Synthesis of 2-Substituted Nitrogen Heterocycles Using *para*-Toluenesulfonyl Iodide in a Key Step

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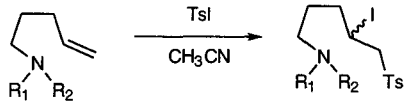
Abstract: *N*-Protected aminoalkenes undergo radical addition of tosyl iodide to give β-iodosulfones which can subsequently be induced to cyclise giving 2-substituted pyrrolidines and piperidines. Incorporation of an α-methylbenzyl group at nitrogen leads to a diastereoselective ring closure where the constituent diastereoisomers can be separated readily giving chiral, non-racemic heterocycles.

Natural products containing saturated nitrogen heterocycles as substructures often display potent and diverse biological activities, and methodologies directed towards their syntheses have been investigated for many years. One popular approach to their preparation has involved closure of the ring by formation of a carbon–nitrogen bond; conjugate addition of a nucleophilic nitrogen substituent onto an activated alkene, in a Michael-type reaction, is one example of this concept that has been exploited by a number of workers.[1] Synthesis of nitrogen heterocycles with an α-(arenesulfonylmethyl) substituent by this strategy has been investigated by the groups of Carretero[2] and Momose[3] using conjugate additions onto a preformed vinyl sulfone as the acceptor. Their reports appeared near the end of our studies extending our arenesulfonyl-halide based synthesis of oxygen heterocycles into the area of pyrrolidine and piperidine synthesis, and therefore we are prompted to communicate details of our investigations which have led to a potentially useful synthesis of chiral, non-racemic 2-substituted nitrogen heterocycles which could be applied to the synthesis of either enantiomer.

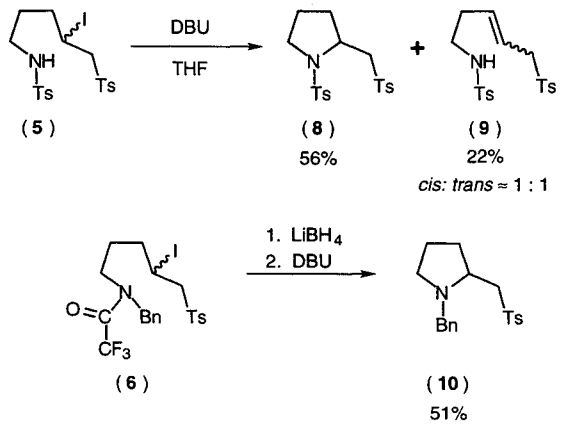
While addition of *para*-toluenesulfonyl iodide to alkenols occurs cleanly and smoothly giving β-iodosulfones in high yields,[4,5] a different profile was observed with the analogous 5-aminopent-1-ene (**1**), where complex mixtures of products were isolated.[6] Presumably the higher nucleophilicity of the amino group, as well as an ambiguous polarisation of the sulfur-iodine bond,[5] led to competing radical and ionic reactions resulting in the observed plethora of products. Introduction of electron-withdrawing protecting groups effectively reduced the nucleophilicity of the nitrogen atom; reaction of the *N*-protected substrates (**2**) to (**4**) with tosyl iodide gave the β iodosulfones (**5**) to (**7**) cleanly and in high yields.[7]



R_1	R_2	Amine	Iodosulfone	Yield (%)
Ts	H	(**2**)	(**5**)	93
CF_3CO	Bn	(**3**)	(**6**)	95
t-Boc	H	(**4**)	(**7**)	85

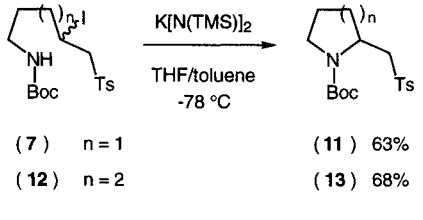
Scheme 1

Following our investigations on oxygen heterocycle synthesis, it was expected that treatment of ε-protected amino β-iodosulfones such as (**5**) with a strong base should allow cyclisation to occur,[7] presumably by *in situ* elimination to give the vinyl sulfone and subsequent conjugate addition of the nitrogen-based anion. In the first instance, the sulfonamide (**5**) underwent cyclisation on treatment with DBU, giving the pyrrolidine (**8**) in 56% yield accompanied by the allyl sulfone (**9**) in 22% yield (Scheme 2). The *N*,*N*-disubstituted compound (**6**) was treated sequentially with $LiBH_4$ and then with DBU, giving the *N*-benzyl heterocycle (**10**) in 51% yield. Slightly lower yields were realised if $Ba(OH)_2$ was used to cleave the trifluoroacetamide.



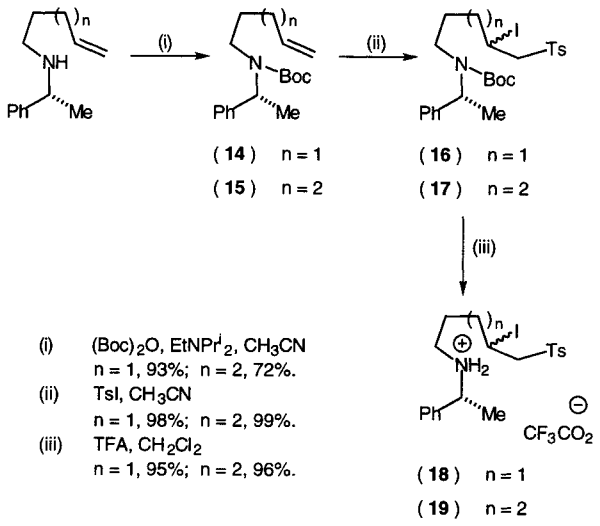
Scheme 2

In the case of the *t*-butoxycarbonyl-protected amine (**7**), cyclisation was promoted with $K[N(TMS)_2]$ (1.5 equivalents) to give the *N*-protected pyrrolidine (**11**) in 63% yield (Scheme 3).[8] This procedure was easily adapted to the synthesis of the piperidine (**13**), which was isolated in 68% yield (58% yield over two steps, from *t*-Boc-protected 6-aminohex-1-ene).



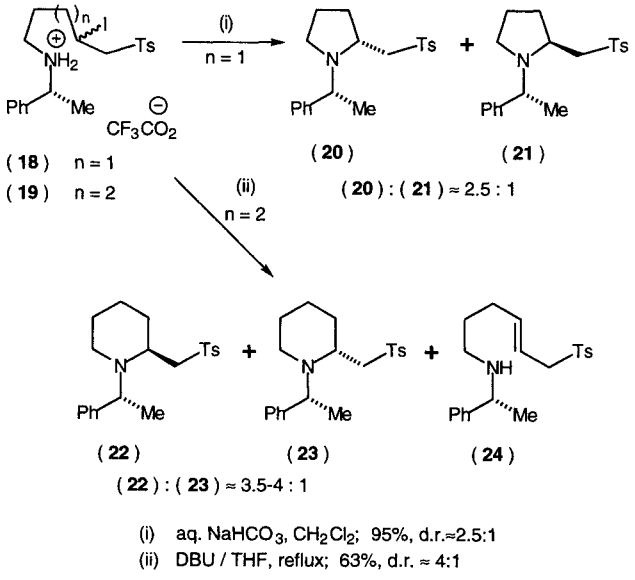
Scheme 3

As the *N*-benzyl compound (**6**) could be converted to the corresponding heterocycle (**10**) successfully, it was of interest to investigate the effect of a chiral directing group on the course of the cyclisation. The commercial availability of both enantiomers of α-methylbenzylamine[9] has meant that this simple reagent has received widespread attention as a chiral directing group in many different applications; diastereoselectivities ranging from moderate to excellent have been reported.[10] Monoalkylation of (*R*)-α-methylbenzylamine with 5-bromopent-1-ene and with hex-5-en-1-yl tosylate occurred readily in DMPU and in high yield under Seebach's conditions,[11] and protection of nitrogen as the *t*-Boc derivative occurred without incident giving the required starting materials (**14**) and (**15**) for the radical additions. Addition of tosyl iodide in CH_3CN gave the 1,2-adducts (**16**) and (**17**) in virtually quantitative yields (Scheme 4).[7] Finally, precursors for cyclisation were obtained readily by cleavage of the carbamates using trifluoroacetic acid (TFA) in CH_2Cl_2, giving the salts (**18**) and (**19**).[12,13]



Scheme 4

Simple neutralisation of the salt (**18**) with aqueous $NaHCO_3$ and CH_2Cl_2 (biphasic) gave the pyrrolidines (**20**) and (**21**) in 95% yield, as a 2.5:1 mixture (Scheme 5).[13] The homologous salt (**19**) was treated with DBU in boiling THF to give the piperidines (**22**) and (**23**) in 63% yield as a 3.5-4:1 mixture, accompanied by the allyl sulfone (**24**).[14] While these selectivities are only modest, two recrystallisations from diethyl ether / light petroleum gave the pyrrolidine (**20**) as a single diastereoisomer in 54% overall yield from the alkene (**14**); the absolute stereochemistry of the major product was established by X-ray crystallography.[15] It is of interest to note that this cyclisation proceeds with the same control over the new stereocentre as the Ag(I)-mediated cyclisation of allenic amines.[16] While the piperidine crystallises less readily, the two diastereoisomers are readily separable by chromatography on silica (20% ethyl acetate / light petroleum) and the absolute stereochemistry of the major product (**22**) has also been determined by X-ray crystallography. It is intriguing that the major diastereoisomer in this case has formed with induction at the new chiral centre giving a product of opposite configuration compared with the pyrrolidine (**20**). While reasons for this switch are currently unclear,



Scheme 5

studies are continuing into the use of alternative chiral directing groups to enhance the levels of diastereoselectivity and possibly establish the cause of this interesting result, as well as the effect of alkene geometry on the sense of the ring closure.

In conclusion, we have developed a new and simple approach to 2-substituted nitrogen heterocycles which can provide chiral, non-racemic material of high purity if a directing group such as α-methylbenzylamine is used. Elaboration of the sidechain using Julia methodology,[17] and simple hydrogenolytic removal of the α-methylbenzyl group providing a free secondary amine,[18] should enable the synthesis of a wide range of chiral, non-racemic 2-substituted nitrogen heterocycles.

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References and Notes

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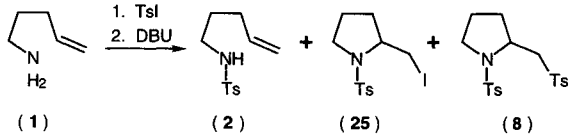
(6) Reaction of alkene (**1**) with tosyl iodide gave complex mixtures (Scheme 6). Addition of one equivalent of tosyl iodide, and then treatment of the crude product with DBU, gave the acyclic sulfonamide (**2**, 20%), an iodocyclisation product (**25**, 9%) and the α-(toluenesulfonylmethyl) pyrrolidine (**8**, 4%).



Scheme 6

(7) Craig, D.C.; Edwards, G.L.; Muldoon, C.A. *Tetrahedron* **1997**, *53*, 6171. The conditions for radical addition of tosyl iodide to alkenols were applied to the protected aminoalkenes.

(8) The general method for cyclisations with $K[N(TMS)_2]$ has been described previously.[7]

(9) Flukabrand™ ChiraSelect Reagent (≥ 99% *e.e.*) is available from the Aldrich Chemical Company: (*R*)-enantiomer, 25 ml £67.60; (*S*)-enantiomer, 25 ml £99.60.

(10) Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **1997**, *38*, 85. Lorthiois, E.; Marek, I.; Normant, J.-F. *Tetrahedron Lett.* **1997**, *38*, 89. Davies, S.G.; Smyth, G.D. *Tetrahedron: Asymmetry* **1996**, *7*, 1001. Davies, S.G.; Smyth, G.D. *Tetrahedron: Asymmetry* **1996**, *7*, 1273. Fox, D.N.A.; Lathbury, D.; Mahon, M.F.; Molloy, K.C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652.

(11) Juaristi, E.; Murer, P.; Seebach, D. *Synthesis* **1993**, 1243.

(12) The crude products contained two mole equivalents of TFA, but could be used without further purification.

(13) Trifluoroacetic acid (15 ml) was added to a solution of the carbamate (**16**) (4.86 g, 8.51 mmol) in dichloromethane (50 ml) at room temperature and under an argon atmosphere. The resulting pink solution was stirred at room temperature for 30 min and the solvent was removed under reduced pressure to give the *salt* (**18**) containing two mole equivalents of TFA as a viscous yellow oil (6.56 g, 95 %); the product was used without further purification. δ_H (300 MHz; $CDCl_3$) 1.69-2.21 (m, 4H, pentyl H), 1.72 (d, *J* 7.2 Hz, 3H, CH_3), 2.46 (s, 3H, $ArCH_3$), 2.69-3.15 (m, 2H, CH_2N), 3.60-3.77 (m, 2H, CH_2S), 4.27-4.49 (m, 2H, CHI, PhCHN), 7.30-7.51 (m, 7H, ArH), 7.75, 7.76 (2 x d, *J* 8.2 Hz, 2H, ArH), 7.83, 8.17, 8.56, 8.93 (4 x bs, 2H, NH_2), 10.11 (bs, 2H, 2 x CF_3CO_2H); *m/z* (electrospray): 472 (M+, 100%), 368 (17). A solution of the ammonium salt (**18**) (2.68 g, 3.30 mmol) in dichloromethane was washed with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with dichloromethane and the combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a viscous yellow oil. Flash chromatography (40% ethyl acetate / light petroleum) gave the *pyrrolidine* as a colourless crystalline solid (1.08 g, 95 %), as a mixture (2.5:1) of two diastereoisomers (**20**) and (**21**) which could not be separated by chromatography. Two recrystallisations from ether / light petroleum gave the major diastereoisomer (**20**) as a colourless crystalline solid (54% overall, m.p. 101-102 °C), $[\alpha]_D$ = + 67.9 ° (*c* = 3.35, $CHCl_3$), (Found: C, 70.0; H, 7.5; N, 3.9. $C_{20}H_{25}NO_2S$ requires C, 69.9; H, 7.3; N, 4.1 %); δ_H (300 MHz; $CDCl_3$) 1.29 (d, *J* 6.9 Hz, 3H, CH_3), 1.59-1.73 (m, 2H, ring H), 1.77-1.91 (m, 2H, ring H), 2.26-2.36 (m, 1H, H5a), 2.47 (s, 3H, $ArCH_3$), 2.69-2.76 (m, 1H, H5b), 3.03 (dd, *J* 13.9, 10.3 Hz, 1H, CH_aS), 3.11-3.19 (m, 1H, H2), 3.31 (dd, *J* 13.9, 1.5 Hz, 1H, CH_bS), 3.62 (q, *J* 6.9 Hz, 1H, PhCHN), 7.06-7.13 (m, 2H, ArH), 7.18-7.26 (m, 3H, ArH), 7.34 (d, *J* 8.2 Hz, 2H, ArH), 7.73 (d, *J* 8.2 Hz, 2H, ArH); δ_C (75.5 MHz; $CDCl_3$) 21.6 ($ArCH_3$, CH_3), 23.1 (CH_2), 30.9 (CH_2), 49.9 (CH_2N), 54.4 (CHN), 60.9 (PhCHN), 61.1 (CH_2S), 126.8 (ArCH), 127.5 (ArCH), 127.9 (ArCH), 128.1 (ArCH), 129.8 (ArCH), 136.9 (Ar), 142.5 (Ar), 144.4 (Ar); *m/z* (EI): 343 (M^+, <1 %), 328 (9), 266 (10), 174 (45), 105 (100), 91 (41).

(14) The allyl sulfone was approximately 30% of the crude product (^1H NMR), and was not isolated. Cyclisation at room temperature gave a lower yield (47%) of the piperidine and relatively more allyl sulfone (≈40%).

(15) Full details of the structures (**20**) and (**22**) have been deposited with the Cambridge Crystallographic Data Centre.

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(17) The Julia olefination was used by Momose and coworkers for introduction of the unsaturated sidechain of the clavepictines.[3]

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