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Tandem cationic cyclisation–aziridinium ion formation–nucleophilic ring opening: new methodology for the stereocontrolled synthesis of substituted pyrrolidines

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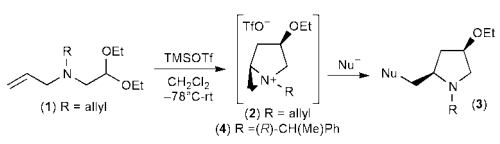
A novel tandem cationic cyclisation–aziridinium ion formation–nucleophilic ring opening procedure has been developed which provides powerful new methodology for the stereocontrolled synthesis of a wide variety of substituted pyrrolidines from acyclic precursors. The intermediate bicyclic aziridinium ions can be isolated and their structure has been confirmed by X-ray crystallography.

Saturated nitrogen heterocycles, including pyrrolidines and piperidines, occur in a wide variety of natural products and biologically active compounds.[1] Their synthesis has attracted much attention over the years, and methods which allow the construction of polysubstituted compounds with stereochemical control are particularly valuable.[2] Our research group has been involved in developing new chemistry of aziridinium ion intermediates, and alongside other workers in the field,[3] have shown them to be versatile, yet underused intermediates in synthetic organic chemistry.[4] Bicyclic aziridinium ions such as (**2**) have been known for some time, and are usually generated from the corresponding pyrrolidine-2-methanols or 3-hydroxypiperidines or halide derivatives thereof.[5] The reaction of these bicyclic aziridinium ions with nucleophiles is very useful synthetically, and is also of mechanistic interest as both pyrrolidine or piperidine products can be formed depending on the regioselectivity of the aziridinium ion cleavage reaction. However this methodology is limited due to the availability of suitable precursors, which are usually derived from proline or piperidine derivatives.

We have recently reported mechanistic and synthetic studies on the Lewis acid mediated nucleophilic cleavage of α-amino acetals.[6] In the course of this work we chose to investigate a range of substitution patterns, including *N*,*N*-diallylamines which were of interest as deprotection could be readily achieved under mild conditions to give the free primary amine.[7] At low temperatures, acetal substitution occurs,[6] however if the intermediate is allowed to warm to rt prior to addition of a nucleophile, then the final product is the substituted pyrrolidine (**3**) *as a single diastereoisomer* (Scheme 1). This can be rationalised by a cationic cyclisation of an *N*-allyl group onto the α-oxocarbenium ion, generated by cleavage of acetal (**1**). The nitrogen atom then intercepts the developing cationic centre directly forming the bicyclic aziridinium ion (**2**), followed by regioselective ring opening by the nucleophile.



Scheme 1

† Author to whom communications regarding X-ray crystallography should be addressed.

The rearrangement to form the aziridinium ion proceeds in high yield, and such intermediates can be observed by ^{1}H NMR prior to addition of the nucleophile. Alternatively, they can be isolated as crystalline tetraphenylborate salts by addition of $NaBPh_4$ to an acetone solution of the triflate salts (**2**) followed by addition of ether to induce precipitation. The aziridinium ions isolated in this way, can be stored indefinitely, and are particularly attractive synthetic intermediates. This also allowed the use of X-ray crystallography to unambiguously determine the relative stereochemistry of the aziridinium ion (**4**) (Fig. 1) derived from *R*-(+)-α-methylbenzylamine, obtained by fractional crystallisation of the crude product mixture.[8]

Previous studies on the reactivity of bicyclic aziridinium ions such as (**2**) suggested that the regioselectivity of the ring opening reaction may be a problem, particularly if pyrrolidines were desired. However, we found that this was generally not the case (Table 1), and that a range of synthetically useful nucleophiles could be employed, leading to the synthesis of a diverse range of 1,2,4-trisubstituted pyrrolidines. Only in the case of oxygen nucleophiles were significant quantities of piperidine products formed, and in such cases, this could be improved by using more reactive synthetic equivalents.

Although these results were encouraging, the methodology did not offer the opportunity for control of absolute stereochemistry unless a resolution was used. We therefore also investigated more complex examples derived from substituted α-amino acetals which overcame this limitation. Examples are shown in Scheme 2.[6,9] In general, good selectivity is observed, which is essentially independent of nucleophile, consistent with the aziridinium ion intermediates (**7**) and (**10**). Importantly, even a substituent as small as a methyl group still allows for a good degree of stereocontrol for formation of aziridinium ion (**10**).

The observed stereocontrol can be rationalised by assuming all substitutents adopt a pseudo-equatorial position in a chair-like transition state in the cyclisation reaction (Fig. 2).

The remaining limitation on this chemistry lies in the nature of the acetal chosen. Although methyl and ethyl acetals are readily accessible, they do not allow for ready deprotection in the presence of sensitive functionality to give the more useful alcohol substituent. To address this problem we synthesised the

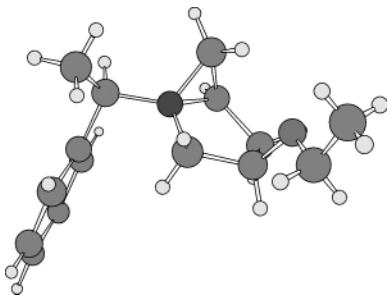


Fig. 1 X-Ray crystal structure of (**4**) (BPh_4 omitted for clarity).

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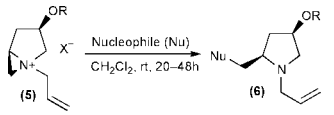
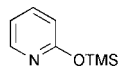
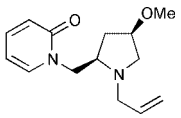
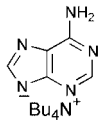
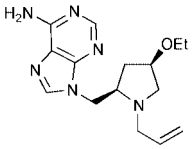
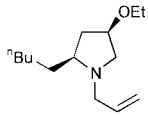
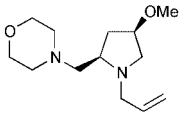
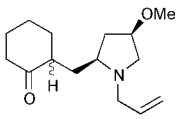
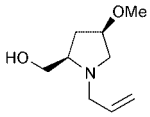
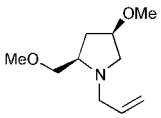
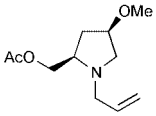
benzyl acetal (**12**). This underwent smooth cyclisation with comparable efficiency and selectivity to other acetals (Scheme 3), and the product benzyl ether (**13**) should now be capable of hydrogenolysis, which would also allow concomitant N-deprotection to the parent substituted 3-hydroxypyrrolidine.

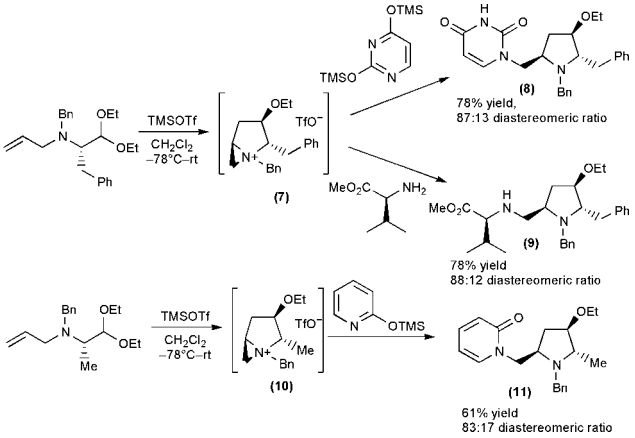
In summary, we have developed a novel tandem cationic cyclisation–aziridinium ion formation–nucleophilic ring opening procedure which provides powerful new methodology for the stereocontrolled synthesis of a wide variety of substituted pyrrolidines.[9] We are currently investigating this reaction further to determine its generality, and to exploit its potential in natural product synthesis. The results of these studies will be reported in due course.

Table 1 Nucleophilic opening of bicyclic aziridinium ions



Entry	R	X[a]	Nucleophile	Product	Yield[b]
1	Me	BPh_4^-			81%
2	Et	TfO^-			65%[c]
3	Et	BPh_4^-	$^nBu_2CuLi$		56%[c]
4	Me	BPh_4^-			77%
5	Me	TfO^-			67%[d]
6	Me	BPh_4^-	NaOH		61% (<10%)
7	Me	TfO^-	MeONa		41% (20%)
8	Me	TfO^-	MeOH		68%[e]
9	Me	BPh_4^-	AcONa		31% (28%)

[a] TfO^- counterion indicates aziridinium ion is generated *in situ*, whereas BPh_4^- counterion indicates preformed salt is used. [b] Yields for X = TfO^- are from the aminoacetal precursor, for X = BPh_4^-, yields are from the purified bicyclic aziridium ion salt; yields in parentheses are for isomeric piperidine. [c] CH_2Cl_2 exchanged for THF prior to addition of nucleophile. [d] 1:1 Mixture of diastereoisomers. [e] 55:45 Mixture of pyrrolidine and piperidine.



Scheme 2

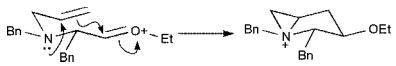
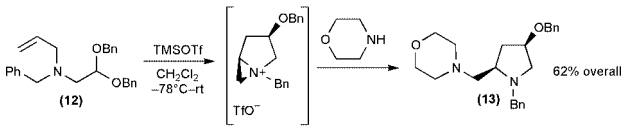


Fig. 2



Scheme 3

We wish to thank the EPSRC and GlaxoSmithKline (Stevenage) for an Industrial CASE award.

Notes and references

1 See for example: A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux and R. J. Nash, *Phytochemistry*, 2001, **56**, 265; D. O'Hagan, *Nat. Prod. Rep.*, 1997, 637.

2 A. Mitchinson and A. Nadin, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2862 and references cited therein. For other recent examples see: D. W. Knight and R. Salter, *Tetrahedron Lett.*, 1999, **40**, 5915; A. M. Palmer and V. Jager, *Synlett*, 2000, 1405; I. A. O'Neil, E. Cleator, N. Hone, J. M. Southern and D. J. Tapolczay, *Synlett*, 2000, 1408.

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4 C. M. Rayner, *Synlett*, 1997, 11.

5 J. Cossy, C. Dumas and D. G. Pardo, *Eur. J. Org. Chem.*, 1999, 1693; K. A. Tehrani, K. van Syngel, M. Boelens, J. Contreras, N. De Kimp and D. W. Knight, *Tetrahedron Lett.*, 2000, **41**, 2507; L. Poitout, Y. Le Merrer and J. C. Depezay, *Tetrahedron Lett.*, 1996, **37**, 1613.

6 M. A. Graham, A. H. Wadsworth, M. Thornton-Pett, B. Carrozzini, G. L. Cascarano and C. M. Rayner, *Tetrahedron Lett.*, 2001, **42**, 2865. This paper also contains details of methods used for synthesis of appropriate precursors.

7 P. J. Kocienski, *Protecting Groups*, Thieme, 1994; see also ref. 4*b*.

8 Only one other X-ray crystal structure of an aziridinium ion has been reported, see: E. Pombo-Villar, J. Boelsterli, M. M. Cid, J. France, B. Fuchs, M. Walkinshaw and H. P. Weber, *Helv. Chim. Acta*, 1993, **76**, 1203. *Crystal data* for (**4**): $C_{39}H_{42}BNO$, M = 551.55, triclinic, a = 9.0282(2), b = 9.7091(2), c = 10.3036(2) Å, U = 791.07(3) Å^3, α = 114.3040(10), β = 97.6460(10), γ = 99.5540(10)°, T = 150 K, space group $P1$, Z = 1, λ(Mo-Kα) = 0.71073 Å, 8491 reflections measured, 5075 unique (R_{int} = 0.0392) which were used in all calculations. μ = 0.067 mm^{-1}, $R_1[I > 2\sigma(I)]$ = 0.0417, final $wR(F^2)$ was 0.1043 (all data). CCDC 160870. See http://www.rsc.org/suppdata/cc/b1/b102124i/ for crystallographic files in .cif format.

9 All new compounds have been characterised by ^{1}H and ^{13}C NMR, IR, MS and gave satisfactory elemental analysis. Stereochemical assignments for compounds (**8**), (**9**) and (**11**) were confirmed by NOE experiments; no attempt has been made to assign the stereochemistry of the minor diastereoisomeric products.