Synthesis of Symmetrical Ketones from Grignard Reagents and 1,1′-Carbonyldiimidazole

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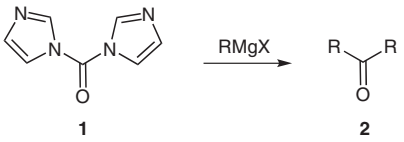
Abstract: Coupling reactions of 1,1′-carbonyldiimidazole with Grignard reagents provide a rapid and straightforward method for the synthesis of symmetrical ketones.

Key words: Grignard reactions, coupling, acylations, 1,1′-carbonyldiimidazole, ketones



Scheme 1

Ketones are highly useful intermediates in organic synthesis for carbon–carbon bond formation and functional group interconversion. Therefore extensive efforts have been made towards the efficient synthesis of this important functionality.[1] One of the most straightforward methods for the synthesis of ketones is the coupling reaction of carboxylic acids or their derivatives with organometallic reagents. However, in spite of the inherent simplicity, its synthetic usefulness is severely limited, mainly due to the simultaneous formation of undesired tertiary and/or secondary alcohols.[2] Thus, a number of techniques have been developed to suppress the formation of tertiary alcohol,[1,3,4] and, in this regard, extensive efforts have been made in our laboratory over recent years.[5]

In connection with this type of synthetic work and with the aim to explore other valuable carbonyl transfer reagents, we considered it to be of interest to further investigate the reactivity of acylazoles with organometallic reagents. Indeed, as recently documented by Staab, Bauer, and Schneider,[6a] acylazolides in general, and *N*-acylimidazoles in particular, are efficient acylating reagents.[6] They have undergone reactions with various nucleophiles, including organometallic reagents, to give a wide range of carbonyl and carboxyl derivatives under mild conditions. However, to the best of our knowledge, the synthesis of ketones directly from the reaction of 1,1′-carbonyldiimidazole with alkyl and aryl Grignard reagents has not been reported in the literature. This observation encouraged us to consider the possibility to develop a simple and general method for the synthesis of a variety of ketones starting directly from Grignard reagents and 1,1′-carbonyldiimidazole (CDI), as a milder and more easily handled substitute of the more toxic phosgene (Scheme 1).

The reaction of Grignard reagents with 1,1′-carbonyldiimidazole (**1**) was optimized for the coupling reaction of **1** with 4-tolylmagnesium bromide. Superior yields of ketone **2b** (80%) were obtained when 2.3 equivalents of the Grignard reagent were added to 1 equivalent of **1** at –80 °C, and the reaction mixture was subsequently warmed to room temperature and kept at the same temperature for one hour (Table 1, entry 2).

The scope of the reaction of 1,1′-carbonyldiimidazole (**1**) with regard to a variation of the Grignard reagent was then investigated (Table 1). The reaction of **1** with phenyl- (entry 1), functionalized aryl- (entries 2–4), as well as hetaryl Grignard reagents (entry 5) were successful and gave the desired ketones **2a**–**e** in good yields when the abovementioned protocol was followed. The coupling reactions of sterically hindered Grignard reagents also gave ketones **2f** and **2g** in good yields (entries 6 and 7), but did not take place at low temperature, implying a lower reactivity of these reagents. To obtain ketones **2f** and **2g** in comparable yields, 2.7 equivalents of the Grignard reagent were added at room temperature, and the reaction mixtures were stirred for three hours at the same temperature. Although our protocol required the use of a slight excess of the organomagnesium reagent (2.3–2.7 equiv), tertiary alcohols **3** were either not obtained as the side products (entries 2, 3, 6, and 7) or were limited at 2–7% (entries 1, 4, and 5), an amount which, however, can easily be removed by column chromatography.

We also investigated the use of alkyl Grignard reagents in the coupling reactions with **1** (Table 1, entries 8–12). These reagents also reacted smoothly to afford the corresponding ketones **2h**–**l** in satisfactory yields. Nevertheless, for the primary alkyl reagents a greater amount of tertiary alcohol **3** formation (5–18%) took place. The ketone **2**/tertiary alcohol **3** product ratio was generally sensitive to the temperature and the amount of excess Grignard reagent used, and may be increased by using a lower excess or two equivalents of Grignard reagent. Our study, however, for the present, was a comparison of the relative performance of several Grignard reagents under fixed conditions.

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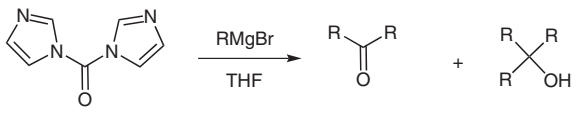
Table 1 Synthesis of Symmetrical Ketones **2**[a]



1 **2** **3**

Entry	R	Temp	Ratio **2/3**[b]	**2**	Yield[c] (%)
1	Ph	–80 °C to r.t.	98:2	**2a**	65
2	4-tolyl	–80 °C to r.t.	100:0	**2b**	80
3	4-$MeOC_6H_4$	–80 °C to r.t.	100:0	**2c**	72
4	4-FC_6H_4	–80 °C to r.t.	93:7	**2d**	65
5	2-thienyl	–80 °C to r.t.	97:3	**2e**	71
6	2-tolyl[d]	r.t.	100:0	**2f**	73
7	1-naphthyl[d]	r.t.	100:0	**2g**	67
8	hexyl	–80 °C to r.t.	85:15	**2h**	55
9	octyl	–80 °C to r.t.	82:18	**2i**	73
10	decyl	–80 °C to r.t.	95:5	**2j**	72
11	dodecyl	–80 °C to r.t.	89:11	**2k**	72
12	cyclohexyl	–80 °C to r.t.	100:0	**2l**	75

[a] Reagents and conditions: RMgBr (2.3 equiv), –80 °C, 30 min, then r.t., 1 h.
[b] The **2/3** ratio of the product mixture was determined by GC analysis.
[c] Yields of products purified by column chromatography.
[d] Reagents and conditions: RMgBr (2.7 equiv), r.t., 3 h.

We have also investigated the possibility of obtaining unsymmetrical substituted ketones. Two different Grignard reagents were added sequentially to 1,1′-carbonyldiimidazole (**1**). However, the addition of one equivalent of phenylmagnesium bromide at –80 °C followed, after 30 minutes, by the addition of one equivalent of 4-tolylmagnesium bromide yielded a mixture of symmetrical and unsymmetrical substituted ketones in comparable amounts (GC analysis). In an effort to expand the scope of this process further, studies on the extension of this strategy to the synthesis of unsymmetrical substituted ketones are currently under investigation.

In conclusion, we have described a new protocol for the *direct* acylation of Grignard reagents, without additional transition-metal catalysts or organic ligands. Aliphatic, aromatic, and heteroaromatic ketones have been synthesized in satisfactory yields by use of a stable and easily accessible acylating agent. We believe that this protocol provides a practical alternative to the existing methods available for the synthesis of ketones by reaction of their corresponding carboxylic acid derivatives with organometallic reagents.

Macherey-Nagel silica gel 60 (particle size 0.040–0.063 mm) was used for column chromatography and Macherey-Nagel aluminum sheets with silica gel 60 F_{254} were used for TLC. GC analysis was performed on a Varian 3900 gas chromatograph equipped with a Supelco capillary column (SLB-5ms, 30 m × 0.25 mm i.d.). GC-MS analysis was performed on a Shimadzu GC-MS-QP5000 gas chromatograph–mass spectrometer equipped with a Supelco capillary column (SLB-5ms, 30 m × 0.25 mm i.d.). ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra of samples in $CDCl_3$ were recorded on a Varian Inova spectrometer.

Ketones 2a–l; General Procedure

A freshly prepared THF soln of RMgBr (2.85 mmol) was added dropwise, under N_2, to a stirred soln of CDI (**1**; 1.24 mmol) in anhyd THF (6 mL) at –80 °C. The resulting mixture was stirred at the same temperature for 30 min, then warmed to r.t. After 1 h, the reaction mixture was quenched with aq NH_4Cl and extracted with EtOAc. The organic extracts were washed with H_2O, dried (Na_2SO_4), and concentrated under vacuum. The residue was purified by column chromatography (silica gel, PE–EtOAc, 95:5); this gave ketones **2a–l**. All products except **2k** are known and commercially available, and were characterized spectroscopically. Spectroscopic data for the known compounds **2a**[7], **2b**[8], **2c**[7], **2f**[7], and **2g**[9] can be found in the literature.

Bis(4-fluorophenyl)methanone (2d)[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.75 (m, 4 H), 7.17–7.09 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.7, 165.3 (d, *J* = 254.4 Hz), 133.6 (d, *J* = 3.0 Hz), 132.4 (d, *J* = 9.2 Hz), 115.5 (d, *J* = 21.9 Hz).

Bis(2-thienyl)methanone (2e)[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (dd, *J* = 3.8, 1.0 Hz, 2 H), 7.67 (dd, *J* = 5.0, 1.0 Hz, 2 H), 7.16 (dd, *J* = 5.0, 3.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7, 142.8, 133.5, 133.1, 127.9.

Tridecan-7-one (2h)[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (t, *J* = 7.4 Hz, 4 H), 1.55–1.45 (m, 4 H), 1.29–1.15 (m, 12 H), 0.82 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.5, 42.7, 31.6, 28.9, 23.8, 22.4, 13.9.

Heptadecan-9-one (2i)[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (t, *J* = 7.4 Hz, 4 H), 1.56–1.46 (m, 4 H), 1.22 (br s, 20 H), 0.83 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.6, 42.7, 31.8, 29.3, 29.2, 29.1, 23.8, 22.6, 14.0.

Henicosan-11-one (2j)[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (t, *J* = 7.4 Hz, 4 H), 1.57–1.47 (m, 4 H), 1.22 (br s, 28 H), 0.84 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.7, 42.8, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 23.9, 22.7, 14.1.

Pentacosan-13-one (2k)[12]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (t, *J* = 7.6 Hz, 4 H), 1.52–1.49 (m, 4 H), 1.23 (br s, 36 H), 0.86 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.8, 42.8, 31.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 23.9, 22.7, 14.1.

MS (EI, 70 eV): *m*/*z* (%) = 252 (2), 213 (8), 197 (31), 169 (2), 152 (5), 127 (3), 123 (3), 109 (6), 96 (11), 95 (10), 85 (14), 83 (10), 71 (42), 69 (14), 59 (19), 58 (44), 57 (66), 55 (43), 43 (100), 41 (56).

Dicyclohexylmethanone (2l)[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48–2.37 (m, 2 H), 1.80–1.66 (m, 8 H), 1.65–1.56 (m, 2 H), 1.35–1.06 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 217.0, 49.1, 28.5, 25.8, 25.7.

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