Novel Acylation of Aliphatic Olefins Promoted by Active Zinc Compounds

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It was found that acylation of a variety of aliphatic olefins with acid chlorides is efficiently promoted by active zinc compounds, which were prepared from a Zn/Cu couple and alkyl iodides. The crude product mixtures were subsequently treated with 1 M KOH in methanol or were subjected to catalytic hydrogenation to afford the corresponding α,β-unsaturated or saturated ketones in good to moderate yields. It was also shown that the reaction fully follows the Markovnikov rule.

The Friedel–Crafts aliphatic acylation has been extensively studied,[2] whereas, owing to low yield and formation of a complex mixture of products, its synthetic utility has been rather limited in contrast with the high potentiality of the corresponding aromatic acylation.

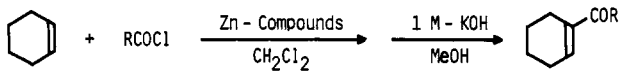
Although recently several new methods[3–5] of improving the yield and selectivity of acylation of olefins by using strongly polarized complexes containing incipient acyl cations have been reported,[6] these methods may be inconvenient for the preparation of α,β- or β,γ-unsaturated ketones due to the instability of acyl-cation complexes, troublesome procedures, and less availability of reagents.

In this paper, we report novel acylation of aliphatic olefins promoted by active zinc compounds to provide facile methods of selective synthesis of α,β-conjugated enones and saturated ketones.

Results and Discussion

Active zinc compounds were prepared by refluxing solutions of alkyl iodides or methylene iodide in methylene chloride containing pure zinc or Zn/Cu couple[7] for 1 h under an atmosphere of nitrogen.

Dropwise addition of acid chlorides (**2**) to solutions of cyclohexene (**1**) and freshly prepared active zinc compounds in methylene chloride at 15–20 °C gave mixture of acylated products, that is, α,β- and β,γ-unsaturated ketones and β-chloro ketones. Subsequent treatment of the crude mixture with 1 M potassium hydroxide in methanol afforded the corresponding 1-acylcyclohexenes **3** in good yields.



1 **2a - g** **3a - g**

The activity of various zinc compounds and Lewis acids in the acylation of **1** with *n*-butyryl chloride (**2c**) is summarized in Table I, which clearly indicates that the zinc compound prepared from Zn/Cu couple and methylene iodide possesses the most effective activity in the synthesis of cyclohexenyl propyl ketone (**3c**). Table II shows the yields of 1-acylcyclohexenes **3a–g** obtained by the reaction of **1** with a variety of acid chlorides, **2a–g**, in the presence of the most active zinc compounds described above or aluminum chloride.

Table I. Reaction of Cyclohexene (1) with *n*-Butyryl Chloride (2c) in the Presence of Various Zinc Compounds and Lewis Acids

zinc compd	temp, °C	% yield[a,b] of 3c
$Zn-CHI_3$	15–20	48
$Zn/Cu-CHI_3$	15–20	47
$Zn-CH_2I_2$	15–20	52
$Zn/Cu-CH_2I_2$	15–20	76
$Zn-CH_3I$	15–20	50
$Zn/Cu-CH_3I$	15–20	48
$Zn-I_2$	15–20	45
$Zn/Cu-I_2$	15–20	58
$AlCl_3$	0–5	55
ZnI_2	0–5	30
$ZnCl_2$	0–5	35

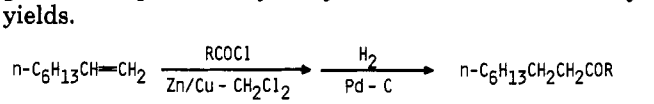
[a] Isolated. [b] The yields based on 1.

Table II. Acylation of Cyclohexene (1) with Acid Chlorides 2a-g Promoted by $Zn/Cu-CH_2I_2$ or Aluminum Chloride

acid chloride	R in RCOCl	% yield[a,b] of 3 method A[c,e]	% yield[a,b] of 3 method B[d,f]	ref
2a	CH_3	68	50	8
2b	C_2H_5	74	40	9
2c	n-C_3H_7	76 (77[f])	60	9
2d	i-C_3H_7	75 (74[f])	30	9
2e	t-C_4H_9	71		
2f	C_6H_5	57	40	10
2g	$CH_2CH_2CO_2CH_3$	68[f]	41	11

[a] Isolated. [b] The yields based on 1. [c] The $Zn/Cu-CH_2I_2$ compound was used. [d] Aluminum chloride was used according to the reported methods.[8–11] [e] The mixture of products was treated with 1 M potassium hydroxide in methanol. [f] The mixture of products was distilled over anhydrous sodium carbonate.

The similar acylation of 1-octene (**4**) and subsequent catalytic hydrogenation of the crude mixture of products gave the expected octyl alkyl ketones **5** in satisfactory yields.



4 **5c**, R=n-C_3H_7 (Y=70%) **5d**, R=i-C_3H_7 (Y=67%)

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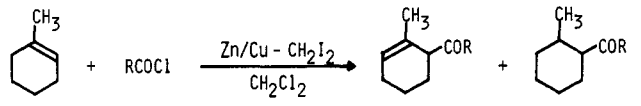
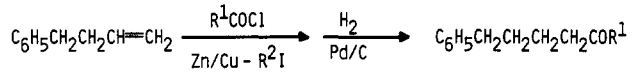
Unconjugated ketones, 1-methyl-6-acylcyclohexenes **7b,d**, were obtained as the major products through the reaction of 1-methylcyclohexene (**6**) with acid chlorides **2b** and **2d** under the similar conditions, being accompanied by a small amount of the corresponding saturated ketones **8b** and **8d**.[12,14]



6 **2b,d** R=C_2H_5 **7b**, 63% **8b**, 4%
R=i-C_3H_7 **7d**, 70% **8d**, 6%

These results indicate that the present acylation fully follows the Markovnikov rule.

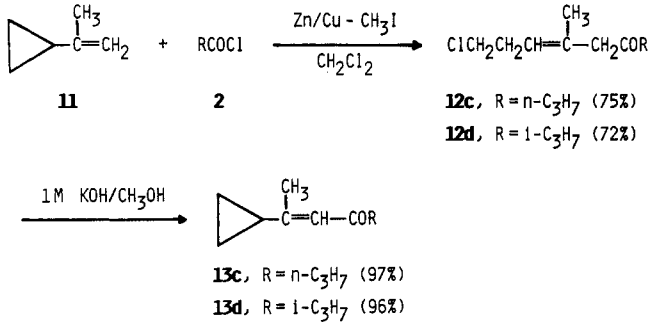
Furthermore, useful selectivity of the present zinc compounds was found in the acylation of 4-phenyl-1-butene (**9**) and 2-cyclopropylpropene (**11**) under the similar conditions. The reaction of **9** with **2c** or **2d** followed by hydrogenation yielded 4-phenylbutyl propyl ketone (**10c**) or 4-phenylbutyl isopropyl ketone (**10d**) in reasonable yield.



9 $R^2 = CH_2I_2$ **10c**, R^1=n-C_3H_7 (54%)
$R^2 = CH_3I$ **10c**, R^1=n-C_3H_7 (43%)
$R^2 = CH_2I_2$ **10d**, R^1=i-C_3H_7 (48%)
$R^2 = CH_3I$ **10d**, R^1=i-C_3H_7 (34%)

None of the aromatic ring-substituted products were detected in the mixture of products. Substitution of the zinc compounds by usual Lewis acids such as zinc chloride or aluminum chloride brought about the formation of small amounts of complex mixtures containing the expected ketones in the yields of 2–5%.

In the reaction of **11** with **2c** or **2d** yielding stereoisomeric mixtures of the ring-opened products **12c** or **12d**, the

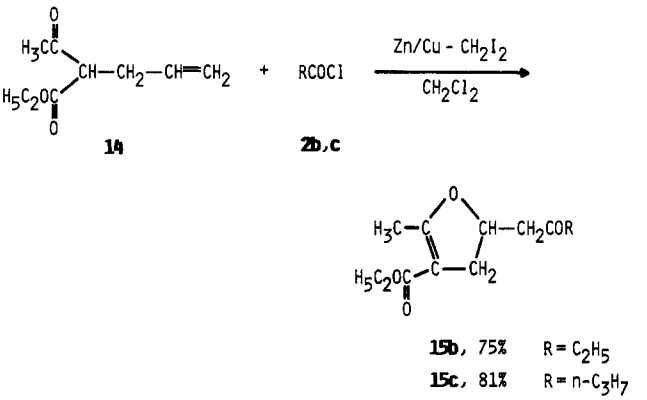


11 **2** **12c**, R=n-C_3H_7 (75%)
12d, R=i-C_3H_7 (72%)

13c, R=n-C_3H_7 (97%)
13d, R=i-C_3H_7 (96%)

active zinc compound prepared from Zn/Cu couple and methyl iodide promotes the reaction more effectively (**12c**, 75%; **12d**, 72%) than the Zn/Cu–CH_2I_2 compound (**12c**, 56%; **12d**, 53%) or zinc chloride (**12c**, 55%; **12d**, 52%). Interestingly, the treatment of the acylated products **12c,d** with 1 M potassium hydroxide in methanol gave recyclized α,β-conjugated enones **13c,d** in almost quantitative yields.

A carboalkoxyl group existing in the starting olefin did not disturb the acylation, but the acyl group was incorporated into the reaction as an enol group, since it was located in a suitable position. Thus, the reaction of ethyl allylacetoacetate (**14**) with acid chloride **2b** or **2c** gave 2,3-dihydrofuran derivative **15b** or **15c** in 75–81% yields.



14 **2b,c**

15b, 75% R=C_2H_5
15c, 81% R=n-C_3H_7

In most reactions described above, Simmons–Smith-type reagent, that is, Zn/Cu–CH_2I_2, gave the best result without showing any cyclopropanation. Although some species derived in situ from the active zinc compounds seem to behave as the unique catalyst in the present acylation, the detailed structures of the species are not clear. It is likely, however, that the active zinc compounds generate the active species little by little in the reaction mixture.

On the basis of high selectivity, better yield, mild conditions, and simple procedure, the present acylation possesses a high potentiality for synthesis of α,β-unsaturated ketones and saturated ketones from aliphatic olefins.

Experimental Section

General Procedure for Acylation of Cyclohexene (1), 1-Octene (4), 1-Methylcyclohexene (6), 4-Phenyl-1-butene (9), 2-Cyclopropylpropene (11), or Ethyl Allylacetoacetate (14) with Acid Chlorides 2a-g in the Presence of the Active Zinc Compounds. The active zinc compounds were prepared as follows.[7] A mixture of 6.54 g (0.10 mol) of zinc dust and 0.99 g (0.01 mol) of cuprous chloride in 30 mL of methylene chloride was refluxed with stirring under an atmosphere of nitrogen for 30 min. After the mixture was cooled to room temperature, 0.05 mol of an alkyl iodide (iodoform, methylene iodide, or methyl iodide) or iodine was added to the mixture, which was then refluxed for an additional 1 h. Into the solution of the freshly prepared active zinc compounds was added in a few minutes a solution of 0.05 mol of an olefin in 10 mL of methylene chloride at 0–5 °C with stirring under an atmosphere of nitrogen. After a short period,[16] a solution of 0.10 mol of an acid chloride in 10 mL of methylene chloride was added dropwise into the stirred mixture in 15 min at 15–20 °C with external cooling. An exothermic reaction took place, and the mixture gradually turned red-brown. The reaction mixture was stirred at room temperature for 2 h and then was refluxed for another 2 h. Then, 30 mL of 10% aqueous sulfuric acid was carefully added into the mixture under cooling with an ice–water bath. The reaction mixture was filtered with suction and extracted (3 × 50 mL of ether). The combined ethereal solution was washed (saturated aqueous $NaHCO_3$), dried ($MgSO_4$), and concentrated to give a mixture of products. The crude mixture of acylated products was subsequently subjected to base-catalyzed treatment or catalytic hydrogenation. The products **7b,d** and **8b,d** were identified by comparison of their gas chromatographic and spectroscopic behaviors with those of authentic samples.[9,15] Each of the products **12c,d** obtained by acylation of **11** was a mixture of two stereoisomers, and the ratio of the stereoisomers determined by gas chromatographic techniques was approximately 7:3 for both products. The major stereoisomers were isolated by preparative gas chromatography, though their stereoconfiguration could not be assigned by spectroscopic analyses.

(12) Saturated ketones **8b,d** may be formed through the reduction of the corresponding β-chloro ketones with the excess amount of zinc. The similar formation of acetylcyclohexane in the $AlCl_3$-promoted acylation of cyclohexene has been reported.[13]

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(14) Compounds **8b,d** were found to be mainly trans isomers by comparison of their gas chromatographic and spectroscopic behaviors with those of authentic samples.[9,15]

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(16) Olefins remained unchanged until the addition of acid chlorides.

The products **15b,c** were also isolated by fractional distillation, and their spectroscopic behaviors were consistent with their assigned structures.

Stereoisomeric mixture of 1-chloro-4-methyl-3-nonen-6-one (12c): bp 101–103 °C (4 mmHg); yield 75%; NMR (CCl_4) δ 5.21 (t, J = 5.2 Hz, 1 H), 3.45 (t, J = 6.1 Hz, 2 H), 2.97 and 3.04 (s, 2 H), 2.25–2.81 (m, 4 H), 1.62 and 1.70 (s, 3 H), 1.21–1.82 (m, 2 H), 0.90 (t, J = 6.3 Hz, 3 H); IR (neat) 1725, 1610, 960 cm^{-1}. Anal. Calcd for $C_{10}H_{17}OCl$: C, 63.65; H, 9.08; Cl, 18.79. Found: C, 63.58; H, 9.11; Cl, 18.98.

Major stereoisomer of 12c: NMR (CCl_4) δ 5.21 (t, J = 5.2 Hz, 1 H), 3.45 (t, J = 6.1 Hz, 2 H), 2.97 (s, 2 H), 2.25–2.62 (m, 4 H), 1.62 (s, 3 H), 1.21–1.71 (m, 2 H), 0.90 (t, J = 6.3 Hz, 3 H); IR (neat) 1725, 1610, 960 cm^{-1}.

Stereoisomeric mixture of 1-chloro-4,7-dimethyl-3-octen-6-one (12d): bp 102–103 °C (4 mmHg); yield 72%; NMR (CCl_4) δ 5.18 (t, J = 5.8 Hz, 1 H), 3.43 (t, J = 6.0 Hz, 2 H), 3.03 and 3.10 (s, 2 H), 2.23–2.82 (m, 3 H), 1.61 and 1.68 (s, 3 H), 1.03 (d, J = 5.8 Hz, 6 H); IR (neat) 1715, 1610, 960 cm^{-1}. Anal. Calcd for $C_{10}H_{17}OCl$: C, 63.65; H, 9.08; Cl, 18.79. Found: C, 63.71; H, 9.07; Cl, 18.74.

Major stereoisomer of 12d: NMR (CCl_4) δ 5.15 (t, J = 5.6 Hz, 1 H), 3.43 (t, J = 6.0 Hz, 2 H), 3.30 (s, 2 H), 2.23–2.59 (m, 3 H), 1.61 (s, 3 H), 1.01 (d, J = 5.6 Hz, 6 H); IR (neat) 1715, 1610, 960 cm^{-1}.

1-(2,3-Dihydro-4-carbethoxy-5-methylfuryl)butan-2-one (15b): bp 132–134 °C (5 mmHg); 75%; NMR (CCl_4) δ 5.40–4.95 (m, 1 H), 4.28 (q, J = 7.1 Hz, 2 H), 2.94 and 2.90 (d, J = 6.0 Hz, 2 H), 2.54 (q, J = 8.0 Hz, 2 H), 2.45 (d, J = 8.0 Hz, 2 H), 2.20 (s, 3 H), 1.31 (t, J = 7.1 Hz, 3 H), 1.09 (t, J = 8.0 Hz, 3 H); IR (neat) 1720, 1710, 1690, 1080 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.94; H, 8.12.

1-(2,3-Dihydro-4-carbethoxy-5-methylfuryl)pentan-2-one (15c): bp 138–140 °C (5 mmHg); yield 81%; NMR (CCl_4) δ 5.32–4.48 (m, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 2.83 and 2.70 (d, J = 7.0 Hz, 2 H), 2.50 (t, J = 8.0 Hz, 2 H), 2.39 (d, J = 8.0 Hz, 2 H), 2.15 (s, 3 H), 1.63 (q, J = 8.0 Hz, 2 H), 1.29 (t, J = 7. 1 Hz, 3 H), 0.96 (t, J = 8.0 Hz, 3 H); IR (neat) 1720, 1710, 1690, 1080 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.10; H, 8.29.

Base-Catalyzed Treatment of 12c,d and of the Crude Mixture of Products Obtained by Acylation of 1. With stirring at 15–20 °C, 5.0 g of **12c,d** or the crude mixture of the products obtained by acylation of **1** with **2a–g** was added into 100 mL of 1 M methanolic potassium hydroxide solution. Then, the mixture was allowed to stand at room temperature until it was transformed into almost a single compound. The course of the reaction was monitored by the gas chromatographic technique. It took 2–3 days in most cases. After the solvent was removed under reduced pressure, the residue was poured into 100 mL of ice-water, and neutralized with glacial acetic acid. The aqueous solution was extracted (3 × 50 mL of ether), and the combined ethereal solution was washed (saturated aqueous $NaHCO_3$), dried ($MgSO_4$) and concentrated to give the α,β-unsaturated ketone **3a–g**, or **13c,d**. The isolated yields of **3a–g** are shown in Table II and their structures were identified by comparison of their spectroscopic behaviors with those of authentic samples.[8-11,17] The gas chromatographic analysis of β-cyclopropyl-α,β-unsaturated ketones **13c,d** showed that both products were mixtures of stereoisomers E and Z, the ratio being 95/5 for both **13c,d**. The major stereoisomers were isolated by preparative gas chromatography and tentatively assigned to be E isomers on the basis of comparison of their NMR spectra with those of the E isomer and the E,Z mixture of 4-cyclopropyl-3-penten-2-one.[18,19]

(*E*)-2-Cyclopropyl-2-hepten-4-one ((*E*)-13c): bp 105–107 °C (25 mmHg); NMR (CCl_4) δ 5.92 (br s, 1 H), 2.28 (t, J = 6.5 Hz, 2 H), 1.89 (s, 3 H), 1.78–1.25 (m, 3 H), 0.90 (t, J = 6.2 Hz, 3 H), 0.91–0.60 (m, 4 H); IR (neat) 1670, 1600 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.46; H, 9.85.

(*E*)-2-Cyclopropyl-5-methyl-2-hexen-4-one ((*E*)-13d): bp 107–108 °C (25 mmHg); NMR (CCl_4) δ 5.93 (br s, 1 H), 2.75–2.23 (m, 1 H), 1.89 (s, 3 H), 1.62–1.32 (m, 1 H), 1.03 (d, J = 6.0 Hz, 6 H), 0.92–0.58 (m, 4 H); IR (neat) 1670, 1600 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.61; H, 9.74.

Catalytic Hydrogenation of the Crude Mixture of Products Obtained by Acylation of 4 or 9. By use of 0.50 g of 10% palladium on carbon as a catalyst, hydrogenation of 5.0 g of the crude mixture of products obtained by acylation of **4** or **9** was carried out in 50 mL of absolute ethanol to give saturated ketones **5c,d** or **10c,d**. The products, octyl propyl ketone (**5c**) and octyl isopropyl ketone (**5d**), showed identical spectroscopic and gas chromatographic behaviors with those of authentic samples.[20,21] The structures of 4-phenylbutyl propyl ketone (**10c**) and 4-phenylbutyl isopropyl ketone (**10d**) were identified by spectroscopic and elemental analyses.

4-Phenylbutyl propyl ketone (10c): bp 134–135 °C (2 mmHg); NMR (CCl_4) δ 7.02 (br s, 5 H), 2.12–2.10 (m, 6 H), 1.89–1.25 (m, 6 H), 0.91 (t, J = 6.0 Hz, 3 H); IR (neat) 1700 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.08; H, 9.89.

4-Phenylbutyl isopropyl ketone (10d): bp 137–138 °C (2 mmHg); NMR (CCl_4) δ 7.12 (br s, 5 H), 2.85–2.18 (m, 5 H), 1.78–1.44 (m, 4 H), 1.03 (d, J = 5.8 Hz, 6 H); IR (neat) 1709 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.41; H, 9.86.

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Registry No. **1**, 110-83-8; **2a**, 75-36-5; **2b**, 79-03-8; **2c**, 141-75-3; **2d**, 79-30-1; **2e**, 3282-30-2; **2f**, 98-88-4; **2g**, 1490-25-1; **3a**, 932-66-1; **3b**, 1655-03-4; **3c**, 30857-53-5; **3d**, 56922-88-4; **3e**, 37720-76-6; **3f**, 17040-65-2; **3g**, 85995-67-1; **4**, 111-66-0; **5c**, 6137-26-4; **5d**, 6315-95-3; **6**, 591-49-1; **7b**, 20937-68-2; **7d**, 20937-65-9; **8b**, 85995-78-4; **8d**, 85995-79-5; **9**, 768-56-9; **10c**, 85995-68-2; **10d**, 85995-69-3; **11**, 4663-22-3; (*E*)-**12c**, 85995-70-6; (*Z*)-**12c**, 85995-76-2; (*E*)-**12d**, 85995-71-7; (*Z*)-**12d**, 85995-77-3; (*E*)-**13c**, 85995-72-8; (*E*)-**13d**, 85995-73-9; **14**, 610-89-9; **15b**, 85995-74-0; **15c**, 85995-75-1; Zn, 7440-66-6.

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