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1,7-Electrocyclisations of stabilised azomethine ylides

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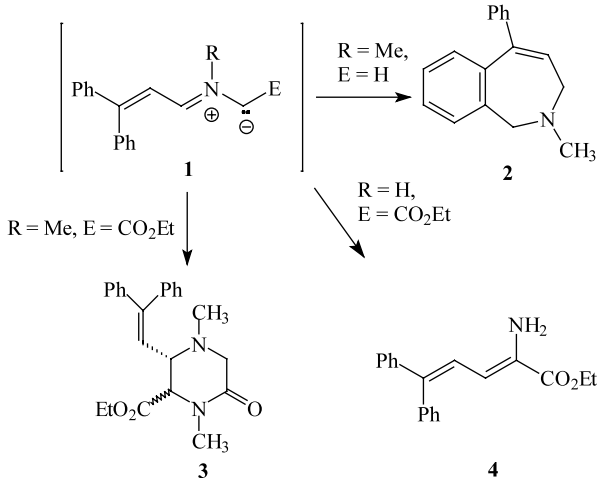
Abstract—Ester-stabilised α,β:γ,δ-unsaturated azomethine ylides **9** were generated by the deprotonation method from isoquinolinium salts **8**. 1,7-Electrocyclisation of these dipoles followed by a 1,5-hydrogen shift, gives tetrahydro[5,6]azepino[2,1-*a*]isoquinolines **10**. © 2003 Elsevier Science Ltd. All rights reserved.

The 1,3-dipolar cycloaddition reaction is one of the most simple approaches for the construction of five membered heterocyclic rings.[1] There are, however, many other synthetically useful reactions of these dipoles, including the 1,5- and 1,7-electrocyclic[2,3] ring closure of appropriately substituted dipolar systems. Recently, we[4] and others[5] published the first examples of the 1,7-electrocyclisation of non-stabilised azomethine ylides with α,β:γ,δ-unsaturation.

During these and further studies we have found significant differences between the reactivity of α,β:γ,δ-unsaturated, non-stabilised ylides **1** (E = H) and α,β:γ,δ-unsaturated, ester-stabilised azomethine ylides **1** (E = CO_2Et). The former dipoles react via a 1,7-electrocyclisation,[6] followed by a [1,5]-hydrogen shift to give dihydrobenzazepines **2**, whilst the latter give other products (**3** or **4**) via novel rearrangements (Scheme 1).[7,8] As a continuation of these studies we have now examined the reactivity of some α,β:γ,δ-unsaturated, ester-stabilised azomethine ylides **9** generated by deprotonation of imminium salts **8**. The synthesis of precursors was carried out according to the Bischler–Napieralski procedure[9] by cyclisation of amide **6** in the presence of $POCl_3$ that resulted in the formation of 3,4-dihydroisoquinolines **7**. Subsequent reaction with bromoalkyl derivatives in anhydrous ether gave the quaternary salts **8a–d** (Scheme 2).



Scheme 1.

Reacting the isoquinolinium salts **8a–d** with triethylamine at ambient temperature, in dry ethanol leads to the formation of 8-substituted-2,3-dimethoxy-13-phenyl-5,6,8,14*a*-tetrahydro[5,6]azepino[2,1-*a*]isoquinolines **11a–d** via azomethine ylide intermediates **9a–d**. Compounds could be isolated by a simple filtration in moderate to good yields. In this reaction the azomethine ylides were produced by dehydrohalogenation of the isoquinolinium salts,[10] which leads via a 1,7-electrocyclisation reaction to the azepine **10** and finally by a [1,5]-hydrogen shift to the products **11a–d**. The stereochemistry of tetracycles **11a–d** was deduced by NOE studies (Scheme 3).

In summary, we have demonstrated the first 1,7-electrocyclisation of electron-withdrawing group stabilised azomethine ylides (**11a** and **11c**), while the explored reaction sequence provides a useful route to the tetrahydro[5,6]azepino[2,1-*a*]isoquinoline ring system.

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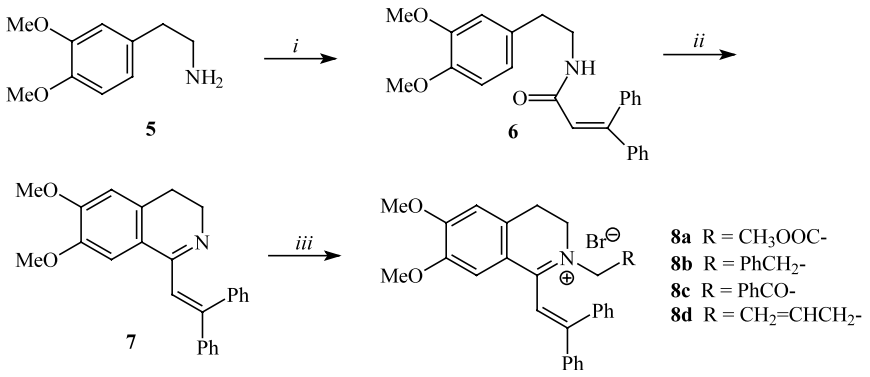
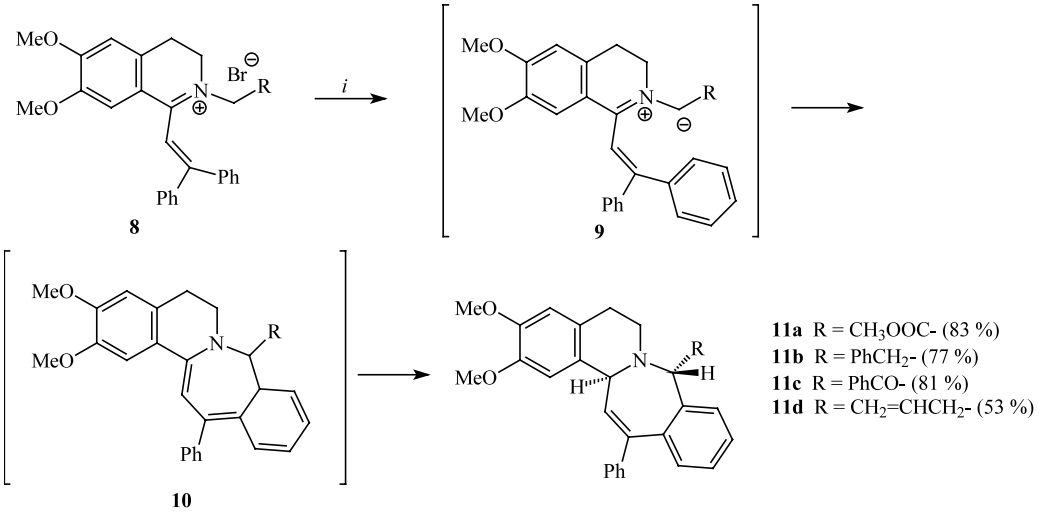


Scheme 2. *Reagents and conditions*: (i) $Ph_2C{=}CHCOCl$, NaOH, Et_2O, H_2O, rt (88%); (ii) $POCl_3$, toluene, reflux (72%); (iii) RCH_2Br, Et_2O, rt (95–100%).



Scheme 3. *Reagents and conditions*: (i) Et_3N, EtOH, rt.

Acknowledgements

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