Azides: Their Preparation and Synthetic Uses

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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 I. 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 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 subdi-
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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

\[ \text{nitrone products} \]

\[ \begin{array}{c}
\text{RN}_3 \xrightarrow{\text{Ar or heat}} \text{RN} - N, \\
\text{rearrangement followed by nucleophilic attack}
\end{array} \]

\[ \text{products} \]

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.

\[ \text{amino substitution} \]

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

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

\[ \text{products} \]

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

\[ \text{RLi} + \text{TsN}_3 \rightarrow \text{RN} - \text{N}=\text{N}=\text{N}-\text{TsLi}^+ \]

b. Diazot Transfer (Section III.I)

However

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

\[ \text{RN}_3 + \text{PR} = \text{PR} \rightarrow \text{RN}=\text{PR} \]

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)

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.
### TABLE 1. Azide Reviews

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An exhaustive review of this topic has just appeared.\(^{18}\)

\[
\begin{align*}
\text{ArSO}_3\text{N}_3 & \rightarrow \text{Z-CH-}Z' \\
\text{Z} & = \text{COR, NO}_2, \text{CN, SO}_2\text{R}, \text{etc.}
\end{align*}
\]

c. Amination (Section III.G)

\[
\begin{align*}
\text{ArLi + RN}_3 & \rightarrow \text{ArNH}_2 \\
\text{R} & = \text{vinyl, Ts, PhSCH}_2, (\text{PhO})_2\text{P(O)}, \text{TMSCH}_2
\end{align*}
\]

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-
an inert atmosphere, the azido adamantane analogue (2, X = Cl) was obtained from 2 (X = Cl or OH) with NaN3/57% sulfuric acid (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/CH2Cl2 at 90 °C, and the tertiary azides (4, X = Br; R = Me, t-Bu) resulted from azide ion displacement of the corresponding bromo compounds (4, X = Br; R = Me, t-Bu). In the latter, other dienes 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.

With alkali metal azides (mainly sodium azide) it is usually helpful to use a polar solvent (typically DMF or DMSO, although acetone or even ethanol 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. Additionally, the azidooxadiazole (4) could be prepared from the bromide 5 only by treatment with lithium azide in DMF or potassium azide.20 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. 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. The generality of this process has not been assayed 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 hexamethylyphosphoramide at 60 °C to give the azido compounds in good to excellent yield under homogeneous, neutral, nonaqueous conditions. Olah and co-workers 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, 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. The crude azides were reduced in situ by the Staudinger process (see section III.A.4). It was claimed 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 liquid–liquid cases. The rates of nucleophilic substitution by N3- (as the chloride or hydroxy group) with poly(1-halogeno-2,4-dinitrobenzenes) is subject to significant catalysis by micelles of cetyltrimethylammonium bromide. 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). 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. Thus, graft polymerization of acryloyl onium salts (A–C=CH2X) 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 claimed 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. The reaction rate is affected by azide ion concentration and the length and hydrophobicity of the onium salt side chain. Hassner has shown that essentially quantitative azidation of activated and nonactivated alkyl halides can be achieved at room temperature with a polymeric
quaternary ammonium azide.

A useful addition for activated primary halides is ultrasound-promoted azidation in aqueous solution. 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. The trimethylsilyl analogue 11 (R = Me3SiCH2CH2CH2) has been similarly prepared. 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. 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. Eliminative azidation has also been observed 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. Propargylic diazides 19 and 20 are similarly obtained. The latter are extremely explosive and must be stored at low temperature; they survive several weeks at -25 °C. The results of a recent study concerning 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 COPh) destabilize the diazide.

2. With Rearrangement

In an attempt to prepare the elusive azidophenylethylene (23), chlorophenylethylene (22) was allowed to react with sodium azide in DMSO for 3 days at 25 °C. Not unexpectedly, 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 halogenoarylethynes.

The ω,ω-dibromocacetophenone derivatives 27 (X = Br) react with 2 equiv of sodium azide to form the aroyl azides 28. The process is apparently not merely displacement of dibromomethane anion but is rationalized as involving rearrangement of the initially formed azide 27 (X = N3) and subsequent extrusion of HCN and N2.

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-buta diene (33). 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. Diazide 33 could also be prepared directly from 29 (1 equiv) by heating (60 °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

\[
\begin{array}{c}
\text{BrCH}_2\text{C}==\text{CBr} \\
\xrightarrow{\text{N}_3^-} \\
\text{N}_3\text{CCH}_2\text{C}==\text{CCH}_2\text{N}_3 \\
\end{array}
\]

(30–32) to 33 could be isolated, the likelihood of their existence was strengthened by the isolation of 2-azido-1,3-butadiene (36) from the reaction of 4-bromo-1,2-butadiene (34) with sodium azide in aqueous methanol for 5 days (Scheme 4). Compound 36 could be more conveniently prepared from 34 and tetramethylguanidinium azide in sulfolane (1.5 h, 55–60 °C). Postulated intermediate, viz., 35, 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. 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). Hydrazonoyl azides (48) and the unstable 1-azido-2-aza-1,3-butadiene derivatives (49) have been prepared in standard fashion by the action of sodium azide on the corresponding chlorides.

SCHEME 4

\[
\begin{array}{c}
\text{CH}_2==\text{CCH}_2\text{X} \\
\xrightarrow{\text{N}_3^-} \\
\text{N}_3\text{CH}_2\text{C}==\text{CCH}_2\text{N}_3 \\
\end{array}
\]

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

Eliminative azidation to form tosyl azide and iso-3. By Displacement at Unsaturated Sites

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

\[
\begin{array}{c}
\text{Me}_2\text{CHC}==\text{N}^-\text{Ts} \xrightarrow{\text{LiN}_3} \text{TsN}_3 + \text{Me}_2\text{CHCN}
\end{array}
\]

\[
\begin{array}{c}
\text{Me}_2\text{C}==\text{C}^-\text{NTs} \xrightarrow{\text{HN}_3} \text{TsN}_3 + \text{Me}_2\text{CHCN}
\end{array}
\]

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

Azidoquinones 55, 56, and 57 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.
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Bis(diisopropylamino)phosphinyl azide is derived from the chloride in the same manner.93

Similarly, aryl-,94 alkyl-,96 and heteroalkylazidoboranes95 (R3BN3) and diazidoboranes96 have been prepared. Dibutylin and dibenzyltin chlorides react with sodium azide to give the dialkytin 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 arylbromodializarines 74 with tetra-butylationmmonium 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 = NH,; 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 = NH) resulted from azide treatment of 78 in MeOH/H2O.105 Interestingly, in DMF/H2O, elimination to form 79 (X = H) occurred.

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,92,93 diphenyl phosphorazidate,94 and trimethylisilyl 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.96

The gem-diazido-87 and triazidosilanes88 Me3Si(N3)2 and PhSi(N3)2 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

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.66

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), 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

42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110
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%). The azide 81 was formed at lower temperature and was shown to be a precursor of 83.

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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, 85, 86 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). Similarly, triazide 89 is obtained by using Na₂N₃/But₄NCI in HMPA. 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 analogues). The 6-azidohexa-2,4-dienoates 90 were also prepared from the corresponding mesylates.

The SN₂ nature of the substitution (i.e., inversion of configuration) is apparent from a number of examples: inter alia, 91 → 92, 93 → 94, 95 → 96, 97 → 98, 99 → 100. Displacement can be extended to activated aromatic systems; thus, oxadiazole 99 (X = N₃) results from treatment of 99 (X = SO₂Me) with NaN₃ in EtOH.

A similar attempt with 100 gave a tetrazole derivative (see section VI.B.4) presumably derived from the initially formed azido compound. 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). 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 adamantane-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 adamantane-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 adamantane-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. Similarly, high yields (95% and 87%, respectively) of the azido sugar 103 and lactone 104 were obtained with sodium azide in DMF at 100 °C and reflux, 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). 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-bromo-benzenesulfonate (brosyl) groups by azide ion. In part, this may be due to the known incidence of competitive $S_N2$ 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.125 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(Ph₃P)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 123.130

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 poly cyclic 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.132 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. An intermediate epoxide is probably involved in the regio- and stereospecific conversion of 136 to 137. Interestingly, the oxirane 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 h (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. 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-

Similar regioselectivity was observed with other 2,3-epoxy alcohols using TMSA and a stoichiometric quantity of Ti(O-i-Pr)₄. TMSA and a catalytic quantity of Ti(O-i-Pr)₄ and TMSA and ZnCl₂. 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. More recently, a 13-compound study of the regioselectivity of ring opening with ammonium azide in analogues of 140 has been reported.

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

The boron trifluoride diethyl etherate catalyzed reaction of 1,2-epoxysilanes (R = H, 1-hydroxy-1-cyclohexyl; R' = Me, Et) with TMSA followed by brief treatment with a trace amount of HCl in methanol afforded (1-azido-2-hydroxyalkyl)silanes in 74-86% yield. Direct conversion of 143 (R = alkyl, R' = 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 treatment with HN₃ in DMF. The hydrazoic acid was generated in situ from TMSA and methanol in DMF. 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.

Under Payne rearrangement conditions epoxy alcohol 147 reacts with excess sodium azide to give azido diol 148 in 52% yield. 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 Ketal}s

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
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With 2 equiv of trimethylsilyl azide, diphenyl ketal 151 (R1 = R2 = Ph) is converted to a tetrazole, presumably via diazide (153) intermediacy. Similar results were obtained with the cy-hydroxy analogues 151 (R1 = CH2OH; R2 = 4-MeOC6H4, 4-MeC6H4; R3 = Me). The necessity for activating substituents is manifest since 151 (R1 = CH2OH; R2 = Ph, 4-ClC6H4; R3 = Me) gave monoazido silyl ether 152 (R1 = CH2OSiMe3). 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. Other Lewis acids can be utilized and recently it was shown that HN3/TiCl4 smoothly converts benzylic, allylic, or tertiary alcohols to the corresponding azides in good yield. Primary alcohols are unaffected and stereochemistry is not maintained, indicative of a carbocation intermediate.

The modified Mitsunobu reaction (156) (Ph3P, DEAD, HN3, 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.

In some cases apparent rearrangement occurs; e.g., the secondary alcohol 6α-hydroxyprogynene (159) reacts with BF3/HN3 to give the 5-azido analogue 161, presumably via HN3 addition to a Δ4-pregnene (160) intermediate. 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.

F. From Carboxylic Acids

The preparation of acyl azides from acyl halides has been previously described (see section ILA). Similar two-step procedures (from the carboxylic acid) have been developed by using the reaction of a mixed anhydride with sodium azide. 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. More recently, N,N-dimethyl(chlorosulfonyl)methaniminium chloride (Me2N−N=CHOS(O)Cl−; from thionyl chloride and DMF) was used as an activating reagent for the reaction of carboxylic acids with NaN3. 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. 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, Hassner has shown that enol and silyl enol ethers react to give azido ethers in good yield. A similar process occurs with trifluoroacetic acid catalysis. Interestingly, TiCl4-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 TiCl₄); mono- or 1,2-dialkyl olefins do not react. These data, in conjunction with the regiospecificity of the addition, are suggestive of a carboxylation intermediate. This premise is further supported by the isolation of a mixture of 5α- and 5β-azidocholesterol from 5-cholesterol. Previously, hydrazolic acid had been shown to add readily only in the case of cyclopropene or in Michael additions to unsaturated carbonyl compounds. A recent example of the latter has been reported. Attempts to add HN₃ to diarylethane in the presence of sulfuric acid led to considerable decomposition due to Schmidt rearrangement (see section III.E).

Pregnenolone acetate (162) reacts with chromyl azide (formed in situ from chromium trioxide and sodium azide) 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. 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. The mechanism was presumed to involve an initial conjugate nucleophilic attack by azide ion and subsequent electrophilic azide addition. Viscinal diazides have also been prepared from alkenes by using Fe(III) and Pb(IV) reagents. The latter converted 1,5-dienes to 1,4-diazides. Recently, modifications of this approach have been reported. Thus, 1,2-diazaides were the major products from treatment of alkenes with NaN₃/Mn(III)(OAc)₃; Mn(III)N₃ species are presumably formed in situ. The mechanism apparently involves ligand transfer to generate a β-azidoalkyl radical which subsequently reacts with a second Mn(III)N₃ species. Similarly, vicinal diazides were formed in 34–85% yield under mild conditions by reaction of the corresponding alkene with PhIO and sodium azide.

The lead tetraacetate/trimethylsilyl azide system has been previously utilized for the introduction of "positive" azide to a large variety of olefins and acetylenes, with isolated trisubstituted steroidal olefins, allylic azides or seco keto nitriles are formed, depending upon temperature. In contrast, isolated disubstituted olefins provide α-azido ketones. 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.

Interestingly, reaction of mesityl oxide with trimethylsilyl azide and ethylene glycol in the presence of SiCl₄ (1%) leads to the azido ketal.

Nucleophilic attack by azide ion or congenic species on nonconjugated alkenes can be facilitated by dimethyl(methylthio)sulfonium tetrafluoroborate. 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. It has been stated that iodine azide usually adds to olefins via a three-membered iodonium ion intermediate whereas bromine azide can add either in an ionic or a free radical fashion, the latter being favored by nonpolar solvents.

Tamura and coworkers have examined the reactions of iodine azide with indoles and benzo[b]furan. Extension to benzo[b]thiophene 1,1-dioxide gave intriguing results. Treatment of 171 with I₂ provided the 3-azido species 172 whereas with Br₂ the 2-azido product 173 was obtained. The formation of 172 presumably involves azide attack on an iodonium intermediate; a similar mechanism has been proposed for open-chain vinyl sulfones.

In contrast, it was suggested that the reaction with bromine azide involves attack of N₃⁻ radical on the double bond and subsequent Br⁻ attack at the benzyllic position. A mixture of azide-containing products was obtained from benzo[b]thiophene and iodine azide but their unstable nature precluded their characterization.

The α,α-dichloro azide (R₁ = R₂ = Ph, R₃ = Cl, R₄ = H) had been prepared by addition of chlorine...
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SCHEME 7

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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. 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 azide structure and the reaction temperature, substantial amounts of the [3,3]-rearrangement product (188) can also be formed.

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.

The reaction of α,β-unsaturated esters and ketones with iodine azide was examined by Hassner and co-workers. 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 shown 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

The addition of iodine azide to 3-methylene-5α-androstane (183) in the presence of oxygen is regioselective but not stereoselective; iodomethyl-containing products 184 and 185 are formed. 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/IN₃. Under a nitrogen atmosphere, products containing an azido-
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 7a-azido-3-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.

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 7a-azido-3-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 SN1 mechanism.205 The preparation of azide polymers by reaction of poly(vinyl nitrate) with sodium or lithium azide has been examined.206

I. From Amines or Hydrazines

Nitrosation of hydrazines is a standard route to azides207 and in this regard, nitrous acid,207,208 nitrosyl chloride,209 and organic nitriles210 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), cyclopropylacyl azides (204),212 long-chain alkoxyacetyl 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.
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.

![Scheme 11](https://example.com/scheme11.png)

**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. A similar process was used to yield the azido β-lactam 231 (69% from 230, LDA as base). Metal-halogen exchange followed by treatment with tosyl azide and subsequent low-temperature fragmentation of the resultant triazenylibromides with sodium pyrophosphate gave the bithienyl azides 232-237 from the corresponding bromo compounds. 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). 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 azide using Quast and Eckert’s procedure.

**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).

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. Treatment of 3-amino-1,2,3-benzotriazin-4(3H)-one (245) with sodium azide in acetic acid gave an excellent yield of the hitherto unknown o-azidobenzohydrazide (246).

**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 to give the corresponding di- and mononitrates 249 and 250, respectively. 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 esters 251 and 252, respectively. Additionally, triester 253 was obtained from 248 and 1,3,5-benzenetricarboxylic acid. 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.

4-Azidophenyl methacrylate (261) was prepared in an analogous fashion by treatment of 4-midophenol (260) with methacrylic acid chloride. Copolymerization of 261 with styrene and (tert-butoxy carbonyl)-amino)ethyl methacrylate was examined. Acetylation can also be performed in the presence of the azido group; acetates 264237 and 265238 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. Acid-catalyzed reaction of 263 with ethanethiol gave the dithioether 267 in 50% yield. Displacement from alkyl halides can also occur. Thus, azido alcohol 254 reacts with \([\text{FC(NO}_2]_2\text{CH}_2\text{NCH}_2\text{Br}\) to give the corresponding ether, and a carbamate results from treatment of \(\text{HOCH(\text{CH}_2\text{N}_3)}_2\) with \((\text{NO}_2]_2\text{CH}_2\text{CH}_2\text{NO})_{19}\).

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/\(\text{Et}_3\text{N}\); a separable 7:1 mixture of 270 and 271, respectively, resulted. An acetonide (273) was obtained by protection of diol 272 with DMP and a catalytic amount of p-toluene-sulfonic acid. Dehydration of the diol 274 with POCl₃/pyridine occurred to form the less substituted double bond (as in 275); none of 276 was observed. Only resinous material resulted when the same transformation was attempted with the amino diol 277; the utility of the azido group as a masked amine (see section III.A) is thus manifest.

In a reaction not directly involving the OH group, azidonaphthols (cf. 278 and 279) couple with aryl diazonium chlorides to provide the corresponding azo products 280 and 281, respectively.
Azides: Their Preparation and Synthetic Uses

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).

The method has been recently utilized for the preparation of azido acrylate precursors to indoles, isoquinolines, thiophenopyrroles, and azaannulenes and related heterocycles (see section VI). The interesting diazido furan 282 and thiophene 283 derivatives (precursors to furo- and thiophenopyrazidines and (from 283 only) an isothiazole) have been prepared similarly.

In general, product stereochemistry about the double bond is not known but is assumed to be Z. Various other bases (inter alia, Na₂CO₃, KOH, or NaOH under phase-transfer conditions) gave unsatisfactory results, as did an attempt at acid-catalyzed condensation using TiCl₄. Extension to azidoacetonitrile and azidonitrile was also unsuccessful. Condensation of ethyl azidoacetate with formylchromanones (cf. 284) did not occur; the hemiacetals 285 were instead obtained. Protection of the keto group as the dioxolane 286 permitted efficient condensation.

However, yields for the condensation are generally good and it has been reported 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 azidocyclop propane 289. A modification of the procedure using the (trimethylsilyl)ethyl ester 288 and DBU/DMF provided 290. The latter could be converted to the parent carboxylic acid 291 by deprotection with tetrabutylammonium fluoride. Base-catalyzed hydrolysis of analogues of 289 to the corresponding carboxylic acids under mild conditions has also been reported. Deprotection of the tert-butyldimethylsilyl ether 292 to the corresponding alcohol 293 has been accomplished by using 5% HF.

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

Nucleophilic attack at the ester function has been reported. 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, and fluoro azide 302 was converted to amide 303 in 84% yield by treatment with ammonia. 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. The Boc group in the latter could be removed subsequently with HCl. Diamide 308 was similarly prepared from 306 and 307.

2-Azidobenzoyl chloride (309, R = Cl) combines with hydrazine 310 to provide benzylidene derivative 311, which can also be prepared from 2-azidobenzoxy hydrazide (309, R = NH₂H). Attempts to synthesize the latter by treatment of methyl o-azidobenzoate (309, R = OMe) with hydrazine hydrate or hydrolysis of 311 were unsuccessful.
(Azidodinitrophenyl)glycine derivative 292 results from the reaction of the corresponding β-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.312 Reaction of the analogous acid fluoride 313 with methanol gave the corresponding ester.249

\[
\begin{align*}
\text{OCF}_2\text{CF}_2\text{CF}_3 & \quad \text{OCF}_2\text{CF}_2\text{CF}_3 \\
\text{N}_2\text{C} &= \text{CFCF}_2\text{OCF(CF}_2\text{)COF} \\
\text{NaCF}_2\text{CFCOF} &
\end{align*}
\]

312 313

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 trifluorooacetic anhydride added to the imine 314 in the presence of triethylamine to provide the azetidin-2-one 315.253 An analogous 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 azetidinones, usually with a high degree of cis stereoselectivity.255,256 Dearylation of 316 to 317 with ceric ammonium nitrate (CAN) occurred in 69% yield under mild conditions.257 The yield of 317 was substantially better than that from potassium persulfate mediated debenzylation of 318 (<25%).258 The dearylation of azidoazetidinones (cf. 319) with CAN (after treatment of 319 with HCl, MeOH, and CH(OMe)3) had been previously reported259 and the intermediacy of a phenol (cf. 320) has been suggested.258 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.255 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 α-keto esters 326 and/or 317 depending on how much oxidant was utilized.258 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 azidoazetidinones bearing a ((methoxycarbonyl)diethyolphosphono)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 DME and esterification of 334 with ethanol/HCl to give 335.242

\[
\begin{align*}
\text{CO} & \quad \text{CO} \\
\text{N}_3\text{OCH}_2\text{COCCF}_3 & \quad \text{N}_3\text{OCH}_2\text{COCCF}_3 \\
\text{Diene} & \quad \text{Diene} \\
\text{333} & \quad \text{333} \\
\text{334} & \quad \text{334} \\
\text{335} & \quad \text{335}
\end{align*}
\]

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

point was different from that obtained by Boulton,269
and repetition of the procedure apparently did not
provide any azide-containing material.265 It is thus
reasonable to conclude that the current synthesis has
afforded authentic material.267

In a reaction analogous to that performed with azido
esters (see section II.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

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 IH NMR 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).267

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

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 per-
iodate and selenoxide elimination (6 h at room tem-
perature) 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 rea-
sonable 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 PbO2 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%,
and the Beckmann fragmentation products 366 and 367 (45% and 47%, respectively). \[ \text{318 Chemical Reviews, 1988, Vol. 88, No. 2} \] Scriven and Turnbull respectively) and the Beckmann fragmentation products 366 and 367 (45% and 47%, respectively). \[ \text{368, R} = \text{OPNB; X} = \text{N}_3 \]

\[ \text{369, R} = \text{Cl; X} = \text{N}_3 \]

\[ \text{370, R} = \text{SPh; X} = \text{N}_3 \]

\[ \text{371, R} = \text{Cl; X} = \text{N}_3 \]

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. \[ \text{266, R} = \text{OPNB; X} = \text{N}_3 \]

\[ \text{368, R} = \text{Cl; X} = \text{N}_3 \]

\[ \text{369, R} = \text{SPh; X} = \text{N}_3 \]

\[ \text{370, R} = \text{SPh; X} = \text{Cl} \]

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-butoxide at 80 °C and 0.1 Torr gave vinyl azide 372, which was transformed to δ-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.

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.

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)COOMe at 35 °C. A similar reaction occurred with 4-hydroxyacetophenone.

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).

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. Many similar processes have been described.
The synthesis of the potential bisintercalating photoaffinity-labeling reagent 393 was achieved in three steps from the thiourea (Scheme 16). 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.

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

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

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 399d → 399d; 48%). Thermolysis of 399a–d in carbon tetrachloride at 80 °C gave moderate to good yields of 1-azidocyclopropanecarboxylate derivatives 400a–d. The latter could be hydrolyzed to carboxylic acids (see section II.L.2a) and subsequently hydrogenated to 1-aminocyclopropanecarboxylic acids (see section III.A).

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

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% deuteriation had occurred. After three repetitions, the degree of deuteriation increased to over 99%.

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).
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functional cross-linking reagents. Formylation of 6-azido-1,3-dimethyluracil provided 5-formyl derivative 407, a useful precursor to fused pyrimidines. 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. 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.

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 characterized adduct 414) with phenyl azide. 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.

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.

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

Attempted azide substitution of the propargyl sulfo- nates 421 gave azido triazoles 422 in low yield (4–24%) rather than the anticipated allenyl azides.

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

The quadricyclanone 425 was converted to the azido silyl ether 426 by treatment with sodium azide and trimethylsilyl chloride. 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. 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.

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

\[ \text{ArCH}_2\text{CH}_2\text{SO}_2\text{N}_3 \xrightarrow{\Delta} \text{ArCH}_2\text{CH}_2\text{N}_3 + \text{SO}_2 \]

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 oxazinium\(^{288}\) and chromylium\(^ {289}\) species and their subsequent conversions to \(\beta\)-tetrazolo-trans-benzal acetophenones and benz[\(\epsilon\)]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,\(^ {292-294}\) Pb\(_3\)P,\(^ {295}\) Na\(_2\)S/NEt\(_3\),\(^ {296}\) diborane,\(^ {297}\) Na\(_2\)S/NEt\(_3\),\(^ {298}\) NaBH\(_4\),\(^ {299}\) Ti(II),\(^ {300}\) Mo(III),\(^ {301}\) Bu\(_3\)SnH,\(^ {302}\) Zn/HCl,\(^ {303}\) 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, \(\beta\)-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 Na/ NH\(_2\)/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-\(\text{H}\)\(_2\)]glycine (435) (in overall 60\% yield) was effected by initial treatment with 5 N H\(_2\)SO\(_4\)/AcOH to give 433 followed by room-temperature permanganate oxidation (to give 434) and catalytic reduction (10\% Pd/C/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 occurred (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\(_2\)O (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 167 and 158 to the amino...
<table>
<thead>
<tr>
<th>entry</th>
<th>RN₃</th>
<th>reductant</th>
<th>conditions*</th>
<th>% yield</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>348, R = H</td>
<td>H₂/PtO₂</td>
<td>AcOH</td>
<td>97.8 exo (from presumed exo azide)</td>
<td>267</td>
</tr>
<tr>
<td>2</td>
<td>108</td>
<td>H₂/PtO₂</td>
<td>toluene</td>
<td>97.4 endo (from presumed endo azide)</td>
<td>123</td>
</tr>
<tr>
<td>3</td>
<td>NaO₂CCH(N₃)CH₂CH₂N(Me)Ad</td>
<td>H₂/PtO₂</td>
<td>EtOH/MeOH, rt, 600 kPa, 3 days</td>
<td>83</td>
<td>304</td>
</tr>
<tr>
<td></td>
<td>(Ad = adamantyl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>H₂/Lindlar</td>
<td>EtOH, rt, 2 h</td>
<td>95-97</td>
<td>270</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>H₂/Lindlar</td>
<td>MeOH, 4 h</td>
<td>quantitative</td>
<td>307</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>H₂/Pd black</td>
<td>EtOH</td>
<td>&gt;80</td>
<td>175</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>H₂/Pd/C</td>
<td>EtOH</td>
<td>&gt;60 (2 steps)</td>
<td>119</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>H₂/Pd/C</td>
<td>EtOH, 1.5 h, rt</td>
<td>46-65</td>
<td>112</td>
</tr>
<tr>
<td>9</td>
<td>103</td>
<td>H₂/Pd/C</td>
<td>AcOH</td>
<td>&gt;60 (2 steps)</td>
<td>119</td>
</tr>
<tr>
<td>10</td>
<td>385</td>
<td>H₂/Pd/C</td>
<td>MeOH, 1 h, 20 °C</td>
<td>90</td>
<td>273</td>
</tr>
<tr>
<td>11</td>
<td>378</td>
<td>H₂/Pd/C</td>
<td>10% KOH, 0 °C</td>
<td>nearly quantitative</td>
<td>49</td>
</tr>
<tr>
<td>12</td>
<td>alkyl azide (alkyl = hexyl, HOCH₂C(Me)(Pr)CH₂CH₂, 2-octyl, H(C₆H₄)₆, PhCH₂(C₆H₅)₆)</td>
<td>H₂/Pd/C</td>
<td>MeOH, rt, 10-15 h</td>
<td>88-94</td>
<td>308</td>
</tr>
<tr>
<td>13</td>
<td>same as above</td>
<td>HCO₂NH₄/Pd/C</td>
<td>MeOH</td>
<td>74-93 (lower yields than entry 12, but avoids use of H₂ gas)</td>
<td>308</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>hydrazine hydrate/ RaneNi</td>
<td>EtOH, 5 min, reflux</td>
<td>32-68 (as acetamido derivative)</td>
<td>130</td>
</tr>
<tr>
<td>15</td>
<td>157, 158, R = n-C₆H₁₂</td>
<td>LAH</td>
<td>quantitative</td>
<td>157</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>98</td>
<td>LAH</td>
<td>quantitative</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>121 + 122</td>
<td>LAH</td>
<td>quantitative</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>LAH</td>
<td>ether, 0 °C</td>
<td>76 (after N-Boc protection)</td>
<td>311</td>
</tr>
<tr>
<td>19</td>
<td>94, R = (R)- or (S)-N₃</td>
<td>LAH</td>
<td>quantitative</td>
<td>113</td>
<td></td>
</tr>
</tbody>
</table>
AzMes: Their Preparation and Synthetic Uses

Chemical Reviews, 1988, Vol. 88, No. 2

3, exo or endo

LAH

ether, 30–55 °C, 4.5 h
(endo → endo amine
only; exo → 4:1
exo:endo amine)

LAH

THF, 60 °C, overnight

H₂O, toluene, PTC 1–6 h,
rt, Ar or ArSO₂ 16 h,
80 °C, alkyl (can be
used as a one-pot halide
to amine conversion)

alkyl, aryl, arylsulfonyl

NaBH₄

rt, 36 h
～30 (as N-acetyl)

1. Ph₃P
2. pyridine, aq NH₃
1. CH₂Cl₂, 0 °C to rt,
4 h
2. MeOH, 40 h, 0–5 °C
60 °C, MeOH
50
rt, 36 h

1. Ph₃P
2. NH₃

96 (more consistent yields
than with H₂/Pd/C)

1. Ph₃P
2. NaOH

96 (more consistent yields
than with H₂/Pd/C)

Cohen, H. L.
J. Polym. Sci.,
1985, 23, 1671

440 + 441, X = N₃

1. Ph₃P
2. H₂O/HCl

pentane, 20 h, rt
2. 1 h, rt

80–85
62–96 (thioether, alkene,
ester, nitro, epoxide, ketal, alkyne all
unaffected)

1. Ph₃P
2. CF₃CO₂H, MeOH
1. (EtO)₂P
2. HCl

rt

0–80 (low yields with
steric hindrance)
[alkyne, alkene, ester
unaffected]

H₂S/NBu₃

CH₂Cl₂, 0 °C, 1.5 h

H₂S/NBu₃

CH₂Cl₂, 0 °C

58.5 (isolated as the
phenoxyacetamido
derivative)

50

56

Na₂SO₄

90–100 °C, 7 h

33

448

Na₂SO₄

60 (as Boc derivative
451) [benzyloxy ether
also cleaved]

36

Na/NH₃

82 (ester in 454 converted
to amide)

322

55

Na₂SO₄

74

273

Na/NH₃

318

37

452–454

Me₅NH, Et₃N, or
MeNH₂

25% aqueous solution,
40–50 °C, 3–5 h

82 (ester in 454 converted
to amide)

322

2-nitro-3-azidopyridine

MeOH, ROH, NaOAc,
KCN, or
NaSC₆H₄Me-4

proton donor
solvents, rt

～25

98

125

275

253c, 315

259

262

239

320

74
<table>
<thead>
<tr>
<th>entry</th>
<th>RN₂</th>
<th>reductant</th>
<th>conditions</th>
<th>% yield</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>aryl, n-hexyl or benzoyl</td>
<td>KHF₄(CO)₄</td>
<td>CO, EtOH, rt, 12 h (benzyl azide → ethyl phenyl carbamate at rt and benzamide at ~40 °C)</td>
<td>70–100 (aryl halide, methoxy unaffected)</td>
<td>323</td>
</tr>
<tr>
<td>40</td>
<td></td>
<td>NaH₂PO₂/Pd/C</td>
<td>rt → 50–65 °C (ketone, alkene, N-oxide, O-benzyl, aryl chloride, benzyl chloride, epoxide all potentially reducible)</td>
<td>73 (ester, cyclic ketone, amide, alkyl chloride, nitrile unaffected)</td>
<td>324</td>
</tr>
<tr>
<td>41</td>
<td>aryl, benzyl, n-butyl, cyclohexyl, Ph₃C, ArCO, ArSO₂</td>
<td>NaTeH</td>
<td>EtOH/Et₂O, rt, 15 min</td>
<td>55–100 (alkene, alkyne, carbonyl, carbazol, amide, ester, nitrile, halooaryl, halooalkyl, sulfone unaffected)</td>
<td>325</td>
</tr>
<tr>
<td>42</td>
<td>aryl</td>
<td>HSCH₂CO₂H/NH₃</td>
<td>EtOH, 50–60 °C</td>
<td>89–100 (nitro, methoxy, chloro unaffected)</td>
<td>326</td>
</tr>
<tr>
<td>43</td>
<td>MeN₅, HOCH₂CH₂N₂</td>
<td>(n-Bu)₅Mo₂Fe₂S₆(SPh)₆</td>
<td>MeOH, THF or H₂O, resp</td>
<td>almost quantitative with careful addition of H⁺ donors</td>
<td>327</td>
</tr>
<tr>
<td>44</td>
<td>PhCH==C(N₅)CO₂Me</td>
<td>Hg/Pt or graphite cathodes + electrons</td>
<td>very low</td>
<td>reasonable yields of a mixture of N-acylated enamines</td>
<td>328</td>
</tr>
<tr>
<td>45</td>
<td>α-azido-styrene</td>
<td>Hg electrode + electrons, Ac₂O</td>
<td>CH₂CN/H₂O, 50 °C</td>
<td>mix of aniline (67) and diphenylurea (23)</td>
<td>329</td>
</tr>
<tr>
<td>46</td>
<td>PhN₅</td>
<td>Fe₉(CO)₉</td>
<td>150 °C, 20 kg cm⁻², 4 h</td>
<td>26–70 (chloro and nitro unaffected)</td>
<td>331</td>
</tr>
<tr>
<td>47</td>
<td>ArN₅</td>
<td>RhCl₃/CO</td>
<td></td>
<td>13–86 (nitro, methoxy unaffected)</td>
<td>332</td>
</tr>
<tr>
<td>48</td>
<td>ArN₅</td>
<td>P₃I₄</td>
<td>C₆H₆ reflux, several hours</td>
<td></td>
<td>333</td>
</tr>
<tr>
<td>49</td>
<td>aryl or alkyl N₅</td>
<td>SnCl₂</td>
<td>MeOH, rt, 0.25–1 h</td>
<td></td>
<td>334</td>
</tr>
</tbody>
</table>

*rt = room temperature.
Azides: Their Preparation and Synthetic Uses

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, except in the case of arylsulfonyl azides. However, it has been shown recently that under phase-transfer conditions efficient reduction of aryl, arylsulfonyl, and alkyl azides can be effected (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 NaH under phase-transfer conditions gave a 72% yield of phenylglycine.58

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

RN₃ + Ph₃P → RN=PPh₃ → RNH₂

Staudinger reaction after its discovery. The same author reported that conversion of the iminophosphorane to the amine could be effected with ammonium hydroxide. This method has been modified to a “one-pot” process by Letsinger and co-workers and recent variants on the latter have allowed preparation of a mitoseine (entry 24) and 3-aminoxetane (105) (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 (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, respectively (entry 28). A seven-compound study of the generality of the process has been reported (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. In one reported case the intermediate phosphazene 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. 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 triethylphosphate, and (c) two-step deprotection using HCl gas in ether (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 H₂S/NET₃ for azide to amine conversion have been limited and mainly in the β-lactams (entries 32 and 33) and carbohydrate fields. 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 35% yield (entry 54). Azidophenol 448 (prepared from 447 by treatment with sodium azide/AcO) reacted with sodium dithionite to give the amine, which
was further transformed in situ\textsuperscript{318} (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.\textsuperscript{76} The aminoquinone (analogous to 57) could be prepared from 449 using Watanabe's method.\textsuperscript{319}

(c) Sodium/Ammonia. Acetonide 273 was reduced with Na/H\textsubscript{2} to amino alcohol 450, which was treated directly with (Boc)\textsubscript{2}O in aqueous NaOH to give the N-protected alcohol 451\textsuperscript{339} (entry 36).

$$\begin{align*}
273 & \rightarrow \\
(1) \text{Na/NaH}_2 & \rightarrow \\
(2) \text{(Boc)}_2O & \rightarrow \\
450, R = H & \rightarrow \\
451, R = \text{Boc} & \rightarrow 
\end{align*}$$

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 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.\textsuperscript{320} This unusual transformation had been previously observed in the pyridine series.\textsuperscript{321} More recently, 2-nitro-3-azidopyridine was reportedly reduced to the amine in 25% yield by NaOH, RONa, KCN, or NaSC\textsubscript{6}H\textsubscript{4}-4-Me in proton-donor solvents\textsuperscript{322} (entry 38). Additionally, with the first two reagents, concomitant reduction and 6-substitution occurred. In contrast, with the stronger nucleophile, NaSC\textsubscript{6}H\textsubscript{4}-4-Me, azide substitution took place and the reaction with KCN also provided a product derived from cyanide addition to the azido group.\textsuperscript{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).\textsuperscript{104,105}

7. By New Methods

Various new reagents for the azide to amine conversion have been developed recently (entries 39-49). Thus, tetracarbonylhydridoferrate (HFe(CO)\textsubscript{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\textsuperscript{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 reduced\textsuperscript{324} (entry 40). A reagent of more general applicability is sodium hydrogen telluride (prepared from tellurium and sodium borohydride), which reduces aryl, benzy1, alkyl, acyl, and sulfonyl azides in good to excellent yield under mild conditions\textsuperscript{326} (entry 41). For aryl azides, mercaptoacetic acid appears to be a very efficient reductant\textsuperscript{326} (entry 42).

Multielectron reduction of methyl azide and 2-hydroxyethyl azide using a (n-Bu\textsubscript{4}N\textsubscript{4})\textsubscript{2}[Mo\textsubscript{6}Fe\textsubscript{6}S\textsubscript{6}-(SPh)\textsubscript{3}] modified glassy carbon electrode provided the appropriate amine plus hydrazine and ammonia (depending on concentration)\textsuperscript{327} (entry 43). This method probably offers little synthetic scope at present. In the same vein, cathodic reduction of \(\alpha\)-azidocinnamic ester\textsuperscript{328} and nonterminal vinyl azides\textsuperscript{329} has been examined. In the former, an excellent yield of \(\alpha\)-amino-cinnamic 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.\textsuperscript{330}

Azidobenzene was converted to a mixture of aniline (67%) and \(N,N\text{'-diphenylurea (23\%) by treatment with Fe\textsubscript{2}(CO)\textsubscript{9} in acetonitrile/water at 50 °C}\textsuperscript{331} (entry 46). Azidoarenes were also converted to the aminoa renes in 26-70% yield by carbon monoxide and water in the presence of a RhCl\textsubscript{3 catalyst\textsuperscript{332} (entry 47) and in 13-96% yield by P\textsubscript{2}I\textsubscript{4}\textsuperscript{333} (entry 48). With the latter, aroyl 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 methanol\textsuperscript{334} (entry 49).

B. Other Reductions

Cyclic and acyclic 2-azido ketones 455 eliminate nitrogen in the presence of catalytic amounts of perbenenate. 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.\textsuperscript{335} Similarly, \(\alpha\)-azido esters 457 react with acetic anhydride in the presence of catalytic amounts of rhodium 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 Ac\textsubscript{2}O/AcOH ratio is employed, monoacetylated ester 458 is the sole product.\textsuperscript{336}
Azides: Their Preparation and Synthetic Uses

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. 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. 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. 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. More recently, Tsuji and co-workers have extensively examined similar reactions of pyridyl, quinolyl, and isoquinolyl azides under acidic conditions, 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.

The same workers have examined the effects of reaction conditions upon the course of such reactions. With hydrohalogenoic 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.

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-glucose (474) over 10% Pd/C gave pyrrolidine 475 in quantitative yield. Similarly, reduction of 476 with H₂/Pd black in ethanol containing sodium acetate at 50 °C, followed by treatment with PhCH₂COCl/NaHCO₃, provided the bicyclic amine 477 in 36% yield. The latter could be further transformed to 478. 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.
Cyclization of azido alcohols 482 to aziridine 483 (>80%) took place when either was heated in THF at 60–65 °C with triphenylphosphine. Under the previously reported conditions (viz., triphenylphosphine in ether at reflux) no cyclization occurred (see section II.A). The process was extended to the preparation of the aza analogue of LTA. Aziridines also result from treatment of 484 and 485 with tri-n-butylphosphine or trimethyl phosphate. Similar results were obtained with a chrysene analogue.

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. 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 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.

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.

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.

Treatment of α-azido ketones 504 with sodium hydrogen telluride at room temperature gives pyrazines 505 in 40–98% yield. 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 catalyst or triphenylphosphine and from ketones and iodine azide.
Azides: Their Preparation and Synthetic Uses

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.356 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 acyl azide 512 in benzene gave isocyanate 513, which could be converted to urea derivatives 514a–e with arylamines or to carbamate 514d with isopropyl alcohol.369 Similarly, urea derivatives 516a–e were prepared by thermolysis of acyl azides 515a–e (obtained from the carboxylic acids with ethyl chloroformate followed by NaN₃) in the presence of ethyl anthranilate.364

Most current utilizations of the Curtius rearrangement have involved isocyanates only as intermediates. Thus, allenic isocyanate 518, formed from thermolysis in benzene (18 h) of 517 (in turn prepared from the carboxylic acid), could be hydrolyzed to amine 519 in 39% overall yield.360 Similarly, some tetrazolylmethyl 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, carboxylactone 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 → acid chloride → acyl azide → 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%) 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 527 and 530, presumably arising from 527 and 528, respectively.

An excellent review of the photochemical (and thermal) rearrangements of heavier main group element (mainly B, Si, Ge, and P) azides has appeared recently. 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) rearrange on photolysis in methanol to form metaphosphonimidates (532), which are trapped by the solvent to give methyl N,P-diarylphosphonamidates (533) in reasonable yield. Methyl phosphinates (534), products of solvolytic azide displacement, and diarylphosphinic amides (535) are also formed.

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 photolysed in DMSO (a known nitrene trap). 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. Similar experiments conducted in the presence of dimethyl sulfoxide (DMS) (and methanol) provided sulfilimine 538 in addition to 533. 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. Thus, irradiation of the azidophosphonium salt 540 (X = PF6) at 254 nm for 15 h at room temperature gave the iminophosphonium salt 541. 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 (Mes3Si=NMes).

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. 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 (98-100%) via a Schmidt reaction on the dicarboxylic acid 543.379 Apparently, 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 dialkyl 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 MeCOCHRCO-X-OH (X = NH₂, CO₂H) with retention of stereochemistry to form iminophosphorane, apparently via an intermediate phosphorus(V) complex.396 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 phosphate 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, phosphaalkene 559 reacted with phenyl azide to give iminomethylene phosphorane 560.400

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

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 nitrites 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,386 ketones,387 ketenes,388 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, triphenylphosphite, 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 phosphate 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, phosphaalkene 559 reacted with phenyl azide to give iminomethylene phosphorane 560.400

Even phosphorus cations can undergo the Staudinger reaction. Thus, azides were shown to react with bis(dialkylamino)phosphonium species to give the corre-
sponding bis(dialkylamino)iminophosphonium compounds (561). More recently, the process has been

\[
(R_2N)_2PAI^+Cl^- + R_2N=POCl \rightarrow \text{products (563)}
\]

extended to the chlorophosphonium salts (562). 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 (R2N-P-N=P).

\[
R_2N\cdot P\cdot N=NR \rightarrow \text{products (564)}
\]

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

\[
\begin{align*}
\text{(565), } X & \text{ lone pair} \\
\text{(566), } X & \text{ NR } (R = 4-ClC_6H_4, 4-NO_2C_6H_4, \text{ Ph, Ts}) \\
\text{(567), } X & \text{ lone pair} \\
\text{(568), } X & \text{ NTs}
\end{align*}
\]

Similar to 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 diazaphospholanes 571.405 In contrast, with p-nitrophenyl or tosyl azide the expected iminodiazaphospholanes resulted in 62–87% yield. Normal Staudinger products were also formed from tetramethyldiazaphospholane 572 and phenyl, p-methoxyphenyl, or p-nitrophenyl azides.

\[
\text{571, } R = \text{H, Me; } R' = \text{Me, Et}
\]

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), amino 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).

\[
\begin{align*}
\text{Ph}_3P\cdot NHR'R'\text{CO}_2^- & \rightarrow (\text{EIO})_2P(O)\text{ONHR'R'CO}_2\text{Et} \\
\text{574} & \text{575} \\
\text{576} & \text{577} \\
\text{578} & \text{579} \\
\text{580}
\end{align*}
\]

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 (Me2N)2P. Trialkyl phosphites react with 577 to give the corresponding iminophosphoranes (578), which are converted to amino 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-diazidothene (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. \(\omega\)-Azido acids gave insoluble zwitterionic products (Ph3P\(\text{+}\)-NH(CH2)2CO\(\text{2-}\)) and under these conditions cyclization was not observed. However, in refluxing pyridine Ph3P\(\text{+}\)-NH(CH2)2CO\(\text{2-}\) did provide 2-pyrollidone in 95% yield.408 More recently, a similar, but milder process was used for the preparation of small peptides. Therein, ethyl diphenylphosphinite (Ph2POEt) proved to be the reagent of choice since on HCl workup its oxide is hydrolyzed to diphenylphosphinic acid, which can be extracted from the
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 Pearson\(^{413}\) 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**

\[
\text{PhSCH}_2\text{N}_3 + \text{RMgBr} \rightarrow \text{PhSCH}_2\text{N} \equiv \text{NNHR} \xrightarrow{\text{KOH}} \text{RNH}_2
\]

R = aryl, alkyl

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 \(\approx\) 590 > 591 > 592 \(\gg\) 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 aryl 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 triazines 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 alkylithium 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 yield.

**SCHEME 22**

\[
\text{ArLi} + \xrightarrow{\text{H}_3\text{O}^+} \text{Ha}^+ \xrightarrow{\text{ArNH}_2}
\]

Ar = aryl, heteroaryl, benzyl, dithianyl
yield (34–85%) (Scheme 23).

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

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

It should be noted that Guntrum has reported that tosyl azide exhibits shock sensitivity similar to that of nitroglycerin. Accordingly, Kelly 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.

2. By Reaction with Alkenes and Related Species

The methylenefluorene derivatives 600 and 601 react with the aryl azides 602a–e, respectively, to give the ring-expanded arylamines 603 (37%) and 604 (36–66%). Products 605 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%). 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.

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. 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 allylamines 620 and 621. Similar reactions occur in the presence of trifluoroacetic acid.

3. By Reaction with Boranes

For some time alkyl azides have been known to react with organoboranes to afford secondary amines. 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). 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% yield (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.)

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

In contrast to the results of thermal and photoiniti-ated 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 carboximidates and/or the corresponding aziridines rather than at the terminal nitrogen, 637

Interestingly, 1-isocynano-2,3,4,6-tetraacetyl-α-D-glucopyranoside reacted to give only the corresponding urea in 75% yield.

SCHEME 26
\[
\begin{align*}
R-N=C+N_3C_2Et & \xrightarrow{hv} R-N=C=N-C_2Et + N_2 \\
R-N=C-N-C_2Et & \xrightarrow{H_2O} RNHCONHCO_2Et
\end{align*}
\]

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

\[
t-Bu_3SiCIN_3 + t-Bu_3SiNa \rightarrow t-Bu_3Si=NSi-t-Bu_3
\]

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

\[
\text{EtOOC}-N=\text{Cl}Na^+ + \text{EtCONCO}_2\text{Et} \rightarrow \text{EtOCONHCO}_2\text{Et} + \text{NaCl} + \text{N}_2
\]

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-, NH3, HO-, MeO-) to form an anion of \( m/z \) 28, to which

\[
\text{Me}_3\text{SiCH}_2\text{N}_3 + \text{B}^- \rightarrow \text{CH}_2=N^- + \text{CN}^- + \text{N}_5^- + \text{Me}_3\text{Si}^-
\]

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 benzyl azides.

\[
\begin{align*}
\text{Ph-Su}^- + \text{Bu}^- & \rightarrow \text{Ph-Su}^- \cdot \text{Bu}^- \\
\text{Bu}^- + \text{Bu}^- & \rightarrow \text{Bu}^- \cdot \text{Bu}^-
\end{align*}
\]

Displacement of the azido group, rather than attack at a nitrogen atom, occurred from treatment of benzensulfinyl azide with nitrogen or sulfur nucleo-philes.447 Thus, with primary or secondary amines, sulfinate was 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 thiosulfimates 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 trifluoro- methyl sulfoxides 650–652 do not iminate with sodium azide in sulfuric acid. However, if the latter is replaced by oleum, the S-(trifluoromethyl)-S-aryl sulfoximides 653–655 are formed.451
**SCHEME 27**

\[ R\text{C}X + \text{PhN}_3 \xrightarrow{\Delta} R\text{C}=\text{NPh} \]

\( R = \text{hindered alkyl}; X = S, Se \)

**SCHEME 28**

\[ \begin{aligned} \text{Z} - \text{C} - \text{Z} & \xrightarrow{\text{ArSO}_3\text{N}_2} \text{Z} - \text{C} - \text{Z'} \\
\text{Z'} & \text{ArSO}_3\text{N}_2 \end{aligned} \]

Sulfoximides 657 are also formed in 50–60% yield by thermolysis of alkoxy carbonyl azides 656 in DMSO.\(^{462}\)

\[ \text{ROCON}_2 \xrightarrow{\text{DMSO}} \text{ROCON} \equiv \text{SOMe}_2 \]

656, \( R = \text{Br, } t\text{-Bu} \)

657

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

**SCHEME 29**

\[ \begin{aligned} \text{R-C-CHR'} & \xrightarrow{\text{TsN}_2} \text{R-C-CR'} \\
\text{R'CO} & \xrightarrow{\text{B}} \text{R'NO}_2 \end{aligned} \]

**to competing reactions (viz., aldol condensation and polymerization) during the attempted preparation of the appropriate enolate ions.** However, various workers 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-EtSO\(_2\)C\(_6\)H\(_4\)N\(_2\)) 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,\(^{463}\) trityl azide,\(^{464}\) \( (\text{azidochloromethyl})\text{dimethylammonium chloride,}^{465}\) trityl azide,\(^{466}\) and 4-nitrophenoxy azide\(^{467}\) 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.\(^{466}\) 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-toluenesulfonylamide 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 azide was shown to be an excellent alternative.

The diazo compounds resulting from these procedures have enjoyed extensive exploitation as carbene or carbeneoid precursors.\(^{471}\) Thus, the diazo esters 661–664 form the corresponding cyclopropanes 665–668, respectively, in 46–84% yield on treatment with CuSO\(_4\) and Cu(acac\(_2\)) in refluxing benzene.\(^{472}\)

**SCHEME 29**

\[ \begin{aligned} \text{R-C-CHR'} & \xrightarrow{\text{TsN}_2} \text{R-C-CR'} \\
\text{R'CO} & \xrightarrow{\text{B}} \text{R'NO}_2 \end{aligned} \]

**Intramolecular cyclopropanation of \( \alpha\)-diazo-\( \beta\)-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
Azide and sodium hydride. The yields were considerably lower when triethylamine was used as base.

\[
\begin{align*}
669, \quad R, R^2 = \text{cyclic}; \quad R' = H; \quad X = \text{CH}_2, \quad O; \quad Y = H_2 \\
670, \quad Y = N_2, \text{rest as above}
\end{align*}
\]

Diazo compound cyclization reactions have been considerably enhanced by the use of rhodium(II) acetate as catalyst. Thus, the novel \(\beta\)-lactam 674 and aza \(\beta\)-lactam analogues 675 and 676 were prepared in excellent yield (75-100\%) by heating the corresponding diazo compounds 671-673 with a catalytic quantity of rhodium(II) acetate. A cephalosporin analogue has been prepared similarly. 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 the case of 671, where \(p\)-carboxybenzenesulfonyl azide was employed.

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

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 \(p\)-toluenesulfonylamide groups. These compounds were not characterized but were suggested to be of the same type as those obtained from reaction of alkylindoles and tosyl azide. 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 \(\beta\)-naphthol and tosyl azide.

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

The trifluoroacetyl group has been utilized similarly, with the advantage that its removal is more facile. 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 (\(R = H, F, C_l; \quad R' = \text{Ph, 2-pyridyl, 2-thienyl}) react with tosyl azide under phase-transfer conditions (benzyltriethylammonium chloride) to give the corresponding 3-diazo-3\(H\)-indoles 687.

Treatment of diketopiperazine derivative 688 (\(X = H_2\)) with \(n\)-butyllithium and tosyl azide gave the corresponding quinone diazide 689 using tosyl azide as base.

\[
\begin{align*}
683 & \quad \text{LDA, \(-78^\circ\) C} \\
684 & \quad \text{TFAE}
\end{align*}
\]

\[
\begin{align*}
684 & \quad \text{ArSO}_2\text{Na} \\
685 & \quad \text{NEt}_3 \\
686 & \quad \text{H}_2\text{O}
\end{align*}
\]

\[
\begin{align*}
679 & \quad \text{N}_2 \\
680 & \quad \text{N}_2
\end{align*}
\]
responding diazo compound 688 (X = N₂), which was used in situ as a synthetic equivalent of amino-carboxycarbene. More routinely, diazopyrazolinones have been prepared by treatment of the parent pyrazolinones with tosyl azide/triethylamine.

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

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 [(PhO)₂P(O)N₃]. The first example of a 6-diazosilacyclohexa-2,4-diene (693) was also prepared by diazo transfer (n-BuLi/tosyl azide).

Diazot 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 (R = PhCH₂) and 694 (R = CH₂C₆H₄Cl-p), where benzaldehyde and phenylacetalddehyde (2:1) and p-chlorobenzaldehyde, respectively, were formed.

Aldehydes 697 (68-83%) also result from the drop-wise addition of thiadiazoloylalkyl azides 696 to concentrated sulfuric acid at -5 to 0 °C.

IV. Applications in Allocyclic 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. The process can be extended to trans-m-azidocinnamate.

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

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).

B. Ring Contractions

Hindered silyl enol ethers undergo ring contraction via triazolines when allowed to react with arylsulfonyl azides under pressure. Enol ethers give cleaner products with greater regiospecificity 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). 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).

Recently, phosphoryl azides have been used to effect the ring contraction of cyclic enamines in moderate to good yield. 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).

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).

D. Rearrangements

On occasion interesting rearrangements occur under Schmidt conditions. Thus, homocuneone (702) reacts with sodium azide in methanesulfonic acid at 0–5 °C (20 min) to yield the unusual cyano dimesylate 704 in ca. 20% yield. 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.

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 sugars (see also section 11.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). Azide 706 may be prepared in four steps from 1,6-anhydro-β-D-mannopyranose (Scheme 33). The last three steps occur in good overall yield. This contrasts with the former method, which involves treatment of 707 under vigorous conditions (see section III.A). Preparations of azido carbohydrates are discussed here, rather than in section II, where considerations of carbohydrate chemistry are paramount.

Four new diazido sugars (708–711) have been made by treatment of the anhydro tosylribopyranosides 712 and 713 with sodium azide. Mesylate 714 reacts with sodium azide to give the azidogalactopyranose derivative 717. 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 715 (see section...
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The synthesis of chemically modified cyclodextrins has been reviewed, and this review contains a section on azido derivatives. Azido carbohydrates are discussed in another general review of hydrazine derivatives of carbohydrates.

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 $\alpha$- and/or $\beta$-glycosidic linkages (for other examples of azide survival, see section II.L). For example, glycosyl bromide 718 has been condensed with the 4-hydroxy group of the glycosyl acceptor 719.

In another paper, the effect of a C-2 azido substituent on the $\beta/\alpha$ ratio in glycosidic bond formation relative to 4-$O$-alkyl functions has been studied. 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). 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). However, the erythro analogue of 720 undergoes elimination of hydrazoic acid to give 721.
SCHEME 36

SCHEME 38

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

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.

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. Conversion of 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).

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 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, Knittel obtained indoles in virtually quantitative yields at 140 °C and azirines at 80 °C (Scheme 39).

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

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 oxopyranog[6]indoles (Scheme 40).

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

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

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). 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 workers studied the effect of oxidants on indole versus isoquinoline formation for a series of azidocinnamates bearing only one substituent ortho to the azidoacryloyl group (Scheme 42). Isoquinoline yield increased from 2 to 52%, and indole
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 azawittig 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

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 azepines542 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
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### 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 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

\[ \text{Scheme 43} \]

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{PhH, room temp. 4-5 h} \\
\text{TEMPO} \\
\end{array}
\]

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

\[ \text{Scheme 44} \]

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{PhH, 1.5 h} \\
\text{R}^2 + \text{H} \\
\end{array}
\]

\[ \text{Scheme 45} \]

\[
\begin{array}{c}
\text{CO}_2\text{Et} \\
\text{DMF} \\
\text{R}^1 + \text{CH}_2\text{OMe} \\
\text{R}^2 + \text{Me} \\
\end{array}
\]

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

\[ \text{Scheme 47} \]

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{N}_3 \\
\text{MeCN} \\
\end{array}
\]

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".

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\begin{array}{c}
\text{N}_3 \\
\text{N}_3
\end{array} & \quad \begin{array}{c}
\text{N}_3 \\
\text{N}_3
\end{array}
\end{align*}
\]

156 °C/PhBr, 98% (19)

hv/107 °C, 18% PhCOMe, 36%

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 zwittazido 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.

\[
\begin{align*}
\text{H} & \quad \text{+} \\
\begin{array}{c}
\text{N}_3 \\
\text{N}_3
\end{array} & \quad \begin{array}{c}
\text{N}_3 \\
\text{N}_3
\end{array}
\end{align*}
\]

\[
90\%
\]

\[
\begin{align*}
\text{PhCOMe} & \quad \text{Me} \\
\text{N}_3 & \quad \text{N}_3
\end{align*}
\]

90%

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.

\[
\begin{align*}
\text{CO}_2\text{Ph} & \quad \text{N}_3 \\
\text{96%}
\end{align*}
\]

(21)

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 appeared555 employing o-azidobithienyls newly available by treatment of lithiobithienyls with tosyl azide and subsequent fragmentation of the intermediate lithium triazene salts.528 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

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

\[
\begin{align*}
\text{PhS} & \quad \text{CO}_2\text{Et} \\
\text{90%}
\end{align*}
\]

(756)

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

\[
\begin{align*}
\text{N}_3 & \quad \text{S} \\
\text{Azide} & \quad \text{SPh}
\end{align*}
\]

(24)

Azide 752 readily cyclizes to a 1,2-dihydro-1-aza-2-borabenzene on standing with phenyl dichloroborane 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 benzocinnoline 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 (particualrly in phenothiazine synthesis) and its mechanism were delineated chiefly by Cadogan and his
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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).566

Azepinobenzothiazoles formed via ring expansion of the azanorcaradiene tautomer of the spiro intermediate are more commonly encountered in systems where X = CH₂. Jones' group5@ 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 anthraisoazolones 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).2418

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)

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 arylnitrene 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
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. One is based on the cyclization of the anils of o-azidobenzaldehyde, an established method (Scheme 53). The synthetically important point here is the conversion of the benzyl alcohol to aldehyde 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 gave much lower yields.

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

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

In contrast, treatment of o-azidobenzaldehyde with sodium hydride in DMF gives an indazol-3-one by base-catalyzed cyclization (Scheme 57). A similar base-catalyzed closure, involving a carbanion, yields indoxyls (eq 31). 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 aryltrimine ions is well-known. Now attack at nitrogen by alkenes followed by Friedel–Crafts reaction has been used to prepare trans-[5]para-1-aza-cyclophanes (Scheme 58).

Abramovitch has trapped aryltrimine ions intramolecularly to provide a potentially general approach to a number of heterocycles that have amino groups β to the ring junction (Scheme 59).

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

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. 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).

A pyrazinone ring system was formed by reaction of pyrrole and an isocyanate (Scheme 62). Note that these acyl azides are best prepared from mixed anhydrides.
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**SCHEME 59**

\[
\begin{align*}
\text{N}_3 & \quad \text{Ph} \\
\text{CO}_2\text{Me} & \quad \text{H}_2\text{N} \\
\rightarrow & \quad \text{Ph} \\
\text{TFMSA} & \quad \text{HCl} \\
& \quad 65\
\end{align*}
\]

**SCHEME 60**

\[
\begin{align*}
\text{N}_3 & \quad \text{CO}_2\text{H} \\
& \quad 0 \degree \text{C} \\
\rightarrow & \quad \text{H}_2\text{O} \\
\text{TFMSA} & \quad (2 \text{ drops} \\
& \quad \text{room temp. 25 h} \\
& \quad \text{TFAA} \\
& \quad 15\% \\
\end{align*}
\]

**SCHEMES 61-65**

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

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

Lwowski and co-workers have studied the reactions of carbamoyl azides extensively. Some recent work
has concerned the photolysis of dialkylcarbamoyl azides in the presence of carbodiimides which yields 769 and 770, the latter by a novel process (Scheme 64). An indazole may be obtained by reacting 770 with benzene.

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 photoreaction of 771 with more azide, which provides the first instance of an intermolecular-assisted loss of nitrogen from a carbamoyl azide.

\[
\begin{align*}
\text{Me}_2\text{N}^+\text{N}^-\text{NCMe}_2 & \quad \text{hv} \quad \text{Me}_2\text{N}^+\text{N}^-\text{NCMe}_2 \\
\end{align*}
\]

5. Sulfonyl Azides

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

\[
\begin{align*}
\text{Me} & \quad \text{SO}_2\text{N}_3 \quad \text{Freon 113} \\
\text{Me} & \quad \text{SO}_2\text{NH}_2 \\
\end{align*}
\]

Dihydropyridines rather than sultams become the main products of FVP of arylethanesulfonyl azides at 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 arylethanesulfonyl azides (Scheme 66).

Solution and flash vacuum pyrolysis of 3-arylpropanesulfonyl azides give seven-membered sultams. Best yields are obtained on solution decomposition in Freon 113.

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).

\[
\begin{align*}
\text{Ar\text{NH}_2\text{CCl}_2\text{H}} & \quad \text{Pd(OAc)}_2\text{, TEP} \\
\text{Ar\text{N}} & \quad \text{NH}_2\text{CO}_2\text{H} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{R} & \quad \text{Cl} \\
\text{R} & \quad \text{Cl} \\
\end{align*}
\]

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). 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).

ω-Azido ketones react with triphenylphosphine under anhydrous conditions to yield five-, six-, or seven-
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SCHEME 69

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

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

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

α-Azidostyrene readily forms iminophosphoranes and on reaction with triphenylphosphine or trimethyl phosphite, respectively. These have been used in the synthesis of azaazulenes (eq 42) and the 1,2-λ3-azaazaphosphorine ring system (Scheme 69).

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

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

SCHEME 70

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

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

α-Azidostyrene readily forms iminophosphoranes and 576 on reaction with triphenylphosphine or trimethyl phosphite, respectively. These have been used in the synthesis of azaazulenes (eq 42) and the 1,2-λ3-azaazaphosphorine ring system (Scheme 69).

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

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

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. 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).
Synthesis of N-unsubstituted triazoles usually entails the selection of an azide (RN₃) 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. (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-diazidonapthalene 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 sydnones, 620

Vinyl azides usually eliminate nitrogen readily to form 2H-azirines rather than cyclize to 4H-triazoles. However, when suitably substituted, they spontaneously cyclize to 4H-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
increasingly important part in heterocyclic synthesis 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^237,237^ 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-Benzoxquinone azide 786 undergoes intramolecular cycloaddition to give triazoline 787, which has been observed directly by ^1H NMR (Scheme 81)^631,632.

Formation of the triazoline can be followed by NMR; after 2.5 h of reaction a trace of 788 and the products 789-791 appear, with 50% triazoline 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 triazoline 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 triazoline (Scheme
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 triazoline 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% 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,643 and reactions of tetrazoles have been reviewed.644

The first report of the synthesis of a 5-unsubstituted 4H-imidazole 796 by photolysis of an alkenyltetrazole has appeared (eq 52).844 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 SnCl2·2H2O 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)teta-
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SCHEME 88

SCHEME 89

SCHEME 90

SCHEME 91

5. Other Cycloadditions

Aryl azidosulfonates add to norbornadiene to provide a new synthesis of the 2-azabicyclo[3.2.1]octadiene system (Scheme 89). Azide cycloaddition reactions continue to be employed for the synthesis of uncommon heterocycles.

C. Ring Expansions and Contractions

1. Schmidt Reaction and Related Processes

The term Schmidt reaction has come to cover a number of interconversions brought about by hydrazoic acid under strongly acidic conditions. Here only cyclic examples are considered. Andrieux and co-workers have treated a series \((n = 1, 2, 3)\) of benzocycloalkanols with \(\text{HN}_3-BF_3\) 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 \(\text{HN}_3/\text{BF}_3\text{-OEt}_2\) unexpectedly gave benzazocine (801) rather than an indole.

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

by Desbene and co-workers for dibenzo[\(b,h\)][1,4]-thiazepines and -thiazepines (cf. Scheme 91). Preference for aryl migration (over secondary alkyl) was observed in the reactions of ketones with sulfuric acid/sodium azide at 64 °C to give cyclic amides 802 and 803 in 80-91% yield. 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, \(R = \text{NO}_2\)) and decreased by a similarly positioned amino function (70%, 803, \(R = \text{NH}_2\)).

A mixture of products (viz., 806 and 807) also resulted from treatment of 805 with sodium azide in polyphosphoric acid. 1,5- and 1,8-dichloroanthraquinones react with hydrazoic acid to give, in each case, both of the theoretically possible lactams. For the corresponding reactions with 1- and 2-chloroanthraquinones, two of the four theoretically possible lactams were identified.
Some other recent applications of the Schmidt reaction in heterocyclic chemistry appear in (eq 54-58).

Treatment of 1,3-dithiolium salts \((X = \text{halogen})\) with azide ion gives thermally unstable 2-azido-1,3-dithiolenes \((808)\), which rearrange with loss of nitrogen to give 1,4,2-dithiazines and N-substituted 2-imino-1,3-dithiolenes (Scheme 92). When \(X = \text{SAr}\), the (thioimino)-1,3-dithiolenes are formed in good yields, e.g., 77% when \(R^1, R^2 = -(CH_2)_4-,\) and \(X = p\)-nitrophenylthio. 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 dithiolyl azides \(^{670}\) 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]annulenes \(^{673}\) and aza[18]annulenes \(^{674}\) by photolysis at low temperature.

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

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-dimiino[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). \(^{679}\)
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SCHEME 97

SCHEME 98

SCHEME 99

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).660

Treatment of isoimidium perchlorates with sodium azide gives acyl azides which undergo Curtius rearrangement and electrocyclic closure to novel 2H-1,3-oxazin-2-ones on heating (Scheme 99).661

5. Nitrene Insertion into Aromatics

The reaction of sulfonyl azides with aromatics was first described by Curtius662 and has been thoroughly investigated by Abramovitch.592,595,598,602,604 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 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).685 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

Wolf695 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.650,656,690,691 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 3H-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 didehydroazepines on irradiation regardless of the position or nature of the substituent. However, photolysis of 2,6-dimethylphenyl azide in the presence of CO in an N\textsubscript{2} matrix at 12 K gives the isocyanate by trapping of the nitrene as rearrangement to didehydroazepine is very inefficient. Pentafluorophenyl azide on irradiation in a matrix at 12 K gives no didehydroazepine 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). 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.

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.

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. Photolysis of the same azide in the presence of methoxide affords 3H-azepin-2-one, presumably via the methoxyazepine (Scheme 100).

However, azides that have a carbonyl-containing ortho substituent undergo ring expansion to azepines in good yield on photolysis in methanol. More recently, azides bearing certain para and meta electron-withdrawing groups also have been found to yield azepines. These observations, plus the fact that aryl azides with o-CN and o-CF\textsubscript{3} groups form azepines, indicate that electronic effects of substituents rather than a special stabilization by an ortho carbonyl group (e.g., 822) dictate the course of these reactions. A mechanism involving nucleophilic attack on a didehydroazepine rather than a benzazirine intermediate has been proposed (Scheme 101).

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

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). Ring expansion of 4-azidopyridines to 5-methoxy 6H-1,4-diazepines has been achieved also by thermolysis. 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. Some of the wide div-
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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 α-nitrosocinnaminitrile (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, 715, 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 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 yield 715 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 Reed 720 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;462 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 amines (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 peptides727-734 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 isocyanate acetate 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 III.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.

**IX. References**

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