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BENZENESULFONYLNITRILE OXIDE

A 1,3-DIPOLE EXHIBITING MODIFIED REACTIVITY IN CYCLOADDITION REACTIONS

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Numerous rate studies have been reported for the cycloaddition of 1,3-dipoles to alkenes and alkynes.[1] From these studies it has been concluded that each class of 1,3-dipoles exhibits a characteristic dipolarophile activity sequence with relatively minor variation for individual 1,3-dipoles within each class.[2] We wish to report, however, that the activity sequence towards alkenes is heavily skewed for benzenesulfonylnitrile oxide[3] compared to typical nitrile oxides. This behavior is attributed largely to the well-known potent electron-attracting ability of the benzenesulfonyl group.

Competition studies indicate that benzenesulfonylnitrile oxide prefers to react with electron-rich alkenes rather than electron-poor ones. For example, reaction is 30 times more rapid with norbornylene than methyl acrylate. Similarly, reaction is 10.6 times faster for n-butyl vinyl ether than methyl acrylate. Table 1 compares our results for a series of alkenes to published results[1a] with benzonitrile oxide. Towards benzonitrile oxide norbornylene is only 1.8 times more reactive than methyl acrylate. Methyl acrylate reacts 4.0 times *faster* with benzonitrile oxide than does n-butyl vinyl ether.

A quantitative measure of the electron-richness of an alkene is provided by its ionization potential.[1b] Huisgen *et al.*[1a] have reported a "U-shaped" plot of ionization potential *vs.* relative alkene reactivity towards benzonitrile oxide. Norbornylene and methyl acrylate lie at opposite ends of this "U". A similar plot for benzenesulfonylnitrile oxide is shown in the Graph. While this plot is marred by scattered values,[4] most points lie on or near a "J-shaped" curve-- a strongly tipped version of the curve reported for benzonitrile oxide.

In all probability, the reactivity of benzenesulfonylnitrile oxide is not diminished towards electron-poor alkenes in an absolute sense. Rather, its reactivity is increased towards all other alkenes. Consistent with this view is the fact that benzenesulfonylnitrile oxide will cycloadd to tetramethylethylene whereas other nitrile oxides normally fail to give this reaction.[5,6] Also, Hammett plots with a positive ρ have been reported for the reactions of styrene and acetonitrile with substituted benzonitrile oxides.[7]

TABLE 1.

RELATIVE REACTIVITY OF ALKENES
TOWARDS CYCLOADDITION.

Alkene	Ph-C≡N→O $k_{(rel)}$[a]	PhO$_2$S-C≡N→O $k_{(rel)}$[b]
norbornylene	49.28	36.74
methyl acrylate	28.52	1.22
methyl methacrylate	12.49	1.44[c]
n-butyl vinyl ether	6.56	12.91[d]
styrene	3.88	4.17
1-hexene	≡ 1.00	≡ 1.00
cyclopentene	0.61	0.83
methyl crotonate	0.28	0.032

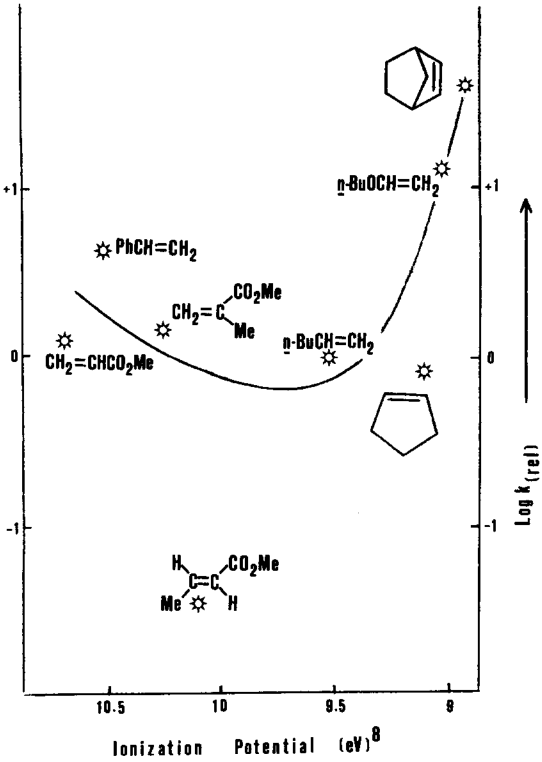
(a) Data taken from ref. 1a.

(b) Determined by nmr; comparison was made to standard samples.[13]

(c) Confirmed by isolation.

(d) PhSO$_2$C≡N→O was generated using Et$_3$N to suppress formation of $n\text{-BuO}\underset{\text{CH}_3}{\text{CH}}\text{ON=CBrSO}_2\text{Ph}$.

GRAPH

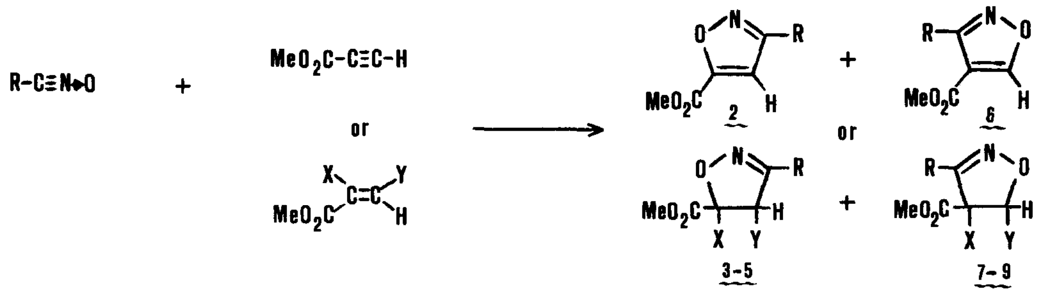


Huisgen has argued that the "U-shaped" reactivity curve exhibited by benzonitrile oxide is evidence for a significant contribution from both the HOMO and LUMO of the nitrile oxide to the cycloaddition pathway.[2,1a,9] Sustmann has classified such 1,3-dipoles as "type 2".[10] Our results indicate a higher degree of LUMO-control for benzenesulfonylnitrile oxide. Apparently this 1,3-dipole falls between the Sustmann type 2 and 3 classifications. We propose "type 2½" as a description of such behavior.

One of the most vexing problems concerning nitrile oxide cycloaddition reactions has been the question of regioselectivity.[2] With most monosubstituted alkenes and alkynes, nitrile oxides react with high regioselectivity to give 5-substituted isoxazolines and isoxazoles, respectively. However, with α,β-unsaturated esters, mixtures of 4- and 5-substituted products are often obtained. This latter observation has been rationalized on the basis of reversed maximum orbital overlaps for the nitrile oxide LUMO-α,β-unsaturated ester HOMO as opposed to the nitrile oxide HOMO-α,β-unsaturated ester LUMO.[2,11] Consequently, the weakly 1,3-dipole LUMO-dominated reactions of benzenesulfonylnitrile oxide should exhibit higher regioselectivity than those of benzonitrile oxide.

The reaction of benzenesulfonylnitrile oxide with several α,β-unsaturated esters has been examined (Table 2). A fair degree of regioselectivity was observed in all cases. Included for

TABLE 2. NITRILE OXIDE REGIOSELECTIVITY



R-	Alkene or Alkyne	5-Carbomethoxy Product	Ratio[a]	4-Carbomethoxy Product
PhO_2S-	$MeO_2CC \equiv C-H$	2a	94:6[b,c]	6a
Ph-	$MeO_2CC \equiv C-H$	2b	72:28	6b
NC-	$MeO_2CC \equiv C-H$	2c	66:34	6c
PhO_2S	$MeO_2C(CH_3)C=CH_2$	3a	100:00[b,c]	7a
Ph-	$MeO_2C(CH_3)C=CH_2$	3b	100:00	7b
PhO_2S-	(*E*)-$MeO_2CCH=CHPh$	4a	12:88[b,c]	8a
Ph-	(*E*)-$MeO_2CCH=CHPh$	4b	30:70	8b
NC-	(*E*)-$MeO_2CCH=CHPh$	4c	15:85	8c
PhO_2S-	(*E*)-$MeO_2CCH=CHCH_3$	5a	62:38[b]	9a
Ph-	(*E*)-$MeO_2CCH=CHCH_3$	5b	34:66	9b
NC-	(*E*)-$MeO_2CCH=CHCH_3$	5c	45:55	9c

(a) Data for benzonitrile oxide and cyanogen N-oxide were taken from ref. 12.

(b) Determined by nmr.

(c) Confirmed by isolation.[13]

comparison are the corresponding reactions for benzonitrile oxide[12] and cyanogen N-oxide.[12a] It is perhaps surprising that a higher degre of regioselectivity was not observed for benzenesulfonyl nitrile oxide. However, α,β-unsaturated esters fall in the area where HOMO contributions from the nitrile oxide would be maximal-- near the left end of the "J-shaped" curve. Therefore, the relative reactivity studies appear to be a more sensitive probe of the nature of these cycloaddition reactions.

In conclusion, both the reactivity and the regioselectivity of benzenesulfonylnitrile oxide are consistent with its classification as a "type 2½" 1,3-dipole.

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REFERENCES AND NOTES

1. Typical examples include: (a) K. Bast, M. Christl, R. Huisgen and W. Mack, *Chem. Ber.*, 106, 3312 (1973). (b) R. Sustmann, *Angew. Chem.*, 84, 887 (1972); *Int. Ed. Eng.*, 11, 838 (1972). (c) R. Huisgen, G. Szeimies and L. Möbius, *Chem. Ber.*, 100, 2494 (1967). (d) A. Dondoni, *Tetrahedron Lett.*, 2397 (1967).
2. For a discussion, see: R. Huisgen, *J. Org. Chem.*, 41, 403 (1976).
3. Generated *in situ* from the following bromo oxime: $PhSO_2(Br)C=NOH$ (**10**). Cycloaddition reactions were carried out by adding a CH_2Cl_2 solution of bromo oxime **10** dropwise over 3 hr to a mixture of aqueous Na_2CO_3 and 10 equivalents of alkene (or 10 equivalents each of two alkenes) in CH_2Cl_2. The bromo oxime **10** was prepared in 30-40% overall yield from benzenesulfonylnitromethane. A mixture of the nitro compound, NaOAc and CH_2Cl_2 at 0-5°C was treated with Br_2 affording a 7:86:7 mixture of non-, mono- and dibrominated product. This crude material was treated at 0°C with excess etheral CH_2N_2 and the resulting nitronic ester refluxed in CH_2Cl_2 for 20 min. The oily crude **10** was crystallized from a concentrated CH_2Cl_2-hexane solution: mp 101-102°C.
4. Ionization potentials do not take into account variation among several differing electronic factors. Steric factors, which should be significant for benzenesulfonylnitrile oxide, have been ignored.
5. Only mesitonitrile oxide has been reported to react with tetramethylethylene. Elevated temperature and a 21 hr reaction time are necessary: Ch. Grundmann, H-D. Frommeld, K. Flory and S. K. Datta, *J. Org. Chem.*, 33, 1464 (1968).
6. Synthetic applications of this and similar results have been submitted for publication.
7. (a) A. Bataglia and A. Dondoni, *Ric. Sci.*, 38, 201 (1968). (b) K. J. Dignam, A. F. Hegarty and F. L. Quain, *J. Org. Chem.*, 43, 388 (1978).
8. Ionization potentials were taken from ref. 1a and the following: (a) R. Sustmann, *Tetrahedron Lett.*, 4271 (1972). (b) G. Hentrich, E. Gunkel and M. Klessinger, *J. Mol. Struct.*, 21, 231 (1974). (c) P. Bischof, J. A. Hashmall, E. Heilbronner and V. Hornung, *Helv. Chim. Acta.*, 52, 1745 (1967).
9. It has been argued that "U-shaped" reactivity curves are evidence for a diradical mechanism. Tipping of these curves so that electron-poor alkenes are the more reactive has been explained assuming uneven formation of extended diradicals: R. A. Firestone, *Tetrahedron*, 33, 3009 (1977), p 3017. In the present study, it is the electron-*rich* alkenes that are the more reactive.
10. (a) R. Sustmann, *Tetrahedron Lett.*, 2717 (1971). (b) See also: K. N. Houk, J. Sims, C. R. Watts and L. J. Luskus, *J. Am. Chem. Soc.*, 95, 7301 (1973).
11. For an alternative explanation see reference 9.
12. (a) M. Christl and R. Huisgen, *Chem. Ber.*, 106, 3345 (1973). (b) M. Christl, R. Huisgen and R. Sustmann, *ibid*, 106, 3275 (1973).
13. Structure assignments were based on ir, nmr and elemental analysis.

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