The Utility of Nitroacetic Acid and its Esters in Organic Synthesis

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In this review a summary of the syntheses and properties of nitroacetic acid and its esters is given. In addition, their chemical reactivity in the light of their synthetic utility leading to numerous types of nitro compounds, amino acids, and heterocyclic systems is described.

1. Introduction and Historical Background

In 1947, Lyttle and Weisblat[1] stated "the chemistry of alkyl nitroacetates has been explored only in a cursory fashion". They added "these esters are promising intermediates for a number of compounds such as amino acids, nitroparaffins, amines, and their derivatives". The subsequent 32 years have seen a tremendous progress in the development of the chemistry of nitroacetates. In this review, the types of reactions they undergo, with an emphasis on their synthetic utility, various methods of preparation, and physical and spectral properties are summarized.

Nitroacetic acid (**1**) and its derivatives have been the subject of investigations by numerous synthetic chemists, with their efforts being largely confined to the methyl (**2**) and the ethyl (**3**) esters. The presence of the active methylene group makes these esters unique intermediates for the formation of carbon-carbon bonds. Consequently, their reactivity often parallels that of other compounds containing an active methylene group. The nitro group of compounds resulting from reaction of the methylene group is readily convertible to the amino group. The nitroacetic esters are, thus, valuable intermediates for the synthesis of esters of 2-nitroalkanoic acids, nitro alcohols, nitro amines, halonitro compounds, di- and trinitro compounds, nitroacrylates, oxazolidines, oxazoles, amino acids, amino alcohols, carbohydrate derivatives, etc.

$O_2N-CH_2-COOR^1$

1 $R^1 = H$
2 $R^1 = CH_3$
3 $R^1 = C_2H_5$
4 $R^1 = C_6H_5CH_2$

Ethyl nitroacetate (**3**) was first prepared in 1900 quite unintentionally[2]; nitration of ethyl 3,3-dimethylacrylate gave an α-nitro compound which decomposed to **3** and acetone when treated with an alkali. Nine years later, the disodium and the dipotassium salts of **1** were prepared[3] by treating nitromethane with aqueous alkali; careful acidification liberated the acid **1**, m.p. 87–89° (dec.). Many early attempts to prepare the free acid had failed on account of its tendency towards ready decarboxylation. In 1923, a general esterification method for **1** and its dipotassium salt was reported[4]. Among the compounds prepared were the ethyl, propyl, isopropyl, isobutyl, and isopentyl esters. The ethyl ester (**3**) was prepared, for example, from the free acid in 70% yield using sulfuric acid as the catalyst, and from the dipotassium salt in 39% yield with hydrogen chloride serving as the catalyst. A detailed discussion of the historical aspects can be found in Ref. [1].

2. Methods of Preparation[5]

2.1. Nitroacetic Esters

Methods for the preparation of nitroacetic acid esters and salts are summarized in Schemes **A** and **B**.

An improvement[6] to the earlier method[4] requires reaction of nitromethane with 50% aqueous potassium hydroxide (Scheme **A**). The dipotassium salt of **1**, obtained in 56% yield, is acidified with sulfuric acid and esterified with methanol or ethanol in the presence of anhydrous sodium sulfate at −55°/26 h. Subsequent standing at 25°/6 days, work up, and distillation gives the methyl or the ethyl ester in 60% yield. Nitromethane is reported[7] to condense with itself to produce methazonic acid (**10**), followed by de-

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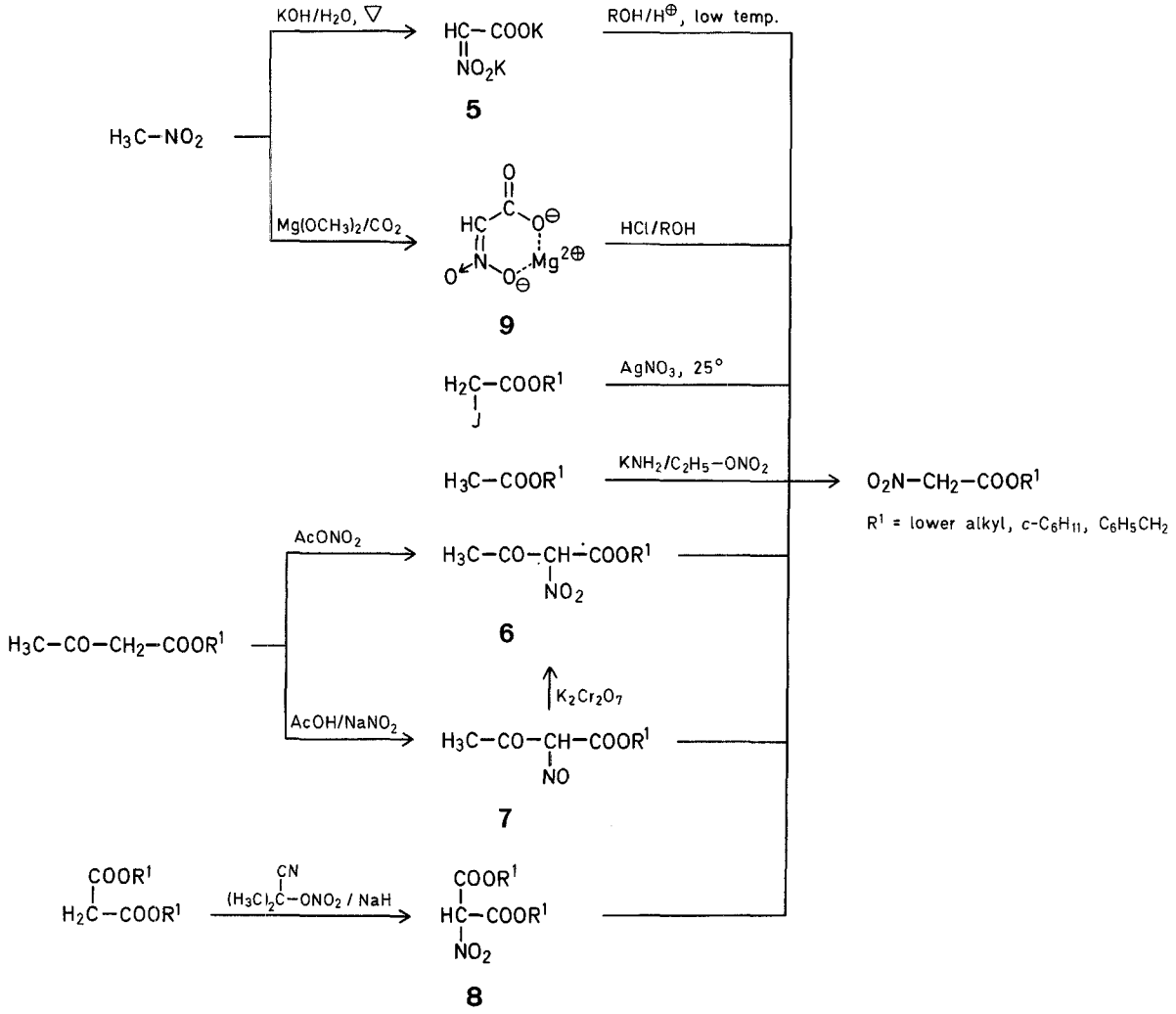
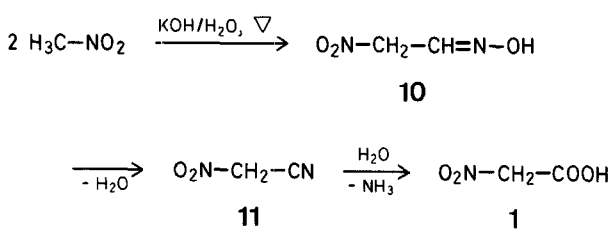


Scheme A



Scheme B (Compounds **1**, **10**, and **11** exist as potassium salts)

hydration to nitroacetonitrile (**11**), and hydrolysis (Scheme **B**). Another procedure[8], utilizing an increased concentration of the alkali, produces a 79–88% yield of the salt. Acidification and esterification are carried out at −15°/1 h followed by stirring at 25°/8 h. This highly recommended procedure[8] gives a 66–70% yield of methyl nitroacetate (**2**) in the esterification step. The ethyl, 1-propyl, and 2-propyl esters can be obtained in this fashion as well[9]. A similar method[10] utilizes potassium hydroxide in 1-butanol. Recrystallization of the resultant salt is necessary prior to esterification. The yields leading to the methyl ester are 71–77% in the first step and 60–66% in the second step. The benzyl ester (**4**) can be obtained in 35–50% yield[11] and 67–75% yield[12].

Benzyl Nitroacetate (4)[11]:

Benzyl alcohol (780 ml) is saturated with dry hydrogen chloride at 0° and to the resultant colourless solution is added, in portions, finely powdered dipotassium nitroacetate (275 g). During the addition, hydrogen chloride is passed into the well-stirred mixture whilst the temperature is allowed to rise to 10°. At this point, when the reaction mixture still contains hydrogen chloride (160 g), the gas supply is stopped and the reaction mixture is stirred for 4 h at 10°. After stirring for 18 h at 0° an equal volume of dichloromethane is added and the mixture is filtered. The filtrate is then washed acid-free with water (8 × 200 ml). The solvents are then removed from the filtrate by distillation from a steam bath at reduced pressure. The residue (250 g) is distilled to give benzyl nitroacetate: yield: 200–220 g (67–75% based on the dipotassium salt used as starting material); b.p. 120–125°/0.1 torr; m.p. 31°.

An earlier method[13] and a modification[14] thereof form the basis for a one-step procedure[15] involving nitration of alkyl (methyl, ethyl, isopropyl, and cyclohexyl) acetoacetates. For example, **3** can be prepared in 94% yield when ethyl acetoacetate is nitrated by 70% (or 99%) nitric acid in acetic anhydride in the presence of sulfuric acid. The resultant ethyl α-nitroacetoacetate (**6**) is then decomposed by ethanol in this patented process[16] (Scheme **A**).

A somewhat related process[17] involves the preparation of ethyl α-isonitrosoacetoacetate (**7**) in 80% yield. Oxidation by chromic acid and hydrolysis gives **3** in 61% yield. Manganese dioxide[18] and peroxytrifluoroacetic acid[19] oxidation gives 30% and 40% yields of **3**, respectively (Scheme **A**).

The general procedures developed for the synthesis of α-nitroalkanoic esters are applicable to the synthesis of nitroacetic esters as well (Scheme **A**). The Kornblum procedure[20] leads to **3** in 77% yield when ethyl iodoacetate is allowed to react with silver nitrite. Nitration of diethyl malonate by acetone cyanohydrin nitrate followed by alkaline cleavage constitutes another method[21] for the synthesis of **3** in 42% yield. The same process from ethyl acetoacetate gives a 52% yield. Carboxylation of nitromethane in the presence of magnesium methyl carbonate followed by esterification leads to **2** in 58% yield[22,23]. Nitration of *t*-butyl acetate with alkyl nitrates in the presence of potassium amide[24] results in the formation of *t*-butyl nitroacetate in 18% yield (Scheme **A**).

2.2. Nitroacetic Acid

The classical[3] method consists of suspending the salt in ether and freeing the acid by treatment with hydrogen chloride with cooling. Use of hydrochloric acid at −5° produces the acid in 20–36% yield[22]. The use of tartaric acid in the acidification step results in a yield of 70–79%[25]. In this way, quantities of up to 17 g with good purity can be obtained. Further purification is achieved by crystallization from chloroform or by sublimation at 68–70°/0.1 torr.

Nitroacetic Acid (1)[25]:
To dipotassium nitroacetate (39.8 g, 1 mol) in water (100 ml) is added a cold solution of tartaric acid (66 g, 2 mol) in water (100 ml) at −10° to −8° (ethanol/Dry Ice bath) within ~20 min to give a final pH of 2. The mixture is filtered, the filtrate saturated with sodium chloride, and extracted with ether (6 × 80 ml; AnalaR), all at 0°. The dried (Na_2SO_4) extracts are evaporated at 5–10° in vacuo to give a yellow oil which is dissolved in chloroform (30 ml), evaporated, and the process repeated. The crystalline product is thoroughly dried at 0°/0.2 torr for 6–7 h; yield: 16–18 g (70–78%); m.p. 86–88° (slow effervescence). The m.p. could be much lower if temperatures during the reaction were allowed to rise above 10°.

3. Physical and Spectral Properties

The physical and spectral properties of nitroacetic acid and the more frequently used esters are summarized in Table 1. When crystallized from hot chloroform or benzene, nitroacetic acid forms[3] long needles melting at 87–89° with decomposition. It dissolves readily in water (with a slow decomposition), ethanol, and ether. Ionization constants of **1**[22] and the X-ray crystallographic structure of the dipotassium salt **5**[26] have been studied.

For detailed discussions of the I.R. spectra see Refs. [27,28]. The pK_a of **3** has been reported as 5.82[29] and 5.62[30], compared to pK_a of 13.3 and 10.79 for diethyl malonate and ethyl acetoacetate, respectively.

4. Chemical Reactivity

4.1. Nitroacetic Esters

4.1.1. Reduction

Esters of glycine are produced upon reduction of the nitro group. As a structural proof, ethyl nitroacetate (**3**) was converted[3] to glycine by the action of sodium amalgam. This transformation was also achieved through catalytic hydrogenation[31,32].

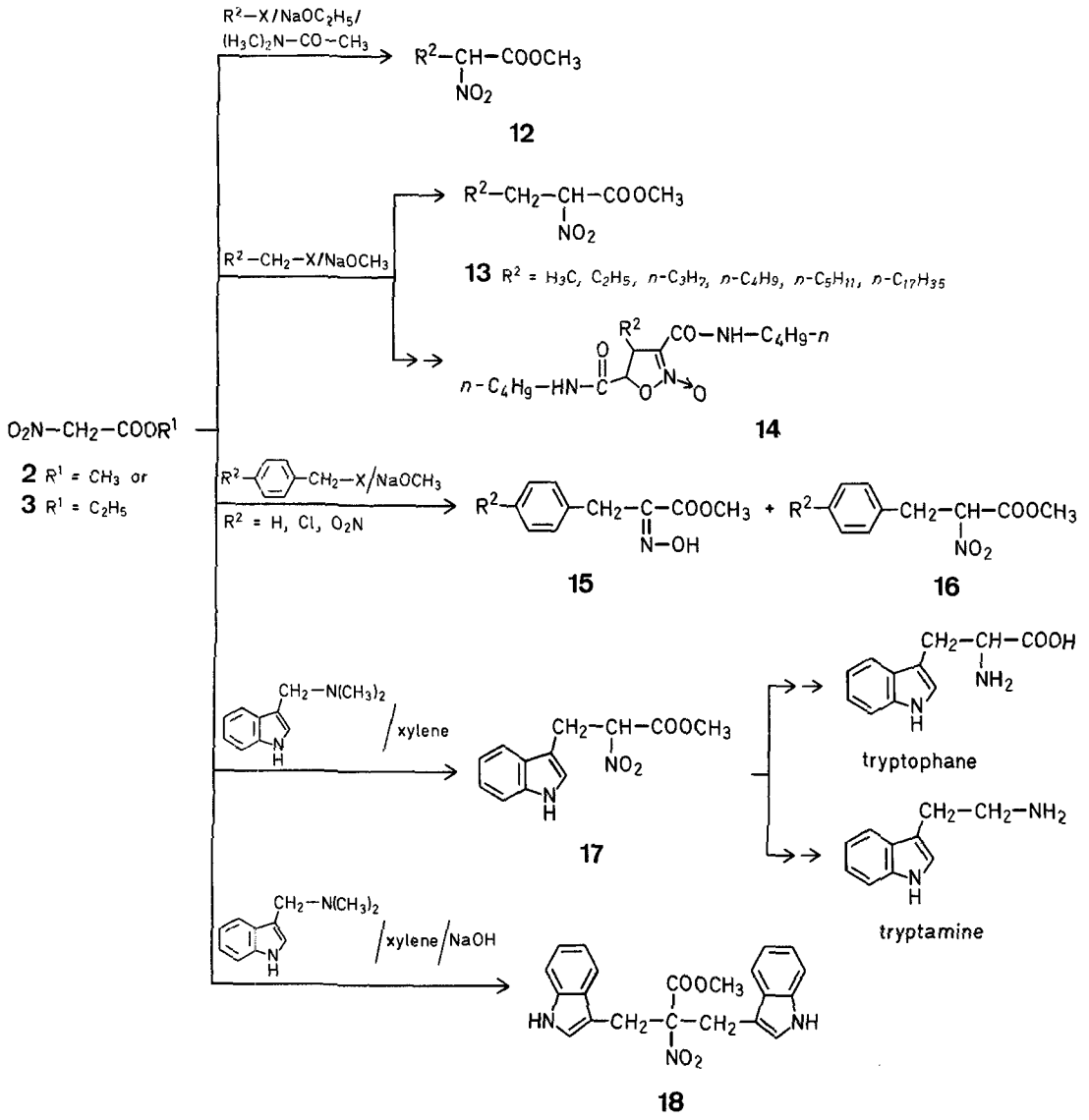
4.1.2. Alkylation

Alkylation reactions of esters of nitroacetic acid are summarized in Schemes **C** and **D**.

Table 1. Physical and Spectral Properties of Nitroacetic Acid and its Esters

Compound	R in O_2N-CH_2-COOR	m.p. or b.p./torr	I.R. ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	U.V. (solvent) λ_{max} [nm] (ε)	M.S. *m/e* (rel. int.)	Ref.
1	H	87–89° (dec.)	1735; 1565; 1390	5.20	(4 molar HCl): 274 (29.8) (0.12 molar NaOH): 275 (11000)	108 (1.3), 107 (1.25), 106 (0.2), 105 (0.3), 64 (10), 63 (14), 62 (8), 61 (4.1), 44 (100)	3, 22, 25
2	CH_3[a]	80–82°/8, 111–113°/25	1776; 1760	3.83 (s, 3H); 5.20 (s, 2H)	—	—	8
3	C_2H_5[b]	70°/1.5	1760; 1567	1.28 (t, 3H); 4.25 (q, 2H); 5.20 (s, 2H)	—	—	6, 15
4	$C_6H_5CH_2$	120–125°/1; m.p. 37°	—	—	—	—	12

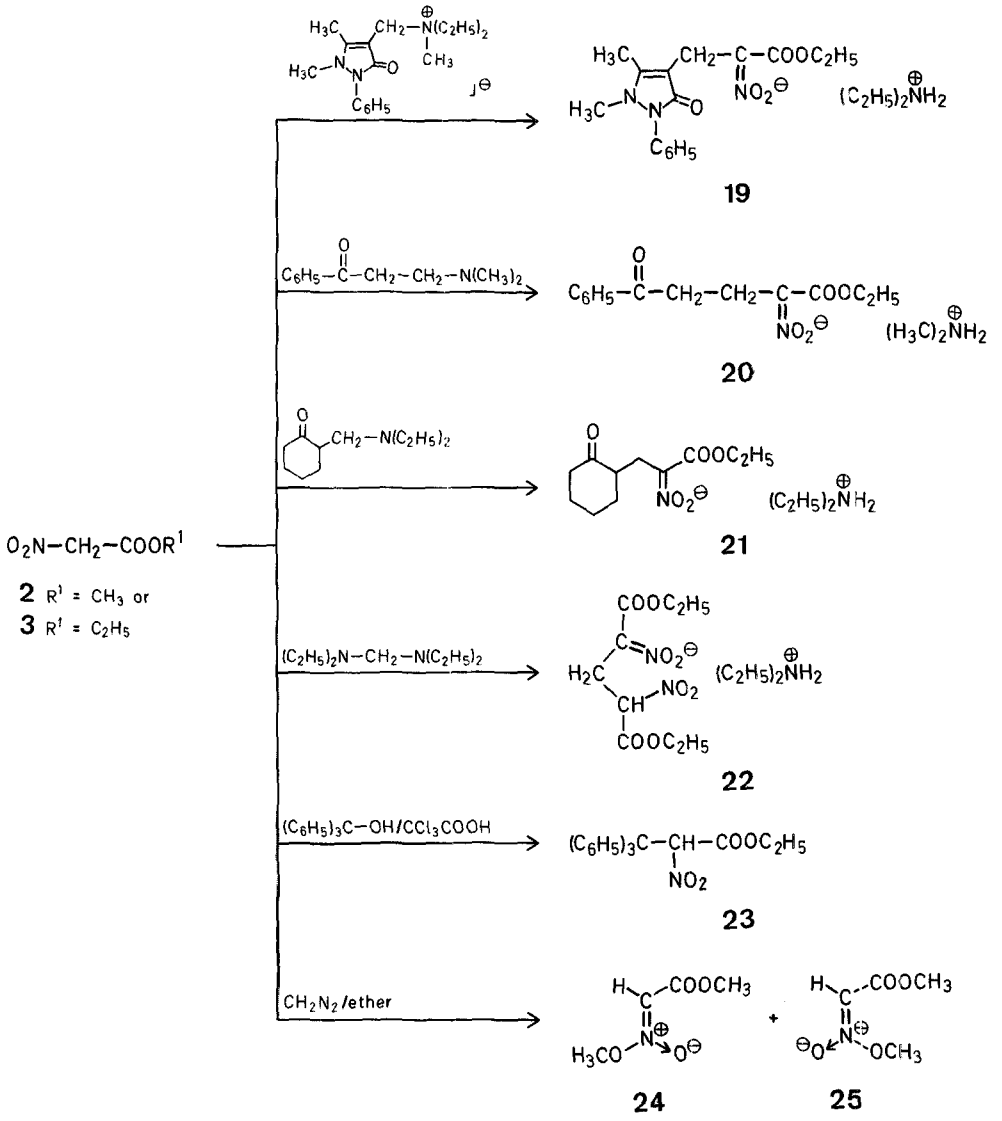
[a] n_D^{20}: 1.4260.
[b] n_D^{20}: 1.4252.



Scheme C

Alkylation with Alkyl Halides: *C*-Alkylation of the silver salt of **3** with methyl iodide produced ethyl 2-nitropropanoate in 28% yield[4]. The sodium salt was alkylated[33] with allyl bromide and crotyl chloride to produce ethyl 2-nitro-4-pentenoate (10–17% yield) and ethyl 2-nitro-4-hexenoate (10% yield), respectively. The *C*- and *O*-alkylations of the sodium salt of **2** in aprotic dipolar solvents, e.g. dimethylacetamide, were studied[34,35]. A number of intermediates **(12)** for the synthesis of α-amino acids were produced *via* *C*-alkylation with substituted alkyl halides, with yields ranging from 11 to 88% (Scheme C). This alkylation failed in protic solvents, however. Later, it was reported that use of *n*-alkyl iodides, in addition to *C*-alkylated products **13**, gave *O*-alkylated products which were isolated as isoxazoline *N*-oxides **14** in 32–43% yields[36]. This study was extended[37] to *p*-substituted benzyl halides to produce 3-phenyl-2-hydroxyiminopropanoates **15** (10–17% yields) and 3-phenyl-2-nitropropanoates **16** (20–37% yields). *C*-Alkylation of **3** was also achieved[38] in the presence of triethylamine to produce a 9–17% yield of the ethyl ester corresponding to **13** (R^2 = lower alkyl or phenyl).

Alkylation with Amines: *C*-Alkylation of **3** by gramine, in refluxing xylene with no additional base present was reported[1] to produce ethyl 2-nitro-3-(3-indolyl)-propanoate **(17)** in 90% yield. These reactants in the presence of sodium hydroxide led, however, to the bis-alkylated product **18**. The identical product **18** was isolated[39] by reacting **3** with gramine methiodide in the presence of sodium ethoxide in ethanol. This bis-alkylation was blocked effectively by substituting diethyl nitromalonate for **3** in the reaction involving gramine[40]. Stirring of **3** with gramine resulted in precipitation of the corresponding salt[41]. A quantitative yield of **17** was realized when the salt was heated under reflux in toluene. The reaction of **3** with diethylaminomethylantipyrine failed to give any *C*-alkylated product[42]. Reaction of the methiodide, however, led[43,44] to the desired product **19** (Scheme D).



Scheme D

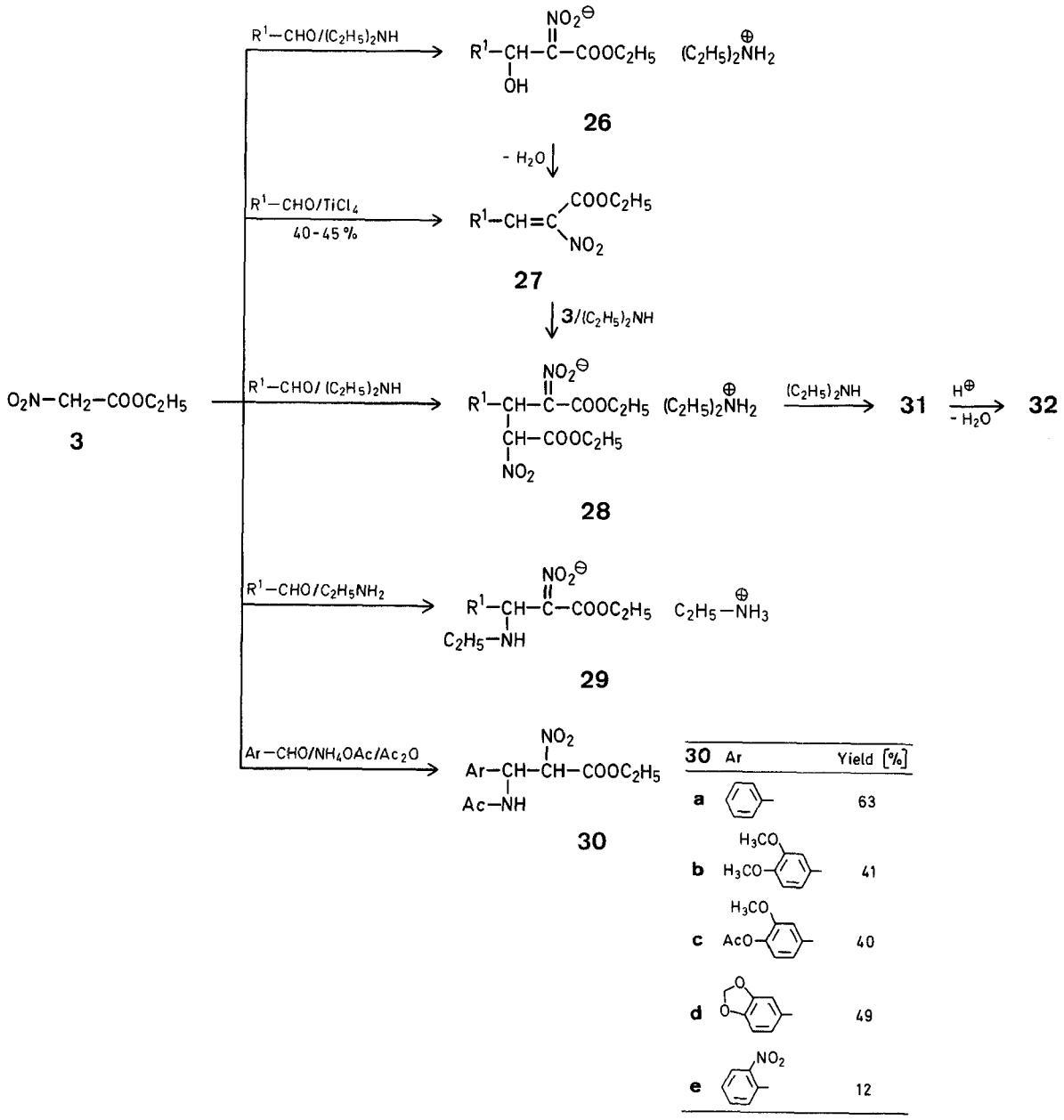
C-Alkylation readily took place on reaction with Mannich bases[43,44,45]. Thus, the reaction of **3** at 0° with 1-dimethylamino-3-phenyl-2-propanone and 2-diethylaminomethylcyclohexanone led to the corresponding *C*-alkylated products **20** and **21**, respectively, isolated as dialkylammonium salts (Scheme **D**). Reaction with bis[diethylamino]methane gave[43] diethyl 2,3-dinitroglutarate diethylammonium salt (**22**). Attempts to condense benzyl nitroacetate (**4**) with 3-diethylamino-3-hydroxyindol-2-one produced dibenzyl 2,4-dinitroglutarate in 8% yield[11]; a mechanism was proposed.

Alkylation with Alcohols: Heating of **3** with trityl alcohol in the presence of trichloroacetic acid resulted in the formation of ethyl 3,3,3-triphenyl-2-nitropropanoate (**23**)[46] in 41% yield (Scheme **D**). Acetic or sulfuric acids were not effective as catalysts in this reaction. Reaction of trityl chloride in the presence of triethylamine gave *C*- and *O*-bis-alkylated products. *C*-Alkylations with other aryl carbinols, e.g. xanthydrol, were also reported[47,48].

Alkylations with Diazomethane: Interaction of **3** with diazomethane led to *O*-alkylated products, i.e. the corresponding methyl ester of nitronic acid[14]. The products[49] derived from **2** were shown to consist of (*E*)- and (*Z*)-isomers **24** and **25** in the ratio of 2:3 (Scheme **D**).

4.1.3. Reaction with Aldehydes, Ketones, and Imino Compounds

Syntheses of amino acids, dinitroglutaric esters, isoxazoles, etc. were effected via condensation of nitroacetic esters with aldehydes, ketones, and Schiff bases. Three types of reaction products with aldehydes were isolated depending upon the reaction conditions: (a) the Henry addition leading to α-nitro-β-hydroxy esters **26**, (b) dehydration of these addition products leading to α-nitroacrylates **27**, and (c) the Michael addition of **3** to **27** producing 2,4-dinitroglutarates **28** (Scheme **E**). These reactions have been extensively studied and were briefly reviewed[45]. For example, condensation of 2-methyl-

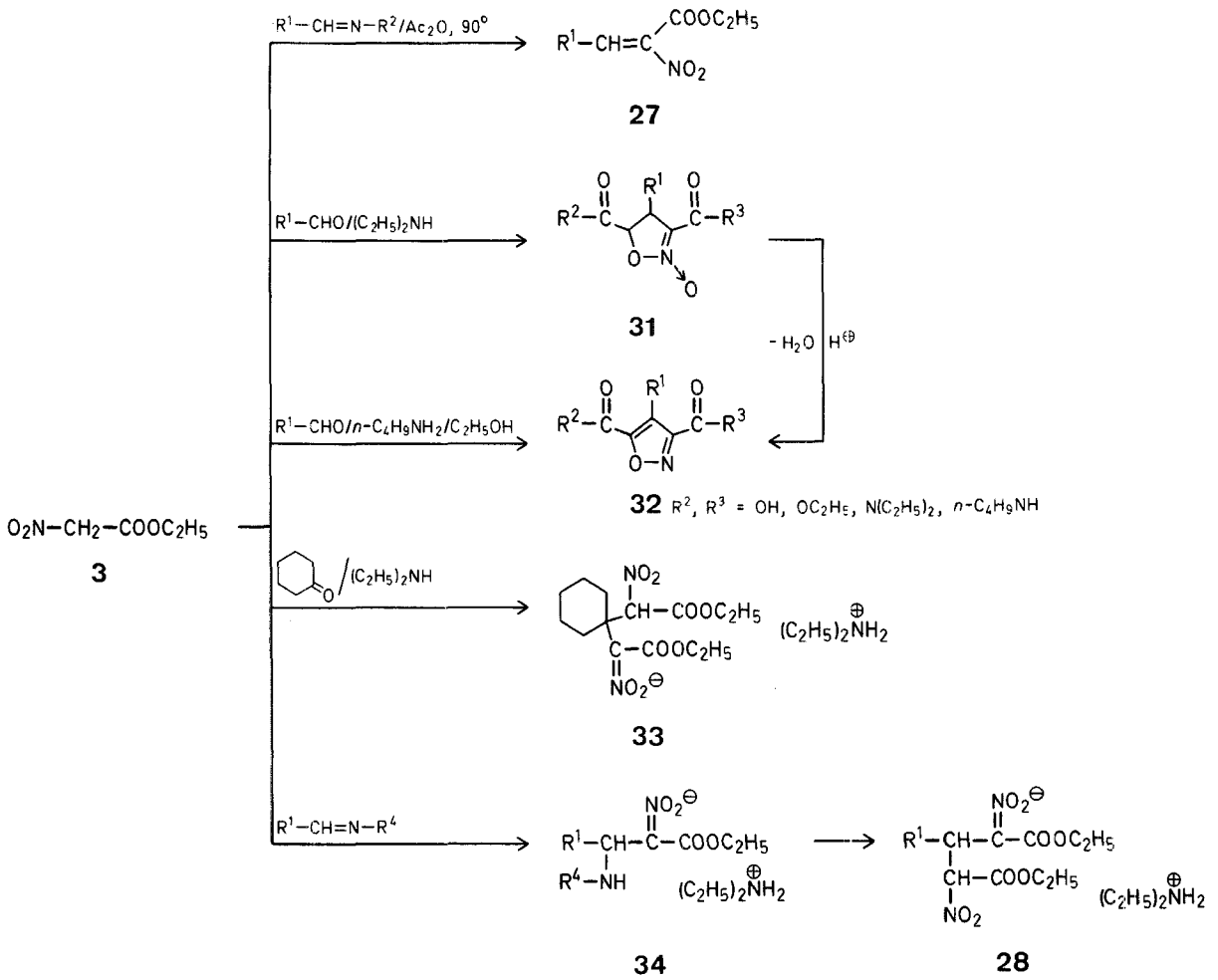


Scheme E

propanal with **3** in the presence of piperidine gave rise to ethyl 2-nitro-3-hydroxy-4-methylpentanoate in 46% yield[50]. Several α-nitro-β-hydroxy ester diethylammonium salts **26** were prepared from aliphatic as well as from aromatic aldehydes, **3**, and diethylamine[51]. These salts were observed to be unstable, changing to the corresponding dinitroglutarates **28**. Substitution of ethylamine (one equivalent) for diethylamine in the reaction led to α-nitro-β-ethylamino esters **29**. Reaction of aromatic aldehydes, ammonium acetate (or acetamide), and **3** in acetic anhydride give rise to 2-nitro-3-acetylamino-3-arylpropanoates **30** in good yields[52].

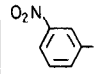
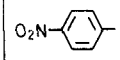
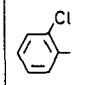
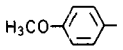
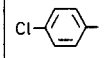
Sodium acetate was used[53,54] to prepare α-nitro-β-hydroxy esters from several aromatic aldehydes. The Knoevenagel condensation of **3** with aromatic and aliphatic aldehydes, in the presence of titanium(IV) chloride and pyridine, gave the corresponding α-nitroacrylates **27** in 40–45% yields (Scheme E). This reaction, also applicable to ethyl acetoacetate, was studied[55]. As mentioned earlier, the Michael addition[51,56] of a second equivalent of **3** led to dinitroglutarates **28**. Their preparation could be carried out, however, in one step (Table 2). For example, at room temperature, mixing one equivalent of butanal with 2 equivalents of **3** and 1 equivalent of diethylamine, led to diethyl 2,4-dinitro-3-propylglutarate diethylammonium salt (**28**, $R^1 = n$-propyl) in 95% yield[51].

Treatment of **28** with an excess of diethylamine converted[56] these compounds to corresponding isoxazolines oxide **31**, which in turn were converted to corresponding isoxazoles **32** in the presence of an acid[57]. These isoxazoles, however, could be prepared in one step in 26–68% yield by reacting 1 mol equivalent of



Scheme F

Table 2. Diethylammonium Salts of Diethyl 2,4-dinitroglutarates **28** (Scheme E)

R¹	Yield [%] of **28**	Ref.	R¹	Yield [%] of **28**	Ref.
n-C_3H_7	95	51		66	56
i-C_3H_7	—	51		60	56
	88	56		97	56
	89	56		62	56
	98	56		82	56
	68	56		83	56

an aldehyde with 2 mol equivalents of **3** in the presence of 6 mol equivalents of *n*-butylamine in refluxing ethanol[58] (Table 3).

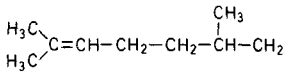
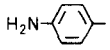
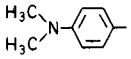
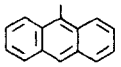
Reaction[57] of cyclohexanone with **3** resulted in formation of **33** in 65% yield (Scheme F). The Henry addition of **3** with fluorinated ketones and aldehydes was also reported[59,60].

A wide variety of Schiff bases was allowed to react with **3** and diethylamine[57]. The resultant unstable adducts **34** underwent facile conversion to the corresponding dinitroglutarate diethylammonium salts **28** (Scheme F). As in the case of aldehydes, treatment of Schiff bases with **3** and an excess of *n*-butylamine produced[58,61] the corresponding isoxazoles **32** in one-step with the yields ranging from 11% to 66%. Several ethyl α-nitrocinnamates (**27**, R = aryl) were prepared[62] by treating Schiff bases with **3** at 90° in the presence of acetic anhydride and assigned (*E*)- and (*Z*)-configurations[63] (Table 4).

4.1.4. Michael Addition

The esters readily undergo addition to nitroolefins and to α,β-unsaturated aldehydes, ketones, esters, and nitriles (Scheme G). For example, reaction[64] of **3** with acrolein, methacrolein, and crotonaldehyde in the presence of sodium ethoxide produced **35**. Potassium hydroxide[65,66], benzyltrimethylammonium hydroxide[67,72], trimethylanilinium benzenesulfonate[68,69], and diethylamine[51,57,70,71] served as effective

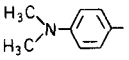
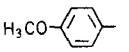
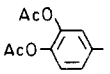
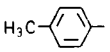
Table 3. 4-Substituted 3,5-Bis-[*n*-butylaminocarbonyl]-1,2-oxazoles **32** (R^2, $R^3 = n\text{-}C_4H_9NH$)[58]

R^1	Yield [%] Aldehyde	Utilizing Schiff Base
H_3C	24	11
$n\text{-}C_3H_7$	23	29
	–	20
	38	66
	42	47
	21	51
	36	57
	–	48
	–	31
	–	52
	–	10
	–	55
	–	50
	–	5
	–	21
	–	44

addition catalysts as well. Reaction of ethyl nitroacetate with potassium fluoride formed the double salt **38** which added readily to acrylonitrile and chalcone leading to ethyl 4-cyano-2-nitrobutanoate (**37**) and ethyl 4-benzoyl-3-phenyl-3-nitrobutanoate (**39**), respectively[73]. Fluorides of rubidium and cesium catalyzed the addition with good yields also. Diethylamine was used in the addition of **3** to acrylonitrile, chalcone (product **39**), 2-(2-furyl)-1-nitroethylene, 2-phenyl-1-nitroethylene, benzalacetone (product **40**), and ethyl cinnamate, with the isolation of products as diethylammonium salts in yields ranging from 54% to 97%[51,57].

A double addition of **2** to dimethyl 7-oxo-7*H*-benzocycloheptene-6,8-dicarboxylate, catalyzed by sodium methoxide, leading to **41** was reported[74]. The addition to nitroacrylates (the Knoevenagel products)

Table 4. Ethyl α-Nitrocinnamates **27** (Scheme F)

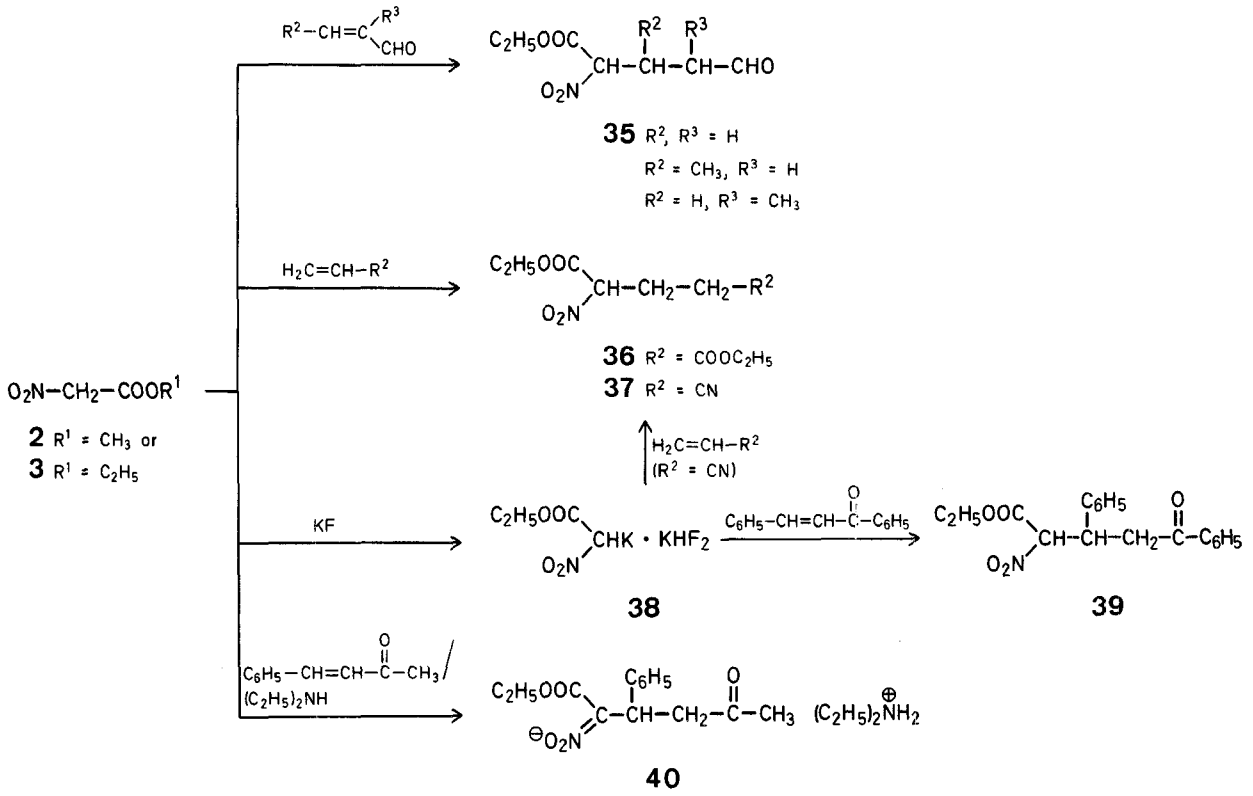
R	Yield [%]	Reference
	78	55
	83	55
	85	55
	64	55
	95	55
	88	55
$i\text{-}C_3H_7$	58	55
$t\text{-}C_4H_9$	40	55
	–[a]	104
	–[a]	104
	76	63
	70	63
	74	63

[a] Methyl ester.

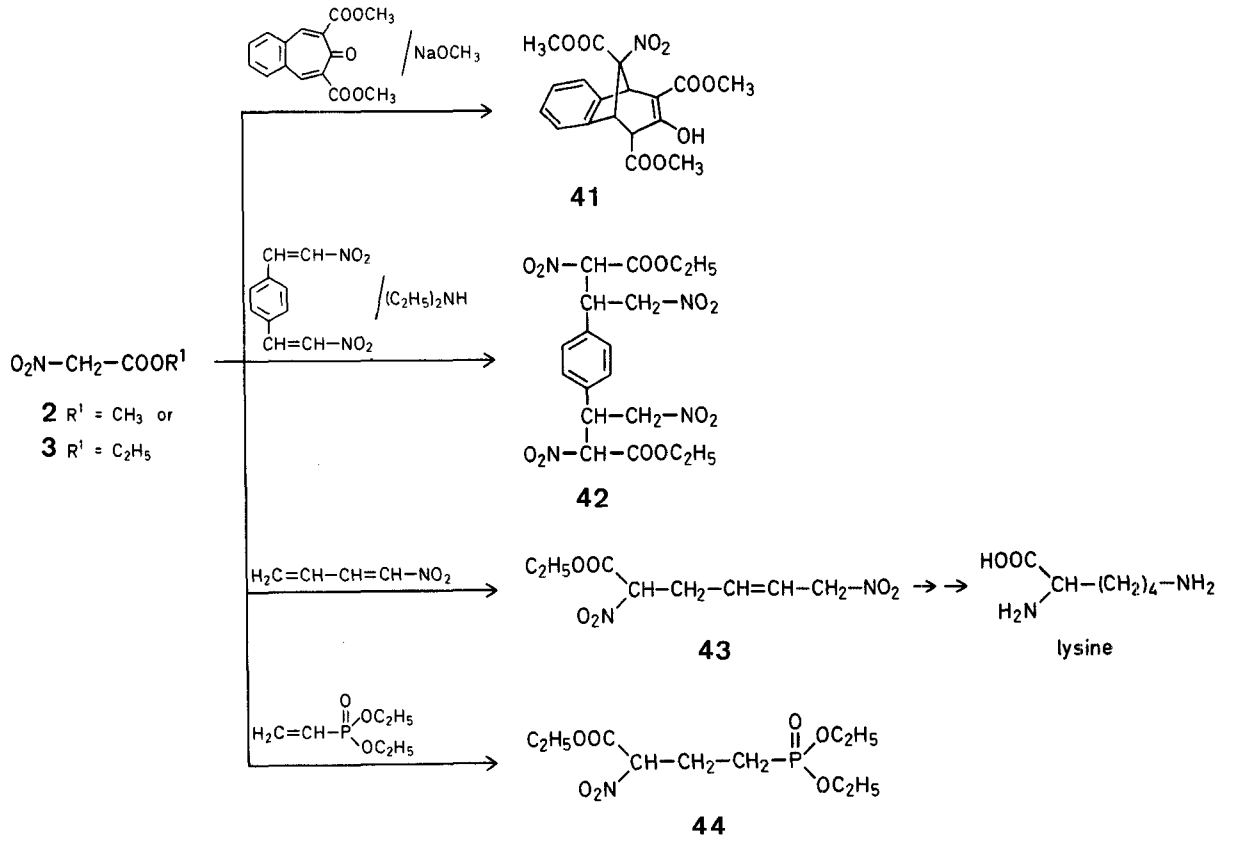
was discussed earlier. The reaction of 1,4-bis[2-nitrovinyl]benzene with **3** gave **42** in the presence of triethylamine[75]. Likewise, addition to 1-nitro-1,4-butadiene led[76] to the 1,4-addition product **43**, and addition to diethyl ethenephosphonate led[77] to **44** in 45% yield (Scheme H).

4.1.5. Alkoxymethylenation

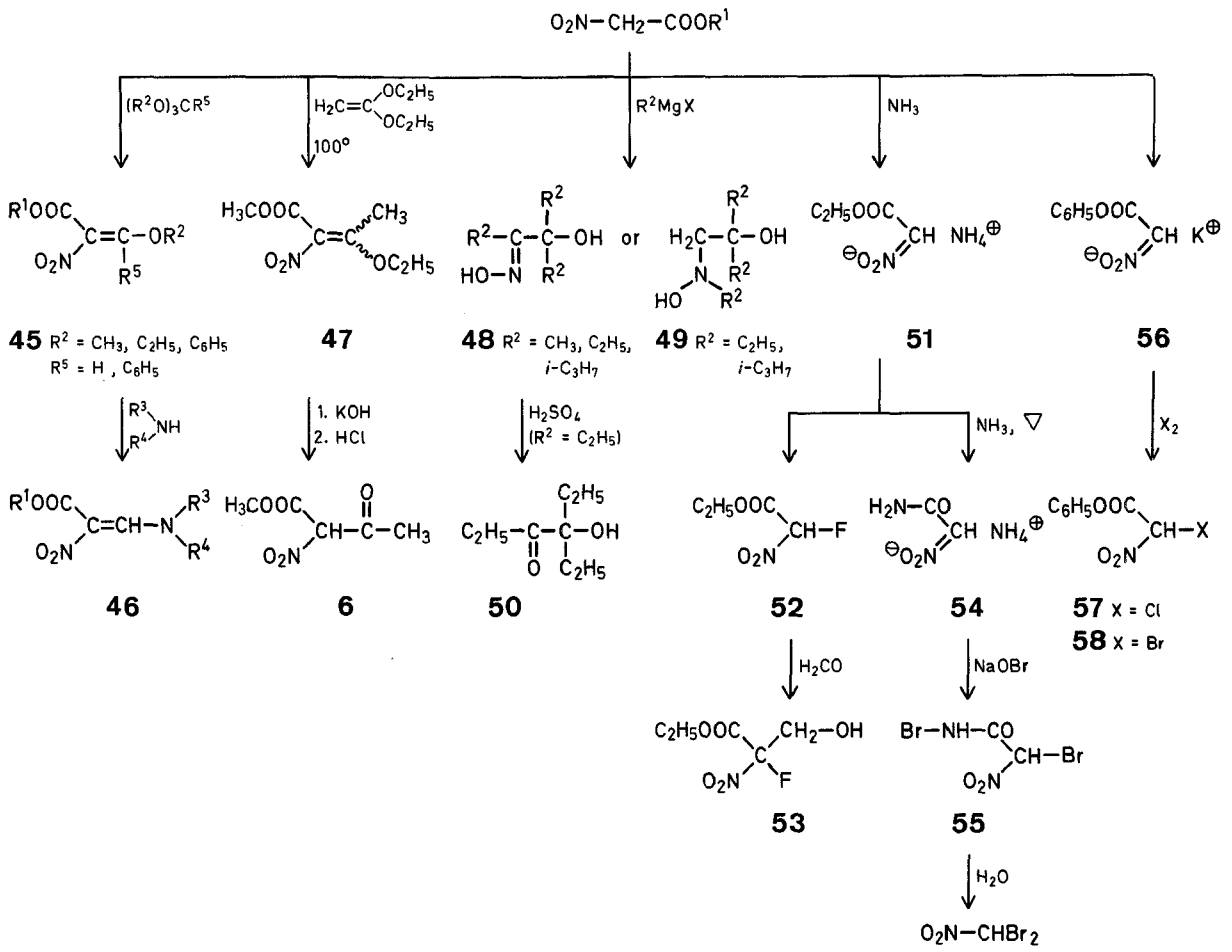
Nitroacetic esters readily form the corresponding alkoxymethylene compounds when heated with alkyl orthoformates in the presence of acetic anhydride[78,79]. Thus, methyl 2-nitro-3-ethoxyacrylate (**45**, $R^2 = C_2H_5$) was prepared[78] in 66% yield (Scheme I). The alkoxy group was readily displaced by amines[80,81,82]. Some of the resulting enamines **46** were intermediates for the synthesis of heterocyclic compounds. Arylenamines **46** (R^4 = substituted and unsubstituted phenyl) were synthesized in one step by heating **3** with triethyl orthoformate and aniline derivatives[80] (Table 5). Condensation of ketene diethylacetal at 100° with **2** gave methyl α-nitro-β-ethoxycrotonate (**47**) in 68% yield[83]. Compound **47** was converted to α-nitroacetoacetate **6** in 65% yield (Scheme I). Refluxing of **3** in triphenyl orthobenzoate leading to **45** ($R^5 = C_6H_5$) was also reported[84]. This reaction failed to occur in the presence of acetic anhydride.



Scheme G



Scheme H



Scheme I

Table 5. Ethyl 3-Arylamino-2-nitroacrylates **46** ($R^1 = C_2H_5$) (Scheme I)

R^3	R^4	Yield [%]	Reference
H	HO-C$_6$H$_4$-	44	80
H	H_3CO-C$_6$H$_4$-	66	80
H	2-H_3CO-C$_6$H$_4$-	80	80
H	2-CH_3O-C$_6$H$_4$-	64	80
H	H_3C-C$_6$H$_4$-	71	80
H	2-H_3C-C$_6$H$_4$-	84	80
H	2-CH_3-C$_6$H$_4$-	68	80
H	C$_6$H$_5$-	76	80
H	Br-C$_6$H$_4$-	94	80
H	Cl-C$_6$H$_4$-	83	80

Table 5. Continued

R^3	R^4	Yield [%]	Reference
H	HOOC-C$_6$H$_4$-	66	80
H	H_3C-CO-C$_6$H$_4$-	93	80
H	O_2N-C$_6$H$_4$-	90	80
H_3C	C$_6$H$_5$-	40	80
H	2-NO_2-C$_6$H$_4$-	61	82
H	2-F_3C-C$_6$H$_4$-	62	82
H	2,6-Cl_2-C$_6$H$_3$-	58	82
H	1-naphthyl	55	82
H	2-naphthyl	61	82

4.1.6. Reaction with Grignard Reagents

The reactions of **3** with methyl-, ethyl-, isopropyl-, and phenylmagnesium halides were studied[85]. The major products isolated were oximes **48** along with small amounts of hydroxylamines **49** (Scheme **I**). Compound **48** ($R^2 = C_2H_5$) was hydrolyzed to the keto alcohol **50**. Reaction of **3** with phenylmagnesium bromide yielded benzophenone and triphenylcarbinol.

4.1.7. Halogenation

Fluorination of the ammonium salt of **3** (**51**) with fluorine and nitrogen (1:30) in water at 5° gave rise to ethyl fluoronitroacetate (**52**)[86] (Scheme **I**). Addition of formaldehyde to **52** gave the nitro alcohol **53**. Bromination[87] of the nitroacetamide ammonium salt **54**, obtained in 70% yield by heating **51** in ammonia, gave *N*,α-dibromonitroacetamide (**55**) in 55% yield. Dibromonitromethane resulted in 61% yield when **55** was heated in water. Compounds **57** and **58** were produced when the potassium salt of phenyl nitroacetate (**56**) was halogenated[88]. The apparent ionization constants of ethyl fluoro- and chloronitroacetates in water were studied[89].

4.1.8. Reaction with Amines

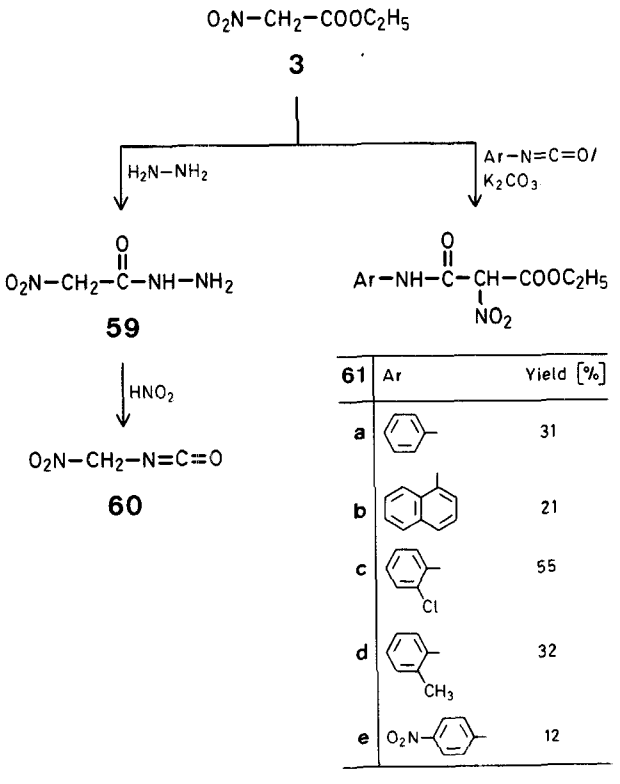
Reaction of alkyl nitroacetates with amines, in general, leads to the corresponding amine salts, which are converted to amine salts of the corresponding amides upon heating. The amines used in the reaction were ammonia[88,90], piperidine[91], and hydrazine[92]. The Curtius reaction[92] of nitroacetyl hydrazide (**59**) gave nitromethyl isocyanate (**60**) via nitroacetazide (Scheme **J**).

4.1.9. Addition Reaction

The reaction[93] of the sodium salt of **3** with aryl isocyanates gave the corresponding *N*-aryl-α-ethoxycarbonyl-α-nitroacetamides **61** in the yields varying from 12% to 55% (Scheme **J**).

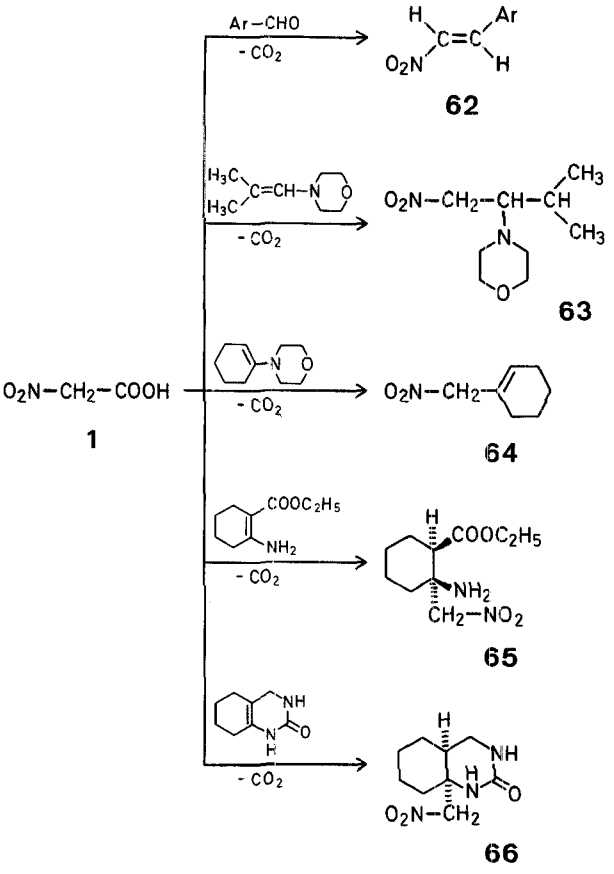
4.2. Nitroacetic Acid

As mentioned earlier, **1** undergoes ready decarboxylation which is complete in 5 minutes at 33° in dimethyl sulfoxide[25]. It is relatively stable in ethanol, ether, or chloroform, in contrast with its behavior in water. Nitroacetic acid (**1**) was used[25] to add the elements of nitromethane to aromatic aldehydes and enamines. The reaction with aldehydes proceeded neat at 65–90° and led to corresponding *trans*-β-nitrostyrenes **62** with occasional formation of nitro alcohols. This method of synthesizing nitrostyrenes was more satisfactory than the standard method involving nitromethane and a base. At considerably lower temperatures, reactions of enamines and **1** led to nitroamine adducts or to nitroolefins (Scheme **K**). For example, reaction of **1** with 2-methyl-1-morpholinoprop-1-ene led to a quantitative yield of **63**,



61	Ar	Yield [%]
a	C6H5	31
b	1-naphthyl	21
c	2-Cl-C6H4	55
d	2-CH3-C6H4	32
e	4-O2N-C6H4	12

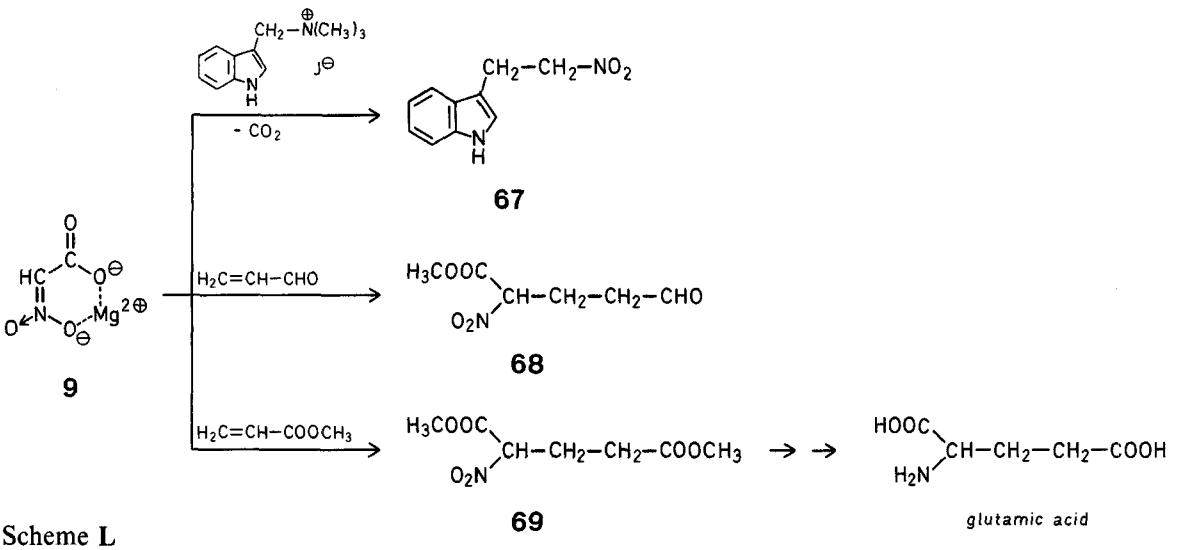
Scheme **J**



Scheme **K**

while reaction with 1-morpholinocyclohex-1-ene led to nitroolefin **64**. The same investigators[94,95] reported a stereospecific *cis*-addition of the elements of nitromethane in a similar fashion to ethyl 3,4,5,6-tetrahydroanthranilate and to 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one giving rise to **65** and **66**, respectively (Scheme K).

The magnesium salt of nitroacetic acid (**9**) was alkylated[22] with gramine methiodide to give 3-(2-nitroethyl)-indole (**67**) in 99% yield. The Michael addition of **9** with acrolein and methyl acrylate followed by esterification gave methyl 2-nitro-4-formylbutanoate (**68**) and dimethyl α-nitroglutarate (**69**), respectively[96]. Treatment[97] of the monopotassium salt of **1** in water with chlorine gave rise to dichloronitromethane in low yield. Fluorination of the monosodium salt of **1**, followed by esterification, gave ethyl fluoronitroacetate and ethyl difluornitroacetate[98] (Scheme L).



Scheme L

Tryptophan[1] and tryptamine[99] were synthesized via *C*-alkylation of gramine (Scheme C). Hydrolysis followed by decarboxylation of product **17** resulted in an 83% yield of 3-(2-nitroethyl)-indole, which was reduced in 82% yield to tryptamine, isolated as hydrochloride[99]. Similarly, reduction of **17** followed by hydrolysis gave tryptophan in 50% yield. The Michael addition product **35** ($R^2 = R^3 = H$) (Scheme G) was acetalized, hydrogenated over Raney nickel, hydrolyzed, and hydrogenated over platinum to produce proline[69] (Table 6). The Michael addition compound **43** (Scheme H) was hydrogenated and hydrolyzed to produce lysine[76]. Phenylalanine was synthesized via electrochemical reduction of methyl α-nitrocinnamate[100].

The Henry addition of **3** with 2-methylpropanal followed by dehydration gave ethyl α-nitro-β-isopropylacrylate which was hydrogenated over platinum to give the ethyl ester of leucine[101]. Threonine was synthesized via the Henry addition of acetaldehyde[102]. Reaction of **3** with glutaraldehyde and *o*-phthalaldehyde in the presence of sodium acetate at 10° in ethanol gave the corresponding nitrodiols which were hydrogenated over Raney nickel to produce 2-ethoxycarbonyl-2-aminocyclohexane-1,3-diol and 2-ethoxycarbonyl-2-aminoindan-1,3-diol, respectively[103] (Table 6).

5. Synthetic Utility

5.1. Amino Acids

The esters of nitroacetic acid are extremely valuable intermediates for the synthesis of numerous amino acids and related compounds (Table 6). The conversion of the nitro group leading to esters of glycine was described in Section 4.1.1. The extensive studies on *C*-alkylation[35] made a large contribution to the development of synthetic routes to several of the amino acids. Treatment of the sodium salt of **2** with alkyl halides led to **12** (Scheme C). Raney nickel hydrogenation, followed by acid hydrolysis led to the formation of the hydrochloride salts of the amino acids listed in Table 6.

Dimethyl α-Nitrosuccinate (12, $R^2 = CH_2COOCH_3$)[35]:

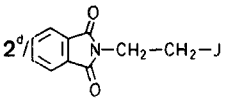
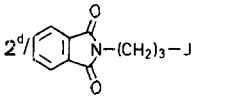
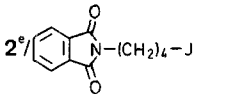
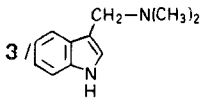
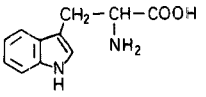
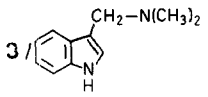
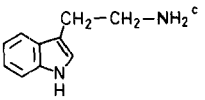
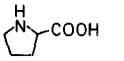
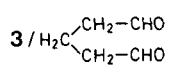
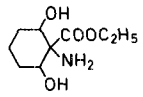
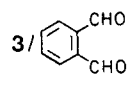
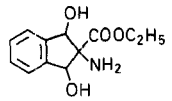
Method A: The sodium salt of methyl nitroacetate (2.0 g, 14.2 mmol) is added to a solution of methyl bromoacetate (2.17 g, 14.2 mmol) in dimethylacetamide (50 ml). This suspension is stirred overnight at room temperature. The reaction mixture is then added to water (150 ml) and extracted with benzene. The extract is subjected to fractional distillation under reduced pressure to give the title compound; yield: 0.63 g (23%).

Method B: 1.03 Normal sodium methoxide solution in methanol (22.8 ml) is added to a solution of methyl nitroacetate (3.1 g, 26.01 mmol) and methyl bromoacetate (4.0 g, 26.1 mmol) in dimethylacetamide (100 ml). The reaction mixture is then treated in a manner similar to that described above to give a yellow syrup. After distillation, compound **12** is obtained; yield: 3.3 g (66%).

5.2. Nitro Compounds

As apparent from Section 4, nitroacetic acid (**1**) and its esters are intermediates for a wide variety of nitro

Table 6. Amino Acids and Derivative Using Nitroacetates

Type of reaction of first step	Reactants used (nitroacetate/other reactant)	Yield [%] of first step	Amino Acid prepared	Ref.
reduction	**3**[a]/H_2	92	H_2N-CH_2-COOH[b]	31
C-alkylation	**2** /$Br-CH_2-COOCH_3$	66	$HOOC-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-CH_2-COOH$[c]	35
	2[d]/$Br-CH_2-CH_2-COOCH_3$	88	$HOOC-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-CH_2-CH_2-COOH$[c]	35
	2[d]/$J-CH_3$	74	$H_3C-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$[c]	35
	2[d]/$J-C_3H_7$-*i*	20	$i\text{-}C_3H_7-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$[c]	35
	2 /$Br-CH_2-C_6H_5$	50	$C_6H_5-CH_2-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$[c]	35
	2[d]/ 	11	$H_2N-(CH_2)_2-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$[c]	35
	2[d]/ 	29	$H_2N-(CH_2)_3-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$[c]	35
	2[e]/ 	12	$H_2N-(CH_2)_4-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$[c]	35
	3 / 	90		1
	3 / 	90		99
Michael addition	**2** /$H_2C=CH-CHO$	85		69
	3 /$H_2C=CH-CH=CH-NO_2$	–	$H_2N-(CH_2)_4-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$[c]	76
	9 /$H_2C=CH-COOCH_3$	–	$HOOC-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-CH_2-CH_2-COOH$	96
Henry addition	**3** /H_3C-CHO	–	$H_3C-\underset{\displaystyle OH}{\underset{\vert}{CH}}-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$[f]	102
	3 /$i\text{-}C_3H_7-CHO$	–	$i\text{-}C_3H_7-CH_2-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-COOH$[g]	101
	3 / 	40		103
	3 / 	71		103

[a] Ethylammonium salt used.
[b] Isolated as ethyl ester, hydrochloride salt.
[c] Isolated as hydrochloride salt.
[d] Sodium salt used.
[e] Silver salt used.
[f] Isolated as ethyl ester, oxalate salt.
[g] Isolated as ethyl ester.

compounds which include dialkyl 2,4-dinitroglutarates, α-nitroacrylates, α-nitrocinnamates, nitro alcohols, nitro amines, nitro olefins, nitrohalo compounds, etc. Diethyl 2,4-dinitroglutarates, in general, were prepared by reacting 1 mol equivalent of an aldehyde, 2 mol equivalents of **3**, and 3 mol equivalents of diethylamine in ethanol or in ligroin at room temperature. The products listed in Table 2 were isolated as crystalline diethylammonium salts[51,56].

Diethyl 2,4-Dinitro-3-*n*-propyl-1,5-pentanedioate Diethylammonium Salt (28, $R^1 = n\text{-}C_3H_7$)[31]:
Butanal (0.7 g, 10 mmol) in petroleum ether is treated with ethyl nitroacetate (2.6 g, 20 mmol) and, after cooling in an ice/water bath, diethylamine (0.8 g, 11 mmol) is added. The reaction mixture is allowed to stand at room temperature for 12 h. The precipitated diethylammonium salt of the ester is filtered under suction and recrystallized from ethanol; yield: 3.7 g (95%); m.p. 104–105°.

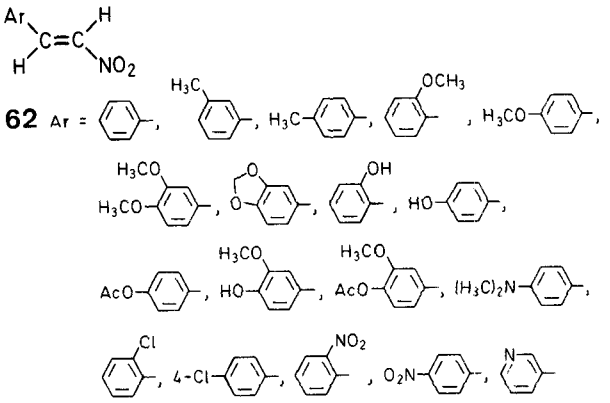
Ethyl α-nitroacrylates were synthesized[55] by reaction of aldehydes with **3** in tetrahydrofuran in the presence of titanium(IV) chloride and a tertiary amine (Table 4).

Ethyl 3-Substituted 2-Nitropropenoates (27):
Titanium(IV) chloride (11 ml, 0.1 mol) in anhydrous tetrachloromethane (25 ml) is added under strict exclusion of moisture to well-stirred cooled (~0°) anhydrous tetrahydrofuran (200 ml). A yellow, flaky precipitate forms. The aldehyde and ethyl nitroacetate (0.05 mol each) are then added neat or as tetrahydrofuran solutions (25 ml). Anhydrous pyridine (16 ml, 0.2 mol) or *N*-methylmorpholine (22 ml, 0.2 mol) in anhydrous tetrahydrofuran (~30 ml) is then added dropwise during 1 to 2 h to the well-stirred, cooled (0°) mixture. If the base is added too quickly an oily precipitate may form. The resultant mixture is then stirred at 0° or allowed to warm to room temperature. After 7–24 h, water (50 ml) and diethyl ether (50 ml) are added. The aqueous layer is extracted with ether (2 × 50 ml), the combined ether extracts are washed with saturated sodium hydroxide solution (50 ml), and the organic phase is dried with magnesium sulfate. The solvent is then removed at 30° under water pump vacuum. The product is purified by distillation through a suitable column or recrystallized; yield: 40–95% (determined by G.L.C.).

A mixture of the *E*- and *Z*-isomers of methyl α-nitrocinnamates was synthesized[104] from aldehyde anils and **2** in acetic anhydride in yields ranging from 85% to 97%.

Methyl α-Nitrocinnamate[104]:
A mixture of *N*-benzylideneaniline (69.5 g), methyl nitroacetate (40 g), and acetic anhydride (72 ml) is heated at 40° for 4 h. Then the mixture is poured into hot (80°) water (2000 ml), and the resultant mixture is carefully stirred. The aqueous layer is separated by decantation, and the oil is diluted with tetrachloromethane (150 ml) and washed twice with hot water. The solution is dried with magnesium sulfate and evaporated in vacuum. For additional purification, the resultant mixture of isomers of the nitro ester (62 g, 90%) is distilled in vacuum, a fraction with b.p. 130–140°/0.5 torr being collected. On standing the nitro ester (*Z*-isomer) crystallized out; yield: 30 g; m.p. 57.5–58° (from chloroform/hexane).

This method was extended[63] to prepare several α-nitroacrylates **27** (Table 4). N.M.R. spectroscopy aided by a shift reagent was used to assign the stereochemistry[63]. Heating of **3** with triethyl orthoformate and aniline dervatives or naphthylamines gave ethyl 3-arylamino-2-nitroacrylates **(46)** as mixtures of *E*- and *Z*-isomers[80,82] (Scheme I and Table 5). Ethyl 1-nitro-2-acetylamino-2-phenylpropanoates **(30**; Scheme E) resulted when **3** was heated with aromatic aldehydes and ammonium acetate in the presence of acetic anhydride[52]. Heating[25] (65–90°) of **1** with aromatic aldehydes, neat in a dry nitrogen atmosphere until decarboxylation was complete, led to 2-nitrostyrenes **62** listed below.



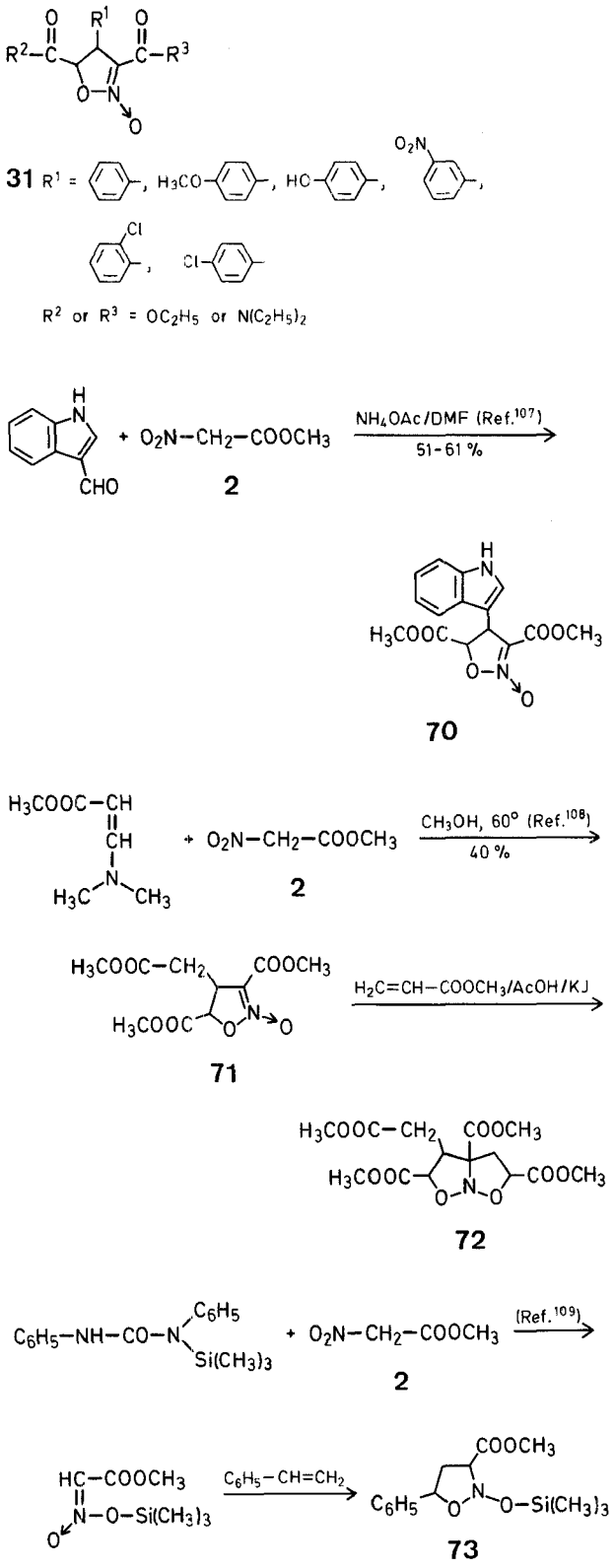
Reaction of Nitroacetic Acid with Aromatic Aldehydes[25]:
The aldehyde (1 mmol) is stirred with nitroacetic acid (2 mmol) under dry nitrogen and the temperature raised slowly until effervescence begins. The mixture is stirred at that temperature (ranging from 65° to 90°) until carbon dioxide evolution ceased (0.75–1.5 h). If the ^{1}H-N.M.R. spectrum indicates complete formation of a β-nitrostyrene, the product is purified by distillation, sublimation, or crystallization and its m.p. or b.p. and I.R. and N.M.R. spectra were compared with those of an authentic sample. If the condensation is not complete, the crude product, after removal of nitromethane by bubbling dry nitrogen through it, is treated with a further quantity of nitroacetic acid (2 mmol) as above, and this process is repeated until a high conversion into the nitrostyrene is obtained.

N-Aryl-2-ethoxycarbonyl-2-nitroacetamides **(61**; Scheme J) were synthesized by reacting equimolar mixtures of isocyanates, **3**, and anhydrous potassium carbonate in refluxing benzene[93]. The potassium salt of methyl formylnitroacetate was obtained in 77% yield when methyl β-ethoxy-α-nitroacrylate was treated with 10% potassium hydroxide in methanol at 0°. This salt was suspended in ether and treated with hydrogen chloride to prepare methyl formylnitroacetate[105]. Trimethyl and triethyl esters of 1,3,5-trinitro-1,3,5-pentanetricarboxylic acid were prepared by reacting 3 mol equivalents of **2** or **3** with 2 mol equivalents of *N,N,N',N'*-tetraethylmethylenediamine in absolute methanol followed by acidification[106].

5.3. Heterocyclic Compounds

A number of isoxazoline *N*-oxides **31** were prepared[56] in 60–90% yield by refluxing diethylammonium salts of diethyl dinitroglutarates (**28**; see below and Scheme E) with diethylamine in ethanol. The additional methods for the synthesis of this ring sys-

tem and its derivatives (**70-73**) are summarized[107,108,109] in Scheme **M**.



Scheme **M**

Isoxazoles **32** were prepared[110,111] by exposing ethyl α-nitroacrylates or diethyl 1,3-dinitroglutarates to an excess of a primary amine. These heterocycles, however, could be conveniently made[58] by reacting one mol equivalent of an aldehyde, 2 mol equivalents of **3**, and 6 mol equivalents of *n*-butylamine in refluxing ethanol (Table 3). An alternate method, which gave higher yields in general, consisted of reacting **3** with Schiff bases.

General Method for the Synthesis of Isoxazoles Using Aldehydes[58]:

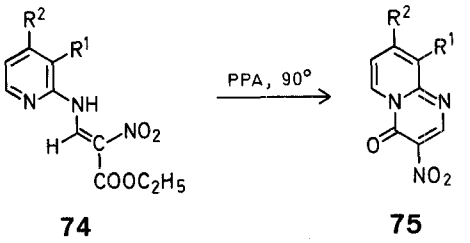
To a mixture of an aldehyde (1.0 equiv.) and ethyl nitroacetate (2.0 equiv.) in absolute ethanol, *n*-butylamine (6 equiv.) is added; the mixture is heated under reflux for 5 h and worked up in a manner similar to that described below.

4-Methyl-3,5-bis[*n*-butylaminocarbonyl]isoxazole[58]:

Into a solution of ethylidene-*n*-butylamine (1.50 h, 0.015 mol) in absolute ethanol (5 ml) is added ethyl nitroacetate (4.03 g, 0.03 mol) under stirring. During this period, considerable heat is evolved; the temperature of the reaction mixture rises to 60° from 18°. *n*-Butylamine (5.53 g, 0.076 mol) is then added to the mixture. When the exothermic reaction has subsided, the reaction mixture is gently heated under reflux for 5 h. After the solution has been left standing at room temperature, the solvent is removed by distillation to give a reddish brown sirup, which is allowed to stand in a refrigerator to give crystals of the title compound; yield: 0.46 g (11%). Recrystallization from ligroin to gives feathery crystals; m.p. 84-86°.

3-Nitro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**75a-d**; Table 7) resulted when compounds **74a-d** were cyclized by the action of polyphosphoric acid at 90° for one hour in a closed vessel[82]. 3-Nitro-4-oxo-4*H*-pyrimido[2,1-*a*]isoquinoline (**75e**) was prepared in 68% yield by reacting 1-aminoisoquinoline with ethyl 3-methoxy-3-nitroacrylate (**76a**) followed by the polyphosphoric acid treatment.

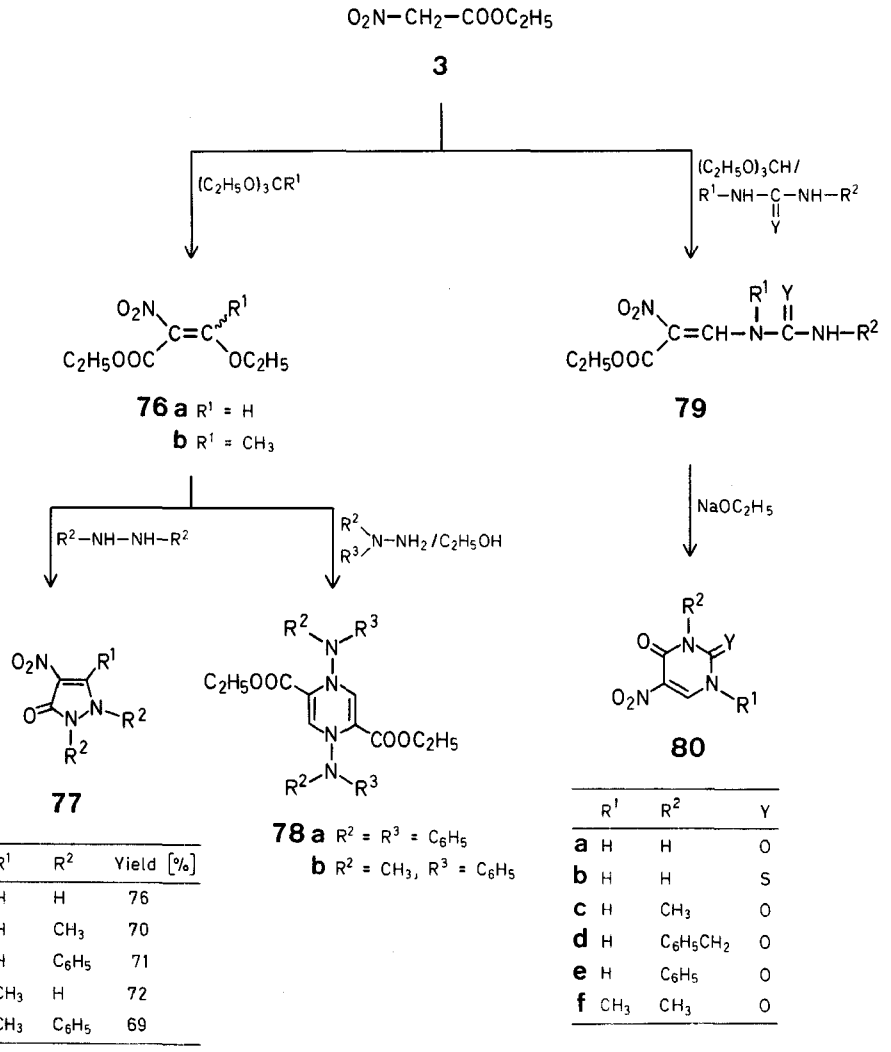
Table 7. 3-Nitro-4-oxo-4*H*-pyrido[1,2-*q*]pyrimidines **75**[82]



Compound	R^1	R^2	Yield [%]
75a	H	H	72
75b	OH	H	62
75c	CH_3	H	65
75d	H	CH_3	67
75e	$-(CH=CH)_2-$		68[a]

[a] Prepared in one step from 1-aminoquinoline.

Two types of heterocycles were generated when **76a** and **76b** were reacted with hydrazines. Dihydropyrazoles **77** (Scheme **N**) resulted when hydrazine and *N,N'*-disubstituted hydrazines were used[81]; while reaction of **76a** with *N,N*-disubstituted hydrazines led to dihydropyrazines **78**.



	R^1	R^2	Yield [%]
a	H	H	76
b	H	CH_3	70
c	H	C_6H_5	71
d	CH_3	H	72
e	CH_3	C_6H_5	69

	R^1	R^2	Y
a	H	H	O
b	H	H	S
c	H	CH_3	O
d	H	$C_6H_5CH_2$	O
e	H	C_6H_5	O
f	CH_3	CH_3	O

Scheme N

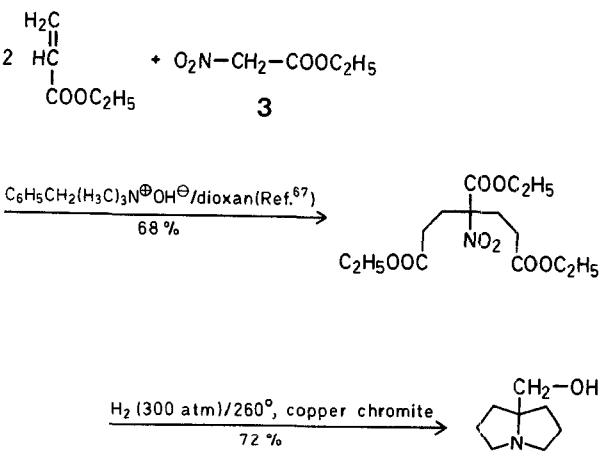
4-Nitro-3-oxo-2,3-dihydropyrazole (77a)[81]:
To a solution of ethyl 3-ethoxy-2-nitropropenoate (**76a**; 6.0 g, 31.7 mmol) in ether (50 ml) is added, drop-wise at room temperature within 10 min with vigorous stirring, a solution of hydrazine hydrate (1.7 g, 33.9 mmol) in anhydrous ethanol (3 ml). The mixture is then heated under reflux for 30 min, the resultant precipitate is filtered under suction, and recrystallized from glacial acetic acid; yield: 3.2 g (76%); yellow crystals; sublimation p. >200°; m.p. (sealed tube): 254°.

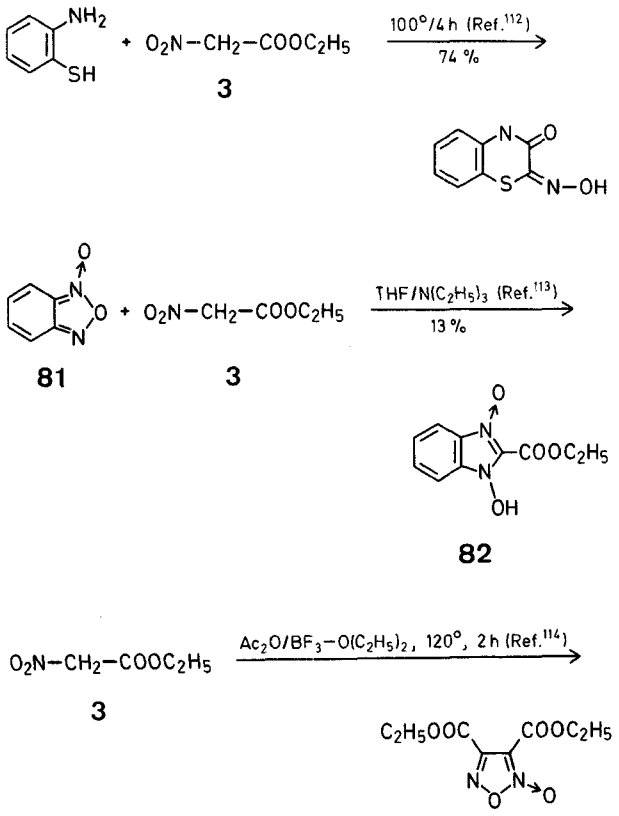
5-Nitrouracils **80** were prepared by base-catalyzed cyclization of **79**, which were synthesized in one step by heating mixtures of **3**, ureas, and ethyl orthoformate (Scheme N).

Ethyl ω-Methylureidomethylenenitroacetate[79]:
A mixture of ethyl nitroacetate (2.66 g, 0.02 mol), ethyl orthoformate (3.70 g, 0.025 mol) and *N*-methylurea (1.48 g; 0.02 mol) is heated at 120°, under continuous removal of ethanol for 20 min. After five minutes, a yellow precipitate separates; the excess orthoester is removed in vacuo, and the residue, after crystallization from ethanol, affords **79** ($R^1 = H$, $R^2 = CH_3$, Y = O); yield: 3.05 g (71%); m.p. 177°.

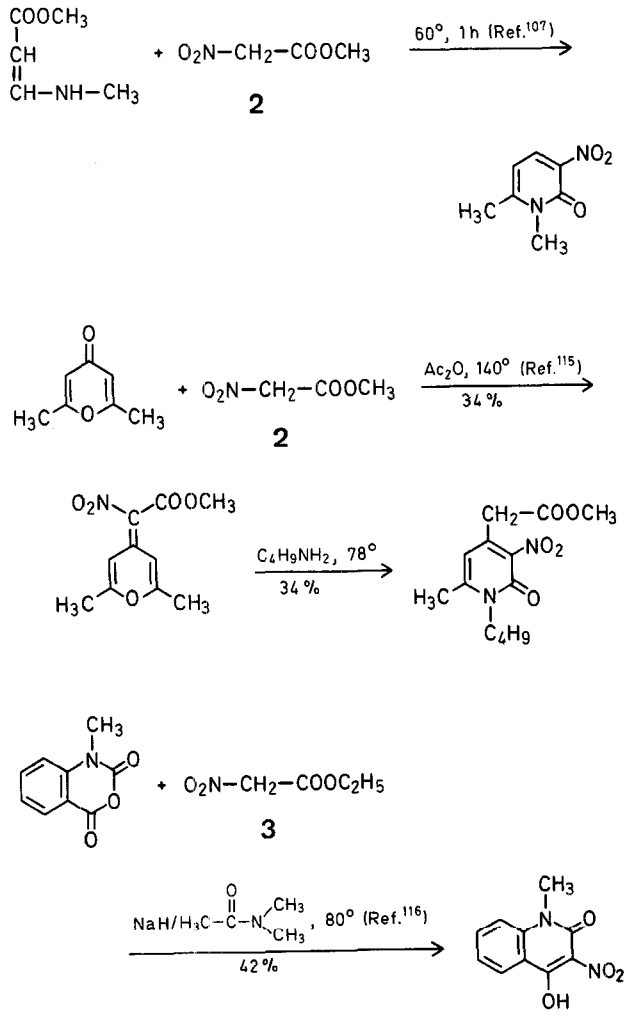
3-Methyl-5-nitrouracil (80c)[79]:
Ethyl ω-methylureidomethylenenitroacetate (1.085 g, 0.005 mol) is heated under reflux with 0.5 molar ethanolic sodium ethoxide solution (10 ml) for 2 h. The residual suspension is evaporated in vacuo, the residue dissolved in hot water (15 ml), the solution treated with charcoal, filtered, and the filtrate acidified with 1 normal hydrochloric acid to give product which separates; yield: 0.851 g (100%); m.p. 272–273°.

Schemes **O** and **P** summarize the synthesis of additional heterocycles and their derivatives. A synthesis of 1-hydroxy-2-ethoxycarbonylbenzimidazole-3-oxide (**82**) was reported[113].





Scheme O

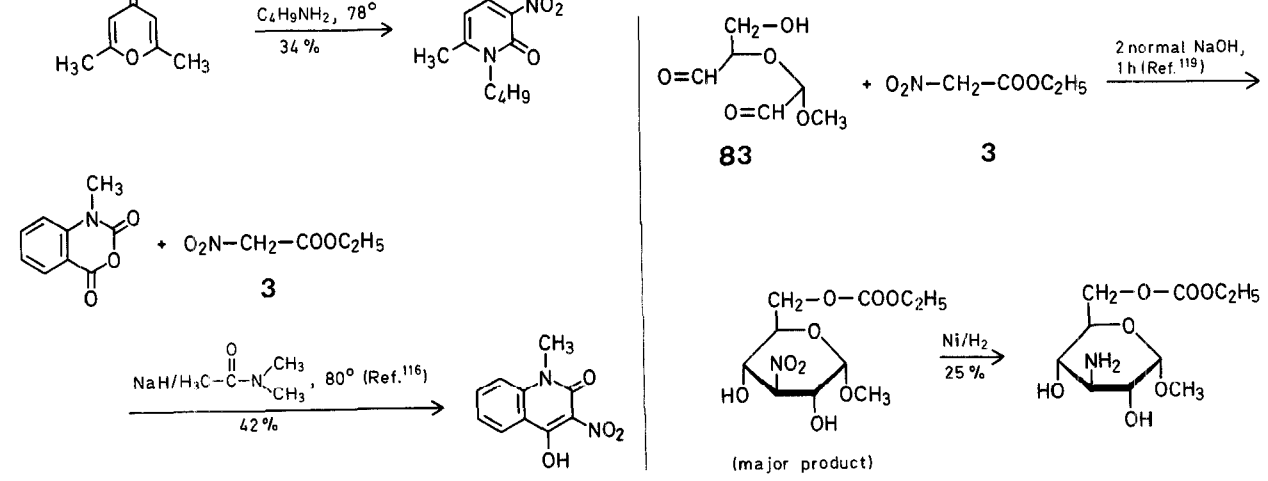


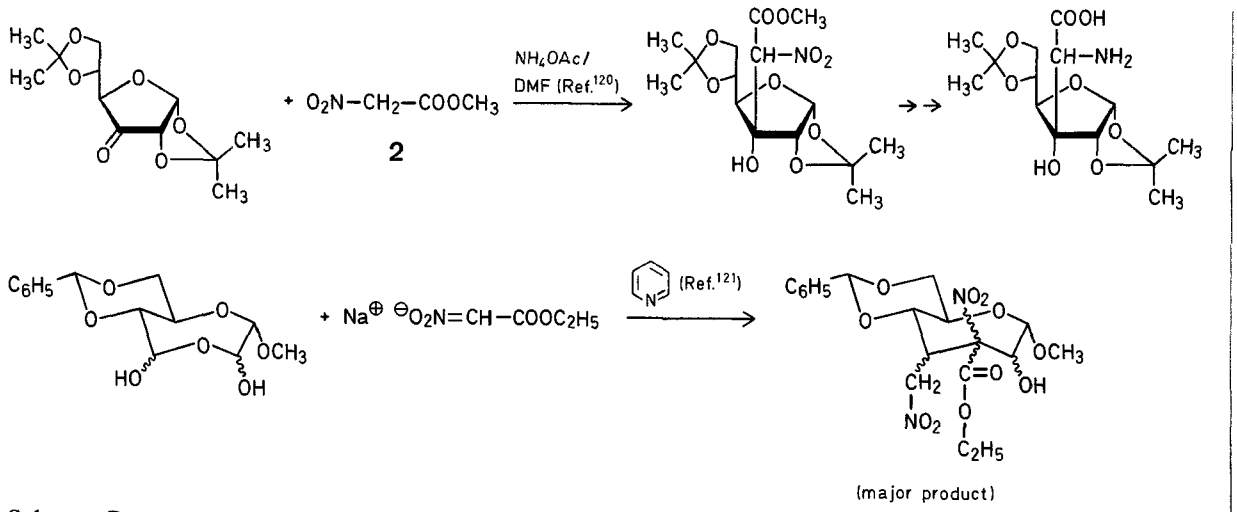
Scheme P

1-Hydroxy-2-ethoxycarbonylbenzimidazole-3-oxide (82)[113]:
A solution containing ethyl nitroacetate (4.22 g, 0.0317 mol), tetrahydrofuran (5 ml), and triethylamine (5 ml) is added to a solution of isobenzofuroxan (**81**; 4.30 g, 0.0317 mol) in tetrahydrofuran (10 ml) containing triethylamine (10 ml). Upon completion of the addition, the reaction mixture is allowed to stand at room temperature for about 4 h whereupon the yellow precipitated solid is filtered, washed, and dried. Recrystallization from ether/acetone gives the product; yield: 1.1 g (13%); m.p. 154.5–156.5°.

5.4. Carbohydrate Derivatives

Alkyl nitroacetates were used for the preparation of nitro and amino carbohydrate derivatives as summarized in Scheme Q. A C→O ethoxycarbonyl shift was observed[119] when **83** was allowed to react with **3**.





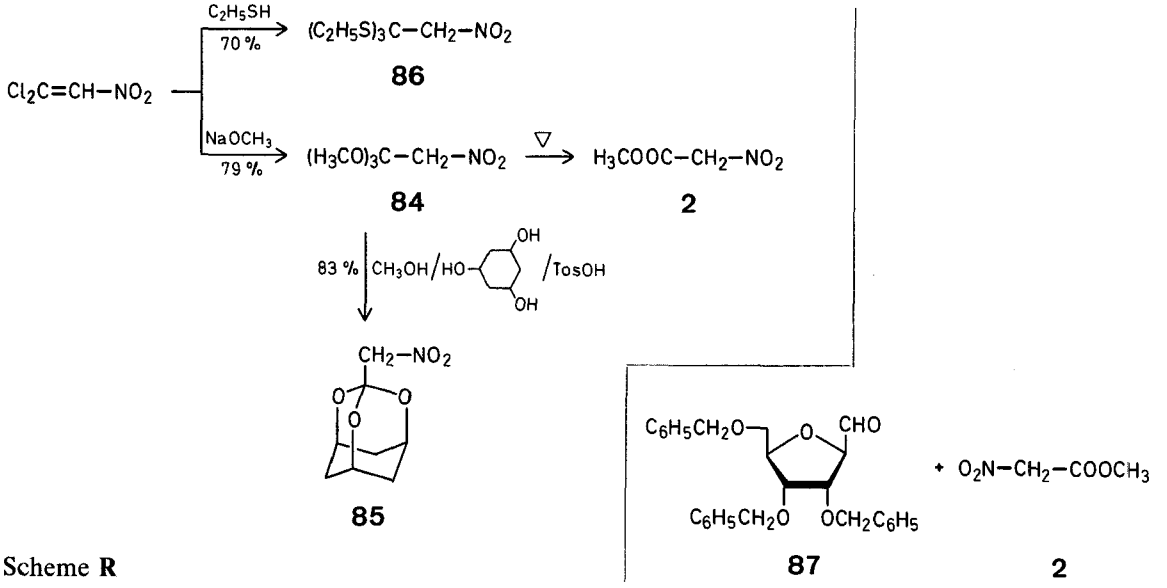
Scheme Q

6. Recent Developments

The references[122-135] received after the completion of the original manuscript are included in this Section.

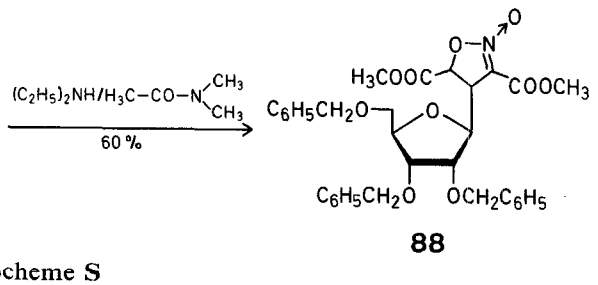
A synthesis of ortho ester **84** and ortho thioester **86** by displacement reactions of 2,2-dichloronitroethylene (Scheme **R**) was reported[122]. Compound **84** led to methyl nitroacetate upon thermal decomposition. Triooxaadamantane **85** resulted (yield 83%) when **84** was transesterified with cyclohexane-1,3,5-triol.

crystallization; the configurations were assigned by spectroscopic methods. A procedure for synthesis of dimethyl nitrosuccinate in 23–27% yield was published[125]. 4-(*C*-Glycosyl)-isoxazoline *N*-oxides, new types of *C*-glycosides, were synthesized[126]. For example, reaction of 1 mol equivalent of 3,4,6-tri-*O*-benzoyl-2,5-anhydro-D-allose (**87**) with 2 mol equivalents of **2** in dimethylacetamide, in the presence of an equivalent of diethylamine, gave a 52% yield of **88** as a mixture of two diastereoisomers[127] (Scheme **S**).



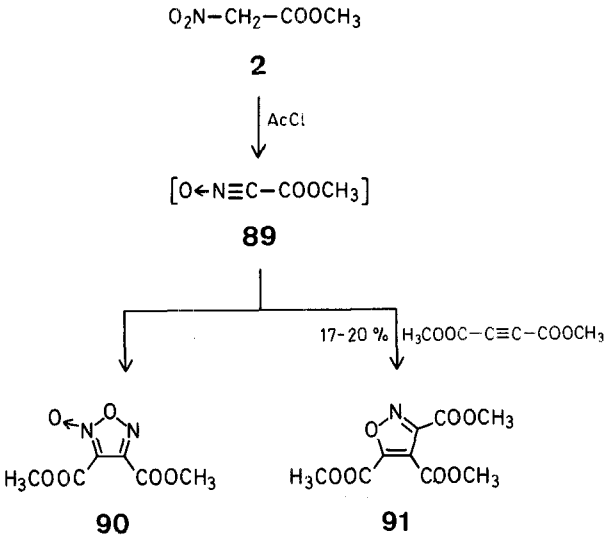
Scheme R

The preparation of methyl-2-nitro-3-[2-(X-furyl)]-acrylates (X = H, CH_3, Br, J, $COOCH_3$, and NO_2) was reported[123] by reacting methyl nitroacetate with appropriate aldehydes in the presence of titanium(IV) chloride (modification of the Lehnert procedure[55] with improved yields ranging from 68–88%). The geometric isomers were separated by fractional



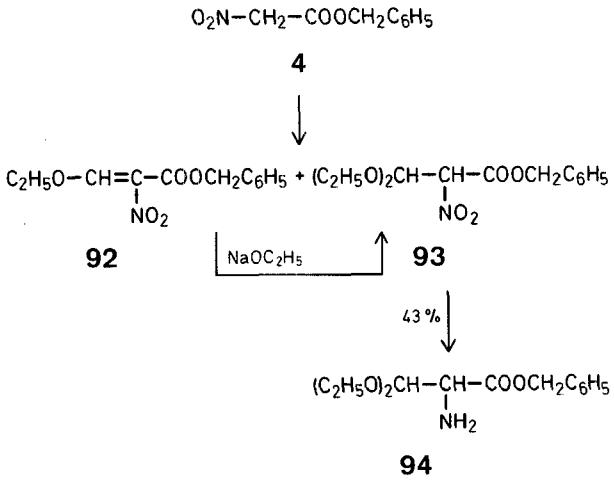
Scheme S

Reaction[128] of **2** in dimethylacetamide with acetyl chloride led to furoxane **90**, which was believed to be formed via dimerization of nitrile oxide **89** (Scheme T). Trapping of this intermediate by dimethyl acetylenedicarboxylate led to isoxazole **91** in 17–20% yield.



Scheme T

Reaction[129] of benzyl nitroacetate (**4**) with triethyl orthoformate in acetic anhydride at 85–90° gave a mixture of **92** and **93**. Sodium ethoxide treatment converted **92** to **93**, making it possible to isolate **93** in quantitative yields (Scheme U). Aluminum amalgam treatment reduced **93** to the amino compound **94** in 43% yield.



Scheme U

Note added in Proof

The ethyl and *t*-butyl esters of **1** were synthesized[136] in low yields from corresponding alkyl bromoacetates by treatment with triethylammonium nitrite in dichloromethane in the presence of 1,1'-(1,3-phenylene)-dipyrrolidine at −35 to −40°.

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Caution: An incident of explosion has been reported when the dipotassium salt was stored in the presence of moisture, D. A. Lyttle, *Chem. Eng. News* **27**, 1473 (1949); *C. A.* **43**, 4855 (1949).
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Caution: In a personal communication to the author, Prof. O. S. Wolfbeis, Institut für Organische Chemie der Karl-Franzens-Universität Graz, Österreich, has reported an incident of a violent explosion during the distillation of ethyl isonitrosoacetate.
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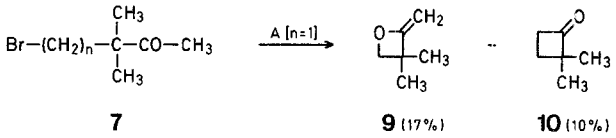
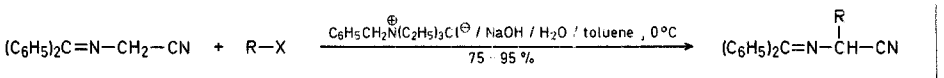
Abstract 5528, *Synthesis* **1979** (7), 554;
The formula scheme for the conversion **7**→**9**+**10** should be as follows:



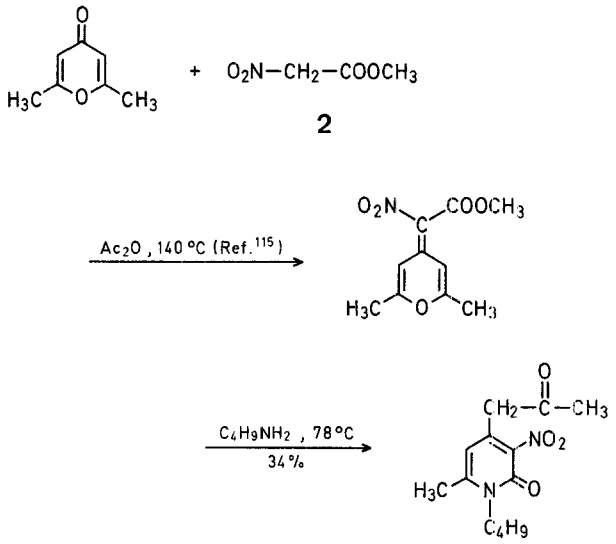
7

Abstract 5556, *Synthesis* **1979** (8), 629;
The formula scheme for the conversion **1**+**2**→**3** shou d be as follows:



1 **2** **3**

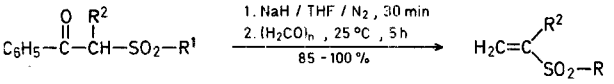
M. T. Shipchandler, *Synthesis* **1979** (9), 666–686;
The second reaction in Scheme **P** (p. 682) should be as follows:



G. Sosnovsky, J. A. Krogh, S. G. Umhoefer, *Synthesis* **1979** (9), 722–724;
The heading for the third column of the Table (p. 723) should be as follows:
Solvent[c]
(Reaction
time[d] [h])

C. Venturello, R. D'Aloisio, *Synthesis* **1979** (10), 790–793;
The last two lines of the third paragraph of the right hand column on page 791 should read as follows:
drazines and of the not easily accessible 3-acetyl-5-methylisoxazole[4].

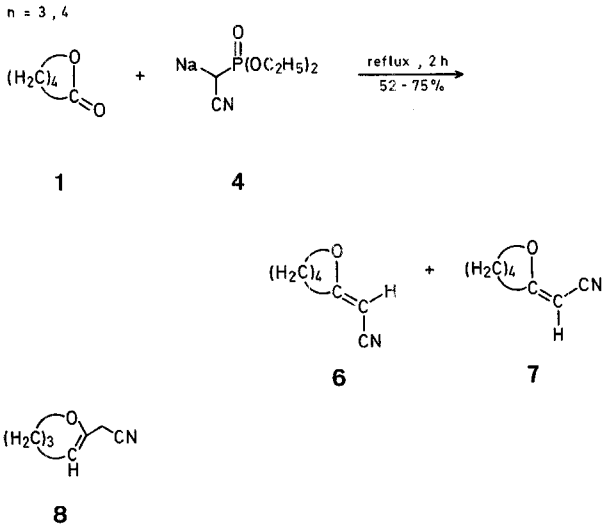
Abstract 5616, *Synthesis* **1979** (10), 840;
The formula scheme for the conversion **1**→**2** should be as follows:



1 **2**

Abstract 5627, *Synthesis* **1979** (11), 917;
The title should be as follows:
[1,4]-Addition of 1,3-Dithianes to 2-Cycloalkenones.

Abstract 5637, *Synthesis* **1979** (11), 920;
The lower part of the formula scheme should be as follows:

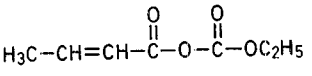


1 **4**

6 **7**

8

C. Goasdoue, R. Couffignal, *Synthesis* **1979** (12), 954–955;
The structure of compound **5** (p. 955) should be as follows:



5

P. Pollet, S. Gelin, *Synthesis* **1979** (12), 977–979;
The correct names for compounds **8** and **9** are 4-oxo-2-phenyl-2,6-dihydro-4*H*-furo[3,4-*d*]-1,2,3-triazoles and 4-oxo-4*H*,6*H*-furo[3,4-*c*][1,2,5]oxadiazoles, respectively.