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A method for generating nitrile oxides from nitroalkanes: a microwave assisted route for isoxazoles

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Abstract—A convenient route has been developed for generation of nitrile oxides in situ from nitroalkanes under very mild conditions using microwave irradiation, using 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) and DMAP as catalyst. Isoxazolines and isoxazoles are obtained in very good yields compared to known methods.

1. Introduction

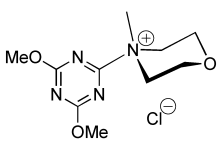
The synthetic and mechanistic aspects of the application of nitrile oxides in [3+2] cycloaddition have been studied extensively.[1] Correspondingly, several procedures have been reported for the generation of nitrile oxides. Nitrile oxides undergo 1,3-dipolar cycloadditions with olefins and acetylenes to provide isoxazolines and isoxazoles, respectively. These products, besides being potential pharmaceutical agents, are also precursors to useful intermediates such as γ-amino alcohols and β-hydroxy ketones.[2] The dehydrogenation of aldoximes via the formation of halogenated derivatives such as hydroximoyl chlorides and bromides, has been frequently employed as effective procedure.[3,4] Reaction of primary nitroalkanes with a dehydrating agent, aromatic isocyanates[5,6] or ethyl chloroformate[7] has been employed too. These methods suffer from limitations owing to the presence of some functional groups in the first case and the relatively high reaction temperature in the other that may cause polymerization of the forming nitrile oxide.

In the past, the treatment of a nitroalkane with di-*tert*-butyl dicarbonate in the presence of small amounts of 4-dimethylaminopyridine (DMAP) has allowed trapping of dipolarophile agents leading to the cycloadduct under milder conditions.[8] During our ongoing studies on the use of [1,3,5]triazine derivatives in organic synthesis,[9,10] in connection with our previous studies[11] on the synthesis of functionalized heterocycles,[12,13] we noted that the use of 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride[14] (DMTMM)[15] in the presence of DMAP as catalyst converted the nitroalkanes to nitrile oxide and consequently can be used for their transformation into isoxazolines or isoxazoles under very mild conditions and in good yields (Fig. 1).

2. Results and discussion

The procedure is based on treatment of DMTMM with four equivalents of the dipolarophile in acetonitrile at 20°C and 0.1 equiv of DMAP, followed after 15 min by addition of the nitroalkane (Scheme 1). After 8–10 h the reaction mixture is quenched with water and worked up to yield the heterocyclic compound.

The formation of the nitrile oxide and consequently that of isoxazolines and isoxazoles is slower than the corresponding method that uses $(Boc)_2O$,[8] requiring longer times for completion. The advantage of this procedure is that the only side product is 4,6-dimethoxy-[1,3,5]triazin-2-ol, readily removed by aqueous work-up. The yields of the reactions are quantitative in all the cases, while the conversions depend on the structure of the substrates (Table 1). In particular, steric hindrance on the alkyl group bound to the dipolarophile and obviously on the 4-position in the heterocyclic compound seems to reduce the rate of the reaction. Heating the reaction mixture at the reflux temperature (82°C) did not increase significantly the rate and the yields decreased drastically, because of formation of by-products.[16]



DMTMM

Figure 1.

Keywords: isoxazoline; solid-phase synthesis; microwave condition.

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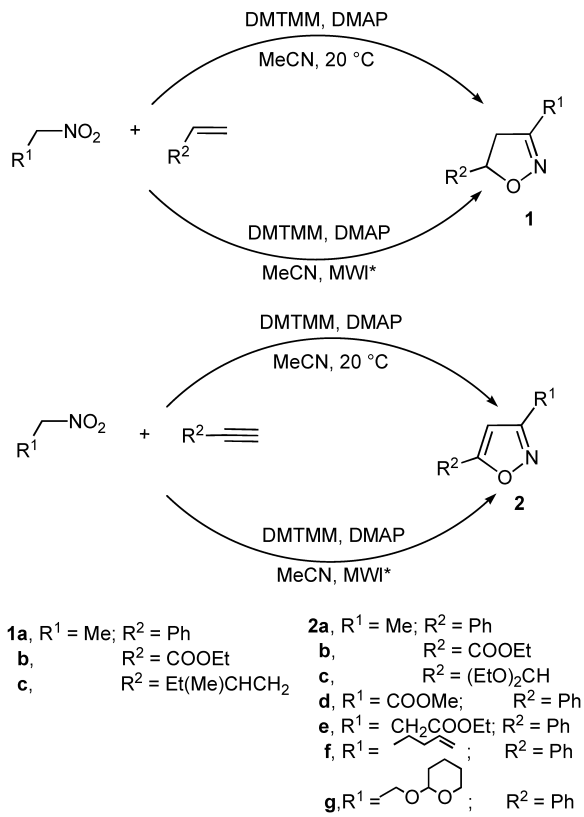


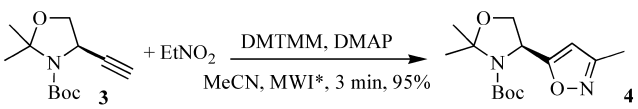
Scheme 1.

Recently, this laboratory has focused on the application of microwave heating in organic synthesis. Carrying out reactions using microwave irradiation conditions,[17] as opposed to conventional heating, has the advantage to shorten the reaction times because of the rapid core heating associated with microwaves. However, this procedure is not always applicable, as often the use of solvents suitable to the microwave conditions represents a real limit, unless to carry out the reaction in a pressure tube.

With the goal of reducing the reaction times, we have therefore repeated all the runs under microwave irradiation, using a self-tunable microwave synthesizer. The MW experiments were performed in a self-tuning single mode CEM DiscoverTM Focused Synthesizer apparatus. The instrument continuously adjusts the applied wattage to maintain the desired temperature.[18] Reactions were performed using a flask equipped with a reflux condenser mounted outside the apparatus. In this case, the use of microwaves was crucial for the success of the reaction. A MeCN solution of DMTMM, 4 equiv. of the dipolarophile, 0.1 equiv. of DMAP and of the nitroalkane were completely converted and pure products **1** and **2** could be recovered after usual work-up (Table 1).

Table 1. Formation of isoxazolines **1** and isoxazoles **2** under conventional or microwave conditions

	Conventional reaction		MWI reaction	
Product	Time (h)	Conv. (%)	Time (min)	Conv. (%)
1a	6	73	3	99
1b	12	87	3	99
1c	6	45	3	99
2a	6	75	3	100
2b	8	65	3	98
2c	10	80	3	95
2d	6	84	3	99
2e	6	68	3	97
2f	10	72	3	92
2g	10	86	3	99



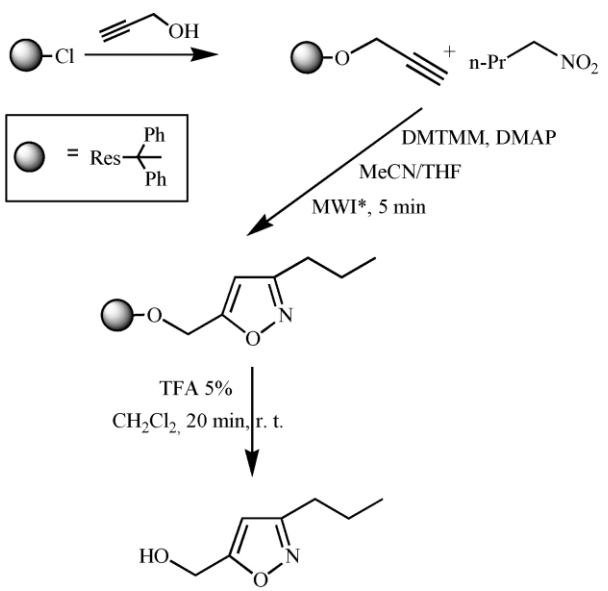
Scheme 2.

The reaction has been tested for the synthesis of α-aminoacids containing the isoxazole moiety.[19] Thus, a sample of (*R*)-4-ethynyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester, **3**,[20] was treated with 4 equiv. of nitroethane in the presence of 1 equiv. of DMTMM and DMAP. After 3 min of microwave irradiation, chemically pure (*S*)-3-methyl-5-(2,2-dimethyl-3-*tert*-butoxycarbonyl-oxazolidin-4-yl)isoxazole, **4**,[19] (>95% yield) was recovered without loss of optical purity[21] (Scheme 2).

This procedure can be conveniently applied to the synthesis on polymeric support too. So, propargyl alcohol was anchored on trityl chloride resin (Scheme 3), controlling the loading by infrared spectroscopy.[11] After being washed, the resin was treated with excess DMTMM and nitroethane in MeCN/THF. Successively, DMAP was added slowly to generate the nitrile oxide, then the mixture irradiated for 5 min (5 cycles of 1 min, and 1 min of rest) and monitored by infrared spectroscopy for the disappearance of the alkyne stretch. The isoxazole, (3-methylisoxazol-5-yl)methanol,[11] was then cleaved off the resin under standard conditions.

3. Conclusion

In conclusion, we have reported an effective and efficient method to perform the formation and the reaction of nitrile



Scheme 3.

oxides from nitroalkanes, using a simple reagent such as DMTMM, through microwave irradiation. Moreover, we have verified that this approach can be also applied to solid-phase synthesis.

4. Experimental

4.1. General

All reagents and solvents employed were reagent grade materials purified by standard methods and distilled before use. Nitrocompounds were commercial products distilled carefully before use and 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) was prepared as described.[15] (*R*)-2,2-Dimethyl-3(*tert*-butoxycarbonyl)-4-ethynyloxazolidine was obtained from L-serine through a described sequence reaction.[9] Elemental analyses were performed on a Perkin–Elmer 420 B analyzer. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) Fourier transform spectra were obtained with a Varian VXR-300 spectrometer using $CDCl_3$ solutions and TMS as an internal standard. Chemical purity was established by HPLC-UV measurements and the structure of known compounds were further corroborated by comparing their ^{1}H NMR data with those of literature.

4.2. General procedure: 3-methyl-5-phenylisoxazole[8,22]

(a) *Conventional procedure*. Acetonitrile (10 mL), DMTMM (0.69 g, 2.5 mmol), 4-dimethylaminopyridine (DMAP) (0.03 g, 0.2 mmol) and phenylacetylene (1.07 mL, 10 mmol) were placed in a flask at room temperature. After 10 min, nitroethane (0.14 mL, 2 mmol) was added dropwise with stirring. The mixture as stirred at room temperature (6 h), then H_2O (10 mL) was added. The mixture was then extracted with diethyl ether, the combined organic layer washed with brine and dried (Na_2SO_4). Removal of diethyl ether in vacuo, gave 0.24 g of chemically pure 3-methyl-5-phenyl isoxazole, **2a** (75%,), ^{1}H NMR; δ 7.75 (d, 2H, Ph), 7.44 (m, 3H, Ph), 6.45 (s, 1H, CH), 2.35 (s, 3H, Me); ^{13}C NMR δ 157.9, 148.1, 136.4, 128.9, 128.0, 126.2, 98.4, 15.3.[8]

(b) *Microwave procedure*. Acetonitrile (10 mL), DMTMM (0.69 g, 2.5 mmol), 4-dimethylaminopyridine (DMAP) (0.03 g, 0.2 mmol) and phenylacetylene (1.07 mL, 10 mmol) were placed in a 100 mL flask at room temperature. After 10 min. nitroethane (0.14 mL, 2 mmol) was added dropwise. The open flask was irradiated at 80°C (by modulation of the power) for 3 min in a self-tuning single mode CEM Discover™ Focused Synthesizer. The solution was cooled rapidly at room temperature by passing compressed air through the microwave cavity for 1 min, then H_2O (10 mL) was added. The mixture was extracted with diethyl ether, the combined organic layer washed with brine and dried (Na_2SO_4). Removal of diethyl ether in vacuo, gave 0.32 g of chemically pure 3-methyl-5-phenyl isoxazole, **2a** (100%).

4.2.1. 3-Methyl-5-phenyl-4,5-dihydroisoxazole (1a).[8,23] From nitroethane and styrene, 0.24 g (73%), [from microwave procedure (MWI). 0.33 g (99%)], ^{1}H NMR; δ 7.33 (m, 5H, Ph), 5.55 (dd, 1H, CH, *J*=8, 9.5 Hz), 3.36 (m, 1H, CH, *J*=8 Hz), 2.80 (m, 1H, CH, *J*=9.5 Hz), 2.03 (s, 3H, Me); ^{13}C NMR δ 166.9, 158.9, 150.2, 136.4, 128.9, 128.0, 126.7, 101.1, 50.3, 33.2.

4.2.2. 3-Methyl-4,5-dihydroisoxazole-5-carboxylic acid ethyl ester (1b).[8,24] From nitroethane and ethyl acrylate, 0.27 g (87%) [MWI 0.31 g (99%)], ^{1}H NMR; δ 4.35 (m, 1H, CH, *J*=5, 11 Hz)), 4.02 (q, 2H, O–CH_2), 3.00 (m, 2H, CH_2, *J*=5, 11 Hz), 2.08 (s, 3H, Me), 1.18 (t, 3H, O–C–Me); ^{13}C NMR δ 172.0, 163.8, 79.1, 60.2, 23.4, 20.1, 13.2.

4.2.3. 3-Methylisoxazole-5-carboxylic acid ethyl ester (2b).[8] From nitroethane and propiolic acid ethyl ester, 0.20 g (65%) [MWI 0.31 g (98%)], ^{1}H NMR; δ 6.78 (s, 1H, CH), 4.22 (q, 2H, O–CH_2), 2.35 (s, 3H, Me), 1.30 (t, 3H, O–C–Me); ^{13}C NMR δ 167.2, 158.9, 150.2, 101.5, 59.1, 13.6, 12.4.

4.2.4. 3-Methyl-5-(2-methylbutyl)-4,5-dihydroisoxazole (1c). From nitroethane and 4-methylhex-1-ene, 0.14 g (45%) [MWI 0.31 g (99%)], ^{1}H NMR (mixture of rotamers) δ 4.61 (m, 1H, CH), 2.95 (m, 1H, CH), 2.51 (m, 1H, CH), 1.96 (s, 3H, Me), 1.72 (m, 1H, CH), 1.62–1.42 (m, 2H, CH_2), 1.39–1.09 (m, 2H, CH_2), 1.84 (m, 6H, Me); ^{13}C NMR (mixture of rotamers) δ 155.0, 79.1, 78.6, 44.5, 44.2, 42.5, 42.1, 31.7, 31.4, 29.8, 29.2, 19.3, 18.8, 13.3, 11.1. $C_9H_{17}NO$ (155.24): calcd C, 69.63; H, 11.04; N, 9.02; found: C, 69.52; H, 11.12; N, 9.02.

4.2.5. 3-Methyl-5-diethoxymethylisoxazole (2c). From nitroethane and propiolaldehyde diethyl acetal, 0.30 g (80%) [MWI 0.35 g (95%)], ^{1}H NMR δ 6.16 (s, 1H, CH), 5.59 (s, 1H, CH), 3.61 (q, 4H, O–CH_2), 2.27 (s, 3H, Me), 1.21 (t, 6H, O–C–Me); ^{13}C NMR δ 174.2, 147.4, 104.2, 94.9, 61.8, 23.7, 14.9. $C_9H_{15}NO_3$ (185.22): calcd C, 58.36; H, 8.16; N, 7.56; found: C, 58.40; H, 8.09; N, 7.54.

4.2.6. 5-Phenylisoxazole-3-carboxylic acid ethyl ester (2d).[20] From ethyl nitroacetate and phenylacetylene, 0.37 g (84%) [MWI 0.44 g (99%)], ^{1}H NMR δ 7.78 (d, 2H. Ph), 7.45 (m, 3H, Ph), 6.59 (s, 1H, CH), 3.56 (q, 2H, O–CH_2), 0.85 (t, 3H, O–C–Me); ^{13}C NMR δ 170.2, 161.9, 150.3, 136.0, 128.9, 126.7, 125.8, 99.1, 62.2. 30.5, 18.7.

4.2.7. (5-Phenylisoxazol-3-yl)acetic acid methyl ester (2e). From 2-nitro methyl propionate and phenylacetaldehyde, 0.29 g (68%) [MWI 0.41 g (97%)], ^{1}H NMR δ 7.88 (d, 2H, Ph), 7.56 (m, 3H, Ph), 6.71 (s, 1H, CH), 3.91 (s, 2H, CH_2), 3.87 (s, 3H, O–CH_3); ^{13}C NMR δ 167.4, 159.2, 149.9, 136.4, 128.9, 128.0, 127.6, 101.2, 49.8, 33.5. $C_{12}H_{11}NO_3$ (217.22): calcd C, 66.35; H, 5.10; N, 6.45: found: C, 66.42; H, 5.23; N, 6.45.

4.2.8. 3-(But-3-enyl)-5-phenylisoxazole (2f). From 5-nitropent-1-ene and phenylacetylene, 0.29 (72%) [MWI 0.37 g (92%)], ^{1}H NMR δ 7.75 (d, 2H, Ph), 7.43 (m, 3H, Ph), 6.38 (s, 1H, CH), 5.88 (m, 1H, HC═, *J*=9, 14.5 Hz), 5.07 (m, 2H, ═CH_2), 2.85 (m, 2H, CH_2), 2.47 (m, 2H, CH_2); ^{13}C NMR δ 169.8, 162.0, 150.9, 130.2, 128.9, 127.4, 125.8, 113.0, 64.4, 19.8. $C_{13}H_{13}NO$ (187.24): calcd C, 78.36; H, 6.58; N, 7.03: found: C, 78.24; H, 6.57; N, 7.03.

4.2.9. 3-(Tetrahydropyran-2-yloxymethyl)-5-phenylisoxazole (2g).[25] From 2-(2-nitroethoxy)tetra-hydropyran and

phenylacetylene, 0.44 (86%) [MWI 0.51 g (99%)],^{1}H NMR δ 7.79 (d, 2H, Ph), 7.46 (m, 3H, Ph), 6.59 (s, 1H, CH), 4.82 (s, 2H, CH_2–O), 4.76 (m, 1H, O–CH) 3.62–3.53 (m, 2H, O–CH_2), 1.74–1.68 (m, 2H, CH_2), 1.55 (m, 4H, CH_2–CH_2); ^{13}C NMR δ 170. 2, 161.9, 129.8, 128.8, 127.5, 126.3, 99.1, 98.4, 65.8, 62.0, 29.9, 25.0, 19.4.

4.2.10. (*S*)-3-Methyl-5-(2,2-dimethyl-3-*tert*-butoxycarbonyl-oxazolidin-4-yl)isoxazole (4). From nitroethane and (*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine, **3**: from microwave procedure as reported above (0.54 g, 96 %), $[\alpha]_D^{20}=-73.5$ (c=1, $CHCl_3$),[19] 0.57 g (99%), mp 53°C, $[\alpha]_D^{25}=-3.1$ (c=3, $CHCl_3$), ^{1}H NMR (mixture of conformers) δ 6.01 (s, 1H,CH), 5.01 (dd, 1H,CH), 4.04 (m, 2H, CH_2), 2.28 (ps, 3H), 1.59 (s, 3H, Me), 1.52 (pd, 3H, Me), 1.49 (s, 4H, C–Me), 1.40 (s, 5H, C–Me); ^{13}C NMR 50°C) δ 159.3, 128.7, 120.4, 101.5, 80.3, 67.3, 59.9, 53.9, 28.8, 26.2, 13.9.

4.3. Procedure for the solid-phase preparation of (3-propylisoxazol-5-yl)methanol

The synthesis was carried out in a manual 20 mL reactor equipped with a sintered glass and using a nitrogen flow for agitation and filtration. A solution of propargyl alcohol **1** (0.41 g, 7.4 mmol) in dry pyridine (3.0 mL) was added dropwise to chlorotrityl resin (0.35 g of a 1.24 mmol/g Novabiochem sample, 0.43 mmol, swollen in CH_2Cl_2) in 7.0 mL of pyridine. The mixture was shaken at room temperature for 48 h, filtered and washed several times with pyridine and dry diethyl ether and dried to afford the corresponding alkyne resin: FT IR (KBr): 3289 cm^{-1}. The resin was then separated in some portions for repeated runs.

To the resin (0.16 mmol), swollen with CH_2Cl_2 and filtered to remove the solvent, it was added MeCN (5.0 mL), THF (2.5 mL), 1-nitrobutane (1.72 mmol) and DMTMM (6.9 mmol): after 2 h, DMAP (0.2 mmol) was added dropwise. Then the suspension was placed into an open flask, the mixture irradiated as above for 5 min and monitored for the disappearance of the alkyne stretch (24 h). The resin was then filtered and washed several times with CH_2Cl_2 affording polymeric isoxazole. Substrate cleavage was accomplished by treating the resin with a freshly prepared TFA–CH_2Cl_2 (5:95) solution at room temperature (20 min). Filtration and resin washing with CH_2Cl_2 gave an organic phase which was washed with Na_2CO_3 aqueous 10% solution and dried (Na_2SO_4).[8a] Removal of the solvent gave the target isoxazole **5** in 82% yield, chemically pure at HPLC; ^{1}H NMR, δ 6.03 (s, 1H, CH), 4.66 (s, 2H, CH_2-O), 2.66 (m, 2H, CH_2), 1.69–1.53 (m, 2H, CH_2), 1.18 (bs, 1H, OH), 0.91 (t, 3H, Me).[11]

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