# A Highly Unusual Condensation Reaction between 3-Chloro-3-methyl-2-butanone and Lithium Diisopropylamide

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*Received August 24, 1984*

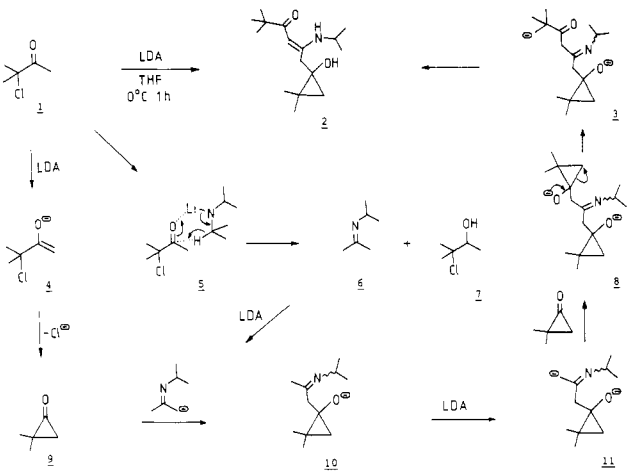
The reaction of lithium diisopropylamide (LDA) with 3-chloro-3-methyl-2-butanone in tetrahydrofuran afforded 2,2-dimethyl-5-[*N*-(isopropyl)amino]-6-(2,2-dimethyl-1-hydroxycyclopropyl)-4-hexen-3-one as the principal reaction product. This compound apparently resulted from addition of two molecules of Favorskii-derived cyclopropanone with *N*-(2-propylidene)isopropylamine, i.e., the oxidation product (Meerwein–Ponndorf–Verley reaction) of LDA.

Lithium diisopropylamide (LDA) is frequently used as a strong, easy-to-handle, nonnucleophilic base in organic synthesis. Especially protons $\alpha$ with respect to a carbonyl or imino group are readily removed by LDA without side reactions. However, it is known that LDA is an efficient single electron donor to $\alpha$-deficient heteroaromatics[3] and molecules which have favorable reduction potentials,[4] but the reported side reactions remain rare. It has been shown that $\alpha$-halo and $\alpha$-methoxy ketones undergo reduction of the carbonyl group by LDA and these results were explained in terms of the N-analogue of the well-known Meerwein–Ponndorf–Verley reduction.[5] More recently, the ketone functionality of ethyl 5-chloro-2-oxopentanoate was also reported to be reduced by LDA at low temperature to the corresponding alcohol function.[6] We would like to disclose now another example of the scarcely reported reduction of an $\alpha$-functionalized ketone by lithium diisopropylamide.

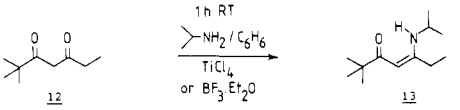
## Results

Treatment of 3-chloro-3-methyl-2-butanone (1) with 2 mol equiv of lithium diisopropylamide in dry tetrahydrofuran (freshly distilled from sodium benzophenone ketyl) at 0 °C gave rise to a vigorous reaction from which, after 1 h reaction time and aqueous workup, a complex reaction mixture was isolated. On standing, a pure crystalline compound precipitated (mp 110 °C) whose mass spectrum suggested an odd number of nitrogen atoms ($M^+$ $m/e$ 267). The infrared spectrum (KBr pellet) indicated an hydroxyl and/or amino (NH) function (3200–3500 $cm^{-1}$), while the strong band at 1587 $cm^{-1}$ was attributed to a carbonyl group in corroboration with the $^{13}C$ NMR spectrum (vide infra). More conclusive structural information was gathered from the $^1H$ NMR spectrum ($CDCl_3$, 360 MHz). The typical AB system at $\delta$ 0.41 and 0.62 ($J$ = 5.7 Hz) could be attributed to nonequivalent methylene protons of a tetrasubstituted cyclopropane unit, while a *tert*-butyl signal was present at 1.16 ppm. Of major importance was the presence of an *N*-isopropyl group, which was characterized by the nonequivalent methyl groups (1.23 and 1.25 ppm, each a doublet with $J$ = 6.5 Hz) and, more specifically, by the methine proton ($\delta$ 3.84) whose multiplicity

**Scheme I**




**Scheme II**




suggested an additional coupling to an amino hydrogen atom. This coupling is not compatible with an ordinary amino functionality but rather refers to an amide or an enaminone. In addition, an AB system at $\delta$ 2.55 and 2.89 ($J$ = 16.2 Hz) is consistent with the nonequivalent hydrogens of a methylene function on a double bond, while an olefinic hydrogen is resonating at $\delta$ 5.30 (s). The $^{13}C$ NMR spectrum ($CDCl_3$, 20 MHz) supports the above mentioned structural units, and differentiates between an amide and an enaminone. The carbonyl resonance at 203.7 ppm is only consonant with a ketone group, but its low stretching vibration in infrared (vide supra) points to a conjugation like in an enaminone. Besides this, the high $\delta$ value of the carbonyl carbon in $^{13}C$ NMR refers to a sterically hindered ketone, such as a pivaloyl moiety. By putting together all structural units discussed above, the compound was identified as 2,2-dimethyl-5-[*N*-(isopropyl)amino]-6-(2,2-dimethyl-1-hydroxycyclopropyl)-4-hexen-3-one (2) (Scheme I).

In order to support this structural elucidation, a model compound with an analogous enaminone skeleton was synthesized. Condensation of pinacolone with ethyl propionate in the presence of sodium hydride in ether[7] gave 2,2-dimethyl-3,5-heptanedione (12) which was reacted with isopropylamine in benzene in the presence of boron tri-

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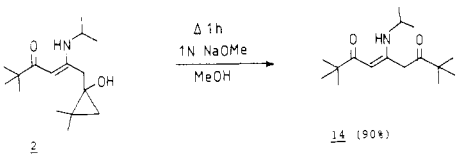
**Scheme III**




fluoride etherate or titanium(IV) chloride to afford 2,2-dimethyl-5-[*N*-(isopropyl)amino]-4-hepten-3-one (**13**) (Scheme II). The latter compound revealed exactly the same spectrometric features (IR, $^1$H NMR, $^{13}$C NMR) as compound **2**.

From an inspection of the structure of compound **2**, it was concluded that the molecule was constructed of two units corresponding to the α-chloro ketone **1** and one unit corresponding to the *N*-isopropyl ketimine of acetone (**6**). The latter compound might originate from oxidation of LDA in a way analogous to the reports discussed in the introductory part. As a matter of fact, during the reduction by LDA of phenacyl bromide, the *N*-isopropyl ketimine of acetone (**6**) has been isolated.[5] This is also an indication that this process is most probably operative in the reaction discussed in this communication (see complex **5**). α-Chloro ketone **1** might be a suitable substrate for the oxidation of LDA, but all efforts to identify any reduction product from **1** (e.g., β-chloro alcohol **7**) or the ketimine **6** failed (preparative TLC, GLC, column chromatography, HPLC). However, it is reasonable to believe that this process leading to ketimine **6** occurs, because this molecule is used as a building block in the final product **2**. The other parts of compound **2** consist of a cyclopropanone adduct, resulting from the initial stages of a Favorskii rearrangement,[8] and a ring-opened cyclopropanone. Therefore, the mechanism of the formation of rearranged compound **2** can be interpreted in terms of an initial 1,3-dehydrochlorination of α-chloro ketone **1** to generate cyclopropanone **9** as an intermediate (Scheme I). This reactive transient species is attacked by the anion of ketimine **6**, generated by means of LDA, to afford adduct **10**, which is again deprotonated by LDA to give dianion **11**. This anion adds to cyclopropanone **9** to furnish adduct **8**, whose protonated species is not isolable. Ring opening generates the most stable carbanion **3**, which on protonation and tautomerism yields the stable enaminone **2**. An alternative way of explaining the transformation of **10** into **2** consists of ring opening of **10** to generate the corresponding enaminone which might be more nucleophilic at the γ-position (with respect to the carbonyl group). Wether or not a dianion is involved is not known yet. A similar reactivity is known for dianions of β-keto esters which are regiospecifically alkylated at the γ-position,[9] but also enaminones behave in an analogous way.[10-12] The addition of such an enaminone anion (or dianion) across the carbonyl group of a cyclopropanone unit **9** affords directly cyclopropanol **2**.

Besides the structural proof and the mechanistic explanation, there is also support of the identity of enaminone **2** by a chemical transformation. Treatment of compound **2** with sodium methoxide in methanol (1 N) under reflux for 1 h afforded the ring-opened compound **14** in 90% yield. The base-induced opening of the cyclopropanol unit occurs in such a way as to produce the most stable intermediate carbanion (cf. the Favorskii rearrangement) and results in the generation of a second pivaloyl unit (Scheme III). It should be mentioned that, apart from the ease with which compound **2** is isolated, the reaction of **1** with LDA is extremely complex in that the liquid reaction mixture (after isolation of **2**) contains at least 30 compounds as evidenced by HPLC analysis. Only one of these compounds could be identified as compound **2**.

The conversion of **1** to **2** is highly dependent upon the reaction conditions. It was noticed that compound **2** was only formed in a reasonable yield (47%) when compound **1** was added rapidly (neat) to the cooled (0 °C) solution of LDA (2 equiv) in THF. The reverse addition did only afford compound **2** in 6% yield.

Finally, attempts to extend this reaction of LDA to other related substrates, e.g., 3-bromo-3-methyl-2-butanone and 1-(1-chlorocyclohexyl)-1-ethanone, failed.[13] Also lithium diethylamide did not afford any isolable compound related to **2**.

The finding that lithium tetramethylpiperidide did not react with α-chloro ketone **1** to give a compound related to **2** is not unexpected, of course.

As a conclusion, this reaction represents the unexpected synthesis of a fairly complex molecule **2** starting from a simple substrate **1**. In view of the current common use of LDA in synthetic organic chemistry, it is of importance to be aware of certain limitations with reactions of bifunctional compounds such as α-chlorinated ketones.

## Experimental Section

IR spectra were measured with a Perkin Elmer Model 1310 spectrophotometer. $^1$H NMR spectra were recorded with Varian T-60 (60 MHz) and Bruker WH-360 FT (360 MHz) spectrometers, while $^{13}$C NMR spectra were obtained from a Varian FT-80 (20 MHz) spectrometer. UV spectra were measured with a Beckman DB spectrophotometer, while mass spectra were recorded with a Varian-MAT 112 mass spectrometer (direct inlet system, 70 eV). 3-Chloro-3-methyl-2-butanone (**1**) was prepared by chlorination of 3-methyl-2-butanone with sulfuryl chloride in dichloromethane (room temperature), after which the reaction mixture was distilled over a 50-cm Vigreux column (bp 116–119 °C (760 mmHg), 82% yield). Lithium diisopropylamide (LDA) was freshly prepared from dry diisopropylamine and butyllithium (in hexane) or methyllithium (in ether) in dry tetrahydrofuran at 0 °C.

**Reaction of 3-Chloro-3-methyl-2-butanone (1) with Lithium Diisopropylamide.** A freshly prepared solution of 0.08 mol of lithium diisopropylamide in 40 mL of dry tetrahydrofuran was treated rapidly (under stirring at 0 °C) with 0.04 mol (4.82 g) of 3-chloro-3-methyl-2-butanone (**1**) (nitrogen atmosphere). After this vigorous reaction the mixture was further magnetically stirred for 1 h after which it was poured into water and extracted three times with ether. The combined organic extracts were dried over potassium carbonate and evaporated under vacuo to afford an oil from which, after standing overnight, a white precipitate was formed. The crystalline material (**2**) was filtered, washed with pentane, and dried: 1.7 g, yield 47%; mp 110 °C.

**Spectrometric data of 2,2-dimethyl-2-[*N*-(isopropyl)-amino]-6-(2,2-dimethyl-1-hydroxycyclopropyl)-4-hexen-3-one (2)**: IR (KBr) 3200–3500 ($\nu_{OH}$ and $\nu_{NH}$), 1587 ($\nu_{C=O}$), 1530 cm$^{-1}$ ($\nu_{C=C}$); UV (MeOH) $\lambda_{max}$ 270 nm; $^1$H NMR ($CDCl_3$, 360 MHz) δ 0.41 and 0.62 (each 1 H, each d, AB, $J$ = 5.7 Hz, cyclopropane $CH_2$), 1.14 and 1.28 (each 3 H, each s, $CMe_2$), 1.16 (9 H, s, *t*-Bu), 1.23 and 1.25 (each 3 H, each d, $J$ = 6.5 Hz, $NCMe_2$), 2.55 and 2.89 (each 1 H, each d, AB, $J$ = 16.2 Hz, $CH_2C$=), 2.8 (1 H, broad s, OH), 3.84 (1 H, septuplet x d, $J$ = 6.5 Hz, $J$ = 8 Hz, NCH), 5.30 (1 H, s, CH=C), 11.13 (1 H, broad d, $J$ = 8 Hz, NH); $^{13}$C NMR ($CDCl_3$, 20 MHz) δ 20.27 (q), 22.24 (q), 22.79 (q), 23.97 (q) (four methyl signals referring to $CMe_2$ and $NCMe_2$), 28.11 (q, $Me_3$),

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25.47 (t, cyclopropane $CH_2$), 36.49 (dd, $CH_2C$=), 41.41 (s, $CMe_3$), 44.36 (d, NCH), 59.68 (s, COH, 87.83 (d, CH=C), 163.32 (s, NC=), 203.73 (s, C=O); Mass spectrum, *m/e* (relative abundance) 267 ($M^+$, 5), 250 (5, OH·), 234 (15), 211 (10), 210 (85, *t*-Bu·), 192 (10), 188 (5), 182 (5), 168 (10), *t*-BuCOCH=C=$N^+$HiPr), 164 (10), 153 (10), 150 (8), 126 (100, *t*-BuCOCH=C=$N^+H_2$), 122 (10), 112 (10), 100 (15), 99 (30), 85 (15), 84 (30), 83 (15), 68 (8), 57 (90, *t*-$Bu^+$), 43 (15), 42 (15), 41 (35), 40 (10). Anal. Calcd: N, 5.23. Found: N, 5.11.

**Condensation of 2,2-Dimethyl-3,5-heptanedione (12) with Isopropylamine.** A magnetically stirred mixture of 1.55 g (0.01 mol) of 2,2-dimethyl-3,5-heptanedione (**12**) and 2.34 g (0.04 mol) of isopropylamine in 15 mL of benzene was treated dropwise either with 0.006 mol of titanium(IV) chloride (dissolved in 5 mL of pentane) or 0.03 mol of boron trifluoride etherate (dissolved in 5 mL of benzene). The reaction flask was protected with a calcium chloride tube. The reaction mixture was stirred for 1 h, after which it was poured into 150 mL of aqueous 2 N sodium hydroxide. The organic phase was isolated and the aqueous layer was extracted twice with ether. The combined organic phases were dried ($Na_2CO_3$) and evaporated in vacuo to afford enaminone **13** in 67% (using $TiCl_4$) or 87% (using $BF_3$·$Et_2O$) yield: bp 125–27 °C (15 mmHg); IR (NaCl) 1610–1560 $cm^{-1}$ (broad strong band, $\nu_{C=O}$); $^1H$ NMR ($CDCl_3$) 1.13 (9 H, s, *t*-Bu), 1.22 (6 H, d, $J$ = 6 Hz, $Me_2$), 1.1 (3 H, covered by *t*-Bu signal, $CH_3$), 2.26 (2 H, q, $J$ = 7.5 Hz, $CH_2C$=), 3.71 (1 H, m, NCH), 5.06 (1 H, s, CH=), 10.8 (1 H, broad signal, NH); $^{13}C$ NMR ($CDCl_3$) 13.08 (q, Me), 24.22 (q, $Me_2$), 25.23 (t, $CH_2$), 28.12 (q, $Me_3$), 41.25 (s, $CMe_3$), 44.06 (d, NCH), 87.91 (d, CH=), 167.50 (s, NC=), 203.34 (s, C=O); mass spectrum, *m/e* (relative abundance) 197 ($M^+$, 8), 140 (100), 122 (8), 93 (39), 57 (17), 56 (17), 55 (8), 44 (15), 43 (23), 42 (16), 41 (35), 40 (9), 39 (8).

**Reaction of Enaminone 2 with Sodium Methoxide in Methanol.** A solution of 50 mg (0.18 mmol) of enaminone **2** in 0.4 mL of 1 N sodium methoxide in methanol was refluxed for 1 h, after which the reaction mixture was poured into water and extracted three times with dichloromethane. The extracts were dried (sodium carbonate) and evaporated under vacuo to give a clear liquid residue. Although the product was more than 95% pure, an additional purification by preparative TLC (hexane/ether 80:20, silica gel $GF_{254}$ (Merck)) provided an analytical sample of compound **14** (40 mg, 90% yield): mp 54 °C; $^1H$ NMR ($CDCl_3$) 1.10 (9 H, s, *t*-Bu), 1.20 (9 H, s, *t*-Bu), 1.20 (6 H, d, $J$ = 6.5 Hz, $Me_2$), 3.43 (2 H, s, $CH_2$), 3.2–3.7 (1 H, m, NCH), 4.92 (1 H, s, CH=C), 10.4 (1 H, broad, NH); $^{13}C$ NMR ($CDCl_3$) 24.06 (q, $Me_2$), 27.46 (q, $Me_3$), 27.96 (q, $Me_3$), 40.66 (t, $CH_2$), 41.31 (s, $CMe_3$), 44.99 (s, $CMe_3$), 45.37 (d, NCH), 90.86 (d, =CH), 158.76 (s, =CN), 203.69 (s, O=CC=C), 209.50 (s, $CH_2C$=O); IR (NaCl) 1722 ($\nu_{t\text{-}BuCOCH_2}$), 1605 (br, $\nu_{t\text{-}BuCOCH=CN}$), 3320 $cm^{-1}$ (w, $\nu_{NH}$); MS, *m/e* (relative abundance) 267 ($M^+$, 2), 211 (3), 210 (27), 126 (6), 58 (8), 57 (100), 45 (10), 44 (5), 43 (14), 42 (8), 41 (27), 40 (22). Anal. Calcd: N, 5.23. Found: N, 5.15.

**Acknowledgment.** We are greatful to the "Commissariaat-Generaal voor de Internationale Culturele Samenwerking" (Belgium) for a postdoctoral research grant for one of us (Mariana Palamareva) and to the National Fund for Scientific Research for Financial support to the laboratory. We are also indebted to Prof. M. J. O. Anteunis, Laboratory of Organic Chemistry, NMR Spectroscopic Unit, Faculty of Sciences, State University of Gent, for recording the 360-MHz $^1H$ NMR spectrum.

**Registry No.** **1**, 5950-19-6; **2**, 97135-62-1; **12**, 20734-29-6; **13**, 97135-63-2; **14**, 97135-64-3; 1-(1-chlorocyclohexyl)-1-ethanone, 1004-55-3; lithium diisopropylamide, 4111-54-0; pinacolone, 75-97-8; ethyl propionate, 105-37-3; 3-bromo-3-methyl-2-butanone, 2648-71-7; lithium diethylamide, 816-43-3.

# Modification of the Catalytic Activity of Zinc Chloride. A Kinetic Investigation in Zinc Chloride–Ether–Dichloromethane Mixtures

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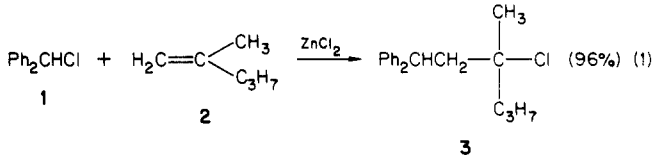
*Received December 28, 1984*

The addition reaction of chlorodiphenylmethane with 2-methyl-1-pentene was studied kinetically in order to characterize the catalytic activities of $ZnCl_2/Et_2O/CH_2Cl_2$ mixtures of different composition. The activity of the heterogeneous $ZnCl_2/CH_2Cl_2$ system is raised by 3–4 orders of magnitude when 0.5 equiv of ether are added. At −70 °C the system is homogeneous for $[Et_2O]/[ZnCl_2] > 1.1$, and the catalytic activity decreases with increasing ether/zinc chloride ratio. At $[Et_2O]/[ZnCl_2]$ ratios greater than 2, the reaction rate depends on the ether/zinc chloride ratio and is almost independent of the absolute concentration of the catalyst.

Zinc chloride is usually considered to be a weak Lewis acid.[1] This view is essentially based on experiments carried out either under homogeneous conditions in donor solvents or under heterogeneous conditions in solvents like chlorinated hydrocarbons. In previous work we have found that addition reactions of chloroalkanes with alkenes, which are not efficiently catalyzed by zinc chloride in *either* dichloromethane *or* ether, readily take place in a mixture of these two solvents.[2,3] In order to quantify this observation, we determined the rates of the zinc chloride catalyzed reactions of chlorodiphenylmethane (**1**) with 2-methyl-1-pentene (**2**) in dichloromethane–ether solutions of variable composition.




## Experimental Section

**Zinc chloride** (commercial product, MERCK) was heated 48 h at 160 °C (0.01 mmHg) and stored in a nitrogen atmosphere.

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