Ring Expansion of 2-Alkenyl Azetidines into Unsaturated Azocanes

Bruno Drouillat, François Couty,* Vanessa Razafimahaléo

Institut Lavoisier de Versailles, UMR CNRS 8180, Universud Paris, Université de Versailles Saint Quentin en Yvelines, 45 Avenue des Etats-Unis, 78035 Versailles Cedex, France
Fax +33(1)39254452; E-mail: couty@chimie.uvsq.fr

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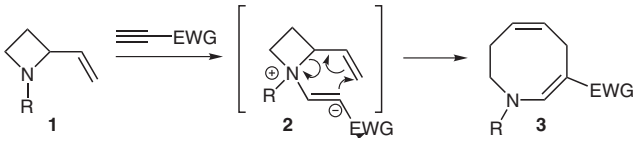
Abstract: Enantiomerically pure 2-alkenyl azetidines undergo a ring expansion into *N*-alkyl-1,2,3,6-azocines upon reaction with activated alkynes (ethyl propiolate or ethynyl *p*-tolyl sulfone). The scope of this ring enlargement, which provides a new entry to functionalized eight-membered ring nitrogen heterocycle, is discussed.

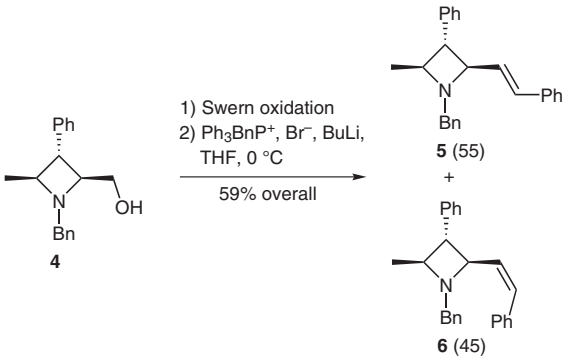
Key words: azetidines, ring expansion, azocanes



Scheme 1 [3,3]-Sigmatropic rearrangement of 2-alkenyl azetidines reacting with activated alkynes would produce unsaturated azocanes

Azetidines are rather underused heterocycles[1] due to their somewhat restricted availability, particularly when an enantiomerically pure starting material is required.[1f] Nonetheless, the strain in these heterocycles makes them particularly interesting candidates for ring opening or ring expansion reactions, which can, in the latter case, give access to larger nitrogen heterocycles. Thus, expansions of azetidines can produce up to seven-membered rings through various reactions such as photolysis[2] (production of pyrroles), cobalt-catalysed carbonylation[3] (production of pyrrolidinones), intramolecular rearrangement[4] (production of pyrrolidines or piperidines), [4+2] cycloadditions[5] (production of piperidines), [2,3]-sigmatropic shifts[6] (production of azepanes), and other processes.[7] However, to the best of our knowledge, the ring expansion of azetidines into azocanes (eight-membered nitrogen heterocycles) has not yet been described. We wish to report in this letter the first example of such a ring expansion based on a [3,3]-sigmatropic rearrangement of 2-alkenyl azetidines reacting with activated alkynes (Scheme 1). The prototype of such a rearrangement was described recently by Back et al,[8] and its feasibility has been evaluated for 3-, 5-, 6- or larger 2-vinyl nitrogen heterocycles,[9] but not with 2-alkenyl azetidines. In addition, this rearrangement did not take place with strained 2-vinyl aziridines, due to competitive ring opening of the intermediate zwitterion **2** by the solvent,[9] a result that casts doubt on the possible use of a strained four-membered ring as a substrate. When starting from azetidines, this ring expansion would give access to unsaturated azocanes, a class of nitrogen heterocycles that has been little studied, probably due to the well-known inherent difficulty in forming such medium-sized heterocycles.[10] Despite their restricted methods of preparation,[11] functionalized azocanes have been used as useful intermediates for the preparation of pyrrolizidinic alkaloids, through ring contraction,[12] or as flexible scaffolds for the preparation of new iminocyclitols.[13]

In order to test this reaction, a set of 2-alkenyl azetidines was selected (see Table 2 below). These compounds were prepared by previously described procedures[6] involving either (i) Swern oxidation of the corresponding 2-hydroxymethyl azetidine, followed by Wittig olefination of the resulting aldehyde (compounds **5**, **6** and **9**–**12**) or (ii) formation of a ketone moiety at C-2, resulting from the reaction of the corresponding 2-cyano azetidine with a Grignard reagent,[14] followed by Wittig olefination (compounds **13** and **14**). All these syntheses occurred with fair yields for unreported compounds **5**, **6**, **9**, **13** and **14**. As an illustration, Scheme 2 highlights the synthesis of stereoisomers **5** and **6**, which were produced with low selectivity, but could be conveniently separated by flash chromatography.



Scheme 2 Example of the preparation of 2-alkenyl azetidines

We first examined the nature of the electrophilic partner and the reaction conditions as regards to the feasibility of this ring expansion. Thus, compound **9** was reacted with an array of Michael acceptors in dichloromethane or, when higher refluxing temperature was desired, 1,2-dichloroethane (Table 1, entries 1–6). This first set of experiments demonstrates the feasibility of this ring expan-

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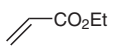
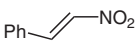
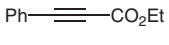
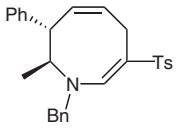
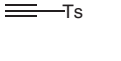
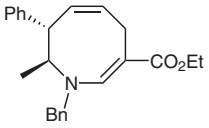
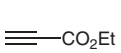
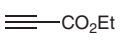
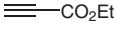
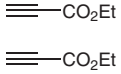
Table 1 Optimisation of the Reaction Conditions with Azetidine **9**

Entry	Electrophile	Conditions				Product [Yield(%)][c]
		Equiv	Solvent	Temp	Time (h)	
1		5	DCE[b]	reflux	24	No reaction
2		1	DCE[b]	reflux	24	No reaction
3		1	DCE[b]	reflux	24	No reaction
4	DMAD[a]	5	neat	r.t.	24	No reaction
5		1	CH_2Cl_2	r.t.	24	 **7** (23)
6		5	CH_2Cl_2	r.t.	24	 **8** (28)
7		5	CH_2Cl_2	reflux	72	**8** (28)
8		5	THF	reflux	72	**8** (26)
9		2	DCE	MW	12	**8** (25)
10		1.5	neat	r.t.	72	**8** (54)
11		1.5	MeCN	r.t.	72	**8** (57)
12		2	EtOH	r.t.	5 d	**8** (82)

[a] DMAD = Dimethyl acetylenedicarboxylate.
[b] No reaction was observed in CH_2Cl_2 at r.t.
[c] Yield refers to isolated pure product.

sion but shows that its scope is restricted to activated monosubstituted alkynes (ethyl propiolate or ethynyl *p*-tolyl sulfone, entries 5 and 6). Since no other products could be isolated from the crude reaction mixtures, the moderate yields obtained for **7** and **8** were attributed to competitive polymerization. Encouraged by these findings, optimization of the reaction conditions using the reaction of **9** with ethyl propiolate was next undertaken (entries 7–12). These data demonstrate that neither using a large excess of electrophile, nor heating the reaction mixture, increased the yields. Instead, running the reaction in more polar solvents (or without any solvent) had a clear effect on the efficiency of the reaction, and ethanol (entry 12) was finally found to be the optimal solvent for this ring enlargement. In this solvent, the reaction occurred smoothly, and the product was isolated in 82% yield.

Next, the scope of this reaction with various starting 2-alkenyl azetidines was studied. The choice of substrates was made with the aim of varying two main parameters in the reacting azetidines: the substitution of the alkene, and the substitution of the azetidine ring, including the effect of the relative configuration of the substituents. As will be discussed in the following paragraphs, these parameters proved to be crucial for the success of this ring enlargement. Thus, the compounds depicted in Table 2 were tested as substrates, using these optimized conditions (2 equiv of activated alkyne, EtOH, r.t.).

Back et al. nicely demonstrated that this reaction goes through an intermediate zwitterion **2**, the formation of which is the rate-limiting step in the case of 2-vinyl piperidines.[9] In our experiments, the low yields obtained with disubstituted alkenes **13**, **14**, **5** and **6** (entries 8–11) are due to competitive opening of this intermediate zwitterion by ethanol, in an S_N2' fashion. With these substrates, the additional substituent on the double bond probably causes severe steric congestion during the electrocyclic [3,3]-sigmatropic rearrangement as shown in Scheme 3 for substrate **14** (entry 9). This results in a slower process, thus promoting competitive opening. Furthermore, it raises the question of whether protonation of the zwitterion by ethanol can become competitive. In this case, the rearrangement would result from a cationic 3-aza-Cope rearrangement, whose activation energy, though being lower than for 3-aza-Cope,[15] is probably higher than that required for the zwitterion (Scheme 3).

Table 2 Scope of the Ring Enlargement with Various Azetidines[a]

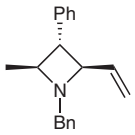
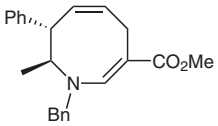
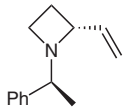
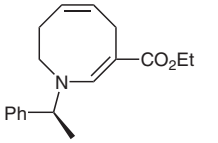
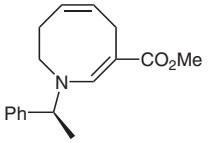
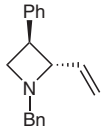
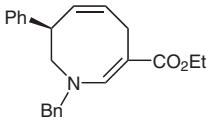
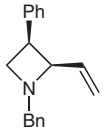
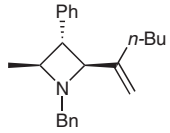
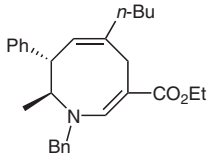
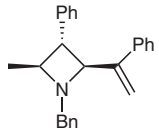
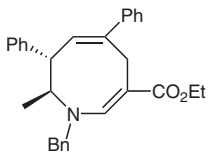
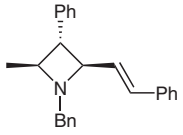
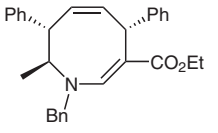
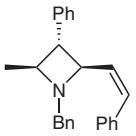
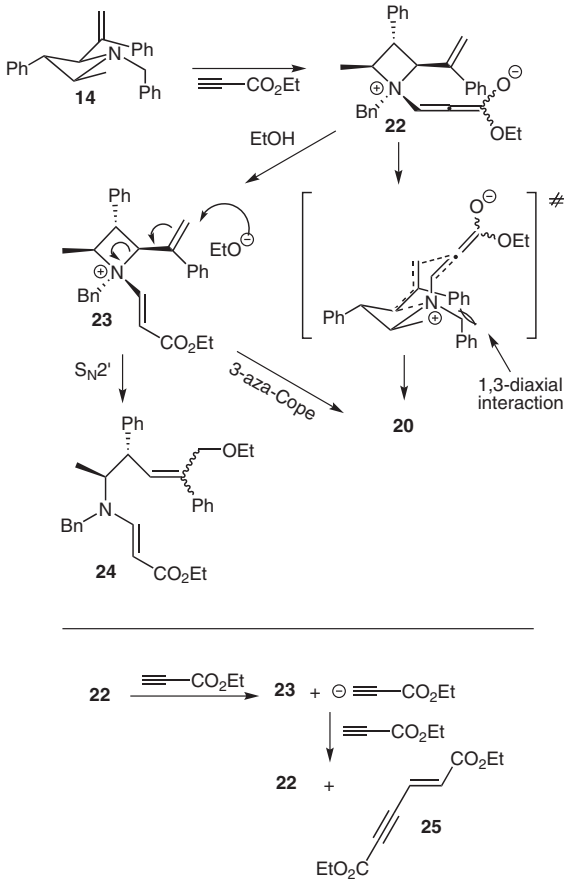
Entry	Starting azetidine	Time (h)	Product	Yield (%)[d]
1	 **9**	5 d	**8**	82
2[b]	**9**	4	**7**	70
3[c]	**9**	24	 **15**	77
4	 **10**	12	 **16**	98
5[c]	**10**	5	 **17**	76
6	 **11**	24	 **18**	45
7	 **12**	24	No azocane isolated[e]	–
8	 **13**	24	 **19**[e]	16
9	 **14**	24	 **20**[e]	38
10	 **5**	6 d	 **21**[e]	8

Table 2 Scope of the Ring Enlargement with Various Azetidines[a] (continued)

Entry	Starting azetidine	Time (h)	Product	Yield (%)[d]
11	 **6**	6 d	No azocane isolated[e]	–

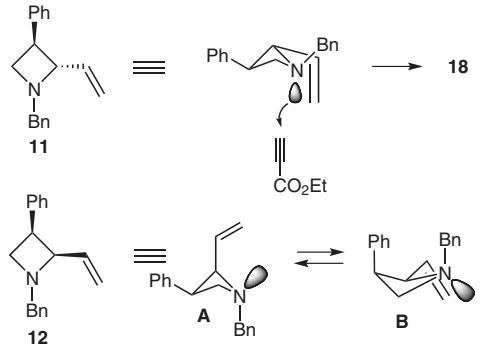
[a] Unless stated, ethyl propiolate was used as the electrophile.
[b] Ethynyl *p*-tolyl sulfone was used in this experiment.
[c] Methyl propiolate was used in this experiment.
[d] Yields refer to isolated pure product.
[e] Products resulting from the opening of the intermediate zwitterion were produced and isolated (see text).

It should be noted that attempts were made to optimize the yield of **20** by using non-protic solvents (CH_2Cl_2, THF, MeCN), in the hope of suppressing the possible protonation of the zwitterion by the solvent. In these experiments, the yield could not be improved, and the enyne **25**, resulting from the deprotonation of ethyl propiolate by the zwitterion,[16] followed by conjugate addition was isolated in some cases. This highlights the basic nature of the zwitterion.



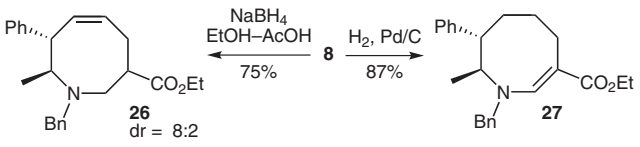
Scheme 3 Identification of the competitive side-reactions in the case of 1,1- or 1,2-disubstituted alkenes

The relative configuration of the stereocenters in the reacting azetidine is also an important parameter. Thus, 2,3-*trans*-vinyl azetidine **11** gave the expected ring expansion product **18** (entry 6), while its 2,3-*cis*-isomer **12** only gave competitive opening (entry 7). This can be understood by an analysis of the conformational preference of the reacting azetidines: **11** indeed reacts through its low-energy 1,2,3-triequatorial conformer to give a zwitterion in which the reacting centers for the ensuing sigmatropic rearrangement are well disposed in a *cis*-relationship. On the other hand, in azetidine **12**, among the four possible conformers and invertomers, only 1,2- or 1,3-diaxial conformers **A** and **B** can lead to a suitable disposition of the substituents for ring enlargement (Scheme 4). If their population is low, and the first step is not reversible, then ring opening becomes the prominent process.



Scheme 4 The relative configuration of the stereocenters in the starting azetidine is a crucial parameter

The unsaturated azocanes produced in this ring expansion are particularly suited for further functionalization since both alkenes could be reduced in a chemoselective and diastereoselective manner. For example, upon treatment with sodium borohydride in the presence of acetic acid, clean reduction of the enaminoester moiety in **8** was achieved, leading to **26** with fair diastereoselectivity. On the other hand, hydrogenation led selectively to **27** (Scheme 5).



Scheme 5 Chemo and diastereoselective reduction of **8**

In summary, we have reported the first example of a four- to eight-membered ring expansion of a nitrogen heterocycle. The scope of this rearrangement is quite narrow and is restricted to 2-vinyl azetidines in which the conformational equilibrium favours a conformer able to produce an intermediate zwitterion in which a *cis*-relationship is observed between the vinyl moiety and the produced allenolate. If these prerequisites are observed, then the ring expansion occurs uneventfully, leading to unsaturated azocanes[17] that can be further functionalized.

Acknowledgment

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(17) **Typical Procedure for the Ring Expansion of 2-Alkenyl Azetidines into Unsaturated Azocanes**: The following procedure for the preparation of azocane **8** is representative. To a solution of azetidine **9** (800 mg, 3.03 mmol) in absolute EtOH (30 mL), was added in one portion, ethyl propiolate (0.62 mL, 6.06 mmol). The reaction mixture was stirred for 5 days and concentrated under reduced pressure. The crude residue was purified by flash chromatography (Pentane–Et_2O, 75:25 + 0.1% Et_3N) to afford **8** as a colourless oil (911 mg, 82%).
Compound **8**: R_f = 0.30 (Pentane–Et_2O, 75:25); $[\alpha]_D^{25}$ –957 (*c* 0.95, CH_2Cl_2); ^{1}H NMR (300 MHz): δ = 0.95 (d, *J* = 6.7 Hz, 3 H, Me), 1.17 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 2.95 (dd, *J* = 12.0, 6.5 Hz, 1 H, H7), 3.41–3.60 (m, 2 H, H4), 4.08 (q, *J* = 7.1 Hz, 2 H, OCH_2), 4.27 (d, *J* = 15.8 Hz, 1 H, NCH*H*), 4.43 (d, *J* = 15.8 Hz, 1 H, NC*H*H), 4.64 (m, 1 H, H8), 5.39 (dd, *J* = 11.1, 6.5 Hz, 1 H, H6), 5.56 (m, 1 H, H5), 7.03 (d, *J* = 7.9 Hz, 1 H, Ar), 7.11–7.27 (m, 9 H, Ar), 7.57 (s, 1 H, H2); ^{13}C NMR (75 MHz): δ = 14.6 (CH_3CH_2), 18.7 (CH_3), 25.1 (C4), 53.3 (NCH_2), 56.0, 57.6 (C7, C8), 59.7 (OCH_2), 94.9 (C3), 125.2, 126.8, 127.5, 128.4, 128.5, 128.6, 132.0 (C5, C6, CHAr), 139.1, 141.2 (CqAr), 151.9 (C2), 170.0 (C=O); MS (ESI): *m*/*z* (%) = 385.3 (20) [M + Na^+], 362.2 (100) [M + H^+]. Compound **7**: white solid; mp 74 °C; R_f = 0.25 (Pentane–Et_2O, 75:25); $[\alpha]_D^{25}$ –548 (*c* 3.3, CH_2Cl_2); ^{1}H NMR (300 MHz): δ = 1.07 (d, *J* = 6.5 Hz, 3 H, Me), 2.47 (s, 3 H, Me), 3.02–3.16 (m, 2 H, H4, H7), 3.74 (dd, *J* = 16.2, 7.5 Hz, 1 H, H4′), 4.44 (d, *J* = 15.8 Hz, 1 H, NCH*H*), 4.58 (d, *J* = 15.8 Hz, 1 H, NC*H*H), 4.64 (m, 1 H, H8), 5.24 (m, 1 H, H5), 5.50 (m, 1 H, H6), 7.03 (m, 2 H, Ar), 7.19–7.44 (m, 10 H, Ar), 7.64 (s, 1 H, H2), 7.72 (d, *J* = 6.7 Hz, 2 H, Ar); ^{13}C NMR (75 MHz): δ = 18.7 (CH_3), 21.5 (CH_3), 25.4 (C4), 53.2 (NCH_2), 56.3, 57.7 (C7, C8), 102.5 (C3), 123.2, 125.5, 127.0, 127.2, 127.3, 127.6, 127.8, 128.3, 128.5, 128.7, 128.8, 129.4, 133.0 (C2, C5, C6, CHAr), 138.8, 139.9, 140.6, 142.4 (CqAr), 149.9 (C2); MS (ESI): *m*/*z* (%) = 466.3 (100) [M + Na^+].