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Selective five- and six-membered cyclic amine syntheses *via* capture of episulfonium ions

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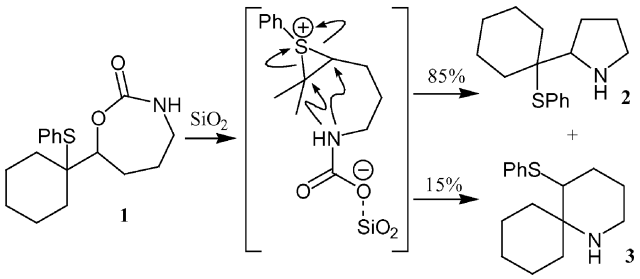
Amide nitrogens open episulfonium ions to form pyrrolidines or piperidines selectively, depending on the nitrogen substituent, in either reversible or irreversible reactions.

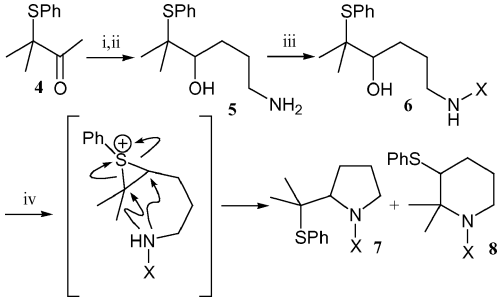
The ring closure reactions of β-hydroxy sulfides and their derivatives containing pendant nucleophiles produce cyclic ethers, lactones, sulfides, amines,[1] carbamates and carbonates by the intramolecular trapping of an episulfonium ion.[2] In the majority of cases, five- or six-membered heterocycles are produced, and in strong-acid catalysed cyclo-etherifications, the more thermodynamically stable ring size is formed in a reversible reaction.[2] Related nitrogen reactions generally occur with irreversible ring-closure,[3–11] although thermodynamic control of stereochemistry, rather than ring-size, can occur using iodonium ions.[6]

The rearrangement of carbamate **1** in the presence of silica gel to give a mixture of five- and six-membered cyclic amines **2** ("unrearranged" where the sulfur has not migrated) and **3** ("rearranged" where the sulfur has migrated) probably occurs with irreversible ring-closure as CO_2 is lost (Scheme 1).[1] The use of nitrogen nucleophiles with less labile electron-withdrawing groups may result in reversible ring closures. Cyanomethylation and reduction of ketone[2] **4** gave amine **5** which could be acylated to give alkyl-carbamates **6a–c**, sulfonamide **6d** and formamide **6e**. Methyl carbamate **6a** was treated with Amberlyst-15 acid resin and a mixture of cyclic products **7a** and **8a** was initially formed (Scheme 2). Prolonged treatment did indeed result in the equilibration of the mixture to give a single product, establishing the reversible addition of a nitrogen nucleophile to an episulfonium ion (Table 1). Exchange of the methyl carbamate group for a dinitro-benzamide allowed determination of the more stable cyclic product, the pyrrolidine-amide, by X-ray crystallography (**10**, Scheme 3).†

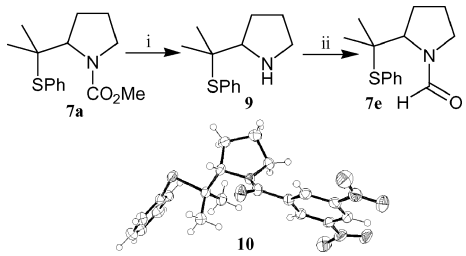


Scheme 1

Reactions of carbamate esters **6b** and **6c** also produced single products on prolonged treatment with acid. Sulfonamide **6d** reacted to give a mixture of products that equilibrated to form only the five-membered ring (Fig. 1). Formamide **6e** initially reacted to form an allylic sulfide by elimination of water,[2] but reprotonation reproduced the episulfonium ion that ring closed to produce an unchanging ratio (15 : 85) of products **7e** and **8e**. The major product was subsequently deformylated and the crystal structure of the hydrochloride salt of amine **11** established that the six-membered ring was the major product in the ring closure (Scheme 4).



Scheme 2 *Reagents and conditions*: i, LDA, THF, HMPA, then $BrCH_2CN$, 62%; ii, $LiAlH_4$, Et_2O, 98%; iii, X = CO_2Me: $ClCO_2Me$, Et_3N, CH_2Cl_2, 76%; X = CO_2Bn: $ClCO_2Bn$, Et_3N, CH_2Cl_2, 56%; X = CO_2Ph: $ClCO_2Ph$, Et_3N, CH_2Cl_2, 71%; X = Ts: TsCl, Et_3N, CH_2Cl_2, 68%; X = CHO: HCO_2CO^tBu, Et_3N, THF, 80%; iv, Amberlyst-15, $CDCl_3$, see Table 1.



Scheme 3 *Reagents and conditions*: i, NH_2NH_2, KOH, 80%; ii, HCO_2CO^tBu, Et_3N, THF, 56%. X-Ray structure of the 3,5-dinitrobenzamide **10** of pyrrolidine **9** (ellipsoids at 50% probability).

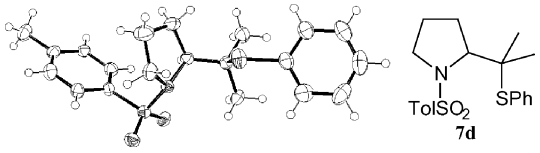
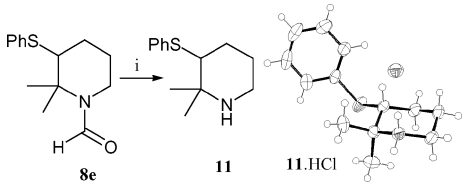


Fig. 1 X-Ray structure of sulfonamide **7d** (ellipsoids at 50% probability).†



Scheme 4 *Reagents and conditions*: i, NH_2NH_2, KOH, 60%. X-Ray structure of the HCl salt of piperidine **11** (ellipsoids at 50% probability).†

The increased stability of unrearranged five-membered ring **7a** compared to rearranged six-membered ring **8a** is in direct contrast to the related cyclic ethers **12** and **13** where the ring size is dominated by the "downhill" migration of the sulfur to the less substituted carbon (Scheme 5).[2] This complete turnover of the dominance of sulfur in a five- to six-membered-ring equilibrium is not known in simple cyclic ethers, and therefore

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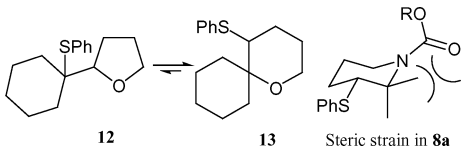
Table 1 Cyclisation of amides **6** (Scheme 2)

Amide	Acyl group X	Cyclisation time/h	Conversion (%)[a]	Product ratio **7 : 8** (%)[a]	Yield (%)[b]
6a	CO_2Me	2	*ca.*25	34 : 66	—
6a	CO_2Me	17	100	40 : 60	—
6b	CO_2Me	120	100	100 : 0	84
6b	CO_2Ph	18	100	45 : 55	—
6b	CO_2Ph	120	100	100 : 0	80
6c	CO_2Bn	18	100	93 : 7	—
6c	CO_2Bn	120	100	100 : 0	88
6d	Tosyl	2	15	33 : 67	—
6d	Tosyl	60	100	100 : 0	56
6e	CHO	19	67	15 : 85	—
6e	CHO	190	100	14 : 86	10

[a] by NMR; [b] isolated yield.

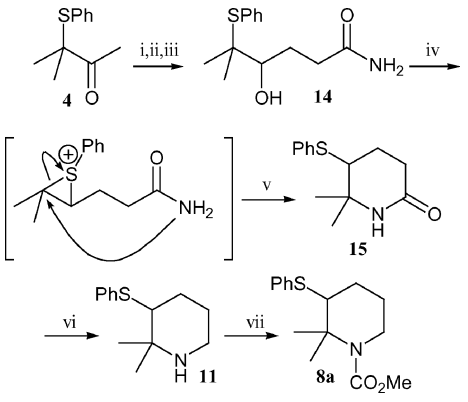
the equilibration of the piperidines to the pyrrolidines was surprising. In carbamates **8a–c** the steric compression of the acyl group and the equatorial methyl group may destabilise the six-membered rings compared to the pyrrolidine isomers (Scheme 5). This destabilisation does not occur in ether **13**.



Scheme 5

Prolonged treatment of formamides **7e** and **8e** with acid did not lead to their interconversion in chloroform at 40 °C, and in d_8-toluene at 100 °C, independently synthesised pyrrolidine **7e** (Scheme 3) only partially equilibrated to give a six-membered ring. This establishes that formamides **7e** and **8e** are far less labile than the carbamates and sulfonamides, and do not equilibrate in the ring-closing reactions. All of the ring-closure reactions in Table 1 indicate that six-membered rings are formed faster than five-membered rings. Generally, in irreversible five- *versus* six-membered-ring closures onto iodonium[5,6] and selenonium[8–10] ions, amide nitrogens attack the more substituted[4,5,9] or benzylic[4,8] electrophilic carbon. This indicates that the nitrogen favours attack at a more cation-like carbon. This is in contrast to sulfur-mediated ring-closure reactions where oxygen attacks the less substituted carbon in non-equilibrating conditions.[2]

Amide **14**, also made from ketone **4**, is similar to amide **6** but has the carbonyl of the amide as part of the main carbon chain (Scheme 6). Treatment of this amide with acid led to a single



Scheme 6 *Reagents and conditions*: i, LDA, THF, HMPA, then $BrCH_2CO_2Et$, 37%; ii, NaOH, H_2O, MeOH; iii, DCC, NHS, THF then NH_3, H_2O, 95% (2 steps); iv, $NaBH_4$, MeOH, 62%; v, TFA, toluene, 74%; vi, $LiAlH_4$, Et_2O; vii, $ClCO_2Me$, Et_3N, CH_2Cl_2, 63% (2 steps).

lactam product. Reduction and acylation produced carbamate **8a**. In this case the inclusion of the carbonyl inside the ring restricts the ring-closing reaction to give only the six-membered lactam. Possibly the additional restriction in torsional angles supplied by the amide of precursor **14** precludes the formation of the five-membered ring.

Previous methods involving the capture of episulfonium ions[1,2] have not proved useful for the selective synthesis of piperidines. Placing the acyl group within the ring results in the selective formation of a six-membered ring (**15**) while an exocyclic acyl group leads to the formation of a five-membered ring (**7**). In both cases the electron withdrawing functionality can be removed providing selective syntheses of pyrrolidine **9** or piperidine **11**.

Acknowledgements

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Notes and references

† *Crystal Data* for **10**: $C_{20}H_{21}N_3O_5S$, $M = 415.46$, orthorhombic, space group $P2_12_12_1$, $a = 6.04760(10)$, $b = 10.1799(3)$, $c = 32.0263(9)$ Å, $U = 1971.67(9)$ Å^3, $Z = 4$, μ(Mo–Kα) = 0.202 mm^{-1}, 7221 reflections measured at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 3248 unique (Rint = 0.033); $R1 = 0.033$, $wR2 = 0.073$ [$I > 2\sigma(I)$]. Absolute structure parameter −0.08(8). The structure was solved with SHELXS-97, and refined with SHELXL-97.[11]
Crystal Data for **7d**: $C_{20}H_{25}NO_2S_2$, $M = 375.53$, orthorhombic, space group $Pca2(1)$, $a = 15.717(3)$, $b = 6.1884(12)$, $c = 39.420(8)$ Å, $U = 3834.1(13)$ Å^3, $Z = 8$, μ(Mo–Kα) = 0.291 mm^{-1}, 11360 reflections measured at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 5387 unique (Rint = 0.044); $R1 = 0.042$, $wR2 = 0.098$ [$I > 2\sigma(I)$]. The structure was solved with SHELXS-97, and refined with SHELXL-97.[11]
Crystal Data for **11**·HCl: $C_{13}H_{20}ClNS$, $M = 257.81$, orthorhombic, space group $Pbca$, $a = 8.5638(3)$, $b = 14.0302(5)$, $c = 23.1201(9)$ Å, $U = 2777.92(18)$ Å^3, $Z = 8$, μ(Mo–Kα) = 0.401 mm^{-1}, 13217 reflections measured at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 3144 unique (Rint = 0.058); $R1 = 0.070$, $wR2 = 0.193$ [$I > 2\sigma(I)$]. The structure was solved with SHELXS-97, and refined with SHELXL-97.[11]
CCDC reference numbers 261090–261092. See http://www.rsc.org/suppdata/ob/b5/b503068b/ for crystallographic data in CIF or other electronic format.

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