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Selenocyclisations of Homoallylic Sulfonamides: A Highly Stereoselective Route to both *cis*- and *trans*-2,5-Dihydropyrroles

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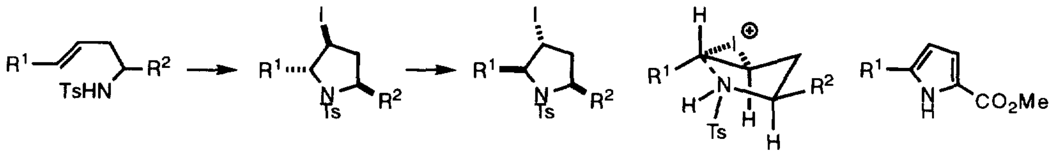
Abstract:- *Overall 5-endo-trig selenocyclisations of homoallylic sulfonamides proceed smoothly and highly stereoselectively, under a selection of conditions, to give excellent yields of selenopyrrolidines and the related trans- or cis-2,5-dihydropyrroles, after oxidation and elimination.*

Keywords: Cyclisation; Selenonium ions; pyrrolidines; sulfonamides.

We have recently reported that homoallylic sulfonamides **1** undergo smooth iodocyclisation upon treatment with three equivalents each of iodine and potassium carbonate in acetonitrile to give the 2,5-*trans*-pyrrolidines **2**. A significant bonus associated with this methodology is that, in the absence of base, the initial products **2** undergo smooth isomerization to the corresponding 2,5-*cis* isomers **3**.[1] Although such cyclisations appear to contravene Baldwin's rules,[2] being formally 5-*endo*-trig processes, the fact that these are electrophile- rather than nucleophile-driven cyclisations suggests that they do not represent true exceptions.[3] The stereochemistry of the initial cyclisation products **2** is consistent with the involvement of a chair-like transition state **4** wherein an equatorial positioning of substituent R^2 is the controlling feature. We have further exemplified this methodology in a new approach to substituted prolines[4] and also demonstrated that a double, base-induced elimination of both hydrogen iodide and toluenesulfinic acid efficiently produces the corresponding pyrrolecarboxylates **5**, when R^2 is an ester group, CO_2Me in the initial products **2** or **3**.[4]



1 **2** **3** **4** **5**

However, attempts to effect other, partial eliminations met with only limited success. For example, exposure of the phenyl pyrrolidine **6** to various basic conditions led to gross mixtures of the 2,5- and 2,3-dihydropyrroles **7** and **8**. This encouraged us to examine the related selenocyclisations of the homoallylic

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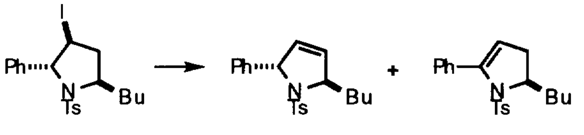
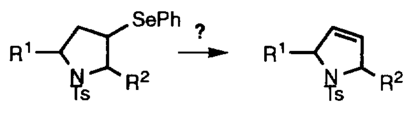
sulfonamides **1** in the hope of generating selenopyrrolidines **9**, hopefully with good stereocontrol, which might be expected to undergo more controlled eliminations, following oxidation to the corresponding selenoxides, to give the 2,5-dihydropyrroles **10**. Herein we report on the success of both of these ideas.

Indications from previous studies of selenocyclisations in general suggest that overall 5-*endo*-trig cyclisations of sulfonamides **1** ought to be viable, *via* episelenonium ions, in view of the utility of this method in tetrahydrofuran synthesis.[5] Similarly, overall 5-*endo*-trig cyclisations of episulfonium ions, albeit formed *via* elimination of a leaving group from β-halo- or -tosyloxy-sulfides, are also established as viable routes to tetrahydrofurans[6] as well as to pyrrolidine ring formation in an approach to the pyrrolizidine ring system.[7]



6 **7** **8**



9 **10**

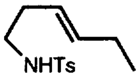
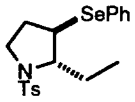
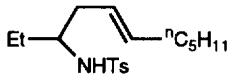
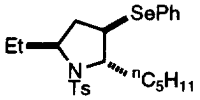
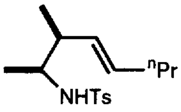
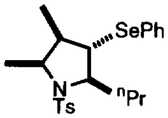
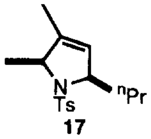
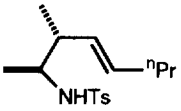
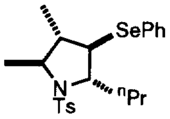
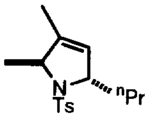
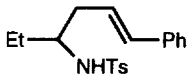
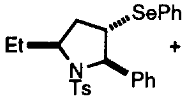
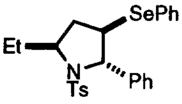
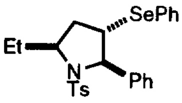
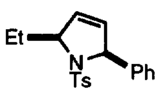
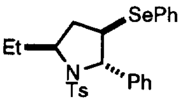
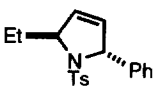
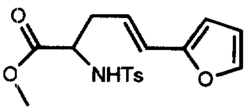
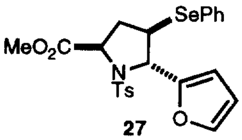
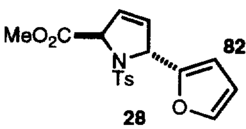
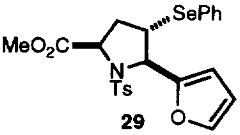
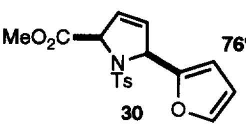
The required homoallylic sulfonamides **1** were prepared as previously described[1,4] and the results obtained are presented in the Table. We were delighted to find that the simple tosylamide **11** underwent rapid and efficient cyclisation upon treatment with phenylselenenyl chloride in dichloromethane at -78°C in less than 1 h to give only the *trans*-pyrrolidine **12**. Similarly, the more substituted analogue **13** was smoothly converted into the selenopyrrolidine **14** as a single diastereoisomer; both cyclisations are consistent with the intermediacy of a transition state corresponding to **4**. However, this was clearly not the case with the dimethyl analogue **15** which led only to the *cis*-2,5-stereochemistry in product **16**. Presumably, as one of the methyl groups would be positioned axially if a conformation based on **4** was involved, an alternative is favoured, perhaps one related to that recently proposed by Lipshutz.[5] The dimethyl diastereoisomer **18** also underwent rapid and highly stereoselective cyclisation to give the seleno-pyrrolidine **19**, the stereochemistry of which is also consistent with a transition state conformation related to **4**, in which both substituents are positioned equatorially.

Both of the latter selenopyrrolidines **16** and **19** underwent smooth oxidation at selenium and subsequent elimination when exposed to 30% hydrogen peroxide in THF at 20°C for 1 h, to give the hoped for 2,5-dihydropyrroles **17** and **20** respectively with preservation of the initial stereochemistry.

Inclusion of an aryl substituent on the alkene function, as in precursor **21**, caused what appeared to be partial isomerization of the initial expected 2,5-*trans* product **23**, in a similar fashion to that observed in the iodocyclisations (see above), leading to a mixture of products [**22** and **23**], even at -78°C. That this was the case, and that isomerization was caused by the hydrogen chloride generated during the cyclisation, was indicated when the precursor **21** was cyclized in the presence of a trace of HCl (conditions B), when only the 2,5-*cis* isomer **22** was formed. Logically, the addition of a base ought to favour formation of the corresponding 2,5-*trans* isomer **23**. This is exactly what we found: when potassium carbonate was added, the *trans*-isomer **23** predominated although the cyclisations were slower and benefited, in terms of the overall stereoselectivity, from the addition of 5 mol% of water, possibly to aid the neutralization of the acid formed (conditions C). Again, both selenopyrrolidines **22** and **23** were readily converted into the 2,5-dihydropyrroles **24** and **25** respectively with complete retention of stereochemistry.

Such cyclisations are also suited to the elaboration of substituted prolines.[4] Following some experimentation, we found that the amino-ester **26** underwent smooth and rapid conversion into the 2,5-*trans*

TABLE : Selenocyclisations of Homoallylic Sulfonamides and Eliminations

Sulfonamide	Conditions	Product(s)	Isolated yield	Eliminations
 11	A	 12	83%	–
 13	A	 14	80%	–
 15	A	 16	84%	 17 76%
 18	A	 19	79%	 20 80%
 21	A	 22 +  23	81% [4:1]	
21	B	 22	77%	 24 81%
21	C	 23	83%	 25 84%
 26	D	 27	83%	 28 82%
26	E	 29	85%	 30 76%

Yields quoted are of isolated, pure products which exhibited satisfactory spectroscopic and analytical data. *Conditions* : A: PhSeCl (1.1 eq), CH_2Cl_2, -78°C, 0.5-1 h; B: as A + cat. 10M HCl; C: as A + K_2CO_3 (1.1 eq) and 5 mol% H_2O, then warm to 20°C; D: PhSeCl (1.1 eq), K_2CO_3 (1.1 eq), THF, -78°C, 2 h; E: as D but all at 20°C.

isomer **27** when exposed to PhSeCl in tetrahydrofuran at -78°C in the presence of potassium carbonate (conditions D). Somewhat unexpectedly, simply by carrying out the cyclisation at ambient temperature, but still in the presence of K_2CO_3 (conditions E), we isolated only the 2,5-*cis* isomer **29**. In both cyclisations, traces of the other isomer were visible, which were readily separated by column chromatography. This variation in conditions may well reflect participation by the furan ring.[8] As expected, both of these latter selenopyrrolidines underwent smooth elimination of the seleno group upon exposure to hydrogen peroxide to give the corresponding dihydropyrroles **28** and **30**, both of which should serve as useful precursors to a range of targets based on highly substituted pyrrolidines.

The foregoing results attest to a delicate balance governing the outcome of these selenocyclisations. This is further emphasized by a recent study of selenocyclisations of homoallylic benzylamines which revealed that the major products were azetidines, arising from a 4-*exo*-trig pathway, accompanied by smaller amounts of β-selenopyrrolidines related to the products reported herein.[9] Again, the outcome of such cyclisations was highly condition dependent and also showed variations with respect to the selenium reagent employed. In the present work, we did not observe the formation of azetidines from any of the substrates examined.

Clearly, there is a considerable degree of variation in the outcome of these cyclisations, depending on the exact substrate and the conditions used. However, the cyclisations usually show excellent levels of stereoselectivity and hence should find use in a number of areas of pyrrolidine synthesis. Further, the subsequent eliminations all proceed with complete selectivity, in favour of the 2,5-dihydropyrroles, a generally observed pattern of elimination of selenoxides away from an adjacent heteroatom. Of course, this may not be the case when an adjacent *syn*-hydrogen is not available [*ie* in epimers of pyrrolidines **16** and **19**]. Studies in this direction are in progress, along with work aimed at determining the best method for obtaining optically pure products from this potentially useful and flexible sequence which usually appears to proceed *via* a transition state geometry related to that (**4**) involved in the corresponding iodocyclisations.

Acknowledgements

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