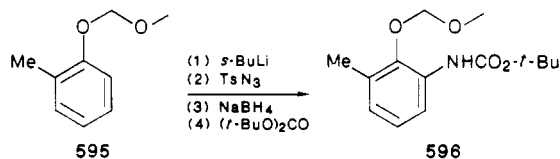


SCHEME 23

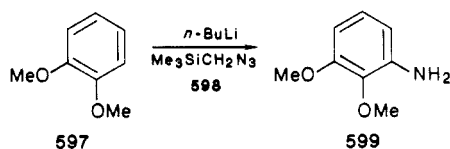


yield (34–85%) (Scheme 23).

Snieckus has reported a modification of this process utilizing tosyl azide and sodium borohydride,⁴¹⁸ and recently this approach was employed in the regiospecific transformation of *o*-methyl(methoxymethoxy)benzene (595) to carbamate 596 in 72% yield.⁴¹⁹



A similar transformation, viz., 597 → 599, has been effected in 78% yield using (trimethylsilyl)methyl azide (598) as the aminating agent.⁴²⁰

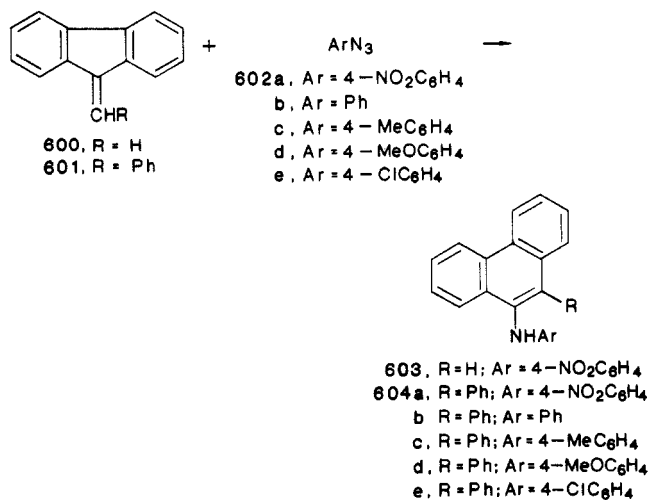


It should be noted that Guntrum⁴²¹ has reported that tosyl azide exhibits shock sensitivity similar to that of nitroglycerin. Accordingly, Kelly⁴²⁰ has suggested that great caution is also advisable in the handling of the analogous reagent 598.

The versatile reagent diphenyl phosphoroazidate [(PhO)₂P(O)N₃] (see section VII) also combines with aryl Grignard or aryllithium reagents to give labile triazenes which can be reduced to the primary amines with sodium bis(2-methoxyethoxy)aluminum hydride or lithium aluminum hydride.⁴²²

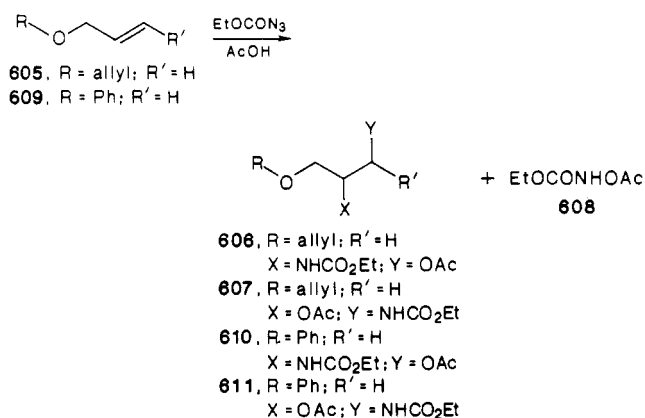
2. By Reaction with Alkenes and Related Species

The methylenefluorene derivatives 600 and 601 react with the aryl azides 602a and 602a–e, respectively, to

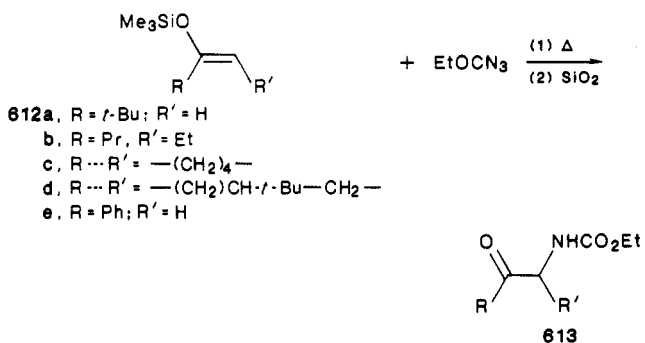


give the ring-expanded arylamines 603 (37%) and 604 (36–66%).⁴²³ Products 603 and 604 presumably arise by thermal breakdown of initially formed triazolines (isolable from 600 and 602b–e). A similar ring expansion has been employed for the formation of heterocyclic (Section VI.B.3) and alicyclic (Section IV.C) systems.

Thermolysis of EtOCON₃ in the presence of 605 using acetic acid as solvent gave 606 (15%), 607 (38%), and 608 (47%).⁴²⁴ The amount of the undesired byproduct 608 could be reduced substantially by employing considerably less acetic acid. With ether 609 a similar thermolysis reaction gave 610 (68%) and 611 (25%).



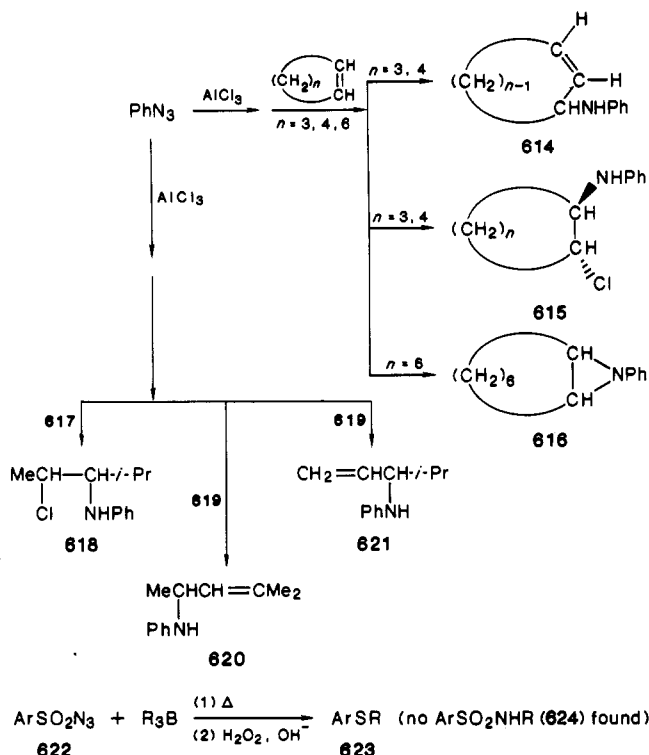
Ethyl azidoformate also combines with enol trimethylsilyl ethers (612). Thus, heating the reagents at 110 °C in a sealed tube, followed by silica gel chromatography, affords *N*-ethoxycarbonyl α -amino ketones (613) in 35–65% yield.⁴²⁵



In the presence of AlCl₃, phenyl azide reacted with cyclohexene or cyclopentene to give *N*-allylanilines (614) and *N*-phenyl- β -chloroamines (615) (approximately 1:1) in 92% and 52% yield, respectively, after aqueous sodium carbonate workup.^{426a} With *cis*-cyclooctene, aziridine 616 (47%) was instead isolated. Under the same conditions, *cis*-4-methylpent-2-ene (617) gave only the chloroamine 618 whereas *trans*-4-methylpent-2-ene (619) provided the arylamines 620 and 621. Similar reactions occur in the presence of trifluoroacetic acid.^{426b}

3. By Reaction with Boranes

For some time alkyl azides have been known to react with organoboranes to afford secondary amines.⁴²⁷ A recent attempted extension of this process to arylsulfonyl azides (622) gave interesting results. Thus,

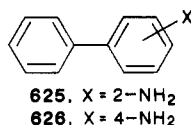


treatment of *p*-tolylsulfonyl or benzenesulfonyl azide with tricyclohexyl-, cyclopentyl-, hexyl-, or *exo*-norbornylborane gave the arylalkyl sulfides (623) in 45–70% yield instead of the expected sulfonamides (624).⁴²⁸ The mechanism is unclear but the necessity for the azido function is manifest since tosyl chloride did not react under these conditions.

4. Via Electrophilic Aromatic Substitution

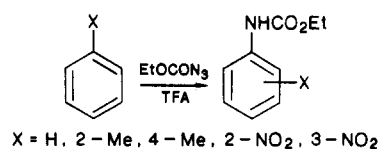
Examples involving cyclization are collected in section VI.A.3. Ethyl azidoformate reacts with benzene, toluene, or nitrobenzene in the presence of trifluoroacetic acid (TFA) to give ethyl *N*-arylcarbamates in 28–66% yield⁴²⁹ (Scheme 24). With toluene, the product mixture consists of the ortho and para carbamates (42% and 24%, respectively), whereas ortho and meta carbamates (17% and 11%, respectively) are obtained from nitrobenzene. More recently, the study was extended to include naphthalene; (*N*-(1- and 2-naphthyl)carbamates were obtained in 42% and 12% yield, respectively) and the effects of other acids (viz., acetic, trichloroacetic, and trifluoromethanesulfonic).⁴³⁰ The latter were less efficient in promoting the reaction than was TFA. The results of the study suggest that the mechanism involves electrophilic aromatic substitution by (ethoxycarbonyl)nitrenium ion.

Similar results were obtained for reactions of phenyl azide with benzene, toluene, or naphthalene in the presence of TFA; diarylamine products resulted.⁴³¹ In the reaction with benzene, C-substitution products, 625 and 626, were also isolated in 11% and 12% yield, respectively.

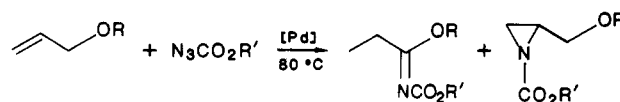


Aromatic *N*-substitution has also been reported for reactions of phenyl azide with benzene, toluene, cum-

SCHEME 24



SCHEME 25



ene, chlorobenzene, bromobenzene, and biphenyl in the presence of a catalytic amount of trifluoromethanesulfonic acid.⁴³² Again, 2- and 4-substituted diarylamines were obtained in reasonable yield. Interestingly, with 1-azidonaphthalene, products of C-substitution resulted from the reactions with benzene and biphenyl.

Thermolysis of trifluoromethanesulfonyl azide in 1:1 mixtures of benzene and substituted benzenes gave trifluoromethanesulfonamide and substituted analogues. The isomer ratios, the total rate ratios, and the partial rate factors for sulfonamidation were determined.⁴³³

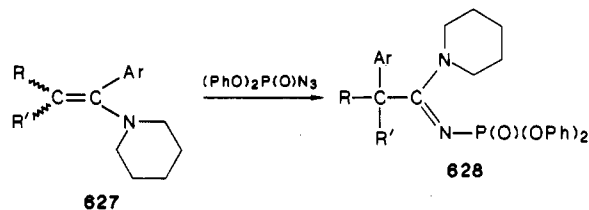
H. With Nucleophiles

Reactions of azides with nucleophiles leading to diazo compounds (Section III.I), amines (Section III.G), or iminophosphoranes (Section III.F) have been described previously.

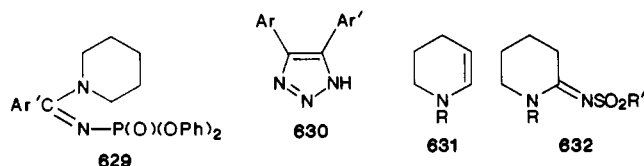
Azidoformates exhibit reactivity toward a variety of nucleophiles at either the acyl group or the terminal nitrogen of the azide moiety.^{13,434}

1. Carbon or Silicon Nucleophiles

A carbon-carbon double bond can play a nucleophilic role; often triazolines result (see section VI.B.2). On occasion, however, triazolines are intermediates and rearrangement products thereof are isolated (see section VI.B.3). α -Amino ketones have been obtained from azides and enamines⁴³⁵ or enol acetates.⁴³⁶ In contrast, the enamines 627 react with diphenyl phosphorazidate (DPPA) to give amidines 628.⁴³⁷ Interestingly, the



pyrrolidine enamines 627 (R = Ar', R' = H) reacted with DPPA to afford 628 as the major product (from 627 (R = Ar = Ph)), a mixture of 628 and 629 (from 627 (R = Ph; Ar = 2-pyridyl)), or the 1,2,3-triazole 630 as the main product (from 627 (R = 2-pyridyl; Ar = Ph)).⁴³⁸ Presumably these products arise by different cleavage modes from the intermediate triazoline.



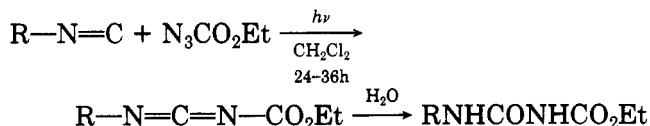
In light of these results it is perhaps surprising that *N*-substituted tetrahydropyridines (cf. 631) form imines (cf. 632) on treatment with aryl- or alkylsulfonyl azides.⁴³⁹

In contrast to the results of thermal and photoinitiated reactions, allylic ethers react with azidoformate in the presence of tetrakis(triphenylphosphine)palladium to give *N*-carboalkoxy imines as well as aziridines (Scheme 25).⁴⁴⁰

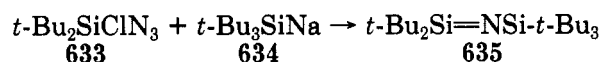
A more recent study of the generality of the reaction has shown that it is successful for acyclic unsaturated ethers in general and is catalyzed much more effectively by PdCl₂(PhCN)₂.⁴⁴¹ Under these conditions imines were formed in good yields (44–100%) and the corresponding aziridines were present in miniscule amounts.

Photolysis of ethyl azidoformate in the presence of some alkyl isonitriles gave carbodiimides and/or the corresponding ureas (Scheme 26).⁴⁴² A mixture of both products was obtained with R = cyclohexyl but with R = *tert*-butyl only the diimide was isolated (60%). Interestingly, 1-isocyano-2,3,4,6-tetraacetyl-β-D-glucopyranoside reacted to give only the corresponding urea in 75% yield.

SCHEME 26

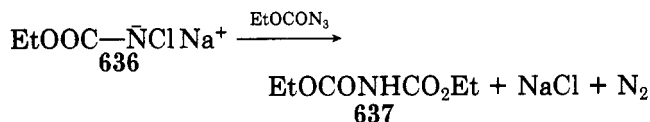


Silaketimine 635 is formed in quantitative yield from the reaction of azido-di-*tert*-butylchlorosilane (633) and (tri-*tert*-butylsilyl)sodium (634) at -78 °C in dibutyl ether.⁴³³



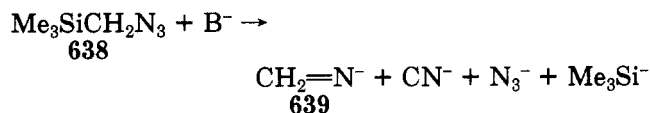
2. Nitrogen Nucleophiles

Ethyl *N*-chlorocarbonate (636) reacts with ethyl azidoformate (to form diethyl iminodiformate (637)) or tosyl azide but not alkyl or aryl azides.⁴⁴⁴ The reactions



are enhanced by the use of Aliquat 336. Apparently, 637 is formed via attack of 636 at the carbonyl group of the azido species rather than at the terminal nitrogen, in agreement with hard and soft acid-base theory.

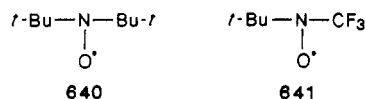
In a flowing afterglow device (trimethylsilyl)methyl azide (638) reacts rapidly with a variety of bases (F⁻, NH₂⁻, HO⁻, MeO⁻) to form an anion of *m/z* 28, to which



was assigned the methanimine structure 639.⁴⁴⁵ Large amounts of cyanide ion and smaller quantities of azide and trimethylsilyl anions were also produced. Amide ion appears to generate the maximum amount of 639.

Nitroxide radicals 640 and 641 were formed from the combination of trifluoromethanesulfonyl azide with

2-nitroso-2-methylpropane.⁴⁴⁶ Similar results were obtained from the reactions of the latter with phenyl, tosyl, and benzoyl azides.

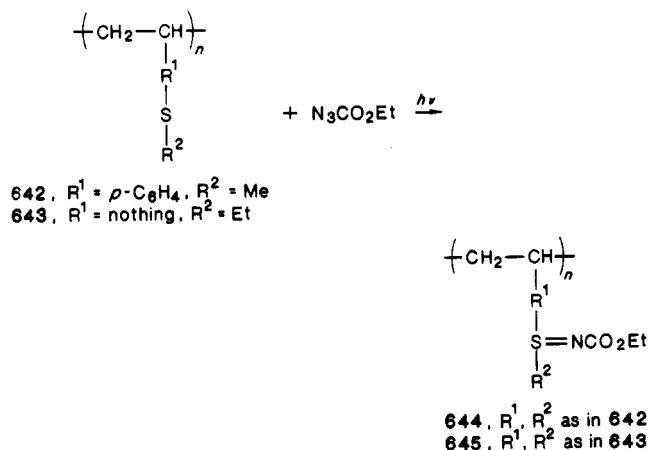


Displacement of the azido group, rather than attack at a nitrogen atom, occurred from treatment of benzenesulfinyl azide with nitrogen or sulfur nucleophiles.⁴⁴⁷ Thus, with primary or secondary amines, sulfenamides were formed in 48–78% yield.

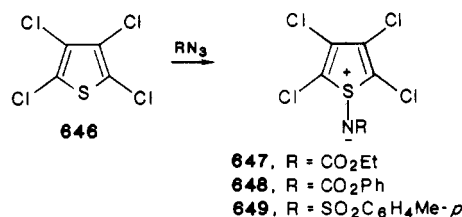
3. Sulfur or Selenium Nucleophiles

As alluded to in the previous section, benzenesulfinyl azide also reacted with thiols (at -20 °C) to give the corresponding thiosulfonates in 41–93% yield.⁴⁴⁷

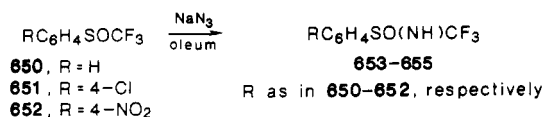
In a process formally equivalent to the Staudinger reaction, sulfides react with azides to give iminosulfuranes.⁴⁴⁸ Recently, this transformation was extended to sulfide-containing polymers.⁴⁴⁹ Thus, 642 and 643 reacted with ethyl azidoformate under photolytic



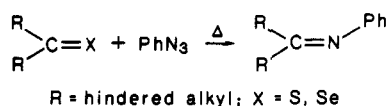
conditions to give the corresponding iminosulfuranes 644 and 645 in 17% and 30% yield, respectively. Similarly, iminosulfuranes 647–649, the first examples of thienium-*S*-imides, were formed (44%, 23%, and 24%, respectively) by thermolysis of the appropriate azides in the presence of tetrachlorothiophene.⁴⁵⁰ Similar intermediates from trithiapentalenes have been proposed (see section VI.C.2).



In contrast to aryl alkyl sulfoxides, aryl trifluoromethyl sulfoxides 650–652 do not iminate with sodium azide in sulfuric acid. However, if the latter is replaced by oleum, the *S*-(trifluoromethyl)-*S*-arylsulfoximides 653–655 are formed.⁴⁵¹



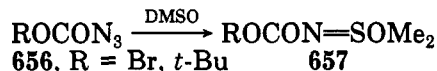
SCHEME 27



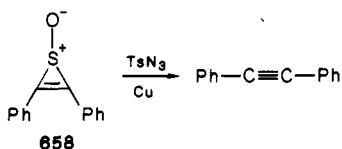
SCHEME 28



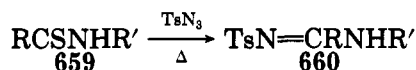
Sulfoximides **657** are also formed in 50–60% yield by thermolysis of alkoxy carbonyl azides **656** in DMSO.⁴⁵²



Diphenylthiirene 1-oxide (**658**) did not react with *p*-toluenesulfonyl azide to form the corresponding sulfoximide; instead diphenylacetylene resulted in 21.7% yield.⁴⁵³



Δ^2 -Thiatriazolines are intermediates in the conversion of thioamides **659** to tosylamidines **660** (68–86%) with tosyl azide.⁴⁵⁴



R = Me, Ph; R' =

H, Ph, 4-tolyl, 4-anisyl, 4-EtOC₆H₄

Similarly, hindered thiones and selenones form *N*-phenylimines in 20–86% yield via thia- and selenatriazolines, respectively, on heating with phenyl azide (Scheme 27).⁴⁵⁵

I. Diazo Transfer

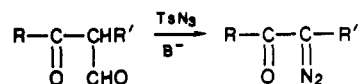
An excellent, comprehensive review of the diazo transfer process has appeared recently.¹⁶ Accordingly, the present compilation is merely a synopsis of the general process with emphasis on recent uses.

The diazo transfer process generally involves attack of a carbon nucleophile upon an arylsulfonyl azide to form a diazo compound (Scheme 28). When the Z and Z' groups are suitably electron withdrawing (e.g., COOR, CHO, COR, CONR₂, CO₂⁻, CN, NO₂, SOR, SO₂R, SO₃R, SO₂NR₂, or one Ar), the carbon nucleophile can be generated by the action of a suitable base on the corresponding activated methylene species.^{16,456} The efficacy of the process has been improved by the use of phase-transfer catalysis.⁴⁵⁷ In the case of a ketone the nucleophilic species can be prepared by conversion to a (dialkylamino)methylene derivative.⁴⁵⁸

Introduction of the diazo group adjacent to a single carbonyl moiety can be achieved indirectly by converting the ketone to an α -formyl ketone and subsequent treatment with tosyl azide under basic conditions (vide infra) (Scheme 29).

Successful diazo transfer to simple aldehydes such as acetaldehyde has not been reported, presumably due

SCHEME 29

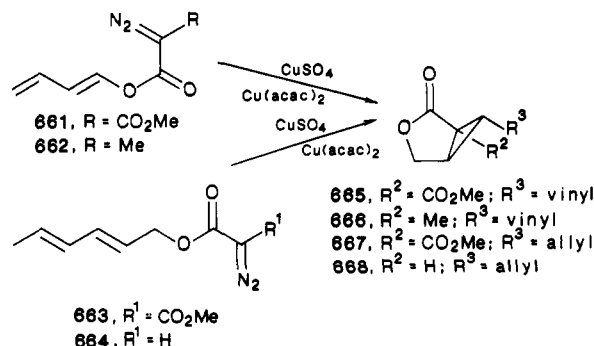


to competing reactions (viz., aldol condensation and polymerization) during the attempted preparation of the appropriate enolate ions. However, various workers⁴⁵⁹ have demonstrated that the lithium enolate of acetaldehyde can be generated in the absence of such complications by the cycloreversion of THF in the presence of *n*-butyllithium, and recently this approach was extended to reaction of the incipient enolate with aryl and tosyl azides.⁴⁶⁰ Except for azides having no electron-withdrawing groups, decomposition ensues within 0.5 h and formamides (22–86%) and amines (0–24%) corresponding to the starting azides can be isolated. The formation of diazomethane was also demonstrated and in two cases (viz., 2-Me- and 2-EtSO₂C₆H₄N₃) this may be of synthetic utility (70% yield).

Tosyl azide is the most commonly employed azide but *p*-dodecylbenzenesulfonyl azide,⁴⁶¹ *p*-carboxybenzenesulfonyl azide,⁴⁶² polymer-bound tosyl azide,⁴⁶² triflyl azide,⁴⁶³ (azidochloromethylene)dimethylammonium chloride,⁴⁶⁴ trisyl azide,⁴⁶⁵ and 4-nitrophenyl azide⁴⁶⁶ have found some use. 4-Cyclopentene-1,3-dione was converted to the diazo congener with 2-azido-3-ethyl-1,3-benzothiazolium tetrafluoroborate in an alkaline medium.⁴⁶⁷ The same reagent and 1-ethyl-2-azidopyridinium tetrafluoroborate have been reported previously.⁴⁶⁸

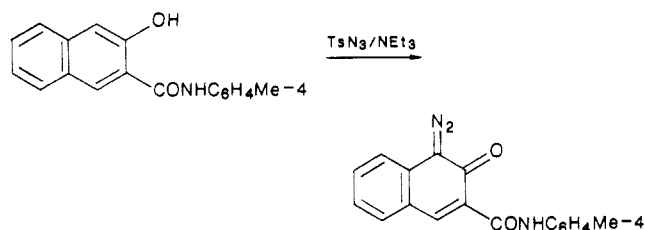
A major factor in the continued search for new diazo transfer reagents has been the difficulty encountered in the separation of the diazo product from excess reagent and 4-toluenesulfonamide following diazo transfer with tosyl azide. Accordingly, 4-carboxybenzenesulfonyl azide has been recommended as a replacement for the latter since it is soluble in base. Recently,⁴⁶⁹ the much less expensive but still base-soluble reagent mesyl azide⁴⁷⁰ was shown to be an excellent alternative.

The diazo compounds resulting from these procedures have enjoyed extensive exploitation as carbene or carbenoid precursors.⁴⁷¹ Thus, the diazo esters **661–664** form the corresponding cyclopropanes **665–668**, respectively, in 46–84% yield on treatment with CuSO₄ and Cu(acac)₂ in refluxing benzene.⁴⁷²

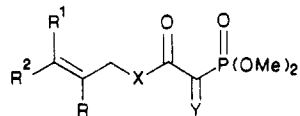


Intramolecular cyclopropanation of α -diazo- β -keto-phosphonates (cf. **670**) using copper powder has also been reported.⁴⁷³ Formation of the diazo compounds **670** from the corresponding activated methylene compounds **669** was effected in 80–96% yield by using tosyl

SCHEME 30



azide and sodium hydride. The yields were considerably lower when triethylamine was used as base.

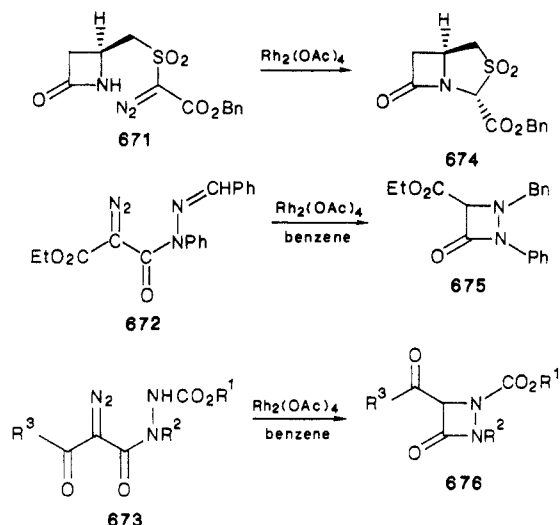


669, $\text{R}, \text{R}^2 = \text{cyclic}$; $\text{R}^1 = \text{H}$; $\text{X} = \text{CH}_2, \text{O}$; $\text{Y} = \text{H}_2$

$\text{R} = \text{H}$; $\text{R}^1 = \text{R}^2 = \text{H}$; $\text{X} = \text{CH}_2, \text{O}$; $\text{Y} = \text{H}_2$

670, $\text{Y} = \text{N}_2$, rest as above

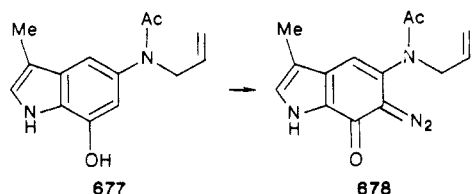
Diazo compound cyclization reactions have been considerably enhanced by the use of rhodium(II) acetate as catalyst. Thus, the novel β -lactam 674 and aza β -lactam analogues 675 and 676 were prepared in ex-



cellent yield (75–100%) by heating the corresponding diazo compounds 671–673 with a catalytic quantity of rhodium(II) acetate.^{474–476} A cephalosporin analogue has been prepared similarly.⁴⁷⁷ The diazo compounds were in turn synthesized in variable yield by diazo transfer to the activated methylene precursors. Tosyl azide was the reagent of choice for this process except for in the case of 671, where *p*-carboxybenzenesulfonyl azide was employed.

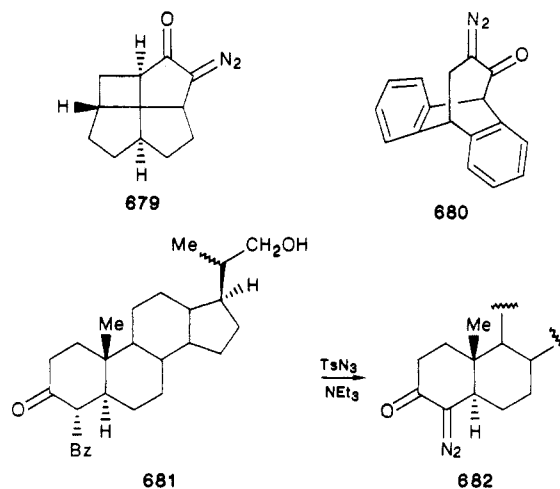
Diazo transfer to phenols has also been reported,⁴⁷⁸ and recently this process was used to prepare 3-(*p*-tolylcarbonyl)-1,2-naphthoquinone 1-diazide (Scheme 30).⁴⁷⁹

An attempt to convert phenol 677 to the corresponding quinone diazide 678 using tosyl azide was unsuccessful; the product mixture consisted primarily



of materials containing two *p*-toluenesulfonamide groups.⁴⁸⁰ These compounds were not characterized but were suggested to be of the same type as those obtained from reaction of alkylindoles and tosyl azide.⁴⁸¹ Successful conversion of 677 to 678 was realized in 45% yield by using *m*-nitrobenzenesulfonyl azide and trifluoroethanol as solvent. The latter had been reported to be an excellent solvent for the diazo transfer reaction between β -naphthol and tosyl azide.⁴⁸²

As briefly mentioned previously, α -formyl ketones can be directly converted to the corresponding α -diazo ketones by treatment with tosyl azide and triethylamine. In this manner Dauben and Walker⁴⁸³ prepared the fenestrane derivative 679 and Banciu⁴⁸⁴ synthesized 680. Some modifications on this process have been reported. Thus, the benzoyl group can perform the same function as the formyl moiety (cf. 681 \rightarrow 682).⁴⁸⁵

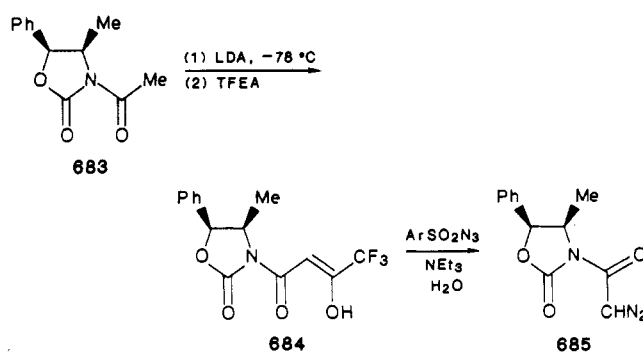


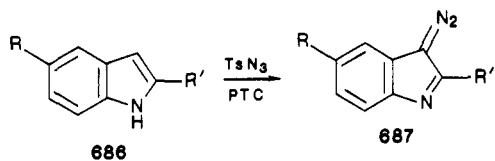
The trifluoroacetyl group has been utilized similarly, with the advantage that its removal is more facile.⁴⁸⁶ Thus, *N*-acetyloxazolidone 683 was converted to 684 with LDA and 2,2,2-trifluoroethyl trifluoroacetate (TFEA) (Scheme 31). Subsequent diazo transfer in the presence of no more than 1 equiv of water gave 685 directly. Direct diazo transfer with 683 was not successful.

Diazo transfer to heterocyclic systems has also been reported. Thus, 2-arylindoles 686 ($\text{R} = \text{H}, \text{F}, \text{Cl}$; $\text{R}' = \text{Ph}, 2\text{-pyridyl}, 2\text{-thienyl}$) react with tosyl azide under phase-transfer conditions (benzyltriethylammonium chloride) to give the corresponding 3-diazo-3*H*-indoles 687.⁴⁸⁷

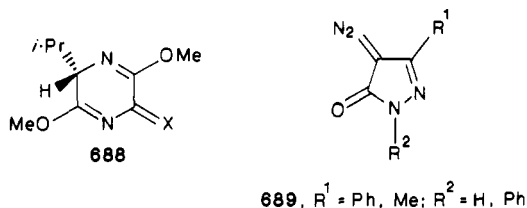
Treatment of diketopiperazine derivative 688 ($\text{X} = \text{H}_2$) with *n*-butyllithium and tosyl azide gave the cor-

SCHEME 31



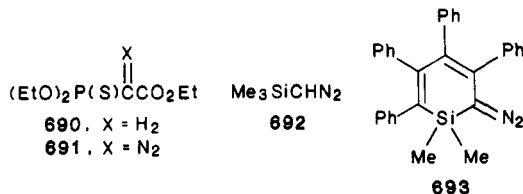


responding diazo compound **688** ($\text{X} = \text{N}_2$), which was



used in situ as a synthetic equivalent of aminocarboxycarbene.⁴⁸⁸ More routinely, diazopyrazolinones **689** have been prepared by treatment of the parent pyrazolinones with tosyl azide/triethylamine.⁴⁸⁹

Ethyl (diethoxythiophosphoryl)diazoacetate (**691**), the first thiophosphoryl diazocarbonyl compound, was prepared in 22% yield by treating **690** with potassium *tert*-butoxide followed by tosyl azide.⁴⁹⁰



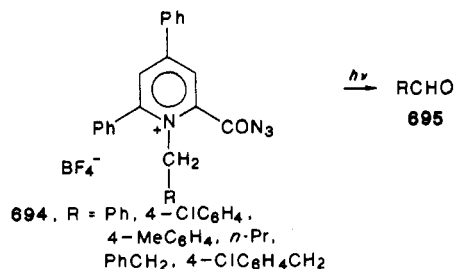
In a variation of the standard diazo transfer process, (trimethylsilyl)diazomethane (**692**) was prepared in 78.6% yield by reaction of [(trimethylsilyl)methyl]magnesium chloride with diphenylphosphoroazidate $[(\text{PhO})_2\text{P}(\text{O})\text{N}_3]$.⁴⁹¹ The first example of a 6-diazosilacyclohexa-2,4-diene (**693**) was also prepared by diazo transfer (*n*-BuLi/tosyl azide).⁴⁹²

Diazo transfer to amines affords azides and this is covered in section II.J.

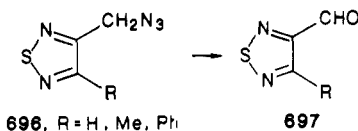
J. Other Reactions

A few azide transformations have been reported that do not fit into the categories described so far.

Thus, irradiation of 1-substituted 2-(azidocarbonyl)-4,6-diphenylpyridinium tetrafluoroborates **694** gave the aldehydes **695** (60–76%) expected from cleavage of the R group except for **694** ($\text{R} = \text{PhCH}_2$) and **694** ($\text{R} = \text{CH}_2\text{C}_6\text{H}_4\text{Cl-}p$), where benzaldehyde and phenylacetaldehyde (2:1) and *p*-chlorobenzaldehyde, respectively, were formed.⁴⁹³



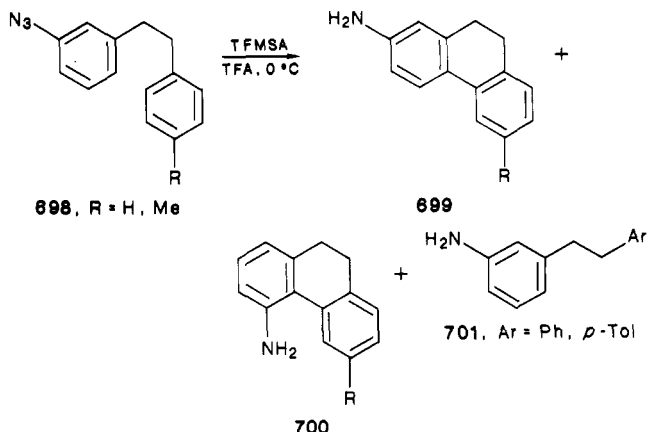
Aldehydes **697** (68–83%) also result from the dropwise addition of thiadiazolylalkyl azides **696** to concentrated sulfuric acid at -5 to 0 °C.⁴⁹⁴



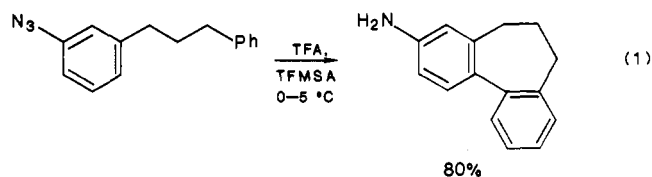
IV. Applications in Allicyclic Chemistry

A. Cyclizations

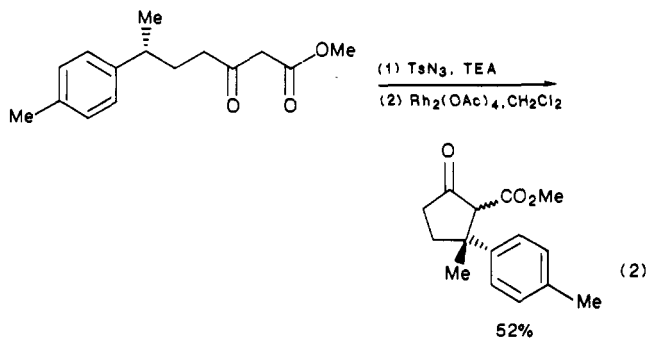
Bibenzyl derivatives **698** react with trifluoromethanesulfonic acid (TFMSA) at 0 °C to give the cyclized species **699** (major) and **700** and small quantities of the hydrogen abstraction products **701**.⁴⁹⁵ The process can be extended to *trans*-*m*-azidocinnamate.



Similar treatment of 3'-azido-1,3-diphenylpropane results in a high-yield cyclization to a seven-membered ring (eq 1).⁴⁹⁶

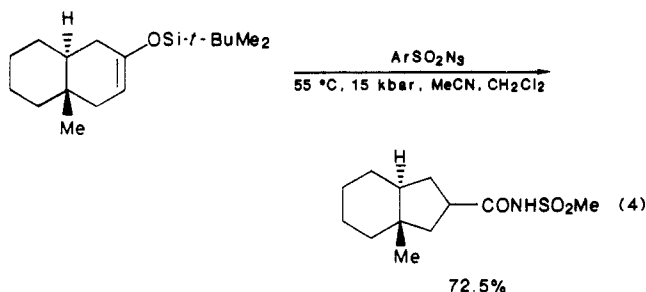
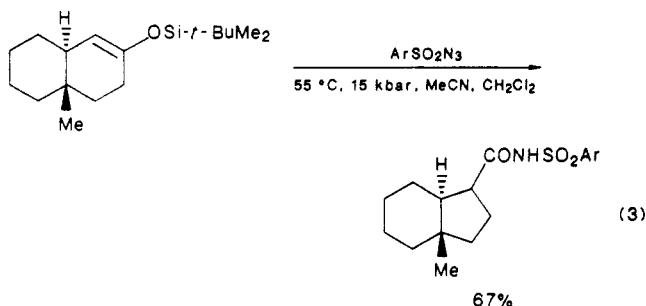


Reaction of tosyl azide with active methylene compounds gives diazo compounds which subsequently may be converted to carbenes with rhodium diacetate (see section III.I for other examples). Recently, this methodology has been extended to provide a generally applicable strategy for the enantioselective construction of a chiral quaternary center (eq 2).⁴⁹⁷

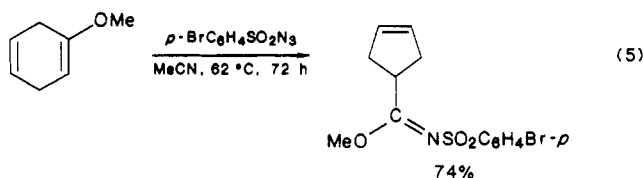


B. Ring Contractions

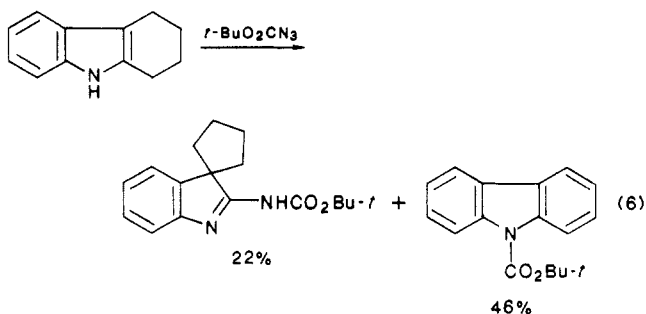
Hindered silyl enol ethers undergo ring contraction via triazolines when allowed to react with arylsulfonyl azides under pressure.⁴⁹⁸ Enol ethers give cleaner products with greater regioselectivity than do enamines (eq 3 and 4).



Methyl enol ethers produced by Birch reduction of anisoles have been found to undergo reaction at ambient pressure and moderate temperature (eq 5).⁴⁹⁹



Recently, phosphoryl azides have been used to effect the ring contraction of cyclic enamines in moderate to good yield.⁵⁰⁰ An interesting variation of this ring contraction, which leads to a spiro product, involves initial addition of *tert*-butyl azidoformate to a tetrahydrocarbazole (eq 6).⁵⁰¹



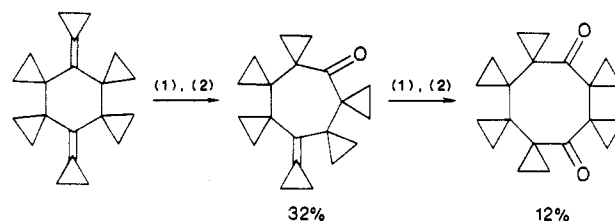
C. Ring Expansions

An interesting ring expansion of alicycles with an exocyclic methylene group involves an azide cycloaddition followed by treatment with base (Scheme 32).⁵⁰²

D. Rearrangements

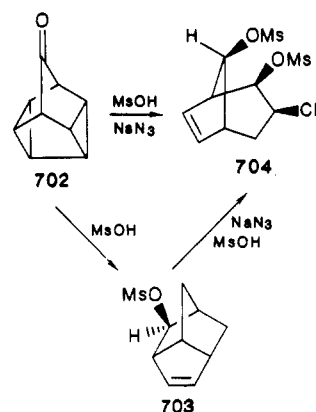
On occasion interesting rearrangements occur under Schmidt conditions. Thus, homocuneone (702) reacts with sodium azide in methanesulfonic acid at $0\text{--}5^\circ\text{C}$ (20 min) to yield the unusual cyano dimesylate 704 in ca. 20% yield.⁵⁰³ It was surmised that acid-catalyzed rearrangement of 702 preceded Schmidt fragmentation and this premise was confirmed by isolation of 703 on treatment of 702 with methanesulfonic acid alone.

SCHEME 32^a



^a (1) $p\text{-NO}_2\text{C}_6\text{H}_4\text{SO}_2\text{N}_3$; (2) KOH , MeOH .

Subsequent conversion of 703 to 704 could then be effected in ca. 40% yield. The homocuneone (702) \rightarrow 8-ketobrendane (703) transformation appears to be fairly general and occurs with a variety of acids and electrophiles. Other rearrangements of alicycles have been reported by the same research group.⁵⁰⁴

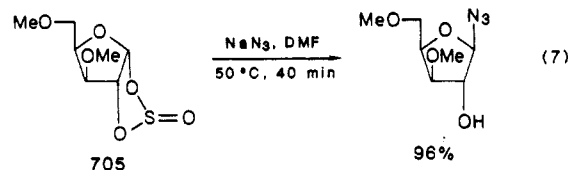


V. Applications in Carbohydrate Chemistry

A. Synthesis

Methods for the introduction of the azido group into sugars have been well studied, as the azido group can be reduced easily under a variety of conditions to afford amino sugars⁵⁰⁵ (see also section III.A). Preparations of azido carbohydrates are discussed here, rather than in section II, where considerations of carbohydrate chemistry are paramount.

Cyclic sulfate 705 undergoes regioselective ring opening to give the trans alcohol (eq 7).⁵⁰⁶

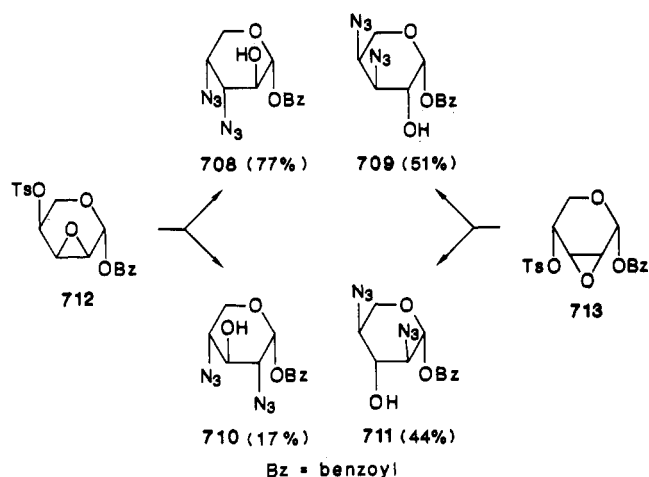
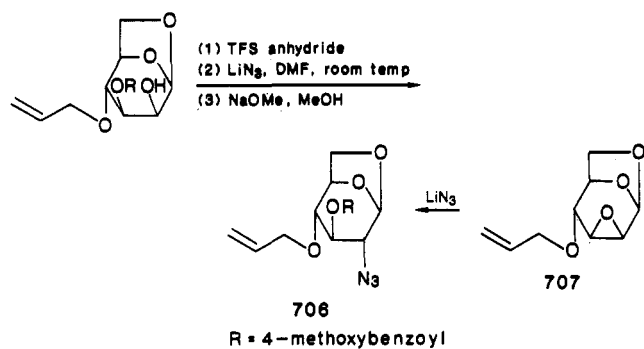


Azide 706 may be prepared in four steps from 1,6-anhydro- $\beta\text{-D}$ -mannopyranose (Scheme 33).⁵⁰⁷ The last three steps occur in good overall yield. This contrasts with the former method, which involves treatment of 707 under vigorous conditions⁵⁰⁸ (see section II.B for another example of triflate replacement).

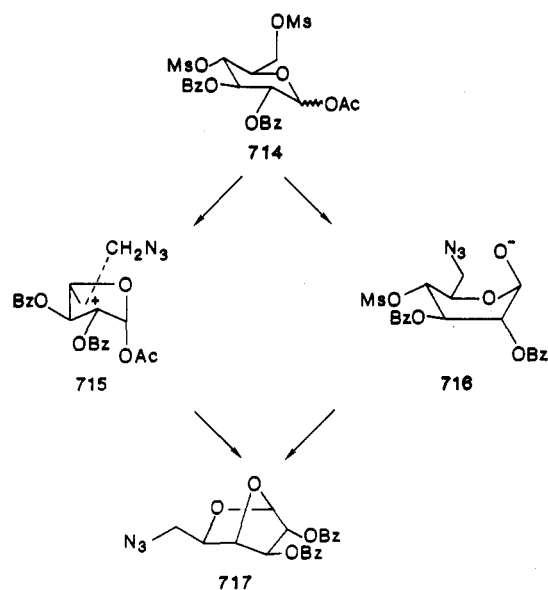
Four new diazido sugars (708–711) have been made by treatment of the anhydro tosylribopyranosides 712 and 713 with sodium azide.⁵⁰⁹

Mesylate 714 reacts with sodium azide to give the azidogalactopyranose derivative 717.⁵¹⁰ Oxygen-17 NMR and oxygen-18 induced shifts in carbon-13 NMR support the intermediacy of azido mesylate 716 rather than the alternative carbenium ion 715⁵¹⁰ (see section

SCHEME 33



II.B for tosylate replacement).

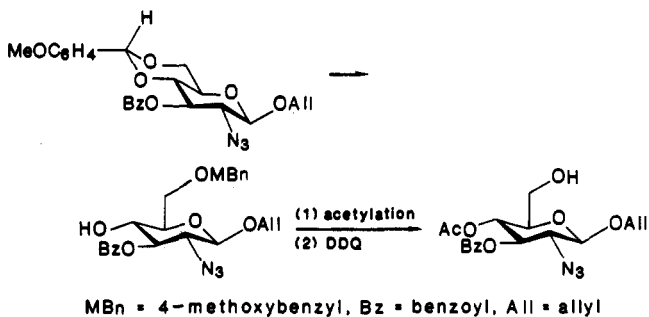


The synthesis of chemically modified cyclodextrins has been reviewed, and this review contains a section on azido derivatives.⁵¹¹ Azido carbohydrates are discussed in another general review of hydrazine derivatives of carbohydrates.⁵¹²

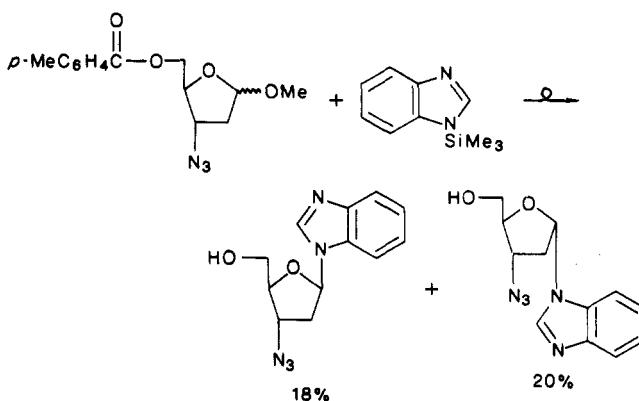
B. Survival of Azido Groups during Other Manipulations

Apart from ease of reduction, the presence of an azido group at C-2 in a sugar has the advantage of nonparticipation during the formation of α - and/or β -glycosidic linkages⁵¹³ (for other examples of azide survival, see section II.L). For example, glycosyl bromide 718 has

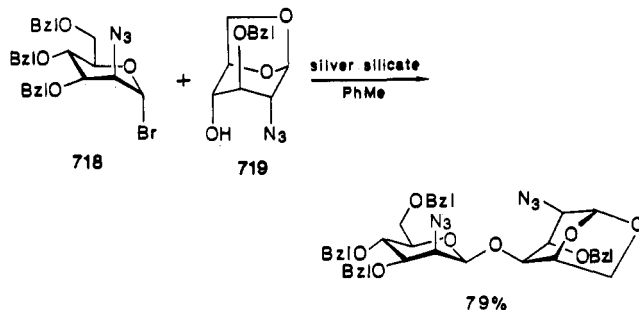
SCHEME 34



SCHEME 35

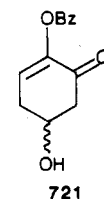
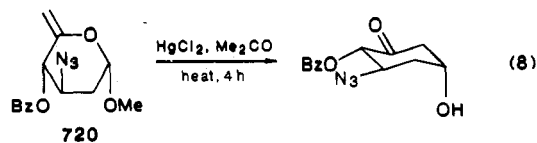


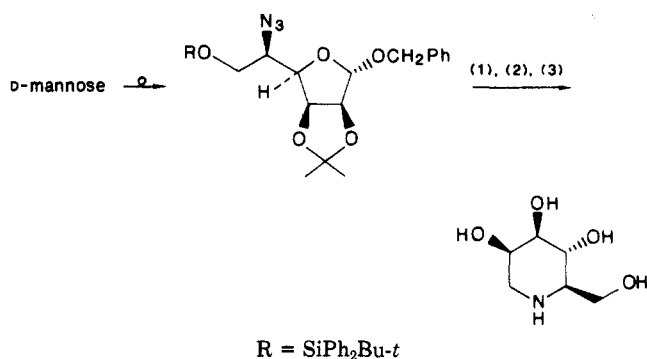
been condensed with the 4-hydroxy group of the glycosyl acceptor 719.⁵¹⁴



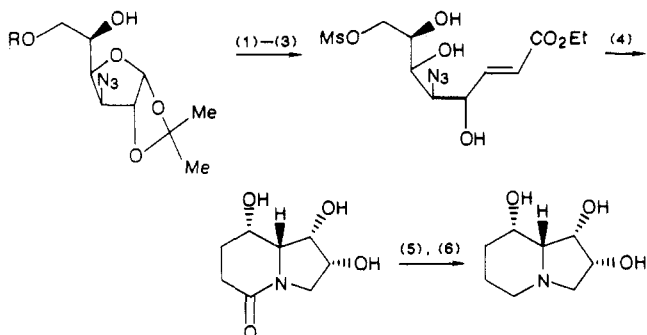
In another paper, the effect of a C-2 azido substituent on the β/α ratio in glycosidic bond formation relative to 4-O-alkyl functions has been studied.⁵¹⁵ Recently, it was found that a 4-methoxybenzylidene acetal could be opened reductively and the so formed 4-methoxybenzyl ether removed by oxidation with DDQ without affecting the C-2 azido function (Scheme 34).⁵⁰⁵ No acetyl ester migration from C-4 was noted.

The azido functionality can survive the Ferrier transformation to provide a 1,3-diaminocyclitol precursor (eq 8).⁵¹⁶ However, the erythro analogue of 720 undergoes elimination of hydrazoic acid to give 721.



SCHEME 36^a

^a (1) Bu₄NF, THF, room temperature; (2) CF₃CO₂H, dioxane, H₂O; (3) palladium hydroxide, H₂, MeOH.

SCHEME 37^a

^a (1) MsCl, pyridine; (2) CF₃CO₂H, H₂O (9:1); (3) Ph₂P=CHCO₂Et, THF; (4) H₂, 10% Pd/C, MeOH; (5) (Me₃Si)₂NH, Me₃SiCl; (6) BH₃·Me₂S, THF.

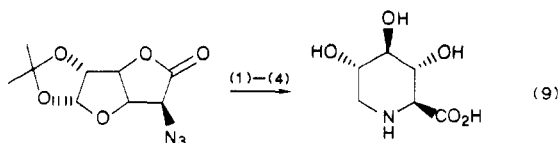
Azides survive glycosidation with 1-(trimethylsilyl)-benzimidazole (Scheme 35).⁵¹⁷

C. Reductive Cyclizations (See Also Section III.C)

1,5-Dideoxy-1,5-imino-D-mannitol can be synthesized from D-mannose via hydrogenation of a 5-azido-5-deoxymannose (Scheme 36). A route from D-glucose has also been described.⁵¹⁸

Two stereoisomers of swainsonine have been synthesized by similar sequences (Scheme 37).⁵¹⁹

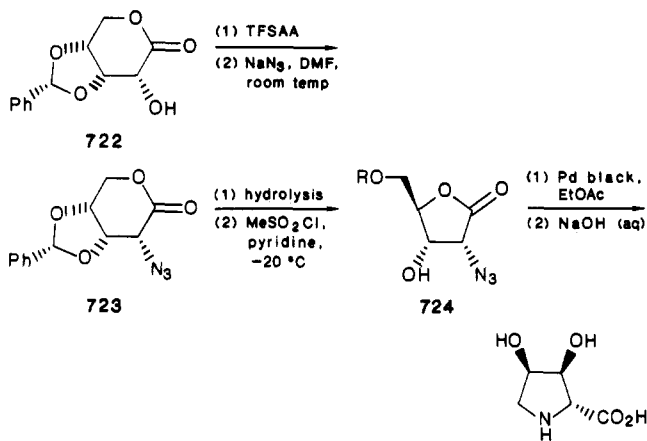
Reductive cyclization of the isopropylidene derivatives of D-glucuronolactone gives a trihydroxypipercolic acid (eq 9).⁵²⁰



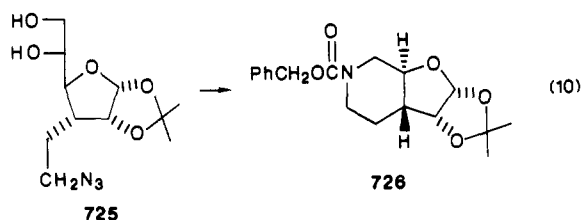
(1) H₂, 10% Pd/C, EtOAc; (2) PhCH₂COCl, NaHCO₃, EtOAc, H₂O; (3) CF₃CO₂H, H₂O, room temperature; (4) H₂, Pd black, H₂O, HOAc (9:1), 4 days

Treatment of D-ribonolactone with benzaldehyde in concentrated hydrochloric acid gives Zinner's lactone (722), the triflate of which rather surprisingly gives azide 723 with retention of configuration.⁵²¹ Conversion to 1,4-lactone 724 and reduction affords 2(R),3(S),4(R)-dihydroxyproline (Scheme 38) (see ref 522 for another example of hydroxypyrrolidine synthesis).

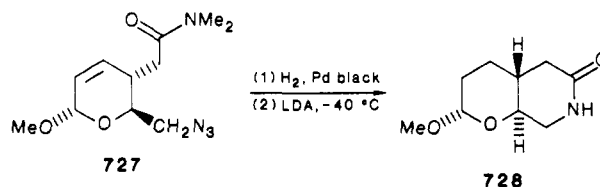
SCHEME 38



Successive treatment of 725 with sodium iodate, hydrogen/palladium black, and PhCH₂OCOC1 provides benzyl carbamate 726 in 66% overall yield.⁵²³



Hydrogenation of azido amide 727 in the presence of palladium black in ethanol reduces both the double bond and the azide to an amine, which can be cyclized to lactam 728 with LDA.⁵²⁴

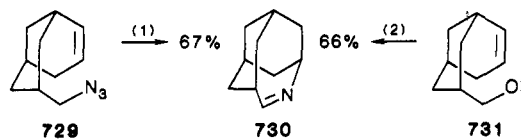


VI. Heterocyclic Synthesis

A. Cyclizations

1. Alkyl Azides

Azide 729 cyclizes to 4-azahomoadamant-4-ene (730) in the presence of methanesulfonic acid; 730 is obtained also from alcohol 731.⁵²⁵



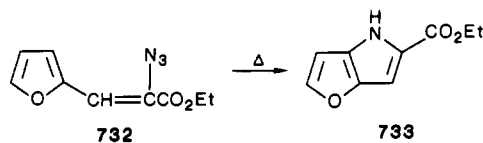
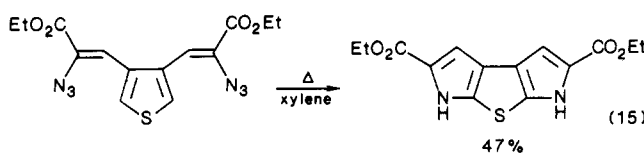
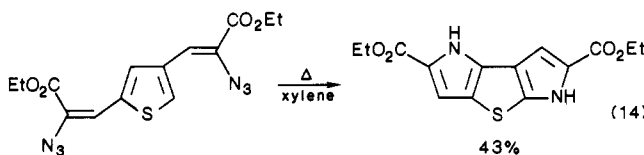
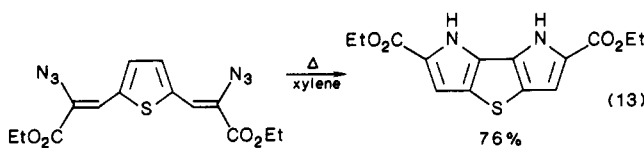
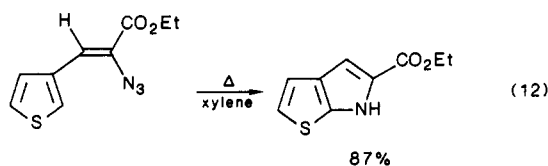
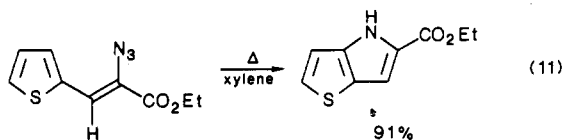
(1) MeSO₃H, CH₂Cl₂, room temperature, 30 min; (2) NaN₃, MeSO₃H, CH₂Cl₂

2. Vinyl Azides

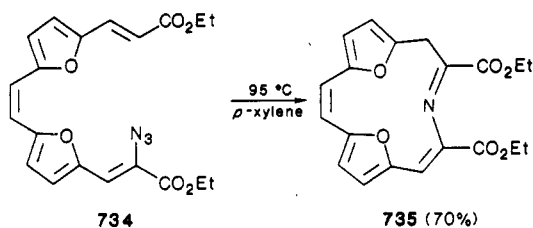
An important method for the construction of five-, six-, and seven-membered fused nitrogen heterocycles, based on the cyclization of azidoacrylate has been developed into a powerful synthetic method by Moody and Rees. Hemetsberger and co-workers^{526,527} found that azidocinnamates, which are readily prepared from the corresponding benzaldehyde, ethyl azidoacetate,

and sodium ethoxide, undergo ring closure to indoles. The intermediate azirine can be observed by NMR when the thermolysis is carried out at 80 °C. Recently, Knittel⁵²⁸ obtained indoles in virtually quantitative yields at 140 °C and azirines at 80 °C (Scheme 39).

Monovinyl (eq 11 and 12)⁵²⁹ and divinyl (eq 13–15) azido thiophenes⁵³⁰ have proved to be useful precursors for the annulation of pyrroles to thiophenes.



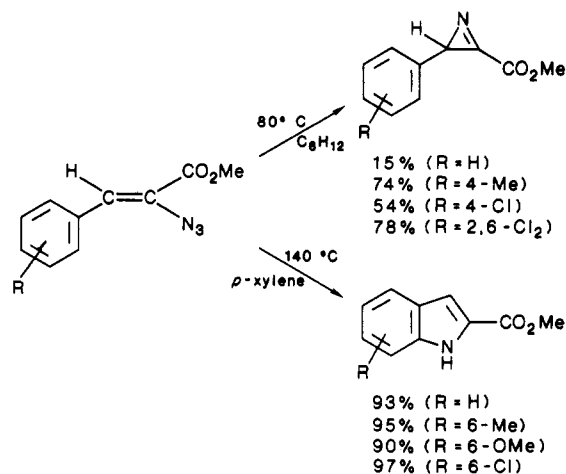
Azido furan **732** predictably undergoes cyclization to furopyrrole **733**.⁵³¹ However, **734** gives the azaannulene **735** by intramolecular cycloaddition without any furopyrrole formation, thus providing a convenient high-yield azaannulene synthesis.⁵³¹



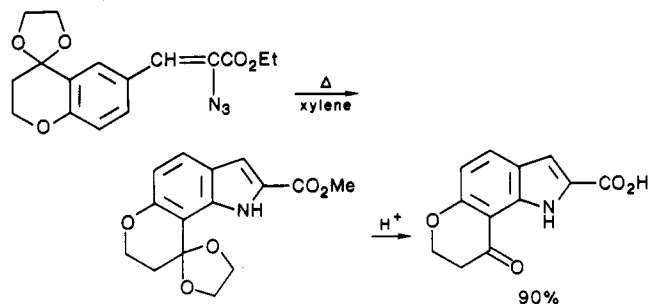
The preparation of acryl azides under strongly basic conditions is confined to aldehydes that cannot undergo competitive condensations. Remote carbonyl groups may be protected to avoid this disadvantage, as for example in the synthesis of oxopyrano[*g*]indoles (Scheme 40).⁵³²

Where cyclization to a five-membered ring is blocked, closure can take place at an *o*-methyl group to give a pyridine ring. (2-Azidoacrylyl)benzofuran **736** undergoes cyclization in quantitative yield to a benzo-

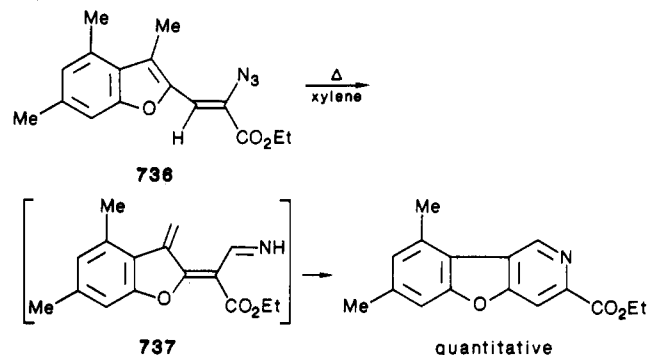
SCHEME 39



SCHEME 40



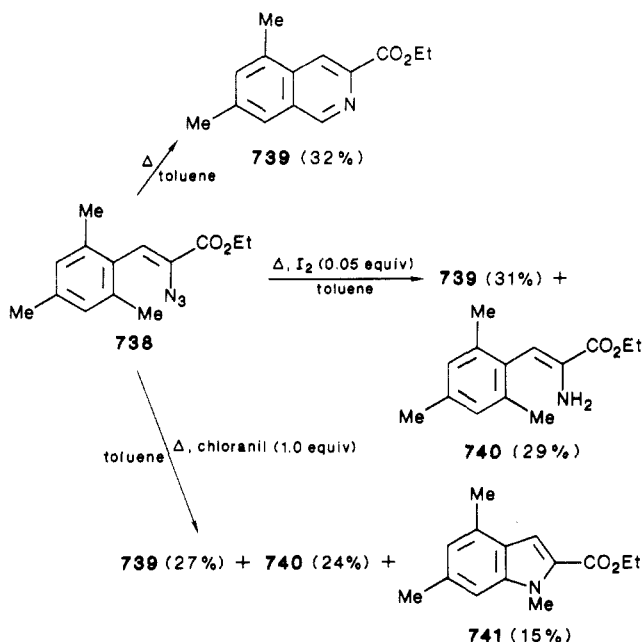
furan[3,2-*c*]pyridine via an enamine (**737**) rather than by direct insertion.⁵³³



Rees, Moody, and co-workers have studied these reactions extensively from both a mechanistic and a synthetic viewpoint. They have found that decomposition of an azidocinnamate (**738**) with blocked ortho positions in the presence of an oxidant profoundly affects the nature of the products (Scheme 41).⁵³⁴

It was hoped that added iodine would oxidize the intermediate dihydropyridine to **739** before H abstraction by nitrene occurred to give enamine **740**. Formation of **741** in the presence of chloranil is interesting as it provides the first instance of indole formation by cyclization to a "blocked" ortho position followed by a methyl shift. The requirement of two ortho blocking groups would limit this as a general isoquinoline synthesis to isoquinolines with a 5-substituent. Therefore, the same workers⁵³⁴ studied the effect of oxidants on indole versus isoquinoline formation for a series of azidocinnamates bearing only one substituent ortho to the azidoacrylyl group (Scheme 42). Isoquinoline yield increased from 2 to 52%, and indole

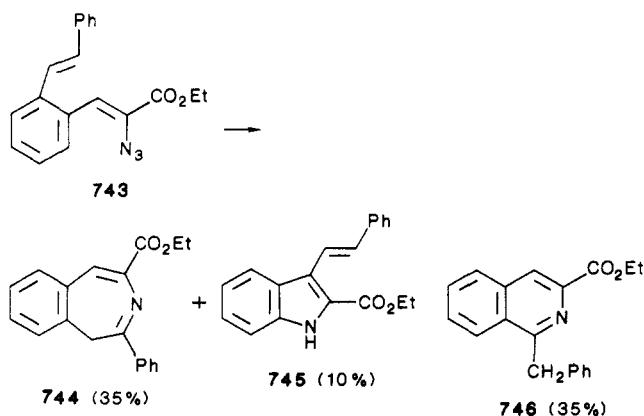
SCHEME 41



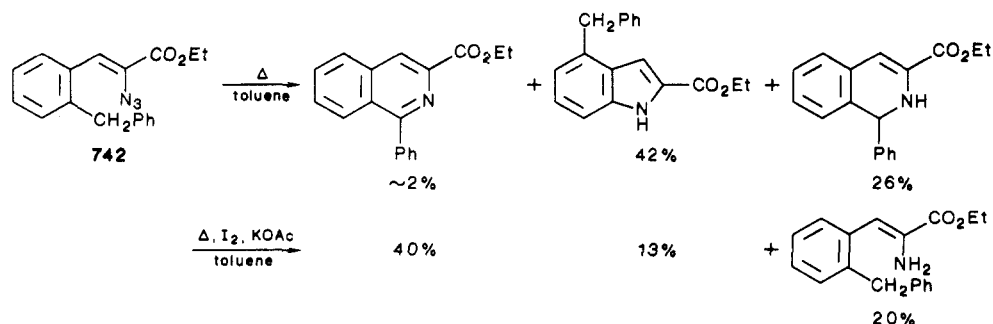
yield fell when thermolysis of **742** was carried out in the presence of iodine and potassium acetate.

The above difficulties were avoided by using azidocinnamates with an ortho carbonyl substituent which on treatment with TEP undergo intramolecular aza-Wittig reaction to give isoquinolines in very high yield (Scheme 43).⁵³⁵ This procedure has the advantage of high-yield, mild conditions, and it offers an alternative to the more common isoquinoline syntheses which require at least one electron-donating substituent in the benzene ring to promote an electrophilic ring closure.

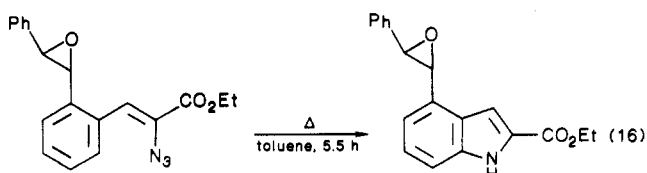
Decomposition of *o*-styrylazidocinnamate **743** in boiling toluene affords benzazepine **744** as well as the anticipated indole **745** and isoquinoline **746**.⁵³⁶



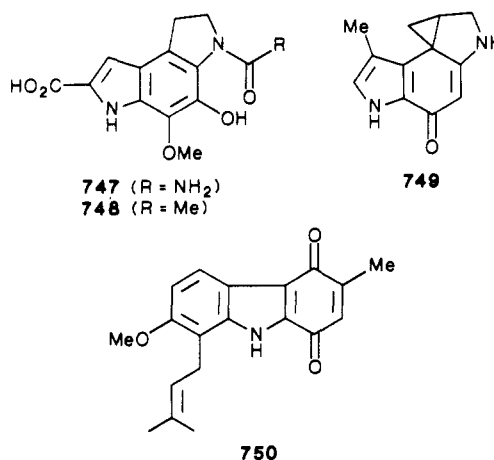
SCHEME 42



Exclusive indole formation can be achieved in good yield by protecting the ortho olefinic substituent as the epoxide (eq 16).⁵³⁷



Azidocinnamate cyclizations provide the key steps (i.e., construction of both pyrrole rings) in the synthesis of the phosphodiesterase inhibitors PDE-I (**747**) and PDE-II (**748**),⁵³⁸ the left-hand unit of the potent anti-tumor agent CC-1065 (**749**),⁵³⁹ and the pyrrole ring of murrayquinone-B (**750**).⁵⁴⁰



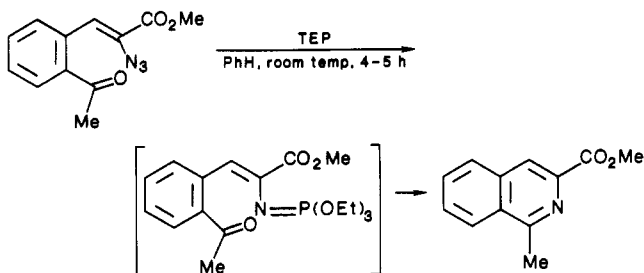
Azepines can be the preferred products of decomposition of azidocinnamates bearing an ortho cycloalkenyl substituent of appropriate ring size.⁵⁴¹ Here intramolecular cycloaddition via a dihydrotriazole intermediate is proposed (Scheme 44).

Moody has annulated pyrroles,⁵⁴² pyridines, and azepines⁵⁴³ to the 2,3-positions of suitably substituted indoles (Scheme 45).

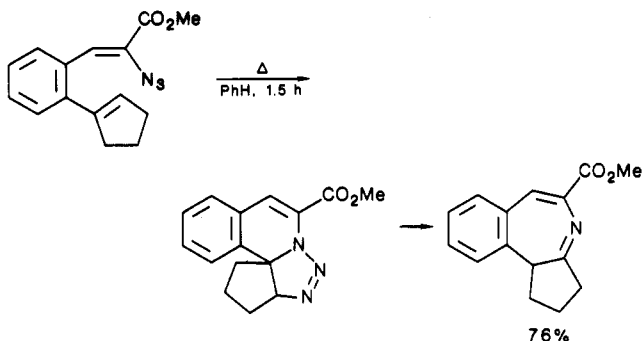
The presence of an *o*-thiophenoxy group in the azidocinnamate results in the formation of a benzothiazine on thermolysis (Scheme 46).⁵⁴⁴

2,5-Diarylpyrroles have been prepared in quite good yields by the hexacarbonylmolybdenum-mediated dimerization of arylvinyl azides. Two possible reaction pathways have been suggested (Scheme 47).⁵⁴⁵

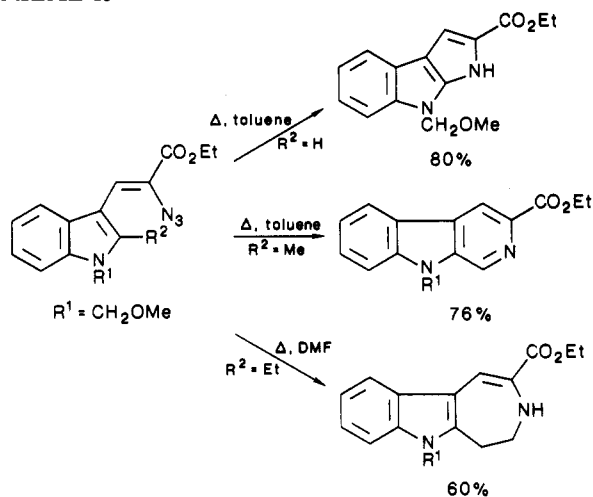
SCHEME 43



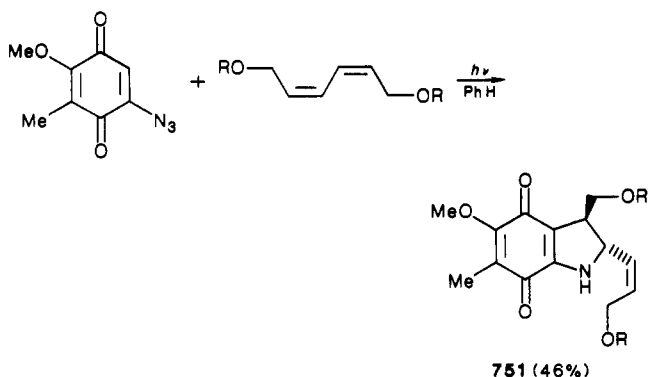
SCHEME 44



SCHEME 45



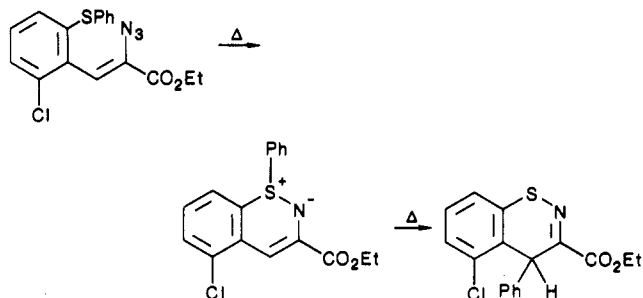
A mitomycin precursor (751) has been prepared with high stereoselectivity by photolysis of an azidoquinone and a *cis,cis*-diene.⁵⁴⁶



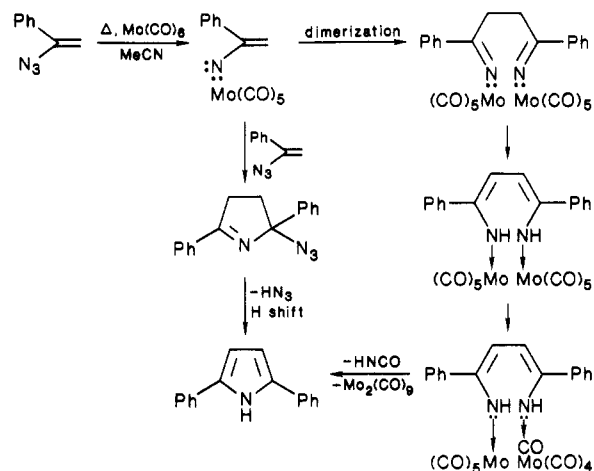
3. Aryl and Heteroaryl Azides

Intramolecular cyclizations of aryl and heteroaryl azides to form five-, six-, and seven-membered rings are well-known general high yield processes. They have

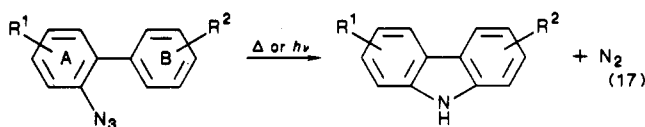
SCHEME 46



SCHEME 47

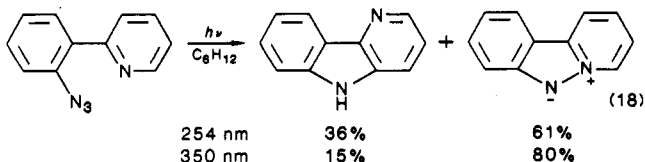


been reviewed several times recently; therefore older work will not be discussed in detail here. The prototype of these reactions, the cyclization of *o*-azidobiphenyl to carbazole, was reported by Smith and Brown in 1951 (eq 17).⁵⁴⁷



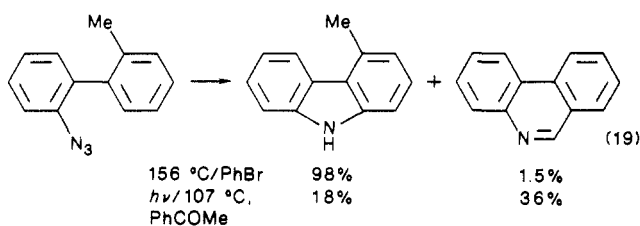
The reaction is typically carried out thermolytically at 150–200 °C in, for example, di- or 1,2,4-trichlorobenzenes or by photolysis.⁵⁴⁸ Yields are usually excellent⁵⁴⁹ regardless of the nature of the substituents attached to rings A and B. However, attachment of ortho substituents (e.g., nitro) that provide the opportunity for a competing non-nitrene reaction does prevent carbazole formation via a singlet nitrene process.

Replacement of ring A or B of the azidobiphenyl by various heterocyclic systems (e.g., thienyl and pyridyl)⁵⁵⁰ also usually leads to good-yield cyclizations on decomposition. The wavelength chosen for photolysis can have a significant effect upon the yields of products formed (eq 18).⁵⁵¹



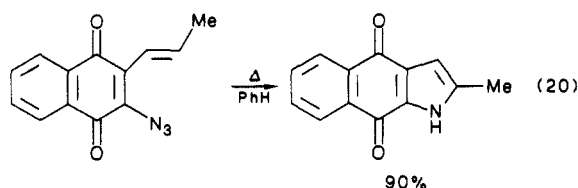
Cyclization onto a suitably placed methyl group is promoted under triplet nitrene forming conditions (eq 19), although carbazole formation is still significant.⁵⁵² However, this process is not as efficient as carbazole

formation under "singlet conditions".

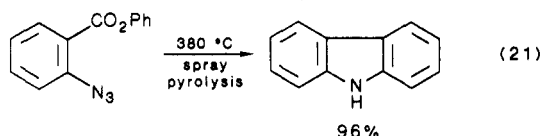


The report of the thermolysis of an azido-1,2-quinone is of interest as it results in the formation of an indoloquinone rather than zwitterido cleavage (Scheme 48).^{553a}

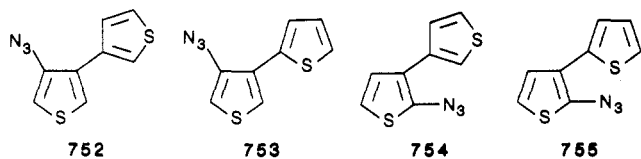
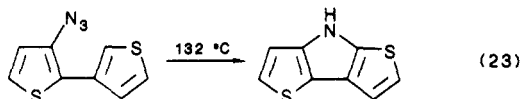
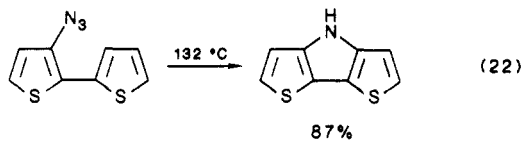
This offers an alternative to the other azide ring closure route to indoloquinone (eq 20),^{553b} and it promises to have generality.



o-Azidobenzoates yield carbazoles on spray pyrolysis with loss of carbon dioxide (eq 21).⁵⁵⁴ This is the first example of the successful decomposition of an azido aromatic having two atoms between the rings. On solution thermolysis this reaction is not observed.

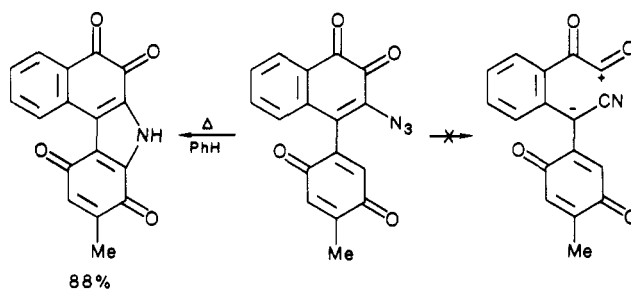


In contrast to the extensive work on carbazole synthesis, little was known of the cyclization of *o*-azidobithienyls to dithienopyrroles. Now an extensive study has appeared,⁵⁵⁵ employing *o*-azidobithienyls newly available by treatment of lithiobithienyls with tosyl azide and subsequent fragmentation of the intermediate lithium triazene salts.²²⁸ Both 3-azido-2,2'-bithienyl and 3-azido-2,3'-bithienyl undergo cyclization readily in high yield in boiling chlorobenzene (eq 22 and 23), but the

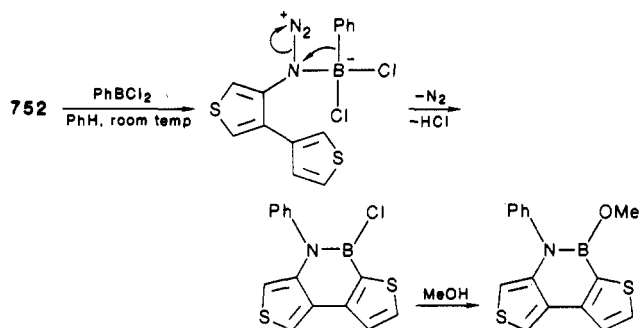


other four isomers 752–755 do not give the analogous cyclic products. Isomers 752 and 753 give polymeric materials, 754 undergoes ring opening, and 755 gives intractable products. These failures were attributed to the lack of availability of low-energy concerted pathways for reaction in these isomers, as has been found in related 2-azidophenyl heterocycles.⁵⁵²

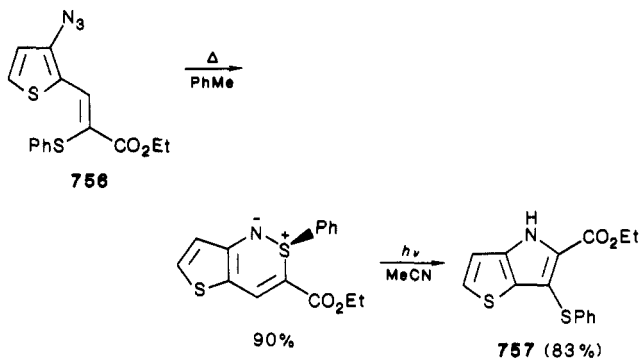
SCHEME 48



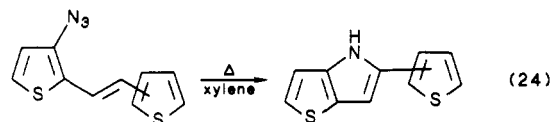
SCHEME 49



Ortho-substituted 3-azidothiophene 756 undergoes cyclization in boiling toluene to afford an azathia-benzene derivative in 90% yield.⁵⁵⁵ On photolysis in acetonitrile the azathia-benzene rearranges to a thienopyrrole (757).^{557–559}



Thermal decomposition of azidodithienylethenes gives thienyl-4*H*-thieno[3,2-*b*]- or -[3,4-*b*]pyrroles in good yield (eq 24).^{560,561}

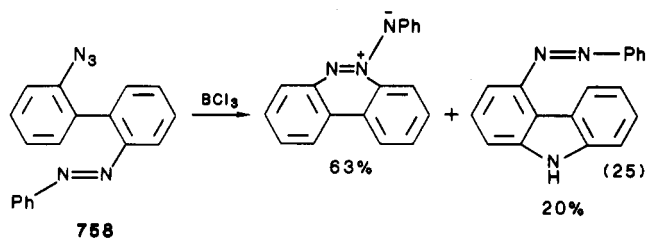


Azide 752 readily cyclizes to a 1,2-dihydro-1-aza-2-borabenzene on standing with phenyldichloroborane at room temperature (Scheme 49).⁵⁶⁴

However, treatment of *o*-azidobiphenyl with boron trichloride in benzene at room temperature gives carbazole in 91% yield.⁵⁶⁴

Substituted *o*-azidobiphenyl 758 gives the *N*-phenylimide of benzo[*c*]cinnoline as the main product on similar treatment (eq 25).⁵⁶⁴

Biaryl azides of the type 759 cyclize initially on decomposition to five-membered rings which undergo a Smiles-like rearrangement to six-membered rings (Scheme 50). The synthetic importance of this method (particularly in phenothiazine synthesis) and its mechanism were delineated chiefly by Cadogan and his

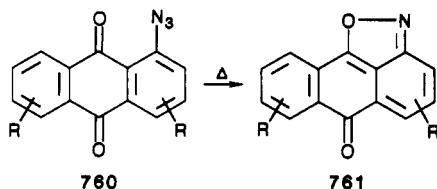


group working on both azide decomposition and phosphorus-mediated deoxygenations of nitro and nitroso compounds.⁵⁶⁵

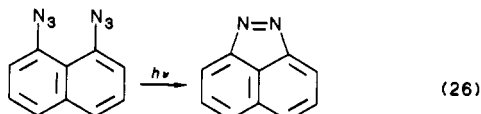
Thiazepines are the major product when the B ring contains two methyl groups ortho to the ring junction (Scheme 51).⁵⁵⁰

Azepinobenzothiazoles formed via ring expansion of the azanorcaradiene tautomer of the spiro intermediate are more commonly encountered in systems where X = CH₂. Jones' group⁵⁶⁶ has compared the effect of thermolysis temperature on solution and flash vacuum thermolysis of *o*-azidodiphenylmethanes. Acridines and acridans are favored at higher temperatures using flash vacuum pyrolysis whereas at lower temperature on solution thermolysis azepinoindoles are the main product (Scheme 52).

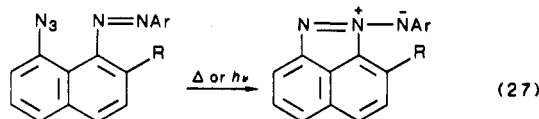
Azides of the type 760 undergo cyclization to anthraisoaxazolones 761 on heating.²²³



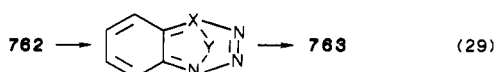
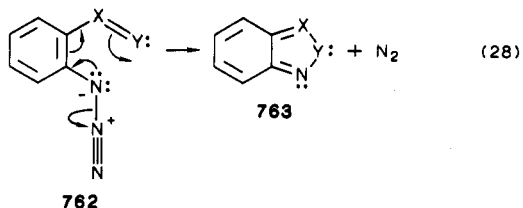
Benzo[*c,d*]indazole has been formed by the photolysis of *peri*-diazidonaphthalene in a rigid matrix at low temperature (eq 26).⁵⁶⁷



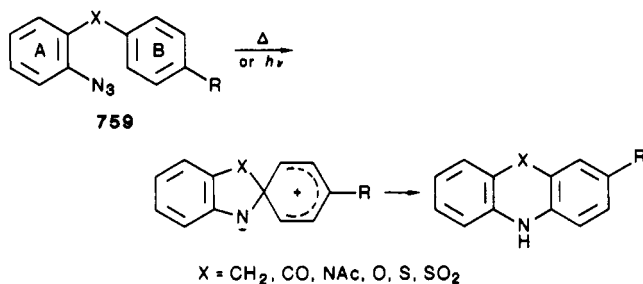
The *N*-arylimine derivative of this ring system, which contains the rare 1,3-dipolar azimine system, has been isolated for the first time (eq 27).^{241a}



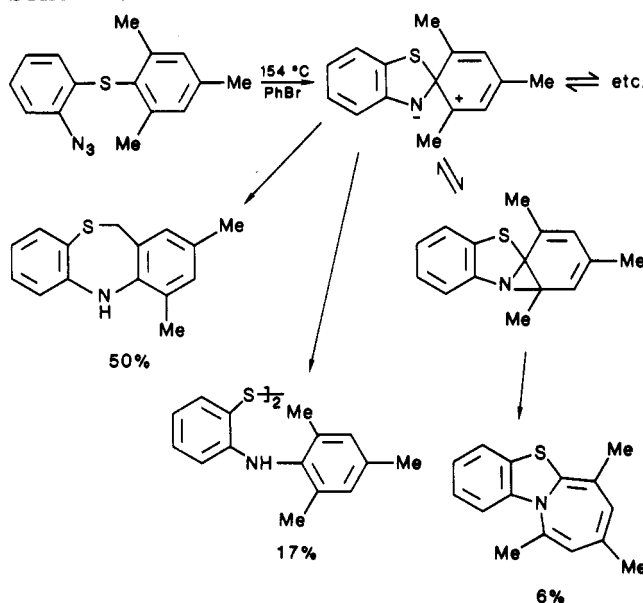
Ring closures of an azido group to an ortho substituent that do not involve an intermediate nitrene have interested azide chemists for some years.⁵⁶⁸ Two mechanisms (one based on a concerted reaction (eq 28),⁵⁶⁹ the other on 1,3-dipolar cyclization (eq 29)⁵⁷⁰)



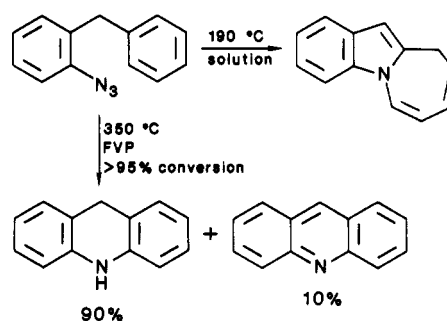
SCHEME 50



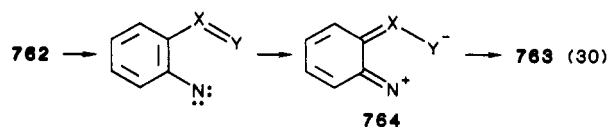
SCHEME 51



SCHEME 52

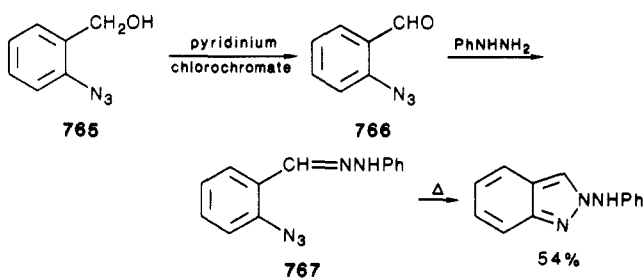


have been proposed based on experimental observations. Now a third mechanism has appeared⁵⁷¹ that, unlike the other two, accounts for the observed order of accelerating effects on azide fragmentation with different ortho substituents, viz., ArN=N- > O=N(O)- > O=C(R)- > RN=C(R)- > R₂C=C(R)-. This new mechanism is based on the notion that charge separation contributes more to the structure of the aryl nitrene than it does to the corresponding azide (eq 30). The

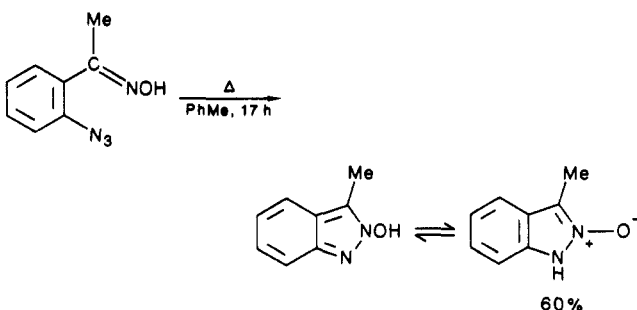


more the transition state resembles the charge-separated structure 764, the easier is ring closure. Furthermore, this process unlike an electrocyclic one does not require the delocalization energy of the new heterocycle that is being formed in the transition state to

SCHEME 53



SCHEME 54



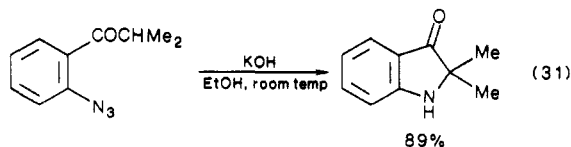
provide the driving force for reaction. These mechanistic considerations should be useful for selecting reaction conditions for synthetic endeavors.

Routes to several hitherto somewhat elusive indazole derivatives have appeared recently.^{262,572-571} One⁵⁷² is based on the cyclization of the anils of *o*-azidobenzaldehyde, an established method (Scheme 53).⁵⁷⁵ The synthetically important point here is the conversion of the benzyl alcohol (765) to aldehyde (766) in 90% yield using Corey's reagent, without detriment to the ortho azido group (see section II.L.1 for other examples). Previous routes to the azidoanils of the type 767 gave much lower yields.⁵⁷⁶

o-Azidoacetophenone oxime cyclizes on reflux in toluene to give a tautomeric 2-hydroxyindazole (Scheme 54).²⁶³

3-Chloroindazole has been made in 91% yield, merely by heating *o*-azidobenzanilide with thionyl chloride (Scheme 55).⁵⁷⁷ This method has recently been extended to give a benzimidazole synthesis (Scheme 56).⁵⁷⁴

In contrast, treatment of *o*-azidobenzanilide with sodium hydride in DMF gives an indazol-3-one by base-catalyzed cyclization (Scheme 57).^{573,578} A similar base-catalyzed closure, involving a carbanion, yields indoxyls (eq 31).^{579,580} Note that low temperature is

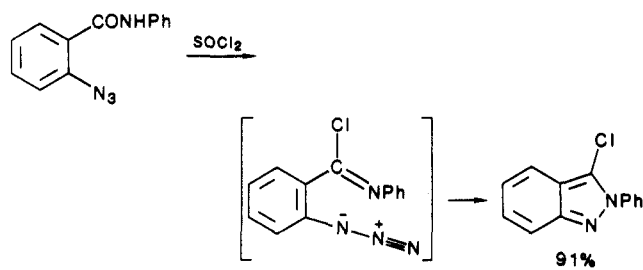


necessary to avoid formation of a benzisoxazole by azide fragmentation. These azide cyclizations offer potentially general routes to several less readily available simple heterocycles.

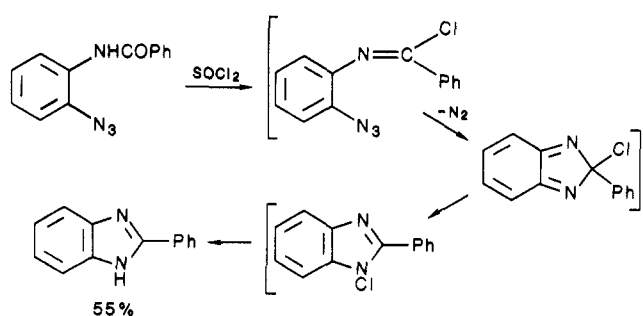
Intermolecular electrophilic attack at ring positions in arylnitrenium ions is well-known.⁵⁸¹ Now attack at nitrogen by alkenes followed by Friedel-Crafts reaction has been used to prepare *trans*-[5]para-1-azacyclophanes (Scheme 58).⁵⁸²

Abramovitch has trapped arylnitrenium ions intramolecularly to provide a potentially general approach

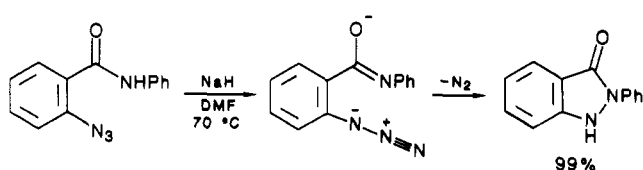
SCHEME 55



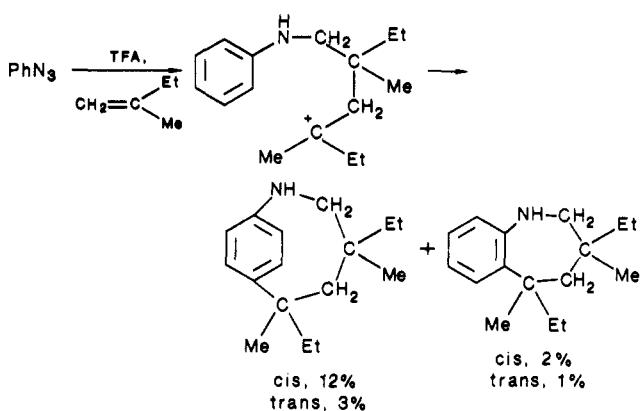
SCHEME 56



SCHEME 57



SCHEME 58



to a number of heterocycles that have amino groups β to the ring junction (Scheme 59).⁴⁹⁵

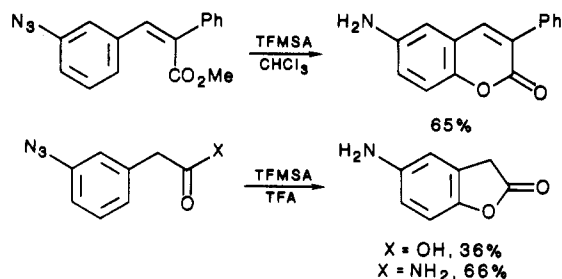
More recently, this lactone synthesis has been extended to the preparation of spiro lactones (Scheme 60).⁵⁸³

4. Acyl Azides

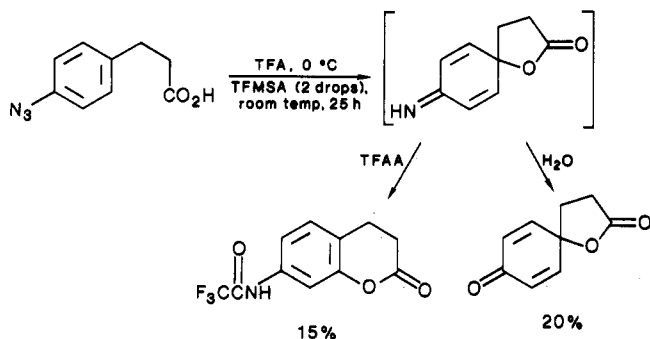
Cyclization of isocyanates, formed by Curtius rearrangement of acyl azides (see section III.D for a further treatment of the Curtius reaction), is a well-established method for the synthesis of heterocycles.³ Therefore, only a few examples will be given. The parent furo-[2,3-*c*]pyridine system has been made for the first time by annulation of a pyridine to furan (Scheme 61).^{160b}

A pyrazinone ring system was formed by reaction of pyrrole and an isocyanate (Scheme 62).⁵⁸⁴ Note that these acyl azides are best prepared from mixed anhydrides.

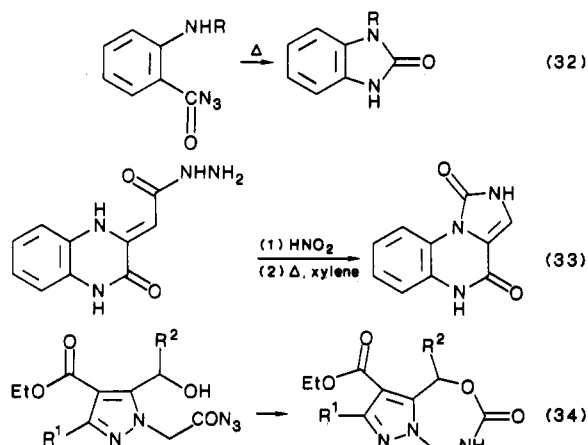
SCHEME 59



SCHEME 60

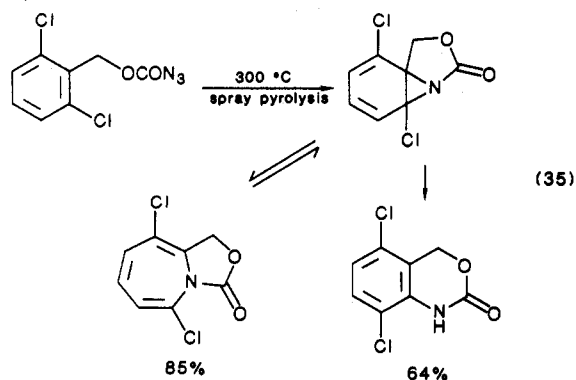


Acyl azide cyclizations via isocyanates may also be used to prepare five-membered (eq 32 and 33)⁵⁸⁵ and seven-membered (eq 34)⁵⁸⁶ rings.



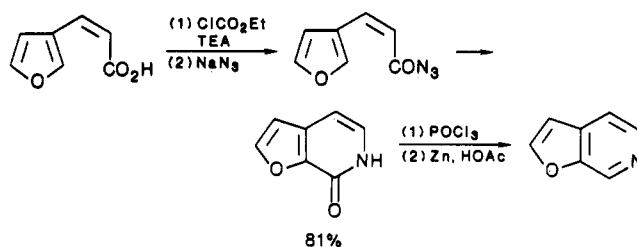
The Meth-Cohn spray pyrolysis technique has been applied successfully to the synthesis of several heterocycles. 4-Azaazulene was obtained in 56% overall yield from the chlorohydrin **768** (Scheme 63).⁵⁸⁷

Spray pyrolysis of benzyl azidoformate at 330 °C gives oxazoloazepines, or their dimers, which on further heating rearrange to benzoxazines (eq 35).⁵⁸⁸

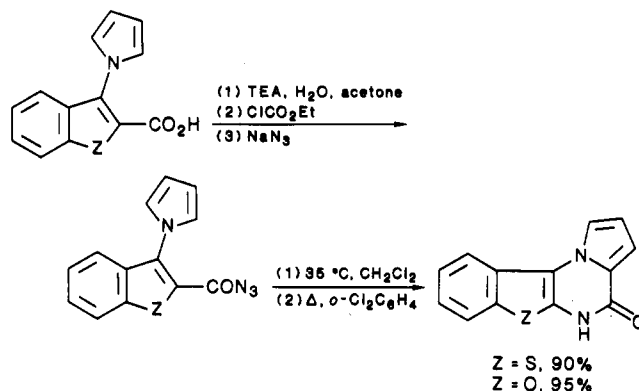


Lwowski and co-workers have studied the reactions of carbamoyl azides extensively.⁵⁸⁹ Some recent work

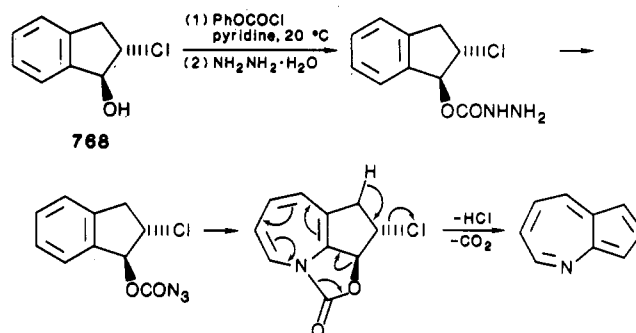
SCHEME 61



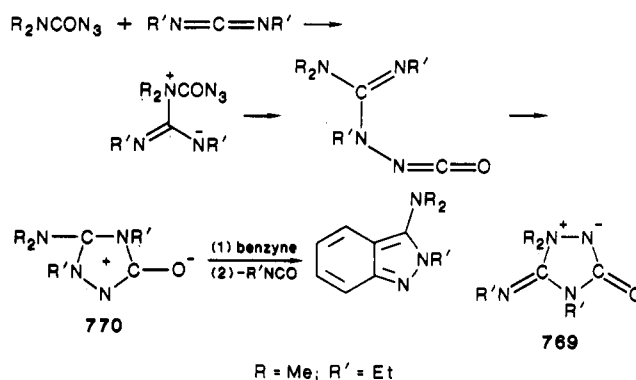
SCHEME 62



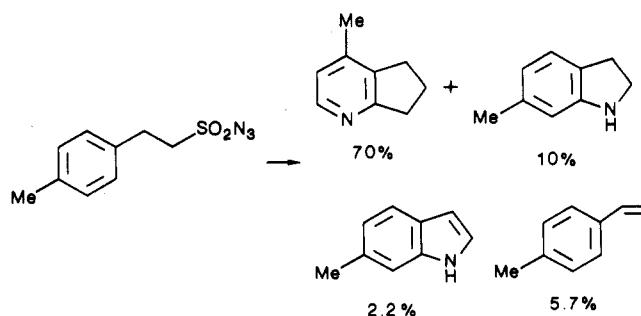
SCHEME 63



SCHEME 64

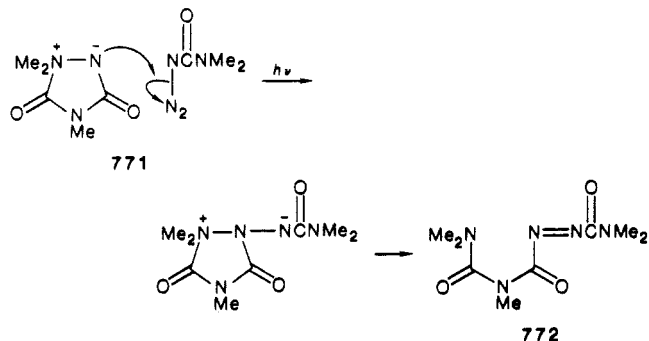


SCHEME 65



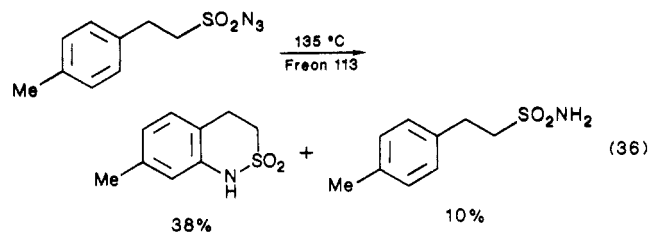
has concerned the photolysis of dialkylcarbamoyl azides in the presence of carbodiimides which yields **769** and **770**,⁵⁹⁰ the latter by a novel process (Scheme 64). An indazole may be obtained by reacting **770** with benzyne.

Dimethylcarbamoyl azide has been photolyzed in the presence of methyl isocyanate to give the ylide **771** and an azo compound **772**. The latter is formed by photo-reaction of **771** with more azide,⁵⁹¹ which provides the first instance of an intermolecular-assisted loss of nitrogen from a carbamoyl azide.



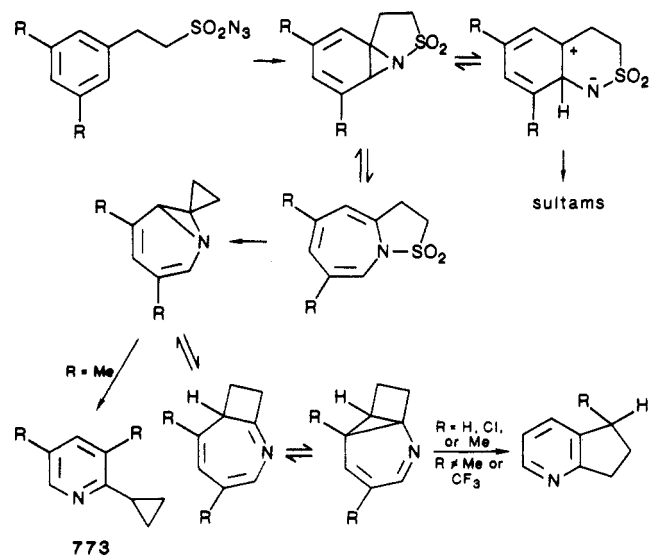
5. Sulfonyl Azides

Abramovitch has made a fundamental study of the intermolecular reactions of arylsulfonyl azides.⁵⁹² The intramolecular reactions of substituted aryethanesulfonyl, arylpropanesulfonyl, and other sulfonyl azides have now been carried out to investigate the corresponding intramolecular reactions. β -Arylethanesulfonyl azides, when thermolyzed in inert solvents such as Freon 113, cyclize to sultams (eq 36).^{83,593} Corresponding sulfonamides, the triplet nitrene hydrogen abstraction products, are also formed.

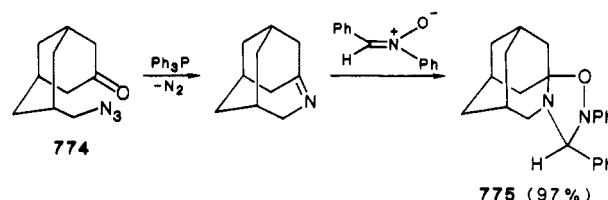


Dihydropyridines rather than sultams become the main products of FVP of aryethanesulfonyl azides at

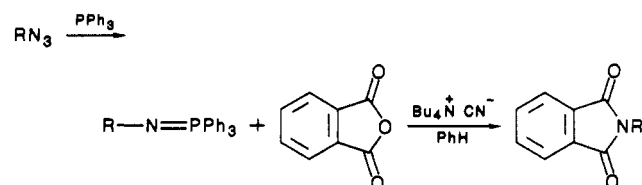
SCHEME 66



SCHEME 67



SCHEME 68



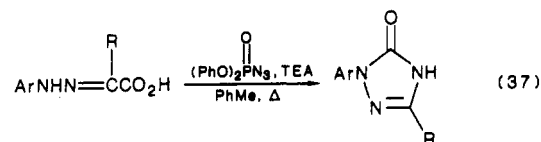
the appropriate temperature (Scheme 65). The nature of products formed varies greatly with the FVP temperature.

A mechanism that accounts for the formation of dihydropyridine and other interesting products (e.g., **773**) has been established by using variously substituted aryethanesulfonyl azides (Scheme 66).⁵⁹⁴

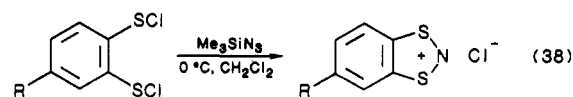
Solution and flash vacuum pyrolysis of 3-arylpropanesulfonyl azides give seven-membered sultams. Best yields are obtained on solution decomposition in Freon 113.⁵⁹⁵

6. Other Azides

1-Aryl-1,2,4-triazolin-5-ones may be prepared from arylhydrazones of α -keto acids by reaction with diphenylphosphoryl azide (eq 37).⁵⁹⁶



Treatment of benzene-1,2-disulfonyl chlorides with trimethylsilyl azide at 0 °C affords benzo-1,3,2-dithiazolium chlorides almost quantitatively (eq 38).⁵⁹⁷



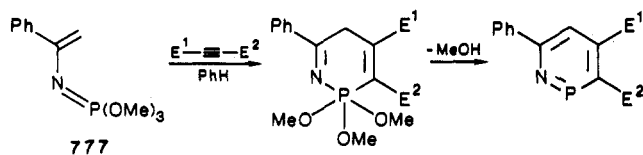
7. Staudinger Reaction and Related Processes

Azides react readily with trivalent phosphorus compounds to give phosphine imines (Staudinger reaction), which can undergo further reaction with, for instance, a carbonyl group (aza-Wittig reaction) (for reduction, see section III.A).⁵⁹⁸ This section contains examples of cyclizations that produce nitrogen and phosphorus heterocycles (see section VI.A.2 for other examples).

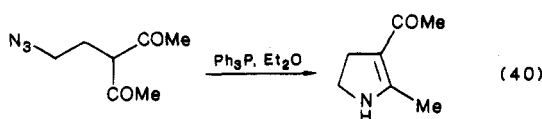
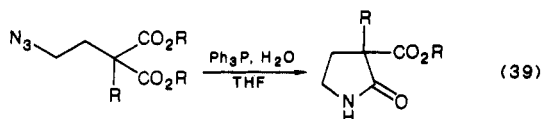
Bridgehead imines are most often prepared from bridgehead azides, but unsymmetrical bridgehead azides give mixtures of imines. A new sequence starting with the azido ketone **774** and involving Staudinger and aza-Wittig reactions followed by trapping affords the bridgehead imine adduct **775** in nearly quantitative yield (Scheme 67).⁵⁹⁹

ω -Azido ketones react with triphenylphosphine under anhydrous conditions to yield five-, six-, or seven-

SCHEME 69

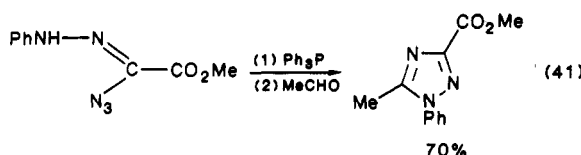


membered cyclic imines.⁶⁰⁰ Azido esters cyclize in good yield to amides under aqueous conditions (eq 39)⁶⁰¹ whereas an azido ketone forms a β -keto ester on reaction with triphenylphosphine under anhydrous conditions (eq 40).⁶⁰¹

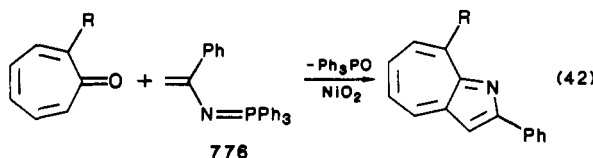


Phthalimido derivatives may be prepared by treatment of the appropriate azide with triphenylphosphine and phthalic anhydride (Scheme 68).⁶⁰² This provides another method for protecting amines and is of great potential for amino carbohydrates.

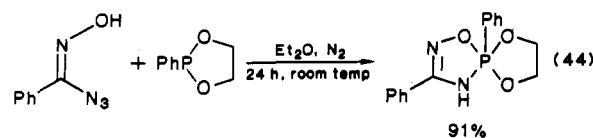
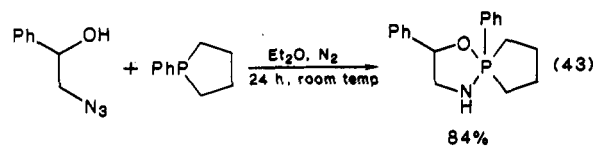
Hydrazonyl azides have been cyclized via an azo-Wittig reaction (eq 41).⁶⁰³



α -Azidostyrene readily forms iminophosphoranes 776 and 777 on reaction with triphenylphosphine or trimethyl phosphite, respectively. These have been used in the synthesis of azaazulenes (eq 42)⁶⁰⁴ and the 1,2- λ^5 -azaphosphorine ring system (Scheme 69).⁶⁰⁵

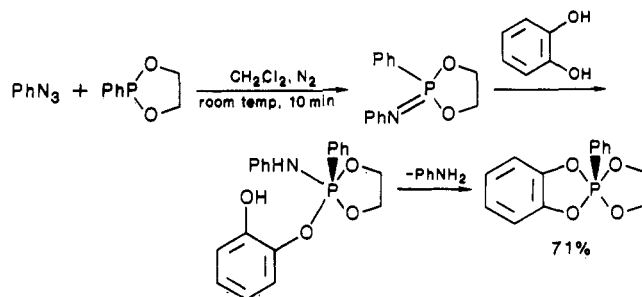


Cadogan and co-workers have shown that treatment of hydroxyalkyl and hydroxamic azides with phosphorus(III) reagents provides a general route to penta-coordinate phosphoranes (eq 43 and 44).⁶⁰⁶

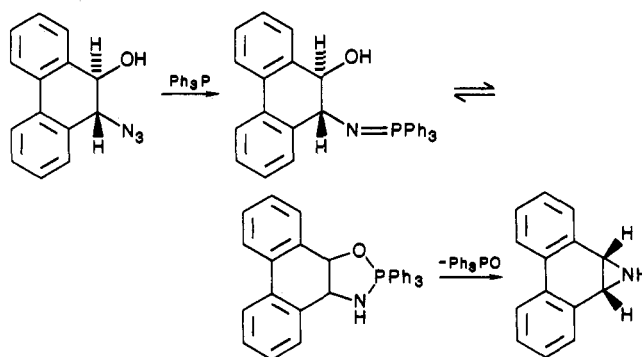


An intermolecular version of the above reaction, involving phenyl azide, has also been described (Scheme 70).⁶⁰⁷

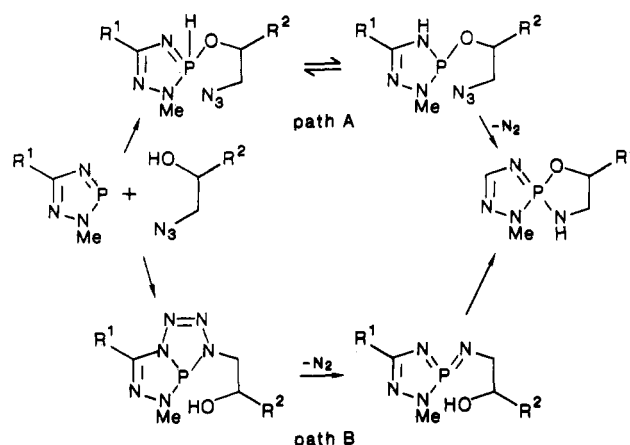
SCHEME 70



SCHEME 71



SCHEME 72



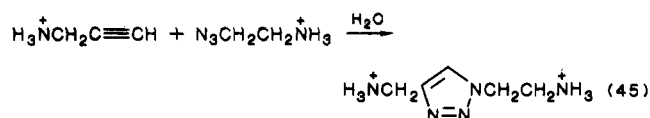
Fused azirines may be obtained via oxazaphospholidines by loss of phosphine oxide (Scheme 71).⁶⁰⁸

Spirophosphazenes have been prepared by the reaction of azido alcohols with triazaphospholes; however, path A is favored over path B (Scheme 72).⁶⁰⁹

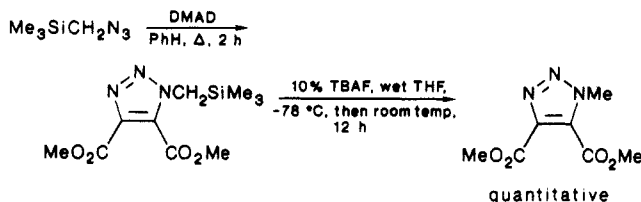
B. Cycloadditions

1. Formation of Stable Triazoles

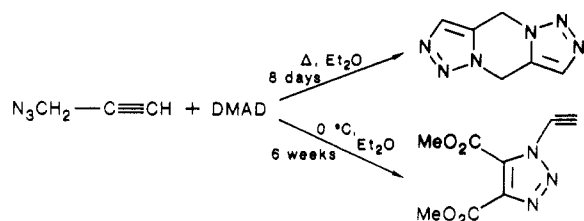
Addition of azides to acetylenes or activated methylene compounds offers two well-established methods for the synthesis of 1,2,3-triazoles.⁶¹⁰⁻⁶¹² Recent work has been concerned with mechanistic examination and synthetic extensions of these reactions. The rather slow cyclization (eq 45) is speeded up when carried out in the presence of cucurbitural (a nonadecacyclic cage compound that can encapsulate substituted ammonium ions).⁶¹³



SCHEME 73



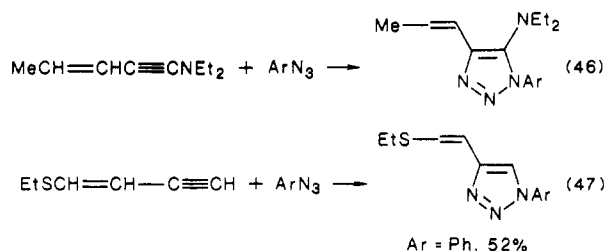
SCHEME 74



Synthesis of *N*-unsubstituted triazoles usually entails the selection of an azide (RN_3) that adds easily to an alkyne and has an *R* group that is easily removable. Benzyl is a favorite group for this purpose but it requires forcing conditions for its removal. 4-Methoxybenzyl azide is reasonably stable and undergoes additions smoothly, and the 4-methoxybenzyl group may be removed relatively easily.⁶¹⁴ (Trimethylsilyl)methyl azide, made from (chloromethyl)trimethylsilane and sodium azide has been used as a methyl azide equivalent (Scheme 73).⁶¹⁵

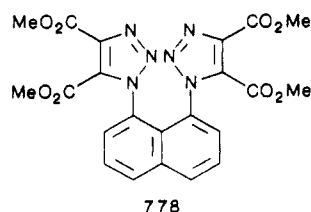
3-Azido-1-propyne adds to DMAD in the cold, but dimerizes on heating in ether (Scheme 74).⁵³

Suitably substituted enynes undergo addition with azides at the triple rather than the double bond as had been observed previously (eq 46 and 47).⁶¹⁶



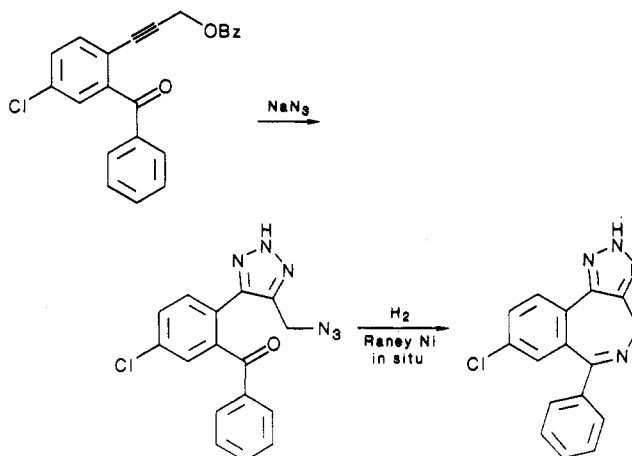
Cycloaddition and substitution by azide ion have proved valuable in triazolobenzazepine synthesis (Scheme 75).⁶¹⁷

Addition of DMAD, its congeners, or enolates of acetoacetic esters to 1,8-diazidonaphthalene gives, e.g., the strained 1,8-bis(triazolyl)naphthalene 778 in high yield.⁶¹⁸

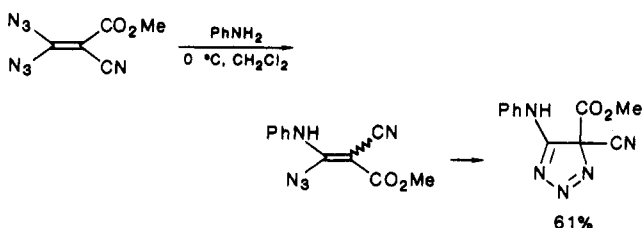


Addition of azides to phosphonium ylides,⁶¹⁹ which proceeds under mild conditions, has been used for the formation of triazoles at a 4-substituent in sydnone,

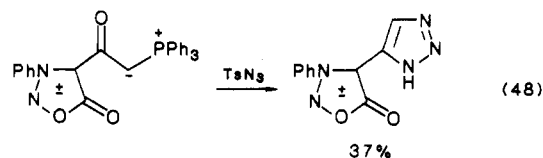
SCHEME 75



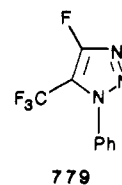
SCHEME 76



which are very sensitive to acid, base, and heat (eq 48).⁶²⁰



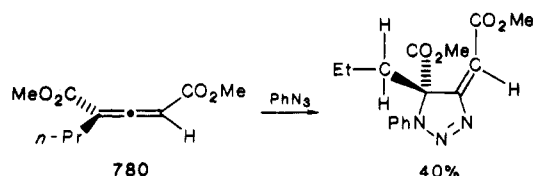
Phenyl azide adds to perfluoropropyne to give mainly 779,⁶²¹ whereas phenyl azide gives an equimolar amount of both regioisomers on addition to phenylpropyne.⁶²²



Vinyl azides usually eliminate nitrogen readily to form 2*H*-azirines rather than cyclize to 4*H*-triazoles. However, when suitably substituted, they spontaneously cyclize to 4*H*-triazoles (Scheme 76).⁶²³

2. Formation of Stable Triazolines

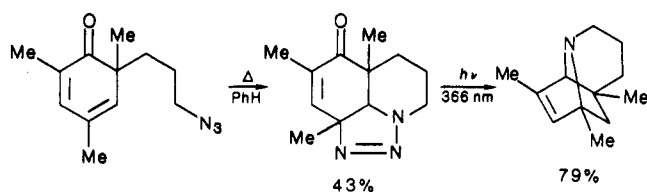
Addition of phenyl, *p*-nitrophenyl, and *o*-methoxyphenyl azides to the allene 780 takes place in a regio- and directiospecific manner.⁶²⁴



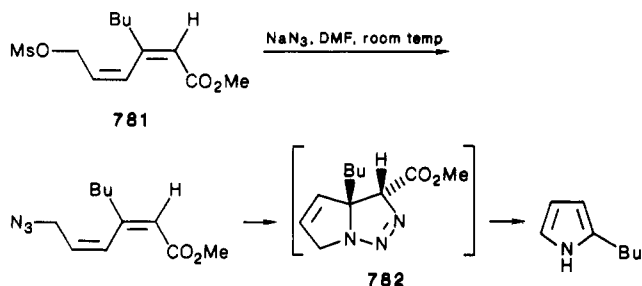
3. Triazolines as Intermediates

(a) Intramolecular Cycloadditions. Intramolecular azide cycloadditions involving triazolines are playing an

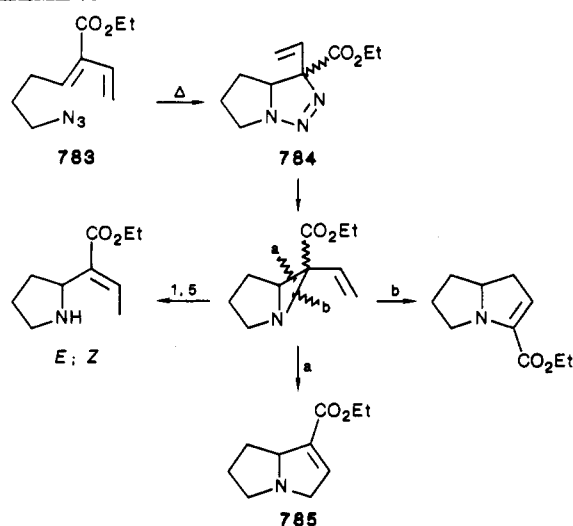
SCHEME 77



SCHEME 78



SCHEME 79

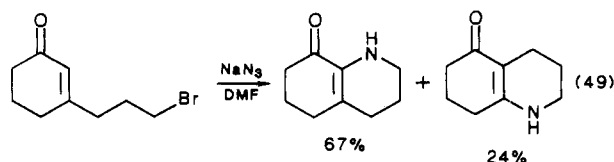


increasingly important part in heterocyclic synthesis,^{625,626} often without the isolation of the azide. A new synthesis of the 2-azatricyclo[4.4.0.0^{2,8}]decenone system has been achieved (Scheme 77).¹⁰⁷

Treatment of mesylate 781 with sodium azide in DMF at room temperature gave 2-butylpyrrole in high yield; presumably the azide undergoes intramolecular cycloaddition via 782 (Scheme 78).¹¹¹

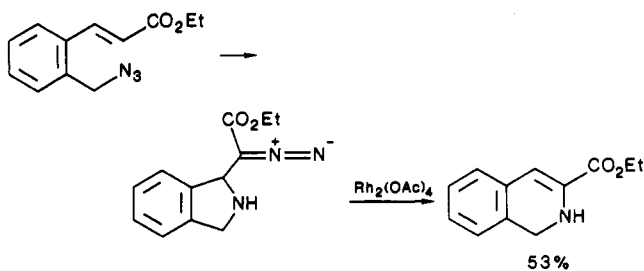
Two groups of workers^{237,627} have found that decomposition of azido diene 783 (Scheme 79) gives access to the pyrrolizidine alkaloids probably via 784, which is similar to 782, providing a formal total synthesis of supinidine (785).

Cycloadditions of alkyl azides, generated in situ, to enones (eq 49)⁶³⁰ and cinnamate esters (Scheme 80)⁶²⁸⁻⁶³⁰ afford a variety of heterocycles via triazole intermediates.

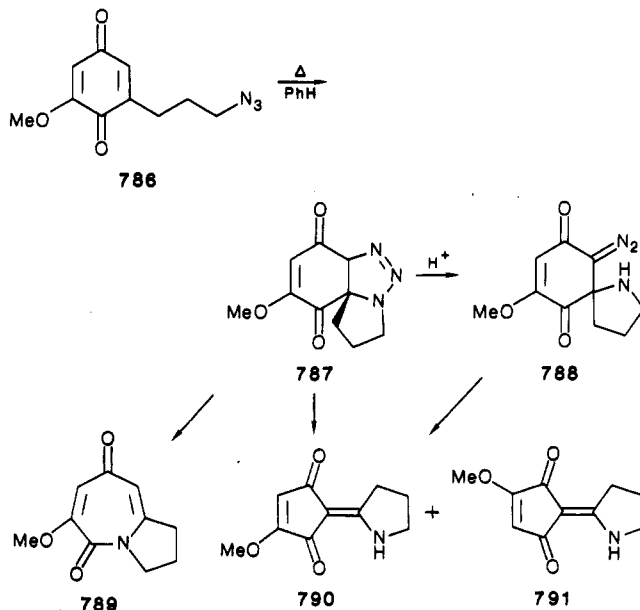


1,4-Benzoquinone azide 786 undergoes intramolecular cycloaddition to give triazolone 787, which has been

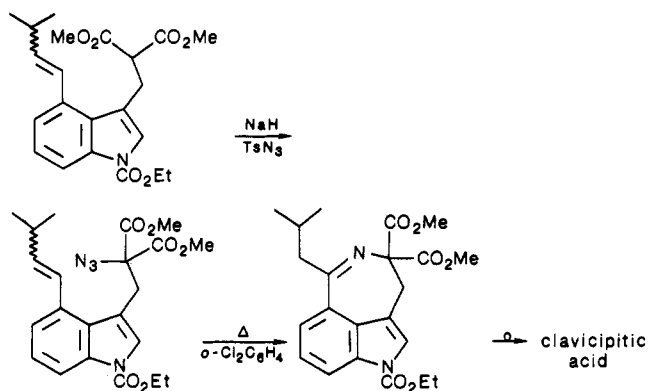
SCHEME 80



SCHEME 81



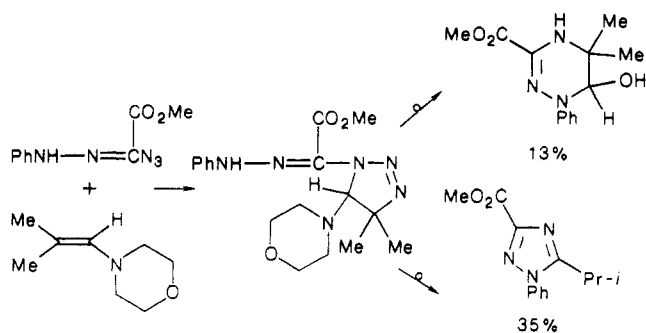
SCHEME 82



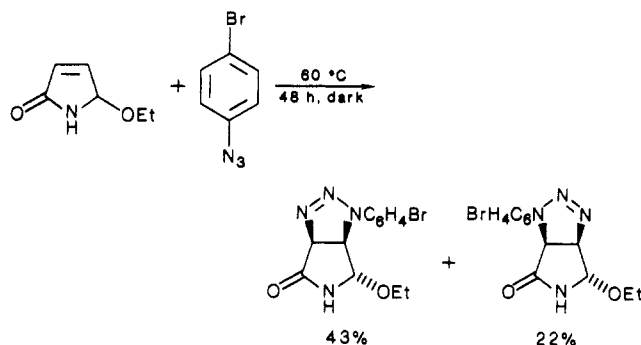
observed directly by ¹H NMR (Scheme 81).^{631,632} Formation of the triazolone can be followed by NMR; after 2.5 h of reaction a trace of 788 and the products 789-791 appear, with 50% triazolone and 25% starting azide. Continued heating at 40 °C results in formation of a 1:1 mixture of azepinedione and the 4-cyclopentene-1,3-diones 790 and 791. If a trace of acid is added, or on silica gel chromatography, the triazolone is quickly converted to 788. The diazo enedione 788 is stable at 40 °C in benzene for 21 h, but may be quantitatively converted to a mixture of 790 and 791 in toluene at reflux, without any azepinedione being detected among the products.

Another total synthesis, that of clavicipitic acids, has been described in which the key feature is the formation of the seven-membered ring via a triazolone (Scheme

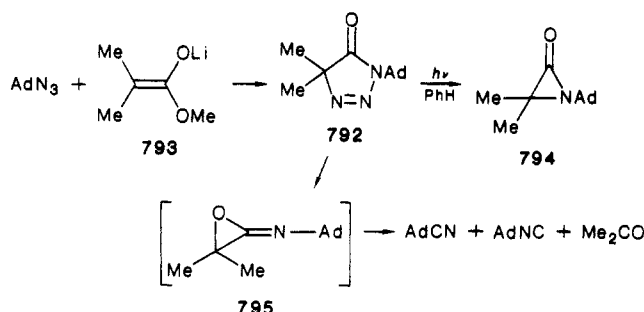
SCHEME 83



SCHEME 84



SCHEME 85



82).²²⁶ The use of the azide transfer reaction (II.J.) for making the starting azide is also noteworthy.

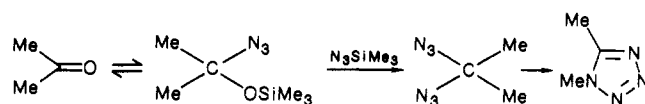
(b) Intermolecular Reactions. Methyl azido(phenylhydrazono)acetate undergoes 1,3-dipolar cycloaddition reactions with various substituted enamines to give ultimately 1,2,4-triazines and 1,2,4-triazoles, probably via triazolone intermediates (Scheme 83).⁶³³

1,3-Dipolar cycloaddition of a series of azides to 1-methyl-1,2,5,6-tetrahydropyridine yields pharmaceutically interesting 1-methylpiperidylidene-2-sulfon-(cyan)amides via initially formed triazolines.⁶³⁴ *p*-Bromophenyl azide adds to 5-ethoxy-3-pyrrolin-2-one to give a mixture of regioisomeric triazolines (Scheme 84).⁶³⁵

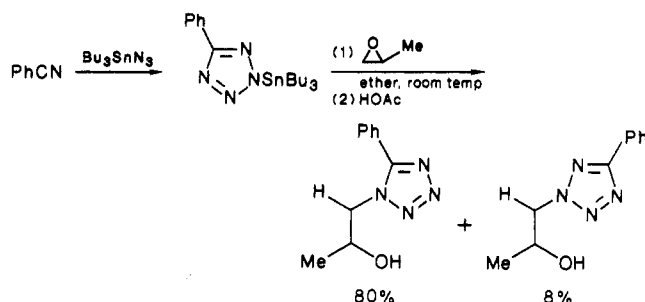
Alkyl azides are known to add to ketone enolates.^{636,637} Therefore, formation of triazol-4-one **792** when adamantyl azide was added to a suspension of **793** in hexane at -78°C and the mixture was allowed to stand at room temperature for 3 h was no surprise (Scheme 85).⁶³⁸ However, **792** on irradiation in dry benzene gave **794**, accompanied by adamantyl isocyanide, a small amount of adamantyl cyanide, and acetone. These other products were accounted for by reaction through **795**.

Treatment of tetracyclone with sodium azide under acidic conditions affords tetraphenylpyridone in 90%

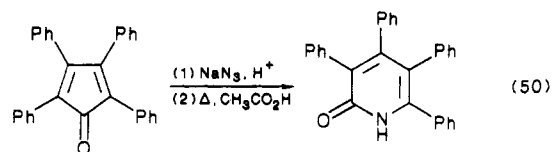
SCHEME 86



SCHEME 87

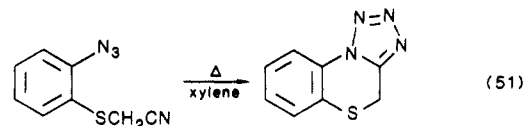


yield. The reaction involves a cycloaddition to a triazole intermediate rather than Schmidt reaction (eq 50).⁶³⁹



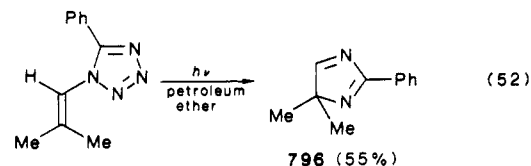
4. Tetrazoles

(a) Intramolecular Formation. Tetrazolo[5,1-*c*]-[1,4]benzothiazines, of pharmaceutical interest, have been synthesized by intramolecular azide cycloaddition to a nitrile (eq 51).⁶⁴⁰ This method is analogous to one described previously,⁶⁴¹ the mechanism of which has been studied recently.⁶⁴²



Imidoyl azides, usually generated in situ by treatment of the chloride with azide, spontaneously cyclize to tetrazoles (the von Braun-Rudolf reaction), unless they contain a stabilizing moiety. Factors that affect such cyclizations have been studied recently,⁶⁴ and reactions of tetrazoles have been reviewed.⁶⁴³

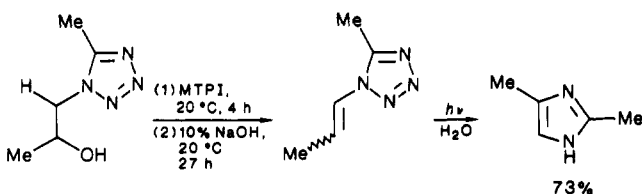
The first report of the synthesis of a 5-unsubstituted 4*H*-imidazole **796** by photolysis of an alkenyltetrazole has appeared (eq 52).⁶⁴⁴ The tetrazole was prepared by azide treatment of an imidoyl chloride obtained by chlorination of an enamide. Mild photolysis conditions are essential as **796** is a most unstable and volatile compound.



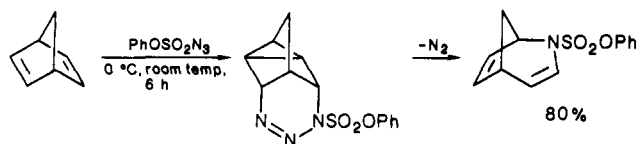
A quantitative yield of 1,5-dimethyltetrazole is formed when a mixture of acetone, 3 equiv of trimethylsilyl azide, and 0.1 equiv of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ is heated at 55°C for 20 h (Scheme 86)⁶⁴⁵ (see section II.D for azide synthesis from ketals).

(b) Intermolecular Reactions. Addition of tributylstannyl azide to nitriles gives 2-(tributylstannyl)tetra-

SCHEME 88



SCHEME 89

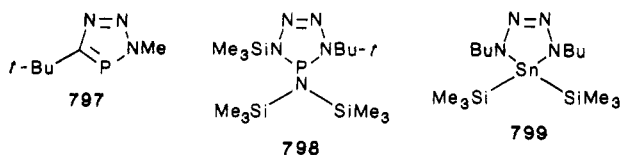


zoles, which react with epoxides to form alcohols with destannylation (Scheme 87). These alcohols may be readily dehydrated; the resulting alkenes give imidazoles on photolysis (Scheme 88).⁶⁴⁶

5. Other Cycloadditions

Aryl azidosulfonates add to norbornadiene to provide a new synthesis of the 2-azabicyclo[3.2.1]octadiene system (Scheme 89).⁶⁴⁷

Azide cycloaddition reactions continue to be employed for the synthesis of uncommon heterocycles 797,⁶⁴⁸ 798,⁶⁴⁹ 799⁶⁵⁰

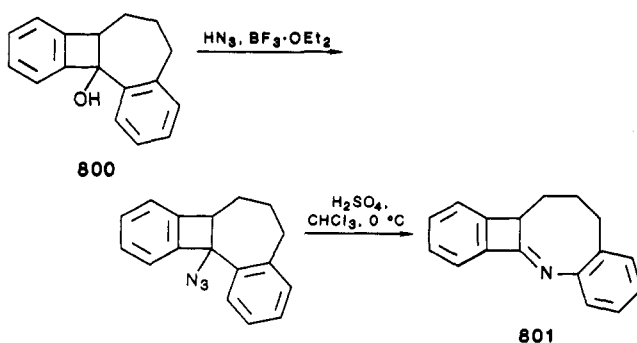


C. Ring Expansions and Contractions

1. Schmidt Reaction and Related Processes

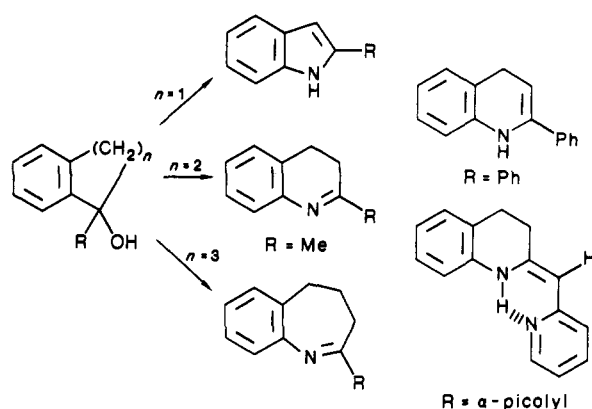
The term Schmidt reaction has come to cover a number of interconversions¹³ brought about by hydrazoic acid under strongly acidic conditions. Here only cyclic examples are considered. Andrieux and co-workers have treated a series ($n = 1$,⁶⁵¹ $n = 2$,⁶⁵² $n = 3$ ⁶⁵³) of benzocycloalkanols with $\text{HN}_3\text{-BF}_3$ and have obtained ring-expanded products (Scheme 90). The position of the isolated double bond in the dihydroquinolines depends upon the nature of R.

Reaction of alcohol 800 with $\text{HN}_3/\text{BF}_3\cdot\text{OEt}_2$ unexpectedly gave benzazocine (801) rather than an indole.⁶⁵⁴

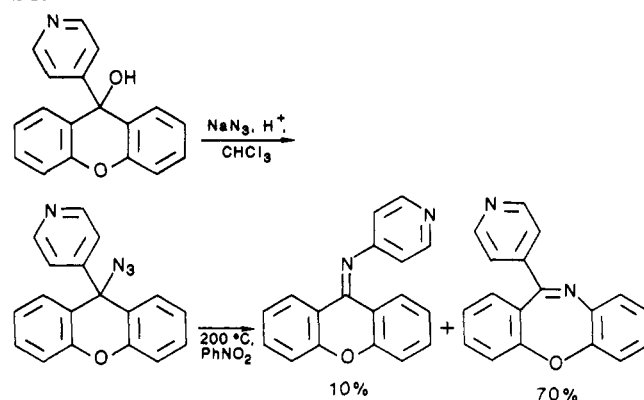


Ring expansion of 9-aryl-9-azidothioxanthenes, first described independently by Loudon⁶⁵⁵ and Coombs,⁶⁵⁶ now has been developed as a general synthetic method

SCHEME 90

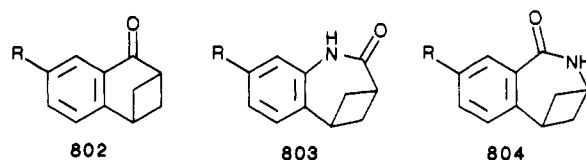


SCHEME 91



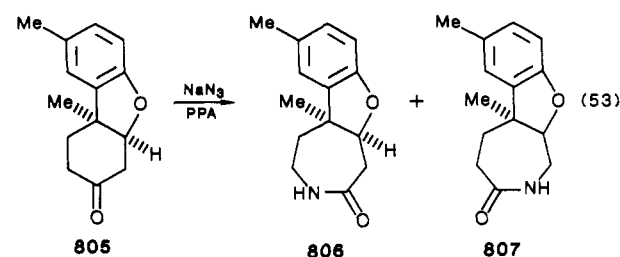
by Desbene and co-workers for dibenzo[*b,f*][1,4]-thiazepines and -oxazepines (cf. Scheme 91).⁶⁵⁷

Preference for aryl migration (over secondary alkyl) was observed in the reactions of ketones 802 with sulfuric acid/sodium azide at 64 °C to give cyclic amides 803 and 804 in 80–91% yield.⁶⁵⁸ The percentage of the

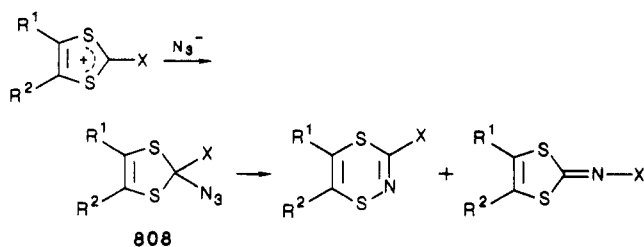


product mixture constituted by the "aryl migration" product 803 (75%, R = H) was increased by the presence of a nitro group at the 7-position in the ketone (80%, 803, R = NO_2) and decreased by a similarly positioned amino function (70%, 803, R = NH_2).

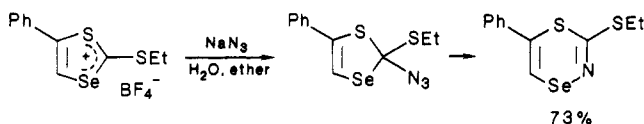
A mixture of products (viz., 806 and 807) also resulted from treatment of 805 with sodium azide in poly(phosphoric acid).⁶⁵⁹ 1,5- and 1,8-dichloroanthraquinones react with hydrazoic acid to give, in each case, both of the theoretically possible lactams.⁶⁶⁰ For the corresponding reactions with 1- and 2-chloroanthraquinones, two of the four theoretically possible lactams were identified.



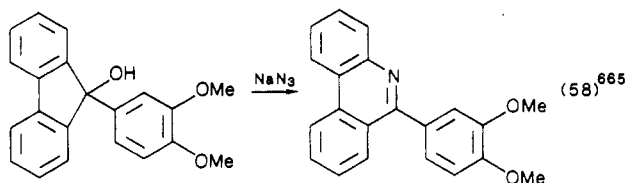
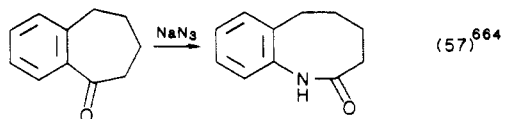
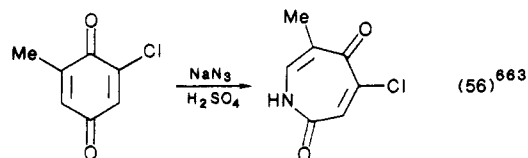
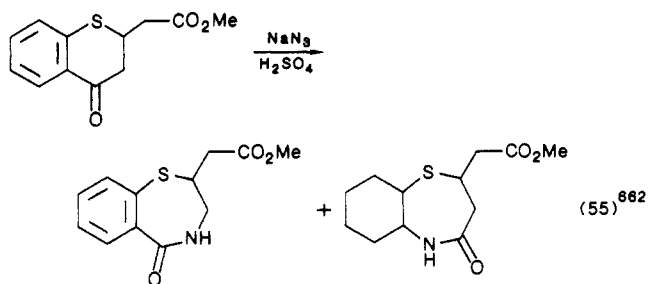
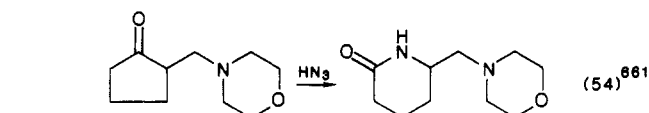
SCHEME 92



SCHEME 93



Some other recent applications of the Schmidt reaction in heterocyclic chemistry appear in (eq 54–58).

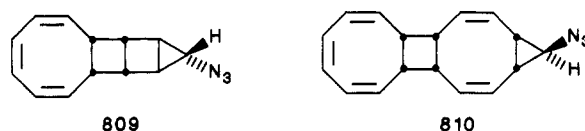


Treatment of 1,3-dithiolium salts ($\text{X} = \text{halogen}$) with azide ion gives thermally unstable 2-azido-1,3-dithioles (808),⁶⁶⁶ which rearrange with loss of nitrogen to give 1,4,2-dithiazines and N-substituted 2-imino-1,3-dithioles (Scheme 92). When $\text{X} = \text{SAr}$, the (thioimino)-1,3-dithioles are formed in good yields, e.g., 77% when R^1 , $\text{R}^2 = -(\text{CH}_2)_4-$, and $\text{X} = p$ -nitrophenylthio.⁶⁶⁷ ((Benzenesulfonyl)imino)dithiole may be produced similarly.⁶⁶⁸

The method described above has recently been extended to afford 1,4,3-thiaselenazines (Scheme 93).⁶⁶⁹

Nakayama and co-workers also have carried out the decomposition of dithioly azides⁶⁷⁰ and their benzo analogues.^{671,672} They found that certain 1,4,2-dithiazines extrude sulfur to give isothiazoles (Scheme 94).

Azides 809 and 810 have been ring expanded to aza-[14]annulenes⁶⁷³ and aza[18]annulenes⁶⁷⁴ by photolysis at low temperature.



Ring expansion of azido perfluorohydrocarbons is rare;⁶⁷⁵ however, 811 undergoes ring expansion readily on flow pyrolysis at 380 °C (Scheme 95).⁶⁷⁶

2. Via Ylide Intermediates

Trithiapentalene 812 reacts with ethyl azidoformate to give dithiazine 813. A mechanism that involves attack by a nitrene to give an ylide was proposed (Scheme 96).⁶⁷⁷

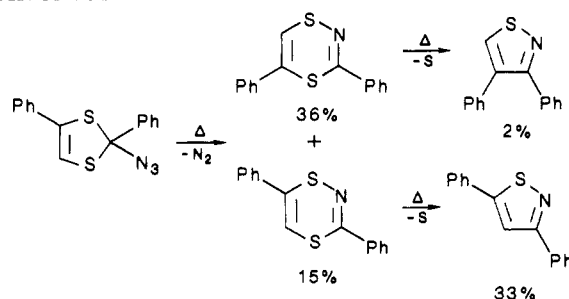
3. By Epoxide Ring Opening

Epoxide ring opening by azide ion plays an important part in the synthesis of the 1,3-diimino[14]annulene 814 (Scheme 97)⁶⁷⁸ (see section II.C.).

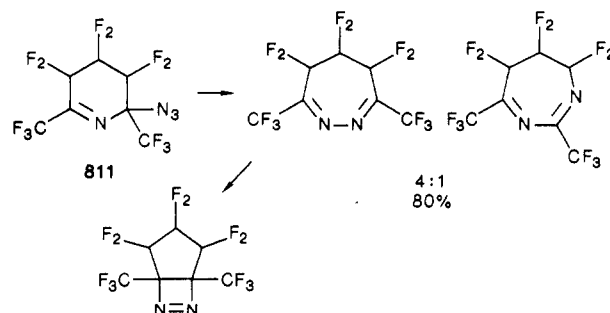
4. Washburne Procedure

Washburne found that certain cyclic anhydrides react with trimethylsilyl azide to give ring expansion via an isocyanate formed by Curtius rearrangement (Scheme 98).⁶⁷⁹

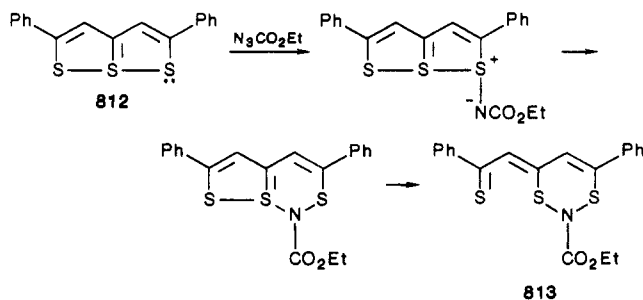
SCHEME 94

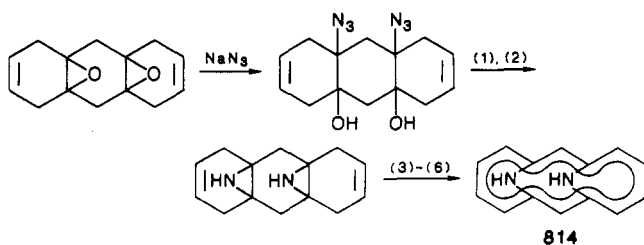


SCHEME 95



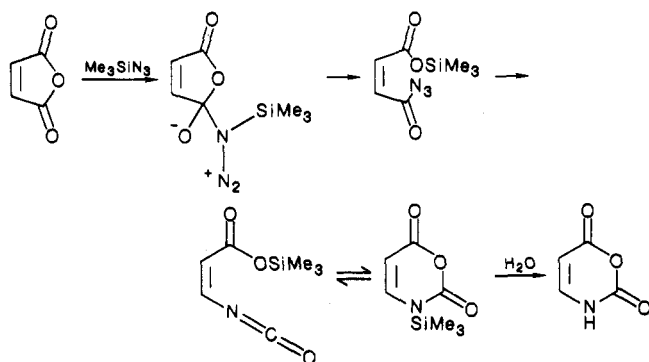
SCHEME 96



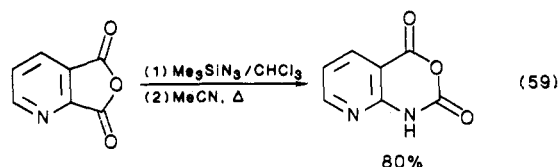
SCHEME 97^a

^a (1) oleum; (2) LAH; °C (3) SOCl₂, TEA, 0 °C; (4) Br₂, CH₂Cl₂, -78 °C, then DBN, THF, -10 °C; (5) DDQ, PhH, Δ; (6) HOAc, HCl.

SCHEME 98



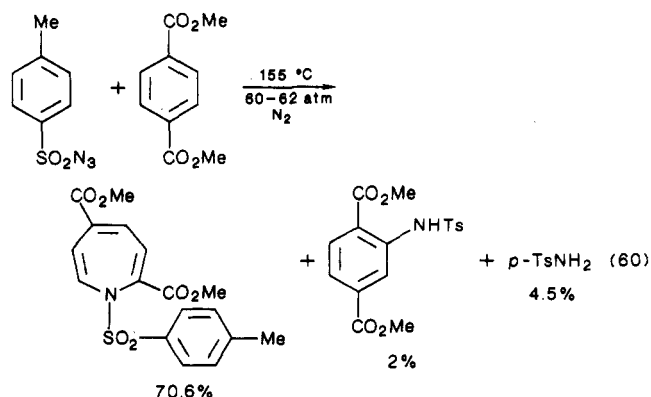
This procedure has recently been extended to permit the expansion of 2,3-pyridinedicarboxylic anhydride to provide a superior route to azaisatoic anhydride (eq 59).⁶⁸⁰



Treatment of isoimidium perchlorates with sodium azide gives acyl azides which undergo Curtius rearrangement and electrocyclic closure to novel 2*H*-1,3-oxazin-2-ones on heating (Scheme 99).⁶⁸¹

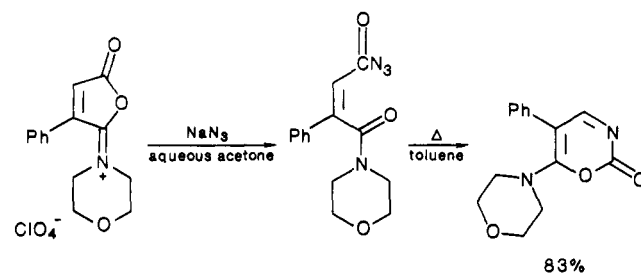
5. Nitrene Insertion into Aromatics

The reaction of sulfonyl azides with aromatics was first described by Curtius⁶⁸² and has been thoroughly investigated by Abramovitch.^{592,593,683,684} Recently, the optimum conditions for azepine formation were described (eq 60) and the operative mechanism under



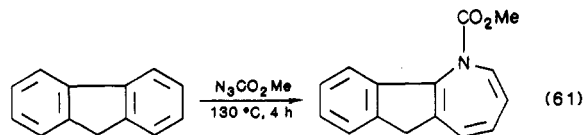
these conditions was discussed.⁶⁸⁵ Control of temperature (between 155 and 160 °C) is a crucial factor for

SCHEME 99

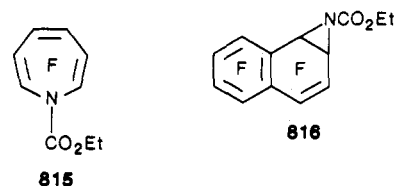


successful ring expansion. The generality of this reaction, however, is limited by the nature of the substituents in the aromatic substrate. Aryl sulfonamides are the main products when aromatic solvents bearing electron-donating groups are used.

Fluorene undergoes expansion to an indenoazepine when it is heated with methyl azidoformate (eq 61).⁶⁸⁶

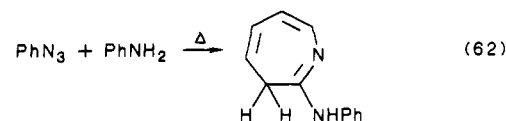


Hexafluorobenzene has been used as an inert solvent for the study of (ethoxycarbonyl)nitrene insertions into C-H bonds; however, thermolysis of ethyl azidoformate in excess hexafluorobenzene at 90 °C for 72 h gives azepine **815**. Ring expansion is also observed on photolysis.⁶⁸⁷ On the other hand, photolysis of ethyl azidoformate in PFN gives adduct **816**, which does not undergo subsequent ring expansion.



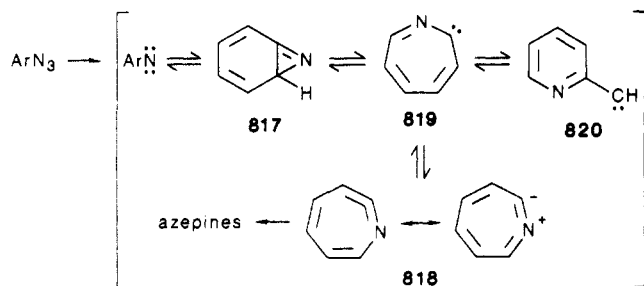
6. Decomposition of Azides in the Presence of Nucleophiles

Wolff⁶⁸⁸ was the first to describe the ring expansion of an aryl azide to an azepine on thermolysis in a nucleophilic solvent (eq 62).



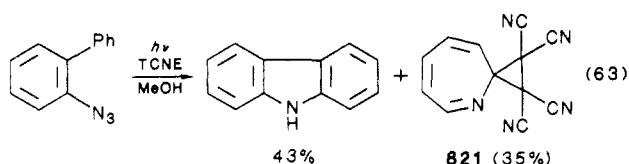
This reaction has been developed a great deal since 1912. Much of this work has been discussed in several detailed reviews.^{550,568,690,691} Therefore, only major points of recent developments will be discussed here.

The mechanism of this reaction has posed a fascinating puzzle over the years. Currently, the precise nature of the intermediate [(**817**, **818**) or other (**819**, **820**)] that undergoes nucleophilic attack is the subject of investigation by several research groups. The latest results indicate that on phenyl azide photolysis dihydroazepine (**818**) is the intermediate formed that undergoes reaction with nucleophiles to ultimately yield 3*H*-azepines. The nature of the products formed has been found to depend dramatically upon azide concentration and the power of the light source⁶⁹² as well as the temperature⁶⁹³ at which the photolysis is carried



out. Several substituted monocyclic aryl azides also have been studied by IR spectroscopy of low-temperature matrices. Series of five meta (F, Cl, CN, Me, MeO) and para (F, Cl, CN, Me, MeO) phenyl azides all yield dihydroazepines on irradiation regardless of the position or nature of the substituent.⁶⁹⁴

However, photolysis of 2,6-dimethylphenyl azide in the presence of CO in an N₂ matrix at 12 K gives the isocyanate by trapping of the nitrene as rearrangement to dihydroazepine is very inefficient. Pentafluorophenyl azide on irradiation in a matrix at 12 K gives no dihydroazepine formation; however, in the presence of CO, isocyanates are formed. Irradiation (at 254 nm) of *o*-azidobiphenyl and TCNE in acetonitrile gives two products, one of which (821) is consistent with the trapping of a 2-azacyclohepta-2,4,6-trienylidene intermediate (eq 63).⁶⁹⁵



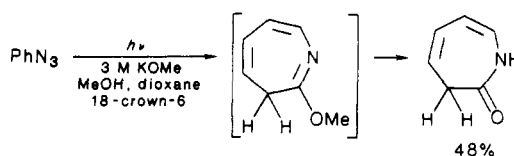
In none of the above work has evidence for involvement of a benzazirine intermediate been obtained. Evidence for azirine formation in the photolysis of bi- and polycyclic aryl azides, however, has been adduced.^{696,697}

Ring expansion of monocyclic aryl azides occurs, on thermolysis or photolysis in an excess of primary or secondary aliphatic amines as solvents, to give fair to good yields of azepines. However, azides that carry an ortho substituent suitable for participation in an assisted cyclization usually do not yield azepines. The cyclization reaction is preferred. Aromatic azides with *p*-methoxy, *o*-nitro, or *p*-nitro substituents usually do not give azepines in synthetically useful yields. However, it should be noted that a *m*-methoxy group has a yield-enhancing effect on azepine formation in the photolysis of *m*-anisyl azide in ethylamine solution.⁶⁹⁸

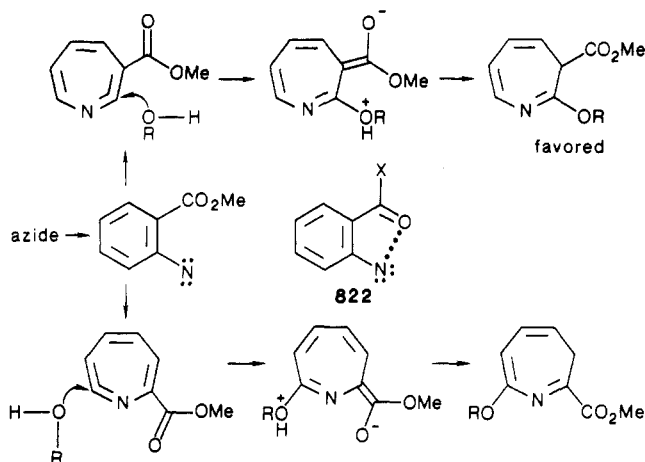
There is only one report of phenyl azide itself undergoing ring expansion on photolysis in methanol to give a methoxyazepine, but in only 10% yield.⁶⁹⁹ Photolysis of the same azide in the presence of methoxide affords 3*H*-azepin-2-one, presumably via the methoxyazepine (Scheme 100).⁷⁰⁰

However, aryl azides that have a carbonyl-containing ortho substituent undergo ring expansion to azepines in good yield on photolysis in methanol.^{701,702} More recently, azides bearing certain para and meta electron-withdrawing groups also have been found to yield azepines.^{234,703-705} These observations, plus the fact that aryl azides with *o*-CN and *o*-CF₃ groups form azepines, indicate that electronic effects of substituents rather than a special stabilization by an ortho carbonyl group

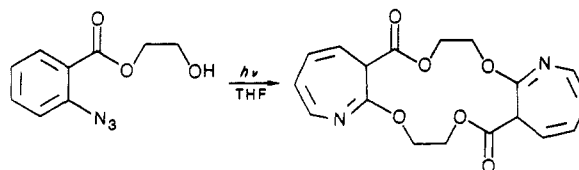
SCHEME 100



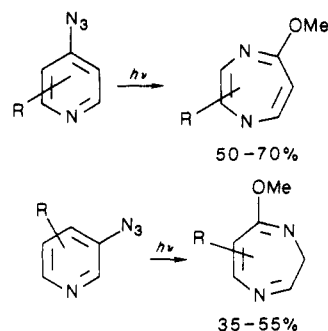
SCHEME 101



SCHEME 102



SCHEME 103



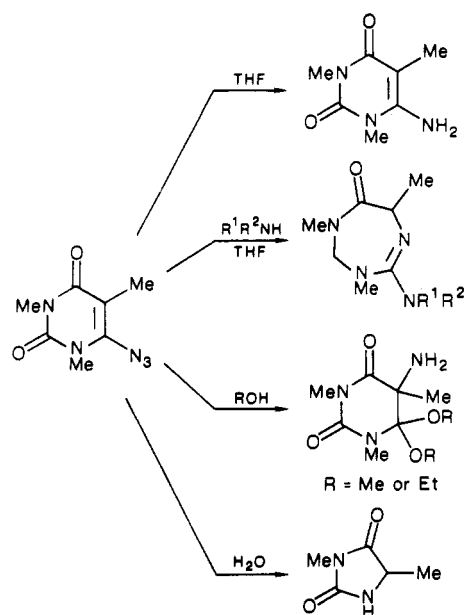
(e.g., 822) dictate the course of these reactions. A mechanism involving nucleophilic attack on a dihydroazepine rather than a benzazirine intermediate has been proposed (Scheme 101).²³⁴

This ring expansion, therefore, promises to have a more general synthetic application than previously thought.⁷⁰⁶ One such extension to the synthesis of a diazepino-14-crown-4 has been reported by Smalley and co-workers (Scheme 102).⁷⁰⁷

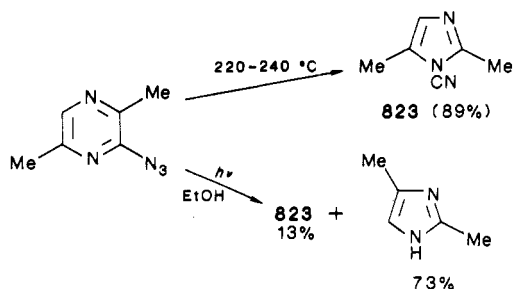
Photolysis of 3- and 4-azidopyridine and some of their methyl derivatives in the presence of methoxide ion yields 1,3- and 1,4-diazepines, respectively (Scheme 103).⁷⁰⁸ Ring expansion of 4-azidopyridines to 5-methoxy 6*H*-1,4-diazepines has been achieved also by thermolysis.⁷⁰⁹ The authors noted that heating conditions (200 °C for 8 min) are fairly critical.

Full details of the work of Hirota's group on the photolytic reactions of substituted azidouracils with nucleophiles have appeared.⁷¹⁰ Some of the wide div-

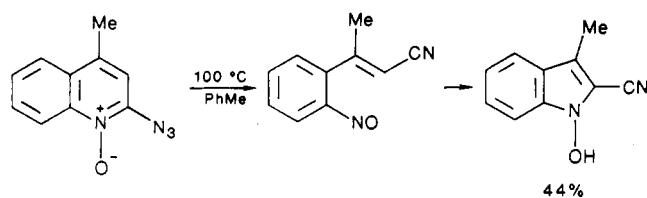
SCHEME 104



SCHEME 105



SCHEME 106



ersity of products is summarized (Scheme 104).

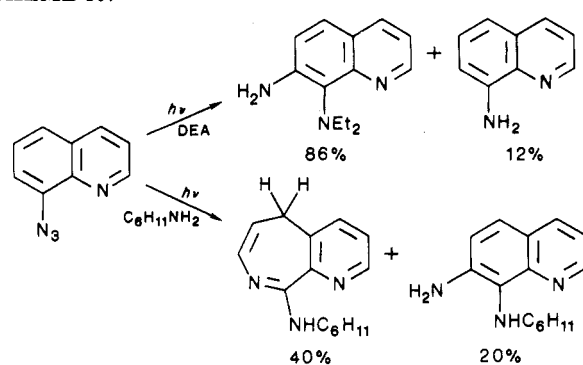
Azidopyrazines undergo ring contraction to imidazoles on pyrolysis or photolysis (Scheme 105).⁷¹¹

2-Azido-4-methylquinoline 1-oxide undergoes ring contraction on decomposition at 100 °C, probably via an *o*-nitrosocinnamitrile (Scheme 106).⁷¹² 3- and 4-pyridine 1-oxides give complex mixtures on thermal or photochemical decomposition in the presence of amines. No products of ring contraction were detected.⁷¹³

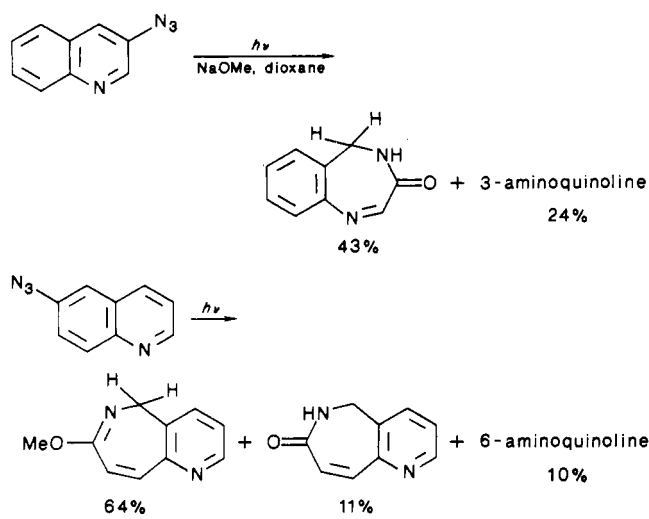
Photolysis of bicyclic aromatic and heterocyclic azides in the presence of amines as a general synthetic route to bicyclic azepines and diazepines is limited by competitive formation of *o*-diamines, which depends upon the position of the azide group and the nature of the amine (Scheme 107).^{714–716} The rearomatization reaction is discussed in section III.B.

Studies of the product distribution from the photolysis of several types of [6,6]-bicyclic aromatic azides in various amines have led to the following synthetically useful generalizations.⁷¹⁴ Reaction of primary amines with α -nitrenes (naphthalene nomenclature) tends to

SCHEME 107



SCHEME 108



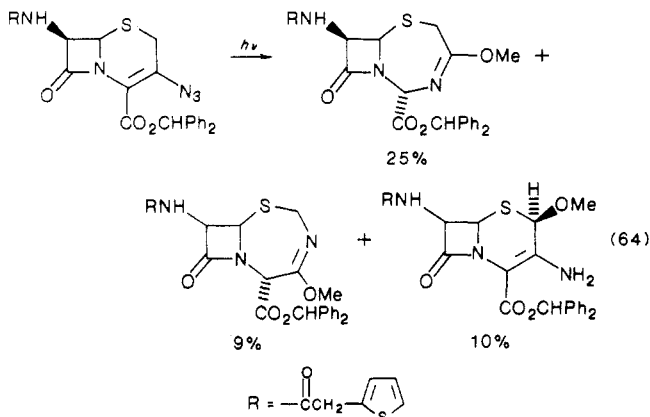
give mainly azepines, occasionally with minor amounts of *o*-diamines. Secondary amines usually afford the parent amine from the α -nitrene (triplet product), unless the starting azide bears a *m*-methoxy substituent, in which case ring expansion to azepines is observed.⁷¹⁵ With β -bicyclic nitrenes *o*-diamines have been obtained from both primary and secondary amines.

Formation of azepines by the photolysis of bicyclic azides in the presence of methoxide ions is a much more general reaction than that in amines.⁷¹⁶ Both α - and β -azides undergo ring expansion to give methoxyazepines or azepinones, and furthermore, the methoxy substituents may be replaced by nucleophiles (Scheme 108).⁷¹⁷

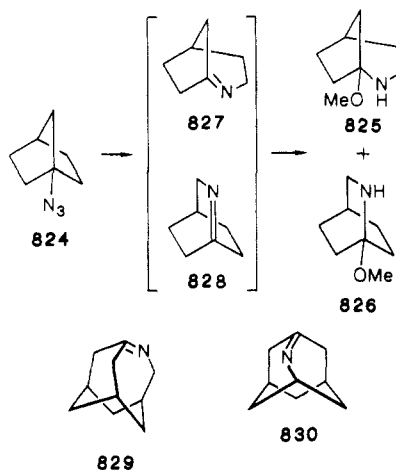
The presence of a methoxy group meta to the azide has an even greater enhancing effect on azepine yield⁷¹⁵ than in the monocyclic series.⁶⁹⁸ Mono- and bicyclic azides also have been decomposed in the presence of alkyl mercaptans to afford *o*-((aminoalkyl)thio) derivatives in modest yields.⁷¹⁸

C(3)-Azidocephams undergo ring expansion on photolysis (eq 64).⁷¹⁹

Some time ago Lwowski and Reed⁷²⁰ found that irradiation of 1-azidobicyclo[2.2.1]heptane (824) in methanol gave 825 and 826 by trapping of the anti-Bredt imines 827 and 828. More recently, the study of bridgehead imines has been given great impetus by the belief that the thermal and photochemical syn-anti and cis-trans isomerization of strained CN double bonds might be involved in vision.⁷²¹ The direct observation of matrix-isolated 4-azahomoadamant-3-ene (829) (formed on matrix photolysis of 1-azidoadamantane)



and 2-azaadamant-1-ene (**830**) (matrix photolysis of 3-azidonoradamantane) has been reported.⁷²²



VII. Azides as Reagents

The two most commonly used azides are sodium azide and hydrazoic acid (usually generated from sodium azide and an acid). This section serves to cross reference the three leading organic azide reagents in which the azide group is attached to a sulfur (principally *p*-toluenesulfonyl azide), phosphorus (diphenyl phosphorazidate (DPPA)), or silicon (trimethylsilyl azide (TMSA)).

A. *p*-Toluenesulfonyl Azide

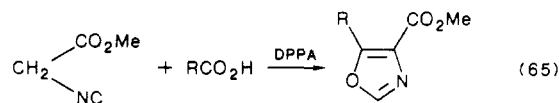
p-Toluenesulfonyl azide is probably the most versatile of the three reagents mentioned above and it participates in most azide reactions.⁷²³ These include amination (sections III.G and VI.C.5), diazo transfer (sections III.I and IV.A.1), azide transfer (sections II.J, VI.A.3, and VI.B.3.a), cycloaddition (section VI.B.1), cycloaddition–ring expansion (section IV.A.3), cycloaddition–ring contraction (section IV.A.2), and ring expansion (section VI.C.5). *p*-Tosyl azide is a shock-sensitive reagent,^{420,421} therefore modified reagents have been developed to avoid this disadvantage. Thus, a polymeric sulfonyl azide has been used for the diazo transfer process.⁴⁶² This approach holds considerable promise for the future.

B. Diphenyl Phosphorazidate

The diversity of reactivity exhibited by DPPA has made this a particularly attractive reagent and its utility has been reviewed.^{724,725}

Recently, it has been employed for the conversion of carboxylic acids to amines (see section III.D) or acyl azides (see section II.F) and enamines to amidines (see section III.H.1). Additionally, DPPA has been used for diazo transfer⁷²⁶ (see section III.I) and as a peptide coupling reagent for the synthesis of several cytotoxic cyclic peptides^{727–731} and a straight-chain peptide precursor to an indole alkaloid.⁷³¹

4-(Methoxycarbonyl)oxazoles can be formed in 57–95% yield by DPPA-mediated C-acylation of methyl isocyanoacetate with carboxylic acids (eq 65).⁷³³



C. Trimethylsilyl Azide

The use of TMSA as a reagent has been reviewed.^{734,735} In the present review, TMSA has been discussed as an azide source for the preparation of azides from halides (section II.A), alkenes (section II.G), epoxides (section II.C), and ketals (section II.D) among others and for cyclizations (section VI.A.6), cycloadditions (section VI.B), and the Washburne procedure (section VI.C.4).

VIII. Prospects

The increasing number of mild methods available for azide synthesis make azides more accessible than ever for synthetic work. One can expect to see techniques like PTC and ultrasonication (section II.A.1) more generally applied in azide synthesis. The scope of some of the newer reactions mentioned in this review will be extended and milder conditions will be found for them. The remarkable stability of the azide group, particularly under oxidative conditions, commends it as a protective group during multistage synthetic sequences (section V.B.).

Before azides are generally accepted as reagents for large-scale synthetic work, an improvement in their stability is required. This would seem to provide an ideal opportunity for the development of polymer-bound reagents. It would add increased safety to all the other advantages offered by such reagents.⁷³⁵ Indeed, polymer-bound tosyl azide has been used for diazo transfer.⁴⁶² Such a reagent also may well be suitable for aminations (section III.G.1) and azide transfer (section II.J.) reactions. In a different way, Hassner has used a polymeric quaternary ammonium azide⁴⁷ for alkyl azide synthesis, and polymeric phosphines have been employed in the Staudinger reaction.⁴⁰⁷

We expect to see an increasing use of azides under all the main headings in this review. If one were asked to select areas for particular attention, those of stereoselective synthesis, reductive cyclization, and metal-assisted azide decomposition applied especially to natural product synthesis would spring to mind.

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