Cyclization Reactions Terminated by Enamides and Enecarbamates

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The formation of five- and six-membered rings using cyclization reactions terminated by enamides and enecarbamates is described.

As part of our programme to develop general methods for the synthesis of azacyclics we have explored the use of enamides and enecarbamates as cyclization terminators for cyclization reactions. Enamides and enecarbamates are reported to react with highly electrophilic reagents such as acylium ions, however, their use as terminators in cyclization reactions has been overlooked to our knowledge.[1] This may be due to the fact that upon cyclization with an electrophile, a highly reactive acyliminium ion would be formed. This electrophilic intermediate might then initiate undesired side reactions. Research in our laboratory has shown quinone methides to be well behaved cyclization terminators,[2] and we elected to explore cyclizations with this initiator that form five- and six-membered rings. With the success of our research, this highly functionalized terminator should find use with other initiators.

The proposed cyclization requries the selective activation of a quinone methide with a Lewis acid in the presence of the nitrogen containing terminator (enamide or enecarbamate). At this stage, it was unclear if an enamide or enecarbamate would be reactive enough to capture the quinone methide prior to Lewis acid mediated decomposition.[3] The results of our study to test the feasibility of cyclizations with endocyclic and exocyclic enamides and enecarbamates are described herein.

Oxidation of phenol **1** to quinone methide **2** was accomplished with Ag_2O[4] (Scheme 1).† Treatment of **2** with $ZnCl_2$ afforded cyclized enecarbamate **4** in 85% yield and hemiaminal **5** in 5% yield. Compound **5** must arise *via* addition of water to the initially formed acyliminium ion **3**. Despite attempts to remove the water formed in the oxidation, **5** was always observed as a minor by-product in the reaction.‡ In spite of this, the carbon–carbon bond formation occurs in high yield.

We next turned our attention to the 5-*exo-trig*-cyclization shown in Scheme 2. Oxidation of phenol **6** to quinone methide **7** followed by treatment with $BF_3{\cdot}OEt_2$ afforded **9** in 70% isolated yield as a single diastereoisomer (mixture of amide

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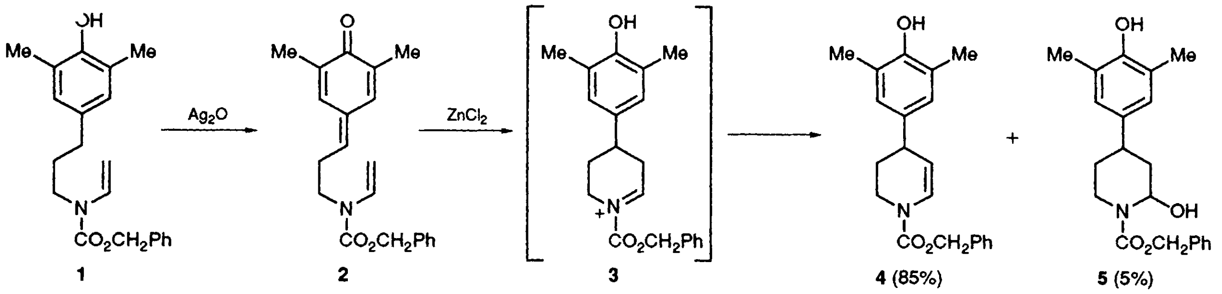
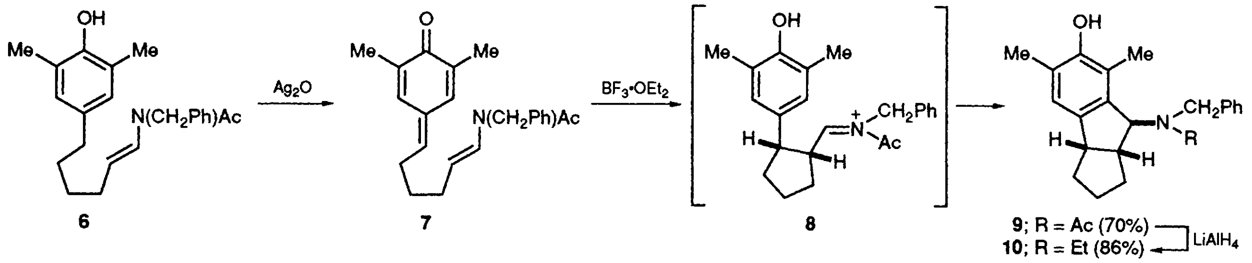
† All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR, mass and high-resolution mass spectroscopy.

‡ Failure to dry the solution of quinone methide **2** resulted in the formation of **5** as the major product.



Scheme 1



Scheme 2

rotational isomers at 25 °C).§ Reduction of **9** (LiAlH$_4$, 86%) afforded amine **10** for characterization. The stereochemistry was assigned on the basis of ^{1}H NMR coupling constants. The formation of **9** must result from the trapping of acyliminium ion intermediate **8** by the electron rich aromatic ring five centres away. This remarkable reaction forms three new stereogenic centres with >95% diastereoisomeric excess (d.e.).

In summary, the 5-*exo-trig*-cyclization of an enecarbamate and the 6-*endo-trig*-cyclization of an enamide onto a quinone methide afforded cyclized products in high yields, and in the case where stereoisomers were possible, excellent stereoselectivity. Based on our results, both enamides and enecarbamates should find application as terminators in cyclization reactions with a wide range of initiators. The scope and limitations of cyclization reactions with this highly functionalized terminator and the application of the methodology to the synthesis of alkaloids will be reported in due course.

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3 The loss of an allylic hydrogen to afford a styrene is a common reaction upon subjecting a quinone methide to a Lewis acid. See reference 2(*c*) and references cited therein.
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§ When ZnCl$_2$ was employed as the Lewis acid the styrene corresponding to **7** was the major product of the reaction.