Application of Electrophile-mediated Cyclisations to the Synthesis of the Hexahydroazepine Ring System

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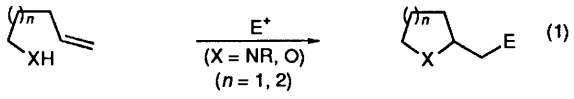
Allenic oxime **6** undergoes efficient Ag^{I}-catalysed cyclisation to give the hexahydroazepine-based nitrone **7**; this reactive 1,3-dipole was subsequently trapped by styrene and *N*-methylmalemide to give the adducts **8** and **9** respectively.

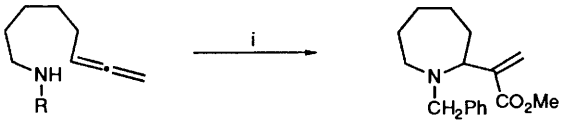
Electrophile-mediated heteroatom cyclisations of the type shown in eqn. (1) have been extensively applied to the synthesis of a host of 5- and 6-membered rings.[1] However, examples[2] of the application of this methodology to the construction of 7-membered heterocyclic rings are rare despite the flexibility that is inherent in this chemistry in terms of the nature of the π-system, the electrophile, and the heteroatom nucleophile.† Although the problems associated with forming medium rings are well recognised, significant success has, nevertheless, been achieved by the application of conventional intramolecular alkylation reactions to this area of heterocyclic synthesis.‡ These alkylation processes do, however, generally involve



(1)

nucleophilic displacement at a primary centre whereas the ring-closure step shown in eqn. (1) is to a more hindered secondary site. Our interest in medium-sized rings has focused on the synthesis of the hexahydroazepine skeleton *via* the application of an electrophile-mediated cyclisation sequence and we have concentrated on substrates incorporating an allene residue which represents both a reactive and synthetically versatile π-component.§

The *N*-benzyl and *N*-(*p*-tolyl)sulphonyl allenic amines **1** and **2**, which are readily available¶ using conventional methods, were examined initially (Scheme 1). Attempts to effect

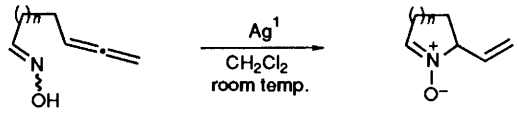


1; R = CH_2Ph
2; R = SO_2Tol **3**

Scheme 1 *Reagents and conditions:* for R = CH_2Ph; i, $PdCl_2(PhCN)_2$, CO, MeOH, Et_3N, room temp., 3 h; 23%.

cyclisation of **1** using Ag^{I}-catalysis ($AgOSOCF_3$, CH_2Cl_2), conditions which have been extensively applied to the synthesis of 5- and 6-membered rings, were all unsuccessful. However, reaction of **1** using Pd^{II} as the electrophilic trigger, in the presence of CO and MeOH (carbonylating conditions), gave the desired 2-alkenyl-substituted hexahydroazepine **3**. Although the yield of this reaction was modest (23%), this observation is significant given the lack of success previously reported for the construction of nitrogen-containing heterocycles based on cyclisations involving alkenyl substrates.[2b] The application of this allene-based methodology to the synthesis of 7-membered rings is, nevertheless, limited and the less nucleophilic sulphonamide **2** was inert towards cyclisation in the presence of both Ag^{I} and Pd^{II}.

In an attempt to improve the efficiency of this electrophile-mediated process we have exploited the high reactivity of the allene π-bond which allows for the use of a wider range of nitrogen nucleophiles than can be accommodated in the corresponding alkenyl-based substrates. For example, the allenic oximes **4** undergo facile Ag^{I}-catalysed cyclisation to give isomerically pure cyclic nitrones **5** in high yield[7] eqn. (2).



(2)

4a; *n* = 1
4b; *n* = 2

5a; *n* = 1
5b; *n* = 2

This Ag^{I}-catalysed reaction fails for alkenyl-containing substrates, although Grigg has, in a complementary process, successfully generated nitrones by the intramolecular *N*-alkylation of oximes using either epoxides or electron-deficient alkenes.[8]

We felt that the facile allene-mediated cyclisations observed in our earlier work would, together with the conformational constraint afforded by the oxime functionality, provide a more efficient route to the hexahydroazepine skeleton and overcome some of the problems encountered with **1** and **2**.

The successful implementation of this methodology is shown in Scheme 2. The allenic oxime **6** (1:1 mixture of *E*- and *Z*-isomers) was treated with $AgBF_4$ ($ClCH_2CH_2Cl$, 80 °C), in the presence of styrene. Cyclisation of **6** took place smoothly to give the nitrone **7** and although this species was not isolated, the corresponding 1,3-dipolar cycloadduct **8** was obtained in 20% yield.[9]

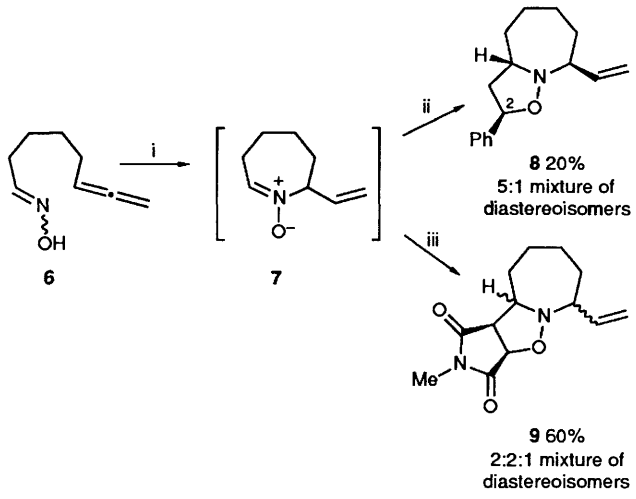
The low yield of **8** appears to be a reflection of the 1,3-dipolar cycloaddition step between the intermediate nitrone **7** and

† For alternative methods to generate medium-sized rings by intramolecular alkylation of allylic halides that also lead *inter alia* to 2-alkenyl heterocyclic products.[3]

‡ Intramolecular alkylation of amine derivatives with primary alkyl halides provides an efficient entry to medium ring *N*-heterocycles although the products of these reactions do lack the synthetic flexibility offered by cyclisations of the type shown in eqn. (1).[4]

§ For leading references to earlier heterocyclisation studies involving allenes, see: refs. 1*a* and 5.

¶ Reduction of hexa-4,5-dienenitrile[6] with Bu^{i}_2AlH followed by reductive amination ($PhCH_2NH_2$–$NaBH_4$) of the resulting aldehyde gave **1**. Reduction of this nitrile ($LiAlH_4$) gave the corresponding amine in good yield which was converted into the sulphonamide **2** using $ClSO_2Tol$ and pyridine. The oxime **6** was obtained by extending previously developed methods.[7] All new compounds have been characterised by standard spectroscopic methods and either elemental analysis or high resolution mass measurement.



Scheme 2 *Reagents and conditions:* i, $AgBF_4$, $ClCH_2CH_2Cl$, room temp.; ii, styrene, 80 °C, 12 h; iii, *N*-methylmaleimide, 80 °C, 9 h

styrene. A more realistic indication of the efficiency of the key cyclisation step was obtained using a more reactive dipolarophile. When the Ag^I-catalysed cyclisation of the oxime **6** was carried out in the presence of *N*-methylmaleimide, a 60% *isolated* yield of cycloadducts **9** was obtained, as a 2:2:1 mixture of three isomers. Furthermore, separation of the *E*- and *Z*-isomers of **6** was unnecessary since *Z*-**6** undergoes facile isomerization under the reaction conditions. Attempts to isolate and characterise the nitrone **7** have failed but this was not entirely unexpected given the relative instability of **5b** when compared to **5a**; this latter nitrone can be readily isolated and purified by flash chromatography.

In summary, electrophile-mediated cyclisations can, under certain circumstances, be applied to the synthesis of the hexahydroazepine skeleton. The problems normally associated with the formation of 7-membered rings using this strategy have been efficiently overcome by exploiting the reactivity of the allene π-bond combined with the favourable conformational constraint associated with the oxime group. Future work in this area will concentrate on the extension of this methodology to include more highly substituted allenic substrates and this is currently underway.

Acknowledgements

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9 The stereochemistry of the major styrene cycloadduct is as shown in **8** and was established by nOe studies. This corresponds to approach of the dipolarophile in an *exo* mode to the less hindered face of nitrone **7** and is consistent with earlier results.[7] The minor isomer of **8** corresponds to the *endo* isomer, *i.e.* epimeric at C-2, the phenyl-bearing centre. Given the lack of selectivity observed, the relative stereochemistry of the *N*-methylmaleimide cycloadducts **9** have not been unambiguously established.

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