SHORT PAPER

Intramolecular cycloadditions of unsaturated nitrilimines containing a sulfinyl group
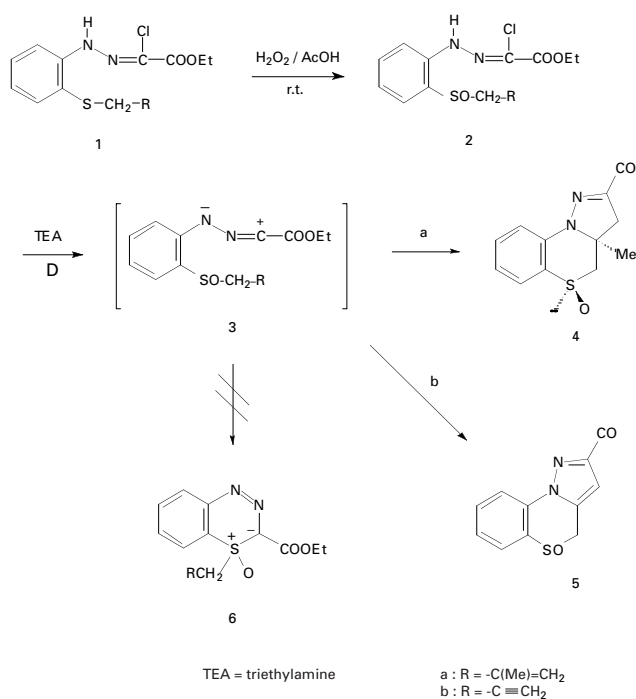
Gianluigi Broggini[a], Luca Bruché*[b], Alessandra Farina[b], Stefano Valdo Meille[b], Giorgio Moltenia and Gaetano Zecchi[a]

[a]*Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, via Golgi 19, 20133 Milano, Italy*

[b]*Dipartimento di Chimica, Politecnico di Milano, via Mancinelli 7, 20131 Milano, Italy*

The intramolecular 1,3-dipolar cycloaddition of nitrilimines **3** allowed the obtainment of 4*H*-pyrazolo[5,1-*c*][1,4]benzothiazine *S*-oxides **4** and **5**.

Intramolecular nitrilimine cycloadditions to multiple bonds have been shown to constitute an efficient and versatile source of multi-ring heterocycles.[1–3] However, in cases where a thioether function is present in the tether connecting the dipole and the dipolarophile moieties, the preferred reaction is the nucleophilic attack of the divalent sulfur on the carbon atom of the dipole, thus forming cyclic sulfonium ylides which then rearrange to stable products.[4] On these grounds, we felt it interesting to examine whether analogous substrates containing a sulfinyl group might produce to the corresponding sulfoxonium ylides. Nitrilimines **3a,b** were chosen to this purpose (Scheme 1).

excess of triethylamine in boiling benzene. The starting material disappeared after 5 h, and only the tricyclic products **4** and **5**, respectively, could be isolated in moderate yields. These products clearly arise from a 1,3-dipolar cycloaddition of the nitrilimine dipole onto the double or the triple carbon-carbon bond. The formation of sulfoxonium ylides of type **6**, that was predicted on the basis of the reported nucleofilicity of the sulfinyl function,[6] was not at all observed. In the case of compound **4**, having two stereogenic centres, only one diastereoisomer was obtained. The crystals of the racemate contain water of crystallization that led to the packing based on hydrogen bonding between a water molecule and the COOEt group. The relative stereochemistry of S and C3a was unambiguously determined, proving that the methyl and the sulfoxide oxygen are in a mutual *anti* relationship (Fig. 1).

The total diastereoselectivity of the cycloaddition, within the experimental error limits, constitutes an interesting result that must be ascribed to the directing effect exerted by the sulfinyl function. The concerted cycloaddition process requires the intramolecular approach of the π-electron systems in parallel planes. On the other end, the reacting molecule reasonably assumes a preferred conformation where the sulfinyl oxygen and the methyl group minimize their mutual steric interactions. As a consequence, the transition state **A** depicted in Fig. 2 is the most accessible, thus justifying the stereoselective formation of cycloadduct **4**.

It is well known that sulfoxides, both in racemic and in enantiopure form, can exert a good stereocontrol in a wide variety of reactions,[7] among which Diels-Alder[8] and 1,3-dipolar[9] cycloadditions occupy a prominent place. However, while some examples of reactions of vinyl and allyl sulfoxides with nitrones or nitrile oxides are reported,[9,10] this is, to the best of our knowledge, the first example involving a nitrilimine. Further experiments on this topic, namely on intermolecular
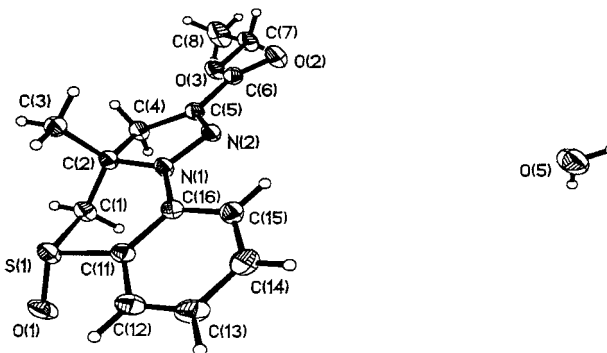

TEA = triethylamine

a : R = -C(Me)=CH₂
b : R = -C≡CH₂

Scheme 1

Results and discussion

Hydrazonoyl chlorides **2a,b** were obtained in good yield by reaction of their precursors **1a,b**[4] with hydrogen peroxide in controlled conditions, in order to avoid further oxidation to sulfones.[5] The *in situ* generation of nitrilimines **3a,b** was performed by treating the hydrazonoyl chlorides **2a,b** with an

---

* To receive any correspondence.
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

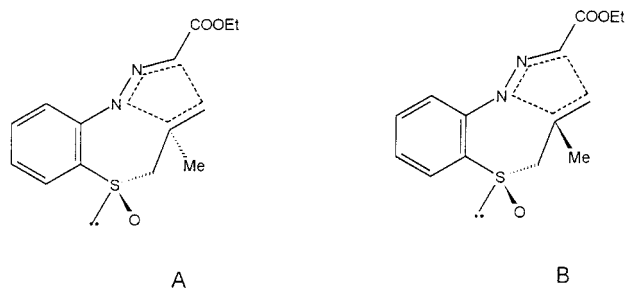**Fig. 1** ORTEP view of compound **4**

Fig. 2 Transition states for the formation of cycloadduct **4**

cycloadditions between vinyl sulfoxides and nitrilimines, are under study and will be reported in due course.

Experimental

Mps were obtained using a Büchi apparatus and are uncorrected. IR spectra were taken with a Perkin-Elmer 377 spectrophotometer. ^{1}H NMR spectra were recorded with a Varian EM-390 instrument in CDCl$_3$ solutions using SiMe$_4$ as an internal standard. Mass spectra were taken on a VG 70 EQ spectrometer. Compounds **1a,b** were prepared as described previously.[4]

Synthesis of hydrazonoyl chlorides **2a,b**: *general procedure.* – 30% aqueous hydrogen peroxide (0.28 mol) was added to a solution of hydrazonoyl chloride **1a,b** (8.0 mmol) in acetic acid (100 ml). After stirring the mixture at room temperature for 1 h, an ice-water mixture (400 ml) was added and then the pH was adjusted to *ca* 7 with Na$_2$CO$_3$. The hydrazonoyl chlorides **2a,b** were isolated by filtration and purified by crystallization from ethanol. **2a**: yield 77%; m.p. 95°C; ν_{max} (Nujol) 3140 and 1730 cm^{-1}; δ_H 1.46 (3 H, t, *J* 7 Hz, CH$_3$), 3.70 and 3.92 (2 H, AB type, *J* 13 Hz, CH$_2$SO), 4.45 (2 H, q, *J* 7 Hz, C*H*$_2$CH$_3$), 4.8–5.1 (2 H, m, =CH$_2$), 6.8–7.6 (3 H, m, ArH), 7.7–7.85 (1 H, m, ArH), 11.5 (1 H, br s, NH); *m/z* 328 (M$^+$) (Found: C, 51.02; H, 5.33; N, 8.45. C$_{14}$H$_{17}$ClN$_2$O$_3$S requires: C, 51.14; H, 5.21; N, 8.52). **2b**: yield 73%; mp 105°C; ν_{max} (Nujol) 3280 and 1720 cm^{-1}; δ_H 1.48 (3 H, t, *J* 7 Hz, CH$_3$), 2.39 (1 H, t, *J* 2.5 Hz, CH), 3.96 and 4.03 (2 H, double AB type, *J*$_{AB}$ 13 Hz, *J* 2.5 Hz, CH$_2$SO), 4.47 (2 H, q, *J* 7 Hz, C*H*$_2$CH$_3$), 6.8–7.9 (4 H, m, ArH), 11.15 (1 H, br s, NH); *m/z* 312 (M$^+$) (Found: C, 50.01; H, 4.10; N, 9.05. C$_{13}$H$_{13}$ClN$_2$O$_3$S requires: C, 49.92; H, 4.19; N, 8.96).

Reaction of hydrazonoyl chlorides **2a,b** *with triethylamine. general procedure:* To a solution of hydrazonoyl chloride **2a,b** (3.0 mmol) in benzene (150 ml), triethylamine (15 mmol) is added. The mixture is refluxed for 5 h, then is washed with 1 M HCl and with water; after drying over sodium sulfate, the residue is chromatographed on a silica gel column with a benzene–ethyl acetate 9:1 mixture as eluent, affording cycloadducts **4** and **5**, respectively. (3a*R*/*S*,5*S*/*R*)-2-ethoxycarbonyl-3a-methyl-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzothiazine *S*-oxide (**4**): yield 28%; m.p. 95°C (from diisopropyl ether); ν_{max} (Nujol) 1700 cm^{-1}; δ_H 1.41 (3 H, t, *J* 7 Hz, CH$_2$C*H*$_3$), 1.52 (3 H, s, CH$_3$), 3.21 (2 H, s, CH$_2$), 3.27 and 3.83 (2 H, AB type, *J* 12 Hz, CH$_2$SO), 4.38 (2 H, q, *J* 7 Hz, C*H*$_2$CH$_3$), 7.0–7.8 (4 H, m, ArH); *m/z* 292 (M$^+$) (Found: C, 57.41; H, 5.59; N, 9.45. C$_{14}$H$_{16}$N$_2$O$_3$S requires: C, 57.52; H, 5.52; N, 9.58). 2-Ethoxycarbonyl-4*H*-pyrazolo[5,1-*c*][1,4]benzothiazine *S*-oxide (**5**): yield 34%; m.p. 193°C (from *n*-pentane-chloroform); ν_{max} (Nujol) 1700 cm^{-1}; δ_H 1.48 (3 H, t, *J* 7 Hz, CH$_3$), 4.21 and 4.62 (2 H, AB type, *J* 16 Hz, CH$_2$SO), 4.50 (2 H, q, *J* 7 Hz, C*H*$_2$CH$_3$), 7.02 (1 H, s, CH), 7.3–7.9 (3 H, m, ArH), 8.1–8.3 (1 H, m, ArH); *m/z* 276 (M$^+$) (Found: C, 56.63; H, 4.29; N, 10.25. C$_{13}$H$_{12}$N$_2$O$_3$S requires: C, 56.51; H, 4.38; N, 10.14).

Crystal data for **4**: C$_{14}$H$_{18}$N$_2$O$_4$S: M$_r$ = 310.36, colourless crystal (1.0 × 0.2 × 0.1 mm), monoclinic, space group P2$_1$/c, *a*=9.992(1), *b*= 16.532(1), *c*=8.946(1) Å, β=91.55(1)° V=1477.2(2) Å^3, Z=4, ρ_{calcd} =1.396 gcm^{-3} , F(000)=656, λ(Cu kα) = 1.54178 Å, μ= 2.113 mm^{-1}, graphite monochromator, θ–2θ scan, T=298 K; of 3316 measured

reflections (4.4 < θ < 68.0) 2578 were independent (R$_{int}$ = 0.0656). Data were collected with a Siemens P4 diffractometer and corrected for Lorentz, polarization and decay effects (three standard reflections were measured every 100 reflections), while no absoption correction was applied. The structure was solved by direct methods (SIR97)[11] and refined on F^2 (SHELXL-97)[12]. All non-hydrogen atom were refined with anisotropic thermal parameters. Hydrogen atoms were inserted at calculated position and refined in the riding mode. wR2=0.1525 and R1 = 0.0561 [for 2070 reflections with I>2σ(I)], GoF=1.068 for 199 parameters. A final difference Fourier map showed no residual density below –0.343 or above 0.532 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-149453. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

References

1 A. Padwa, *in 1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984, vol. 2, chap. 12.
2 A. Padwa and A.M. Schoffstahl, in *Advances in Cycloaddition*, ed. D.P. Curran, YAI Press, London, 1990, vol. 2, p. 1.
3 G. Broggini, G. Molteni and G. Zecchi, *Heterocycles*, 1998, **47**, 541.
4 L. Bruché, L. Garanti and G. Zecchi, *J.Chem.Soc., Perkin Trans. 1*, 1981, 2245; L. Bruché, L. Garanti and G. Zecchi, *J.Chem.Soc., Perkin Trans. 1*, 1984, 2535.
5 L. Bruché, L. Garanti and G. Zecchi, *J.Chem.Res.*, 1986, (*S*) 210, (*M*) 1890; L. Bruché and G. Zecchi, *J.Chem.Soc., Perkin Trans. 1*, 1987, 399.
6 C.J.M. Stirling, in *Organic Chemistry of Sulfur*, ed. S. Oae, Plenum Press, New York, 1977, ch. 9, p. 519.
7 G.H. Posner, in *Asymmetric Synthesis*, ed. J.D. Morrison, Academic Press, New York, 1983, p. 225; G.H. Posner, in *The Chemistry of Sulphoxides and Sulphones*, eds. S. Patai, Z. Rappoport and C.J.M. Stirling, Wiley, New York, 1988, ch. 16; G.H. Posner, *Acc.Chem.Res.*, 1987, **20**, 72 and references therein; A.J. Walker, *Tetrahedron: Asymmetry*, 1992, **3**, 961; A.D. Westwell, M. Thornton-Pett and C.M. Rayner, *J.Chem.Soc., Perkin Trans. 1*, 1995, 847 and references therein; M.C. Carreño, *Chem.Rev.*, 1995, **95**, 1717; G.D. Solladié, in *Houben-Weyl, Methods of Organic Chemistry, Stereoselective Synthesis*, eds. G. Helmchen, R.W. Hoffmann, J. Mulzer and E. Schaumann, 1996, vol. E 21, p. 1056 and p. 1793.
8 J.L. Carretero, J.L. Garcia Ruano, A. Lorente and F. Juste, *Tetrahedron: Asymmetry*, 1993, **4**, 177 and references therein; M.A. Brimble, L.J. Duncalf and D.C.W. Reid, *Tetrahedron: Asymmetry*, 1995, **6**, 263.
9 T.Koizumi, H. Hirai and E. Yoshii, *J.Org.Chem.*, 1982, **47**, 4004; T. Takahashi, A. Fujii, J. Sugita, T. Hagi, K. Kitano, Y. Arai, T. Koizumi and M. Shiro, *Tetrahedron: Asymmetry*, 1991, **2**, 1379; C. Louis and C. Hootelé, *Tetrahedron: Asymmetry*, 1995, **9**, 2149.
10 P. Bravo, L. Bruché, A. Farina, G. Fronza, S.V. Meille and A. Merli, *Tetrahedron: Asymmetry*, 1993, **4**, 2131; P. Bravo, L. Bruché, G. Fronza and A. Merli, *Gazz.Chim.Ital.*, 1994, **124**, 275; P. Bravo, L. Bruché, M. Crucianelli, A. Farina, S.V. Meille, A. Merli and P. Seresini, *J.Chem.Res.*, 1996, (*S*) 348, (*M*) 1901; P. Bravo, L. Bruché, P. Seresini and M. Zanda, *J.Heterocycl.Chem.*, 1997, **34**, 489. A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, M. C. Burla, G. Polidori, M. Camalli, R. Spagna, SIR97, Program for Crystal Structure Solution, Università di Bari. G. M. Sheldrick, SHELXL-97, Program for Crystal Structure Refinement, Universität Göttingen, 1997.