

The Direct Synthesis of the Cyclic Sulphamidate of (*S*)-Prolinol: Simultaneous *N*-Protection and Activation towards Nucleophilic Displacement of Oxygen.

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Abstract: The preparation of the cyclic sulphamidate of (*S*)-prolinol has been achieved by reaction with sulphuryl chloride at low temperature. This material has been shown to be susceptible to acid catalysed nucleophilic attack to furnish 2-(*N,N*-dialkylamino)methyl- and 2-(methoxymethyl)pyrrolidines after hydrolysis of the intermediate sulphamic acid derivatives.

It has been reported that cyclic sulphamidates **1** undergo nucleophilic substitution at oxygen with secondary amines (Figure 1), albeit under forcing conditions (EtOH, R₂NH, 130°C, steel bomb, 3h).²

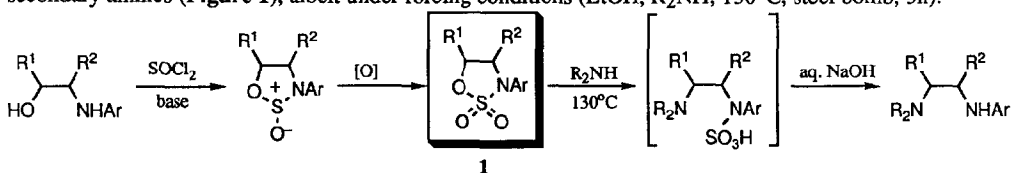
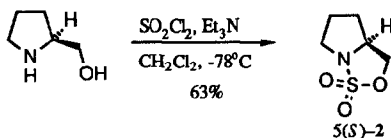


Figure 1

The previous workers obtained the cyclic sulphamidates **1** by oxidation of the corresponding sulphimidite precursors with potassium permanganate, whilst others have used ruthenium tetroxide to carry out such oxidations.³ In another instance, the sulphamidate derivative of serine has been obtained *via* DCC mediated closure of the *O*-sulphate⁴ and this derivative is currently being investigated in studies parallel to those reported here.⁵ In addition, a cyclic sulphamidate has been postulated as an intermediate in the unexpected fluorination of a *N*-trimethanesulphonyl- β -amino alcohol.⁶

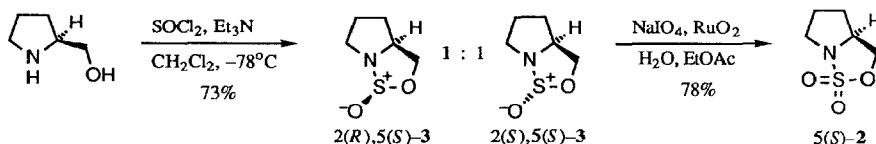
We reasoned that a straightforward preparation of sulphamidate ester derivatives of readily available homochiral β -amino alcohols, permitting concomitant protection of the nitrogen moiety and conversion of the hydroxyl into a leaving group, should form the basis of a convenient, enantiospecific approach to amine derivatives if milder substitution conditions than those previously reported¹ could be developed. However, the most direct approach to cyclic sulphamidates, namely reaction of β -amino alcohols with sulphuryl chloride, has not been reported, the only published attempt to carry out such a conversion leading to the isolation of an aziridine after chromatography.⁷

Our initial attempts at direct preparation of the sulphamidate of (*S*)-prolinol (**2**) failed until the reaction was carried out at -78°C.



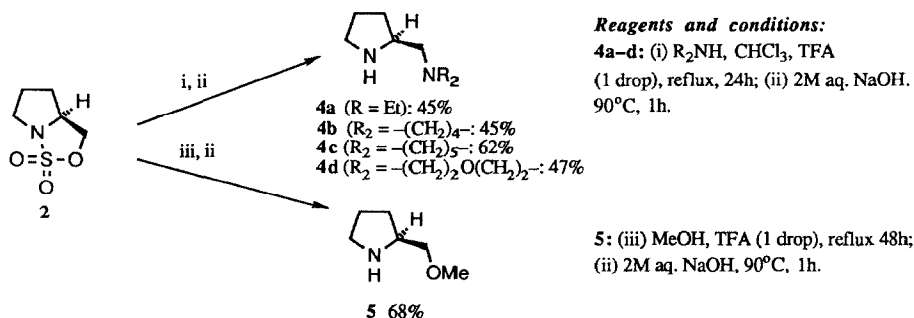
At this temperature (*S*)-prolinol reacted with sulphuryl chloride in dichloromethane containing two equivalents of triethylamine to furnish 5(*S*)-**2** in 63% yield after rapid purification by dry flash chromatography followed by recrystallisation from ether {m.p. 46–8°C; $[\alpha]_{\text{D}}^{20} +43.2$ (c 1.02, CHCl_3)}.

In a stepwise approach to **2**, the known cyclic sulphamidite **3**⁸ could be obtained as a 1:1 mixture of epimers at the sulphur in 73% distilled yield from (*S*)-prolinol by this low temperature modification. Oxidation of the mixture ($\text{NaIO}_4 / \text{RuO}_2$, EtOAc, 0°C) furnished **2** in 78% yield (57% overall from (*S*)-prolinol).



The relative stereochemistry of the epimers has been previously assigned by Lowe and co-workers⁸ by virtue of the anisotropy of the sulphoxide group.⁹ Rapid decomposition on silica thwarted attempts at chromatographic isolation of both epimers but, on standing, 2(*R*),5(*S*)-**3** was found to decompose more rapidly leaving the ether soluble material highly enriched (*ca.* 95%) in 2(*S*),5(*S*)-**3**. Pure 2(*S*),5(*S*)-**3** $\{[\alpha]_{\text{D}}^{20} -44.3$ (c = 2.78 CH_2Cl_2) $\}$ could then be isolated from this enriched mixture by rapid dry flash chromatography.

Attempts at carrying out substitutions on substrates **2** and **3** with anionic nucleophiles (MeMgBr , PhLi , MeONa) under a wide variety of conditions proved unsuccessful. However, heating a solution of **2** in refluxing chloroform with diethylamine, followed by removal of solvent and treatment with aqueous base,² permitted the isolation of 2-(*N,N*-diethylamino)methylpyrrolidine (**4a**) in 28% yield. This yield was increased to 45% on the addition of one drop of trifluoroacetic acid to the reaction mixture $\{[\alpha]_{\text{D}}^{20} = +10$ (c = 0.44, CHCl_3) $\}$.^{10a,b} In a similar manner 2-(pyrrolidinomethyl)pyrrolidine (**4b**) $\{[\alpha]_{\text{D}}^{20} = +13.0$ (c = 1.36, EtOH) $\}$ ^{10a,b,c} 2-(piperidinomethyl)pyrrolidine (**4c**) $\{[\alpha]_{\text{D}}^{20} = +15.2$ (c = 2.4, EtOH) $\}$ ^{10a,b,c} and 2-(morpholinomethyl)pyrrolidine (**4d**) $\{[\alpha]_{\text{D}}^{20} = +18.4$ (c = 2.99 EtOH) $\}$ ^{10a,b,c} were isolated in 45%, 62% and 47% distilled yields respectively. In all cases the yield of material, pure by n.m.r. analysis, was quantitative prior to the distillation. Extending this procedure, 2-(methoxymethyl)pyrrolidine (**5**) was obtained in 66% isolated yield $\{[\alpha]_{\text{D}}^{20} = +2.8$ (c = 0.60, CHCl_3) $\}$ ¹¹ by refluxing **2** in methanol containing one drop of trifluoroacetic acid, followed by removal of solvent and base hydrolysis (Scheme).



Scheme

The sulphamidate **2** is a crystalline material and is stable for extended periods of storage at room temperature. Homochiral diamines **4a-d** have found application as chiral bases^{12,10c} and also for complexation

with hydride reagents to obtain enantioselective reducing agents.^{10b,13} This direct approach to the enantioselective preparation of bidentate ligands such as **4a-d** and **5** from prolinol appears to have potential for further application and we will report our findings in due course.

Experimental Procedures

Preparation of sulphamidate 2: Method 1: (S)-prolinol (505 mg, 5 mmol) and triethylamine (1.42 mL, 2 equiv.) were dissolved in dichloromethane (30 mL), cooled to -78°C and to this stirred mixture was added sulphuryl chloride (419 mg, 0.41 mL) in CH_2Cl_2 (30 mL) dropwise by syringe. The mixture was maintained at this temperature for 3h, allowed to warm to room temperature and stirred for a further 10h. The mixture was washed with aq. HCl (2 x 10 mL), brine (10 mL), dried and the solvent removed *in vacuo*. Purification by dry flash chromatography, eluting with pentane / ether gradient, followed by recrystallisation (ether) furnished 5(S)-**2** as colourless needles (523 mg, 63%). m.p. $46-8^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{20} +43.2$ ($c = 1.02$, CHCl_3); Found, C 36.4, H 5.8, N 8.5, S 19.6%, $\text{C}_5\text{H}_9\text{NO}_2\text{S}$ requires C 36.8, H 5.6, N 8.6, S 19.9%; ν_{max} 1370, 1185 cm^{-1} ; δ_{H} (300 MHz, CDCl_3) 1.82 (1H, m), 2.19 (1H, m), 1.96 (2H, m), 3.27 (1H, dt, J 7.1 Hz, J' 11.5 Hz), 4.28 (1H, m), 3.68 (1H, dt, J 5.9 Hz, J' 11.5 Hz), 4.05 (1H, dd, J 6.0 Hz, J' 8.7 Hz), 4.55 (1H, dd, J 6.9 Hz, J' 8.7 Hz); δ_{C} (50.3 MHz, CDCl_3) 25.0, 31.1, 51.0, 62.4, 71.8; m/z (C.I., NH_3) 181 (MNH_4^+), 164 (MH^+).

Method 2: A solution of (S)-prolinol (3.03 g, 30 mmol) and triethylamine (8.6 mL, 2 equiv.) in dichloromethane (80 mL) was added dropwise over thirty minutes to a stirred solution of thionyl chloride (2.18 g, 2.26 mL, 31 mmol) in dichloromethane (80 mL) under nitrogen at -78°C . This temperature was maintained for three hours and then allowed to rise slowly to room temperature overnight. The solvent was evaporated and the brown residue was triturated several times with ether (4 x 75 mL) and dichloromethane (20 mL). The organic extracts were combined and concentrated *in vacuo* to give an oily residue which was purified by short path distillation (bath temp. 110°C / 0.4 mm Hg) to give the epimeric mixture of sulphamidites **3** as a colourless liquid (3.21 g, 72%). Found C 41.0, H 6.4, N 9.4%; $\text{C}_5\text{H}_9\text{NO}_2\text{S}$ requires C 40.8, H 6.2, N 9.5%; ν_{max} 1165 cm^{-1} ; m/z (C.I. NH_3) 148 (MH^+), 70; 2(R),5(S)-**3**: δ_{H} (200 MHz) 1.60-2.10 (4H, m), 3.20-3.50 (2H, m), 4.18 (1H, dd, J 8.5 Hz, J' 3.0 Hz), 4.20-4.32 (1H, m), 4.86 (1H, dd, J 8.5 Hz, J' 6.5 Hz); δ_{C} 24.9, 30.9, 47.9, 64.6, 74.1. 2(S),5(S)-**3**: $[\alpha]_{\text{D}}^{20} -44.3$ ($c = 2.78$, CH_2Cl_2) 1.90-2.05 (4H, m), 2.87 (1H, m), 3.50 (1H, m), 3.97-4.32 (3H, m), 4.44 (1H, dd, J 4.9 Hz, J' 6.3 Hz); δ_{C} 28.1, 28.4, 44.5, 65.5, 71.2. To an aqueous solution of sodium periodate (0.5 M, 12 mL) and ruthenium dioxide (9.5 mg) was added a solution of sulphamidite **3** (240 mg, 1.65 mmol, diastereoisomeric mixture) in ethyl acetate (10 mL). The mixture was stirred at 0°C in a sealed flask for 30 min, transferred to a separating funnel and the organic layer removed. The aqueous layer was washed with ethyl acetate (2 x 15 mL) and the organic extracts were combined. Isopropyl alcohol (3 mL) was added to destroy any ruthenium tetroxide remaining in the organic layer, the mixture was filtered, dried and concentrated *in vacuo* to give a white solid which was recrystallised from ether to furnish pure **2** (208 mg, 78%).

Representative Procedure for reaction of 2 with amines: Preparation of 2-(S)-(N,N-diethylaminomethyl)pyrrolidine (4a): A solution of **2** (173 mg, 1.1 mmol), and Et_2NH (1.0 mL, 9 equiv.) in chloroform (15 mL) containing trifluoroacetic acid (1 drop) was refluxed for 24 h. Removal of solvent and excess diethylamine (*in vacuo*) from the deep red solution gave a residue which was heated to 90°C with aq. NaOH (2 M, 10 mL) for 1h. After cooling, the solution was extracted with ether (4 x 10 mL), and the organic extracts were combined, dried and concentrated at reduced pressure to give 2-(S)-(N,N-diethylaminomethyl)pyrrolidine (**4a**) as a pale

yellow oil. Purification by short path distillation (bath temp 60°C / 0.35 mm Hg) gave pure **4a** (72 mg, 45%) with spectroscopic data identical with those in the literature [α]_D²⁰ +10.0 (*c* = 0.44, CHCl₃).^{10a,b} The same procedure permitted the isolation of 2(*S*)-(pyrrolidinomethyl)pyrrolidine (**4b**) in 45% distilled yield, [α]_D²⁰ +13.0 (*c* = 1.36, EtOH),^{10a,b,c} 2-(*S*)-(piperidinomethyl)pyrrolidine (**4c**) in 62% distilled yield [α]_D²⁰ +15.2 (*c* = 2.40, EtOH),^{10a,b,c} and 2-(*S*)-(morpholinomethyl)pyrrolidine (**4d**) in 47% distilled yield [α]_D²⁰ +18.4 (*c* = 2.99, EtOH).^{10a,b,c}

Preparation of 2-(S)-(methoxymethyl)pyrrolidine (5): To a solution of **2** (266 mg) in methanol (10 mL) was added one drop of trifluoroacetic acid. The solution was refluxed for 48 hours, and the methanol was then removed at reduced pressure. The remaining material was dissolved in aq. NaOH (2 M, 15 mL) and heated to 90°C for 1 h with stirring. After cooling, the solution was extracted with ether (3 x 15 mL), the organic extracts were combined, dried and concentrated at reduced pressure to give essentially pure 2-(*S*)-(methoxymethyl)pyrrolidine (**5**) (124 mg, 66%) with spectroscopic data identical with those in the literature. A sample was further purified by short path distillation (bath temp. 45°C / 15 mm Hg), [α]_D²⁰ +2.8 (*c* = 0.60, CHCl₃).¹¹

References

1. For the sake of brevity in this paper, we use the trivial nomenclature of *sulphamidate* to describe the [3.3.0]-1-aza-2-thia-3-oxabicyclooctane-2,2-dioxide system (**2**) and *sulphamidite* to describe the [3.3.0]-1-aza-2-thia-3-oxabicyclooctane-2-oxide system (**3**).
2. Z. Zubovics, L. Tody, A. Varro, G. Rablozky, M. Kurthy, P. Duortsak, G. Jerkovich, and E. Tomori, *Eur. J. Med. Chem.*, 1986, **21**, 370.
3. B. Cuthbert and G. Lowe, *J. Chem. Soc., Chem. Commun.*, 1989, 1702.
4. Y. Noda, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 1554.
5. J. E. Baldwin, A. C. Spivey, and C. J. Schofield, *Tetrahedron Asymmetry*, Accompanying paper.
6. T. Lyle, C. Magill, and S. Pitzenberger, *J. Amer. Chem. Soc.*, 1987, **109**, 7890.
7. J. Deyrup and C. Moyer, *J. Org. Chem.*, 1969, **34**, 175.
8. Previously prepared in 38% yield from (*S*)-prolinol by reaction with thionyl chloride / pyridine in benzene at 0 -- -10°C: G. Lowe and M. A. Reed, *Tetrahedron Asymmetry*, Accompanying paper.
9. T. Nishiyama and F. Yamada, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 3073; T. Nishiyama, F. Yamada, and H. Samukawa, *Bull. Soc. Chem. Jpn.*, 1975, **48**, 1878.
10. (a) T. Sone, K. Hiroi, and S. Yamada, *Chem. Pharm. Bull.*, 1973, **21**, 2331; (**4a**) [α]_D²⁰ +13.4 (*c* = 1.14, EtOH); (**4b**) [α]_D²⁰ +8.5 (*c* = 2.4, EtOH); (**4c**) [α]_D²⁷ +17.8 (*c* = 1.28, EtOH), (**4d**) [α]_D²⁵ 10.4 (*c* = 10, EtOH); (b) M. Asami, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 721; (**4a**) [α]_D²⁸ +14.5 (*c* = 1.10, EtOH); (**4b**) [α]_D²⁹ +8.2 (*c* = 2.38, EtOH); (**4c**) [α]_D²⁸ +19.1 (*c* = 1.04, EtOH) (**4d**) [α]_D³⁰ +17.6 (*c* = 9.98, EtOH); (c) S. K. Hendie and J. Leonard, *Tetrahedron*, 1987, **43**, 3289, (**4b**) [α]_D²⁵ +8.3 (*c* = 2.4, EtOH); (**4c**) [α]_D²⁵ +1.8 (*c* = 2.2, C₆H₆); (**4d**) [α]_D²⁵ +10.4 (*c* = 10, EtOH). The optical rotations of the diamines (**4a-d**) are heavily solvent and concentration dependent.
11. D. Seebach, H. Kainowski, B. Bastani,, G. Crass, H. Daum, N. P. Dupreez, V. Ehrig, W. Langer, C. Nussler, H. Oei, and M. Schmidt, *Helv. Chim. Acta*, 1977, **60**, 301. [α]_D²⁰ +3.0 (*c* = 2.0, C₆H₆).
12. T. Mukaiyama, *Tetrahedron*, 1981, **37**, 4111; T. Mukaiyama, K. Tomimori, and T. Oriyama, *Chem. Lett.*, 1985, 813.
13. (a) M. Asami, *Chem. Lett.*, 1984, 829; (b) M. Asami, *Bull. Chem. Soc. Jpn*, 1990, **63**, 1402.