A New Route to Nitrile Oxides from Primary Alkylhalides for *in situ* Dipolar Cycloadditions

Dilipkumar Maiti and Pranab K. Bhattacharya*

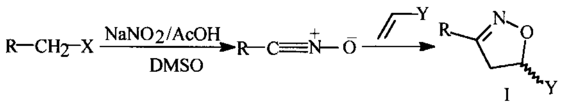
Medicinal Chemistry Division, Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Calcutta 700 032, INDIA

Fax 91-33-4730284/4735197; Email: IICHBIO@GIASCIL 01. VSNL.NET.IN

Received 26 November 1997

Abstract: A new route to nitrile oxide preparation from primary alkylbromide, chloride, nitrite and their cycloadditions with olefins to form isoxazolines in a single pot are described.

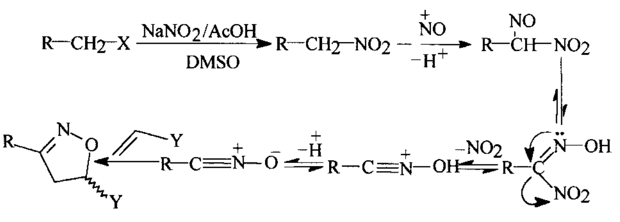
Conversion of organic functionalities in organic synthesis is still a focal point of thinking. Halogens are widely used in aliphatic systems to introduce various other functionalities. For example, treatment of alkylhalides with sodium nitrite gives rise to alkylnitro compounds along with nitrite esters.[1-3] We report herein the formation of nitrile oxides from alkylbromide, chloride and nitrite when treated with sodium nitrite[2] and acetic acid in dimethyl sulfoxide (DMSO) medium.[4] The nitrile oxides thus formed by this easy methodology, were made to react *in situ* with various olefins; both electron deficient and electron rich, such as acrylate, vinylacetate, vinyl pyridine and styrene (Table) to form respective isoxazolines (I, Scheme 1). Only one regioisomer (I) was formed in these cycloaddition reactions.



Scheme 1

The importance of nitrile oxides in organic chemistry is well documented,[5] particularly for the use in 1,3 dipolar cycloaddition by both the intra- and intermolecular pathway. Both of the well known oxidative and dehydrative methods of nitrile oxide preparation are multistep processes.[5a] So far there is only one route known for the formation of carbethoxy fulmide (carbethoxy foromonitrile oxide, CEFNO) in the literature[6] and our route is the second one.

We have prepared nitrile oxides from alkylhalides and it clearly reveals that the only possible pathway of the reaction is through the nitro and then nitrolic acid intermediate (Scheme 2) which was rightly assumed by Mioskowski[3b] and Kornblum[3a] et al. We also confirmed the hypothesis by using two nitro compounds for the preparation of nitrile oxides. It is interesting to note that if the reactions are studied at low temperature (-20°C) in DMF, only the corresponding nitro compounds were formed not the nitrile oxides.



Scheme 2

Acknowledgement

Thanks are due to CSIR and UGC , India for financial assistance as well as a research fellowship to one of the authors (DKM). Thanks are also due to the Director, IICB for various help.

Table

Entry No.	R	X	Y	Yield (%)	Comp. No.
1	p-$NO_2C_6H_4$	Br	CO_2Et	65	**1**
2	p-ClC_6H_4	Br	CO_2Et	62	**2**
3	m-$NO_2C_6H_4$	Br	CO_2Et	57	**3**
4	$C_6H_5CH_2$	Br	CO_2Et	55	**4**
5	CO_2Et	Cl	CO_2Me	52	**5**
6	C_6H_5	Cl	CO_2Me	52	**6**
7	C_6H_5	Br	CO_2Me	68	**6**
8	C_6H_5	Br	OCOMe	53	**7**
9	C_6H_5	Br	2-Py	45	**8**
10	CO_2Et	Br	OCOMe	53	**9**
11	CO_2Et	Br	C_6H_5	35	**10**
12	C_6H_5	NO_2	CO_2Me	48	**6**
13	$C_6H_5CH_2$	NO_2	CO_2Et	58	**4**

References and Notes

1. (a) Kornblum, N. Organic Reactions: Cope, A.C., Ed.; John Wiley: London, 1962, vol.12, pp. 101-56. (b) Coombes, R.G. Comprehensive Organic Chemistry: The Synthesis and Reactions of Organic Compounds: Barton, D.H.R.; Ollis, W.D., Eds.; Pergamon Press: Oxford, 1979, vol 2, 305-381.
2. McCullough, K.J. Encyclopedia of Reagents for Organic Synthesis: Paquette, L.A., Ed., John Wily & Sons: New York, 1995, vol 7, pp 4604-09.
3. (a) Kornblum, N.; Weaver, W.M. *J. Am. Chem. Soc.* **1958**, *80*, 4333-37. (b) Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234-35.
4. **General Procedure** : The alkylhalide (0.01 mole), DMSO (50 ml) and acetic acid (10ml) were taken together and cooled to 0°C. Sodium nitrite (2.1g, 0.03mole) was added to it and the suspension was stirred vigorously. The substituted olefin (0.03 mole) was added and stirred at room temperature for about 15-25 hr. The reaction mixture was diluted with cold water. The product was extracted with ether (4x50ml) and the combined ether layer was washed with brine (3x10ml) and dried passing through anhydrous sodium sulfate. The crude products were separated by silica gel column chromatography. In some cases the products were purified by crystallization in appropriate solvent or by evaporative distillation at low pressure. Always, small amounts of nitrile oxide hydrolysed product and HNO_2 addition product to olefin were also found as byproducts.

Comp. No. 1. : Colorless needle shaped solid(ether). **m.p.** 74°C (γ_{max} / cm^{-1}, KBr): 3084, 2932, 1736, 1656, 1589, 1516, 1462, 1438, 1345, 1259, 1153, 1106, 1016, 900. **^{1}HNMR** ($CDCl_3$, 100 MHz): δ 1.32 (3H, t, J=7Hz), 3.64 (1H, d, J=2Hz), 3.74 (1H, s), 4.30 (2H, q, J=7Hz), 5.28 (1H, dd, J=8Hz), 7.88 (2H, d, J=8Hz), 8.32 (2H, d, J=8Hz).

^{13}CNMR ($CDCl_3$, 25MHz): δ 14.0(q), 38.05(t), 62.22(t), 78.85(d), 123.97(d), 127.59(d), 134.52(s), 154.47(s), 169.46(s).

EIMS (m/z, 70 ev): 264(M^+), 233, 232, 218, 204, 190(bp), 174, 163, 144, 132.

Comp. No. 2. : Colorless solid (ether) **m.p.** 66°C
I.R. (γ_{max} / cm^{-1}, KBr): 3104, 2988, 2944, 1740, 1597, 1557, 1490, 1436, 1399, 1374, 1345, 1249, 1222, 1093, 1027. **^{1}HNMR (**$CDCl_3$, 100MHz): δ 1.34 (3H, t, J=7Hz), 3.60 (1H, d, J=2Hz), 3.68 (1H,s), 4.30 (2H, q, J=7Hz), 5.22 (1H, dd, J=8Hz), 7.44 (2H, d, J=8Hz) 7.68 (2H, d, J=8Hz). **^{13}CNMR** ($CDCl_3$, 25 MHz): δ 13.9(q), 38.4(t), 61.8(t), 78.2 (d), 127(s), 128(d), 128.8(d), 136.2(s), 154.9(s), 169.7(s). **EIMS** (m/z, 70 ev): 254(M^+), 222, 194, 193, 182, 180(bp), 154, 152, 137, 126.

Comp. No.3 : Colorless solid(methanol). **m.p.** 53^o C
I.R. (γ_{max} / cm^{-1}, KBr): 3088, 2982, 2928, 1747, 1532, 1479, 1441, 1353, 1300, 1246, 1210, 1092, 1021, 968, 915. **^{1}HNMR (**$CDCl_3$, 100MHz): δ 1.34 (3H, t, J=7Hz), 3.66 (1H, d, J=2Hz), 3.76 (1H, s), 4.31 (2H, q, J=7Hz), 5.28 (1H, dd, J=8Hz), 7.66 (1H ,t) 8.05-8.52 (3H, m).
^{13}CNMR ($CDCl_3$, 25MHz): δ 13.8(q), 38.0(t), 61.8(t), 78.5(d), 121.2(d), 124.4(d), 129.7(d), 130.2(s), 132.2(d), 148.1(s), 154.3(s), 169.3(s). **EIMS** (m/z, 70 ev): 264(M^+), 233, 232, 191, 190(bp), 175, 163, 153, 136.

Comp. No. 4. : Colorless liquid.
I.R. (γ_{max} / cm^{-1} , neat): 3062, 3015, 2982, 2932 1741, 1603, 1557, 1494, 1451, 1375, 1326, 1274, 1206, 1032, 853, 809, 743. **^{1}HNMR** ($CDCl_3$, 300MHz): δ 1.27 (3H, t, J=7.9Hz), 3.08 (2H, d, J=8.4Hz) 3.32 (1H, d, J=2Hz), 3.69 (2H, s), 4.16 (2H, q, J=7.9Hz), 4.93 (1H, dd, J=1.5,8.4Hz), 7.32 (5H, m). **^{13}CNMR** ($CDCl_3$, 75MHz): δ 13.97, 33.43, 40.23, 61.71, 77.34, 127.17, 128.68, 128.89, 135.09, 157.24, 170.21.

Comp. No. 5. : Colorless liquid.
I.R. (γ_{max} / cm^{-1}, neat): 3060, 2954, 2850, 1745, 1600, 1485, 1440, 1380, 1255, 1132. 1019, 920,820, 782, 746. **^{1}HNMR** ($CDCl_3$, 100MHz): δ 1.40 (3H, t, J=7.2Hz), 3.52 (1H, d, J=2.4Hz), 3.58 (1H,s), 3.86 (3H,s), 4.20 (2H, q, J=7.2Hz), 5.26 (1H, dd J=2.4,8.4Hz) **^{13}CNMR** ($CDCl_3$, 75MHz): δ 13.79, 37.38, 52.56, 62.17, 68.27, 151.76, 158.78, 169.33, 173.11. **EIMS** (m/z, 70 ev): 201(M^+), 189,185, 175, 170, 163, 151, 148, 120, 101, 95, 85, 69.

Comp. No. 8. : Brown colored solid(methanol) **m.p.** 88°C
I.R. (γ_{max} / cm^{-1} , KBr): 2924, 1588, 1466, 1436, 1354, 1323, 1145, 995, 953. **^{1}HNMR (**$CDCl_3$ 100MHz): δ 3.68 (1H,d,J=2Hz), 3.8(1H, d, J=4Hz), 5.86 (1H, dd, J=8Hz), 7.12-7.88 (8H, m), 8.6 (1H, d, J=5 Hz). **^{13}CNMR** ($CDCl_3$, 75MHz): δ 41.35, 82.34, 120.52, 122.87, 126.76, 128.62, 129.14, 130.13, 136.98, 149.26, 156.43, 159.78. **EIMS** (m/z, 70 ev): 224(M^+), 207, 194, 193(bp), 167, 165, 146, 144, 131, 121, 105, 91.

Comp.No. 9. : Colorless liquid.
I.R. (γ_{max} / cm^{-1}, neat): 3080, 2954, 2892, 1753, 1710, 1564, 1354, 1257, 1216. 1019, 933, 887. **^{1}HNMR** ($CDCl_3$, 100MHz): δ 1.40 (3H, t, J=7Hz), 2.10 (3H, s), 3.32 (1H, d, J=2Hz), 3.40 (1H, d, J=7.5Hz), 4.40 (2H, q, J=7Hz), 6.84 (1H, dd J=1.5Hz) **^{13}CNMR** ($CDCl_3$, 75MHz): δ 13.98(q), 20.77(q), 39.77(t), 62.48(t), 96.34(d), 151.85(s), 161.2(s), 169.09(s). **EIMS** (m/z, 70 ev): 201 (M^+), 172, 159, 158(bp), 141, 129, 104, 103, 95, 83.

5. (a) Basel, Y.; Hassner, A.; *Synthesis*, **1997**, 309-12. (b) Kanemasa, S.; Tsuge, O. *Heterocycles*, **1990,** *30*, 719-36 and references cited therein. (c) de Blas, J.; Carretero, J. C.; Dominguez, E. *Tetrahedron Asym.* **1995**, *6*, 1035-38. (d) Xiang, Y.; Schinazi, R. F.; Zhao, K. *J. Org. Chem.* **1997**, *62*, 88-92.

6. Kozikowski, A.P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366-372.