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An investigation of the scope of the 1,7-electrocyclization of α,β:γ,δ-conjugated azomethine ylides

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ABSTRACT

Substituents on the diene component have little influence on the periselectivity of the cyclizations of α,β:γ,δ-conjugated azomethine ylides, with 1,7-electrocyclizations predominating. In some cases, subtle changes to these substituents can, however, influence the product formed, through their effect on the relative energies of the transition states for the 1,5- (6π) and 1,7-electrocyclization (8π) processes. The most striking changes in periselectivity occur for phenylethenyl-substituted azomethine ylides **3d**–**f**, which can give either a pyrroline **4d**,**f** or dihydrobenzazepine **6e**, depending upon the alkene configuration.

1. Introduction

Azomethine ylides, e.g., **3**, Scheme 1, can be used in the preparation of a range of heterocycles through 1,3-dipolar cycloadditions,[1] 1,5-electrocyclizations,[2] or 1,7-electrocyclizations,[3,4] and routes to these versatile intermediates include the decarboxylation of iminium salts,[5] the ring-opening of aziridines,[6] and the 1,2-prototropy of α-imino esters.[7] In continuation of our previous studies on these allyl anion type 1,3-dipoles, we describe here an investigation of the scope of the 1,7-electocyclization of α,β:γ,δ-conjugated azomethine ylides **3**. In all cases, the azomethine ylides **3** in this study were generated by the decarboxylation of an iminium salt **2** formed by the condensation of an aldehyde **1** and sarcosine (*N*-methylglycine), Scheme 1.

2. Results and discussion

Generation of the (*E*)-azomethine ylides **3a**–**c**, from the corresponding aldehydes **1a**–**c**, led to the expected formation of the pyrrolines **4a**–**c** via a 1,5-electrocyclization, Scheme 2 (pyrrole **5** was obtained as a minor product of the cyclization of azomethine ylide **3a**). Isomerization of the double bond, from (*E*)-**3c** to (*Z*)-**3c′**, and subsequent 1,7-electrocyclization onto the aryl ring, was only observed for the 4-chloro derivative **3c**, from which a minor amount of the dihydrobenzazepine **6c** was also obtained.

The 1,7-electrocyclization of the azomethine ylide **3e**, in which the configuration of the β-phenylethenyl group is (*Z*), gave the dihydrobenzazepine **6e**. Intriguingly, the azomethine ylides **3d**,**f** in which only the configuration of the β-phenylethenyl substituent has changed, to (*E*), were found to undergo 1,5-electrocyclization, giving the pyrrolines **4d**,**f** in good to excellent yield, Scheme 3.

As can be seen from Fig. 1, the (*E*)-configuration of the phenylethenyl substituent results in a greatly reduced separation between the methylene terminus of the azomethine ylide **3d** and the quaternary carbon to which it cyclizes in a 1,5-electocyclization (6π), resulting in a dramatically lower energy barrier for this process and a change in the periselectivity, to give the pyrroline product **4d** of a 1,5-electrocyclization. Molecular modelling of this process, Table 1 and Fig. 2, confirms the similar energy barriers for the 1,7-electrocyclizations of both dipoles (**3d** and **3e**), Fig. 2 (blue); the increased energy barrier for the 1,5-electrocyclization for the (*Z*)-alkenyl substituted dipole **3e**, Fig. 2b (red), resulting in a 1,7-electrocyclization for this reactive intermediate (to give benzazepine **6e**); and the lower energy barrier for the 1,5-electrocyclization

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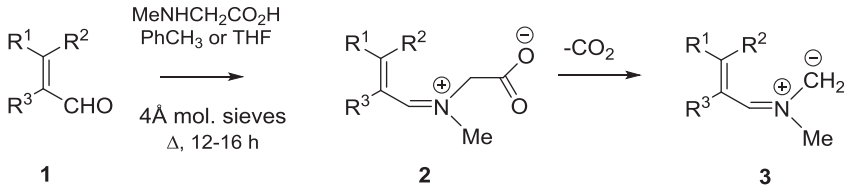
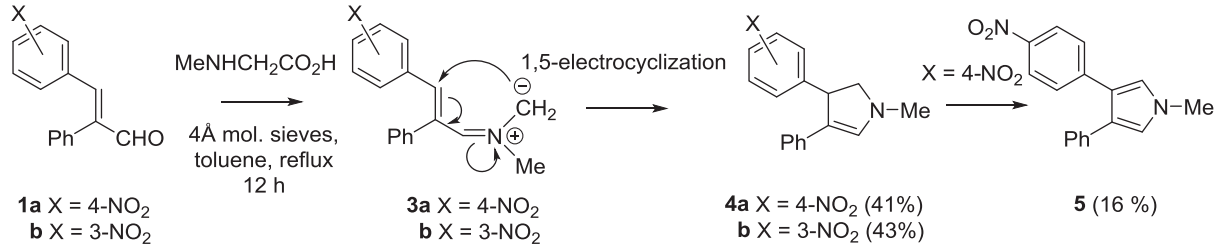
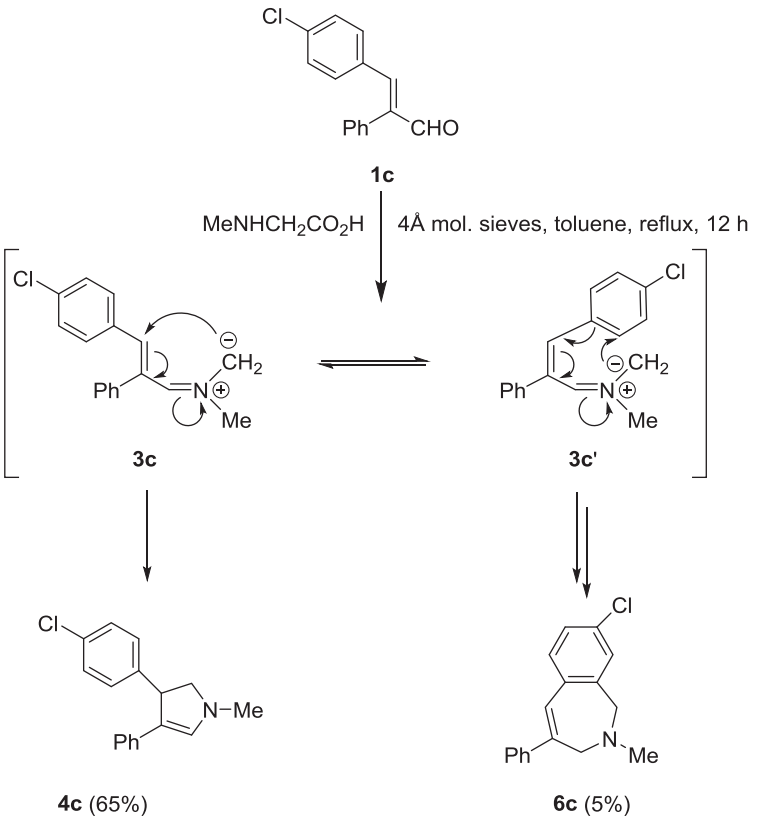


Scheme 1.





Scheme 2.

of the (*E*)-alkenyl substituted dipole **3d**, Fig. 2a (red), resulting in a 1,5-electrocyclization (to give pyrroline **4d**).

Generation of azomethine ylide **3g** (from aldehyde **1g**) again led to the formation of the benzazepine **6g**, while the bromo derivative **3h** (from **1h**) gave a mixture of the benzazepine **6h** and the pyrrole **11** (formed by a 1,5-electrocyclization to the bromopyrroline followed by dehydrobromination), Scheme 4.

The azomethine ylides **3i**–**l** underwent 1,7-electrocyclization to the dihydroazepines **6i**–**l**, with no evidence for the formation of the pyrroline products of a 1,5-electrocyclization, Scheme 5. The azomethine ylide in which the α,β-bond is the 2,3-position of a thiophene ring **3m** also underwent a 1,7-electrocyclization, to give the dihydrothieno[3,2-*c*]azepine **6m**, Scheme 6, as did the azomethine ylides in which this bond is aromatic **3n-u** (to give the dihydro[2] benzazepines **6n**–**u**), Scheme 7. The intermediacy of azomethine ylides in these processes was shown by the trapping of azomethine ylide **3o** (R=Ph) with *N*-phenylmaleimide to give a single diastereoisomer of the cycloadduct **12**, Scheme 8, with the relative stereochemistry being confirmed by the observation of a NOE between H-2a and H-3.

For the azomethine ylide **3v** (containing a (*Z*)-alkene substituent), no electrocyclization was observed, Scheme 9, while the corresponding (*E*)-alkenyl substituted azomethine ylide **3o** gave the dihydro[2]benzazepine **6o** in good yield. The 1,7-electrocyclization of azomethine ylide **3v** is presumably blocked by the bulky *cis*-phenyl group and more rigid unsaturated system