Ring-expansion of tertiary cyclic α-vinylamines by tandem conjugate addition to (*p*-toluenesulfonyl)ethyne and formal 3-aza-Cope rearrangement†

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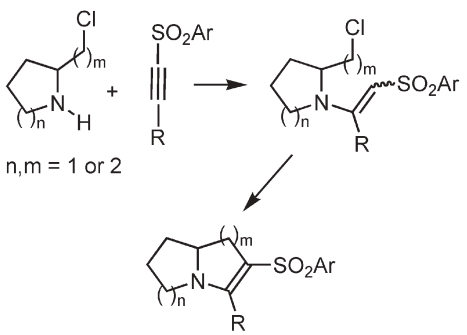
A novel ring-expansion protocol is based on the conjugate additions of cyclic α-vinylamines to (*p*-toluenesulfonyl)ethyne, followed by aza-Cope rearrangements of the resulting zwitterions, to afford medium and large-ring cyclic amines under remarkably mild conditions.

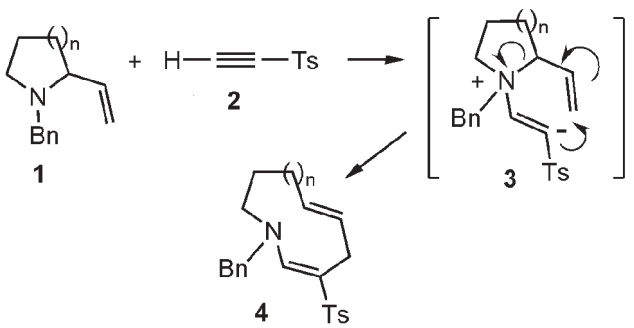
Compounds containing medium and large rings are often difficult to synthesize by direct ring-closure protocols such as intramolecular alkylation or acylation. The formation of medium-sized rings is impeded by unfavourable combinations of Pitzer, transannular and large-angle strain in the products. Furthermore, closure of large rings is accompanied by an unfavourable loss of entropy.[1] The ring-expansion of a more readily available cyclic starting material of normal ring size can provide an effective alternative to direct ring-closures.[2] We recently discovered a series of novel cyclizations that are based upon the conjugate additions of primary or secondary amines to acetylenic sulfones,[3] followed by intramolecular akylation or acylation (*e.g.*, see Scheme 1). These processes provided access to a series of piperidines, pyrrolizidines, indolizidines, quinolizidines, decahydroquinolines and quinolones, including (−)-pumiliotoxin C,[4a] various other dendrobatid alkaloids,[4b] myrtine,[4c] (−)-lasubine II[4c] and two quinolone alkaloids from the medicinal plant *Ruta chalepensis*.[4d] We now report that the conjugate additions of cyclic, tertiary amines containing α-vinyl substituents (*e.g.* **1**) to the acetylenic sulfone **2**, are spontaneously followed by a formal 3-aza-Cope rearrangement of the zwitterions **3**. This results in facile ring-expansions of the initial amine by four members to afford the corresponding medium-ring or macrocyclic amines **4** (Scheme 2). Similar ring systems are found in a number of natural products that display interesting biological activity.[5]



Scheme 1 Cyclizations of chloroamines with acetylenic sulfones.

In general, aza-Cope rearrangements[6,7] and related processes[8,9] proceed with difficulty and require strongly elevated temperatures that limit their synthetic usefulness. In some instances, catalysis with Brønsted or Lewis acids has been used to facilitate the process. Alternatively, cationic variations of the aza-Cope rearrangement, where a quaternary nitrogen atom is present, proceed under milder conditions. We therefore reasoned that the zwitterionic conjugate addition product **3** in Scheme 2 would rearrange under especially mild conditions and provide a convenient means for transforming readily available α-vinyl *N*-benzylpyrrolidines, piperidines, morpholines, azepines and other cyclic amines into sulfone-functionalized products containing medium or large rings. In contrast to the present results with cyclic α-vinylamines, the [3,3]sigmatropic rearrangements of acyclic allylamines with acetylenic sulfone **2** were reported to fail, except in the case of silylated hydroxylamine derivatives.[7b] Other rearrangements of the conjugate addition products of allylamines with dimethyl acetylenedicarboxylate have also been reported.[10]

The results of the ring-expansions of the cyclic α-vinylamines with **2** are shown in Table 1. The required α-vinylamines **1a**,[11] **1b**[11] and **7a**,[12] as well as acetylenic sulfone **2**,[13] were obtained by minor variations of literature methods. The preparation of the remaining starting materials **1c**, **1d**, **5**, **7b** and **9** is described in the supplementary information.† All of the reactions listed in Table 1 were performed in dichloromethane, with conditions ranging from



Scheme 2 Aza-Cope rearrangement of cyclic α-vinyl amines with acetylenic sulfone **2**.

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† Electronic supplementary information (ESI) available: procedures, characterization data, ^{1}H and ^{13}C NMR spectra for new products; X-ray structure data for compound **4b**. See DOI: 10.1039/b607713g

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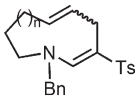
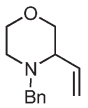
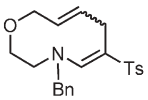
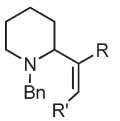
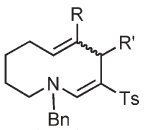
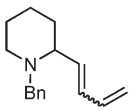
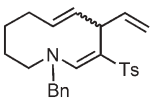
Table 1 Ring expansion of α-vinyl cyclic amines with **2**

Starting amine	Product (yield)	Conditions[a,b] (temp., time)
		
1a (n = 1)	**4a** (87%)	0 °C, 0.5 h
1b (n = 2)	**4b** (91%)	0 °C, 0.5 h
1c (n = 3)	**4c** (89%)	0 °C, 0.5 h
1d (n = 9)	**4d** (63%)	RT, 30 h
		
5	**6** (87%)	RT, 12 h
		
7a R = H; R' = Me	**8a** (89%)	RT, 12 h
7b R = Me; R' = H	**8b** (86%)	Reflux, 8 h
		
9	**10** (58%)	RT, 12 h

[a] All reactions were performed in dichloromethane. [b] RT = room temperature.

0.5 h at 0 °C for **4a–4c** to 8 h at reflux for **8a**. A typical procedure is available in the supplementary information.† The reactions of **1a–1d** indicate that simple cyclic α-vinylamines can be converted into either medium-ring (**4a–4c**) or macrocyclic (**4d**) products in excellent to good yields, respectively. The method can be used to incorporate other heteroatoms, as shown by the formation of **6** from the morpholine derivative **5**. Additional substituents are tolerated at either the α- or β-position of the vinyl moiety, as exemplified by the preparation of the methyl-substituted products **8a** and **8b**, formed with only a modest reduction in reaction rate compared to the rate of the corresponding unsubstituted amine **1b**. The dienylamine **9** also underwent a [3,3] rearrangement instead of the analogous [3,5] process, although in somewhat diminished yield.

Based on the olefinic coupling constant J_{cis} = 11.3 Hz, we conclude that the 9-membered product **4a** has the 5*Z* configuration. On the other hand, the 10-membered homologue **4b** was obtained as a 95 : 5 mixture of 5*E* and 5*Z* isomers, based on integration of the NMR signals from H-2 at δ 7.62 and 7.53, respectively. The 5*E*-configuration of the major isomer was indicated by X-ray crystallography (Fig. 1),§ which also confirmed the expected 2*E* configuration. The 10-membered oxazecine **6** was similarly obtained as a mixture of E : Z isomers in the ratio of 9 : 1 (integration of H-2 signals at δ 7.67 and 7.59, respectively), with the major isomer identified by its H-5/H-6 coupling constant J_{trans} = 15.9 Hz. The 11-membered homologue **4c** was obtained as the pure E isomer (J_{trans} = 15.7 Hz). Overlapping olefinic NMR signals and the unavailability of suitable crystals for X-ray structures precluded the unambiguous determination of 5*E*/*Z* geometry for **4d**, **8a**, **8b** and **10**, although we assume that the *E*-configuration was favoured in these examples.

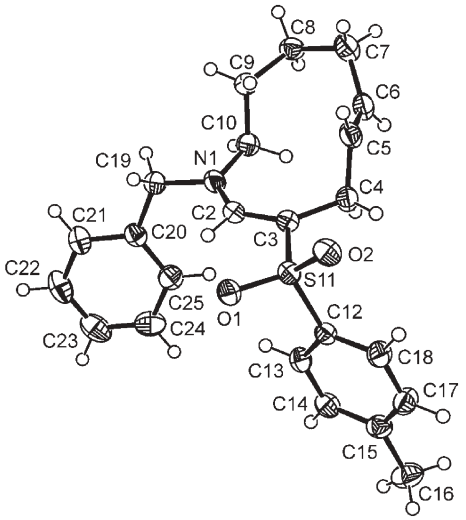
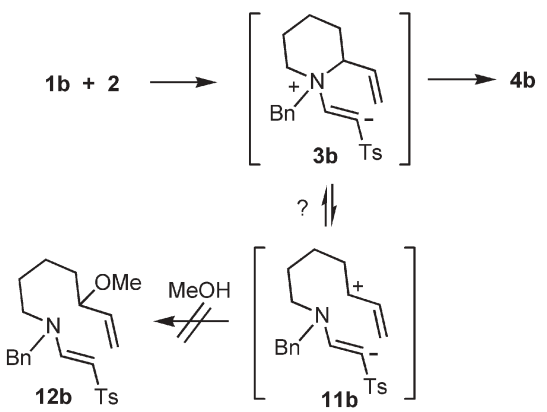


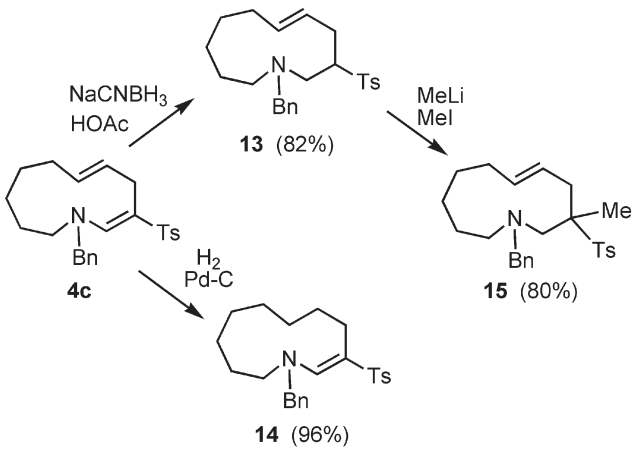
Fig. 1 ORTEP diagram of **4b** with displacement ellipsoids plotted at 50% probability level; 3 disordered H-atoms at 0.5 occupancy each around C16 have been ignored.

Normal 3-aza-Cope reactions are [3,3]sigmatropic rearrangements that proceed in a concerted manner and involve the interaction of *p*-orbitals at the respective terminal positions of the vinyl and allyl moieties of the precursor amine. The present reaction is somewhat different because it presumably requires the interaction of a sulfone-stabilized vinyl anion with an alkene *p*-orbital in intermediate **3**. There is no direct evidence that the present reaction is concerted and other mechanisms, such as a dissociative process proposed earlier for related aza-Cope reactions,[10a,b] followed by recombination, cannot be ruled out. However, attempts to trap the corresponding dissociated intermediate **11b** with nucleophilic solvents such as methanol failed and neither **12b** nor its ω-methoxy isomer were formed (Scheme 3). Similarly, attempts to detect **3b** or other intermediates by monitoring the reaction of **1b** with **2** by ^{1}H NMR spectroscopy in $CDCl_3$ were unsuccessful, probably because the formation of intermediate **3b** is rate-limiting and the subsequent step or steps are too fast to allow observable accumulation of **3b** or other intermediates.

A selection of further transformations that are possible for the products is illustrated with **4c** in Scheme 4. Thus, the enamine and



Scheme 3 Dissociative mechanism for the formation of **4b**.



Scheme 4 Further transformations of **4c**.

isolated alkene moieties can each be reduced selectively with sodium cyanoborohydride or by catalytic hydrogenation to afford **13** and **14**, respectively, while the sulfone moiety of **13** can be employed to introduce an additional substituent *via* alkylation of the corresponding α-carbanion, as in the case of **15**.

In summary, these preliminary experiments indicate that the ring-expansions of cyclic α-vinylamines with acetylenic sulfone **2** proceed under remarkably mild conditions without the need for catalysts. They provide efficient and convenient access to cyclic amines with medium or large rings, tolerate the presence of other heteroatoms and substituents, and permit further useful transformations of the products.

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Notes and references

§ *Crystal data:* $C_{23}H_{27}NO_2S$, M = 381.52, crystal system = orthorhombic, space group = *Pbca*. Unit cell dimensions: a = 17.003(4), b = 11.331(4), c = 21.365(7) Å, V = 4116(2) Å^3, Z = 8, MoKα radiation (λ = 0.71073 Å), T = 173(2) K, μ = 0.175 mm^{-1}, number of reflections measured = 8795, unique reflections = 4661, observed reflections ($I > 2.0\ \sigma$ I) = 3640, R_{int} = 0.022, R = 0.0430 and wR = 0.1052 for observed data. CCDC 609578. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b607713g

1 M. B. Smith and J. March, *March's Advanced Organic Chemistry—Reactions, Mechanisms and Structure*, Wiley, New York, 5th edn., 2001, pp. 184–186 and 280–281.

2 M. Hesse, *Ring Enlargement in Organic Chemistry*, VCH, Weinheim, 1991.

3 For a review of acetylenic and allenic sulfones, see: T. G. Back, *Tetrahedron*, 2001, **57**, 5263.

4 (*a*) T. G. Back and K. Nakajima, *J. Org. Chem.*, 1998, **63**, 6566; (*b*) T. G. Back and K. Nakajima, *J. Org. Chem.*, 2000, **65**, 4543; (*c*) T. G. Back, M. D. Hamilton and V. J. J. Lim, *J. Org. Chem.*, 2005, **70**, 967; (*d*) T. G. Back, M. Parvez and J. E. Wulff, *J. Org. Chem.*, 2003, **68**, 2223.

5 Examples include (*a*) the motuporamines: D. E. Williams, P. Lassota and R. J. Andersen, *J. Org. Chem.*, 1998, **63**, 4838; (*b*) halitulin and related compounds: Y. Kashman, G. Koren-Goldshlager, M. D. G. Gravalos and M. Schleyer, *Tetrahedron Lett.*, 1999, **40**, 997; (*c*) palustrine and other spermidine alkaloids: B. B. Touré and D. G. Hall, *J. Org. Chem.*, 2004, **69**, 8429 and references cited therein.

6 For reviews see: (*a*) D. Enders, M. Knopp and R. Schiffers, *Tetrahedron Asymmetry*, 1996, **7**, 1847; (*b*) S. Blechert, *Synthesis*, 1989, 71; (*c*) N. M. Przheval'skii and I. I. Grandberg, *Russian Chem. Rev.*, 1987, **56**, 477; (*d*) R. P. Lutz, *Chem. Rev.*, 1984, **84**, 205.

7 For recent examples of 3-aza-Cope rearrangements of acyclic allyl vinyl amines, see: (*a*) D. Fiedler, R. G. Bergman and K. N. Raymond, *Angew. Chem. Int. Ed.*, 2004, **43**, 6748; (*b*) M. J. S. Gomes, L. Sharma, S. Prabhakar, A. M. Lobo and P. M. C. Glória, *Chem. Commun.*, 2002, 746; (*c*) D. F. McComsey and B. E. Maryanoff, *J. Org. Chem.*, 2000, **65**, 4938; (*d*) A. S. Cardoso, A. M. Lobo and S. Prabhakar, *Tetrahedron Lett.*, 2000, **41**, 3611; (*e*) M. A. Walters, *J. Org. Chem.*, 1996, **61**, 978.

8 For recent examples of 2-aza-Cope rearrangements of 3-alkenyliminium species, see: (*a*) Z. D. Aron and L. E. Overman, *Org. Lett.*, 2005, **7**, 913; (*b*) K. M. Brummond and J. Lu, *Org. Lett.*, 2001, **3**, 1347.

9 For recent examples of aza-Claisen rearrangements, see: (*a*) J.-F. Zheng, L.-R. Jin and P.-Q. Huang, *Org. Lett.*, 2004, **6**, 1139; (*b*) S. G. Davies, A. C. Garner, R. L. Nicholson, J. Osborne, E. D. Savory and A. D. Smith, *Chem. Commun.*, 2003, 2134; (*c*) J. Kang, T. H. Kim, K. H. Yew and W. K. Lee, *Tetrahedron Asymmetry*, 2003, **14**, 415; (*d*) U. M. Lindström and P. Somfai, *Chem. Eur. J.*, 2001, **7**, 94; (*e*) Y.-G. Suh, S.-A. Kim, J.-K. Jung, D.-Y. Shin, K.-H. Min, B.-A. Koo and H.-S. Kim, *Angew. Chem., Int. Ed.*, 1999, **38**, 3545.

10 (*a*) E. Vedejs and M. Gingras, *J. Am. Chem. Soc.*, 1994, **116**, 579; (*b*) A. L. Schwan and J. Warkentin, *Can. J. Chem.*, 1988, **66**, 1686; (*c*) K. A. Kandeel and J. M. Vernon, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2023.

11 Compounds **1a** and **1b** were previously investigated in aza-Cope rearrangements with chromium carbene complexes: C. J. Deur, M. W. Miller and L. S. Hegedus, *J. Org. Chem.*, 1996, **61**, 2871.

12 S. Nazabadioko, R. J. Pérez, R. Brieva and V. Gotor, *Tetrahedron: Asymmetry*, 1998, **9**, 1597.

13 Z. Chen and M. L. Trudell, *Synth. Commun.*, 1994, **24**, 3149.