Synthesis and Stability of the Cyclic Sulfamidate of *N*-Trityl-L-Serine Methyl Ester

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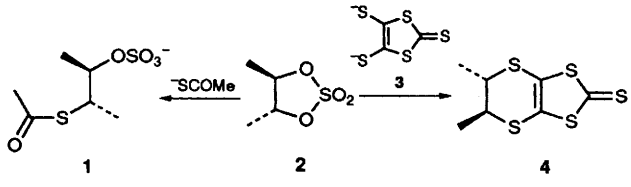
The title compound **12**, prepared in three steps from L-serine methyl ester, is thermally stable <50 °C; the formation of the cyclic sulfamidite **9**, rather than acyclic products, in the reaction of thionyl chloride with *vic*-amino alcohol **7** is far more dependent on reaction conditions than with less crowded molecules.

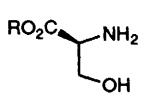
The cyclic sulfate ester of (2*R*)(3*R*)-butane-2,3-diol **2** undergoes stereospecific ring opening at carbon with one equivalent of nucleophile, *e.g.* with thioacetate to give the monoalkyl sulfate anion **1**. Furthermore, **2** reacts with the bis-nucleophile **3** by stereospecific displacement of the SO_4^{2-} ion to form the six-membered ring in **4**.[1] These appear to be general reactions for cyclic sulfate esters of *vic*-diols.[2–4] We have extended this chemistry to the cyclic sulfamidates of *vic*-amino alcohols and, in particular, that of L-serine methyl ester **5** to open a route to the synthesis of new amino acid derivatives. Substitution of one amino H atom in **5** (*e.g.* with benzyl to give **6**) was necessary for the subsequent reaction with thionyl chloride to form cyclic sulfamidite **8** (as a mixture of two diastereoisomers). Subsequent oxidation with a source of ruthenium(VIII) gave the cyclic sulfamidate **11**, which underwent ring opening at C-5 with a range of nucleophiles.[5] Similar, results have been reported for the *tert*-butyl ester of L-serine.[6]

In a search for a more readily removable *N*-protecting group we targeted the cyclic sulfamidate of *N*-trityl-L-serine methyl ester **12**. It has been reported[7] that such compounds are unstable to loss of SO_3, *e.g.* the benzyl ester analogue **13** often decomposed during preparation from cyclic sulfamidite **10** [by ruthenium (VIII) catalysed oxidation] to give aziridine **18**. However, this seemed unlikely for the L-threonine analogue as the reported[7] loss of SO_3 would require an inversion of configuration at C-5.† We find that treatment of the *N*-trityl-L-serine methyl ester **7** with thionyl chloride and pyridine in tetrahydrofuran (THF) at 0 °C for 2 h yields the corresponding cyclic sulfamidite **9** (as a mixture of two diastereoisomers) in 90% yield‡. (The ^1H and ^{13}C NMR spectra of **9** differ markedly from those reported for the corresponding *N*-trityl benzyl ester **10**.[7]) Subsequent oxidation with sodium periodate/aqueous acetonitrile in the presence of catalytic ruthenium(III) chloride gives the corresponding cyclic sulfamidate **12** in 48% yield.§ This material is completely unchanged on heating in dry acetonitrile to 50 °C for at least 2 h. The ^{13}C NMR spectrum of **12** shows characteristic signals for the two ring C atoms (δ C-4 58.8, C-5 66.2) in close agreement to those observed in the corresponding *N*-benzyl analogue **11** (δ 57.0, 66.2), the structure of which has been determined by X-ray crystallography.[5] The ^1H–^{13}C correlation spectrum confirms the assignment of these two resonances of **12**, and the FAB MS shows a highest *m/z* of 344 assigned as $M-SO_3^+$, and a base peak corresponding to the trityl cation.

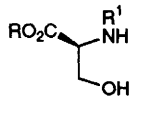
The sensitivity of the reaction of *N*-trityl *vic*-amino alcohols, such as **7**, with thionyl chloride to choice of base and solvent



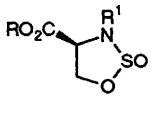
1 **2** **4**



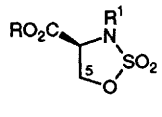
5; R = Me



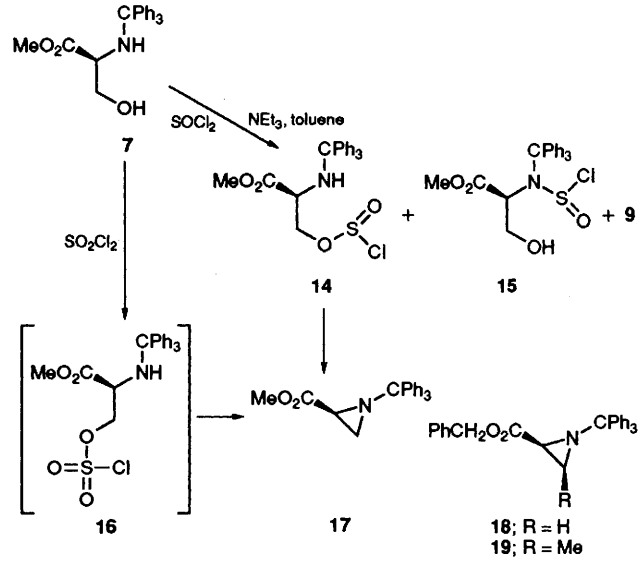
6; R = Me, R¹ = $PhCH_2$
7; R = Me, R¹ = Ph_3C



8; R = Me, R¹ = $PhCH_2$
9; R = Me, R¹ = Ph_3C
10; R = $PhCH_2$, R¹ = Ph_3C



11; R = Me, R¹ = $PhCH_2$
12; R = Me, R¹ = Ph_3C
13; R = $PhCH_2$, R¹ = Ph_3C



7 **14** **15** **16** **17** **18**; R = H **19**; R = Me

† This is partly obscured in the original paper, due to a slip in the presentation of the stereochemistry.

‡ **6** (2.00 g), dissolved in dry THF (40 ml) at 0 °C, was treated with redistilled $SOCl_2$ (1.0 ml) followed by pyridine (1.7 ml) and stirred for 15 h at 0 °C. The reaction mixture was diluted further with THF (100 ml) and filtered. Chromatography of the concentrated filtrate on silica, eluting with diethyl ether, gave **9** (1.67 g, 90%) as a mixture of diastereoisomers.

§ **9** (351 mg) in MeCN (2 ml) was mixed at 0 °C with $Ru^{III}Cl_3 \cdot xH_2O$ (6 mg), $NaIO_4$ (368 mg) and water (2 ml) and then stirred at room temp. until the reaction mixture turned from brown to dark-green. Extraction with $CHCl_3$ (3 × 20 ml), washing the combined organic layers with brine, further drying ($MgSO_4$) and evaporation *in vacuo* gave **12** (174 mg, 48%), which recrystallised from MeCN as colourless rods, m.p. 166–168 °C, $[\alpha]_{589}^{25}$ −13.6 (*c* 0.4, CH_2Cl_2). δ 7.64–7.28 (m, Ph_3C), 4.65 (dd, *J* 3.0, 8.8 Hz, 4-H), 4.27 (dd, *J* 3.0, 8.5 Hz, 5-H_α), 3.80 (s, Me), 3.50 (dd, *J* 8.5, 8.8 Hz, 5-H_β); ^{13}C NMR ($CDCl_3$) δ 168.3 (CO_2Me), 140.6–136.5 (Ph_3C), 78.8 (Ph_3C), 66.2 (C-5), 58.8 (C-4), 52.1 (Me); IR ν/cm^{-1} (Nujol) 3040m, 1760s, 1370s, 1355s; FAB MS (glycerol–thioglycerol matrix) *m/z* 344 (12%, M − SO_3 + H^+), 326 (16), 243 (100, Ph_3C^+); satisfactory microanalyses (C, H, N) were obtained.

has been responsible for this confusion over the properties of the corresponding cyclic sulfamidates. Thus, using the conditions employed for the benzyl ester series ($SOCl_2$, Et_3N, toluene, 0 °C),[7] we found that the methyl ester **7** no longer gave one product but a mixture of three products, which behaved very similarly on chromatographic separation. Although it was not possible to separate these materials completely, we propose from NMR and IR spectral data of the purest fractions that they were the *O*-chlorosulfinyl derivative **14** (ν 3350 cm^{-1}), the *N*-chlorosulfinyl derivative **15** (ν 3450 cm^{-1}) and cyclic sulfimidite **9**, in an approximate ratio of 2:2:1. Furthermore, the NMR spectra for **14** were very similar to those for the substance formerly[7] assigned as the benzyl ester of the *N*-trityl cyclic sulfamidate.¶ Variation in the composition of this mixture accounts for the lack of reproducibility in the subsequent oxidation reaction reported for the benzyl ester series,[7] and an intramolecular S_N2 reaction of the *O*-chlorosulfonyl analogue (formed from **14** in the oxidation step), accounts for the formation of aziridine **18**. Furthermore, we found that treatment of amino alcohol **7** with sulfuryl chloride furnished the corresponding aziridine **17**, presumably by ring closure of the corresponding $-OSO_2Cl$ derivative. (This mechanism accounts for the formation of the *cis* substituted aziridine **19** in the L-threonine series.)

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¶ Compound **14** contains two stereogenic centres (S and C-4) and exists in two diastereoisomeric forms

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