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Sulfonamides as novel terminators of cationic cyclisations

Charlotte M. Haskins and David W. Knight*
Chemistry Department, Cardiff University, P.O. Box 912, Cardiff, UK CF10 3TB.
E-mail: knightdw@cf.ac.uk

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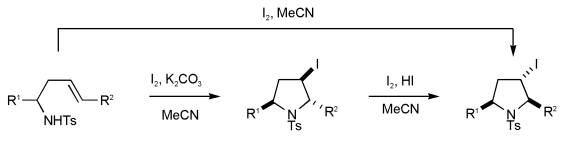
Trifluoromethanesulfonic (triflic) acid is an excellent catalyst for inducing *overall* 5-*endo* cyclisation of homoallylic sulfonamides [*e.g.* 4] to give pyrrolidines [*e.g.* 5]. In competitive experiments, pyrrolidines or homopiperidines are formed in preference to piperidines, even when the latter would be obtained by trapping a tertiary carbocation. Cationic cascades terminated by a sulfonamide group are viable for the efficient formation of polycyclic systems.

Despite being disfavoured by Baldwin's rules,[1] 5-*endo*-trig cyclisations involving electron-deficient intermediates such as iodonium ions[2] have made a considerable contribution to synthetic methodology; it is likely that these are not exceptions to the rules, being electrophile rather than nucleophile-driven. Our own studies have uncovered a highly stereocontrolled synthesis of pyrrolidines using such cyclisations of (*E*)-homoallylic sulfonamides **1** which, when exposed to iodine in the presence of potassium carbonate, are converted rapidly into the corresponding 2,5-*trans*-iodopyrrolidines **2** in excellent yields, probably *via* a chair-like transition state (Scheme 1).[3] In contrast, omission of a base results in exclusive formation of the corresponding 2,5-*cis* isomers **3**, indicative of an isomerization of the initially-formed kinetic isomers **2** to the thermodynamic isomers **3**. This idea was confirmed when examples of 2,5-*trans*-pyrrolidines **2** were exposed to iodine–hydrogen iodide mixtures when conversion into the *cis*-isomers **3** occurred rapidly.[3] Selenocyclisations of sulfonamides **1** show similar features.[4] This chemistry led us to speculate that it might be possible to trigger such cyclisations using acid. Herein, we report the successful outcome of our initial studies in this area.

The required precursors [**4**,**6** *etc.*; Table 1] were readily obtained in good overall yield using the Stork procedure[5] followed by *N*-protecting group exchange. Examples of the corresponding aldehydes **14** and alcohols **16** were then obtained by reduction. Initial experiments using the prenyl derivative **4b** indicated the viability of the idea in that the desired product **5b** was observed upon exposure to a variety of proton sources. Following some experimentation, we discovered that using trifluoromethanesulfonic (triflic) acid in chloroform represented optimum conditions for inducing cyclisation. Some definitive results are presented in Table 1. Both prenyl derivatives **4** underwent rapid and very clean cyclisation when exposed to 0.4 equivalents of triflic acid at 0 °C to give essentially quantitative yields of the pyrrolidines **5**. In contrast, the cinnamyl derivatives **6** required slightly more demanding conditions (0.6 eq. TfOH, 25 °C, 4 h) before similar yields of the 5-phenyl derivatives **7** were obtained. Understandably, cyclisation of the corresponding crotyl analogue **8** required heating to reflux to achieve complete reaction; the excellent yields of the resulting pyrrolidines **9** were however retained. *spiro*-Pyrrolidines can also be prepared using this chemistry: the ylidenecyclohexane derivative **10** gave an excellent return of the expected product **11** under the mildest set of conditions. Given that the reaction pathway involves alkene protonation and carbocation generation, it was not surprising to find that the isomeric cyclohexene derivative **12** gave the related *spiro*-pyrrolidine **13** under similar conditions. This observation will provide an additional degree of flexibility in terms of precursor synthesis. Aldehyde functions, at least when not having an α-proton, survive the acidic conditions, as shown by the very clean conversion of the *N*-tosyl alaninal derivative **14** into the corresponding pyrrolidine carboxaldehyde **15**. However, suitably positioned hydroxyl groups compete with the sulfonamide as carbocation traps. Thus, the alaninol derivative **16** gave a *ca.* 1:1 mixture of the pyrrolidinemethanol **17** and the aminopyran **18**, indicating a not unexpected limitation of this methodology.

We then examined the stereochemical features of the cyclisation, using the cinnamyl derivatives **6** (Table 2). In the case of the glycinate **6a**, our initial experiments (Table 1) gave



Scheme 1

Table 1

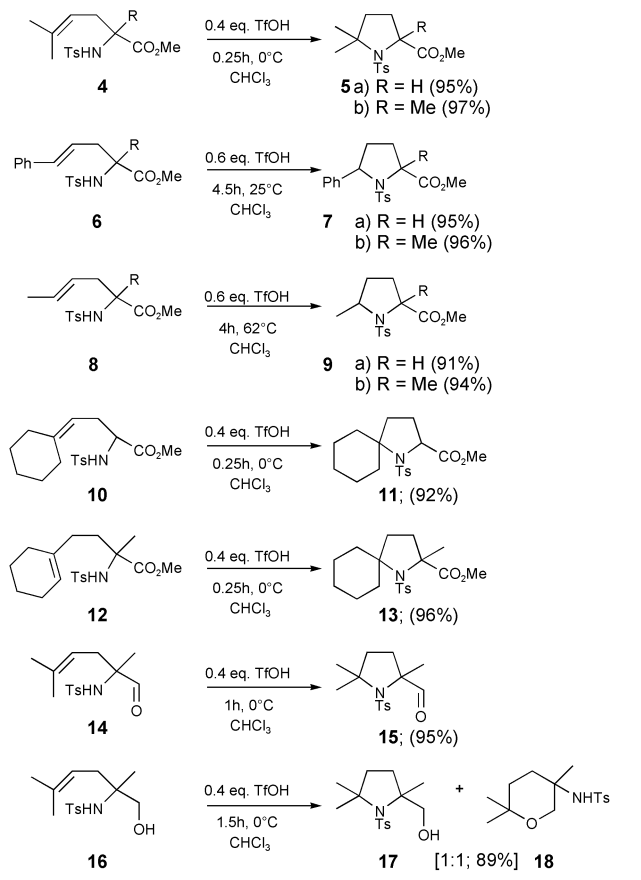


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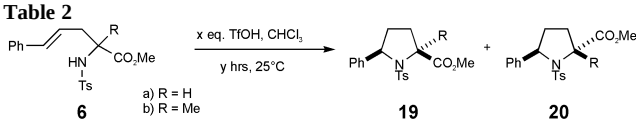
Table 2



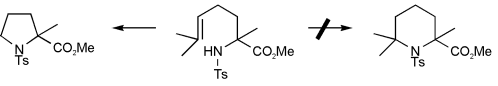
6 **19** **20**

x eq. TOH	*y* h	**19a**:**20a**		*x* eq. TfOH	*y* h	**19b**:**20b**	
0.6	4.5	1	1	0.6	4.0	2.9	1
1.0	2.0	1	1	1.5	2.0	3.5	1
2.0	1.5	> 20	1	2.0	1.5	4.0	1
5.0	1.0	> 20	1	5.0	1.0	9.0	1

a 1 : 1 mixture of the *cis*- and *trans*-pyrrolidine carboxylates **19a** and **20a**.[6] Increasing the amount of triflic acid to two equivalents resulted in the almost exclusive formation of the *cis*-isomer **19a**. That this thermodynamically more stable isomer is obtained predominantly under these conditions suggests that a similar isomerization process can take place to that observed during the iodocyclisations (Scheme 1).[3,4] Similarly, treatment of the alanine-derived sulfonamide **6b** with excess triflic acid also led to a synthetically useful preponderance of the '*cis*'-isomer **19b** although to obtain this, five rather than two equivalents of acid were required.

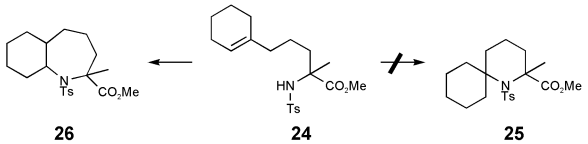
When we attempted to extend the methodology to syntheses of piperidine derivatives [*e.g.* **23**], we found that formation of such six-membered rings is particularly *disfavoured*. For example, exposure of the homoprenyl derivative of alaninate **21** to triflic acid gave only the pyrrolidines **22** (*cis:trans* ~ 3 : 2) (Scheme 2),[6] despite the implication that a less stable secondary carbocation is involved. Similarly, treatment of the cyclohexenyl derivative **24** with catalytic triflic acid did not give the *spiro*-piperidine **25** but rather the 6/7 ring system **26** (Scheme 3). In all the above examples, isolated yields were in excess of 90%.

Finally, we were intrigued by the possibility that similar chemistry could be applied to related polyene systems using a sulfonamide group to terminate the cascade, in a further development of the classical biomimetic studies of Johnson.[7] We were delighted to find that the geranyl derivatives **27** underwent rapid cyclisation at 0 °C to give *ca*. 90% isolated yields of the *trans*-annulated pyrrolidines **28**, both as 3 : 2 mixtures, epimeric at the amino-ester stereogenic centre (Scheme 4). This assignment of structure was confirmed by a single crystal X-ray crystallographic determination of a separated sample of the major isomer of the glycine derivative **28a**. Under the same conditions, the corresponding farnesyl derivatives **29** also gave excellent returns of the tricyclics **30**, but now in isomer ratios of *ca* 3 : 3 : 1 : 1; the major products were the *trans*-fused pair, epimeric at the amino-ester centre. The two geranylgeranyl derivatives **31** also underwent smooth cyclisations to give the azasteroid derivatives **32** in 80–83% isolated yields, although as a gross mixture of stereoisomers (Scheme 4).[8]



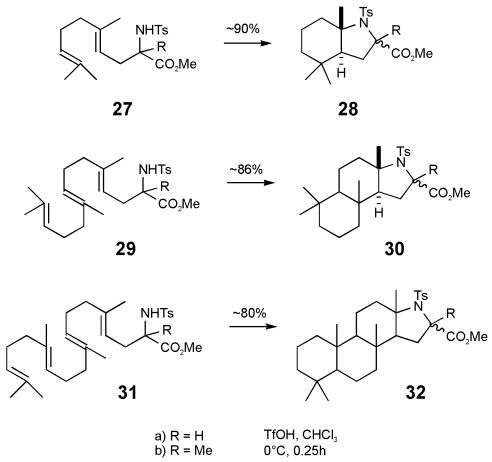
22 **21** **23**

Scheme 2



26 **24** **25**

Scheme 3



27 **28** **29** **30** **31** **32**

Scheme 4

In conclusion, we have established that acid-catalysed *overall* 5-*endo*-trig cyclisations of homoallylic sulfonamides are useful for the rapid and efficient assembly of pyrrolidines, and are likely to be of some generality but which will clearly be limited to substrates having other functionality which is stable to triflic acid. Similarly general may be an isomerization process which leads to a considerable predominance of the more thermodynamically stable isomers, using an excess of the acid. Finally, the method has some potential for the elaboration of polycyclic systems by cation cyclisation cascades terminated by the sulfonamide function although, again, other functional group sensitivity to triflic acid will have to be kept in mind in future applications.[9]

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Notes and references

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8 Detailed mass spectral analyses of cyclised products **28**, **30** and **32** provided excellent additional evidence for these structural assignments. We are grateful to Dr N. J. Haskins for these data which will be published elsewhere.
9 Full analytical and spectroscopic data consistent with the proposed structures have been obtained for all structures reported herein.