6-Phenylsulfonyl-2,10-diazabicyclo[4.4.0]dec-1-ene—a Readily Accessible, Prototypical Bicyclic Amidine for Studies in Molecular Recognition and Catalysis

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The title compound is synthesised in two steps from commercially available starting materials; the amidine and its complex with a chiral carboxylic acid are characterised using X-ray crystallography.

Amidinium and guanidinium units have figured prominently in studies of anion recognition, being able to satisfy the electrostatic and H-bonding requirements of various oxoanions through formation of complexes **1**.[1,2] Bicyclic systems of general form **2** have attracted particular attention.[1] They are preorganised for oxoanion recognition at a specific site, and their conformationally restricted frameworks may be used to position additional functionality, sometimes in quite elaborate architectures.[1b,e,f] In the latter part of this work it has been guanidinium (X = N) rather than amidinium (X = CR) units which have predominated, probably owing to synthetic considerations.† The published syntheses of bicyclic amidines such as **3**[1a] and **4**[3] require rather vigorous conditions and are not well-suited to the preparation of complex, multifunctional analogues. We now report the preparation of the title amidine **5** *via* a mild and simple procedure which could be adaptable to a range of related structures, including chiral variants with potential as enantioselective catalysts.[1h]

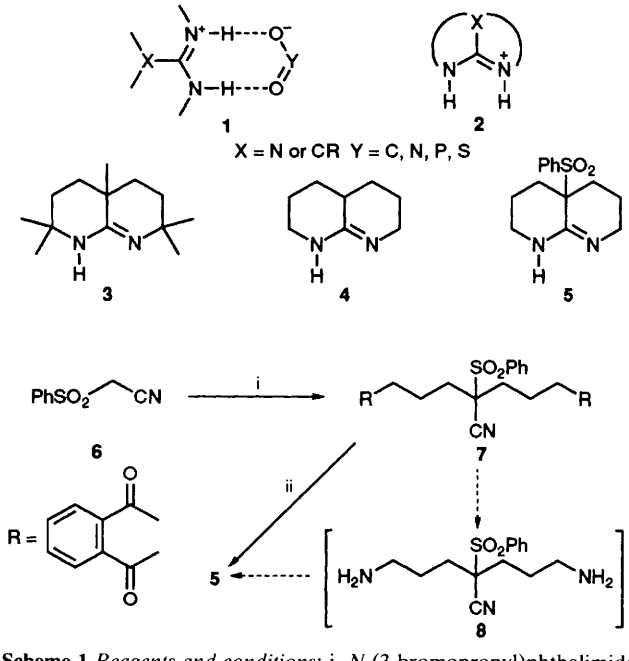
As shown in Scheme 1, our synthesis of **5** required just two steps from commercially available (phenylsulfonyl)acetonitrile **6**. Bis-alkylation of **6** with *N*-(3-bromopropyl)phthalimide, employing DBU as base,[4] gave **7** in 87% yield. Treatment of **7** with $NaBH_4$ then AcOH, following the procedure of Osby *et al.*,[5] was expected to give diamine **8**. Instead, we were pleased to find that bicyclisation occurred under the reaction conditions to give **5** directly in 65% yield. Both **7** and **5** were purified by crystallisation, without recourse to chromatography.

Amidine **5** was characterised by microanalysis, spectroscopic methods‡ and X-ray crystallography (Fig. 1).§ The crystals, which were obtained from MeCN, were found to contain dimeric units connected by pairs of NH···N hydrogen bonds (intermolecular H···N distances of 2.33 Å).¶ An unexpected feature of the structure is the pyramidal arrangement of bonds around the tricoordinate nitrogen, N(2). A survey of the amidine structures present in the Cambridge Crystallographic Database revealed that the anticipated planar coordination pattern is indeed more common. However, the results in this case may indicate that pyramidalisation is not too costly in energetic terms.

X-Ray crystallography was also used to confirm the ability of **5** to interact specifically with carboxyl groups, as in **1** (Y =C). Treatment of the amidine with an equimolar quantity of *S*-naproxen **9** in $CHCl_3$ followed by evaporation and recrystallisation from $CHCl_3$–MeCN yielded a 1:1 complex as colourless needles. The X-ray crystal structure of this material, shown in Fig. 2,‖ indicated that proton transfer had taken place to give the naproxenate of $\mathbf{5H}^+$ as an ion pair, connected *via* two NH···O hydrogen bonds with H···O distances of 1.761 and 1.765 Å, respectively. As might be expected, both nitrogens in this structure exhibit planar coordination.

The basicity of **5** was assessed in terms of its ability to interact with nitroalkanes. In earlier work we had used ^1H NMR to study mixtures of nitroethane and Eschenmoser's bicyclic amidine **3** in C_6D_6 and CD_3CN, and had obtained evidence of substantial proton transfer in both solvents.[1h] In similar experiments with **5**, no proton transfer could be detected, implying that the sulfonyl group does cause a significant reduction in basicity. However, **5** did prove able to catalyse the addition of nitroethane to but-1-en-3-one, albeit at a lesser rate than **3**.

The straightforward synthesis of **5** and the mild conditions involved suggest that this simple amidine could serve as



Scheme 1 *Reagents and conditions*: i, *N*-(3-bromopropyl)phthalimide (2.2 equiv.), DBU (2.2 equiv.), DMF, 80 °C, 40 min; ii, $NaBH_4$, Pr^iOH, H_2O, room temp., 24 h, followed by addition of AcOH, 80 °C, 3 h

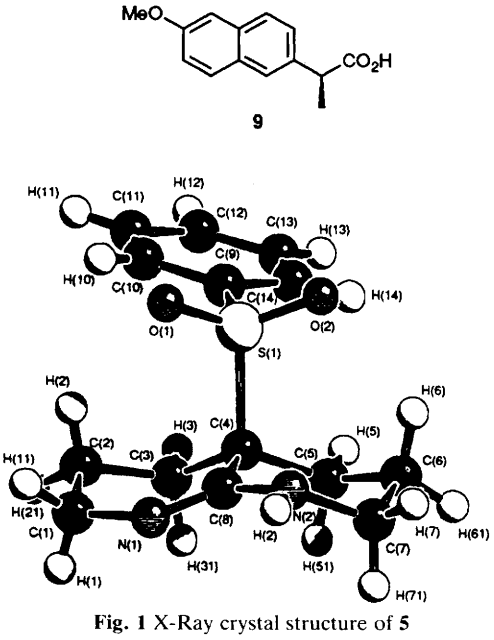


Fig. 1 X-Ray crystal structure of **5**

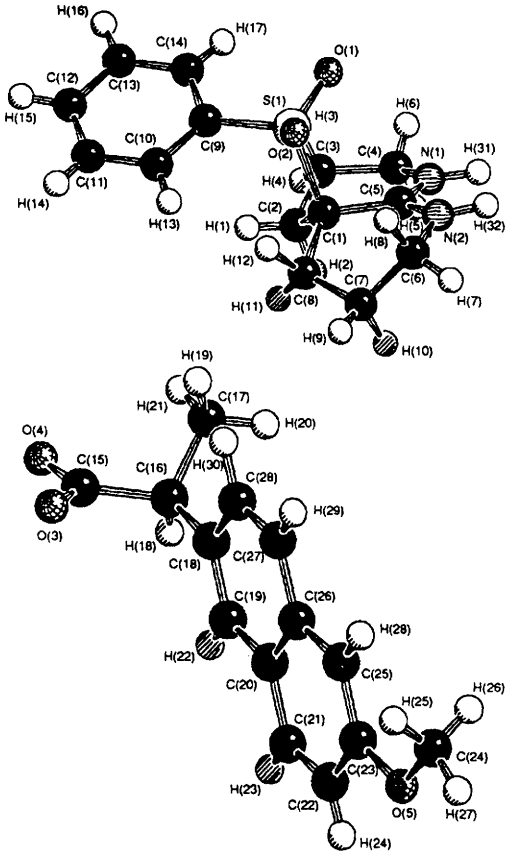


Fig. 2 X-Ray crystal structure of **5H**$^+$ naproxenate

prototype for a series of more elaborate bases, including analogues with a variety of functional groups. **5** Itself has potential in the crystallisation and handling of carboxylic and other oxoacids, following the precedent set by the pentamethyl bicyclic amidine **3**.[6] The phenylsulfonyl amidine has similar lipophilicity to **3**, but is simpler to prepare and easier to store and handle, being far less vulnerable to reaction with atmospheric carbon dioxide.

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Footnotes

† In other respects, the amidiniums are relatively attractive. Being more acidic than the guanidiniums they should be stronger H-bond donors, and there is scope for variation at the amidinium 'α-carbon' (X = CR) which is not available for X = N.

‡ *NMR data* for **5**: δ_H($CDCl_3$, 300 MHz) 7.97–7.51 (5 H, m, SO_2Ph), 3.29–3.20 (2 H, m, NCH_2), 3.04–2.95 (2 H, m, NCH_2), 2.53–2.34 (2 H, m, CH_2), 2.11–2.01 (2 H, m, CH_2), 1.74–1.65 (2 H, m, CH_2), 1.52–1.44 (2 H, m, CH_2); δ_C($CDCl_3$, 75.87 MHz) 156.06 (–N=C–N–), 137.15, 134.04, 130.33, 128.83, 63.74 ($PhSO_2$–*C*), 43.94, 32.19, 20.04.

§ *Crystal data* for **5**: $C_{14}H_{18}O_2N_2S$, M = 278.3694, monoclinic, a = 7.3096(6), b = 12.0184(6), c = 15.332(1) Å, β = 91.510(4)°, U = 1346.5(1) Å^3 (by least-squares refinement of the setting angles of 25 reflections, 16 < θ < 18°), space group $P2_1n$ (alternative setting of $P2_1c$, No. 14), Z = 4, D_c = 1.373 g cm^{-3}, F(000) = 592. λ = 0.71069 Å, μ(Mo-Kα) = 1.95 cm^{-1}. 2592 reflections in the range 1 < θ < 25° were measured on an Enraf-Nonius CAD4 diffractometer using ω-2θ scan mode and graphite monochromated Mo-Kα radiation. The data were merged to give 2302 unique reflections (R_{merg} = 0.0114) of which 2221 had $|F_{obs}| > 4\sigma|F_{obs}|$ and were used in structure solution and refinement. The structure was solved using the direct method of SHELXS and refined by full-matrix least-squares analysis to final R and R_w values of 0.0390 and 0.0507, respectively. All of the atoms were located and allowed to refine with the non-hydrogen atoms given anisotropic temperature factors. The final difference map had a highest peak of 0.25 e Å^{-3}.

¶ *cf.* The dimeric structure proposed in ref. 1(*i*) for a 'dibenzoguanidine' in $CDCl_3$ solution.

‖ *Crystal data* for **5H**$^+$ *naproxenate*: $C_{28}H_{32}O_5N_2S$, M = 508.6324, orthorhombic, a = 5.8526(6), b = 16.166(1), c = 26.694(3) Å, U = 2525.6(5) Å^3, space group $P2_12_12_1$ (No. 19), Z = 4, D_c = 1.334 g cm^{-3}, F(000) = 1080. λ = 0.71069 Å, μ(Mo-Kα) = 1.29 cm^{-1}. A colourless crystal of approximate dimensions 0.3 × 0.3 × 0.3 mm^3 was mounted on an Enraf-Nonius CAD4 diffractometer, and the intensities of 2591 reflections in the range 1 < θ < 25° were measured using the ω-2θ scan mode and graphite monochromated Mo-Kα radiation. The data were merged to give 2564 unique reflections (R_{merg} = 0.0312) of which 2016 had $|F_{obs}| > 4\sigma|F_{obs}|$ and were used in structure solution and refinement. The structure was solved using the direct method of SHELXS-86 and refined by full-matrix least-squares analysis to a conventional R factor of 0.0338. The non-hydrogen atoms were refined with anisotropic temperature factors while the hydrogen atoms were located and their positions allowed to refine with isotropic temperature factors. Atomic coordinates, bond lengths and angles, and thermal parameters for both compounds, have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

References

1 For bicyclic systems, see *e.g.* (*a*) F. Heinzer, M. Soukup and A. Eschenmoser, *Helv. Chim. Acta*, 1978, **61**, 2851; (*b*) F. P. Schmidtchen, *Tetrahedron Lett.*, 1989, **30**, 4493; (*c*) A. Gleich, F. P. Schmidtchen, P. Mikulcik and G. Müller, *J. Chem. Soc., Chem. Commun.*, 1990, 55; (*d*) A. Echavarren, A. Galán, J.-M. Lehn and J. de Mendoza, *J. Am. Chem. Soc.*, 1989, **111**, 4994; (*e*) A. Galán, D. Andreu, A. Echavarren, P. Prados and J. de Mendoza, *J. Am. Chem. Soc.*, 1992, **114**, 1511; (*f*) G. Deslongchamps, A. Galán, J. de Mendoza and J. Rebek Jr., *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 61; (*g*) E. J. Corey and M. Ohtani, *Tetrahedron Lett.*, 1989, **30**, 5227; (*h*) P. H. Boyle, M. A. Convery, A. P. Davis, G. D. Hosken and B. A. Murray, *J. Chem. Soc., Chem. Commun.*, 1992, 239, (*i*) J.-L. Chicharro, P. Prados and J. de Mendoza, *J. Chem. Soc., Chem. Commun.*, 1994, 1193; (*j*) P. H. Boyle, A. P. Davis, K. J. Dempsey and G. D. Hosken, *J. Chem. Soc., Chem. Commun.*, 1994, 1875.

2 For other systems, see *e.g.* (*a*) B. Dietrich, T. M. Fyles, J.-M. Lehn, L. G. Pease and D. L. Fyles, *J. Chem. Soc., Chem. Commun.*, 1978, 934; (*b*) M. W. Göbel, J. W. Bats and G. Dürner, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 207; (*c*) A. Terfort and G. von Kiedrowski, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 654; (*d*) J. Smith, K. Ariga and E. V. Anslyn, *J. Am. Chem. Soc.*, 1993, **115**, 362; (*e*) E. Fan, S. A. Van Arman, S.Kincaid and A. D. Hamilton, *J. Am. Chem. Soc.*, 1993, **115**, 369.

3 S. Löfås and P. Ahlberg, *J. Heterocycl. Chem.*, 1984, **21**, 583; K. Janne and P. Ahlberg, *Synthesis*, 1976, 452.

4 *cf.* H. Oediger and F. Möller, *Liebigs Ann. Chem.*, 1976, 348.

5 J. O. Osby, M. G. Martin and B. Ganem, *Tetrahedron Lett.*, 1984, **35**, 2093.

6 D. Sternbach, M. Shibuya, F. Jaisli, M. Bonetti and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 634; S. E. Denmark, *J. Org. Chem.*, 1981, **46**, 3144; P. Mohr, M. Tori, P. Grossen, P. Herold and C. Tamm, *Helv. Chim. Acta*, 1982, **65**, 1412; W. Oppolzer, C. Chapuis, D. Dupuis and M. Guo, *Helv. Chim. Acta*, 1985, **68**, 2100.