Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5347–5350
Tetrahedron Letters

Studies on the [2,3]-Stevens rearrangement of aziridinium ions

Gareth J. Rowlands* and William Kentish Barnes

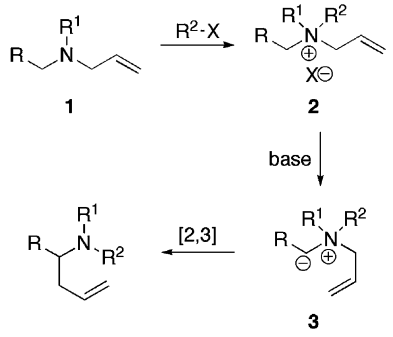
Department of Chemistry, University of Sussex, Falmer, Brighton BN1 9QJ, UK

Received 15 April 2004; revised 13 May 2004; accepted 18 May 2004

Abstract—The aziridinium ylide generated by the intramolecular reaction of a metal carbenoid tethered to a vinylaziridine undergoes [2,3]-Stevens rearrangement to furnish the indolizidine skeleton. It is essential that the correct nitrogen invertomer is used or a competing [1,5]-hydrogen shift predominates. During the preparation of a second system a 'one-pot' acylation-[3,3]-Claisen rearrangement was observed, delivering a seven-membered lactam.

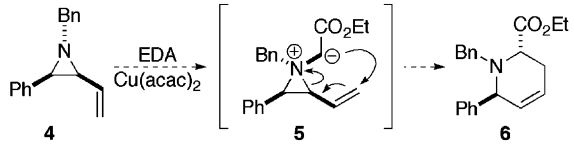
Saturated nitrogen heterocycles, including piperidines, occur in a wide variety of natural and biologically relevant compounds.[1] Thus development of novel routes to this structural motif is an important area of research. In recent years the aziridinium ion has become a significant and versatile synthetic intermediate, as it readily undergoes ring-opening with a variety of nucleophiles.[2] Surprisingly there have been few reports of intramolecular attack upon aziridinium ions.[3]

The [2,3]-Stevens rearrangement is a synthetically useful C–C bond forming reaction of *N*-allyl quaternary ammonium ylides **3**.[4] Conventionally the desired ylides are formed via quaternisation of an amine **1** followed by treatment with a base (Scheme 1).[5] The ammonium salt **2** can be isolated or the sequence performed in 'one pot'.[6] Alternatively ammonium ylides can be formed under essentially neutral conditions via tertiary amine insertion into a metal carbenoid. Several groups have studied the synthesis of reduced cyclic amines via the intramolecular generation and rearrangement of ammonium ylides.[7–9] West and co-workers[8] has prepared quinolizidine alkaloids via a [1,2]-Stevens rearrangement. In a series of elegant papers Clark et al.[9] has utilised the [2,3]-Stevens rearrangement to form a variety of heterocycles via tandem intramolecular cyclisation-rearrangement or intramolecular cyclisation-ring expansion.



Scheme 1.

We were interested in utilising an aziridinium ion in the [2,3]-Stevens rearrangement as an approach to tetrahydropyridines **6** (Scheme 2), versatile synthetic building blocks for the preparation of substituted piperidines. At the outset of this work[10] there had been no reports of this reaction, and even now there is only one simple example.[9c] Our initial approach is outlined in Scheme 2. It was believed that the aziridinium ion might decompose via a [1,5]-hydrogen shift[11,12] so we wanted to avoid its isolation. Therefore ylide **5** was to be prepared from vinylaziridine **4** via the reaction of a metal carbenoid.



Scheme 2.

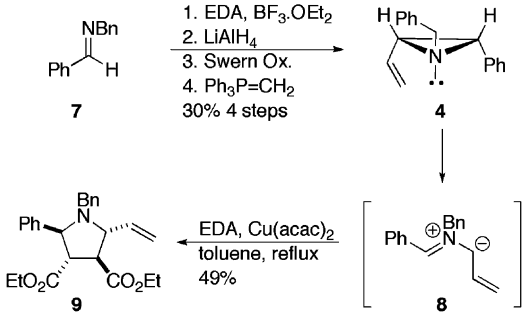
Keywords: Vinylaziridine; Aziridinium; Ylide; Carbene; [2,3]-Stevens rearrangement.

* Corresponding author. Tel.: +44-1273-678-242; fax: +44-1273-677-196; e-mail: g.rowlands@sussex.ac.uk

0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.05.087

There have been two previous reports on the generation of aziridinium ylides via the interaction of an *N*-alkyl aziridine with a carbene.[13] Hata and Watanabe found that treatment of *N*-phenethylaziridine with ethyl diazoacetate (EDA) in the presence of $Cu(acac)_2$ led to fragmentation of the aziridine to give ethylene and an imine via *syn*-elimination instead of the anticipated [1,2]-Stevens rearrangement. We reasoned that a vinylaziridine would undergo the desired [2,3]-Stevens rearrangement instead of decomposition. The [1,2]-rearrangement is symmetry forbidden and there is little thermodynamic driving force for the ring expansion of an aziridine to an azetidine. Alternatively, a vinylaziridine would allow the ring expansion to proceed via a symmetry allowed process with considerable release of ring-strain during the expansion from a 3-ring to a 6-ring. The anionic variant, the [2,3]-aza-Wittig reaction proceeds smoothly on account of this driving force.[11,14] As a result we decided to reinvestigate the reaction of *N*-alkyl aziridines with metal carbenoids and here report the factors that effect the efficiency of this reaction.

The desired *N*-benzyl vinylaziridine **4** was readily prepared from imine **7** in four steps (Scheme 3). The aza-Darzens-like reaction of EDA and **7** under Lewis acid catalysis gave the *cis*-aziridine ester in good yield.[15] The ester was converted to the desired vinyl substituent in three steps. The poor yield is due to the instability of both the aldehyde intermediate and the vinylaziridine **4**. NOE analysis indicated that the vinylaziridine exists as one nitrogen invertomer with the benzyl group residing on the opposite face of the aziridine to the two substituents. This is the ideal conformation for the interaction of the amine with the metal carbenoid as the resultant ylide would form on the same face as the alkene.



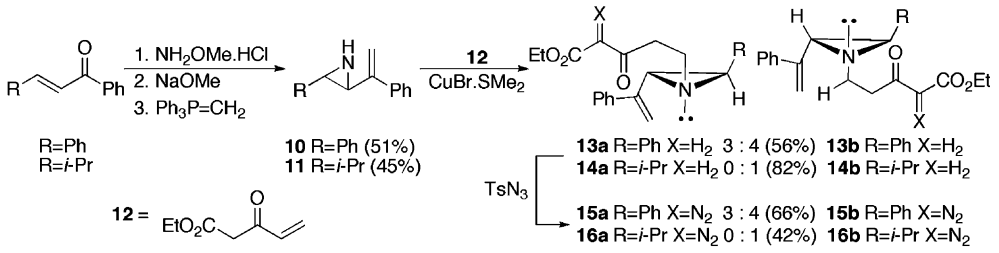
Scheme 3.

With the vinylaziridine **4** in hand we turned our attention to the proposed intermolecular ylide generation-rearrangement reaction (Scheme 2). Treatment of **4** with EDA in the presence of either $Cu(acac)_2$ or $Rh_2(OAc)_4$ in a variety of solvents at room temperature led to no reaction other than dimerisation of EDA to give diethyl fumarate and recovery of unreacted **4** (>80%). On heating, a reaction did occur, but not as desired. The highly substituted pyrrolidine **9** was isolated in moderate yield (Scheme 3). Presumably thermal ring-opening of the vinylaziridine gives the azomethine ylide **8**, in which the vinyl moiety acts as an anion stabilising group. 1,3-Dipolar cycloaddition with the fumarate formed via the dimerisation of EDA then furnishes the pyrrolidine **9**. The generation of an azomethine ylide from an aziridine is well known[16] when the ylide is stabilised by a carbonyl moiety but is rare with other functionality.

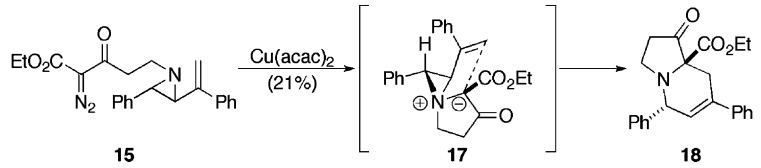
Failure of the desired reaction could be attributed to two possibilities; firstly catalyst deactivation via coordination of the amine and metal centre.[17] This argument might explain the surprising stability of the vinylaziridine under the reaction conditions compared to normal storage! Coordination would prevent nitrogen inversion and thus inhibit the [1,5]-hydrogen shift. Normally deactivation is overcome by heating, a possibility not open to us due to the thermal instability of **4**. Alternatively, steric hindrance might prevent interaction of the amine and the metal carbenoid; the necessicity for three eclipsing substituents on the same face of an aziridine combined with the required *endo* orientation of the alkene group may be too energetically unfavourable.

With the failure of the intermolecular variant we decided to turn our attention to the intramolecular variant.[9c] It was hoped that by tethering the diazo moiety to the amine, quaternisation would be more favourable. The methodology would also allow an elegant, direct entry into the indolizidine skeleton via a tandem cyclisation-ylide generation-rearrangement reaction. This would offer a considerable advantage over the analogous aza-Wittig reaction, which required an additional five steps to create the second ring of the indolizidine skeleton.[14b]

The *N*-unsubstituted vinylaziridines **10** and **11** were prepared in good yield (Scheme 4).[14d] *N*-alkylation proved more problematic. Extensive optimisation allowed the synthesis of **13** and **14** via Lewis acid activated conjugate addition with copper(I) bromide. Interestingly, the two vinylaziridines behaved very differently. Compound **13** could be isolated in 56% after 7 days at



Scheme 4.



Scheme 5.

room temperature. NOE analysis revealed that the *N*-alkyl aziridine existed as a 3:4 **13a**:**13b** mixture of nitrogen invertomers favouring the undesired invertomer **13b** in which the *N*-alkyl substitutent and the vinyl moiety are *cis*. Surprisingly no [1,5]-hydrogen shift was observed. Alkylation of **11** proceeded in a mere 30 min to give **14b** as a single nitrogen invertomer in 82% yield. If the reaction was left longer the only product isolated was that resulting from a [1,5]-hydrogen shift. Clearly, in **14b** the isopropyl group forces the *N*-alkyl substituent *cis* to the vinyl group thus encouraging ring-opening. At present we have no explanation for the incredible difference in reactivity. Addition of the diazo moiety to **13** via reaction with tosyl azide proceeded in good yield to give **15**. Once again compound **14** was more problematic due to decomposition via the [1,5]-hydrogen shift.

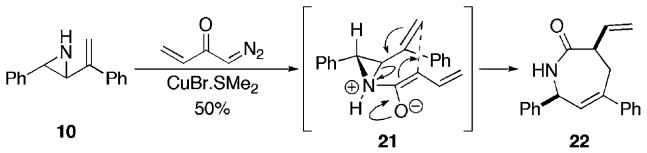
The tandem cyclisation-ring expansion reaction was then investigated. Compound **15** did not react with any catalyst at room temperature but we were pleased to isolate the desired bicyclic amine **18** in 21% upon heating the reaction to reflux in acetonitrile (Scheme 5). The relative stereochemistry was confirmed by NOE and can be understood if the reaction is assumed to proceed via formation of ylide **17**. [2,3]-Stevens rearrangement then occurs with the ester functionality orientated away from the aziridine substituents, placing it on the opposite face to the phenyl group.

Whilst the yield appears low it is easily rationalised. The starting material exists as a 3:4 mixture of nitrogen invertomers. Only the ylide **17** formed *cis* to the alkene moiety can undergo the rearrangement, which means only invertomer **15a** can proceed profitably. As this invertomer only accounts for 43% of the material the yield is restricted. Nitrogen inversion in aziridines is very slow due to the increased s character of the lone pair whilst the [1,5]-hydrogen shift is greatly accelerated at the higher temperatures employed here.[12] Therefore we believe invertomer **15b** undergoes the [1,5]-hydrogen shift more rapidly than nitrogen inversion. The resulting imine then decomposes under the reaction conditions. The overall yield is further compromised by the thermal instability of both starting material and product.

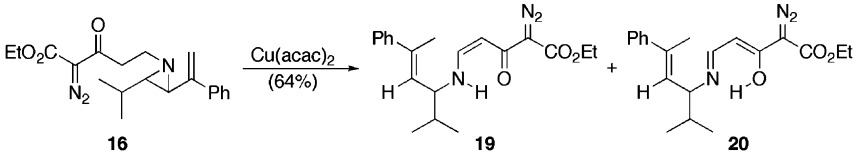
The importance of having the correct invertomer is borne out by the reaction of **16**, which exists as only the undesired invertomer. At reflux **16** rapidly undergoes a [1,5]-hydrogen shift to give an imine that tautomerises to the enamine **19** and enol **20** that can be isolated in good yield (Scheme 6). The presence of the diazo moiety indicates that the shift is more favourable than ylide formation.

Introduction of an alternative tether was investigated. Attempted conjugate addition of vinylaziridine **10** to diazomethylvinyl ketone under our standard conditions did not yield the desired cyclisation precursor but the lactam **22** was obtained as a single diastereoisomer in moderate yield (Scheme 7). Presumably reaction of the vinylaziridine with the ketene formed from the Wolff rearrangement of the diazo ketone generates enolate **21** that undergoes a [3,3]-Claisen rearrangement to give the lactam **22**. The relative stereochemistry can be understood if the reaction is assumed to proceed via a boat-like transition state **21** as described by Somfai[18] for the base-promoted cyclisation of *N*-acyl vinylaziridines. This reaction offers a 'one-pot' variant of Somfai's work.[18] Further studies are required to evaluate the scope of this 'one-pot' reaction of ketenes and vinylaziridines and will be reported in due course.

In conclusion, we have shown that the aziridinium ion can be used in the rapid preparation of the indolizidine skeleton. In order to prevent a competitive [1,5]-hydrogen shift it is crucial that the correct nitrogen invertomer is formed. This places a structural limitation on this methodology. The failure of the intermolecular variant and difficulty in handling vinylaziridines has led us to investigate a method for producing these species in situ. This work will be reported in due course.



Scheme 7.



Scheme 6.

Acknowledgements

We would like to thank Dr. Tony Avent for the NOE analysis. This work was supported by the EPSRC (GR/N38329/01).

References and notes

1. (a) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742–760; (b) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 719–741; (c) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862–2892; (d) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446.
2. (a) Andrews, D. R.; Dahanukar, V. H.; Eckert, J. M.; Gala, D.; Lucas, B. S.; Schumacher, D. P.; Zavialov, I. A. *Tetrahedron Lett.* **2002**, *43*, 6121–6125; (b) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 1435–1437; (c) Cossy, J.; Gomez Pardo, D. *Chemtracts* **2002**, *15*, 579–605; (d) Graham, M. A.; Wadsworth, A. H.; Thornton-Pett, M.; Rayner, C. M. *Chem. Commun.* **2001**, 966–967; (e) O'Brien, P.; Towers, T. D. *J. Org. Chem.* **2002**, *67*, 304–307; (f) Piotrowska, D. G.; Wróblewski, A. E. *Tetrahedron* **2003**, *59*, 8405–8410.
3. Graham, M. A.; Wadsworth, A. H.; Zahid, A.; Rayner, C. M. *Org. Biomol. Chem.* **2003**, *1*, 834–849.
4. (a) Coldham, I. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Elsevier Science: Oxford, 1995; Vol. 1, pp 377–424; (b) Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 913–974.
5. (a) Bailey, T. S.; Bremner, J. B.; Carver, J. A. *Tetrahedron Lett.* **1993**, *34*, 3331–3334; (b) Gulea-Purcarescu, M.; About-Jaudet, E.; Collignon, N.; Saquet, M.; Masson, S. *Tetrahedron* **1996**, *52*, 2075–2086; (c) Mageswaran, S.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans.1* **1981**, 1953–1962; (d) Neeson, S. J.; Stevenson, P. J. *Tetrahedron Lett.* **1988**, *29*, 3993–3996; (e) Ollis, W. D.; Sutherland, I. O.; Thebtaranonth, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1963–1968; (f) Sweeney, J. B.; Tavassoli, A.; Carter, N. B.; Hayes, J. F. *Tetrahedron* **2002**, *58*, 10113–10126; (g) Zhang, C.; Maeda, Y.; Shirai, N.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 25–28.
6. (a) Arboré, A. P. A.; Cane-Honeysett, D. J.; Coldham, I.; Middleton, M. L. *Synlett* **2000**, 236–238; (b) Coldham, I.; Middleton, M. L.; Taylor, P. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2951–2952; (c) Smith, S. C.; Bentley, P. D. *Tetrahedron Lett.* **2002**, *43*, 899–902.
7. Wright, D. L.; Weekly, R. M.; Groff, R.; McMills, M. C. *Tetrahedron Lett.* **1996**, *37*, 2165–2168.
8. (a) Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, *53*, 16565–16574; (b) West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892–6894; (c) West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6051–6056; (d) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420–8421.
9. (a) Clark, J. S.; Hodgson, P. B. *J. Chem. Soc., Chem. Commun.* **1994**, 2701–2702; (b) Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3312–3324; (c) Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Blake, A. J.; Cooke, P. A.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3325–3337.
10. Kentish Barnes, W. D.Phil. Thesis, University of Sussex, 2002.
11. Coldham, I.; Collis, A. J.; Mould, R. J.; Rathmell, R. E. *Tetrahedron Lett.* **1995**, *36*, 3557–3560.
12. (a) Åhman, J.; Somfai, P.; Tanner, D. *J. Chem. Soc., Chem. Commun.* **1994**, 2785–2786; (b) Somfai, P.; Åhman, J. *Tetrahedron Lett.* **1995**, *36*, 1953–1956.
13. (a) Hata, Y.; Watanabe, M. *Tetrahedron Lett.* **1972**, 2830–3827; (b) Hata, Y.; Watanabe, M. *Tetrahedron Lett.* **1972**, 4659–4660.
14. (a) Åhman, J.; Somfai, P. *J. Am. Chem. Soc.* **1994**, *116*, 9781–9782; (b) Åhman, J.; Somfai, P. *Tetrahedron Lett.* **1995**, *36*, 303–306; (c) Åhman, J.; Jarevång, T.; Somfai, P. *J. Org. Chem.* **1996**, *61*, 8148–8159; (d) Coldham, I.; Collis, A. J.; Mould, R. J.; Rathmell, R. E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2739–2745.
15. Casarrubios, L.; Perez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358–8359.
16. (a) Dell, C. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873–3905; (b) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 1069–1109; (c) Coldham, I.; Collis, A. J.; Mould, R. J.; Robinson, D. E. *Synthesis* **1995**, 1147–1150.
17. Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094–5102.
18. Lindström, U. M.; Somfai, P. *Chem. Eur. J.* **2001**, *7*, 94–98.