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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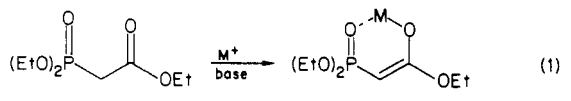
Received August 1, 1984

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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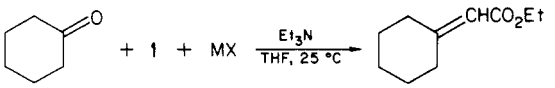
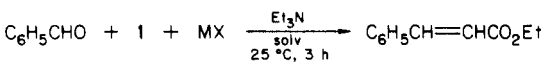
Table I. Reaction of Cyclohexanone with 1 in the Presence of Metal Halides[a]



entry	MX, mmol	yield,[b] %
1	none	0
2	LiCl (10)	19 (50)
3	LiBr (10)	39 (85)
4	$MgCl_2$ (10)	52 (86)
5	$MgBr_2$ (5)	50 (48)
6	$MgBr_2$ (10)	62 (85)
7	$MgBr_2$ (20)	70
8	$MgBr_2$ (10)	90[c]
9	$MgBr_2$ (10)	0[d]
10	NaI (10)	0
11	$ZnCl_2$ (10)	0.5
12	$AlCl_3$ (10)	0
13	$FeCl_3$ (10)	0
14	$CuCl_2$ (10)	0

[a] Reaction at 25 °C with 10 mmol of cyclohexanone, 10 mmol of Et_3N, 10 mmol of 1, and 10 mL of THF for a period of 3 h, except where noted. [b] Yield of ethyl cyclohexylideneacetate determined by ^1H NMR analysis. Yields in parentheses are for 24-h reaction periods. [c] 20 mmol of Et_3N was used. [d] No Et_3N was used.

Table II. Reaction of Benzaldehyde with 1 in a Variety of Solvents[a]



solvent	MX	yield,[b] %
acetonitrile	LiCl	77
	LiBr	93
	$MgCl_2$	15
	$MgBr_2$	71
diethyl ether	LiCl	77
	LiBr	71
	$MgBr_2$	80
tetrahydrofuran	LiCl	86
	LiBr	96
	$MgBr_2$	81
methylene chloride	LiCl	56
	LiBr	70
	$MgBr_2$	47
dimethylformamide	LiBr	25
	$MgBr_2$	10

[a] Reaction at 25 °C with 10 mmol of benzaldehyde, 10 mmol of 1, 10 mmol of Et_3N, and 10 mL of solvent for a period of 3 h. [b] GLC yields of ethyl cinnamate.

due to a more complete formation of the magnesium enolate (2, M = MgX) compared to the lithium enolate (2, M = Li; eq 1).

The reaction of benzaldehyde with phosphonate 1 in the presence of magnesium or lithium halides and triethylamne was examined in a variety of solvents (eq 2). None of the

$$C_6H_5CHO + 1 + MX \xrightarrow[\text{solv 25 °C, 12 h}]{Et_3N} C_6H_5CH{=}CHCO_2Et \quad (2)$$

MX = LiCl, LiBr, or $MgBr_2$

metal halides was completely soluble in the mixture of benzaldehyde and solvent under our standard conditions. However, addition of phosphonate 1 invariably resulted in complete dissolution of the salt and homogeneous solutions. As can be seen from the results shown in Table II, most of the common organic solvents give satisfactory results. It is noteworthy that the reaction can be conducted in methylene chloride, a solvent which is incompatible with the usual strong bases used in the HWE reaction. The low conversions realized in dimethylformamide solution possibly reflect the high coordinating power of this solvent for metal ions, disfavoring formation of the internally coordinated enolate 2.

The reaction of a variety of aldehydes and ketones with 1 in the presence of either $MgBr_2$ or LiBr was conducted on a preparative scale with the results shown in Table III. Excellent yields are obtained with aldehydes or with the reactive ketone cyclohexanone. However, simple methyl ketones such as acetophenone or acetone fail to react. The unreactivity of such ketones under standard HWE conditions has been noted previously.[2] In all cases, the unsaturated ester product was the *E* isomer. None of the corresponding Z isomer was detected either by GLC or ^1H NMR analysis under conditions judged sufficient to detect 2% of this isomer. A similar high *E*/*Z* ratio was reported by Masamune and Roush.[4]

Conclusions

HWE procedures using LiBr or $MgBr_2$ and triethylamine appear to give yields of unsaturated esters comparable to those reported for other, stronger, bases[2,4] at least with the simple substrates described here. The present procedure seems especially suitable for large scale preparations where the use of triethylamine possesses significant handling or cost advantages over other bases.

Experimental Section

Tetrahydrofuran was distilled from sodium/benzophenone just prior to use. Triethylamine was distilled from calcium hydride. Diethyl ether was taken directly from a freshly opened can of anhydrous ether. Acetonitrile was distilled from calcium hydride. Dimethylformamide was distilled from phosphorus pentoxide. Methylene chloride was taken from a freshly opened bottle of anhydrous methylene chloride. ^1H NMR data were obtained on a Varian T-60 spectrometer at 60 MHz. Chemical shifts are reported on the δ scale relative to an internal Me_4Si standard.

Table III. Reaction of a Variety of Carbonyl Compounds with 1 in the Presence of Triethylamine and Metal Halides[a]

CO compd	metal halides	(solv)	product	yield,[b] %
C_6H_5CHO	LiBr	(CH_3CN)	$C_6H_5CH{=}CHCO_2Et$	84
	$MgBr_2$	(THF)		85
$(CH_3)_2CHCHO$	LiBr	(CH_3CN)	$(CH_3)_2CHCH{=}CHCO_2Et$	80
	$MgBr_2$	(THF)		40
n-$C_6H_{13}CHO$	LiBr	(CH_3CN)	*n*-$C_6H_{13}CH{=}CHCO_2Et$	75
	$MgBr_2$	(THF)		100
cyclohexanone	LiBr	(CH_3CN)	$(CH_2)_5C{=}CHCO_2Et$	85
cyclopentanone	LiBr	(CH_3CN)	$(CH_2)_4C{=}CHCO_2Et$	15
$C_6H_5CH{=}CHCHO$	LiBr	(CH_3CN)	$C_6H_5CH{=}CH{-}CH{=}CHCO_2Et$	65
CH_3COCH_3	LiBr	(CH_3CN)		0
	$MgBr_2$	(THF)		0
$C_6H_5COCH_3$	LiBr	(CH_3CN)		0
	$MgBr_2$	(THF)		0

[a] Reaction at 25 °C for 12 h, 25-mmol scale (carbonyl compound:1:Et_3N:metal halide = 1:1:1.1:1.2). [b] Isolated yield, based on weight of distilled product.

Gas chromatographic analyses were performed on a Varian 920 chromatograph equipped with a 6 ft × 0.25 in. stainless-steel column packed with 15% SE-30 on Chromosorb W. GC yields were obtained by using *n*-alkanes as internal standards.

Lithium bromide (aldrich Chemical Co., 99+%) was dried in an abderhalden flask over refluxing xylene at 0.3 torr.

Magnesium bromide was prepared from dibromoethane and magnesium and dried under vacuum at 150 °C.[6]

Zinc chloride (Aldrich Chemical Co., 98%) was dried with thionyl chloride followed by removal of excess $SOCl_2$ under high vacuum.[7]

Lithium chloride (Aldrich Chemical Co., 99%) was dried in an abderhalden flask over refluxing xylene at 0.3 torr.

The remaining metal salts were obtained as anhydrous materials from commercial sources. All metal salts were stored in a dessicator and transferred under argon in a glovebag. In several experiments, magnesium or lithium halides were transferred and weighed in the atmosphere without the protection of a glovebag or drybox, and triethylamine and solvents were taken directly from freshly opened bottles without prior purification. These modifications gave no significant change in yields compared to the general procedure below.

Triethyl phosphonoacetate was prepared from ethyl bromoacetate and triethylphosphite.[8]

HWE Reaction. General Procedure. The following procedure, with modification of scale, is representative of the procedure used to obtain the results in Tables I–III: a 50-mL flask with a septum inlet and magnetic stir bar was flame dried and flushed with argon. Anhydrous metal salt, 30 mmol, was weighed in a glovebag and transferred under a stream of argon to the flask. Solvent, 25 mL, and triethyl phosphonoacetate (25 mmol, 5.54 g) was added and the mixture stirred 5 min. Triethylamine (28 mmol, 3.9 mL) was added and the mixture stirred an additional 10 min. The carbonyl compound was then added dropwise (5 min), and the reaction mixture was stirred overnight. After being quenched with dilute aqueous HCl, the reaction mixture was extracted with ether (3 × 25 mL). The organic extracts were combined and dried over $MgSO_4$, and the solvent was removed under vacuum. Samples for GC or ^1H NMR analyses were taken, and the crude product was purified by short path distillation.

Ethyl cinnamate[1b] was prepared from 1 and benzaldehyde: bp 75 °C (0.2 mmHg); ^1H NMR ($CDCl_3$) δ 1.30 (t, 3 H), 4.18 (q, 2 H), 6.33 (d, 1 H), 6.7–7.7 (m, 6 H).

Ethyl 4-methyl-2-pentenoate[1b] was prepared from 1 and isobutyraldehyde: bp 60 °C (30 mmHg); ^1H NMR ($CDCl_3$) δ 0.96–2.48 (m, 9 H), 2.4 (septet, 1 H), 4.16 (q, 2 H), 5.75 (d, 1 H), 7.0 (d of d, 1 H).

Ethyl 2-nonenoate[9] was prepared from 1 and heptaldehyde: bp 72 °C (2 mmHg); ^1H NMR ($CDCl_3$) δ 0.8–1.1 (m, 3 H), 1.1–1.7 (m, 1 H), 1.9–2.5 (m, 2 H), 4.2 (q, 2 H), 5.75 (d, 1 H), 6.95 (m, 1 H).

Ethyl cyclohexylideneacetate[10] was prepared from 1 and cyclohexanone: bp 50 °C (0.2 mmHg); ^1H NMR ($CDCl_3$) δ 1.23 (t, 3 H), 1.4–1.8 (m, 6 H), 1.9–2.5 (m, 2 H), 2.7–3.1 (m, 2 H), 5.5 (s, 1 H).

Ethyl cyclopentylideneacetate[11] was prepared from 1 and cyclopentanone: bp 85 °C (10 mmHg), ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H), 1.8 (m, 6 H), 2.5 (m, 2 H), 4.2 (q, 2 H), 5.8 (m, 1 H).

Ethyl 5-phenyl-2,4-pentadienoate[10] was prepared from 1 and cinnamaldehyde: bp 90 °C (0.2 mmHg); ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 4.2 (q, 2 H), 5.95 (d, 1 H), 6.7–7.6 (m, 8 H).

Registry No. 1, 867-13-0; Et_3N, 121-44-8; LiBr, 7550-35-8; $MgCl_2$, 7786-30-3; $MgBr_2$, 7789-48-2; LiCl, 7447-41-8; PhCHO, 100-52-7; $PhCH{=}CHCO_2Et$, 103-36-6; $(CH_3)_2CHCHO$, 78-84-2; n-$C_6H_{13}CHO$, 111-71-7; PhCH=CHCHO, 104-55-2; $CH_3C(O)CH_3$, 67-64-1; $PhC(O)CH_3$, 98-86-2; $(CH_3)_2CHCH{=}CHCO_2Et$, 2351-97-5; n-$C_6H_{13}CH{=}CHCO_2Et$, 17463-01-3; $(CH_2)_4C{=}CHCO_2Et$, 1903-22-6; $PhCH{=}CHCH{=}CHCO_2Et$, 1552-95-0; ethyl cyclohexylideneacetate, 1552-92-7; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1.

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Intramolecular Diels–Alder Reaction of 1-Nitrodeca-1,6,8-trienes

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Received August 7, 1984

Nitro trienes **1**, **2**, and **3** are prepared from nona-5,7-dien-1-ols **6**, **10**, and **14**, respectively, via a three-step sequence involving PCC oxidation, nitro aldol condensation, and dehydration. Intramolecular Diels–Alder reaction of nitro trienes **1** and **2** preferentially affords endo cycloadducts possessing the trans ring fusion (9:1 trans/cis) while cyclization of **3** gives exclusively the trans-fused perhydroindene skeleton (**25c**/**25d**, 9:1). In contrast, (*Z*)-nitroolefins **4** and **5**, which are found to undergo cyclization at room temperature, produce a nearly 1:1 mixture of cis- and trans-fused cycloadducts.

Nitroaliphatic compounds have proven both versatile and unique as synthetic intermediates, particularly with regard to the extensive utility of the nitro group in organic functional group interconversions.[1] This utility is augmented by the many synthetic routes which access nitroaliphatics.[1,2] Of these routes, the intermolecular [4 + 2] cycloaddition of a nitroolefin and a 1,3-diene is the most reliable method for the stereoselective construction of

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