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# Carbenium ion trapping using sulfonamides: an acid-catalysed synthesis of pyrrolidines by intramolecular hydroamination

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ABSTRACT

Cyclisations of homoallylic sulfonamides proceed smoothly via carbenium ion generation using trifluoromethanesulfonic (triflic) acid, the ease of cyclisation being directly related to the ion stability to give good to excellent yields of the corresponding pyrrolidines. Both toluene- and nitrophenyl-sulfonyl groups are suitable for all substrates tested whereas the corresponding carbamates are only useful in cases of tertiary and highly stabilised carbenium ions. Polyene-derived sulfonamides can also be cyclised to the corresponding polycyclic systems in remarkably high yields, in reactions reminiscent of related cascades encountered in terpene biosynthesis.

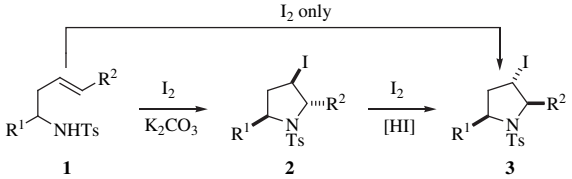


## 1. Introduction

The central importance of nitrogenous compounds to the manipulation of biological systems in general has meant that the development of methods for the efficient introduction of this element into organic compounds continues to occupy a pivotal position in synthetic methodology.[1] One only has to consider the impact that the Buchwald–Hartwig and related amination reactions[2] have had, especially in the Pharmaceutical sector, since their introduction. More generally, although a long established principle, new ways to carry out overall alkene hydroamination, the addition of the elements of nitrogen at the amine oxidation level and hydrogen to an alkene,[3] in a selective and mild manner have come to great prominence of late, by reason of the significant contribution that such methodology could have to this area.

In principle, one way to multiply the synthetic methods available to prepare a selected structural feature is to reverse the polarity associated with to a particular functional group.[4] The nucleophilicity inherent in a typical alkene bond can be reversed, for example, by epoxidation, which can allow it then to be attacked by various nucleophilic species. Closely related are more transient intermediates generated by the positioning of a halogen or selenium atom across the alkene, thereby achieving a similar reversal of polarity and hence intramolecular attack by a suitably positioned nucleophile such as an alcohol or attenuated amine group. These are, of course, the very familiar halo- or seleno-cyclisations processes for ring closure, which can operate in a number of modes, including 5- and 6-*exo* as well as 5-*endo* examples.[5] During our studies of such cyclisations,[6,7] we were stimulated to search for alternatives to both molecular iodine and selanyl halides for a number of reasons, not the least of which were the fact that a relatively large excess (3 equiv) of iodine is required and general limitations for scale up in both cases, especially when using the selenium-based reagents, where cost and disposal become limiting considerations. The idea to attempt to form pyrrolidines and perhaps *N*-heterocycles with other ring sizes using such chemistry but with alternative activating agents for the alkene arose from two observations.

Firstly, we found that overall 5-*endo-trig* iodocyclisations of homoallylic sulfonamides **1**, which give very largely the 2,5-*trans*-iodopyrrolidines **2** under basic conditions (Scheme 1), gave *only* the corresponding 2,5-*cis* diastereomers **3** if the base was omitted.[7] By starting with a single enantiomer of the precursor [**1**; $R^1$=Et; $R^2$=Bu], we were able to establish that formation of the latter most likely occurs by cycloreversion of the initially formed and hence kinetic isomers **2** back to precursor **1** and subsequent cyclisation to




**Scheme 1.**

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eventually produce only the thermodynamically more stable 2,5-*cis*-isomers **3**. Presumably, the trigger for this is protonation of the *trans*-pyrrolidines at nitrogen by the hydrogen iodide formed as the cyclisation proceeds and which is now not removed as no base is present. A key implication is therefore that at least some of the regenerated starting material **1** remains unprotonated in the presence of this strong acid and hence is able to participate as a nucleophile in subsequent iodocyclisations.

A second significant observation was made during extensions of this methodology to the formation of highly substituted proline analogues **4**, which, in extreme cases, required prolonged exposure to excess iodine in order to achieve complete conversion into the desired iodopyrrolidines **5** (Fig. 1).[8] When such cyclisations were carried out in the absence of base, the products **5** were sometimes accompanied by small amounts of the de-iodopyrrolidines **6**. We were unsure as to how these were formed, but reasoned that one possibility was that direct acid-catalysed cyclisation was occurring to a limited extent. Therefore, when we began to investigate alternative electrophilic triggers for this type of cyclisation in general, the prospects for using protons, the simplest of electrophiles, for this purpose was one of the first to be investigated.

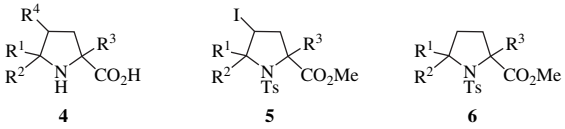
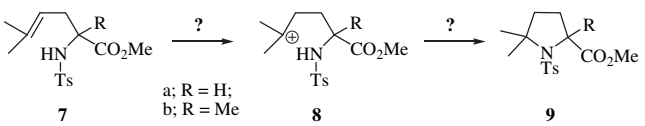



**Figure 1.**

Herein, we report in full on the successful outcome of this idea and on some of its key features. Although the initial concept of this methodology was that it was a pyrrolidine synthesis, it can of course also be viewed as an intramolecular hydroamination process, as will be discussed later, in which the amine is the nucleophile and the alkene in effect the electrophile.[9,10]

## 2. Results and dicussion

Our first experiments were focused not unnaturally on substrates, which were particularly well set up to undergo such cyclisations, on the grounds that if these could not be successfully transformed into pyrrolidines, then the whole idea was perhaps not a viable proposition (Scheme 2). We therefore chose the prenyl derivatives **7**, which were readily prepared using the convenient Stork procedure (see below),[11] along with the very stable *p*-toluenesulfonyl (tosyl) group to attenuate the reactivity of the amino group. Protonation of the prenyl group was expected to give the stabilised tertiary carbenium ions **8**, which looked well set up to be trapped by the nearby sulfonamide group at least some of which, as argued above, would not be protonated and hence would be available to trap the positive ion to give the desired pyrrolidines **9**. In addition, in the case of precursor **7b**, a helpful steric compression ('Thorpe–Ingold' effect) may also contribute.

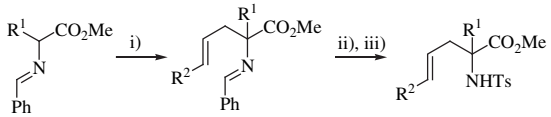



**Scheme 2.**

Initial trials met with success: when the sulfonamides **7** were refluxed with 1 equiv of *p*-toluenesulfonic (tosic) acid in chloroform, ethyl acetate or toluene, complete and reasonably clean conversions into the hoped-for pyrrolidines **9** were observed. Temperatures in excess of 70 °C were essential with this acid; in refluxing dichloromethane, no cyclisation occurred. Cyclisations were generally incomplete if less than 1 equiv of the acid was used. However, later trials using less substituted precursors such as those derived from cinnamyl or crotyl halides failed to produce such cyclisation products (see below). Other trials using acetic acid or trifluoroacetic acid also failed to produce any cyclisation products as did hydrogen chloride in methanol. It was only when we turned to a so-called super acid,[12] trifluoromethanesulfonic acid (triflic acid; TfOH, $CF_3SO_3H$) that success was achieved. This then became the reagent of choice for all subsequent experiments detailed below.

A brief optimisation study soon established that the two model substrates **7a**,**b** underwent very rapid and clean cyclisations to give the hoped-for pyrrolidines **9a**,**b** in essentially quantitative yields upon exposure to around half an equivalent of triflic acid in ice-cold chloroform for no more than 15 min. Using less acid (0.1 and 0.03 equiv) resulted in much lower conversions under the same conditions (28% and 8%, respectively). At a very low temperature (−78 °C), no cyclisation occurred using up to 1 equiv of acid while at −40 °C, conversions into pyrrolidines **9a**,**b** reached around 70% using 0.4 equiv of acid during up to 6 h. We therefore adopted the initial conditions of 0.4 equiv of triflic acid in chloroform or dichloromethane at 0 °C for around 15 min as our standard protocol for this type of substrate, which is expected to give relatively stabilised tertiary carbenium ions **8**.

We next tested the generality of this chemistry by using substituents that were somewhat less able to provide such stabilisation of a positive charge. All these and most subsequent substrates were synthesised using the Stork procedure featuring alkylation of the carbanion derived from the benzaldehyde Schiff's base of methyl glycinate or alaninate **10** (Scheme 3).[11] Yields of the intermediate imines **11** were generally excellent when using allylic bromides; use of the corresponding iodides was necessary in cases of less activated, non-allylic alkenyl halides.




**10** a) $R^1$ = H; b) $R^1$ = Me

**11** a) $R^1$ = H; $R^2$ = Ph; b) $R^1$ = Me; $R^2$ = Ph; c) $R^1$ = H; $R^2$ = Me; d) $R^1$ = $R^2$ = Me

**12**

**Scheme 3.** (i) LDA, THF, −78 °C, then add alkyl halide, −78 °C, 1 h then 20 °C, 1 h; (ii) 1 M HCl, $Et_2O$, 2 h, 20 °C; (iii) *p*-TsCl, $Et_3N$, DMAP (cat.), $CH_2Cl_2$, 20 °C, 16 h.

While the subsequent acid-catalysed imine hydrolysis was simple, we have great difficulty in obtaining decent yields of the final *N*-tosylated derivatives **12**, partly due to bis-tosylation.[13]

After some experimentation, we found conditions under which cyclisations of all four new precursors **12a**–**d** derived from combinations of glycine and alanine, together with cinnamyl and crotyl bromides, proceeded very smoothly to give excellent yields of the expected pyrrolidines **13a**–**d**. The results of these and the foregoing experiments using the prenyl derivatives **7a**,**b** are collected in Table 1. These initial cyclisations followed an approximate pattern expected from the likely carbenium ion stability [cf. ion **8**] in the sense that, while the prenyl derivatives **7a**,**b** underwent rapid cyclisation at 0 °C, the cinnamyl derivatives **12a**,**b** required reactions at ambient temperature and the crotyl analogues **12c**,**d** reflux temperature. This would seem to roughly equate to tertiary alkyl, benzylic and secondary alkyl carbenium ion stabilities. However, where relevant (see Experimental section), the reactions shown in Table 1 were not particularly stereoselective. We have briefly examined this feature and have obtained results, which suggest these initial products are best regarded as kinetic mixtures (Table 2).

Firstly, the stereochemical assignments shown in Table 2 were based upon our previous deductions made from both NMR and X-ray