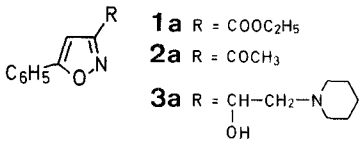
## Convenient Synthesis of Alkyl Ketones from Carboxylic Esters

Ikuo KIKKAWA*, Tadahiko YORIFUJI

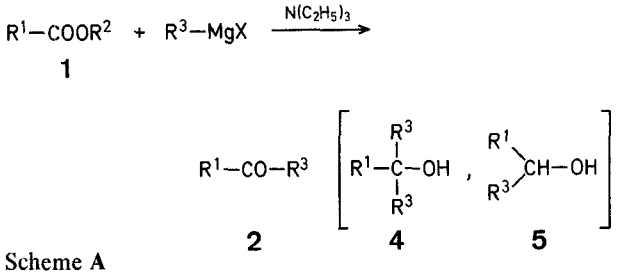
*Shionogi Research Laboratories, Shionogi & Co. Ltd., Osaka 553, Japan*

The one-step synthesis of ketones by the Grignard reaction of carboxylic esters in a hydrocarbon or ether solvent is usually unsatisfactory owing to the formation of undesired tertiary alcohols, although the use of low temperatures and excess substrates improves the selectivity of ketone formation in some cases[1]. The Grignard reaction of aliphatic esters in hexamethylphosphoric triamide has been reported to be useful for preparing aliphatic ketones via their ketonic enolates[2a]. However, the high carcinogenicity and difficult availability of the solvent would make this process prohibitive for preparative use. Other methods reported include the reaction of acyl chlorides[2b] with $R-MgX/CdX_2$ and of acids[2c] with alkyllithium reagents (2 equiv).

We needed to explore an industrial process for converting the easily available ester **1a**[3] into ketone **2a**, a key intermediate in production of perioxal (**3a**), a new, non-steroidal, anti-inflammatory agent[4].



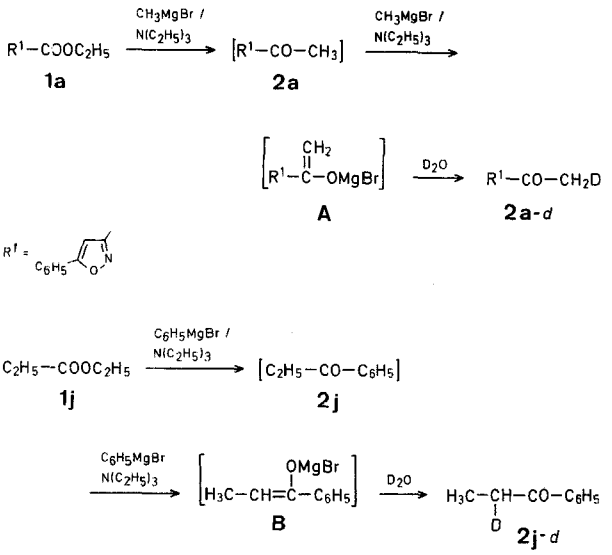

With the expectation that a base would facilitate the formation of the intermediary ketonic enolate, we have studied the reaction of **1a** with methylmagnesium bromide in the presence of an amine at 5–10 °C and found that the use of six or more molar equivalents of a tertiary aliphatic amine such as triethylamine, tri-*n*-butylamine, or *N*-methylpiperidine was effective for giving the ketone **2a** in excellent yield, whereas use of a weaker aromatic base such as pyridine or dimethylaniline was not effective.




Scheme **A**

To clarify the scope and limitation of this procedure, the reactions of various esters **1** with Grignard reagents in the presence of triethylamine were examined (Scheme **A** and Table 1). The reaction in the absence of triethylamine under the same conditions gave the corresponding tertiary alcohols **4** as major products (51–88% yields), except for the reaction of **1a** with *n*-butylmagnesium bromide which gave **4c** and **5c** in 19 and 41% yield, respectively. The present procedure is most satisfactory when the aliphatic Grignard reagent has a lower reducing ability and the ester does not have enolizable $\alpha$-hydrogen(s). The low yields of ketones **2f** and **2g** can be explained by partial enolization of the corresponding starting esters having $\alpha$-hydrogen(s). The moderate yields of products **2e** and **2i** may be due to a lower reactivity of the ester carbonyl conjugated with an electron-releasing group. In the reaction of **1a**, ethyl propanoate, and ethyl phenylacetate with phenylmagnesium bromide, no and high enolization of intermediate ketones **2d** and **2j** and facile formation of the ester enolate can account for formation of alcohol **4d** and ketone **2j** and recovery of the starting ester, respectively.

These diverse results were well interpreted by assuming that triethylamine forms a complex with the Grignard reagent to lower its reactivity and facilitates enolization of the intermediate ketones and of the starting esters when enolizable. Formation of unreactive enolates such as **A** and **B** from intermediate ketones in the present procedure is supported by isolation of deuterated ketones **2a**-*d* and **2j**-*d* as major products on deuterolysis as shown in Scheme **B**.




Scheme **B**

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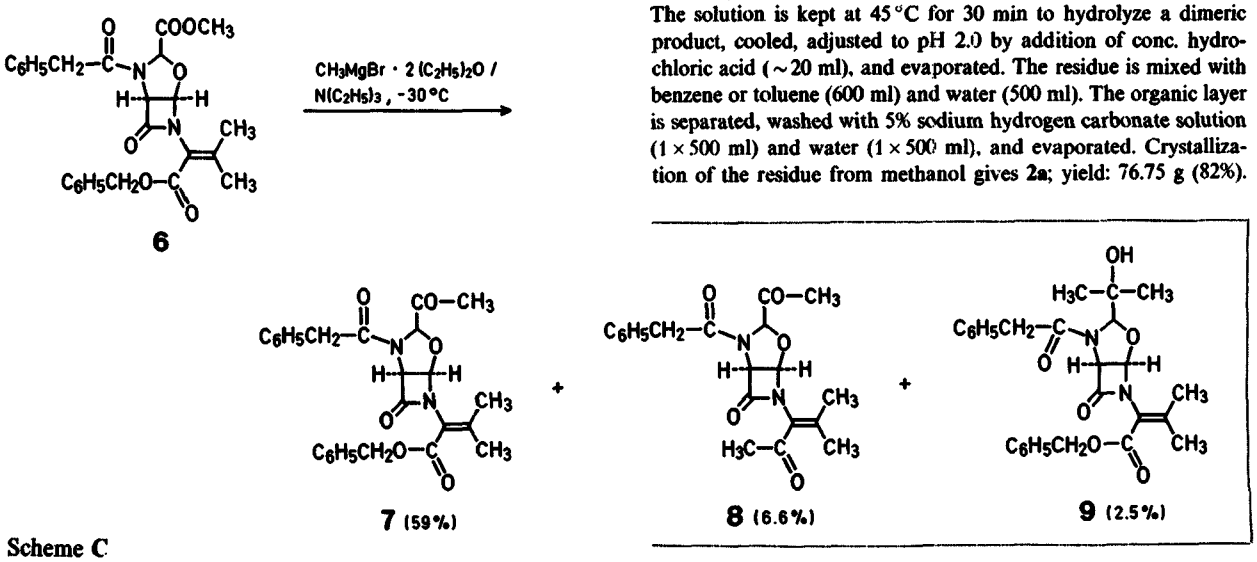
An advantage of this new procedure is demonstrated by the successful conversion of ester **6** having other reactive functional groups into ketone **7**, an important intermediate in 1-oxacephem synthesis[5] (Scheme C). The appropriate Grignard reaction in hexamethylphosphoric triamide[2a] did not give the desired product **7** at all.




Scheme C

Melting points and boiling points are uncorrected. $^1$H-N.M.R spectra were recorded on a Varian T-60 or EM 360 spectrometer with TMS as internal standard. I.R. spectra were obtained using a JASCO IRA-1 spectrophotometer.

**3-Acetyl-5-phenylisoxazole (2a) and 3-(1-Hydroxy-1-methylethyl)-5-phenylisoxazole (4a); Typical Procedure:**

A solution of methyl bromide (104.4 g, 1.1 mol) in benzene or toluene (350 ml) is added dropwise at 20–30 °C under nitrogen to a suspension of magnesium turnings (24.31 g, 1 mol) in benzene or toluene (100 ml) containing tetrahydrofuran (144 g, 2 mol) and a catalytic amount of iodine. After stirring of the mixture for 2 h triethylamine (303.6 g, 3 mol) is added. To the resulting mixture is added dropwise a solution of 3-ethoxycarbonyl-5-phenylisoxazole (**1a**; 108.61 g, 0.5 mol) in benzene or toluene (1000 ml) at 5–10 °C in 1 h. The reaction mixture is stirred at 5–10 °C for 2 h and treated then with 4 normal hydrochloric acid (688 ml, 2.75 mol). The organic layer is washed with water (1 × 300 ml), 5% aqueous sodium hydrogen carbonate solution (1 × 500 ml), and water (2 × 500 ml), and evaporated. The residue is dissolved in a mixture of methanol (2000 ml) and 20% aqueous potassium hydroxide solution (30 ml). The solution is kept at 45 °C for 30 min to hydrolyze a dimeric product, cooled, adjusted to pH 2.0 by addition of conc. hydrochloric acid (~20 ml), and evaporated. The residue is mixed with benzene or toluene (600 ml) and water (500 ml). The organic layer is separated, washed with 5% sodium hydrogen carbonate solution (1 × 500 ml) and water (1 × 500 ml), and evaporated. Crystallization of the residue from methanol gives **2a**; yield: 76.75 g (82%).

Column chromatography of the residue from the mother liquor on silica gel (eluent: ethyl acetate) affords **4a**; yield: 5.65 g (5.6%).

Acidification of the alkaline layer with conc. hydrochloric acid followed by filtration and washing with water gives 3-carboxy-5-phenylisoxazole; yield: 7.47 g (7.9%); m.p. 160.5–161.5 °C; identical with an authentic sample prepared by alkaline hydrolysis of **1a**.

**Deuterolysis of the Product from Ester 1a; 3-(Acetyl-$d_3$)-5-phenylisoxazole (2a-$d$):**

Ester **1a** (1.086 g, 5 mmol) in toluene (10 ml) is reacted with methylmagnesium bromide diethyl etherate (10 mmol) in toluene (10 ml) and triethylamine (4.2 ml, 30 mmol) as described above. Deuterated water (4 ml) is added slowly while maintaining the temperature below 20 °C. Anhydrous magnesium sulfate (~5 g) is added,

**Table 1.** Reaction of Esters **1** with Grignard Reagents in the Presence of Triethylamine[a] (Scheme A)

| Ester 1 | | Grignard reagent | Unreacted | No of | Yield [%] of Products[c] | | |
|---|---|---|---|---|---|---|---|
| $R^1$ | $R^2$ | $R^3$—MgX | 1 [%][b] | Products | 2 | 4 | 5 |
| **1a** | | $CH_3MgBr \cdot 2THF$ | 8 | **a** | 82 | 6 | 0 |
| **1a** | | $CH_3MgJ \cdot 2(C_2H_5)_2O$ | —[d] | **a** | 70 | 17 | 0 |
| **1a** | | $C_2H_5MgBr \cdot 2(C_2H_5)_2O$ | —[d] | **b** | 72 | 6.9 | 0 |
| **1a** | | $C_2H_5MgJ \cdot 2(C_2H_5)_2O$ | 12 | **b** | 68 | 7 | 0 |
| **1a** | | $n\text{-}C_4H_9MgBr \cdot 2THF$ | —[d] | **c** | 41 | 8 | 15 |
| **1a** | | $C_6H_5MgBr \cdot 2(C_2H_5)_2O$ | —[d] | **d** | 0 | 82 | 0 |
| 4-$H_3CO$—$C_6H_4$ | $CH_3$ | $CH_3MgBr \cdot 2(C_2H_5)_2O$ | 31 | **e** | 45 | 0 | 0 |
| $n\text{-}C_7H_{15}$ | $CH_3$ | $CH_3MgBr \cdot 2(C_2H_5)_2O$ | 20 | **f** | 25 | 0 | 0 |
| $c\text{-}C_6H_{11}$ | $CH_3$ | $CH_3MgBr \cdot 2(C_2H_5)_2O$ | 19 | **g** | 27 | 0 | 0 |
|  | $CH_3$ | $CH_3MgBr \cdot 2THF$[e] | —[d] | **h** | 80 | 0 | 0 |
| $C_6H_5CH{=}CH$ | $CH_3$ | $CH_3MgBr \cdot 2THF$[f] | —[d] | **i** | 49 | 0 | 0 |
| $C_2H_5$ | $C_2H_5$ | $C_6H_5MgBr \cdot 2(C_2H_5)_2O$ | —[d] | **j** | 77 | 0 | 0 |
| $C_6H_5CH_2$ | $C_2H_5$ | $C_6H_5MgBr \cdot 2(C_2H_5)_2O$ | 93 | — | 0 | 0 | 0 |

[a] Unless otherwise stated, reaction conditions are the same as those described in the Typical Procedure.
[b] Yield of the corresponding acid isolated (see experimental).
[c] Yield of isolated product.
[d] Not determined.
[e] Molar ratio of ester: $CH_3MgBr$: $N(C_2H_5)_3$ = 1:5.5:22.
[f] Molar ratio of ester: $CH_3MgBr$: $N(C_2H_5)_3$ = 1:3:18.

**Table 2.** Physical Data for Compounds **2**, **4**, and **5**

| Product | m.p. [°C] (solvent) or b.p. [°C]/torr | Molecular formula[a] or Lit. m.p. or b.p./torr | I.R. ($CHCl_3$) $\nu$ [$cm^{-1}$] | $^1$H-N.M.R. ($CDCl_3$/TMS) $\delta$ [ppm] |
|---|---|---|---|---|
| **2a** | 100° (methanol) | 99°[4] (PE) | — | |
| **2b** | 88° (*n*-hexane) | $C_{12}H_{11}NO_2$ (201.2) | 1705 | 1.23 (t, 3H, $J$=7.0 Hz); 3.09 (q, 2H, $J$=7.0 Hz); 6.86 (s, 1H); 7–8 (m, 5H) |
| **2c** | 76° (ether/PE) | $C_{14}H_{15}NO_2$ (229.3) | 1704 | 0.9–2.0 (m, 7H); 3.08 (m, 2H); 6.85 (s, 1H); 7–8 (m, 5H) |
| **2e** | 37° (ether/*n*-hexane) | 38°[6] | — | — |
| **2f** | 194°/760 | 195°/760[7] | — | — |
| **2g** | 58°/80 | 57°/80[8] | — | — |
| **2h** | 92°/12 | 94°/11[9] | — | — |
| **2i** | 39° (*n*-hexane) | 40–42°[10] | — | — |
| **2j** | 104°/17 | 105°/17[11] | — | — |
| **2a-*d*** | | $C_{11}H_8DNO_2$ (188.2) | — | 2.73 (t, 2H); 6.85 (s, 1H); 7–8 (m, 5H) |
| **2j-*d*** | | $C_9H_9DO$ (136.2) | 1676 | —[b] |
| **4a** | 82° (ether/PE) | $C_{11}H_{13}NO_2$ (203.2) | 3525, 3380, 1616, 1595, 1577, 1500 | 1.65 (s, 6H); 3.70 (s, 1H); 6.60 (s, 1H); 7–8 (m, 5H) |
| **4b** | 87° (*n*-hexane) | $C_{14}H_{17}NO_2$ (231.3) | 3680, 3500 | 0.92 (t, 6H, $J$=7.0 Hz); 1.92 (q, 4H, $J$=7.0 Hz); 2.67 (broad, 1H); 6.48 (s, 1H); 7–8 (m, 5H) |
| **4c** | 73° (ether/PE) | $C_{18}H_{25}NO_2$ (287.4) | 3600 | 0.7–2.2 (m, 18H); 2.58 (broad, 1H); 6.47 (s, 1H); 7–8 (m, 5H) |
| **4d** | 127° (ether/*n*-hexane) | $C_{22}H_{17}NO_2$ (327.4) | 3385 | 3.85 (s, 1H); 6.40 (s, 1H); 7–8 (m, 15H) |
| **5b** | 135°/0.2 | $C_{12}H_{13}NO_2$ (203.2) | 3600, 3400 | 1.00 (t, 3H, $J$=7.0 Hz); 1.83 (q, 2H, $J$=7.0 Hz); 3.54 (s, 1H); 4.80 (t, 1H, $J$=7.0 Hz); 6.52 (s, 1H); 7–8 (m, 5H) |
| **5c** | 49° (ether/PE) | $C_{14}H_{17}NO_2$ (231.3) | 3600 | 0.7–2.0 (m, 9H); 3.35 (broad, 1H); 4.89 (m, 1H); 6.55 (s, 1H); 7–8 (m, 5H) |

[a] The microanalyses of all compounds were in satisfactory agreement with the calculated values (C ±0.21, H ±0.14, N ±0.26).

[b] The $^1$H-N.M.R. spectrum is too complicated for assignment. Its $^1$H-decoupled $^{13}$C-F.T.-N.M.R. spectrum ($CDCl_3$, 15 MHz) showed a signal at $\delta$=31.4 ppm (t, $^1J_{CD}$=19 Hz) for the $CH_3CH(D)$ group.

the mixture filtered through a layer of anhydrous magnesium sulfate, and the filtrate evaporated. Chromatography of the residue (0.90 g) as described above gives the deuterated ketone **2a-*d***; yield 0.717 g (76%).

$^1$H-N.M.R. ($CDCl_3$): $\delta$=2.63 (t, 2H, $CH_2D$); 6.85 (s, 1H, H-4); 7.3–8.0 ppm (m, 5$H_{arom}$).

**Deuterolysis of Ketone 2a:**

Ketone **2a** (0.936 g, 5 mmol) is substituted for the ester **1a** in the above reaction to give a residue (0.965 g). T.L.C. analysis (benzene/ethyl acetate/*n*-hexane 1:1:3) shows that the residue is a ~8:2 mixture of **2a-*d*** and an aldol dimer containing a trace of alcohol **4a**. Crystallization of the residue from methanol gives **2a-*d***; yield: 0.490 g (54%); whose $^1$H-N.M.R. spectrum is almost identical with that of the sample of **2a-*d*** obtained above.

**Deuterolysis of the Product from Ethyl Propanoate (1j); 2-Deuterio-1-oxo-1-phenylpropane (2j-*d*):**

Ethyl propanoate (0.506 g, 5 mmol) in benzene (5 ml) is reacted with phenylmagnesium bromide diethyl etherate in benzene (10 mmol) and triethylamine (4.2 ml, 30 mmol), and the reaction mixture is worked up as described above to give a residue (0.823 g). Chromatography of the residue on silica gel (eluent: benzene/hexane 1:1) affords the deuterated ketone **2j-*d***; yield 0.455 g (67%).

$^1$H-N.M.R. ($CDCl_3$): $\delta$=1.1–1.4 (m, 3H, $CH_3$); 2.7–3.25 [m, 1H, $CH(D)CH_3$]; 7.2–8.2 ppm (m, 5$H_{arom}$).

**Conversion of Diester 6 to 7+8+9:**

To a mixture of methylmagnesium bromide diethyl etherate (40 mmol), triethylamine (16.7 ml, 120 mmol), and toluene (17.8 ml), prepared as described above, is added a solution of **6**[5] (4.785 g, 10 mmol) in toluene (25 ml) at −30 °C in 15 min. After being stirred at −30 °C for 15 min, the reaction mixture is poured into a mixture of 2 normal hydrochloric acid (88 ml, 176 mmol), ethyl acetate (100 ml), and ice (~40 g). The organic layer is separated, washed with cold 0.5 normal hydrochloric acid (80 ml) and cold water (3×80 ml), dried with anhydrous sodium sulfate, and evaporated. The residue (5.0 g) is chromatographed on silica gel (eluent: benzene/ethyl acetate) to give four fractions A, B, C, and D.

A – Starting diester **6**; yield: 0.558 g (12%).

B – Monoketone **7**; yield: 2.684 g (59%); syrup.

| | | | | |
|---|---|---|---|---|
| $C_{26}H_{26}N_2O_6$ | calc. | C 67.52 | H 5.67 | N 6.06 |
| (462.5) | found | 67.73 | 5.60 | 5.87 |

I.R. ($CHCl_3$): $\nu$=1783 ($\beta$-lactam C=O); 1740 (acetyl C=O); 1730 (ester C=O); 1670 $cm^{-1}$ (amide C=O).

$^1$H-N.M.R. ($CDCl_3$): $\delta$=1.83 and 2.17 [each s, 3H, $C(CH_3)_2$]; 2.27 (s, 3H, $COCH_3$); 3.90 (s, 2H, $C_6H_5CH_2CON$); 5.13 and 5.97 (each d, 1H, $J$=4 Hz, $\beta$-lactam H); 5.22 (s, 2H, $COOCH_2C_6H_5$); 6.10 (s, 1H, oxazolidine H); 7.33 ppm (s, 10$H_{arom}$).

C – Diketone **8**; yield: 0.245 g (6.6%); syrup.

| | | | | |
|---|---|---|---|---|
| $C_{20}H_{22}N_2O_5$ | calc. | C 64.85 | H 5.99 | N 7.56 |
| (370.4) | found | 65.02 | 5.83 | 7.49 |

I.R. ($CHCl_3$): $\nu$=1783 ($\beta$-lactam C=O); 1740 (acetyl C=O); 1688 (conjugated acetyl C=O); 1670 $cm^{-1}$ (amide C=O).

$^1$H-N.M.R. ($CDCl_3$): $\delta$=1.83 and 2.07 [each s, 3H, $C(CH_3)_2$]; 2.27 and 2.33 (each s, 3H, $COCH_3$); 3.93 (s, 2H, $C_6H_5CH_2CON$); 5.28 and 5.93 (each d, 1H, $J$=4 Hz, $\beta$-lactam H); 6.13 (s, 1H, oxazolidine H); 7.33 ppm (s, 5$H_{arom}$).

D – Alcohol **8**; yield: 0.118 g (2.5%); m.p. 112–114 °C (from ether).

| | | | | |
|---|---|---|---|---|
| $C_{27}H_{30}N_2O_6$ | calc. | C 67.76 | H 6.32 | N 5.85 |
| (478.5) | found | 67.54 | 6.32 | 5.81 |

I.R. ($CHCl_3$): $\nu = 3400$ (OH); 1748 ($\beta$-lactam C=O); 1730 (ester C=O); 1680 $cm^{-1}$ (amide C=O).

$^1$H-N.M.R. ($CDCl_3$): $\delta = 1.28$ and 1.30 [each s, 3H, $C(OH)(CH_3)_2$]; 1.95 and 2.13 [each s, 3H, $-C(CH_3)_2$]; 2.88 (s, 2H, $C_6H_5CH_2CON$); 4.77 (s, 1H, OH); 5.25 (s, 2H, $COOCH_2C_6H_5$); 5.33 and 5.75 (each d, 1H, $J = 4$ Hz, $\beta$-lactam H); 5.80 (s, 1H, oxazolidine H); 7.33 ppm (s, 10 $H_{arom}$).

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