Efficient Dealkoxycarbonylation of Some β-Ketoesters by Halides of Group IIa Metals

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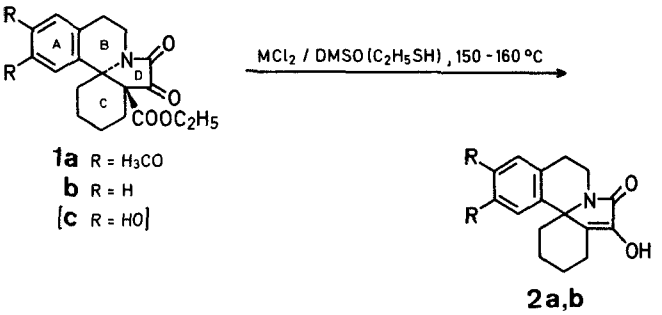
Removal of an ester group from a β-ketoester to give a ketone is one of the basic procedures in organic synthesis. Among the reagents (without involving hydrolysis of an ester group) hitherto reported[1-5] for this purpose, alkali metal halides in dipolar aprotic solvents[4] are particularly interesting, since the reaction is carried out under neutral conditions and is thus applicable to compounds which are sensitive to acids and bases. Although the importance of nucleophiles in the reaction has been noticed, the role of counter cations is still obscure[1,4e]. We now report that halides of group IIa metals (including alkaline earth metals) are superior to alkali metal halides for this purpose.

4a-Ethoxycarbonyl-11,12-dimethoxy-5,6-dioxo-1,2,3,4,4a,5,8,9-octahydro-6*H*-indolo[7a,1-*a*]isoquinoline (**1a**) is resistent to acid hydrolysis; on alkaline treatment the ring D is opened. Treatment with aluminium chloride/dimethyl sulfide[6a] resulted only in cleavage of the aromatic methoxy groups giving rise to **1c**. Heating of **1a** with sodium chloride/dimethyl sulfoxide[2a] afforded the desired ketone **2a**[8] but in only 30% yield even under optimum conditions (170 °C, 24 h).

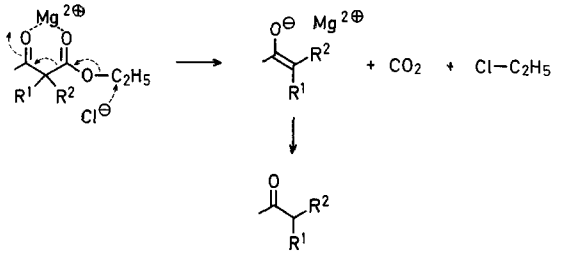
Deethoxycarbonylation took place smoothly when **1a** was heated with excess magnesium or calcium chloride in dimethyl sulfoxide at 150–160 °C for 5–6 h, giving **2a** in 50–60% yield. Similarly, the related compound **1b** gave the deethoxycarbonylated compound **2b** in 50–60% yield on similar treatment. The hydrates, $MgCl_2 \cdot 6H_2O$ and $CaCl_2 \cdot 2H_2O$ worked as well. Copper(I) chloride and the halides of bivalent metals other than those of group IIa, such as $NiCl_2$, $ZnCl_2$, $MnCl_2$, and $SnCl_2$ had no effect.



1a R = H_3CO
b R = H
[**c** R = HO]

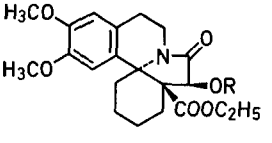
2a,b

On comparing the chlorides of group IIa metals, the order of effectiveness for the dealkoxycarbonylation of **1b** to **2b** in dimethyl sulfoxide/ethanethiol at 155–160 °C for 3 h was found to be $CaCl_2 \cdot 2H_2O$ (47% yield of isolated, pure **2b**) ≈ $MgCl_2 \cdot 6H_2O$ (44%) > $BeCl_2$ (34%) > $BaCl_2 \cdot 2H_2O$ (24%). This suggests that a suitable molecular size of the cation is necessary to gain efficient dealkoxycarbonylation. Therefore, we assume the cyclic participation of the bivalent cation to a β-ketoester group as shown below, though details of the mechanism are still not clarified.



Solvent effects on the conversion of **1b** to **2b** with $MgCl_2 \cdot 6H_2O$ at 160 °C for 3 h were also studied and the following results obtained: hexamethylphosphoric triamide (63% yield of isolated, pure **2b**) > dimethyl sulfoxide (50%) > dimethylformamide (39%) ≫ sulfolane and tetrahydrothiophene (no reaction). Tetrahydrothiophene and sulfolane had no effect, indicating that the reaction mechanism is different from that of dealkoxylation with the tetrahydrothiophene/aluminium halide system (HASB combination)[6a].

Addition of ethanethiol is sometimes useful to prevent coloration of the reaction mixture, but it may often produce side reactions such as thiolation[6b]. Thus, performance of the reaction under nitrogen or argon is recommended, and magnesium chloride/hexamethylphosphoric triamide is the combination of choice. Compared to a sodium chloride/dimethyl sulfoxide system[4], dealkoxycarbonylation by the present system usually occurs at lower temperatures and is completed within a shorter time. Proving that the reaction is specific to β-ketoesters (and probably also to geminal esters), the compounds **3a** and **3b** were recovered unchanged under the same reaction conditions.



3a R = H
b R = H_3C-SO_2-

The Table summarizes the examples of dealkoxylcarbonylation achieved by this method (including **4a** and **4b**). All compounds

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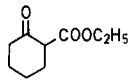
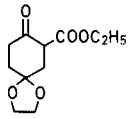
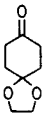
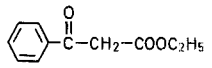
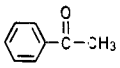
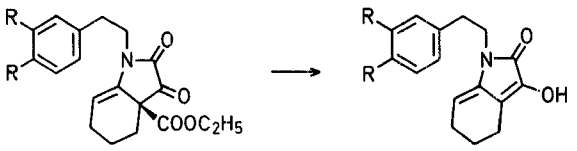
Table. Dealkoxycarbonylation of β-Ketoesters with Magnesium Chloride

Substrate	Product	Reaction conditions Solvent/temperature[a]/time	Yield [%] of Product
1a	**2a**	HMPT/150–155 °C/2 h	73
1b	**2b**	HMPT/150 °C/3 h	63
4a	**5a**	DMSO/150 °C/1 h	54
4b	**5b**	DMSO/150 °C/1 h	51
6 	**7** 	HMPT/140–150 °C/1 h	84[b] (85–95)[4a]
8 	**9** 	HMPT/150 °C/2 h	92[b]
10 	**11** 	DMSO/150 °C/1 h	41[c]

[a] Bath temperature.
[b] Calculated from G.L.C. peak areas.
[c] Yield from isolation as tosylhydrazone (m.p. 151–152 °C).

examined smoothly gave the deethoxycarbonylated products in satisfactory yields. Simple β-ketoesters **6**, **8**, and **10** were smoothly deethoxycarbonylated as expected. However the yields of **7**, **9**, and **11** achieved were comparable to those obtained by the previous methods. Therefore the present modification is particularly useful for the hindered β-ketoesters which are difficult to deethoxycarbonylate by the previously known methods.



4a R = H_3CO
b R = H

5a,b

Compounds **1a**, **1b**, **3a**, **3b**, **4a**, and **4b** were prepared according to Ref.[7].

Dealkoxycarbonylation of β-Ketoesters using Magnesium Chloride; General Procedure:

A mixture of the β-ketoester (1.0 mmol) and magnesium chloride (5 mmol) is heated with stirring at 140–160 °C for 3–6 h by one of the following ways;

(a): in dimethyl sulfoxide (10 ml) under argon;
(b): in dimethyl sulfoxide (10 ml) and ethanethiol (1 ml);
(c): in hexamethylphosphoric triamide (7 ml) under argon.

The product is isolated by one of the following procedures:

A: (dimethyl sulfoxide solvent): The mixture is acidified with 1 normal hydrochloric acid (~50 ml) and extracted with chloroform or dichloromethane (3 × 30 ml). Evaporation of the solvent from the dried (sodium sulfate) extract gives the dealkoxycarbonylated product, which is purified, if necessary, by column chromatography on silica gel, eluting with chloroform containing an appropriate amount of ethyl acetate. In the cases of **1a** and **1b**, the products are taken up in 2 normal sodium hydroxide solution (100 ml). Acidification of the alkaline layer with concentrated hydrochloric acid (to pH 2) and extraction with chloroform (4 × 30 ml) gives the dealkoxycarbonylated products **2a** and **2b**. In the case of **10**, diethyl ether (3 × 50 ml) is used for extraction.

B (hexamethylphosphoric triamide solvent): The solvent is evaporated in vacuo. The residue is dissolved in benzene (200 ml) which is washed with 1 normal hydrochloric acid (100 ml), dried with sodium sulfate, and concentrated. Crystallization of the residue from an appropriate solvent, or column chromatography on silica gel, as described above, gives the pure product.

11,12-Dimethoxy-5,6-dioxo-1,2,3,4,4a,5,8,9-octahydro-6H-indolo[7a,1-a]isoquinoline (**2a**; 14,15-dimethoxy-7,8-dioxoerythrinan): m.p. 179–180 °C from ethyl acetate (Lit.[8], m.p. 180 °C); acetate m.p. 146–148 °C from ether (Lit.[8], m.p. 148 °C).

I.R. (KBr): ν = 1765 (w); 1680 (sh); 1660 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 3.85 (s, 3H); 3.87 (s, 3H); 6.39 (s, 1H); 6.68 (s, $1H_{arom}$); 7.05 ppm (s, $1H_{arom}$).

5,6-Dioxo-1,2,3,4,4a,5,8,9-octahydro-6H-indolo[7a,1-a]isoquinoline (**2b**; 7,8-dioxoerythrinan); m.p. 219 °C from methanol; prisms.

$C_{16}H_{17}NO_2$	calc.	C 75.27	H 6.71	N 5.49
(255.3)	found	75.14	6.63	5.67

I.R. (KBr): ν = 1760 (w); 1685 (sh); 1650 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 7.0–7.6 ppm (m, $4H_{arom}$).

1-[2-(3,4-Dimethoxyphenyl)-ethyl]-2,3-dioxo-2,3,3a,4,5,6-hexahydroindole (**5a**); red gum (Lit.[3], unstable crystals; m.p. 143 °C).

M.S.: m/e = 315 (M^+).

I.R. ($CHCl_3$): ν = 3200; 1668 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 3.85 (s, 6H); 5.38 (t, 1H, J = 4.5 Hz); 6.6–6.7 ppm (m, $3H_{arom}$).

2,3-Dioxo-1-(2-phenylethyl)-2,3,3a,4,5,6-hexahydroindole (**5b**); red gum.

M.S.: m/e = 255 (M^+).

I.R. ($CHCl_3$): ν = 3300; 1720–1680 (br) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 5.38 (t, 1H, J = 4.5 Hz); 7.18 ppm (s, $5H_{arom}$).

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