Pergamon

Tetrahedron Letters 43 (2002) 9649–9652

TETRAHEDRON
LETTERS

# An unprecedented outcome of the lithium–ammonia reduction of enones: the formation of cyclopropanols

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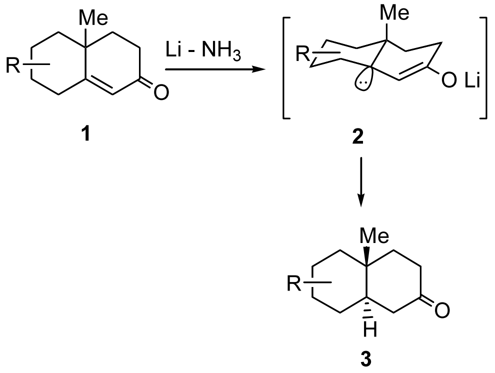
Received 14 October 2002; revised 16 October 2002; accepted 21 October 2002

**Abstract**—An unusual process takes place during the lithium–ammonia reduction of a variety of cyclic enones bearing an ester group in the γ-position, furnishing cyclopropanols. The reason for this unprecedented outcome has been attributed to the through-space stabilization of a developing cyclopropyl radical by interaction with the neighboring ester substituent. © 2002 Elsevier Science Ltd. All rights reserved.

The lithium–ammonia (L–A) reduction of α,β-ethylenic ketones, disclosed by Birch in the early 1950s, has been from the outset recognized as a potent tool in the field of synthetic organic chemistry, leading to its rapid expansion, as evidenced by the abundant documentation devoted to the subject. Perhaps the most attractive feature of this reaction is its remarkable stereochemical outcome. In this respect, in 1964, in a seminal series of structural studies, Stork unraveled the stereochemistry of L–A reduction of a variety of enones that have had considerable impact upon the direction of subsequent synthetic efforts in the area.[1] Of particular significance was the observation that the stereochemical course of L–A reduction of octalones **1**, furnishing the *trans*-fused decalones **3**, is determined by the transient angular carbanions **2**, adopting the conformation of lowest energy prior to protonation (Scheme 1).[2]

In this communication, we report that an unprecedented process occurs during the L–A reduction of octalone **5**, affording the fused cyclopropanol **6**. Since it appeared that this unusual outcome might be due to the fact that an angular carbomethoxy group is present in starting material **5**, the L–A reductions of related α-enones **7** and **9**, both bearing in the γ-position an ester group at a quaternary carbon center, were also examined. In fact these reductions paralleled completely the conversion [**5**→**6**], giving cyclopropanols **8** and **10**, respectively, a result in accord with our expectation.

In recent synthetic endeavors directed towards the elaboration of decalin-based scaffolds,[3] the L–A reduction of (±)-octalone **5**, prepared by allylic oxidation[4] of alkene **4**,[5] was investigated. Much to our surprise, when the reduction of **5** was conducted with 7 equiv. of Li in



**Scheme 1.**

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*Keywords*: cyclopropanation; enones; reduction; radical and radical reactions; molecular modeling/mechanics.

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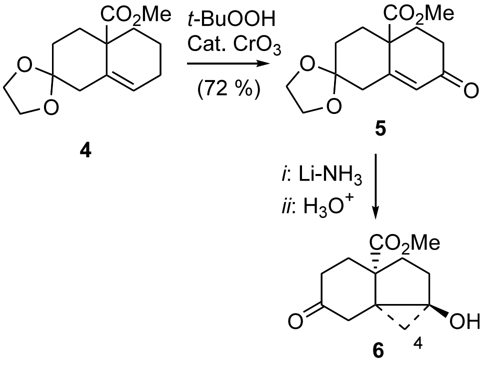
PII: S0040-4039(02)02382-1

$NH_3$ at −30°C in the presence of THF–$Et_2O$ (5 min stirring, then quenching with $NH_4Cl$, followed by hydrolytic workup with 3 M HCl), we could not observe any trace of the expected *trans*-decalone. However, the tricyclic derivative (±)-**6** was isolated after chromatographic purification on silica gel in 73% yield, and its structure was confirmed as follows. The presence of a cyclopropane nucleus in **6** was first revealed in the $^1H$ NMR spectrum by a characteristic pattern for protons at C-4 (doublet of doublet at $\delta$ 0.61 ppm, $J=6.6$, 1.6 Hz and doublet at $\delta$ 1.03 ppm, $J=6.6$ Hz). This was further supported by the HMBC spectral analysis, exploiting a dual set of correlations between these two protons and the cyclopropane carbon at C-4 ($\delta$ 19.4 ppm) (Scheme 2). Finally, the full structure of **6**, including the *syn* relationship between the cyclopropane nucleus and the angular carbomethoxy group, was unequivocally assigned by single-crystal X-ray diffraction analysis (Fig. 1).[6]

The reason for the occurrence of the intriguing cyclopropanation process [**5**→**6**] seeming mainly due to the presence of an angular ester group in starting octalone **5**, we next decided to examine the L–A reduction of related tricyclic enone (±)-**7**, a key intermediate in the synthesis of diterpenoids of the cyathin family.[7] In agreement with our prediction, the reduction of **7** with 3 equiv. of Li in $NH_3$ at −30°C in the presence of 1 equiv. of EtOH gave the tetracyclic derivative (±)-**8**, as a single diastereomer in 61% yield. $^1H$ and $^{13}C$ NMR spectroscopic studies including HMBC experiments, which revealed correlation peaks between the C-6 carbon atom ($\delta$ 13.8 ppm) and the methylene protons at C-6 (multiplet at $\delta$ 0.75 ppm and multiplet at $\delta$ 0.84 ppm), established the presence of a cyclopropane nucleus in compound **8**. The depicted *exo* arrangement of the cyclopropane ring (*syn* to the angular carbomethoxy group), although not definitively secured, was assigned on the basis of energy difference between stereomers, a severe steric hindrance affecting the *endo* isomer (Scheme 3).



**Scheme 2.**

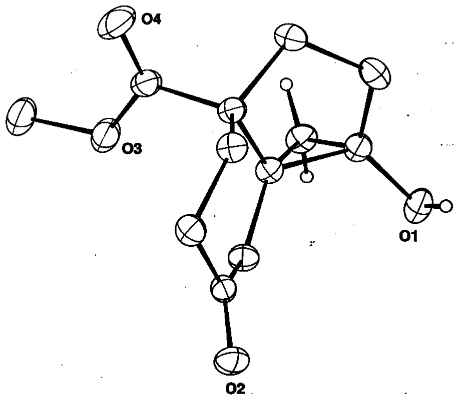
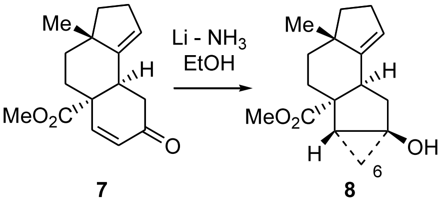


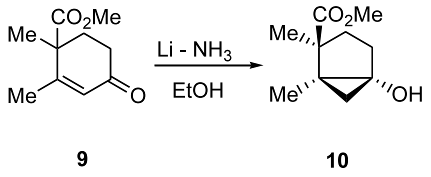
**Figure 1.** ORTEP view of **6** with labeled oxygen atoms. Thermal ellipsoids are scaled to 50% probability level. Hydrogen atoms shown are drawn to an arbitrary scale.



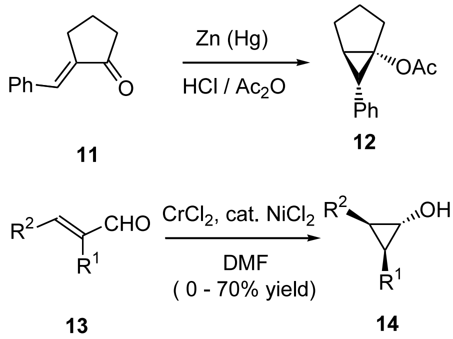
**Scheme 3.**

A similar transannular cyclopropanation has also been encountered in the L–A reduction of Hagemann's ester (±)-**9**.[8] Treatment of this enone with 7 equiv. of Li in $NH_3$ at −30°C in the presence of 1 equiv. of EtOH thus produced, in a 65% yield, diastereomerically pure fused cyclopropanol (±)-**10** ($^1H$ NMR: cyclopropane protons: doublet at $\delta$ 0.40 ppm, $J=6.4$ Hz and doublet at $\delta$ 0.87 ppm, $J=6.4$ Hz). The configurational assignment of **10** was based on mechanistic considerations (vide infra) (Scheme 4).

The tendency toward cyclopropanol formation during the L–A reduction of octalone **5** and related enones **7** and **9** having been proved, the remaining consideration lay in the elucidation of the mechanism of this cyclopropanation. There existed, as prior art, two compelling examples of reduction of α,β-ethylenic carbonyl compounds promoted by a metal or a lower valence state of a metal ion, leading to cyclopropanols. The first evidence deals with the Clemmensen-type reduction of enones.[9] For instance, when 2-benzylidenecyclopentanone (**11**) was subjected to zinc amalgam in the presence of hydrochloric acid and acetic anhydride, the fused cyclopropanol acetate **12** was formed with a 50% yield.[9a] The second example, illustrated by equation [**13**→**14**] demonstrates the occurrence of a cyclopropanation process in the chromium(II)-mediated reduction of α,β-ethylenic aldehydes[10] (Scheme 5).

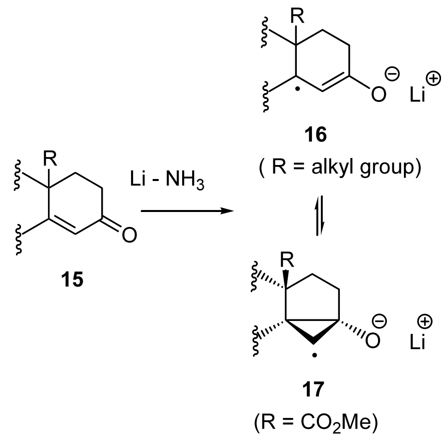


**Scheme 4.**



Scheme 5.

Turning our attention to the mechanism of the current cyclopropanation, semi-empirical molecular orbital calculations using MOPAC program (version 5.0)[11] were undertaken, keeping in mind that the L–A reduction of enones **15** primarily involves radical anion intermediates **16**, resulting from the transfer of one electron from the metal to the conjugate carbonyl moiety of enones (Scheme 6). Following the idea of testing the possible stabilization, through the aid of a neighboring ester group, of cyclopropyl radicals **17**, valence bond isomers of **16**, the computational studies were performed on the two pairs of epimeric delocalized radicals **A** and **B** (angularly substituted by a methyl group) and **C** and **D** (angularly substituted by a carbomethoxy group). By way of comparison, calculations were also carried out on parent allylic radicals **E** and **F**. Incidentally, it should be pointed out that the electron density encountered in optimized structures **A**–**F** (Fig. 2) was consistent with the atomic charge distribution of a radical anion. At the RHF/AM1 level,[12] the enthalpy of formation of species **A**, where the cyclopropane ring is *syn* to the angular methyl, is 4.7 kcal/mol below the *anti* isomer **B**. In the carbomethoxy-substituted series, the energy difference between the two epimers was found to be substantially enhanced, the *syn* isomer **C** being 8.4 kcal/mol more stable than the *anti* isomer **D**, an outcome which may be rationalized by assuming that species **C** benefits from the aforementioned stabilization. Regarding the electronic structure of species **A**–**D**, the presence of an important negative atomic charge at two cyclopropane carbon centers reflects an homoconjugative orbitals overlapping within the cyclopropoxide system. In this respect, a striking difference in electron density between these two centers was observed in the case of the *syn* species **C**, *the cyclopropane summit in close spatial proximity to the angular carbomethoxy group turned out to be the less charged (−0.23 versus −0.48)*. In light of these results, one may infer that the transannular cyclopropanation occurring in the L–A reduction of enones **5**, **7** and **9** originates in the through-space stabilization of a transient cyclopropyl radical by interaction with a neighboring ester substituent.



Scheme 6.

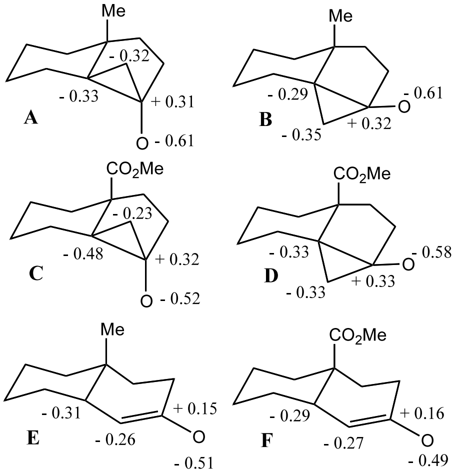


**Figure 2.** Relevant atomic charges calculated at the AM1 level in delocalized radicals **A**–**F**.

To conclude, we have established that an unusual process takes place in the L–A reduction of a variety of cyclic enones bearing an ester group in the γ-position, furnishing cyclopropanols. The reason for this unprecedented outcome has been attributed to the through-space stabilization of a developing cyclopropyl radical with the aid of the ester substituent. In addition to its mechanistic interest, this reaction offers a novel access to cyclopropanols, although of restricted applicability. Methods of preparation of cyclopropanols are relatively scarce; one of the most potent is the condensation of the so-called Kulinkovich reagents (mixture of Grignard reagents with titanium tetra-*iso*propoxide) with alkyl carboxylates.[13]

## Acknowledgements

Financial support for this work was provided by the European Union Training and Mobility for Researchers program (Contract No. ERBFMRXCT 96-0011).

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6. Compound **6**: colorless solid; mp 135°C. Crystal data for 1a-hydroxy-6-oxo-octahydro-cyclopropa[*c*]indene-3a-carboxylic acid methyl ester: white crystal of 0.2×0.31×0.35 mm, $C_{12}H_{16}O_4$, $M_w=224.3$; monoclinic, space group $P2_1/c$, $Z=4$, $a=9.060(9)$, $b=8.866(8)$, $c=14.554(5)$ Å, $\beta=107.25(5)°$, $V=1116$ Å$^3$, $d_{calcd}=1.334$ g cm$^{-3}$, $F(000)=480$, $\lambda=0.710693$ Å (Mo K$\alpha$), $\mu=0.100$ mm$^{-1}$; 3310 reflections measured ($-12\leq h\leq 0$, $0\leq k\leq 12$, $-19\leq l\leq 20$) on a Nonius CAD4 diffractometer. The structure was solved with SIR92[14] and refined with SHELXL-97.[15] Hydrogen atoms riding. Refinement converged to $R(gt)=0.0595$ for the 1863 observed reflections having $I\geq 2\sigma(I)$, and $wR(gt)=0.1546$, goodness-of-fit $S=0.979$. Residual electron density: −0.339 and 0.255 e Å$^{-3}$. Full crystallographic results have been deposited as Supplementary Material (CIF file) at the Cambridge Crystallographic Data Centre, UK (CCDC 194806).
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