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The Unexpected Preferential Formation of 1-Alkyl-1-Phenyl-2-Propanones on Monoalkylation of the 1-Phenyl-2-Propanone Dianion

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THE UNEXPECTED PREFERENTIAL FORMATION
OF 1-ALKYL-1-PHENYL-2-PROPANONES
ON MONOALKYLATION OF THE
1-PHENYL-2-PROPANONE DIANION

by

Jack M. Hinkley

A Thesis
Submitted to the
Faculty of the Graduate College
in partial fulfillment
of the
Degree of Master of Arts

Western Michigan University
Kalamazoo, Michigan
August 1978

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Jack M. Hinkley

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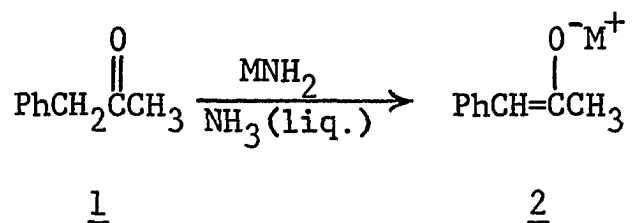
TABLE OF CONTENTS

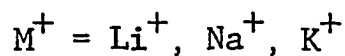
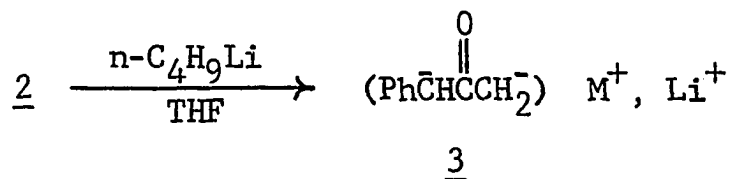
	PAGE
INTRODUCTION	1
HISTORICAL	3
RESULTS AND DISCUSSION	25
TABLE I ALKYLATION OF THE POTASSIUM ENOLATE <u>2a</u> WITH ALKYL HALIDES	30
TABLE II ALKYLATION OF THE 1-PHENYL-2- PROPANONE DIANION (<u>3</u>) WITH ALKYL HALIDES	36
TABLE III CARBANION H NMR CHEMICAL SHIFT DATA (δ)	41
TABLE IV TRIMETHYLSILOXYPROPENE H NMR CHEMICAL SHIFT DATA (δ)	58
EXPERIMENTAL	59
REFERENCES	78
VITA	82

INTRODUCTION

In 1967 Hauser, Mao, and Miles¹ described in a communication the successful preparation of several ketone derived dianions that hitherto had not been reported. Included in this communication was the preparation of the dianion of 1-phenyl-2-propanone (3). Previously, it had been shown that potassium amide in liquid ammonia readily converted 1-phenyl-2-propanone (1) to the enolate salt 2 ($M^+ = K^+$) but failed to effect dimetalation to form 3.² It was found, however, that 3 was readily obtained by sequential metalation of 1-phenyl-2-propanone with an alkali amide and n-butyllithium according to the route shown in Scheme I.¹

Scheme I



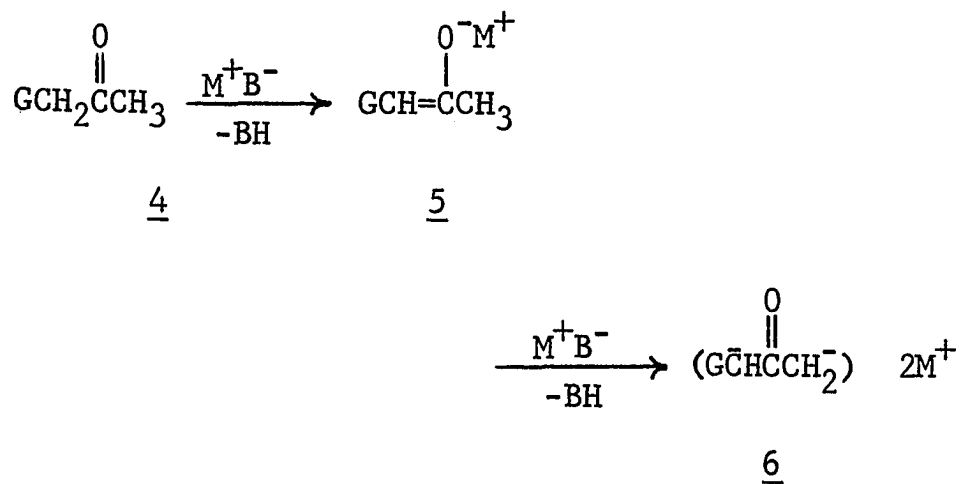


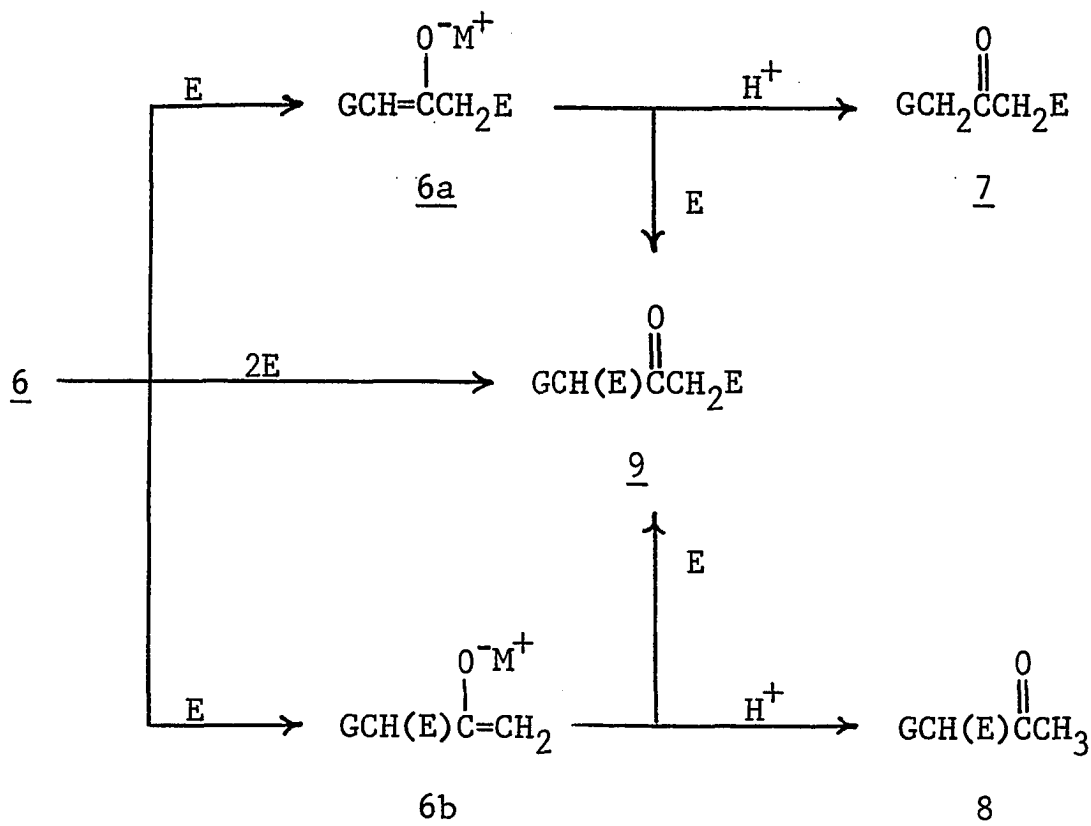
Although several reactions of 3 with electrophiles were described, no reactions with alkylating agents were reported nor have such reports describing the alkylation of 3 or related dianion systems appeared in the more recent literature.³ Because of this lack of information, a study of the monoalkylation of the 1-phenyl-2-propanone dianion was initiated.

HISTORICAL

Substituted acetones of the general type 4, where G is a methylene activating and anion stabilizing substituent, are converted with high regioselectivity to the corresponding enolate anions 5 on reaction with one equivalent of strong base.⁴ Conceptually, removal of the less acidic proton from the methyl group (C₃) of 5 should result in the formation of the 1,3-dianion 6. As this species possesses two reactive carbon centers, reaction at these centers with a limited amount of an electrophile E may lead to three possible products as shown in Scheme II.

Scheme II



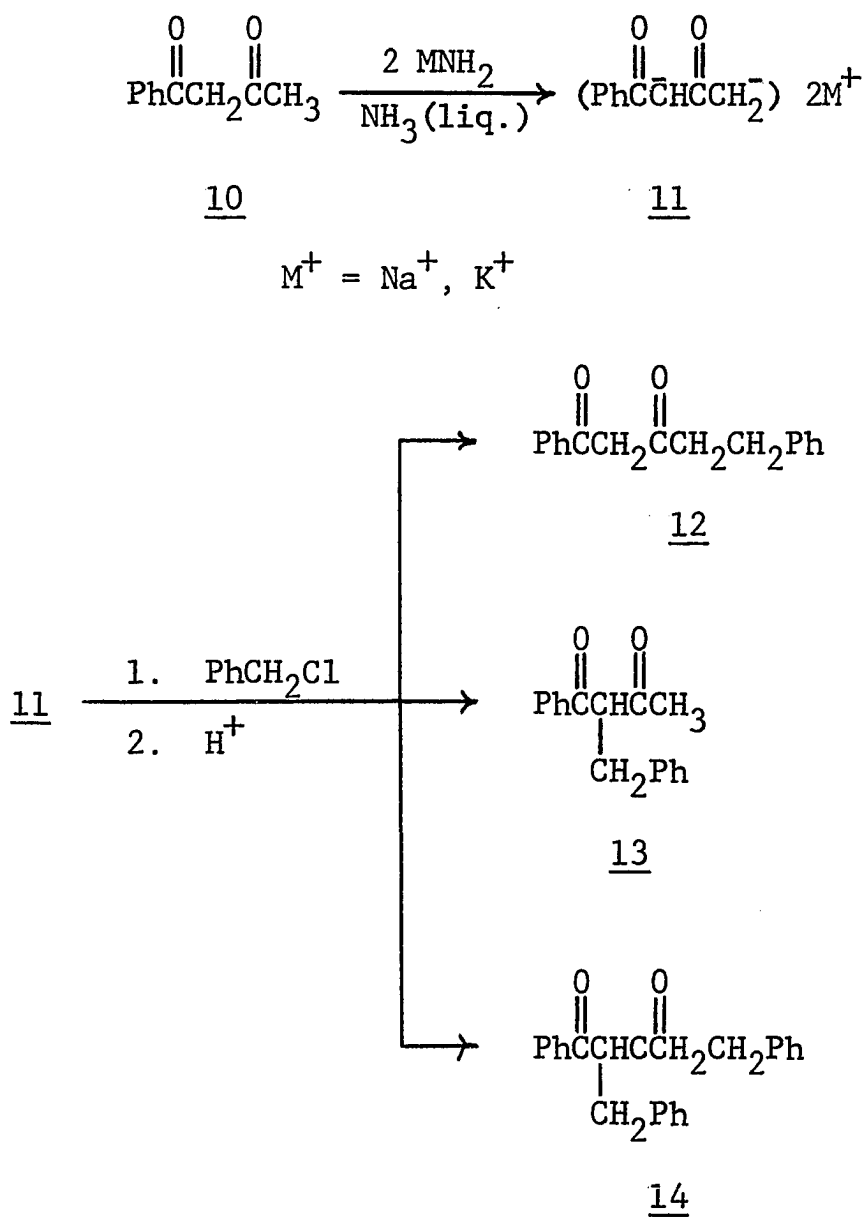


Reaction exclusively at the terminal position (C_3) would lead to the formation of gamma substituted derivatives 7; reaction exclusively at C_1 would lead to the formation of alpha substituted derivatives 8; and reaction at both C_1 and C_3 either simultaneously or sequentially via the two possible enolate anions, 6a and 6b would lead to the formation of 1,3-disubstituted derivatives 9.

One of the first examples of a dianion of the general type 6 to appear in the literature was reported by Hauser and Harris in 1958.⁵ It was shown that 1-phenyl-1,3-butanedione (10) could be converted to the corresponding

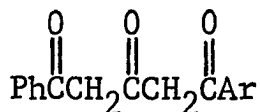
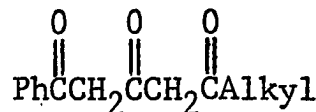
1,3-dianion 11 by the action of two equivalents of potassium amide in liquid ammonia. Subsequently, an extensive study of the reactions of this dianion with a large number of electrophiles was made.

Scheme III

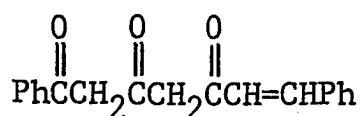
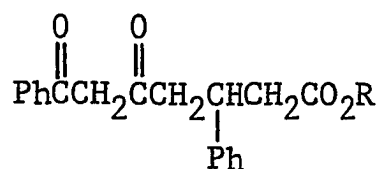


Alkylation of 11 with benzyl chloride led to the exclusive formation of 1,5-diphenyl-1,3-pentanedione (12) the product of C₃ substitution.⁵ Neither the C₁ substitution product, 1-phenyl-2-(phenylmethyl)-1,3-butanedione (13), nor the product of 1,3-disubstitution, 1,5-diphenyl-2-(phenylmethyl)-1,3-pentanedione (14) were observed. Previously, 13 was obtained by reacting the sodium enolate of 1-phenyl-1,3-butanedione with benzyl chloride.⁶

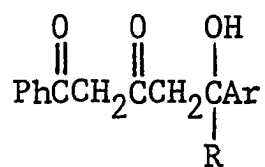
Acylation of the dipotassium salt of 11 was effected with ethyl benzoate⁵ and other aromatic esters⁷ to give 1,5-diaryl-1,3,5-pentanetriones 15. The 5-alkyl analogues 16 were obtained on reaction of alkanolic acid ethyl esters with the dilithium salt.⁸ Reaction of 11 with methyl

1516

cinnamate gave a mixture of the triketone 1,7-diphenyl-1-hepten-3,5,7-trione (17), and methyl 5,7-dioxo-3,7-diphenylheptanoate (18a).⁹ The mode of reaction proved to be sensitive to the ease of displacement of the alcohol moiety as 17 was obtained in high yield from phenyl cinnamate while 18b was the only product obtained from t-butyl cinnamate.

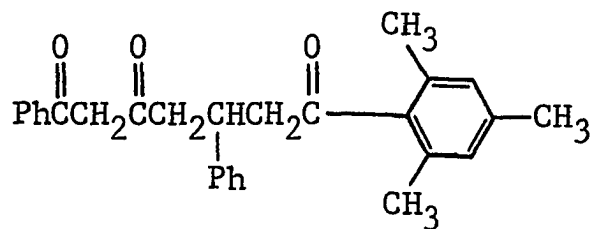
1718 a) R = CH₃b) R = t-C₄H₉

Benzaldehyde⁵ and p-methoxybenzaldehyde¹⁰ reacted with 11 to give the hydroxydiones 19a and 19b. Similarly, benzophenone reacted with the disodium salt and acetophenone reacted with the dilithium salt of 11 to give the hydroxydiones 19c and 19d.¹⁰ The reaction of 11 with 1,3-diphenyl-2-propen-1-one also proceeded via 1,2-addition to give the unsaturated hydroxydione 19e. However, the reaction of 11 with 3-phenyl-1-(2,4,6-trimethylphenyl)-2-propen-1-one gave only the triketone 20, the product of 1,4-addition.¹¹

19 a) R = H, Ar = Phb) R = H, Ar = p-(CH₃O)C₆H₄

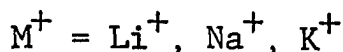
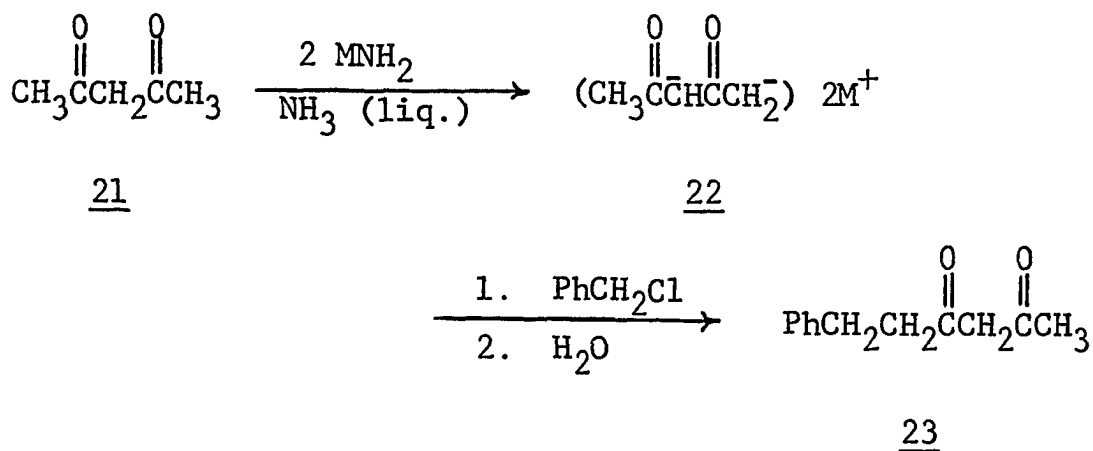
c) R = Ar = Ph

d) R = CH₃, Ar = Phe) R = PhCH=CH₂, Ar = Ph

20

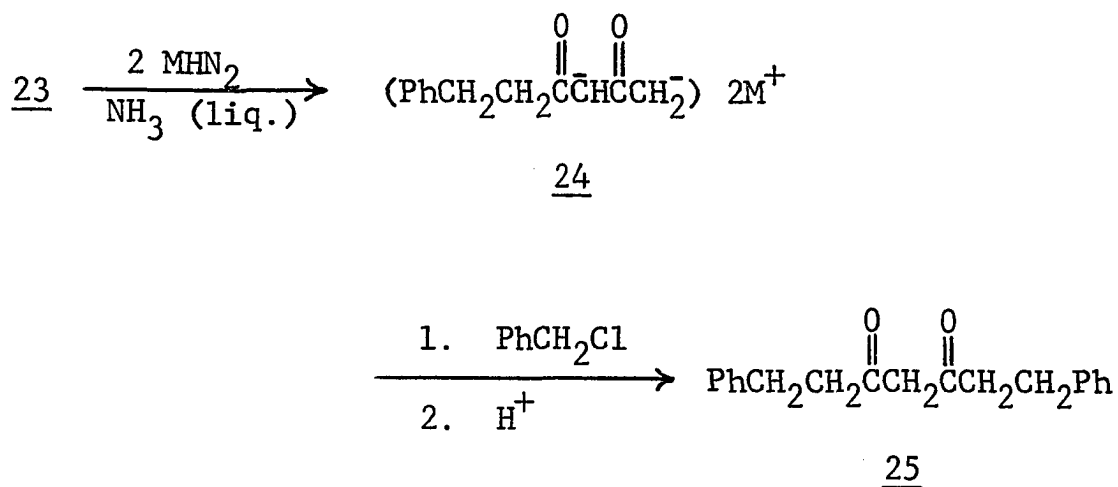
A second substituted acetone of the general type 4 shown to be readily converted to a 1,3-dianion of the general type 6 by two equivalents of an alkali amide in liquid ammonia is 2,4-pentanedione (21).⁵ Several 2,4-pentanedione homologues also have been converted to the corresponding 1,3-dianions by this method and the synthetic applications of these dianions have been reviewed.¹²

Scheme IV



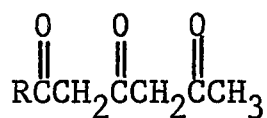
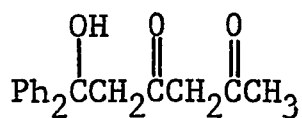
Reaction of 22 with one equivalent of benzyl chloride gave 1-phenyl-3,5-hexanedione (23) as the sole product.⁵ This in turn was converted to the dianion 24 which on benzylation gave 1,7-diphenyl-3,5-heptanedione (25).¹³ No other alkylation products were detected. Reaction of the

Scheme V



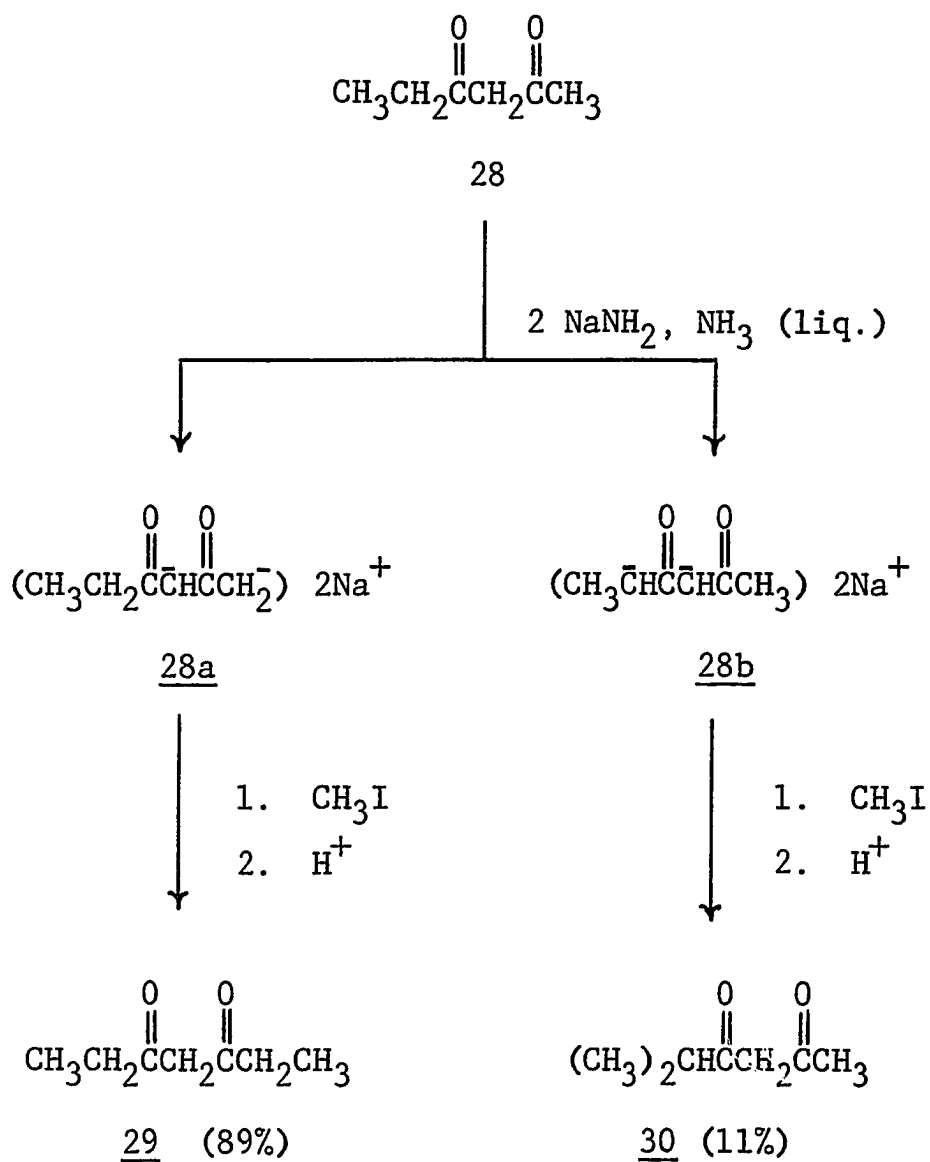
dianion 22 with several alkyl halides gave a series of 1-alkyl-2,4-pentanediones which are less readily accessible by other methods.¹⁴ These in turn have been converted to 1,5-dialkyl-2,4-pentanediones through alkylation of the corresponding 1,3-dianions.¹²

1,3,5-Triketones 26 were obtained from the dianion 22 on reaction with esters of aryl⁶ and alkyl⁸ carboxylic acids. Reaction with benzophenone led to the formation of 1,1-diphenyl-1-hydroxy-3,5-hexanedione (27).⁹

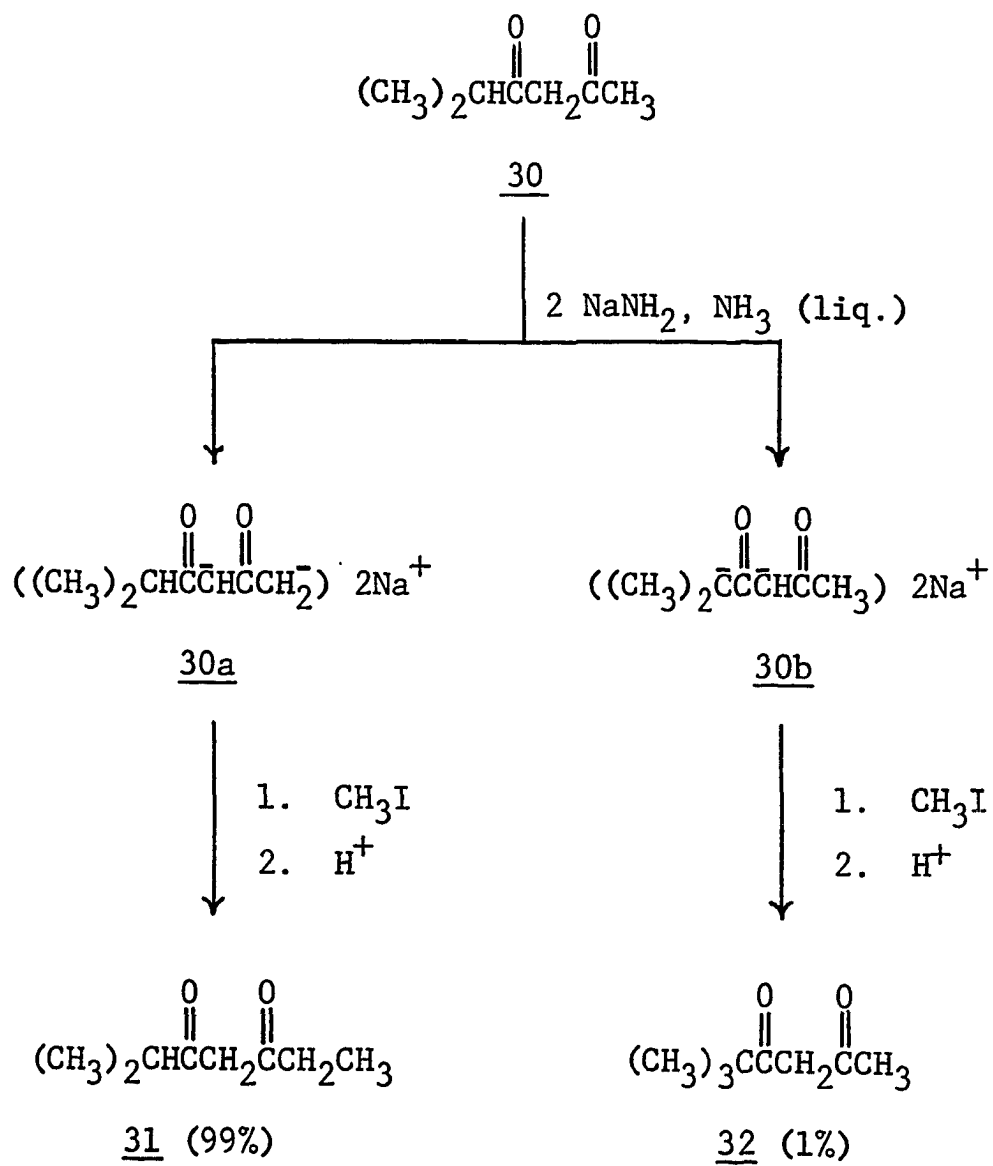
2627

Where two different sites with similar relative basicities could be developed, it was found that more than one dimetalated species could arise from the parent ketone. Dimetalation of 2,4-hexanedione (28) with sodium amide followed by addition of one equivalent of iodomethane gave 89% 3,5-heptanedione (29) and 11% 5-methyl-2,4-hexanedione (30)¹⁵ (Scheme VI). These products were shown to arise from two distinct dianions which under the reaction conditions were not interconverted, so that the product ratio is not representative of a mixture of 28a and 28b at equilibrium but rather is representative of the relative basicities of the two sites of secondary ionization. As shown in Scheme VII, repetition of this reaction with the disodium salt of 30 gave 99% 6-methyl-3,5-hexanedione (31) and 1% 5,5-dimethyl-2,4-hexanedione (32)¹⁵ which reflected the increased basicity of the C₅ carbon induced by the methyl substituent.¹⁶ The disodium salt of 1-phenyl-2,4-pentanedione (33), when reacted with one equivalent of iodomethane, 1-iodobutane, or benzyl chloride, gave only the corresponding 1-alkyl-1-phenyl-3,4-pentanediones 34, the C₁ position being activated by the phenyl substituent.

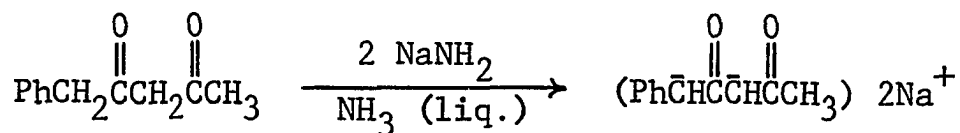
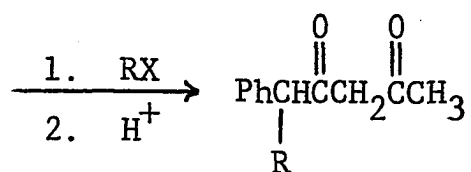
Scheme VI



Scheme VII

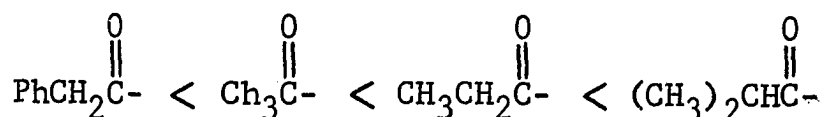


Scheme VIII

3334

But if the phenyl substituent is on the carbon beta to the carbonyl, the alpha position is not activated, since benzylation of the dipotassium salt of 1-phenyl-3,5-hexanedione (24) gave exclusively the symmetrical diketone 1,7-diphenyl-3,5-heptanedione (25)¹³ (Scheme V).

Through competitive metalation of mixtures of certain 1,3-diketones and analysis of the products obtained on alkylation, it was determined that the relative basicities of the sites of secondary ionization increased according to the following order of substituents on the parent acetone:

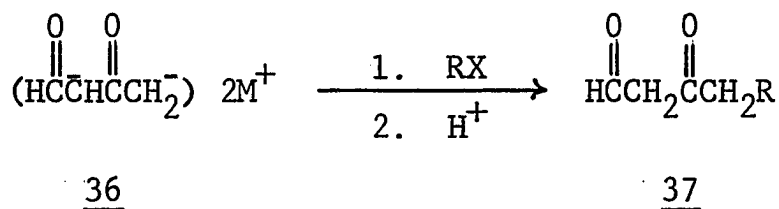


Competitive alkylation of mixtures of the corresponding 1,3-dianions of 1,3-diketones incorporating these groups established that the relative reactivities of the secondary sites towards alkylation also increased according to the same sequence, with the relative reactivity of propionyl and isobutyryl being of the same order of magnitude.¹⁷

The extensive studies by Hauser and coworkers of the reactions of 1,3-dianions derived from 1,3-diketones established that the site of secondary ionization is also the more reactive center giving on reaction with electrophiles products of the general type 7 rather than products of the general type 8. These findings prompted investigations of other stabilized 1,3-dianion systems of type 6. Thus, substituted acetones 4, where G is either an aldehyde, ester, sulfone, sulfoxide, sulfide, or dialkylphosphonate have been converted to corresponding 1,3-dianions and reacted with various electrophiles.

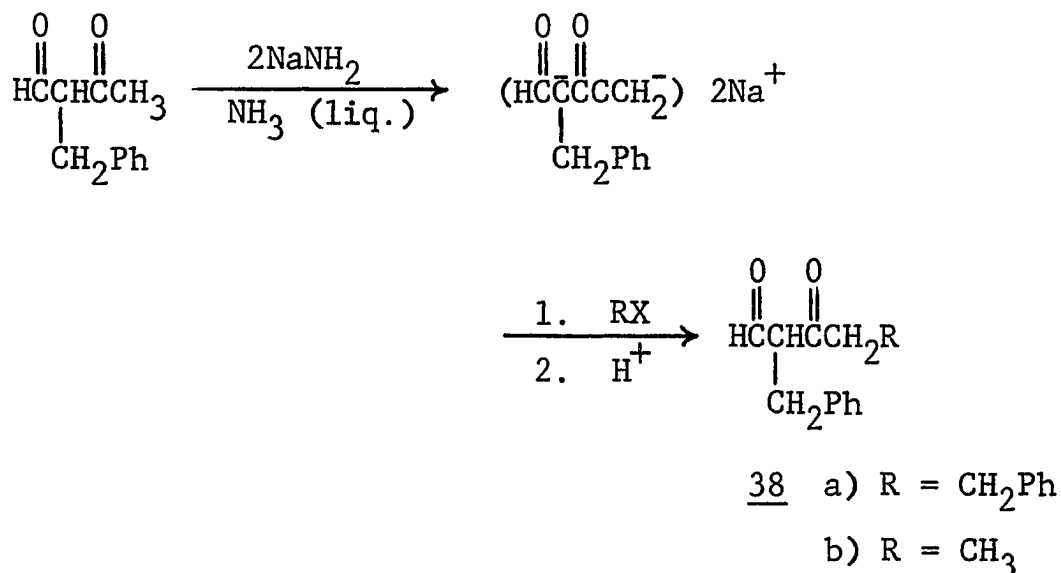
The 3-oxobutanal dianion (36) was obtained on reaction of the sodium enolate of 3-oxobutanal with an alkali amide in liquid ammonia.¹⁸ Reaction with several alkyl halides gave a series of 4-alkyl-3-oxobutanals 37.¹⁸ Alkylation of the 2-(phenylmethyl)-3-oxobutanal dianion also occurred at the terminal carbon (C₄) as benzyl chloride and iodomethane

Scheme IX

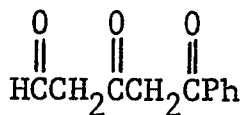
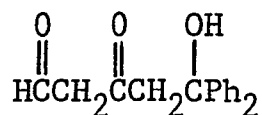


gave the respective 4-alkyl derivatives 38a and 38b.¹⁸

Scheme X

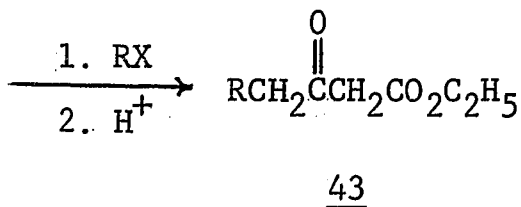
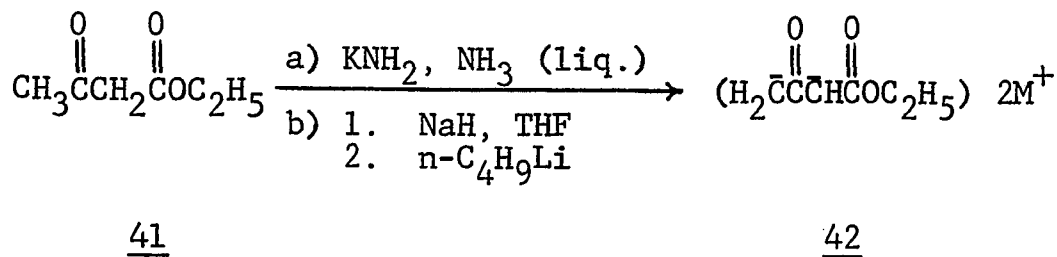


Evidence for alkylation at C₂ was not found. Reaction of 36 with methyl benzoate gave 5-phenyl-3,5-dioxopentanal (39) and the 1,2-addition product, 5,5-diphenyl-5-hydroxy-3-oxopentanal (40) was obtained from the reaction of 36 with benzophenone.¹⁹

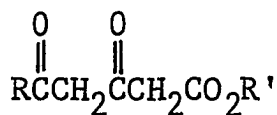
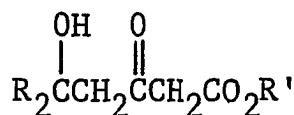
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Ethyl 3-oxobutanoate (41), as well as other 3-oxobutanoate esters have been converted to their corresponding 1,3-dianions either on reaction with potassium amide in liquid ammonia²⁰ or in tetrahydrofuran by sequential metalation with sodium hydride followed by n-butyllithium.²¹ Alkylation was found to occur exclusively at the terminal carbon (C₄) giving 4-alkyl-3-oxobutanoate esters 43 with higher yields obtained by the latter method.^{21,22} The 1,3-dianions of 3-ketoesters bearing on alkyl substituent at either C₂ or C₄ also reacted with alkyl halides at the terminal position.²²

Scheme XI

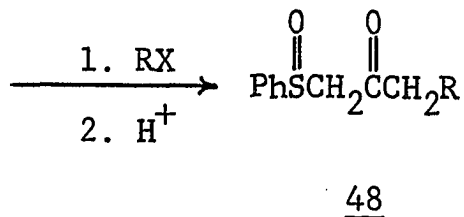
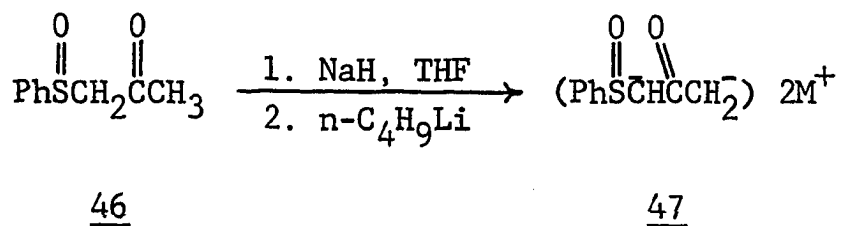


The dianion 42 reacted with esters to give 3,5-diketooesters 44²³ and with ketones and aldehydes to give hydroxyketoesters (45).^{24,25}

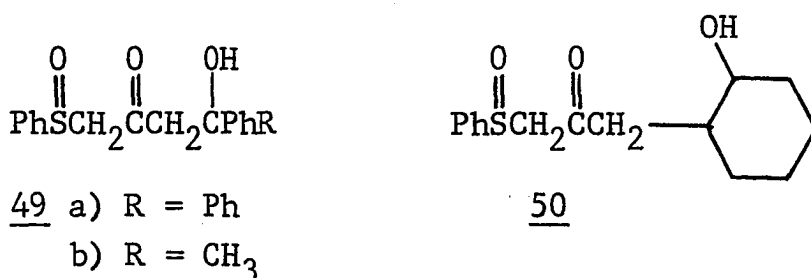
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Phenyl (2-oxopropyl)-sulfoxide (46) when reacted in tetrahydrofuran with sodium hydride followed by n-butyl lithium gave the corresponding 1,3-dianion 47.^{26,27} Alkylation of 47 occurred exclusively at the terminal position (C₃) to give 48 and evidence for alkylation at C₁ or

Scheme XII

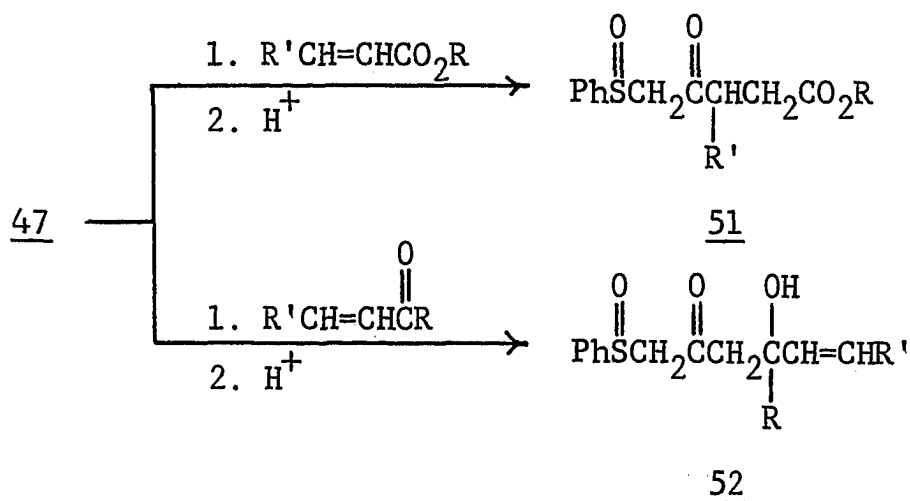


1,3-dialkylation was not found.²⁶ Analogues of 46 bearing an alkyl substituent at either C_1 ²⁸ or C_3 ²⁶ when converted to their corresponding 1,3-dianions also reacted at the terminal position with alkyl halides to give products of C_3 substitution. Reaction of 47 with benzophenone and acetophenone gave the 1,2-addition products, 49a and 49b. Cyclohexene oxide gave the hydroxyketosulfoxide 50.²⁶



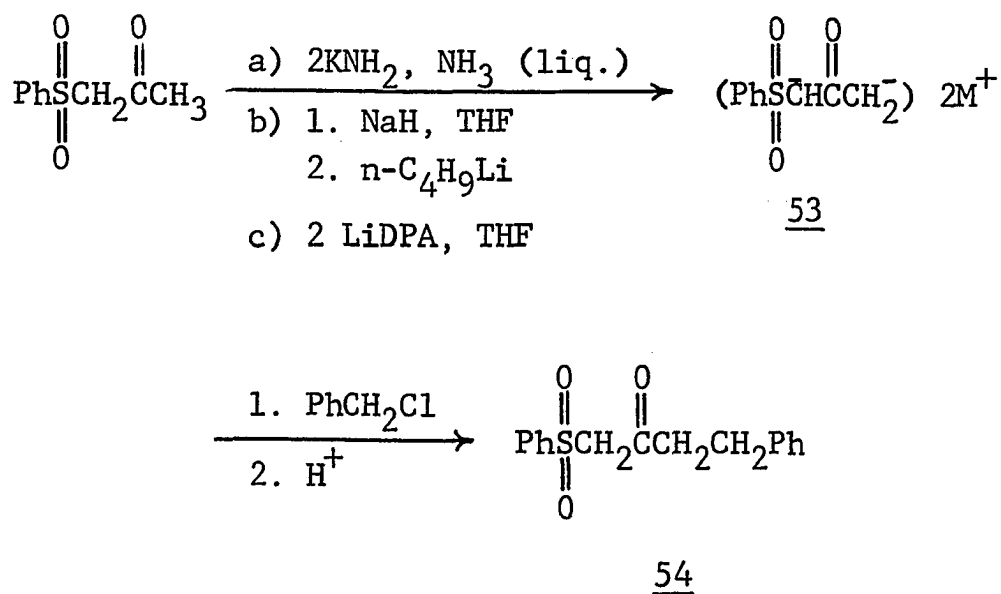
α, β -Unsaturated esters were found to react with 47 to yield solely 4-ketoesters 51, whereas α, β -unsaturated ketones gave exclusively the 1,2-addition products 52.²⁷

Scheme XIII



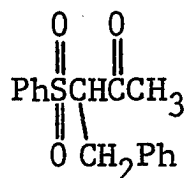
The phenyl (2-oxopropyl)-sulfone dianion (53) was obtained on reaction of the parent ketone with potassium amide in liquid ammonia.²⁸ It was also shown that dimetalation could be effected with sodium hydride followed by n-butyllithium in tetrahydrofuran or by lithium diisopropylamide.³⁰ Addition of benzyl chloride resulted in alkylation at the terminal carbon (C₃) to give the ketosulfone 54.²⁹ Alkylation of the monoanion with benzyl chloride

Scheme XIV

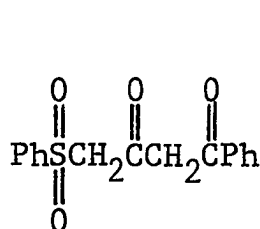


gave only the isomeric C₁ substitution product 55.²⁹ Acylation at C₃ was realized with methyl benzoate giving the

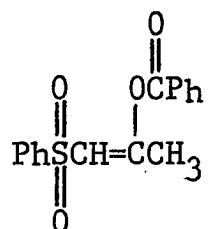
diketosulfone 56, while the reaction of the monoanion with benzoyl chloride gave only the O-acylation product 57.²⁹



55



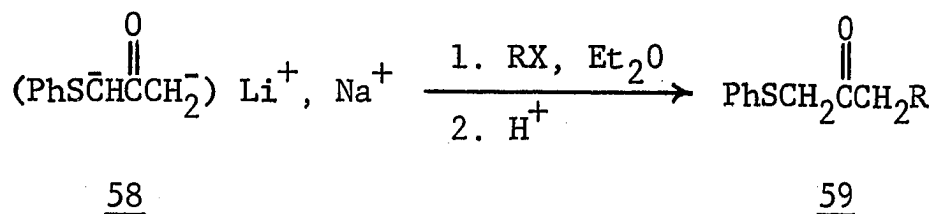
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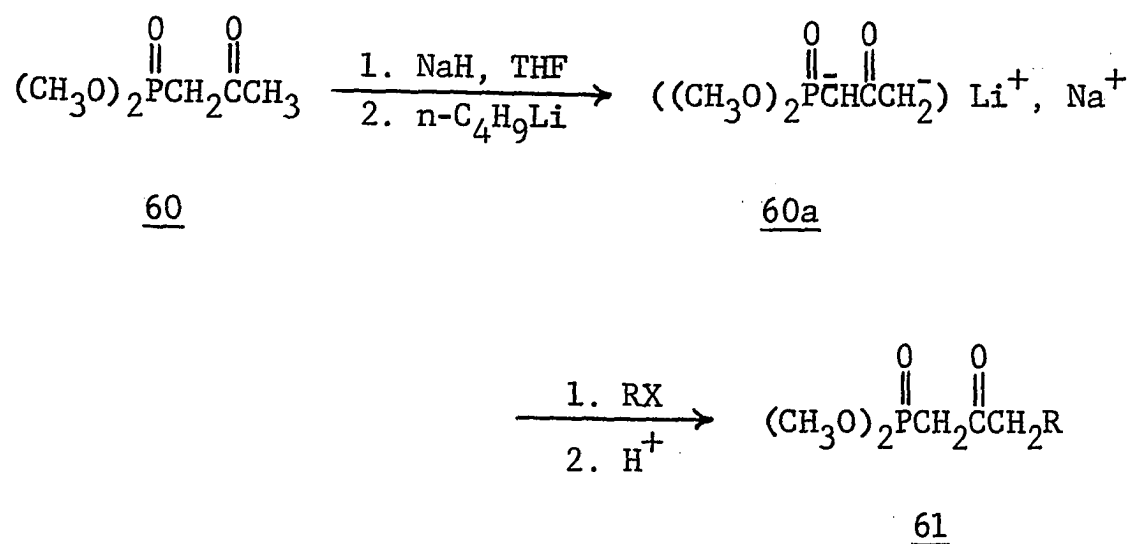
The phenyl (2-oxopropyl)-thiane dianion (58), generated by sequential metalation with sodium hydride and n-butyl lithium reacted with alkyl halides at the terminal carbon (C₃) to give a series of chain extended derivatives 59.³¹

Scheme XV



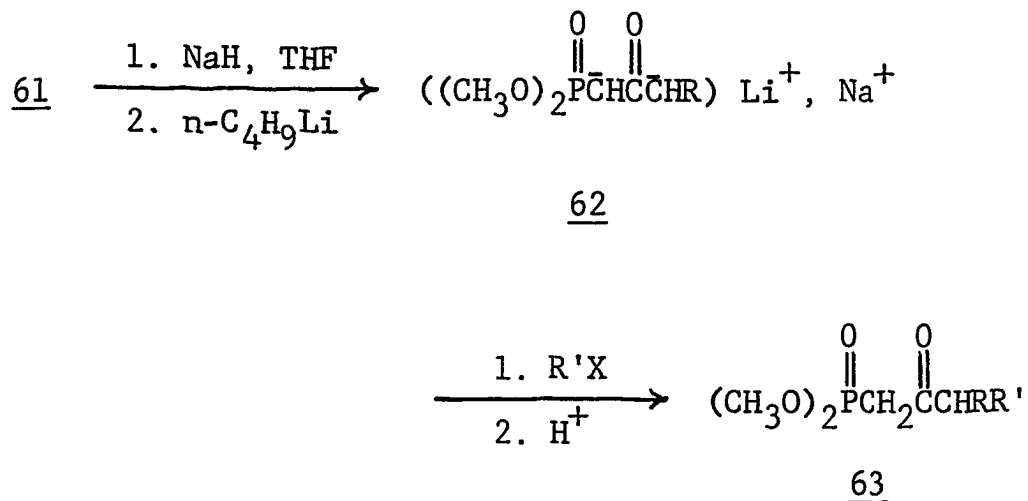
Dimethyl (2-oxopropyl)-phosphonate (60) was converted to the corresponding 1,3-dianion in a similar manner.³² Reaction with alkyl halides gave exclusively products of C₃ substitution 61.

Scheme XVI



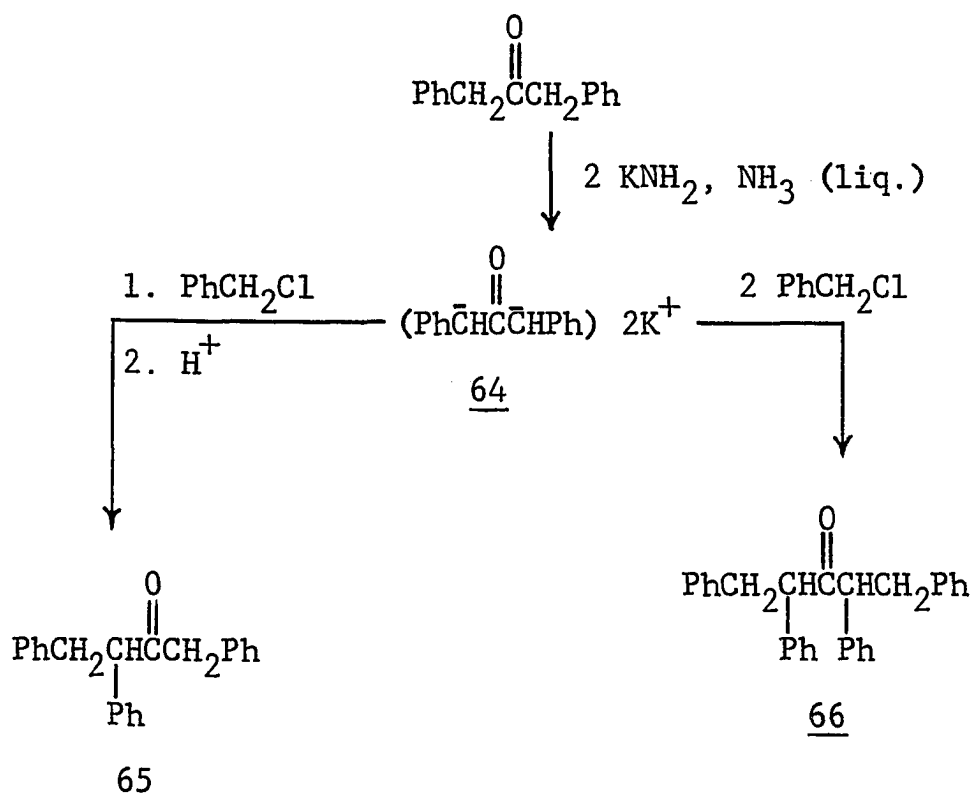
A second alkyl group was introduced at C₃ by reacting the 1,3-dianion generated from 61 with a second alkyl halide to give disubstituted derivatives 63.^{32,33}

Scheme XVII



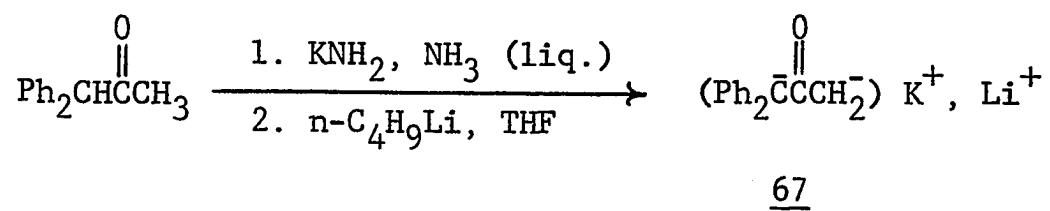
In addition to 1-phenyl-2-propanone (1), other aryl-acetones have been converted to their respective dianions. Thus, 1,3-diphenyl-2-propanone was converted to the dianion 64 with potassium amide in liquid ammonia which on reaction with either one or two equivalents of benzyl chloride give, respectively, the products of mono- and dibenzylation 1,2,4-triphenyl-3-butanone (65) and 1,2,4,5-tetraphenyl-3-pentanone (66).⁵

Scheme XVIII



1,1-Diphenyl-2-propanone was converted to the corresponding 1,3-dianion 67 by sequential metalation with potassium amide in liquid ammonia followed by n-butyllithium in tetrahydrofuran but was not reacted with alkylating agents.¹ A study of the reactions of this dianion with limited amounts of alkylating agents, since completed,³⁴ was undertaken by another member of our research group after the findings of the study to be discussed forthwith were obtained by this author.

Scheme XIX



RESULTS AND DISCUSSION

The published procedure of Hauser, Mao and Miles for the conversion of 1-phenyl-2-propanone (1) to the corresponding dianion 3¹ is a two step reaction involving formation of the alkali enolate with an alkali amide in liquid ammonia followed by the reaction of this intermediate with n-butyllithium in tetrahydrofuran (THF) as shown in Scheme I. Griffiths³¹ modified this procedure by using sodium hydride with THF as the solvent to form the enolate salt, thus eliminating the need to change solvent systems. A limitation of sodium hydride in this type of reaction is its low reactivity, principally due to its low solubility in most organic solvents.³⁵ Because of this, attempts to form sodium enolates from readily enolizable ketones often is severely impeded by competing self-condensation.³⁶ Although the alkali enolates of 1 are stable towards self-condensation, it was anticipated that ketones which do form reactive enolate salts would be converted to their respective dianions and their reactions studied. For a generally applicable method to achieve this conversion, the reagent required to form the intermediate enolate anion was one that was readily handled and possessed sufficient reactivity to readily ionize the ketone without competing side reactions. The

reagent of choice proved to be potassium hydride which was recently shown by Brown³⁷ to readily convert enolizable ketones, including acetone, to potassium enolates without competitive side reactions.

Formation and Reactions of the Potassium Enolate
of 1-Phenyl-2-Propanone (2)

Following the procedure of Brown,³⁸ 1-phenyl-2-propanone was added to a stirred suspension of potassium hydride in THF under a nitrogen atmosphere to give an orange-red solution of the potassium enolate 2. The reaction was vigorous and exothermic but could be regulated by controlling the rate of addition and with cooling. In several instances the reaction was monitored by collection of the hydrogen evolved. The reaction ceased once the theoretical amount of gas was collected indicating that the ketone had completely reacted. Neutralization with H₂O gave only 1-phenyl-2-propanone. Analysis of the reaction mixture by gas chromatography (gc) failed to show evidence of any side reaction products.

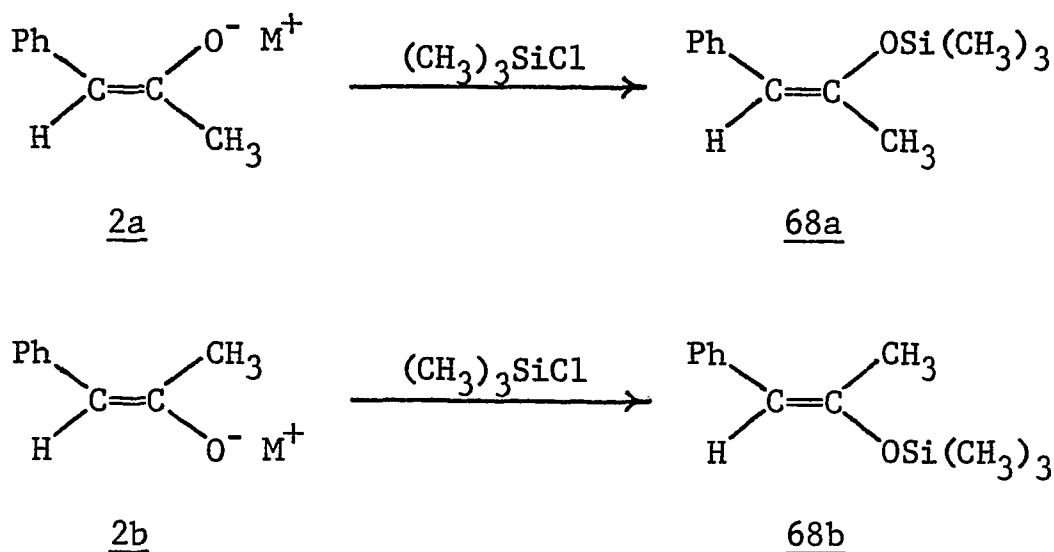
Ionization was found to proceed smoothly in bis-(methoxy)-ethane but was substantially slower in diethyl ether (Et₂O). Addition of small amounts of THF to diethyl ether had a significant catalytic effect and red-orange solutions of 2 (M⁺ = K⁺) were readily obtained. This

apparently is not due to increased solubilization of the solid hydride as potassium hydride is reportedly "completely insoluble" in THF.³⁷ Rather, this may be due to complexation of potassium hydride by THF in a manner much like the complexation of alkali salts by macrocyclic polyethers.³⁹ Several reactions were run in diethyl ether containing by volume 15% THF as the cosolvent. This mixed solvent system will subsequently be referred to as THF-Et₂O.

Ionization of 1 can give two possible geometric isomers of the enolate salt 2, one possessing the Z configuration (2a) and the other possessing the E configuration (2b) which differ in the spatial relationship between the phenyl group and oxygen around the C₁-C₂ bond. The isomer ratios of 2a and 2b generated under various conditions have been determined by trapping with chlorotrimethylsilane.^{40,41} Reaction of the potassium enolate generated from 1 with potassium hydride in both THF and THF-Et₂O gave as the only product Z-1-phenyl-2-(trimethylsiloxy)-1-propene (68a) indicating that the enolate anion obtained under these conditions possessed only the Z configuration. This is consistent with the results reported for the ionization of 1 with sodium hydride as trimethylsilylation gave 98% 68a and 2% 68b.⁴⁰

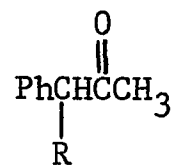
Structure assignment of this product was made through the NMR spectrum which in deuteriochloroform showed a broad

Scheme XX



multiplet centered at δ 7.33 that integrated for five protons and assigned to the phenyl group and a singlet at δ 5.38 that integrated for one proton and assigned to the vinylic proton. This compared closely with the published spectrum of the Z-isomer 68a in carbon tetrachloride³⁵ which showed a similar broad multiplet for the absorptions of the phenyl protons and a singlet at δ 5.32 for the absorption of the vinylic proton. The NMR spectrum of the E isomer 68b in CCl_4 was also published and was characterized by a slightly broadened singlet absorption for the phenyl protons and a sharp singlet absorption at δ 5.77 for the vinylic proton.³⁵ From this it was concluded that the enolate anion formed on metalation of 1 with potassium hydride was largely, if not exclusively, the Z-isomer 2a.^{40,41}

The potassium enolate 2a was reacted with several alkyl halides in both THF and THF-Et₂O to give a series of 1-alkyl-1-phenyl-2-propanones 69. The results are sum-



69

marized in Table I. Reaction with iodomethane preceeded rapidly and smoothly to give in good yield 3-phenyl-2-butanone. The other alkyl halides reacted less rapidly, often requiring reaction periods of eighteen to twenty-four hours. The long reaction times were feasible due to the stability of the enolate anion towards condensation with the reaction product and also because of the decreased acidity of the remaining benzylic proton of the product. Thus, proton exchange equilibria commonly observed between more reactive enolate anions, such as that of cyclohexanone and its alkylation products,³⁶ were not observed in this case as analysis by gc of the crude reaction products did not reveal evidence for 1,1-dialkylation or condensation.

A large difference in reactivity was observed between benzyl chloride and benzyl bromide. Benzyl chloride failed to react with 2a after 1.5 hours whereas 3,4-diphenyl-2-butanone was isolated in 60% yield from the reaction.

TABLE I
ALKYLATION OF THE POTASSIUM ENOLATE 2a WITH ALKYL HALIDES

<u>RX</u>	<u>Solvent</u>	<u>Time (hrs)</u>	<u>Product</u>	<u>Yield (%)^a</u>	<u>Reference</u>
CH ₃ I	THF	2.0	3-Phenyl-2-butanone	69	58
CH ₃ I	THF-Et ₂ O ^b	1.0	3-Phenyl-2-butanone	76	58
C ₂ H ₅ I	THF-Et ₂ O ^b	18.0	3-Phenyl-2-pentanone	87	58
n-C ₄ H ₉ I	THF	18.0	3-Phenyl-2-heptanone	77	58
n-C ₄ H ₉ I	THF-Et ₂ O ^b	20.0	3-Phenyl-2-heptanone	76	58
(CH ₃) ₂ CHBr	THF	24.0	4-Methyl-3-phenyl-2-butanone	(60) ^c	
(CH ₃) ₂ CHBr	THF-Et ₂ O ^b	36.0	4-Methyl-3-phenyl-2-butanone	(15) ^c	
PhCH ₂ Br	THF	1.5	3,4-Diphenyl-2-butanone	60	58
PhCH ₂ Cl	THF	1.5	3,4-Diphenyl-2-butanone	(n.r.) ^c	

^aIsolated. ^b15% THF by volume in diethyl ether. ^cNormalized yields as determined by gas chromatography.

of 2a with benzyl bromide over the same period. This was of some interest as benzyl chloride is commonly used as a benzylating agent often with enolate anions. A comparison of the relative reactivities of several alkyl halides was made by Conia⁴² and benzyl bromide was found to be approximately thirty-seven times as reactive as benzyl chloride. The greater polarizability of bromine may well account for the difference in relative reactivities of these benzyl halides.

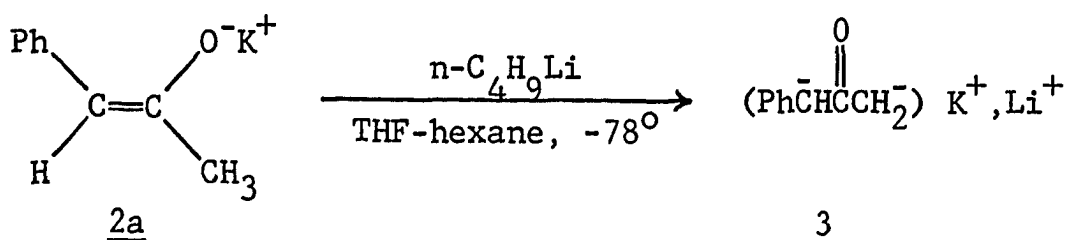
The effects of solvent on the rate of alkylation of 2a were qualitatively demonstrated in the reactions of 2a with 2-bromopropane in both THF and THF-Et₂O. Although this reaction proceeded slowly in both solvents at room temperature, product formation, as determined by gas chromatography, was approximately 60% complete after twenty-four hours in THF and about 15% complete after thirty-six hours in THF-Et₂O. The only other component present was 1-phenyl-2-propanone. The slow rate of reaction can be partially attributed to the low relative reactivity of 2-bromopropane and also to the difference in solvation of the potassium salt of 2a by the two solvent systems. Zook and Relahan have examined the reactions of alkyl halides with sodium enolates of primary and secondary alkyl ketones¹⁶ and found that the rate of alkylation increased with increasing solvation power of the ether solvent.⁴³ In addition, House and coworkers reported that

the lithium and sodium salts of 2a exist as solvent separated ions in THF and primarily as contact ion pairs in diethyl ether³⁵ reflecting the significantly higher solvation power of THF. The difference in rates of product formation in 2-propylation of 2a with 2-bromopropane found suggests that 2a ($M^+ = K^+$) may also exist as solvent separated ions in THF and primarily as contact ion pairs in THF-Et₂O.

Formation and Reactions of the 1-Phenyl-2-Propanone Dianion (3)

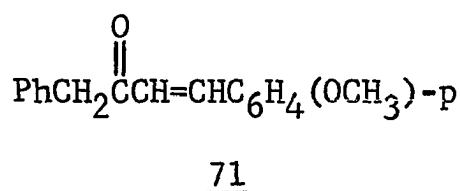
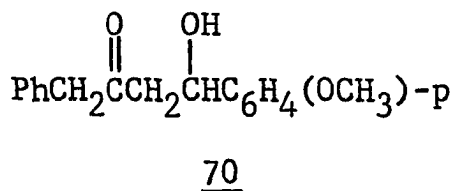
Addition of a slight excess over one equivalent of n-butyllithium in hexane to a solution of 2a ($M^+ = K^+$) in either THF or THF-Et₂O at -78° resulted in immediate formation of the 1-phenyl-2-propanone dianion (3) obtained as an intensely dark red solution. The reported procedure called for addition to take place at ambient temperature,¹ however, cleavage of THF is minimized by lowering the reaction temperature.⁴⁴ The dianion 3 appeared to be quite stable over long periods and did not undergo loss or change of color on warming.

Scheme XXI



Reaction of 3 with p-methoxybenzaldehyde gave the unreported beta-hydroxyketone 70 in 44% yield which in turn was dehydrated to the unsaturated ketone 71.¹

Attempts to obtain 1,3,7-triphenyl-1,6-heptanedione, the reported product isolated from the reaction of 3 with 1,3-diphenyl-2-propen-1-one,¹ were unsuccessful. The unidentified product was obtained as a white solid with a melting point of 183-185°; the reported melting point of the Michael addition product was 114°.¹



The main part of this investigation involved the reactions of the dianion 3 with alkyl halides. When a slight excess of one equivalent of iodomethane was added to a solution of 3 in THF at 0°, the intense red color of the dianion soon disappeared and a white precipitate formed. After neutralization and workup, analysis of the crude product by gc revealed the presence of a two component mixture consisting of 3-phenyl-2-butanone, the product of C₁ alkylation identified by comparison of the retention time with that of an authentic sample, and a component tentatively identified as 1-phenyl-2-butanone the product of alkylation at C₃, in a ratio of 3 to 2.

Alkylation under similar conditions with iodoethane and 1-iodobutane again led to the formation of two component product mixtures with only traces of 1-phenyl-2-propanone detected by gc. Unexpectedly (vide supra), the amount of C_1 alkylation increased. Iodoethane gave a product mixture where the C_1 alkylation product predominated by a ratio of approximately 5.7 to 1, and 1-iodobutane gave a product mixture where the C_1 alkylation product predominated by a ratio of approximately 19 to 1. These C_1 alkylation products, 3-phenyl-2-pentanone and 3-phenyl-1-heptanone were also identified by comparison of the retention times with those of authentic samples. Since the completion of this study the minor products obtained have been conclusively established as being the products of C_3 alkylation by other members of this research group.³⁴ These initial results indicated that unlike other acetone derived dianions (6), alkylation of 3 was governed by other factors.

The dianion 3 was next reacted with a series of alkyl halides, both primary and secondary, that varied widely in relative reactivities. A solution of 3 in either THF or THF-Et₂O was treated with a slight excess of one equivalent of alkyl halide under conditions similar to those described above, and after allowing the reaction to proceed for a prescribed period, usually four hours, it was quenched with H₂O. When feasible, the products obtained were

purified by distillation under reduced pressure and characterized by physical and chemical means. The results are summarized in Table II. Attempts to maximize yields were not made and with one exception, 4-methyl-3-phenyl-2-hexanone, all compounds prepared by this method have been described in the literature.

With the exception of the highly reactive alkyl halides, alkylation generally occurred preferentially and often with high regiospecificity at C_1 . Iodomethane and benzyl bromide gave a mixture of products in which the C_1 substitution product predominated only slightly. It was found that alkylation of C_1 increased with increasing length of the alkyl chain. Regioselectivity also increased as the number of substituents on the halogen bearing carbon was increased. A representative example is 2-bromopropane which gave almost exclusively 4-methyl-3-phenyl-2-pentanone (68% isolated yield). Those alkyl halides which are prone to base catalysed elimination such as 2-bromobutane and bromocyclohexane gave good yields of C_1 substitution products which suggests that under these conditions elimination occurred only to a limited extent.

When the leaving group was changed from either bromide to chloride or iodide to chloride the increased regioselectivity towards alkylation at C_1 was observable experimentally only when a large change in relative reactivities was elicited. Thus, in benzylation, benzyl bromide gave

TABLE II
ALKYLATION OF 1-PHENYL-2-PROPANONE DIANION (3)
WITH ALKYL HALIDES

<u>RX</u>	<u>Solvent</u>	<u>Time (hrs)</u>	<u>Product</u>	<u>Yield (%)^a</u>	<u>Reference</u>
CH ₃ I	THF	2	3-Phenyl-2-butanone	(65) ^b	
			1-Phenyl-2-butanone	(35)	
CH ₃ CH ₂ I	THF	4	3-Phenyl-2-pentanone	79	58
CH ₃ CH ₂ I	THF-Et ₂ O	4	3-Phenyl-2-pentanone	54	58
n-C ₄ H ₉ I	THF	4	3-Phenyl-2-heptanone	58	58
n-C ₄ H ₉ I	THF-Et ₂ O	1	3-Phenyl-2-heptanone	54	58
n-C ₄ H ₉ Cl	THF	8	3-Phenyl-2-heptanone	82	58
(CH ₃) ₂ CHBr	THF	4	4-Phenyl-3-phenyl-2-pentanone	68	58
(CH ₃) ₂ CHBr	THF-Et ₂ O	6	4-Phenyl-3-phenyl-2-pentanone	59	58
(CH ₃) ₂ CHCH ₂ Br	THF	4	5-Methyl-3-phenyl-2-pentanone	72	58
CH ₃ CH ₂ CHBr CH ₃	THF	4	4-Methyl-3-phenyl-2-hexanone	65	

TABLE II (CONTINUED)
 ALKYLATION OF 1-PHENYL-2-PROPANONE DIANION (3)
 WITH ALKYL HALIDES

<u>RX</u>	<u>Solvent</u>	<u>Time (hrs)</u>	<u>Product</u>	<u>Yield (%)^a</u>	<u>Reference</u>
cyclo-C ₅ H ₉ Br	THF	3	1-Cyclopentyl-1-phenyl-2-propanone	62	60
cyclo-C ₆ H ₁₁ Br	THF	4	1-Cyclohexyl-1-phenyl-2-propanone	61	61
cyclo-C ₆ H ₁₁ CH ₂ Br	THF	4	4-Cyclohexyl-3-phenyl-2-butanone	71	62
PhCH ₂ Cl	THF	3	3,4-Diphenyl-2-butanone	47	58
PhCH ₂ Br	THF	3	Mixture ^{b,d}		
o-tolyl-CH ₂ Br	THF	3	Mixture ^{b,d}		

^aIsolated. ^bAs determined by gas chromatography. ^cSatisfactory physical and analytical data were obtained for this compound. ^dProducts were not identified.

a product mixture which contained in only slight excess the product of C₁ alkylation 3,4-diphenyl-2-butanone whereas benzyl chloride showed high selectivity for alkylation at C₁ and 3,4-diphenyl-2-butanone (47%) was isolated on purification. When 1-chlorobutane was used in place of 1-iodobutane little increase in selectivity was observed experimentally as 1-iodobutane already demonstrated a high regioselectivity for alkylation at C₁. It should be noted that 1-iodobutane has a much lower relative reactivity than benzyl bromide.⁴²

Whether regioselective alkylation at C₃ could be achieved by using extremely reactive alkylating agents was not determined. Such reagents, for example Meerwein's reagent, may instead give products of O-alkylation⁴⁵ or even O,C-dialkylation.

The solvent media which was found to greatly influence the rate of alkylation of the potassium enolate 2a appeared to have little effect on the rate of alkylation of the dianion 3. Isolated yields of C₁ substituted products from iodoethane, 1-iodobutane, and 2-bromopropane in THF-Et₂O ranged from 50-60% over reaction times of under six hours. These product yields are comparable to those obtained with the same reagents in THF. Determination of the role of THF in solvation of the dianion 3 has yet to be made, so it is not known whether the reactivity of the dianion is for the most part independent of general

solvent effects or whether in THF-Et₂O this dianion is selectively solvated by THF perhaps increasing the solubility and leading to enhanced reactivity.

The formation of the dianion 3 was reasonably well established by Hauser and coworkers.¹ They offered substantiating evidence of dianion formation by deuteration of the reaction intermediate obtained after addition of n-butyllithium to a solution of 2 in THF. The amount of deuterium incorporated as calculated from the NMR spectrum was reported to be 0.95-0.98D at C₃ and 1.00D at C₁. This was repeated in this study to determine the extent of conversion of 2a to 3 but it was found that the deuterium content at C₁ and C₃ varied and was caused by deuteriumhydrogen exchange during workup.

Regiospecific alkylation of a stabilized acetone derived dianion 6 at C₁ has not been observed previously. Only exclusive alkylation at C₃ of 6 has been found to occur (vide supra). Since alkylation at C₁ is the expected mode for the enolate anion 2a, it remained to be established beyond doubt that the reactive intermediate being alkylated was indeed the dianion 3 rather than a different reactive intermediate such as one similar to the enolate anions 2a or 2b.

To obtain the required information NMR spectroscopy was employed. The NMR spectrum of the potassium enolate 2a was recorded in THF with tetramethylsilane as the

external standard. The absorptions of the ortho, meta and para ring protons, centered at δ 6.73 were clearly distinguishable, each split into a complex multiplet. The absorption signal of the vinyl proton was a sharp singlet at δ 4.50 (Table III). This spectrum is comparable to the spectrum published by House and coworkers³⁵ of the Z-isomer 2a ($M^+ = Na^+$) recorded in THF which also shows the very complex splitting pattern of the phenyl protons centered at δ 7.10 and the sharp singlet of the vinyl proton at δ 4.93. The upfield shift of the vinyl proton when the counter ion is changed from Na^+ to K^+ is indicative of an increase in negative charge at C_1 .³⁵ The spectrum lends added support to the assignment of the Z configuration to the potassium enolate by trimethylsilylation.

Following this, the NMR spectrum of the solution obtained from the reaction of 2a with n-butyllithium was recorded in THF-hexane. In this spectrum, the region upfield from δ 3.80 was almost completely obscured by resonance absorptions of THF and hexane. The absorptions of the phenyl ring protons were not obscured and showed a marked upfield shift from the positions of the signals of the ring protons of 2a. Absorptions that could be attributed to the presence of 2a or 2b were not found in this spectrum as neither the complex splitting pattern of the phenyl protons characteristic of 2a nor the slightly broadened singlet exhibited by the phenyl protons of 2b³⁵

TABLE III
CARBANION H NMR CHEMICAL SHIFT DATA (δ)

Anion	Counter-ion	Recording Solvent	Absorptions				Ref.
			Phenyl	H ₁	H ₂	H ₃	
<u>2a</u>	K ⁺	THF	6.27 (1H, m, para) 6.73 (2H, m, meta) 7.32 (2H, m, ortho)	4.50 (s)	--	-- ^a	--
<u>2a</u>	Na ⁺	THF	6.7 ^b (m, para) 7.1 ^b (m, meta) 7.5 ^b (m, ortho)	4.93 (s)	--	-- ^a	35
<u>2a</u>	K ⁺	NH ₃ (liq.)	6.57 (para) 7.01 (meta) 7.64 (ortho)	4.67 (s)	--	1.72 (3H)	55
<u>2a</u> ^c	M ⁺ ^f	THF/hexane	6.25 (m, para) 6.72 (m, meta) 7.30 (m, ortho)	4.50 (s)	--	-- ^a	--
<u>2a</u> ^d	M ⁺ ^f	THF-d ₈ / hexane	6.25 (m, para) 6.70 (m, meta) 7.28 (m, ortho)	4.50 (s)	--	2.02	64
<u>2b</u>	Li ⁺	DME ^e	6.8 ^b (s)	5.25 (s)	--	--	35
<u>3a</u>	K ⁺ , Li ⁺	THF/hexane	5.43 (brd m, para) 6.30 (brd m, ortho and meta)	-- (a)	--	-- ^a	--

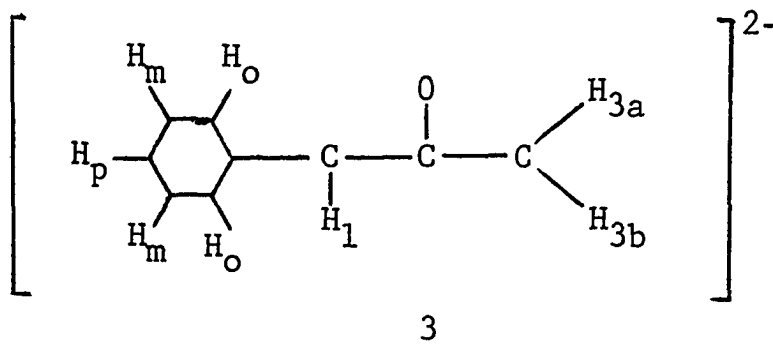
TABLE III (CONTINUED)
CARBANION H NMR CHEMICAL SHIFT DATA (δ)

Anion	Counter-ion	Recording Solvent	Absorptions				Ref.
			Phenyl	H ₁	H ₂	H ₃	
<u>3a</u>	K ⁺ , Li ⁺	THF-d ₈ /hexane ^e	5.47 (1H, brd m, para) 6.33 (4H, brd m, ortho and meta)	3.82 (1H, brd s)	--	2.60 (2H, brd d)	--
<u>74a</u>	Li ⁺	THF-d ₈	5.70 (m, para) 6.3 ^b (m, para) 6.6 ^b (m, meta)	4.1 (d) ^b	6.7 (m) ^b	2.9 (m) ^b	56
<u>74c</u>	K ⁺	THF-d ₈	6.70 (para)	--	--	--	56
<u>74a</u>	K ⁺	NH ₃ (liq.)	5.48 (para) 5.90 (1H, ortho) 6.2-6.5 (3H, ortho, meta)	4.22 (1H)	6.63 (1H)	2.93 (1H) 3.39 (1H)	55
<u>72</u>	M ⁺ ^f	THF/hexane	6.73 (brd m)	--	--	--	--

^aProton absorptions obscured by solvent absorptions. ^bEstimated from the published spectrum. ^cFrom titration with D₂O. ^dFrom titration with H₂O.
^eDimethoxyethane. ^fWhether the counterion is either Li⁺ or K⁺ is not known.

were found. In addition, signals assignable to the vinylic protons which should also be observable were not found. From this it was concluded that the conversion of 2a to the dianion 3 was complete, and, as the NMR spectrum did not change with time, reprotonation at C₃ was not taking place.

A complete spectrum of the dianion 3 was recorded in THF-d₈/hexane at a temperature of 43° and with tetramethylsilane as an external standard. The following absorptions were observed: a multiplet, somewhat broadened and poorly resolved, centered at δ 6.33(4H), assigned to the ortho and meta ring protons; a broad multiplet centered at δ 5.47(1H) assigned to the para ring proton; a broad singlet at δ 3.82(1H) assigned to H₁; and a partially resolved doublet centered at δ 2.60(2H) assigned to H_{3a} and H_{3b}.

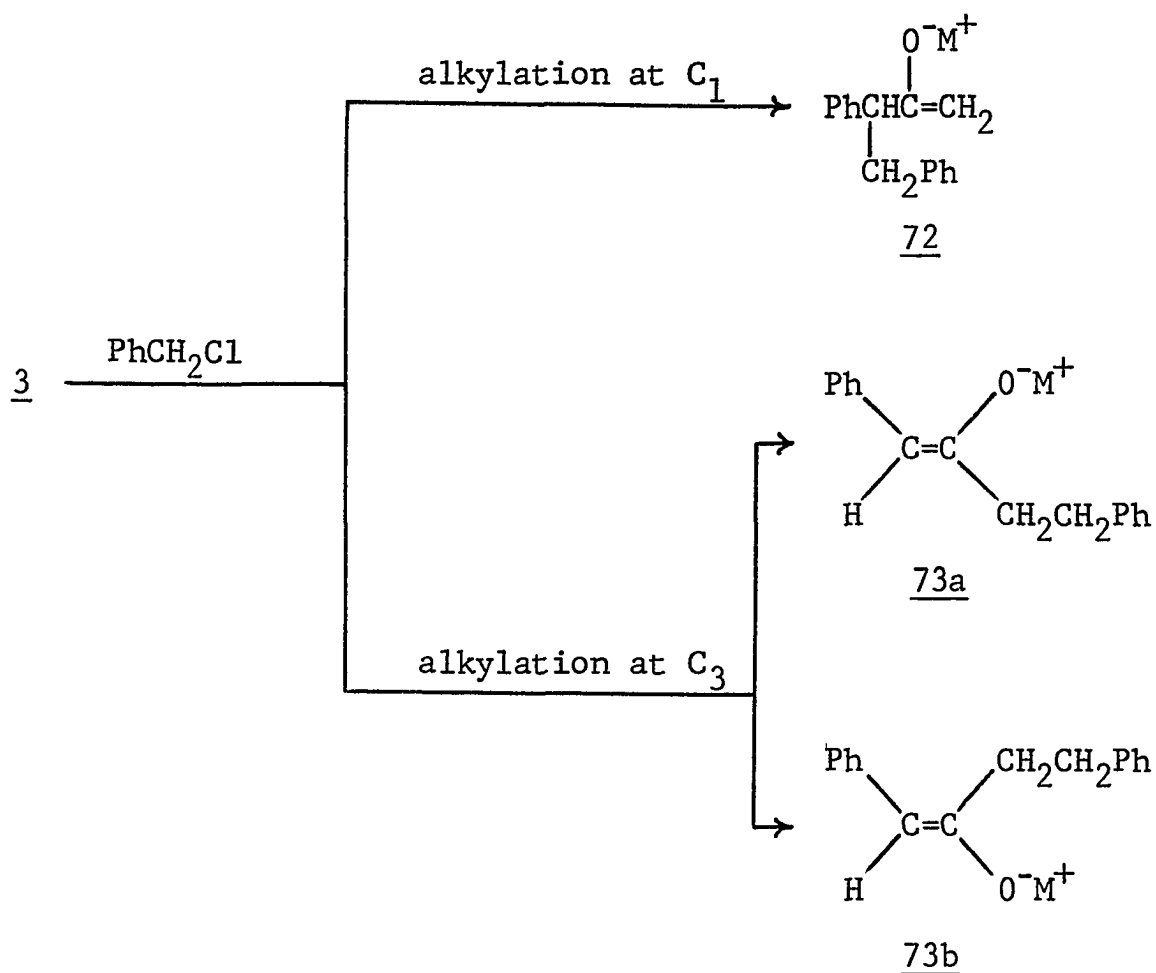


With the evidence for complete dianion formation and lack of reprotonation obtained by NMR, the possibility that the C₁ alkylation products originated by alkylation of an enolate anion was discounted. Supporting evidence

that these products originated by alkylation of the dianion 3 was also obtained through the use of NMR.

A solution of the dianion 3 was prepared as before in THF-hexane and the NMR spectrum recorded. The expected resonance absorption pattern of the phenyl protons was observed. Benzyl chloride was added to the stirred solution until the intense red color of the dianion had permanently disappeared. The NMR spectrum of the resulting solution was then recorded (Table III). It was expected that benzylation at C_3 would give rise to an enolate anion, either 73a or 73b whose NMR spectrum would resemble the NMR spectrum of either 2a or 2b. Such a spectrum would be readily identifiable by the presence of a signal due to the absorption of the vinylic proton on C_1 and should be located close to the positions of the vinylic proton signals of either 2a or 2b as it is not expected that the isolated benzyl group would have an extensive influence on the environment of the C_1 proton. If, however, alkylation took place at C_1 to give 72 the environment around C_1 would be greatly altered. The absorptions of the phenyl protons should collapse into a singlet reflecting the loss of charge delocalized into the ring. The absorption of the C_1 proton, now a methine hydrogen, should be located considerably upfield from the region of the C_1 vinylic proton absorptions. The signals of the two C_3 vinylic protons should also be located further upfield.⁴⁶ The NMR spectrum

Scheme XXII



of the solution did display resonance absorptions that were expected for the enolate anion formed on benzylation at C_1 . Other than the resonance absorptions of THF and hexane that obscured the region of the spectrum upfield from δ 3.8, the only signals observed were a broad absorption at δ 6.73 and a broad singlet at δ 6.81 and are clearly attributable to the protons of the two phenyl rings. The NMR spectrum of the E-isomer 73b would be expected to have singlets for the phenyl proton absorptions, as in the spectrum of 2b

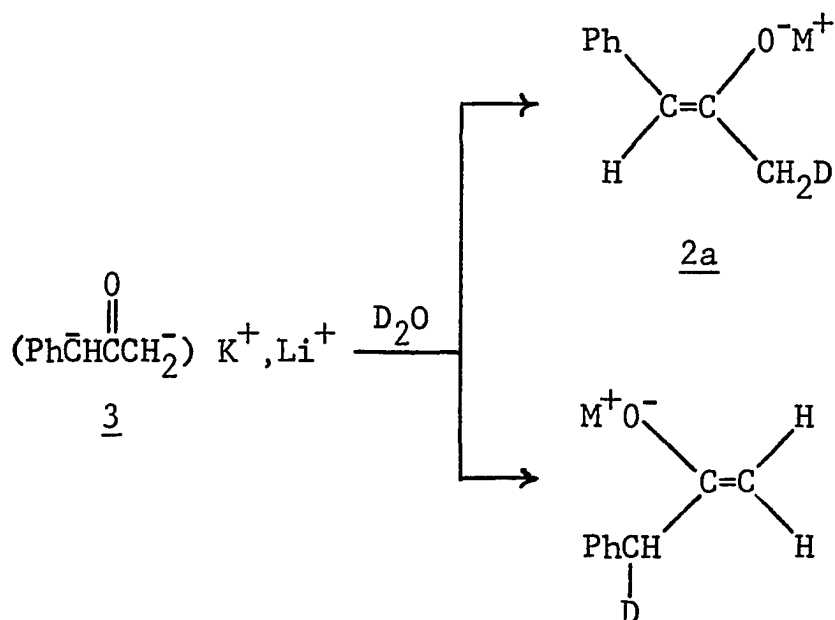
only a slightly broadened singlet for the phenyl proton absorptions was observed. In addition, an observable absorption due to the vinylic proton should also have been observed in the spectrum of 73b. As it was not, benzylation at C_1 giving rise to 72 must have occurred and with very high regiospecificity.

Additional support for the formation of 72 has been obtained since by other members of this research group by trapping with chlorotrimethylsilane the intermediate obtained on the reaction of 3 with 2-bromopropane to yield 4-methyl-3-phenyl-2-(trimethylsiloxy)-1-pentene.³⁴

The site of initial protonation of the dianion 3 was determined also by NMR in a manner similar to the determination of the site of alkylation. A solution of 3 was prepared in THF-hexane and D_2O was then added until the intense red color was completely discharged giving a light red solution. The NMR spectrum of this solution compared very closely with the spectrum of 2a ($M^+ = K^+$) with the distinctive multiplets of the ortho, meta and para ring protons and the singlet of the vinylic proton located at δ 4.50 (Table III). From this spectrum it was determined that initial protonation of the dianion 3 occurred exclusively at C_3 to give only the Z-isomer of the enolate anion 2a. This is in keeping with the principle of microscopic reversibility since the dianion 3 has been shown to arise from the deprotonation of 2a at C_3 .

In general, various studies have shown that a ketone of the general type 4 when converted to its corresponding dianion 6 via the enolate anion 5 reacts with alkylating agents, carbonyl compounds, esters, conjugated systems and epoxides at the site of secondary ionization. In none

Scheme XXIII

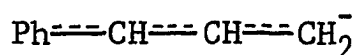


of the systems previously studied was alkylation of the methine carbon observed. The high reactivity of the secondary site indicates that the initial charge formed on secondary ionization remains largely localized at this site maintaining the high basicity of this position.

As with other dianions derived from ketones of the general type 4, the dianion of 1-phenyl-2-propanone (3) underwent 1,2-addition at the terminal position.¹ Also, it was established that the initial site of protonation

was at the terminal position. Reaction with alkyl halides, however, led to preferential alkylation at C₁ whereas alkylation of all other ketone dianion systems is at the position analogous to C₃. It must be concluded, then, that the dianion 3 is a type of reactive intermediate different from other dianion systems derived from ketones of the general type 4, and is, in fact, representative of a heretofore unrecognized class of stabilized ketone dianions.

The unusual chemistry displayed by the dianion 3 is not without analogous precedent as the chemistry of the propenylbenzene anion (74) on comparison proves to be quite similar. Campbell and Young⁴⁷ showed that quenching of 74



74

(M⁺ = Na⁺) in liquid ammonia with the proton donors ammonium chloride, methanol, and phenylethyne gave approximately 85% 1-propenylbenzene and 15% 2-propenylbenzene. Quenching of the sodium salt of 74 in pentane with methanol gave 74% 2-propenylbenzene and 26% 1-propenylbenzene⁴⁸ suggesting that in less polar solvents protonation occurred preferentially at C₁ rather than C₃. As excess sodium amide was present in the reaction mixture, the possibility that equilibration occurred could not be discounted. Herbrandson

and Mooney⁴⁹ observed similar results on quenching of the lithium salt of 71 in liquid ammonia with ammonium chloride and in diethyl ether with methanol. In the former case, 80% 1-propenylbenzene and 20% 2-propenylbenzene was obtained and in the latter case approximately 54% 1-propenylbenzene and 48% 2-propenylbenzene were obtained.

Acetophenone reacted with the sodium salt of 74 in liquid ammonia,⁵⁰ as did benzophenone with the lithium salt of 74 in diethyl ether,⁴⁹ at C₃ to give, respectively, 1,4-diphenyl-4-hydroxy-1-pentene and 4-hydroxy-1,4,4-triphenyl-1-butene.

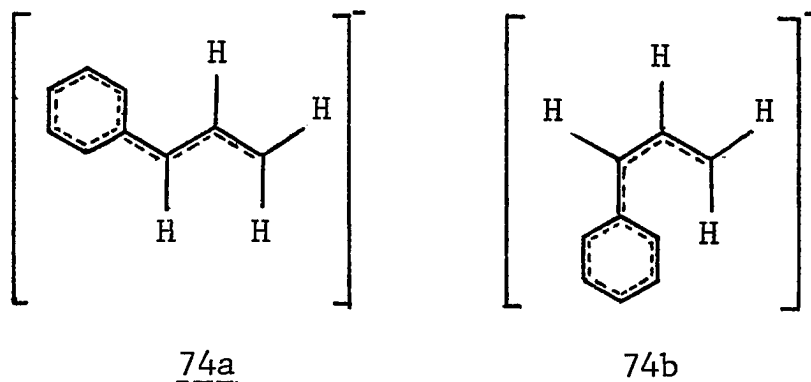
Reaction of 74 ($M^+ = Na^+$) in liquid ammonia with benzyl chloride gave 3,4-diphenyl-1-butene,⁵¹ the product of alkylation at C₁. Methylation with several methylating agents, including iodomethane was shown to occur almost exclusively at C₁.⁵² In addition, alkylation of 74 ($M^+ = Na^+$) in liquid ammonia with allylic halides gave mainly products of C₁ substitution^{53,54} without rearrangement of the allylic moiety indicating that alkylation proceeded by an S_N2 mechanism.⁵⁴ The same reactions when run in pentane did yield products of both C₁ and C₃ substitution and with some rearrangement of the allylic moiety and it was suggested that this reaction in a less polar solvent was partially S_N1 in character.⁴⁸

The NMR spectrum of the carbanion 74 has been recorded in both liquid ammonia⁵⁵ and tetrahydrofuran⁵⁶ with lithium,

sodium and potassium as the counterions. The resonance absorptions of the ortho and meta ring protons were found between δ 5.90 and δ 6.70, the ortho proton absorptions being slightly upfield from the absorptions of the meta protons. The absorption of the para ring proton was found approximately 0.5 ppm upfield from the signals of the other ring protons (Table III). In liquid ammonia, with potassium as the counterion, the absorption of the para proton appeared at δ 5.48.⁵⁵ In THF, with lithium or sodium as the counterions, this absorption appeared at δ 5.70⁵⁶ and with potassium as the counterion, this absorption was found at δ 5.63.⁵⁶ The large upfield shift of the phenyl proton absorptions when compared with the phenyl proton absorptions of the neutral molecule (δ 7.10 for 1-propenylbenzene and 2-propenylbenzene)⁵⁷ is attributed to extensive delocalization of the negative charge into the ring. The large upfield shift of the para proton absorption is an indication of the degree of charge delocalization and consequently the degree of association of the carbanion and its counterion which is dependent on both the nature of the counterion and the solvation power of the solvent.

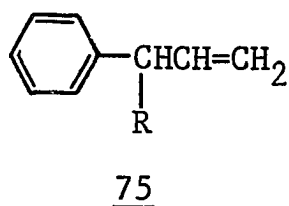
The structure of the propenylbenzene anion in solution as deduced from the NMR spectra was reported to be planar with the C_1 and C_2 hydrogens oriented trans (74a).^{55,56} A planar structure with the C_1 and C_2 hydrogens oriented

cis (74b) was considered to be subject to steric crowding.⁵⁵ The relationship of 1-phenyl-2-propanone and

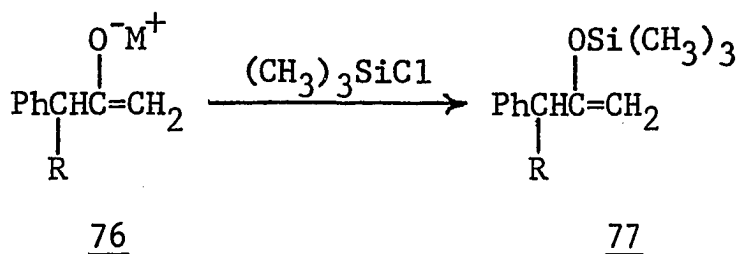


1-propenylbenzene is readily apparent as the tautomeric enol of this ketone is 2-hydroxy-1-propenylbenzene. Enolate anion formation can be considered simply as conversion of the alcohol to the alkoxide salt, with 2a being analogous to trans-1-propenylbenzene. Secondary ionization by removal of a proton at C_3 from 2a is comparable to ionization of 1-propenylbenzene to the propenylbenzene anion (74a). Both the 1-phenyl-2-propanone dianion (3) and the propenylbenzene anion (74a) have been shown to react with carbonyl compounds at the terminal carbon (C_3) via 1,2-addition. Reaction of 3 with H_2O ³⁴ was shown to occur exclusively at C_3 . Reaction of 74a with proton donors, occurred preferentially at C_3 in liquid ammonia while in less polar solvents C_1 protonation increased. Also, both 3 and 74a were found to react with alkyl halides preferentially at C_1 with the propenylbenzene anion

giving neutral products 1-alkyl-1-phenyl-2-propenes (75)

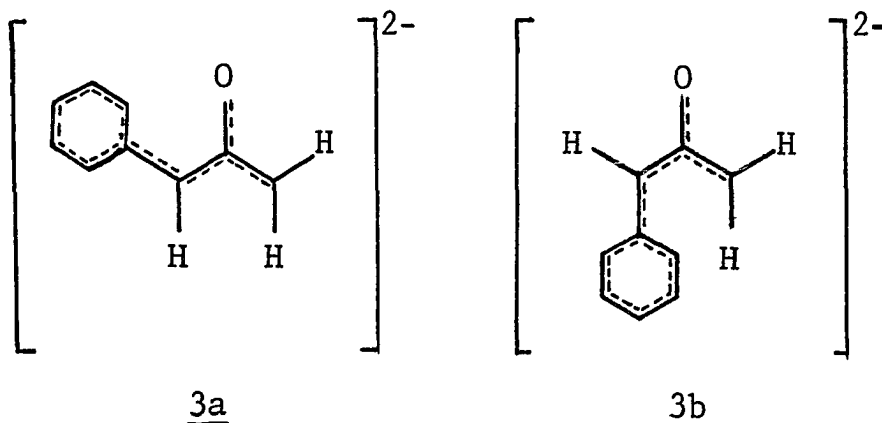


and 3 on monoalkylation giving the enolate anion 76. The formation of this intermediate was substantiated by trapping 76 ($\text{R} = \text{CH}(\text{CH}_3)_2$) with chlorotrimethylsilane to give the trimethylsiloxypropene 77.³⁴ The NMR spectrum of the



intermediate obtained on titration of 3 with benzyl chloride did not have the C_1 vinylic proton absorption expected for the analogous enolate anion of 2a bearing the benzyl substituent at C_3 . Alkylation of the propenylbenzene anion is thought to proceed via an $\text{S}_\text{N}2$ mechanism. Although not proven, alkylation of the dianion 3 should proceed via a similar mechanism.

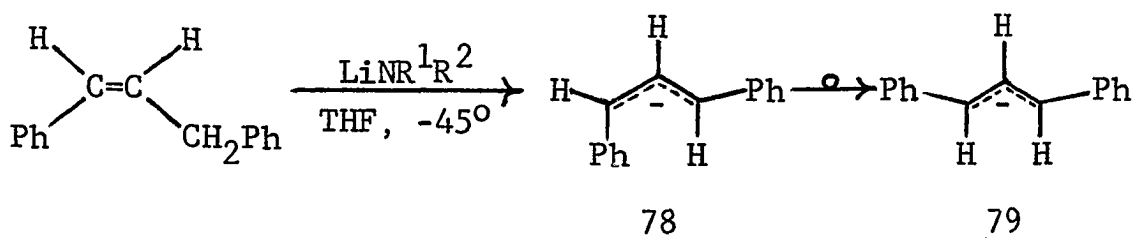
In the NMR spectra of 3 and 74a similarities are also found. In both spectra the absorptions of the ortho and meta protons are found together although the chemical shifts vary, with the absorption of the para proton found approximately 0.5 ppm upfield. The absorptions of the C_1 and C_3 protons also have comparable chemical shifts (Table III). As the solution structure of the propenylbenzene anion is planar with the C_1 and C_2 hydrogens oriented trans, along with the close similarities of the NMR spectra of 3 and 74a, it is probable that the solution structure of 3 is also planar with the C_1 hydrogen and the C_2 oxygen oriented trans across the C_1 - C_2 bond (3a). It is also probable that the solution structure 3b with the phenyl ring and the C_2 oxygen oriented trans across the



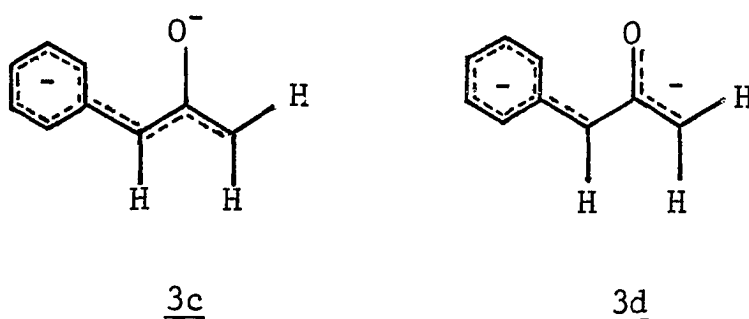
C_1 - C_2 bond would be subject to steric crowding as is 74b and would not be a favored conformation. Only recently has the unstable Z,E-1,3-diphenylpropenyl anion

(78) been observed and only at temperatures below -45° as rapid rearrangement to the more stable E,E-isomer (79) occurs at higher temperatures.⁵⁷

Scheme XXIV

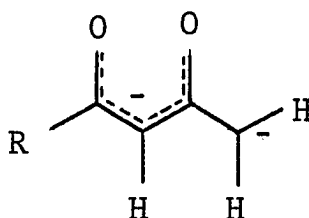


Two major resonance reference structures are suggested for the 1-phenyl-2-propanone dianion, 3c and 3d.



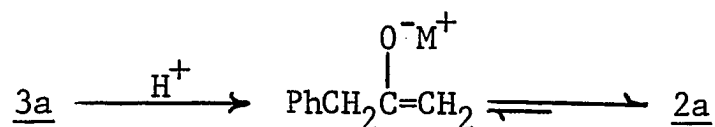
The resonance reference structure 3c is similar to 74a with one negative charge localized on oxygen and the other negative charge highly delocalized over C_1 , C_2 and C_3 and the phenyl ring. This is in keeping with the observed similarities in the chemistry and the NMR spectra of 74a and 3.

Subtle differences in the product distribution on protonation of 74a and 3 and on methylation with iodomethane in polar solvents are observed. The former carbanion undergoes almost exclusive C_1 methylation and gives a mixture of 1- and 2-propenylbenzene and the latter carbanion undergoes exclusive protonation at C_3 and gives a mixture of C_1 and C_3 methylation products which suggests not a significant difference in the charge density at C_1 , but rather, reflects a difference in the charge density at C_3 . An increased charge density at C_3 may be indicative of the importance of 3d as a resonance reference structure. The charge density on C_3 must still be considerably less than the charge density on the terminal carbon of the dianions of 1,3-diketones 80⁴⁶ as in these systems alkylation and other reactions with electrophiles occur exclusively at the terminal position.



80

The mode of protonation of 3a is as yet not well defined. Initial protonation at C_1 followed by rapid equilibration to 2a is not considered likely in view of the



results of alkylation-silylation.³⁴ Such a proton shift may also lead to formation of 2b which should be detectable by NMR and by trapping with chlorotrimethylsilane. Protonation of 74a is not well understood either⁴⁹ and it appears that the position of protonation under kinetically controlled conditions is dependent on the reaction solvent. In liquid ammonia the carbanion 74a on protonation with a variety of proton donors afforded 1-propenylbenzene in excess of 90%,^{48,49} whereas, protonation in less polar solvents gave largely 2-propenylbenzene.^{48,49}

In summary, it has been found that limited amounts of alkyl halides reacted with the potassium, lithium salt of the 1-phenyl-2-propanone dianion (3) preferentially and often with high regiospecificity at C₁ in both THF and THF-Et₂O. The relative amount of C₁ alkylation was found to depend upon the ease of displacement of the leaving group. 1,2-Addition at C₃ by p-methoxybenzaldehyde, first reported by Hauser and coworkers¹ was confirmed by isolation of 4-hydroxy-4-(p-methoxyphenyl)-1-phenyl-2-butanone (70) which was dehydrated to the reported alkenone 71. Reaction with H₂O and D₂O occurred exclusively at C₃ to

give the enolate anion 2a which possesses the Z-configuration. It was concluded that the chemistry of the dianion 3 was best explained in terms of the chemistry of the propenylbenzene anion rather than in terms of the chemistry shown by other stabilized ketone dianion systems and is representative of a hitherto unrecognized class of stabilized ketone dianions.

TABLE IV
TRIMETHYLSILOXYPROPENE H NMR CHEMICAL SHIFT DATA (δ)

<u>Compound</u>	<u>Solvent</u>	<u>Absorptions</u>				<u>Reference</u>
		<u>Phenyl</u>	<u>H₁</u>	<u>H₃</u>	<u>Si(CH₃)₃</u>	
<u>68a</u>	CDCl ₃	6.95-7.57 (m)	5.38 (1H, s)	1.90 (3H, s)	0.15	--
<u>68a</u>	CCl ₄	6.9 - 7.6 ^a (m)	5.32 (1H, s)	--	--	35
<u>68b</u>	CCl ₄	7.2 ^a (s)	5.77 (1H, s)	--	--	35
<u>77</u> ^b	--	7.12 (m)	2.77 (1H, d)	4.03 (2H, d)	--	65

^aEstimated from the published spectrum. ^bR = CH(CH₃)₂.

EXPERIMENTAL

General

Potassium hydride was obtained as either a 22.5% or a 35% suspension by weight in light mineral oil from Alfa Inorganics, Inc. n-Butyllithium was obtained as either a 2.20 molar or a 2.45 molar solution in hexane from the Ventron Corporation. 1-Phenyl-2-propanone was obtained from Matheson, Coleman and Bell and distilled before use. The alkyl halides were obtained from various commercial sources and used without further purification. Diethyl ether and tetrahydrofuran were dried by refluxing over sodium hydride followed by distillation. Hexane was dried similarly over sodium.

All preparative reactions were carried out in a 250 mL three-neck Morton flask fitted with a pressure equalizing addition funnel, condenser, septum, and magnetic stirrer under a nitrogen atmosphere. All glassware used was oven dried. The mineral oil was removed from potassium hydride by washing the suspension with two 20 mL portions of hexane as described by Brown,³⁸ then the reaction solvent was added. The amounts of KH used in each experiment are recorded as dry weights. All products prepared, with the exception of 4-methyl-3-phenyl-2-hexanone are

described in the literature and their derivatives prepared by standard methods.

All boiling points and melting points are uncorrected. The melting points were obtained with a Thomas-Hoover melting point apparatus. The infrared spectra were recorded with a Beckman IR-8 infrared spectrophotometer. The NMR spectra were recorded with a Varian A-60A nuclear magnetic resonance spectrophotometer in chloroform with tetramethylsilane as the internal standard. The NMR spectra of the carbanions were recorded in the reaction solvent with tetramethylsilane as the external standard. Gas chromatographic analysis of the crude reaction mixtures was done using a Varian Aerograph 2700 gas chromatograph.

Procedures

Preparation and Alkylation of the Potassium Enolate of 1-Phenyl-2-propanone (2a). 3-Phenyl-2-butanone. Method A.

Following the procedure of Brown,³⁸ a solution of 1-phenyl-2-propanone (2.68 g, 20 mM) in 20 mL of dry THF was added dropwise to a stirred suspension of potassium hydride (1.04 g, 26 mM) in 20 mL of dry THF which gave after gas evolution ceased a clear orange-red solution of the potassium salt of 2a. After stirring for an additional 10 minutes, the solution was cooled to 0-5° (ice-H₂O) and iodomethane (3.88 g, 27 mM) dissolved in 20 mL of dry THF was added. Stirring was continued for two hours during which

time a heavy white precipitate (KI) formed as the red color disappeared. To this solution 100 mL of diethyl ether was added along with 20 mL of H₂O and the layers were separated after stirring 5 minutes. The organic layer was washed successively with dilute HCl and saturated NaHCO₃ solution and dried (Na₂SO₄). Concentration under reduced pressure and distillation gave 2.04 g (69%) of 3-phenyl-2-butanone: bp 68-70° (1.8 torr), (lit⁵⁸ bp 106-110° (22 torr)); IR 1704 cm⁻¹; NMR (CDCl₃) δ 1.35 (d, 3, PhCHCH₃), 1.98 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 3.74 (q, 1, PhCH) 7.24 (s, 5, Ph); semicarbazone: mp 173-174° (lit⁵⁹ mp 170-172°).

3-Phenyl-2-butanone. Method B.

1-Phenyl-2-propanone (2.68 g, 20 mM) was added dropwise from a syringe to a stirred suspension of potassium hydride (1.04 g, 26 mM) in 90 mL of THF-diethyl ether (15% THF by volume). After gas evolution ceased, a clear reddish-orange solution of the potassium salt of 2a was obtained. After cooling to -78° (dry ice-2-propanol) iodomethane (3.88 g, 27 mM) was added from a syringe. After 5 minutes, the temperature was brought to 0-5° (ice-H₂O). The solution was stirred for one hour. The color soon dissipated and a heavy white precipitate (KI) formed. To this was added 20 mL H₂O, the layers separated and the organic layer washed with H₂O until the washes were neutral

to litmus. The solution was dried (Na_2SO_4) and concentrated under reduced pressure to an aromatic oil. Distillation gave 2.96 g (76%) of 3-phenyl-2-butanone: bp $78-79^\circ$ (3.6 torr), (lit⁵⁸ bp $106-110^\circ$ (22 torr)); IR 1704 cm^{-1} ; NMR (CDCl_3) δ 1.35 (d, 3, PhCHCH_3), 1.97 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 3.74 (q, 1, PhCH), 7.24 (s, 5, Ph); semicarbazone: mp $169-171^\circ$, (lit⁵⁹ $170-172^\circ$).

3-Phenyl-2-pentanone

The potassium salt of 2a, prepared according to method B, was reacted with iodoethane (4.20 g, 27 mM) for 18 hours to give 2.82 (87%) of 3-phenyl-2-pentanone: bp $74-76^\circ$ (2.2 torr), (lit⁵⁸ $116-119^\circ$ (23 torr)); IR 1710 cm^{-1} ; NMR (CDCl_3) δ 0.81 (t, 3, CH_2CH_3), 2.00 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 1.50-2.38 (m, 2, CHCH_2CH_3), 3.55 (t, 1, PhCHCH_2), 7.25 (s, 5, Ph); semicarbazone: mp $186-188^\circ$, (lit⁵⁸ mp $190-191^\circ$).

3-Phenyl-2-heptanone

The potassium salt of 2a, prepared according to method A, was reacted with 1-iodobutane (4.60 g, 25 mM) for 18 hours to give 2.95 g (77%) of 3-phenyl-2-heptanone: bp $74-75^\circ$ (0.7 torr), (lit⁵⁸ bp $131-135^\circ$ (16 torr)); IR 1707 cm^{-1} ; NMR (CDCl_3) δ 0.61-2.61 (m, 9, $\text{n-C}_4\text{H}_9$), 2.02 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 3.62 (q, 1, PhCH), 7.25 (s, 5, Ph); semicarbazone: mp $156-157^\circ$, (lit⁵⁸ mp $156-157^\circ$).

The potassium salt of 2a, prepared according to method B, was reacted with 1-iodobutane (5.00 g, 27 mM) for 20 hours to give 2.88 g (76%) of 3-phenyl-2-butanone: bp 100-102° (3.6 torr); semicarbazone: mp 156-158°.

3,4-Diphenyl-2-butanone

The potassium salt of 2a, prepared according to method A, was reacted with benzyl bromide (4.00 g, 23 mM) for 1.5 hours to give 2.68 g (60%) of 3,4-diphenyl-2-butanone: bp 110-112° (0.4 torr), (lit⁵⁸ bp 119-122° (1 torr)); IR 1705 cm⁻¹; NMR (CDCl₃) δ 1.85 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 3.12 (m, 2, PhCH₂CH), 3.95 (t, 1, PhCHCH₂), 7.05 (s, 5, Ph), 7.15 (s, 5, Ph); oxime: mp 134-135°, (lit⁵⁸ mp 133-134°).

Reaction of 2a ($\text{M}^+ = \text{K}^+$), prepared according to method A, with benzyl chloride (2.86 g, 24 mM) for 1.5 hours gave an oil as the crude product. Gas chromatographic analysis showed that this oil contained benzyl chloride, and 1-phenyl-2-propanone as the sole components. Evidence for the expected product 3,4-diphenyl-2-butanone was not found.

Reaction of 2a ($\text{M}^+ = \text{K}^+$) with 2-bromopropane

The potassium salt of 2a, prepared according to method A, was reacted with 2-bromopropane (3.60 g, 30 mM) for 24 hours at ambient temperature. The oil isolated from this

reaction was analyzed by GC and was found to contain two major components. In order of elution, these were identified as 1-phenyl-2-propanone (40%) and 4-methyl-3-phenyl-2-butanone (60%).

The potassium salt of 2a, prepared according to method B, was reacted with 2-bromopropane (3.32 g, 27 mM) for 36 hours at ambient temperature. The oil isolated from this reaction was analyzed by GC and found to contain two major components. In order of elution, these were identified as 1-phenyl-2-propanone (85%) and 4-methyl-3-phenyl-2-butanone (15%).

Z-1-Phenyl-2-(trimethylsiloxy)-1-propene (67a)

According to method A, a solution of 2a ($M^+ = K^+$) was prepared in THF from potassium hydride (1.04 g, 26 mM) and 1-phenyl-2-propanone (2.68 g, 20 mM) and cooled to 0-5° (ice-H₂O). Triethylamine (2.63 g, 26 mM) followed by chlorotrimethylsilane (3.26 g, 30 mM) was added directly into the stirred solution by syringe, after which the orange-red color of the solution was discharged and a white precipitate immediately formed. After stirring for one hour, the solvent was removed under reduced pressure and the residue taken up in pentane. This was filtered through celite, decolorized with activated charcoal and concentrated under reduced pressure to a colorless mobile liquid.

Distillation gave 1.79 g (44%) of Z-1-phenyl-2-(trimethylsiloxy)-1-propene: bp 74-77° (1.4 torr), (lit⁴⁰ bp 81° (2.0 torr)); IR 1660 cm⁻¹; NMR (CDCl₃) δ 0.19 (s, 9, Si(CH₃)₃), 1.92 (s, 3, C-CH₃), 5.38 (s, 1, PhCH=C), 7.00-7.45 (m, 5, Ph).

The potassium salt of 2a was prepared according to method B from potassium hydride (1.04 g, 26 mM) and 1-phenyl-2-propanone (2.68 g, 20 mM) then cooled to 0-5°. Triethylamine (2.63 g, 26 mM) followed by chlorotrimethylsilane (3.26 g, 30 mM) were then added directly into the stirred solution by syringe. After stirring for one hour, the solvent was removed under reduced pressure and the residue taken up in pentane. Filtration through celite gave a pale yellow solution which was concentrated under reduced pressure to a mobile liquid. Distillation gave 3.00 g (73%) of Z-1-phenyl-2-(trimethylsiloxy)-1-propene: bp 89-94° (3.6 torr); NMR (CDCl₃) δ 0.19 (s, 9, Si(CH₃)₃) 1.93 (s, 3, CH₃), 5.38 (s, 1, PhCH=C), 7.02-7.45 (m, 5, Ph).

Preparation of the 1-phenyl-2-propanone dianion (3) in THF.
Reaction with iodoethane.

The potassium salt of 2a was prepared in THF according to method A by dropwise addition of a solution of 1-phenyl-2-propanone (3.36 g, 25 mM) in 20 mL of dry THF to a stirred suspension of potassium hydride (1.20 g, 30 mM) in 25 mL of THF. The resulting clear orange-red solution was stirred

for 10 minutes, then cooled to -78° (dry ice-2-propanol). n-Butyllithium in hexane (29 mM, 12 mL, 2.40 mM/mL) was then added dropwise by syringe and immediately reacted to give an intense dark red solution of the dianion 3. After stirring for 20 minutes, the temperature was brought to $0-5^{\circ}$ (ice- H_2O) and a solution of iodoethane (4.68 g, 30 mM) in 20 mL of dry THF was added dropwise. Reaction was almost immediate with discharge of the color and formation of a heavy white precipitate. After stirring 4 hours, 15 mL of H_2O were added followed by 150 mL of diethyl ether. After separation, the organic phase was washed repeatedly with H_2O until the washes were neutral to litmus. After drying ($MgSO_4$), the solution was concentrated under reduced pressure to give the crude product. Gas chromatographic analysis showed only a small trace of 1-phenyl-2-propanone and two major components in a ratio of 85 to 15. The larger fraction was the first to elute and was identified as 3-phenyl-2-pentanone on comparison of retention times with an authentic sample. The smaller fraction was not identified. Distillation gave 3.80 g (79%) of purified 3-phenyl-2-pentanone: bp $86-90^{\circ}$ (3.3 torr); (lit⁵⁸ $116-119^{\circ}$ (23 torr)); IR 1707 cm^{-1} ; NMR ($CDCl_3$) δ 0.82 (t, 3, CH_2CH_3), 1.93 (m, 2, $CHCH_2CH_3$), 2.00 (s, 3, $\overset{O}{\parallel}CCH_3$), 3.58 (t, 1, $PHCHCH_2$), 7.25 (s, 5, Ph); semicarbazone: mp $185-186^{\circ}$, (lit⁵⁸ mp $190-191^{\circ}$).

Preparation of the 1-phenyl-2-propanone dianion (3) in the THF-diethyl ether. Reaction with iodoethane.

The potassium salt of 2a was prepared in 90 mL of THF-diethyl ether (15% THF by volume) according to method B from potassium hydride (1.04 g, 26 mM) and 1-phenyl-2-propanone (2.68 g, 20 mM) as a clear orange solution. On cooling to 0-5° (ice-H₂O) n-butyllithium in hexane (22 mM, 10 mL, 2.25 mM/mL) was added dropwise by syringe which immediately reacted to give a dark red solution. After stirring for 45 minutes, a solution of iodoethane (3.42 g, 22 mM) in 20 mL of dry diethyl ether was added dropwise. As the color was discharged a heavy white precipitate formed. After stirring for 1 hour, 10 mL of H₂O was added, the layers separated, and the organic layer washed with H₂O. Drying (Na₂SO₄) and concentration under reduced pressure gave the crude product as a mobile liquid. Distillation gave 1.69 g (54%) of 3-phenyl-2-pentanone: bp 79-83° (2.6 torr); NMR (CDCl₃) 0.81 (t, 3, CH₂CH₃), 1.93 (m, 2, CHCH₂CH₃), 2.01 (s, 3, C(=O)CH₃), 3.58 (t, 1, PhCH), 7.25 (s, 5, Ph).

Reaction of 3 with 1-iodobutane

The dianion 3 was prepared in THF as described previously and reacted with 1-iodobutane (5.52 g, 30 mM) for 4 hours. The crude product was analyzed by gas chromatography and was found to contain two major components in a

ratio of 95 to 5. The larger fraction which eluted first was shown to be 3-phenyl-4-heptanone by comparison of the retention time with that of an authentic sample. The smaller fraction was not identified. Distillation gave 2.80 g (59%) of purified material. Bp $87-91^{\circ}$ (1.3 torr) (lit⁵⁸ bp $131-135^{\circ}$ (16 torr)); IR 1707 cm^{-1} ; NMR (CDCl_3) δ 0.60-2.61 (m, 9, $n\text{-C}_4\text{H}_9$), 2.00 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 3.62 (q, 1, PhCH), 7.25 (s, 5, Ph); semicarbazone: mp 151° , (lit⁵⁸ mp $156-157^{\circ}$).

The dianion 3 prepared in THF- Et_2O (15% THF by volume) as described previously was reacted with 1-iodobutane (4.10 g, 22 mM) to give 2.00 g (53%) of 3-phenyl-2-heptanone: bp $94-97^{\circ}$ (2.0 torr); NMR (CDCl_3) δ 0.59-2.60 (m, 9, $n\text{-C}_4\text{H}_9$), 2.01 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 3.64 (q, 1, PhCHCH-), 7.25 (s, 5, Ph).

Reaction of the dianion 3 with iodomethane

A solution of the dianion 3 prepared in THF- Et_2O as described previously was cooled to -78° (dry ice-isopropanol) and reacted with iodomethane (2.84 g, 20 mM) for 1 hour then at $0-5^{\circ}$ (ice- H_2O) for 3 hours. Analysis of the crude product isolated from this reaction by gas chromatography showed the presence of two major components in a ratio of 65 to 35. The major fraction which eluted first was shown to be 3-phenyl-2-butanone by comparison of the retention

time with that of an authentic sample. The other component was not identified.

This reaction was repeated as described except that iodomethane (3.12 g, 22 mM) was added at 0° and stirred for 2.5 hours. Gas chromatographic analysis of the crude product showed the presence of two components in a ratio of 68 to 32. The larger fraction was found to be 4-methyl-3-butanone by comparison of the retention time with that of an authentic sample.

Reaction of the dianion 3 with 2-bromopropane

A solution of the dianion 3 was prepared in THF as described previously and reacted with 2-bromopropane (3.81 g, 30 mM) for 4 hours. From this was obtained 3.00 g (68%) of 4-methyl-3-phenyl-2-pentanone: bp 78-82° (2.2 torr), (lit⁵⁸ bp 109-114° ()); IR 1703 cm⁻¹; NMR (CDCl₃) δ 0.83 (q, 6, CH(CH₃)₂), 2.02 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 2.48 (m, 1, CHCH(CH₃)₂), 3.58 (t, 1, PhCHCH), 7.25 (s, 5, Ph); semicarbazone: mp 148-149° (lit⁵⁸ mp 153-154°).

A solution of the dianion 3 was prepared in THF-Et₂O as described previously and reacted with 2-bromopropane (2.46 g, 20 mM) for 6 hours. From this was obtained 2.08 g, (59%) of 4-methyl-3-phenyl-2-pentanone: bp 73-76° (1.6 torr); NMR (CDCl₃) δ 0.83 (q, 6, CH(CH₃)₂), 2.01 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 2.48 (m, 1, CHCH(CH₃)₂), 3.58 (t, 1, PhCHCH), 7.25 (s, 5, Ph); semicarbazone: mp 147-149°.

Reaction of the dianion 3 with 1-chlorobutane

A solution of the dianion 3 was prepared in THF as described previously and reacted with 1-chlorobutane (2.78 g, 30 mM) for 8 hours. From this was obtained 3.39 g (70%) of 3-phenyl-2-heptanone: bp 89-94° (1.6 torr), (lit⁵⁸ bp 131-135° (16 torr)); IR 1707 cm⁻¹; NMR (CDCl₃) δ 0.61-2.61 (m, 9, n-C₄H₉), 2.00 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 3.62 (q, 1, PhCHCH₂), 7.25 (s, 5, Ph); semicarbazone: mp 154-155°, (lit⁵⁸ mp 156-157°).

Reaction of the dianion 3 with 2-methyl-1-bromopropane

A solution of the dianion 3 was prepared in THF as described previously and reacted with 2-methyl-1-bromopropane (4.11 g, 30 mM) for 4 hours. From this was obtained 3.42 g (72%) of 5-methyl-3-phenyl-2-hexanone: bp 81-85° (1.5 torr), (lit⁵⁸ bp 119-124° (14 torr)); IR 1705 cm⁻¹; NMR (CDCl₃) δ 0.73-2.55 (m, 9, -CH₂CH(CH₃)₂), 2.00 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 3.73 (q, 1, PhCHCH₂), 7.25 (s, 5, Ph); semicarbazone: mp 115-116° (lit⁵⁸ mp 116-118°).

Reaction of the dianion 3 with 2-bromobutane

A solution of the dianion 3 was prepared in THF as described previously and reacted with 2-bromobutane (4.11 g, 30 mM) for 4 hours. From this was obtained 3.10 g (63%)

of 4-methyl-3-phenyl-2-hexanone: bp 96-100° (3.6 torr); IR 1712 cm⁻¹; NMR (CDCl₃) δ 0.57-1.74 (m, 8, CH(CH₃)CH₂CH₃), 2.03 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 2.33 (m, 1, CHCH(CH₃)CH₂), 3.52 (t, 1, PhCHCH), 7.25 (s, 5, Ph).

Semicarbazone: mp 141-144°.

Anal. Calcd for C₁₄H₂₁N₃O: C, 67.88; H, 8.56; N, 16.99. Found: C, 67.88; H, 8.58; N, 17.15.

2,4-Dinitrophenylhydrazone: mp 87-90°.

Anal. Calcd for C₁₉H₂₂N₄O₄, 0.5 H₂O: C, 60.15; H, 5.84; N, 14.76. Found: C, 60.26; H, 5.85; N, 14.62.

Reaction of the dianion 3 with bromocyclopentane

A solution of the dianion 3 was prepared in THF as described previously and reacted with bromocyclopentane (4.47 g, 30 mM) for 3 hours. From this was obtained 3.10 g (62%) of 1-cyclopentyl-1-phenyl-2-propanone: bp 100-105° (1.1 torr), (lit⁶⁰ bp 110-127° (2.5 torr)); IR 1703 cm⁻¹; NMR (CDCl₃) δ 0.63-2.89 (m, 9, cyclo-C₅H₉), 2.03 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 3.50 (t, 1, PhCH), 7.26 (s, 5, Ph); 2,4-dinitrophenylhydrazone: mp 114-115° (lit⁶⁰ mp 116-118°).

Reaction of the dianion 3 with bromocyclohexane

A solution of the dianion 3 was prepared as described previously and reacted with bromocyclohexane (4.90 g, 30 mM)

for 4 hours. From this was obtained 3.30 g (61%) of 1-cyclohexyl-1-phenyl-2-propanone: bp 110-113° (1.1 torr), (lit⁶² bp 132-136° (2.5 torr)); IR 1712 cm⁻¹; NMR (CDCl₃) δ 0.56-2.00 (m, 11, cyclo-C₆H₁₁), 2.04 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 3.36 (d, 1, PhCH), 7.16 (s, 5, Ph); 2,4-dinitrophenylhydrazone: mp 151-152°, (lit⁶¹ mp 155-156°).

Reaction of the dianion 3 with bromomethylcyclohexane

A solution of the dianion 3 was prepared in THF as described previously and reacted with bromomethylcyclohexane (5.31 g, 30 mM) for 4 hours. From this was obtained 4.10 g (73%) of 4-cyclohexyl-3-phenyl-2-butanone: bp 117-121° (1.0 torr); NMR (CDCl₃) δ 0.55-2.24 (m, 13, CH₂C₆H₁₁), 2.00 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 3.79 (t, 1, PhCH), 7.27 (s, 5, Ph); 2,4-dinitrophenylhydrazone: mp 122-123°, (lit⁶² mp 126-127°).

Reaction of the dianion 3 with benzyl chloride

A solution of the dianion 3 was prepared on THF as described previously and reacted with benzyl chloride (4.70 g, 30 mM) for 4 hours. From this was obtained 2.90 g (52%) of 3,4-diphenyl-2-butanone: bp 115-120° (0.5 torr), (lit⁵⁸ bp 119-122° (1.0 torr)); IR 1704 cm⁻¹; NMR (CDCl₃) δ 1.89 (s, 3, $\overset{\text{O}}{\parallel}\text{CCH}_3$), 3.12 (m, 2, PhCH₂CH), 3.90 (t, 1,

PhCH $\underline{\text{CH}}$ CH₂), 7.04 (s, 5, Ph), 7.17 (s, 5, Ph); 2,4-dinitrophenylhydrazone: mp 113-113.5° (lit⁶³ mp 115-117°).

Reaction of the dianion 3 with benzyl bromide

A solution of the dianion 3 was prepared in THF as described previously and reacted with benzyl bromide (5.13 g, 30 mM) for 3 hours. From this the crude product was obtained as a pungent oil. Gas chromatographic analysis of this oil showed that three major components were present in about equal amounts. The presence of 3,4-diphenyl-2-butanone as one of the major components was ascertained by comparison of retention times with an authentic sample.

Reaction of the dianion 3 with p-methoxybenzaldehyde

A solution of the dianion 3 was prepared from potassium hydride (2.04 g, 26 mM), 1-phenyl-2-propanone (2.68 g, 20 mM) and n-butyllithium in hexane (24 mM, 10 mL, 2.40 mM/mL) in 100 mL of THF. A solution of p-methoxybenzaldehyde (2.72 g, 20 mM) in 30 mL of THF was added dropwise at 0-5° and stirred for 2 hours. After neutralizing with H₂O, the layers were separated and dried (Na₂SO₄). Concentration under reduced pressure gave a red oil which crystallized on trituration with pentane to give 2.20 g (44%) of crude 4-hydroxy-4-(p-methoxyphenyl)-1-phenyl-2-butanone (70).

Recrystallization from benzene-petroleum ether gave a cream white solid: mp 78-79°; NMR (CDCl₃) δ 2.73, (s, 1, $\text{CHCH}_2\overset{\text{OH}}{\overset{\text{O}}{\parallel}}\text{C}$), 2.85 (d, 1, $\overset{\text{OH}}{\overset{\text{O}}{\parallel}}\text{CCH}_2\text{C}$), 3.23 (brd s, 1, OH), 3.67 (s, 2, PhCH₂), 3.77 (s, 3, OCH₃), 5.05 (t, 1, CH(OH)-CH₂), 7.00 (m, 4, p-(CH₃O)-C₆H₄), 7.23 (s, 5, Ph). Anal. Calcd for C₁₇H₁₈O₃: C, 75.56; H, 6.71. Found: C, 75.27; H, 6.74.

The hydroxyketone 70 (1.50 g, 5.5 mM) and p-toluene-sulfonic acid monohydrate (0.25 g, 1.3 mM) were dissolved in 75 mL of benzene and heated at reflux for 4 hours. On cooling, the solution was washed with two 10 mL portions of sat. NaHCO₃ and dried (Na₂SO₄). Concentration under reduced pressure gave 0.90 g (65%) of 1-p-methoxyphenyl-4-phenyl-1-buten-3-one (71): mp 94-97° (lit¹ mp 99-101°); NMR (CDCl₃), δ 3.79 (s, 3, OCH₃), 3.90 (s, 2, PhCH₂), 6.65-7.83 (m, 6, p-CH₃O-C₆H₄CH=CH), 7.26 (s, 5, Ph).

Reaction of the dianion 3 with 1,3-diphenyl-1-propen-3-one

A solution of the dianion 3 was prepared in 40 mL of THF from potassium hydride (1.66 g, 41 mM), 1-phenyl-2-propanone (5.36 g, 40 mM) and n-butyllithium in hexane (48 mM, 20 mL, 2.40 mM/mL). To this was added a solution of 1,3-diphenyl-1-propen-3-one (8.32 g, 40 mM) in dry THF and stirred for 1 hour. This was then neutralized with 20 mL of H₂O, separated and washed with dilute HCl and saturated

NaHCO₃ solution. Drying and concentrating under reduced pressure gave a white crystalline solid. Mp 183-185°, (lit¹ 113-114°). The product was not further characterized.

NMR Spectrum of the potassium enolate 2a

The potassium enolate 2a was prepared by addition by syringe of 1-phenyl-2-propanone (2.68 g, 20 mM) to a stirred suspension of potassium hydride (1.04 g, 26 mM) in 20 mL of THF. 469 mL (volume uncorrected) of H₂ was collected over H₂O with 448 mL being the calculated theoretical volume. The NMR spectrum of this solution was recorded using tetramethylsilane as an external standard. The absorptions were as follows: δ 4.50 (s, 1, H₁), 6.27 (m, 1, para), 6.73 (m, 2, meta), 7.32 (m, 2, ortho). The region upfield from δ 4.0 was obscured by solvent absorptions. The remainder of the solution was neutralized with H₂O. Analysis by gas chromatography showed only one component, that being 1-phenyl-2-propanone.

NMR Spectrum of the dianion 3a

The potassium enolate 2a was prepared by addition by syringe of 1-phenyl-2-propanone (0.53 g, 4.0 mM) to a stirred suspension of potassium hydride (0.21 g, 5.2 mM) in 3 mL of THF. After stirring 10 minutes, the solution was cooled to -78° (dry ice, isopropanol) and n-butyllithium

in hexane (4.8 mM, 2 mL, 2.40 mM/mL) was added. The deep red solution was stirred for 30 minutes then brought to room temperature. The NMR spectrum of this solution was recorded using tetramethylsilane as an external standard. The absorptions were as follows: δ 5.43 (brd m, 1, para), 6.30 (brd m, 4, ortho and meta).

This was repeated in THF- d_8 /hexane. The absorptions were as follows: δ 2.60 (brd d, 2, C- \underline{CH}_2), 3.82 (brd s, 1, PhCH-), 5.47 (brd m, 1, para), 6.33 (brd m, 4, ortho and para).

Titration of the dianion 3 with D_2O

To the remainder of the solution in THF-hexane prepared above D_2O was added dropwise from a syringe until the intense red solution had permanently changed to a red-orange solution. The NMR spectrum was recorded and the absorptions were as follows: δ 4.50 (s, 1, PhCH=C), 6.25 (s, para), 6.70 (m, meta), 7.28 (m, ortho).

Titration of the dianion 3 with benzyl chloride

A solution of the dianion 3 was prepared from potassium hydride (0.21 g, 5.2 mM), 1-phenyl-2-propanone (0.53 g, 4.0 mM) and n-butyllithium in hexane (4.8 mM, 2 mL, 2.40 mM/mL) as described above. At 0° benzyl chloride was added until the intense red color had permanently disappeared.

The NMR spectrum of the resulting solution with tetramethylsilane as the external standard had the following absorptions: δ 6.73 (brd m), 6.81 (brd m). The region upfield from δ 4.0 was obscured by solvent absorptions.

REFERENCES

1. C. M. Mao, C. R. Hauser, and M. L. Miles, J. Am. Chem. Soc., 89, 5303 (1967).
2. C. R. Hauser and T. M. Harris, J. Am. Chem. Soc., 81, 5303 (1959).
3. H. O. House, "Modern Synthetic Reactions," second edition, W. A. Benjamin, Inc., Menlo Park, California, 1972, p. 555.
4. ibid., pp. 492-570.
5. C. R. Hauser and T. M. Harris, J. Am. Chem. Soc., 80, 6360 (1958).
6. E. R. Trotman, J. Chem. Soc., 127, 88 (1925).
7. R. J. Light and C. R. Hauser, J. Org. Chem., 25, 538
8. S. D. Work and C. R. Hauser, J. Org. Chem., 28, 725 (1963).
9. F. B. Kirby, T. M. Harris, and C. R. Hauser, J. Org. Chem., 28, 2266 (1963).
10. R. J. Light and C. R. Hauser, J. Org. Chem., 26, 1716 (1961).
11. R. J. Light, T. M. Harris, and C. R. Hauser, J. Org. Chem., 26, 1344 (1961).
12. T. M. Harris and C. M. Harris, Org. React., 7, 155 (1969).
13. T. M. Harris and C. R. Hauser, J. Am. Chem. Soc., 81, 1160 (1959).
14. R. B. Meyer and C. R. Hauser, J. Org. Chem., 25, 158 (1960).
15. K. G. Hampton, T. M. Harris, and C. R. Hauser, J. Org. Chem., 31, 663 (1966).
16. H. D. Zook and W. L. Rellahan, J. Am. Chem. Soc., 79, 881 (1957).

17. K. G. Hampton, T. M. Harris, and C. R. Hauser, J. Org. Chem., 31, 1036 (1966).
18. T. M. Harris, S. Boatman, and C. R. Hauser, J. Am. Chem. Soc., 85, 3273 (1963).
19. T. M. Harris, S. Boatman, and C. R. Hauser, J. Am. Chem. Soc., 87, 3186 (1965).
20. J. F. Wolfe, T. M. Harris, and C. R. Hauser, J. Org. Chem., 29, 3245 (1964).
21. L. Weiler, J. Am. Chem. Soc., 92, 6702 (1970).
22. S. N. Huckin and L. Weiler, J. Am. Chem. Soc., 96, 1082 (1974).
23. S. N. Huckin and L. Weiler, Tetrahedron Letters, 2405 (1972).
24. S. N. Huckin and L. Weiler, Tetrahedron Letters, 4835 (1971).
25. S. N. Huckin and L. Weiler, Can. J. Chem., 52, 2157 (1974).
26. P. A. Grieco and C. S. Pogonowski, J. Org. Chem., 39, 732 (1974).
27. I. Kuwajima and H. Iwasawa, Tetrahedron Letters, 107 (1974).
28. P. A. Grieco and C. S. Pogonowski, Chem. Commun., 497 (1974).
29. W. I. O'Sullivan, D. F. Tavernes, and C. R. Hauser, J. Am. Chem. Soc., 83, 3453 (1961).
30. F. Cooke and P. Magnus, Chem. Commun., 519 (1976).
31. J. S. Griffiths, "Alkylations and Self-Condensations of Certain N,N-Dialkyltoluamides. A New Method for the Preparation of 2-Isloxazolin-5-Ones. Condensation of Multiple Anions Formed By the Consecutive Use of Different Bases," Ph.D. Dissertation, Duke University, 1971, pp. 102-107; Diss. Abst. Int. B, 32, 5103 (1972).
32. P. A. Grieco and C. S. Pogonowski, J. Am. Chem. Soc., 95, 2071 (1973).

33. P. A. Grieco and C. S. Pogonowski, Synthesis, 425 (1973).
34. G. B. Trimitsis, J. M. Hinkley, R. TenBrink, M. Poli, G. Gustafson, J. Erdman, and D. Rop, J. Am. Chem. Soc., 99, 4838 (1977).
35. H. O. House, R. A. Auerbach, M. Gall and N. P. Peet, J. Org. Chem., 38, 514 (1973).
36. H. O. House, Rec. Chem. Prog., 28, 99 (1967).
37. C. A. Brown, J. Org. Chem., 39, 1324 (1974).
38. C. A. Brown, J. Org. Chem., 39, 3913 (1974).
39. C. J. Pedersen and H. K. Frensdorff, Angew. Chem. Internat. Edit. Eng., 11, 16 (1972).
40. H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, J. Org. Chem., 34, 2324 (1969).
41. G. F. Stork and P. F. Hudrlik, J. Am. Chem. Soc., 90, 4462, 4464 (1968).
42. J. M. Conia, Rec. Chem. Prog., 24, 43 (1963).
43. H. D. Zook, T. J. Russo, E. F. Farand, and D. S. Stoltz, J. Org. Chem., 36, 2222 (1968).
44. H. Gilman and G. L. Schwebke, J. Organometal. Chem., 4, 483 (1965).
45. G. J. Heiszwolf and H. Kloosterziel, Rec. Trav. Chim., 89, 1153 (1970).
46. M. L. Miles, C. G. Moreland, D. M. von Schriltz, and C. R. Hauser, Chem. Ind., 2098 (1966).
47. T. W. Campbell and W. G. Young, J. Am. Chem. Soc., 69, 698 (1947).
48. R. W. Mixer and W. G. Young, J. Am. Chem. Soc., 78, 3379 (1956).
49. H. F. Hebrandson and D. S. Mooney, J. Am. Chem. Soc., 79, 5809 (1947).
50. R. H. DeWolfe, D. E. Johnson, R. I. Wagner, and W. G. Young, J. Am. Chem. Soc., 79, 4798 (1957).

51. T. Ando and N. Tokua, Bull. Chem. Soc. Jap., 31, 1026 (1957).
52. W. S. Murphy, R. Boyer, and E. A. O'Riorden, Tetrahedron Letters, 4157 (1971).
53. H. Levy and A. C. Cope, J. Am. Chem. Soc., 66, 1684 (1944).
54. W. G. Young, M. Kosmin, R. Y. Mixer, and T. W. Campbell, J. Am. Chem. Soc., 74, 608 (1952).
55. G. J. Heiszwolf and H. Kloosterziel, Rec. Trav. Chim., 86, 1345 (1967).
56. V. R. Sandel, S. V. McKinley, and H. H. Freedman, J. Am. Chem. Soc., 90, 495 (1968).
57. G. Boche and D. R. Schneider, Tetrahedron Letters, 3657 (1976).
58. E. M. Schultz, J. B. Bicking, S. Mickey, and F. S. Crossley, J. Am. Chem. Soc., 75, 1072 (1953).
59. J. Levy and A. Tabrant, Bull. Chim. Soc., Fr., 49, 1776 (1931).
60. G. N. Walker and A. Alkalay, J. Org. Chem., 36, 491 (1971).
61. C. A. Buehler, H. A. Smith, K. V. Nayak, and T. A. Magee, J. Org. Chem., 26, 1573 (1961).
62. A. I. Meyers and A. C. Kovalsky, Tetrahedron Letters, 4809 (1969).
63. A. Terada and Y. Kishida, Chem. Pharm. Bull., 18, 490 (1970).
64. G. B. Trimitsis and M. Poli, Unpublished Spectrum.
65. G. B. Trimitsis, Unpublished Spectrum.

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