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THE GENERATION AND REACTION OF ENOLATE ANIONS WITH TRIETHYLAMINE IN THE PRESENCE OF MAGNESIUM OR LITHIUM HALIDES

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Michael Anthony Nowak

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Doctoral degree in Chemistry

Michael W. Rathke
Major professor

Date August 5, 1985

THE GENERATION AND REACTION OF ENOLATE ANIONS WITH TRIETHYLAMINE IN THE PRESENCE OF MAGNESIUM OR LITHIUM HALIDES

BY

MICHAEL ANTHONY NOWAK

A DISSERTATION

Submitted to

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ABSTRACT

Bis(trimethylsilyl) malonate, in the presence of triethylamine and lithium or magnesium halides, is converted to its enolate anion. Under these conditions, the enolate anion is C-acylated in good yields with a variety of acid chlorides or ethyl octanoyl carbonate. Important exceptions are the hindered acid chloride pivaloyl chloride, which gives a fifty percent yield of C-acylated product, and crotonyl chloride, which gives no C-acylated product. Under these conditions, acyl imidazoles give modest yields of C-acylated product. Subsequent hydrolysis and decarboxylation of the acylation product gives β-keto acids or methyl ketones.

In the presence of triethylamine and lithium or magnesium halides, triethylphosphonoacetate reacts with a variety of aldehydes to give α,β-unsaturated esters in excellent yields. Under the same conditions, triethylphosphonoacetate is unreactive towards simple methyl ketones.

Compared to other procedures which employ strong bases, these procedures are inexpensive, safe and convenient, especially for large-scale preparations. They are also particularly attractive for use with base-sensitive substrates.

In memory of my father, Edward Nowak.

ACKNOWLEDGEMENTS

The author wishes to thank Professor Michael W. Rathke for his patience and his guidance throughout the course of this work. I consider it a privilege having been associated with him. I would like to express special thanks to Professor William Reusch for serving as second reader.

I would like to thank my wife, Nanette, for always being there and believing in me. I would like to thank my Mom, Stan J. and my families in New York and Michigan for their faith, interest and continuing support.

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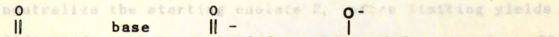
CHAPTER I

THE ACYLATION OF BIS(TRIMETHYLSILYL) MALONATE USING TRIETHYLAMINE AND MAGNESIUM OR LITHIUM HALIDES

INTRODUCTION

Carbon-carbon bond forming reactions are the backbone of synthetic organic chemistry. Base-promoted removal of a proton alpha to a carbonyl group gives a resonance-stabilized enolate anion (eq. 1). Subsequent reaction with an electrophile (eq. 2) constitutes one of the most frequently used methods of effecting such bond-forming reactions.



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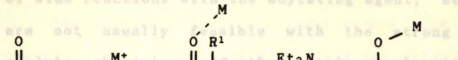
For the past decade, synthetic applications of enolate reactions have emphasized the use of very powerful bases, primarily the lithium dialkylamides ($pK_a > 35$).[1]

It is well known that complexation of a metal cation to a ligand can enhance the acidity of the ligand.[2] If metal complexation with carbonyl compounds would enhance their acidity sufficiently so that enolate formation could be promoted by weak bases such as the tertiary amines ($pK_a \sim 10$), then a new route to enolate chemistry would be available

(eq. 3). The synthetic advantages of such a route to enolate species are most apparent for acylation reactions.



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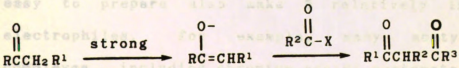
The standard procedure for acylation reactions involves a two-step sequence (eq. 4). In the first step, an enolate anion is generated using a strong base such as a metal alkoxide, lithium alkyl or lithium dialkylamide. The second step involves addition of an acylating agent. This procedure is plagued by the fact that the product 3 is a stronger acid than starting compound 1 and thus may neutralize the starting enolate 2, often limiting yields to fifty percent.[3] One solution to this problem is to effect the reaction in a single step using two equivalents of base



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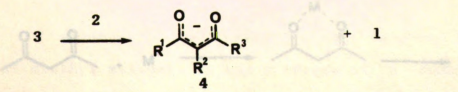
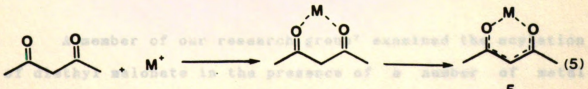


to produce enolate **4** stoichiometrically. However, because of side reactions with the acylating agent, such procedures are not usually feasible with the strong bases used in enolate chemistry. If the metal complexation route of equation 3 were successful, the weak but tolerant tertiary amine bases would accommodate the high acidity of the acylation product but avoid reaction with the acylating agent.

Initial investigation of this proposed enolate chemistry began with the relatively acidic (pK_a~15)[4] β-dicarbonyl compounds. Formation of enolate complexes from this class of compounds seems relatively straightforward, not only because of their high intrinsic acidity, but also because the chelating nature of the enolate should provide a strong driving force for bonding with an appropriate metal ion (eq. 5). Unfortunately, the same factors which make **5** easy to prepare also make **5** relatively inert towards electrophiles. For example, many acetyl acetonate complexes, including chromium acetyl acetonate **6**, are weak nucleophiles[5] which undergo typical enolate reactions only



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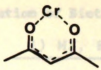
with powerful electrophiles, such as Friedel-Crafts reagents, or at elevated temperatures.



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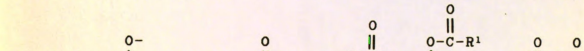
The objective of this investigation was to identify carbonyl substrates and metal ions for which complex 5 has sufficient stability to be formed in useful concentrations by weak bases but also is able to react with a variety of electrophiles. The last step in equation 5 is a proton-exchange reaction, and the overall driving force of the reaction depends on the stability of the metal oxygen bond in 5. The greatest chance for success would appear to be with magnesium or zinc where the metal ions have appreciable complexing ability for oxygen ligands and where their enolates and known to possess sufficient reactivity towards a number of electrophiles.[2a] Also, magnesium enolates are known to have a low tendency to acylate at oxygen rather than carbon[6], and oxygen acylation is often a significant problem in acylation reactions of ambident enolate anions (eq. 6).



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A member of our research group[7] examined the acylation of diethyl malonate in the presence of a number of metal salts (Table 1). The malonate esters are one of the least acidic members of the β-dicarbonyl class of compounds (pK_a~14). Nevertheless, diethyl malonate was acylated in

TABLE 1. Acylation of Diethyl Malonate.[a]

$$EtO_2CCH_2CO_2Et \xrightarrow[2)\ PhC(=O)Cl]{1)\ MX,\ Et_3N} (EtO_2C)_2CHC(=O)Ph$$

Entry	MX	Yield Product, %	Recovered Starting Material, %
1	---	0	87
2	$ZnCl_2$	0	93
3	$CuCl_2$	0	99
4	$FeCl_3$	0	63
5	$MgCl_2$	85	8
6	$MgCl_2$	0	98[b]
7	LiCl	0	---
8	LiBr	88	---

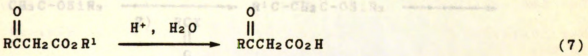
a) All entries except entry 8 are taken from:

Cowan, Patrick, Ph.D. dissertation, Michigan State University, 1983.

b) Reaction carried out in the absence of triethylamine.

good yields in the presence of magnesium chloride and triethylamine (pK_a~10).[1a] Control experiments demonstrated the necessity of both the metal salt and Et_3N for the success of the reaction. The resulting acylation products may be of interest to synthetic organic chemists, but more importantly, the methodology should be applicable to similar systems.

There are three general routes to β-keto acids: acid[15,16] or base-promoted hydrolysis[17] of the corresponding keto ester (eqs. 7,8), carboxylation[18-21] of ketone enolate anions (eq. 9) and acylation[9,22] of carboxylic acid dianions (eq. 10). A serious problem associated with the acid-



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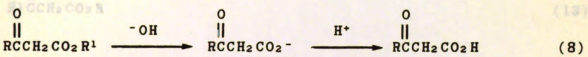

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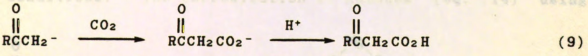

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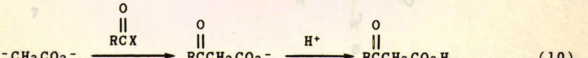

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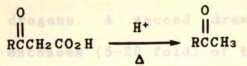
catalyzed hydrolysis of keto esters is that subsequent decarboxylation of the keto acid (eq. 11) may occur.



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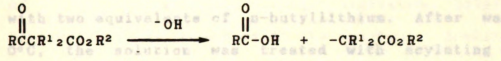
Alkaline hydrolysis of β-keto esters avoids this decarboxylation but is complicated by possible retro-Claisen cleavage of the β-keto ester (eq. 12). An alternative approach, the acylation of silyl acetates (eq. 13), gives



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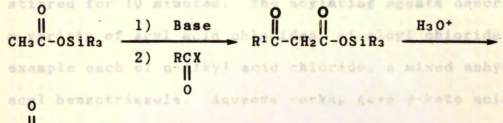

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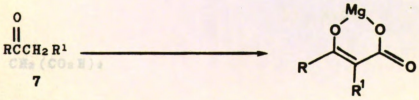
keto esters that are readily hydrolyzed under neutral conditions.[23] The carboxylation of ketones (eq. 14) using

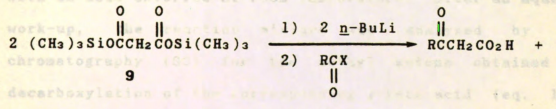


(14)

magnesium methyl carbonate (MMC)[17] in dimethylformamide (DMF) solution gives keto acids, and formation of complex 8 appears to provide the thermodynamic driving force for this reaction. Consequently, a necessary requirement for using

MMC is that starting ketone 7 contain at least two alpha hydrogens. A second drawback to using MMC is the large excesses (5-20 fold) of the reagent required to obtain good yields.

The synthesis of β-keto acids via acylation of bis(trimethylsilyl) malonate 9 (a synthon of trimethylsilyl acetate) using two equivalents of the strong base n-butyllithium (eq. 15) has been described.[24] Two equivalents of 9 in an ethereal solvent were cooled to -60°C and treated with two equivalents of n-butyllithium. After warming to 0°C, the solution was treated with acylating agent and stirred for 10 minutes. The acylating agents described are a variety of aryl acid chlorides, pivaloyl chloride, and one example each of n-alkyl acid chloride, a mixed anhydride and acyl benzotriazole. Aqueous workup gave β-keto acids in 63-93% yield.



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Substrate 9, which is structurally similar to diethyl malonate, is ideally suited for metal cation complexation, and routes to enolate chemistry via weak tertiary amine bases should be applicable here. In addition, after acylation, the readily hydrolyzable silicon esters should

provide an easy route to β-keto acids and to methyl ketones by decarboxylation of the corresponding β-keto acid.

RESULTS AND DISCUSSION

Because of the similarity of the substrates, investigation of the acylation of **9** began with the conditions found suitable for the acylation of diethyl malonate.[7] An initial set of experiments provided a survey of solvent systems using magnesium chloride and triethylamine as promotors of the reaction. Addition of **9** to a stirred slurry of magnesium chloride in the solvent resulted in complete dissolution of the magnesium chloride. The resulting homogeneous solution was then treated with triethylamine and a precipitate formed immediately. After stirring ten minutes, the heterogeneous mixture was mixed with an acid chloride at room temperature. After an aqueous work-up, the reaction mixture was analyzed by gas chromatography (GC) for the methyl ketone obtained by decarboxylation of the corresponding β-keto acid (eq. 16).

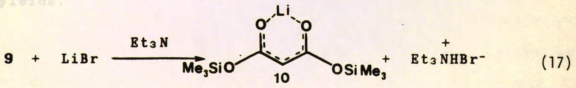
$$Me_3SiO_2CCH_2CO_2SiMe_3 \xrightarrow[2)\ RCOCl\ \ 3)\ H_3O^+]{1)\ MgCl_2,\ Et_3N} RCOCH_3 \qquad (16)$$

In this manner bis(trimethylsilyl) malonate was acylated with benzoyl chloride in good yield in either diethyl ether or acetonitrile solution. Since diethyl ether can be purchased as anhydrous material, it was selected as the solvent of choice. Attempts to acylate **9** with other acid chlorides under the conditions described gave only poor to

moderate yields of acylation product. The results of these initial experiments are summarized in Table 2.

The ability of other metal salts to promote the reaction was then examined. Lithium bromide proved to be an effective alternative to magnesium chloride. Use of lithium bromide offered two advantages: 1) Lithium bromide is easier to obtain and handle in the anhydrous state. 2) The lithium enolate should be more reactive than the corresponding magnesium enolate.

We wished to verify that these acylation reactions were proceeding via an enolate intermediate by isolating **10**. Addition of triethylamine to a solution of lithium bromide and bis(trimethylsilyl) malonate in diethyl ether immediately gave a precipitate. No precipitate formed in the absence of lithium bromide. After stirring ten minutes, the precipitate was isolated and dried under high vacuum; the filtrate was concentrated under high vacuum. The precipitate accounted for 99% of the theoretical weight of triethylamine hydrobromide (eq. 17) and exhibited a ^{1}H NMR



(17)

spectrum identical to that of triethylamine hydrobromide. Mass spectral analysis of the precipitate also gave a spectrum corresponding to the relatively volatile triethylamine hydrobromide ($Et_3NH^+Br^-$). The filtrate residue gave a ^{1}H NMR spectrum exhibiting silicon methyls and a singlet 0.55 ppm upfield from the alpha proton signal

TABLE 2. Reaction of Bis(trimethylsilyl) Malonate with Acid Chlorides Using $MgCl_2$

$$Me_3SiO_2CCH_2CO_2SiMe_3 \xrightarrow[2)\ RCOCl \\ 3)\ H_3O^+]{1)\ MgCl_2,\ Et_3N} RCOCH_3$$

Entry	Reaction Time	Solvent	R	Yield, %
1	1 hour	CH_3CN	Ph	90
2	1 hour	Et_2O	Ph	90
3	1 hour	CH_2Cl_2	Ph	32
4	1 hour	THF	Ph	50
5	1 hour	Et_2O	$CH_3CH{=}CH_2$	0
6	1 hour	Et_2O	$n\text{-}C_7H_{15}$	15
7	1 hour	Et_2O	i-Pr	6
8	18 hours	Et_2O	i-Pr	15
9	18 hours	CH_2Cl_2	i-Pr	52

Standard Reaction Conditions: 5 mmol scale: 1.0 equiv. BSM, 1.05 equiv. $MgCl_2$, 2.1 equiv. Et_3N, 5.0 mL solvent. After 10 min., 1.0 equiv. RCOCl. All yields are GC yields.

of bis(trimethylsilyl) malonate. Comparison with the ^{1}H NMR spectrum of **10** prepared by reaction with n-butyllithium confirmed that enolate formation had taken place.

Acylation reactions of bis(trimetylsilyl) malonate, using the lithium bromide procedure, were examined under a number of different reaction conditions (Table 3). Efforts to improve the yields focused on reaction conditions which were likely to promote enolate formation and minimize possible side reactions. Diethyl ether remained the solvent of choice. Coloration of the reaction mixture occurred when either isobutyryl chloride or crotonyl chloride was added to the reaction flask. This suggested that side reactions were occurring, possibly ketene formation. Weaker bases than triethylamine proved ineffective in promoting the reaction. The reaction temperature was an important factor. Best yields were obtained when the malonate ester, lithium bromide and triethylamine were stirred for several minutes at room temperature and then cooled to 0°C before addition of the acid chloride.

One problem frequently encountered in acylation reactions of enolate species is competition of O-acylation with C-acylation (eq. 6). The failure to detect any C-acylated material derived from pivaloyl chloride suggested that O-acylation might be the predominant reaction with hindered acylating agents. Likewise, the modest C-acylation yields obtained with isobutyryl chloride might be attributed to competing O-acylation. Consequently, it was important to determine if in fact O-acylation was responsible for our

TABLE 3. Reaction of Bis(trimethylsilyl) Malonate with Acid Chlorides Using LiBr.

$$Me_3SiO_2CCH_2CO_2SiMe_3 \xrightarrow[2)\ RCOCl\ \ 3)\ H_2O]{1)\ LiBr,\ Et_3N} RCOCH_2CO_2H \text{ or } RCOCH_3$$

Entry	Reaction Time	Temperature	Solvent	R	Yield, %
1	18 hours	25	Et_2O	Ph	57
2	18 hours	25	CH_2Cl_2	Ph	45
3	18 hours	25	CH_3CN	Ph	55
4	18 hours	25	Et_2O	Ph	0[a]
5	18 hours	25	CH_2Cl_2	Ph	0[a]
6	18 hours	0	Et_2O	Ph	60[b]
7	1 hour	0	Et_2O	Ph	88[c]
8	1 hour	0	Et_2O	i-Pr	50[d]

Same reaction conditions as Table I, with LiBr in place of $MgCl_2$.

a. Pyridine used as base.

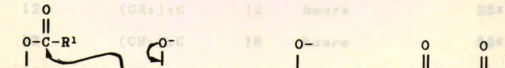
b. Base added after RCOCl.

c. Isolated yield.

d. Base added at 25° and stirred for 10 minutes, then cooled to 0°.

limited success with this procedure by isolating and identifying possible O-acylation products. To this end, isobutyryl chloride was added to a stirred reaction mixture containing **9**, lithium bromide and triethylamine in diethyl ether at 0°C. The crude reaction mixture was analyzed by gas chromatographic mass spectroscopy (GC/MS). No O-acylation product could be detected. ^{1}H NMR analysis of the crude reaction mixture did not reveal the presence of O-acylated product because: 1) The ^{1}H NMR spectrum of the O-acylated product is expected to be nearly identical to that of a mixture of **10** and isobutyryl chloride. 2) If the two spectra were distinguishable, the CH_2 signal of the ammonium salt would be superimposed on the enolate (vinyl) hydrogen. Attempts to isolate O-acylated material from the crude reaction mixture were unsuccessful. Thus, there is no direct evidence of O-acylation.

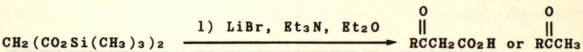
In difficult cases, successful C-acylations can often be accomplished by using excess starting enolate[25], which then reacts with the O-acylation product to give the desired C-acylation product together with the starting enolate (eq. 18). The acylation reactions were, therefore, re-examined



(18)

under a variety of conditions using a slight excess (5%) of bis(trimethylsilyl) malonate, lithium bromide, and triethylamine (Table 4). For those acid chlorides which had

TABLE 4. Acylation of Bis(trimethylsilyl) Malonate Using Lithium Bromide



Entry	R	Reaction Time	Yield (%)
1	Ph	1 hour	85
2	n-C_7H_{15}	1 hour	91
3	n-C_7H_{15}	1 hour	80[f]
4	n-C_7H_{15}	1 hour	84[a,f]
5	n-C_7H_{15}	1 hour	65[b,f]
6	n-C_7H_{15}	1 hour	42[c,f]
7	n-C_7H_{15}	1 hour	45[d,f]
8	$(CH_3)_2CH$	1 hour	50
9	$(CH_3)_2CH$	1 hour	30[c]
10	$(CH_3)_2CH$	1 hour	12[e]
11	$(CH_3)_3C$	1 hour	0
12	$(CH_3)_3C$	12 hours	35[g]
13	$(CH_3)_3C$	18 hours	50[g]
14	$(CH_3)_3C$	40 hours	10[g]

TABLE 4, continued

Entry	R	Reaction Time	Yield (%)
15	$CH_3CH=CH_2$	1 hour	0
16	$(CH_3)_2CH$	0.25 hour	0[h]

a) Two full equivalents of lithium bromide used.
b) Malonate ester, base and lithium bromide were stilled at 0°, not room temperature.
c) Ratio of reagents used is 1.1 BSM: 1.05 LiBr: 2.1 Et_3N: 1.0 RCOCl.
d) Reaction mixture allowed to stir three hours before addition of RCOCl.
e) $(i\text{-Pr})_2NEt$ used in place of Et_3N.
f) Isolated yield of keto acid.
g) Isolated yield of methyl ketone.
h) Using method of van der Baan[24], obtained complex mixture of products.

given acceptable yields of C-acylated product, a small increase in yield was observed over standard reaction times. Larger excesses of these reagents had little effect (<5%) on the yields. Allowing the malonate ester, lithium bromide and base to stir for longer periods of time before addition of the acid chloride did not improve the yields. Extended reaction times also gave no increase in yields with most acylating agents, except for pivaloyl chloride. In the latter case, pinacolone could be isolated in yields up to 50% but excessively long reaction times (40 hours) resulted in lower yields.

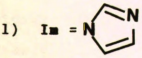
It is interesting to note that our attempt to acylate bis(trimethylsilyl) malonate with isobutyryl chloride using a literature procedure that generates the enolate with n-butyllithium was unsuccessful. Efforts to isolate the keto acid using the literature procedure failed. Gas chromatographic analysis for the corresponding methyl ketone revealed a complex mixture of products. Gas chromatographic-mass spectral analysis identified 3-methyl-2-butanone as an insignificant component of the reaction mixture.

The acylation of bis(trimethylsilyl) malonate using lithium bromide with other acylating agents was next examined (Table 5). Acyl imidazoles **11** and mixed carboxylic acid anhydrides (acyl carbonates) **12**, may be prepared directly from the corresponding carboxylic acid

TABLE 5. Reaction of Bis(trimethylsilyl) Malonate with Acyl Carbonates and Imidazoles.

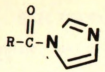
$$Me_3SiO_2CCH_2CO_2SiMe_3 \xrightarrow[2)\ RCOX\ \ 3)\ H_2O]{1)\ MX,\ Et_3N} RCOCH_2CO_2H \text{ or } RCOCH_3$$

Entry	RCOX[1]	Reaction Time	Temp.	Yield[2], %
1	PhCOIm	18 hours	25°	0
2	i-PrCOIm	18 hours	25	<5
3	$C_7H_{15}COIm$	18 hours	25	13*
4	PhCOIm	1 hour	0	0
5	$C_7H_{15}COIm$	24 hours	0--RT	58*
6	i-PrCOIm	24 hours	0--RT	0
7	i-PrCOIm	18 hours	0--RT	0[3]
8	i-PrCOIm	1 hour	67	0
9	$PhCOCO_3Et$	1 hour	0	0
10	$C_7H_{15}COCO_3Et$	1 hour	0	35*
11	$C_7H_{15}COCO_3Et$	1 hour	0--RT	65*

1) Im = 

2) Yields are GC yields except where noted by "*". Entries so marked are isolated yields.

3) $MgCl_2$ used in place of LiBr.



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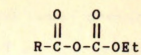


12

under relatively mild conditions. The acyl imidazoles, which are much weaker acylating agents than acid chlorides, gave acceptable yields of acylation product only after extended reaction periods. No acylation product was obtained using ethyl benzoyl carbonate but ethyl octanoyl carbonate provided 3-oxodecanoic acid in relatively good yield.

In summary, a new procedure has been developed for the acylation of readily hydrolyzable malonic esters providing a new route to β-keto acids and methyl ketones. The procedure is safe, convenient and economical, particularly on a large scale. Using these procedures, the reaction can be carried out in a single step without complications due to reaction of the base with the acylating agent.

EXPERIMENTAL

MATERIALS

Acetonitrile, diisopropyl amine and triethylamine were distilled from calcium hydride prior to use. Tetrahydrofuran was distilled from sodium/benzophenone prior to use. Diethyl ether was taken from a freshly opened can of anhydrous ether. Methylene chloride was taken from a freshly opened bottle of anhydrous methylene chloride. Lithium bromide (Aldrich Chemical Company, 99%) was dried in an abderhalden flask over refluxing xylene at 0.3 torr. It was stored and weighed under argon in a glove bog and dried *in situ* by treatment with chlorotrimethylsilane for ten minutes followed by removal of all volatile materials under high vacuum. All acid chlorides were obtained from Aldrich Chemical Company and were purified by distillation. Acyl imidazoles were prepared by the method of Staab.[26] Carbonates were prepared just prior to use from ethyl chloroformate and the corresponding carboxylic acid in diethyl ether according to the procedure of Tarbell and Rice.[27] The ethyl chloroformate was obtained from Aldrich Chemical Company and was used without further purification. The carboxylic acids were obtained from Aldrich Chemical Company and purified by distillation except benzoic acid which was purified by sublimation. n-Butyllithium was obtained from Aldrich Chemical Company as a 1.6M solution in hexane and was used directly.

Bis(trimethylsilyl) malonate (28) was prepared from malonic acid and two equivalents of chlororimethylsilane. b.p. 50-52 (0.3 torr). ^{1}H NMR: δ 3.26 (s, 1H), 0.1 (s, 9H).

METHODS OF ANALYSIS

Gas chromatographic analyses were performed on a Varian 920 chromatograph equipped with a 6 ft. X 0.25 in. stainless steel column packed with 15% SE-30 on Chromasorb-W or on a Hewlett Packard 5880A chromatograph equipped with a 12.5 meter X 0.25 mm capillary column using crossed linked dimethylsilicone as the liquid phase. GC yields were obtained using n-alkanes as internal standards. ^{1}H NMR data were obtained using a Finnigan 4000 EI GC/MS mass spectrometer. Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 599 grating infrared spectrometer using a polystyrene reference.

General Procedure for the Acylation of Bis(trimethylsilyl) malonate.

A 50 mL round bottom flask fitted with an efficient stirrer, a septum inlet and a gas inlet tube with mercury bubbler was flame dried under argon and charged with 5.5 mmol of anhydrous metal salt. To this was added 10 mL of anhydrous solvent and 5.25 mmol of bis(trimethylsilyl) malonate. 5.5 mmol of triethylamine was added dropwise and a precipitate formed immediately. After stirring ten minutes,

the flask was cooled to 0°C and 5.0 mmol of an acylating agent was added. (Acid chlorides were added dropwise, slowly; carbonates were added in one portion as the crude freshly-prepared reaction mixture.)

General Procedure for the Preparation of Methyl Ketones.

After the reaction mixture described above was stirred for one hour, it was quenched with 4 mL 5M HCl and then refluxed for one hour. To this mixture was added an appropriate n-alkane as an internal standard. The mixture was then extracted with ether (3 X 10 mL), the organic layers were combined and dried ($MgSO_4$), and this product was analyzed by gas chromatography.

General Procedure for the Preparation of β-Keto Acids.

After the reaction mixture described above was stirred for one hour, it was quenched with 10 mL cold saturated aqueous $NaHCO_3$ and stirred for ten minutes in an ice bath. The aqueous layer was separated and acidified to pH 2-3 by the dropwise addition of cold 4M H_2SO_4. The resulting precipitate was extracted with ether (3 X 10 mL), the organic layers were combined, dried ($MgSO_4$), and filtered. The solvent was removed *in vacuo* (avoid excessive heat) and the re-sulting white solid proved of sufficient purity to be used directly.

Benzoyl Acetic Acid: m.p. 101-102 (lit. m.p. 101-102)[29]; ^{1}H NMR ($CDCl_3$): δ 4.1 (s, 2H), 5.7 (enol H), 7.25-7.6 (m, 3H), 7.7-8.05 (m, 2H).

2-Oxodecanoic Acid: m.p. 76-77; ^{1}H NMR ($CDCl_3$): 0.9-1.1 (m, 3H), 1.2-2.0 (br s, 12H), 3.6 (s, 1H), 10.6 (s, 1H) enol proton not observed; m/s (m/e): 186 (M^+), 142 ($-CO_2$), 127, 85, 71, 58 (base), 43; IR (KBr): 3500-3300 (br), 2915, 2850, 1730, 1710, 1435.

Isolation of 10 Using Lithium Bromide and Triethylamine.

A 50 mL flask was fitted with a septum inlet, magnetic stirrer, a filter stick and a gas inlet tube. The flask was flame dried under a stream of argon. The flask was charged with lithium bromide (5 mmol, 0.44g) and diethyl ether (5 mL). Bis(trimethylsilyl) malonate (5 mmol, 1.3 mL) was added and the solution stirred 5 minutes. Triethylamine (5 mmol, 0.7 mL) was added dropwise and a white precipitate formed immediately. After stirring ten minutes, the mixture was filtered. The precipitate was collected and dried in a dessicator under vacuum (1 torr). The filtrate was concentrated under high vacuum (0.3 torr) giving a white residue. The dry precipitate exhibited the following: ^{1}H NMR (CD_3CN): δ 3.2 (q, 3H), 1.5 (t, 3H); m/s (m/e) 101 (Et_3N), 80 (HBr^{79}), 82 (HBr^{81}). The filtrate exhibited the following: ^{1}H NMR (CCl_4): δ 2.7 (s), 0.1 (s).

Characterization of 10 Prepared Using n-Butyllithium.

A 50 mL flask was fitted with a septum inlet, magnetic stirrer and gas inlet tube. The flask was flame dried under argon. Diethyl ether (10 mL) and bis(trimethylsilyl) malonate (1.3 mL, 5 mmol) was introduced via syringe and the solution was cooled to -78°C. n-Butyllithium (5 mmol, 3.125 mL 1.6M solution in hexane) was added dropwise. The solution was stirred ten minutes and slowly brought to room temperature. All volatile components were removed under high vacuum to give a white solid. ^{1}H NMR ($CDCl_3$): δ 2.8 (s), 0.1 (s).

Attempted Acylation of 9 with Isobutyryl Chloride Using n-Butyllithium.

This procedure for the acylation of **9** with acid chlorides (but not isobutyryl chloride) is described in the literature.[24] A 50 mL flask was fitted with a magnetic stirrer, septum inlet and gas inlet tube and was flame dried under argon. The flask was charged with bis(trimethylsilyl) malonate (10 mmol, 2.6 mL) and diethyl ether (20 mL) and the solution cooled to -78°C. n-Butyl-lithium (10 mmol, 6.25 mL 1.6M solution in hexane) was added dropwise and the solution warmed to 0°C. Isobutyryl chloride (5 mmol, 0.52 mL) was added dropwise and the reaction mixture stirred for ten minutes. Standard aqueous work-up fails to provide any β-keto acid. Repeating the acylation procedure followed by work-up previously described as the general procedure for the preparation of methyl ketones gave a gas chromatograph

exhibiting fifteen unassignable signals and a 4% yield of 3-methyl-2-butanone. GC/MS did not prove useful in determining the identity of the numerous by-products.

CHAPTER II

The Horner-Wadsworth-Wittig Reaction Using Triethylamine and Magnesium or Lithium Halides

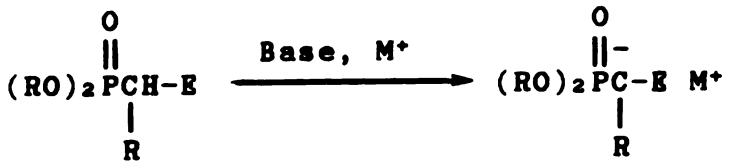
INTRODUCTION

One of the most important tools available to the synthetic organic chemist for the construction of carbon-carbon bonds is the Wittig olefination reaction (eq. 19).

(19)

It provides an easy method for linking two synthons of any size which bear various functional groups. The Wittig reaction and its modifications provide a major advantage over other olefin-forming reactions by introducing the double bond regiospecifically.

The Horner-Wadsworth-Emmons modification of the Wittig reaction (eqs. 20-23) employs phosphonate esters **12** bearing an additional-electron withdrawing group, E. One of the most important Horner-Wadsworth-Emmons reagents, triethylphosphonoacetate, **19**, employs an ester function as the electron-withdrawing group. Triethylphosphonoacetate and compounds similar to it have been used to prepare a variety of natural products including prostaglandins[30], juvenile hormones[31], and a number of isoprenoid compounds[32]



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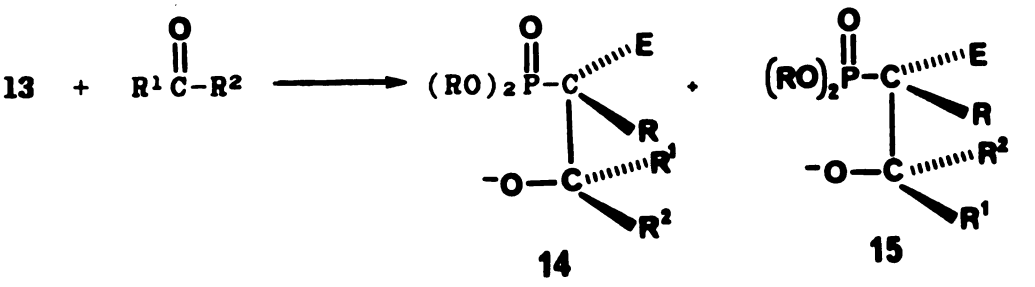
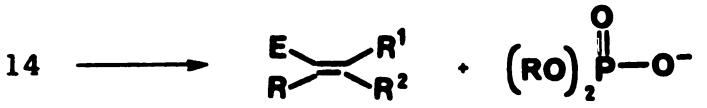


(21)

including β-carotene.[33] The Horner-Wadsworth-Emmons reaction has been applied intramolecularly in the synthesis of ring compounds containing cycloalkenones[34] and butenolide moieties.[35] The Horner-Wadsworth-Emmons reaction with epoxides yields substituted cyclopropanes.[36] The phosphonate olefination has been employed in a number of industrial



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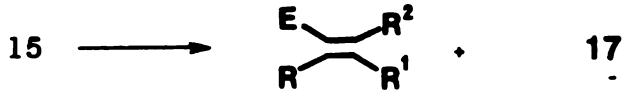
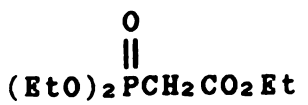


(23)

processes and bis-phosphonates have been examined as polymerizing reagents.[37]

The Wittig reaction, using **19**, results, overall, in the same product obtained by an aldol condensation using an ester enolate followed by dehydration (eq. 24).[1,38] In contrast to aldol routes, the Horner-Wadsworth-Wittig reaction using **19** furnishes the olefinic product regiospecifically and in one step with a high degree of stereochemical control about the newly-formed double bond. Acid catalyzed dehydration of β-hydroxy esters is sometimes complicated by formation of the β,γ-unsaturated ester.[39] Base-promoted elimination of the acetate derived from the β-



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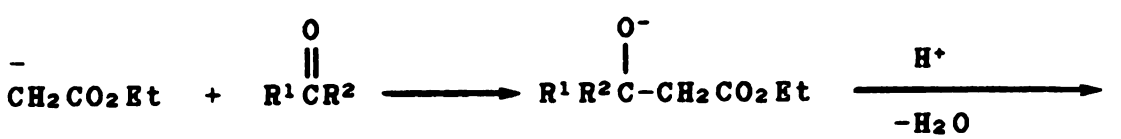
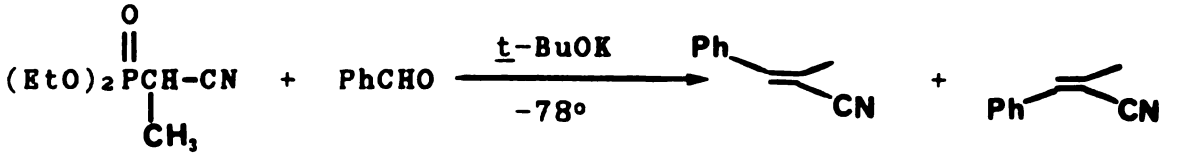
hydroxy ester overcomes this problem[40] but introduces an extra step.



$$R^1R^2C{=}CH_2CO_2Et \qquad (24)$$

The position of the carbon-carbon double bond formed by the phosphonate Wittig reaction can be predicted with a high degree of certainty, with double-bond migrations to give β,γ-unsaturated esters having been reported only in rather unique, isolated cases.[41]

The stereochemistry of the newly formed double bond is less predictable. Unstabilized Wittig reagents generally give Z olefins and stabilized Wittig reagents generally give E olefins. From early studies, it was believed that phosphonate olefinations gave exclusively E olefins. However, the mechanism of phosphonate olefinations has since been established (eqs. 20-23) and the olefin product stereochemistry depends on a number of factors. The aldol product of a β-phosphono ester ($E=CO_2R^3$) with a carbonyl substrate has never been isolated. β-Hydroxyphosphononitriles corresponding to 14 and 15 (eq. 21, E=CN) have been isolated and separated. Subsequent treatment with base indicates the aldol condensation is reversible (eq. 21) and control experiments show that collapse of 14 and 15 (eqs. 22 and 23) is highly stereospecific.[42] Although postulated, there is no evidence that 14 and 15 interconvert directly. Thus, the stereochemistry of the pro-duct olefin depends on the relative rates of formation and decomposition of 14 and 15.[42] In general, thermodynamically-controlled olefination reactions give E olefins while kinetically-controlled olefinations give Z olefins. Thus, the E/Z ratio of the product olefin is dependent on temperature (eqs. 25-27) and the ability of the counter cation[42a] to stabilize the intermediate oxyanion



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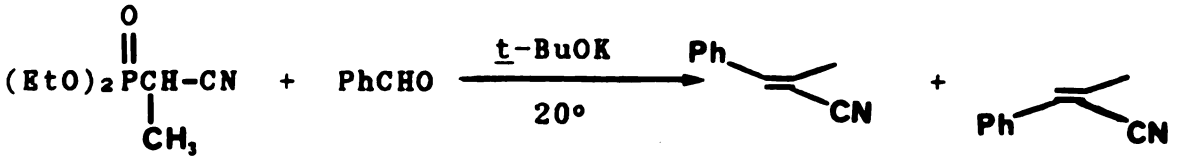

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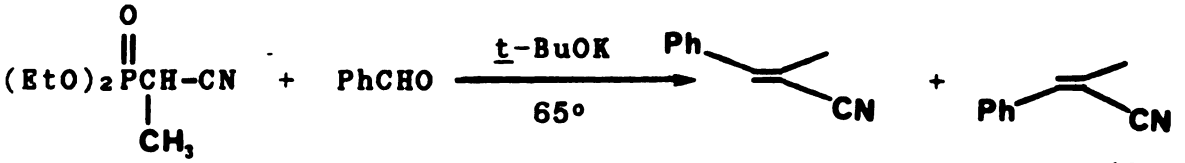

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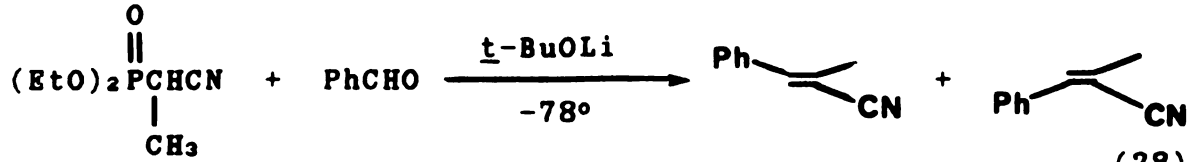
(eqs. 28-30). Steric effects depend on the bulk of both the phosphonate reagent[43,44] and the carbonyl substrate (eqs. 31 and 32).[43b] The bulk of the phosphonate reagent is dependent on both the size of the side chain (eqs. 33 and 34)[43b] and the size of the additional electron-withdrawing group.[44] Equations 35-38 illustrate that the size of the nitrile



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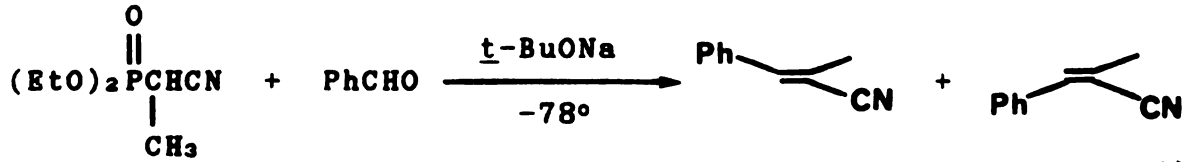

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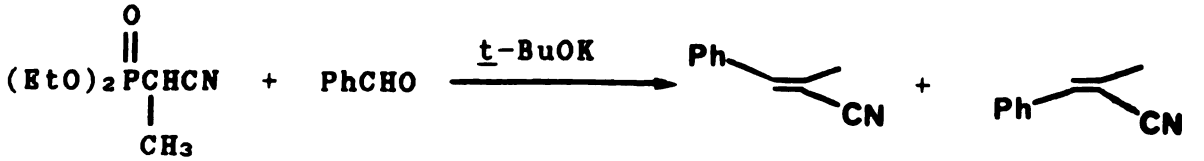

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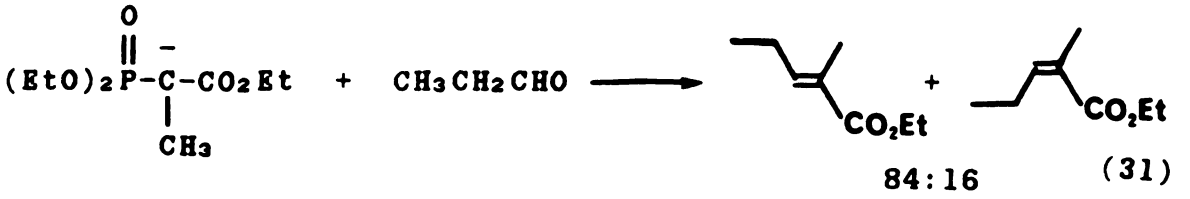
group is comparable to methyl, but the carbomethoxy group has a greater effective size than methyl. The solvent[44,45] has also been shown to influence the stereochemical outcome of the reaction.

The Horner-Wadsworth-Emmons-Wittig reaction has some strict steric requirements. This means that the phosphonate anions are more reactive towards aldehydes than ketones, and certain ketones are completely unreactive towards the phosphonate anion. In steroidal systems, for example, the phosphonate anion **20** reacts with 3-keto steroids but does not react with 6-keto, 7-keto, 17-keto or 20-keto steroids.[46] Similarly, **20** is unreactive towards 20-oxo-21-methyl steroids but does react with 20-oxo-21-hydroxy pregnanes. Presumably, the aldol step is reversible; but the formation of a cyclic product drives the reaction to completion.[47] Simple cyclohexanones are normally reactive towards **20**, but cyclohexanones bearing substituents at the 2 position are unreactive if the substituent is constrained to an equatorial position.[46,48] Reaction of the bridged ketone **21** with **20** gives poor yields of unsaturated ester. This is one example example where the Reformatsky reaction, followed

by base-promoted elimination of the acetate, was the preferred route to the unsaturated ester.[49] Phosphonate



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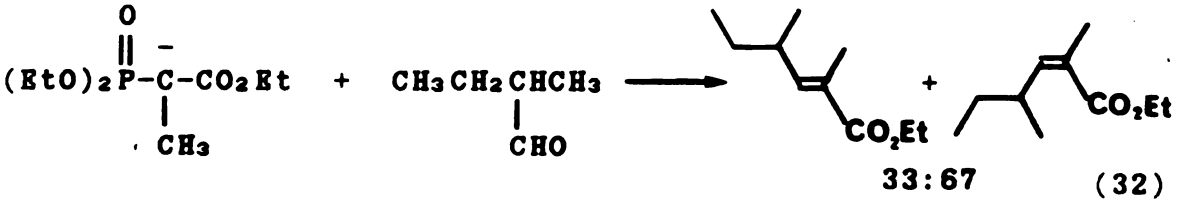
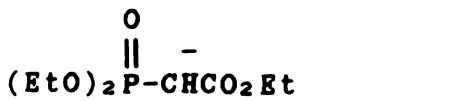


(32)

olefinations with readily enolizable aldehydes or ketones, such as acetophenone, often give poor yields of olefins.

In comparison with the normal (phosphine) Wittig reaction, the Horner-Wadsworth-Emmons modification offers some significant advantages. The phosphonate reagents are easier to prepare[50], usually by the Arbuzov reaction or the Michaelis-Becker reaction. The former, involving reaction of a trialkyl phosphite with an alkyl halide, is the most commonly used route. Reagent 19, for example, is prepared readily and in high yields from triethylphosphite and ethyl bromoacetate. The phosphonate is easily modified by alkylation or acylation of the phosphonate anion.[51] Isolation of the olefinic product is simplified because unlike phosphine oxides, the phosphate ester by-product 17 is easily removed by aqueous extraction. The utility of the phosphonate olefination is attested to by the extensive reviews recently afforded it.[52]

Standard procedures for generating the phosphonate anion **20** use strong bases such as sodium hydride, lithium



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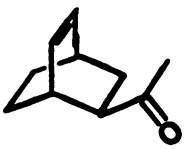
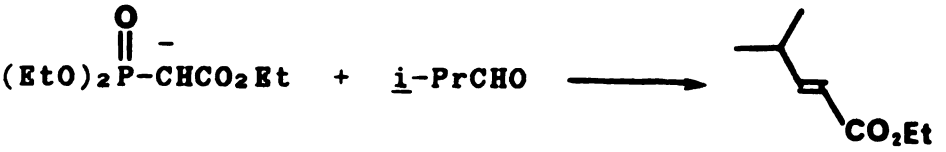


21

diisopro-pylamide, or metal alkoxides which are expensive and/or may react with sensitive functional groups in reagent or substrate. Since compound **19** is structurally similar to malonate esters, it appeared to be a likely candidate for acidity enhancement through metal cation coordination, allowing anion formation with weak bases. Clearly, a procedure for carrying out the phosphonate olefination under



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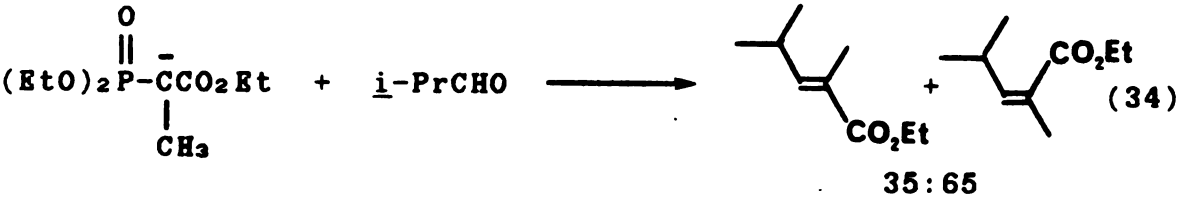

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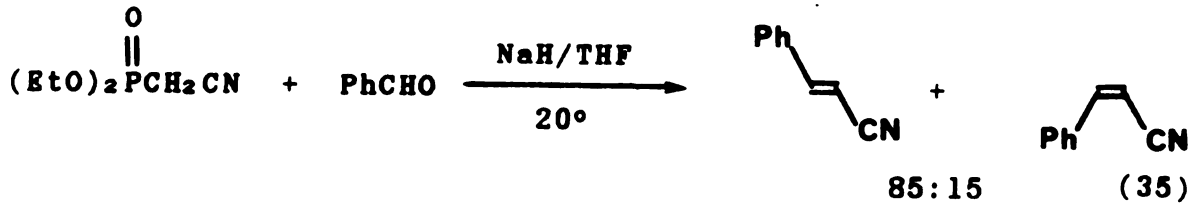
mild conditions would be of significant value. The stability of the metal complex **22**, formed via that route (eq. 39), should overcome the problems associated with readily enolizable substrates in the Wittig reactions. A weak base promoted olefination procedure would offer significant advantages in terms of cost and convenience.

The diethoxyphosphinyl group is inferior to the carboethoxy group in increasing the acidity of alpha hydrogens. The pK of triethylphosphonoacetate is 2.5 pK units greater than diethylmalonate (19.2 vs. 16.7 in dimethylsulfoxide solution).[53] Although the exact nature of charge delocalization in **22** is not well defined, the phosphinyl group undoubtedly makes a contribution. The structure and reactivity of **22** appears to be dependent on a number of factors including solvent system, the metal cation M, and the base used to generate **22**.[54] The stability of **22**, and thus the acidity of **19**, is greatly influenced by the nature of the metal ion M in **22**. The pK of triethylphosphonoacetate in the presence of potassium cation (dimethylsulfoxide solution) has been estimated at 19.2 and in the presence of lithium cation (diglyme solution) at 12.2.[53a] Presumably, the difference in acidity is attributable to tighter chelation of lithium cation resulting in a stronger metal-oxygen bond in the resulting enolate. Phosphonate **23**, for example, which has no



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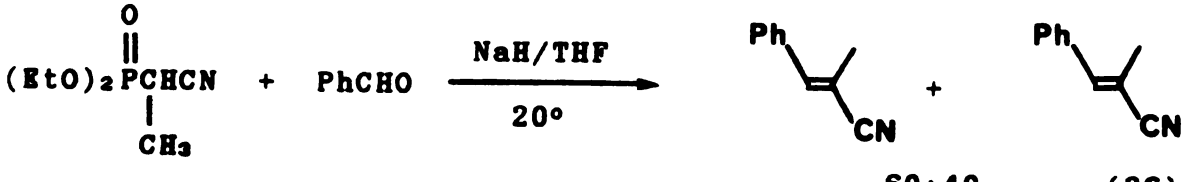

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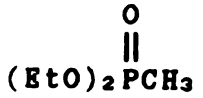
carboethoxy group, is expected to be a poorer chalating agent for metal cations and its acidity shows a less-pronounced dependency on the metal cation present (4 pK units difference for the lithium and potassium complexes). The selection of the metal ion M in **22** is important. While **22** must be stable enough to form in useful concentrations with weak bases, it must possess sufficient reactivity towards carbonyl compounds. While more electropositive metals (sodium, potassium) make **22** more nucleophilic, less electropositive metals (lithium, magnesium) appear to result in a more facile cycloelimination step (eqs. 20 and 21) in Wittig olefinations.[56]

The addition of metal salts has been reported to retard the phosphine Wittig reaction by complexing with an intermediate in the reaction[57] but there are reports that some nucleophilic substitutions at the phosphoryl group, similar to the one in the cycloelimination step of the phosphonate olefination reaction, are accelerated by added cations.[58]

Nearing completion of this study, an independent report appeared in the literature[59] describing a procedure for carrying out the Horner-Wadsworth-Emmons-Wittig reaction using the relatively expensive tertiary amine bases diisopropylethylamine (pK~10) or diaza[5.2.0]bicycloundec-7-ene (DBU, pK~11.6) and lithium chloride. The method was



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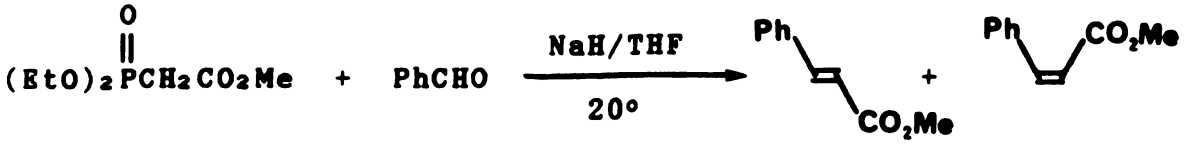
demonstrated with three aldehydes that were readily enolizable or base sensitive. The method proved successful where the standard strong base conditions failed.



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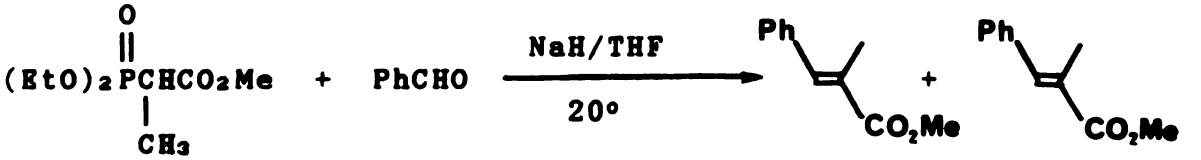

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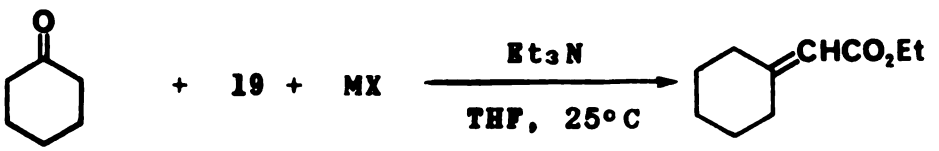
RESULTS AND DISCUSSION

The ability of triethylphosphonoacetate to undergo the Horner-Wadsworth-Emmons-Wittig reaction using triethylamine and a number of metal salts was examined. Cyclohexanone was stirred with triethylphosphonoacetate and triethylamine in the presence of a number of metal halides (eq. 39) in tetrahydrofuran solution (Table 6). After aqueous workup, the presence of the expected product, ethyl cyclohexylidene acetate, **24** was determined by gas chromatography. Magnesium and lithium halides are effective in promoting the reaction.

TABLE 6. Reaction of Cyclohexanone with 19 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

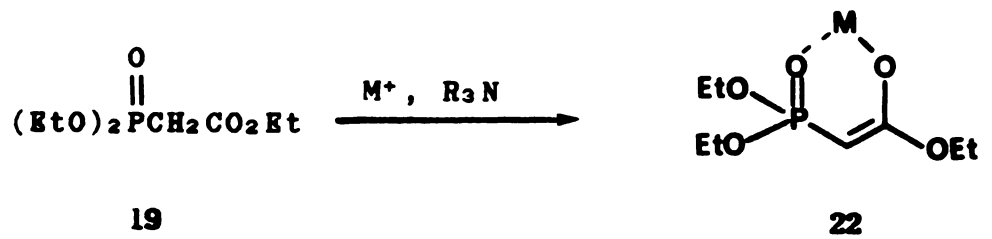
a) Reaction at 25°C with 10 mmol cyclohexanone, 10 mmol Et_3N, 10 mmol 19, 10 mL THF for a period of 3 h, except where noted.

b) Yield of ethyl cyclohexylidene acetate determined by ^1H NMR analysis. Yields in parentheses are for 24 h reaction periods.

c) 20 mmol Et_3N was used.

d) No Et_3N was used.

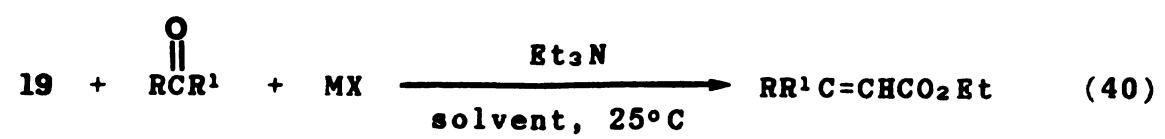
Control experiments demonstrate the need for both the metal salt and the base. The magnesium halides appear to be more effective promoters of the reaction than lithium halides (Table 6, entries 2,3,6,7). Since lithium enolates are



19 22 (39)

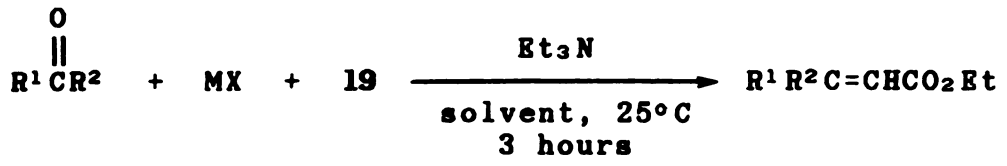
generally more reactive than magnesium enolates, this difference may be due to the magnesium enolate (22, M=Mg) forming faster than the lithium enolate (22, M=Li). The reaction appears to require stoichiometric amounts of metal salt. Excellent yields of ethyl cyclohexylidene acetate 24 are obtained over relatively short reaction times with an excess of triethylamine. However, excellent yields may also be obtained using stoichiometric amounts of base over longer reaction times (24 hours).

The reaction of triethylphosphonoacetate with cyclohexanone of benzaldehyde (eq. 40) was examined (Table 7) using a variety of solvents (acetonitrile, diethyl ether,



(40)

TABLE 7. Reaction of Carbonyl Compounds with 19 in a Variety of Solvents.[a]



Solvent	O R¹CR²	MX	Yield[b,c]
Yield, %[b]			
Acetonitrile	Benzaldehyde	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	81
Methylene chloride		LiCl	56
		LiBr	70
		$MgBr_2$	47
Dimethylformamide		LiBr	25
		$MgBr_2$	10
Benzene		LiBr	93

Table 7, continued

Solvent Yield, %[b]	R^1CR^2 (O)	MX	Yield[b,c]
Benzene	Cyclohexanone	$MgBr_2$	82
Ethanol		$MgBr_2$	30
Water		$MgBr_2$	0

a) Reaction at 25° with 10 mmol carbonyl substrate, 10 mmol 19, 10 mmol Et_3N, 10 mL solvent for a period of 3 hours.

b) GLC yields of ethyl cinnamate or ethyl cyclohexylidene acetate.

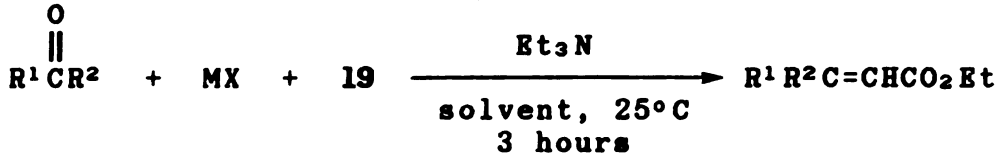
c) Only <u>trans</u> ethyl cinnamate detected.

tetrahydrofuran, methylene chloride, dimethylformamide, benzene, glyme, ethanol). Only lithium chloride was completely soluble in any of the solvents. However, addition of triethylphosphonoacetate invariably resulted in complete dissolution of the salts and homogeneous solutions. Addition of triethylamine to solutions containing magnesium halides resulted in instantaneous formation of a precipitate. Addition of triethylamine to solutions containing lithium halides resulted in no observable change in the reaction mixture. Addition of the carbonyl substrate to a solution of **19**, lithium halide and triethylamine resulted in the rapid formation of the same precipitate.

Most common solvents give satisfactory results. It is interesting that while yields are low, the reaction occurs in some protic solvents (ethanol). It is noteworthy that the reaction can be carried out in methylene chloride, a solvent incompatible with the strong bases usually employed in the Horner-Wadsworth-Wittig reaction. The low conversions realized in dimethylformamide solution probably reflect the high coordination power of the solvent for metal ions, disfavoring formation of the internally coordinated enolate **22**.

The reaction of a variety of aldehydes and ketones with triethylphosphono-acetate in the presence of either magnesium bromide or lithium bromide was conducted on a preparative scale with the results shown in Table 8. Excellent yields are obtained with aldehydes or the reactive

TABLE 8. Reaction of a Variety of Carbonyl Compounds with 19 in the Presence of Triethylamine and Metal Halides.[a]



Carbonyl Compound	Metal Halides	(solvent)	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)	$C_6H_5CH=CHCH=CHCO_2E$	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:19:Et_3N:metal halide-1:1:1.1:1.2).

b) Isolated yield, based on weight of distilled product.

ketone cyclohexanone. However, simple methyl ketones such as acetophenone or acetone fail to react.

In all cases, the unsaturated ester product was the conjugated E isomer. No β,γ-unsaturated ester was detected and none of the corresponding Z isomer was detected by GC or ^{1}H NMR analysis under conditions judged sufficient to detect 0.5% of the other isomers. Similar high E/Z ratios have been reported for the Horner-Wadsworth-Emmons Wittig reaction.[59] The procedure appears to be somewhat tolerant of less than rigorous exclusion of moisture from the reaction flask. In a number of experiments, anhydrous metal salts were weighed in the atmosphere and solvents and triethylamine could be used directly from a freshly opened bottle without significant losses (<5%) in yields of olefination product.

We attempted to verify that the reaction was proceeding via production of the phosphonate anion. When magnesium or lithium bromide is added to triethylphosphonoacetate, its ^{1}H NMR spectrum exhibits a small downfield shift (0.16 ppm) of the alpha hydrogens. When triethylamine is added to a solution of triethylphosphonoacetate, the alpha hydrogen doublet (JP-H=24Hz) coalesces into a broad singlet. A mixture of triethylphosphonoacetate, lithium bromide and triethylamine exhibits a pair of quartets around 3.2ppm and 2.4ppm. The alpha hydrogens are no longer observable. This is indicative of an equilibrium with a rapid proton exchange between the enolate and triethylamine. ^{1}H NMR analysis of a heterogeneous mixture of triethylphosphonoacetate, magnesium

bromide and triethylamine exhibits one quartet at δ 3.2 indicative of quantitative ammonium salt formation. No signal is observed for the alpha protons of triethylphosphono-acetate. Filtration of a mixture of triethylphosphonoacetate, triethylamine and magnesium bromide gave, after evaporation of all volatile components, a precipitate identified as triethylamine hydrobromide and a white solid exhibiting the following ^{1}H NMR: δ 4.4 (m), 3.3 (d, J=20 Hz), 1.4 (m). Comparison of these spectra with the ^{1}H NMR spectrum reported for the calcium enolate[54a] of 19 and examination of solvent effects on the chemical shifts in the lithium enolate[54c] of 19 led to the conclusion that the white solid was the magnesium enolate of 19 (22, M=Mg).

Opposed to this is a report[59] that 19, in the presence of lithium chloride (LiCl) and diazabycyclo[5.4.0]undec-7-ene (DBU) in acetonitrile-δ3 solution, gives a 31P NMR spectrum that exhibits two ^{31}P signals. The authors' interpretation is that two LiCl/19/DBU complexes exist and that one of them is in-terconverting to 22 (M=Li) at a rate comparable to the NMR time scale.

Procedures for the Horner-Wadsworth-Emmons Wittig reaction with aldehydes using lithium bromide or magnesium bromide and triethylamine give yields of unsaturated esters comparable to those procedures using other, stronger bases.[52a,59] The negative results obtained with ketones using this procedure, while disappointing, are not entirely unsatisfactory. With a few exceptions, especially cyclohexanones, the phosphonate Wittig reactions using 19

with ketones are difficult. There are reports in the literature that metal salts inhibit the normal Wittig reaction, presumably by forming unreactive complexes with an intermediate in the reaction. However, our results with lithium and magnesium salts have been entirely satisfactory. This new procedure for the phosphonate Wittig reaction seems especially useful for large scale preparations where triethylamine possesses significant handling and cost advantages over other bases.

EXPERIMENTAL

MATERIALS

Tetrahydrofuran was distilled from sodium/benzophenone just prior to use. Acetonitrile and triethylamine were was distilled from calcium hydride. Dimethyl formamide was distilled from phosphorous pentoxide. Diethyl ether was taken directly from a freshly opened can of anhydrous ether. Methylene chloride was taken from a freshly opened bottle of anhydrous methylene chloride. Lithium bromide (Aldrich Chemical Company, 99+%) was dried in an abderhalden flask over refluxing xylene at 0.3 torr. Magnesium bromide was prepared from dibromoethane and magnesium metal and dried under vacuum at 150°C.[60] Zinc chloride (Aldrich Chemical Company, 98%) was dried with thionyl chloride followed by removal of excess thionyl chloride under high vacuum.[61] Lithium chloride (Aldrich Chemical Company, 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 glove bag. Triethylphosphonoacetate was prepared from ethylbromoacetate and triethylphosphite.[50]

METHODS OF ANALYSIS

^{1}H NMR data were obtained on a Varian T-60 spectrometer at 60MHz. Chemical shifts are reported on the delta scale

relative to an internal tetramethylsilane standard. Gas chromatographic analyses were performed on a varian 920 chromatograph equipped with a 6 ft. X 0.25 in. stainless steel column packed with 15% SE-30 on Chromasorb W. GC yields were obtained using n-alkanes as internal standards. NMR yields were obtained using acetophenone as internal standard.

General Procedure for the Phosphonate Olefination Reaction.

The following procedure, with modification of scale, is representative of the procedure used to obtain the results in Tables 5-7. A 50 mL flask with a septum inlet and magnetic stirrer was flame dried under argon. Anhydrous metal salt (30 mmol) was weighed in a glove bag and transferred under a stream of argon to the flask. Solvent (25 mL) and triethylphosphonoacetate (25 mmol, 5.54g) were added and the mixture stirred 5 minutes. Triethylamine (28 mmol, 3.9 mL) was added and the mixture stirred an additional 10 minutes. the carbonyl compound was then added and the reaction mixture stirred overnight. After quenching with dilute aqueous HCl, the reaction mixture was extracted with ether (3 X 25 mL). The organic extracts were combined and dried over magnesium sulfate.

General Procedure Used to Survey Metal Salts.

To the combined extracts described above was added a known quantity of acetophenone as internal ^1H NMR standard.

The solvent is removed *in vacuo*. Yields are based on the relative integration of product olefin to acetophenone.

General Procedure Used to Survey Solvent Systems.

To the combined extracts described above was added a known quantity of n-alkane as internal GC standard. The solution was then analyzed by GC for product olefin.

General Procedure for the Isolation of Unsaturated Esters.

The combined extracts described above were filtered and the solvent removed *in vacuo*. The crude product was purified by short-path distillation.

Ethyl cinnamate[62] was prepared from 19 and benzaldehyde: b.p. 75°C (0.2 torr); ^{1}H NMR ($CDCl_3$): δ 1.3 (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[62] was prepared from 19 and isobutyraldehyde: b.p. 60°C (30 torr); ^{1}H NMR ($CDCl_3$): δ 0.96-2.48 (m, 9 H), 2.4 (septet, 1 H), 4.16 (q, 2 H).

Ethyl-2-noneoate[63] was prepared from 19 and heptaldehyde: b.p. 72°C (2 torr); ^{1}H 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 cyclohexylidene acetate[64] was prepared from 19 and cyclohexanone: b.p. 50°C (0.2 torr); ^{1}H NMR ($CDCl_3$): δ 1.23 (t, 3 H), 1.4-1.8 (m, 6 H), 1.9-2.5 (m, 2 H), 5.5 (s, 1 H).

Ethyl cyclopentylidene acetate[65] was prepared from 19 and cyclopentanone: b.p. 85°C (10 torr); ^{1}H 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[64] was prepared from 19 and cinnamaldehyde: b.p. 90°C (0.2 torr); ^{1}H 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).

^{1}H NMR Study of Triethylphosphonoacetate/Lithium Bromide/Triethylamine Mixture.

Triethyl phosphonoacetate (1.0 M, CD_3CN solution) exhibits the following ^{1}H NMR spectrum: δ 4.1 (m), 3.10 (d, J=22 Hz), 1.3 (t), 1.2 (t).

Triethylphosphonoacetate (0.5 mmol, 0.09 mL) was added to CD_3CN (0.5 mL) and lithium bromide (0.5 mmol, 0.044g) stirring under argon. The homogeneous solution was transferred to an NMR tube that had been flushed with argon. The solution exhibits the following ^{1}H NMR spectrum: δ 4.33-3.83 (m), 3.10 (d, J=22Hz), 1.30 (t), 1.20 (t).

Triethylphosphonoacetate (0.5 mmol, 0.09 mL) was added to an NMR tube containing triethylamine (0.5 mmol, 0.07 mL) in CD_3CN solution (0.5 mL). The solution exhibited the following ^{1}H NMR spectrum: δ 4.1 (m), 2.93 (br s), 2.4 (q), 1.4-0.9 (m).

Triethylamine (0.5 mmol) was added to an NMR tube containing a solution of a solution of lithium bromide (0.5

mmol) and triethylphosphonoacetate (0.5 mmol) in CD_3CN (0.5 mL). The sample exhibited the following ^1H NMR spectrum: δ 4.45-3.97 (m), 3.2 (q), 2.4 (q), 1.4-0.83 (m).

^1H NMR Study of Triethylphosphonoacetate/Triethylamine/ Magnesium Bromide Mixture.

Triethylamine (0.07 mL, 0.5 mmol) was added to an NMR tube containing a solution of triethylphosphonoacetate (0.5 mmol, 0.09 mL) and magnesium bromide (0.5 mmol, 0.052g) in CD_3CN (0.5 mL). A white precipitate formed instantly. The sample exhibited the following ^1H NMR spectrum: δ 4.45-3.9 (m), 3.2 (q), 1.4-0.83 (m).

Isolation of the Magnesium Enolate of Triethyl-phosphonoacetate.

A 50 mL flask fitted with a septum inlet, gas inlet tube with bubbler, magnetic stirrer and filter stick was flame dried under argon. The flask was charged with 5 mmol (0.92g) of anhydrous magnesium bromide which had been weighed and transferred under argon. Anhydrous diethyl ether (5 mL) and triethylphosphonoacetate (5 mmol, 0.97 mL) was added via syringe and the mixture stirred 5 minutes. Triethylamine (5 mmol, 0.70 mL) was added dropwise and a white precipitate formed instantaneously. After stirring ten minutes, the mixture was filtered. The filtrate was concentrated under high vacuum overnight and gave a white solid. The precipitate was dried in a vacuum dessicator overnight.

Filtrate residue: ^{1}H NMR ($CDCl_3$): δ 4.5-4.2 (m), 3.3 (d, J=20Hz), 1.5-1.1 (m).

Precipitate: ^{1}H NMR ($CDCl_3$): δ 3.2 (q), 1.45 (t); m/s (m/e): 101 (-HBr), 86 (base), 82 (HBr^{81}), 80 (HBr^{79}).

BIBLIOGRAPHY

BIBLIOGRAPHY

1. For the use of lithium dialkylamides in organic synthesis, see: (a) House, H. "Modern Synthetic Reaction", W. A. Benjamin, Inc., Menlo Park, 2nd ed., 1972. (b) Chevrot, C.; Perichon, J. *Bull. Soc. Chim. Fr.* 1977, 5-6 pt. *1*, 421.

2. (a) Houghton, R. P. "Metal Complexes in Organic Chemistry", Cambridge University Press, Cambridge 1979. (b) Mehrorta, R.; Gaur, D. P. "Metal β-Diketonates and Allied Derivatives", Academic press, San Francisco, 1978.

3. Rathke, M. W.; Deitch, J. *Tetrahedron Lett.* 1971, *12*, 2953.

4. Reutov, O. A.; Beletskaya, I. P.; Butin, K. P. "CH-Acids", Pergamon Press, Oxford, 1978.

5. (a) Collman, J. P.; et. al. *Chem. and Ind.* 1960, 1213. (b) Collman, J. P.; et. al. *J. Org. Chem.* 1963, *28*, 1449. (c) Collman, J. P. *Angew. Chem. Int. Ed.* 1965, *4*, 132.

6. Augustine, R. L. "Carbon-Carbon Bond Formation", Marcel Dekker, Inc., New York, 1979, Vol. 1, p.250-263.

7. Cowan, P. J. "The Acylation of Trimethylsilyl Acetate", Ph.D. Dissertation (1983), Michigan State University.

8. Wissner, A. *J. Org. Chem.* 1979, *44*, 4617.

9. Kuo, Y. N.; Yahner, J. A.; Ainsworth, C. *J. Am. Chem. Soc.* 1971, *93*, 6321.

10. Crombie, L.; Hemesley, P.; Pattenden, G. *Tetrahedron Lett.* 1968, 3021.

11. Herbert, R. B.; Jackson, F. B.; Nicholson, I. T. *J. Chem. Soc. Chem. Comm.* 1976, 450.

12. Pollack, R. M. in Gandor R. D.; Schowen, R. I. "Transition States of Biochemical Processes", Plenum Press, New York, 1978, p.46.

13. Logue, M. W.; Pollack, R. M.; Vitullo, V. P. *J. Am. Chem. Soc.* **1950**, *72*, 1231.

14. (a) Oshry, L.; Rosenfeld, S. M. *Org. Prep. and Proceed.* **1982**, 251. (b) Brown, J. M. "Oxo Carboxylic Acids", Sec. 9.5 in Barton, D.; Ollis, W. D. "Comprehensive Organic Chemistry", Pergamon Press, Oxford, **1979**.

15. Stenhagen, E. *Ark. Kimi.* **1951**, *3*, 381.

16. Mitz, M. A.; Axelrod, A. E.; Hoffman, K. *J. Am. Chem. Soc.* **1950**, *72*, 1231.

17. Logue, M. W. *J. Org. Chem.* **1974**, *39*, 3455.

18. Stiles, M. *J. Am. Chem. Soc.* **1959**, *81*, 2598.

19. Bottachio, G.; Chiusoli, G. P. *Chem. Commun.* **1966**, 618.

20. Bottachio, G.; Chiusoli, G. P.; Felicioli, M. G. *Gazz. Chim. Ital.* **1973**, *103*, 105.

21. Tirpak, R. "Acylation of Ketone Enolates and Their Trimethylsilyl Derivatives", Ph.D. Dissertation, 1982, Michigan State University.

22. Krapcho, A. P.; Kashdan, D. S.; Jahugen, E. G. E., Jr. *J. Org. Chem.* **1977**, *42*, 1189.

23. (a) Cowan, P. J.; Rathke, M. W. *Synth. Commun.* **1981**, *13*, 183. (b) Moreau, J. L.; Couffignol, R.; Arous-Chtara, R. *Tetrahedron* **1981**, 307.

24. Barnick, J. F. W. K.; van der Baan, J. L.; Bickelhaupt, J. *Synthesis* **1979**, *10*, 787.

25. See Reference 1a, p.763.

26. Staab, H. A. *Chem. Ber.* **1957**, *90*, 1321.

27. Tarbell, D. S.; Rice, J. A. *J. Org. Chem.* **1957**, *22*, 245.

28. Schmidt, U.; Schwochau, M. *Monatsch. Chem.* **1967**, *98*, 1492.

29. Miyano, M.; Dorn, C. R. *J. Org. Chem.* **1972**, *37*, 1818.

30. (a) Plantema, O. G.; deKonig, H.; Huisman, H. O. *J. Chem. Soc. Perk. I* **1978**, 304. (b) Taub, D.; et. al. *Chem. Commun.* **1970**, 1258. (c) Corey, E. J.; et. al. *J. Org. Chem.* **1972**, *37*, 3043.

31. (a) Dahm, K. H.; Trost, B. M.; Roller, H. J. *J. Am. Chem. Soc.* **1967**, *93*, 5292. (b) Schultz, H.; Sprung, I. *Angew. Chem. Intern. Ed. Engl.* **1969**, *8*, 271. (c) Braun, B. H.; et. al. *J. Econ. Entomol.* **1968**, *61*, 866. (d) Cavill, G. W. K.; Laing, D. G.; Williams, P. J. *Aust. J. Chem.* **1969**, *22*, 2145. (e) Cochrane, J. S.; Hanson, J. R. *J. Chem. Soc. Perk. I* **1972**, 361.

32. Vig, O. P.; Anand, R. C. *Indian J. Chem.* **1969**, 1111.

33. Surmatis, J. D.; Thommen, R. *J. Org. Chem.* **1969**, *34*, 559.

34. (a) Clark, R. D.; Kozar, L. G.; Heathcock, L. H. *Synth. Commun.* **1975**, *5*, 1. (b) Grieco, P. A.; Pogonowski, C. S. *Synthesis* **1973**, 425. (c) Henrick, C. A.; et. al. *J. Am. Chem. Soc.* **1968**, *90*, 5926.

35. Lehman, H. G.; Wiechert, R. *Angew. Chem. Int. Eng. Ed.* **1968**, *7*, 300.

36. Sturtz, G. *Bull. Soc. Chim. Fr.* **1965**, 2349.

37. (a) BASF AG Germ. Pat. 1,108,219 (1959) and 1,112,072. (b) Drefahl, G.; Hoerhold, H. H.; Wildner, H. E.: Germ. Pat. 51,436 (Chem. Abstr. 66:105346h).

38. Rathke, M. W. *Organic Reactions* **1975**, *22*, 423.

39. Shriner, R. L. *Organic Reactions* **1942**, *1*, 1.

40. Fung, K. H.; Schmalzl, K. J.; Mirrington, R. N. *Tetrahedron Lett.* **1974**, 1733.

41. (a) Quin, C. D.; et. al. *J. Org. Chem.* **1971**, *36*, 1495. (b) Wadsworth, W. S., Jr.; Emmons, W. D. *Organic Synthesis* **1965**, *45*, 44. (c) Sunberg, R. J.; Holcombe, I. O. *J. Org. Chem.* **1969**, *34*, 3273.

42. (a) Redjal, A.; Seyden-Penne, J. *Tetrahedron Lett.* **1974**, 1733. (b) Lefebvre, G.; Seyden-Penne *J. Chem. Soc. Chem. Commun.* **1970**, 1308. (c) Lavielle, G.; Carpentier, M.; Savignac, P. *Tetrahedron Lett.* **1973**, 173. (d) Deschamps, B.; Lefebvre, G.; Seyden-Penne, J. *Tetrahedron* **1972**, *28*, 4209. (e) Danion, D.; Carrie, R. *Tetrahedron* **1972**, *28*, 4223.

43. (a) Jones, G.; Maisay, R. F. *J. Chem. Soc. Chem. Commun.* **1968**, 543. (b) Kinstle, J. H.; Mandanas, B. Y. *Chem. Commun.* **1968**, 1699. (c) Sasaki, K. *Bull. Chem. Soc. Jap.* **1966**, *39*, 2703.

44. Bottkin-Strzalko, T. *Tetrahedron*, **1973**, *29*, 4199.

45. (a) Normont, H.; Sturtz, G. *Compt. Rend. C.* **1963**, *256*, 1800. (b) Gallagher, G.; Webb, R. L. *Synthesis* **1974**, 122. (c) Deschamps, B.; Lefebvre, G.; Redjel, A.; Seyden-Penne, J. *Tetrahedron* **1973**, *29*, 2437. (d) Bottkin-Strzalko, T.; Seyden-Penne, J. *Tetrahedron Lett.* **1972**, 1945. (e) Danion, D.; Carrie, R. *Tetrahedron* **1972**, *28*, 4223.

46. Bose, A. K.; Dahill, R. T., Jr. *J. Org. Chem.* **1965**, *30*, 505.

47. Fritsch, W.; Stache, V.; Ruschig, H. *Ann.* **1966**, *699*, 195.

48. Harding, K. E.; Tseng, C. Y. *J. Org. Chem.* **1975**, *40*, 929.

49. Merrington, R. N.; Scmalzl, K. J. *J. Org. Chem.* **1972**, *37*, 2871.

50. Kosolapoff, G. M. "Organophosphorous Compounds", Wiley, New York, **1950**, Chap. 7.

51. (a) Clark, R. D.; Kozar, L. G.; Heathcock, C. H. *Synthesis* **1975**, 635. (b) Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071.

52. (a) Wadsworth, W. S., Jr. *Organic Reactions* **1978**, *25*, 73. (b) Walker, B. J. "PO-Activated Olefinations", Chap. 3 in Cadogan, J. I. G. "Organophorous Reagents in Organic Synthesis", Academic Press, London, **1979**.

53. (a) Petrov, E. S.; et. al. *Zh. Obsch. Khimii* **1975**, *45*, 1529. (b) Petrov, E. S.; et. al. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1976**, 534.

54. (a) Kirilov, M.; Petrov, G. *Monatsch. Chem.* **1972**, *103*, 1651. (b) Bottin-Strzalko, T.; Seyden-Penne, J.; Simmonin, M. P. *J. Chem. Soc. Chem. Commun.* **1976**, 905.

55. (a) Mesyats, S. P.; et. al. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1974**, 2497. (b) Mesyats, S. P.; et. al. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1974**, 2489.

56. Redjel, A.; Seyden-Penne, J. *Tetrahedron Lett.* **1974**, *16*, 1733.

57. Schlosser, M. *Angew. Chem. Int. Ed. Eng.* **1968**, *7*, 650.

58. (a) Wadsworth, W. S., Jr.; Larsen, S.; Horten, H. L. *J. Org. Chem.* **1973**, *38*, 256. (b) Wadsworth, W. S., Jr. *J. Org. Chem.* **1973**, *38*, 2921.

59. Masamune, S.; Roush, W. R.; et. al. *Tetrahedron Lett.* **1984**, *25*, 2183.

60. Ashby, E. C.; Arnott, R. C. *J. Organomet. Chem.* **1968**, *14*, 1.

61. Pray, A. R. "Inorganic Synthesis", Wiley, New York, 1973, Coll. Vol. V, p.1536.

62. Wadsworth; W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

63. Bory, S.; Lin, D. J.; Fetizon, M. *Bull. Soc. Chim. Fr.* **1971**, 1298.

64. Takanishi, H.; Fijiwara, K.; Ohta, M. *Bull. Chem. Soc. Jap.* **1962**, *35*, 1498.

65. Richardt, C.; Panse, P.; Eichler, S. *Chem. Ber.* **1967**, *100*, 1144.