An Improved Method for Preparation of Nitrile Oxides from Nitroalkanes for In Situ Dipolar Cycloadditions[1]

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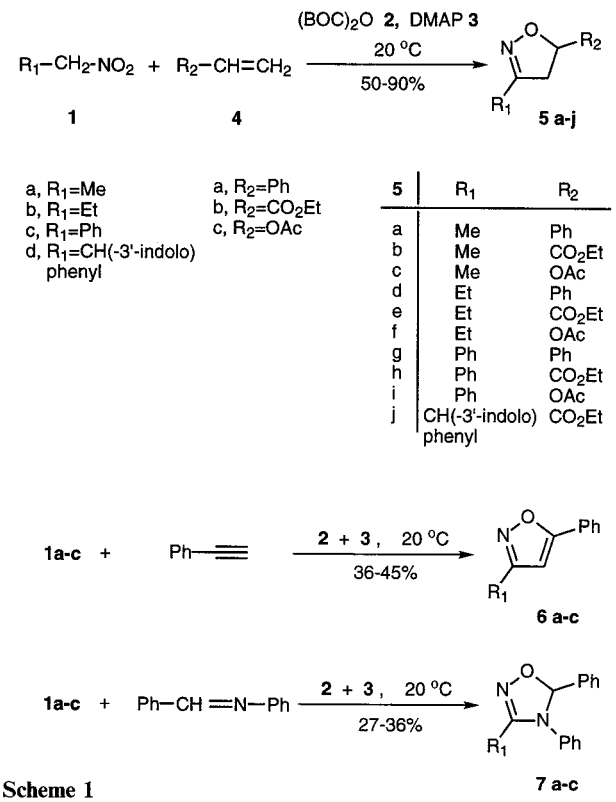
A new method has been found for generation of nitrile oxides in situ from nitroalkanes under mild conditions. Thus, reaction of nitroalkanes **1** with di-*tert*-butyl dicarbonate (**2**) and 4-dimethylaminopyridine (**3**) as catalyst in the presence of dipolarophiles at room temperature afforded cycloadducts (e.g. **5**, **6**, and **7**) in improved yields compared to known methods. Solvent effects were also noted.

Nitrile oxides are important intermediates in the synthesis of 4,5-dihydroisoxazoles and of many 5-membered heterocyclic systems via dipolar cycloadditions.[2] In turn, reductive cleavage of the N–O bond of 4,5-dihydroisoxazoles has proved to be a useful route to oxo alcohols, amino ketones, pyridines, and a number of natural products.[3] The two most widely used routes to nitrile oxides involve: (1) reaction of aldoximes, with oxidizing agents[4] or halogenating species,[5] (in the latter case the reaction proceeds via hydroximoyl chlorides, followed by elimination of HCl with base) or (2) reaction of primary nitroalkanes with a dehydrating agent, e.g. aromatic isocyanates in the Mukaiyama method[6] or ethyl chloroformate in the Shimizu method.[7] Both methods suffer from limitations; in case (1) the halogenating reagent may disallow the presence of some functional groups, in case (2) heating to ca. 80 °C is usually required, leading sometimes to low yields of products and to nitrile oxide dimerization or polymerization.

We report here an improved procedure for in situ generation of nitrile oxides from primary nitroalkanes at room temperature and their in situ regioselective conversion to dihydroisoxazole **5**. Thus, treatment of a nitroalkane **1** with di-*tert*-butyl dicarbonate [$(BOC)_2O$, **2**] (or ethyl chloroformate) in the presence of 0.1 molar equivalents of 4-dimethylaminopyridine (DMAP, **3**) and an excess of a dipolarophile trapping agent at room temperature for 2–3 hours led to the cycloadduct, generally in much improved yields and under milder conditions than in the Mukaiyama or Shimizu procedure. When carried out in the presence of an alkene **4** (bearing an electron-withdrawing or -donating group, see Scheme 1), an alkyne or an imine, the cycloaddition led to 4,5-dihydroisoxazoles **5**, isoxazoles **6** or to 4,5-dihydro-1,2,4-oxadiazoles **7** respectively (see Table).

For example, reaction of nitroethane (**1a**) with styrene (**4a**, 5 equiv) using di-*tert*-butyl dicarbonate (1.5 equiv) and DMAP (0.1 equiv) in acetonitrile at 20 °C for 3 hours gave dihydroisoxazole **5a** in 90% yield. By comparison, reaction of **1a** with **4a** using phenyl isocyanate was carried out by heating to 80 °C to give 79% of **5a**.[6] In another example, 1-nitropropane (**1b**) reacted with styrene (**4a**) to give dihydroisoxazole **5d** in 76% yield by using di-*tert*-butyl dicarbonate (**2**) and DMAP **3** as catalyst at room temperature, while using phenyl isocyanate or ethyl chloroformate at 80 °C led to the dihydroisoxazole **5d** in 57.5% or 6% yield, respectively.[6,7]



Scheme 1

Table. Reaction of **1** and Dipolarophile in the Presence of **2** and **3** at 20 °C (Procedure A), see Scheme 1

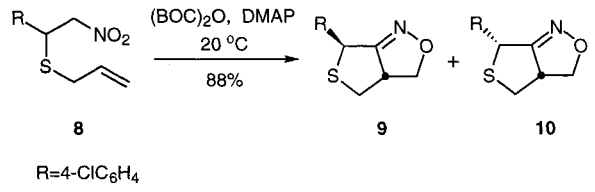
Nitroalkane	Dipolarophile	Product	Yield[a] (%)	Lit.[b] (%)	Lit.[c] (%)
1a	**4a**	**5a**	90		79
	4b	**5b**	90		
	4c	**5c**	50		53.5
	phenylacetylene	**6a**	37		
	N-benzylideneaniline	**7a**	27		10
1b	**4a**	**5d**	76	6	57.5
	4b	**5e**	87		
	4c	**5f**	57		89
	phenylacetylene	**6b**	36	6	
	N-benzylideneaniline	**7b**	35		18
1c	**4a**	**5g**	68[d]	22	
	4b	**5h**	90[d]	64[e]	
	4c	**5i**	75[d]	20	
	phenylacetylene	**6c**	45[d]	25	
	N-benzylideneaniline	**7c**	36[d]		
1d	**4b**	**5j**	88		

[a] Determined by ^1H NMR and confirmed by isolation of **5a** and **5b**.
[b] Shimizu method[7] using ethyl chloroformate at 80 °C.
[c] Mukaiyama method[6] using phenyl isocyanate at 80 °C.
[d] Using ethyl chloroformate instead of **2** at 20 °C (procedure B).
[e] From methyl acrylate.

In case of phenylnitromethane **(1c)** the use of ethyl chloroformate and DMAP was found to give much higher yields of the cycloadducts than without DMAP and allowed the reaction to be performed at room temperature. For example, reaction of phenylnitromethane **(1c)** with vinyl acetate **(4c)** using ethyl chloroformate (1.2 equiv) and DMAP (0.1 equiv) in chloroform at 20 °C afforded the cycloadduct **5i** in 75 % yield, while in the absence of DMAP no reaction occurred at 20 °C and heating to 80 °C was required to give only 20 % of the dihydroisoxazole (Table). In all reactions of phenylnitromethane, using di-*tert*-butyl dicarbonate **(2)** instead of ethyl chloroformate gave much lower yields of cycloadducts (10–15 %).

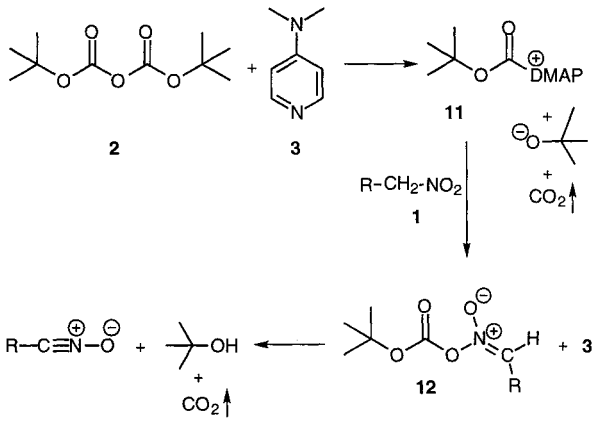
Similarly, reaction of nitroethane **(1a)** with ethyl acrylate using ethyl chloroformate (1.2 equiv) and DMAP (0.1 equiv) in chloroform at 20 °C afforded dihydroisoxazole **5a** in 60 % yield. In the absence of DMAP, heating to 80 °C was required and the yield of **5a** was less than 17 %. When di-*tert*-butyl dicarbonate **(2)** and DMAP were used in hexane/MeCN (9:1) at 20 °C the yield increased to 90 %.

Using di-*tert*-butyl dicarbonate **(2)** and DMAP **3** was found to be superior over phenyl isocyanate also in intramolecular cycloadditions. 1-Allylthio-1-(4-chlorophenyl)-2-nitroethane (**8**, Scheme 2) undergoes intramolecular nitrile oxide–olefin cycloaddition (INOC) when treated with di-*tert*-butyl dicarbonate (**2**, 1.6 equiv) and DMAP **3** (0.1 equiv) in toluene for 2 hours at room temperature to provide the fused dihydroisoxazoles **9** and **10** (1:1 ratio) in 88 % yield. The same reaction, but using phenyl isocyanate for 3 days at room temperature, afforded 62 % of the product.[8]



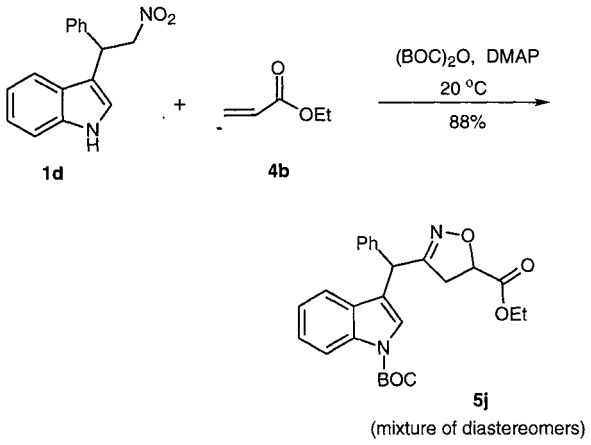
Scheme 2

Our method is based on the rationalization that formation of nitrile oxides from nitroalkanes involves generation of a nitronate ester, e.g. **12** in Scheme 3, followed by base-catalyzed elimination of a carboxylate unit. DMAP is known to be an excellent catalyst for esterification of alcohols by acid anhydrides[9] and should enhance the apparent rate determining step, namely formation of the nitronate ester and thus allow the reaction to occur at room temperature. Furthermore, DMAP is a strong base and should serve equally well in the elimination of the nitronate to nitrile oxide and mono *tert*-butyl carbonate. Decomposition of the latter gives a strong base (*tert*-butoxide) that helps in the elimination step. A further advantage of our new procedure, besides the lower temperature, is that in the case of di-*tert*-butyl dicarbonate the only side products are environmentally friendly CO_2 and *t*-BuOH (see Scheme 3), while in the case of phenyl isocyanate, diphenylurea is an undesirable side product.



Scheme 3

An additional advantage of this new method is that the use of di-*tert*-butyl dicarbonate allows the reaction to be carried out with substrates that contain NH or OH groups without prior protection so that cycloaddition will lead to protected *N*-Boc or *O*-Boc products. For example cycloaddition of 1-(1*H*-indol-3-yl)-2-nitro-1-phenylethane **(1d)** with ethyl acrylate **(4b)** using di-*tert*-butyl dicarbonate **(2)** and DMAP afforded the *N*-Boc protected indolyl substituted dihydroisoxazole **5j** as two diastereomers of unassigned stereochemistry in 88 % yield (Scheme 4).



Scheme 4

We found that the choice of solvent also influences the yield, sometimes dramatically. The solvent effect is due in part to the solubility of the *N*-alkoxycarbonylpyridinium salt **11** (in Scheme 3) formed initially in the reaction between DMAP and **2**. This was demonstrated by isolation of such a salt when hexane only was used as the solvent; in this case there was almost no dihydroisoxazole product formed. In general, a polar solvent (MeCN) was preferred with di-*tert*-butyl dicarbonate **(2)** and chloroform was preferred when ethyl chloroformate was used to generate the nitrile oxides.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Brucker AC-200 or on a Brucker AM-300 spectrometer, using TMS as an internal standard. MS were performed with a Finnigan 4021 spectrometer by electron impact (EI) or chemical ionization (CI) with a beam energy of 60–70 eV. HRMS (CI in methane) were recorded at 60–70 eV on VG-Fisions "AutoSpec" spectrometer. Column chromatography was performed on Merck silica gel 60 (230–240 mesh) using a petroleum ether/Et_2O gradient as eluent. TLC was carried out on precoated Merck silica gel aluminum plates 60F-254.

Solvents $CHCl_3$ (AR), hexane (AR), toluene (AR) and MeCN (HPLC) were used without additional purification. Starting materials were commercially available (Aldrich), except phenylnitromethane[10] **(1c)** and 1-(1*H*-indol-3-yl)-1-phenyl-2-nitroethane[11] **(1d)** which were prepared according to previously described procedures. Dilute HCl used was less than 5% aq HCl.

The yield of the cycloaddition products **5a–j**, **6a–c** and **7a–c**, was determined by ^{1}H NMR. The ratio between the nitroalkane and an internal standard (fluorene) was calculated before the reaction was carried out. At the end of the reaction the ratio between the two benzylic hydrogens (δ = 3.9) of fluorene and H_4 or H_5 of the cycloadduct was determined by integration. The products **5a** and **5b** were also isolated in order to confirm the calculated yield. The products were purified by chromatography for spectral measurements. Compounds **5a**,[12] **5c**,[6] **5d**,[12] **5f**,[6] **5g**,[13] **5h**,[14] **5i**,[13] **6a**,[15] **6b**,[16] **6c**,[15] **7a**,[6] **7b**,[6] and **7c**,[15] were identified on the basis of the melting points and the spectral data (^{1}H and ^{13}C NMR and MS). In case of **9** and **10**,[8] the yield and the relative ratio were determined by ^{1}H NMR, using fluorene as internal standard, without isolation of the products.

General Procedure A; Using Di-*tert*-butyl Dicarbonate [$(BOC)_2O$] and 4-Dimethylaminopyridine (DMAP) Catalyst:

Di-*tert*-butyl dicarbonate (0.33 g, 1.5 mmol) and dipolarophile **4a–c** (5 mmol), or phenylacetylene (5 mmol), or *N*-benzylideneaniline (1.5 mmol) were dissolved in MeCN (5 mL) or MeCN/hexane (1:4, 5 mL in case of **5b**) and DMAP (0.012 g, 0.1 mmol) was added. The nitro compound **1a,b** (1 mmol) dissolved in MeCN (5 mL) was added in portions over a period of 1 h at r.t. to the dipolarophile solution and the reaction was allowed to proceed for a further 3 h. The mixture was evaporated (the yield was determined by NMR) and purification of the product (see Table) was carried out by column chromatography (10–30% Et_2O/petroleum ether gradient).

In the case of **9** and **10**, a toluene solution (5 mL) of $(BOC)_2O$ (0.532 g, 1.6 mmol) was added in one portion to a toluene solution (5 mL) of 1-(allylthio)-1-(4-chlorophenyl)-2-nitroethane (**8**, 0.257 g, 1 mmol) and DMAP (0.012 g, 0.1 mmol) and the reaction was allowed to proceed for 2 h. The mixture was evaporated and the yield (88%) and the ratio between **9** and **10**[8] (1:1) were determined by ^{1}H NMR.

General Procedure B; Using Ethyl Chloroformate and DMAP Catalyst:

Et_3N (0.12 g, 1.2 mmol), DMAP (0.012 g, 0.1 mmol) and dipolarophile **4a–c** (5 mmol), or phenylacetylene (5 mmol), or *N*-benzylideneaniline (1.5 mmol) were dissolved in $CHCl_3$ (5 mL). The solution of phenylnitromethane (**1c**, 0.137 g, 1 mmol) and ethyl chloroformate (0.13 g, 1.2 mmol) in $CHCl_3$ (5 mL) was added in portions to the dipolarophile solution over 1 h at r.t. and the reaction was allowed to run for a further 3 h. The reaction mixture was washed with water and dil HCl, dried ($MgSO_4$) and evaporated (the yield was determined by NMR). Purification of the product (see Table) was carried out by column chromatography (10–30% Et_2O/petroleum ether gradient).

Ethyl 3-Methyl-4,5-dihydroisoxazole-5-carboxylate (5b):

Procedure A was repeated using nitroethane (**1a**, 0.075 g, 1 mmol) in MeCN (5 mL) and ethyl acrylate (**4b**, 0.5 g, 5 mmol) in MeCN/hexane (1:4, 5 mL) to afford **5b** (see Lit[12] for the methyl ester) as a yellowish oil in 90% yield.

^{1}H NMR: δ = 3.22, 3.23 and 4.97 (ABX system, J_{AB} = 18 Hz, J_{AX} = 4.5 Hz, J_{BX} = 13.5 Hz, H_A and H_B are $2H_4$ and H_x is H_5), 4.24 (q, J = 7 Hz, 2 H, O–CH_2–), 2.03 (t, J = 1 Hz, 3 H, C_3–CH_3), 1.31 (t, J = 7 Hz, 3 H, O–C–CH_3).

^{13}C NMR: δ = 170.33 (s, –CO_2–), 154.60 (s, C_3), 77.18 (d, C_5), 61.69 (t, O–CH_2–), 42.34 (t, C_4), 13.99 (q, O–C–CH_3), 12.52 (q, C_3–CH_3).

MS: (EI) m/z (%) = 158 (MH^+, 22), 140 ($MH^+ - H_2O$, 9), 112 (MH^+ – EtOH, 4), 84 (MH^+ – $EtCO_2H$, 100).

HRMS: m/z calcd for $C_7H_{12}NO_3$ (MH^+): 158.0840. Found 158.0817.

Ethyl 3-Ethyl-4,5-dihydroisoxazole-5-carboxylate (5e):

Procedure A was repeated using 1-nitropropane (**1b**, 0.089 g, 1 mmol) and ethyl acrylate (**4b**, 0.5 g, 5 mmol) to afford **5e** (see Lit[12] for the methyl ester) as a yellowish oil in 87% yield.

^{1}H NMR: δ = 4.96 (t, J = 9 Hz, 1 H, H_5), 4.24 (q, J = 7 Hz, 2 H, O–CH_2–), 3.22 (dt, J = 9, 1 Hz, 2 H, $2H_4$), 2.40 (qt, J = 7.5, 1 Hz, 2 H, C_3–CH_2–), 1.31 (t, J = 7 Hz, 3 H, O–CH_2–CH_3), 1.19 (t, J = 7.5, 3 H, C_3–CH_2CH_3).

^{13}C NMR: δ = 169.96 (s, –CO_2–), 158.94 (s, C_3), 76.57 (d, C_5), 61.19 (t, O–CH_2–), 40.36 (t, C_4), 20.40 (t, C_3–CO_2–), 13.63 (q, O–C–CH_3), 10.31 (q, C_3–C–CH_3).

MS: (EI) m/z (%) = 343 (MMH^+, 100), 172 (MH^+, 96), 154 (28), 98 (MH^+ – $EtCO_2H$, 13).

HRMS: m/z calcd for $C_8H_{14}NO_3$ (MH^+): 172.1030. Found: 172.0974.

Ethyl 3-[1-*tert*-Butoxycarbonyl-1*H*-indol-3-yl(phenyl)methyl]-4,5-dihydroisoxazole-5-carboxylate (5j):

Procedure A was repeated (except that 0.66 g, 3 mmol of di-*tert*-butyl dicarbonate were used) using 1-(1*H*-indol-3-yl-1-phenyl-2-nitroethane (**1d**, 0.266 g, 1 mmol prepared from indole and styrene[11]) and ethyl acrylate (**4b**, 0.5 g, 5 mmol) to give, by order of elution, the two separated diastereomers $\mathbf{5j_1}$ and $\mathbf{5j_2}$ as yellowish oils in 88% yield.

$\mathbf{5j_1}$: ^{1}H NMR: δ = 8.13 (d, J = 8 Hz, 1 H, $H_{7\ ind.}$), 7.55 (s, 1 H, $H_{2ind.}$), 7.35–7.19 (m, 7 H), 7.11 (t, J = 7.5 Hz, 1 H), 5.41 (s, 1 H, $H_{benzylic}$), 4.98 (dd, J = 11.5, 6 Hz, 1 H, H_5), 4.20 (q, J = 7 Hz, O–CH_2–), 3.30 (dd, J = 17.5, 6 Hz, 1 H, H_4), 3.14 (dd, J = 17.5, 11.5 Hz, 1 H, H_4), 1.67 (s, 9 H, *t*-butyl), 1.25 (t, J = 7 Hz, 3 H, O–C–CH_3).

^{13}C NMR: δ = 170.13 (s, –CO_2–), 158.77 (s, C_3), 149.57 (s, –NCO_2–), 137.89 (s, C_{ipso}), 135.67 (s, $C_{7a\ ind.}$), 129.28 (s, $C_{3a\ ind.}$), 128.87 (d, 2 × *Co*), 128.43 (d, 2 × *Cm*), 127.65 (d, *Cp*), 124.56 (d, $C_{2\ ind.}$), 124.50 (d, $C_{5\ ind.}$), 122.53 (d, $C_{6\ ind.}$), 119.73 (d, $C_{4\ ind.}$), 118.75 (s, $C_{3\ ind.}$), 115.28 (d, $C_{7\ ind.}$), 83.85 (s, O–*C*-*t*-butyl), 77.56 (d, C_5), 61.79 (t, O–CH_2–), 41.73 (d, $C_{benzylic}$), 39.77 (t, C_4), 28.17 (q, *t*-butyl), 14.02 (q, O–C–CH_3).

MS: (CI/NH_3) m/z (%) = 466 (MNH_4^+, 100), 499 (MH^+, 37).

HRMS: m/z calcd for $C_{26}H_{28}N_2O_5$ (M^+): 448.1980. Found: 448.1998.

$\mathbf{5j_2}$: ^{1}H NMR: δ = 8.12 (d, J = 8 Hz, 1 H, $H_{7\ ind.}$), 7.50 (s, 1 H, $H_{2ind.}$), 7.39–7.25 (m, 7 H), 7.16 (t, J = 7.5 Hz, 1 H), 5.39 (s, 1 H, $H_{benzylic}$), 4.98 (dd, J = 11, 6.5 Hz, 1 H, H_5), 4.23 (q, J = 7 Hz, O–CH_2–), 3.29 (dd, J = 17, 6.5 Hz, 1 H, H_4), 3.19 (dd, J = 17, 11 Hz, 1 H, H_4), 1.66 (s, 9 H, *t*-butyl), 1.28 (t, J = 7 Hz, 3 H, O–C–CH_3).

^{13}C NMR: δ = 170.13 (s, –CO_2–), 158.75 (s, C_3), 149.57 (s, –NCO_2–), 137.87 (s, C_{ipso}), 135.63 (s, $C_{7a\ ind.}$), 129.30 (s, $C_{3a\ ind.}$), 128.81 (d, 2 × *Co*), 128.26 (d, 2 × *Cm*), 127.55 (d, *Cp*), 124.75 (d, $C_{2\ ind.}$), 124.63 (d, $C_{5\ ind.}$), 122.63 (d, $C_{6\ ind.}$), 119.64 (d, $C_{4\ ind.}$), 118.60 (s, $C_{3\ ind.}$), 115.34 (d, $C_{7\ ind.}$), 83.96 (s, O–*C*-*t*-butyl), 77.66 (d, C_5), 61.82 (t, O–CH_2–), 41.58 (d, $C_{benzylic}$), 40.24 (t, C_4), 28.19 (q, *t*-butyl), 14.07 (q, O–C–CH_3).

MS: (CI/NH_3) m/z (%) = 466 (MNH_4^+, 100), 449 (MH^+, 45).

HRMS: m/z calcd for $C_{26}H_{28}N_2O_5$ (M^+): 448.1980. Found: 448.1998.

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