Direct Easy Synthesis of Ketones from Carboxylic Acids and Chlorinated Compounds†

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Introduction

The reaction of organolithium compounds with carbon dioxide is a standard procedure to prepare carboxylic acids.[1a] In general, small amounts of a ketone are obtained in this process as a byproduct. However, the preparation of ketones[1b] from carboxylates and organolithium compounds can be achieved only under prolonged reflux,[2] using sonication,[3] or in the presence of cerium(III) chloride.[4] Methodologies for ketone synthesis involving other carboxylic acid derivatives of the type RCOX and alkyllithium compounds give usually tertiary alcohols as the main reaction products, and α-deprotonation is often a serious limitation.[5,6] On the other hand, we have recently discovered that the combination of an arene-catalyzed lithiation[7] with Barbier-type conditions[8] (carrying out the lithiation process in the presence of an electrophile) is a versatile methodology to prepare very reactive lithium intermediates, useful species in synthetic organic chemistry. Thus, for instance, unstable functionalized organolithium compounds[9,10] or polylithium synthons[11] can be prepared under very mild reaction conditions. In this paper, we apply the mentioned combination to prepare ketones directly from carboxylic acids and chlorinated derivatives.

Results and Discussion

We first studied the best reaction conditions to carry out the transformation using benzoic acid (**1a**) and *sec*-butyl chloride (**2b**) as reagents (Scheme 1). After varying several parameters such as the temperature (Table 1, entries 1 and 2), reaction time (Table 1, entries 1 and 3, and 7 and 8), arene catalyst (Table 1, entries 1, 5, and 9), filtration of the lithium excess before the final hydrolysis (Table 1, entries 6 and 7), prior formation of the corresponding carboxylate [with *n*-butyllithium (Table 1, entries 1−5) or lithium (Table 1, entries 6−9], or the direct use of the carboxylic acid (Table 1, entry 10), as well as different ways to perform the reaction (Table 1, footnote *a*, methods A−F), we concluded that the best results were obtained using method F, which involves adding the mixture of benzoic acid and *sec*-butyl chloride in THF to the dark green lithium suspension in THF containing a ∼10% of naphthalene at temperatures ranging between 0 and 20 °C for 10 min.

Scheme 1

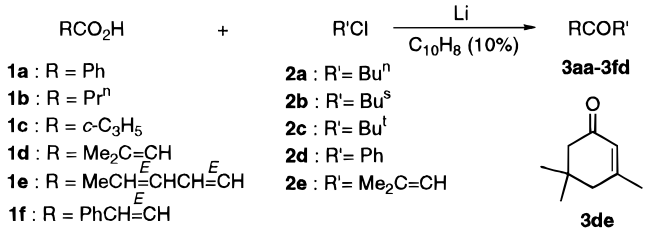

Table 1. Reaction of Benzoic Acid with *sec*-Butyl Chloride: Preparation of Bu^{s}COPh

entry	carboxylate formation	reaction conditions			
		T (°C)	time	method[a]	yield (%)[b]
1	Bu^{n}Li	0→20	3 h	A	57
2	Bu^{n}Li	−78→20	2 h	A	18
3	Bu^{n}Li	0→20	2 h	A	47
4	Bu^{n}Li	0→20	3 h	B	0
5	Bu^{n}Li	0→20	3 h	C	70
6	Li	0→20	3 h	D	70
7	Li	0→20	3 h	D[c]	61
8	Li	0→20	10 min	D[c]	49
9	Li	0→20	2 h	E	48
10	*d*	0→20	10 min	F[c]	97

[a] A catalytic amount of naphthalene (1:0.1 molar ratio) was always used unless noted. Method A: $PhCO_2Li$ + Bu^{s}Cl added to Li + naphthalene. Method B: $PhCO_2Li$ added to the mixture of Bu^{s}Cl + Li + naphthalene. Method C: $PhCO_2Li$ + Bu^{s}Cl added to Li + DTBB. Method D: $PhCO_2Li$ added to Li, then successive addition of naphthalene and Bu^{s}Cl. Method E: $PhCO_2Li$ added to Li, then addition of Bu^{s}Cl. Method F: $PhCO_2H$ + Bu^{s}Cl added to Li + naphthalene. [b] GLC yield. [c] Lithium excess was filtered off before the final hydrolysis. [d] No carboxylate formation prior the lithiation step (see Method F).

The reaction of different carboxylic acids **1** with representative chlorinated derivatives **2** to give the expected ketones **3**, following the above-mentioned protocol, is shown in Scheme 1, and the corresponding results are summarized in Table 2. In all reactions, a portion of the starting carboxylic acid **1** remained unreacted, so the real yields are higher if corrected for unreacted carboxylic acid (Table 2, footnote *b*).

We applied this methodology to the preparation of *trans*-chalcone **3fd** starting from cinnamic acid (**1f**) and chlorobenzene (**2d**) (Table 2, entry 11); using sorbic acid (**1e**) and the chlorinated precursor **2d**, the expected unsaturated ketone **3eb** was isolated in low yield, due probably to a partial decomposition of this final reaction product under the reductive reaction conditions. Finally, we tried to prepare phorone (2,6-dimethylhepta-2,5-dien-4-one) using the methodology shown in Scheme 1, by reaction of 3-methylbut-2-enoic acid (**1d**) with 2-methylprop-1-enyl chloride (**2e**). However, instead of phorone, we obtained isophorone (**3de**) as the only reaction product

† This paper is dedicated to Prof. Nino Fava on his 73rd birthday.

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(10) For the last paper from our laboratory, see: Guijarro, A.; Mancheño, B.; Ortiz, J.; Yus, M. *Tetrahedron* **1996**, *52*, 1643.

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Table 2. Preparation of Ketones 3 from Carboxylic Acids 1 and Chlorinated Derivatives 2

						product[a]		
entry	starting acid	starting chloride	**1**/**2** molar ratio	time	no.	R	R′	yield (%)[b]
1	**1a**	**2a**	1:1.2	15 min	**3aa**	Ph	Bu^n	50 (56)
2	**1a**	**2b**	1:1.2	10 min	**3ab**	Ph	Bu^s	75 (96)
3	**1a**	**2c**	1:2	25 min	**3ac**	Ph	Bu^t	32 (40)
4	**1a**	**2d**	1:1.2	1.5 h	**3ad**	Ph	Ph	63 (98)
5	**1b**	**2a**	1:2	3.5 h	**3ba**	Pr^n	Bu^n	31 (40)
6	**1b**	**2d**	1:2	2 h	**3bd**	Pr^n	Ph	41 (53)
7	**1c**	**2a**	1:2	40 min	**3ca**	c-C_3H_5	Bu^n	62 (73)
8	**1c**	**2d**	1:2	2 h	**3cd**	c-C_3H_5	Ph	53 (63)
9	**1d**	**2e**	1:2	1 h	**3de**	*c*	*c*	20 (50)
10	**1e**	**2b**	1:2	6 h	**3eb**	MeCH=CHCH=CH	Bu^s	15 (28)
11	**1f**	**2d**	1:2	2 h	**3fd**	PhCH=CH	Ph	45 (60)

[a] All products **3** were >96% pure (GLC and 300 MHz ^{1}H NMR), except **3eb** (92%). [b] Isolated yield after column chromatography (silica gel, hexane/diethyl ether) based on the starting carboxylic acid **1**; in parentheses is the corresponding isolated yield based on the consummed carboxylic acid **1**. [c] See text and Scheme 1.

in low yield (Table 2, entry 9). This easy isomerization, under basic conditions, is surprising considering that the reported conditions for such process are far more drastic and tedious (formation of the corresponding silyl enol ether followed by heating at 220 °C in the presence of a Pd(II) catalyst and final acidic hydrolysis).[12]

From a mechanistic point of view, we think that the initially *in situ*-generated lithium carboxylate reacts with the alkyllithium, formed by a rapid naphthalene-catalyzed lithiation of the starting chlorinated material, in a Barbier-type process.

In conclusion, and taking into account the results described in this paper, we consider that this methodology represents an easy way to prepare ketones from carboxylic acids and chlorinated materials (alkyl, alkenyl, or phenyl chloride). In no cases were tertiary alcohols detected as byproducts.

Experimental Section

General. For general information, see ref 11h.

Preparation of Compounds 3. General Procedure. A solution of the carboxylic acid **1** (2.5 mmol) and the chlorinated compound **2** (3 or 5 mmol, see Table 2 for the molar ratio) in THF (5 mL) was added dropwise to a previously prepared deep green suspension of lithium powder (14 mmol) and naphthalene (0.25 mmol) in THF (5 mL) at 0 °C and under argon. The mixture was warmed to 20 °C and stirred for the time specified in Table 2. The excess of lithium was filtered (the nonpyrophoric residue was destroyed by standing the glass fritted funnel in contact with the air moisture under a hood), and the filtrate was hydrolyzed with a saturated solution of $NaHCO_3$. The resulting mixture was extracted with diethyl ether (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated (15 mmHg). The residue was purified by column chromatography (silica gel; hexane/diethyl ether) to yield products **3**. Yields are included in Table 2. Compounds **3aa**,[13] **3ac**,[14] **3ad**,[15] **3bd**,[16] **3cd**,[17] **3de**,[18] and **3fd**[19] were characterized by comparison of their physical and spectroscopic data (IR, ^{1}H and ^{13}C NMR, and MS) with those of the corresponding commercially available samples. For the rest of the compounds **3**, physical and spectroscopic data, as well as references, follow.

***sec*-Butyl Phenyl Ketone (3ab):**[20] R_f 0.66 (hexane/diethyl ether 4:1); IR (film) 3040, 1597, 1687 cm^{-1}; ^{1}H NMR δ 0.82 (t, J = 7.4 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H), 1.35−1.44, 1.69−1.79 (2m, 2H), 3.32−3.41 (m, 1H), 7.33 (m, 2H), 7.43 (m, 1H), 7.86 (m, 2H); ^{13}C NMR δ 11.7, 16.7, 26.6, 42.0, 128.1, 128.5, 136.8, 142.7, 204.0; MS m/z (relative intensity) 162 (M^+, 8), 40 (100).

***n*-Butyl *n*-Propyl Ketone (3ba):**[21] R_f 0.71 (hexane/diethyl ether 4:1); IR (film) 1713 cm^{-1}; ^{1}H NMR δ 0.91 (t, J = 7.0 Hz, 6H), 1.25−1.37 (m, 2H), 1.52−1.63 (m, 4H), 2.35−2.42 (m, 4H); ^{13}C NMR δ 13.6, 13.7, 17.2, 22.3, 25.9, 42.5, 44.6, 211.3; MS m/z (relative intensity) 128 (M^+, 13), 43 (100).

***n*-Butyl Cyclopropyl Ketone (3ca):**[22] R_f 0.33 (hexane/diethyl ether 9:1); IR (film) 1693 cm^{-1}; ^{1}H NMR δ 0.82−0.87, 0.97−1.02 (2m, 4H), 0.92 (t, J = 7.3 Hz, 3H), 1.27−1.44 (m, 2H), 1.55−1.64 (m, 2H), 1.88−1.97 (m, 1H), 2.52−2.56 (t, J = 7.3 Hz, 2H); ^{13}C NMR δ 10.5, 13.9, 20.3, 22.4, 26.2, 43.2, 211.3; MS m/z (relative intensity) 126 (M^+, 8), 69 (100).

(*E*,*E*)-2-Methyl-4,6-nonadien-4-one (3eb):[23] R_f 0.18 (hexane/diethyl ether 9:1); IR (film) 1693, 1633 cm^{-1}; ^{1}H NMR δ 0.88 (t, J = 7.3 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H), 1.66−1.75, 1.76−1.87 (2m, 2H), 2.03 (d, J = 2.3 Hz, 3H), 2.60−2.71 (m, 1H), 6.12−6.27, 7.14−7.27 (2m, 4H); ^{13}C NMR δ 11.7, 16.2, 18.8, 26.3, 45.9, 126.4, 130.4, 140.2, 142.7, 204.3; MS m/z (relative intensity) 152 (M^+, 7), 95 (100).

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