A Novel Synthesis of Ketones Using 4,6-Pyrimidyl Diesters

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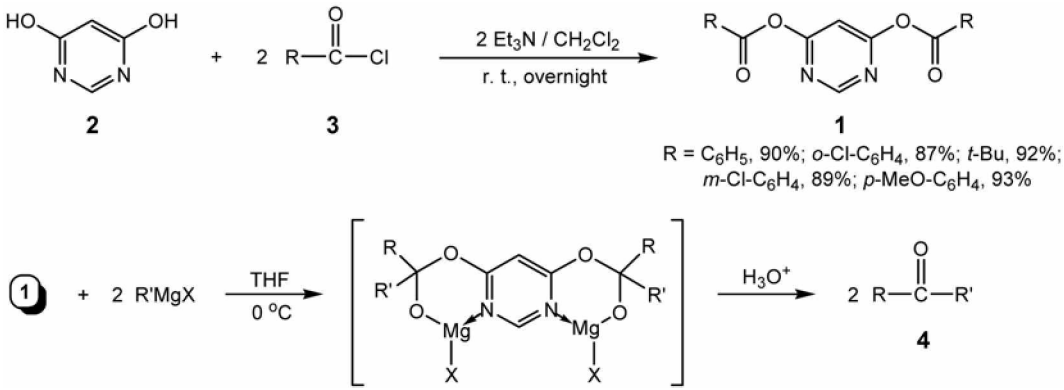
The acylation of organometallics with carboxylic acid derivatives has been generally adopted as a chemoselective method of ketones formation.[1] Several types of acylating agents have been developed to avoid overaddition of organometallics to the desired ketones, suppressing by-products such as tertiary alcohols. The reaction of active esters having 2-pyridyl ligands such as *S*-(2-pyridyl)thioates,[2] 2-pyridyl esters,[3] and *N*-methyl-*N*-(2-pyridyl)amides[4] with Grignard reagents affords 6-membered chelates, which are dissociated to form the ketones by acidic hydrolysis. The treatment of 2-acyloxy-3-methylpyrazines[5] and 3-(*N*-acyl-*N*-methylamino)-1-methylimidazolium iodides[6] with organolithiums or Grignard reagents also gave ketones, but 2 equiv of organometallics were required. Among acylating agents to prepare ketones, *N*-methoxy-*N*-methylamides (Weinreb amides)[7] have been widely used because they react with both organolithiums and Grignard reagents to form various ketones including ynones and β-diketones *via* 5-membered chelates without forming side products.

The synthesis of ketones has been accomplished by the reaction of carboxamides or trifluoro esters with organometallics. *N,N*-Dimethylacetamides,[8] *N*-acylaziridines,[9] and ethyl trifluoroacetate[10] reacted cleanly with both organolithiums and Grignard reagents to form the ketones upon acidic workup of the tetrahedral intermediates, where no significant amounts of overaddition products were not detected. The reaction of benzimidazole methiodide[11] and benzoyl cyanides[12] with Grignard reagents also afforded the methyl ketones and diaryl ketones, respectively. Alternatively ketones were prepared from the nucleophilic addition of Grignard reagents to nitriles[13] and *N*-(ethoxymethylene)-aniline,[14] but the former proceeds in high temperature and the latter requires the additional step of dehydrogenation.

Although several groups have been employed as selective acylating agents, only one acyl group in the acylating agents has been transferred. There is no report on the development of acylating agents which produce 2 equiv of ketones from one acylating agent with Grignard reagents. In this paper we wish to report that 2 equiv of ketones can be efficiently prepared from 4,6-pydimidyl diesters and Grignard reagents in high yields.

4,6-Pyrimidyl diesters **1** were readily prepared by the addition of 2 equiv of acid chlorides **3** to a mixture solution of 1 equiv of 4,6-dihydroxypyrimidine **2** and 2 equiv of triethylamine in methylene chloride at room temperature (Scheme 1). This reaction proceeded slowly because **2** was slightly soluble in methylene chloride. After completion of the reaction, the mixture was separated by aqueous workup and pure **1** was obtained after recrystallization from 20% EtOAc/*n*-hexane. However, 4,6-pyrimidyl dipivalate was partially decomposed during aqueous workup and it was separated by dissolving in THF after evaporation of methylene chloride, followed by filtering off triethylamine hydrochloride, in 92% yield.

The successful synthesis of ketones **4** using **1** was accomplished by the reaction with Grignard reagents in THF at 0 °C. It was determined that 2 equiv of Grignard reagents converted **1** to the corresponding ketones without concomitant addition to the products. For example, the addition of 2 equiv of isobutylmagnesium chloride to a solution of 1 equiv of 4,6-pyrimidyl dibenzoate in THF at 0 °C led to the formation of the precipitate, which was hydrolyzed with

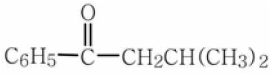
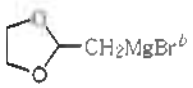
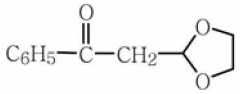
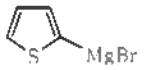
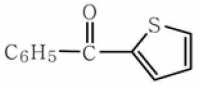
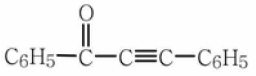
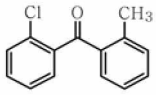
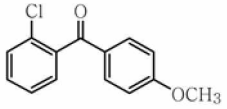
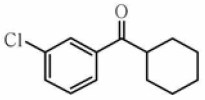
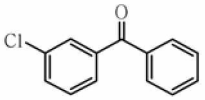
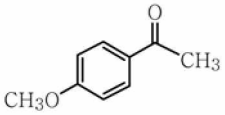
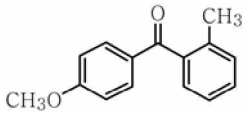
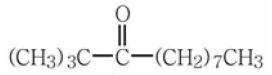
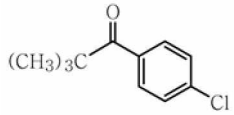
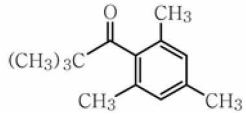


Scheme 1

saturated NH_4Cl solution to give 3-methylbutyrophenone in 92% yield. There was no observable side product such as the corresponding tertiary alcohol due to the subsequent nucleophilic addition of Grignard reagent to the desired ketone. The success of this acylation seemed to result from the formation of the 6-membered chelate between magnesium cation of Grignard reagent and carbonyl oxygen/ring nitrogen of **1**, which was dissociated to give **4** after acidic hydrolysis.

As shown in Table 1, various ketones were efficiently synthesized by this method in high yields (76-93%). The reaction worked well with both aliphatic and aromatic Grignard reagents. Electron withdrawing (**4e-4h**) and electron donating group (**4i**. **4j**) in 4,6-pyrimidyl dibenzoate didn't influence on the nucleophilic acyl substitution of **1** by Grignard reagents. Significantly. the reactions are not limited to primary and secondary Grignard reagents. Thus. the reaction of 4,6-pyrimidyl dipivalate with 2-mesitylmagnesium bromide afforded the sterically hindered 2',4',6'-trimethyl-2.2-dimethylpropiophenone (**4m**) in 84% yield. However,

Table 1. Preparation of ketones from 4,6-pyrimidyl diesters and Grignard reagents[a]

Entry **4**	R	R'MgX	Products	Isolated yield, %
a	C_6H_5	$(CH_3)_2CHCH_2MgCl$		92
b				76
c				88
d		C_6H_5-C≡C-MgCl		83
e	*o*-Cl-C_6H_4	*o*-CH_3-C_6H_4MgCl		85
f		*p*-CH_3O-C_6H_4MgBr		87
g	*m*-Cl-C_6H_4	*c*-$C_6H_{11}MgCl$		89
h		C_6H_5MgBr		90
i	*p*-CH_3O-C_6H_4	CH_3MgBr		92
j		*o*-CH_3-C_6H_4MgCl		93
k	$(CH_3)_3C$	$CH_3(CH_2)_7MgCl$		87
l		*p*-Cl-C_6H_4MgBr		91
m		2,4,6-$(CH_3)_3$-C_6H_2MgBr[c]		84

[a]The reaction was carried out at 0 °C for 10 min. [b]The reaction was carried out at room temperature for 1.5 h. [c]The reaction was carried out between 0 °C and room temperature for 0.5 h.

the reaction of 4,6-pyrimidyl dibenzoate with (1,3-dioxolan-2-ylmethyl)magnesium bromide was completed in 1.5 h at room temperature to give α-(1,3-dioxolan-2-yl)acetophenone (**4b**) in 76% yield, reflecting on the decreased nucleophilicity.

In conclusion the present method provides a novel synthesis of various ketones from **1** and Grignard reagents. It offers advantages: (i) the reactions are clean, (ii) the reaction times are short, and (iii) 2 equiv of ketones is synthesized from 1 equiv of **1** in high yields; thus may be utilized in many synthetic applications.

Experimental Section

Preparation of 4,6-pyrimidyl dibenzoate (General procedure). To a solution of 4,6-dihydroxypyrimidine (561 mg, 5.0 mmol) and triethylamine (1.46 mL, 10.5 mmol) in methylene chloride (40 mL) was added benzoyl chloride (1.41 g, 10.0 mmol) at room temperature. After being stirred overnight, the mixture was poured into saturated $NaHCO_3$ solution (40 mL), extracted with methylene chloride, and washed with brine (40 mL). The aqueous phase was reextracted twice with methylene chloride (2 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized from 20% EtOAc/*n*-hexane to give 4,6-pyrimidyl dibenzoate (1.44 g, 90%): mp 97-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.21-8.24 (m, 4H), 7.65-7.72 (m, 2H), 7.50-7.57 (m, 4H), 7.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 163.2, 159.0, 134.6, 130.6, 128.8, 128.0, 105.5; FT-IR (KBr) 3062, 1746 (C=O), 1569, 1368, 1243, 1049, 696 cm^{-1}.

Preparation of 3-methylbutyrophenone 4a (General procedure). To a solution of 4,6-pyrimidyl dibenzoate (481 mg, 1.5 mmol) in THF (15 mL) was added isobutylmagnesium chloride (0.5 M in THF, 6.0 mL, 3.0 mmol) at 0 °C. After being stirred for 10 min, the mixture was quenched with saturated NH_4Cl solution (3 mL) and THF was evaporated *in vacuo*. The mixture was poured into saturated NH_4Cl solution (30 mL) and extracted with methylene chloride (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by vacuum distillation using Kugelrohr apparatus to give **4a** (448 mg, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93-7.97 (m, 2H), 7.53-7.56 (m, 1H), 7.43-7.48 (m, 2H), 2.83 (d, J = 6.9 Hz, 2H), 2.30 (septet, J = 6.7 Hz, 1H), 1.00 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 137.4, 132.9, 128.5, 128.1, 47.5, 25.2, 22.8; FT-IR (film) 3061, 2957, 2870, 1685 (C=O), 1598, 1448, 1406, 1385, 1365, 1284, 1213, 1006, 752, 691 cm^{-1}; Ms *m/z* (%) 162 (M$^-$, 17), 120 (30), 105 (100), 77 (43), 51 (11).

α-(1,3-Dioxolan-2-yl)acetophenone (4b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 7.1 Hz, 2H), 7.53-7.59 (m, 1H), 7.41-7.46 (m, 2H), 6.52 (dd, J_1 = 14.3 Hz, J_2 = 6.8 Hz, 1H), 4.56 (t, J = 4.7 Hz, 2H), 4.24 (dd, J_1 = 14.3 Hz, J_2 = 2.3 Hz, 1H), 4.07 (dd, J_1 = 6.8 Hz, J_2 = 2.3 Hz, 1H), 4.02 (t, J = 4.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 151.5, 133.1, 129.7, 128.4, 87.1, 65.9, 63.2; FT-IR (film) 3063, 2955, 2877, 1722 (C=O), 1618, 1452, 1366, 1274, 1111, 823, 711 cm^{-1}; Ms *m/z* (%) 192 (M$^-$, 1), 149 (83), 105 (100), 77 (51).

Phenyl 2-thienyl ketone (4c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 4.9 Hz, 1H), 7.64 (d, J = 3.8 Hz, 1H), 7.56-7.61 (m, 1H), 7.47-7.53 (m, 2H), 7.14-7.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.2, 143.6, 138.1, 134.9, 134.2, 132.3, 129.2, 128.4, 128.0; FT-IR (KBr) 3099, 1633 (C=O), 1597, 1411, 1286, 1052, 842, 715 cm^{-1}; Ms *m/z* (%) 188 (M$^-$, 100), 111 (97), 105 (33), 77 (34).

1,3-Diphenyl-2-propyn-1-one (4d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21-8.25 (m, 2H), 7.67-7.70 (m, 2H), 7.63-7.67 (m, 1H), 7.39-7.54 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 136.9, 134.1, 133.1, 130.8, 129.6, 128.7, 128.6, 120.1, 93.1, 86.9; FT-IR (film) 3061, 2198, 1637 (C=O), 1597, 1285, 1012, 757, 696 cm^{-1}; Ms *m/z* (%) 206 (M$^+$, 61), 178 (100), 176 (16), 129 (68).

2-Chloro-2'-methylbenzophenone (4e): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.44 (m, 4H), 7.28-7.37 (m, 3H), 7.15-7.22 (m, 1H), 2.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 139.6, 139.5, 136.9, 132.0, 131.9, 131.8, 131.5, 131.3, 130.3, 129.9, 126.7, 125.5, 21.2; FT-IR (film) 3064, 3021, 2965, 2926, 1671 (C=O), 1589, 1434, 1301, 1055, 926, 743 cm^{-1}; Ms *m/z* (%) 232 (M$^+$+2, 11), 231 (13), 230 (M$^-$, 32), 229 (39), 195 (100), 141 (7), 139 (21), 119 (28), 91 (33).

2-Chloro-4'-methoxybenzophenone (4f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.0 Hz, 2H), 7.40-7.47 (m, 2H), 7.32-7.40 (m, 2H), 6.93 (d, J = 7.0 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 164.5, 139.4, 132.9, 131.5, 131.2, 130.4, 129.8, 129.3, 127.1, 114.3, 55.9; FT-IR (KBr) 3057, 3013, 2973, 1657 (C=O), 1598, 1433, 1255, 1150, 1021, 862, 762 cm^{-1}; Ms *m/z* (%) 248 (M$^+$+2, 14), 246 (M$^-$, 41), 139 (12), 135 (100), 77 (11).

3-Chlorophenyl cyclohexyl ketone (4g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.90 (m, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.50-7.53 (m, 1H), 7.40 (dd, J_1 = 7.8 Hz, J_2 = 7.8 Hz, 1H), 3.15-3.24 (m, 1H), 1.70-1.92 (m, 5H), 1.23-1.56 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 138.4, 135.3, 133.0, 130.3, 128.7, 126.7, 46.1, 29.7, 26.3, 26.1; FT-IR (film) 3067, 2931, 2854, 1681 (C=O), 1449, 1204, 980, 894, 800, 730 cm^{-1}; Ms *m/z* (%) 224 (M$^+$+2, 6), 222 (M$^-$, 18), 187 (35), 167 (19), 141 (36), 139 (100), 113 (10), 111 (30).

3-Chlorobenzophenone (4h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76-7.80 (m, 3H), 7.39-7.77 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 139.3, 136.9, 134.6, 132.8, 132.3, 130.0, 129.9, 129.6, 128.5, 128.1; FT-IR (KBr) 3064, 1662 (C=O), 1568, 1446, 1284, 1077, 897, 780, 764, 719, 697 cm^{-1}; Ms *m/z* (%) 218 (M$^-$+2, 19), 216 (M$^+$, 54), 141 (10), 139 (29), 113 (7), 111 (20), 105 (100), 77 (40).

4-Methoxyacetophenone (4i): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 163.5, 130.6, 130.3, 113.7, 55.5, 26.4; FT-IR (film) 3004, 2967, 1674 (C=O), 1601, 1358, 1258, 1172, 1027, 834 cm^{-1}; Ms *m/z* (%) 150 (M$^+$, 32), 135 (100), 107 (15), 92

(16), 77 (25).

2-Methyl-4'-methoxybenzophenone (4j): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 9.1 Hz, 2H), 7.35-7.40 (m, 1H), 7.21-7.35 (m, 3H), 6.93 (d, J = 9.1 Hz, 2H), 3.87 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 164.1, 139.6, 136.6, 132.9, 131.2, 130.9, 130.2, 128.3, 125.6, 114.1, 55.9, 20.2; FT-IR (film) 3064, 3014, 2961, 1655 (C=O), 1598, 1458, 1257, 1149, 1028, 846, 750 cm^{-1}; Ms *m/z* (%) 226 (M^-, 33), 225 (71), 195 (100), 135 (40), 91 (19), 77 (15).

2,2-Dimethyl-3-undecanone (4k): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (t, J = 7.3 Hz, 2H), 1.50-1.60 (m, 2H), 1.23-1.32 (m, 10H), 1.13 (s, 9H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.2, 44.1, 36.5, 31.9, 29.5, 29.4, 29.2, 26.4, 24.0, 22.7, 14.1; FT-IR (film) 2957, 2926, 1707 (C=O), 1465, 1365, 1073, 723 cm^{-1}; Ms *m/z* (%) 198 (M^+, 3), 141 (66), 71 (38), 57 (100).

4'-Chloro-2,2-dimethylpropiophenone (4l): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 7.7 Hz, 2H), 7.38 (d, J = 7.7 Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0, 137.6, 136.9, 129.9, 128.7, 44.5, 28.4; FT-IR (film) 3072, 2971, 2932, 1675 (C=O), 1588, 1476, 1399, 1366, 1189, 1091, 961, 839 cm^{-1}; Ms *m/z* (%) 196 (M^-, 2), 141 (37), 139 (100), 111 (20), 85 (3), 57 (15).

2',4',6'-Trimethyl-2,2-dimethylpropiophenone (4m): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 2H), 2.23 (s, 3H), 2.13 (s, 6H), 1.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.8, 140.0, 137.7, 132.4, 128.8, 45.2, 28.5, 21.3, 20.8; FT-IR (film) 2968, 2931, 1687 (C=O), 1476, 1378, 1364, 1146, 929, 850 cm^{-1}; Ms *m/z* (%) 204 (M^+, 1), 148 (12), 147 (100), 119 (20), 91 (9).

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