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The synthesis of β-*N*-tosylamino hydroxylamines via the ring opening of *N*-tosylaziridines and their use in reverse Cope cyclisations

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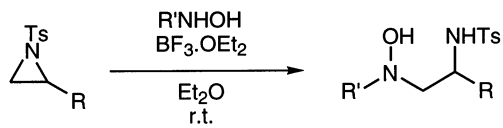
Abstract—*N*-Tosylated aziridines have been found to undergo high yielding and regioselective ring opening with hydroxylamines in diethyl ether in the presence of boron trifluoride diethyl ether complex to give β-*N*-tosylamino hydroxylamines. Suitable substrates were shown to undergo reverse-Cope cyclisations to give amino functionalised pyrrolidine and piperidine *N*-oxides.

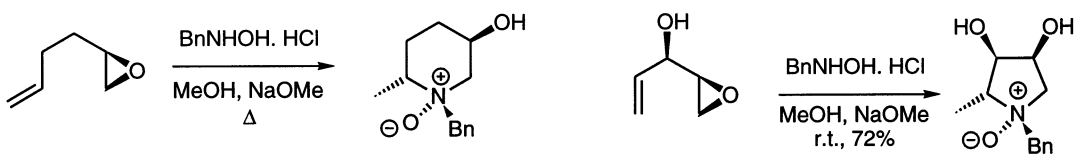
The reverse-Cope cyclisation is emerging as a powerful method for the synthesis of a range of functionalised nitrogen heterocycles.[1,2] Previous utilisation of the reverse-Cope cyclisation has been hampered by the paucity of general methods for the stereocontrolled synthesis of the requisite hydroxylamines. Methods previously utilised to synthesise hydroxylamines[3] include the alkylation of hydroxylamine, the reduction of nitro and nitroso compounds, oximes and nitrones, additions to nitrones, the oxidation of secondary amines and Mitsunobu chemistry. We have previously shown that the precursor hydroxylamines can be synthesised from the ring opening of unsaturated epoxides with *N*-benzyl hydroxylamine.[1] The subsequent reverse-Cope cyclisations yielded hydroxylated pyrrolidine and piperidine *N*-oxide derivatives (Scheme 1).

We now wish to report that *N*-tosylated aziridines undergo a regioselective ring opening with *N*-alkylated hydroxylamines. We were surprised to find no literature precedent for this transformation and so used our previously reported epoxide ring opening methodology as a starting point for this work. We have examined the ring opening of a number of *N*-tosylated aziridines[4] with three different *N*-alkylated hydroxylamines under a range of reaction conditions and found the reaction to be both regioselective and high yielding. The optimum conditions for this transformation involve taking a *N*-tosylated aziridine in diethyl ether at 1 M concentration and treating it with the relevant hydroxylamine in the presence of boron trifluoride diethyl ether complex (20 mol%) (Scheme 2). The desired β-*N*-tosylamino-*N*-alkylhydroxylamines were obtained in good yields after flash column chromatography.

The products of this reaction, β-*N*-tosylaminohydroxylamines, can be considered to be differentially functionalised 1,2-diamines, an important family of compounds in synthetic chemistry.[5]



Scheme 2.



Scheme 1.

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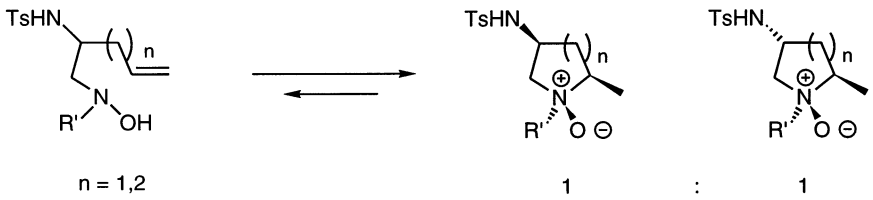
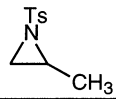
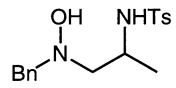
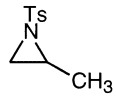
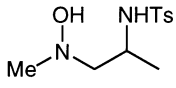
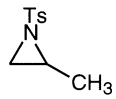
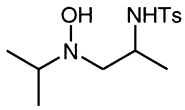
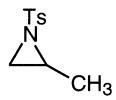
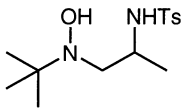
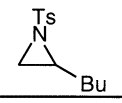
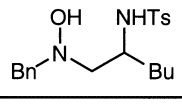
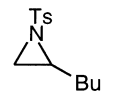
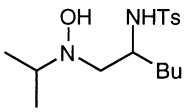
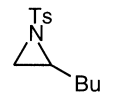
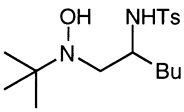
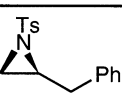
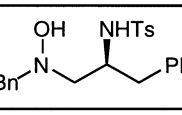
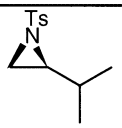
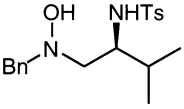
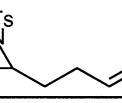
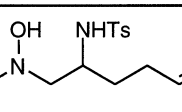


Scheme 3.

Table 1. The $BF_3{\cdot}OEt_2$ promoted ring opening of *N*-tosyl aziridines with *N*-alkylated hydroxylamines and their subsequent reverse-Cope cyclisation (where relevant)

Entry	Substrate	Conditions	Product	% Yield
1		BnNHOH (1.1eq), Et_2O (1M) $BF_3.OEt_2$ (20 mol%), 20h		**68**
2		MeNHOH. HCl(5eq), K_2CO_3 (5eq), Et_2O (1M) $BF_3.OEt_2$ (20 mol%), 48h		**48**
3		^{i}PrNHOH.HCl (1.1eq), K_2CO_3 (1.1eq) Et_2O (1M) $BF_3.OEt_2$ (20 mol%), 36h		**72**
4		^{t}BuNHOH.HCl (1.1eq), K_2CO_3 (1.1eq) Et_2O (1M) $BF_3.OEt_2$ (20 mol%), 36h		**59**
5		BnNHOH (1.1eq), Et_2O (1M) $BF_3.OEt_2$ (20 mol%), 20h		**93**
6		^{i}PrNHOH.HCl (1.1eq), K_2CO_3 (1.1eq) Et_2O (1M) $BF_3.OEt_2$ (20 mol%), 48h		**63**
7		^{t}BuNHOH.HCl (1.1eq), K_2CO_3 (1.1eq) Et_2O (1M) $BF_3.OEt_2$ (20 mol%), 60h		**77**
8		BnNHOH (1.1eq), Et_2O (1M) $BF_3.OEt_2$ (20 mol%), 24h		**78**
9		BnNHOH (1.1eq), Et_2O (1M) $BF_3.OEt_2$ (20 mol%), 30h		**75**
10		BnNHOH (1.1eq), Et_2O (1M) $BF_3.OEt_2$ (20 mol%), 18h		**74**

In appropriate examples of this ring opening reaction, with correctly situated unsaturation in the aziridine containing substrate, we observed reverse-Cope cyclisation to the corresponding pyrrolidine and piperidine *N*-oxides[6] (Scheme 3). The cyclisation to form the five-membered adducts occurs at room temperature and the intermediate β-*N*-tosyl-amino-*N*-alkyl-hydroxylamines could not be isolated; however, the formation of the piperidine ring is not a spontaneous process and the intermediate β-*N*-tosyl-amino-*N*-alkyl-hydroxylamine is readily isolated. Cyclisation to form the piperidine *N*-oxide required heating in methanol for a period of 48 h.

The reverse-Cope cyclisation affords the cyclic products as a 1:1 mixture of diastereoisomers Structures have been assigned to these products by ^{1}H NMR analysis and they have been shown to have a *syn* relationship between the *N*-oxide function and the methyl group in accordance with previous studies[1] (Table 1).

In conclusion, we report a novel route into β-*N*-tosyl-amino-*N*-alkyl-hydroxylamines via the ring opening of *N*-tosylated aziridines with *N*-protected-hydroxylamines in a simple, regioselective and high yielding transformation. In appropriate cases the products of this reaction can undergo reverse-Cope cyclisation to give both amino functionalised pyrrolidine and piperidine *N*-oxides.

Acknowledgements

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6. **Preparation of *N*-benzyl-3-*N*-tosylamino-5-methyl-pyrrolidine *N*-oxide via an in-situ ring opening/reverse-Cope cyclisation**. To a solution of 2-allyl-1-tosylaziridine (0.237 g, 1.00 mmol) in anhydrous diethyl ether (1 mL) was added boron trifluoride diethyl ether complex (0.025 mL, 20 mol%) and *N*-benzyl hydroxylamine (0.135 g, 1.10 mmol) under a nitrogen atmosphere. The reaction was stirred for 72 h at room temperature before being dissolved in methanol (10 mL), adsorbed onto silica gel and purified by flash column chromatography (EtOAc:MeOH, 4:1) to afford the two diastereoisomers of the title compound in a circa 1:1 ratio as white solids (0.162 g, 0.45 mmol), (0.155 g, 0.43 mmol). Isomer 1 had ^{1}H NMR (400 MHz, CD_3OD) 1.23 (3H, d, $J=6$ Hz), 1.7 (1H, m), 2.25 (1H, m), 2.3 (3H, s), 2.4 (1H, dd, $J=2$ Hz, 12 Hz), 3.35 (1H, sept, $J=6$ Hz), 3.48 (1H, dd, $J=9$ Hz, 13 Hz), 4.03 (1H, d, $J=15$ Hz), 4.19 (1H, d, $J=15$ Hz), 7.2 (2H, d, $J=6$ Hz), 7.32 (5H, m), 7.55 (2H, d, $J=8$ Hz). Isomer 2 had ^{1}H NMR (400 MHz, CD_3OD) 1.23 (3H, d, $J=6$ Hz), 1.68 (1H, m), 2.05 (1H, m), 2.32 (3H, s), 3.05 (2H, m), 3.58 (1H, m), 3.92 (1H, m), 4.18, (2H, ab, $J=13$ Hz, 18 Hz), 7.27 (2H, d, $J=8$ Hz), 7.34 (5H, m), 7.58 (2 H, d, $J=8$ Hz); IR (Nujol) 3408, 2918, 1462, 1377, 1330 cm^{-1}; *m*/*z* (FAB$^+$) 361.2 (100%), acc. mass $C_{19}H_{24}N_2O_3S$ requires: 361.15859, found: 361.15890.