HETEROCYCLES, Vol. 22, No. 10, 1984

SYNTHESIS OF 3-BENZENESULFONYL-ISOXAZOLINES AND ISOXAZOLIDINES

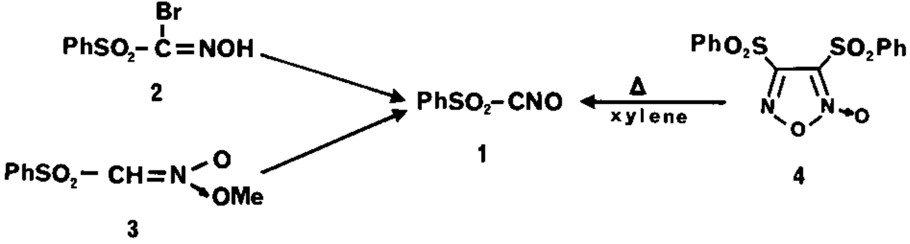
Claudio Bellandi, Marco De Amici and Carlo De Micheli*
Institute of Medicinal Chemistry, Viale Abruzzi, 42 - 20131 Milano
Remo Gandolfi
Department of Organic Chemistry, Viale Taramelli, 12 - 27100 Pavia

Abstract - Isoxazoline derivatives 5-8 were obtained in moderate yields upon refluxing a chloroform solution of electron-rich or moderate electron-poor dipolarophiles and nitronic ester 3. Electron-poor dipolarophiles react with 3 yielding N-methoxyisoxazolidines 9-11.

The variety of synthetic transformations available for Δ^2-isoxazolines increased the interest in the chemistry of nitrile oxides especially in the field of natural product synthesis.[1]

One of the most promising nitrile oxides is, in this context, benzenesulfonylnitrile oxide 1 due to the possibility of its heterocyclic derivatives to be functionalized by replacement of the benzenesulfonyl group with different substituents as shown by Wade and coll.[2]

Scheme 1



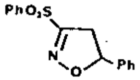
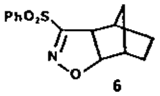
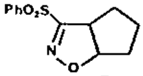
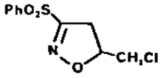
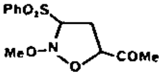
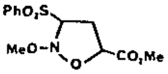
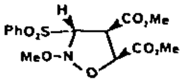
The limitation in the use of such a 1,3-dipole is mainly due to the difficulty in the synthesis of the corresponding hydroxamoyl bromide 2, the most used precursor, obtained from phenylsulfonylnitromethane in a low yield three step process.[2,3] On the other hand, the cycloreversion of furoxan 4 generates 1 under severe reaction conditions only.[4] Up to now the simplest method of producing 1 is the base-induced elimination of methanol from nitronic ester 3.[5]

Since such a methodology has been applied to a limited number of reactions we decided to further explore the generation of nitrile oxide 1 from nitronic ester 3, in the course of investigations devoted to the synthesis of muscimol and AT-125.

As nitrile oxides can be generated by thermal elimination of hydrochloric acid from hydroxamoyl chlorides,[6,7] we took into account the possibility of producing nitrile oxide 1 by thermal elimination of methanol from nitronic ester 3.[8] Consequently we refluxed a toluene solution of 3 and norbornene: cycloadduct 6 was isolated in moderate yield (41%). We tried different reaction conditions by using the following solvents: benzene, chloroform, ethanol, and ether and in all the tested conditions but one we obtained 6 in similar yields. Upon refluxing the reactants in ether, even for a long time, no cycloadduct was isolated or detected.

Table 1

Results of the 1,3-Dipolar Cycloadditions of Nitronic Ester 3

Dipolarophile	Cycloadduct[10]		Yield (%)
1) Styrene	 5	mp 84-85	56
2) Norbornene	 6	mp 85-86	43(72)[a]
3) Cyclopentene	 7	oil	27
4) Allyl chloride	 8	oil	31
5) Methyl Vinyl Ketone	 9	mp 121-123	56
6) Methyl acrylate	 10	mp 100-101	70
7) Dimethyl maleate	 11	mp 133-134	30

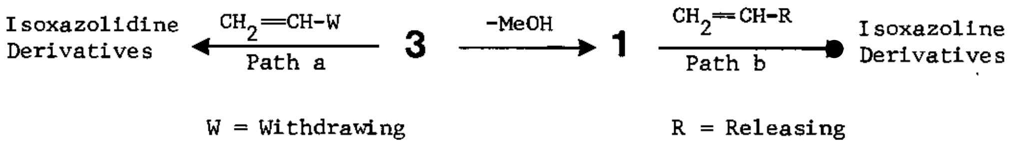
[a] This yield has been obtained by reacting 3 and norbornene in a molar ratio 5:1

Table 1 gathers the results of the cycloadditions carried out under the mildest conditions that is at reflux in chloroform as reported in the typical procedure.[9] Our procedure employs the 1,3-dipole as the limiting reagent, consequently all the reactions have been carried out with a five fold excess of dipolarophile. The yields are based on the nitrile oxide precursor phenylsulfonylnitromethane used to prepare nitronic ester 3 and refer to pure, isolated products.[12] Reaction 2) has also been carried out with a five fold excess of 1,3-dipole and the yield (in parenthesis) increased significantly. This methodology can be fruitfully used with precious dipolarophiles.

It is interesting to notice that electron-poor dipolarophiles yield N-methoxy-isoxazolidines 9-11 whereas electron-rich or moderate electron-poor dipolarophiles produce Δ^2-isoxazolines 5-8.

At first sight it seemed that compounds 5-8 could be derived from N-methoxy-isoxazolidines through the thermal elimination of methanol. Such a possibility was discarded because we did not observe any formation of the isoxazoline derivative by refluxing a toluene solution of 10. We believe that reactions 1-4 and 5-7 in Table 1 follow two different reaction paths:

Scheme 2



A direct cycloaddition occurs (path a) when nitronic ester 3 reacted with an electron-poor dipolarophile. On the other hand electron-rich or moderate electron-poor dipolarophiles slow down the reaction rate along path a. Consequently 3 decomposes to 1 and the reaction proceeds along path b.

As a matter of fact, it is well documented[13] that cycloadditions of nitronic esters with electron-poor dipolarophiles e.g. dimethyl maleate belong to Type I of Sustmann's classification.[14] Consequently electron-poor dipolarophiles are suitable partners for nitronic ester 3.

On the other hand, a study of the reactivity of nitrile oxide 1[15] shows that its reactions are in between Type II and III of the above mentioned classification. Therefore 1 can be efficiently trapped with electron-rich or moderate electron-poor dipolarophiles.

A study of the cycloaddition of 3 with triple bonds was undertaken in order to deepen our knowledge on the reactivity of such a 1,3-dipole and to test the applicability of this methodology to the synthesis of natural products.

ACKNOWLEDGMENT

Financial support from the National Ministry of Education is gratefully acknowledged. Thanks are also due to Prof. P.A. Wade for a research sample of phenylsulfonyl nitromethane.

REFERENCES AND NOTES

1) G. Desimoni, G. Tacconi, A. Barco and G.P. Pollini, Natural Products Synthesis through Pericyclic Reactions, A.C.S. Monographs, 1983, **180**.

2) P.A. Wade and H.R. Hinney, J.Am.Chem.Soc., 1979, **101**, 1319.

3) R.V. Stevens and R.P. Polniaszek, Tetrahedron, 1983, **39**, 743.

4) R.A. Whitney and E.S. Nicholas, Tetrahedron Letters, 1981, 3371.

5) P.A. Wade and M.K. Pillay, J.Org.Chem., 1981, **46**, 5425.

6) C. Grundmann and P. Grünanger, "The Nitrile Oxides", Springer-Verlag N.Y., 1971.

7) G. Bianchi, R. Gandolfi and P. Grünanger "The Chemistry of Functional Groups", Suppl. C - Ed. Z. Rappoport - J. Wiley and Sons, 1983.

8) Nitronic anhydrides have been used as nitrile oxides precursors; the corresponding nitrile oxide is generated "in situ" by release of acetic acid. For leading papers in this area see Ref. 7.

9) Typical procedure: A solution of nitronic ester 3 (5 mmol) in $CHCl_3$ (10 ml) is added dropwise to a solution of the dipolarophile (20 mmol) in chloroform (10 ml) under reflux, and stirring. The reaction mixture is kept under reflux for 4h, then the solvent evaporated and the residue chromatographed over a silica gel column.

10) Structural assignments are based on ^1H-NMR spectra and elemental analyses. In particular the ^1H-NMR spectrum of 6 allowed the attribution of the exo-structure. ^1H-NMR ($CDCl_3$) δ 8.2-7.5 (m, 5H, $PhSO_2$), 4.7 (dd, 1H, H-2, $J_{2,6}$= 10 Hz, $J_{1,2}$= 1.5 Hz), 3.5 (dd, 1H, H-6, $J_{2,6}$= 10Hz, $J_{6,7}$= 1.3Hz), 2.7 (m, 2H, H-1 and H-7), 1.4 (m, 6H, H-8, H-9, and H-10).
The ^1H-NMR spectra of cycloadducts 9-11 showed a singlet corresponding to three protons at 3.45 δ characteristic of an N-methoxy group.[11]
Structure 11 has been assigned to the product of reaction 7) by considering the very close chemical shifts of its methoxycarbonyl groups. 11: ^1H-NMR ($CDCl_3$) δ 8.2-7.5 (m, 5H, $PhSO_2$), 5.3 (d, 1H, H-3, $J_{3,4}$= 6Hz), 5.1 (d, 1H, H-5, $J_{4,5}$= 11Hz), 4.2 (dd, 1H, H-4, $J_{3,4}$= 6Hz, $J_{4,5}$= 11Hz), 3.75 and 3.85 (s, 6H, CO_2Me), 3.45 (s, 3H, N-OMe).
Similar considerations did not allow to define the reciprocal spatial arrangements of the substituents in compounds 9 and 10.

11) R. Greé and R. Carrié, Bull.Soc.Chim.France, 1975, 1319

12) 3 has been obtained from phenylsulfonylnitromethane and excess diazomethane.[2]

13) R. Greé, F. Tonnard and R. Carrié, Tetrahedron Letters, 1974, 135 and Bull.Soc. Chim.France, 1975, 1325.

14) R. Sustmann and H. Trill, Angew.Chem.Int.Ed., 1972, **11**, 838.

15) P.A. Wade and H.R. Hinney, Tetrahedron Letters, 1979, 139.

Received, 18th May, 1984