J. Org. Chem. **1997,** *62,* 4327−4329

Lewis Acid-Promoted Coupling Reactions of Acid Chlorides with Organoaluminum and Organozinc Reagents

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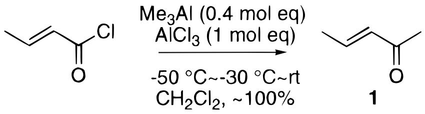
Received February 11, 1997[⊗]

An efficient synthesis of α,*β*-unsaturated ketones by the reaction of acid chlorides with trialkylaluminum (1/3 mole equiv) in the presence of $AlCl_3$ (1 mol equiv) is described. Dialkylzincs were also useful and are easier to prepare than trialkylaluminum. Reaction of RCOCl with $R'AlCl_2$ or R'_2AlCl gave R′COR, without $AlCl_3$, in high yield.

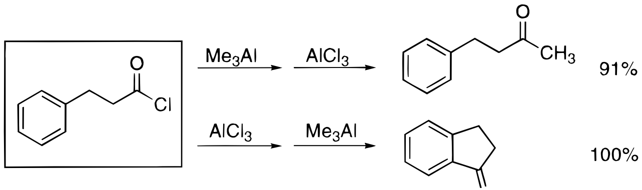
The coupling reactions of alkylmetal reagents and acid halides provide a useful method for synthesizing ketones.[1−3] During our study of the Diels−Alder reaction,[4] we became interested in reacting acid chlorides with organoaluminum reagents to give ketones in a single operation. Inspired by some earlier reports,[2,3] we developed a practical method for producing (*E*)-pent-3-en-2-one (**1**) (Scheme 1), a useful precursor for some silyloxy dienes, by reacting crotonyl chloride and triethylaluminum.[5] In this report, we describe this reaction in detail and its extension to an organozinc reagent.

When a CH_2Cl_2 solution of trimethylaluminum (0.4 equiv) was added to a solution of crotonyl chloride and aluminum chloride (1.0 equiv) in CH_2Cl_2, alkylation proceeded to give (*E*)-pent-3-en-2-one (**1**) quantitatively (Table 1). The presence of aluminum chloride was essential; without aluminum chloride, only 9% of **1** was obtained. Although aluminum fluoride and gallium chloride were less effective, methylaluminum chloride and dimethylaluminum chloride were effective for the alkylation of crotonyl chloride.

Scheme 1



Scheme 2



The reaction of phenylpropionyl chloride with trimethylaluminum was interesting from a mechanistic point of view. When a solution of aluminum chloride was added to a mixture of the acid chloride and trimethylaluminum, the desired propiophenone was obtained in 91% yield (Scheme 2). However, the addition of trimethylaluminum to a mixture of aluminum chloride and the acid chloride under the same conditions gave 1-indanone quantitatively. These results suggested that the reaction did not proceed via the simple acylinium ion complex (A in Figure 1), but rather proceeded via the acyl chloride−AlR'_3 complex (B) activated by the AlClXY species (X, Y = Cl or alkyl) as shown in Figure 1. A bulky aluminum reagent, such as trioctylaluminum, also worked without any problems.

The general procedure, which has been reported previously,[5] was generally reproducible for the preparation of a few grams of **1**. However, we encountered a serious problem when we tried to prepare a large quantity (>10 g) of **1**. Specifically, the product was contaminated by a varying amount of 3-chloropentan-2-one, and it was difficult to separate these compounds because of their close boiling points. The amount of contaminating chloro ketone depended on the workup prodedures (**1**:chloro ketone = 1:1−10:1), such as the washing time using aqueous base and the time necessary for removal of CH_2Cl_2 under atmospheric pressure. Finally, we established two procedures for the large-scale preparation of **1**. One procedure consists of the elimination of hydrogen chloride from the chloro ketone to **1**, basically as described in ref 6. The product obtained using this protocol sometimes contained a trace amount of *β*,*γ*-unsaturated ketone.

Since the addition of HCl to **1** appeared to occur when CH_2Cl_2 was removed by distillation under atmospheric pressure, the second procedure included the rapid distillation of a mixture of CH_2Cl_2 and **1** under reduced pressure at less than 50 °C using a cold trap (−78 °C). The solvents were then distilled in the presence of quinoline. Purification of the residue by distillation under vacuum gave on the order of 30 g of pure **1**.

Regarding the preparation of organometallic reagents, dialkylzinc reagents are much easier to prepare and sometimes more stable than trialkylaluminums.[1,7] Thus, we next focused our attention on the use of dimethylzinc

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[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1997.

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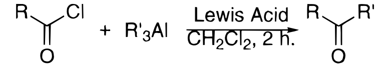
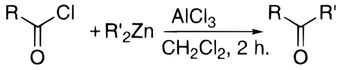
S0022-3263(97)00244-2 CCC: $14.00

Table 1. Reaction of Acid Chlorides with Trialkylaluminum

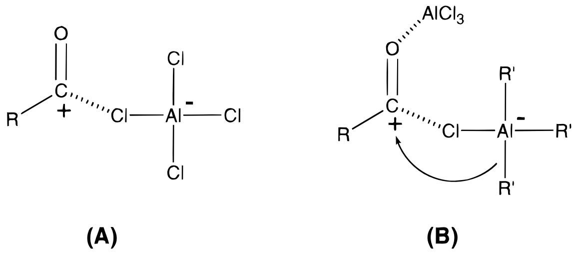


entry	RCOCl	R'_3Al	Lewis acid	product	yield (%)
1	$CH_3CH=CHCOCl$	Me_3Al	$AlCl_3$	$CH_3CH=CHCOCH_3$ (**1**)	100
2	$CH_3CH=CHCOCl$	Me_3Al		$CH_3CH=CHCOCH_3$ (**1**)	9
3	$CH_3CH=CHCOCl$	Me_3Al	AlF_3	$CH_3CH=CHCOCH_3$ (**1**)	25
4	$CH_3CH=CHCOCl$	Me_3Al	$GaCl_3$	$CH_3CH=CHCOCH_3$ (**1**)	48
5	$CH_3CH=CHCOCl$	$MeAlCl_2$		$CH_3CH=CHCOCH_3$ (**1**)	100
6	$CH_3CH=CHCOCl$	Me_2AlCl		$CH_3CH=CHCOCH_3$ (**1**)	77
7	$CH_3CH=CHCOCl$	Oct_3Al	$AlCl_3$	$CH_3CH=CHCOC_8H_{17}$ (**2**)	88
8	$C_8H_{17}COCl$	Oct_3Al	$AlCl_3$	$C_8H_{17}COC_8H_{17}$ (**3**)[9]	100

Table 2. Reaction of Acid Chlorides with Dialkylzincs



entry	RCOCl	R'_2Zn	product	yield (%)
1	$CH_3CH=CHCOCl$	Me_2Zn	$CH_3CH=CHCOCH_3$ (**1**)[5]	100
2	$PhCH=CHCOCl$	Et_2Zn	$PhCH=CHCOC_2H_5$ (**4**)[10]	71
3	$C_7H_{15}COCl$	Et_2Zn	$C_7H_{15}COC_2H_5$ (**5**)[11]	94
4	$CH_3CH=CHCOCl$	Et_2Zn	$CH_3CH=CHCOC_2H_5$ (**6**)[5]	77
5	$PhCOCl$	Et_2Zn	$PhCOC_2H_5$ (**7**)[12]	86
6	$PhCH_2COCl$	Et_2Zn	$PhCH_2COC_2H_5$ (**8**)[13]	99



(A) (B)

Figure 1.

instead of trimethylaluminum in this transformation. As expected, the ketone (**1**) was obtained quantitatively under comparable reaction conditions. Without aluminum chloride, **1** was not obtained at all. Various catalysts have been reported to be effective in the reaction of acid chlorides with organoaluminum reagents,[3] while only a palladium catalyst has been effective in the reaction of acid chlorides with organozinc reagents.[7,8] The results of the current study are summarized in Table 2 and clearly demonstrate its general synthetic utility.

In summary, we have developed a novel synthetic method for ketones: i.e., the Lewis acid-promoted reaction of acid chlorides with dialkylzincs, as well as a comparable reaction with alkylaluminum chlorides. The ease of preparation and the stability of dialkylzincs compared to trialkylaluminum make these reactions useful for ketone synthesis.[14]

Experimental Section

Acid chlorides, trialkylaluminum, and dialkylzinc were used as obtained from commercial sources. Dichloromethane and THF were freshly distilled over CaH_2 and sodium/benzophenone, respectively. All of the reactions were usually carried out under an argon atmosphere in well-dried glassware, unless noted otherwise. Column chromatography was performed using Merck silica gel 60.

Typical Procedure for the Reaction of Acid Chloride with Trialkylaluminum. To a cooled (−50 °C) suspension of $AlCl_3$ (31.3 mmol) in CH_2Cl_2 (25 mL) was added a solution of the acid chloride (31.3 mmol) in CH_2Cl_2 (10 mL) over 15 min under an argon atmosphere. The mixture was stirred for about 1 h and cooled to −30 °C. A solution of trialkylaluminum (12.6 mmol) in CH_2Cl_2 (13 mL) was added over 30−60 min. The mixture was then kept at rt for 2 h, recooled to 0 °C, and quenched by the addition of water. The organic layer was separated, and the aqueous layer was washed with Et_2O. The combined organic layer was washed with 5% aqueous $NaHCO_3$ and then with water and finally dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel to give the corresponding ketone. Each product was characterized by IR, NMR, and mass spectroscopy.

Typical Procedure for the Reaction of Acid Chloride with Methylaluminum Dichloride or Dimethylaluminum Chloride. To a cooled (−30 °C) solution of crotonyl chloride (31.3 mmol) in CH_2Cl_2 (35 mL) was added a solution of methylaluminum dichloride (37.5 mmol) or dimethylaluminum chloride (18.8 mmol) in CH_2Cl_2 (13 mL) over 30 min. The mixture was then kept at rt for 2 h, recooled to 0 °C, and quenched by the addition of water. The workup as above gave a residue that was subjected to distillation under reduced pressure to afford (*E*)-pent-3-en-2-one (**1**) (31.4 mmol and 24.1 mmol, 100% and 77%, respectively; bp 40 °C/30 mmHg) as a colorless oil: IR (neat) cm^{-1} 3040, 2980, 2330, 1720, 1700, 1680, 1640, 1450, 1380, 1360, 1320, 1290, 1280, 1260, 1190,

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1040, 1020 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.92 (3H, dd, $J = 6.9, 1.7$ Hz), 2.24 (3H, s), 6.10 (1H, dd, $J = 15.9, 9.1$ Hz), 6.83 (1H, dq, $J = 13.8, 6.7$ Hz).

4-Phenylbutan-2-one. A solution of trimethylaluminum (1.05 M, *n*-hexane solution, 7.99 mL, 8.35 mmol) and CH_2Cl_2 (12 mL) at −50 °C over 30 min was added to a solution of 3-phenylpropionyl chloride (3.52 g, 20.87 mmol) in CH_2Cl_2 (50 mL). After the mixture was stirred for 1 h at under the previously described reaction conditions, aluminum chloride (2.78 g, 20.87 mmol) was added. The mixture was stirred for 1.5 h at room temperature and poured over ice. Usual workup gave a residue that was purified with silica gel column chromatography (AcOEt:*n*-hexane, 1:10) to afford 4-phenylbutan-2-one[15] (2.82 g, 91%).

Preparation of ∼30 g of (*E*)-Pent-3-en-2-one. A solution of 1.0 M $MeAlCl_2$ in hexane (574 mL) was added dropwise to a solution of crotonyl chloride (478.3 mmol) in CH_2Cl_2 (400 mL) at −30 °C. After being stirred for an additional 1 h, the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was poured over ice (500 g), and the separated organic layer was washed with saturated K_2CO_3 (aq) (300 mL) and brine (200 mL × 3). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was distilled under reduced pressure (room temperature/120 mmHg to 50 °C/20 mmHg). After quinoline (10 mL) was added to the distillate, the remaining CH_2Cl_2 was removed by distillation under atmospheric pressure. Distillation of the residue under reduced pressure gave (*E*)-pent-3-en-2-one (44−47 °C/40 mmHg, 30.72 g, 76.3%).

Typical Procedure for the Reaction of Acid Chloride with Dialkylzinc. To a cooled (−50 °C) suspension of $AlCl_3$ (31.3 mmol) in CH_2Cl_2 (25 mL) was added a solution of the acid chloride (31.3 mmol) in CH_2Cl_2 (10 mL) over 15 min under an argon atmosphere. The mixture was stirred for ∼1 h and cooled to −30 °C. A solution of dialkylzinc (18.8 mmol) in CH_2Cl_2 (19 mL) was added over 30−60 min. The mixture was then kept at rt for 2 h, recooled to 0 °C, and quenched by the addition of water. Usual workup afforded a residue that was subjected to distillation under reduced pressure or purified by column chromatography on silica gel to give the corresponding ketone. Each product was characterized by IR, NMR and mass spectroscopy.

(*E*)-2-Dodecen-4-one (2): *Rf* = 0.66 (*n*-hexane:AcOEt = 10:1); IR (KBr) cm^{-1} 2940, 2855, 1695, 1685, 1460, 1440, 1380, 1280, 1200; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 0.87 (3H, m), 1.28 (12H, m), 1.90 (3H, dd, $J = 6.8, 1.7$ Hz), 2.51 (2H, d, $J = 7.6$ Hz), 6.12 (1H, dd, $J = 15.7, 1.7$ Hz), 6.84 (1H, dd, $J = 15.7, 6.7$ Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 14.05, 18.16, 22.61, 24.29, 29.11, 29.30, 29.36, 31.79, 40.04, 131.95, 142.21, 200.74; LRMS (FAB) *m*/*z* 183 (20), 141 (100%); HRMS (EI) calcd for $C_{12}H_{22}O$ (M^+) 182.1761, found 182.1761.

Acknowledgment. Financial support from the Ministry of Education, Science and Culture in the form of a Grant-in Aid for Scientific Research and from the Fujisawa Foundation is gratefully acknowledged. We also thank Ms R. Hara at the Chemical Analysis Center of Chiba University for measuring mass spectral data.

Supporting Information Available: NMR spectra of **1** and **2** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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