This is to certify that the

dissertation entitled

I. ACYLATION OF TRIMETHYLSILYL ACETATE. A SYNTHETIC ROUTE TO β-KETO ACIDS AND METHYL KETONES.
II. ACYLATION OF CARBON ACIDS UNDER ESSENTIALLY NEUTRAL CONDITIONS.
III. AN INTRODUCTORY STUDY OF THE CARBOMETHOXYLATION OF KETONES USING WEAK BASES.

presented by

Patrick J. Cowan

has been accepted towards fulfillment
of the requirements for

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Michael Ratcke
Major professor

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CHAPTER I

ACYLATION OF TRIMETHYLSILYL ACETATE.
A SYNTHETIC ROUTE TO β-KETO ACIDS
AND METHYL KETONES.

CHAPTER II

ACYLATION OF CARBON ACIDS UNDER
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CHAPTER III

AN INTRODUCTORY STUDY OF THE CARBOMETHOXYLATION
OF KETONES USING WEAK BASES.

By

Patrick J. Cowan

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ABSTRACT

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I. Trimethylsilyl acetate was acylated with a variety of acid chlorides to give, after solvolysis and subsequent decarboxylation, excellent yields of methyl ketones. The β-keto acids 3-oxo-3-phenylpropanoic acid and 4,4-dimethyl-3-oxopentanoic acid were prepared in 97% and 81% yield, respectively, by acylation of trimethylsilyl acetate with benzoyl chloride and pivaloyl chloride. Acetylation of trimethylsilyl butanoate gave, after hydrolysis and decarboxylation, 2-pentanone in 47% yield. Trimethylsilyl

2-methylpropanoate failed to react with acetyl chloride.

II. Magnesium chloride and triethylamine were used to promote the acylation of diethyl malonate, ethyl acetoacetate, and acetylacetone. Excellent yields of C-acylated products, commonly known as triacylmethanes, were obtained in most cases. Acylation of acetylacetone with isobutyryl chloride gave a mixture of triacylmethanes resulting from transacylation reactions. Substituting collidine for triethylamine was found to suppress the transacylation reactions.

III. The carbomethoxylation of cyclohexanone and acetophenone was accomplished with carbomethoxy imidazole in the presence of triethylamine, magnesium chloride, and sodium iodide to give 2-carbomethoxycyclohexanone and methyl benzoylacetate, respectively, each in 64% yield. Carbomethoxylation of diethyl ketone gave a mixture of three β-dicarbonyl compounds which were identified as dimethyl methylmalonate (37), methyl-3-oxo-2-methylpentanoate, and 4-methyl-3,5-heptanedione (36). Compounds 36 and 37 are thought to arise from bis carbomethoxylation of diethyl ketone.

To my family and NO.

ACKNOWLEDGMENTS

I wish to express my deep appreciation to Dr. Michael W. Rathke for his guidance, encouragement, and, most importantly, his friendship throughout the course of my graduate career.

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ACYLATION OF TRIMETHYLSILYL ACETATE. A SYNTHETIC ROUTE TO β-KETO ACIDS AND METHYL KETONES.

Introduction

β-Keto acids are important intermediates for the preparation of ketones[1,2] and for the synthesis of a variety of natural products[3,4]. These compounds have also been used extensively for the studies of the mechanism of decarboxylation[5,6].

β-Keto acids have in general been synthesized by three methods: acid[7,8] or base[9] catalyzed hydrolysis of the corresponding β-keto esters, carboxylation of the appropriate enolate anions[10-12], and acylation of dianions of carboxylic acids[2,13].

Although alkaline hydrolysis of β-keto esters has been used successfully to prepare several of the corresponding aromatic[14] and aliphatic[15,16] β-keto acids (eq 1), it has proven to be unreliable as a general method[8,10]. Alkaline hydrolysis is often complicated by competing attack of the base at the ketone function, leading to retro Claisen cleavage of the β-keto ester[8,10] (eq 2).

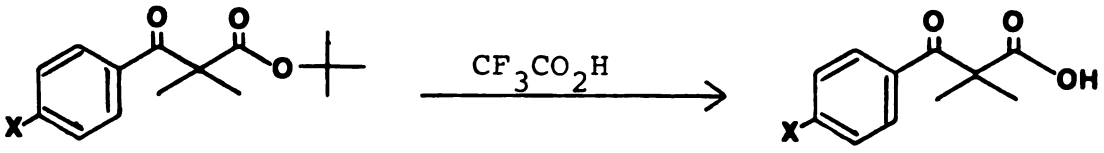
Acid hydrolysis of methyl esters (eq 3) has been effective in the preparation of several long chain β-keto acids[8].

$$RCOCH_2CO_2R^1 \xrightarrow{^-OH} RCOCH_2CO_2^- \xrightarrow{H^+} RCOCH_2CO_2H \quad (1)$$

$$RCCR_2COR^1 \xrightarrow{^-OH} RCOH + {}^-CR_2COR^1 \quad (2)$$

$$RCOCH_2CO_2CH_3 \xrightarrow[HOAc]{HCl} RCOCH_2CO_2H \quad (3)$$

Recently Logue[10] has described the conversion of tert-butyl-β-benzoylisobutyrates to the corresponding β-keto acids by treatment with trifluoroacetic acid[10] (eq 4). Acid catalyzed thermal decomposition of the desired β-keto acid is often a serious problem in the acid catalyzed hydrolysis of β-keto esters[5,6] (eq 5).

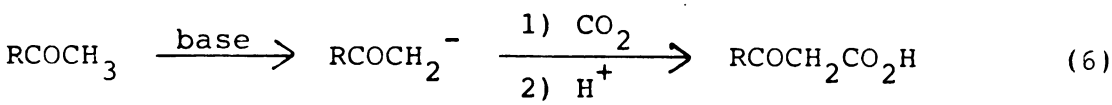


(4)

X = H, CH_3, OCH_3, Cl

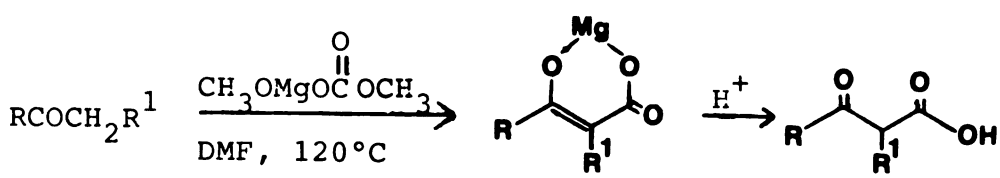
$$RCOCH_2CO_2R^1 \xrightarrow{H^+} RCOCH_2CO_2H \xrightarrow{H^+} RCOCH_3 + CO_2 \quad (5)$$

The reaction of enolate anions with carbon dioxide also leads to β-keto acids. Both aliphatic and aromatic β-keto acids have been prepared by deprotonation of the appropriate ketones with a suitable base in inert polar solvents, followed by reaction with carbon dioxide[10-12] (eq 6).



$$RCOCH_3 \xrightarrow{base} RCOCH_2^- \xrightarrow[2)\ H^+]{1)\ CO_2} RCOCH_2CO_2H \qquad (6)$$

Stiles and Finkbeiner[10] have demonstrated that methyl magnesium carbonate (MMC) in dimethylformamide (DMF) solution is capable of carboxylating ketones which have alpha hydrogens (eq 7). Although MMC gives good yields of β-keto acids

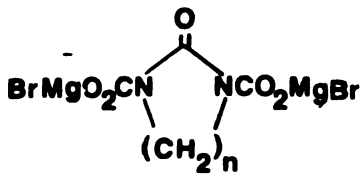


$$RCOCH_2R^1 \xrightarrow[DMF,\ 120°C]{CH_3OMgOC(=O)OCH_3} \text{Mg-chelate} \xrightarrow{H^+} R\text{-}CH(R^1)\text{-}C(=O)\text{-}CH_2\text{-}C(=O)OH \qquad (7)$$

in many cases, optimum yields require large excesses (5-20 fold) of the reagent.

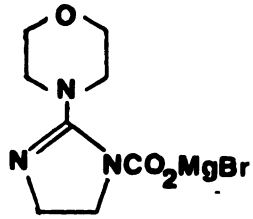
Separate studies by Sakurai[17] and Matsumura[18,19] have shown that complexes 1, 2, and 3 act effectively as carbon dioxide carriers in the carboxylation of active methylene compounds under mild conditions (eq 8). These procedures give moderate to fair yields (44-65%) of β-keto acids.

Acylation of dianions of carboxylic acids has also been



n = 2,3

1



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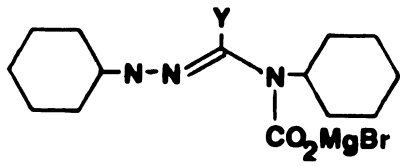


3

$$RCCH_2R^1 + \underset{\sim}{1} \xrightarrow[2)\ H^+]{1)\ DMF} RCCHCO_2H \quad (8)$$

shown to be a viable route to β-keto acids. In 1971, Ainsworth and Kuo[2] reported a route to β-keto acids in which intermediates formed in the reaction of carboxylic acid dianions with esters were trapped using trimethylchlorosilane (TMCS). The resulting trimethylsilyl esters were solvolyzed under neutral conditions to give good yields of β-keto acids (eq 9).

$$R_2\bar{C}CO_2^- + R^1CO_2CH_3 \longrightarrow R^1COCR_2CO_2^- \xrightarrow{TMCS} R^1COCR_2CO_2Si(CH_3)_3 \xrightarrow{CH_3OH} R^1COCR_2CO_2H \quad (9)$$

Recently van der Baan and coworkers[20] have described the preparation of β-keto acids in good yields by acylation and subsequent hydrolysis and decarboxylation of the mono anion of bis(trimethylsilyl) malonate (**4**, eq 10).

$$2\ (Me_3SiO_2C)_2\bar{C}H + RCOCl \longrightarrow (Me_3SiO_2C)_2\bar{C}{-}COR \xrightarrow[0°C]{H_2O} \qquad (10)$$
$$\text{(4)}$$
$$(HO_2C)_2CHCOR \xrightarrow{-CO_2} RCOCH_2CO_2H$$

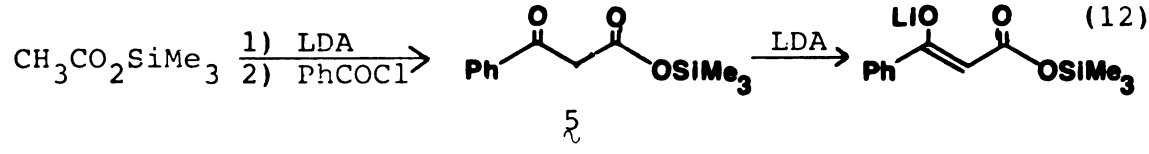
Previous work in this laboratory has demonstrated that enolates of monocarboxylic esters react with acid chlorides to yield β-keto esters[21]. In fact, the lithium enolate of trimethylsilyl acetate is a synthetic equivalent of enolate **4**. Consequently, a less expensive and more direct route towards the synthesis of β-keto acids would be the direct acylation of a lithium enolate of a trimethylsilyl ester followed by solvolysis to the desired compound (eq 11).

$$RCH{=}C(OLi)OSiMe_3 + R^1COCl \longrightarrow R^1COCH(R)CO_2SiMe_3 \longrightarrow R^1COCH(R)CO_2H \qquad (11)$$

Thus, we have studied the synthetic utility of the acylation of trimethylsilyl esters for the formation of β-keto acids.

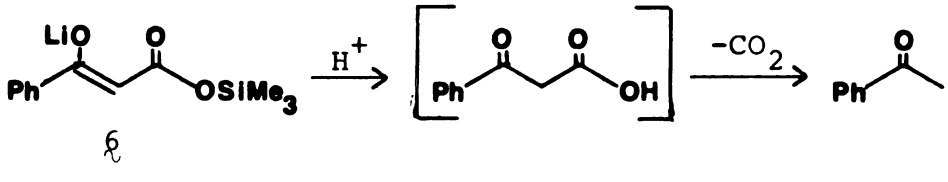
Results and Discussion

The lithium enolate of trimethylsilyl acetate [prepared by reaction of trimethylsilyl acetate with two equivalents of lithium diisopropylamide (LDA)] was reacted with one equivalent of benzoyl chloride. Two equivalents of LDA were necessary as the second equivalent is consumed by the acidic intermediate, β-keto siloxy ester 5, (eq 12). Due



5 (12)

to the susceptibility of β-keto acids to decarboxylation, it was decided not to analyze the reaction by isolation of the β-keto acid obtained by solvolysis of 6. Instead, the reaction yield was determined by solvolysis and subsequent decarboxylation of 6, followed by GC analysis for the corresponding methyl ketone (eq 13). Following this procedure,



6 (13)

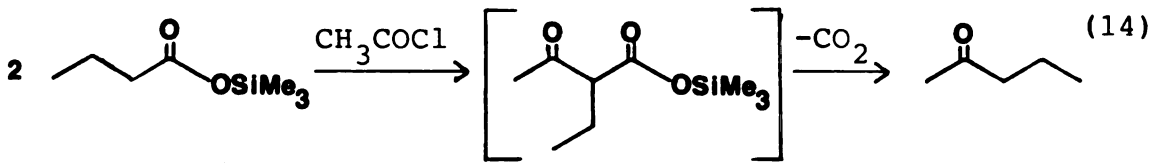
acetophenone was obtained in 98% yield (GC).

To test the general applicability of the method, the lithium enolate of trimethylsilyl acetate was reacted with a variety of acid chlorides. For optimum yields, most cases

required use of 1.5 equivalents of trimethylsilyl acetate. As can be seen in Table 1, the majority of the acid chlorides tested gave the corresponding methyl ketone in approximately 90% yield.

To test the applicability of the method to the preparation of β-keto acids, we prepared and isolated 3-oxo-3-phenylpropanoic acid and 4,4-dimethyl-3-oxopentanoic acid in 97% and 81% yield, respectively. The lower yield obtained with 4,4-dimethyl-3-oxopentanoic acid was probably due to partial decarboxylation of the sensitive β-keto acid.

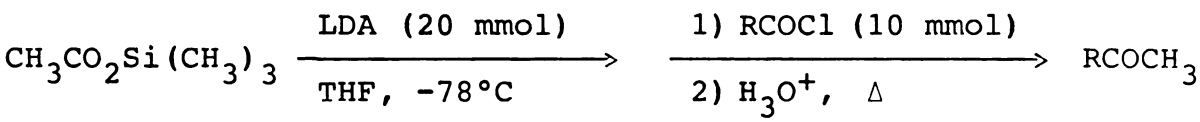
We next attempted to extend this methodology to other trimethylsilyl esters. Trimethylsilyl butanoate was reacted with acetyl chloride to give, after hydrolysis and decarboxylation, 2-pentanone in 47% yield (GC, eq 14). However, tri-



(14)

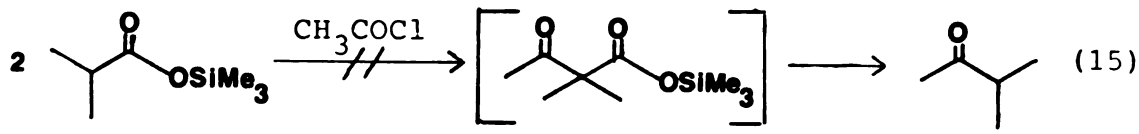
methylsilyl 2-methylpropanoate failed to react with acetyl chloride to give the expected 3-methyl-2-butanone (eq 15). These results suggest that substitution at the alpha position of trimethylsilyl acetate sterically hinders C-acylation of the corresponding enolate. As the nucleophillic carbon of the trimethylsilyl ester enolate becomes more hindered, O-acylation probably becomes the predominant reaction pathway.

Table 1. Acylation of Trimethylsilyl Acetate.



RCOCl	mmol $CH_3CO_2Si(CH_3)_3$	Yield (%)[a]
C_6H_5COCl	10	98
	15	76
	20	26
$o\text{-}CH_3C_6H_4COCl$	10	70
	15	88
$(CH_3)_3CCOCl$	15	94
	20	60
$(CH_3)_2CHCOCl$	15	99
$n\text{-}C_3H_7COCl$	10	49
	15	77

a) Yields determined by GC, using an internal standard.



(15)

In conclusion, this procedure offers a useful, high-yield route to β-keto acids and methyl ketones by acylation of trimethylsilyl acetate. This method, however, is not directly applicable to the acylation of trimethylsilyl esters other than trimethylsilyl acetate (with acid chlorides). Perhaps the use of acylating agents less reactive than acid chlorides would solve this problem[22].

Experimental

Materials

Diisopropylamine was distilled from CaH_2 prior to use. THF was distilled from the sodium ketyl of benzophenone prior to use. Trimethylsilyl esters were prepared from the corresponding carboxylic acid and bis(trimethylsilyl) acetamide by the method described by Klebe[23]. Acid chlorides (excluding o-$CH_3C_6H_4COCl$)[24] were obtained from Aldrich Chemical Co. and distilled prior to use.

Methods of Analysis

^1H NMR data were obtained on a Varian T-60 spectrometer at 60 MHz. Chemical shifts are reported in parts per million

on the delta scale relative to TMS internal standard. Gas chromatographic analysis were performed with a Varian 920 chromatograph equipped with a 6 ft. by 0.25 in. stainless steel column packed with Carbowax 20 M terephthalic acid on acid washed Chromosorb P.

General Procedure for the Acylation of Trimethylsilyl Esters

A flame-dried 50 mL flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was flushed with argon and immersed in an ice bath. 12.5 mL (20 mmol) of 1.6 M n-butyllithium in hexane was injected followed by dropwise addition of 2.82 mL (20 mmol) of diisopropylamine. The solvent was removed under reduced pressure, leaving lithium diisopropylamide as a white solid. The base was dissolved in 10 mL THF and cooled to -78°C. The appropriate amount of trimethylsilyl ester (see Table 1, 20 mmol for trimethylsilyl butanoate and trimethylsilyl 2-methylpropanoate) was added dropwise and the resulting solution was stirred for 15 minutes at -78°C. After addition of 10 mmol of acid chloride, the reaction was warmed to room temperature and stirred for 15 minutes. The solvent was removed under reduced pressure leaving a slightly yellow solid.

General Procedure for the Preparation of Methyl Ketones

The solid obtained above was dissolved in 10 mL CH_2Cl_2. 3 mL 6 M HCl was added and the resulting mixture was refluxed for 2 hours. The mixture was extracted with three 5 mL portions of CH_2Cl_2, the combined organic layers were dried over

$MgSO_4$ and analyzed by GC (dodecane as an internal standard) for methyl ketone.

General Procedure for the Isolation of β-Keto Acids

The slightly yellow solid isolated above was dissolved in 10 mL of CH_2Cl_2 and cooled to 0°C. 6 M HCl was slowly added to bring the pH of the solution to approximately 1. The mixture was extracted with three 5 mL portions of CH_2Cl_2, the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give the crude β-keto acid. The crude product was dissolved in diethyl ether and washed with a small quantity of water to remove minor amounts of triethylamine hydrochloride. The organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure leaving the β-keto acid as a colorless solid. The product was recrystallized from $CHCl_3$/pentane.

3-oxo-3-phenylpropanoic acid: Yield 1.57g (97%); m.p. 98-99°C (lit. 101-102°C)[25]; ^1H NMR ($CDCl_3$), δ 4.12 singlet ($PhCOCH_2CO_2H$), 5.72 singlet ($-C=CHCO_2H$), 7.25-8.05 multiplet (C_6H_5-CO). Ketone/enol ratio = 3:1.

4,4-dimethyl-3-oxopentanoic acid: Yield 1.16g (81%); m.p. 43-45°C (lit. 47-49°C)[26]; ^1H NMR ($CDCl_3$), δ1.17 singlet [$(CH_3)_3CCO$], 3.60 singlet ($-COCH_2CO_2H$), 5.07 singlet ($-C=CH-CO_2H$). Ketone/enol ratio = 14:1.

Chapter II

ACYLATION OF CARBON ACIDS UNDER ESSENTIALLY NEUTRAL CONDITIONS

Introduction

A standard procedure for the C-acylation of carbon acids, 7, is the formation of the conjugate base, 8, followed by reaction with an acid chloride (or anhydride) in a second, separate step (eq 16). A problem inherent in this approach is that the acylation product, 9, is always a stronger acid than 7 and thus may neutralize a portion of anion 8 in a subsequent acid-base reaction[21] (eq 17).

$$\underset{7}{R_2CH_2} + \text{base} \longrightarrow \underset{8}{R_2\bar{C}H} \xrightarrow{R^1COCl} \underset{9}{R_2CHCOR^1} \qquad (16)$$

$$8 + 9 \longrightarrow 7 + \underset{10}{R_2\bar{C}COR^1} \qquad (17)$$

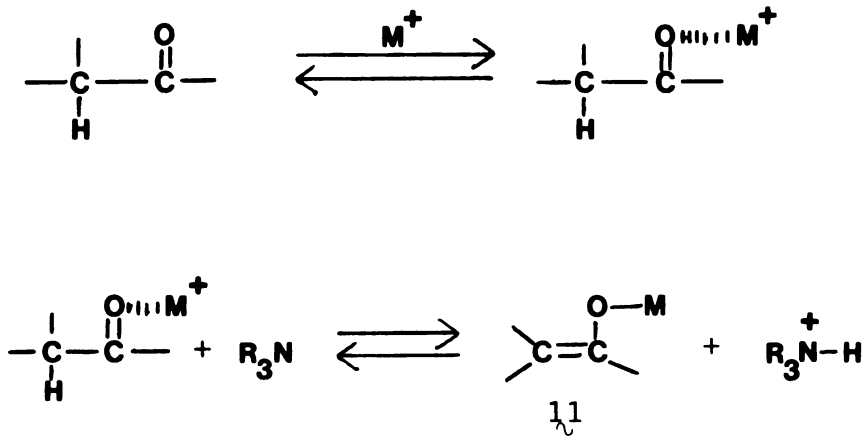
One solution to this problem is to effect a single-step reaction of carbon acid 7 with an acid chloride in the presence of two equivalents of base, producing product enolate 10 stoichiometrically (eq 18). A critical requirement for the success of this procedure is that the base must not consume the acid chloride during the reaction. This restriction appears to have limited the application of the

$$7 + R^1COCl \xrightarrow{\text{base}} 9 \xrightarrow{\text{base}} 10 \qquad (18)$$

single-step procedure to those very strong carbon acids (e.g. Meldrum's acid)[27] whose anions can be generated almost quantitatively by the weak but relatively tolerant tertiary amine bases.

It is well known that complexation of a metal ion to a ligand can enhance the acidity of that ligand[28]. Accordingly, we considered that one way to extend the single-step acylation procedure to weaker carbon acids would be to use metal complexation to enhance the acidity of carbon acids to the point where useful concentrations of enolates could be generated with tertiary amine bases (Figure 1). Clearly,

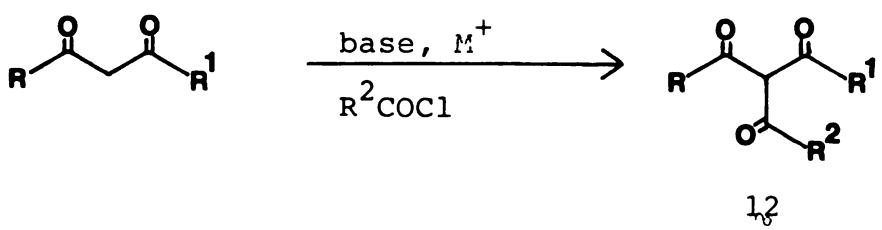
Figure 1. Metal Complexation to Carbon Acids.



11

only the last step in Figure 1 is a proton exchange reaction and the overall driving force of the reaction depends on the stability of the metal-oxygen bond in enolate 11. Thus, our objective was to find metal ions for which 11 would be of sufficient stability to be formed in useful concentrations by weak bases but of sufficient reactivity to be attacked by a variety of acylating agents.

We chose to use β-dicarbonyl compounds as the carbon acids for our initial study of the use of metal chelation in a one-step acylation procedure using weak bases. The products of such a reaction, commonly known as triacylmethanes (12, eq 19), have been found to be useful intermediates in

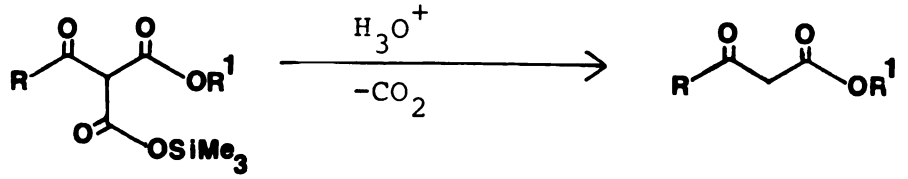


(19)

12

the preparation of dyes, insecticides, and auxiliary agents for lacquers and leathers[29]. Triacylmethanes have also been used as intermediates in the synthesis of β-keto acids[9,20] (eq 10) and β-keto esters[30-35] (eqs 20 and 21). Triacetylmethane (12, $R=R^1=R^2=CH_3$) has been used as a heat stabilizer in plastics[36] and also as a food preservative[37].

Triacylmethanes are generally synthesized by reaction of a preformed metal complex of a β-dicarbonyl compound with an



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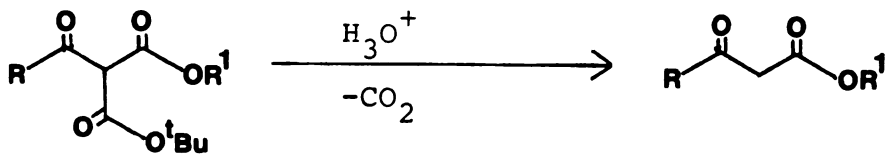
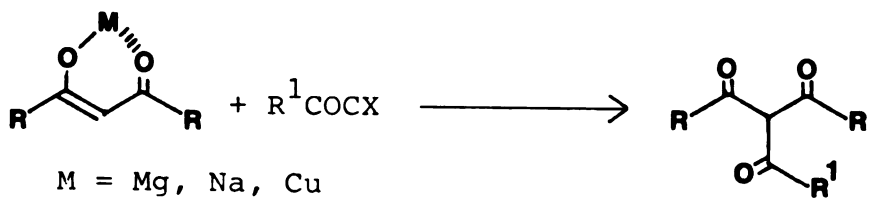


(21)

acylating agent (eq 22)[38-47]. For example, diethyl acetyl-

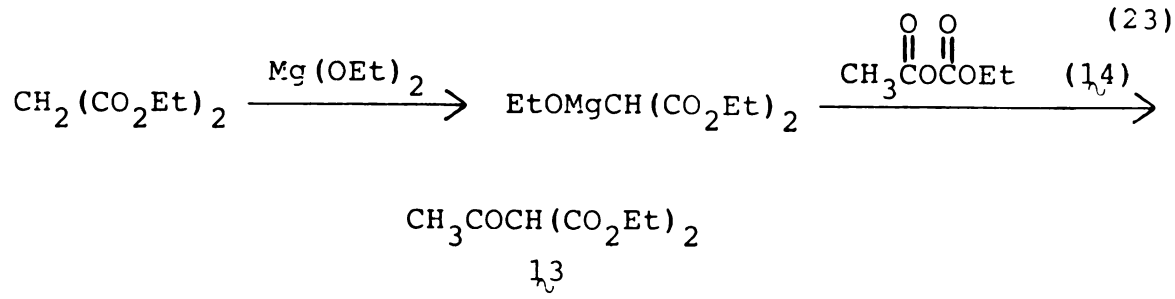


M = Mg, Na, Cu

(22)

malonate (13) has been synthesized in 54% yield by treatment of the magnesium enolate of diethyl malonate with the mixed anhydride 14 (eq 23)[38]. Viscontini[39] has described the synthesis of ethyl-3-oxo-2-acetylbutanoate in 73% yield by a similar procedure (eq 24). Triacetylmethane has been synthesized from acetylacetone and acetyl chloride (eq 25)[40].

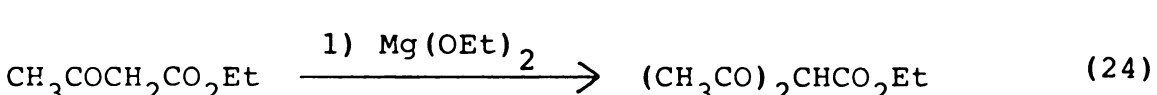
The formation of enolates of β-dicarbonyl compounds using weak bases (e.g. tertiary amines) in the presence of metal complexing agents should be relatively simple, not only



(23)

$$CH_2(CO_2Et)_2 \xrightarrow{Mg(OEt)_2} EtOMgCH(CO_2Et)_2 \xrightarrow[14]{CH_3COCOEt} CH_3COCH(CO_2Et)_2$$

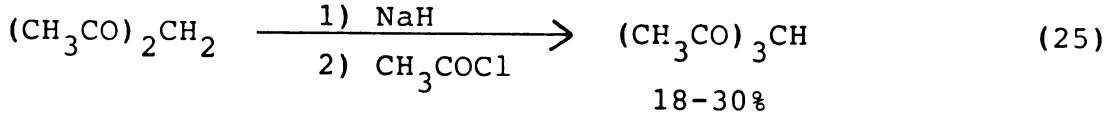
13



(24)

$$CH_3COCH_2CO_2Et \xrightarrow[2)\ CH_3COCl]{1)\ Mg(OEt)_2} (CH_3CO)_2CHCO_2Et$$

73%

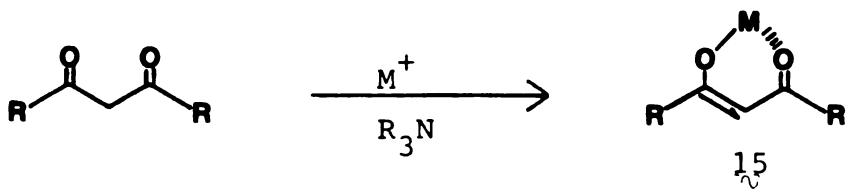


(25)

$$(CH_3CO)_2CH_2 \xrightarrow[2)\ CH_3COCl]{1)\ NaH} (CH_3CO)_3CH$$

18-30%

because of the high intrinsic acidity of the β-dicarbonyl compounds, but also because their chelating nature should favor the formation of a metal complex (15, eq 26). A



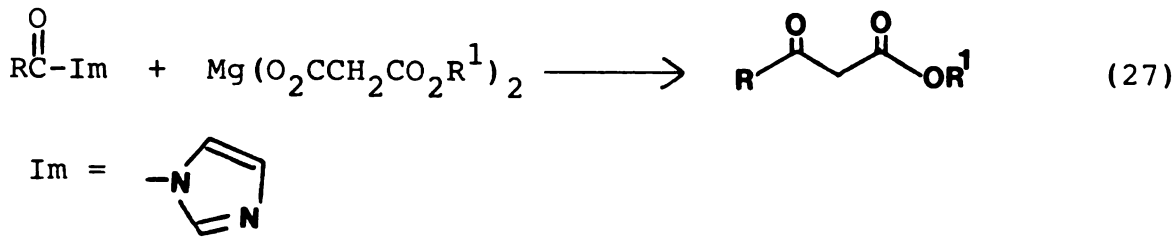
(26)

15

variety of metal complexes, 15, have been known for more than a century. Unfortunately, the same factors which make

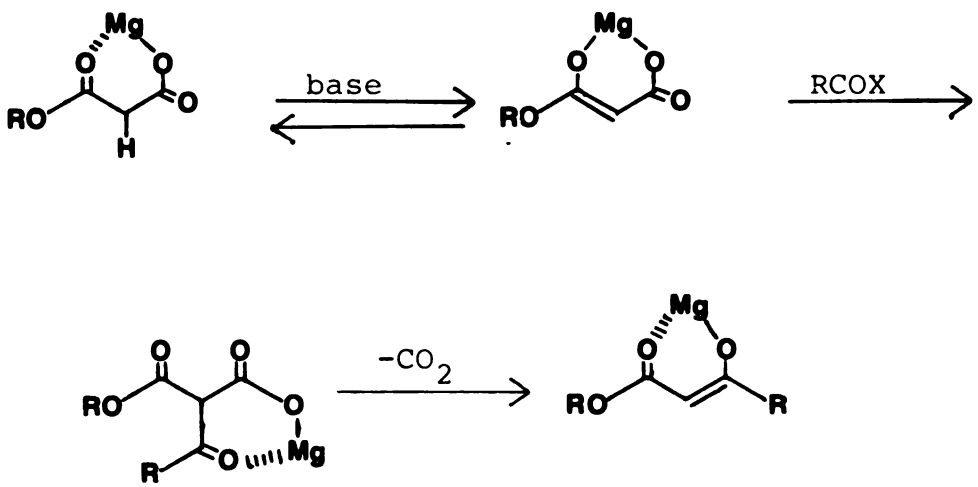
15 easy to prepare also render it relatively inert in synthetically useful reactions with electrophiles. For example, most transition metal complexes (15, M=transition metal) do not react with electrophiles such as acid chlorides and aldehydes. On the other hand, the more reactive lithium and sodium complexes (15, M=Li,Na) must usually be prepared with relatively strong bases, such as the corresponding metal alkoxides. The greatest chance for success would appear to be with magnesium or zinc complexes (15, M=Mg,Zn) where the complexes are known to possess sufficient reactivity for reaction with a variety of electrophiles[28] and where the metal ions have appreciable complexing power for oxygen ligands, favoring the formation of complexes (15, M=Mg,Zn) in the presence of weak bases. Magnesium enolates are also known to have a high tendency to acylate at carbon rather than at oxygen[48].

Results reported by Masamune[49] and Kobuke[50] for the acylation of magnesium salts of malonate half-esters provide examples of these concepts (eq 27). Compound 16 (Figure 2)



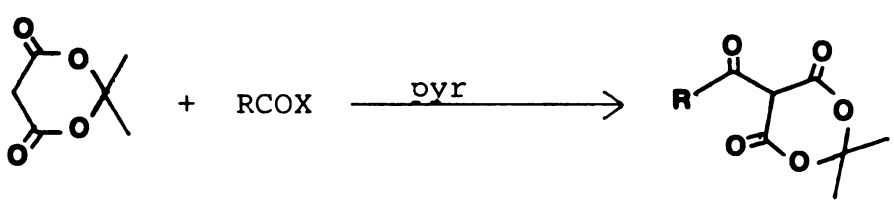
(27)

Figure 2. Acylation of Magnesium Salts of Malonate Half-Esters.



is ideally structured for acidity enhancement by an efficient internal metal complexation. Presumably the weak base necessary for enolate formation is provided by imidazole (deliberately added by Kobuke and present as a by-product of acyl imidazole formation in Masamune's reaction).

We also note that with very acidic dicarbonyl compounds, such as Meldrum's acid[27] (17, eq 28), the acylation reaction



(28)

17

can be conducted with weak bases in the absence of metal ions, and that this represents an exceedingly useful

acylation procedure. In a sense, one of our goals was to extend this procedure by means of metal complexation to less acidic β-dicarbonyl compounds.

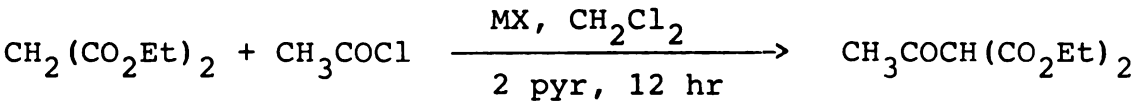
Results and Discussion

Initial experiments involved the reaction of diethyl malonate with acetyl chloride in the presence of pyridine and a variety of metal salts (MX, Table 2). Diethyl malonate was chosen as the substrate for the initial study since it is one of the least acidic members of the β-dicarbonyl family of compounds and thus should provide the most stringent test of this method.

In the absence of metal salt (Entry 1, Table 2), diethyl malonate was recovered nearly quantitatively. In addition, the reaction mixture turned black shortly after addition of the acetyl chloride, presumably due to ketene formation. When the reaction was repeated on a preparative scale (Entry 6, Table 3; note: triethylamine used as base), no C-acylated product was formed in the absence of added metal salt. These results indicate that diethyl malonate is too weak an acid to form useful enolate concentrations in the presence of pyridine or triethylamine.

The reaction of diethyl malonate with acetyl chloride in the presence of pyridine was repeated in the presence of added metal salts (MX, Table 2). In the presence of LiCl, $CuCl_2$, $ZnCl_2$, or $FeCl_3$, diethyl malonate was recovered nearly

Table 2. Survey of Metal Catalysts in the Acylation of Diethyl Malonate.

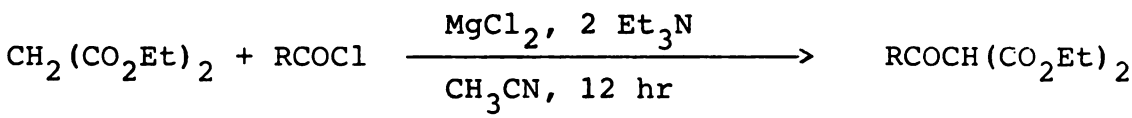


Entry	MX	Recovered S.M. (%)[a]
1	—	87
2	$ZnCl_2$	93
3	$CuCl_2$	99
4	$FeCl_3$	63
5	LiCl	91
6	$MgCl_2$	8
7[b]	$MgCl_2$	98

a) GC yields.

b) Reaction carried out in the absence of pyridine.

Table 3. Acylation of Diethyl Malonate.



Entry	RCOCl	Yield (%)[a]
1	CH_3COCl	85
2	C_6H_5COCl	89
3	$(CH_3)_2CHCOCl$	92
4	$(CH_3)_3CCOCl$	90
5	$n\text{-}C_3H_7COCl$	86
6[b]	CH_3COCl	0

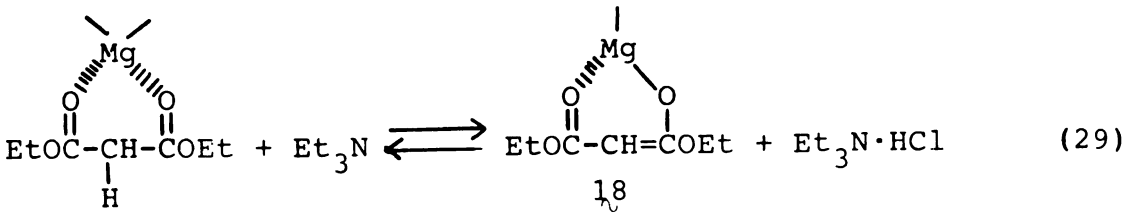
a) Isolated yields.

b) Reaction carried out in the absence of magnesium chloride.

quantitatively. Also, the reaction mixture turned black shortly after the addition of acetyl chloride. With $MgCl_2$, however, the reaction mixture remained colorless and only 8% of diethyl malonate was recovered. Attempts to isolate diethyl acetylmalonate (12, R=R=OEt, $R^2=CH_3$), however, gave relatively low yields, 61%. Replacement of pyridine (pKa ≅ 5.0)[51] with the stronger base, triethylamine (pKa ≅ 10.0)[51] increased the isolated yield of diethyl acetylmalonate to 85%. Excellent yields of C-acylated product were also obtained for a variety of acid chlorides using triethylamine in the presence of $MgCl_2$ (Table 3). These results indicate that the $MgCl_2$ is in some way (presumably by chelating to diethyl malonate) enhancing the acidity of diethyl malonate to the point where its enolate may be generated by the weak base triethylamine.

A ^1H NMR study was conducted to verify that the enolate of diethyl malonate was in fact formed on treatment with triethylamine in the presence of $MgCl_2$. One equivalent of triethylamine was added to a 0.5 M solution of diethyl malonate in CD_3CN, and ^1H NMR analysis revealed no change in the methylene singlet of diethyl malonate (for a more complete description of the ^1H NMR, see the experimental section). On addition of one equivalent of magnesium chloride to the triethylamine-diethyl malonate system, a precipitate formed. ^1H NMR analysis showed that the methylene singlet of diethyl malonate had disappeared and the methylene quartet of triethylamine had shifted downfield by approximately 0.5 ppm. This observation may be attributed to

enolate formation with rapid proton exchange between diethyl malonate and triethylamine[52] (eq 29). Finally, enolate 18



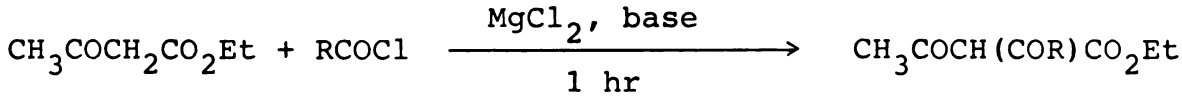
(29)

was isolated in approximately 40% yield by reaction of a 0.5 M CH_3CN solution of diethyl malonate with triethylamine and $MgCl_2$. We interpret this result as an enhancement of the acidity of diethyl malonate by complexation with $MgCl_2$.

To test the generality of this procedure, the acylation reaction using $MgCl_2$ was examined with ethyl acetoacetate as the substrate. As in the case of diethyl malonate, no C-acylated product was isolated when ethyl acetoacetate was reacted with acetyl chloride in the absence of $MgCl_2$ (Entry 10. Table 4). Reaction of the ethyl acetoacetate with acetyl chloride in the presence of $MgCl_2$ and triethylamine in CH_3CN gave only a 10% yield of the expected C-acylated product (Entry 1, Table 4). Changing the solvent to methylene chloride (CH_2Cl_2) had almost no effect on the yield of C-acylated product. However, when the reaction was repeated using pyridine as a base in CH_3CN, the yield of C-acylated product increased to 73% (Entry 3, Table 4). Changing the solvent to CH_2Cl_2 with pyridine as the base further increased the yield to 91% (Entry 4, Table 4).

The low yield of C-acylated product obtained when

Table 4. Acylation of Ethyl Acetoacetate.



Entry	RCOCl	Base[a]	Solvent	Yield (%)[b]
1	CH_3COCl	Et_3N	CH_3CN	10
2	CH_3COCl	Et_3N	CH_2Cl_2	13
3	CH_3COCl	pyr	CH_3CN	73
4	CH_3COCl	pyr	CH_2Cl_2	91
5	C_6H_5COCl	pyr	CH_2Cl_2	81
6	$(CH_3)_2CHCOCl$	pyr	CH_2Cl_2	77
7	$(CH_3)_3CCOCl$	pyr	CH_2Cl_2	18
8[c]	$(CH_3)_3CCOCl$	pyr	CH_2Cl_2	75
9	$n\text{-}C_3H_7COCl$	pyr	CH_2Cl_2	78
10[d]	CH_3COCl	pyr	CH_2Cl_2	0

a) 2 Equivalents of base used in all cases.

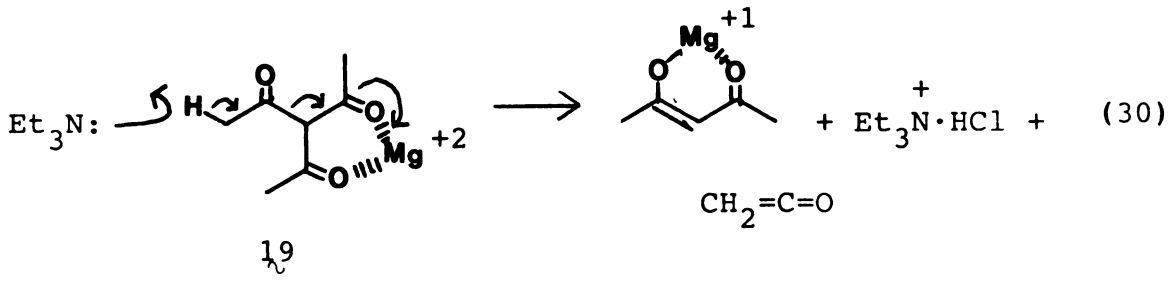
b) Isolated yields.

c) Reaction stirred for 12 hr.

d) Reaction carried out in the absence of magnesium chloride.

triethylamine was used as the base may be due to side reactions of triethylamine with acetyl chloride to form ketene. This side reaction would be expected to be more prevalent when using ethyl acetoacetate as the substrate rather than diethyl malonate since the magnesium enolate of the stronger acid, ethyl acetoacetate (pKa ≅ 10)[51], is expected to be less nucleophillic and to react at a slower rate with acetyl chloride than the magnesium enolate of the weaker acid, diethyl malonate (pKa ≅ 14)[51].

An alternative explanation for the low yield of C-acylated product obtained with triethylamine is illustrated in equation 30. Triacylmethanes are known to be readily



19 (30)

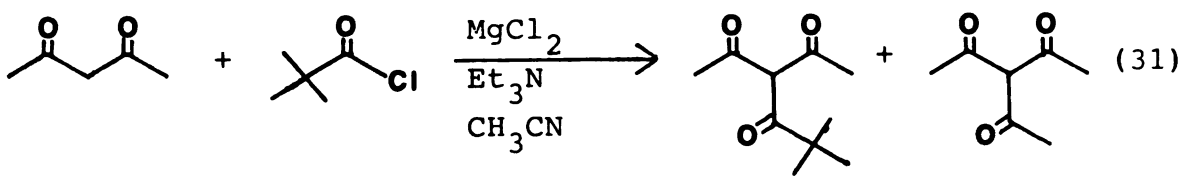
cleaved by base with cleavage normally occurring at an acetyl function[42]. Thus, triethylamine may react with the C-acylated product 19 to form ketene and the magnesium enolate of ethyl acetoacetate. This cleavage would be expected to be much slower with the weaker base, pyridine.

Under the standard conditions of 2 equivalents of pyridine and 1 equivalent of $MgCl_2$ in CH_2Cl_2, ethyl acetoacetate was reacted with a variety of acid chlorides. With the exception of pivaloyl chloride, all the acid chlorides

examined gave excellent yields of C-acylated product after a reaction time of one hour (Table 4). Pivaloyl chloride gave only an 18% yield of C-acylated product after one hour, but after a 12 hour reaction time the yield increased to 75%.

Acylation of acetylacetone, using the procedure developed for ethyl acetoacetate, gave excellent yields of the corresponding C-acylated product, provided that the acid chloride was relatively unhindered (Table 5). In cases where the acid chloride has no alpha protons available for ketene formation, yields were increased using triethylamine as the base and lengthening the reaction time from 1 to 12 hours (Entries 5 and 6, Table 5).

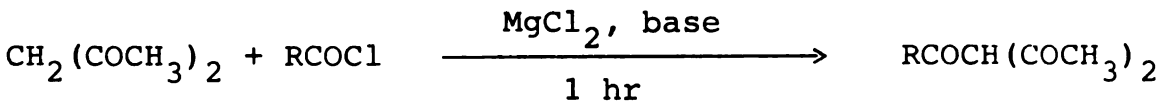
Acylation of acetylacetone with relatively hindered acid chlorides (i.e. isobutyryl and pivaloyl chloride) led to a mixture of triacylmethanes. Reaction of acetylacetone with pivaloyl chloride gave not only the expected diacetyl pivaloylmethane (≅30%, 20, eq 31) but also a small amount



20 21 (31)

(≅1% by GC) of triacetylmethane (21, eq 31). Use of isobutyryl chloride as the acylating agent gave not only the expected diacetyl isobutyrylmethane (≅40%, 22) but also small amounts of triacetylmethane (≅15%, 21) and

Table 5. Acylation of Acetylacetone.



Entry	RCOCl	Base[a]	Solvent	Yield (%)[b]
1	CH_3COCl	pyr	CH_2Cl_2	83
2	C_6H_5COCl	pyr	CH_2Cl_2	78
3[c]	C_6H_5COCl	pyr	CH_2Cl_2	79
4[c]	C_6H_5COCl	pyr	CH_3CN	79
5[c]	C_6H_5COCl	Et_3N	CH_3CN	98
6	$(CH_3)_3CCOCl$	pyr	CH_2Cl_2	5
7[c]	$(CH_3)_3CCOCl$	Et_3N	CH_3CN	30[d]
8	$(CH_3)_2CHCOCl$	pyr	CH_2Cl_2	40[e]
9[f]	CH_3COCl	pyr	CH_2Cl_2	g

a) 2 Equivalents of base used in all cases.

b) Isolated yields.

c) Reaction stirred for 12 hr.

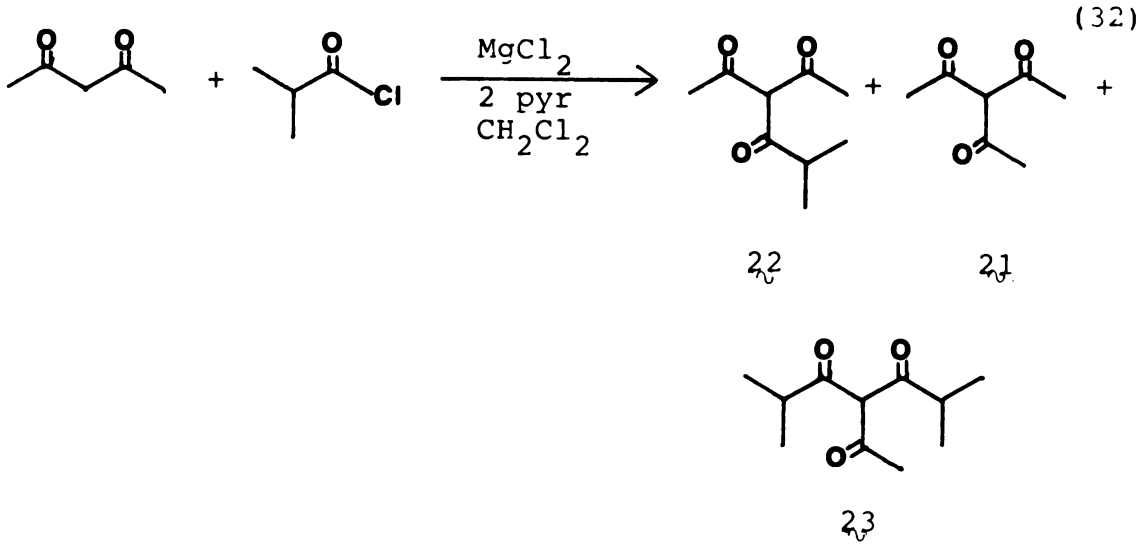
d) ≅1% (GC) triacetylmethane.

e) ≅15% triacetylmethane, ≅5% diisobutyryl acetylmethane.

f) Reaction carried out in the absence of magnesium chloride.

g) 37% Isolated yield of O-acylated acetylacetone.

diisobutyryl acetylmethane (≅5%, 23, eq 32). A possible



(32)

explanation for the occurrence of the anomalous triacylmethanes (21, eq 31; 21 and 23, eq 32) is offered in Figure 3. Acetylacetone is acylated to give the expected triacylmethane 25. Previous studies have shown that if R is a bulky group, the triacylmethane 25 exists almost exclusively in the keto form[53]. If 25 is in the keto form, it can act as an acylating agent and react with 24 to give triacetylmethane (21) and enolate 26[34]. Enolate 26 can then react with remaining acid chloride to give the disubstituted triacylmethane 27.

In order to determine optimum conditions for the reaction of acetylacetone with isobutyryl chloride, the reaction was run under a variety of conditions and the products determined by GC. As can be seen in Table 6, although the reaction is faster in CH_2Cl_2 solution, less of the

Figure 3. Transacylation of Acetylacetone.

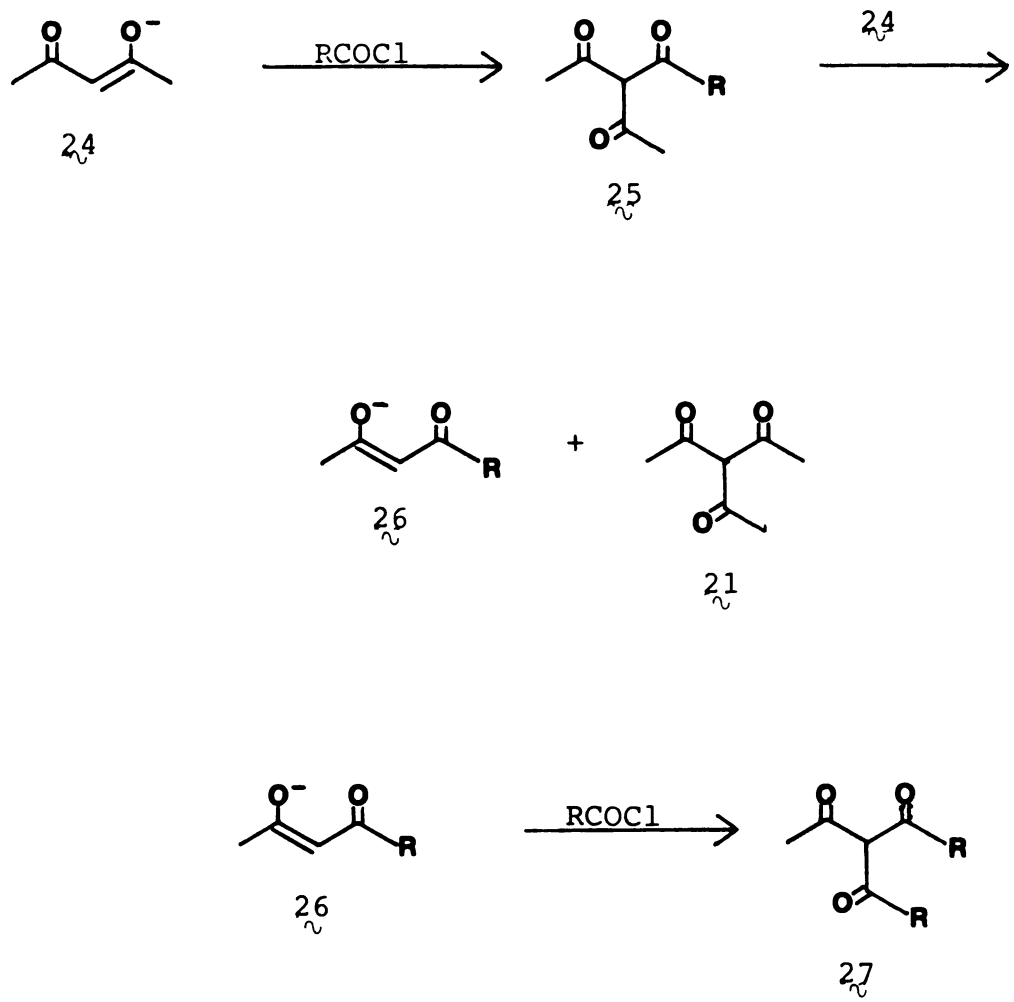
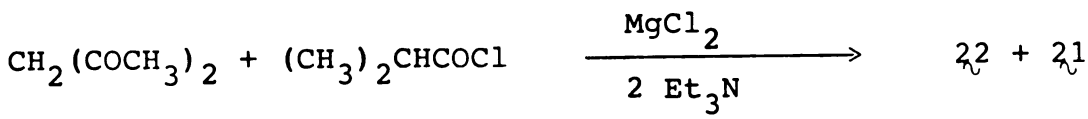


Table 6. Reaction of Acetylacetone with Isobutyryl Chloride, a Solvent Study.



Entry	Solvent	Reaction Time (hr)	Yield (%)[a] 22	21
1	CH_3CN	0.25	11	—
2	CH_3CN	0.50	55	1
3	CH_3CN	1.0	55	5
4	CH_2Cl_2	0.25	50	1
5	CH_2Cl_2	1.0	56	10
6	CH_2Cl_2	12.0	28	15

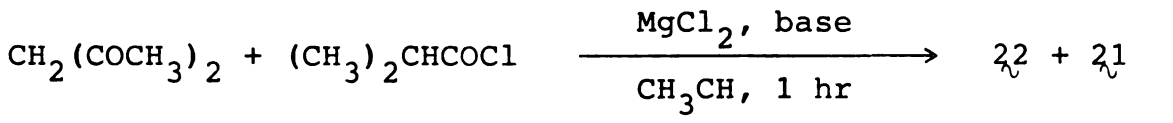
a) GC yields.

anomalous triacetylmethane (21) was formed when the reaction was conducted in CH_3CN (Entries 3 and 5, Table 6). Thus, all subsequent reactions were performed in CH_3CN.

A survey of various bases (triethylamine, pyridine, dimethyl aniline, diethyl aniline, lutidine, and collidine) revealed collidine as the most efficient of the bases tested in the acylation of acetylacetone with isobutyryl chloride (Table 7). Not only did collidine give the highest yield of product (77% GC, 60% isolated), analysis of the reaction mixture revealed that essentially no triacetylmethane was formed (≅1% GC). This result is especially surprising since lutidine, which differs from collidine only by not having a methyl group at the 4 position, gave only a 51% yield (GC) of product (22) and a significant amount of triacetylmethane (≅10% GC). It appears, therefore, that the use of collidine as a base somehow suppresses the transacylation reactions which lead to the formation of triacetylmethane. Collidine was also shown to give almost identical yields of C-acylated product as pyridine in the acylation of acetylacetone with acetyl chloride (81% isolated yield of triacetylmethane) and benzoyl chloride (78% isolated yield of diacetyl benzoylmethane).

As mentioned previously, Masamune[49] and Kobuke[50] have shown that magnesium salts of malonate half-esters can be acylated with acyl imidazoles (eq 21). We therefore studied whether acyl imidazoles might also be used in our acylation procedure. It should be noted that acyl imidazoles can be

Table 7. Survey of Bases in the Acylation of Acetylacetone with Isobutyryl Chloride.



Entry	Base[a]	Yield (%)[b] 22		21
1	Et_3N	55		5
2	pyr	46		10
3	$PhNMe_2$	68		1
4	$PhNEt_2$	49		5
5	lutidine	51		10
6	collidine	77	(60%)[c]	1

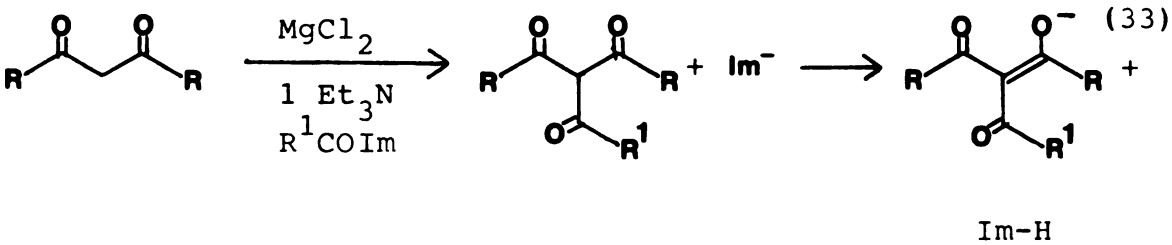
a) 2 Equivalents of base used in all cases.

b) GC yields.

c) Isolated yield.

prepared directly from the corresponding carboxylic acid whereas some acid chlorides cannot be prepared directly from the corresponding acid. Thus, the successful use of acyl imidazoles would increase the versatility of our procedure.

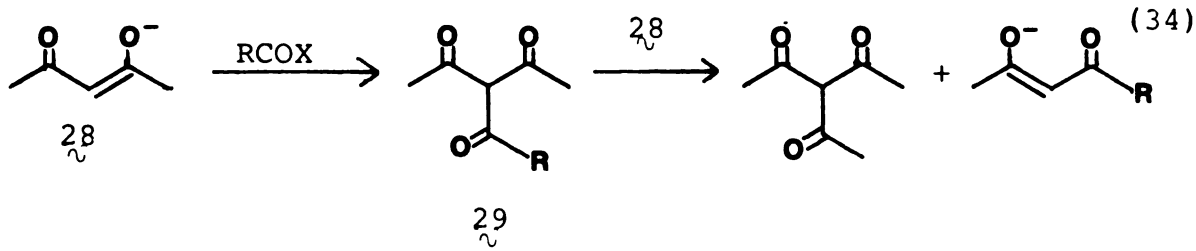
With acyl imidazoles only one equivalent of added base should be necessary, since the imidazole anion released in the reaction could act as the second equivalent of base needed to convert the highly acidic triacylmethane to its conjugate base (eq 33). Unfortunately, reaction of acetyl-



(33)

acetone with isobutyryl imidazole gave none of the expected diacetyl isobutyrylmethane (22, eq 32); only triacetylmethane was observed (GC). This result may be due to the fact that acyl imidazoles are less reactive than the corresponding acid chlorides. As the reactivity of the added acylating agent decreases, one would expect the triacylmethane (29, eq 34) to become competitive as an acylating agent, thus decreasing the yield of 29, and, at the same time, increasing the amount of triacetylmethane formed.

As was the case with both diethyl malonate and ethyl acetoacetate, no C-acylated product was formed when the acetylation of acetylacetone was conducted in the absence of



(34)

added $MgCl_2$ (Entry 9, Table 5). Unlike the previous cases, however, a 37% yield of O-acylated acetylacetone was isolated. This result demonstrates the tendency of magnesium enolates to acylate at carbon rather than at oxygen since, in the presence of added $MgCl_2$, no O-acylated product was observed.

In conclusion, the procedure which we have developed offers an extremely mild method for the acylation of β-dicarbonyl compounds. Although there have been previous reports of the acylation of magnesium enolates of β-dicarbonyl compounds, it was necessary to preform and isolate the magnesium enolate; usually be reaction of the β-dicarbonyl compound with magnesium alkoxides. Also, many of the previous methods require two equivalents of the magnesium enolate per equivalent of acylating agent; the second equivalent acting as a base and reacting with the product triacylmethane. In our acylation procedure, the magnesium enolate is generated in situ and reacted, without prior isolation, with one equivalent (based on the starting β-dicarbonyl compound) of acid chloride in a one-pot reaction. This not only decreases the amount of time needed to prepare

the triacylmethane, but also decreases the cost of the reaction since a 1:1, not a 2:1 ratio of β-dicarbonyl to acylating agent is sufficient. In fact, triacetylmethane, which is used extensively in industry, can be prepared using our procedure for approximately $10/mole (cost based on materials used, does not include man hours). This same compound is listed by Aldrich at a price of $1,000/mole (available in 5g samples). Thus, our procedure offers not only an exceptionally mild method (essentially neutral conditions) for the acylation of β-dicarbonyl compounds, but is also extremely economical.

Experimental

Materials

Reagent grade methylene chloride was dried over 4A molecular sieves. Acetonitrile was distilled from calcium hydride as were all the commercially available amines. Copper (II) chloride was obtained as an anhydrous reagent from Fisher Scientific Co. The remaining Lewis acids were obtained as anhydrous reagents from Aldrich Chemical Co. Diethyl malonate, ethyl acetoacetate, acetylacetone, and the acid chlorides were also obtained from Aldrich Chemical Co., and were purified by simple distillation. Isobutyryl imidazole was prepared from isobutyryl chloride and imidazole by the method described by Staab[54].

Methods of Analysis

^{1}H NMR data were obtained on a Varian T-60 spectrometer at 60 MHz. Chemical shifts are reported in parts per million on the delta scale relative to TMS internal standard. Mass spectral data were acquired with a Finnigan Model 4000 electron impact GC/Mass spectrometer. Gas chromatographic analysis were performed with a Varian 920 chromatograph equipped with a 6 ft. by 0.25 in. stainless steel column packed with 15% SE-30 on Chromosorb W.

General Acylation Procedure Used to Survey Various Lewis Acids

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 dry methylene chloride, diethyl malonate (10 mmol, 1.52 mL), and pyridine (20 mmol, 1.60 mL). The Lewis acid (10 mmol) was added and the resulting heterogeneous mixture was stirred for 15 minutes. The flask was immersed in an ice bath and acetyl chloride (10 mmol, 0.72 mL) was introduced into the flask via the septum inlet. After stirring the reaction mixture for 15 minutes at 0°C, the cooling bath was removed and the mixture was stirred for 12 hours. After cooling to 0°C, the reaction was quenched with 5 mL of 6 M HCl. The resulting solution was washed three times with 5 mL of diethyl ether and the combined ether extracts were dried ($MgSO_4$). The ether solution was analyzed by GC (dodecane as an internal standard) for unreacted diethyl malonate.

General Procedure for the Acylation of Diethyl Malonate

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 (2.38g) of anhydrous magnesium chloride. Dry acetonitrile (25 mL) was added to the flask. To the resulting heterogeneous mixture was added 25 mmol (3.80 mL) 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 stirring for 15 minutes at 0°C, 25 mmol of acid chloride was added. The resulting mixture was stirred 1 hour at 0°C and 12 hours at room temperature. After cooling to 0°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 ($MgSO_4$), filtered, and the solvent removed under vacuum. The resulting residue was purified by bulb to bulb distillation.

Diethyl acetylmalonate was prepared from diethyl malonate and acetyl chloride. Bulb to bulb distillation (90°C/0.25 mm) gave 4.7976g of a clear liquid which was shown to be a mixture of diethyl malonate and diethyl acetylmalonate. ^1H NMR analysis revealed that the mixture contained approximately 21 mmol (85%) of diethyl acetylmalonate. ^1H NMR ($CDCl_3$), δ1.1-1.5 (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 (b.p. 140°C/0.25 mm). ^{1}H NMR ($CDCl_3$), δ1.1-1.3 (t, J=7Hz, 6H), 4.0-4.4 (q, J=7Hz, 4H), 5.3 (s), 7.3-7.9 (m, 5H), 13.1 (s). MS: (m/e) 264 ($M^{\cdot+}$), 105 ($PhCO^+$).

Diethyl isobutyrylmalonate was prepared from diethyl malonate and isobutyryl chloride in 92% yield (b.p. 100°C/0.4 mm). ^{1}H NMR ($CDCl_3$), δ1.0-1.5 (m, 12H), 2.5-3.0 (m, 1H), 4.0-4.4 (m, 4H), 4.6 (s), 13.2 (s). MS: (m/e) 230 ($M^{\cdot+}$), 187 ($M^{\cdot+}$ - $CH(CH_3)_2$), 159 ($M^{\cdot+}$ - $(CH_3)_2CHCO$), 159, 141, 87, 71, 43.

Diethyl n-butyrylmalonate was prepared from diethyl malonate and n-butyryl chloride in 86% yield (b.p. 100°C/0.4 mm). ^{1}H NMR ($CDCl_3$), δ0.7-2.0 (m, 11H), 2.1-2.7 (m, 2H), 4.0-4.5 (m, 4H), 13.3 (s). MS: (m/e) 230 ($M^{\cdot+}$), 187 ($M^{\cdot+}$ - $CH_2CH_2CH_3$), 159 ($M^{\cdot+}$ - $CH_3CH_2CH_2CO$), 141, 87, 71, 43.

Diethyl pivaloylmalonate was prepared from diethyl malonate and pivaloyl chloride in 90% yield (b.p. 100°C/0.4 mm). ^{1}H NMR ($CDCl_3$), δ1.1-1.4 (m, 15H), 4.0-4.4 (m, 4H), 4.9 (s, 1H). MS: (m/e) 245 ($M^{\cdot+}$ + 1), 159 ($M^{\cdot+}$ - $(CH_3)_3CCO$), 85, 57, 41.

^{1}H 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 (0.76 mL) of diethyl malonate. A ^1H NMR of the resulting solution was taken.

^1H NMR (CD_3CN), δ1.0-1.4 (m, 6H), 3.3 (s, 2H), 3.9-4.3 (m, 4H).

The NMR sample was returned to the flask and 5 mmol (0.66 mL) of triethylamine was added. A ^1H NMR was taken of the resulting solution.

^1H NMR (CD_3CN), δ0.8-1.4 (m, 15H), 2.2-2.7 (m,6H), 3.3 (s, 2H), 3.9-4.3 (m, 4H).

The NMR sample was returned to the flask and 5 mmol (0.48g) of anhydrous magnesium chloride was added. The resulting heterogeneous mixture was stirred for 15 minutes at room temperature. As the mixture was stirred it became more viscous. An aliquot of the mixture was removed, filtered, and a ^1H NMR was taken of the filtrate.

^1H NMR (CD_3CN), δ1.0-1.4 (m, 15H), 2.8-3.3 (m, 6H), 3.8-4.2 (m, 5H).

Isolation of the Magnesium Enolate of Diethyl Malonate

A 0.5 M diethyl ether solution (20 mL; 10 mmol) of diethyl malonate was prepared under an atmosphere of argon. To this solution were added 10 mmol (1.39 mL) of triethylamine and 10 mmol (0.95g) of anhydrous magnesium chloride. The resulting heterogeneous mixture was stirred for 1.5 hours. The mixture was filtered under an atmosphere of argon and the solvent was removed from the filtrate under

reduced pressure leaving 0.86g of a white solid.

^{1}H NMR ($CDCl_3$), δ0.9-1.4 (m, 6H), 3.7-4.3 (m, 5H).

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 (2.38g) of dry magnesium chloride. Dry solvent (25 mL, CH_3CN or CH_2Cl_2, see Table 4) 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 4) was added through the septum inlet. After stirring for 15 minutes at 0°C, 25 mmol of acid chloride was added. The resulting mixture was stirred for 15 minutes at 0°C and 1 hour at room temperature. After cooling to 0°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 ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The resulting residue was purified by bulb to bulb distillation.

Ethyl-3-oxo-2-acetylbutanoate was prepared from ethyl acetoacetate and acetyl chloride in 91% yield (b.p. 45°C/0.2 mm). ^{1}H NMR ($CDCl_3$), δ1.3 (t, J=7Hz, 3H), 2.4 (s, 6H), 4.3 (q, J=7Hz, 2H), 17.5 (s, 1H). MS: (m/e) 172 (M^+), 157 ($M^+ - CH_3$), 129 ($M^+ - CH_3CO$), 98, 85, 43.

Ethyl-3-oxo-2-benzoylbutanoate was prepared from ethyl acetoacetate and benzoyl chloride in 81% yield (b.p. 140°C/0.25 mm). ^{1}H NMR ($CDCl_3$), δ0.7-1.4 (m, 3H). 2.0-2.4 (s, total 3H), 3.7-4.3 (m, 2H), 5.3 (s), 7.2-7.9 (m, 5H), 12.9 (s), 16.3 (bs). MS: (m/e) 234 ($M^{\cdot+}$), 233 ($M^{\cdot+}$ - H), 219 (M^+ - CH_3), 187, 105 ($PhCO^+$), 77, 43.

Ethyl-3-oxo-2-acetyl-4-methyl pentanoate was prepared from ethyl acetoacetate and isobutyryl chloride in 77% yield (b.p. 55°C/0.2 mm). ^{1}H NMR ($CDCl_3$), δ1.0-1.5 (m, 9H), 2.3 (s, 3H), 2.9-3.4 (m, 1H), 4.0-4.5 (m, 2H), 17.3 (s, 1H). MS: (m/e) 200 (M^+), 185 (M^+ - CH_3), 155, 71.

Ethyl-3-oxo-2-acetylhexanoate was prepared from ethyl acetoacetate and n-butyryl chloride in 78% yield (b.p. 54°C/0.2 mm). ^{1}H NMR ($CDCl_3$), δ0.8-2.0 (m, 8H), 2.3 (s, 3H), 2.3-2.8 (m, 2H), 4.1-4.5 (m, 2H), 17.4 (s, 1H). MS: (m/e) 201 (M^+ + 1), 185 (M^+ - CH_3), 157 (M^+ - 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 (b.p. 65°C/0.25 mm). ^{1}H NMR ($CDCl_3$), δ1.1-1.5 (m, 12H), 2.3 (s, 3H), 4.0-4.4 (m, 2H), 5.0 (s, 1H). MS: (m/e) 214 ($M^{\cdot+}$), 199 (M^+ - CH_3), 173, 155, 131, 85.

General Procedure for the Acylation of Acetylacetone

Acetylacetone was acylated in a manner identical to that described for ethyl acetoacetate substituting 25 mmol

(2.57 mL) of acetylacetone for 25 mmol of ethyl acetoacetate.

Triacetylmethane was prepared from acetylacetone and acetyl chloride in 83% yield (b.p. 55°C/0.5 mm). ^{1}H NMR ($CDCl_3$), δ2.1 (s, 6H), 2.3 (s, 3H), 16.7 (s, 1H). MS: (m/e) 142 (M^+), 127 ($M^+ - CH_3$), 100 ($M^+ - CH_2{=}C{=}O$), 85, 67, 43.

Benzoyl diacetylmethane was prepared from acetylacetone and benzoyl chloride in 98% yield (b.p. 125°C/0.25 mm). ^{1}H NMR ($CDCl_3$), δ2.0 (s, 6H), 7.4-8.0 (m, 5H), 16.6 (s, 1H). MS: (m/e) 204 (M^+), 189 ($M^+ - CH_3$), 161 ($M^+ - CH_3CO$), 147, 127, 105, 85, 77, 43.

Pivaloyl diacetylmethane was prepared from acetylacetone and pivaloyl chloride. Bulb to bulb distillation (50°C/ 0.05 mm) yielded 1.6972g of a clear liquid. ^{1}H NMR analysis showed the liquid to be a 3:1 mixture of pivaloyl diacetylmethane : triacetylmethane giving a 30% ^{1}H NMR yield of pivaloyl diacetylmethane.

^{1}H NMR ($CDCl_3$), δ1.1-1.3 (m, 9H), 2.2-2.4 (s, total 6H), 5.6 (s) + 15.4 (bs, total 1H). MS: (m/e) 184 (M^+), 142 ($M^+ - CH_2{=}C{=}O$), 127 ($M^+ - C(CH_3)_3$), 101, 85, 57, 43.

Isobutyryl diacetylmethane was prepared from acetylacetone and isobutyryl chloride following the procedure described above and using the reagents listed in Entry 6 of Table 7. Bulb to bulb distillation (b.p. 40°C/0.1 mm) yielded 2.67g of a clear liquid. ^{1}H NMR analysis revealed

the liquid to be a 12:1 mixture of isobutyryl diacetylmethane and triacetylmethane giving a 60% ^{1}H NMR yield of isobutyryl diacetylmethane. ^{1}H NMR δ1.0-1.3 (m, 6H), 2.1-2.3 (m, 6H), 2.4-3.2 (m, 1H), 5.0 (s) + 16.5 (s) + 16.7 (s, total 1H). MS: (m/e) 171 (M^+ + 1), 152, 127 (M^+ - CH_3CO), 85, 71, 43.

Diisobutyryl acetylmethane was formed as a by-product in the reaction of acetylchloride with isobutyryl chloride and was identified by its GC/MS: (m/e) 198 (M^+), 155 (M^+ - CH_3CO), 137, 128, 113, 85, 71, 43.

Acetylacetone enol acetate was prepared from acetylacetone and acetyl chloride in the absence of magnesium chloride in 37% yield (b.p. 38°C/0.25 mm). ^{1}H NMR δ2.0-2.4 (m, 11H), 5.8 (s) + 6.1 (s, total 1H). 143 (M^+ + 1), 127 (M^+ - CH_3), 101, 85, 43.

GC Study of the Acylation of Acetylacetone with Isobutyryl Chloride

Acetylacetone was reacted with isobutyryl chloride according to the procedure described for the acylation of ethyl acetoacetate. Following acid work-up, the combined ether extracts were dried ($MgSO_4$) and analyzed for isobutyryl diacetylmethane by GC (tetradecane as an internal standard).

Acylation of Acetylacetone with Isobutyryl Imidazole

Acetylacetone was reacted with isobutyryl imidazole in CH_2Cl_2 with triethylamine according to the procedure for the

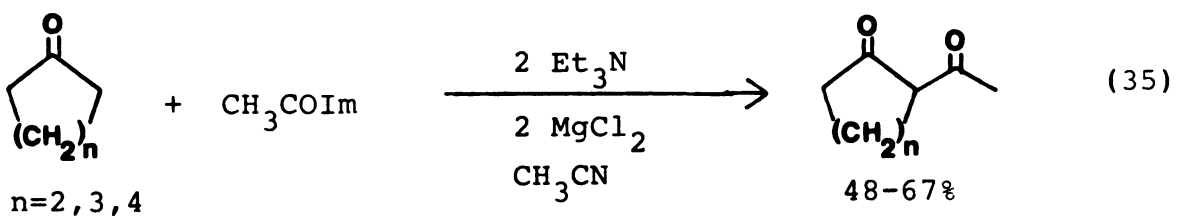
acylation of ethyl acetoacetate. GC analysis revealed triacetylmethane as the only product.

Chapter III

AN INTRODUCTORY STUDY OF THE CARBOMETHOXYLATION OF KETONES USING WEAK BASES

Introduction

After our success in acylating β-dicarbonyl compounds with acyl halides, using triethylamine and $MgCl_2$ to promote enolate formation, we decided to extend the procedure to the acylation of ketones. Previous work in this laboratory[55] has shown that the acetylation of cyclic ketones with acyl imidazoles, using triethylamine and $MgCl_2$ to promote enolate formation, gave C-acylated products in moderate yields (eq 35). However, acyclic ketones failed to react under these



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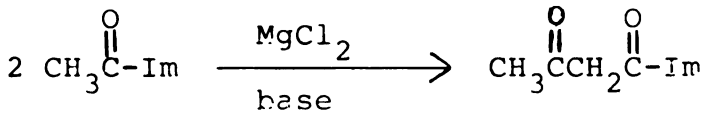
conditions.

A possible explanation for the low yield of C-acylated products from reactions involving acetyl imidazole is a self-condensation similar to the Claisen ester condensation (eq 36). Staab has observed such a reaction in an attempted synthesis of t-butyl acetate from acetyl imidazole and



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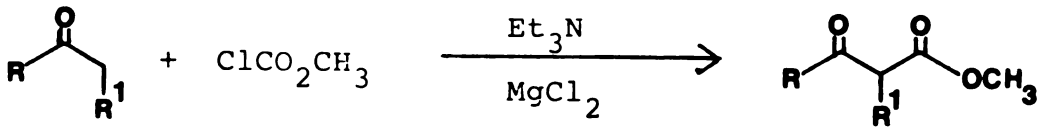
t-butanol in the presence of sodium t-butoxide[56]. Clearly, use of an acylating agent which lacked alpha protons would eliminate this side reaction.

We chose to study the reaction of ketones with methyl chloroformate in the presence of triethylamine and $MgCl_2$ (eq 37). Methyl chloroformate does not have protons alpha to the



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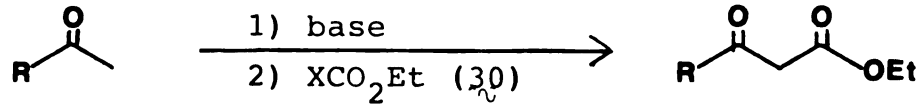
carbonyl function and thus cannot undergo a condensation reaction of the type shown in equation 36.

Carboalkoxylations of ketones to form β-keto esters have been accomplished by reaction of ketones with diethyl carbonate (30, X=OEt) or ethyl chloroformate (30, X=Cl) in the presence of such bases as sodium ethoxide or sodium hydride (eq 38)[57]. Diethyl oxalate (31, eq 39) and ethyl diethoxyphosphinyl formate (32, eq 40) have also been employed as acylating reagents in the carboethoxylation of ketones.

All of the carboalkoxylation reactions referred to above require the use of a strong base to form the ketone enolate.



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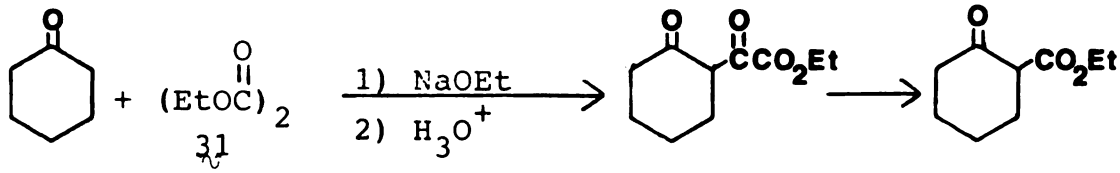

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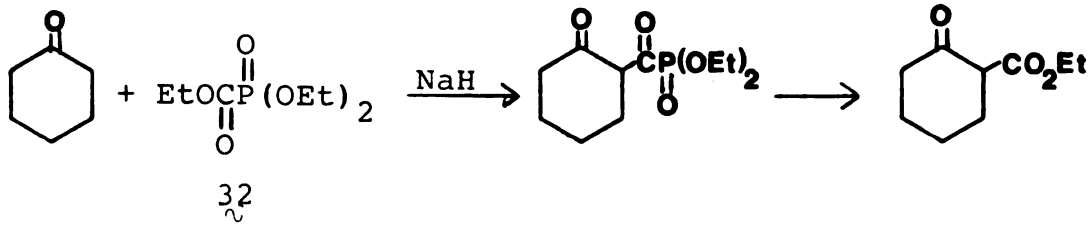

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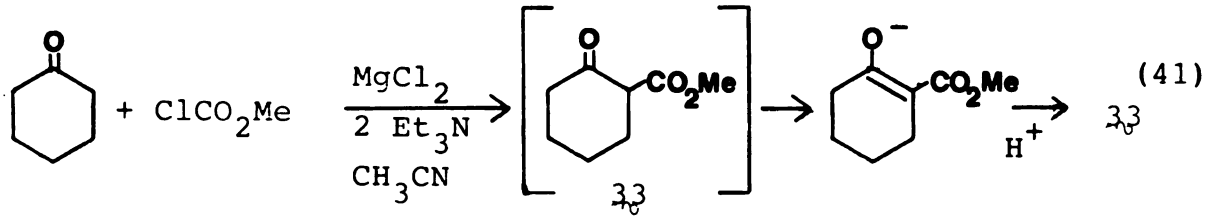
Also, to insure a good yield of product, many of the procedures require the use of excess ketone enolate. We thought that these problems could be avoided if the procedure which we developed for the acylation of β-dicarbonyl compounds could be extended to the carboalkoxylation of ketones (eq 37). The development of such a mild carboalkoxylation procedure would provide a useful alternative to the conventional procedures.

Results and Discussion

Cyclohexanone was reacted with methyl chloroformate in the presence of $MgCl_2$ and triethylamine in CH_3CN solution (eq 41). It was necessary to use two equivalents of tri-



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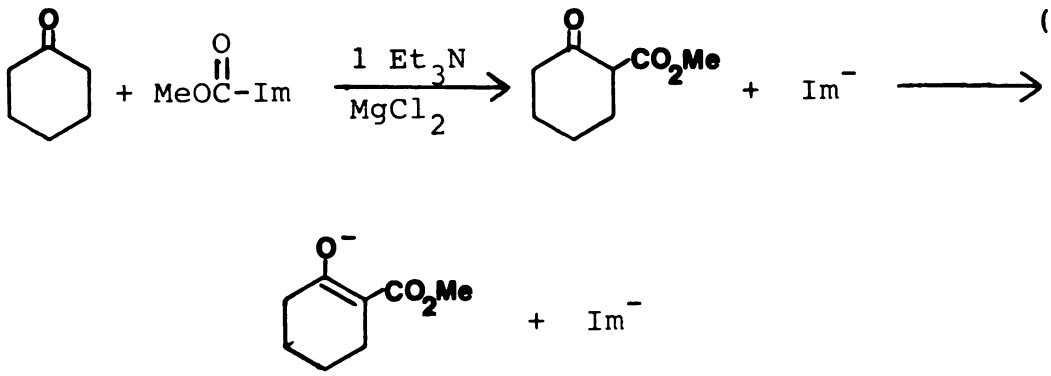
ethylamine, as the second equivalent is consumed by the acidic β-keto ester product 33. The resulting white suspension was allowed to stir overnight before quenching with aqueous HCl. Unfortunately, analysis of the reaction mixture (GC) revealed no β-keto ester (33) was formed.

Previous work in our laboratory had revealed that in the acetylation of cyclohexanone under similar conditions, acetyl imidazole gave a much higher yield of 2-acetyl cyclohexanone (67%) than acetyl chloride (28%, eq 35, n=4). Thus, we decided to attempt the carbomethoxylation using carbomethoxy imidazole as the acylating agent (eq 42). Only one equivalent of triethylamine was used, as the imidazole anion which is released can act as the second equivalent of base and react with the β-keto ester 33. Unfortunately, this procedure provided only a 9% isolated yield of 33.

A possible explanation for the low yield of product observed here may be the occurrence of a side reaction between $MgCl_2$ and the imidazole produced in the reaction (eq 43).



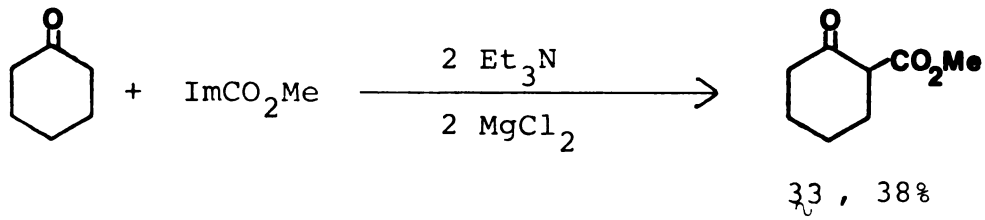
(42)

$$MgCl_2 + H\text{-}Im + Et_3N \longrightarrow Et_3N\cdot HCl + ClMg\text{-}Im \quad (43)$$

(34)

The chloromagnesium imidazole (34) produced in this reaction would be a less active Lewis acid than $MgCl_2$ and therefore should not be as effective as $MgCl_2$ in promoting enolate formation of cyclohexanone. A possible solution to this problem would be to add a second equivalent of $MgCl_2$ to the reaction mixture. Also, because amines weakly chelate to $MgCl_2$[28], a second equivalent of triethylamine would probably be needed. When these conditions were applied to this reaction, only a 38% yield of 33 was obtained (eq 44).

We next reacted cyclohexanone with carbomethoxy imidazole in the presence of a 2:1 mixture of sodium iodide and $MgCl_2$, with triethylamine as the base (eq 45). It was assumed that this mixture would generate magnesium iodide, which, being a stronger Lewis acid than $MgCl_2$, would better promote enolate



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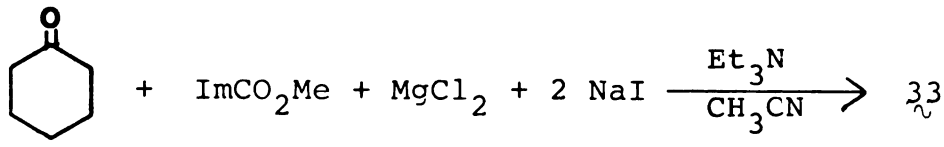
33 , 38%



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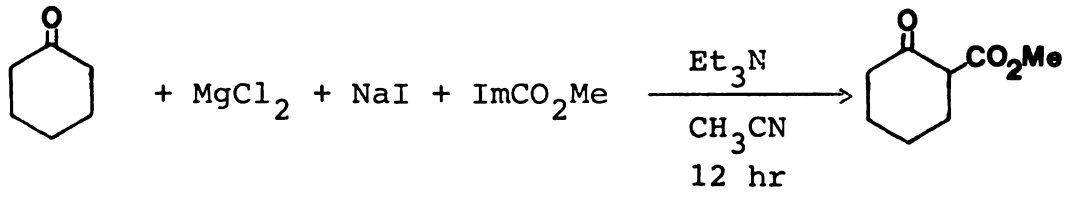
formation from cyclohexanone. The result of this change was an increase in the yield of 33 from 9% (Entry 2, Table 8) to 47% (Entry 6, Table 8). Further adjustments of the reaction conditions increased the yield of 33 to 64%. The optimum reaction conditions were found to be a 2:2:1 ratio of $MgCl_2$: triethylamine:sodium iodide and these conditions were employed for all our further studies.

Extension of this procedure to the carbomethoxylation of acetophenone gave a 64% isolated yield of methyl benzoylacetate. Carbomethoxylation of diethyl ketone (5 mmol scale), however, gave a mixture of three β-dicarbonyl compounds with a combined weight of 0.40g (≅56%, eq 46). The compounds were identified by GC/mass spectrometry and by ^1H NMR analysis of GC isolated samples. A possible explanation for the occurrence of products 36 and 37 is offered in

Table 8. Carbomethoxylation of Cyclohexanone.

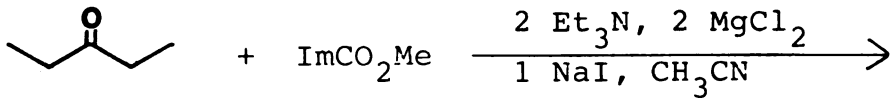


	# of equivalents			
Entry	$MgCl_2$	NaI	Et_3N	Yield
1[b]	1	-	2	0
2	1	-	1	9
3	2	-	1	26
4	2	-	2	38
5	1	2	1	47
6[c]	1	2	1	41
7	2	2	1	36
8	2	2	2	64
9	2	4	2	59
10	2	1	2	64
11	2	0.2	2	48
12[b]	1	2	2	0

a) Based on 5.0 mmol of cyclohexanone.

b) Methyl chloroformate used in place of carbomethoxy imidazole.

c) Refluxed overnight.



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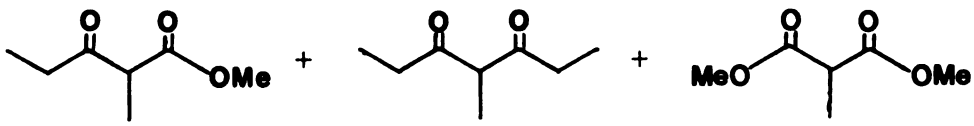


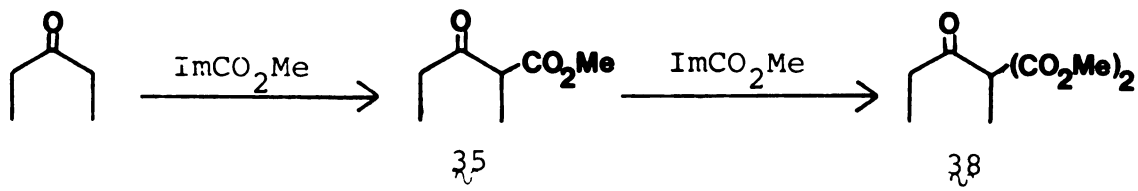
35 36 37

Figure 4. Diethyl ketone may be bis acylated to give the triacylmethane 38. Triacylmethanes, especially those which are unable to enolize, have been known to act as acylating agents[34]. Thus, the triacylmethane 38 may acylate diethyl ketone to give 36 and 37 after acidification. Triethylamine may also react with 38 in a manner similar to that of equation 30 to give ketene 39 and the β-dicarbonyl 37. This may explain why 37 qualitatively appears to be the major product (analyzed by GC).

The transacylation reactions shown in Figure 4 are not expected to occur in the carbomethoxylation of cyclic ketones. Should bis carbomethoxylation of the cyclic ketone occur, the resulting triacylmethane 40 would probably react with remaining ketone enolate 41 to give two equivalents of the expected product 42 (eq 47). Alternatively, triacylmethane 40 may be hydrolyzed during the acidic work-up (eq 48).

In conclusion, this procedure has the potential to be a

Figure 4. Carbomethoxylation of Diethyl Ketone.



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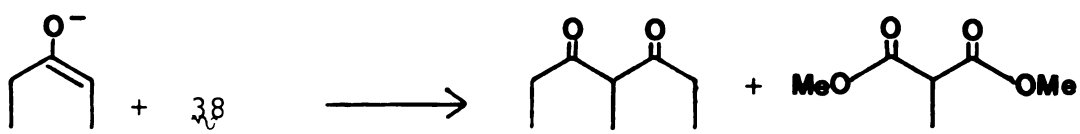

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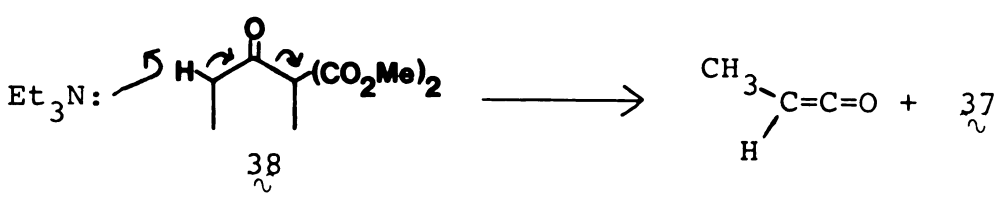

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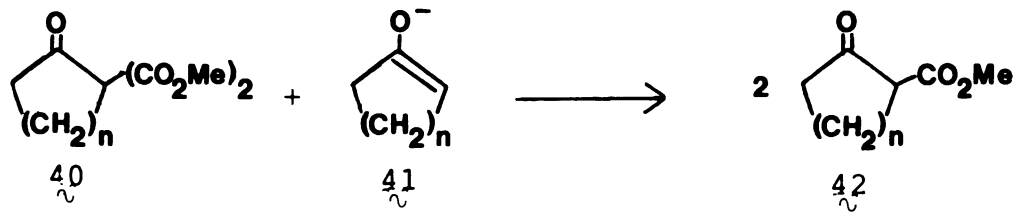
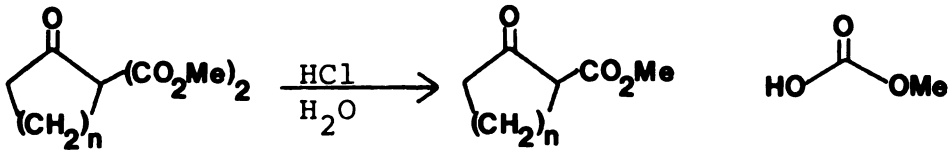


40 41 42 (47)



(48)

mild and convenient method of carbomethoxylating cyclic ketones. Additional study is required, however, to increase the generality and effectiveness of this procedure, especially in the carbomethoxylation of non-cyclic ketones. Perhaps the use of a less reactive carbomethoxylating agent will eliminate the transacylation reactions in the carbomethoxylation of diethyl ketone.

Experimental

Materials

Acetonitrile and triethylamine were distilled from calcium hydride. Methyl chloroformate was obtained from Aldrich Chemical Co. and distilled prior to use. Carbomethoxy imidazole was prepared from methyl chloroformate and imidazole by the method described by Moodie[57]. Sodium iodide,

purchased from J.T. Baker Chemical Co., was dried by heating under vacuum prior to its use. Magnesium chloride, acquired as the anhydrous reagent from Aldrich Chemical Co., was stored in a glove bag under argon. All ketones used in this investigation were commercially available and were distilled from calcium hydride prior to use.

Methods of Analysis

^{1}H NMR data were obtained on a Varian T-60 spectrometer at 60 MHz. Chemical shifts are reported in parts per million on the delta scale relative to TMS internal standard. Mass spectral data were acquired with a Finnigan Model 4000 electron impact GC/Mass spectrometer. Gas chromatographic analysis were performed with a Varian 920 chromatograph equipped with a 6 ft. by 0.25 in. stainless steel column packed with 15% SE 30 on Chromosorb W.

General Procedure for the Carbomethoxylation of Cyclohexanone

A flame-dried 50 mL round bottom flask equipped with a septum inlet, magnetic stirrer, and mercury bubbler was flushed with argon and charged with 5 mL of CH_3CN and 0.52 mL (5.0 mmol) of cyclohexanone. The appropriate amounts of magnesium chloride, sodium iodide, and triethylamine (see Table 8) were added and the resulting heterogeneous mixture was stirred for 15 minutes. Carbomethoxy imidazole (5.0 mmol, 0.48g) was added and the resulting white mixture was stirred overnight at room temperature. The reaction mixture

was quenched with 4 mL of 6 M HCl and the resulting solution was washed three times with 5 mL of diethyl ether. The combined ether extracts were dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The resulting residue was purified by bulb to bulb distillation.

2-Carbomethoxycyclohexanone was prepared by the procedure described above (10 mmol $MgCl_2$, 10 mmol triethylamine, 5.0 mmol NaI) in 64% yield (b.p. 110°C/1.4 mm). ^1H NMR ($CDCl_3$), δ1.3-2.5 (m, 8H), 3.2-3.5 (m) + 12.0 (s, total 1H), 3.7 (s, 3H).

Carbomethoxylation of Acetophenone

A flame-dried 50 mL round bottom flask equipped with a septum inlet, magnetic stirrer, and mercury bubbler was flushed with argon and charged with 5 mL of CH_3CN and 0.59 mL (5.0 mmol) of acetophenone. Magnesium chloride (0.95g, 10 mmol), sodium iodide (0.75g, 5.0 mmol), and triethylamine (1.40 mL, 10 mmol) were added to the flask and the resulting heterogeneous mixture was stirred for 15 minutes. Carbomethoxy imidazole (0.48g, 5.0 mmol) was added and the resulting mixture was stirred overnight at room temperature. The reaction mixture was quenched with 4 mL of 6 M HCl and the resulting solution was washed three times with 5 mL of diethyl ether. The combined ether extracts were dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The resulting residue was purified by bulb to bulb distillation giving a 64% yield of methyl benzoylacetate (b.p.

175°C/1.4 mm). ^{1}H NMR ($CDCl_3$), δ3.70 (s) and 3.77 (s, total 3H), 4.00 (s) and 5.67 (s, total 2H), 7.30-8.00 (m, 5H). MS: (m/e) 178 ($M^{\cdot+}$), 147 ($M^{\cdot+}$ - OCH_3), 105 ($PhCO^+$), 77, 51.

Carbomethoxylation of Diethyl Ketone

Diethyl ketone was carbomethoxylated according to the procedure described above, substituting diethyl ketone (0.53 mL, 5.0 mmol) for acetophenone. After acidic work-up, the solution was washed three times with 5 mL of diethyl ether. The combined ether extracts were dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure giving 0.40g of a slightly yellow liquid. Analysis (GC) revealed three products which were purified by GC preparation and identified by their mass spectrum and ^{1}H NMR.

Methyl-3-oxo-2-methylpentanoate (35): ^{1}H NMR ($CDCl_3$), δ1.07 (t, J=7Hz, 3H), 1.33 (d, J=7Hz, 3H), 2.53 (q, J=7Hz, 2H), 3.50 (q, J=7Hz, 1H), 3.71 (s, 3H). MS: (m/e) 144 ($M^{\cdot+}$), 115 ($M^{\cdot+}$ - CH_2CH_3), 113 ($M^{\cdot+}$ - OCH_3), 88, 57.

4-Methyl-3,5-heptanedione (36): ^{1}H NMR ($CDCl_3$), δ1.03 (t, J=7Hz, 6H), 1.30 (d, J=7Hz, 3H), 2.47 (q, J=7Hz, 4H), 3.70 (q, J=7Hz, 1H). MS: (m/e) 142 ($M^{\cdot+}$), 113 ($M^{\cdot+}$ - CH_2CH_3), 86, 57.

Dimethyl methylmalonate (37): ^{1}H NMR ($CDCl_3$), δ1.38 (d, J=7Hz, 3H), 3.60 (q, J=7Hz, 1H), 3.71 (s, 6H). MS: (m/e) 146 ($M^{\cdot+}$), 115 ($M^{\cdot+}$ - OCH_3), 87 ($M^{\cdot+}$ - CH_3OCO), 72, 59.

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