Heterocyclisation *via* 1,3-Cyclic Sulfates. Asymmetric Synthesis of (+)-Sedridine

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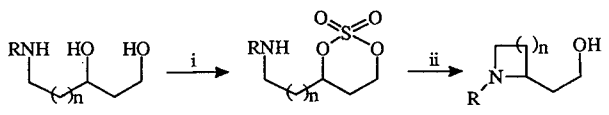
Received 23 September 1996

Abstract. 1,3-Cyclic sulfates (**1b-d**) participate in heterocyclisation reactions to give pyrrolidines (**2b**) and piperidines (**2c/d**). Cyclic sulfate activation, when coupled to the enantio- and diastereoselective generation of 1,3-diols, provides a synthesis of (+)-sedridine (**9**).

The use of cyclic sulfates to activate diols towards nucleophilic attack provides an efficient and versatile process offering potential in heterocyclic synthesis.[1] While 1,2-cyclic sulfates (2,2-dioxide-1,3,2-dioxathiolanes), like epoxides, undergo cyclisation reactions with heteroatom nucleophiles,[2] the 1,3-homologues have yet to be fully evaluated within this context.[3] In this communication we describe the synthesis and cyclisation of 1,3-cyclic sulfates (2,2-dioxide-1,3,2-dioxathianes) as a route to representative 2-(2-hydroxyethyl)pyrrolidines and piperidines. In addition, we illustrate a more general feature of this chemistry by a synthesis of (+)-sedridine.

A series of 1,3-cyclic sulfates (**1a-c**), carrying a sulfonamide moiety as the latent nucleophile, were prepared in 77-88 % yield from the corresponding 1,3-diol using the two-step protocol developed by Sharpless[4] (***Scheme 1***). In order to proceed efficiently, the cyclisation step required sulfonamide activation. This was achieved using NaH (in THF at r.t.) and the heterocyclic products (**2**) were then isolated following an anhydrous acidic work-up (to cleave the intermediate sulfate ester). The results are shown in Table 1.

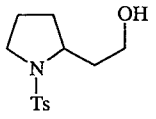
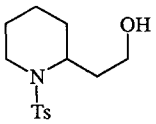
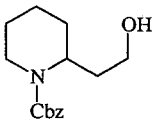


(**1a**) n=1, R=Ts 88 %
(**1b**) n=2, R=Ts 77 %
(**1c**) n=3, R=Ts 87 %
(**1d**) n=3, R=Cbz 87 %

(**2**)

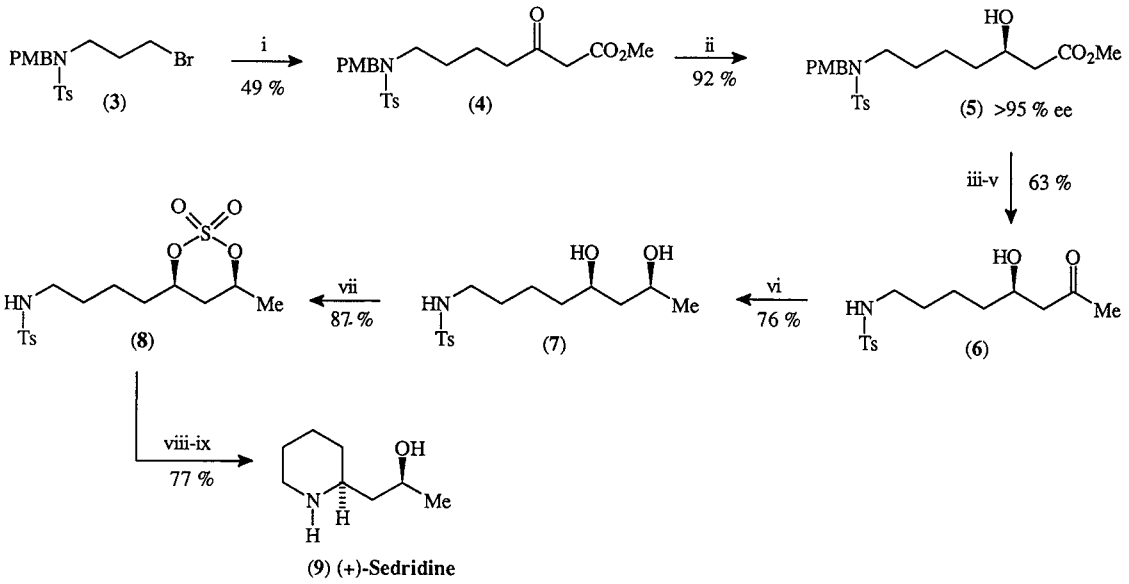
Scheme 1. *Reagents*: i, $SOCl_2$ then $RuCl_3$ (cat.), $NaIO_4$; ii, NaH, THF, r.t. then concentrated HCl

Table 1

1,3-Cyclic sulfate (1)	Heterocyclic Product (2) (% yield)
(**1a**)	complex mixture of products
(**1b**)	 (**2b**) 65 %
(**1c**)	 (**2c**) 99 %
(**1d**)	 (**2d**) 61 %

The 3-(2-aminoethyl) derivative (**1a**) did not give an identifiable heterocyclic product (azetidine or piperidine) under these conditions. The homologue (**1b**) did, however, undergo regioselective cyclisation and the 2-substituted pyrrolidine (**2b**) was isolated in 65 % yield. Cyclisation of the 3-(4-aminobutyl) variant (**1c**) was very efficient and provided piperidine (**2c**) in almost quantitative yield. The *N*-Cbz substrate (**1d**) has been evaluated as an alternative *N*-nucleophile but piperidine formation (to give (**2d**)) was lower yielding and significantly slower when compared to the cyclisation of the sulfonamide analogue (**1c**).[5]

A very important feature associated with the use of 1,2-diol activation *via* cyclic sulfates is the ability to couple a potent level of electrophilic reactivity with highly efficient asymmetric dihydroxylation[6] (to prepare the precursor 1,2-diol). While this has proved to be a powerful combination, a related and equally potent synergy is available with 1,3-cyclic sulfates. This is based on asymmetric reduction of a β-dicarbonyl to establish the absolute stereochemistry of the requisite 1,3-diol precursor. Exemplification of this strategy is presented in



Scheme 2. *Reagents:* i, $MeCOCH_2CO_2Me$, NaH followed by *n*-BuLi, then (**3**); ii, $[(R)\text{-(BINAP)}RuCl_2]_2.NEt_3$, H_2 (200 psi), aq. HCl (cat.), MeOH; iii, CAN, $MeCN/H_2O$; iv, $LiCH_2SO_2Ph$ (5 eq.), THF; v, Bu_3SnH, AIBN, PhMe; vi, Et_2BOMe then $NaBH_4$; vii, $SOCl_2$ then $RuCl_3$, $NaIO_4$; viii, NaH, THF then H_3O^+; ix, Na, liq. NH_3.

Scheme 2 by a stereocontrolled synthesis of (+)-sedridine (**9**), a piperidine alkaloid originally isolated from *Sedum acre*.[7]

Regiospecific alkylation[8] of methyl acetoacetate with the *N*-protected 3-bromopropylamine (**3**) gave (**4**) in 49 % yield. Efficient asymmetric reduction of β-ketoester (**4**) was achieved using the method reported by King[9] to give the (*3R*)-hydroxyester (**5**) in 92 % yield and in >95 %e.e.[10] Oxidative cleavage of the *p*-methoxybenzyl (PMB) moiety from (**5**) followed by conversion of the methyl ester to the corresponding β-hydroxyketone (**6**) was achieved in 3 steps and in 63 % overall yield. *Syn*-selective[11] reduction of ketone (**6**) proceeded with complete control of stereochemistry and conversion of the resulting 1,3-diol (**7**) to 1,3-cyclic sulfate (**8**) was carried out in the usual way. Exposure of (**8**) to NaH followed by an acidic work-up and subsequent reductive cleavage of the sulfonamide residue gave (+)-sedridine (**9**)[12] in 77 % overall yield from (**8**).

In summary, 1,3-cyclic sulfates provide viable substrates for *N*-heterocyclisation reactions leading to 5- and 6-membered rings. A more important general feature of this methodology is an ability to harness this electrophilic reactivity to the efficient methods now available for the enantio- and diastereoselective synthesis of 1,3-diols. As a consequence, it is clear that 1,3-cyclic sulfates, like their 1,2-diol counterparts, also offer significant potential in asymmetric synthesis.

Acknowledgements. We thank EPSRC and AgrEvo UK Ltd. for a CASE award and acknowledge the use of the EPSRC's Chemical Database Service at Daresbury.[13]

References and Notes

1. Lohray, B. B. *Synthesis* **1992**, 1035.
2. Kalanter, T. H.; Sharpless, K. B. *Acta Chem. Scand.* 1993, **47**, 307; Beauchamp, T. J.; Powers, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc.* 1995, **117**, 12873.
3. For an example of a cyclisation reaction of a 1,3-cyclic sulfate leading to an oxetane, see Denmark, S. E. *J. Org. Chem.* 1981, **46**, 3144.
4. Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* 1988, **110**, 7538.
5. Cyclisation of (**1c**) was complete within 1h, but under the same conditions (temperature and substrate concentration) cyclisation of (**1d**) occurred over 24h. In the absence of NaH, substrates (**1b-d**) still undergo cyclisation, to give (**2b-d**) respectively, but this latter process is much slower.

   The following basic experimental protocol was used for heterocyclisation reactions. A solution of cyclic sulfate (**8**) (273 mg, 0.72 mmol) in THF (25 cm^3) at r.t. was treated with NaH (35mg, 60 % dispersion in oil, 0.87 mmol). After 45 min the excess of NaH was destroyed by dropwise addition of ethanol, and concentrated hydrochloric acid (0.1 cm^3) was added. At this point a colourless precipitate formed. After 20 min the mixture was diluted with H_2O (10 cm^3) and most of the THF was removed *in vacuo*. The product was extracted with CH_2Cl_2 (3 x 20 cm^3) and

the extracts were dried ($MgSO_4$) and concentrated. Filtration through a pad of silica gel (eluting with EtOAc-hexane, 1:1) gave *N*-tosyl sedridine (214 mg, 99 %) as a colourless oil which crystallised on standing.

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7. *Isolation of (+)-sedridine* (**9**): (a) Beyerman, H. C.; Muller, Y. M. F. *Rec. Trav. Chim.* 1955, **74**, 1568. (b) Schöpf, C.; Unger, R. *Experimentia* 1956, **12**, 19. *Assignment of absolute configuration of (+)-sedridine*: (c) Butruille, D.; Fodor, G.; Saunderson Huber, C.; Letourneau, F. *Tetrahedron* 1971, **27**, 2055 and references therein. *Asymmetric syntheses of (+)-sedridine (other than methods involving resolution)*: (d) Murahashi, S.; Imada, Y.; Kohno, M.; Kawakami, T. *Synlett*, **1993**, 395. (e) Louis, C.; Hootelé, C. *Tetrahedron: Asymmetry* 1995, **6**, 2149.

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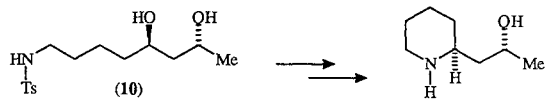
9. King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* 1992, **57**, 6689.

10. Attempts to achieve an asymmetric reduction of (**4**) using bakers' yeast failed under both aqueous and non-aqueous reaction conditions. The enantiomeric excess of (**5**) was determined by ^1H NMR using the Mosher ester derivative, with (±)-(**5**) being used as a standard.

11. *Syn*-Selective reduction: Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O; Shapiro, M. J. *Chemistry Lett.* **1987**, 1923. Reduction of (**6**) to give the *anti*-diol (**10**) (in 72 %d.e.) was achieved using $Me_4NB(OAc)_3H$ (Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* 1988, **110**, 3560). *Anti*-diol (**10**) has been converted to (-)-allosedridine using the same procedures as illustrated in Scheme 2.



(-)-Allosedridine

12. Synthetic (+)-sedridine (**9**) was isolated, following sublimation, as a colourless solid m.p. 82-83 °C {lit.[7a,d] 83-84 °C}; $[\alpha]_D^{22}$ + 25 (c 1.32, EtOH) {lit., $[\alpha]_D^{20}$ + 28.6 (c 2.28, EtOH)[7a]; $[\alpha]_D^{24}$ + 28.5 (c 2.32, EtOH)[7d]; $[\alpha]_D^{22}$ + 26 (c 1.3, EtOH)[7e]}.

13. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. J. *J. Chem. Inf. Comput. Sci.* 1996, **36**, 746.