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Observations on the reductive ring opening reactions of alkylidenecyclopropyl ketones promoted by lithium in liquid ammonia

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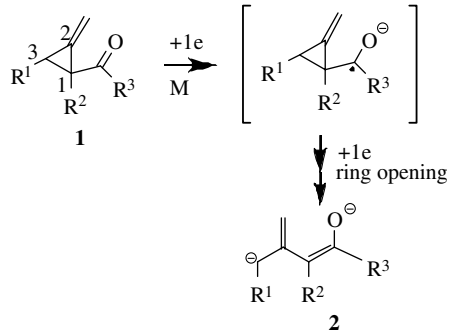
Abstract—The regio- and stereochemical outcome of the reductive ring opening reactions of alkylidenecyclopropyl ketones is a function of substrate structure.

Whilst the cyclopropylcarbinyl homoallylic radical rearrangement has unquestionably served in a wide variety of useful synthetic sequences,[1] ring opening reactions of alkylidenecyclopropane congeners have, by way of contrast, received little attention. For this reason, we therefore elected to examine the sequential single electron transfer induced reduction of some alkylidenecyclopropyl ketones (**1**) as outlined in a general form in Scheme 1.

As implied in Scheme 1, we anticipated that the inclusion of the additional sp^2 centre at C-2 in **1** with its consequential weakening of the C1–C3 bond relative to a simple cyclopropane would favour C1–C3 cleavage and hence the formation of a single regioisomeric enolate dianion intermediate **2**. Such an outcome would also of course be ultimately preferred in terms of allylic stabilisation. From a stereochemical standpoint, however, as illustrated in Figure 1 for the important case of formation of a tetrasubstituted enolate, it was of interest to note that the outcome would be dependent on the preferential collapse of either the *cisoid* or *transoid* conformer of the reactive intermediate. Figure 1 also



Scheme 1.

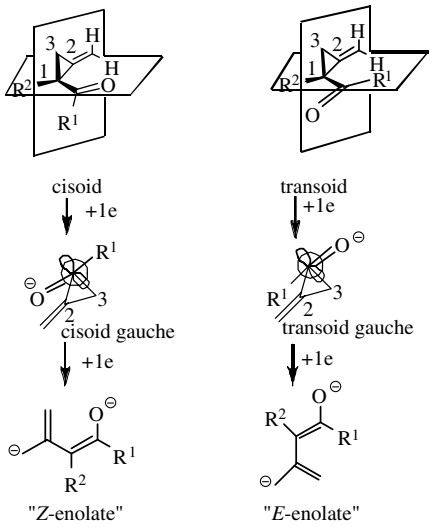


Figure 1.

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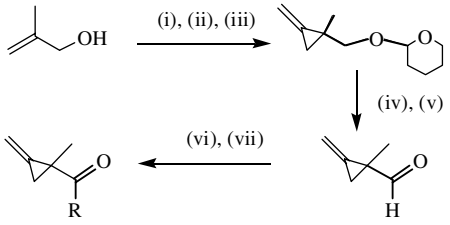


Scheme 2. Reagents and conditions: (i) dihydropyran, HCl 48 h 70%; (ii) *n*BuLi, CH_3CHCl_2, Et_2O, −35 °C (iii) KO^{t}Bu, DMSO, 70 °C, 18 h, 43%; (iv) TsOH, MeOH, 70%; (v) PDC, CH_2Cl_2, rt, 20 h, 95%; (vi) RMgX, Et_2O, 0 °C, R = $nC_{12}H_{25}$, 50%; R = cyclohexyl, 20%; R = Ph, 41%; (vii) PDC, pyridinium trifluoroacetate, CH_2Cl_2, rt, R = $nC_{12}H_{25}$, 93%, R = cyclohexyl, 92%, R = Ph, 80%.

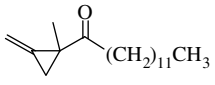
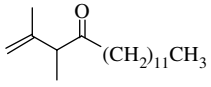
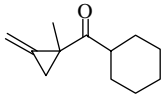
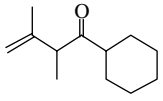
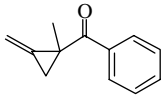
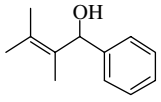
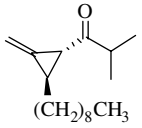
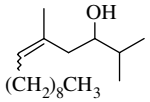
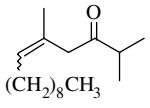
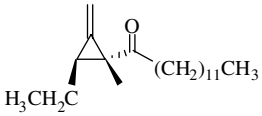
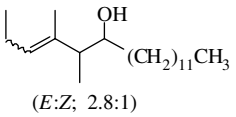
emphasises the intriguing situation that the stereoelectronic requirements for an effective enolate formation through correct orbital alignment of the C1–C3 bond would lead in the first instance, to an 'allylic' intermediate, which does not benefit from overlap with the orthogonal π—cloud of the alkylidene cyclopropane.

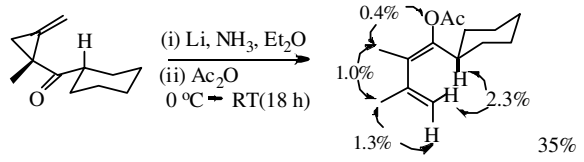
With the above thoughts in mind, a number of simple monocyclic alkylidene cyclopropyl ketones were prepared by the straightforward sequence illustrated in Scheme 2. More highly substituted derivatives were readily accessible in similar fashion from the appropriately substituted isomer of the starting allylic alcohol.

With a selection of appropriate ketones in hand, our attention was then directed towards the reductive ring opening sequence. In the first instance, as a consequence of our own studies in developing tandem radical ring opening reactions of bicyclic cyclopropyl ketones using samarium diiodide,[2] we elected to examine the use of this powerful reducing agent. To our surprise, however, under a range of conditions, complex reaction mixtures were produced. For this reason, we then chose to use the more traditional combination of lithium in liquid ammonia as reductant. The preliminary results for a series of reactions involving the dropwise addition of a solution of the alkylidene cyclopropyl ketone in ether to a solution of lithium in liquid ammonia followed by protic work-up with ammonium chloride are shown in Table 1 and revealed several features of interest.

Thus, whilst the anticipated cleavage of the weaker C1–C3 distal bond was observed for all cases studied, subsequent product evolution is clearly dependent on substrate structure. In particular, whilst the examples shown in entries 1 and 2 yielded the expected β–γ unsaturated ketones, over-reduction to give alcohols can be noted in entries 3–5. This latter phenomenon has been observed previously both by Dauben[3] and by Norin[4] in the lithium ammonia reduction of cyclopropyl ketones and was assumed to arise via further rapid reduction and protonation steps during work-up. For those substrates which possess additional alkyl substituents on the alkylidenecyclopropane ring (entries 4 and 5), it was of interest to note that regiospecific protonation of the allylic anion fragment leading to the more substituted alkene had occurred. In terms of stereoselective trisubstituted alkene formation however, only a

Table 1.

Entry	Substrate	Product(s)	Yield (%)
1			78
2			63
3			48
4			41
			41
5		 (*E*:*Z*; 2.8:1)	59



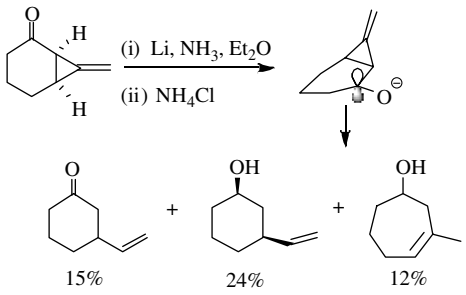
Scheme 3.

modest preference for formation of the *E* isomer was noted. From a mechanistic perspective, the ring opening reaction of the benzoyl substituted alkylidene cyclopropane (entry 3) is certainly the most intriguing, especially since it is known that dissolving metal reduction of the related benzoyl cyclopropane leads only to benzyl cyclopropane without any evidence for the ring opened product.[5] This latter observation has also been supported by detailed kinetic measurements which indicate that, at the one electron reduction level, the equilibrium between the ketyl radical anion and the open form lies strongly in favour of the former.[6] For the case of an alkylidenecyclopropane, however, irrespective of whether ring opening occurs after the delivery of one or two electrons to the carbonyl group, essentially irreversible ring opening is clearly favoured, not only on kinetic grounds by the greater release of strain, but also in thermodynamic terms by the formation of an allylic intermediate. The isolation of the tetrasubstituted allylic alcohol rather than the homoallylic alcohol is also surprising, and at this stage, no clear mechanistic rationale can be advanced for the timing of this isomerisation sequence.

Given that the immediate precursor, prior to protic work-up, should be the thermodynamic lithium enolate of a conjugated ketone, it was of interest to examine the stereochemical outcome of the ring opening sequence, especially in terms of the more problematic case of tetrasubstituted enolate geometry. The results for a preliminary experiment involving trapping with acetic anhydride are shown in Scheme 3, and the isolation of the *E* enol acetate, as confirmed by the NOE measurements shown, is indicative of ring opening via the *transoid* gauche conformer.

Finally, albeit that cleavage of the distal bond is overwhelmingly favoured both on kinetic and thermodynamic grounds, it was of especial interest, as implied in Scheme 4, to study the behaviour of a simple bicyclic system in which the dictates of stereoelectronic control could override these factors and favour production of the higher energy vinylic intermediate via proximal bond cleavage.[7] The results for the ring opening of 7-methylenebicyclo[4.1.0]heptan-2-one are shown in Scheme 4 and reveal a 3:1 preference in favour of the six-membered ring products.

In summary, the foregoing examples have hopefully provided some indication that the reductive ring opening of suitably constituted monocyclic alkylidenecyclo-



Scheme 4.

propyl ketones proceeds via distal cleavage and hence offers a novel regio- and stereoselective route to thermodynamic enolates.

By way of contrast, stereoelectronic factors can dominate the ring opening in a fused bicyclic system, albeit that the degree of regioselectivity is less than in the case of their cyclopropyl congeners.

Acknowledgement

We are grateful to the EPSRC for the provision of a studentship (to S.Z.).

References and notes

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