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A MILD OXIDATION OF NITRILE OXIDES: A NEW SYNTHETIC ROUTE TO NITROSO CARBONYL INTERMEDIATES(*)

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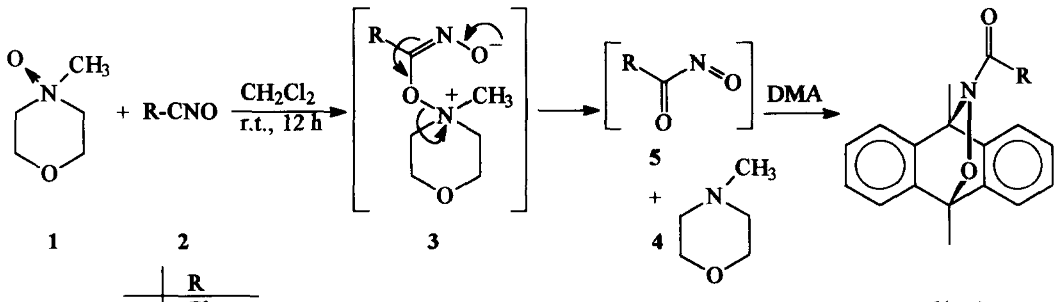
Abstract: Addition of N-methyl morpholine N-oxide (NMO) to a nitrile oxide solution in dichloromethane at room temperature in the presence of a diene affords nitroso carbonyl adducts in fair yields.

The extensive work by G. W. Kirby has shown that the periodate oxidation of hydroxamic acids affords transient nitroso carbonyl intermediates which can be trapped with dienes to give dihydro-1,2-oxazines.[1] In recent years these intermediates have attracted increasing attention and the potential of nitroso carbonyls as very reactive dienophiles in Hetero Diels-Alder (HDA) cycloadditions has been and is still explored in great detail. The HDA cycloadditions often represent the pivotal reaction step in total syntheses of natural products, because of their high stereo- and regio-selective outcome and the convenient introduction of multifunctionality by reductive cleavage of the N-O bond of the adducts.[2-5]

Aside from the oxidation of hydroxamic acids with periodate salts[1-6], few other methods are available; hydroxamic acids have been used as exclusive starting material and the main oxidizing agents are silver oxide and lead oxide in ethyl acetate[7] and oxalyl chloride/dimethyl sulfoxide in dichloromethane at -78 °C, known as Swern-Moffat oxidation.[8] Other oxidizing agents have been reported in literature[9] but they seem not to be satisfactory because of the specific reaction conditions required and of the low yields with respect to the classical periodate oxidation.



	R
a	Ph
b	*p*.Cl-Ph
c	2,4,6-Me$_3$-Ph

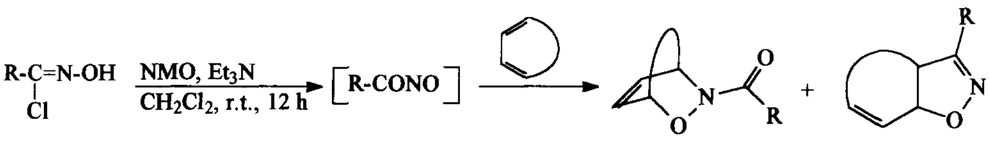
Scheme

(*) Dedicated to Prof. Paolo Grünanger on the occasion of his 70th birthday.

We found that nitroso carbonyl intermediates can be efficiently generated by the mild oxidation of nitrile oxides with a tertiary amine N-oxide (Scheme). The nucleophilic oxygen[10] of the tertiary amine N-oxide **1** adds to the electrophilic carbon[11] of the nitrile oxide **2** affording a zwitterionic adduct **3** whose fragmentation then lead to the tertiary amine **4** and the nitroso carbonyl intermediate **5**, which is trapped with 9,10-dimethylanthracene (DMA) as a HDA cycloadduct **6**.

Addition of N-methyl morpholine N-oxide (NMO, 1.1 equiv.) to a nitrile oxide R-CNO solution in dichloromethane in the presence of a slight excess (1.5 equiv.) of DMA affords the DMA adducts **6(a-c)** in excellent yields (Procedure A). Adduct **6a** (mp 125-6 °C from petroleum ether, 82%) is identical with an authentic sample prepared according to the literature procedure.[12] Similar adducts have been obtained with p-chlorobenzonitrile oxide, **6b** (mp 128-9 °C dec. from ligroin, 95%) and with mesitonitrile oxide, **6c** (mp 183-5 °C from ethanol, 60%).[13]

Table



6(a-n) **7(d-l)**

Entry	R	*Adducts*	mp °(C)[(a)]	yield %
a) DMA				
1	Ph	**6a**[(b)]	125-6	90
2	*p*.Cl-Ph	**6b**	128-9	97
3	2,4,6-Me$_3$-Ph[(c)]	**6c**	183-5	60
b) Cyclohexadiene				
4	Ph	**6d**[(b)]	103-4	81
5	*p*.ClPh	**6e**	88-90	77
6	*p*.Br-Ph	**6f**	68-69	79
7	*p*.Me-Ph	**6g**	97-8	72
8	*p*.MeO-Ph	**6h**	68-70	77
9	*p*.NO$_2$-Ph	**6i**	128-9	86
10	*m*.NO$_2$-Ph	**6j**	oil	70
11	2,4,6-Me$_3$-Ph[(c)]	**6k**	98-100	65
12	CH$_3$	**6l**	oil	57
c) Cyclopentadiene				
13	Ph	**6m**[(b)]	72-4	68
14	2,4,6-Me$_3$-Ph[(c)]	**6n**	109-110	60

(a). Colorless crystals from diisopropyl ether except for **6b** (from ligroin); (b). lit. see ref. 12; (c). procedure A.

The reactions can be more conveniently performed starting from hydroximoyl halides and generating the nitrile oxides *in situ*. By adding triethylamine (1 equiv. or even a catalytic amount) to a dichloromethane solution of hydroximoyl halides and NMO (1.1 equiv.) in the presence of a suitable diene (1.5 equiv.), fair yields of the nitroso carbonyl cycloadducts **6(a-n)** could be obtained (Procedure B, Table).

Besides DMA, 1,3-cyclohexadiene and 1,3-cyclopentadiene can serve as efficient and less expensive trapping agents since the oxidation of the nitrile oxides is much faster than their cycloadditions to these dienes under these conditions. Fair yields of the HDA adducts to 1,3-cyclohexadiene **6(d-l)**[14] were obtained (see Table). The nitrile oxide cycloadducts **7(d-l)** to this dipolarophile are formed in low yields (1-7%). Fair yields of HDA adducts to 1,3-cyclopentadiene **6(m,n)**[15] were obtained too, in spite of the high dipolarophilic activity of cyclopentadiene towards nitrile oxides.[11]

A slight excess of NMO reduce somehow the yields of the adducts **6**; with 1.5-2 equivs. of NMO, adduct **6d** is obtained in about 70% yield. Other solvents can be used to perform the oxidation of nitrile oxides with NMO and similar results have been obtained with chloroform, acetonitrile and ethyl acetate (**6d**: 70-80%; **7d**: 3-10% yield). Protic solvents slow down the oxidation and in methanol adducts **6d** and **7d** are formed in a 38% and 52% yield, respectively.

Entry 12 of the table specifies the oxidation of an aliphatic nitrile oxide, CH_3CNO, generated *in situ* from the corresponding hydroximoyl chloride. The HDA adduct to cyclohexadiene **6l** was isolated as a distillable oil (90 °C/0.1 mmHg bulb to bulb) in a 57% yield along with a little amount of the cycloadduct **7l**, (4%).

Since a variety of methods are available to convert aldoximes into hydroximoyl halides,[11] this mild oxidation seems to us a very promising and convenient procedure for the generation of the transient nitroso carbonyl intermediates.

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13. Adduct **6b**: ^{1}H-nmr ($CDCl_3$): δ 2.05 and 2.75 (s, 3H+3H, *CH*$_3$); 7.1-7.6 (m, aromatics) ppm. Adduct **6c**: ^{1}H-nmr ($CDCl_3$): δ 1.7-2.0 (s, 9H, *2,4,6-CH*$_3$-Ph); 2.2 and 2.9 (s, 3H+3H, *CH*$_3$); 6.7 (s, 2H, 2,4,6-CH$_3$-*Ph*); 7.2-7.6 (m, aromatics) ppm.

14. Adducts **6(e-j)** show similar ^{1}H-nmr signals for the carbocyclic moiety ($CDCl_3$): δ 1.55 and 2.3 (m, 2H+2H, *H-7* and *H-8*); 4.8 and 5.3 (bs, 1H+1H, *H-4* and *H-1*); 6.5 and 6.7 (bs, 1H+1H, *H-5* and *H-6*). Other signals: **6e**, δ 7.3 and 7.6 (d, 2H+2H, AA'BB' syst. aromatics); **6f**, δ 7.6 (m, 4H, aromatics); **6g**, δ 2.35 (s, 3H, *CH*$_3$); 7.2 and 7.6 (d, 2H+2H, AA'BB' syst. aromatics); **6h**, δ 3.8 (s, 3H, *OCH*$_3$); 6.9 and 7.7 (d, 2H+2H, AA'BB' syst. aromatics); **6i**, δ 7.8 and 8.2 (d, 2H+2H, AA'BB' syst. aromatics); **6j**, δ 7.5-8.6 (m, 4H, aromatics).

    Adduct **6k**: ^{1}H-nmr ($CDCl_3$): δ 1.5 and 2.3 (m, 2H+2H, *H-7* and *H-8*); 2.2-2.4 (s, 9H, *2,4,6-CH*$_3$-Ph); 4.2 and 4.57 (m, 1H+1H, *H-4* and *H-1*); 5.0 and 5.6 (m, 1H+1H, *H-5* and *H-6*); 6.85 (bs, 2H, 2,4,6-CH$_3$-*Ph*).

    Adduct **6l**: ^{1}H-nmr ($CDCl_3$):δ 1.5 and 2.15 (m, 2H+2H, *H-7* and *H-8*); 1.96 (s, 3H, *CH*$_3$CO); 4.76 and 5.27 (bs, 1H+1H, *H-4* and *H-1*); 6.52 and 6.63 (m, 1H+1H, *H-5* and *H-6*).

15. Adduct **6n**: ^{1}H-nmr ($CDCl_3$): δ 1.93 and 2.09 (bs, 1H+1H, *H-7*); 2.2-2-3 (s, 9H, *2,4,6-CH*$_3$-Ph); 4.55 and 5.23 (bs, 1H+1H, *H-4* and *H-1*); 5.48 and 5.62 (bs, 1H+1H, *H-5* and *H-6*); 6.87 (bs, 2H, 2,4,6-CH$_3$-*Ph*).

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