Procedures for the Acylation of Diethyl Malonate and Ethyl Acetoacetate with Acid Chlorides Using Tertiary Amine Bases and Magnesium Chloride

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In the presence of magnesium chloride and 2 equiv of triethylamine, diethyl malonate is C-acylated in excellent yields by acid chlorides. A variety of other metal chlorides were ineffective. Similarly, ethyl acetoacetate is C-acylated by acid chlorides in the presence of magnesium chloride and 2 equiv of pyridine.

A standard procedure for the C-acylation of active methylene compounds **1** is conversion to the enolate **2** in a first step, followed by reaction with an acid chloride in a second, separate, step (eq 1).[2] A problem inherent in this approach is that the acylation product **3** is always a stronger acid than **1** and thus may neutralize a portion of the enolate (eq 2). One solution to this problem is a

$$\underset{\mathbf{1}}{CH_2(COX)_2} \xrightarrow{\text{base}} \underset{\mathbf{2}}{(-)CH(COX)_2} \xrightarrow{RCOCl} \underset{\mathbf{3}}{RCOCH(COX)_2} \quad (1)$$

$$3 + 2 \rightarrow 1 + RCOC^-(COX)_2 \quad (2)$$

$$CH_2(COX)_2 + 2\text{base} + RCOCl \rightarrow RCOC^-(COX)_2 \xrightarrow{H_3O^+} 3 \quad (3)$$

single-step acylation conducted in the presence of 2 equiv of base (eq 3). A requirement for success with this latter procedure is that the base must not react destructively with the acid chloride. This seems to have restricted application of the single-step procedure to the acylation of those very strong carbon acids (e.g. Meldrum's acid, $pK_a = 5$)[3] whose enolates can be formed quantitatively by the relatively mild tertiary amine bases.

We considered that one way to extend the single-step acylation procedure to weaker carbon acids would be to use metal complexation to enhance acidity to the point where tertiary amine bases could be used.[4] We report here the results of our study of single-step acylations of diethyl malonate and ethyl acetoacetate using magnesium chloride to enhance acidity.

Results and Discussion

Diethyl Malonate Acylations. Addition of acetyl chloride to an acetonitrile solution of diethyl malonate containing 2 equiv of either pyridine or triethylamine did not give detectable amounts of acylation (12 h, 25 °C). Diethyl malonate was recovered nearly quantitatively, and the reaction mixtures turned black soon after being mixed, presumably due to the formation of ketene-derived products. Evidently the amount of enolate formed from diethyl malonate ($pK_a = 14$) using pyridine ($pK_a = 5.0$) or triethylamine ($pK_a = 10.0$) bases[2] is too small to obtain useful acylation rates. In contrast, similar reaction mixtures containing one equivalent of $MgCl_2$ remained nearly colorless and quenching produced high yields of diethyl acetylmalonate (eq 4). Replacing $MgCl_2$ with a variety

Table I. Acylation of Diethyl Malonate

$$CH_2(CO_2Et)_2 + RCOCl \xrightarrow[CH_3CN,\ 12\ h,\ 25\ °C]{MgCl_2,\ 2Et_3N} \xrightarrow{H_3O^+} RCOCH(CO_2Et)_2$$

entry	RCOCl	isolated yield,[a] %
1	CH_3COCl	0[b]
2	CH_3COCl	42[c]
3	CH_3COCl	85
4	$(CH_3)_2CHCOCl$	92
5	$(CH_3)_3CCOCl$	90
6	n-C_3H_7COCl	86
7	C_6H_5COCl	89

[a] Reactions conducted on 25-mmol scale; 1:1:1:2 diethyl malonate, acid chloride, $MgCl_2$, and Et_3N. Yields based on weight of distilled product. [b] No Et_3N added. [c] One equivalent of Et_3N was added.

$$CH_2(CO_2Et)_2 + MgCl_2 + 2R_3N + CH_3COCl \xrightarrow[25\ °C,\ CH_3CN]{12\ h} \xrightarrow{H_3O^+} CH_3COCH(CO_2Et)_2$$
61% (R_3N = pyridine)
85% (R_3N = Et_3N) (4)

of other metal chlorides ($ZnCl_2$, $CuCl_2$, $FeCl_3$, LiCl, $TiCl_4$, $AlCl_3$) was unsuccessful. Reaction mixtures again turned black shortly after addition of acetyl chloride, and diethyl malonate was recovered nearly quantitatively.

Results obtained for the acylation of diethyl malonate with a variety of acid chlorides in the presence of $MgCl_2$ are shown in Table I. In the absence of base, no acylation is observed (entry 1). As expected from the stoichiometry of eq 3, use of only 1 equiv at base gives decreased yields of product (compare entries 2 and 3).

An ^1H NMR study was conducted to verify that the magnesium enolate of diethyl malonate is formed under the reaction conditions. The appearance and position of the methylene signal of diethyl malonate in CD_3CN was unchanged upon addition of 1 equiv triethylamine. Addition of 1 equiv of $MgCl_2$ to the triethylamine–diethyl malonate solution gave a heterogeneous mixture. Filtration of the mixture gave a solid identified as triethylamine hydrochloride (0.15 equiv). An ^1H NMR spectrum of the filtrate possessed signals (δ 1.2, 3.1) identical with those of triethylamine hydrochloride (0.85 equiv). The signals for the ethyl protons of diethyl malonate were shifted slightly downfield, and the signal for the methylene protons was no longer visible. These observations are consistent with formation of a magnesium enolate, **4**, with

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Table II. Acylation of Ethyl Acetoacetate

$CH_3COCH_2CO_2Et$ +

$$RCOCl \xrightarrow[1\ h,\ 25\ °C]{MgCl_2,\ base,\ H_3O^+} RCOCH(COCH_3)CO_2Et$$

entry	RCOCl	base	solvt	isolated yield,[a] %
1	CH_3COCl	Et_3N	CH_3CN	10
2	CH_3COCl	Et_3N	CH_2Cl_2	13
3	CH_3COCl	pyridine	CH_3CN	73
4	CH_3COCl	pyridine	CH_2Cl_2	91
5	CH_3COCl	Et_3N	CH_3CN	(15)[b]
6	CH_3COCl	pyridine	CH_2Cl_2	0[c]
7	$(CH_3)_2CHCOCl$	pyridine	CH_2Cl_2	77
8	$(CH_3)_3CCOCl$	pyridine	CH_2Cl_2	18 (75)[d]
9	n-C_3H_7COCl	pyridine	CH_2Cl_2	78
10	C_6H_5COCl	pyridine	CH_2Cl_2	81

[a] Yield based on weight of distilled product from reactions conducted on 25-mmol scale; 1:1:1:2 ethyl acetoacetate, acid chloride, $MgCl_2$, and Et_3N. [b] No $MgCl_2$ was added, product is enol acetate. [c] No $MgCl_2$ was added. [d] Yield after 12-h reaction.

rapid proton exchange between enolate and triethylamine hydrochloride (eq 5).[5]

$$CH_2(CO_2Et)_2 + MgCl_2 + Et_3N \rightleftharpoons ClMgCH(CO_2Et)_2 + Et_3N{\cdot}HCl \quad (5)$$
$$4$$

Ethyl Acetoacetate Acylations. Ethyl acetoacetate was reacted with acid chlorides under a variety of conditions with the results shown in Table II. The most satisfactory yields were obtained by using pyridine as the base and methylene chloride as the solvent. Under these conditions no acylation is observed in the absence of $MgCl_2$ (entry 6). With the stronger base triethylamine reaction does occur in the absence of $MgCl_2$ but only O-acylated product is formed (entry 5).

Conclusions

The reaction of diethyl malonate or ethyl acetoacetate with tertiary amine bases and $MgCl_2$ provides a remarkably simple and economical entry into the enolate chemistry of these useful carbon acids. Diethyl malonate and ethyl acetoacetate have previously been acylated by a variety of procedures;[2,6] perhaps the most useful are based on enolate formation with magnesium ethoxide.[7] The present procedure gives equal or higher yields of product with significant advantages in cost and simplicity of operation. We are examining the scope of this acylation procedure with a variety of related carbon acids.

Experimental Section

Reagent grade methylene chloride was stored over 4-Å molecular sieves. Acetonitrile, triethylamine, and pyridine were all distilled from calcium hydride before use and stored under nitrogen. Diethyl malonate, ethyl acetoacetate, and all acid chlorides were obtained from Aldrich Chemical Co. and were purified by simple distillation. Anhydrous metal halides were obtained from Aldrich and stored in a glovebag under argon. Magnesium chloride from Aldrich, "anhydrous, 98+%", was used directly to obtain the results reported in Tables I and II. In several cases, control experiments using magnesium chloride dried by a literature procedure[7] with thionyl chloride were performed and no difference was observed. ^1H NMR spectra were recorded on a Varian T-60 spectrometer and are reported in parts per million relative to Me_4Si. Mass spectra were obtained with a Finnegan 4000 GC/MS. Gas chromatographic analysis were performed with a Varian 920 chromatograph equipped with a 6 ft × 0.25 in. column packed with 15% SE-30 on Chromosorb W.

General Procedure for the Acylation of Diethyl Malonate. The following procedure illustrated for the acylation of diethyl malonate with acetyl chloride in the presence of $MgCl_2$ is representative of the procedure used to examine other metal chlorides and to obtain the results of Table I. A flame-dried 100-mL round-bottom flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was flushed with argon. Magnesium chloride, 25 mmol (2.38 g), was weighed in a vial in a glovebag, and the contents of the vial were added to the flask under a slight flow of argon. Dry acetonitrile (25 mL) was added to the flask. To the resulting heterogeneous mixture was added 25 mmol (3.80 mL) of diethyl malonate. The reaction flask was immersed in an ice bath, and 50 mmol (6.97 mL) of triethylamine was added via the septum inlet. After the solution was stirred for 15 min at O °C, 25 mmol of acid chloride was added. The resulting mixture was stirred 1 h at O °C and 12 h at room temperature. After being cooled to O °C, the reaction mixture was quenched with 15 mL of 5 M HCl. The resulting solution was washed three times with 20 mL of diethyl ether. The combined ether extracts were dried ($MgSO_4$). An aliquot was removed for GC analysis for recovered diethyl malonate and product. The ether was removed under vacuum, and the residue was subjected to simple vacuum distillation.

Diethyl acetylmalonate was prepared from diethyl malonate and acetyl chloride. Bulb to bulb distillation (90 °C (0.25 mm)) gave 4.3 g (85%) of diethyl acetylmalonate: ^1H NMR ($CDCl_3$) δ 1.1–1.5 (m, 6H), 2.2 + 2.3 (s, total 3H), 4.0–4.5 (m, 4H), 13.3 (s) MS: (m/e) 203 (M^+· + 1), 187 (M^+· – CH_3), 160 (M^+· – O=C=CH_2), 115, 86, 69, 43.

Diethyl benzoylmalonate was prepared from diethyl malonate and benzoyl chloride in 89% yield (bp 140 °C (0.25 mm)): ^1H NMR ($CDCl_3$) δ 1.1–1.3 (t, J = 7 Hz, 6 H), 4.0–4.4 (q, J = 7 Hz, 4 H), 5.3 (s), 7.3–7.9 (m, 5 H), 13.1 (s); MS, m/e 264 (M^+·), 105 ($PhCO^+$·).

Diethyl isobutyrylmalonate was prepared from diethyl malonate and isobutyryl chloride in 92% yield (bp 100 °C (0.4 mm)): ^1H NMR ($CDCl_3$) δ 1.0–0.5 (m, 12 H), 2.5–3.0 (m, 1 H), 4.0–4.4 (m, 4 H), 4.6 (s), 13.2 (s); MS, m/e 230 (M^+·), 187 (M^+· – $CH(CH_3)_2$), 159 (M^+· – $(CH_3)_2CHCO$), 159, 141, 87, 71, 43.

Diethyl *n*-butyrylmalonate was prepared from diethyl malonate and n-butyryl chloride in 86% yield (bp 100 °C (0.4 mm)): ^1H NMR ($CDCl_3$) δ 0.7–2.0 (m, 11 H), 2.1–2.7 (m, 2 H), 4.0–4.5 (m, 4 H), 13.3 (s); MS, m/e 230 (M^+·), 187 (M^+· – $CH_2CH_2CH_3$), 159 (M^+· – $CH_3CH_2CH_2CO$), 141, 87, 71, 43.

Diethyl pivaloylmalonate was prepared from diethyl malonate and pivaloyl chloride in 90% yield (bp 100 °C (0.4 mm)): ^1H NMR ($CDCl_3$) δ 1–1.4 (m, 15 H), 4.0–4.4 (m, 4 H), 4.9 (s, 1 H); MS, m/e 245 (M^+ + 1), 159 (M^+· – $(CH_3)_3CCO$), 85, 57, 41.

^1H NMR Study of the Diethyl Malonate/Magnesium Chloride System. A flame-dried 50-mL round-bottom flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was flushed with argon and charged with 10 mL of CD_3CN and 5 mmol (0.75 mL) of diethyl malonate. An ^1H NMR of the resulting solution was taken. ^1H NMR (CD_3CN): δ 1.2 (t, 6 H), 3.3 (s, 2 H), 4.1 (q, 4 H).

The NMR sample was returned to the flask, and 5 mmol (0.66 mL) of triethylamine was added. An ^1H NMR was taken of the resulting solution. ^1H NMR (CD_3CN): δ 1.0 (t, 9 H), 1.2 (t, 6 H), 2.5 (q, 6 H), 3.3 (s, 2 H), 4.1 (q, 4 H).

The NMR sample was returned to the flask, and 5 mmol (0.48 g) of anhydrous magnesium chloride was added. The resulting heterogeneous mixture was stirred for 15 min at room temperature. As the mixture was stirred, it became more viscous. An aliquot of the mixture was removed and filtered, and an ^1H NMR was taken of the filtrate. ^1H NMR (CD_3CN): δ 1.1 (t, 9 H), 1.2 (t, 6 H), 3.1 (q, 6 H), 4.0 (t, b s, 5–6 H).

General Procedure for the Acylation of Ethyl Acetoacetate. A flame-dried 100-mL round-bottom flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was flushed with argon and charged with 25 mmol (2.38 g) of dry magnesium chloride. Dry solvent (25 mL, CH_3CN or CH_2Cl_2, see Table II)

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was added to the flask. To the resulting heterogeneous mixture was added 25 mmol (3.19 mL) of ethyl acetoacetate. The reaction flask was immersed in an ice bath, and 50 mmol of base (pyridine or triethylamine, see Table II) was added through the septum inlet. After the mixture was stirred for 15 min at O °C, 25 mmol of acid chloride was added. The resulting mixture was stirred for 15 min at O °C and 1 h at room temperature. After being cooled to O °C, the reaction was quenched with 15 mL of 6 M HCl. The resulting solution was washed three times with 20 mL of diethyl ether. The combined ether extracts were dried ($MgSO_4$), and an aliquot was removed for GC analysis. The ether was removed, and the residue was purified by simple vacuum distillation.

Ethyl 3-oxo-2-acetylbutanoate was prepared from ethyl acetoacetate and acetyl chloride in 91% yield (bp 45 °C (0.2 mm)): ^{1}H NMR ($CDCl_3$) δ 1.3 (t, J = 7 Hz, 3 H), 2.4 (s, 6 H), 4.3 (q, J = 7 Hz, 2 H), 17.5 (s, 1 H); MS, m/e 172 ($M^{+\cdot}$), 157 ($M^{+\cdot} - CH_3$), 129 ($M^{+\cdot} - CH_3CO$), 98, 85, 43.

Ethyl 3-oxo-2-benzoylbutanoate was prepared from ethyl acetoacetate and benzoyl chloride in 81% yield (bp 140 °C (0.25 mm)): ^{1}H NMR ($CDCl_3$) δ 0.7–1.4 (m, 3 H), 2.0–2.4 (s, total 3 H), 3.7–4.3 (m, 2 H), 5.3 (s), 7.2–7.9 (m, 5 H), 12.9 (s), 16.3 (*b s*); MS, m/e 234 ($M^{+\cdot}$), 233 ($M^{+\cdot} - H$), 219 ($M^{+\cdot} - CH_3$), 187, 105 ($PhCO^{+\cdot}$), 77, 43.

Ethyl 3-oxo-2-acetyl-4-methylpentanoate was prepared from ethyl acetoacetate and isobutyryl chloride in 77% yield (bp 55 °C (0.2 mm)): ^{1}H NMR ($CDCl_3$) δ 1.0–1.5 (m, 9 H), 2.3 (s, 3 H), 2.9–3.4 (m, 1 H), 4.0–4.5 (m, 2 H), 17.3 (s, 1 H); MS, m/e 200 ($M^{+\cdot}$), 185 ($M^{+\cdot} - CH_3$), 155, 71.

Ethyl 3-oxo-2-acetylhexanoate was prepared from ethyl acetoacetate and *n*-butyryl chloride in 78% yield (bp 54 °C (0.2 mm)): ^{1}H NMR ($CDCl_3$) δ 0.8–2.0 (m, 8 H), 2.3 (s, 3 H), 2.3–2.8 (m, 2 H), 4.1–4.5 (m, 2 H), 17.4 (s, 1 H); MS, m/e 201 ($M^{+\cdot} + 1$), 185 ($M^{+\cdot} - CH_3$), 157 ($M^{+\cdot} - CH_3CO$), 139, 129, 111, 71, 43.

Ethyl 3-oxo-2-acetyl-4,4-dimethylpentanoate was prepared from ethyl acetoacetate and pivaloyl chloride in 75% yield (bp 65 °C (0.25 mm)): ^{1}H NMR ($CDCl_3$) δ 1.1–1.5 (m, 12 H), 2.3 (s, 3 H), 4.0–4.4 (m, 2 H), 5.0 (s, 1 H); MS, m/e 214 ($M^{+\cdot}$), 199 ($M^{+\cdot} - CH_3$), 173, 155, 131, 85.

Registry No. CH_3COCl, 75-36-5; $(CH_3)_2CHCOCl$, 79-30-1; $(CH_3)_3CCOCl$, 3282-30-2; n-C_3H_7COCl, 141-75-3; C_6H_5COCl, 98-88-4; $CH_3C(OAc)=C(Ac)CO_2Et$, 27593-44-8; magnesium chloride, 7786-30-3; diethyl malonate, 105-53-3; triethylamine, 121-44-8; diethyl acetylmalonate, 570-08-1; diethyl benzoylmalonate, 1087-97-4; diethyl isobutyrylmalonate, 21633-78-3; diethyl *n*-butyrylmalonate, 21633-79-4; diethyl pivaloylmalonate, 22524-02-3; ethyl acetoacetate, 141-97-9; ethyl 3-oxo-2-acetylbutanoate, 603-69-0; ethyl 3-oxo-2-benzoylbutanoate, 569-37-9; ethyl 3-oxo-2-acetyl-4-methylpentanoate, 79322-87-5; ethyl 3-oxo-2-acetylhexanoate, 63765-76-4; ethyl 3-oxo-2-acetyl-4,4-dimethylpentanoate, 96808-02-5; pyridine, 110-86-1.

The Horner–Wadsworth–Emmons Modification of the Wittig Reaction Using Triethylamine and Lithium or Magnesium Salts

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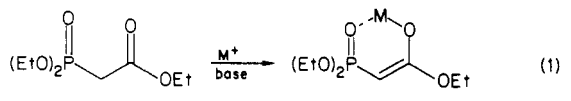
A variety of aldehydes were converted into the corresponding α,β-unsaturated esters using triethyl phosphonoacetate and triethylamine in the presence of lithium or magnesium halides. Under the same conditions, simple methyl ketones were unreactive.

The Horner–Wadsworth–Emmons (HWE) modification of the Wittig reaction utilizes metal enolates, **2**, derived from triethyl phosphonoacetate, **1**, or related phosphonates (eq 1).[1] Relatively strong bases such as *n*-butyllithium,



1 2 (1)

potassium *tert*-butoxide, or sodium hydride are commonly used for the preparation of **2**.[2] However, the stability of **2**, and thus the acidity of **1**, is greatly influenced by the nature of the metal ion, M, in **2**, suggesting that in the presence of the appropriate metal ion much weaker bases could be used in the HWE reaction.[3] A recent report by Masamune, Roush, et al. describing the HWE reaction in the presence of lithium chloride and either DBU or diisopropylethylamine[4] prompted us to report our own, related, study of the HWE reaction in the presence of magnesium or lithium halides using the weaker but much less expensive base triethylamine.

Results and Discussion

Cyclohexanone was reacted with phosphonate **1** in the presence of triethylamine and a variety of metal halides in tetrahydrofuran (THF) solution. As can be seen from the results in Table I, no reaction occurs in the absence of either triethylamine or metal halide (entries 1 and 9). Magnesium halides (entries 4 and 6) appear to be more active promoters of the reaction than lithium halides (entries 2 and 3). Since lithium enolates are generally more reactive than magnesium enolates, this difference may be

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