REACTIONS OF ENOLATE ANIONS

By

Alan A. Millard

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ABSTRACT

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Lithium ester enolates react with aryl and vinyl halides in the presence of $NiBr_2$ activated by *n*-butyllithium to give α-aryl and α-vinyl esters in excellent yields. The reaction occurs with retention of stereochemistry at the halogen bearing carbon when configurational isomers of β-bromostyrene are reacted with the ester enolates. The lithium enolate of N,N-dimethylacetamide reacts with 1-bromopropene to give the α-vinyl acetamide. Enolates of ketones and ketone derivatives fail to give any significant yields of α-aryl compounds when reacted with phenyl iodide.

Addition of a ketone to a suspension of one equivalent of KH for every enolizable hydrogen followed by one equivalent of methyl iodide for every enolizable hydrogen gives the permethylated ketone in good yield. Methyl iodide also reacts with KH to give methane. The permethylated ketones also react with KH to give the corresponding alcohols.

Lithium ester enolates and lithium ketone enolates are oxidatively coupled using $FeCl_3$ as the oxidant to yield γ-ketoesters. With most ketone and ester combinations there

is no self-coupling of either the ketone or ester enolates. When self-coupling does occur, it occurs only with the ester enolates and then in less than 5% yield.

To Sally

ACKNOWLEDGEMENT

The author wishes to extend his appreciation to a friend, Dr.Michael W. Rathke, who also happens to be an excellent chemist and teacher. His guidance throughout this work was invaluable and he will be a lifelong inspiration.

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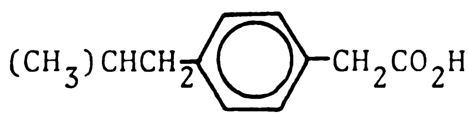
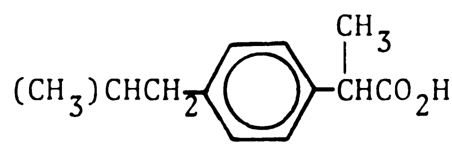
ARYLATION AND VINYLATION OF LITHIUM ESTER ENOLATES

Introduction

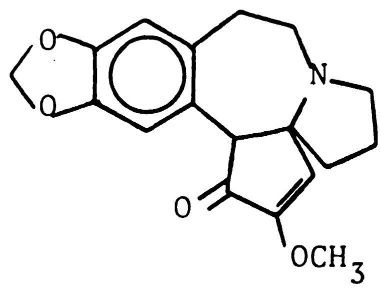
Carbonyl compounds with α-aryl groupings occur widely in biologically and pharmacologically important molecules. Cephalotaxinone (1), ibufenac (2) and ibuprofen (3) are several examples of these compounds.



Ibufenac



Ibuprofen

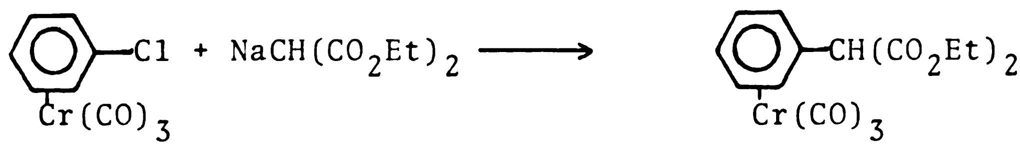


Cephalotaxinone

Displacement of an aryl halide by an enolate would lead directly to the desired product. However, this reaction does not take place under normal reaction conditions (eq 1).

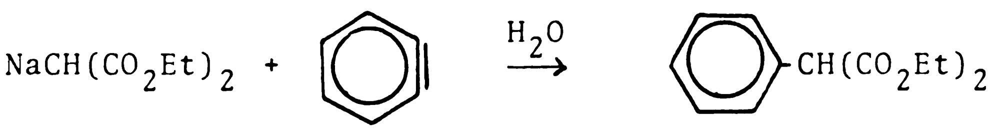
$$C_6H_5X + \;>C{=}C{<}^{OM}_{R} \longrightarrow \text{N. R.} \qquad (1)$$

Most approaches, to date, to the synthesis of these compounds have entailed the combination of an enolate (or its equivalent) with some electron deficient aryl species (eq 2).



(2)

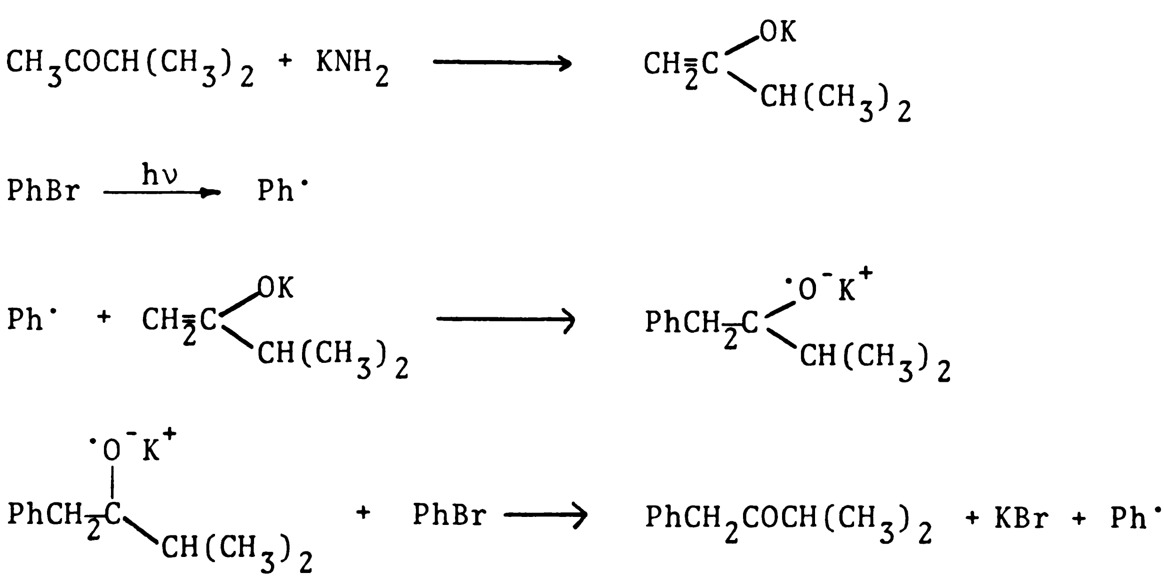
The trapping of sodiomalonate (4) with benzyne is a closely related method (eq 3).



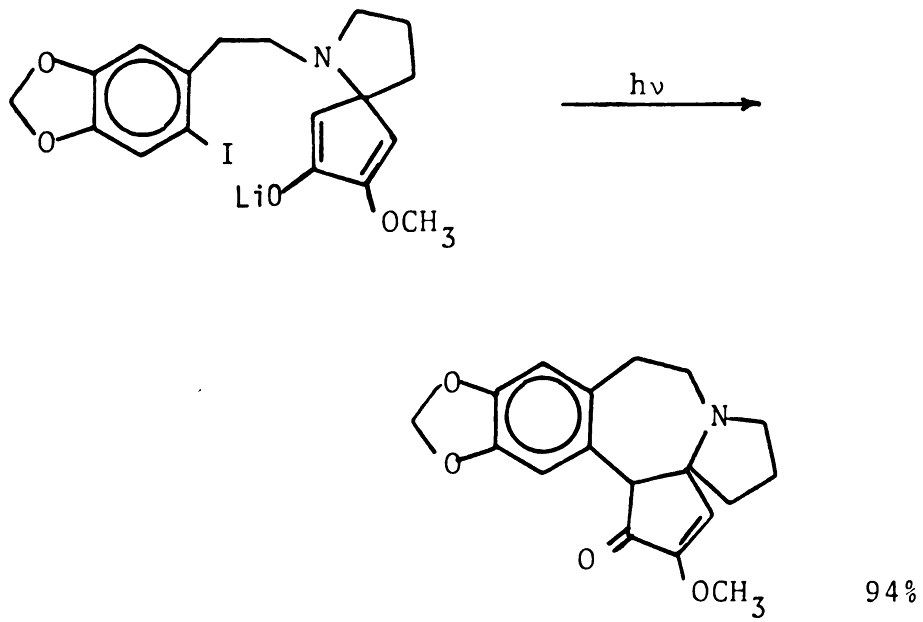
(3)

Rossi and Bunnett reported (5) a method for the trapping of photogenerated aryl radicals with ketone enolates. Scheme I below outlines this (the SRN_1) reaction.

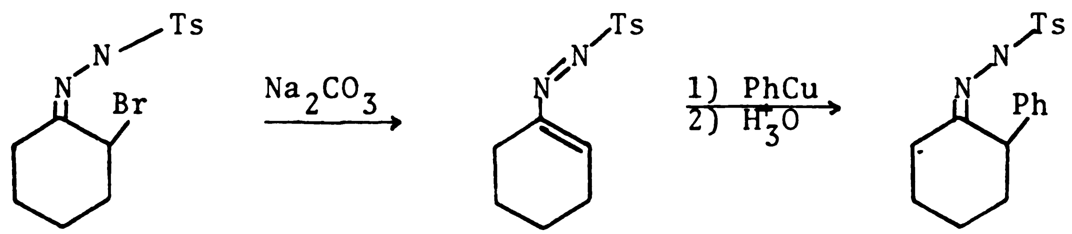
<u>Scheme I</u>



Semmelhack et al. (1) used this reaction in the synthesis of cephalotaxinone.



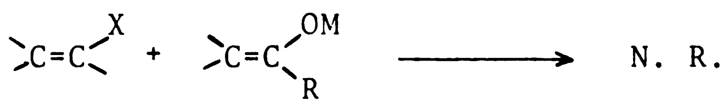
An entirely different approach is the method proposed by Sacks and Fuchs (6). Their scheme is the reaction of an enolonium (α-ketocation) synthon with an electron rich aryl species. Treatment of an α-haloketone derivative (tosylhydrazone) with base followed by phenyl copper or lithium diphenylcuprate or excess phenyl copper occurs as shown below (eq 4).



(4)

The hydrazones can be converted to the ketones by standard techniques.

α-Vinylation can be considered in a manner similar to the presentation of the problem of α-arylation as discussed by Sacks and Fuchs (6). As with α-arylation, the easiest route to α-vinyl-carbonyl compounds would be direct displacement of a vinyl halide with an enolate as shown in equation 5. Again, as with the arylation, the reaction does not give any of the desired product.



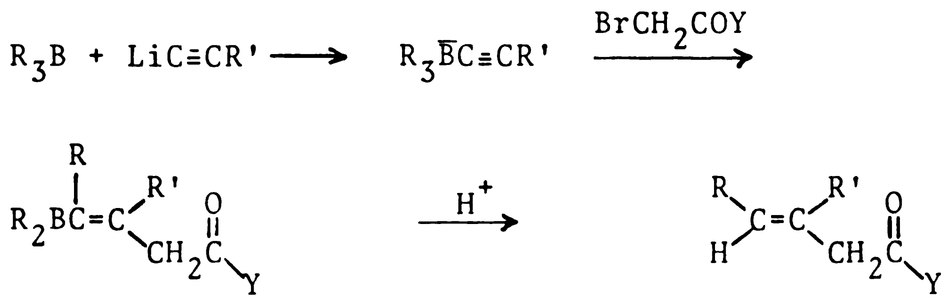
(5)

However, α-vinylation can also be brought about by the α-protonation (7) or the α-alkylation (4) of an enolate of an α-β unsaturated carbonyl compound as shown in equations 6 and 7, respectively.

(6)

(7)

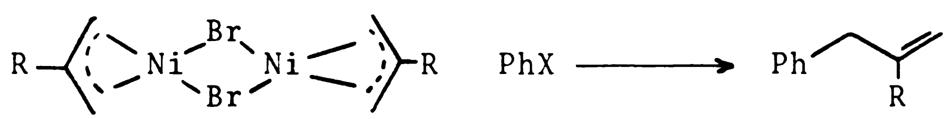
In fact, this is a standard technique for the preparation of these compounds. A method has been reported (8), however, that mimics the charge affinity inversion scheme of Sacks and Fuchs and is outlined in equation 8.



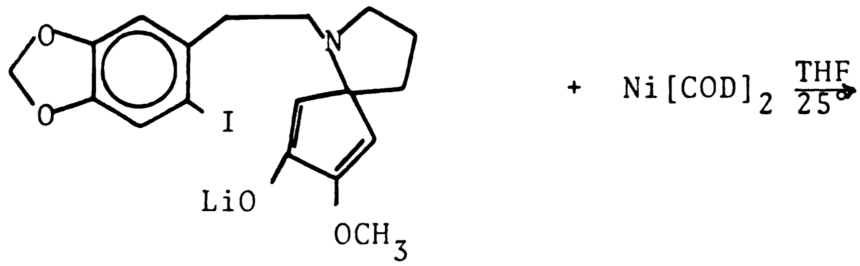
(8)

where Y = alkoxide or alkyl

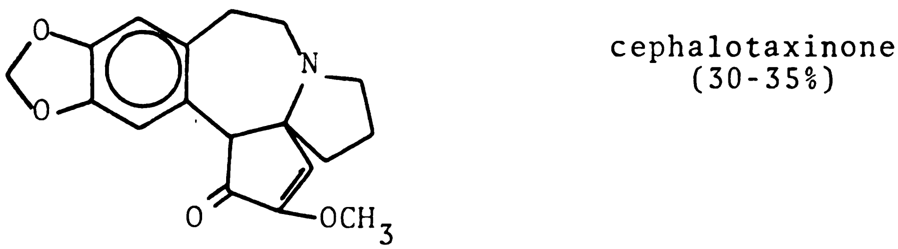
Nickel π-allyl compounds are known to react with alkyl, aryl, and vinyl halides (9) as shown below.



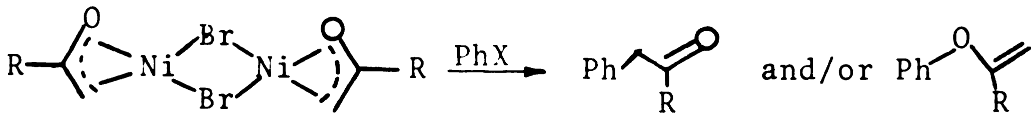
Nickel (0) species are known to react directly with aryl halides to form aryl nickel (II) halide compounds. These compounds react with anionic compounds such as cyanide (10) or Grignard (11) to lead to overall carbon substitution of the halide. Attempts by Semmelhack (1) to use a nickel (0) species as a catalyst in the synthesis of cephalotaxinone gave the desired product in 30-35% yield (eq 9).



(9)



We considered that generation of an oxygen analogue of the nickel π-allyl compound and subsequent reaction with a vinyl or aryl halide might produce the desired α-vinyl or α-aryl carbonyl compound (eq 10).



(10)

We attempted the substitution of phenyl iodide with lithio *tert*-butyl acetate in the presence of nickel (II) bromide. We discovered that substitution would indeed occur provided the ester enolate was generated in the presence of excess *n*-butyllithium. Consequently, a study of the substitution of aryl and vinyl halides with lithium ester enolates was initiated.

We also expanded the study to the substitution of these halides with ketone enolates and enolates of ketone derivatives under similar conditions.

Results

Reaction of the lithium enolates (12) of *tert*-butyl acetate, *tert*-butyl propanoate, ethyl isobutyrate, and *tert*-butyl phenylacetate with various aryl and vinyl halides proceeded smoothly, in the presence of $NiBr_2/n\text{-}BuLi$ as shown in equation 11 to give the corresponding α-aryl or α-vinyl esters in good to excellent yield (Table I).

$$C_6H_5X + Li\overset{|}{\underset{|}{C}}\text{-}CO_2R \xrightarrow[-78°C \text{ to r.t.}]{NiBr_2/0.2n\text{-}BuLi} \xrightarrow{H_3O} C_6H_5\overset{|}{\underset{|}{C}}\text{-}CO_2R \qquad (11)$$

The lithium enolate of ethyl crotonate (7) reacted under similar conditions to give a γ-aryl or γ-vinyl α-β unsaturated ester exclusively (eq 12).

$$\bar{C}H_2CH{=}CHCO_2Et + C_6H_5I \xrightarrow[-78°C \text{ to r.t.}]{NiBr_2/n\text{-}BuLi} C_6H_5CH_2CH{=}CHCO_2Et \qquad (12)$$

The enolates were produced by the dropwise addition of the ester to lithium diisopropylamide in THF at -78°C.

$$RCH_2CO_2R' + [(CH_3)_2CH]_2NLi \xrightarrow[-78°C]{THF} RCH{=}C\begin{matrix} \diagup OLi \\ \diagdown OR' \end{matrix} + [(CH_3)_2CH]_2NH$$

Formation of the enolate of ethyl crotonate required the amide in THF to be treated with one equivalent of hexamethylphosphortriamide thirty minutes prior to the addition of the ester.

$$[(CH_3)_2CH]_2NLi + [(CH_3)_2N]_3P{=}O \xrightarrow[30min]{-78°C} \xrightarrow{CH_3CH{=}CHCO_2Et} CH_2{=}CHCH{=}C\begin{matrix} \diagup OLi \\ \diagdown OEt \end{matrix}$$

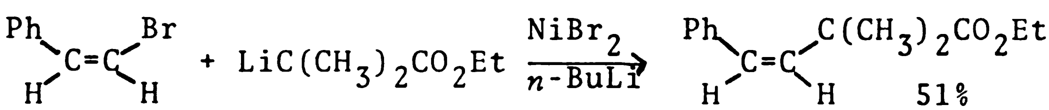
The catalyst was prepared by suspending $NiBr_2$ in THF, cooling to -78°C followed by rapid addition of 0.2 equivalents of *n*-butyllithium. This mixture was then treated with halide followed by a 1.0*M* solution of ester enolate in THF.

Various other reducing agents were used to activate the $NiBr_2$ and the results are listed in Table II. No detectable reaction occurred in the absence of either nickel (II) bromide or reducing agent.

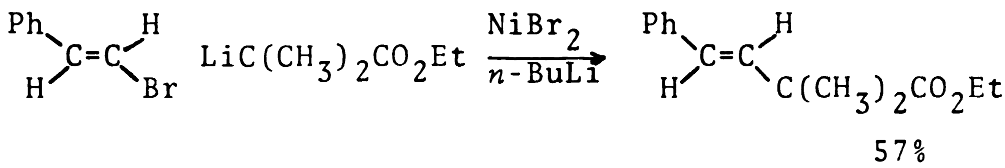
$$PhBr + LiCH_2CO_2C(CH_3)_3 \xrightarrow[0.0\,n\text{BuLi}]{NiBr_2} \text{N.R.}$$

$$PhBr + LiCH_2CO_2C(CH_3)_3 \xrightarrow[0.2\,n\text{BuLi}]{0.0\,NiBr_2} \text{N.R.}$$

The stereochemistry of the reaction was studied by reacting lithio ethyl isobutyrate with configurational isomers of β-bromostyrene. The reaction occurred with complete retention of configuration at the halogen bearing carbon (eqs 13 and 14).



(13)



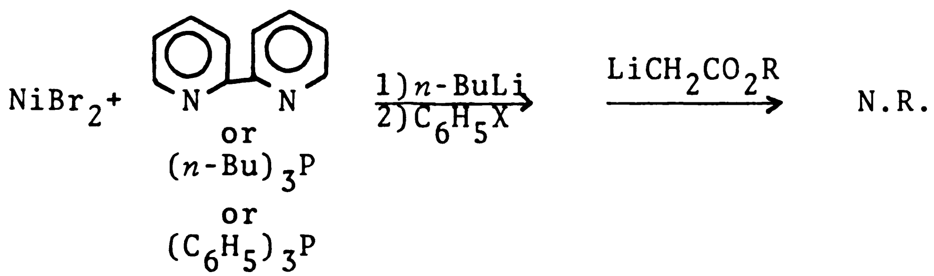
(14)

Optimal yields for a general procedure were obtained with a full equivalent of nickel (II) bromide; however, the catalytic nature of the reaction is shown in equation 15. The result shows a 350% yield of vinylation product based on either nickel (II) bromide or *n*-butyllithium.

$$\underset{10\ \text{mmol}}{CH_3CH{=}CHBr} + \underset{10\ \text{mmol}}{LiCH_2CO_2C(CH_3)_3} + \underset{2\ \text{mmol}}{NiBr_2} + \underset{2\ \text{mmol}}{nC_4H_9Li} \longrightarrow$$

$$\underset{7\ \text{mmol}}{CH_3CH{=}CHCH_2CO_2C(CH_3)_3} \qquad (15)$$

A number of substitution reactions of aryl halides by phosphine or cyclooctadiene complexes of nickel (0) have been reported (1,13). We found that addition of triphenyl or tri-*n*-butyl phosphine or 2,2'-bipyridine to suspensions of $NiBr_2$ before or after addition of *n*-butyllithium gave totally inactive material (eq 16).



(16)

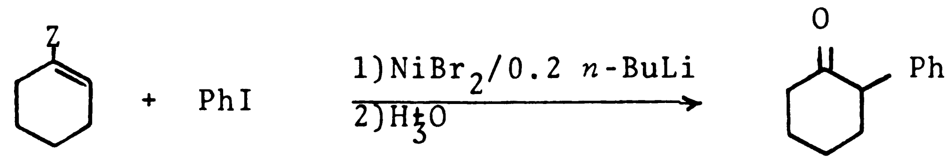
Furthermore, no substitution product was obtained from the reaction of lithio *tert*-butyl acetate with 1-bromopropene using tetrakis(tri-*n*-butylphosphine) nickel (0) (14) or bis(cyclooctadienyl) nickel (0) (15) as catalyst (eq 17).

$$CH_3CH{=}CHBr + LiCH_2CO_2C(CH_3)_3 \begin{cases} \xrightarrow{Ni(COD)_2} & N.R. \\ \xrightarrow[{[(n\text{-}Bu)_3P]_4Ni}]{} & N.R. \end{cases} \tag{17}$$

The lithium enolate of N,N-dimethylacetamide (16) reacted with 1-bromopropene to give the α-vinylacetamide in 50% yield (eq 18)

$$LiCH_2CON(CH_3)_2 + CH_3CH{=}CHBr \xrightarrow[0.2n\text{-}BuLi]{NiBr_2} \underset{50\%}{CH_3CH{=}CHCH_2CON(CH_3)_2} \tag{18}$$

Attempts at either arylation or vinylation of the lithium enolate of cyclohexanone gave none of the desired products. A survey of ketone derivatives was initiated. The reaction conditions were similar to the conditions used in the previously outlined experiments. The results of the survey are shown below.



Z	product yield
-OLi	0%
$LiNC(CH_3)_3$	0%
LiNOLi	0%
$LiNN(CH_3)_2$	16%

It is interesting to note that the reaction of lithio *tert*-butyl acetate with phenyllithium in the presence of $NiBr_2$ gave not only biphenyl but also a small amount of *tert*-butyl phenylacetate (eq 19).

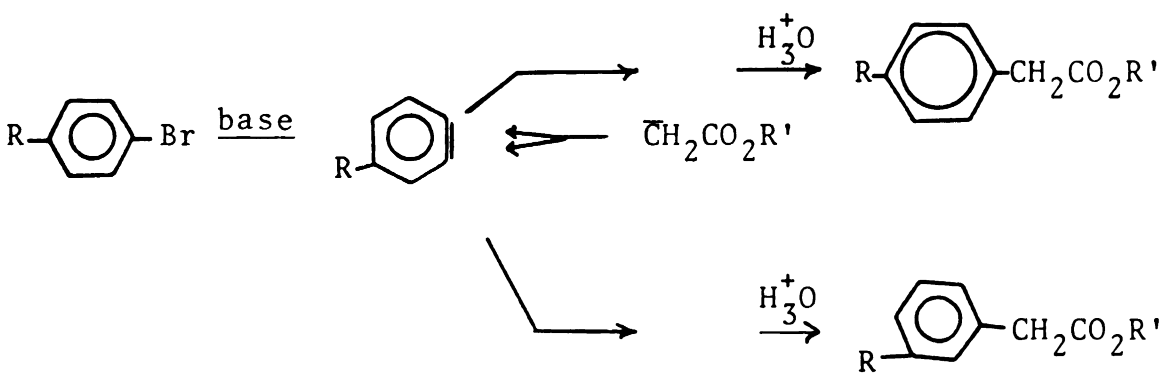
$$LiCH_2CO_2C(CH_3)_3 + PhLi \xrightarrow{NiBr_2} \underset{65\%}{Ph\text{-}Ph} + \underset{3\%}{PhCH_2CO_2C(CH_3)_3} \qquad (19)$$

Discussion

The direct α-arylation and α-vinylation of ester enolates with the corresponding halides in the presence of nickel (II) bromide activated by *n*-butyllithium provides a convenient alternative to the methods presented previously in the introduction. The reaction conditions are mild, the starting materials are readily available and the yields are usually excellent with the halides studied. There are few, if any, side products and the desired products are readily isolated by distillation or chromatography.

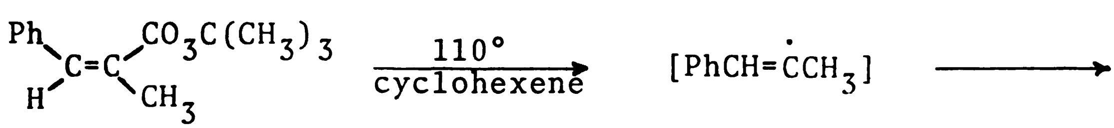
The results obtained allow comments about the mechanism to be made. The possibility of the addition of the enolate to the benzyne (17) molecule can be eliminated. Benzynes generated from substituted benzenes when reacted with an enolate should give a product mixture as shown in Scheme II.

Scheme II



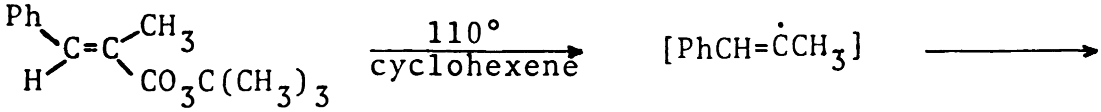
A number of substituted halobenzenes were reacted with lithio *tert*-butyl acetate and each gave a single product with the substitution occurring exclusively at the halogen bearing carbon (Table III).

Singer and Kong (18) reported in 1966 that vinyl radicals substitute almost exclusively to give cis products (eqs 20 and 21).



$PhCH{=}CHCH_3$ (20)

45.2 ±3.1%, cis only

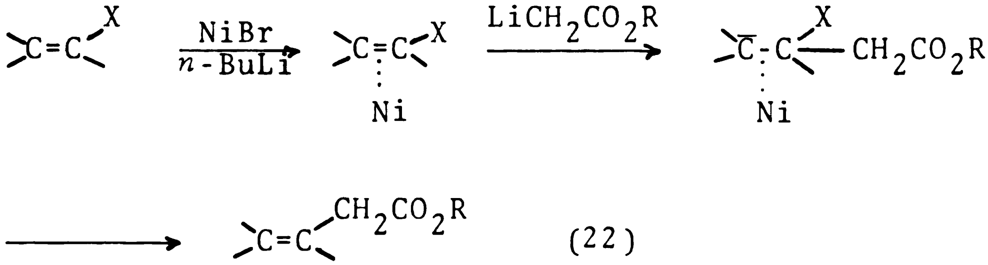


PhCH=CHCH$_3$ (21)

46.4 $\pm$ 0.2%, cis only

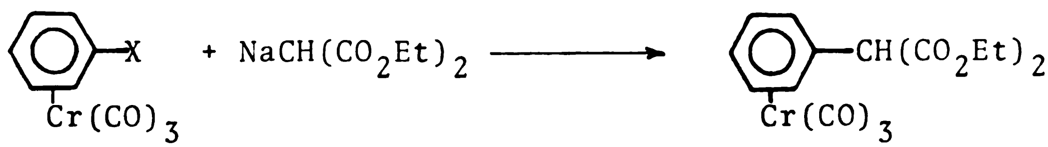
The retention of configuration obtained with the β-bromostyrene isomers probably rules out a radical pathway, at least for these halides (eqs 13 and 14).

A classic nucleophilic aromatic substitution mechanism operative on a nickel activated π-system, as in equation 22, could be postulated.



(22)

The reactivity (19) as a function of the halogen found for $Cr(CO)_3$ activated aryl halides is, however, opposite to that observed in the present study (Table I). The iodo compound was more reactive than the bromo, which was more reactive than the chloro. The fluoro compound did not react at all. These results are opposite to those outlined below:



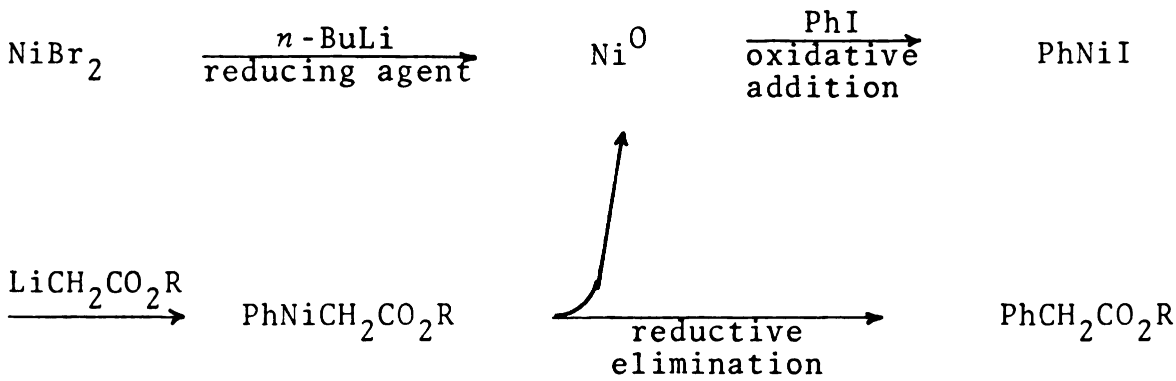
$\xrightarrow[0°]{I_2}$ $PhCH(CO_2Et)_2$

X=I	very low conversion		
X=Cl	25°	48h	5%
	50°	24h	51%
X=F	25°	24h	63%
	50°	20h	95%

A number of substitution reactions aryl halides promoted by phosphine or cyclooctadiene complexes of nickel (0) have been reported (1,13). Oxidative addition of the aryl halide to nickel (0) is considered to be a key step in these reactions (20). Our results show, however, that addition of strong ligands to $NiBr_2$ suspensions gave inactive material. No substitution products were obtained when nickel (0) complexes, tetrakis(tri-*n*-butylphosphine nickel (0) and bis(1,5-cyclooctadienyl) nickel (0) were used as catalysts. If the reaction does proceed through a nickel (0) species, it appears that the absence of a strongly coordinating ligand plays an essential role in its success.

A mechanism involving a nickel (0) is depicted in Scheme III below. The mechanism shown is postulated as the one operating in this reaction. The strongest ligand in the system is the solvent.

Scheme III



Experimental

I Materials

Esters

All of the esters with the exception of *tert*-butyl propanoate were commercially available and were used without further purification. The *tert*-butyl propanoate was prepared from propanoic anhydride and *tert*-butyl alcohol by the procedure described in *Org. Syn.*, *3*, 141.

Organic Halides

All of the aryl halides and all of the vinyl halides with the exception of *cis*-β-bromostyrene were commercially available and were used without further purification. The *cis*-β-bromostyrene was prepared by the procedure of S. J. Cristol and W. P. Morris, *J. Am. Chem. Soc.*, *75*, 2645(1953).

Nickel (II) Salts

The nickel (II) bromide was obtained from Ventron Corp. It was placed in a desiccator over $CaSO_4$ and evacuated for at least sixteen hours prior to use. The nickel (II) bromide·glyme complex was also obtained from Ventron Corp. and it was used without further purification.

II Preparation of Aryl and Vinyl Esters

The esters were prepared in a manner similar to that described for *tert*-butyl 3-pentenoate or ethyl 2,2-dimethyl-4-phenyl-3-butenoate. All GLC analyses were performed on a Varian Model 920 Gas Chromatograph using 1/4"x6' Se-30 column with the appropriate internal standards.

A. Preparation of *tert*-Butyl 3-Pentenoate

A 50 ml flask equipped as in Figure 1 was flame dried under a stream of dry argon. To this flask was added 4.0 ml (6.4 mmol) of 1.6*M* commercial solution of *n*-butyllithium in hexane. The flask was cooled in an ice bath and 0.90 ml (6.4 mmol) of diisopropylamine was added dropwise with stirring. The ice bath was then removed and when the reaction was judged complete (no more butane evolution, approximately 20 minutes), a vacuum was then applied until the hexane was removed completely. The flask was flushed with dry argon and 6.4 ml of THF was added. After dissolution the white powder of lithium diisopropylamide was complete; the flask was cooled in a dry ice/acetone bath. The *tert*-butyl acetate (0.86 ml; 6.4 mmol) was added dropwise. A 100 ml flask was also equipped as in Figure 1. After flame drying, 1.3985 gm, 6.4 mmol of anhydrous nickel (II) bromide was added through a powder funnel and 6.4 ml of THF was added via syringe. The flask was immersed in a dry ice/acetone bath and 0.8 ml, 1.28 mmol of 1.6*M* *n*-butyllithium in hexane was injected. The black suspension was stirred for five minutes, then 0.55 ml, 6.4 mmol of 1-bromopropene was added via syringe. The lithio *tert*-butyl acetate solution was then added through teflon tubing via argon pressure. The cooling bath was then removed and the reaction allowed to warm to room temperature. Thirty minutes after the dry ice/acetone bath was removed it was reapplied and the reaction quenched by the addition of 6.4 ml of 6*N* hydrochloric acid. Pentane was added and the mixture stirred until the organic layer was nearly colorless. GLC analysis of the organic layer established the presence of *tert*-butyl 3-pentenoate in 99% yield.

All α-aryl and α-vinyl esters as well as the α-vinyl acetamide were prepared by the above method from the appropriate carbonyl compound and halide. The only exceptions to this procedure are described below.

B. Preparation of Ethyl 2,2-Dimethyl-4-phenyl-3-butenoate Using $NiBr_2$· glyme

The lithium enolate of ethyl isobutyrate was prepared in the manner described above. The 100 ml flask was charged with 1.9753 gm, 6.4 mmol $NiBr_2$·glyme complex and 6.4 ml THF. The mixture was cooled in a dry ice/acetone bath and then 3.80 ml, 6.08 mmol of 1.6*M* *n*-BuLi solution was injected. The above procedure was then followed using 6.4 mmol *cis*-β-bromostyrene and lithio ethyl isobutyrate. Glpc analysis showed the presence of ethyl *cis*-2,2-dimethyl-4-phenyl-3-butenoate in 50% yield. The above procedure was repeated using *trans*-β-bromostyrene. Glpc analysis showed the presence of ethyl *trans*-2,2-dimethyl-4-phenyl-3-butenoate in 57% yield.

C. Preparation of Ethyl 2,5-Heptadienoate

The preparation of lithium diisopropylamide was as described above. One equivalent (1.12 ml, 6.4 mmol) of hexamethylphosphortriamide was added rapidly via syringe. Thirty minutes later 0.79 ml, 6.4 mmol of ethyl crotonate was added dropwise. Procedure A was then followed and GLC analysis showed a 40% yield of ethyl 2,5-heptadienoate.

III Procedure Using Reducing Agents Other Than *n*-Butyllithium

Various reducing agents were used to activate the $NiBr_2$ and the subsequent mixtures were used to catalyze the reaction of lithio *tert*-butyl acetate with 1-bromopropene. The procedure that was used for -BuLi was also used for the following commercially available reducing agents: methyllithium, phenyllithium, *tert*-butyllithium and triethylaluminum. Methyl magnesium iodide that was made by standard techniques in diethyl ether was also used in the same manner.

Lithium aluminum hydride was also used for the reduction of $NiBr_2$ and the procedure is described in the following.

The $NiBr_2$ was suspended in THF at 25°C. One equivalent of $LiAlH_4$ was then added to this suspension through a powder funnel. After five minutes, the mixture turned black. It was then cooled to -78°C and treated successively with 1-bromopropene and lithio *tert*-butyl acetate as previously described. GLC analysis of the quenched reaction mixture showed the presence of the desired product in 22% yield.

Product Analysis

All GLC analyses were performed on a Varian 920 Chromatograph using 1/4 inch by 6 foot stainless steel column packed with 2.5% Se-30 on Chromosorb G NAW. The aryl and vinyl esters were examined by NMR spectroscopy in carbon tetrachloride solution using $(CH_3)_4Si$ as internal standard.

tert-Butyl 3-Pentenoate

NMR: 5.3δ (m,2H), 2.8δ (m,2H), 1.6δ (m,3H), 1.4δ (s,9H)

tert-Butyl Phenylacetate

NMR: 7.0δ (s,5H), 3.3δ (s,2H), 1.3δ (s,9H)

Ethyl *cis*-2,2-Dimethyl-4-phenyl-3-butenoate

NMR: 7.1δ (bs,5H), 6.3δ (d,J=12Hz,1H), 5.5δ (d,J=12Hz,1H), 3.6δ (q,2H), 1.3δ (s,9H), 1.0δ (t,3H)

Ethyl *trans*-2,2-Dimethyl-4-phenyl-3-butenoate

NMR: 7.1δ (bs,5H), 6.2δ (s,2H), 4.1δ (q,2H), 1.3δ (s,9H), 1.2δ (t,3H)

Ethyl 2,5-Heptadienoate

NMR: 6.7δ (d,t,1H), 5.5δ (bm,3H), 4.0δ (q,2H), 2.8δ (m,2H), 1.6δ (m,3H), 1.2δ (t,3H)

tert-Butyl *p*-Methoxyphenylacetate

NMR: 6.8δ (q,4H), 3.7δ (s,3H), 3.3δ (s,2H), 1.4δ (s,9H)

N,N-Dimethyl-3-pentenamide

NMR: 5.4δ (m,2H), 2.8δ (m,8H), 1.6δ (m,3H)

Table I. Reaction of Lithium Ester Enolates with Aryl and Vinyl Halides

Enolate	Halide	Product[a]	Yield, %[b]
$LiCH_2CO_2C(CH_3)_3$	C_6H_5I	$C_6H_5CH_2CO_2C(CH_3)_3$	73
	C_6H_5Br		41
	C_6H_5Cl		3
	$CH_3CH{=}CHBr$	$CH_3CH{=}CHCH_2CO_2C(CH_3)_3$	99
	$CH_2{=}CBrCH_3$	$CH_2{=}C(CH_3)CH_2CO_2C(CH_3)_3$	94
	$CH_3CH{=}CBrCH_3$	$CH_3CH{=}C(CH_3)CH_2CO_2C(CH_3)_3$	60
	$C_6H_5CH{=}CHBr$	$C_6H_5CH{=}CHCH_2CO_2C(CH_3)_3$	83
$Li(CH_3)CHCO_2C(CH_3)_3$	$CH_3CH{=}CHBr$	$CH_3CH{=}CHCH(CH_3)CO_2C(CH_3)_3$	53
$Li(CH_3)_2CCO_2C_2H_5$	$CH_3CH{=}CHBr$	$CH_3CH{=}CHC(CH_3)_2CO_2C_2H_5$	72
$Li(C_6H_5)CHCO_2C_2H_5$	C_6H_5I	$(C_6H_5)_2CHCO_2C_2H_5$	46
$LiCH_2CH{=}CHCO_2C_2H_5$	$CH_3CH{=}CHBr$	$CH_3CH{=}CHCH_2CH{=}CHCO_2C_2H_5$	40

[a]All products exhibited spectral data in accordance with assigned structures.

[b]Glpc yields.

Table II. Activation of $NiBr_2$ with Reducing Agents

Reducing Agent	Yield, %[a]
$CH_3CH_2CH_2CH_2Li$	99
CH_3Li	76
C_6H_5Li	63
$(CH_3)_3CLi$	51
CH_3MgI	54
$(C_2H_5)_3Al$	12
$LiAlH_4$	22

[a]Product from the reaction of lithio t-butyl acetate and 1-bromo-propene. Glpc yields.

Table III. Reactions of Para-substituted Aryl Halides

Para-substituent	Halogen	Yield, %[a]
H-	Br-	43
Cl-	Br-	54
CH_3O-	Br-	41
CH_3-	Br-	46
CH_3O-	I-	61
Cl-	I-	30
Br-	Br-	29
F-	Br-	55

[a]Product is appropriate para-substituted t-butyl phenyl acetate Glpc yield. All compounds exhibited spectral data in accordance with para-substituted structures.

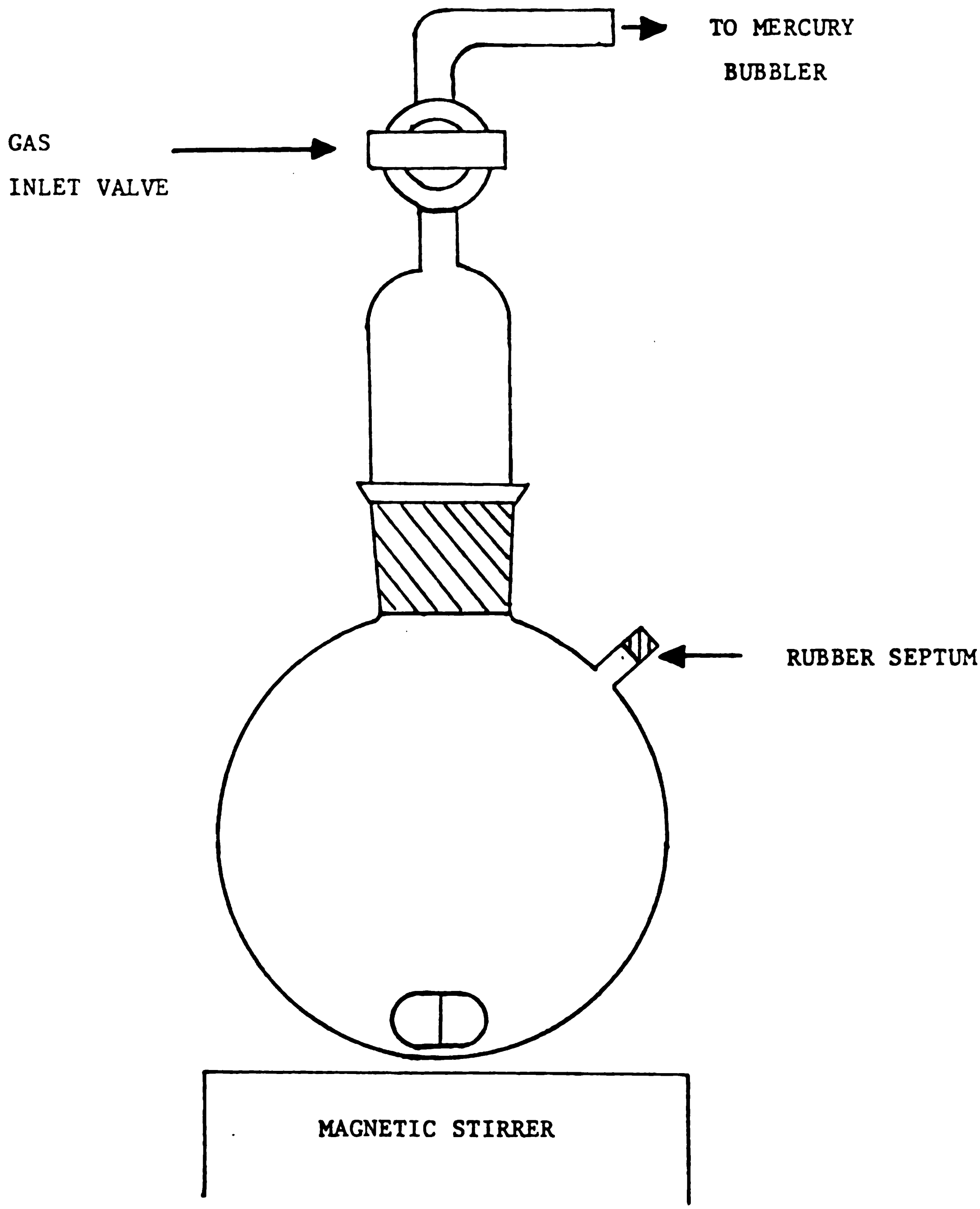


Figure 1. Reaction Apparatus

CHAPTER II

PERMETHYLATION OF KETONES

Introduction

Traditionally, permethylated ketones are prepared by sequential reaction of the ketone with portions of sodamide and methyl iodide (21) (eq 23).

$$(CH_3)_2CHCOCH(CH_3)_2 + NaNH_2 \longrightarrow (CH_3)_2C{=}C\begin{smallmatrix}ONa\\CH(CH_3)_2\end{smallmatrix}$$

$$\xrightarrow{CH_3I} (CH_3)_3CCOCH(CH_3)_2 \xrightarrow{NaNH_2} \begin{smallmatrix}NaO\\(CH_3)_3C\end{smallmatrix}C{=}C(CH_3)_2$$

$$\xrightarrow{CH_3I} (CH_3)_3CCOC(CH_3)_3 \qquad (23)$$

More recent methods use such bases as sodium alkoxide (22) or sodium hydride (23). In most cases, the overall yield for the replacement of all enolizable hydrogens does not exceed 50%.

Charles A. Brown (24) reported a procedure for preparing potassium ketone enolates using KH (eq 24).

$$RCOCH_2R' + KH \longrightarrow \begin{smallmatrix}KO\\R\end{smallmatrix}C{=}CHR' + H_2 \qquad (24)$$

Charles Brown's report (25) that KH reacted only sluggishly with CH_3I suggested a simple route to permethylated ketones. Treatment of a ketone with one equivalent of KH and CH_3I for every enolizable hydrogen at 25° might lead to the desired product (eq 25).

$$RCH_2COR' + KH \longrightarrow RCH{=}C(OK)R' \xrightarrow{CH_3I}$$

$$RCH(CH_3)COR' \xrightarrow{KH} RC(CH_3){=}C(OK)R' \xrightarrow{CH_3I}$$

$$RC(CH_3)_2COR' \qquad (25)$$

Results

With slight modification of the procedure proposed in the introduction the desired results were achieved. We discovered, however, in the course of our survey some results that were somewhat different than those reported by Charles Brown.

We found that potassium hydride reacts with methyl iodide at 25°C to give methane. The reaction does not go to completion, however. When 10 mmol of potassium hydride was treated with 10 mmol of methyl iodide, a total of 3.7 mmol of gas (measured with a gas buret, analyzed by GLC) was given off in less than one minute. No further methane was formed after two hours. GLC analysis of the solution confirmed the presence of 6.3 mmol of residual methyl iodide. Addition of 10 mmol of cyclohexane to the KH suspension resulted in the rapid evolution of 6.3 mmol of hydrogen gas.

We also found that potassium hydride will reduce ketones to alcohols. A side product in the permethylation of cyclohexanone was the methyl ether of 2,2,6,6-tetramethylcyclohexanol. This reduction was confirmed by stirring mixtures of 2,2,6,6-tetramethylcyclohexanone containing equivalent amounts of potassium hydride and analyzing quenched aliquots for 2,2,6,6-tetramethylcyclohexanol. After five hours, ten per cent of the ketone was reduced and 50% in 24 hours.

Two procedures were used for the permethylation of ketones. The first involved the addition of the ketone to a ten per cent excess of potassium hydride. Methyl iodide, in 10% excess, was then added slowly to the reaction mixture. GLC analysis of the reaction mixtures was then performed.

Cyclobutanone, cyclopentanone, cyclohexanone and acetophenone were permethylated using the above procedure. Cycloheptanone and 4-heptanone were trimethylated and acetone was pentamethylated using the above procedure. In these latter cases, the reason for incomplete permethylation is slow reaction of the pentultimate methylated ketone with potassium hydride. With cycloheptanone and acetone, refluxing the reaction mixture for one hour followed by cooling and addition of the final equivalent of methyl iodide gave the permethylated ketones in good yields. This latter procedure was ineffective, however, with 4-heptanone. In fact, no hydrogen was evolved when a sample of 3,3,5-trimethyl-4-heptanone was refluxed for six hours with potassium hydride.

The starting ketone was recovered quantitatively after the addition of methyl iodide. The results of our survey are shown in Table IV.

Discussion

Evidently, potassium hydride does reduce methyl iodide at room temperature, but the reaction stops far short of completion. We have no direct evidence on the reason for incomplete reduction, but the following experiment was particularly revealing.

A suspension of 15 mmol of KH in THF was treated with 5.0 mmol 2,2,6-trimethylcyclohexanone. Five mmol of hydrogen was evolved over a five minute period. Injection of 5.0 mmol of methyl iodide did not produce any gas evolution. GLC analysis of a small aliquot of the reaction mixture revealed the presence of 4.9 mmol of 2,2,6,6-tetramethylcyclohexanone. At this point, the suspension was treated with an additional 10 mmol of methyl iodide and 3.6 mmol of methane was formed. Again, the presence of residual KH (6.4 mmol) and methyl iodide (6.4 mmol) was established.

The incomplete reduction of methyl iodide by KH is probably not due to product KI since KI is also formed (presumably in a similar state) by reaction of the ketone enolate with methyl iodide. The incomplete reduction is not due to the presence of a highly reactive form of KH unless this highly reactive form does not preferentially react with the ketone. The incomplete reduction is probably not due to a trace amount of inhibitor in the methyl iodide unless the inhibitor is removed by the ketone enolate. Most importantly, from our point of view, the potassium enolate of 2,2,6-trimethylcyclohexanone is remarkably reactive to methyl iodide and this reaction is much faster than the reduction of methyl iodide with potassium hydride.

The reduction of permethylated ketones is not without precedence. A similar reduction of non-enolizable ketones by sodium hydride has been described (26). The reduction, however, is slow. Therefore, if care is taken to control reaction temperature this technique is highly useful for the synthesis of these compounds.

Experimental

I Materials

Ketones

All ketones were commercially available and were purified by simple distillation.

Methyl Iodide

The commercial methyl iodide was distilled and stored in a brown bottle with a septum inlet over copper wire in a refrigerator.

Potassium Hydride

Potassium hydride was commercially available from Ventron Corp. as a 25-30% mineral oil dispersion. The dispersion was standardized by measuring the gas given off when a sample of known volume was treated with water.

II Reaction of Methyl Iodide with Potassium Hydride

A 50 ml round-bottomed flask equipped as in Figure 1 was flame dried under a stream of dry argon. The flask was charged with 1.86 ml (10 mmol) of KH dispersion and 10 ml THF. Methyl iodide (0.6 ml, 10 mmol) was injected. A total of 93 ml (3.7 mmol) of gas were volved in one minute. No further gas was evolved after two hours. GLC analysis (2.5% $AgNO_3$ and 7% paraffin on Al_2O_3) of a sample of gas indicated the presence of methane. *n*-Pentane (10 mmol) was added to the reaction mixture as internal standard and GLC analysis (1.5% OV-101) of an aliquot established the presence of 6.3 mmol of methyl iodide.

III Permethylation of Ketones

A. Permethylation of Cyclohexanone

A 500 ml flask equipped as in Figure 2 was flame dried under a stream of dry argon and charged with 40 ml (216 mmol) of KH dispersion in mineral oil. The flask was immersed in a water bath maintained at 25°C. THF (220 ml) was injected followed by dropwise addition of cyclohexanone (5.2 ml, 50 mmol) over a five minute period. After five minutes of a-ditional stirring, methyl iodide (13.5 ml, 216 mmol) was added dropwise over a fifteen minute period. After fifteen minutes of additional stirring, the reaction mixture was cautiously treated with 15 ml of saturated potassium carbonate in water. The aqueous layer was extracted once with ether (15 ml) and the combined organic layers were dried over anhydrous K_2CO_3. The dried organic layer was subjected to simple distillation and 6.25 gm, 81% yield of 2,2,6,6-tetramethylcyclohexanone (bp 183-185°C) was obtained.

When the above procedure was performed on a scale one-tenth of the above, GLC analysis with the proper internal standard showed the presence of the permethylated ketone in 96% yield. The above procedure was used to permethylate cyclobutanone, cyclopentanone, and acetophenone and to trimethylate 4-heptanone.

B. Permethylation of Acetone

A 50 ml flask was equipped as in Figure 2 and dried under argon as previously described. The flask was charged with 1.1 ml, 5.94 mmol of KH in mineral oil and 6.0 ml THF. The flask was immersed in a water bath and acetone (67 μl, 0.9 mmol) was added dropwise over a two minute period. After fifteen minutes of additional stirring, methyl iodide (0.29 ml, 4.68 mmol) was added slowly. After the addition was complete, the water bath was replaced by a heating mantle and the reaction refluxed for one hour and then cooled to 25°C under a stream of argon. The remaining methyl iodide (78 μl, 1.26 mmol) was then added and after ten minutes additional stirring, the mixture was treated as described previously. GLC analysis established the presence of 2,2,4,4-tetramethyl-3-pentanone in 72% yield. When the above procedure was repeated on a ten-fold scale followed by careful fractional distillation, the desired product was obtained in 66% yield. The above procedure was used to permethylate cycloheptanone.

Product Analysis

The ketones synthesized above were isolated by preparative GLC and analyzed by NMR and IR. All the IR were obtained neat and the NMR were in carbon tetrachloride and used $(CH_3)_4Si$ as internal standard.

2,2,4,4-Tetramethylcyclobutanone

NMR:1.7δ (s,2H), 1.2δ (s,12H); IR:1780cm^{-1} (C=O)

2,2,5,5-Tetramethylcyclopentanone

NMR:1.7δ (s,4H), 1.0δ (s,12H); IR:1745cm^{-1} (C=O)

2,2,7-Trimethylcycloheptanone

NMR:1.2-2.0δ (bm,9H), 1.0δ (s,6H), 0.9δ (d,3H); IR:1710cm^{-1} (C=O)

2,2,4-Trimethyl-3-pentanone

NMR:3.0δ (heptet,J=8Hz,1H), 1.1δ (s,9H), 1.0δ (d,J=8Hz,6H); IR:1675cm^{-1} (C=O)

2,2-Dimethylpropiophenone

NMR:7.5δ (m,2H), 7.2δ (m,3H), 1.3δ (s,9H); IR:1675cm^{-1} (C=O)

3,3,5-Trimethyl-4-heptanone

NMR:2.7δ (m,1H), 1.4δ (m,4H), 1.0δ (s,6H), 0.8δ (m,3H); IR:1695cm^{-1} (C=O)

2,2,7,7-Tetramethylcycloheptanone

NMR:1.6δ (s,8H), 1.1δ (s,12H)

2,2,4,4-Tetramethyl-3-pentanone

NMR:1.2δ (s); IR:1670cm^{-1} (C=O)

Table IV. Methylation of Ketones with KH and CH_3I at 25°C

Ketone	Product	Yield[a]
cyclobutanone	2,2,4,4-tetramethylcyclobutanone	79
cyclopentanone	2,2,5,5-tetramethylcyclopentanone	100(83)
cyclhexanone	2,2,6,6-tetramethylcyclohexanone	96(81)
cycloheptanone	2,2,7-trimethylcycloheptanone	75
cycloheptanone[b]	2,2,7,7-tetramethylcycloheptanone	62(50)
acetone	2,2,4-trimethyl-3-pentanone	90
acetone[b]	2,2,4,4-tetramethyl-3-pentanone	72(66)
acetophenone	2,2-dimethylpropiophenone	100(81)
4-heptanone	3,3,5-trimethyl-4-heptanone	86(66)

[a]GLC yields, isolated yields (distillation) in parentheses.

[b]Reaction mixture refluxed for one hour prior to addition of final equivalent of methyl iodide.

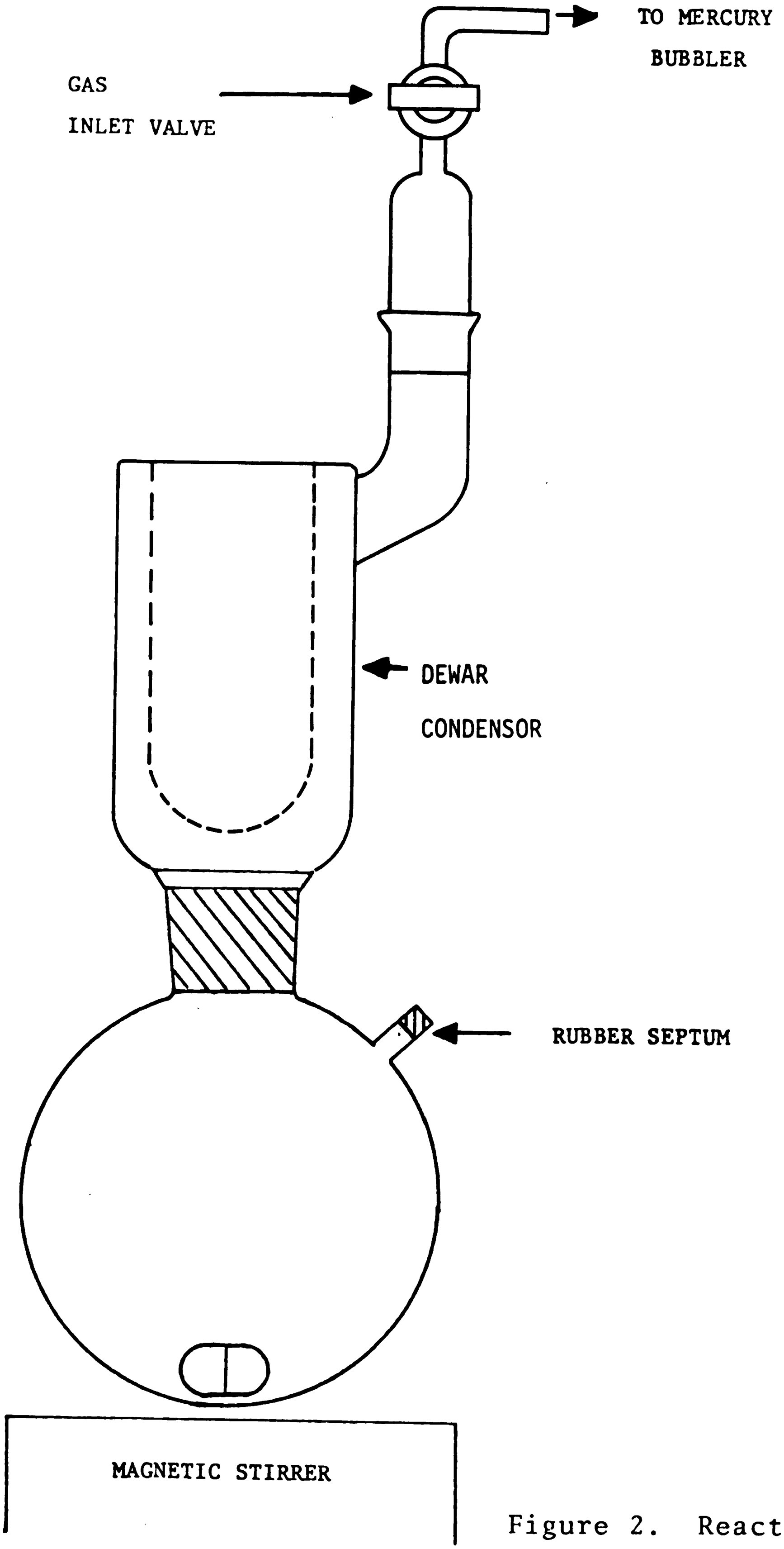


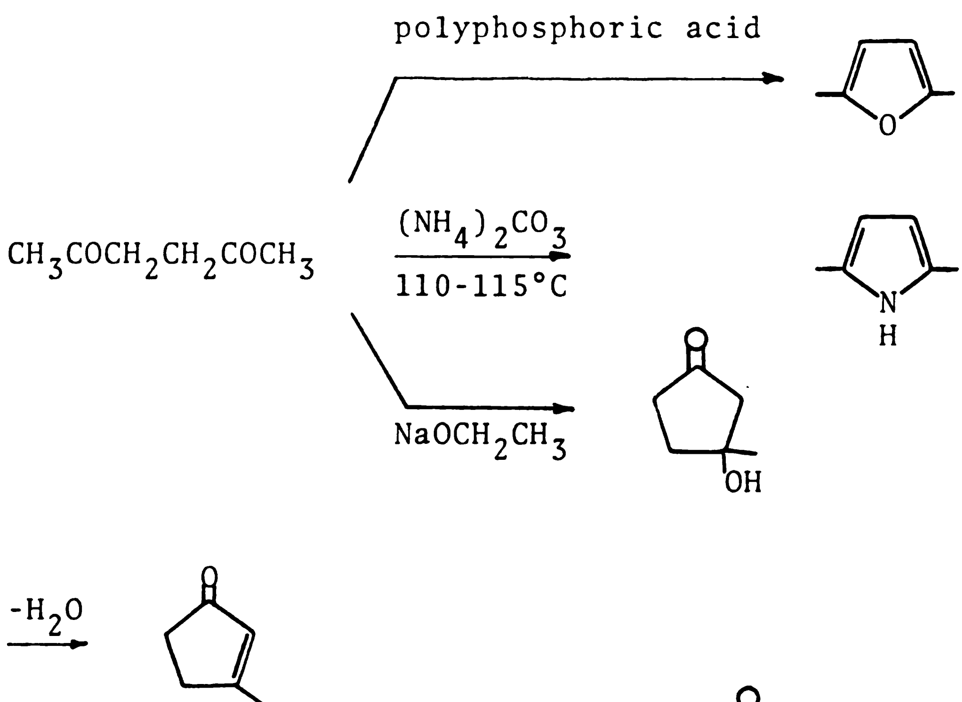
Figure 2. Reaction Apparatus

CHAPTER III

THE CROSS-COUPLING OF KETONE ENOLATES AND ESTER ENOLATES

Introduction

1,4-Dicarbonyl compounds have long been important intermediates in organic synthesis. The 1,4-diketones can be used in the synthesis of furans (27), pyrroles (28), and cyclopentenones (29) (eq 26). The latter compounds are precursors to prostaglandins (30) as are the cyclopentan-1,3-diones (31) derived from the γ-ketoesters (eq 27).



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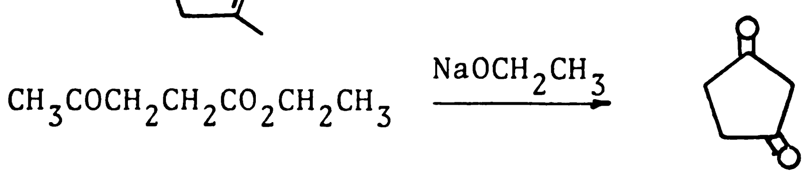


(27)

Dicarbonyl compounds are usually formed in condensation reactions. However, 1,4 disposition of two carbonyl groups cannot be brought about by simple condensation reaction of two carbonyl compounds.

There is a method for making 1,4-dicarbonyl compounds through a condensation of an enolate of a nitro compound with a carbonyl compound (eq 28).

$$\underset{\underset{NO_2}{|}}{R\text{-}\bar{C}\text{-}H} + CH_2{=}CHCOR' \longrightarrow \underset{\underset{NO_2}{|}}{RCHCH_2CH_2COR'}$$

$$\xrightarrow{TiCl_3} RCOCH_2CH_2COR' \qquad (28)$$

The charge affinity inversion at the carbon bonded to the nitro group in the starting material is an essential element in this condensation to give a 1,4-dicarbonyl compound.

One of the most effective methods for the synthesis of 1,4-diketones was reported by Ito and co-workers (32). Lithium ketone enolates are oxidatively coupled (eq 29) with cupric chloride.

$$CH_2{=}C\begin{matrix}\diagup OLi\\ \diagdown R\end{matrix} + CuCl_2 \longrightarrow RCOCH_2CH_2COR \qquad (29)$$

Cupric bromide was used previously (33) to couple lithium ester enolates to give succinate diesters (eq 30).

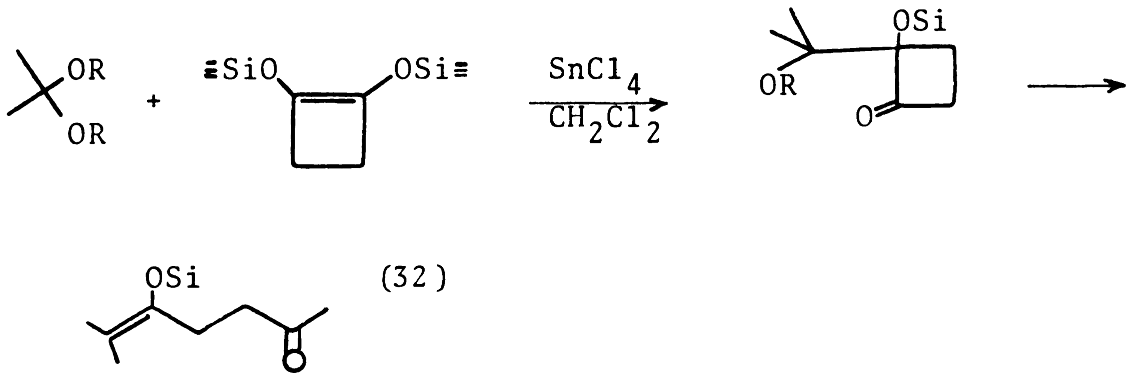
$$CH_2{=}C\begin{matrix}\diagup OLi\\ \diagdown OR\end{matrix} + CuBr_2 \longrightarrow RO_2CCH_2CH_2CO_2R \qquad (30)$$

Many other techniques have been used to form γ-ketoesters. Ho reported (34) the following sequence (eq 31) as a method for the formation of these esters.

$$RCH{=}CHNR'_2 + CH_2{=}CHCO_2Et \longrightarrow \underset{\underset{NR'_2}{\|}}{RC}CH_2CH_2CO_2Et$$

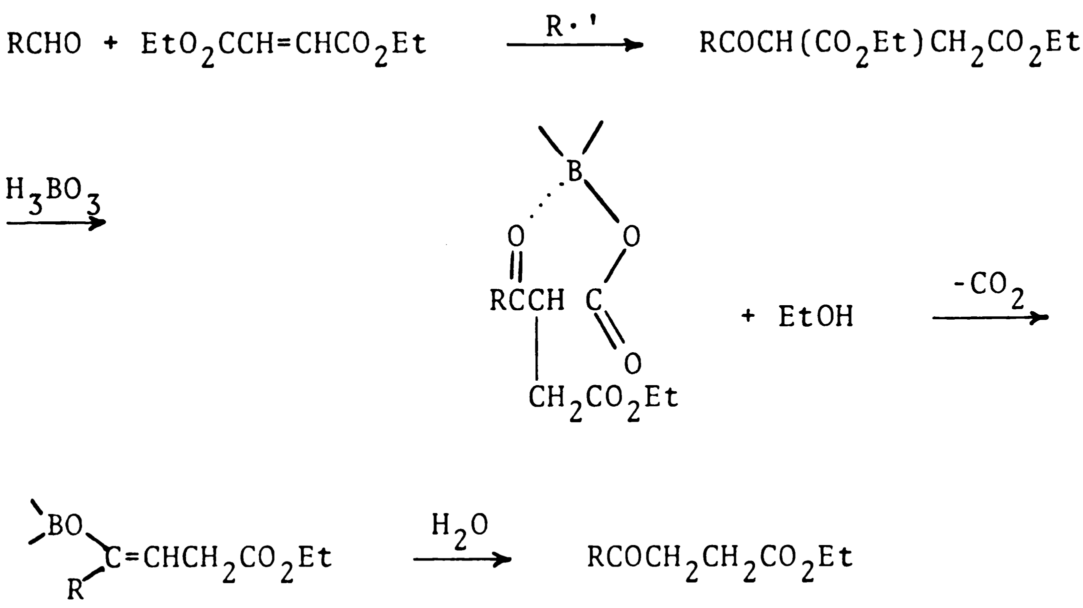
$$\xrightarrow[CuCl]{O_2} RCOCH_2CH_2CO_2Et \qquad (31)$$

Kuwajima and co-workers (35) reported an interesting route to γ-ketoesters (eq 32).



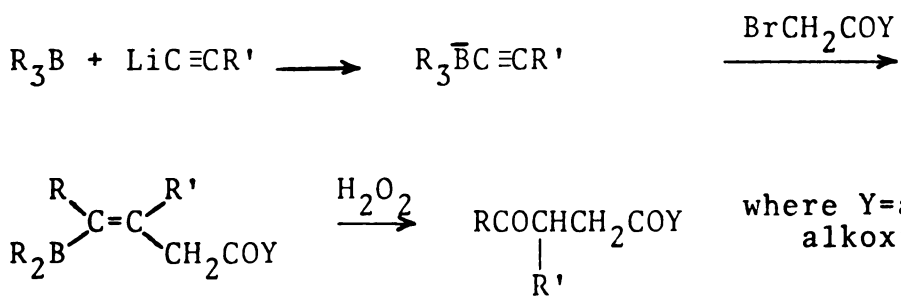
(32)

Yet another technique for the formation of γ-ketoesters was reported (36) by Wehrli and Chu (eq 33).



(33)

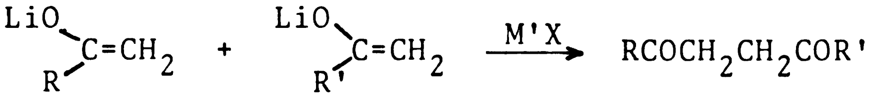
Perhaps the most versatile method for the synthesis of 1,4-dicarbonyl compounds that has been reported is the sequence by Pelter and co-workers (37) (eq 34).



where Y=alkyl or alkoxide (34)

This technique can be used not only to make γ-ketoesters and 1,4-diketones, it can also be used to make β-γ unsaturated ketones and esters (37).

All of the above techniques are useful for the synthesis of the desired compounds. There are, however, limitations to all of the methods. The simpler techniques give only symmetrical products. If an unsymmetrical product is desired, a multistep process is needed. We considered the possibility of achieving unsymmetrical products by the cross-coupling of two different enolates using transition metal oxidants (eq 35).

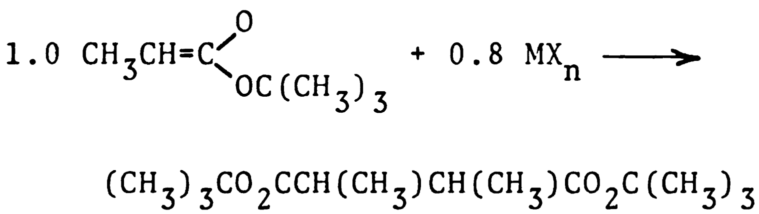


(35)

It would appear that the highest probability of success would be when the two enolates differ greatly in character. Consequently, we chose to study the cross-coupling of ester enolates with ketone enolates.

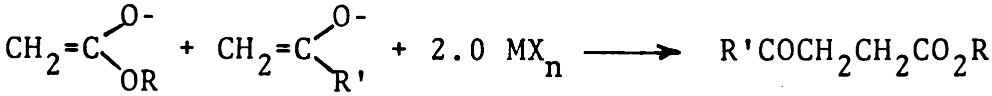
Results

A survey was taken to determine the activity of a number of transition metal salts. If the salt showed activity in the model reaction (eq 36), then it was used in an attempt to cross-couple a ketone and an ester enolate. The results of the survey are shown in Table V.



(36)

The metal that gave the highest yield in the above reaction was used first in an attempt to cross-couple (eq 37) the enolates.



(37)

The most active salt, cupric bromide, gave a complex mixture of products.

The next most active salt, anhydrous ferric chloride, was then used. A reaction using lithio *tert*-butyl acetate and lithio cyclohexanone gave a single product. The product was identified as *tert*-butyl 2-oxocyclohexylacetate. It was produced in a 44% yield. Attempts were made to increase the yield of this reaction.

We discovered that this reaction was extremely sensitive. The THF that was used in these reactions had to be distilled from lithium aluminum hydride in order to maximize the yield. The *n*-butyllithium that was used had to be free of any turbidity or the yields dropped dramatically.

Once the optimum conditions for this reaction were established, attempts were made to increase the yield. The first course of action was to change the iron (III) salt to see if the change in anion would increase the yield either by increasing the activity of the iron or its solubility in organic solvents. When $Fe(2\text{-ethylhexanoate})_3$ and $Fe(acac)_3$ were used as catalysts, the yield dropped to zero. Ferric bromide did give some of the desired product but the yield dropped to 32%.

At this point, a reaction whose products were more easily monitored on the gas chromatograph was used to extend the investigation. The reaction of lithio *tert*-butyl acetate with lithio pinacolone was used as the model reaction. Under conditions identical to those used in the previous reaction, this reaction gave *tert*-butyl

4-oxo-5,5-dimethylhexanoate in 65% yield. All subsequent attempts to increase the yield of cross-coupling were then directed toward this reaction.

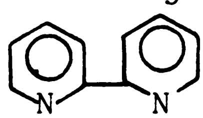
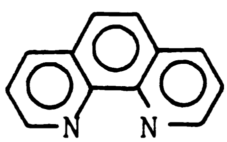
If the reaction is visualized as attack of an ester activated by iron onto a ketone enolate and the competing reaction is dimerization of two activated esters, then addition of the iron solution slowly to the enolate solution should increase the possibility of an activated ester reacting with a ketone enolate before it encounters another activated ester.

If the product reacted with any enolate to form undetectable condensation products, the yield would decrease. And if the coupling reaction was faster than the condensation, then lowering the reaction temperature might increase the product yield. Several experiments were performed where the temperature and duration were varied and the effects of these variations are tabulated below.

Temp °C	Time	Yield %
-78	60 min	14
-78	19 h	48
-38	60 min	58
0	60 min	58

The concentration and stoichiometry of the reactants could control the rate of product formation. Several experiments that varied the stoichiometry and concentration were performed. Altering the amount of $FeCl_3$ by factors of 0.5, 1.5 and 2.0 produced yields of 5%, 30% and 26%, respectively. Increasing the portion of one enolate by 20% with respect to the other enolate gave a yield of 60% for excess ketone enolate and 51% for excess ester enolate. Increasing the concentration of the enolate solution from 1.0*M* to 2.0*M* in total enolate decreased the yield to 38%. Ironically, the same yield was produced when the concentration of the enolates was reduced to 0.1*M* in total enolate.

A ligand could increase the solubility of the iron in THF so a series of experiments was performed to see if the yield increased. The results of that survey are shown below.

Ligand	Yield %
$(n\text{-Bu})_3P$	10
	48
	50

When the previous results were obtained, we decided to try the reaction with amine free enolates. That experiment gave the desired product in 57% yield.

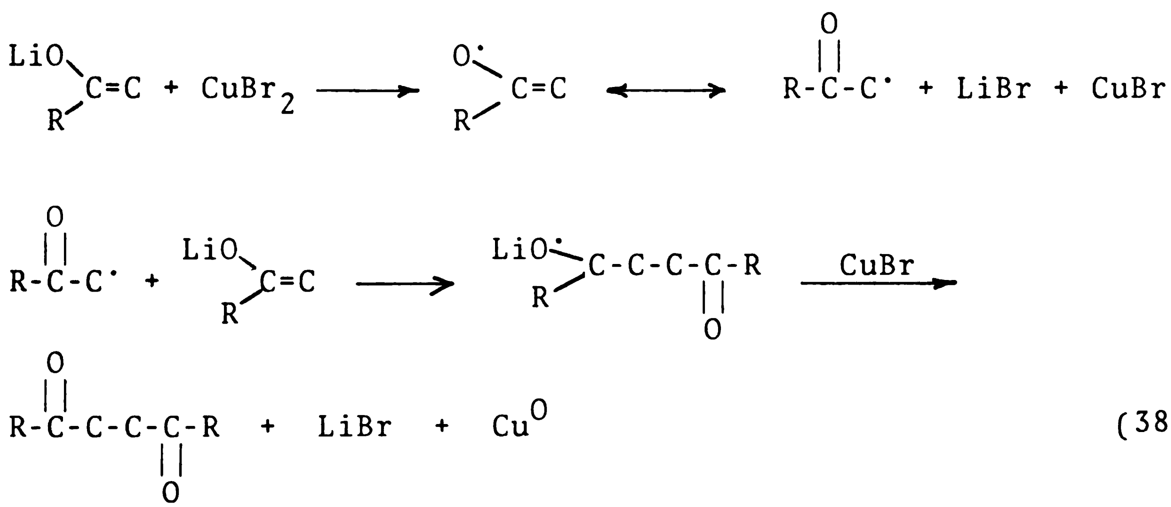
After all these attempts to increase the yield failed a survey of the coupling of different ketones and esters was initiated. The results of that survey are shown in Table VI.

An attempt to cross-couple the pinacolone and acetate enolates with iodine gave a 90% yield of diester and a 10% yield of diketone with no cross-coupling observed.

In an attempt to gain insight into the reaction mechanism, the ketyl of 2,2,6,6-tetramethylcyclohexanone (38) was treated with both water and $FeCl_3$ in THF followed by water. The first experiment gave the expected 50:50 ratio of the starting ketone and the corresponding alcohol. The second experiment, however, gave an 80:20 ratio of ketone to alcohol.

Discussion

The oxidative coupling of enolates can be thought of as a two electron process (eq 38) as shown below using cupric bromide as an example.



(38)

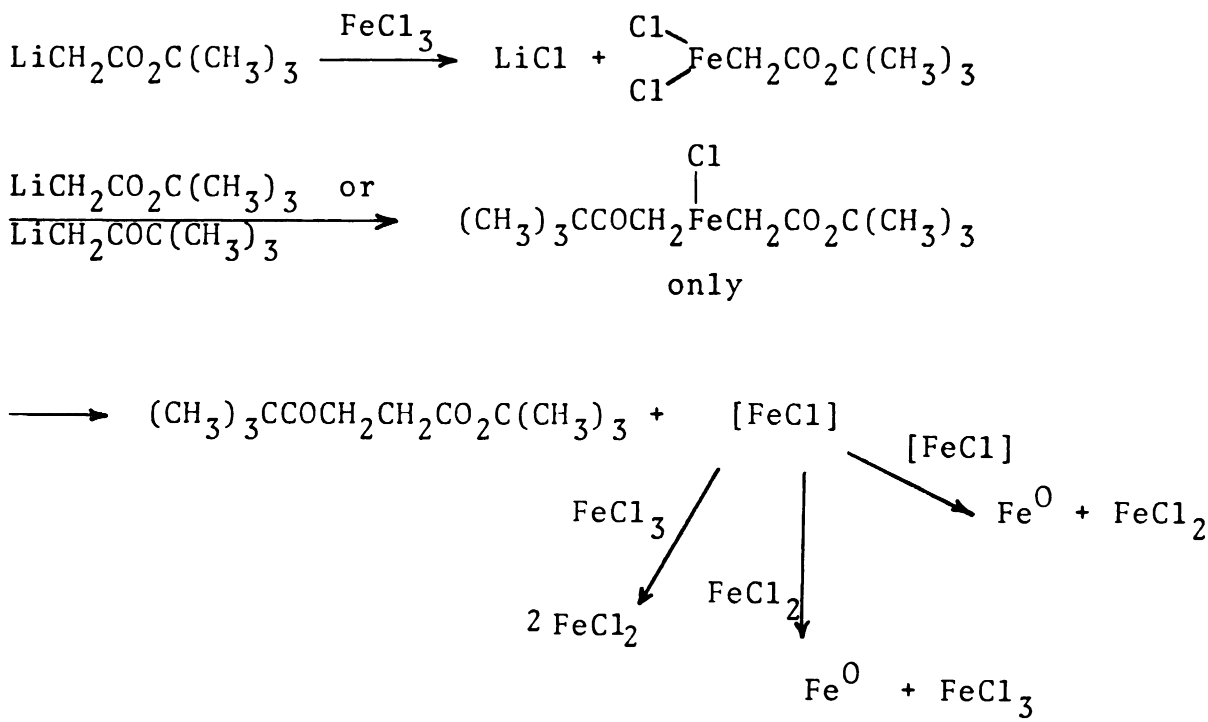
In our system, the starting metal is in the plus three oxidation state. Therefore, if the same type mechanism is operating then a final product would be an unknown iron (I) compound. This difficulty can be rationalized by postulating a transient iron (I) species interacting with another such species to form known iron (0) and iron (II) compounds. An iron (I) species could also react with an iron (III) compound to form two iron (II) species.

Another rationalization is that only iron (III) species oxidize the intermediate ketyl. Indeed, independently generated ketyl anions (38) when treated with $FeCl_3$ in THF followed by aqueous acid gave an 80:20 mixture of ketone to alcohol. Aqueous acid alone gave the expected 50:50 mixture of ketone to alcohol.

If iron (III) compounds are the only reagents oxidizing the anions, then one $FeCl_3$ molecule per anion is the minimum amount of iron needed to give a quantitative yield of product. Reducing the $FeCl_3$ by half caused the yield to drop off from 65% to 5%. Increasing the amount of $FeCl_3$ by factors of 1.5 and 2.0 did not increase the yield. Indeed, the yield was decreased to 30% and 26%, respectively. This decrease in yield was not due to reaction of the product with the excess $FeCl_3$. The isolated product was treated with $FeCl_3$ and no decrease in the amount of product was observed.

A reasonable mechanism consistent with these data can be postulated (Scheme IV). An iron compound with an ester and a ketone enolate attached could reductively eliminate the cross-coupled product and form an iron (I) compound. The iron (I) compound would then immediately react with $FeCl_3$ to form two iron (II) compounds. As the amount of iron (III) decreased the iron (I) could react with either an iron (II) or another iron (I) to form iron (III) and iron (0) or two iron (II) compounds, respectively. For this mechanism to operate, there must be a highly selective step somewhere in the scheme. The easiest to rationalize is a step where only one enolate is attached to the iron and the resultant compound is highly selective for the addition of the other enolate. Scheme IV is shown using pinacolone and *tert*-butyl acetate.

Scheme IV



Experimental

I Materials

Carbonyl Compounds

The esters were obtained commercially and used without further purification. The ketones were also commercially available and were purified by distillation prior to use.

Iron (III) Salts

The $FeCl_3$ was obtained from J. T. Baker & Co. They purified the compound by triple sublimation. All manipulations of this compound were done under argon in a glove bag or a glove box. All the rest of the iron (III) compounds were obtained from Ventron Corp. and used without further purification.

Solvent

It was extremely important that the THF used in these experiments be distilled from $LiAlH_4$ prior to use. THF distilled from the sodium ketyl of benzophenone decreased the yield of products.

n-Butyllithium

Extreme care must be taken to exclude air from the commercial *n*-butyllithium used in these experiments. Prolonged contact with air resulted in a cloudy *n*-butyllithium solution. This cloudy solution greatly decreased the yield of products.

II Preparation of γ-Ketoesters

The cross-coupling of pinacolone with *tert*-butyl acetate is representative. Two reaction flasks were set up as in Figure 1. Each was flame dried under a stream of argon. One flask was charged with 3.4 ml (5.44 mmol) of 1.6*M* *n*-BuLi in hexane. Pentane, 5 ml, was added and the solution cooled to 0°C. Diisopropylamine (0.77 ml; 5.44 mmol) was then added dropwise over a five minute period. The cooling bath was then removed and when gas evolution ceased (approximately 15 minutes later) the hydrocarbon solvent was removed *in vacuuo*. The resultant white powder was dissolved in 5.6 ml of THF and cooled to 0°C. Pinacolone (0.34 ml; 2.72 mmol) was added dropwise. After a five minute interval the reaction was cooled to -78°C and 0.36 ml (2.72 mmol) of *tert*-butyl acetate was added dropwise. Ferric chloride (0.882 gm; 5.44 mmol) was then added to the other flask. After dissolution of the $FeCl_3$ was complete the solution was cooled to -78°C. The enolate solution was then added to the $FeCl_3$ solution through teflon tubing via argon pressure. The cooling bath was then removed and the purple solution allowed to reach room temperature. The reaction mixture was then once again cooled to -78°C and treated successively with 5.6 ml of 3.0*M* HCl, pentane and 0.75 ml (2.72 mmol) *n*-pentadecane. The organic layer was then separated and dried over anhydrous K_2CO_3 and subjected to GLC analysis which showed the presence of *tert*-butyl 4-oxo-5,5-dimethylhexanoate in 65% yield. All the other γ-ketoesters were prepared exactly as described above from the appropriate ketone and ester.

Product Analysis

The products were isolated by preparative GLC and identified by ^{1}H NMR. All the NMR were taken in CCl_4 with $(CH_3)_4Si$ as internal standard.

tert-Butyl 2-Oxocyclohexylacetate

NMR:2.8-1.6δ (bm/11H), 1.4δ (s,9H)

tert-Butyl 4-Oxopentanoate

NMR:2.4δ (m,4H), 2.1δ (s,3H), 1.4δ (s,9H)

tert-Butyl 4-Phenyl-4-oxobutanoate

NMR:7.8δ (m,2H), 7.3δ (m,3H), 3.1δ (t,2H), 2.5δ (t,2H), 1.4δ (s,9H)

tert-Butyl 5,5-Dimethyl-4-oxohexanoate

NMR:2.5δ (dd,4H), 1.4δ (s,9H), 1.2δ (s,9H)

tert-Butyl 3,3,5,5-Tetramethyl-4-oxohexanoate

NMR:2.4δ (s,2H), 1.4δ (s,9H), 1.3δ (s,6H), 1.2δ (s,9H)

tert-Butyl 3,3,5-Trimethyl-4-oxohexanoate

NMR:3.0δ (heptet,1H), 2.4δ (s,2H), 1.4δ (s,9H), 1.2δ (s,6H), 1.0δ (d,6H)

tert-Butyl 2,5,5-Trimethyl-4-oxohexanoate

NMR:2.6δ (m,3H), 1.4δ (s,9H), 1.2δ (s,12H)

Ethyl 2,2,5,5-Tetramethyl-4-oxohexanoate

NMR:4.0δ (q,2H), 2.6δ (s,2H), 1.2δ (m,18H)

Ethyl 5,5-Dimethyl-4-oxohexanoate

NMR:4.0δ (q,2H), 2.6δ (m,4H), 1.2δ (t and s,12H)

Methyl 5,5-Dimethyl-4-oxohexanoate

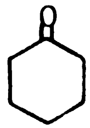
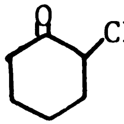
NMR:3.6δ (s,3H), 2.6δ (m,4H), 1.2δ (s,9H)

Table V. Reaction of $LiCH(CH_3)CO_2C(CH_3)_3$ with 0.8 Metal Salt

Metal Salt	Yield, %[a]
$CuBr_2$	64
MnO_2	0
CrO_3	8
$MnBr_2$	0
$KMnO_4$	0
$NaIO_4$	0
$FeCl_3$	55
$Pb(OAc)_4$	14
$Tl(OAc)_3$	0
$AgNO_3$	6
$CoBr_2$	0
$FeCl_2$	0
WCl_6	24
$PdCl_2$	38
$Co(acac)_3$	35 $[(CH_3)_3CO_2CCH_2CH_2CO_2C(CH_3)_3]$

[a]GLC yields of $(CH_3)_3CO_2CCH(CH_3)CH(CH_3)CO_2C(CH_3)_3$.

Table VI. Cross-coupling of Ketones and Esters

Ester	Ketone	Product	Yield, %
$CH_3CO_2C(CH_3)_3$		 $CH_2CO_2C(CH_3)_3$	44
	$(CH_3)_3COCH_3$	$(CH_3)_3COCH_2CH_2CO_2C(CH_3)_3$	65
	$(CH_3)_3COCH(CH_3)_2$	$(CH_3)_3COC(CH_3)_2CH_2CO_2C(CH_3)_2$	53
	$(CH_3)_2CHCOCH(CH_3)_2$	$(CH_3)_2CHCOC(CH_3)_2CH_2CO_2C(CH_3)_3$	65
$CH_3CO_2CH_2CH_3$	$(CH_3)_3COCH_3$	$(CH_3)_3COCH_2CH_2CO_2CH_2CH_3$	50
$CH_3CO_2CH_3$		$(CH_3)_3COCH_2CH_2CO_2CH_3$	45
$CH_3CH_2CO_2C(CH_3)_3$		$(CH_3)_3COCH_2CH(CH_3)CO_2C(CH_3)_3$	22
$(CH_3)_2CHCO_2CH_2CH_3$		$(CH_3)_3COCH_2C(CH_3)_2CO_2CH_2CH_3$	12
$CH_3CO_2C(CH_3)_3$	$(CH_3)_2CO$	$CH_3COCH_2CH_2CO_2C(CH_3)_3$	20
	$C_6H_5COCH_3$	$C_6H_5COCH_2CH_2CO_2C(CH_3)_3$	17

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