

The synthesis of azabicyclo[4.2.1]nonenes by the addition of a cyclopropenone to 4-vinyl substituted 1-azetines—*isomers of the homotropane nucleus*

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Abstract—The conversion of 4-vinyl substituted β -lactams into 4-vinyl substituted 1-azetines and their subsequent reaction with diphenylcyclopropenone (DPP) results in the formation of a highly functionalised 7-azabicyclo[4.2.1]nonene. This heterocyclic system is an isomer of the homotropane (9-azabicyclo[4.2.1]nonene) nucleus, which is the core structure of a class of alkaloid natural products that includes anatoxin-a. The key processes involved are two ring expansions, one of which constitutes a formal [3+2] cycloaddition and the other of which is an unusual aza-Cope (amino-Claisen) [3,3]-sigmatropic rearrangement.
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The homotropane (9-azabicyclo[4.2.1]nonane) nucleus **1** (Fig. 1) is a core component in several important alkaloid natural products¹ such as anatoxin-a **2**^{1b,2} and its synthetic analogues,³ which have a high affinity for the nicotinic acetylcholine receptor (nAChR). Other examples of alkaloids in the homotropane class include the bivalve marine toxin pinnamine **3**,^{2d,4} and bis-homopibatidine **4**,⁵ which is a homologue of the potent analgesic epibatidine.^{1a} In this letter we report an unexpected synthesis of the related 7-azabicyclo[4.2.1]nonene nucleus **5**, an interesting isomer of the 9-azabicyclo[4.2.1]nonene nucleus that is present in anatoxin-a **2**.

Our work began as part of an ongoing series of projects concerned with the synthesis and reactions^{6,7} of β -lac-

tam and β -sultam heterocycles and their use as inhibitors of the serine proteases.^{8,9} As part of this work, we synthesised, by the standard chlorosulfonyl isocyanate to alkene cycloaddition,¹⁰ the known 4-vinyl β -lactams **6**,¹⁰ typically in ~75% yield. Thiation of these β -lactams with Lawesson’s reagent¹¹ was facile, giving 4-vinyl-2-thioxo analogues **7** in 75–90% yield, which were then converted into the corresponding 1-azetines **8a** ($R^1 = R^2 = H$), **8b** ($R^1 = H, R^2 = Me$) and **8c** ($R^1 = R^2 = Me$) in 40–60% yield¹² using a solution of triethyloxonium tetrafluoroborate¹³ (Meerwein’s reagent) in dichloromethane (Scheme 1).

We next sought to use the 1-azetines **8** as a template for cycloaddition reactions in order to produce the bicyclic heterocycles represented by general structure **9** shown

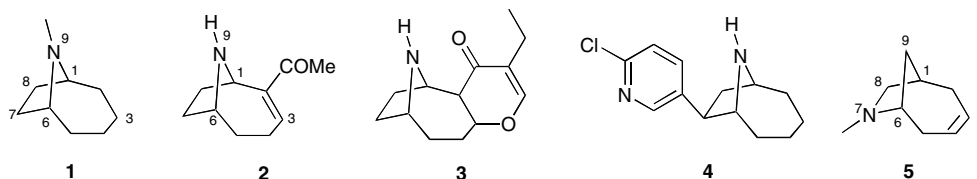
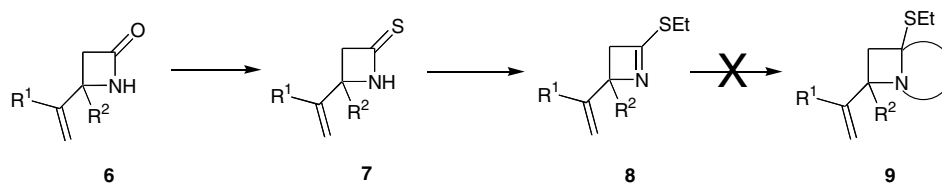


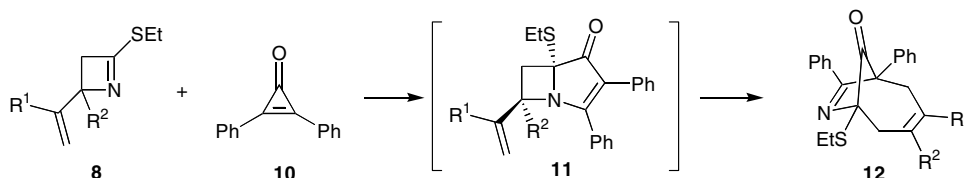
Figure 1. Some important homotropanes **2–4** and 7-azabicyclo[4.2.1]nonene nucleus **5**.

Keywords: β -Lactam; Cyclopropenone; 1-Azetine; Homotropane; Aza-Cope.

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Scheme 1. The synthesis of 4-vinyl-1-azetines **8**.

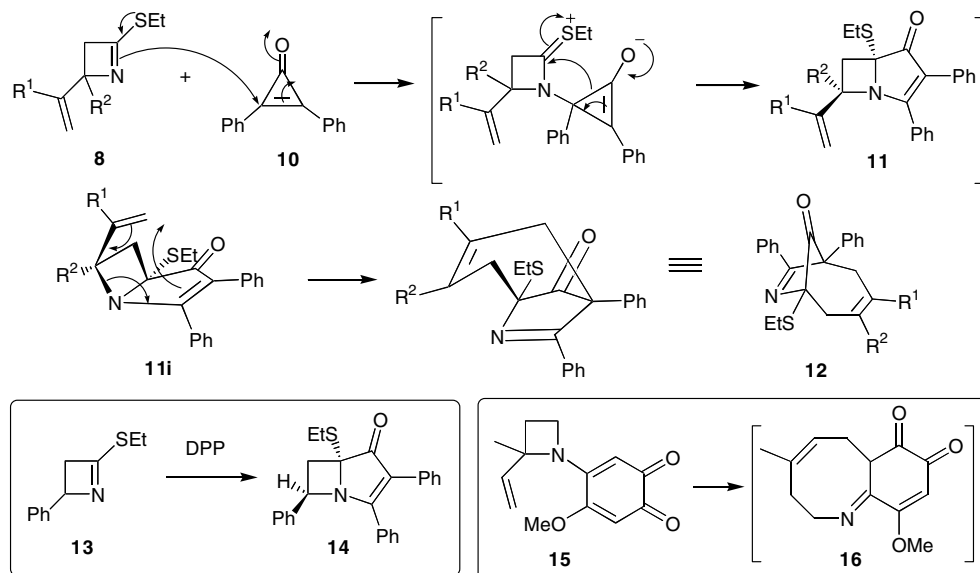


Scheme 2. Synthesis of 7-azabicyclo[4.2.1]nonanes **12**.

in Scheme 1, in order to explore their chemical and biological reactivities. On the basis of the known^{7a,14–16} reactivity of electron rich imines towards diphenylcyclopropenone, we started by investigating the formal [2+3] cycloaddition of 1-azetines **8** with diphenylcyclopropenone **10** (DPP), a reaction which we anticipated would form cycloadducts **11** (Scheme 2). In the event, the products that were isolated from this reaction were not the expected cycloadducts **11**, but were rather the ring expanded 7-azabicyclo[4.2.1]nonanes **12a** ($R^1 = R^2 = H$), **12b** ($R^1 = H, R^2 = Me$) and **12c** ($R^1 = R^2 = Me$), as shown in Scheme 2, isolated in yields of 51–62%.

The structures of these new products were very clear from 1D and 2D NMR studies, which showed, for example, in the case of compound **12a**, the absence of the distinctive vinylic CH_2 expected in compound **11a**, the presence of the $CH_2-CH=CH-CH_2$ linkage of the new ring system, an extremely distinctive quaternary sp^3 car-

bon–phenyl linkage, and a characteristic quaternary sp^3 carbon–ethylthio linkage.^{17,18} A mechanistic rationale for the formation of 7-azabicyclo[4.2.1]nonanes **12** is shown in Scheme 3. We believe that the expected reaction of the 1-azetines **8** with DPP **10** occurs by the mechanism^{14–16} shown in Scheme 3 to give the expected azabicyclo[3.2.0]heptene **11**. The final process in the reaction is an aza-Cope (amino-Claisen) [3,3]-sigmatropic rearrangement as shown in Scheme 3. Aza-Cope rearrangements in such a bicyclic ring system are unprecedented and we believe they are facilitated by strain relief and by the fact that the azabicyclo[3.2.0]heptene ring system has an inherent ‘half-open book’ conformation at the ring junction, as shown in structure **11i**, which allows the vinyl substituent and second alkene to overlap. Such a proposal necessitates that the vinylic and SEt groups in species **11** adopt a *trans* relationship, with the larger SEt group on the less hindered convex face of the molecule. In a bid to demonstrate the validity of such an azabicy-



Scheme 3. Suggested mechanism for the formation of 7-azabicyclo[4.2.1]nonanes **12**.

clo[3.2.0]heptene intermediate, we reacted the 1-azetine **13** with DPP and obtained the expected adduct **14** in high yield, an adduct that cannot undergo [3,3]-sigmatropic rearrangement, and which showed the expected *trans* relationship between the Ph and SEt groups (strong NOE enhancement between the SEt and *cis*-H). Monocyclic α -vinyl-azetidino systems, exemplified by compound **15** (Scheme 3), have been shown by other workers¹⁹ to undergo strain-promoted facile aza-Cope (amino-Claisen) [3,3]-sigmatropic rearrangement to give azocines **16**, after opening of the four-membered ring, lending credence to our proposition of strain-relief.

In summary, a very short entry to the 7-azabicyclo[4.2.1]nonane nucleus has been reported from the reaction of 4-vinyl-1-azetines with a cyclopropenone. The 7-azabicyclo[4.2.1]nonane nucleus is an interesting analogue of the 9-azabicyclo[4.2.1]nonane system that is present in the important alkaloids anatoxin-a, pinnamine and bis-homoepibatidine.

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- All new compounds gave satisfactory ¹H/¹³C NMR spectra, mass spectra and HRMS/microanalysis.
- Typical experimental and spectroscopic details for compounds **12**: To a stirred solution of 2-ethylthio-4-vinyl-1-azetine **8** (0.1–0.5 g) in anhydrous acetonitrile (10–20 mL) was added, with stirring and under an atmosphere of dry nitrogen, a solution of diphenylcyclopropenone (1.0 M equiv) in acetonitrile (5–20 mL). The mixture was stirred at room temperature until the reaction was complete (one week) and the solvent was removed by rotary evaporation. The crude product was purified by flash silica column chromatography (petroleum ether–ethyl acetate/2:1). As an example, 6-ethylthio-3,4-dimethyl-1,8-diphenyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one **12c** was obtained as a dark orange solid (0.271 g, 62% yield), mp 177–181 °C, from 1-azetine **8c** (0.195 g, 1.16 mmol) and DPP (0.240 g, 1.16 mmol). δ_{H} (400 MHz, CDCl₃): 1.28 (3H, t, *J* = 7.4, CH₃CH₂), 1.695 (3H, s, Me), 1.700 (3H, s, Me), 2.55 (1H, dq, *J* = 11.3, 7.4, CH₂CH₃), 2.66 (1H, dq, *J* = 11.5, 7.5, CH₂CH₃), 2.76 (1H, d, *J* = 16.8, CH₂CMe), 2.85 (1H, d, *J* = 16.8, CH₂CMe), 2.97 (1H, d, *J* = 16.3, CH₂CMe), 3.22 (1H, d, *J* = 16.2, CH₂CMe), 7.14 (2H, dd, *J* = 6.5, 1.6, 2 × ArH), 7.23–7.30 (3H, m, 3 × ArH), 7.32–7.39 (3H, m, 3 × ArH), 7.66 (2H, dd, *J* = 7.5, 1.0, 2 × ArH). δ_{C} (100 MHz, CDCl₃): 14.3 (Me), 23.3 (Me), 23.6 (Me), 23.8 (CH₂), 42.5 (CH₂), 46.0 (CH₂), 63.5 (q), 83.0 (q), 124.0 (q), 125.2 (q), 127.1 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 129.0 (CH), 130.8 (CH), 132.2 (q), 136.7 (q), 173.7 (q), 215.1 (q). ν_{max} (thin film, cm⁻¹): 3057 (m), 2986 (m), 2930 (m), 1737 (s), 1566 (m), 1446 (s), 1374 (m), 1266 (s), 1245 (s), 1046 (m), 739 (s), 700 (s). EI⁺ mass spectrum

(*m/z*, %): 376 ([M⁺+1], 5%), 375 ([M]⁺, 10%), 347 (28%), 318 (45%), 293 (50%), 264 (100%), 178 (74%), 105 (25%), 91 (40%), 77 (48%), 41 (38%). HRMS [CI+(NH₃)]: Found [M+H⁺] 376.1730, C₂₄H₂₆NOS requires 376.1732.

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