A New Versatile Synthesis of Esters from Grignard Reagents and Chloroformates

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Abstract: Cross-coupling reactions of chloroformates with organocopper reagents, derived from Grignard reagents, cuprous bromide and lithium bromide, provide a rapid and straightforward method for the synthesis of esters.

Key words: organometallic reagents, cross-coupling, chemoselectivity, esters

Esters are usually synthesized as a two-component reaction from an alcohol with the corresponding carboxylic acid. Numerous and well-established methods for this synthetic route are known.[1]

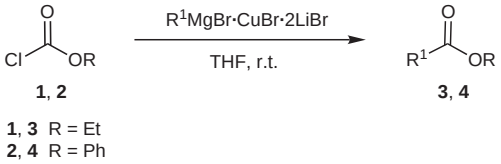
As a part of our extensive work[2] in the area of direct acylation of organometallics,[3] we have recently shown that organocopper reagents derived from Grignard reagents, cuprous bromide and lithium bromide are highly chemoselective reagents.[4–6] Thus, a chemoselective cross-coupling of these reagents with monoesters of dicarboxylic acid chlorides,[4] with α-acetoxy carboxylic acid chlorides[5] and with tartaric acid dichloride,[6] enabled us to achieve a straightforward method for the synthesis of a variety of ketoesters, enantiopure α-acetoxy ketones and C_2-symmetric 1,4-diketones, respectively.

In connection with this type of synthetic work and with the aim to further explore the scope and limitations of our procedure, we considered of interest to investigate on the reactivity of chloroformates, presenting an ester and chloride functionality on the same electrophilic site, toward the above-mentioned organocopper reagents.

Alkoxycarbonylating reagents such as alkyl pyrazole-1-carboxylates or alkyl 1-imidazolecarboxylates were conveniently used in cross-coupling reactions with Grignard reagents to afford esters in good yields.[7,8] However, to the best of our knowledge, the literature gives few reports on the syntheses of esters directly from the reaction of chloroformates with alkyl and aryl Grignard reagents.[9–11] The yields of desired esters are usually low, though superior yields have been reported with the complexes 'PhMgBr/TDA-1' in THF at –15 °C[9a] or by use of dinuclear bridged complexes as catalysts.[9b] Additionally, good yields of esters are obtained by converting in situ the chloroformates to the corresponding acyl tributylphosphonium chlorides.[12] However, the reaction is limited to PhMgBr and MeMgBr and the scope of this method has not been fully explored.

So, we first explored a wide range of aliphatic as well as aromatic organocopper reagents in the coupling reactions with ethyl chloroformate. In all the cases examined the cross-coupling reaction proved to be highly chemoselective and only the replacement of chloride functionality occurred. This result prompted us to devise a straightforward method for synthesizing a variety of esters in high yields and under mild reaction conditions.

We were pleased to find that, under the conditions of our methodology, a host of Grignard reagents reacted smoothly with ethyl or phenyl chloroformate (Scheme 1) to give the corresponding esters in good to excellent yields.[13]



1, **2**

1, **3** R = Et
2, **4** R = Ph

3, **4**

Scheme 1

In particular, as can be seen from the results depicted in Table 1, it should be noted that the reaction of ethyl chloroformate with phenyl- (entry 1), functionalized aryl- (entries 2–4), including sterically hindered species (entry 3), as well as heteroaryl Grignard reagents (entry 5) were successful and gave desired esters **3a**–**e** in good to excellent yields. Moreover, the reaction of aliphatic and alicyclic Grignard reagents (entries 6–9), leading to the esters **3f**–**i**, was also compatible with functional groups such as alkene or aldehyde function, in protected form, presents on the backbones of the Grignard reagent.

A variation of the alcohol component on the chloroformate was next examined. As can be seen from the results in Table 1 (entries 1, 3, 4, 6, 8) the reactions of the phenyl chloroformate with alkyl and aryl Grignard reagents performed particularly well and tend to give the esters **4** in higher yields than those obtained with ethyl chloroformate. In all the reactions examined small amounts of homocoupling product accompanied the cross-coupling products shown in Table 1, which, however, can be easily removed by column chromatography. Another side reaction was the formation of unsymmetrical carbonate.[14] This

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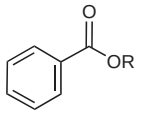
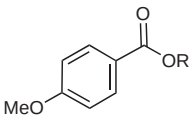
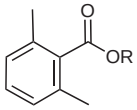
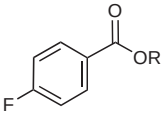
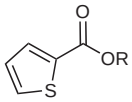
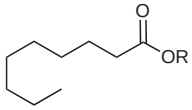
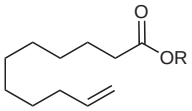
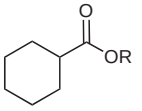
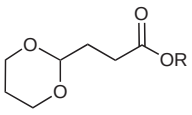
Table 1 Esters **3** and **4** by the Reactions of Chloroformates **1** and **2** with Grignard Reagents

Entry	Grignard reagents R^1	Esters[a] **3**, **4** (yields, %)
1	Phenyl	 **3a** (84); **4a** (84)
2	*p*-Methoxyphenyl	 **3b** (70)
3	2,6-Dimethylphenyl	 **3c** (84); **4c** (98)
4	*p*-Fluorophenyl	 **3d** (71); **4d** (88)
5	2-Thienyl	 **3e** (60)
6	*n*-Octyl	 **3f** (71); **4f** (76)
7	9-Decenyl	 **3g** (72)
8	Cyclohexyl	 **3h** (70); **4h** (84)
9	2-(1,3-Dioxan-2-yl)ethyl	 **3i** (97)

[a] All compounds exhibited spectral data consistent with the assigned structure; yields refer to products purified by chromatography.

byproduct was generally <4%, and in some cases product purification by chromatography was complicated by its similar polarity to compounds **3** and **4**.

In summary the results described in the present study demonstrate that the cross-coupling of ethyl or phenyl chloroformate with Grignard reagents, in the presence of cuprous bromide and lithium bromide, provides a useful tool for the preparation of esters in a rapid and convenient process. It should be pointed out that this new procedure provides esters from alkyl and aryl halides by C_1-carbon-chain extension. Therefore, esters which are otherwise difficult to produce, especially when the acid cannot be synthesized easily,[11] may be obtained in this way. The simplicity of the operations involved and the ready availability of the starting materials suggest that this route to esters represents a practical alternative to currently existing methodology and will enjoy widespread application.

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(13) **Typical Experimental Procedure**
A THF solution (10 mL) of anhyd LiBr (0.665 g, 7.66 mmol) was added at r.t., under nitrogen, to CuBr (0.549 g, 3.83 mmol). A freshly prepared THF solution of 2,6-dimethylphenylmagnesium bromide (4.7 mL, 3.83 mmol) and soon afterwards phenyl chloroformate (0.4 mL, 3.19 mmol) in THF (5 mL) were quickly added to the stirred solution of salts. The mixture was stirred at r.t. for 15 h, quenched with sat. aq NH_4Cl and extracted with EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (silica gel, PE–EtOAc, 9.8:0.2) leading to phenyl 2,6-dimethylbenzoate **4c** (0.707 g, 98% yield). The residual solid was crystallized from hexane giving white crystals of **4c**, mp 50–51 °C. IR (KBr): ν_{max} = 1744, 1600, 1587, 1491, 1466, 1261, 1244, 1182, 1105, 1053, 916, 764, 731, 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.41 (m, 2 H), 7.32–7.22 (m, 4 H), 7.10 (d, *J* = 7.2 Hz, 2 H), 2.48 (s, 6 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.3, 150.6, 135.2, 132.9, 129.8, 129.6, 127.7, 126.1, 121.5, 19.9. MS: *m/z* (%) = 226 (<1) [M^+], 133 (100), 105 (27), 77 (13), 65 (6), 51 (5). The side product phenyl 2,6-dimethylphenyl carbonate (<2%) was identified by the comparison with mass spectral data of an authentic sample independently synthesized: MS: *m/z* (%) = 242 (99) [M^+], 198 (62), 197 (25), 183 (97), 165 (49), 155 (18), 148 (44), 121 (27), 120 (100), 105 (32), 103 (20), 94 (20), 92 (48), 91 (72), 79 (40), 78 (22), 77 (73), 51 (25).

(14) At present, the formation of this side product is not yet clear and is subject to further investigations.