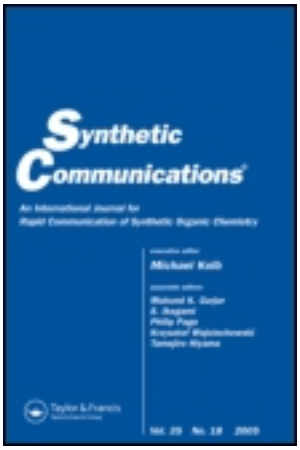

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Intermolecular 1,3-Dipolar Cycloadditions of Preformed Nitrile Oxides with Phenyl Vinyl Sulphone[1]

K. M. Lokanatha Rai [a] & A. Hassner [b]
[a] Department of Chemistry, Mysore, Manasagangothri, Mysore, 570 006, India
[b] Department of Chemistry, Bar-Ilan University, Ramat Gan, 52900, Israel

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INTERMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS OF PREFORMED NITRILE OXIDES WITH PHENYL VINYL SULPHONE[1]

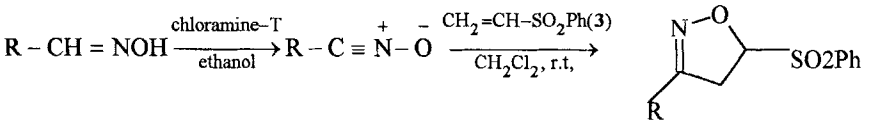
K.M. Lokanatha Rai*[a] and A. Hassner[b]
[a]Department of Chemistry, Mysore, Manasagangothri, Mysore 570 006 India,
[b]Department of Chemistry, Bar-Ilan University, Ramat Gan 52900, Israel

Abstract: Dipolar cycloadditions of nitrile oxides **2**, isolated from the oxidative dehydrogenation of aldoximes by chloramine-T, with vinyl sulphone **3** are discussed.

Dipolar cycloadditions of nitrile oxides with olefinic compounds are of synthetic interest since the product isoxazolines are versatile intermediates for the synthesis of bifunctional compounds.[2] The usual synthesis of nitrile oxides involves the oxidative dehydrogenation of aldoximes using oxidants such as lead tetraacetate,[3] alkali hypohalites,[4] N-bromosuccinimide in dimethylformamide followed by base treatment,[5] chloramine-T (CAT),[6] mercuric acetate[7] or 1-chlorobenzotriazole[8] as well as the reaction of nitro compounds with an aryl isocyanate.[9] Little is known about the synthesis of sulphur containing isoxazolines directly from aldoximes via 1,3-dipolar cycloaddition. The known compounds are all obtained by the cycloaddition of a nitrile oxide generated *in situ* either from a hydroximyl halide or from a nitroalkane with corresponding alkenes.[2c] It is very difficult to obtain the above compounds directly from aldoximes. Often one cannot use oxidants such as NBS, lead tetraacetate, NaOCl, CAT etc. For instance, the sulphonyl group is converted to sulphoximines when CAT is used as oxidant.[10]

* To whom correspondence should be addressed

Another problem is the isolation of the nitrile oxide. This problem was solved by reacting aldoximes with CAT in ethanol at room temperature,[6] which leads to nitrile oxides that are stable in alcohol at room temperature for 5 to 8 h. For



1 2 4

a) R=C_6H_5; b) R=Me-C_6H_4; c) R=MeO-C_6H_4; d) R=$(OCH_2O)C_6H_3$; e) R=$(MeO)_2C_6H_3$; f) $(MeO)_3C_6H_2$; g) R=n-propyl

example, 3,4,5-trimethoxybenzonitrile oxide **2f** can be stored in the solid state for 6 to 7 h in the refrigerator.

When we attempted the cycloaddition of phenyl vinyl sulphone **3** with oxime **1f** *in situ* in the presence of CAT, a mixture of products was obtained from which the desired cycloadduct **4f** was isolated in 30% yield. However, when we preformed nitrile oxide **2f** by reaction of **1f** with CAT in ethanol and reacted it with phenyl vinyl sulphone[3] in dichloromethane, we succeeded in obtaining the cycloadduct **4f** in high yield. This procedure we used for the synthesis of **4a-f**. In a typical procedure, nitrile oxide **2**, isolated from aromatic aldoxime **1** using chloramine-T, was treated with vinyl sulphone **3** in dichloromethane at room temperature. The reaction was completed within 20 to 30 min. The same reaction when carried out in ethanol proceeded very slowly at room temperature. For example after 36 h at room temperature, **2f** reacted with **3** in ethanol to give **4f** as a crystalline solid in 85% yield, while in dichloromethane as solvent the reaction was finished in 15 min to give **4f** in 90% yield. In contrast, aliphatic nitrile oxide **2g** produced the cycloadduct **4g** in dichloromethane at room temperature within 10 min but in very low yield (10-15%) together with dimeric product; in alcohol medium there was not further improvement in the cycloadduct formation.

The structure proof for the isoxazolines **4a-f** was achieved by ^{1}H, ^{13}C NMR and mass spectral data. For instance, S-CHO absorption was found as a doublet of doublets at δ 5.56 ppm for **4a**. The mass spectrum of **4a** showed a base peak at m/e (MH^{+}-142) which corresponds to the loss of $PhSO_2H_2$ and the next highest peak was at m/e 143. The relative intensity of the molecular peak was very low.

EXPERIMENTAL

General: ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on a Bruker AM 300 MHz FT spectrometer using CDCl3 using tetramethylsilane as internal reference. The chemical shifts are expressed in δ, coupling constants J are given in hertz. Mass spectra were obtained on a Finnigan 4021 mass spectrometer at an ionizing energy of 35 eV. Thin layer chromatography (TLC) was done with pre-coated silica gel G plates (Kieselgel 60, F254 Merck) using chloroform as eluent.

General Procedure for the Isolation of Nitrile Oxides 2: Oxime (1 mmol) dissolved in alcohol (5 mL) was treated with chloramine-T (1.2 mmol) at room temperature. After 2 min swirling, the solvent was evaporated. The residue was extracted into ether, washed with 1N NaOH (1x10 mL), brine solution (2x15 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded nitrile oxide **2** in good yield (70 to 90%).[6] In ^{13}C NMR of **2f** (mp 66-69 °C) the nitrile oxide carbon absorbs at 104.69 ppm.

General Procedure for the Cycloaddition: Typical procedure for generation of 3-phenyl-5-phenylsulphonyl-4,5-dihydroisoxazole **4a**: A solution of nitrile oxide **2a** (45 mg, 0.38 mmol) in dichloromethane (5 mL) was treated with phenyl vinyl sulphone **3** (71 mg, 0.4 mmol) at room temperature and kept aside for 30 to 60 min. Evaporation of the solvent yielded an oily substance, which was dissolved in a minimum amount of chloroform. This was poured into petroleum ether and the precipitated solid was filtered. TLC showed a single spot. Repeated crystallization from chloroform-petroleum ether yielded (100 mg, 92%) of **4a** as a crystalline solid, mp 137-138 °. ^{1}H NMR δ 3.81 (dd, J=18 Hz, 1H, 4-H), 4.09 (dd, J=18 Hz,

1H, 4-H), 4.56 (dd, J=18 Hz, 1H, 4-H), 5.56 (dd, J=10 Hz, 1H, 5-H), 7.42 (m, 3H, ArH), 7.60 (m, 4H, ArH), 7.68 (m, 1H, ArH), 8.02 (m, 2H, ArH); ^{13}C NMR δ 36.88 (t, 4-C), 93.30 (d, 5-C, 127.04 (d, 2″,6″-C), 128.85 (d, 3″, 5″-C), 129.21 (d, 3′,5′-C), 129.75 (d, 2′,6′,-C), 131.08 (d, 4″-C), 134.55 (4′-C), 143.5 (s, 1″-C). 156.01 (s, 3-C). Mass spectrum: m/e (relative intensity for $C_{15}H_{13}NO_3S$ 287 (M^+, 1.2), 144 (100), 143 (20).

3-(p-Toluyl)-5-phenylsulphonyl-4,5-dihydroisoxazole 4b: Obtained from **2b** (50 mg, 0.37 mmol) and **3** (71 mg, 0.4 mmol) as a white crystalline solid in 91% yield (100 mg), mp 133=134 °. ^{1}H NMR δ 2.38 (s, 3H, CH_3), 3.78 (dd, J=18 Hz, 1H, 4-H), 4.05 (dd, J=18 Hz, 1H, 4-H, 5.55 (dd, J=10 Hz, 1H, 5-H), 7.23 (d, 2H, 3′,5′-H), 7.55 (m, 5H, 2′,6′-H, ArH), 8.02 (m, 2H, ArH), ^{13}C NMR δ 21.46 (q, CH_3), 36.97 (t, 4-C), 93.90 (d, 5-C), 124.41 (s, 1′-C), 126.98 (d), 3′,5′-C), 127.45 (d, 2V,6″-C), 129.21 (d, 3″,5″-C), 129.52 (d, 2″, 6″-C), 129.73 (d, 4″-C), 135.21 (s, 4′-C), 141.54 (s, 1″-C), 156.85 (s, 3-C). Mass spectrum: m/e (relative intensity) for $C_{16}H_{15}NO_3S$ 302 (MH^+, 0.5), 160 (MH^+-142, 100), 143 (32).

3-(p-Methoxyphenyl)-5-phenylsulphonyl-4,5-dihydroisoxazole 4c: Obtained from **2c** (54 mg, 0.36 mmol) and **3** (65 mg, 0.39 mmol) as a white crystalline solid in 85% yield (98 mg), mp 128-130 °. ^{1}H NMR δ 3.78 (dd, J = 16 Hz, 1H, 4-H), 3.85 (s, 3H, OCH_3), 4.05 (dd, J = 16 Hz, 1H, 4-H), 5.55 (dd, J=10 Hz, 1H, 5-H), 6.91 (d, 2H, 3′,5′-H), 7.55 (m, 5H, ArH), 8.00 (m, 2H, ArH), ^{13}C NMR δ 37.11 (t, 4-C), 55.42 (q, OCH_3), 93.27 (d, 5-C), 114.20 (s, 1′-C), 114.29 (d, 3′,5′-C), 128.43 9d, 2″,6″-C), 128.72 (d, 3″,5″-C), 129.21 (d, 2″,6″-C), 129.76 (d, 4″-C), 156.35 (s, 4′-C), 161.75 (s, 3-C). Mass spectrum: m/e (relative intensity) for $C_{16}H_{15}NO_4S$ 318 (MH^+, 0.5), 176 (MH^+-142, 100), 143 (25).

3-(3′,4′-Methylenedioxyphenyl)-5-phenylsulphonyl-4,5-dihydroisoxazole 4d: Obtained from **2d** (60 mg, 0.37 mmol) and **3** (70 mg, 0.4 mmol) as a white crystalline solid in 91.6% yield (110 mg), mp 165-166 °. ^{1}H NMR δ 3.76 (dd, J=18 Hz, 1H, 4-H), 4.03 (dd, J=18 Hz, 1H, 4-H), 5.53 (dd, J=10 Hz, 1H, 5-H), 6.03 (s, 2H, OCH_2O), 6.82 (d, 1H, ArH), 7.08 (dd, 1H, ArH), 7.18 (s, 1H, ArH), 7.58 (bt,

2H, ArH), 7.68 (bq, 1H, ArH), 8.00 (dd, 2H, ArH), ^{13}C NMR δ 37.03 (t, 4-C), 93.28 (d, 5-C), 101.60 (t, OCH_2O), 106.64 (d, 5′-C), 108.31 (d, 2′-C), 122.25 (d, 6′-C), 129.21 (d, 3″,5″-C), 129.73 (d, 2″,6″-C), 134.52 (d, 4″-C), 141.60 (s, 1″-C), 147.60 (s, 3′-C), 148.20 (s, 4′-C), 156.85 (4′-C). Mass spectrum: m/e (relative intensity) for $C_{16}H_{13}NO_5S$ 332 (MH^+, 1), 190 (MH^+-142, 100), 143 (21), 124(8). HRMS Calcd. $C_{16}H_{13}NO_5S$: 331.0688. Fd: (M+1) 332.0599, $C_{16}H_{13}NO_5S$: Calcd. C 58.01; H 3.96; N 4.23. Fd: C 7.77; H 3.98; N 4.15.

3-(2′,4′-Dimethoxyphenyl)-5-phenylsulphonyl-4,5-dihydroisoxazole 4e:

Obtained from **2e** (50 mg, 0.28 mmol) and **3** (50 mg, 0.3 mmol) as a white crystalline solid in 88.5% yield (85 mg), mp 126-128°. ^{1}H NMR δ 3.83 (s, 2H, CH_3), 3.85 (s, 3H, CH_3), 3.94 (dd, J=18 Hz, 1H, 4-H), 4.04 (dd, J=18 Hz, 1H, 4-H), 5.49 (dd, J=10 Hz, 1H, 5-H), 6.44 (s, 2H, ArH), 7.53 (m, 3H, ArH), 7.66 (m, 1H, ArH), 8.00 (bs, 2H, ArH); ^{13}C NMR δ 39.40 (t, 4-C), 55.49 (q, OCH_3), 93.60 (d, 5-C), 98.57 (d, 2′-C), 105.41 (d, 5′-C), 129.09 (d, 3″,5″-C), 129.84 (d, 2″,6″-C), 130.62 (d, 6′-C), 134.33 (s, 4″-C), 146.20 (s, 3′-C), 155.92 (s, 4′-C), 159.09 (s, 3-C). Mass spectrum: m/e (relative intensity for $C_{17}H_{17}NO_5S$ 348 (MH^+, 0.8), 206 (MH^+-142, 100), 143 (17), 125 (8).

3-(3′,4′-5′-Trimethoxyphenyl)-5-phenylsulphonyl-4,5-dihydroisoxazole 4f:

Obtained from **2f** (120 mg, 0.57 mmol) and **3** (85 mg, 0.5 mmol) as a white crystalline solid in 90% yield (160 mg), mp 141-142°. ^{1}H NMR δ 3.78 (dd, J=18 Hz, 1H, 4-H), 3.88 (s, 9H, OCH_3), 4.10 (dd, J=18 Hz, 1H, 4-H), 5.55 (dd, J=10 Hz, 1H, 5-H), 6.86 (s, 2H, ArH), 7.20 (m, 3H, ArH), 8.01 (dd, 2H, ArH), ^{13}C NMR δ 36.88 (t, 4-C), 56.35 (q, OCH_3), 93.30 (d, 5-C), 104.57 (d, 2′,6′-C), 129.27 (d, 3″,5″-C), 129.75 (d, 2″,6″-C), 134.12 (d, 4′-C), 140.60 (s, 3′,5′-C), 153.00 (s, 1′-C), 156.85 (s, 3-C); Mass spectrum: m/e (relative intensity) for $C_{18}H_{19}NO_6S$ 378 (MH^+, 1), 236 (MH^+-142, 100), 210 (2), 194 (23), 143 (28), 125 (6). HRMS Calcd. $C_{18}H_{19}NO_6S$ 377.1105. Fd. (M+1): 378.1002.

3-Propyl-5-phenylsulphonyl-4,5-dihydroisoxazole 4g: Obtained from **2g** and **3** as an oil in 15% yield. ^{1}H NMR δ 0.95 (t, 3H, CH_3), 1.55 (m, 2H, CH_2), 2.45 (m,

2H, CH_2), 3.40 (dd, J=18 Hz, 1H, 4-H), 3.63 (dd, J=18 Hz, 1H, 4-H), 5,40 (dd, J=10 Hz, 1H, 5-H), 7.63 (m, 3H, ArH), 7.95 (dd, 2H, ArH).

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