ATTEMPTED SYNTHESES OF 1,4-DIKETONES

By

Patrick J. Cowan

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ABSTRACT

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Lithium and potassium ketone enolates failed to react with α-haloketones to give the corresponding 1,4-diketone. Lithium ketone enolates also did not react with γ-halo-α-ketoesters under a variety of conditions.

Lithio methyl acetate reacted with lithio chloroacetyl Meldrum's acid to give methyl-4-Meldrum's acid acetoacetate in 83% yield. The same product was formed with lithio bromoacetyl Meldrum's acid in place of lithio chloroacetyl Meldrum's acid. Reaction of lithio methyl acetate with lithio iodoacetyl Meldrum's acid failed to give any alkylation product.

Acetyl Meldrum's acid did not react with chloroacetone to give acetonyl acetyl Meldrum's acid. However, acetonyl Meldrum's acid, prepared in 87.4% yield from chloroacetone and Meldrum's acid, reacted with acetyl chloride to give acetonyl acetyl Meldrum's acid in 99.5% yield. Acetyl chloride, however, was the only acid chloride which reacted with acetonyl Meldrum's acid. All attempts to cleave the Meldrum's acid ring of acetonyl acetyl Meldrum's acid failed.

To

My Parents, whose love and support made this project possible.

ACKNOWLEDGEMENTS

The author wishes to express his deep appreciation to Dr. Michael W. Rathke for his inspiration, patience, and guidance throughout this project.

The author further expresses his appreciation to his fellow students for both the professional interest and companionship which they have extended to him.

Finally, the author wishes to thank his parents and family for their continued encouragement, love, and interest throughout this effort.

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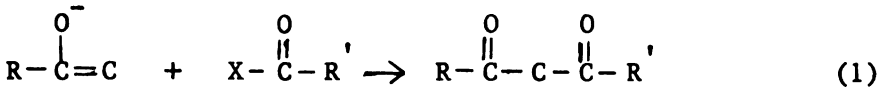
CHAPTER I

REACTIONS OF ENOLATES WITH α-CHLOROKETONES

Introduction

1,4-Dicarbonyl compounds are important intermediates for the synthesis of organic compounds. For example, 1,4-diketones are precursors to pyrroles[1], furans[2], and cyclopentenones[3,4]. Cyclopentenones, in turn, are precursors to prostaglandins[4].

The synthesis of 1,3 and 1,5-dicarbonyl compounds can be accomplished by simple aldol (Eq 1) or conjugate aldol (Eq 2) condensation reactions. 1,4-Dicarbonyl compounds, however, are not amenable to such simple approaches.



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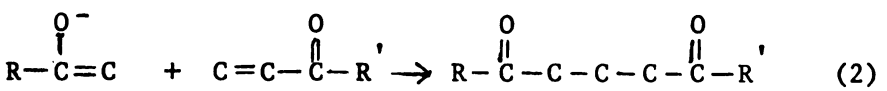


(2)

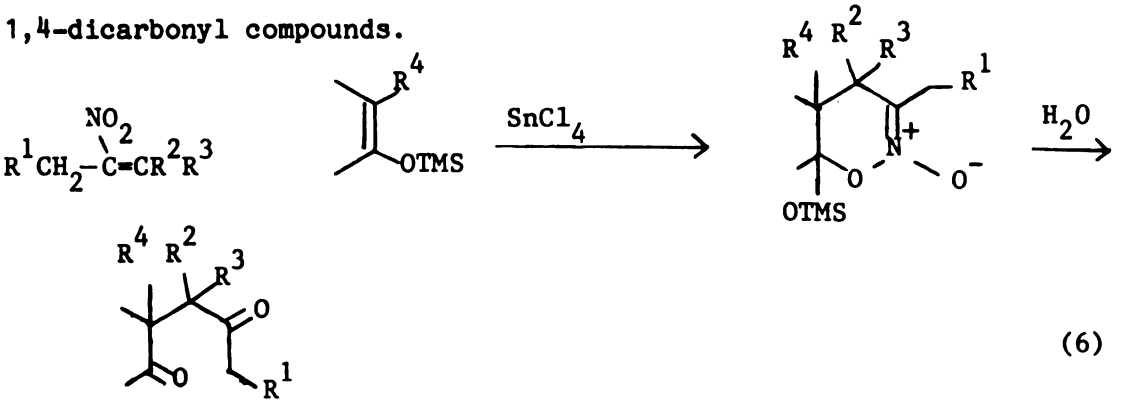
1,4-Dicarbonyl compounds have been synthesized by the addition of acyl anion equivalents, such as nitro-stabilized carbanions[1,3] (Eq 3), lithium di[bis(phenylthio)methyl]copper[5] (Eq 4), and acyl carbonylnickelate[6] (Eq 5), to α,β-unsaturated carbonyls.

$$R\bar{C}H(NO_2) + C{=}CHCOR' \rightarrow R\text{-}CH(NO_2)CH_2CH_2COR' \xrightarrow{TiCl_3} RCOCH_2CH_2COR' \quad (3)$$

$$[(PhS)_2\overset{R}{\overset{|}{C}}]_2CuLi + C{=}C\text{-}\overset{O}{\overset{\|}{C}}\text{-}R' \rightarrow (PhS)_2\overset{R}{\overset{|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}R' \xrightarrow[H_2O]{\substack{4CuO\\2CuCl_2}} RCOCH_2CH_2COR' \quad (4)$$

$$[RCONi(CO)_3]^-Li^+ + C{=}C\text{-}\overset{O}{\overset{\|}{C}}\text{-}R' \rightarrow RCOCH_2CH_2COR' \quad (5)$$

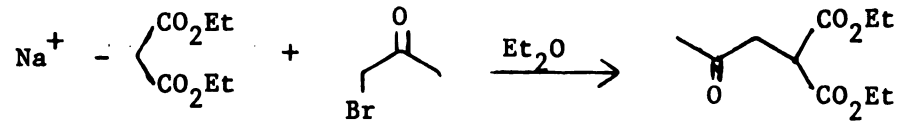
Yoshikoshi and coworkers[7] used a $SnCl_4$ catalysed addition of trimethylsilyl enol ethers to α,β-unsaturated nitroalkenes (Eq 6) to form 1,4-dicarbonyl compounds.



(6)

A particularly attractive approach, at least conceptually, to 1,4-dicarbonyl compounds is the direct alkylation of enolates with α-haloketones. This reaction has been accomplished with the enolates of diethyl malonate[8] (Eq 7) and barbituric acid[9] (Eq 8). The reaction of an enolate of a simple ketone with a α-haloketone, however, has never been reported.

An alternate approach to 1,4-dicarbonyl compounds is the alkylation of enolates with masked α-haloketones. Miyano[10] reacted methallyl iodide with a ketone enolate to obtain the corresponding alkylation product (1) which was converted to a 1,4-dicarbonyl compound (Eq 9).



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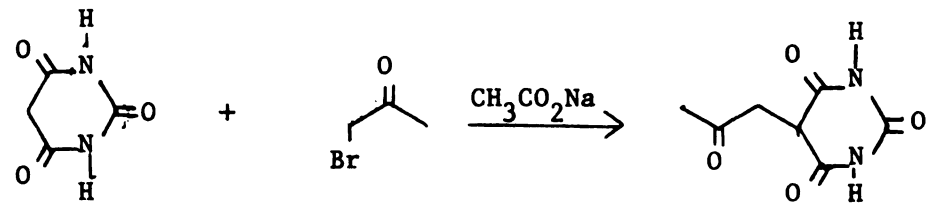

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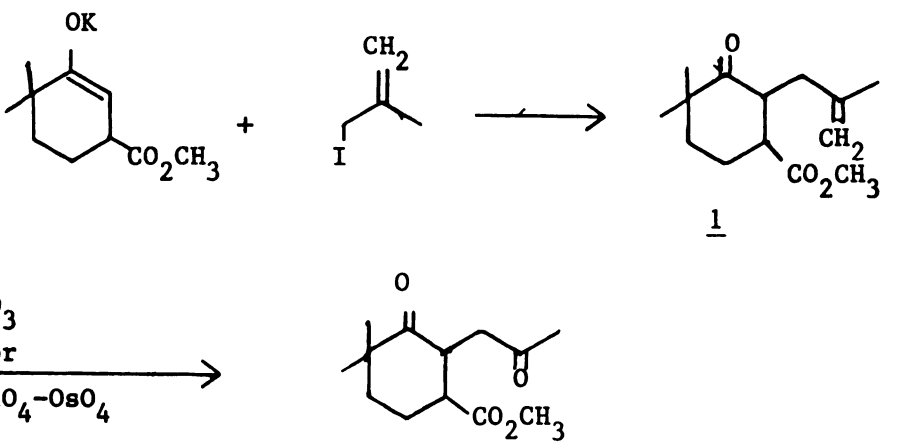
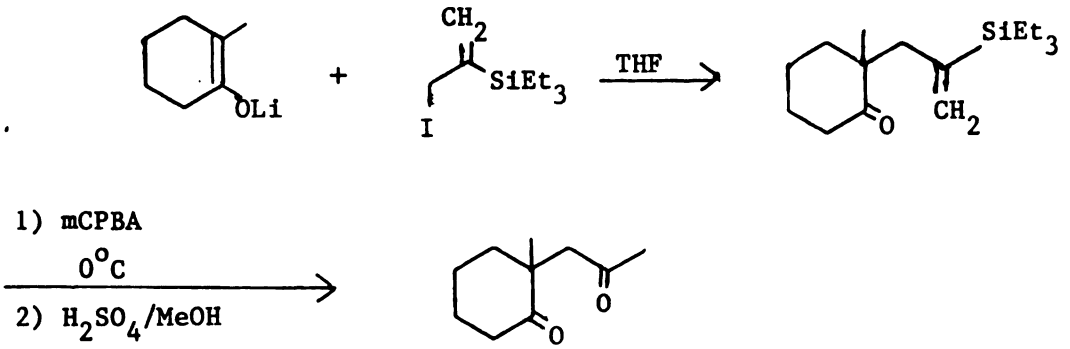


(9)

Stork and Jung[11] reacted 3-iodo-2-triethylsilyl-1-propene with enolates to give the corresponding alkylation product which was converted to a 1,4-diketone (Eq 10).

Jacobson and coworkers[12] have developed a procedure to synthesize 1,4-diketones from lithioenamines and 2-methoxyallyl bromide (Eq 11). The inconvenient synthesis required to prepare 2-methoxyallyl bromide represents the major disadvantage of this method. Conventional methods of preparing enol ethers from ketones give only minor amounts of the desired regioisomer (Eq 12). A pyrolytic cracking procedure was employed



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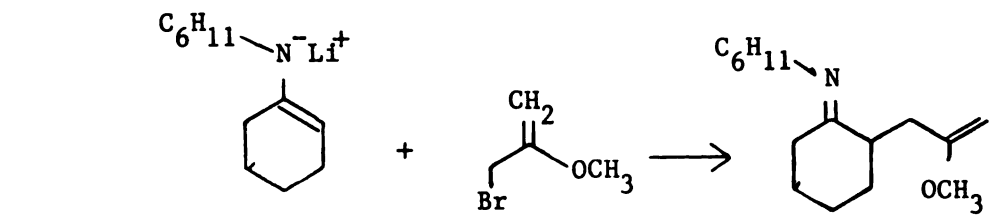

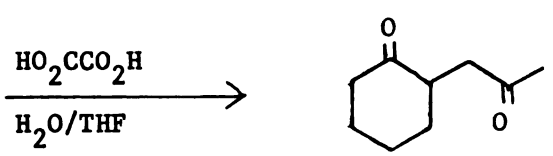

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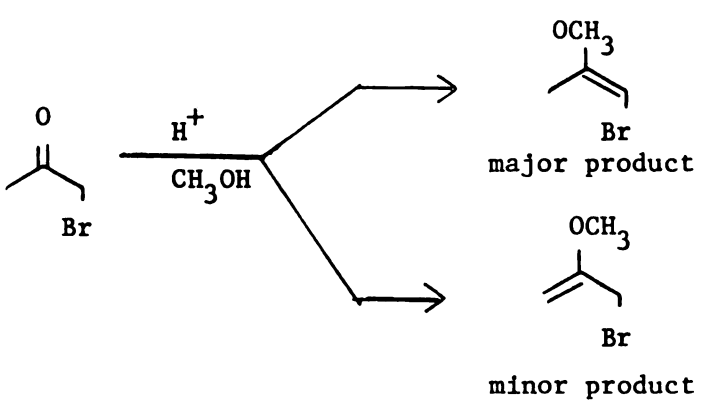
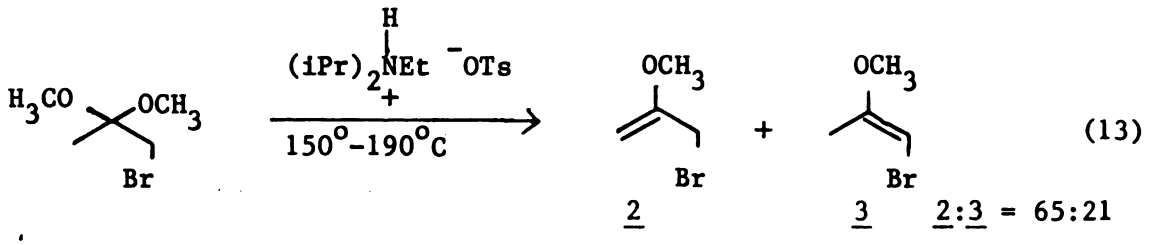


(12)

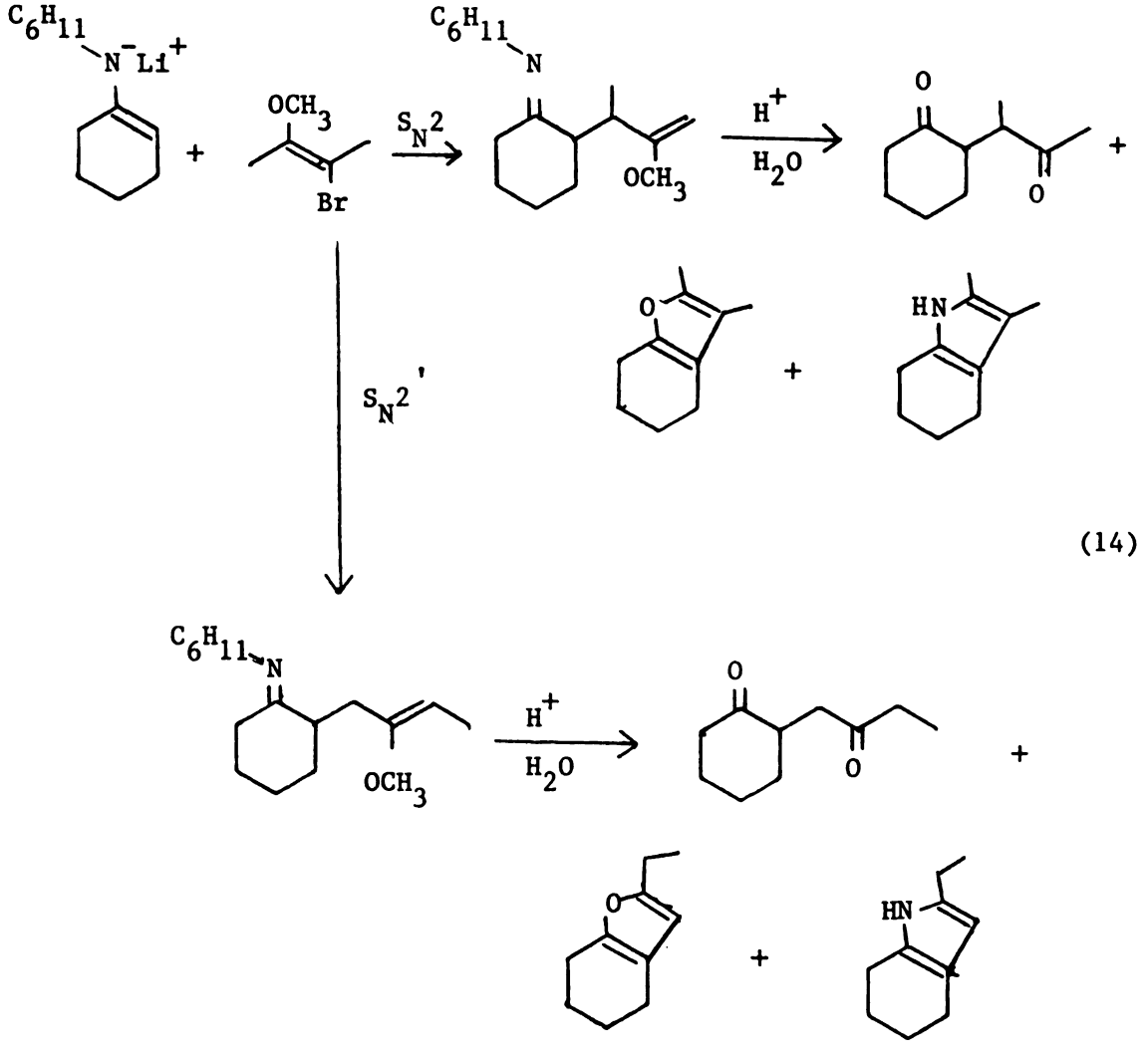
to synthesize the desired vinyl ether (Eq 13). This procedure is not only time consuming but it is also restricted to relatively small scale preparations of 2-methoxyallyl bromide.



(13)

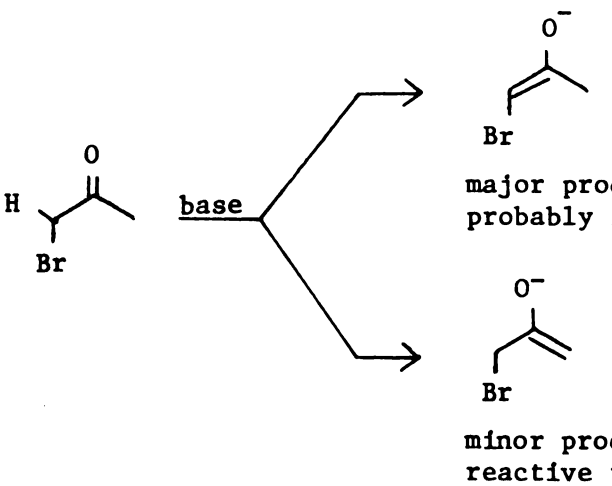
2 3 2:3 = 65:21

An additional difficulty was encountered when the sequence was attempted with 3-bromo-2-methoxy-1-butene (prepared from 3-bromo-2,2-dimethoxybutane)[13]. Here a mixture of S_N2 and S_N2' products were obtained in an approximate ratio of 4:1 (Eq 14). Also, hydrolysis of the intermediate alkylation product sometimes gave a mixture of the 1,4-diketone and the corresponding furan and pyrrole (Eq 14).[13]



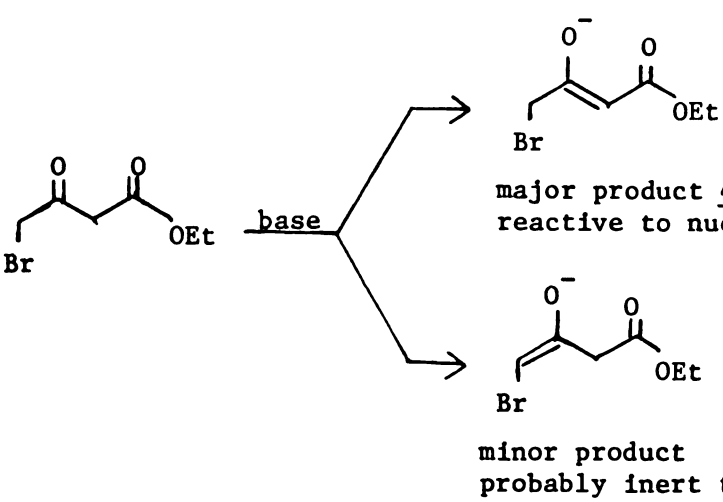
(14)

A simpler method of protecting the carbonyl group of an α-haloketone is conversion of the carbonyl function to the enolate. The appreciably greater acidity of the α-hydrogens (compared to the α^1-hydrogens) of α-haloketones is a serious obstacle to direct application of this approach (Eq 15). However, γ-halo-β-ketoesters should give the desired enolate



(15)

because of the increased acidity of the α^1-hydrogens (Eq 16). Alkylation of 4 with enolates followed by decarboxylation should give a 1,4-diketone (Eq 17).



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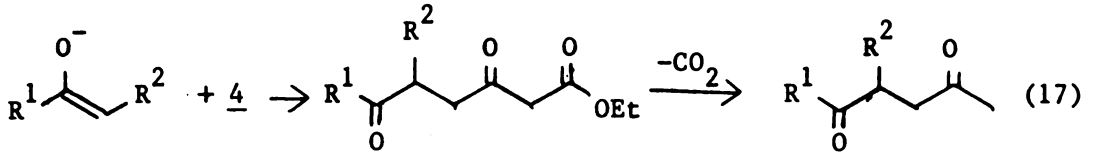
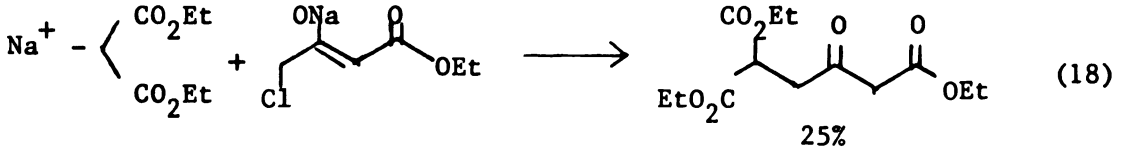


(17)

Kato[14] has reported the reaction of ethyl-4-halo-acetoacetate enolates with the enolates of diethyl malonate (Eq 18) and methyl cyanoacetate (Eq 19). However, the reaction of a simple ketone enolate (as shown in Eq 20) or ester enolate (as shown in Eq 21) with the enolate of a γ-halo-β-ketoester has never been reported.



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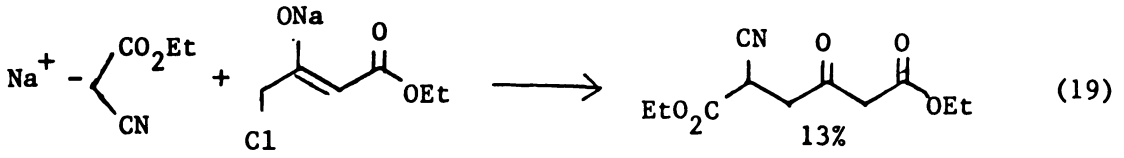

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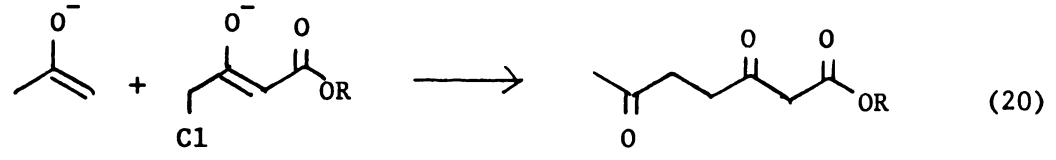

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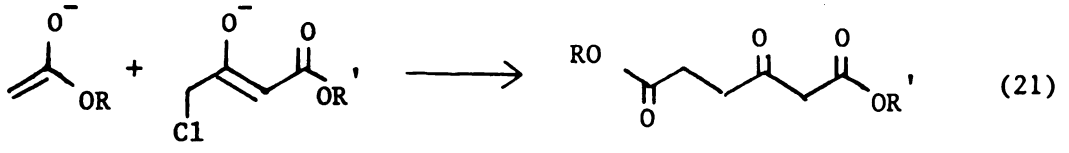


(21)

We began our survey of routes to 1,4-diketones with a brief study of the direct alkylation of ketone enolates with α-chloroacetone (Eq 22).

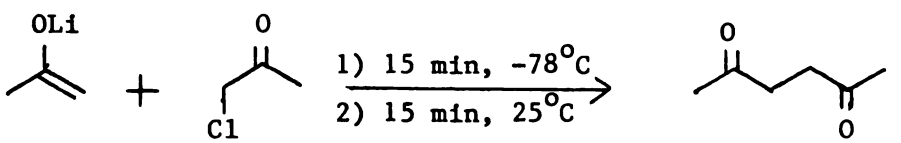
(22)

After this brief study, we turned our attention to the reaction of ketone enolates with γ-chloro-β-ketoesters.

Results

Reactions of Ketone Enolates with α-Chloroacetone

An equivalent of chloroacetone was reacted with an amine-free tetrahydrofuran (THF) solution of lithio acetone at -78°C (Eq 23). GLC



(23)

analysis established an 11.7% yield of 2,5-hexadione. The reaction was repeated in the presence of 0.1 equivalents of dilithium tetrachlorocuprate (Li_2CuCl_4) and in the presence of 1.1 equivalents of triethylborane. The yields of 2,5-hexadione were found to be 13.9% and 5.6% respectively. Under all conditions the reaction mixture turned red immediately after the chloroacetone was added.

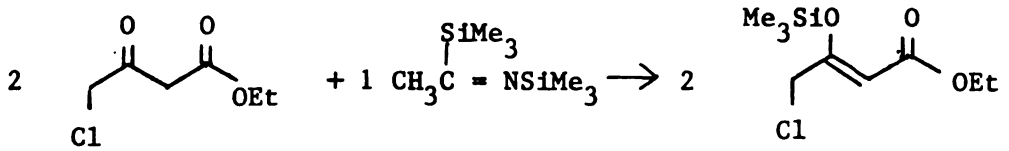
Potassio acetone was prepared by addition of one equivalent of potassium hydride to a THF solution of acetone. An equivalent of chloroacetone was added (the reaction mixture turned red) and analysis

revealed no 2,5-hexadione had formed. The reaction was repeated in the presence of 1.1 equivalents of triethylborane and analysis revealed a 0.75% yield of 2,5-hexadione.

Inverse formation of potassio acetone, i.e. addition of acetone to a suspension of KH in THF, followed by reaction with chloroacetone in the presence of 1.1 equivalents of triethylborane gave only trace amounts (<1%) of 2,5-hexadione.

Reactions of Ketone Enolates with γ-Halo-β-Ketoesters

We next studied reactions of enolates with γ-halo-β-ketoester derivatives. The first substrate chosen was the trimethylsilyl enol ether of ethyl-4-chloroacetoacetate (5) which was prepared from ethyl-4-chloroacetoacetate and bis-trimethylsilyl acetamide in 51.5% isolated yield (Eq 24).



(24)

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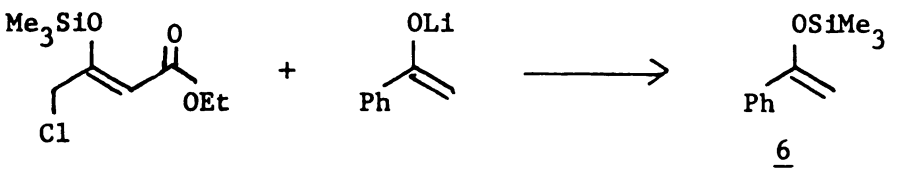
One equivalent of 5 was added to a THF solution of lithio acetophenone at -78°C (Eq 25). GLC analysis revealed one new component which

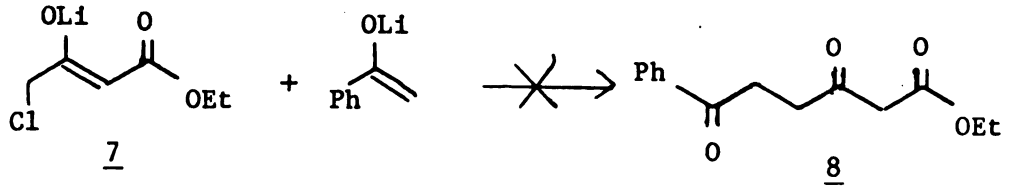


(25)

6

was identified as the trimethylsilyl enol ether of acetophenone (6). The reaction was repeated with amine-free lithio acetophenone with the same results.

The next substrate chosen was lithio ethyl-4-chloroacetoacetate (7). The reaction of lithio acetophenone with 7 (Eq 26) failed to give any alkylation product (8) whether 7 was prepared *in situ* or the enolates

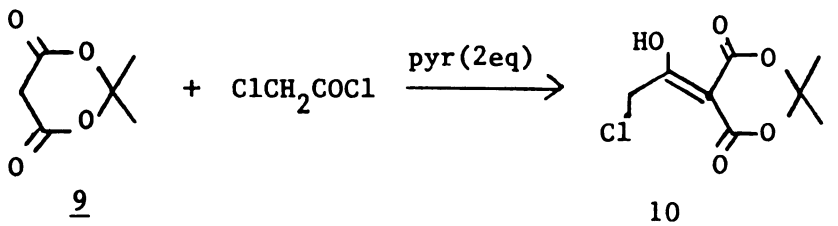


(26)

were prepared separately and then allowed to react.

The copper II and nickel II enolates of ethyl-4-chloroacetoacetate were prepared. Both enolates failed to give any alkylation product when reacted with one equivalent of lithio acetophenone.

We next attempted to activate the α-chloroketo compound by incorporating it with Meldrum's acid (9). The desired compound, chloroacetyl Meldrum's acid (10), was prepared in 99.2% isolated yield by the reaction of chloroacetyl chloride with Meldrum's acid (9) in the presence of 2.0 equivalents of pyridine (Eq 27). The reaction of lithio chloroacetyl Meldrum's acid (11) with lithio acetophenone (Eq 28) failed to give any alkylation product under a variety of conditions.



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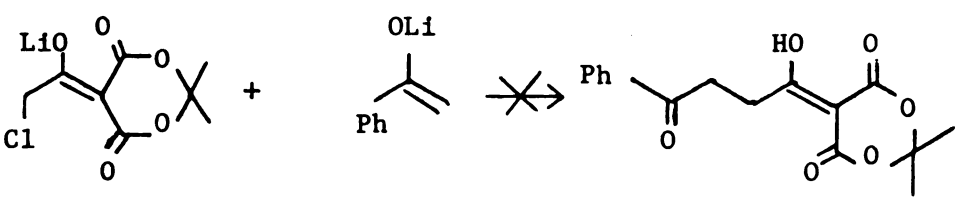
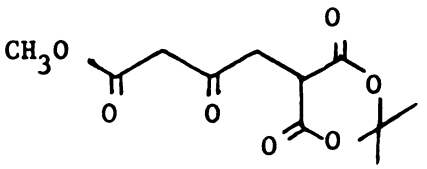


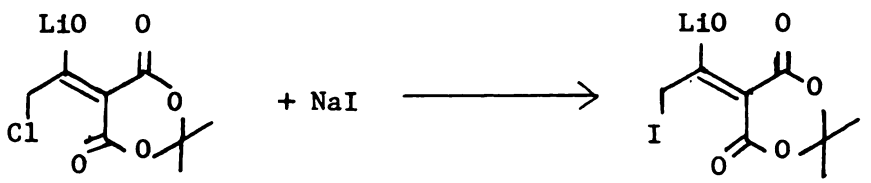
(28)

We next reacted an ester enolate with 11. One equivalent of lithio methyl acetate was added to a THF solution of 11. After work-up, methyl-4-Meldrum's acid acetoacetate (12) was isolated in 83% yield. The same



12

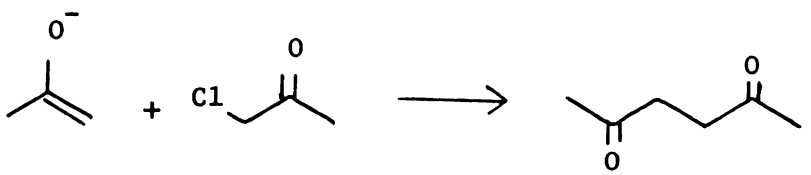
product was formed with bromoacetyl Meldrum's acid in place of chloroacetyl Meldrum's acid. Reaction of lithio methyl acetate with lithio iodoacetyl Meldrum's acid (prepared from 11 and sodium iodide, Eq 29) failed to give any alkylation product.



(29)

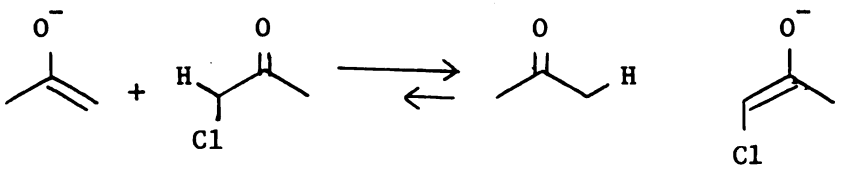
Discussion

We began our survey of routes to 1,4-diketones with a brief study of the direct alkylation of ketone enolates with chloroacetone (Eq 30). We



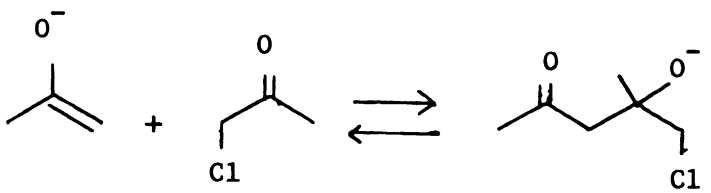
(30)

expected two difficulties with this reaction; proton exchange (Eq 31) and condensation of the ketone enolate with chloroacetone (Eq 32). It is clear that in order to maximize the yield of the 1,4-diketone (Eq 30), the rates of the two competing reactions (Eq 31 and 32) must be decreased as much as possible.



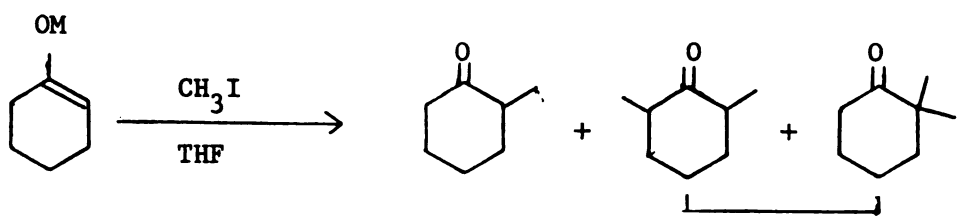
(31)

$pK_a \approx 17$ $pK_a \approx 20$



(32)

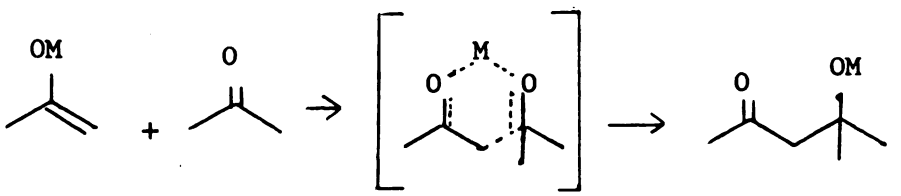
It has been shown that the use of enolates containing highly covalent metal-oxygen bonds decreases the rate of proton exchange. For example, lithium forms tighter metal-oxygen bonds than sodium or potassium, and lithium enolates have been shown to reduce the extent of polyalkylation, which is a result of proton exchange[15,16] (Eq 33).



(33)

M =		
Na	50%	22%
Li	72%	7%

While the use of enolates containing covalent metal-oxygen bonds decreases the rate of proton exchange (Eq 33), the use of an enolate with a non-coordinating metal may decrease the rate of the condensation reaction (Eq 32). Aldol type condensations are thought to occur via a transition state in which the metal functions as a bidentate ligand coordinating to the oxygen atoms[17] (Eq 34). The use of a non-coordi-

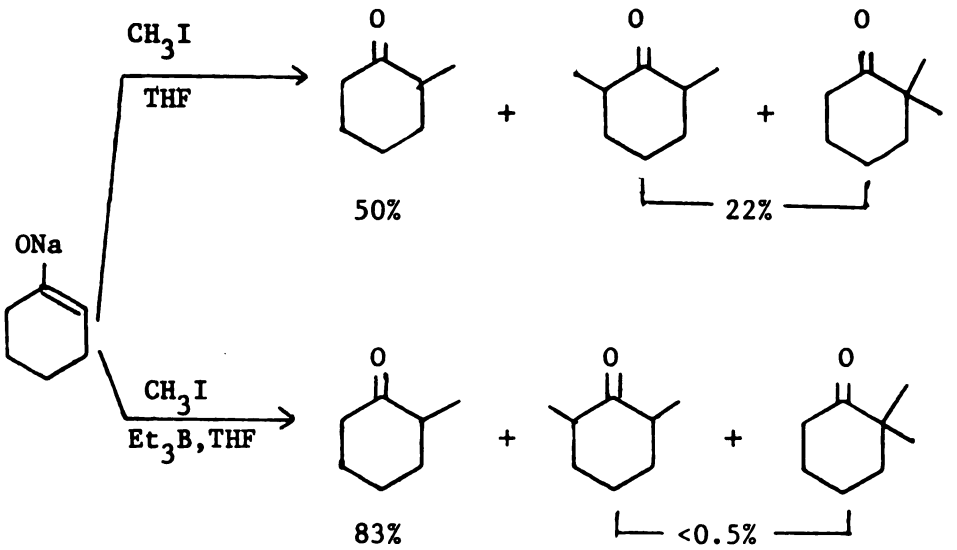


(34)

nating metal (i.e. potassium) would lower the stability of the transition state and thus decrease the rate of the condensation reaction (Eq 32).

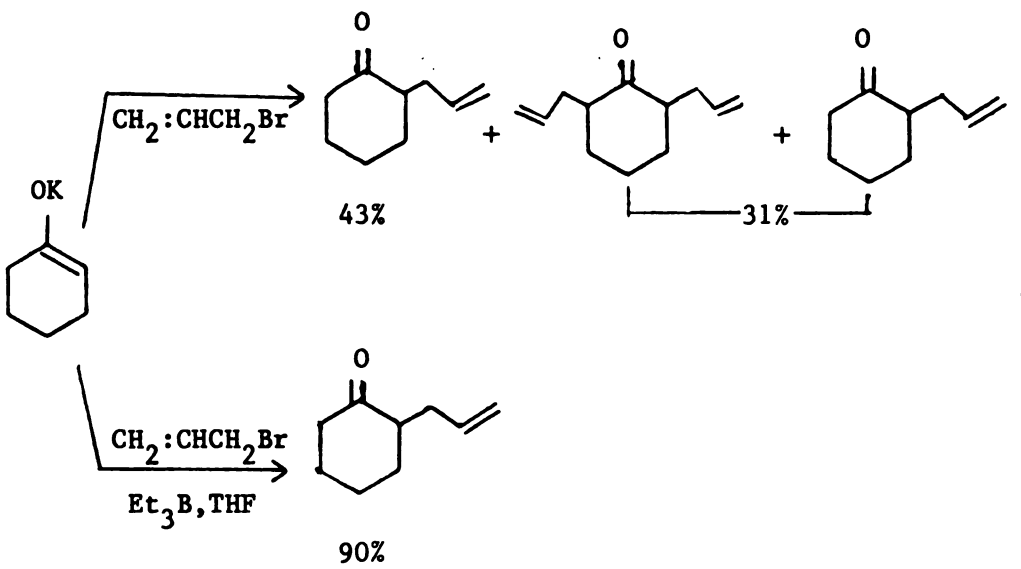
We studied the reaction of chloroacetone with both the lithium and potassium enolates of acetone. Use of the lithium enolate should decrease the rate of proton exchange (Eq 31) while the use of the potassium enolate should decrease the rate of condensation (Eq 32). Chloroacetone reacted with lithio acetone to give an 11.7% yield of 2,5-hexadione. The reaction of potassio acetone with chloroacetone gave no alkylation product. This may be due to an increase in the rate of proton exchange between potassio acetone and chloroacetone.

Lindert[16] has reported that triethylborane serves as an effective additive to decrease polyalkylation in the reaction of the sodium enolate of cyclohexanone with methyl iodide (Eq 35). Later Negishi[18] reported



(35)

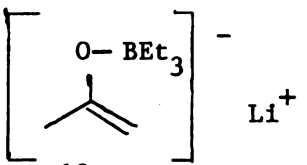
that addition of triethylborane to potassium enolates also serves to decrease polyalkylation (Eq 36). It is thought that triethylborane



(36)

functions by coordinating to the ketone enolate giving an enolate with increased selectivity for alkylation verses proton exchange. We considered that addition of triethylborane to the reaction of lithio acetone and chloroacetone would decrease the rate of proton exchange; however,

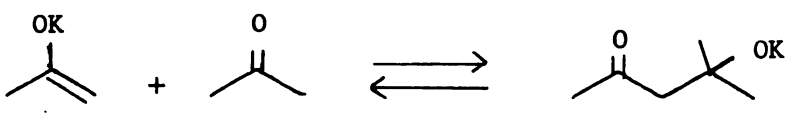
when the reaction was carried out in the presence of 1.1 equivalents of triethylborane, 2,5-hexadione was produced in only 5.6% yield. The fact that triethylborane did not increase the yield of the alkylation product is not surprising in that Negishi has reported that triethylborane does not coordinate to lithium enolates[19]. Thus, although triethylborane is present in the reaction mixture, the reative species is lithio acetone, not the triethylborane complex 13. The reaction of potassio acetone with



13

chloroacetone in the presence of 1.1 equivalents of triethylborane gave 2,5-hexadione in 0.75% yield.

The potassium enolates used in the experiments described above were prepared by addition of potassium hydride to a THF solution of acetone. This method has the disadvantage that as the potassium hydride is initially added, a small amount of potassio acetone is in the presence of a large amount of unreacted acetone and a condensation reaction could result (Eq 37). This problem could be avoided if the enolate is formed



(37)

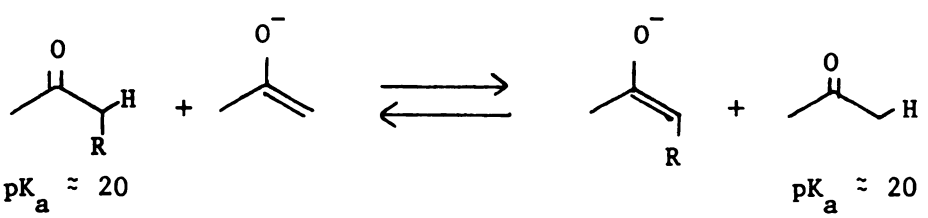
by inverse addition, i.e. addition of acetone to a solution of potassium hydride. However, when potassio acetone formed by inverse addition was reacted with chloroacetone in the presence of 1.1 equivalents of triethylborane only a trace amount of 2,5-hexadione was formed.

Kochi[20] has reported dilithium tetrachlorocuprate (Li_2CuCl_4) catalyzes the cross coupling of Grignard reagents and alkyl bromides (Eq 38).

$$R - MgX + R^1\text{-}Br \xrightarrow[THF]{Li_2CuCl_4} R\text{-}R^1 \qquad (38)$$

We considered the use of Li_2CuCl_4 would also catalyze the reaction of an enolate with a α-chloroketone. However, the reaction of lithio acetone with chloroacetone in the presence of 10% Li_2CuCl_4 gave 2,5-hexadione in essentially the same yield as the reaction carried out in the absence of Li_2CuCl_4.

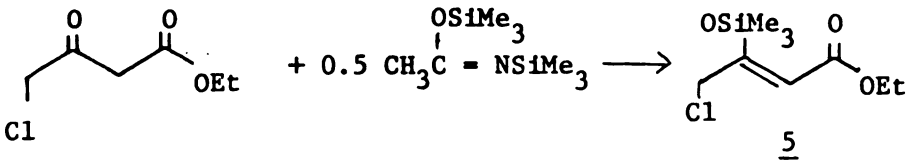
Although triethylborane inhibits proton exchange between acids with similar pK_a's (Eq 39), this additive may be unable to inhibit proton



(39)

exchange between acids with significantly different pK_a's (Eq 31). Protection of the carbonyl function of the α-haloketone would prevent both the proton exchange (Eq 31) and condensation (Eq 32) side reactions.

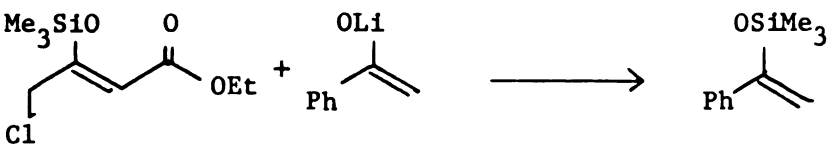
We decided to protect the carbonyl carbon of the α-haloketone as its silyl enol ether. The substrate chosen was the trimethylsilyl enol ether of ethyl-4-chloroacetoacetate (5). This previously unreported compound was prepared in 51.5% yield from ethyl-4-chloroacetoacetate and bis-trimethylsilyl acetamide (Eq 40). Reaction of 5 with one equivalent of



(40)

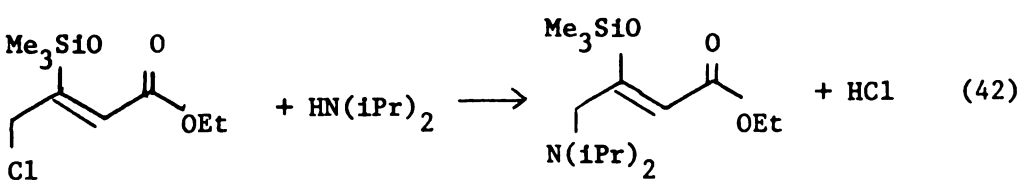
5

lithio acetophenone resulted in the transfer of the trimethylsilyl group from the ketoester to the ketone (Eq 41). One factor that may account



(41)

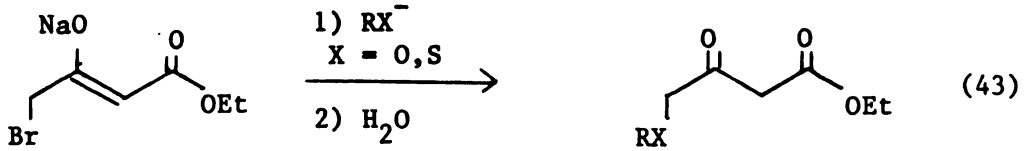
for this transfer is that the diisopropylamine present from the formation of the lithio acetophenone may react with 5 at the γ-carbon and thus prevent any further reaction at this site (Eq 42). In order to prevent



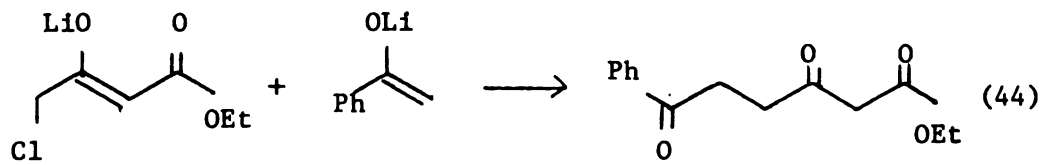
(42)

this reaction, the amine-free enolate of acetophenone was prepared and reacted with 5; however, the trimethylsilyl enol ether of acetophenone was again produced.

Kellogg and Troostwijk[21] have reported the alkylation of the sodium enolate of ethyl-4-bromoacetoacetate with various sulfur and oxygen nucleophiles (Eq 43). In this reaction the carbonyl function of the α-haloketone is protected as its enolate. We attempted to extend this method to the preparation of 1,4-diketones by reacting the lithium enolate of ethyl-4-chloroacetoacetate with lithio acetophenone (Eq 44);



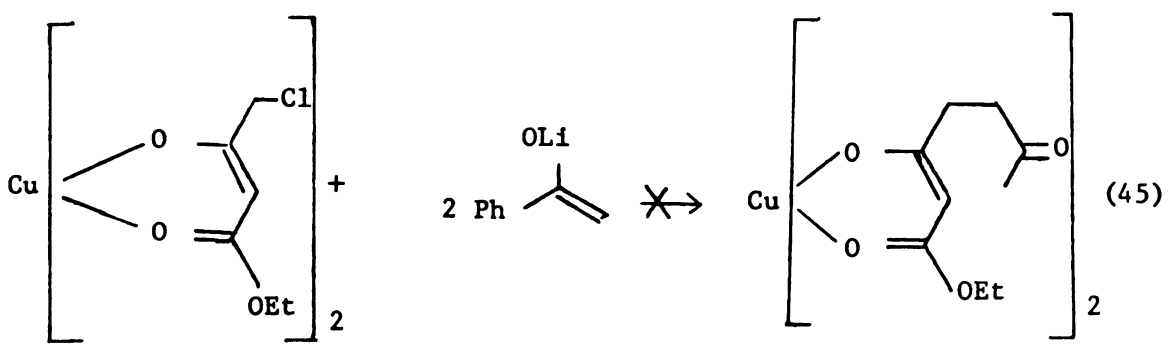
(43)



(44)

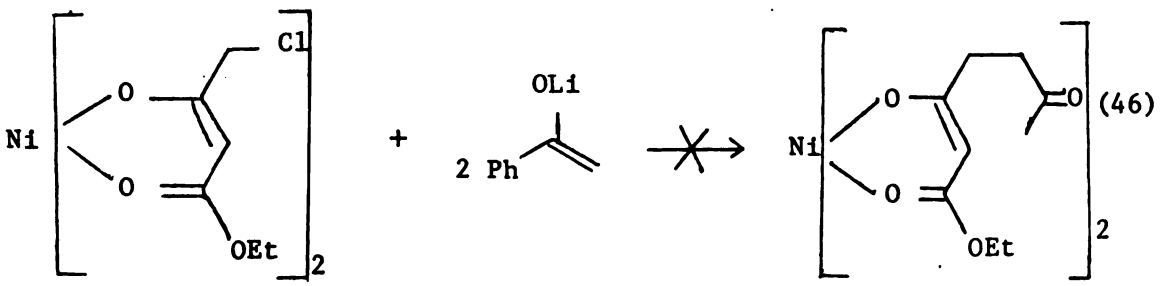
however, the reaction failed to give any alkylation product under a variety of conditions.

We next prepared the copper II enolate of ethyl-4-chloroacetoacetate and reacted it with lithio acetophenone (Eq 45) with the expectation



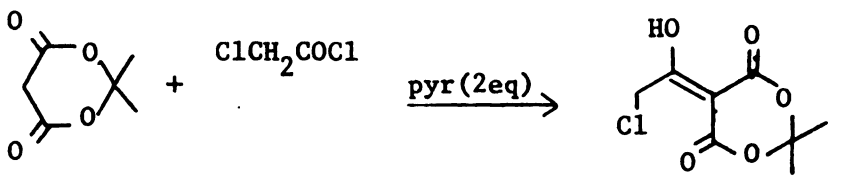
(45)

that the copper II enolate would be more reactive than the lithium enolate. However, the reaction failed to give any alkylation product. Use of the nickel II enolate also failed to give any alkylation product (Eq 46).



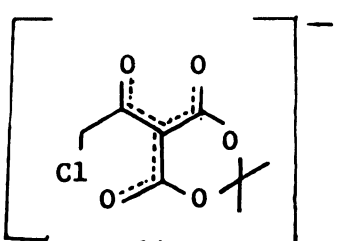
(46)

Chloroacetyl Meldrum's acid (10) was prepared in essentially quantitative yield from Meldrum's acid (9) and chloroacetyl chloride (Eq 47).

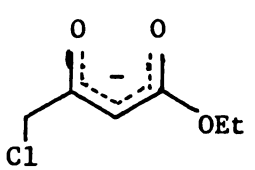


(47)

We suspected that the carbon containing the chlorine in the enolate of chloroacetyl Meldrum's acid (14) would be more susceptible towards nucleophilic attack by enolates than was carbon 4 in the enolate of ethyl-4-chloroacetoacetate (15) because of 14's higher degree of delocalization. Reaction of 14 with an enolate should give 16; which after

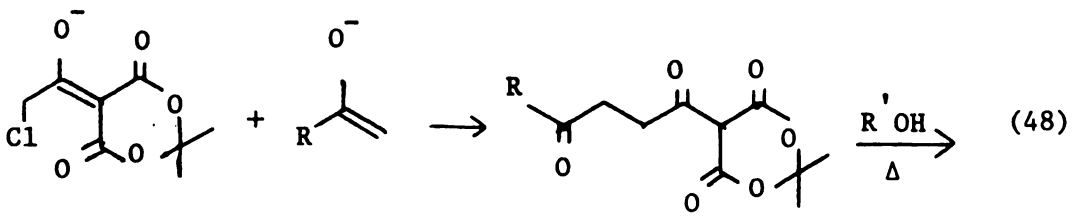


14



15

cleavage of the Meldrum's acid ring by alkoholysis[22] followed by decarboxylation, should give the 1,4-diketone 17 (Eq 48). However, the



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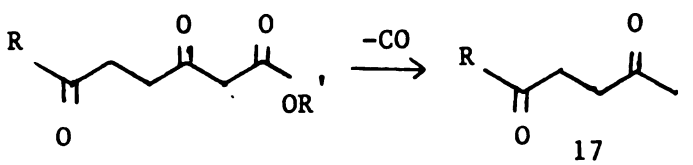
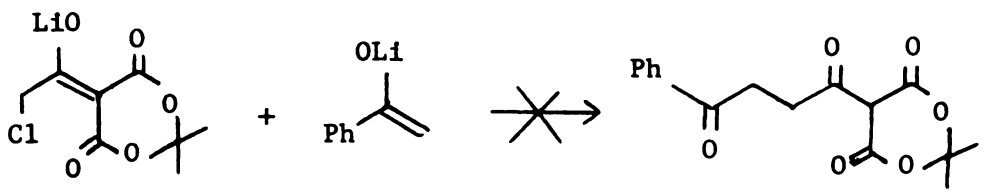


17

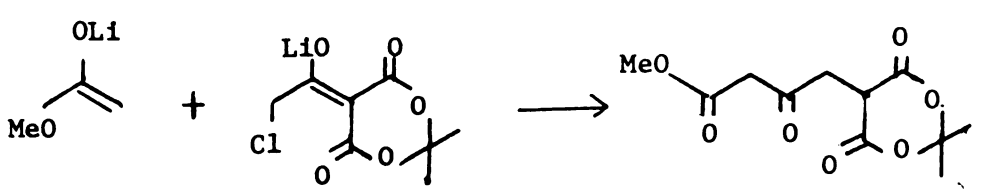
reaction of lithio acetophenone with lithio chloroacetyl Meldrum's acid (18) failed to give any alkylation product under a variety of conditions (Eq 49).



(49)

18

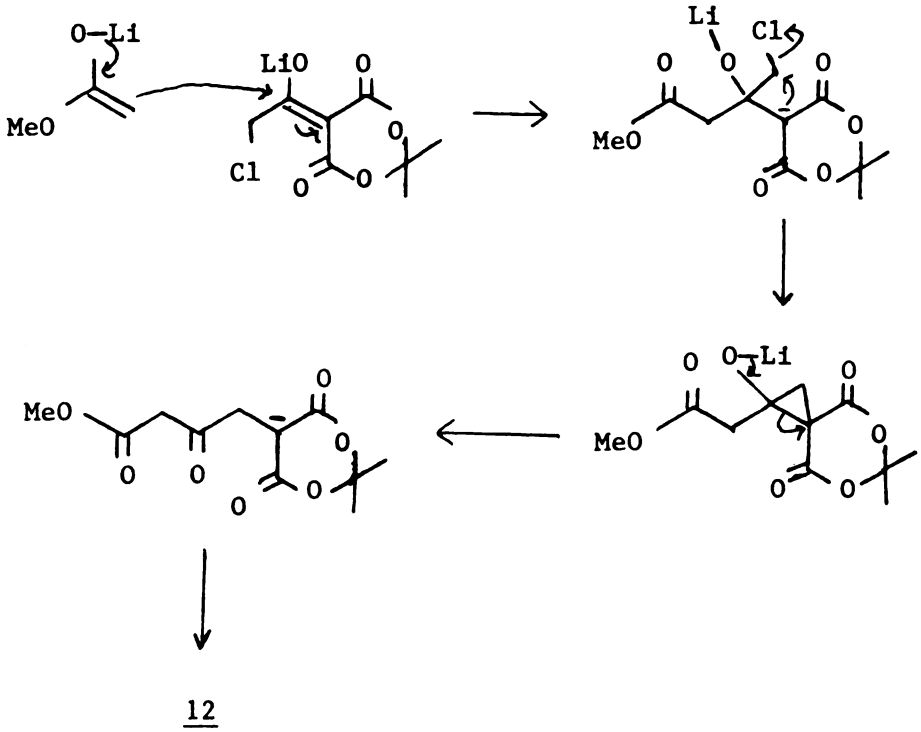
We next decided to try reacting an ester enolate with 18. Ester enolates were chosen because of their increased reactivity over ketone enolates towards alkylation. Reaction of lithio methyl acetate with 18 gave methyl-4-Meldrum's acid acetoacetate (12) in 85% yield (Eq 50).



(50)

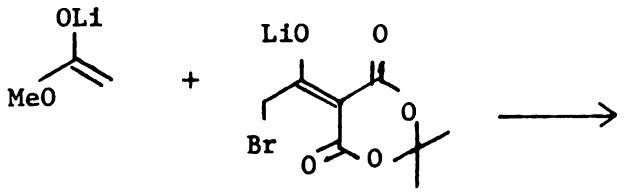
18 12

This product may arise by addition of lithio methyl acetate to the double bond in 18 followed by a Favorskii rearrangement (Eq 51). We changed the



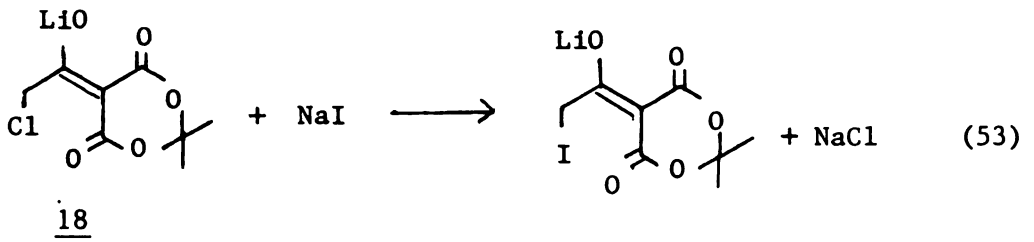
(51)

halogen from chlorine to bromine with the expectation that by making the terminal carbon more electrophilic the lithio methyl acetate would alkylate at that position rather than add to the double bond. However, reaction of lithio methyl acetate with lithio bromoacetyl Meldrum's acid also gave 12 (Eq 52, yield undetermined).



(52)

Finally, we prepared lithio iodoacetyl Meldrum's acid (19) from 18 and sodium iodide (Eq 53). The brown precipitate that formed during the



18 (53)

reaction was isolated and solubility tests showed the precipitate to be sodium chloride, indicating that 19 had been formed. Reaction of 19 (prior to the separation of NaCl) with lithio methyl acetate failed to give any alkylation product. This may have been due to the high salt concentration present in the reaction mixture.

Experimental

I. Materials

n-Butyllithium, Aldrich, was purchased as a 1.6 M hexane solution and standardized by the method of Watson and Eastham[24]. The commercially available compounds diisopropyl ketone, diisopropylamine, chloroacetone, acetone, pyridine, acetophenone, and methyl acetate were distilled from calcium hydride and stored under argon. Tetrahydrofuran (THF) was distilled from sodium and benzophenone and stored under argon. Ethyl-4-chloroacetoacetate, chloroacetyl chloride, and bromoacetyl bromide were purchased from Aldrich and used without further purification. Triethylborane was purchased from Gallery and handled under argon. Meldrum's acid was prepared from malonic acid, acetic anhydride, and

acetone by the method of Davidson and Bernhard[25]. Bis-trimethylsilyl acetamide was prepared from acetamide and chlorotrimethylsilane by the method of Kelbe, Finkeiner, and White[26]. Potassium hydride was purchased as a 24.7% dispersion in oil.

II. Reaction of Lithium Enolates with Chloroacetone

A. Preparation of Lithium Diisopropylamide (LDA)

A 25 ml round-bottomed flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was flushed with argon, immersed in an ice bath, and charged with 3.13 ml (5.0 mmol) 1.6 M n-butyllithium solution and 3.2 ml n-pentane. Stirring was initiated and 0.70 ml (5.0 mmol) diisopropylamine was added dropwise. The ice bath was removed and the mixture was stirred for five minutes. The solvent was removed under vacuum to yield LDA as a white powder.

B. Reaction of Amine-Free Lithio Acetone with Chloroacetone

The following procedure is representative of the preparation of an amine-free lithium enolate solution: LDA (5.0 mmol), prepared as previously described, was dissolved in 5.0 ml THF and cooled to 0°C. Acetone (0.37 ml; 5.0 mmol) was added dropwise and stirred for 15 minutes. The ice bath was removed and the solvent and amine were evaporated under vacuum. After most of the solvent and amine had been evaporated, a warm (approximately 40°C) water bath was placed under the reaction flask and the remaining solvent and amine were evaporated, leaving the lithium ketone enolate as a white powder. The enolate was dissolved in 5.0 ml THF and cooled to -78°C in a Dry Ice/acetone bath. Stirring was initiated and 0.45 ml (5.0 mmol) chloroacetone was added

over a period of approximately 2 minutes. The reaction was stirred for 15 minutes at -78°C, the cooling bath was removed, and the reaction was stirred for an additional 20 minutes. As the reaction mixture warmed, the color of the mixture turned dark red. n-Tridecane was added as an internal GLC standard. The reaction was quenched with 2.0 ml H_2O and the organic phase analyzed by GLC (carbowax 20 M on Chromosorb W, column temperature 125°C). 2,5-Hexadione was observed in 11.7% yield.

C. Preparation of Dilithium Tetrachlorocuprate (Li_2CuCl_4) Solution

A 1.0 M THF solution of Li_2CuCl_4 was prepared from lithium chloride and copper (II)-chloride as described by Kochi[27].

D. Reaction of Lithio Acetone with Chloroacetone in the Presence of 10% Li_2CuCl_4

A 1.1 M THF solution (4.5 ml; 5.0 mmol) of amine-free lithio acetone was prepared at -78°C as previously described. To this solution was added 0.5 ml (0.5 mmol) 1.0 M THF solution of Li_2CuCl_4 giving a dark green solution. Chloroacetone (0.45 ml; 5.0 mmol) was slowly added and the reaction was stirred for 1 hour at -78°C (the color of the reaction mixture was reddish-brown). The cooling bath was removed and the reaction was stirred for an additional 15 minutes. The reaction was worked up and analyzed as previously described. 2,5-Hexadione was observed in 13.9% yield.

E. Reaction of Lithio Acetone with Chloroacetone in the Presence of Triethylborane

A 1.0 M THF solution (5.0 ml; 5.0 mmol) of amine-free lithio acetone was prepared at 0°C as previously described. Triethylborane (0.77 ml; 5.5 mmol) was added and the reaction was stirred for 10 minutes

at 0°C. Chloroacetone (0.45 ml; 5.0 mmol) was slowly added (reaction mixture turned red) and the reaction was stirred for 15 minutes at 0°C. The cooling bath was removed and the reaction was stirred for an additional 15 minutes. n-Tetradecane was added as an internal standard. The reaction was quenched with 1.85 ml (5.55 mmol) 3 N NaOH, cooled to 0°C, and 1.85 ml (5.55 mmol) 30% H_2O_2 was slowly added. The organic phase was analyzed by GLC. 2,5-Hexadione was observed in 5.6% yield.

III. Reaction of Potassium Enolates with Chloroacetone

A. Standardization of KH

A 25 ml round-bottomed flask equipped with septum inlet, magnetic stirrer, and a gas buret was charged with 10.0 ml of acetone. KH (1.00 ml; 24.7% in oil) was added dropwise and the gas evolution was measured by the gas buret. 147.5 ml (6.15 mmol) of gas was evolved per 1.00 ml KH.

B. Reaction of Potassio Acetone with Chloroacetone

The following procedure is representative of the preparation of potassium enolate solutions: a 25 ml round-bottomed flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was flushed with argon, immersed in an ice bath, and charged with 0.37 ml (5.0 mmol) acetone and 5.0 ml THF. Stirring was initiated and 0.81 ml (5.0 mmol) 6.15 M KH was slowly added over approximately 1 minute. Chloroacetone (0.45 ml; 5.0 mmol) was slowly added (the reaction mixture turned dark red) and the reaction was stirred 15 minutes at 0°C. The cooling bath was removed and the reaction was stirred for an additional 15 minutes. GLC analysis showed no 2,5-hexadione had formed.

C. Reaction of Potassio Acetone with Chloroacetone in the Presence of Triethylborane

A 1.0 M THF solution (5.0 ml; 5.0 mmol) of potassio acetone was prepared at 0°C as previously described. Triethylborane (0.77 ml; 5.5 mmol) was added and the reaction was stirred for 5 minutes. Chloroacetone (0.45 ml; 5.0 mmol) was slowly added and the reaction was stirred for 15 minutes at 0°C. The cooling bath was removed and the reaction was stirred for an additional 15 minutes. 2,5-Hexadione was observed in 0.75% GLC yield.

D. Inverse Formation of Potassio Acetone and Its Reaction with Chloroacetone in the Presence of Triethylborane

The procedure previously described was followed except that the potassio acetone was prepared by slow addition of 0.37 ml (5.0 mmol) acetone to a suspension of 0.81 ml (5.0 ml) 24.7% KH in 5.0 ml THF at 0°C. GLC analysis revealed a trace (<1%) of 2,5-hexadione.

IV. Reaction of Ethyl-4-Chloroacetoacetate Derivatives with Lithio Acetophenone

A. Preparation of 5

A 250 ml round-bottomed flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was purged with argon, immersed in an ice bath, and charged with 100 ml n-pentane and 13.5 ml (100 mmol) ethyl-4-chloroacetoacetate. Bis-trimethylsilyl acetamide (12.8 ml; 50 mmol) was added and the ice bath was removed. A white precipitate formed after approximately 5 minutes. The reaction was stirred for 30 minutes, filtered, and the solvent removed from the filtrate under vacuum. The

yellow liquid residue was distilled (70°-72°C, 6.5 mm mercury) yielding 11.88 g (51.5 mmol; 51.5% yield) of 5.

B. Product Analysis

GLC analyses were performed on a Varian Model 920 gas chromatograph equipped with an 8 ft. x 0.25 in. stainless steel column packed with 3% SE-30 on Chromosorb G. ^{1}H NMR spectra were determined on a Varian T-60 using tetramethylsilane as an internal standard. Mass spectra were taken with a Finnigan 4000 with INCOS data system.

^{1}H NMR ($CDCl_3$): δ 0.4 (s, 9H), δ 1.3 (t, 3H); δ 4.2 (q, 2H); δ 4.5 (s, 2H); δ 5.1 (s, 1H)

C. Reaction of 5 with Lithio Acetophenone

The following procedure is representative of the preparation of a lithium enolate solution: LDA (5.0 mmol), prepared as previously described, was dissolved in 5.0 ml THF and cooled to -78°C in a Dry Ice/acetone bath. Acetophenone (0.59 ml; 5.0 mmol) was added and the reaction was stirred for 15 minutes after which 1.03 ml (5.0 mmol) 5 was added. The reaction was stirred for 5 minutes at -78°C. The cooling bath was removed and the reaction was stirred for 3 hours periodically analyzing aliquots by GLC (column temperature 175°C). GLC analysis revealed one new component. The new component was GLC prepped and ^{1}H NMR analysis revealed the component to be the trimethylsilyl enol ether of acetophenone (6).

^{1}H NMR ($CDCl_3$): δ0.5 (s, 9H); δ4.5 (d, 1H); δ5.0 (d, 1H); δ7.2-7.8 (m, 5H)

D. Reaction of 5 with Amine-Free Lithio Acetophenone

Amine-free lithio acetophenone (5.0 mmol) was prepared from LDA (5.0 mmol) and acetophenone (0.59 ml; 5.0 mmol) as previously described and dissolved in THF (5.0 ml) at -78°C. Compound 5 (1.03 ml; 5.0 mmol) was added and the reaction was stirred for 5 minutes at -78°C. The cooling bath was removed and the reaction was followed by GLC. Analysis revealed the formation of 6.

E. Reaction of 7 with Lithio Acetophenone

A 1.0 M THF solution (5.0 ml; 5.0 mmol) of lithio acetophenone was prepared at -78°C as previously described. A THF solution of 7 was prepared as follows: a 25 ml round-bottomed flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was purged with argon, immersed in a Dry Ice/acetone bath, and charged with 5.0 ml THF and 0.68 ml (5.0 mmol) ethyl-4-chloroacetoacetate. n-Butyllithium (3.13 ml; 1.6 M in pentane; 5.0 mmol) was added and the reaction was stirred for 15 minutes. The ester enolate solution was transferred to the ketone enolate solution and the reaction was stirred for 15 minutes at -78°C. The cooling bath was removed and the reaction was stirred for 30 minutes. The reaction was quenched with 7.5 ml 2 M aqueous HCl solution, the organic phase was separated, dried ($MgSO_4$), filtered, and concentrated under vacuum. Analysis by ^{1}H NMR revealed acetophenone and ethyl-4-chloroacetoacetate.

F. Reaction of Lithio Acetophenone with 7 Prepared In Situ

LDA (10.0 mmol) was prepared as previously described, dissolved in THF (5.0 ml), and cooled to -78°C with a Dry Ice/acetone bath. Acetophenone (0.59 ml; 5.0 mmol) was added and the reaction was stirred for 15 minutes at -78°C. Ethyl-4-chloroacetoacetate (0.68 ml; 5.0 mmol) was added and the reaction was stirred for 15 minutes at -78°C. The cooling bath was removed and the reaction was stirred overnight. Cupric acetate (0.50 g) was added forming a green precipitate. The reaction mixture was filtered and the filtrate was concentrated under vacuum. Analysis by ^{1}H NMR revealed only starting materials.

G. Reaction of Ethyl-4-Chloroacetoacetate with 2.0 Equivalents of Lithio Acetophenone

A 1.0 M THF solution (10.0 ml; 10.0 mmol) of lithio acetophenone was prepared at -78°C as previously described. Ethyl-4-chloroacetoacetate (0.68 ml; 5.0 mmol) was added and the reaction was stirred for 15 minutes at -78°C. The cooling bath was removed and the reaction was stirred for 3 hours and concentrated under vacuum. The reaction was quenched with 10.0 ml 2 M HCl, extracted with diethyl ether, the organic phase dried ($MgSO_4$), filtered, and concentrated under vacuum. Analysis by ^{1}H NMR revealed only starting materials.

H. Preparation of Copper II Complex of Ethyl-4-Chloroacetoacetate

A 100 ml Erlenmeyer flask equipped with a magnetic stirrer was charged with 50 ml H_2O and 2.00 g (10.0 mmol) $Cu(OAc)_2 \cdot H_2O$ giving a blue solution. Ethyl-4-chloroacetoacetate (2.70 ml; 20 mmol) was added and the solution was stirred for 15 minutes forming a green precipitate. The

mixture was filtered, the green precipitate was washed with diethyl ether, and dried in a vacuum dessicator yielding 2.74 g (7.01 mmol; 70.1% yield) of the copper II complex.

I. Reaction of Copper II Ethyl-4-Chloroacetoacetate with Lithio Acetophenone

A 1.0 M THF solution (10.0 ml; 10.0 mmol) of lithio acetophenone was prepared at -78°C as previously described. Copper II ethyl-4-chloroacetoacetate (1.95 g; 5.0 mmol) was added and the reaction was stirred for 15 minutes at -78°C. The cooling bath was removed and the reaction was stirred for 15 minutes. While the reaction mixture was warming, a brown precipitate formed which was filtered and washed with acetone. The brown precipitate was found to be insoluble in dilute H_2SO_4.

J. Preparation of Nickel II Complex of Ethyl-4-Chloroacetoacetate

A 100 ml Erlenmeyer flask equipped with a magnetic stirrer was charged with 50 ml H_2O and 2.49 g (10.0 mmol) $Ni(OAc)_2 \cdot 4H_2O$. One equivalent (0.40g; 10.0 mmol) NaOH was added giving a milky solution to which 2.70 ml (20.0 mmol) ethyl-4-chloroacetoacetate was added. The reaction was stirred for 5 minutes forming a green precipitate which was filtered, washed with diethyl ether, and dried in a vacuum dessicator.

K. Reaction of Nickel II Ethyl-4-Chloroacetoacetate with Lithio Acetophenone

A 1.0 M THF solution (10.0 ml; 10.0 mmol) of lithio acetophenone was prepared at -78°C as previously described. Nickel II ethyl-4-chloroacetoacetate (1.93 g; 5.0 mmol) was added and the solution was stirred for 15 minutes at -78°C. The cooling bath was removed and the

reaction was stirred overnight. The solution was filtered (a green precipitate was present) and the filtrate was concentrated under vacuum. ^{1}H NMR analysis showed the filtrate to be acetophenone.

V. Reaction of Chloroacetyl Meldrum's Acid with Enolates

A. Preparation of Chloroacetyl Meldrum's Acid (10)

A 500 ml three neck round-bottomed flask equipped with a mechanical stirrer, addition funnel, and mercury bubbler was purged with argon and immersed in a Dry Ice/acetone bath. The flask was charged with 36.0 g (250 mmol) Meldrum's acid, 40.5 ml (500 mmol) pyridine, and 250 ml methylene chloride. Stirring was initiated and 19.9 ml (250 mmol) chloroacetyl chloride was added via the addition funnel over a period of 3 hours. The cooling bath was removed and the reaction was stirred for an additional 1.5 hours. The reaction was quenched with 250 ml 2 M HCl, the organic phase washed 2 x 100 ml 2 M HCl then 2 x 100 ml H_2O, dried ($MgSO_4$), filtered, and the solvent removed under vacuum giving 50.57 g (247 mmol; 99.2%) chloroacetyl Meldrum's acid (slightly yellow). ^{1}H NMR analysis showed 10 to be sufficiently pure to be used without further purification.

Chloroactyl Meldrum's Acid

^{1}H NMR ($CDCl_3$): δ 1.8 (s, 6H); δ 4.8 (bs, 2H); δ 15.3 (s, 1H)

B. Reaction of Lithio Chloroacetyl Meldrum's Acid (11) with Lithio Acetophenone

LDA (10.0 mmol) was prepared as previously described and dissolved in 120 ml THF at -78°C. Acetophenone (0.59 ml; 5.0 mmol) was added and the reaction was stirred for 15 minutes. Chloroacetyl

Meldrum's acid (1.10 g; 5.0 mmol) was added and the reaction was stirred 15 minutes at -78°C then 6 hours at room temperature. The reaction mixture was quenched with 7.5 ml (15 mmol) 2 M HCl, the organic phase was dried ($MgSO_4$), filtered, and concentrated under vacuum giving a brown precipitate which smelled like acetophenone. Analysis of the brown precipitate (^1H NMR) showed it to be chloroacetyl Meldrum's acid and acetophenone.

C. Reaction of 11 with Lithio Acetophenone, Amine-Free

A 1.0 M THF solution (5.0 ml; 5.0 mmol) of amine-free lithio acetophenone was prepared as previously described. A THF solution of 11 was prepared as follows: n-butyllithium (6.66 ml; 1.5 M; 5.0 mmol) was added to a THF (5.0 ml) solution of chloroacetyl Meldrum's acid (1.10 g; 5.0 mmol) at -78°C. This solution was stirred for 15 minutes at -78°C and the solvent was removed under vacuum to give 11 as a yellow solid. The solid 11 was suspended in 10.0 ml THF at -78°C and the lithio acetophenone solution was added. The cooling bath was removed and the reaction was stirred for 3 hours. The reaction was quenched with 15 ml 2 M HCl, the organic phase was dried ($MgSO_4$), filtered, and concentrated under vacuum yielding a light brown solid. ^1H NMR analysis showed the solid to be acetophenone and chloroacetyl Meldrum's acid.

The reaction was repeated with the following changes: after the lithio acetophenone was added to 11 the reaction was stirred 3 hours at -78°C and worked up without allowing the reaction to warm up. Work-up yielded a yellow solid which was recrystallized from CH_2Cl_2/n-pentane (50:50) giving a white solid. ^1H NMR analysis showed the solid to be chloroacetyl Meldrum's acid.

The reaction was repeated again with the following changes: after the two enolates were combined, the reaction was stirred 1 hour at -78°C, the cooling bath was removed, and the reaction was stirred for 1.5 hours. Acidic work-up gave a yellow oil which was shown to be acetophenone and chloroacetyl Meldrum's acid by ^{1}H NMR analysis.

D. Reaction of 11 with Lithio Methyl Acetate

A 1.0 M THF solution (52.4 ml; 52.4 mmol) of lithio methyl acetate and a 2 M THF solution (25 ml; 52.4 mmol) of 11 were prepared at -78°C as previously described. The solution of 11 was added to the lithio methyl acetate solution over a period of approximately 10 minutes. A white precipitate formed when the enolates were combined. The reaction was stirred for 15 minutes at -78°C, the cooling bath was removed, and the reaction was stirred for 3 hours. The reaction was quenched with 75 ml 2 M HCl, the organic phase was washed (2 x 50 ml 2 M HCl; 2 x 50 ml H_2O), dried ($MgSO_4$), filtered, and the solvent removed under vaccuum giving 11.22 g of a slightly yellow solid. Analysis showed the solid to be 12.

^{1}H NMR ($CDCl_3$): δ 1.8 (s, 6H), δ 3.3 (d, 2H), δ 3.5 (s, 2H), δ 3.7 (s, 3H), δ 3.8 (t, 1H)

MS: m/e 243 (M^+ - 15)

IR (nujol mull): 1710 cm^{-1} (C=O), 1730 cm^{-1} (C=O), 1760 CM^{-1} (C=O)

E. Preparation of Bromoacetyl Meldrum's Acid

Bromoacetyl Meldrum's acid was prepared from Meldrum's acid (7.20 g; 50 mmol), pyridine (8.10 ml; 100 mmol), and bromoacetyl bromide (4.57 ml; 52.5 mmol) following the procedure for the preparation of chloroacetyl Meldrum's acid. Bromoacetyl Meldrum's acid (7.07 g; 58.1% yield) was isolated as a brown solid. ^{1}H NMR analysis showed the compound to be sufficiently pure to be used without further purification.

Bromoacetyl Meldrum's Acid

^{1}H NMR ($CDCl_3$): δ1.7 (s, 6H), δ4.6 (s, 2H), δ14.8 (bs, 1H)

F. Reaction of Lithio Bromoacetyl Meldrum's Acid with Lithio Methyl Acetate

The procedure for the reaction of 11 with lithio methyl acetate was followed substituting bromoacetyl Meldrum's acid for chloroacetyl Meldrum's acid. Compound 12 was isolated as a yellow solid.

G. Preparation of Lithio Iodoacetyl Meldrum's Acid

To a 0.5 M THF solution (10 ml; 5.0 mmol) of 11 at -78°C was added a solution of 0.75 g (5.0 mmol) of NaI in 25 ml THF. The reaction was stirred for 15 minutes at -78°C, the cooling bath was removed, and the reaction was stirred for 1 hour. A light brown precipitate formed as the reaction warmed to room temperature. The reaction was filtered and the filtrate was concentrated under vacuum to give 0.80 g of a yellow solid. ^{1}H NMR analysis of the yellow solid revealed two peaks.

^{1}H NMR (D_2O, external TMS standard): δ 1.6 (s, 6H), δ 4.3 (s, 2H)

Solubility tests of the brown precipitate indicated it to be LiCl. The results of the tests are listed below.

Solvent	Results
Acetone	Insoluble
NH_4OH	Soluble
NH_4OH + $AgClO_4$	Precipitate forms

H. Reaction of Lithio Iodoacetyl Meldrum's Acid with Lithio Methyl Acetate

A THF solution (25 ml; 5.0 mmol) of lithio iodoacetyl Meldrum's acid was prepared as described above with the following changes: after the reaction was stirred at room temperature for 1 hour, the solution was cooled to -78°C without removing the solvent. A THF solution (5.0 ml; 5.0 mmol) of lithio methyl acetate was added to the lithio iodoacetyl Meldrum's acid solution and the resulting solution was stirred for 30 minutes at -78°C. The cooling bath was removed and the reaction was stirred for 1 hour. The reaction mixture was filtered and the solvent was removed from the filtrate under vacuum giving an orange solid. ^1H NMR analysis revealed two singlets.

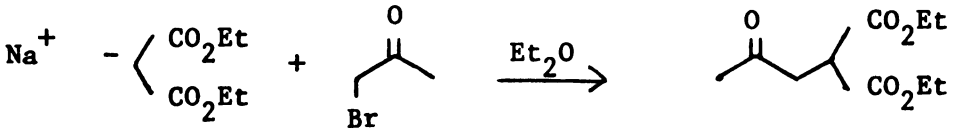
^1H NMR (D_2O, external TMS standard): δ 1.6 (s, 6H), δ 4.3 (s, 2H)

CHAPTER II

REACTIONS OF MELDRUM'S ACID DERIVATIVES

Introduction

The reaction of an enolate with an α-haloketone has been accomplished using α-haloacetone and the enolates of diethyl malonate[8] (Eq 54) and barbituric acid[9] (Eq 55). This type of reaction could be used for



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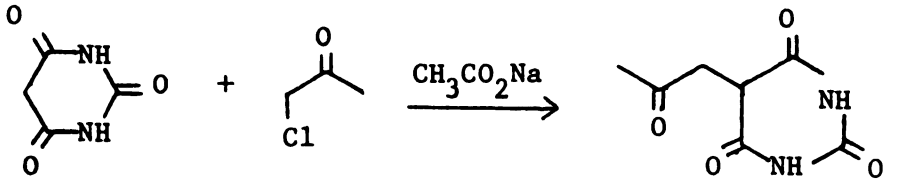
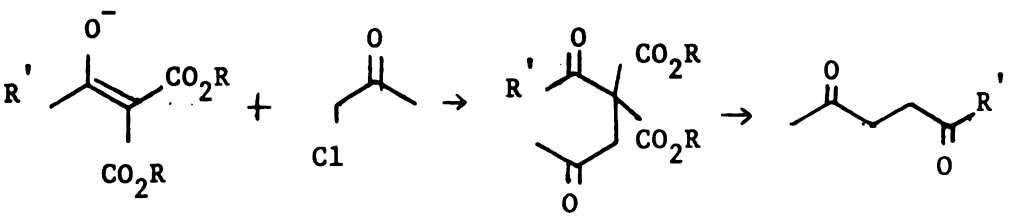


(55)

the synthesis of 1,4-diketones provided the active methylene compounds were properly substituted. For example, reaction of the enolate of 2-acyl malonate (20) with chloroacetone should give 2-acyl-2-acetonyl malonate (21), which could be decarboxylated to give the desired 1,4-diketone (Eq 56).

Alternatively, compounds such as 2-acetonyl malonate could be used to synthesize 1,4-diketones. For example, the reaction of the enolate of 2-acetonyl malonate with an acid chloride should also give 21 (Eq 57).



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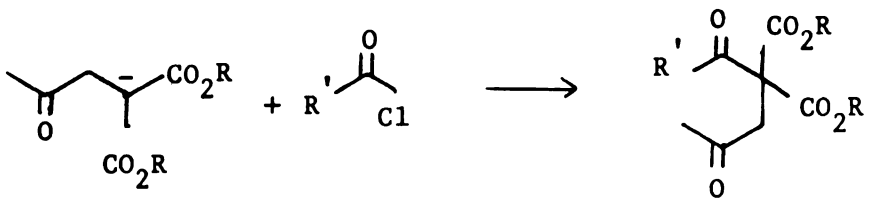
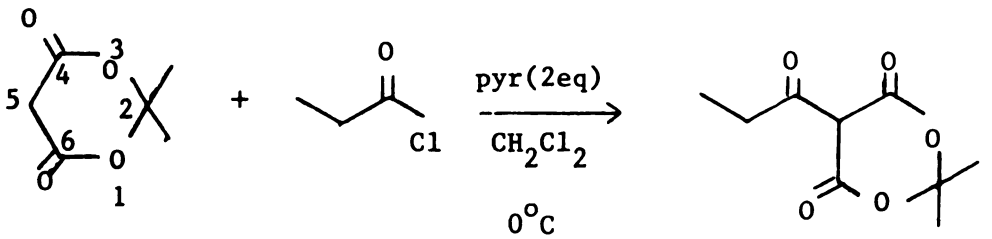
20 21



(57)

21

In contrast with acyclic malonic esters (pK_a 13.7)[22] and acetoacetate esters (pK_a 10.7)[22], Meldrum's acid (9) reacts with electrophiles (at carbon 5) even in the absence of a strong base because of its remarkably high acidity (pK_a 4.97)[22]. For example, Meldrum's acid reacts with propionyl chloride in the presence of pyridine to give propionyl Meldrum's acid (22) in almost quantitative yield (Eq 58)[22].

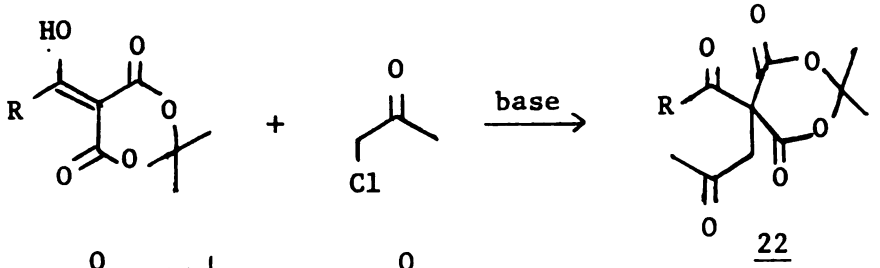


(58)

9

Because of the exceptionally mild conditions needed to react Meldrum's acid with electrophiles, we proposed to study the use of Meldrum's acid for the synthesis of 1,4-diketones. Both of the methods described

above for the synthesis of 1,4-diketones (Eq 56 and 57) were studied with Meldrum's acid in place of the malonic ester (Eq 59 and 60). Either



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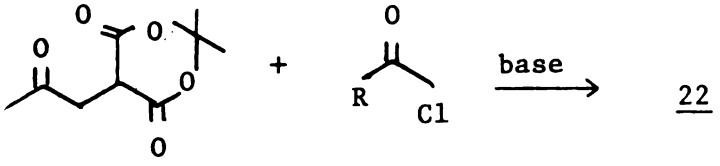
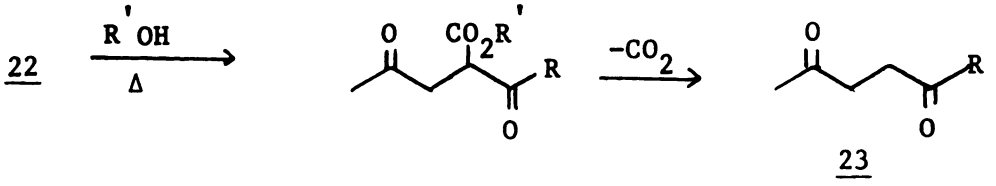


(60)

method should give the same product, 22, which, after cleavage of the Meldrum's acid ring by alkoholysis, followed by decarboxylation, should give the desired 1,4-diketone 23 (Eq 61).



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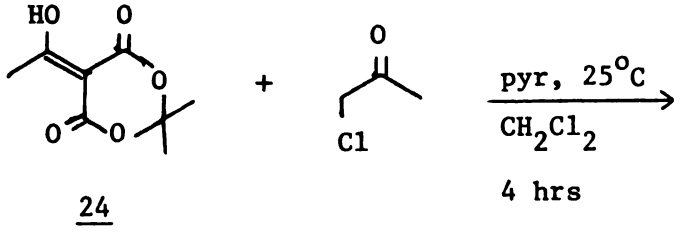
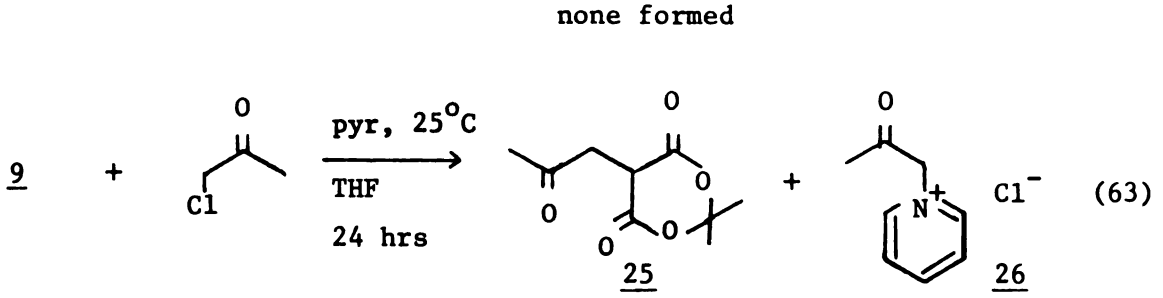
Results

Acetyl Meldrum's acid (24) was reacted with chloroacetone in the presence of one equivalent of pyridine (Eq 62). GLC analysis revealed that the chloroacetone remained unchanged after 4 hours.



(62)

We next decided to study the synthesis of 1,4-diketones via the route shown in equation 60. For our first attempt to synthesize acetonyl Meldrum's acid (25), Meldrum's acid (9) was reacted with chloroacetone in the presence of one equivalent of pyridine. The reaction mixture was filtered after 24 hours and a solid was isolated. ^{1}H NMR analysis showed the solid to be N-acetonyl pyridinium chloride (26; Eq 63).



(63)

Results of related experiments to synthesize acetonyl Meldrum's acid (25) are shown in Table I. The best yield of 25 (87.4%) was obtained with 1.1 equivalents of triethylamine in diethyl ether.

We next attempted to synthesize acetonyl acetyl Meldrum's acid (27) from acetonyl Meldrum's acid (25; Eq 64). Results of experiments to synthesize 27 are shown in Table II. The best yield of 27 (99.5%) was obtained with 2.0 equivalents of pyridine in methylene chloride.

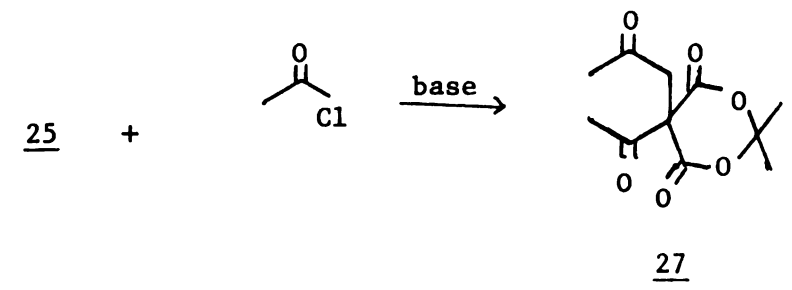


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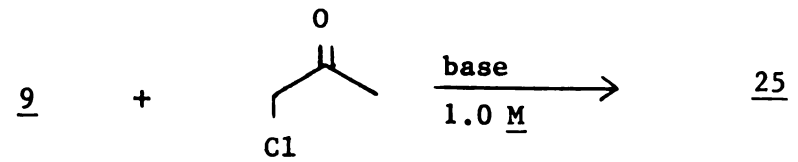
Table I. Preparation of Acetonyl Meldrum's Acid (25)



Solvent	Base(equivalents)	Conditions (0^{o}C, Time)	Yield(%)
THF	pyridine (1.0)	25^{o}, 24 hr	N.R.[a,b]
CH_2Cl_2	pyridine (1.0)	25^{o}, 24 hr	N.R.
MeOH	NaOH (1.0)	25^{o}, 2 hr; 40^{o}, 8 hr	67.4
CH_2Cl_2	Et_3N (1.0)	25^{o}, 18 hr	25
THF	Et_2N (1.0)	25^{o}, 12 hr	56.4
$CHCl_3$	Et_3N (1.0)	61^{oc}, 12 hr	N.R.
Et_2O	Et_3N (1.0)	25^{o}, 24 hr	78.4
THF	Et_3N (1.0)	25^{o}, 24 hr	62.9[d]
THF	Et_3N (1.1)	25^{o}, 24 hr	77.4
Et_2O	Et_3N (1.1)	25^{o}, 24 hr	87.4

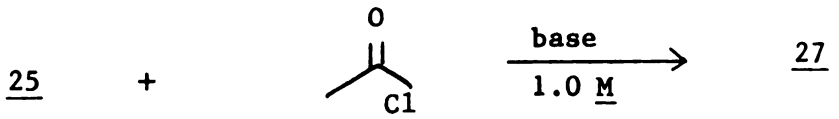
[a] N.R. = No Reaction

[b] Isolated 26

[c] Reflux temperature

[d] 1.1 equivalents of chloroacetone used

Table II. Reaction of Acetonyl Meldrum's Acid with Acetyl Chloride



Solvent	Base(equivalents)	Conditions (°C, Time)	Yield (%)
CH_2Cl_2	pyridine (1.0)	0°, 10 min; 25°, 10 min	(2.6g)[a]
CH_2Cl_2	pyridine (1.0)	0°, 1 hr; 25°, 1 hr	92.5
Et_2O	pyridine (1.0)	0°, 1 hr; 25°, 1 hr	N.R.[b]
Et_2O	Et_3N (1.0)	0°, 1 hr; 25°, 1 hr	(0.61 g)[c]
CH_2Cl_2	pyridine (2.0)	0°, 15 min	99.5[d]

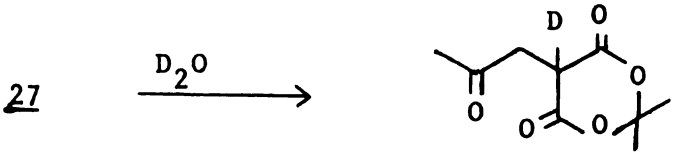
[a] ^1H NMR revealed 3:1 27:25

[b] N.R. = No Reaction

[c] ^1H NMR revealed 1:2 27:25

[d] 1.1 equivalents of acetylchloride used

During our study to optimize the yield of 27, we noticed that a small amount of 25 was present in the reaction mixture after acidic work-up. We suspected that 27 hydrolysed to 25 in the presence of water. To check this assumption, one equivalent of pyridine was added to a chloroform-d solution of 25 at 0°C. The solution was stirred for 15 minutes and 1.1 equivalents of acetyl chloride were added. Aliquots were periodically removed from the reaction mixture and analyzed by ^{1}H NMR. Analysis showed a 1:1 ratio of 27:25 after 1 hour. A second equivalent of pyridine was added and ^{1}H NMR analysis revealed 27 as the only component present. Deuterium oxide (D_2O) was added to the NMR sample and analysis indicated the presence of appreciable amounts of 25-d (Eq 65). Armed with this knowledge, we found the best yield of 27 (99.5%) was obtained when the organic phase of the reaction mixture was immediately separated from the aqueous phase after quenching.

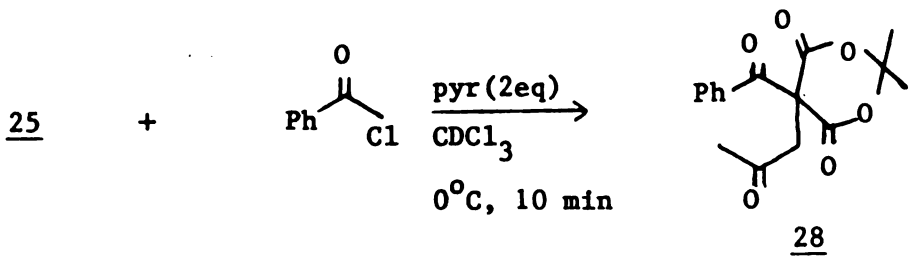


(65)

25-d

We next attempted to prepare acetonyl benzoyl Meldrum's acid (28) from acetonyl Meldrum's acid (25) (Eq 66). As shown by the results in Table III, we were unable to synthesize 28 under a variety of conditions.

We also attempted to react 25 with crotonyl chloride (Eq 67), isobutyryl chloride (Eq 68), and pivaloyl chloride (Eq 69). However, all three acid chlorides failed to react under the conditions shown in equation 67.



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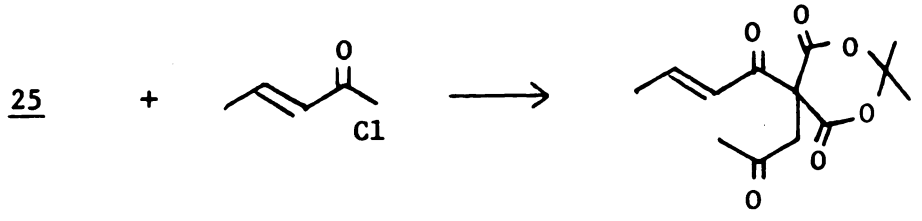

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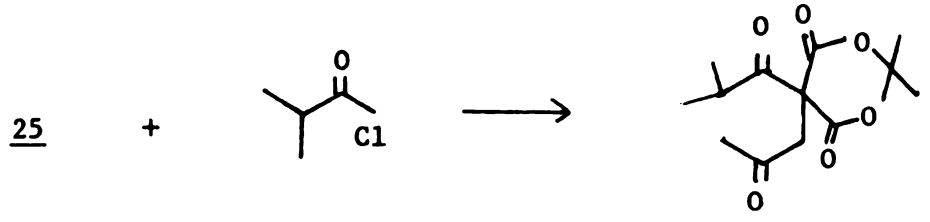

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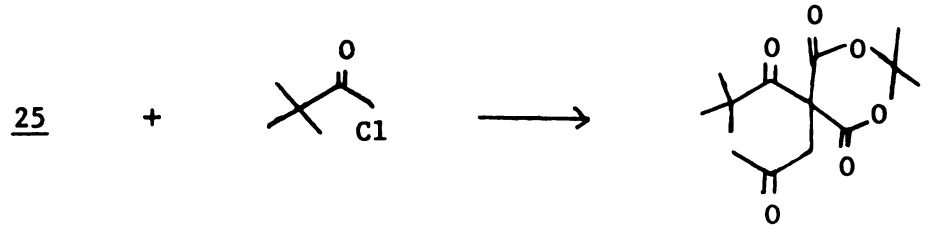
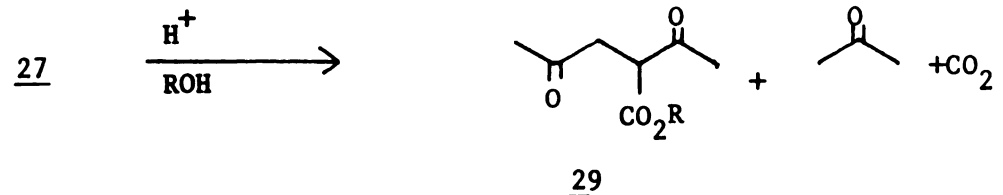


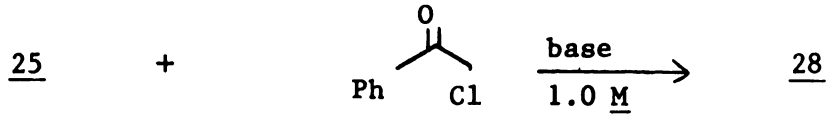
(69)

We next attempted to cleave the Meldrum's acid ring of 27 to give the 1,4-diketone 29 (Eq 70). One equivalent of $BF_3 \cdot OEt_2$ was added to a



(70)

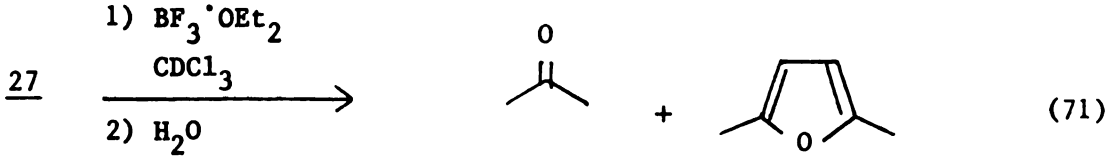
Table III. Reaction of Acetonyl Meldrum's Acid with Benzoyl Chloride



Solvent	Base(equivalents)	Conditions (^{o}C, Time)	Yield(%)
CH_2Cl_2	pyridine (1.0)	0°, 1 hr; 25°, 1 hr	N.R.[a]
CH_2Cl_2	Et_3N (1.0)	0°, 1 hr; 25°, 1 hr	N.R.
Et_2O	Et_3N (1.0)	0°, 1 hr; 25°, 1 hr	N.R.
CH_2Cl_2	pyridine (2.0)	0°, 10 min; 25°, 10 min	N.R.
$CDCl_3$	$PhN(CH_3)_2$ (1.0)	0°, 30 min	N.R.
$CDCl_3$	$(^{i}Pr)_2NEt$ (1.0)	0°, 30 min	N.R.

[a]No Reaction

chloroform-d solution of 27. Water (1.7 equivalents) was added and the reaction was stirred overnight. ^{1}H NMR analysis of the reaction mixture revealed the presence of acetone and 2,5-dimethyl furan (Eq 71). No

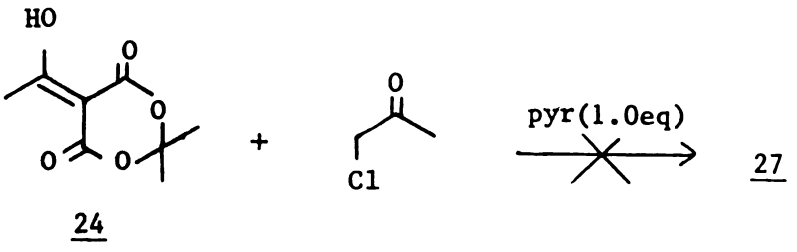


(71)

reaction occured when the reaction time was shortened to 30 minutes. When the amount of $BF_3 \cdot OEt_2$ added was decreased to 0.1 equivalents, analysis revealed unreacted 27 and a small amount of acetonyl Meldrum's acid (25). Finally, when the reaction was repeated with trifluoroacetic acid (instead of $BF_3 \cdot OEt_2$), analysis revealed acetonyl Meldrum's acid (25) as the only product. No acetonyl acetyl Meldrum's acid (27) was present in the reaction mixture.

Discussion

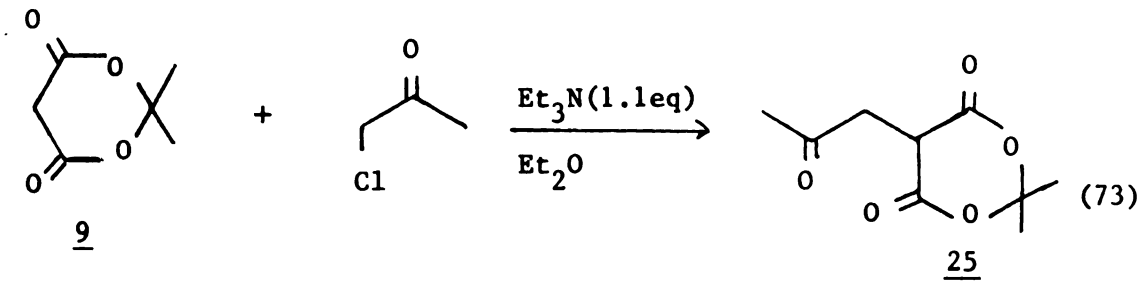
Acetonyl Meldrum's acid (24) failed to react with chloroacetone after 4 hours at room temperature (Eq 72). The acidity constant of 24 is



(72)

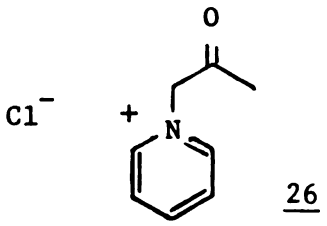
surely less than the pK_a of Meldrum's acid (9; $pK_a \approx 5$); thus the anion of 24 is probably an extremely weak nucleophile and unable to react with chloroacetone.

Meldrum's acid (9) itself, however, reacts smoothly with chloroacetone to give acetonyl Meldrum's acid (25) in good yield provided triethylamine is used as base (Eq 73). Acetonyl Meldrum's acid (25) was

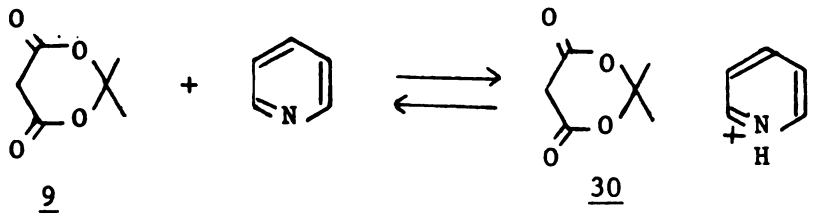


(73)

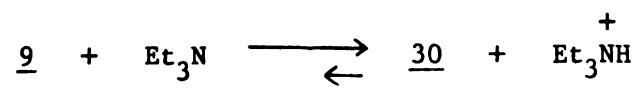
not formed when pyridine was used as the base; instead N-acetonyl pyridinium chloride (26) was isolated. The failure of the reaction under



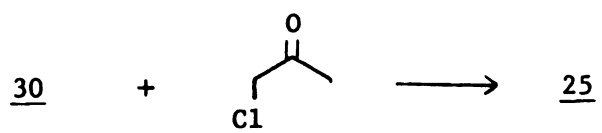
these conditions is probably due to the lower basicity of pyridine (pK_a 5.23) compared to triethylamine (pK_a 10.7). Pyridine reacts reversibly with Meldrum's acid (pK_a 5.2, Eq 74), thus significant amounts of pyridine are available for reaction with chloroacetone to form 26. Triethylamine, on the other hand, reacts with Meldrum's acid (9) almost irreversibly (Eq 75) and enolate 30 is the only nucleophile present in solution for reaction with chloroacetone (Eq 76).



9 30 (74)

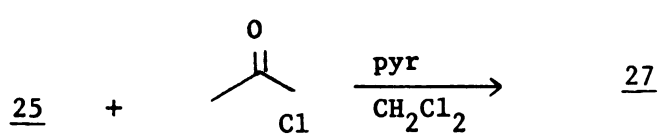


9 + Et_3N ⟶⟵ 30 + $Et_3\overset{+}{N}H$ (75)



30 + 25 (76)

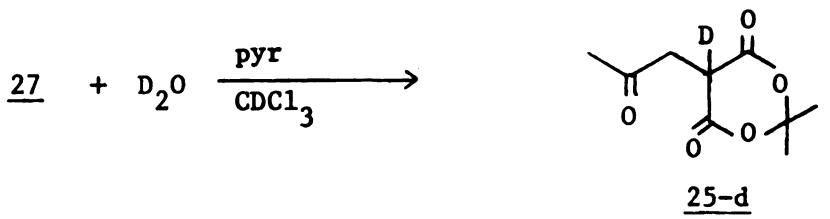
Acetonyl acetyl Meldrum's acid (27) was formed in nearly quantitative yield by reaction of acetonyl Meldrum's acid (25) with acetyl chloride (1.1 equivalents) and pyridine (2.0 equivalents; Eq 77). The



25 + 27 (77)

reaction was repeated with chloroform-d as the solvent so the reaction could be followed by ^1H NMR. The reaction was initiated with only one equivalent of pyridine present. ^1H NMR analysis revealed a 1:1 ratio of 27:25. A second equivalent of pyridine was then added and analysis

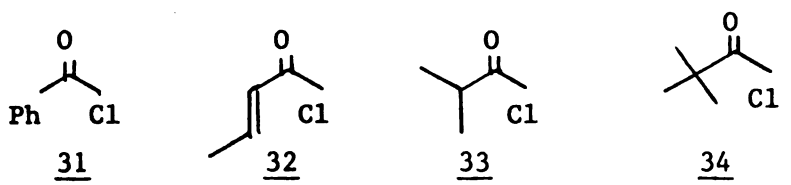
showed mainly 27 with only a trace amount of 25 present in the reaction mixture. The second equivalent of pyridine is probably needed as an HCl trap. A few drops of D_2O were added to the NMR sample and analysis revealed a considerable amount of 27 had hydrolysed to 25-d (Eq 78).



25-d (78)

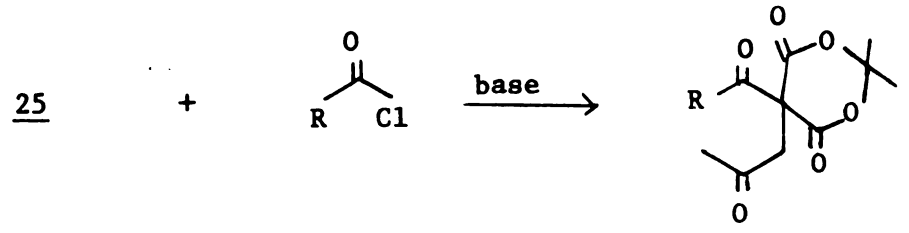
Here the second equivalent of pyridine present from the original reaction mixture probably causes a base catalysed hydrolysis of 27. Armed with this knowledge, we found the best yields of 27 (99.5%) were obtained by quenching the reaction mixture with 2 M HCl and immediately separating the organic phase.

Benzoyl chloride (31), crotonyl chloride (32), isobutyryl chloride (33), and pivaloyl chloride (34) all failed to react with acetonyl



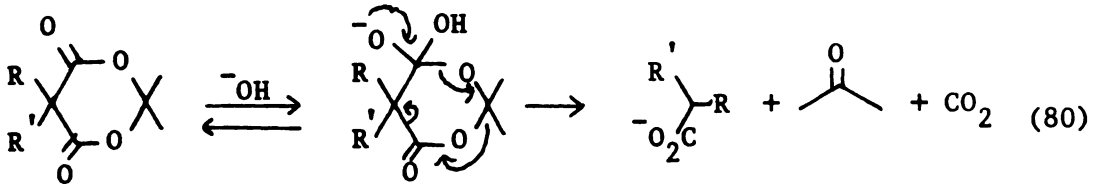
31 32 33 34

Meldrum's acid. The failure of these acid chlorides to react with acetonyl Meldrum's acid is possibly due to steric factors. In the acylation of acetonyl Meldrum's acid a quaternary carbon is formed (Eq 79) and as the acid chloride becomes bulkier, the reaction is less likely to occur.



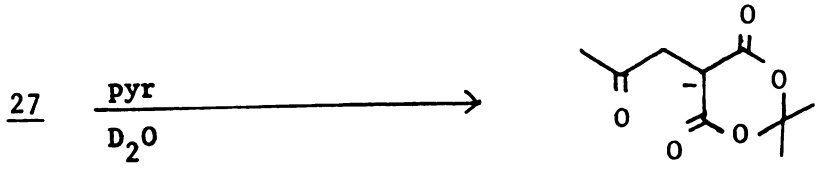
(79)

Finally we attempted to cleave the Meldrum's acid ring of 27 to complete a synthesis of a 1,4-diketone. Pihlaja and Ketola[23] have reported the base catalysed decomposition of disubstituted Meldrum's acid derivatives (Eq 80). Base catalysed hydrolysis of 27, however, led



(80)

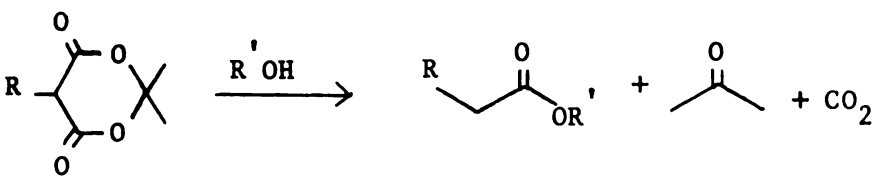
to cleavage of the acetyl group (Eq 78), not the Meldrum's acid ring. This result is not surprising since attack of the base at the acetyl function would lead to the formation of the stable anion 35 (Eq 81).



35

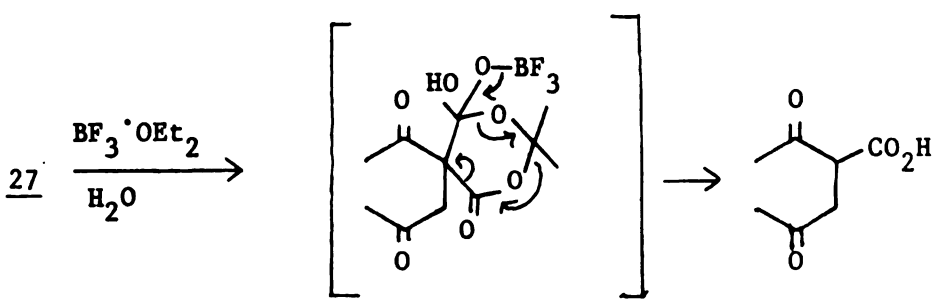
(81)

Yonemitsu[22] has reported the acid hydrolysis of 5-substituted Meldrum's acid derivatives (Eq 82). To hydrolyse 27 we chose boron trifluoride as the acid because of its high Lewis acidity.



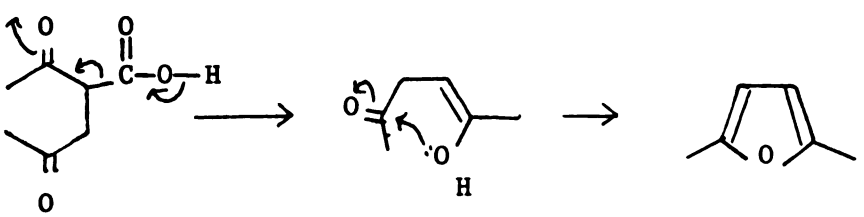
(82)

Compound 27 gave acetone and 2,5-dimethyl furan as products after reacting with one equivalent of $BF_3 \cdot OEt_2$ and water for 24 hours. These products can be explained by the acid hydrolysis of the Meldrum's acid ring (Eq 83) followed by cyclization of the intermediate diketone 36 (Eq 84).



(83)

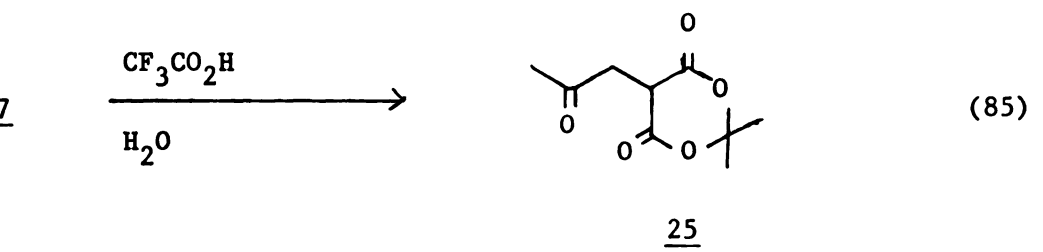
36



(84)

If the amount of $BF_3 \cdot OEt_2$ used is decreased to 0.1 equivalents, compound 27 remains largely unreacted. Thus, it appears that a full equivalent of $BF_3 \cdot OEt_2$ is needed to hydrolyse the Meldrum's acid ring.

Reaction of 27 with trifluoroacetic acid in the presence of water gave exclusive formation of acetonyl Meldrum's acid (25) after 24 hours (Eq 85). Thus it appears that the mode of hydrolysis which compound 27



(85)

25

will undergo, i.e. equation 83 verses equation 85, depends on the acid used. This brief preliminary study indicates the use of a protic acid will hydrolyse the acetyl function whereas the use of an aprotic Lewis acid will hydrolyse the Meldrum's acid ring.

In conclusion, the synthesis of 1,4-diketones from the reaction of Meldrum's acid with α-haloketones and acid chlorides is not promising. However, in reacting chloroacetone with Meldrum's acid a γ-keto ester was formed (Table I). If conditions could be found to hydrolyse the Meldrum's acid ring, the reactions of an α-haloketone with Meldrum's acid may be useful as a general synthetic approach to γ-keto esters.

Experimental

I. Materials

Meldrum's acid, chloroacetone, pyridine, triethylamine, diethyl ether, and THF were prepared or obtained as described in Chapter I. N,N-Diisopropylethylamine, N,N-dimethylaniline, and all acid chlorides were

purchased from Aldrich and used without further purification. Boron trifluoride etherate was obtained from Baker and distilled prior to use. Trifluoroacetic acid was purchased from Alfa. Acetyl Meldrum's acid was obtained from Rob Tirpak who prepared it from Meldrum's acid and acetyl chloride according to Yonemitsu's procedure[22].

II. Reaction of Acetyl Meldrum's Acid (24) with Chloroacetone

A. Preparation of Acetyl Meldrum's Acid

Acetyl Meldrum's acid was obtained from Rob Tirpak of this laboratory and used without further purification.

B. Reaction of 24 with Chloroacetone

A 25 ml round-bottomed flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was purged with argon and charged with 1.86 g (10.0 mmol) acetyl Meldrum's acid and 10 ml CH_2Cl_2. Pyridine (0.80 ml; 10 mmol) was added and the reaction was stirred for 15 minutes. Chloroacetone (0.80 ml; 10 mmol) was added and the reaction was followed by GLC analysis (column temperature 110°C). No chloroacetone reacted after 4 hours.

III. Reaction of Acetonyl Meldrum's Acid with Acid Chlorides

A. Preparation of Acetonyl Meldrum's Acid (25)

A 25 ml round-bottomed flask equipped with septum inlet, magnetic stirrer, reflux condensor, and mercury bubbler was purged with argon and charged with 1.44 g (10.0 mmol) Meldrum's acid and 5.0 ml anhydrous diethyl ether. Triethylamine (1.53 ml; 11.0 mmol) was added giving a milky suspension which was stirred for 10 minutes. While

stirring two layers formed; the bottom layer was clear and the top layer was milky white. Chloroacetone (0.80 ml; 10 mmol) was slowly added and the reaction mixture began to reflux. A white precipitate formed approximately one minute after the chloroacetone was added. The reaction was stirred overnight, quenched with 5 ml H_2O, and filtered. The white precipitate isolated was washed with pentane and dried giving 1.75 g (8.74 mmol; 87.4 % yield) of 25. (Results of additional attempts to synthesize 25 are summarized in Table I).

^{1}H NMR ($CDCl_3$): δ 1.9 (s, 6H), δ 2.3 (s, 3H), δ 3.3 (d, 2H), δ 3.9 (t, 1H)

B. Reaction of 25 with Acid Chlorides

The reaction of 25 with acetyl chloride in CH_2Cl_2 is representative: a 50 ml round-bottomed flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was purged with argon and charged with 2.00 g (10.0 mmol) 25 and 10 ml CH_2Cl_2. Pyridine (1.61 ml; 20.0 mmol) was added and the reaction mixture was cooled to 0°C. Acetyl chloride (0.79 ml; 11.0 mmol) was added dropwise giving a clear yellow solution. The reaction mixture was stirred 15 minutes at 0°C, quenched with 10 ml 2 M HCl, the organic phase immediately separated, dried ($MgSO_4$), and concentrated giving 2.41 g (99.5 mmol; 99.5%) of a slightly yellow solid which was shown to be 27.

^{1}H NMR ($CDCl_3$): δ 1.7 (s, 3H), δ 1.9 (s, 3H), δ 2.2 (s, 3H), δ 2.3 δ (s, 3H), δ 3.6 (s, 2H)

C. A Study of the Reaction of 25 with Acetyl Chloride

A 25 ml round-bottomed flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was purged with argon and charged with 1.00 g (2.5 mmol) 25 and 2.5 ml $CDCl_3$. The reaction mixture was cooled to 0°C and one equivalent of pyridine (0.20 ml; 2.5 mmol) was added. Acetyl chloride (1.98 ml; 2.75 mmol) was added and the reaction was stirred at 0°C. Aliquots were periodically removed and analyzed by ^1H NMR. After 1 hour at 0°C, analysis revealed a 1:1 ratio of 27:25. After 1 hour at 0°C, a second equivalent of pyridine (0.20 ml; 2.5 mmol) was added. Analysis (^1H NMR) revealed 27 as the only component present in the reaction mixture (besides pyridine). Deuterium oxide (approximately 3 drops) was added to the NMR sample and analysis indicated the presence of appreciable amounts of 25-d.

IV. Attempts to Cleave the Meldrum's Acid Ring of 27

A. Reaction of 27 with $BF_3 \cdot OEt_2$

A 5 ml round-bottomed flask equipped with septum inlet, magnetic stirrer, and mercury bubbler was purged with argon and charged with 0.242 g (1.00 mmol) 27 and 1 ml $CDCl_2$. One equivalent of $BF_3 \cdot OEt_2$ (0.123 ml; 1.00 mmol) was added and the reaction was stirred for 5 minutes. Water (0.03 ul; 1.7 mmol) was added and the reaction was stirred overnight. Analysis of the organic phase indicated the presence of acetone and 2,5-dimethylfuran. No 27 was present in the reaction mixture.

^{1}H NMR ($CDCl_3$): δ 2.2 (acetone), δ 4.1 (s, 6H), δ 6.1 (bs, 2H)

The reaction was repeated using 0.1 equivalents of $BF_3 \cdot OEt_2$. Analysis (^{1}H NMR) revealed unreacted 27 and a small amount of 25.

B. Reaction of 27 with Trifluoroacetic Acid

A small amount of 27 was dissolved in $CDCl_3$ in an NMR tube. Approximately 3 drops of trifluoroacetic acid and 6 drops of D_2O was added to the NMR tube, the mixture was shaken, and analyzed by ^{1}H NMR. Analysis revealed no reaction had occurred. Approximately 6 drops of acetone-d_6 was added to the NMR tube, the tube was shaken and allowed to stand overnight at room temperature. ^{1}H NMR analysis revealed 25 as the only Meldrum's acid derivative present in the reaction mixture.

^{1}H NMR ($CDCl_3$): δ 2.2 (acetone), δ 4.1 (s, 6H), δ 6.1 (bs, 2H)

The reaction was repeated using 0.1 equivalents of $BF_3 \cdot OEt_2$. Analysis (^{1}H NMR) revealed unreacted 27 and a small amount of 25.

B. Reaction of 27 with Trifluoroacetic Acid

A small amount of 27 was dissolved in $CDCl_3$ in an NMR tube. Approximately 3 drops of trifluoroacetic acid and 6 drops of D_2O was added to the NMR tube, the mixture was shaken, and analyzed by ^{1}H NMR. Analysis revealed no reaction had occurred. Approximately 6 drops of acetone-d_6 was added to the NMR tube, the tube was shaken and allowed to stand overnight at room temperature. ^{1}H NMR analysis revealed 25 as the only Meldrum's acid derivative present in the reaction mixture.

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