This is to certify that the

dissertation entitled

Chapter I The Synthesis and Reactions of Sterically Hindered Silyl Enol Ethers
Chapter II The Reactions of α-Azido Esters with Base
Chapter III The Phenylation of Ketone Enolates with Diphenyliodonium Salts

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Paul A. Manis

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Major professor

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THE SYNTHESIS AND REACTIONS OF STERICALLY HINDERED SILYL ENOL ETHERS

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THE PHENYLATION OF KETONE ENOLATES WITH DIPHENYLIODONIUM SALTS

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Paul A. Manis

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Submitted to
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ABSTRACT

CHAPTER I
THE SYNTHESIS AND REACTIONS OF STERICALLY HINDERED SILYL ENOL ETHERS

CHAPTER II
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CHAPTER III
THE PHENYLATION OF KETONE ENOLATES WITH DIPHENYLIODONIUM SALTS

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I. A new class of highly hindered silylating agents for ketones has been developed and utilized in the synthesis of silyl enol ethers. Applications of these sterically hindered silyl enol ethers in synthesis and their stability relative to standard silyl enol ethers have been explored.

II. The reactions of α-azido esters with various bases have been explored. These α-azido esters are found to react with catalytic amounts of lithium ethoxide to form biologically interesting dehydroamino esters, and, after hydrolysis, α-keto esters.

III. The reactions of enolates of ketones with diphenyliodonium salts have been investigated. Diphenyliodonium hexafluorophosphate is found to be a useful phenylating reagent for ketone lithium enolates generated under aprotic conditions.

ACKNOWLEDGEMENTS

I wish to express my heartfelt gratitude to Dr. Michael Rathke for making my stay at MSU a most pleasant learning experience. I also wish to thank members of the Rathke group, past and present, for making the lab a fun place to be: Chip, Nate, Rob, Zak, Ihor, Pat, and Rob. I would also like to thank Dot for getting me through the bureaucracy in one piece, and Julie, for keeping me entertained.

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TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

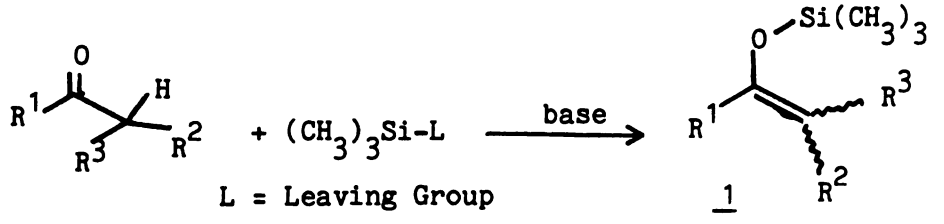
TMS	Trimethylsilyl
TBDS	*tert*-Butyldimethylsilyl
DPS	(2,6-Di-*tert*-butylphenoxy)dimethylsilyl
TPS	(2,4,6-Tri-*tert*-butylphenoxy)dimethylsilyl
LDA	Lithium Diisopropylamide
THF	Tetrahydrofuran
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
t-Boc	*tert*-Butoxycarbonyl
DBU	1,8-Diazabicyclo [5.4.0] undec-7-ene

CHAPTER I

THE SYNTHESIS AND REACTIONS OF STERICALLY HINDERED SILYL ENOL ETHERS

INTRODUCTION

The first reported synthesis of trialkylsilyl enol ethers of simple ketones appeared in 1958[1]. Trimethylsilyl (TMS) enol ethers of simple ketones 1 were first synthesized by Kruger and Rochow[2] in 1964. In the short time since their discovery, TMS enol ethers have been shown to be important synthons for the preparation of enones[3], α-hydroxy ketones[4], β-hydroxy ketones[5], 1,4-diketones[6], α-halo ketones[7], and other functionalized carbonyl compounds[8] (Figure 1). While TMS enol ethers may be prepared by a variety of methods[9], the most common approach to their synthesis involves reaction of a ketone with a silylating reagent, usually in the presence of a base (eq 1). Some of



(1)

the reagents that have been used to perform this reaction include chlorotrimethylsilane with base[10], trimethylsilyl iodide with base[11],

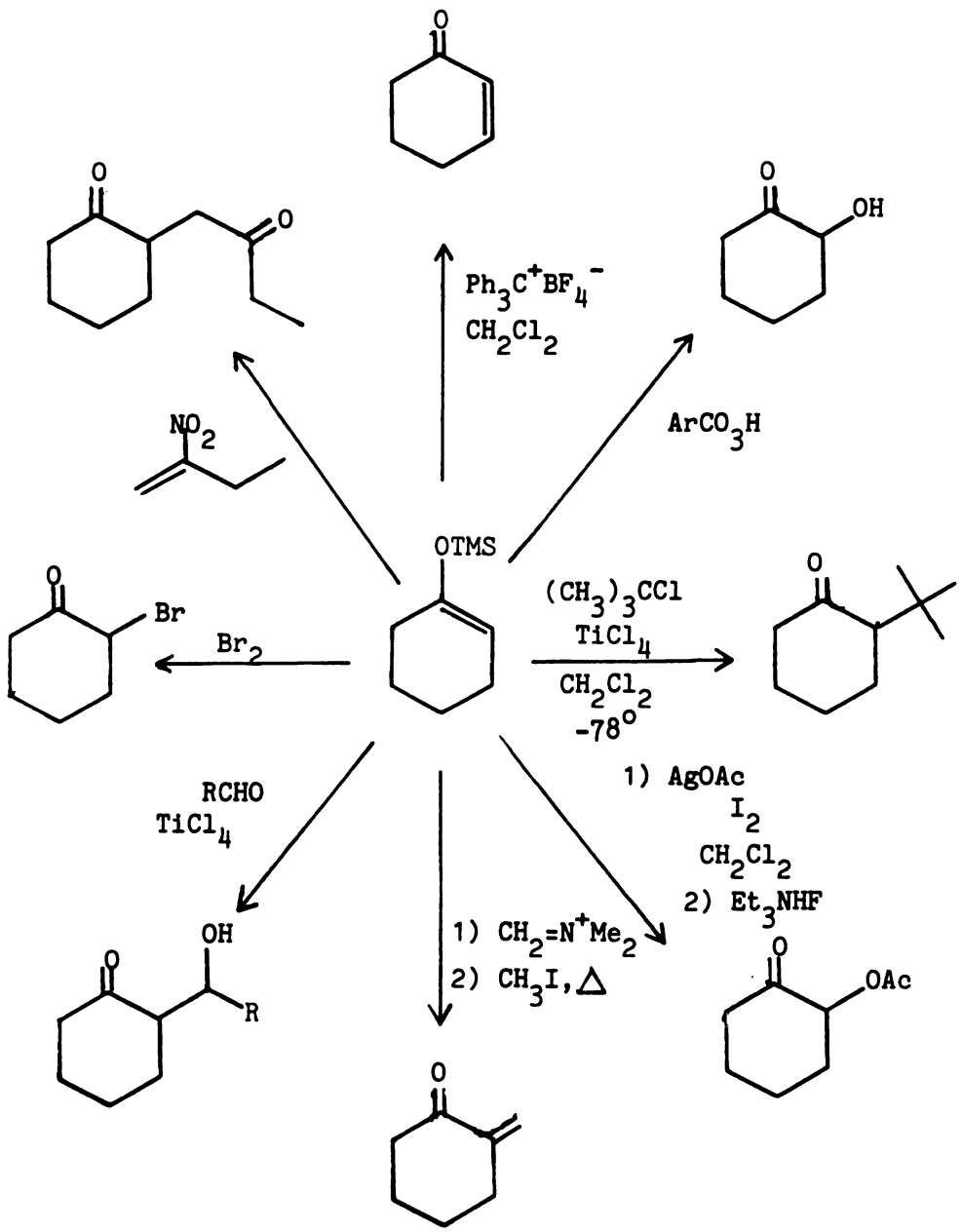
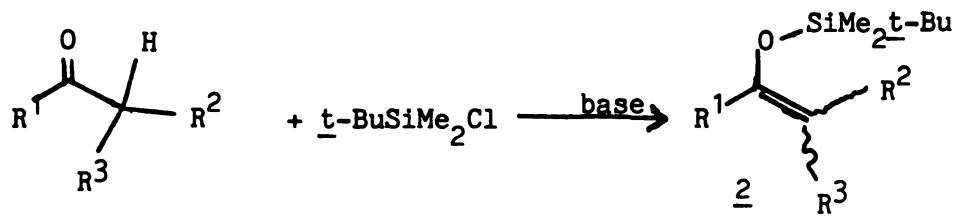


Figure 1. Some Reactions of TMS Enol Ethers

hexamethyldisilazane with imidazole[12], trimethylsilyl triflate[13], bis-trimethylsilyl acetamide[14], N,N-dimethylamino trimethylsilane[15], and ethyl trimethylsilyl acetate[16]. This diversity of reagents provides easy access to TMS enol ethers; unfortunately, TMS enol ethers are very susceptible to hydrolysis[17a,b], and this limits their usefulness. The stability of silyl enol ethers to hydrolysis may be improved by synthesis of the tert-butyldimethylsilyl derivatives 2[17] (eq 2); these more



(2)

hindered silyl enol ethers are hydrolysed much more slowly than the TMS derivatives[17a,b]. However, the requisite tert-butyldimethylsilyl (TBDS) chloride is considerably more expensive than the corresponding trimethylsilylating reagent[18]. We therefore desired to develop a hindered silylating agent which would give enol ether derivatives with a hydrolytic stability similar to TBDS derivatives, but at a more reasonable cost.

TBDS chloride is prepared by the reaction of tert-butyllithium with dichlorodimethylsilane[19] (eq 3). The necessity for using the alkyllithium reagent to form the carbon-silicon bond is the major reason

$$(CH_3)_2SiCl_2 + (CH_3)_3CLi \longrightarrow (CH_3)_3CSi(CH_3)_2Cl \qquad (3)$$

for the high cost of TBDS chloride.

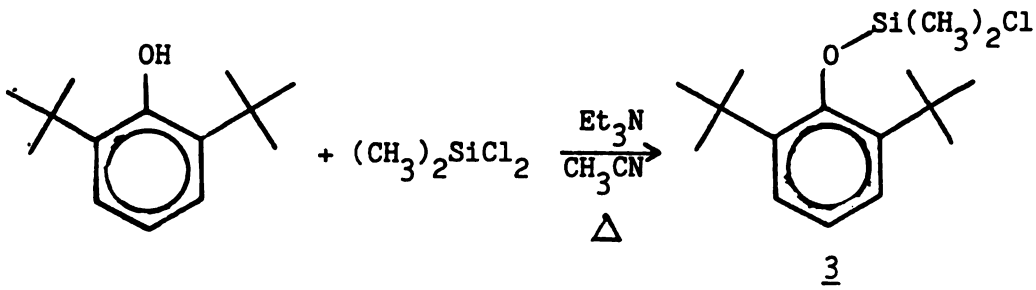
It has been known for some time that the silicon-chlorine bond is easily replaced by a silicon-oxygen bond through reaction with alcohols[20] (eq 4). Since there are many commercially available inexpensive

$$SiCl_4 + nROH \longrightarrow SiCl_{(4-n)}(OR)_n \qquad (4)$$

alcohols, the reaction of an appropriate hindered alcohol with a silyl chloride would appear to be an alternative to the use of alkyllithium reagents. In addition, replacement of an Si-C bond with an Si-O bond might alter the properties of silyl enol ethers due to overlap of oxygen lone pairs with the empty silicon d-orbitals. We proposed to react a hindered, inexpensive alcohol with a silyl chloride to obtain a silylating agent for ketones.

RESULTS AND DISCUSSION

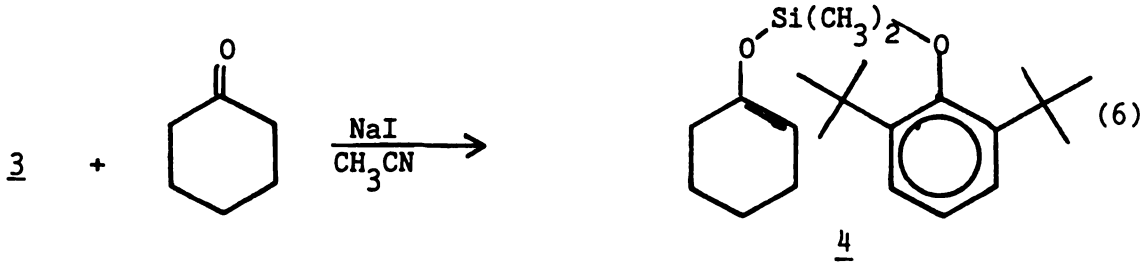
2,6-Di-tert-butylphenol is a commercially available and inexpensive alcohol[21]. Reaction of this phenol with dichlorodimethylsilane and triethylamine in refluxing acetonitrile gave a 75% yield of the desired (2,6-di-tert-butylphenoxy)dimethylsilyl chloride (DPS chloride, 3, eq 5). It was our hope that the hindrance afforded by the large



(5)

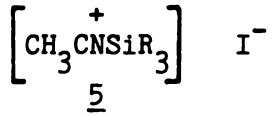
3

di-tert-butylphenoxy substituent would allow the synthesis of hindered, hence more stable, silyl enol ethers. The white, crystalline DPS chloride was reacted with cyclohexanone according to the procedure of Duboudin[11] in an attempt to synthesize the silyl enol ether 4 (eq 6).

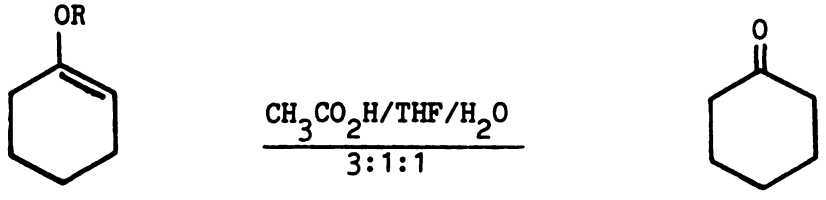


(6)

This procedure, which has been used to synthesize trimethylsilyl enol ethers, is thought to generate a complex silylating reagent 5 more



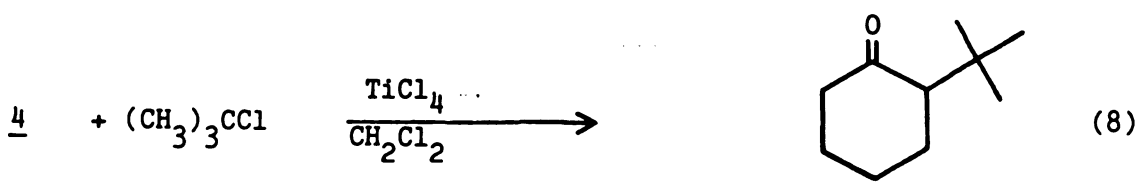
potent than the silyl chloride[22]. After 3 hours, a mixture of the desired 4 and cyclohexanone was observed by GLC in approximately equal amounts. An increase in the reaction time to 6 hours resulted in complete reaction, and after aqueous workup, 4 was isolated in 87% yield. We then compared the rate of acid induced hydrolysis of 4 with the corresponding TBDS enol ether (eq 7). The DPS enol ether proved to be more resistant to acid hydrolysis than the TBDS derivative.



(7)

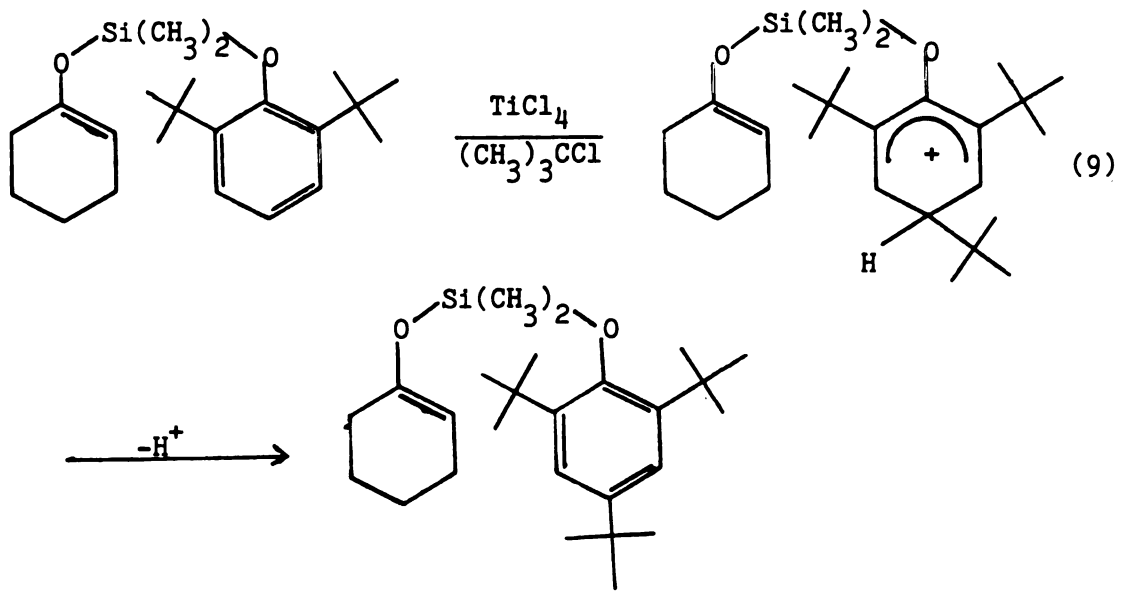
R = TBDS	1 h	90%
R = DPS	1 h	10%

In order to replace the use of TMS enol ethers, DPS enol ethers must undergo the same reactions in comparable yields. We decided to investigate the tert-butylation reaction[23] of silyl enol ethers to see if 4 underwent reaction in a manner comparable to the TMS enol ether (eq 8). The results were disappointing, only 15% of the desired α-tert-butylcyclohexanone was observed; the remainder of the material was



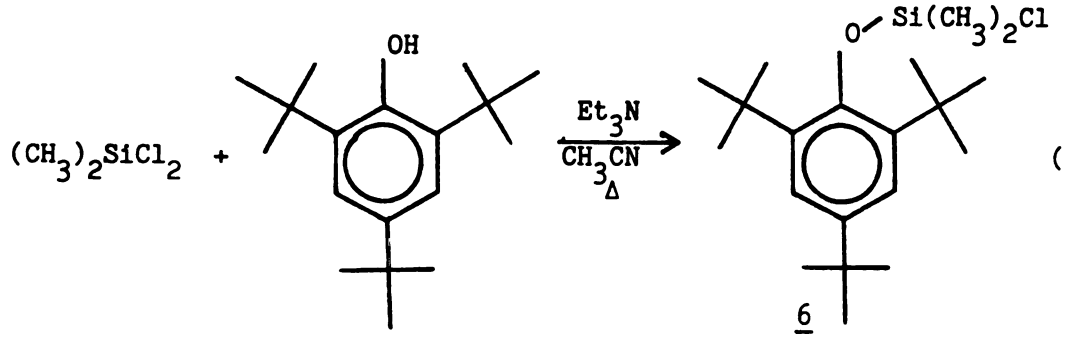
(8)

recovered as cyclohexanone. These results were not improved by varying the Lewis acid employed, reaction temperature or time. We considered that the poor yields might be due to competing tert-butylation of the aromatic ring (eq 9). The acid thus generated could hydrolyze enol



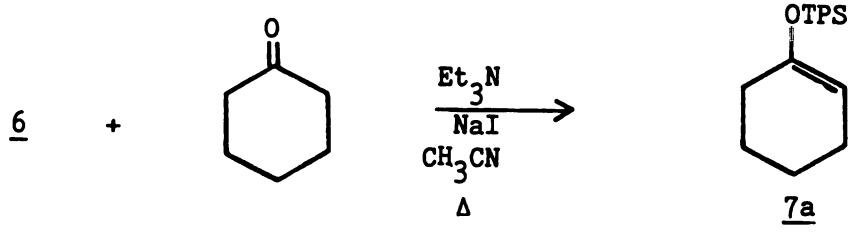
(9)

ether 4, accounting for the large amount of recovered ketone. If this was indeed the case, an obvious solution would be to replace the 2,6-disubstituted phenol with a 2,4,6-trisubstituted phenol. The reaction of 2,4,6-tri-tert-butylphenol, also a commercially available and inexpensive alcohol[24], with dichlorodimethylsilane provided (2,4,6-tri-tert-butylphenoxy)dimethylsilyl chloride (TPS chloride, 6) in 93% yield (eq 10), as a white crystalline solid (mp 79-80°C). Silyl chloride 6



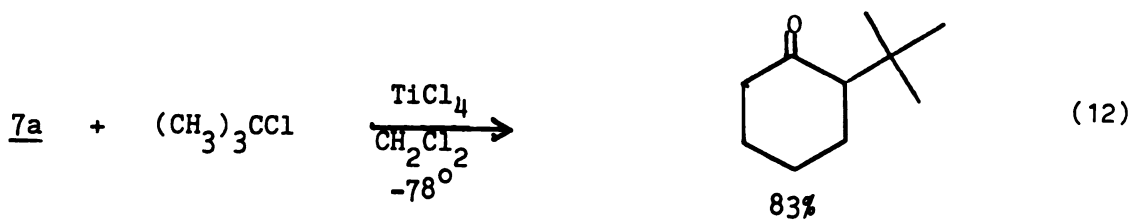
(10)

when reacted with cyclohexanone in the presence of triethylamine gave the silyl enol ether 7a in 91% yield (eq 11). Compound 7a, reacts with



(11)

tert-butyl chloride to give the corresponding α-tert-butyl ketone in 83% yield (eq 12). This marked improvement in yield would appear to support the hypothesis outlined in equation 9.

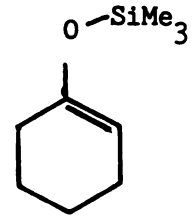
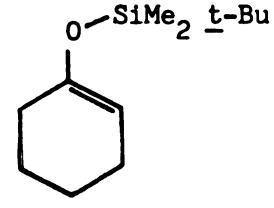
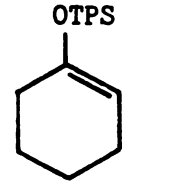


(12)

Next, the hydrolytic stability of 7a was compared to the corresponding TMS and TBDS enol ether derivatives under a wide variety of conditions. The results are summarized in Table I. It can be seen that the TPS enol ether is markedly more resistant to acid hydrolysis than the TMS enol ether. In fact, hydrolysis conditions B demonstrate that the TPS enol ether is even more resistant to acid hydrolysis than the TBDS derivative. These results demonstrate the potential of the TPS enol ethers as a protecting group for ketones. The last entry in Table I demonstrates that KF on Celite in acetonitrile is capable of removing the TPS group to regenerate the ketone quantitatively. The TPS group can thus be introduced and removed efficiently.

The general nature of the synthesis of TPS enol ethers was demonstrated by the reaction of TPS chloride with several ketones. These results are summarized in Table II. TPS enol ethers are obtained in good to excellent yields. As expected, mixtures of stereoisomers were obtained where such mixtures are possible (cf. 7f, 7h). The regiochemical aspects of this reaction were not examined. Where a single isomer is obtained, the product is a white, crystalline solid which can be stored, apparently indefinitely, without special protection from moisture or air. In this respect, TPS enol ethers are a distinct improvement over TMS enol ethers. An extension of the tert-butylation reaction (eq 12)

Table I. Cleavage of Silyl Enol Ethers

Silyl Enol Ether	Cleavage Conditions[a]	Reaction Time (h)	% Ketone[b]
	A	1	20
	A	6	100
	B	0.25	100
	C	1	5
	A	1	0
	A	6	0
	B	0.25	80
	B	1	100
	C	1	0
 7a	A	1	0
	A	6	0
	B	0.25	10
	B	1	70
	B	2	100
	C	1	0
	D	1	100

[a] A: HOAc/THF/H_2O, 1:10:1; B: THF/1 M HCl (aq), 20:1; C: THF/1 M NaOH (aq), 20:1; D: KF on Celite 1:1, 2 M in CH_3CN. Reactions mixtures with solutions A, B, and C are homogeneous.

[b] Determined by GLC using an internal standard (see experimental).

Table II. Formation of TPS Enol Ethers

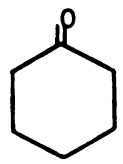
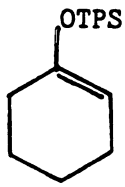
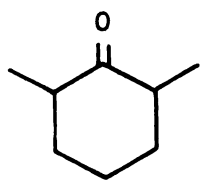
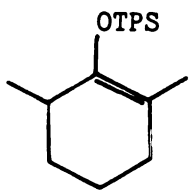
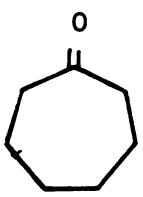
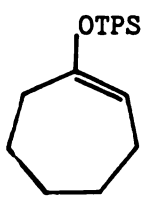
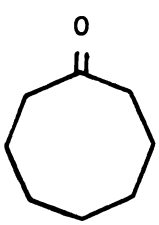
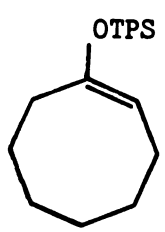
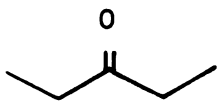
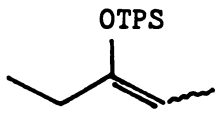
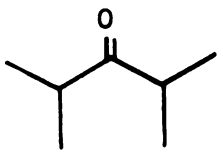
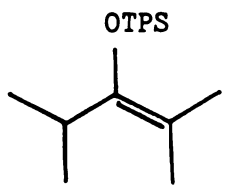
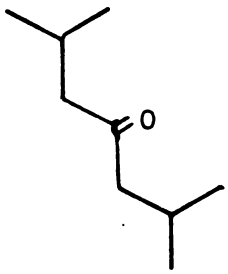
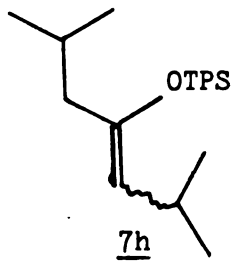
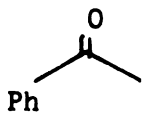
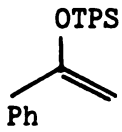
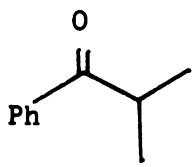
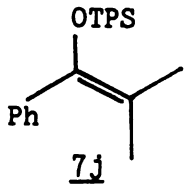
Ketone	Reaction Time[a], h	Product	mp°C	% Yield[b]
	1	 7b	66-68	88
	1	 7a	69.5-70.5	91
	8	 7c	87.5-88.5	81
	1.5	 7d	51-52	92
	2	 7e	65.6-67	91

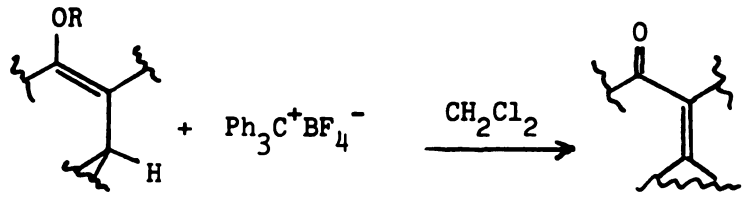
Table II (cont'd)

	1.5	 7f	oil	73[c]
	6	 7g	74-75	95
	6	 7h	oil	86[c]
	3	 7i	96-96.5	87
	6	 7j	85-86	81

[a]Reaction times are not optimized.
[b]Yield of isolated product after purification.
[c]Mixture of E and Z isomers.

to some of the enol ethers described in Table II, resulted in the synthesis of several α-tert-butyl ketones (Table III). The results are comparable to those obtained for TMS enol ethers[23].

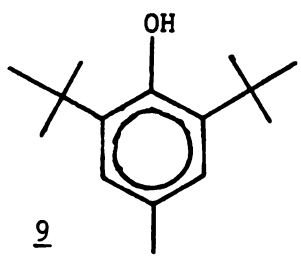
Finally, we investigated the trityl tetrafluoroborate oxidation of silyl enol ethers to the corresponding enones[3a] (eq 13). A major



(13)

problem with this reaction sequence is recovery of unoxidized ketone. While the source of the ketone has not been determined, it appears to arise from fluoride cleavage of the Si-O bond[25]. Use of the TPS enol ethers appears to offer improved results over the TMS derivatives (Table IV, reference 3a)

These reactions demonstrate that TPS chloride is a valuable hindered silylating agent for ketones, and that TPS enol ethers are a viable alternative to TMS and TBDS enol ethers in t-butylation and oxidation reactions. Finally, there are a number of very inexpensive hindered phenols such as butylated hydroxy toluene (BHT, 9) and butylated hydroxy anisole (BHA, 10), that are currently used in foods as antioxidants, which could be expected to provide silylating reagents with similar properties to TPS chloride at an even lower cost.



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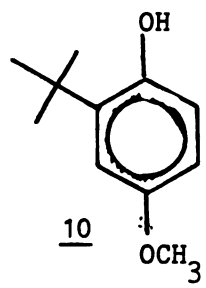

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Table III. t-Butylation of TPS Enol Ethers

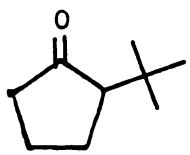
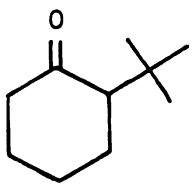
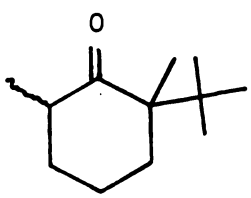
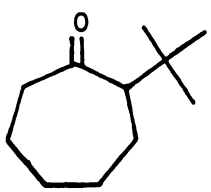
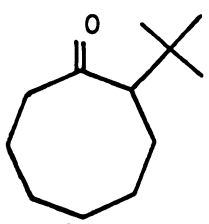
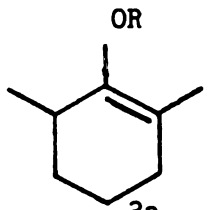
Silyl Enol Ether	Product	Yield (%)
7b	 8a	71
7a	 8b	83
7c	 8c	76
7d	 8d	79
7e	 8e	83

Table IV. Oxidation of TPS Enol Ethers

Silyl Enol Ether	Yield (%) Enone	Ketone
		
R = TMS[3a]	50	15
R = TPS	55	10
		
R = TMS[3a]	64	34
R = TBDS[3a]	35	5
R = TPS	91	6
		
R = TMS[3a]	60	18
R = TPS	75	10

[a]Yield determined by GLC (see experimental).

EXPERIMENTAL

Acetonitrile, triethylamine, and all ketones were distilled from calcium hydride before use and stored under argon. tert-Butyl chloride, titanium tetrachloride, and dichlorodimethylsilane were distilled before use and stored under argon. Sodium iodide was flame-dried under vacuum immediately before use. Acetonitrile, triethylamine, acetophenone, and sodium iodide were obtained from Fisher Chemical. 3-Pentanone and 2,6-dimethyl-4-heptanone were obtained from Matheson Coleman and Bell. Titanium tetrachloride was purchased from Alfa-Ventron. All other ketones, 2,6-di-tert-butylphenol, 2,4,6-tri-tert-butylphenol, tert-butyl chloride, chlorotrimethylsilane, and dichlorodimethylsilane were obtained from Aldrich Chemical Co.. tert-Butyldimethylsilyl chloride was prepared by the method of Corey[19]. TMS and TBDS enol ethers were prepared by the method of Duboudin[11]. Trityl tetrafluoroborate was prepared according to the procedure of Dauben[26]. All reactions were carried out under an argon atmosphere. Gas chromatographic analyses were performed on a Varian 920 chromatograph equipped with a 4 ft x 0.25 in column packed with 15% SE-30 on acid-washed Chromsorb P (except where noted). ^1H NMR spectra were recorded on Bruker WM-250 and Varian T-60 spectrometers at 250 MHz and 60 MHz respectively with $CDCl_3$ as the solvent and are reported in parts per million in the δ scale relative to internal Me_4Si. Infrared spectra were recorded on a Perkin-Elmer 237 B spectrometer as solutions with $CHCl_3$ as the solvent and a polystyrene standard. Low resolution electron impact mass spectra were obtained with a Finnegan 4000 GC/MS at 70 eV. High resolution mass spectra were obtained with a Varian CH-5

double-focusing mass spectrometer at the Michigan State University Department of Biochemistry Mass Spectrometry Faciltiy. Elemental analyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, MI. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are uncorrected.

Preparation of DPS Chloride (3)

Triethylamine (38.5 mL, 275 mmol), 2,6-di-tert-butylphenol (51.6 g, 250 mmol) and dichlorodimethylsilane (34.1 mL, 275 mmol) were dissolved in 300 mL of acetonitrile then heated under reflux for 21 h. The solution was cooled, filtered, and the filter cake washed with 100 mL of ether. The solution was concentrated in vacuo and combined with the ether wash. The combined solutions were filtered, then concentrated in vacuo. The crude yellow solid obtained was recrystallized from heptane, affording 55.8 g (75%) of DPS chloride as white prisms: mp 95.5-96°C; ^{1}H NMR (60 MHz) 6.62-7.23 (m, 3H), 1.42 (s, 18H), 0.70 (s, 6H); EI-MS m/e 298 (M^+), 283, 247, 191, 175, 131, 93, 75, 57.

Preparation of Cyclohexanone DPS Enol Ether (4)

Triethylamine (21 mL, 150 mmol), cyclohexanone (10.4 mL, 100 mmol), and DPS chloride (30 g, 100 mmol) were added to a suspension of sodium iodide (15 g, 100 mmol) in 100 mL of dry acetonitrile. The mixture was stirred for 6 h at room temperature, then diluted with 250 ml of ether and washed with water (2 x 100 ml). The ether solution was dried with $MgSO_4$, then concentrated in vacuo. The residue was distilled (Kugelrohr) affording a clear, colorless, highly viscous oil: bp 160°

(0.05 torr); ^{1}H NMR (60 MHz) 6.56-7.23 (m, 3H), 4.78 (m, 1H), 1.20-2.20 (m, 8H), 1.38 (s, 18H), 0.35 (s, 6H); CI-MS (CH_4) m/e 401 (M+41), 389 (M+29), 361 (M + 1), 345, 333, 305, 262, 247.

Hydrolysis Studies: Cyclohexanone DPS Enol Ether 4 vs. TBDS Enol Ether

5 mmol of each silyl enol ether was dissolved in 5 mL of a 3:1:1 solution of acetic acid/water/THF. After 1 h, a decane standard was added, the solution was extracted with 10 mL of ether, and analyzed for cyclohexanone by GLC. The DPS enol ether was less than 10% hydrolyzed while the TBDS enol ether was nearly completely (> 90%) hydrolyzed.

tert-Butylation of Cyclohexanone DPS Enol Ether 4

This procedure was adopted from the work of Chan, et al.[23b]. tert-Butyl chloride (0.60 mL, 5.5 mmol) was dissolved in 5 mL CH_2Cl_2 and cooled to -78°C. Titanium tetrachloride (0.60 mL, 5.5 mmol) was added. To this mixture was added dropwise a solution of cyclohexanone DPS enol ether (1.80 g, 5.0 mmol) in 3 mL of CH_2Cl_2. The solution was stirred for 1 h at -78°C, then quenched with 10 mL of water. The organic layer was washed with 2 x 10 mL water, dried with $MgSO_4$, and analyzed by GLC after addition of standard. α-tert-Butylcyclohexanone was present in 13% yield, while cyclohexanone was present in 40% yield. These results were virtually unchanged by longer reaction time, higher temperatures (-40°, 0°, 25°), changes in concentration, or use of excess tert-butyl chloride or titanium tetrachloride.

Preparation of (2,4,6-Tri-tert-butylphenoxy)dimethylsilyl Chloride

2,4,6-Tri-tert-butylphenol (131 g, 0.5 mol), triethylamine (84 mL, 0.6 mol) and dichlorodimethylsilane (67 mL, 0.55 mol) were dissolved in 500 mL of acetonitrile and refluxed overnight. The reaction was then allowed to cool to ambient temperature, and concentrated in vacuo. The residue was dissolved in 500 mL of pentane, and washed (3 x 100 mL) with water. The solution was dried with $MgSO_4$, decolorized with Norit-A, and filtered through Celite. The clear, lightly colored solution was concentrated, giving 165 g (93%) of 3 as white crystals: mp 79-81°C; ^1H NMR (250 MHz) 7.28 (s, 2H), 1.44 (s, 18H), 1.30 (s,9H), 0.73 (s, 6H); IR: 2945, 1420, 1260, 1200, 1120 cm^{-1}; EI-MS m/e 354 (M^+), 339, 303. The crystals may be recrystallized from heptane giving white needles melting at 80-81°C. We found that this last step was unnecessary for subsequent use of 3 to prepare silyl enol ethers. Anal. Calcd for $C_{20}H_{35}OSiCl$: C, 67.77; H, 9.94; O, 4.51; Cl, 9.99; m/e 354.2146. Found: C, 67.68; H, 10.05; O, 4.34; Cl, 9.85; m/e 354.2152.

General Procedure for Preparation of TPS Enol Ethers (7)

TPS Enol Ether of Acetophenone (7i) Acetophenone (2.92 mL, 25 mmol), triethylamine (6.3 mL, 37.5 mmol), sodium iodide (4.95 g, 27 mmol), and TPS chloride (8.9 g, 25 mmol) were dissolved in 25 mL of acetonitrile and refluxed for 3 h. After cooling to ambient temperature, the mixture was diluted with 50 mL of pentane, and washed 2 x 25 mL with water. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by either bulb-to-bulb distillation or recrystallization[13] from hexanes giving 9.9 g (86%) of 4i as white

crystals: mp 96-96.5°C; ^{1}H NMR (250 MHz) 7.05-7.67 (m, 7H), 4.90 (d, 1H, J=2.5 Hz), 4.45 (d, 1H, J=2.5 Hz), 1.43 (s, 18H), 1.28 (s, 9H), 0.43 (s, 6H); IR 1665 cm^{-1} (C=C); CI-MS[14] m/e 479 (M+41), 467 (M+29), 439 (M + 1), 423, 383. Anal. Calcd for $C_{24}H_{33}O_2Si$: C, 76.66; H, 9.65; O, 72.9; Si, 6.40; m/e (M-57) 381.2250. Found: C, 76.56; H, 9.71; O, 7.02; Si, 6.46; m/e (M-57) 381.2237.

Using the same procedure, the following TPS enol ethers were prepared:

TPS Enol Ether of Cyclohexanone (7a) 9.5 g (91%), white crystals: mp 69.5-70.5°C; ^{1}H NMR (250 MHz) 7.25 (s, 2H), 4.88 (m, 1H), 1.2-2.1 (m, 8H), 1.43 (s, 18H), 1.29 (s, 9H), 0.37 (s, 6H); IR 1665 cm^{-1} (C=C); EI-MS m/e 416 (M^+), 401, 360, 345, 303, 155, 75, 57. Anal. Calcd for $C_{26}H_{44}O_2Si$: C, 74.94; H, 10.64; O , 7.68; Si, 6.73; m/e 416.3111. Found: C, 75.08; H, 10.69; O, 7.79; Si, 6.88; m/e 416.3141.

TPS Enol Ether of Cyclopentanone (7b) 8.8 g (88%), white crystals: mp 66-68°C; ^{1}H NMR (250 MHz) 7.25 (s, 2H), 4.68 (m, 1H), 1.2-2.4 (m, 6H), 1.44 (s, 18H), 1.29 (s, 9H), 0.39 (s, 6H); IR 1645 cm^{-1} (C=C); EI-MS m/e 402 (M^+), 387, 331, 303, 247, 75, 57; mass spectrum, calcd 402.2954, obsd 402.2959.

TPS Enol Ether of 2,6-Dimethylcyclohexanone (7c) 9.0 g (81%), white crystals: mp 87.5-88.5°C; ^{1}H NMR (250 MHz) 7.26 (s, 2H), 1.2-2.2 (m, 7H), 1.57 (s, 3H), 1.45 (s, 18H), 1.30 (s, 9H), 1.06 (d, 3H, J = 6.8 Hz), 0.36 (s, 3H), 0.28 (s, 3H); IR 1680 cm^{-1} (C=C), EI-MS m/e 444 (M^+), 387, 303, 75, 57. Anal. Calcd for $C_{28}H_{48}O_2Si$: C, 75.61; H, 10.88; O, 7.19; Si, 6.31; m/e 444.3424. Found: C, 75.41; H, 10.78; O, 7.14 ; Si, 6.38; m/e 444.3421.

TPS Enol Ether of Cycloheptanone (7d) 9.9 g (92%), white crystals: mp 51-52°C; ^{1}H NMR (250 MHz) 7.25 (s, 2H), 5.01 (t, 1H, J=6.7 Hz), 1.2-2.3 (m, 10 H), 1.43 (s, 18H), 1.29 (s, 9H), 0.36 (s, 6H); IR 1650 cm^{-1} (C=C); EI-MS m/e 430 (M^+), 415, 373, 303, 169, 75, 57; mass spectrum, calcd 430.3267, obsd 430.3278.

TPS Enol Ether of Cyclooctanone (7e) 10.1 g (91%), white crystals: mp 65.5-67°C, ^{1}H NMR (250 MHz) 7.25 (s, 2H), 4.77 (t, 1H, J=8.4 Hz), 1.2-2.3 (m, 12H), 1.44 (s, 18H), 1.29 (s, 9H), 0.36 (s, 6H); IR 1660 cm^{-1} (C=C); EI-MS m/e 444 (M^+), 429, 387, 336, 321; mass spectrum, calcd 444.3424, obsd 444.3461.

TPS Enol Ether of 3-Pentanone (7f) 7.4 g (73%), oil consisting of E and Z isomers; bp 120°C (0.2 torr); ^{1}H NMR (60 MHz) (partial) 4.63 (q, J=6 Hz) and 4.55 (q, J=6 Hz) E and Z vinyl H; IR 1670 cm^{-1} (C=C); EI-MS m/e 404 (M^+), 389, 347, 319, 303, 143, 75, 57; mass spectrum, calcd 404.3111, obsd 404.3110.

TPS Enol Ether of 2,4-Dimethyl-3-pentanone (7g) 10.3 g (95%), white crystals: mp 74-75°C; ^{1}H NMR (250 MHz) 7.26 (s, 2H), 2.87 (m, 1H, J=6.6 Hz), 1.68 (s, 3H), 1.66(s, 3H), 1.44 (s 18H), 1.30 (s, 9H), 0.98 (d, 6H, J=6.6 Hz), 0.30 (s, 6H); IR 1670 cm^{-1} (C=C); EI-MS m/e 432 (M^+), 417, 376, 319, 303, 263, 75; mass spectrum, calcd 432.3424, obsd 432.3404.

TPS Enol Ether of 2,6-Dimethyl-4-heptanone (7h) 9.9 g (86%), oil consisting of E and Z isomers; bp 160°C (0.2 torr); ^{1}H NMR (60 MHz) (partial) 4.53 (d, J=9.9 Hz) and 4.31 (d, J=9.8 Hz) E and Z vinyl H; EI-MS m/e 460 (M^+), 445, 403, 321, 303, 247, 75, 57; mass spectrum, calcd 460.3737, obsd 460.3743.

TPS Enol Ether of Isobutyrophenone (7j) 9.5 g (81%), white crystals: mp 85-86°C; ^{1}H NMR (250 MHz) 7.2-7.4 (m, 7H), 1.77 (s, 3H), 1.67 (s, 3H), 1.45 (s, 18H), 1.29 (s, 9H), 0.086 (s, 6H); IR 1660 cm^{-1} (C=C); EI-MS m/e 466 (M^+), 451, 409, 353, 303, 205, 131, 75, 57; mass spectrum, calcd 466.3267, obsd 466.3271.

Hydrolysis Studies These studies were conducted on the TPS, TMS, and TBDS enol ethers of cyclohexanone by dissolving 1 mmol of silyl enol ether in 2.5 mL of solution A, B, C, or D. After the indicated time, the standard, decane, was added and 10 mL of ether was used to extract the solution (except for solution D, which was anlayzed directly), the solution was washed with 1 x 5 mL of H_2O, dried with $MgSO_4$, and analyzed by GLC.

General Procedure for the Preparation of α-tert-Butylketones 8[23b]

α-tert-Butylcyclohexanone (8b) Cyclohexanone TPS enol ether (2.08 g, 5.0 mmol) and tert-butyl chloride (0.60 mL, 5.5 mmol) were dissolved in 5 mL of CH_2Cl_2 and cooled to -78°C. Titanium tetrachloride (0.60 mL, 5.5 mmol) was added dropwise and the solution stirred for 2 h at -78°C. The reaction was quenched with 5 mL of water and warmed to room temperature. The organic layer was dried with $MgSO_4$ and analyzed by GLC relative to a hexadecane standard, indicating the presence of α-tert-butylcyclohexanone in 83% yield.

α-tert-Butylcyclopentanone (8a) This compound was prepared as above. GLC analysis showed α-tert-butylcyclopentanone in 71% yield.

α-tert-Butyl-2,6-dimethylcyclohexanone (8c) This compound was prepared as above. GLC analysis showed 8c in 76% yield.

α-tert-Butylcycloheptanone (8d) This compound was prepared as above. GLC analysis showed 8d in 79% yield.

α-tert-Butylcyclooctanone (8e) This compound was prepared as above. GLC anlaysis showed 8e in 83% yield.

General Procedure for the Trityl Tetrafluoroborate Oxidation of TPS Enol Ethers[3a]

Trityl Tetrafluoroborate Oxidation of 7a A solution of 4b (2.08 g, 5 mmol) in 2.5 mL of CH_2Cl_2 was added dropwise to a suspension of trityl tetrafluoroborate (1.80 g, 5.5 mmol) in 2.5 mL of CH_2Cl_2 over 1 min at 25°C. After 10 min the reaction was quenched with 10 mL of water. The CH_2Cl_2 layer was dried ($MgSO_4$) and the internal standard, n-hexadecane, was added. GLC analysis (4 ft x 0.25 in column packed with 15% Carbowax 20 M terephthalate on Chromsorb W) showed cyclohexenone (91%) and cyclohexanone (6%).

Oxidation of 7b Cyclopentanone TPS enol ether was reacted as above. GLC analysis (as above) indicated the presence of cyclopentenone (75%) and cyclopentanone (15%).

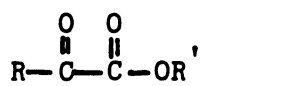
Oxidation of 7c 2,6-Dimethylcyclohexanone TPS enol ether was reacted as above. GLC analysis (as above) showed 2,6-dimethyl-2-cyclohexenone (82%) and 2,6-dimethylcyclohexanone (13%).

CHAPTER II

THE REACTIONS OF α-AZIDO ESTERS WITH BASE

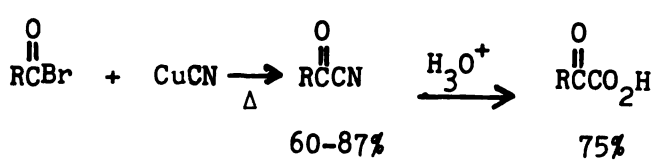
INTRODUCTION

α-Keto esters 11a and acids 11b are molecules of biological



11a R' = alkyl
11b R' = H

significance. They are the biological precursors to amino acids[27], and have also been isolated as steroid metabolites[28]. In addition, these compounds have been employed as synthons for the construction of side chains of biologically active β-lactams[29], and in the synthesis of dipeptides[30]. However, methodology for the synthesis of this important functionality is somewhat limited in its utility and generality. Classically, α-keto acids have been prepared by the hydrolysis of acyl cyanides[31] (eq 14), the hydrolysis of oxime esters[32] (eq 15), the



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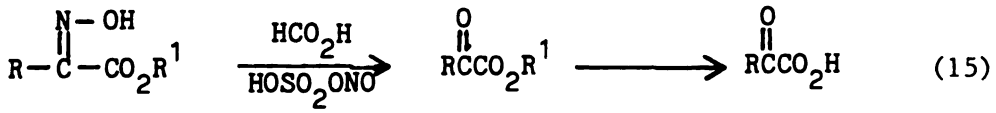

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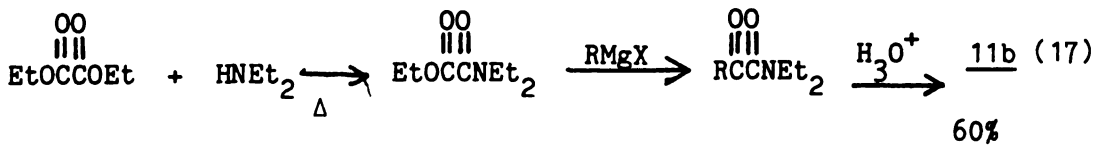
hydrolysis of oxalo acid esters[33] (eq 16) and by reaction of Grignard

(16)

reagents with diethyl oxamates[34] (eq 17). In addition, various specific



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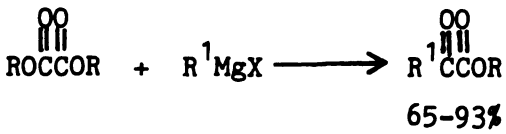
syntheses have been developed[32,35], including the permanganate oxidation of an α-hydroxy acid[36], and the dimethyl sulfoxide oxidation of an α-bromo ester[37]. The generality of these particular reactions has not been explored. Some more recent developments include the selenium dioxide oxidation of α-bromo ketones[38] and methyl ketones[39], the oxidation of α,α-dibromo ketones with pyridine N-oxide[40] (eq 18), and the reaction of Grignard reagents with both dialkyl oxalates[41] (eq 19) and

(18)



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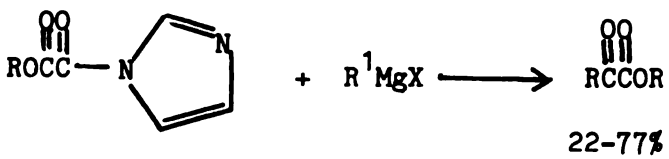
alkyl α-oxo-1 H-imidazole-1-acetates[42] (eq 20). Both Seebach[43a] and



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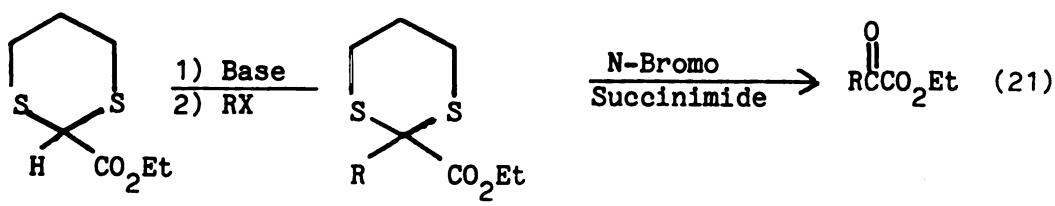
Eliel[43b] have used metallated dithianes derived from ethyl glyoxalate as an acyl anion equivalent in the synthesis of α-keto esters and acids (eq 21). This method would clearly be unsuitable for R = aromatic, as



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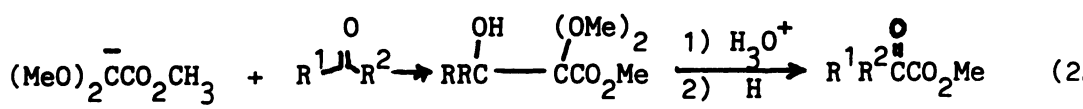
well as cases where competing elimination of HX becomes a factor (2° & 3° RX). Neef and Eder report the use of the anion from α,α-dimethyoxy methylacetate in aldol condensations with ketones[44] (eq 22). Dehydration, reduction, and deketalization completes the synthesis of α-keto



(22)

esters but the authors report that these are not trivial reactions, and yields are often poor. A potentially useful synthesis of α-keto esters involves the osmium tetroxide oxidation of alkynyl ethers[45] (eq 23).

$$R{-}C{\equiv}C{-}OR^1 \xrightarrow[KClO_4]{OsO_4} \underset{80\%}{RCCO_2R^1} \qquad (23)$$

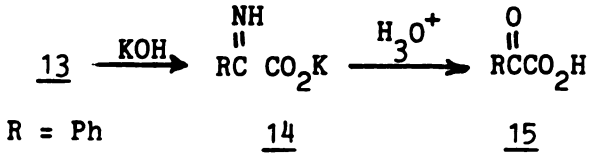
However, osmium tetroxide is extremely toxic[46], and the utility of catalytic quantities of osmium in this sequence has yet to be demonstrated.

Of all the previously mentioned syntheses, only the dimethylsulfoxide oxidation of α-bromo esters[37] involves manipulation at the α-carbon of an ester containing all of the carbon atoms present in the target α-keto ester. This procedure has only been applied successfully in the reaction of ethyl α-bromo (or chloro) acetate and propionate; there is a report that it fails for more complicated molecules[47]. We decided that a desirable procedure for the synthesis of α-keto esters would involve performing chemistry at the α-carbon of a readily available ester precursor.

M.O. Foster extensively investigated the chemistry of α-azido esters 12 almost seventyfive years ago[48]. He observed that careful hydrolysis of 12 allowed isolation of the corresponding carboxylates 13, and ultimately, the α-azido acids (eq 24). Further treatment with

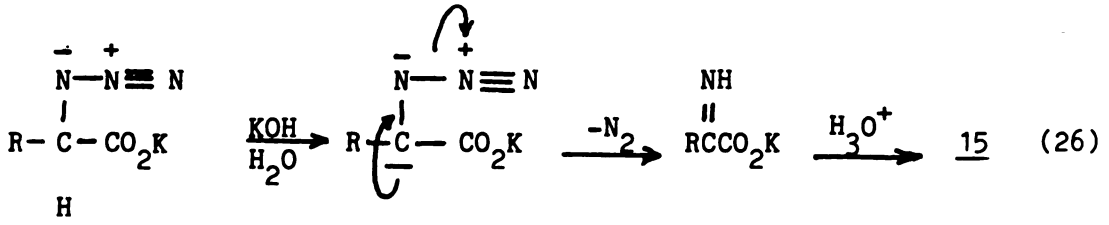
$$\underset{12}{RCHCO_2H} \xrightarrow[H_2O]{KOH} \underset{13}{RCHCO_2K} \xrightarrow[KOH]{excess} N_2 + ? \qquad (24)$$

base resulted in evolution of nitrogen, although a full equivalent was not obtained. He suspected the intermediacy of an α-imino acid 14, and for R = Ph was able to isolate benzoyl formic acid (15, R = Ph, eq 25).



(25)

It appears that hydroxide is a strong enough base to remove the α-proton from the α- azido carboxylate to provide an intermediate carbanion which can evolve nitrogen, leading to a species such as 14 which is hydrolyzed to 15 (eq 26). Although Forster did not attempt to investigate these reactions in detail, it occured to us that by the choice of appropriate reaction conditions, we might achieve a general synthesis of α-keto esters from α-azido esters.



(26)

RESULTS AND DISCUSSION

It was apparent to us that a successful synthesis of α-keto esters from α-azido esters would depend in part on the availability of the precursor α-azido esters themselves. There are reports in the literature on the synthesis of α-azido esters 16 from the corresponding α-halo compounds and sodium azide in an aqueous medium[49] (eq 27). We

$$\underset{\text{R-C(Br)HCO}_2\text{R}^1}{} + \text{NaN}_3 \longrightarrow \underset{\text{16}}{\text{R-C(N}_3\text{)HCO}_2\text{Et}} \qquad (27)$$

found, however, that the use of N,N-dimethylformamide as the solvent allowed shorter reaction times and also facilitated the isolation of 16. The α-bromo esters are available from the esters by a variety of means[50]; therefore, the α-azido esters were quite accessible. We envisioned a sequence such as that described in equation 26, where the base utilized would be chosen such that it would not hydrolyze the ester. We reasoned that the esters would be easier to isolate and handle than the corresponding acids, which could suffer decarboxylation[32].

Treatment of ethyl-2-azidopropionate 17 with triethylamine did not result in evolution of nitrogen even at reflux temperatures (eq 28).

$$\underset{\text{17}}{\text{CH}_3\text{CH(N}_3\text{)CO}_2\text{Et}} + \text{Et}_3\text{N} \xrightarrow[\text{THF}]{\Delta} \text{No Reaction} \qquad (28)$$

The reaction of 17 with one equivalent of sodium hydroxide in aqueous tetrahydrofuran (THF) resulted in hydrolysis of the ester, but no evolution of nitrogen (eq 29). We concluded from these results that a

$$\underline{17} + NaOH \xrightarrow[THF]{H_2O} CH_3\overset{N_3}{\overset{|}{C}}HCO_2Na \qquad (29)$$

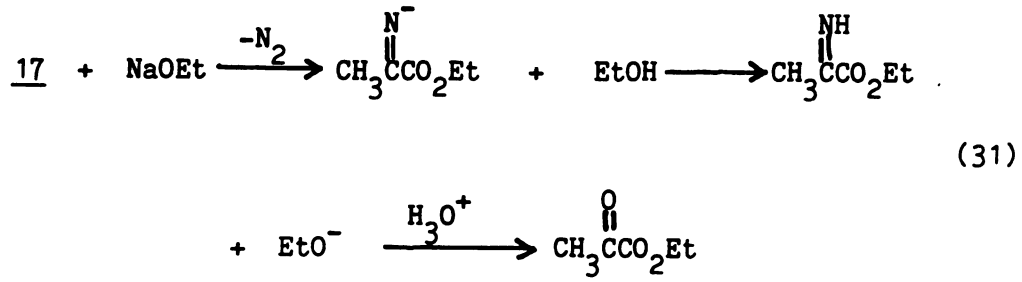
non-aqueous base system was needed, and that simple amine bases were not powerful enough to deprotonate α-azido esters such as 17. Treatment of 17 with lithium diisopropylamide (LDA) in THF at Dry Ice temperature resulted in the evolution of approximately one-half the expected volume of nitrogen. Aqueous workup of the reaction mixture afforded an intractable tar. We concluded that the problem was the instability of the proposed intermediate 18 under the reaction conditions.

$$CH_3\overset{N^-}{\overset{\|}{C}}CO_2R \xrightarrow{H_2O} CH_3\overset{NH}{\overset{\|}{C}}CO_2R \qquad (30)$$

18

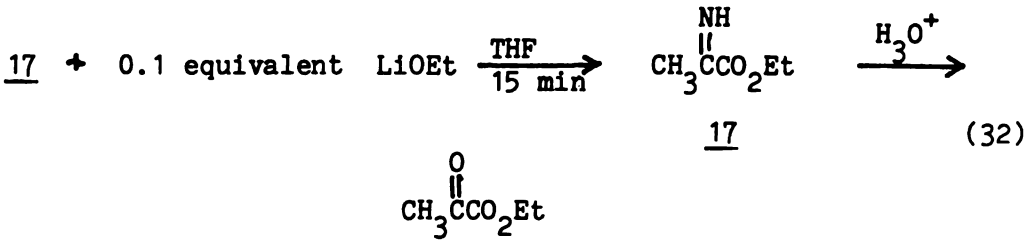
Under aqueous reaction conditions, 18 should be rapidly protonated (eq 30). With anhydrous LDA/THF, however, this anion would not be protonated, and could be expected to react further to give polymeric products. As a result of this reasoning, we concluded that the base used had to be sufficiently powerful so as to remove the α-hydrogen from an α-azido ester and had to provide a conjugate acid capable of protonating the intermediate imine anion 18. We decided initially to investigate sodium

ethoxide in ethanol as a base/solvent system. The reaction of 17 with sodium ethoxide in ethanol resulted in slow (8 h) and quantitative evolution of nitrogen. Hydrolysis of the reaction mixture gave a 10% yield of ethyl pyruvate (eq 31). An examination of equation 31 reveals



(31)

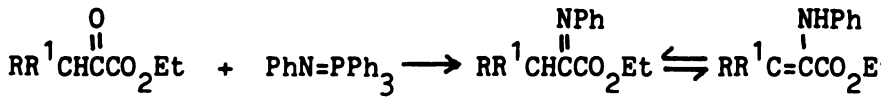
that it should be possible to use a catalytic amount of ethoxide. We also reasoned that the rate of reaction should be increased by the use of a non-protic solvent. This would eliminate the hydrogen bonding present between the base (sodium ethoxide) and solvent, allowing the base to act more effectively. Finally, we switched from sodium to lithium ethoxide because we found it to be very convenient to generate the latter from ethanol and n-butyllithium. Ultimately, we found that treatment of 17 with 0.1 equivalents of lithium ethoxide in THF resulted in rapid (15 min) and complete evolution of nitrogen. Workup with aqueous acid gave a 50% yield of ethyl pyruvate (eq 32). Several α-azido esters were treated in this fashion, and α-keto esters were



(32)

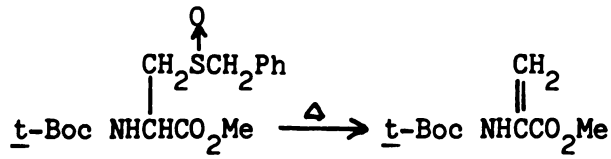
obtained in good yields (Table V). This procedure appears to be applicable to the synthesis of a variety of α-keto esters.

We next turned our attention to the intermediate imino esters (i.e. 19). These compounds are of considerable interest[51], because of their postulated intermediacy in amino acid synthesis[52] and their presence in microbial peptides[53]. The methodology for the synthesis of imino (and their tautomers, enamino) esters has been limited to the reaction of α-keto esters with Wittig-type reagents[54] (eq 33) or elimination of HX



(33)

from appropriately substituted α-amino esters[55-57] (eqs 34-36). It has



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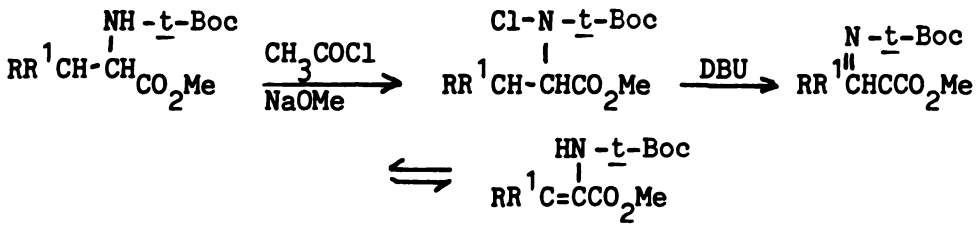

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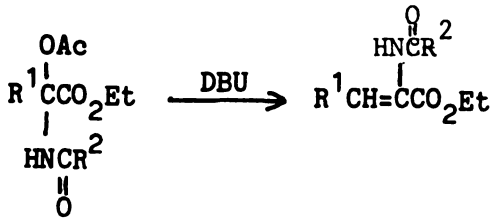

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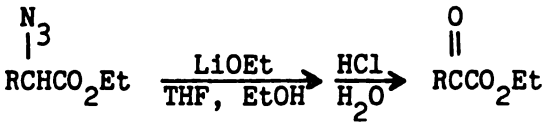
Table V. Formation of α-Keto Esters from α-Azido Esters



16 11a

R	reaction time,[a] min	% yield[b]
CH_3	15	50
CH_3CH_2	20	86
$(CH_3)_2CH$	30	94
Ph	2	91
$PhCH_2$	45	94[c]

[a]Time for complete evolution of nitrogen at 25°C.
[b]GLC yields, determined with internal standard, unless otherwise noted. In all cases, removal of solvent left a residue of essentially pure (^1H NMR analysis) α-keto ester.
[c]Yield of distilled product.

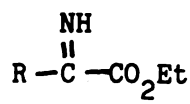
also been reported α-nitro-α,β-unsaturated esters can be reduced directly to the imino esters by treatment with aluminum amalgam in refluxing ether[58] (eq 37). We thought that synthesis of these α-dehydroamino esters from α-azido esters would be a general and useful method nicely complementing currently available techniques.

$$RR^1C(NO_2)CO_2Et \xrightarrow[\text{Ether}]{\text{Al-Hg}} RR^1C(NH_2)CO_2Et \rightleftharpoons RR^1CHC(=NH)CO_2Et \quad (37)$$

It seemed to us that omission of the aqueous workup from our α-keto ester synthesis would allow isolation of the dehydroamino esters. Attempts to isolate ethyl 2-iminopropanoate (19) by distillation of unhydrolyzed reaction mixtures were unsuccessful. The pot contents turned dark on heating and eventually formed a nonvolatile tar. However, careful evaporation of solvent at 25°C from freshly prepared reaction mixtures gave a residue of essentially pure 19 as judged by ^{1}H NMR analysis (the only apparent impurity being lithium ethoxide). Alternatively, addition of triethylamine and acetyl chloride to the unhydrolyzed reaction mixture gave a 60% isolated yield of the corresponding N-acetyl derivative 20 (eq 38).

$$\underline{17} \xrightarrow[\text{THF}]{\text{LiOEt}} \underline{19} \xrightarrow[\text{Et}_3\text{N}]{CH_3C(=O)Cl} \underset{\underline{20}}{CH_2=C(NHC(=O)CH_3)CO_2Et} \quad (38)$$

More simply, verification of α-dehydroamino ester formation was obtained by reaction of 16 with lithium ethoxide in carbon tetrachloride solution. Direct ^1H NMR analysis of the reaction mixtures indicated quantitative formation of α-dehydroamino esters 21, R = Me, Et(a mixture of imino and enamino esters was formed), and Ph .



21

In view of the fact that α-azido esters are readily available in two steps from the corresponding ester, this methodology[59] appears to offer significant advantages over previously published procedures for the synthesis of both dehydroamino esters and α-keto esters.

EXPERIMENTAL

THF was distilled from a sodium-benzophenone ketyl still under argon. Other solvents were distilled before use. Acetyl chloride, ethyl 2-bromobutanoate, and 2-bromo-2-phenylacetic acid were obtained from Aldrich Chemical. Ethyl 2-bromo-3-methylbutanoate was prepared by the method of Rathke[50a]. 2-Bromo-3-phenylpropanoic acid was prepared by the method of Marvel[50b] and esterified by standard procedures. All reactions were conducted under argon atmosphere. Gas chromatographic data were obtained on a Varian 920 chromatograph equipped with a 4 ft x 0.25 in column packed with 10% Carbowax 20 M terephthalate on Chromsorb G. ^1H NMR spectra were recorded on a Varian T-60 spectrometer at 60 MHz using $CDCl_3$ as the solvent (except where noted) and are reported in parts per million in the scale relative to internal Me_4Si. Infrared

spectra were taken on a Perkin-Elmer 237 B spectrometer, using polystyrene as a reference. Electron impact-mass spectra were obtained at 70 eV with a Finnegan 4000 GC/MS. Melting points and boiling points are uncorrected. Yields of the azides are not maximized and ranged from 50-85%.

General Procedure for Preparation of Azides (16)

Ethyl 2-Azidopropanoate[49a] (16, R = Me) Ethyl 2-bromopropanoate (65 mL, 0.50 mol) was added to a suspension of sodium azide (49 g, 0.76 mol) in 50 mL of dimethylformamide at 25°C and stirred for 2.5 h. After addition of 200 mL of water, the solution was extracted with two 50-mL portions of CH_2Cl_2. The combined organic layers were washed with 200 mL of water, dried ($MgSO_4$), and concentrated in vacuo. Distillation afforded 51.01 g (72%) of 16 (R = Me) as a clear, colorless oil: bp 36-40°C (0.5 torr); ^{1}H NMR 4.18 (q, J = 7 Hz, 2H), 3.90 (q, J = 7 Hz, 1H), 1.42 (d, J = 7 Hz), and 1.28 (t, J = 7 Hz) (total 6H); IR (neat) 2100 (s, CN_3), 1745 (s, C=O) cm^{-1}; EI-MS m/e 143 (M^+), 73, 70, 56, 42.

Ethyl 2-Azidobutanoate (16, R = Et) This compound was prepared as above: bp 38-40°C (0.15 torr); ^{1}H NMR 4.20 (q, J = 7 Hz, 2H), 3.73 (t, J = 6 Hz, 1H), 1.82 (m, 2H), 1.30 (t, J = 7 Hz) and 1.00 (t, J = 7 Hz) (total 6H); IR (neat) 2100 (s CN_3), 1745 (s, C=O) cm^{-1}; EI-MS m/e 157 (M^+), 84, 73, 69, 56.

Ethyl α-Azidoisovalerate[49b] (16, R = $(CH_3)_2CH$) This compound was prepared as above: bp 45-45.5°C (0.35 torr); ^{1}H NMR 4.13 (q, J = 7 Hz, 2H), 3.57 (d, J = 6 Hz, 1H), 2.08 (m, 1H), 1.27 (t, J = 7 Hz) and 1.00 (dd, J = 7 Hz) (total 9H); IR (neat) 2090 (s, CN_3), 1730 (s, C=O) cm^{-1}; EI-MS m/e 171 (M^+), 102, 70, 43.

Ethyl 2-Azidophenylacetate[49c] (16, R = Ph) This compound was prepared as above: bp 85-88°C (0.05 torr); ^{1}H NMR 7.28 (s, 5H), 4.87 (s, 1H), 4.08 (q, J = 7 Hz, 2H), 1.10 (t, J = 7 Hz, 3H); IR (neat) 2100 (s, CN_3) 1735 (s, C=O) cm^{-1}; EI-MS m/e 205 (M^+), 163, 132, 104, 77, 51.

Ethyl 2-Azido-3-phenylpropanoate[49d] (16, R = $PhCH_2$) This compound was prepared as above: bp 107-107.5°C (0.05 torr); ^{1}H NMR 7.10 (s, 5H), 3.8-4.3 (m, 3H), 2.85-3.10 (m, 2H), 1.15 (t, J = 7 Hz, 3H); IR (neat) 2100 (s, CN_3), 1700 (s, C=O) cm^{-1}; EI-MS m/e 219 (M^+), 191, 176, 91.

General Procedure for Preparation of Dehydroamino Esters (21)

Ethyl 2-Iminopropanoate (21, R = Me) Ethanol (0.05 mL, 0.8 mmol) was added to n-butyllithium (1.6 M, 0.32 mL, 0.5 mmol) in hexane. The mixture was dissolved in 5 mL of CCl_4 at 25°C. Ethyl 2-azidopropanoate (16, R = Me) was added dropwise and stirred at 25°C until 125 mL (5 mmol) of N_2 was evolved (20 min). Benzene (0.22 mL, 2.5 mmol) was added, and the yield was determined by ^{1}H NMR[60] analysis: yield 100%; ^{1}H NMR (CCl_4) 10.91 (br s, 1H), 4.24 (q, J = 7 Hz, 2H), 2.29 (s, 3H), 1.41 (t, J = 7 Hz, 3H).

Ethyl 2-Iminobutanoate (21, R = Et) This solution was prepared as above: yield 100%[60] (mixture of imine and enamine); partial ^{1}H NMR (CCl_4) for imine, 2.64 (q, J = 8 Hz, 2H); partial ^{1}H NMR (CCl_4) for enamine, 5.54 (q, 1H, J = 7 Hz), 1.70 (d, 3H, J = 7 Hz).

Ethyl 2-Iminophenylacetate (21, R = Ph) This solution was prepared as above: yield 100%[60]; ^{1}H NMR (CCl_4) 10.5 (s, 1H), 7.3-8.0 (m, 5H), 4.20 (q, J = 7 Hz, 2H), 0.85 (t, J = 7 Hz, 3H).

N-Acetyl-2,3-dehydroalanine (20) Imine 21 (R = Me) was prepared as above. Triethylamine (0.77 mL, 5.5 mmol) was added and the solution cooled to 0°C. Acetyl chloride (0.54 mL, 5.5 mmol) was added dropwise. The mixture was filtered, concentrated in vacuo, and the residue purified by bulb-to-bulb distillation, giving 0.42 g (58%) of pale yellow oil; ^{1}H NMR 8.20 (br s, 1H), 6.58 (s, 1H), 5.90 (br s, 1H), 4.40 (q, J = 7 Hz, 2H), 2.27 (s, 1H), 1.46 (t, J = 7 Hz, 3H).

General Procedure for Preparation of α-Keto Esters (11a)

Ethyl 2-Oxobutanoate(11a, R = Et, R' = Et) Ethanol (0.05 mL, 0.8 mmol) was added to n-butyllithium (1.6 M, 0.32 mL, 0.5 mmol) in hexane. The mixture was dissolved in 5 mL of THF and stirred at 25°C. Ethyl 2-azidobutanoate (0.76 mL, 5.0 mmol) was added dropwise. After 20 min at 25°C, 125 mL (5 mmol) of N_2 had evolved, and the reaction was quenched with 2 mL of 3 N HCl. The solution was extracted with two 10 mL portions of ether. The combined organic layers were dried (K_2CO_3) and concentrated in vacuo. The yield was 86% as determined by GLC: ^{1}H NMR 4.13 (q, J = 7 Hz, 2H), 2.70 (q, J = 7 Hz, 2H), 1.23 (t, J = 7 Hz, 3H), 1.00 (t, J = 7 Hz, 3H); 2,4-DNP, mp 139-140.5°C (lit.[61] mp 141-142°C); EI-MS m/e 310 (M^+).

Ethyl Pyruvate (11a, R = Me, R' = Et) This compound was prepared as above: yield 50%; ^{1}H NMR 4.31 (q, J = 7 Hz, 2H), 2.45 (s, 3H), 1.50 (t, J = 7 Hz, 3H); 2,4-DNP, mp 154.5-155°C (lit.[62] mp 154.5-155°C); EI-MS m/e 296 (M^+).

Ethyl α-Oxoisovalerate (11a, R = $(CH_3)_2CH$, R' = Et) This compound was prepared as above: yield 94%; ^{1}H NMR 4.25 (q, J = 7 Hz, 2H), 3.20 (m, 1H), 1.35 (t, J = 7 Hz, 3H), 1.17 (d, J = 7 Hz, 6H); 2,4-DNP, mp

172.5-173.5°C (lit.[63] mp 171.5-172°C); EI-MS m/e 324 (M^+).

Ethyl Phenylglyoxlate(11a, R = Ph, R' = Et) This compound was prepared as above: Yield 91%; ^{1}H NMR 7.20-8.00 (m, 5H), 4.37 (q, J = 7 Hz, 2H), 1.23 (t, J = 7 Hz, 3H); 2,4-DNP, mp 161-162.5°C (lit.[64] mp 162-163.5°C); EI-MS m/e 358 (M^+).

Ethyl Phenylpyruvate (11a, R = $PhCH_2$, R' = Et) This compound was prepared as above. The residue was purified by bulb-to-bulb distillation, affording a 94% yield of clear, light yellow oil identified as the keto ester containing a small amount of enol[65]: ^{1}H NMR of keto form, 7.25 (s, 5H), 4.30 (q, J = 7 Hz, 2H), 4.15 (s, 2H), 1.40 (t, J = 7 Hz, 3H); 2,4-DNP, mp 132.5-133°C (lit.[66] mp 132.5-133°C); EI-MS m/e 372 (M^+).

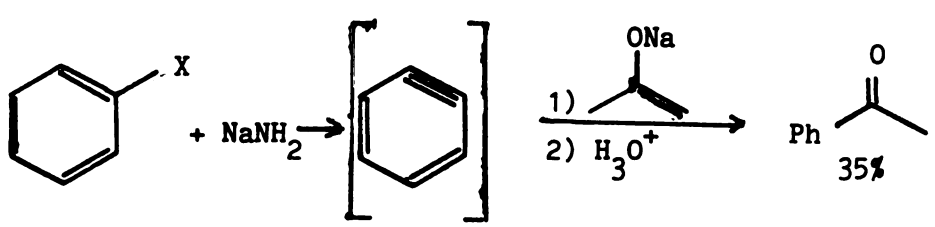
CHAPTER III

THE PHENYLATION OF KETONE ENOLATES WITH DIPHENYLIODONIUM SALTS

INTRODUCTION

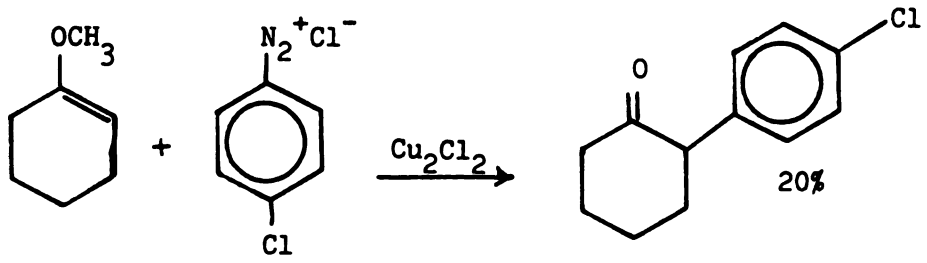
The introduction of an aryl group alpha to a carbonyl is an important chemical reaction. Molecules containing the α-aryl ketone moiety, such as cephalotaxinone 22, are important intermediates for the synthesis of a number of biologically interesting molecules[67]. As a result, there are many examples in the literature of attempts to α-arylate ketones.

Many α-aryl ketone syntheses involve phenylation of the corresponding ketone enolate or equivalent. The reaction of ketone enolates with benzyne generated from halobenzenes results in moderate yields (28-75%) of α-phenylated product[68] (eq 39). Enol ethers and acetates react with



(39)

diazonium salts in the presence of Cu^{I} to give α-phenyl ketones in fair yield[69] (eq 40,41). Heck has reported[70] that enol esters react with in



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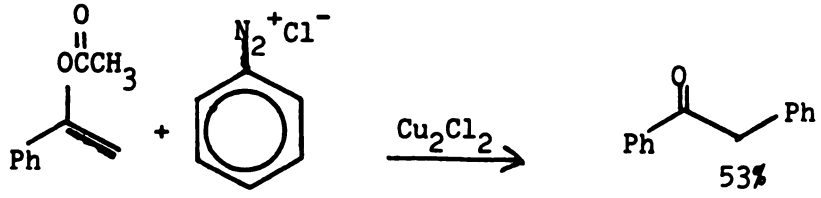
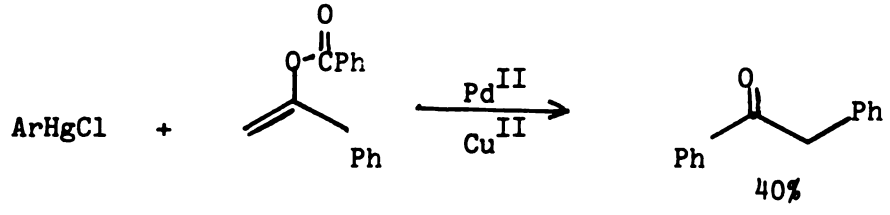


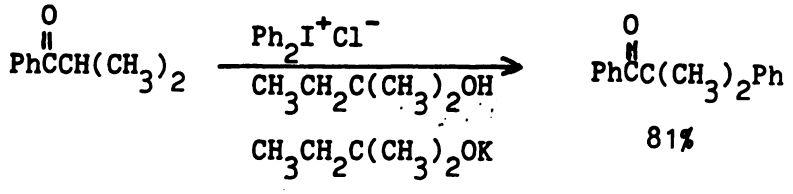
(41)

situ generated aryl palladium compounds to give phenylated products (eq 42). However, the aryl palladium compounds are synthesized from toxic



(42)

aryl mercury compounds. Beringer has extensively investigated the reactions of iodonium salts with various nucleophiles[71]. Reaction of these iodonium salts with simple ketone enolates gives mixed results[72] (eq 43,44). This reaction is postulated to proceed via a radical coupling mechanism[73].

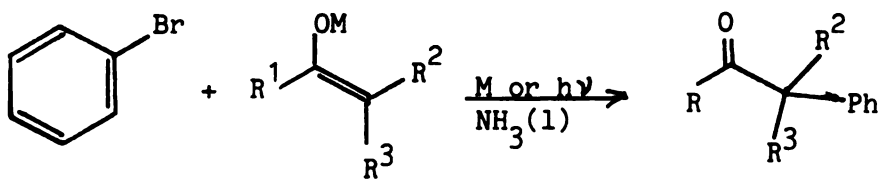


(43)

$$PhCCH_2CH(CH_3)_2 \xrightarrow[CH_3CH_2C(CH_3)_2OK]{Ph_2I^+Cl^-,\ CH_3CH_2C(CH_3)_2OH} PhCCHPhCH(CH_3)_2 \quad (44)$$

23%

Bunnett has done much work in the area of the aromatic ($S_{RN}1$) reaction[74]. He has found that phenyl radicals generated either photolytically or chemically will react with enolates in a radical chain process to give α-phenyl ketones[75] (eq 45). Semmelhack has used this

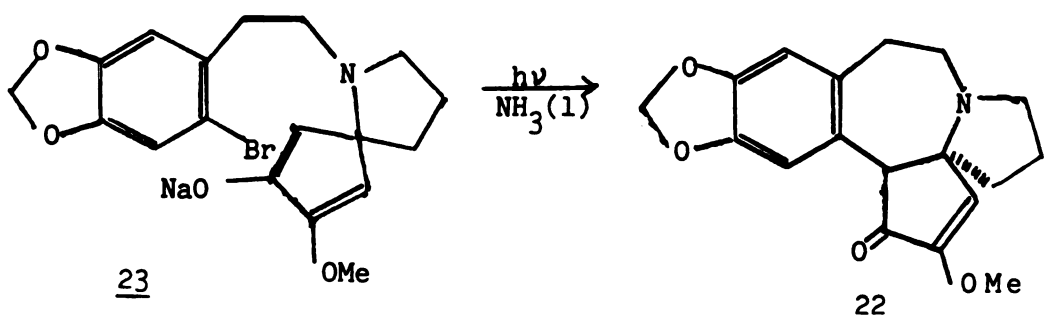


M = K or Na

0-95%

(45)

procedure in a key bond forming step as part of a cephalotaxine synthesis[76] (eq 46). Semmelhack[77] has also attempted the same reaction using bis(1,5-cyclooctadiene)nickel(0) $[Ni(COD)_2]$ to arylate the enolate 23 (eq 47).

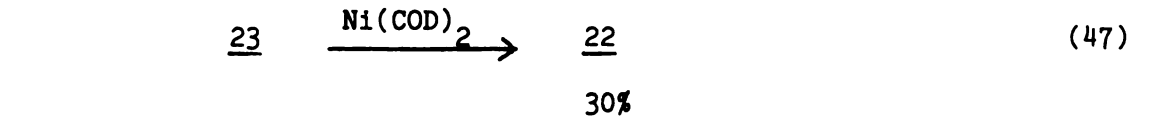


23

22

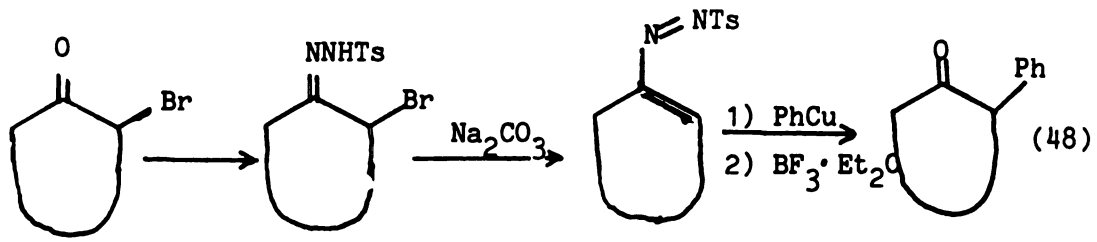
94%

(46)



(47)

Finally, Semmelhack[76] has also attempted the benzyne approach (eq 39). This reaction converts 23 to 22 in only 15% yield. Fuchs[78] has taken a different route. Instead of reacting a ketonic nucleophile with an arylating agent, he generates an "enolate cation" and phenylates with phenylcopper. His "enolate cation" is generated from a α-bromo tosylhydrazone, which in turn arises from the corresponding α-bromoketone (eq 48). This sequence works for cyclic and acyclic ketones, and various substituted aryl copper reagents were used effectively.



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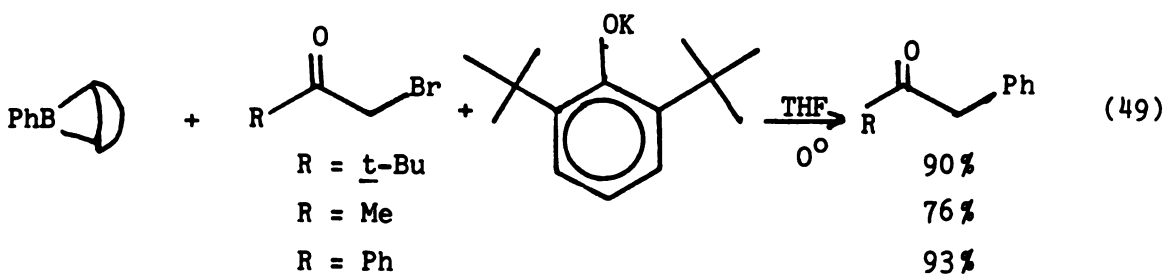
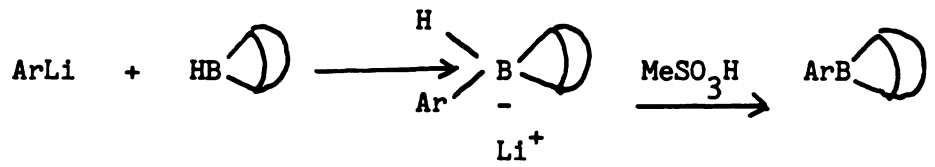
Brown[79] has developed a potentially useful synthesis of α-aryl ketones by reaction of aryl boranes with α-bromoketones (eq 49). The



(49)

aryl boranes are readily prepared from 9-borabicyclo [3.3.1] nonane and the appropriate aryllithium[80] (eq 50), thus making this route very



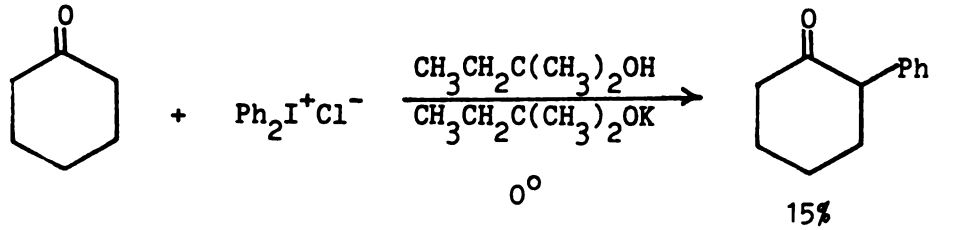
(50)

attractive. Several other procedures involving the arylation of β-keto esters have also been developed[81].

We were particularly intrigued by the Beringer procedure[72] (eq 43,44). A major disadvantage of this route, aside from the variability in yields, is that the particular base/solvent system will generate thermodynamic enolate mixtures[82]; thus, unsymmetrical ketones with α- and α'-hydrogens will lead to mixture of products. We proposed to investigate the reaction of enolates generated by strong bases in aprotic solvents with diphenyliodonium salts.

RESULTS AND DISCUSSION

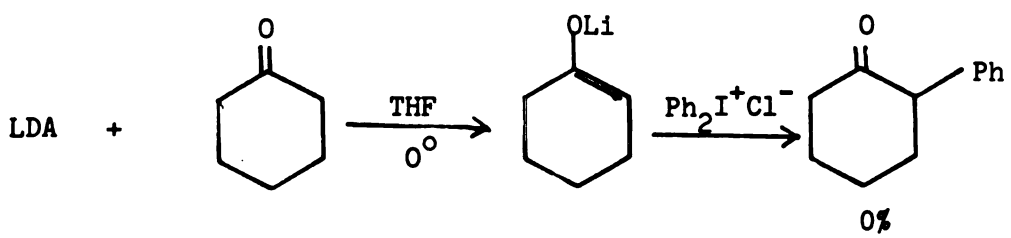
Our studies began by first attempting to use Beringer's procedure[72] with cyclohexanone (eq 51) as our test ketone. We observed



(51)

formation of 15% of α-phenyl cyclohexanone and 50% recovered cyclohexanone. This is consistent with Beringer's observation that isovalerophenone is phenylated in only 23% yield (eq 44) and may be explained in terms of radical stability: the expected intermediate for both cyclohexanone and isovalerophenone is a 2^{o} radical, which is less stable than the radical generated from isobutyrophenone (3^{o}). It is not clear whether the difficulty lies in formation of the radical or in the subsequent reaction.

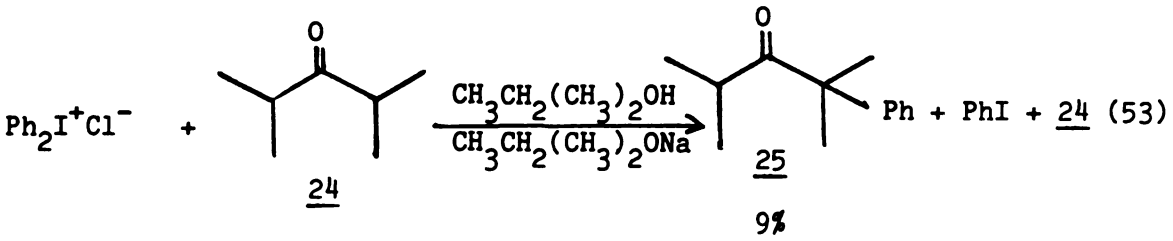
We then turned our attention to strong base/aprotic solvent systems. Lithium diisopropylamide (LDA) is a strong base that completely converts ketones to enolates under aprotic conditions[82]. We used LDA in a variety of solvents, including tetrahydrofuran (THF), dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), and 1,2-dimethyoxyethane (glyme). The enolate of cyclohexanone, generated with LDA in THF, was reacted with $Ph_2I^+Cl^-$ (eq 52). No α-phenyl cyclohexanone was observed.



(52)

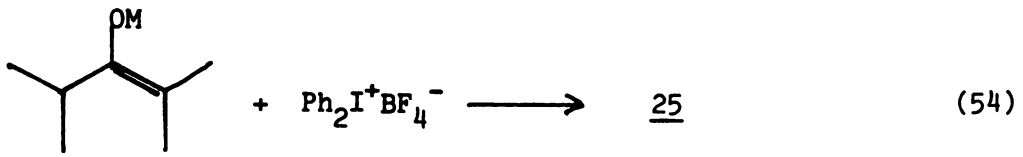
We attempted this reaction in a variety of solvents and at several temperatures. The enolate was generated with LDA in THF, concentrated <u>in vacuo</u> and dissolved in the appropriate solvent. The results, summarized in Table VI, reveal that this reaction does not work well.

We decided to examine a system similar to one where Beringer's reaction worked well, (i.e. 3^{o} α-carbon) and so looked at reactions of diisopropyl ketone 24. When 24 was reacted according to Beringer's procedure[72], a small amount of 2-phenyl-2,4-dimethyl-3-pentanone 25 was observed (eq 53, Table VII). When we varied the metal cation, the solvent, or the



temperature, only small variations in the yield of 25 were observed (Table VII). In all cases, a full equivalent of iodobenzene was observed by GLC, and 24 was also present in 45-60%. It is possible that the phenyl radicals that are generated abstract a hydride from the solvent, although this seems unlikely as the yield is not improved by using excess iodonium salt (Table VII).

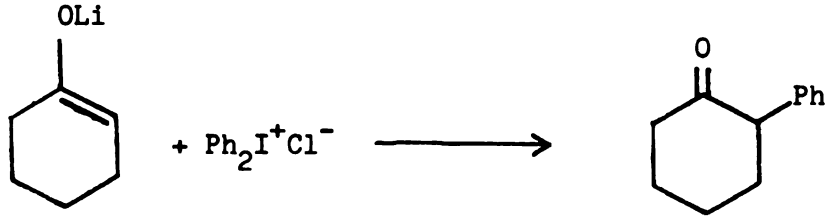
The next variable we changed was the iodonium salt. Diphenyliodonium tetrafluoroborate[83] was reacted with the lithium enolate of 24 under a variety of conditions (eq 54, Table VIII). The results vary, but are



better than reaction with diphenyliodonium chloride.

Finally, we synthesized diphenyliodonium hexafluorophosphate. This salt was reacted with metal enolates of 24 under a variety of

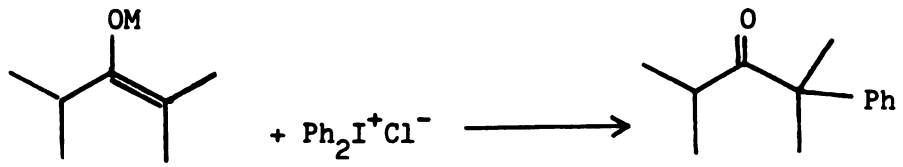
Table VI. Reaction of the Lithium Enolate of Cyclohexanone with Diphenyliodonium Chloride[a]



Solvent	Temp. °C	Yield (%)
THF	0°	0
DMF	25°	2
DMSO	25°	0
$CH_3CH_2C(CH_3)_2OH$	0°	15

[a]These reactions were conducted with amine-free enolate.

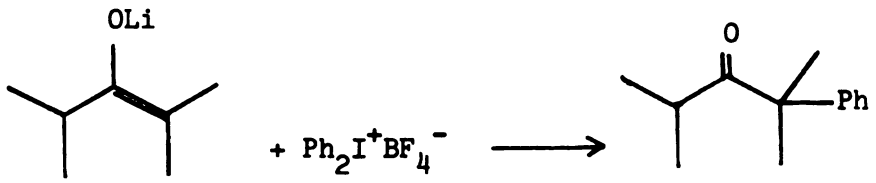
Table VII. Reaction of the Enolate of Diisopropyl Ketone with Diphenyliodonium Chloride[a]



Metal (M)	Solvent	Temp. °C	Yield (%)
Li	$CH_3CH_2C(CH_3)_2OH$	0°	18
Na	$CH_3CH_2C(CH_3)_2OH$	0°	9
Li	$CH_3CH_2C(CH_3)_2OH$		14
Na	$CH_3CH_2C(CH_3)_2OH$		13
K	$CH_3CH_2C(CH_3)_2OH$		9
Li	DMSO	0°	10
Na	DMSO	0°	0
Li	THF	0°	13
Na	THF	0°	5
Li	Glyme		15
K	Glyme		15

[a]These reactions were conducted with amine-free enolate.

Table VIII. Reaction of the Lithium Enolate of Diisopropyl Ketone with Diphenyliodonium Tetrafluoroborate[a]



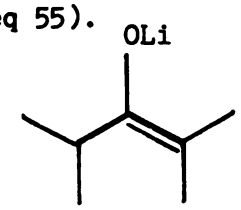
Equivalents $Ph_2I^+BF_4^-$	Solvent	Temp. °C	Yield (%)
1	THF	-78°	12
2	THF	-78°	11
0.5	THF	-78°	9[c]
0.1	THF	-78°	50[c]
1	THF	-78°	40
1	THF	0°	5
1	DMSO	-78°	23
1	DMSO	0°	10
1[b]	THF	-78°	32

[a]These reactions were conducted with amine-free enolate.

[b]Enolate and $Ph_2I^+BF_4^-$ concentrations were 0.2 M for this reaction. All other concentrations are 1 M.

[c]Yield based on amount of $Ph_2I^+BF_4^-$.

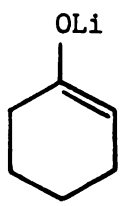
conditions (Table IX). $Ph_2I^+PF_6^-$ is highly soluble in THF as compared to $Ph_2I^+Cl^-$, and hence was added as a solution in THF to THF solutions of the enolate. The best results were obtained when a 2M solution of $Ph_2I^+PF_6^-$ in THF was added to a 1M solution of enolate in THF at -78° (eq 55).



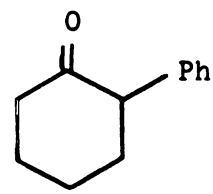
$$+\ Ph_2I^+PF_6^- \xrightarrow[-78^\circ]{THF} \underline{25} \qquad (55)$$

15 min 40%

The lithium enolate of cyclohexanone was reacted with $Ph_2I^+PF_6^-$ under a variety of conditions (Table X). As with 24, the best results are obtained when the lithium enolate of cyclohexanone is reacted with $Ph_2I^+PF_6^-$ in THF at -78°C (eq 56). Curiously, the best yield is



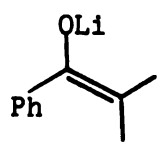
$$+\ Ph_2I^+PF_6^- \xrightarrow[-78^\circ]{THF}$$



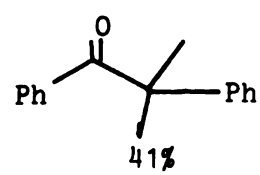
(56)

15 min 42%

virtually identical to that of the diisopropyl ketone reaction. Under these reaction conditions, it appears that radical stability is not an important factor. Finally, isobutyrophenone was reacted under the same conditions (eq 57). Again, the yield is the same as for both cyclohexanone and diisopropyl ketone.



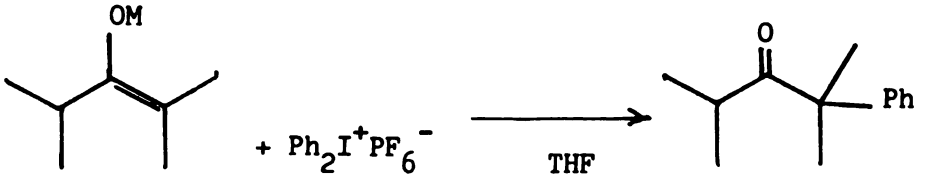
$$+\ Ph_2I^+PF_6^- \xrightarrow[-78^\circ]{THF}$$



(57)

15 min 41%

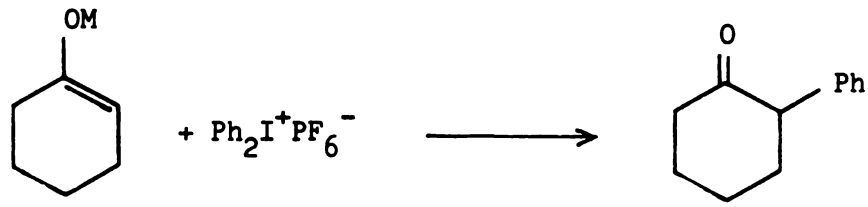
Table IX. Reaction of the Enolate of Diisopropyl Ketone with Diphenyliodonium Hexafluorophosphate in THF.



Metal (M)	Temp. °C	Time (h)	Amine[a]	Enolate	Ph_2I^+	Yield (%)
Li	-78°	1	No	1 M	1 M	38
Li	-78°	1	No	1 M	2 M	40
K	-78°	1	No	1 M	2 M	0
Li	0°	1	No	1 M	2 M	12
Li	-78°	2	No	1 M	2 M	38
Li	-78°	1	Yes	1 M	2 M	37
Ni[b]	-78°	1	No	1 M	2 M	35
Co[c]	-78°	1	No	1 M	2 M	0

[a]Diisopropylamine from LDA (see experimental).
[b]Generated by addition of $NiBr_2$ to lithium enolate.
[c]Generated by addition of $CoBr_2$ to lithium enolate.

Table X. Reaction of the Enolate of Cyclohexanone with Diphenyliodonium Hexafluorophosphate.



Metal (M)	Solvent	Temp. °C	Yield (%)
Na	$CH_3CH_2C(CH_3)_2OH$	0°	0
Li	Glyme	-78°	42
Li	Glyme	0°	15
Li	DMSO	25°	0
Li	THF	-78°	42

Although the yields are moderate, it appears that diphenyliodonium hexafluorophosphate is a good phenylating agent for ketone enolates generated under kinetic conditions[81], thus nicely complementing Beringer's[72] procedure.

EXPERIMENTAL

THF was distilled from a sodium-benzophenone ketyl still. All other solvents were distilled from calcium hydride before use. Cyclohexanone, diisopropyl ketone, and isobutyrophenone were obtained from the Aldrich Chemical Co. and distilled from calcium hydride before use. Diphenyliodonium salts were prepared by the procedure of Beringer[83]. Gas chromatographic data were obtained on a Varian 920 chromatograph equipped with a 4 ft x 0.25 in column packed with 2.5% SE-30 on Chromsorb W. ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer at 60 MHz using $CDCl_3$ as the solvent and are reported in parts per million in the δ scale relative to internal Me_4Si.

Preparation of Potassium Hexamethyldisilazide

Potassium hydride (5 M, 20 ml, 100 mmol) in oil was washed 3 x 20 mL with pentane, the solvent being carefully removed *via* syringe. After the final wash, the residue was concentrated *in vacuo*, then dissolved in 20 mL of THF. Hexamethyldisilazane (24 mL, 115 mmol) was added, and the reaction was stirred for 1 h. The majority of the solvent was removed *via* syringe, and the residue concentrated *in vacuo* affording 15 g (75%) of potassium hexamethyldisilazide as an off-white solid which was stored under argon.

Generation of Lithium Enolates

Lithium Enolate of Diisopropyl Ketone n-Butylithium (2.4M, 2.08 mL, 5.0 mmol) was dissolved in 2.5 mL of pentane at 0°C. Diisopropylamine (0.71 mL, 5.0 mmol) was added dropwise. The solution was stirred for 15 min at 0°C, then concentrated in vacuo. The white residue was dissolved in 5 mL of THF and cooled to 0°C. Diisopropyl ketone (0.70 mL, 5.0 mmol) was added dropwise at 0°C, and the solution was stirred for 15 min. At this point, if amine free enolate was desired, the solution was concentrated in vacuo, then redissolved in the appropriate solvent.

Lithium Enolates of Cyclohexane and Isobutyrophenone These enolates were prepared as above.

Generation of Sodium Enolates

Sodium Enolate of Cyclohexanone Sodium (0.12 g, 5.0 mmol) was dissolved in 25 mL of t-amyl alcohol. Cyclohexanone (0.52 mL, 5.0 mmol) was added and the solution was cooled to 0°C.

Sodium Enolate of Diisopropyl Ketone This enolate was prepared as above.

Generation of Potassium Enolate

Potassium Enolate of Diisopropyl Ketone Hexamethyldisilazane (0.61 g, 3.0 mmol) was dissolved in 5 mL of THF. Diisopropyl ketone (0.42 mL, 3.0 mmol) was added dropwise. The solution was stirred for 1 h, then concentrated in vacuo. The enolate was redissolved in the appropriate solvent.

Phenylations of Enolates

Phenylation of Cyclohexanone Lithium Enolate The lithium enolate of cyclohexanone (5 mmol) was prepared as above and dissolved in 5 mL of THF. The reaction was cooled to -78°C. Diphenyliodonium hexafluorophosphate (2.13 g, 5.0 mmol) was dissolved in 2.5 mL of THF and added dropwise to the enolate. The reaction was stirred for 15 min at -78°C, then allowed to warm to room temperature and quenched with 10 mL of 1 M HCl. The solution was extracted with 10 mL of ether, dried with $MgSO_4$, and analyzed by GLC which showed a 42% yield of 2-phenylcyclohexanone: NMR 6.90-7.20 (m, 5H), 3.20-3.85 (m, 1H), 1.50-2.80 (m, 8H).

Phenylation of Diisopropyl Ketone Lithium Enolate This reaction was conducted as above, affording a 41% yield of 2-phenyl-2,4-dimethyl-3-pentanone: NMR 7.08 (s, 5H), 2.4-2.9 (m, J = 6 Hz, 1H), 1.45 (s, 6H), 1.90 (d, J = 6 Hz, 6H).

Phenylation of Isobutyrophenone Lithium Enolate This reaction was conducted as above, affording a 41% yield of α-phenylisobutyrophenone: NMR 6.80-7.45 (m, 10H), 1.55 (s, 6H).

Other reactions were conducted in analagous fashion by dissolving the desired enolate in the appropriate solvent, and adding iodonium salt. Diphenyliodonium chloride was added neat. (See Tables VI-X for specific combination of reagents).

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