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New Conditions for the Generation of Nitrile Oxides from Primary Nitroalkanes

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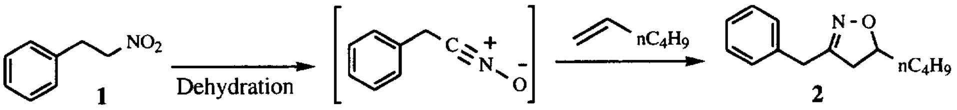
Abstract: Original dehydrating reagents for the efficient formation of nitrile oxides from primary nitro compounds are reported. Burgess salt, DAST, acetic anhydride and oxalyl chloride were shown to be useful reagents to perform this transformation.

Few reactions rival the 1,3 dipolar cycloaddition process in the number of bonds that undergo transformation during the reaction, yielding products considerably more complex than the reactants[2]. Among dipoles, nitrile oxides readily cycloadd to a wide variety of alkenes to generate isoxazolines[3] which represent an extremely useful class of heterocycles. The presence of a nitrogen and an oxygen atom within the ring has made this heterocycle a versatile structure for the synthesis of many functionalities such as β-hydroxyketones, γ-aminoalcohols, β,γ-unsaturated oximes, or β-hydroxy nitriles[4]. Although the reaction between nitrile oxides and various dipolarophiles is well documented[5], intense research is still in progress to optimize regio- and stereo-control *via* chelating agent mediation[6].

Nitrile oxides are in most cases highly reactive intermediates wich are generated *in situ* in the presence of the dipolarophile. They can undergo either cycloaddition to form isoxazoles or dimerisation to give furoxans[7]. Two general routes for the generation of nitrile oxides are usually used: dehydrogenation of aldoximes *via* formation of hydroxamoyl halides[8] or dehydration of primary nitro compounds. The latter method is however the most useful due to its easy set up using 4-chlorophenylisocyanate as described by Mukaiyama in 1960[9]. Eventhough several other methods for the dehydration of primary nitro compounds were reported (p-TsOH in refluxing mesitylene[10], sodium acetate in acetic anhydride at 70 °C[11], ethyl chloroformate or benzenesulfonyl chloride in the presence of triethylamine[12]), none of them supplanted Mukaiyama's procedure. During the course of our studies directed toward the synthesis of complex natural products, we noticed serious drawbacks of these processes, including the requirement of high temperatures, extended reaction times and large excesses of reagent leading to the formation of by-products which are difficult to remove.

We report in this communication our investigations to find more efficient reagents in order to overcome these limitations. For the purpose of this study we evaluated various dehydating agents for their ability to perform the generation of nitrile oxides on a model system (scheme 1).



scheme 1

To compare the performance of the reagents under comparable conditions, 2-phenyl-1-nitroethane was used as a precursor of nitrile oxide and 1-hexene as the dipolarophile. The reactions were carried out in the presence of an excess of 1-hexene to avoid any furoxan formation[13]. The influence of reaction time, temperature, amount of dehydrating agent and amount of base were studied. The results are reported in the following table.

entry	reagent	base	solvent	Conc. (1)	Temp. (2)	Time(3)	ratio 1/2(4)
1	 (3 eq.)	Et_3N, 5 eq.	Benzene	0.3	20	16	95 / 5
2	 (3 eq.)	Et_3N, 5 eq.	Benzene	0.3	60	8	30 / 70
3	BURGESS (3 eq.)	Et_3N, 5 eq.	Toluene	0.1	50	2	5 / 95
4	BURGESS (3 eq.)	Et_3N, 5 eq.	Toluene	0.1	20	2	90 / 10
5	BURGESS (1.5 eq.)	Et_3N, 2 eq.	Toluene	0.2	50	2	45 / 55
6	DAST (3 eq.)	Et_3N, 5 eq.	THF	0.1	-30 ↗ 50	2	5 / 95
7	DAST (1.5 eq.)	Et_3N, 2 eq.	THF	0.2	-30 ↗ 20	2	60 / 40
8	Ac_2O (3 eq.)	Et_3N, 5 eq. DMAP 1.5 eq.	CH_2Cl_2	0.1	0 ↗ 20	2	25 / 75
9	$(COCl)_2$ (1.5 eq.)	Et_3N, 5 eq. DMAP 1.5 eq.	CH_2Cl_2	0.1	-65 ↗ 20	2	30 / 70
10	$POCl_3$ (3 eq.)	Et_3N, 5 eq.	$CHCl_3$	0.1	20	2	10 / 90

(1) Concentration (mol/l) of nitro compound 1; (2) Reaction temperature in ° C; (3) Reaction time in hours; (4) Ratio determined by ^1H NMR of the crude mixture. Isolated yields are given in the text.

4-chlorophenylisocyanate led to the formation of very small amounts of the desired isoxazole at room temperature (entry 1) and only in a fair yield (70%) in 8 hours at 60 °C (entry 2). Under comparable conditions (50 °C), Burgess salt[14] afforded the cycloadduct in 85% isolated yield (entry 3). Lower yields, respectively 10% and 50% were obtained by decreasing the temperature (20 °C) or the amount of reagent (1.5 eq.) (entries 4 and 5). The same trend recured when using DAST[15]. Thus 91% isolated yield of isoxazole was obtained at 50 °C (entry 6), while at 20 °C and when reducing the amount of DAST to 1.5 eq. the yield dropped to 40% (entry 7).

Acetic anhydride also proved to be efficient to perform this reaction: in the presence of triethylamine and DMAP, the desired product was isolated in 70% yield (entry 8). Similar results were obtained with oxalyl chloride (65%) under comparable conditions (entry 9). In addition to their efficiency comparable to that of 4-chlorophenylisocyanate, the latter reagents offer major advantages: easy access, low cost and by-products easy to eliminate. Finally, phosphorus oxychloride allowed to perform this reaction as expected: in accordance with literature results[16] the product was recovered in 80% isolated yield (entry 10).

In summary, the formation of nitrile oxides appears to be a very sensitive reaction. The amount of dehydrating agent as well as the temperature dramatically influence the yield of the reaction. The general trend is an increase in yield with the increase of temperature and / or the amount of dehydrating agent. The addition time of the reagents seems to have very little influence on the outcome of the reaction. We also noticed that at higher concentrations of the nitro compound or at lower amount of dipolarophile furoxan formation became predominant.

Several other dehydrating agents such as 1-methyl-2-chloropyridinium[17], thionyl chloride, triflic anhydride[18], dicyclohexyl carbodiimide, triphenylphosphine oxide / triflic anhydride[19], butyltin oxide[20] and Swern or Mitsunobu conditions were tried. None of these reagents allowed the reaction to proceed. In every case, the starting nitro compound was quantitatively recovered.

In conclusion, we describe new conditions to carry out the dehydration of primary nitroalkanes into the corresponding nitrile oxides. The most efficient reagent on the model system and on complex molecules was DAST. Isolated yield reached 91% under experimental conditions where the classical isocyanate method gave only moderate yields.

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References and Notes.

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13. Typical procedure: A solution of dehydrating reagent (0.99 mmol, 3 eq.) in dry methylene chloride (0.8 ml) was slowly added at 0 °C to a mixture of nitro **1** (0.050g, 0.33 mmol, 1 eq.), triethylamine (0.17g, 0.2 ml, 5 eq.) and 1-hexene (0.14 g, 0.2 ml, 5 eq.), in 2.5 ml of dry methylene chloride. The reaction was allowed to warm up to the desired temperature. The reaction was monitored by TLC. After aqueous work up, product **2** was purified by silica gel chromatography (Rf. 0.4; hexane/ethyl acetate 7/3). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.3 (m, 5H), 4.5 (m, 1H), 3.7 (s, 2H), 2.8 (dd, J = 17 Hz, J = 10.4 Hz, 1 H), 2.4 (dd, J = 17 Hz, J = 8.4 Hz, 1 H), 1.9-0.7 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 128.7, 127.0, 80.7, 41.3, 34.8, 34.3, 27.5, 22.5, 13.9; IR υ cm^{-1} (neat): 2930, 2859, 1495, 1954, 1432, 1335, 1075, 1029, 905.

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