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Lithium–liquid ammonia mediated carbocyclisation of δ,ε-unsaturated esters: annulation of cyclopentanones

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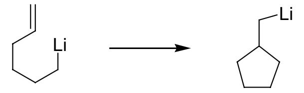
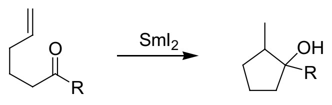
Abstract—Lithium–liquid ammonia mediated carbanion cyclisation of δ,ε-unsaturated esters leading to cyclopentanes, fused as well as spiro, via annulation is described.

The synthetic potential of cyclisation of 5-hexenyllithium, generated from the corresponding iodide or arylselenide by treatment with butyllithium, to generate cyclopentylmethyllithium (Eq. 1) has been exploited recently by several research groups.[1] In a similar manner the utility of samarium iodide for the generation of dianions from aldehydes/ketones and their cyclisation (Eq. 2) has also been well studied.[2] It is well known that electron transfer (e.g., alkali metal in liquid ammonia) to esters results in the formation of either acyloin products (Eq. 3) or the Bouveault–Blanc reduction to primary alcohols (Eq. 4).[3]



(1)



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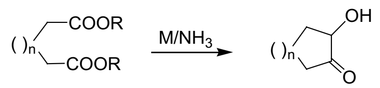
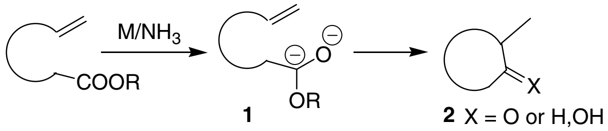


(3)

$$\mathrm{RCOOR'} \xrightarrow{\mathrm{M/NH_3}} \mathrm{RCH_2OH} \qquad (4)$$

However, cyclisation of esters via generation of carbanions (at the carbonyl carbon) and their addition to unactivated double bonds has not been properly explored.[4] Herein, we report the cyclisation of δ,ε-unsaturated esters leading to cyclopentanols under alkali metal in liquid ammonia reduction conditions.



1

2 X = O or H,OH

It was contemplated that reaction of an ester with an alkali metal in liquid ammonia would form a dianion **1**, which could add to an appropriately located olefin resulting in the formation of a cyclic compound **2**. To test the validity of the hypothesis, the reaction of the, δ,ε-unsaturated ester **4a**, obtained from cyclohexylidene-ethanol[5] **3a** via an *ortho* ester Claisen rearrangement and a one carbon homologation, was investigated. Addition of a THF solution of the ester **4a** to a suspension of lithium (10–15 equiv) in liquid ammonia followed by workup with ammonium chloride furnished a mixture of the secondary and primary alcohols **5a** and **6a** (along with a small amount of the corresponding aldehyde **7a**), which on oxidation with PCC–silica gel furnished a 3:1 mixture of the cyclopentanone **8a** and the aldehyde **7a** in 84% yield, which were separated on a silica gel column.[6] On the other hand, slow addition of lithium (6 equiv) to a solution of the ester **4a** in liquid ammonia and dry THF followed by workup, oxidation and separation on a silica gel column furnished predominantly the cyclopentanone **8a** in 90% yield along with 6% of the aldehyde **7a**. In order to probe the possibility of the aldehyde

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Keywords: Lithium in liquid ammonia; Carbanion cyclisation; Cyclopentane annulation.

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Table 1. Cyclisation of δ,ε-unsaturated esters[6,7]

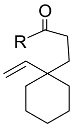
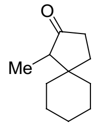
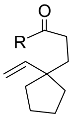
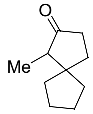
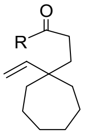
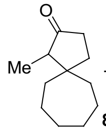
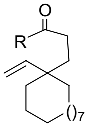
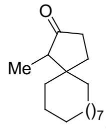
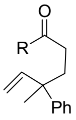
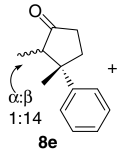
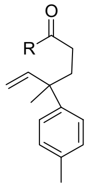
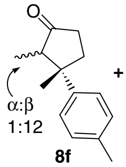
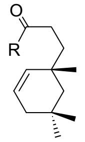
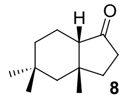
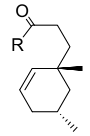
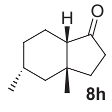
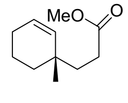
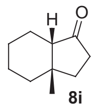
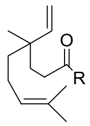
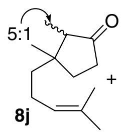
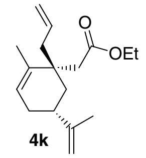
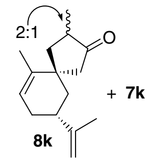
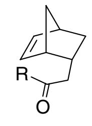
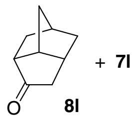
Entry	Ester/aldehyde		Method[a]	Products (**8**+**7**)	% Yield[b] (ratio **8**:**7**)
aa		**4a** R = OMe	A	 + **7a** **8a**	84 (3:1)
ab		**4a** R = OMe	B		96 (15:1)
ac		**7a** R = H	A		74 (2:1)
ba		**4b** R = OMe	A	 + **7b** **8b**	73 (3:2)
bb		**4b** R = OMe	B		94 (15:2)
bc		**7b** R = H	A		66 (4:3)
ca		**4c** R = OMe	A	 + **7c** **8c**	85 (3:1)
cb		**4c** R = OMe	B		96 (10:1)
cc		**7c** R = H	A		72 (3:2)
da		**4d** R = OMe	A	 + **7d** **8d**	81 (6:1)
db		**4d** R = OMe	B		98 (24:1)
dc		**7d** R = H	A		73 (3:2)
dd		**7d** R = H	B		94 (4:3)
ea		**4e** R = OMe	A	 + **7e** **8e**	84 (9:2)
eb		**4e** R = OMe	B		93 (1:0)
ec		**4e** R = OMe	B[c]		92 (1:0)
ed		**4e′** R = $\mathrm{O}^i\mathrm{Pr}$	B		92 (1:0)
ee		**7e** R = H	B		91 (1:2)
fa		**4f** R = OMe	A	 + **7f** **8f**	86 (1:0)
fb		**4f** R = OMe	B		96 (1:0)
fc		**7f** R = H	A		75 (2:1)
fd		**7f** R = H	B		88 (4:7)
ga		**4g** R = OMe	A	 + **7g** **8g**	95 (5:6)
gb		**4g** R = OMe	B		93 (11:5)
gc		**7g** R = H	A		96 (2:7)
ha		**4h** R = OMe	A	 + **7h** **8h**	95 (2:1)
hb		**4h** R = OMe	B		92 (7:2)
hc		**7h** R = H	A		90 (5:11)
i		**4i**	B	 + **7i** **8i**	95 (8:3)
ja		**4j** R = OMe	A	 + **7j** **8j**	88 (7:2)
jb		**4j** R = OMe	B		96 (11:1)
jc		**7j** R = H	B		94 (2:3)

Table 1 (*continued*)

Entry	Ester/aldehyde	Method[a]	Products (**8**+**7**)	% Yield[b] (ratio **8**:**7**)
ka	 **4k**	A	 2:1 + **7k** **8k**	75 (3:1)
kb		B		88 (4:1)
kc		A[d]		70 (5:2)
kd		A[e]		62 (7:2)
la	 **4l** R = OMe	A	 + **7l** **8l**	90 (4:1)
lb	**4l** R = OMe	B		94 (5:1)
lc	**7l** R = H	A		70 (5:2)

[a] Method A: addition of a THF solution of **4** or **7** to a suspension of Li in liquid NH_3; Method B: addition of Li to a solution of **4** or **7** in liquid NH_3 and THF; in both the methods the alcohol mixture **5** and **6** obtained was oxidised with PCC–silica gel and separated on silica gel.

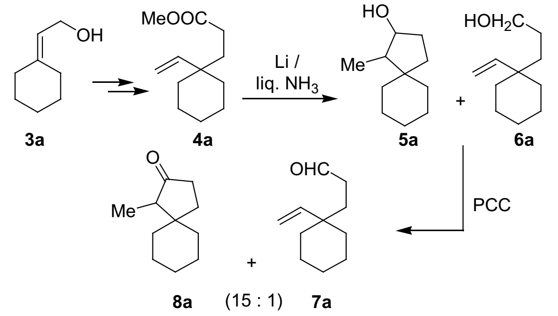
[b] Yield for two steps (cyclisation and oxidation).

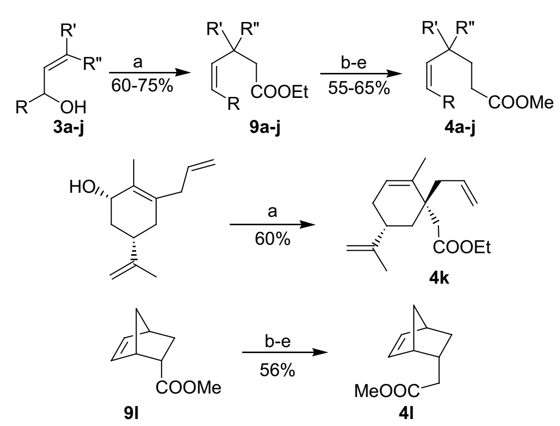
[c] In the presence of *tert*-butanol.

[d] Sodium is used instead of lithium.

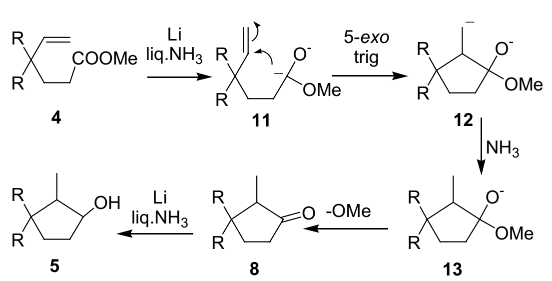
[e] Potassium is used instead of lithium.

7a as an intermediate in the conversion of the ester **4a** into the secondary alcohol **5a**, the reaction was carried out with the aldehyde **7a**. However, reaction of the aldehyde **7a** in liquid ammonia with lithium followed by oxidation furnished a 2:1 mixture of the cyclopentanone **8a** and the aldehyde **7a**, in 74% yield, which suggests that the aldehyde **7a** may not be the intermediate (or more than one pathway is involved) in the conversion of the ester **4a** into the secondary alcohol **5a**.



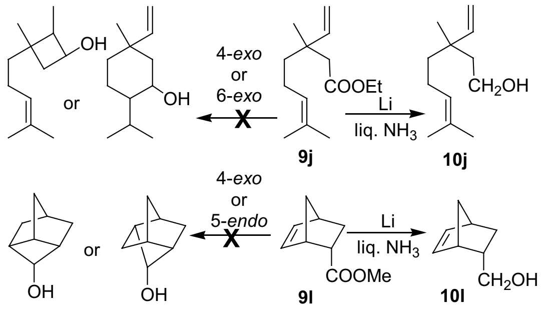


Scheme 1. Reagents and conditions: (a) $MeC(OEt)_3$, EtCOOH, sealed tube, 180 °C, 60 h; (b) 5% NaOH, $MeOH–H_2O$ (1:1), reflux, 8 h; (c) $(COCl)_2$, C_6H_6, rt, 1 h; (d) CH_2N_2, Et_2O, 0 °C → rt, 3 h; (e) hν, MeOH, 1 h.

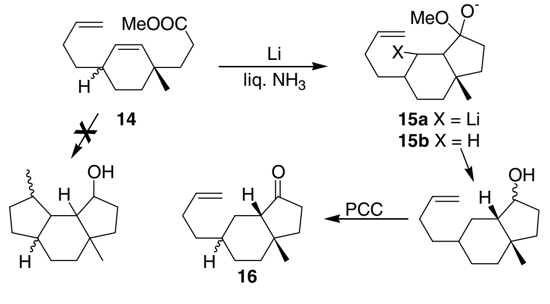


Scheme 2.

To establish the generality of the reaction, a series of olefinic esters **4b–l** were subjected to it and the results are summarised in Table 1. Esters **4a–l** were prepared by conventional methods[7] as depicted in Scheme 1. Reactions using both methods were carried out. In all the cases, the mixture of the alcohols **5** and **6**, obtained in the reaction with lithium and liquid ammonia of the esters **4**, was oxidised with PCC–silica gel in methylene chloride and the ketone **8** and aldehyde **7** separated by silica gel column chromatography. It was found that in all the cases, addition of lithium to a solution of the ester **4** in liquid ammonia and THF (method B) led to efficient cyclisation as compared to the addition of the ester **4** to a suspension of lithium in liquid ammonia (method A). It is worth noting, that there is only a marginal influence of the metal among lithium, sodium and potassium (entries kc and kd) on the course of the reaction. Similarly, no significant change was observed by the presence of an external proton donor such as *tert*-butanol (entry ec), and no change was observed by changing the methyl to ethyl or isopropyl esters. For comparison, the corresponding aldehydes **7b–l** were also subjected to the reaction with lithium–liquid ammonia followed by oxidation. Cyclisation was found to be more facile with the esters **4** than the aldehydes **7**. Even a bridged compound, such as brendane **8l** was found to form efficiently. It is worth mentioning that the cyclopentanone **8f**, obtained as a 12:1 diastereomeric mixture, is a well-established precursor for the sesquiterpenes, laurene and epilaurenes, α-cuparenone and cuparene.[6]



To test the feasibility of cyclisation leading to either six- or four-membered rings, reaction of the diene ester **9j** was carried out. However, no product from cyclisation was noticed in the reaction of the ester **9j** in liquid ammonia with lithium; this only generated the Bouveault–Blanc reduction product, the primary alcohol **10j**, which clearly indicated that the reaction is proceeding via the dianion (if the reaction was proceeding via the radical anion, then 6-*exo* cyclisation would have been noticed) and is highly suitable only for the generation of cyclopentane rings. In a similar manner, the bicyclic ester **9l** also failed to cyclise and generated only the primary alcohol **10l**. On the basis of these results a tentative mechanism is depicted in Scheme 2. The ester **4** forms the dianion **11**, which undergoes a 5-*exo*-*trig* cyclisation to generate the alkyllithium **12**, which is rapidly protonated by ammonia analogous to the 1,4-reduction of conjugated ketones. The resulting alkoxide **13** eliminates the methoxy group to form the cyclopentanone **8**, which under the reaction conditions is reduced to the corresponding alcohol **5**.



A tandem carbanion cyclisation was also attempted for the generation of a tricyclic system starting from diene ester **14**, obtained from 6-(3-butenyl)-3-methylcyclohex-2-enone. The reaction of the diene ester **14** in liquid ammonia with lithium followed by oxidation, however, generated only the bicyclic compound **16** in 76% yield,[8] indicating that the protonation of the intermediate alkyllithium **15a** by ammonia is much faster than the second cyclisation. Since tandem reactions are very facile with radicals, the failure of the generation of the tricyclic compound in the present reaction also suggests that the reaction is proceeding via a dianion.[9]

In conclusion, intramolecular addition of carbanions, generated from esters under lithium–liquid ammonia reduction conditions, to unactivated olefins is described, which resulted in the development of an efficient cyclopentane annulation methodology. Contrary to the general reactivity pattern, the cyclisation is found to be more facile with esters than with the corresponding aldehydes. The synthetic utility of this reaction in the construction of simple, fused, spiro and bridged cyclopentanoid systems has been demonstrated. Currently, we are investigating the application of this methodology to natural product synthesis.

References and Notes

1. Krief, A.; Bousbaa, J. *Tetrahedron Lett.* **1997**, *38*, 6291; Bailey, W. F.; Mealy, M. J.; Wiberg, K. B. *Org. Lett.* **2002**, *4*, 791; Clayden, J.; Kenworthy, M. N. *Org. Lett.* **2002**, *4*, 787, and references cited therein.
2. Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 745; Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.
3. Kaiser, E. M. *Synthesis* **1972**, 391, and references cited therein.
4. To the best of our knowledge there is only one report on the intramolecular addition of esters to olefins under alkali metal in liquid ammonia conditions assisted by an α-hydroxy group (claimed as radical anion mediated addition), see: Cossy, J.; Gille, B.; Bellosta, V. *J. Org. Chem.* **1998**, *63*, 3141–3146.
5. Srikrishna, A.; Nagaraju, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 311.
6. Yields (unoptimised) refer to isolated and chromatographically pure compounds. All the compounds described in this manuscript exhibited spectral data (IR, ^{1}H and ^{13}C NMR and mass) consistent with their structures. Spectral data for the ketone **8a**: IR (neat): ν_{max}/cm^{-1} 1739. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 2.30–2.00 (3H, m), 1.88 (1H, q, *J* 6.9 Hz), 1.75–1.30 (8H, m), 1.30–1.10 (3H, m), 0.92 (3H, d, *J* 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 218.9 (C), 55.1 (CH), 42.3 (C), 37.6 (CH_2), 34.2 (CH_2), 29.7 (CH_2), 28.5 (CH_2), 26.0 (CH_2), 22.4 (CH_2), 22.1 (CH_2), 8.0 (CH_3). HRMS: *m*/*z* for $C_{11}H_{19}ONa$ (M^++Na+1): Calcd 190.1333. Found 190.1331.
7. For **8a**: Eilbracht, P.; Acker, N.; Haedrich, I. *Chem. Ber* **1988**, *121*, 519; for **8b**: Wender, P. A.; White, A. W. *J. Am. Chem. Soc.* **1988**, *110*, 2218; for **8e**: Dygutsch, D. P.; Eilbracht, P. *Tetrahedron* **1996**, *52*, 5461; for **8f**: Chavan, S. P.; Patil, S. S.; Ravindranathan, T. *Tetrahedron* **1999**, *55*, 13417; for **8i**: Jung, M. E.; Johnson, T. W. *Tetrahedron* **2001**, *57*, 1449; for **8l**: Majerski, Z.; Hamersak, Z. *J. Org. Chem.* **1984**, *49*, 1182.
8. In addition 16% of the corresponding aldehyde was also obtained.
9. In addition, the 6-*endo* cyclisation, a dominant reaction with the 5-substituted-5-hexenyl radicals, with δ-substituted esters was not observed, which also further supports the absence of a radical intermediate in these cyclisations. See: Srikrishna, A.; Kumar, P. R.; Ramasastry, S. S. V. *Tetrahedron Lett.* **2003**, *44*, See: doi:10.1016/j.tetlet.2003.10.165.