Synthetic Applications and Mechanism Studies of the Decarbalkoxylations of Geminal Diesters and Related Systems Effected in Me_2SO by Water and/or by Water with Added Salts[1]

A. Paul Krapcho,* J. F. Weimaster, J. M. Eldridge,[2] E. G. E. Jahngen, Jr.,
A. J. Lovey, and W. P. Stephens

Department of Chemistry, The University of Vermont, Burlington, Vermont 05401

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The decarbalkoxylations of geminal diesters, β-keto esters, and α-cyano esters by water–Me_2SO and/or water–Me_2SO with added salts is a convenient preparative route, leading to esters, ketones, and nitriles, respectively. This type of reaction has been studied using a variety of substrates and diverse salts. The diesters $C_6H_5CH(CO_2CH_2CH_3)_2$, $C_6H_5CH_2(CO_2CH_2CH_3)_2$, and $CH_3CONHCH(CO_2CH_2CH_3)_2$ decarbethoxylate on being refluxed in wet Me_2SO. Monosubstituted β-keto esters also decarbethoxylate under these conditions. Diesters such as $CH_3CH_2CH(CO_2CH_2CH_3)_2$ and $CH_3CH_2CH(CO_2CH_3)_2$ undergo a much slower decarbalkoxylation in refluxing wet Me_2SO. Substrates such as $(CH_3)_2CHCH(CO_2CH_2CH_3)_2$ and the disubstituted diesters $(CH_3CH_2)_2C(CO_2CH_2CH_3)_2$, $C_6H_5C(CH_3)C(CO_2CH_2CH_3)_2$, and $(CH_3CH_2)_2C(CO_2CH_3)_2$ undergo no decarbalkoxylations on being heated for long periods in H_2O–Me_2SO. The addition of salts such as KCN, NaCl, or LiCl to the H_2O–Me_2SO dramatically enhances the decarbalkoxylation rates of these substrates. The CH_3CH_2CN–CH_3CH_2OH product ratios have been determined for several mono- and disubstituted geminal diesters using KCN–H_2O–Me_2SO. Relative rates of decarbalkoxylations have been determined for various substrates and salts. Comparative rate data have been obtained for several substrates in H_2O or D_2O in Me_2SO in the presence and absence of salts. Mechanistic interpretations which involve competitive $B_{AL}2$ and $B_{AC}2$ cleavages which are dependent on substrate structure are presented to rationalize the experimental data.

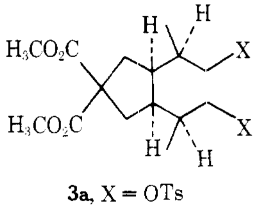
During the past several years we have reported studies of the synthetic applications of the decarbalkoxylations of malonate esters 1 to esters 2 (and the related β-keto esters and α-cyano esters) using NaCN in refluxing Me_2SO,[3] NaCl in wet Me_2SO,[4,5] and wet Me_2SO.[5,6]

$$\underset{\mathbf{1}}{R^1R^2C(CO_2R^3)_2} \rightarrow \underset{\mathbf{2}}{R^1R^2CHCO_2R^3}$$

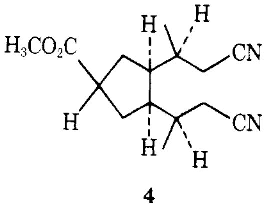
We now wish to report additional experimental data which further extends the synthetic utility of this extremely useful and versatile reaction and sheds some light on the mechanistic aspects.

Introduction

In an attempt to convert the ditosylate **3a** into the dinitrile **3b**, **3a** was treated with excess KCN in Me_2SO at 90 °C (12 h). Under these conditions, the tosylate groups were not only displaced, but a decarbomethoxylation occurred to produce 4 in a good yield.[7] Dinitrile **3b** could be prepared from **3a** if the KCN–Me_2SO (or NaCN) reaction mixture was maintained at room temperature (6 days). The application of the NaCN–Me_2SO reagent combination for effecting decarbalkoxylations was then studied by us utilizing several mono- and disubstituted malonate esters.[3] For example, treatment of $CH_3CH_2(CO_2CH_2CH_3)_2$ with 2 equiv of NaCN in Me_2SO (160 °C, 4 h) leads to ethyl butyrate (80%). Several advantages of this procedure include the facts that functional groups such as ketals or esters which are sensitive to acidic or basic conditions survive the reaction and isomerizations of double bonds do not occur.



3a, X = OTs
b, X = CN



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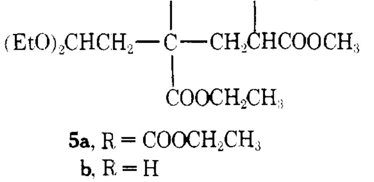
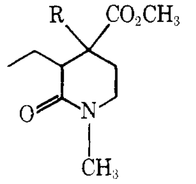


$$(EtO)_2CHCH_2-\underset{\underset{COOCH_2CH_3}{|}}{\overset{\overset{R}{|}}{C}}-CH_2\overset{\overset{CH_2CH_3}{|}}{C}HCOOCH_3$$

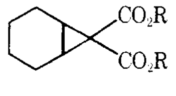
5a, R = $COOCH_2CH_3$
b, R = H

Since the introduction of this procedure, many applications of its synthetic utility to complex molecules have been reported.[8] The decarbethoxylation of **5a** yields **5b**.[8a]

Modifications of this procedure using cyanide salts, other substrates, and dipolar aprotic solvents have subsequently been reported.[9–12] DMF and NaCN have been used in the conversion of **6a** to **6b**.[9] Of mechanistic interest is the result that **7a** on treatment with 2 equiv of KCN in DMF yields **7b** (65%).[10]



6a, R = CO_2CH_3
b, R = H



7a, R = CH_3
b, R = H

Our further studies of this reaction showed that NaCl–H_2O–Me_2SO effected decarbalkoxylations of malonate esters, β-keto esters, and α-cyano esters.[4,5,6] Applications of this salt to effect decarbalkoxylations have appeared in other synthetic routes.[13,14]

Certain substrates undergo reaction when heated with wet Me_2SO without added salts.[5,6] Bernhard in 1894 had observed that hot water could effect decarbalkoxylations of doubly activated esters such as diethyl benzoylmalonate.[15] A recent application of this procedure reports that diethyl propionylmalonate with boiling water yields ethyl propionylacetate.[16] Meerwein[17] in 1913 reported that β-keto esters yield ketones on being treated with water in a sealed tube (200 °C, 0.5 h) and later reported the conversion of 8 to 9.[18] The procedure failed for β-keto esters with no α hydrogens. A modification of this procedure using basic aluminum oxide in aqueous dioxane has recently been reported.[21,22]

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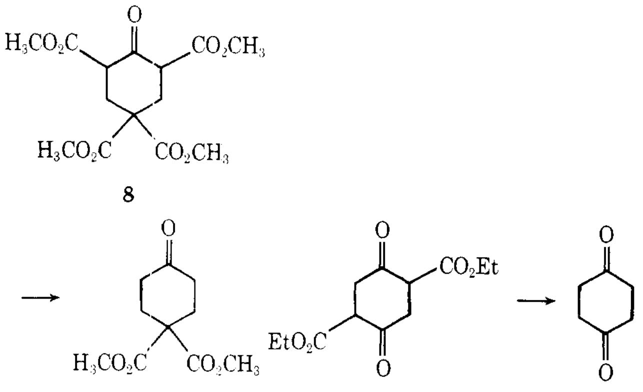
Table I. Decarbalkoxylations of Geminal Diesters by H_2O–Me_2SO

1			Registry no.	Heating period, h[a]	% monoester
R^1	R^2	R^3			
C_6H_5	H	CH_3CH_2[b]	83-13-6	3	90[c]
$C_6H_5CH_2$	H	CH_3CH_2[d]	607-81-8	4	61[e]
CH_3CONH	H	CH_3CH_2[f]	1068-90-2	3.5	70
CH_3	H	CH_3CH_2[g]	009-08-5	3	32[h]
CH_3CH_2	H	CH_3CH_2[d]	133-08-5	2	7[i,j]
CH_3CH_2	H	CH_3CH_2[k]		4.5	20[i]
CH_3CH_2	H	CH_3[l]	26717-67-9	2	32[i,m]
$(CH_3)_2CHCH_2$	H	CH_3CH_2[d]	10203-58-4	2.5	13[i]
$(CH_3)_2CH$	H	CH_3CH_2[d]	759-36-4	2	1[i]
c-C_6H_{11}	H	CH_3CH_2[d]	2163-44-2	2	1[i]
CH_3	CH_3	CH_3CH_2[n]	1619-62-1	2	1[i,o]
CH_3CH_2	CH_3CH_2	CH_3CH_2[n]	77-25-8	2	1[i]
CH_3CH_2	CH_3CH_2	CH_3[n]	27132-23-6	4.5	2[i]
C_6H_5	CH_3	CH_3CH_2[n]	34009-61-5	16	3[i]

[a] The total reaction time is the period beginning when heat was begun and when the refluxing mixture started to cool. All reactions were run in round-bottom flasks with magnetic stirring with a mantle. [b] Diester (0.03 mol) and water (0.06 mol) in 25 mL of Me_2SO. [c] The product was isolated by a water quench, extraction into pentane, and concentration of the pentane extract. Product identification was done by ^1H NMR, IR, and GLC comparisons. Yields are based on isolated products. [d] Substrate and water (0.03 mol each) in 50 mL of Me_2SO. [e] After 8 h and workup as in c, a 70% yield of ethyl phenylpropionate could be isolated (contained about 5% starting diester). [f] Substrate (0.01 mol) and water (0.02 mol) in 10 mL of Me_2SO. The product was isolated by distillation of the Me_2SO under water-aspirator pressure and the distillation of the ethyl acetamidoacetate under vacuum-pump pressure. [g] Diester (0.05 mol) and water (0.10 mol) in 50 mL of Me_2SO. [h] Low-boiling material was distilled from the reaction pot and washed with cold water, and the ester was isolated. [i] An aliquot was quenched with water, extracted with pentane and analyzed by VPC. [j] Fourteen percent monoester after 4 h of total heating. [k] As in d, except DMF as solvent. [l] Diester (0.003 mol) and water (0.03 mol) in 5 mL of Me_2SO. [m] Forty-two percent of ester after an additional hour of heating. [n] Substrate and water (0.015 mol each) in 25 mL of Me_2SO. [o] After 21 h of total heating, perhaps 3% reaction. Paraformaldehyde formed in the condenser.



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9

10

11

Halolytic decarbalkoxylations of activated esters have been reported with various iodide salts and dipolar aprotic or polar aprotic solvents.[24–31] The popular use of iodides in these types of reactions appears to be attributable to their prior applications to cleavages of methyl esters.[11d,32]

Many other halide salts have found use in decarbalkoxylation procedures.[12a,33,34] Internal alkylative decarboxylations have been accomplished with salts such as NaCl, NaBr, KCl and tetramethylammonium bromide in solvents such as Me_2SO and HMPT.[29] External alkylative decarboxylations have been accomplished with LiCl in HMPT.[29b] The use of tetramethylammonium acetate in decarbalkoxylations in Me_2SO[8c] and HMPT[35] have recently appeared.

Decarbalkoxylations of activated esters with ethanolic sodium ethoxide have been reported by Thorpe,[36] Ingold,[37] and Cope and McElvain.[38] Amines in refluxing xylene[14d,39,40] or toluene[41] have also found use in these types of reactions.

Results and Discussion

Water–Me_2SO Studies. Experiments were performed on a variety of geminal diesters to ascertain the limitations of the decarbalkoxylation process using water in Me_2SO (and in one case DMF). The results are tabulated in Table I.

An examination of the data presented in Table I reveals the following pertinent points: (1) substrates with electron-withdrawing substituents such as diethyl phenylmalonate, diethyl benzylmalonate, and diethyl acetamidomalonate undergo decarbethoxylations fairly readily in H_2O–Me_2SO; (2) *n*-alkyl-substituted diethyl malonates and diethyl isobutylmalonate undergo slow decarbalkoxylations, while dimethyl ethylmalonate proceeds about four times faster than the corresponding diethyl ester; (3) substrates such as diethyl isopropylmalonate and diethyl cyclohexylmalonate show little tendency to decarbethoxylate (substituents adjacent to the carbon bearing the geminal diester groups presumably sterically inhibit water attack at one of the ester carbonyl groups); and (4) diethyl and dimethyl disubstituted malonates undergo practically no decarbalkoxylations when heated in H_2O–Me_2SO.[42]

Data has also been obtained for decarbalkoxylations of β-keto esters in H_2O–Me_2SO and these data are summarized in Table II.

The data in Table II reveal that many β-keto esters which contain an α hydrogen undergo rapid decarbalkoxylations in wet Me_2SO. Other dipolar aprotic solvents such as DMF can also be utilized.[5]

Salt Effect Studies. In those geminal diesters which undergo slow decarbalkoxylations in H_2O–Me_2SO (Table I), the addition of salts such as KCN or NaCl accelerates ester formation.[4,5] To more fully probe into the nature of the accelerating effect of salts, various substrates were studied using a variety of salts and conditions. Individual diesters are tabulated in the following tables.

The experimental data for the decarbalkoxylation of diethyl ethylmalonate are summarized in Table III.

It can be seen from the data in Table III that the addition of 2 equiv of NaCl or 1 or 2 equiv of LiCl dramatically increases the rate of ester formation. The different effect seen for LiCl and NaCl is probably due to the greater solubility of LiCl in Me_2SO in comparison to NaCl (heterogeneous). With this particular malonate ester the reaction also proceeds rapidly in DMF as solvent when 1 or 2 equiv of LiCl are

Table II. Decarbalkoxylations of β-Keto Esters Using Water–Me_2SO

Substrate[a]	Registry no.	Ketone, %[c]
2-Carbalkoxycyclohexanone[b]		87
2-Carbethoxycyclooctanone	4017-56-5	70
2-Carbethoxycyclododecanone	4017-60-1	85
2,5-Dicarbomethoxy-1,4-cyclohexanedione	6289-46-9	60 (dione)
$C_6H_5COCH_2COOCH_2CH_3$	94-02-0	70
$CH_3COCH(CH_3)COOCH_2CH_3$	609-14-3	70[d]
$CH_3COC(CH_3)_2COOCH_2CH_3$	597-04-6	e

[a] Substrate (0.03 mol) and water (0.06 mol) in 25 mL of Me_2SO which was heated for 4 h except in entries 1 and 2 which were heated for 3 h. [b] Thirty-five percent methyl ester and 65% ethyl ester. [c] Quenched with water, extracted with pentane, and isolated. [d] Yield calculated from ^1H NMR of crude product. [e] Only starting material recovered in higher than 90% yield.

Table III. Decarbethoxylations of Diethyl Ethylmalonate

Salt, equiv[a]	Heating period, h	% monoester[b]
None	0.5	2
None[c]	4.5	20
1 LiCl	1	84
2 LiCl	0.5	60
	2.0	92
	4.0	99[d]
2 LiCl[e]	0.5	45
2 NaCl	0.5	40
	2.0	72
	4.5	99[d]
2 KCN	1.5	94[f]
1 LiCl[c]	4.5	70
2 LiCl[c]	4.5	83

[a] Diester and water (0.03 mol each) in 50 mL of Me_2SO (0.6 M in substrate). [b] Aliquot quenched with cold water, saturated with NaCl, extracted with pentane, and analyzed by GLC. [c] As in a, except 50 mL of DMF as solvent. [d] Distilled low-boiling materials from the reaction pot and quenched with water, and the ester separated (about 90% isolated yields). [e] As in a, except 5 equiv of H_2O. [f] Distilled material which showed no starting material (90%).

Table IV. Monosubstituted Malonates with Added Salts

1			Equiv of salt	Heating period, h	% ester[b]
R^1	R^2	R^{3a}			
$(CH_3)_2CHCH_2$	H	CH_3CH_2	None	2.5	13
			2 LiCl	4.0	99[c]
$(CH_3)_2CH$	H	CH_3CH_2	None	2.0	1
			2 LiCl	4.0	96[c]
c-C_6H_{11}	H	CH_3CH_2	None	2.0	1
			2 NaCl	3.0	91
				4.0	99[c]

[a] Diester (0.015 mol) and water (0.015 mol) in 25 mL of Me_2SO. [b] GLC analysis of a pentane extract after quenching an aliquot with water and pentane extraction. [c] Distillation from the reaction mixture and washing with water led to about 90% yields of isolated pure ester.

Table V. Decarbomethoxylations of Dimethyl Diethylmalonate

Equiv of salt	Heating period, h	% monoester
None[a]	4.5	2[b]
2 NaCl[a]	4.5	98[c]
2 LiCl[d]	4.0	99[c,e]
2 LiCl[d]	0.5	90[b]
2 KCN[d]	0.5	99[b]
2 LiCl[f]	4.2	98[b]
1 Li_2CO_3[f]	16	6[b]
2 $LiOAc\cdot 2H_2O$[f]	4.0	6[b]
1 $MgCl_2\cdot 6H_2O$[f]	4.0	30[b]
2 LiF[f]	4.0	1[b]
1 $LiI\cdot H_2O$[f]	4.0	g

[a] Diester and water (0.015 mol each) in 25 mL of Me_2SO. [b] GLC analysis of a quenched aliquot. [c] Distilled from the reaction, water washed, and dried (90% isolated yields). [d] Diester and water (0.03 mol each) in 50 mL of Me_2SO. [e] Li_2CO_3 (35%) was also isolated. On distillation, an 80% yield of ester was obtained. [f] Diester and water (0.03 mol each) in 50 mL of DMF. [g] GLC and ^1H NMR of material collected in a Dean–Stark trap indicated the presence of about 30% CH_3I. A 40% yield of Li_2CO_3 could also be isolated.

present. Lithium chloride is an excellent salt for use in preparative decarbalkoxylations.

The decarbomethoxylation of dimethyl ethylmalonate also proceeds rapidly in water–Me_2SO–LiCl. In 0.5 h, 98% decarbomethoxylation occurs (0.6 M substrate, water, and LiCl), while only 32% monoester forms in 2 h (0.6 M substrate and water).

Other monosubstituted malonate esters which undergo slow decarbethoxylations in H_2O–Me_2SO proceed rapidly and in excellent yields when 2 equiv of LiCl or NaCl are present. Some malonate ester decarbethoxylations of this type are summarized in Table IV.

Since the decarbalkoxylations of the dimethyl and diethyl disubstituted malonates barely proceed on heating in H_2O–Me_2SO, several substrates were studied to optimize the rates and yields of the esters which are produced. Data for dimethyl diethylmalonate using a variety of salts and solvents are listed in Table V.

From the data tabulated in Table V it can be seen that the decarbomethoxylation of this particular diester proceeds readily in H_2O–Me_2SO with NaCl, LiCl, or KCN, and also with LiCl in DMF–H_2O. As the reaction proceeds with LiCl as the salt, Li_2CO_3 precipitates during the reaction and can be isolated from the mixture in 30–40% yields.[43] The remainder of CO_2 is evolved [trapped via $BaCO_3$ with a $Ba(OH)_2$ trap]. Li_2CO_3 exhibits little effect on the rate of decarbomethoxylation in H_2O–DMF (Table V, entry 7). The salt LiF (perhaps present as tight ion pairs) exerts no accelerating effect. Lithium acetate is somewhat effective and $MgCl_2$ is reasonably effective. In the case of $LiI\cdot H_2O$ in DMF, the isolation of CH_3I is mechanistically significant (vide supra).

Comparative data for decarbethoxylations of diethyl diethylmalonate are tabulated in Table VI. Substrates of this type (disubstituted) are the most difficult to decarbethoxylate.

The data in Table VI indicate that the most effective decarbethoxylation combination for this substrate is the H_2O–Me_2SO medium with addition of 2 equiv of KCN or LiCl. Sodium chloride is not as effective as LiCl, since longer heating periods are necessary with the former. Since 0.5 equiv of LiCl in entry 4 leads to 60% reaction after 8 h, Cl^- must be regenerated or a pathway not using Cl^- is competitive. The rate depends on the LiCl concentration, as a fourfold concentration increase doubles the product yield (vide supra for mechanistic data bearing on this point). Once again Li_2CO_3 can be isolated in 35–40% yields in the runs using LiCl, and the remaining CO_2 is lost as the gas.

The decarbethoxylations of diethyl dimethylmalonate and

Table VI. Decarbethoxylations of Diethyl Diethylmalonate

Equiv of salt^{a}	% monoester
None	1^{b}
2 LiCl	80^{c}
2 LiCl	98^{d}
0.5 LiCl	40^{e}
2 LiCl^{f}	23^{b}
2 NaCl	$30^{b,g}$
2KCN	$43^{b,h}$

[a] Substrate and water (0.03 mol each) in 50 mL of Me_2SO. Entries 2, 4, 5, and 6 were heated for 4 h; entry 1, 2 h; entry 3, 6 h; and entry 7, 1 h. [b] GLC analysis of a water-quenched aliquot and extracted into pentane. [c] Distillation of the ester from the reaction followed by addition of water and separation of the ester layer. An 85% yield of monoester was obtained which contained only a trace of starting material. A 35% yield of Li_2CO_3 was isolated by filtration of the residue after distillation. [d] Isolated yield after distillation and washing with water. A 30% yield of Li_2CO_3 was isolated. [e] After 8 h total heating, about 60% monoester. [f] As in *a*, except 50 mL of DMF. [g] After 22 h a quenched aliquot showed 85% monoester. This reaction mixture is homogeneous. [h] After 5-h total heating, no starting material is present.

Table VII. Decarbethoxylations of Diethyl Dimethylmalonate

Equiv of salt	% monoester
None^{a}	1^{b}; 3 (21 h)
1 Na_2SO_4^{a}	3^{b}
1 HOAc^{a}	$1^{b,c}$
1 NaOAc^{a}	60^{b}
1.5 $LiOAc\cdot 2H_2O$^{a}	60^{b}
1 LiCl^{d}	$70^{b,e}$
2 LiCl^{d}	97^{f}
1 $KF\cdot 2H_2O$^{d}	18^{b}; 56 (20 h)
0.2 $Na_3PO_4\cdot 12H_2O$^{g}	30^{b}; 75 (22 h)
1 KI^{a}	22^{b}; 50 (20 h)
1 KBr^{a}	40^{b}; 67 (20 h)
1 KCl^{a}	$40^{b,h}$; 72 (20 h)
1 NaCl^{a}	$40^{b,h}$; 70 (20 h)
1 KCN^{a}	$98^{b,e}$

[a] Diester (0.015 mol) and H_2O (0.03 mol) in 25 mL of Me_2SO. All reactions were run for 4 h except entry 1 (2 h) and entry 7 (5 h). [b] GLC analysis of a quenched aliquot. [c] Also paraformaldehyde from Me_2SO decomposition. [d] As in *a*, except 0.015 mol of H_2O. [e] Eighty percent yields of ester on distillation (99% purity). [f] Ninety percent yield on distillation. [g] No water added. [h] Heterogeneous at start of reaction.

Table VIII. Decarbethoxylations of Diethyl 1,1-Cyclobutanedicarboxylate

Equiv of salt	% monoester
0.5 $LiOAc\cdot 2H_2O$^{a}	80^{b}; 85 (6.5 h)
1 $LiI\cdot 2H_2O$^{a}	$93^{b,c}$
2 LiF^{d}	1^{b}
2 LiBr^{d}	$92^{b,e}$
2 NaCl^{d}	60^{b}
2 LiCl^{d}	$99^{b,f}$

[a] Diester (0.015 mol) and Me_2SO (25 mL) heated for 3 h. [b] GLC analysis of an aqueous quench. [c] Distillation and workup gave pure ester (80%). [d] Diester (0.015 mol) and water (0.03 mol) in 25 mL of Me_2SO heated for 3 h. [e] Distillation and workup gave ester (90% yield, 98% purity). [f] Distillation and workup gave pure ester (85%).

diethyl 1,1-cyclobutanedicarboxylate were also studied using a variety of salts and conditions. The pertinent experimental findings for the former substrate are listed in Table VII.

The data for the cyclobutyl diester is summarized in Table VIII.

As can be noted from the data in Tables VII and VIII, the decarbethoxylations of these substrates can be accomplished by a wide variety of salts. Only Na_2SO_4 (insoluble in the medium) and LiF fail to accelerate the reaction. Acetates (lithium and sodium) are effective but the reaction is not catalyzed by acetic acid. Lithium halides are more effective than the corresponding potassium or sodium halides (except for LiF where KF appears to work more effectively). For the data tabulated in Table VIII, the best decarbethoxylating agent appears to be LiCl, with LiI or LiBr somewhat less effective.

The decarbethoxylation of diethyl dimethylmalonate by $Na_3PO_4\cdot 12H_2O$ is of interest. It appears that the effectiveness of this salt may be due to the high pH of its aqueous solutions and perhaps a catalysis of the decarbethoxylation by a hydrolysis–decarboxylation pathway.

Several other substrates were also investigated for preparative purposes using LiCl in Me_2SO and the results are listed in Table IX.

Mechanism Studies: (a) H_2O and D_2O Isotope Effects in the Presence and Absence of Salts. The fact that certain β-keto esters and geminal diesters which possess electron-withdrawing groups on the α carbon undergo decarbalkoxylations in H_2O–Me_2SO indicates that a neutral water hydrolysis is occurring. The deuterium isotope effects were studied by comparison of the rates of decarbalkoxylations in H_2O–Me_2SO and D_2O–Me_2SO in the presence and absence of salts. The data are summarized in Table X.

The data in Table X reveal a k_{H_2O}/k_{D_2O} of 2.7 for diethyl phenylmalonate and 2.2 for dimethyl ethylmalonate (no added salts). However, in the presence of the salts LiCl or KCN the k_{H_2O}/k_{D_2O} values are close to unity. In the absence of salts it would appear that the mechanism is of a water-catalyzed nucleophilic attack by water (or a kinetic equivalent) at the ester carbonyl ($B_{AC}2$) similar to the mechanism proposed for neutral (water-catalyzed) hydrolysis of other acyl activated esters.[44] The salts do not appear to be functioning as general base catalysts.[45] In those substrates which do not react with H_2O–Me_2SO, steric factors may prevent water attack at the ester carbonyl.

The absence of a significant isotope effect in the presence of LiCl or KCN is consistent with a nucleophilic catalysis mechanism ($B_{AC}2$ route via a tetrahedral intermediate) involving the nucleophile, or a $B_{AL}2$ route involving the nucleophile.[46,47,48] Of course the total mechanistic route could proceed via the simultaneous occurrence of both routes.

The decarbalkoxylation procedure in D_2O–Me_2SO is a useful preparative route to α-deuterated esters.[49]

(b) CH_3CH_2CN: Alcohol Ratios Using KCN–H_2O–Me_2SO and Various Diesters. Since the most effective decarbalkoxylation reagent system studied by us is the KCN–H_2O–Me_2SO combination, it was of interest to determine the nitrile/alcohol ratios for various substrate structures from the mechanistic point of view. The experimental data for several malonate esters are tabulated in Table XI.

It might also be noted at this point that K_2CO_3 could be isolated in ca. 40% yields from several of the runs listed in Table XI and CO_2 was also evolved as evidenced by trapping as $BaCO_3$. The data presented in Table XI clearly indicate that the mechanistic pathway is dependent on substrate structure. The formation of CH_3CN (from the disubstituted dimethyl ester) and CH_3CH_2CN (from the diethyl esters) can only arise from a $B_{AL}2$ cleavage as depicted in Scheme I.[47]

A concerted decarbalkoxylation to directly yield carbanion **13** must also be considered. It would appear that this process

Table IX. Preparative Decarbethoxylations Using LiCl-Water-Me$_2$SO

1			Registry	
R^1	R^2	R^3	no.	% monoester
CH$_3$(CH$_2$)$_2$CH$_2$	CH$_3$(CH$_2$)$_2$CH$_2$	CH$_3$CH$_2$	596-75-8	90^b
CH$_3$CH$_2$	C$_6$H$_5$	CH$_3$CH$_2$	76-67-5	80^{b,c}
CH$_3$(CH$_2$)$_2$CH$_2$	H	CH$_3$CH$_2$	133-08-4	75^d; 95 (3 h)^b

[a]Substrate and water (0.03 mol each) and LiCl (0.06 mol) in 50 mL of Me$_2$SO. Entries 1 and 2 were isolated by a water quench and extraction with pentane. The heating times were: entry 1, 6 h; entry 2, 4 h; and entry 3, 0.5 h. [b] Isolated yields with less than 1% starting material. [c] A 60% yield of monoester was found by GLC of a quenched aliquot if 50 mL of DMF was used as the solvent. [d] GLC analysis of a quenched aliquot.

Table X. Decarbalkoxylations in Me$_2$SO with D$_2$O or H$_2$O

1			k_{H_2O}/k_{D_2O}^{b}		
R^1	R^2	R^{3a}	1 equiv of LiCl	1 equiv of KCN	No salt
C$_6$H$_5$	H	CH$_3$CH$_2$	1.09	1.10	2.7
CH$_3$CH$_2$	H	CH$_3$CH$_2$	0.96	1.08	
CH$_3$CH$_2$	H	CH$_3$			2.2
CH$_3$CH$_2$	CH$_3$CH$_2$	CH$_3$CH$_2$	1.0	1.0	No rxn

[a] Three millimole each of malonate ester, H$_2$O or D$_2$O, and salt (if any) in 10 mL of dry Me$_2$SO. [b]Average values for duplicate or triplicate determinations.

would be energetically favorable for those substrates with electron-withdrawing groups that could stabilize the developing carbanionic center. The previous study of Asoaka et al.[29b] indicates that the intermediate **12** (R^1 = R^2 = CH$_3$) can be trapped if the reaction is performed in HMPT with LiCl in the presence of benzyl bromide to yield the monobenzyl diester **14** (30%). An 18% yield of the dibenzyl ester was also isolated. In other cases, the carbanion **13** can be trapped in the presence of benzyl bromide. The formation of acylcyclopropanes by treatment of α-acyl-γ-butyrolactones with various nucleophiles are examples of $B_{AL}2$ cleavages followed by decarboxylations and intramolecular cyclizations of the carbanions which are formed.[29] The conversion of **7a** to **7b** leads to intermediate **15** which is energetically difficult to decarboxylate, and it undergoes a further conversion to the diacid.[10]

The pathway outlined in Scheme I appears to be the dominant mechanistic route for disubstituted malonate esters. The higher nitrile/alcohol ratios seen for the diethyl- vs. the dimethyl-substituted diethylmalonate points to a steric hindrance to attack of the nucleophile at one of the ester carbonyl groups. However, in all cases (except for the dimethyl ester listed) the isolation of ethanol indicates that the $B_{AC}2$ mechanism is competitive. Scheme II presents the mechanism for this route.

Scheme I

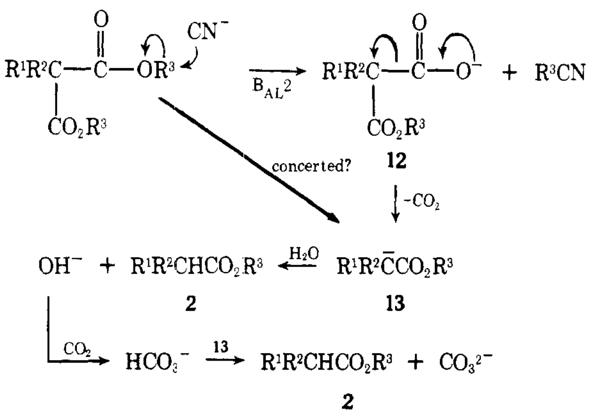
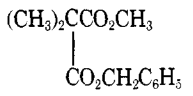


Table XI. Nitrile/Alcohol Ratios from Decarbalkoxylations with NaCN

1			CH$_3$CH$_2$CN/
R^1	R^2	R^3	Alcohol^a
CH$_3$CH$_2$	H	CH$_3$CH$_2$^{b}	0.4^c
CH$_3$	H	CH$_3$CH$_2$^{d}	0.5
CH$_3$	CH$_3$	CH$_3$CH$_2$^{d}	1.4
CH$_3$CH$_2$	CH$_3$CH$_2$	CH$_3$CH$_2$^{b}	4.3
CH$_3$CH$_2$	CH$_3$CH$_2$	CH$_3$^{b}	c,e

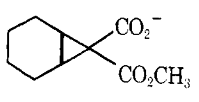
[a]GLC analysis of low-boiling material distilled from the reaction after the specified heating period. [b] Substrate (0.03 mol), KCN (0.06 mol), and H$_2$O (0.03 mol) in 50 mL of Me$_2$SO. Heating periods for each tabular entry: 1, 1.5 h; 2 and 3, 8 h; 4, 5 h; and 6, 0.5 h. [c] No starting material was detectable. [d] Substrate (0.03 mol), KCN (0.045 mol), and H$_2$O (0.03 mol) in 50 mL of Me$_2$SO. [e] Only CH$_3$CN was detectable. No CH$_3$OH could be detected by GLC.

Intermediates such as ethyl cyanoformate would be expected to undergo rapid hydrolysis in H$_2$O-Me$_2$SO.[50] It might be pointed out that ester exchanges appear to be catalyzed by KCN in alcohols.[51]



$$\underset{CO_2CH_2C_6H_5}{(CH_3)_2CCO_2CH_3}$$

14



15

Most simple esters hydrolyze with acyl-oxygen cleavages ($B_{AC}2$) via presumed tetrahedral intermediates. However, in hindered esters the $B_{AL}2$ route can eclipse the usual $B_{AC}2$ pathway.[52] In symmetrical transesterifications such as the treatment of methyl benzoate with sodium methoxide in methanol, good yields of dimethyl ether can be obtained.[52c] Under certain conditions the ElcB mechanism via a ketene intermediate must be considered for those substrates with at least one α hydrogen.[53] Variations in the alkoxyl group of the

Scheme II

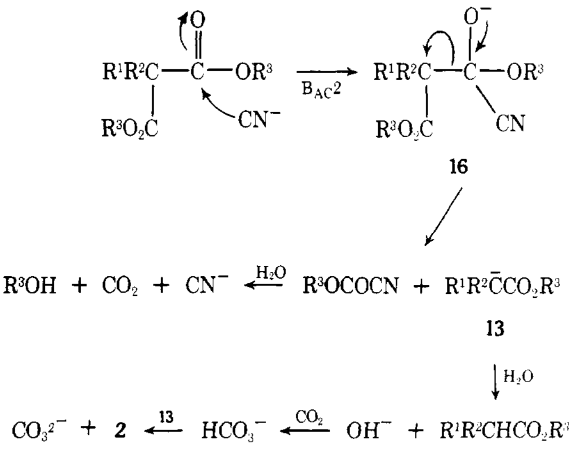


Table XII. LiCl Concentration Variation Study

Equiv of LiCl[a]	k_{rel}[b]
1	1
2	1.6
3	2.2
4	2.6
5	3.3
6	3.6
7	3.7
8	4.0
9	4.1
10	4.3

[a] Three millimole each of diethyl diethylmalonate, water, and LiCl (or multiple thereof) in 10 mL of dry Me_2SO. [b] $k_{rel} = k_{conc}/k_{1equiv}$ (see Experimental Section).

ester have less effect on the $B_{AC}2$ route than the $B_{AL}2$ route.[47] The nucleophilic species must also play a role in the mechanistic pathway.[54]

The observation that methanol could not be detected in the decarbomethoxylation of dimethyl diethylmalonate by $KCN-H_2O-Me_2SO$ indicates that this substrate reacts via the $B_{AL}2$ pathway outlined in Scheme I. The other diesters listed in Table XI exhibit dual pathways in which disubstituted malonates react predominantly via the $B_{AL}2$ route, while monosubstituted malonates react predominantly via the $B_{AC}2$ route.[55]

(c) LiCl Concentration Variations. In order to assess the kinetic effect of the nucleophile, the decarbethoxylation of diethyl diethylmalonate was studied using $LiCl-H_2O-Me_2SO$. This substrate was chosen since it was anticipated that the dominant route would be of the $B_{AL}2$ type. The LiCl concentrations were varied over a range of 1 to 10 equiv per equivalent of diester, and the data are summarized in Table XII.

It can be seen from the data that the rate is dependent on the concentration of LiCl but does not exhibit a first-order dependency of LiCl concentration. The largest rate increase is seen up to the addition of 5 equiv of LiCl, and further concentration increase lead to much smaller enhancements of the decarbethoxylation rate. It is probable that ion pairing or association is playing a role in controlling the apparent nucleophilicity and observed rates.[56]

(d) Relative Rates with Various Salts. Relative rates of ester decarbethoxylation can give information on whether the $B_{AC}2$ mechanism is operative (alkoxyl group variations have small effects) or whether the $B_{AL}2$ route is operative (comparison to S_N2 routes).[47a] Competition experiments were performed on several methyl and ethyl diesters and the relative rate data are tabulated in Table XIII.

From the data presented in Table XIII, it is reasonable to conclude that monoalkyl-substituted malonates on treatment with $LiCl-H_2O-Me_2SO$ are undergoing cleavages via a dominant $B_{AC}2$ attack of Cl^- on one of the ester carbonyl groups ($k_{CH_3}/k_{CH_3CH_2} = 4$).[47a,57] The relative rate of 30.5 found for the $KCN-H_2O-Me_2SO$ reaction on diethyl ethylmalonate appears to be inconsistent with the nitrile/alcohol ratio data in Table XI and is anomalous. Perhaps with KCN a more dominant role for the $B_{AL}2$ route is being exerted for the dimethyl ester and an enhanced value of the relative rate ratio is seen. The relative rates of 17.1 (LiCl) and 35.1 (KCN) for the decarbalkoxylations of the diethyl-substituted malonates are consistent with a dominant pathway for $B_{AL}2$ cleavages.[58,59]

(e) Salt Effects. It was of interest to examine a series of salts with a single diester under comparable reaction conditions to ascertain the best salt to be utilized for preparative purposes. The relative rates for various salts were studied in H_2O-Me_2SO using diethyl diethylmalonate (perhaps in each case undergoing a dominant $B_{AL}2$ cleavage). The relative rate data are tabulated in Table XIV.

Although the rate differences listed in Table XIV are small and the relative nucleophilicities can vary with solvation, nature of the cation, and nature of the transition state,[56d,60] it is tempting to attempt to rationalize the experimental data using HSAB principles[61] and symbiosis.[8c,61,62]

If one assumes that all nucleophiles are cleaving this malonate ester predominantly via a $B_{AL}2$ pathway (Scheme I), the order of rates with the cation Li^+ (hard) constant is $Cl^- > Br^- > I^-$, which is the order of decreasing hardness.[63] However, the position of OAc^- (hard) is out of order, as it might have been expected that OAc^- being harder than Cl^- would exert a larger symbiotic effect (in addition a symmetrical-like transition state with respect to entering and leaving group[8c]) than Cl^-. The relative position of CN^- (soft, and used as the K^+ salt which could alter the nucleophilicity somewhat) would be higher than Cl^- and thus constitutes an anomaly. Steric effects could play a role in hindering approach of a multiatomic anion such as OAc^- and comparison to halide anions may be unjustified. The question of loose and tight transitions states along with symbiotic effects might well have to be considered.[56d]

It can be seen from the data in Table XIV that little rate differences are found in the comparison of LiCl vs. $(CH_3)_4NCl$ and LiOAc and $(CH_3)_4NOAc$. The unreactivity of CuCl (soluble in Me_2SO) might simply be due to ion pairing or solution as Cu_2Cl_2 with reduced nucleophilicity of Cl^-. It would appear that LiCl should be used in preference to LiI in dipolar aprotic solvents to effect more rapid displacements.

Table XIII. Competition Experiments Using Various Malonate Esters

Ester pair[a]	Salt	$k_{CH_3}/k_{CH_3CH_2}$[b]
$CH_3CH_2CH(CO_2CH_3)_2$ $CH_3CH_2CH(CO_2CH_2CH_3)_2$	LiCl	3.9 ± 0.1[c]
$CH_3CH_2CH(CO_2CH_3)_2$ $CH_3CH_2CH(CO_2CH_2CH_3)_2$	KCN	30.5[d]
$(CH_3CH_3)_2C(CO_2CH_3)_2$ $(CH_3CH_2)_2C(CO_2CH_2CH_3)_2$	LiCl	17.1 ± 0.1[c]
$(CH_3CH_2)_2C(CO_2CH_3)_2$ $(CH_3CH_2)_2C(CO_2CH_2CH_3)_2$	KCN	35.1[d]

[a] Three millimole each of diesters, salt, and water in 10 mL of dry Me_2SO with refluxing for periods of 15, 6, 45, and 45 min, respectively. [b] Calculated from: $k_{CH_3}/k_{CH_3CH_2} = \log (xCH_3/x_0CH_3)/\log (xCH_3CH_2/x_0CH_3CH_2)$, where x = % unreacted diester (determined by GLC) and $x_0 = 100$ for the diesters. See, for example: P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 5430 (1956). [c] Average values for two runs and standard deviations. [d] Single determination.

Table XIV. Relative Rates of Salts in Decarbethoxylations

Salt[a]	k_{salt}/k_{LiCl}	k_{salt}/k_{LiI}
LiCl	1	3.1
$(CH_3)_4NCl$	0.75	2.3
CuCl[b]		
LiI	0.32	1
$(CH_3)_4NI$[c]		
LiBr	0.65	2.0
LiOAc	0.56	1.8
$(CH_3)_4NOAc$	0.34	1.0

[a] Performed in a common oil bath with one run containing 1 equiv of LiCl and the other 1 equiv of the listed salt. Substrate in all cases was diethyl diethylmalonate. Relative rates were determined as previously reported (see Table XIII and Experimental Section). [b] Soluble but no reaction after heating for 2 h. [c] Several side products and much decomposition. Not analyzed further.

Conclusions

Certain activated esters have been shown to undergo rapid decarbalkoxylations in wet Me_2SO while other substrates require the presence of salts. The data indicate that LiCl–H_2O–Me_2SO is an excellent salt for preparative decarbalkoxylations. The decarbalkoxylation mechanism is a blend of $B_{AL}2$ and $B_{AC}2$ pathways which are dependent on substrate structure and nucleophile type. A variety of salts can be effectively used in this process.

Experimental Section

All GLC analyses were performed using a DC-200 Chromosorb column with helium as the carrier gas and are corrected for any structural response change. The analyses were performed using a Gow-Mac 69-100 or an Aerograph A-90P chromatograph.

Materials. Me_2SO was kindly supplied by Crown-Zellerbach (Camas, Washington) or was purchased from Fisher Scientific Co. (certified grade) or Mallinckrodt (AR grade). The Me_2SO was dried by distillation from CaH_2 under reduced pressure and it was stored over molecular sieves. All salts (reagent grade) were used as received except for preliminary drying in a few cases. All malonate esters and most β-keto esters were commercially available from Aldrich, Eastman Organics, Pfaltz and Bauer, or ICN Life Sciences Group (K & K). The β-keto esters, 2-carbethoxycyclooctanone, and 2-carbethoxycyclododecanone were prepared according to the procedure described by Krapcho et al.[64] All ketones and esters which were prepared have been previously reported in the literature and compared favorably with the physical properties previously recorded and exhibited IR and NMR spectra consistent with their structures.

(A) Typical Preparative Runs. (a) 2, R^1 = H, R^2 = $(CH_3)_2CH$, R^3 = CH_3CH_2. In a 100-mL rb flask equipped with a magnetic spin bar and a reflux condenser are placed diethyl isopropylmalonate (6.1 g, 0.03 mol), Me_2SO (50 mL, Mallinckrodt AR, as received), water (0.5 mL), and LiCl (2.5 g, 0.06 mol). The solution is heated to refluxing using a mantle with stirring for 4 h. During this period, the mixture becomes turbid and pale yellow. A quenched aliquot and GLC analysis indicated only about 4% malonate ester. The mixture was distilled up to 185 °C to obtain about 10 g of distillate. Cold water was added to this distillate and the ester layer was removed by a pipet to yield 4.0 g of crude ester (GLC analysis showed less than 1% starting diester and trace amounts of low-boiling materials). Distillation (bp 129–132 °C, lit. bp 131–133 °C[65]) yielded 3.5 g of ester (90%).

(b) 2, R^1 = R^2 = R^3 = CH_3CH_2. Diethyl diethylmalonate (6.4 g, 0.03 mol), Me_2SO (50 mL, Fisher certified, as received), water (0.5 g, 0.03 mol), and LiCl (2.5 g, 0.06 mol) were placed in a 100-mL rb flask fitted with a gas-exit tube leading into a $Ba(OH)_2$ solution, a magnetic spin bar, and a heating mantle. The solution was heated at refluxing for a total period of 6 h. During this period, a turbidity appears and the mixture becomes yellow and the color then disappears. The mixture is then distilled up to 185 °C to yield about 7 g of distillate. The distillate is washed with ice water and the ester layer collected (4.1 g, 95%). GLC shows less than 1% starting diester and traces of short retention time materials (bp 148–151 °C, lit. bp 151 °C[65]). Filtration of the residue after the distillation of the ester from the reaction pot gave Li_2CO_3 (0.7 g, 30% of the CO_2 trapped as this salt) which was identified by an IR comparison to an authentic sample. Some CO_2 was also evolved as evidenced by much $BaCO_3$ formation in the $Ba(OH)_2$ during the course of the reaction.

Using procedures as in a and b above, ethyl cyclobutanecarboxylate, methyl 2-ethylbutyrate, ethyl cyclohexylacetate, ethyl isobutyrate, ethyl 4-methylvalerate, and ethyl hexanoate can be prepared.

(c) Ethyl 2-Phenylpropionate (2, R^1 = C_6H_5, R^2 = H, R^3 = CH_3CH_2). Diethyl phenylethylmalonate (7.9 g, 0.03 mol, Eastman practical grade), Me_2SO (50 mL, Mallinckrodt, AR), water (0.5 g, 0.03 mol), and LiCl (2.5 g, 0.06 mol) were placed in a 100-mL rb flask equipped with a magnetic stirrer and fitted with a condenser. The mixture was heated at refluxing for 4 h. At this point, a brown color had developed and suspended solid (Li_2CO_3) was evident. The mixture was poured into 200 mL of ice water and the aqueous layer was saturated with NaCl. The ester was extracted with 4 × 30 mL of pentane, and the yellow pentane extract was dried over Na_2SO_4 and concentrated to yield 4.6 g (80%) of ester which on GLC contained less than 0.5% starting material. Distillation under reduced pressure gave a bp of 120–125 °C/25 mm (lit. bp 123–124 °C/27 mm[65]). Ethyl hydrocinnamate and ethyl 2-*n*-butylhexanoate were isolated using a similar workup.

(B) Analytical Runs. All tabular data were obtained by quenching the reaction at a specified interval in cold water (usually a 2-mL aliquot), saturating the water with NaCl, extraction with pentane, and GLC analysis of the pentane extract.

(C) D_2O and H_2O Runs. Two runs were performed simultaneously in the same oil bath, and both reactions were quenched with water, extracted with pentane, and analyzed by GLC. In the water run, 3

Table XV. Decarbalkoxylations Using H_2O or D_2O in Me_2SO

	1				Rxn time,	% diester[c]	% diester[c]	
R^1	R^2	R^3[a]	Salt	Temp[b]	h	in H_2O	in D_2O	k_{H_2O}/k_{D_2O}[d]
C_6H_5	H	CH_3CH_2	None	177	0.75	20.9	51.2	2.4
			None	177	0.50	30.2	67.1	3.0
			LiCl	182	0.50	13.6	15.1	1.06
			LiCl	157	0.25	75.7	77.8	1.11
			KCN	157	0.25	17.9	20.8	1.10
CH_3CH_2	H	CH_3	None	185	4.0	39.6	66.5	2.27
			None	185	4.0	50.7	72.7	2.13
CH_3CH_2	H	CH_3CH_2	LiCl	175	0.50	66.5	66.6	1.00
			LiCl	180	0.50	67.2	67.1	0.99
			KCN	175	0.30	43.8	46.7	1.08
CH_3CH_2	CH_3CH_2	CH_3CH_2	LiCl	192	2.0	55.8	55.3	0.98
			LiCl	192	1.5	62.9	63.7	1.03
			KCN	192	2.0	16.7	19.2	1.08
			KCN	189	0.75	42.2	42.8	1.02

[a] In most cases, the pairs were run twice, sometimes for different periods of time. [b] Oil bath temperature, ±2 °C. [c] Average values for three GLC analyses with excellent agreement for each analysis. [d] k_{H_2O}/k_{D_2O} = log [% diester (H_2O)/100]/log [% diester (D_2O)/100].

Table XVI. Competition Experiments

Diester pairs, 1			Rxn[a]		% dimethyl[b]	% diethyl[b]	
R^1	R^2	R^3	time	Salt	remaining	remaining	$k_{CH_3}/k_{CH_3CH_2}$
CH_3CH_2	H	CH_3CH_2	0.3	LiCl	27.9	73.0	4.06
CH_3CH_2	H	CH_3	0.25	LiCl	18.6	64.5	3.84
			0.08	KCN	23.8	95.4	30.5
CH_3CH_2	CH_3CH_2	CH_3CH_2	0.75	LiCl	20.5	91.1	17.0
CH_3CH_2	CH_3CH_2	CH_3	0.50	LiCl	23.0	91.8	17.2
			0.75	KCN	7.0	92.7	35.1

[a] Timing starts with CO_2 evolution, in hours. [b] Average values for triplicate GLC analysis (agreements in all cases better than 2%).

Table XVII. LiCl Concentration Studies Using Diethyl Diethylmalonate

Rxn time,[a] h	% diester[b] Stdn, 1 equiv of LiCl	% diester[b] xLiCl	Ratio xLiCl/LiCl	k_{rel}[c]	Av k_{rel}
1.5	58.2	42.7	2	1.57	1.56
2.0	51.9	36.2	2	1.55	
1.5	61.0	32.7	3	2.26	2.21
2.0	54.8	27.4	3	2.15	
1.5	59.6	24.3	4	2.73	2.67
1.0	70.0	39.5	4	2.60	
0.9	75.9	40.2	5	3.30	3.30
1.0	71.7	33.2	5	3.31	
1.0	70.4	28.3	6	3.60	3.59
1.06	65.5	22.0	6	3.58	
1.0	71.2	28.6	7	3.69	3.66
0.75	78.1	40.9	7	3.62	
0.75	83.4	49.3	8	3.90	4.02
0.80	77.8	35.4	8	4.14	
0.75	77.9	35.1	9	4.16	4.14
0.80	78.9	37.7	9	4.12	
0.75	78.9	34.7	10	4.47	4.38
1.0	70.5	22.4	10	4.28	

[a] Heated in an oil bath at 190 ± 2 °C. [b] Average of duplicate GLC analysis with a precision of better than ±0.5%. [c] k_{rel} = log [% diester (xLiCl)/100]/log [% diester (1 equiv of LiCl)/100].

Table XVIII. Decarbethoxylations of Diethyl Diethylmalonate

Reaction time, h	Salt	% diester[a] in LiCl run	% diester[a] in salt run	k_{salt}/k_{LiCl}[b]	Av k_{rel}
1.5	$(CH_3)_4NCl$	78.7	82.3	0.77	0.74
2.0		69.9	77.4	0.71	
1.5	$LiI \cdot H_2O$	65.6	87.1	0.33	0.32
2.0		58.8	84.5	0.32	
1.5	LiBr	66.0	77.6	0.64	0.66
2.0		54.9	66.7	0.68	
1.5	LiOAc	63.5	76.5	0.59	0.57
2.0		58.3	74.3	0.55	
2.0	$(CH_3)_4NOAc$	57.7	83.2	0.33	0.34
2.5		52.9	80.7	0.34	

[a] Average values of duplicate GLC analysis. [b] k_{salt}/k_{LiCl} = log [% diester (salt)/100]/log [% diester (LiCl)/100].

mmol each of diester, H_2O, and salt (if present) was dissolved in Me_2SO (10 mL, dry) in a 25-mL rb flask equipped with a condenser and a magnetic stirrer. The D_2O run was prepared in an identical fashion, except that D_2O was used. Both runs were immersed in the oil bath and worked up in an identical fashion. A summary of the experimental data is listed in Table XV.

(D) Competition Experiments. Three millimoles of each diester, H_2O, and salt was dissolved in Me_2SO (10 mL, Mallinckrodt AR, as received) in a 25-mL rb flask equipped with a magnetic spin bar and a condenser. The mixture was then heated to refluxing for the specified period, quenched, and analyzed by GLC. The experimental results are listed in Table XVI.

(E) LiCl Concentration Effect Study. Duplicate runs were performed simultaneously in the same oil bath. In the standard comparison run diethyl diethylmalonate (3 mmol), LiCl (3 mmol), and H_2O (3 mmol) were dissolved in 10 mL of Me_2SO (dry). In the run to assess the salt effect the only variation was the amount of LiCl added. Both runs were heated for identical periods and analyzed as previously. The data are tabulated in Table XVII.

(F) Salt Effects. In a 25-mL rb flask was placed diethyl diethylmalonate (3 mmol), LiCl (3 mmol), H_2O (3 mmol), and 10 mL of Me_2SO (dry). Another run is prepared in similar fashion, except containing another salt (3 mmol). Both runs are simultaneously immersed in an oil bath preheated to 190 ± 2 °C. After the specified reaction period, the reactions are quenched in water and analyzed by VPC. These data are summarized in Table XVIII.

Acknowledgment. The financial support of the Humphrey Chemical Co., North Haven, Conn., is gratefully acknowledged.

Registry No.—Me_2SO, 67-68-5; 2-carbomethoxycyclohexanone, 41302-34-5; 2-carbethoxycyclohexanone, 01655-07-8; diethyl 1,1-cyclobutanedicarboxylate, 3779-29-1.

References and Notes

(1) Presented in part at the 172nd American Chemical Society National Meeting, San Francisco, Calif., Aug. 30–Sept. 3, 1976, ORGN Abstract 196.

(2) National Science Foundation Undergraduate Research Participant, Summer 1975.

(3) (a) A. P. Krapcho, G. A. Glynn, and B. J. Grenon, *Tetrahedron Lett.*, 215 (1967). (b) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis", Vol. 2, Wiley-Interscience, New York, N.Y., p 381 (1969).

(4) A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 957 (1973).

(5) (a) A. P. Krapcho, E. G. E. Jahngen, Jr., A. J. Lovey, and F. W. Short, *Tetrahedron Lett.*, 1091 (1974). (b) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis", Vol. 5, Wiley-Interscience, New York, N.Y., p 265 (1975).

(6) C. L. Liotta and F. L. Cook, *Tetrahedron Lett.*, 1095 (1974). It is stated in this paper that "sodium chloride appears to be an unnecessary reagent".

(7) A. P. Krapcho and B. P. Mundy, *Tetrahedron*, **26**, 5437 (1970).

(8) (a) J. Harley-Mason and Atta-ur-Rahman, *Chem. Ind.* (*London*), 1845 (1968). (b) W. S. Johnson, C. A. Harbert, and R. D. Stipanovic, *J. Am. Chem. Soc.*, **90**, 5279 (1968). (c) W. S. Johnson, C. A. Harbert, B. E. Ratcliffe, and R. D. Stipanovic, *ibid.*, **98**, 6188 (1976). (d) F. Texier and R. Carrie, *Bull. Soc. Chim. Fr.*, 258 (1972). (e) E. J. Corey and H. A. Kirst, *J. Am. Chem. Soc.*, **94**, 667 (1972). (f) E. E. van Tamelen and R. J. Anderson, *ibid.*, **94**, 8225 (1972). (g) E. E. van Tamelen, M. P. Seiler, and W. Wierenga, *ibid.*, **94**, 8229 (1972). (h) F. Collonges and G. Descotes, *Tetrahedron Lett.*, 1117 (1973). (i) R. V. Venkateswaran, I. Gupta, and P. K. Ghoshal, *Indian J. Chem., Sect. B*, **14**, 243 (1976). (j) W. Kirmse, J. Knist, and H.-J. Ratajczak, *Chem. Ber.*, **109**, 2296 (1976).

(9) L. J. Dolby and H. Biere, *J. Org. Chem.*, **35**, 3843 (1970).

(10) B. W. Peace and D. S. Wulfman, *Synthesis*, 137 (1973).

(11) (a) B. M. Trost and T. J. Dietsche, *J. Am. Chem. Soc.*, **95**, 8200 (1973). (b) B. M. Trost, T. J. Dietsche, and T. J. Fullerton, *J. Org. Chem.*, **39**, 737 (1974). (c) B. M. Trost and L. Weber, *ibid.*, **40**, 3617 (1975). (d) J. E. McMurry and G. B. Wong, *Synth. Commun.*, **2**, 389 (1972).

(12) (a) P. Müller and B. Siegfried, *Tetrahedron Lett.*, 3565 (1973). (b) P. Müller and B. Siegfried, *Helv. Chim. Acta*, **57**, 987 (1974). (c) A. Greene and P. Crabbé, *Tetrahedron Lett.*, 2215 (1975).

(13) (a) O. P. Vig, S. S. Bari, O. P. Sood, and S. D. Sharma, *Indian J. Chem., Sect. B*, **14**, 438 (1976). (b) J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron Lett.*, 4035 (1975).

(14) (a) P. Goswani, R. V. Venkateswaran, and P. C. Dutta, *Indian J. Chem., Sect. B*, **14**, 299 (1976). (b) S. Torii, H. Tanaka, and T. Mandai, *J. Org. Chem.*, **40**, 2221 (1975). (c) P. M. McCurry and K. Abe, *Tetrahedron Lett.*, 1387 (1974). (d) B. S. Huang, E. J. Parish, and D. H. Miles, *J. Org. Chem.*, **39**, 2647 (1974). Certain substrates would probably decarbalkoxylate with H_2O–Me_2SO without added NaCl.

(15) (a) A. Bernhard, *Justus Liebigs Ann. Chem.*, **282**, 153 (1894). (b) D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1286 (1944). These authors claim that this reaction proceeds in a poor yield, but they also report the addition of a small amount of sulfuric acid which might have effected the further decarbethoxylation of the initially formed β-keto ester to acetophenone.

(16) J. B. Paine III, W. B. Kirshner, D. W. Moskowitz, and D. Dolphin, *J. Org. Chem.*, **41**, 3857 (1976), and references cited therein. The ethyl propionylacetate is contaminated with about 20% diethyl malonate (from acyl cleavage).

(17) H. Meerwein, *Justus Liebigs Ann. Chem.*, **398**, 242 (1913), reports that substrates such as 2-carbomethoxycyclopentanone and ethyl benzoylacetate yield ketones on treatment with water under these conditions. It was also reported that diethyl phenylmalonate on heating with water in a bomb at 250 °C undergoes a decarbethoxylation to yield ethyl phenylacetate, but this ester is partially hydrolyzed under the rigorous reaction conditions.

(18) H. Meerwein and W. Schürmann, *Justus Liebigs Ann. Chem.*, **398**, 196 (1913).

(19) (a) A. T. Nielsen and W. R. Carpenter, *Org. Synth.*, **5**, 288 (1973). (b) H. Musso and D. Döpp, *Chem. Ber.*, **97**, 1147 (1964).

(20) J. R. Vincent, A. F. Thompson, Jr., and L. I. Smith, *J. Org. Chem.*, **3**, 603 (1939). A few pieces of glass were added to the water.

(21) A. E. Greene, A. Cruz, and P. Crabbé, *Tetrahedron Lett.*, 2707 (1976). This method appears to proceed satisfactorily for cyclic β-keto esters with at least one α hydrogen. Long periods of heating are required for most compounds and this procedure would appear to offer no advantages to the method described in ref 5.

(22) Other related but nonaqueous decarbalkoxylations of β-keto esters include: J. M. Lalancette and A. Lahance, *Tetrahedron Lett.*, 3903 (1970), boric anhydride at 150 °C; P. A. Wehrli and V. Chu, *J. Org. Chem.*, **38**, 3436 (1973), boric acid at 150–170 °C.

(23) For examples, see: J. R. Johnson and F. D. Hager, *Org. Synth.*, **1**, 351 (1944).

(24) (a) F. Elsinger, *Org. Synth.*, **5**, 76 (1973), and references cited therein. (b) J. Kossanyi, B. Furth, and J. P. Morizur, *Tetrahedron Lett.*, 3459 (1973).

(25) (a) K. Kondo, T. Umemoto, Y. Takahatake, and D. Tunemoto, *Tetrahedron Lett.*, 113 (1977). (b) D. Tunemoto, N. Araki, and K. Kondo, *ibid.*, 109 (1977).

(26) (a) I. T. Harrison, V. R. Fletcher, and J. H. Fried, *Tetrahedron Lett.*, 2733 (1974). (b) K. Kondo, E. Hiro, and D. Tunemoto, *ibid.*, 4489 (1976).

(27) (a) D. Y. Chang, S. H. Lee, and H. C. Lee, *J. Org. Chem.*, **32**, 3716 (1967). (b) D. Y. Chang, C. F. Yam, S. Y. Chan, S. H. Lee. and H. C. Lee, *ibid.*, **31**, 3267 (1966).

(28) G. A. Smith and D. H. Williams, *J. Chem. Soc., Perkin Trans. 1*, 2811 (1972).

(29) (a) S. Takei and Y. Kawano, *Tetrahedron Lett.* 4389 (1975). (b) M. Asaoka, K. Miyake, and H. Takei, *Chemistry Lett.*, 1149 (1975).

(30) J. J. Wilczynski and H. W. Johnson, Jr., *J. Org. Chem.*, **39**, 1909 (1974), obtained methyl acetate in a 35% yield.

(31) E. S. Behare and R. B. Miller, *J. Chem. Soc. D*, 402 (1970).

(32) (a) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960), and references cited therein. (b) P. D. G. Dean, *J. Chem. Soc.*, 6655 (1965). (c) P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970).

(33) P. Ykman and H. K. Hall, Jr., *Tetrahedron Lett.*, 2429 (1975).

(34) N. Ono, H. Eto, R. Tamura, and J. Hayami, *Chem. Lett.*, 757 (1976).

(35) (a) B. M. Trost and T. R. Verhoeven, *J. Org. Chem.*, **41**, 3215 (1976). (b) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **98**, 630 (1976).

(36) F. B. Thole and J. F. Thorpe, *J. Chem. Soc.*, **99**, 2183, 2187 (1911).

(37) C. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, **115**, 143 (1919).

(38) A. C. Cope and S. M. McElvain, *J. Am. Chem. Soc.*, **54**, 4311, 4319 (1932).

(39) D. H. Miles and B. S. Huang, *J. Org. Chem.*, **41**, 208 (1976), and references cited therein. Side reactions and poor conversions in certain disubstituted systems render these processes less useful.

(40) E. J. Parish, B. S. Huang, and D. H. Miles, *Synth. Commun.*, **5**, 341 (1975).

(41) F. Texier, E. Marchand, and R. Carrié, *Tetrahedron*, **30**, 3185 (1974). Competitive amide formation except in a few methyl esters distracts from the preparative use of this method.

(42) T. M. Santosusso and D. Swern, *J. Org. Chem.*, **41**, 2762 (1976); acids generated in Me_2SO decomposition do not appear to catalyze this reaction.

(43) It is reported in ref 9 that in the conversion of **6a** to **6b** with KCN–DMF that only 13% of the calculated CO_2 is evolved. The white precipitate which was reported as being formed is probably K_2CO_3.

(44) (a) J. F. J. Engbersen and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **97**, 1563 (1975). (b) T. H. Fife and D. M. McMahon, *ibid.*, **91**, 7481 (1969).

(45) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **83**, 1743 (1961).

(46) For a compilation of solvent isotope effects, see: S. L. Johnson, "Advances in Physical Organic Chemistry", Vol. 5, V. Gold, Ed., Academic Press, New York, N.Y., 1967, p 281.

(47) (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2nd ed, Cornell University Press, Ithaca, N.Y., 1969, p 1131; for a review of ester hydrolysis mechanisms. (b) For reviews, see: A. J. Kirby, *Compr. Chem. Kinet.*, **10**, 57 (1972); R. E. J. Talbot, *ibid.*, 209 (1972).

(48) For data on Me_2SO, see: H. H. Szmant, "Dimethyl Sulfoxide", S. W. Jacob, E. E. Rosenbaum, and D. C. Wood, Ed., Marcel Dekker, New York, N.Y., 1971.

(49) For example, heating diethyl ethylmalonate with D_2O–Me_2SO leads to ethyl butyrate with an 80–90% incorporation of D at the α carbon. Further studies of the syntheses of other deuterated esters and ketones will be reported shortly.

(50) (a) D. H. R. Barton and C. P. Forbes, *J. Chem. Soc., Perkin Trans. 1*, 1614 (1975). (b) D. H. R. Barton, B. J. Garner, and R. H. Wightman, *J. Chem. Soc.*, 1855 (1964).

(51) K. Mori, M. Tominaga, T. Takigawa, and M. Matsui, *Synthesis*, 790 (1973). The conversion of methyl palmitate to ethyl palmitate in the presence of 0.65% KCN in ethanol occurs overnight. An acyl cyanide intermediate may be involved.

(52) (a) F. C. Chang and N. F. Wood, *Tetrahedron Lett.*, 2969 (1964). (b) L. R. C. Barclay, N. D. Hall, and G. A. Cooke, *Can. J. Chem.*, **40**, 1981 (1962). (c) J. F. Bunnett, M. M. Robison, and F. C. Pennington, *J. Am. Chem. Soc.*, **72**, 2378 (1950). (d) C. A. Bunton, A. E. Comyns, J. Graham, and J. R. Quayle, *J. Chem. Soc.*, 3817 (1955).

(53) (a) R. F. Pratt and T. C. Bruice, *J. Am. Chem. Soc.*, **92**, 5956 (1970). (b) B. Holmquist and T. C. Bruice, *ibid.*, **91**, 2993, 3003 (1969); hydrolysis of malonate esters are reported.

(54) E. W. Thomas and T. I. Crowell, *J. Org. Chem.*, **37**, 744 (1972).

(55) In ref 27a, the decarbethoxylations of $CH_3COOR^1R^2CO_2Et$ with $CaI_2{\cdot}2H_2O$ for $R^1 = R^2 = H$ and $R^1 = H$, $R^2 = CH_3$ gave EtI/EtOH ratios of 1.7 and 11.7, respectively. In the case of $R^1 = R^2 = CH_3$ only EtI was isolated in a 78% yield. These results are consistent with a dominant $B_{AL}2$ attack of I^- in the disubstituted case and a greater contribution of $B_{AC}2$ attack in the mono- and unsubstituted cases.

(56) (a) P. Müller and B. Siegfried, *Helv. Chim. Acta*, **55**, 2400, 2965 (1972). In HMPT, no linear dependence on LiCl concentration was found in the S_N2

displacement on ethyl tosylate. (b) J. F. Normant and H. Deshayes, *Bull. Soc. Chim. Fr.*, 1001 (1969). (c) S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Lett.*, **9**, 24 (1960); solvents and nature of cation drastically effect apparent nucleophilicities. (d) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969); a review on protic–dipolar aprotic solvent effects on rates of bimolecular processes.

(57) Although media effects are important, the alkaline hydrolysis of methyl acetate vs. ethyl acetate exhibits a $k_{CH_3}/k_{CH_3CH_2}$ of about 2 (ref 47a).

(58) The $k_{CH_3}/k_{CH_3CH_2}$ for a simple ester with $B_{AL}2$ cleavage has been reported as 49 using molten thiocyanate salts (ref 54).

(59) (a) A. J. Streitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962, p 73; average values for a series of S_N2 displacements of about 30. (b) A $k_{CH_3}/k_{CH_3CH_2}$ of 17 was reported for the alkylative decarbalkoxylation of a *N*-carbalkoxypyrazole with Cl^- (ref 30). (c) A $k_{CH_3}/k_{CH_3CH_2}$ of 72 was reported for the decarbalkoxylation of 2-benzyl-2-carboalkoxycyclopentanone with NaCN–HMPT (ref 12a).

(60) C. L. Liotta and E. E. Grisdale, *Tetrahedron Lett.*, 4205 (1975), and references cited therein.

(61) (a) A volume containing reprints of important papers in this area has recently been published: R. G. Pearson, Ed., "Hard and Soft Acids and Bases", Dowden, Hutchinson, and Ross, Inc., Stroudsburg, Pa., 1973. (b) T. L. Ho, *Chem. Rev.*, **75**, 1 (1975). (c) J. F. Bunnett and J. D. Reinheimer, *J. Am. Chem. Soc.*, **84**, 3284 (1962), and references cited therein. (d) For a paper criticizing symbiotic effects, see: W. S. Trahanovsky and M. P. Doyle, *Chem. Commun.*, 1021 (1967). See also ref 56d.

(62) L. B. Engemyr and J. Songstad, *Acta Chem. Scand.*, **26**, 4179 (1972): symbiotic effects are greater for S_N2 displacements in dipolar aprotic solvents than in protic media.

(63) (a) In ref 12a for displacements of 2-benzyl-2-carbomethoxycyclopentanone in HMPT with LiCl or LiBr the relative reactivities are reported to be 2.4:1. (b) In ref 30 the alkylative decarboxylation of *N*-carbomethoxypyrazoles were studied in Me_2SO and the k_{X^-}/k_{I^-} rate ratios are 5.1, 3.0, and 1.0 for Cl^-, Br^-, and I^-, respectively. (c) R. Fuchs and K. Mahendran, *J. Org. Chem.*, **36**, 730 (1971); S_N2 reactions for unassociated X^- for primary alkyl *p*-toluene sulfonates are listed as $Cl^-/Br^-/I^-$ = 8:3:1 (Me_2SO) with the tetra-*n*-butylammonium cation.

(64) A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, *Org. Synth.*, **5**, 198 (1973).

(65) I. Heilbron, et al., Eds., "Dictionary of Organic Compounds", Oxford University Press, New York, N.Y., Vol. 1–5, 1965; all esters are listed except **2** ($R^1 = R^2$ = *n*-butyl, R^3 = ethyl) which is reported in M. Rouchi-Laridjani and M. Vilkas, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **254**, 1090 (1962), and ester 2 (R^1 = phenyl, R^2 = H, and R^3 = ethyl) which is reported in H. Laato and R. Isotalo, *Acta Chem. Scand.*, **21**, 2119 (1967).

Vinyllithium Reagents from Arenesulfonylhydrazones

A. Richard Chamberlin, Jeffrey E. Stemke, and F. Thomas Bond*

Department of Chemistry, University of California at San Diego, La Jolla, California 92093

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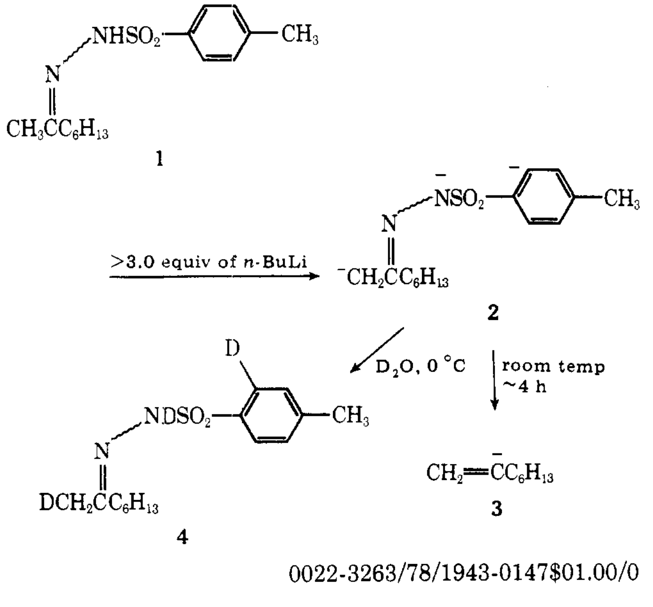
2,4,6-Triisopropylbenzenesulfonylhydrazones of a wide range of ketones serve as a convenient source of vinyllithium reagents. Treatment with 2.0–3.0 equiv of alkyllithium reagent at −78 °C in TMEDA–hexane followed by warming to 0 °C rapidly generates the vinyl anions in most cases. The reagents so formed can be trapped with a variety of electrophiles. This procedure leads to a convenient synthesis of allylic alcohols, di-, tri-, and tetrasubstituted olefins, acrylic acids, acrylic aldehydes, vinylsilanes, and vinyl bromides.

Organolithium reagents have become increasingly important in synthetic organic chemistry.[1] We report here an extremely facile method for generation of a variety of vinyllithium derivatives and trapping of them with an assortment of electrophilic reagents. Our initial studies, portions of which have been reported in preliminary form,[2,3] used the reaction of tosylhydrazones with excess *n*-butyllithium in TMEDA–hexane solvent systems for generation of vinyllithium reagents. This procedure represented a modification of the valuable and widely used Shapiro olefin synthesis[4] by allowing the vinyl anion intermediate[5] to be trapped by externally added electrophiles.

The procedure is illustrated in Scheme I for the tosylhydrazone (**1**) of 2-octanone. Treatment of **1** with excess base generates almost exclusively the 1-octenyl anion (**3**). In solvents (hexane or ether) normally used for the olefin synthesis, **3** is protonated either by solvent[4,6] or, in the case of hexane where the reaction is heterogeneous, by the tosylhydrazone.[7] Use of TMEDA as solvent overcomes this problem, but requires the use of 3 equiv or more of alkyllithium reagent if workup is to produce the desired product. This is shown in Table I for D_2O workup of the reaction. The yield of olefin is invariably high, but deuterium incorporation on workup clearly requires excess base beyond the 2 equiv needed for stoichiometric dianion formation.

Scheme I



The source of this problem has now been shown to be an *o*-aryl hydrogen of the tosyl group.[3,8] Specifically, treatment of **1** at −78 °C with >3.0 equiv of *n*-butyllithium in TMEDA–hexane, followed by D_2O quench, results in the incorporation of two deuterium atoms, one on nitrogen (washed out on workup) and one on the α-methyl group. If, however, the reaction mixture is warmed to 0 °C and then quenched before decomposition to **3** becomes significant, trideuterated tosylhydrazone **4** is obtained. NMR examination of the recovered tosylhydrazone shows that metalation[9] has occurred in the ortho position. A similar directed ortho metalation by an SO_2NHCH_3 group has been reported.[10] Such metalation is facilitated by the use of the strongly basic *n*-butyllithium/TMEDA solvent system and is necessary if **3** is to be trapped by externally added electrophiles. Otherwise, the vinyl anion **3** metalates the remaining dianion, giving 1-octene. Excess *n*-butyllithium (typically 3.5–4.5 equiv) must therefore be used with tosylhydrazones, and this in turn necessitates the use of excess electrophile and the separation of side products which result from attack of the *n*-butyllithium on the electrophile.

These problems can be overcome and the reaction greatly facilitated by the use of easily prepared[11] 2,4,6-triisopropyl-

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