Recent synthetic applications of the dealkoxycarbonylation reaction. Part 1. Dealkoxycarbonylations of malonate esters

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Abstract
The purpose of this review is to update (publications from 1981 to mid 2006) the synthetic applications of dealkoxycarbonylations of malonate esters, β-keto esters (and related esters with α-substituted electron-withdrawing functionalities) induced by heating with water or with water in the presence of salts (such as NaCN, NaCl or LiCl) in dipolar aprotic solvents. The presentation will be divided in two parts. In Part 1, discussion will focus on the dealkoxycarbonylations of malonate esters. Part 2 (to follow as a separate paper) will deal with the dealkoxycarbonylations of β-keto esters and α-cyano esters (and related analogues).

Keywords: Dealkoxycarbonylations, Krapcho, decarbalkoxylations, malonate esters

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1. Introduction

Activated esters, which include such substrates as malonates, β-ketoesters and α-cyanoesters, are of considerable importance in organic synthesis. We have reported in a number a publications that these substrates (and other activated analogues) undergo dealkoxycarbonylations on being heated in dipolar aprotic solvents (such as DMSO or DMF) in the presence of water, or in some substrates with water in the presence of added salts (such as NaCN, NaCl or LiCl) to yield the corresponding esters, ketones and nitriles. This procedure is facile, avoids harsh acidic and
alkaline conditions and tolerates many protecting groups. In addition, this methodology is much more convenient than the classical procedures for accomplishing these transformations.

\[
\begin{array}{c}
\text{R}_1Y\text{CO}_2\text{R} \\
\text{salt, H}_2\text{O,} \\
\text{Dipolar Aprotic Solvent} \\
\rightarrow \\
\text{R}_1Y\text{H}
\end{array}
\]

\(Y = \text{COOR, COR, CN, NO}_2, \text{SO}_2\text{R}\)

This overall process is a formal loss of \(\text{CO}_2\text{R}\) and protonation of the intermediate carbanion (a dealkoxycarbonylation or a decarbalkoxylation).

Two previous reviews of the synthetic applications of this methodology and mechanistic considerations were published in 1982.\(^{1,2}\) Subsequently, this procedure has been referred to as the Krapcho reaction or the Krapcho dealkoxycarbonylation.\(^{3-8}\)

A recent check of the Science Citation Index Expanded (1982 to mid 2006) indicated about 1100 citations to the papers published by the Krapcho group dealing with the dealkoxycarbonylation procedure. The goal of the present review is to update the literature on the more recent strategies of this methodology in synthesis. Because of the large numbers of published papers, the author is going to be somewhat selective in the illustrative synthetic examples chosen from the literature.

### 2. Mechanistic Considerations

Mechanistically, the dealkoxycarbonylation constitutes an ester hydrolysis followed by decarboxylation and subsequent protonation of a carbanion species or a concerted dealkylative decarboxylation followed by protonation of the incipient carbanion. The mechanism is clearly dependent on whether the substrate is heated in the dipolar aprotic solvent with water or water in the presence of salts. Some mechanism details have been discussed in the prior review.\(^{1}\) The overall mechanistic pathway is dependent on the substrate structure and the reaction conditions.\(^{3-9}\)

The cleavages of the aziridinyl malonate 1 have been studied using NaCN or NaCl in aqueous DMSO. In the case of NaCN in DMSO and water (110°C, 6 h), the product was 2 (49%). In the use of DMSO, NaCl and water (150°C, 2 h), the product was 3 (31%). A mechanistic rationalization possibly involving N-participation is proposed.\(^{10}\)
3. Esters

3.1. From mono substituted malonate esters

3.1.1. Water alone

As noted in our previous review,\(^1\) the dealkoxycarbonylations of a number of mono substituted malonates can be accomplished by heating in a dipolar aprotic solvent such as DMF or DMSO with added water to yield the corresponding mono esters. Additional examples of this methodology continue to be reported.

The diester \(4-(R)\) on heating in DMSO and water (170\(^\circ\)C, 13 h) yielded the monoester \(5-(S)\) (80%).\(^{11}\)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{CH(CO}_2\text{Et})_2 & \quad \rightarrow \quad \text{Ph} \\
4-(R) & \quad \text{CH}_2\text{CO}_2\text{Et} \\
5-(S) & 
\end{align*}
\]

The keto diester \((+)-6\) on being heated in wet DMSO (190\(^\circ\)C, 5 h) underwent decarbomethoxylation to afford the keto ester \((+)-7\) (60%). In a similar manner the \((-)\) diester enantiomer could be converted into the \((-)\) ester.\(^{12}\)

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\text{CH(CO}_2\text{Et})_2 & \quad \rightarrow \quad \text{CH}_2\text{CO}_2\text{Et} \\
(+)-6 & \quad (+)-7
\end{align*}
\]

The dealkoxycarbonylations of malonic esters have been performed using microwave irradiation under solvent free solid-liquid phase transfer conditions. For example treatment of \(8\) with LiBr and water, LiBr, water and a PTC agent such as Aliquat 336, or NBu\(_4\)Br and water under microwave conditions (10 min at 30 W) led to the deethoxycarbonylated product \(9\) in 70%, 85% and 96% yields, respectively.\(^{13a,b}\)

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Et} \\
\text{H} & \quad \text{H} \\
\text{8} & \quad \rightarrow \quad \text{Ph} \\
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
9 & 
\end{align*}
\]

The dealkoxycarbonylations of several mono-substituted malonates have been shown to proceed in wet DMF under microwave conditions. For example, the conversion of diester \(10\) to ester \(11\) (84%) was accomplished at 160\(^\circ\)C for 20 min.\(^{14}\)
The deethoxycarbonylation of 12 in HMPA and water (120°C, 2.5 h) afforded 13 (94%).

3.1.2. Water – salts

The dealkoxycarbonylations of a wide variety of substituted malonate esters have been reported using DMSO or DMF, water and salts such as NaCl, LiCl and NaCN. Numerous protective groups in the substrate are tolerated under the reaction conditions. The reactions are roughly classified according to the structure of the substituents.

3.1.2.1. From alkyl, alkenyl, alkynyl and allenic malonate esters. The diester 14-(S) on treatment with DMSO, NaCl and water (155°C, 48 h) led to ester 15-(S) (89%), along with a small amount (6%) of the corresponding acid.

To ascertain the isotope effect on pheromonal activity, the aggregation pheromone of the red flour beetle, deuterated analogues of 4,8-dimethyldecanal were synthesized. Treatment of 16 with DMSO, LiCl and water (reflux, 48 h) led to the deuterated analogue 17 (53%) which was subsequently transformed into 4-trideuteriomethyl-8-methyldecanal.

The deethoxycarbonylations of carbon-14 labelled malonate esters 18a and 18b can be readily accomplished on treatment with LiBr, Aliquat 336 and water under microwave irradiation (200°C, 10 min) to afford 19a and 19b, respectively. The synthesis of 19a (60%) and 19b (57%) could also be accomplished in a one-pot route based on a solvent–free alkylation of...
the carbon-14 labeled diethyl malonate followed by a microwave activated
deethoxycarbonylation in the presence of LiBr, Aliquat 336 and water.\textsuperscript{18}

\[ \text{R}^{14}\text{CH(CO}_2\text{Et)}_2 \rightarrow \text{R}^{14}\text{CH}_2\text{CO}_2\text{Et} \]

\( a, \text{R} = \text{C}_{10}\text{H}_{21} \quad b, \text{R} = \text{C}_{18}\text{H}_{37} \)

Treatment of racemic \textbf{20} (51.3 kg) with DMSO, NaCl and water (137-148°C, 8.5 h) led to
the \( \beta \)-cyano ester \textbf{21} (86%). This substrate was evaluated as an intermediate in the synthesis of
the anticonvulsant (S)-3(aminomethyl)-5-methylhexanoic acid.\textsuperscript{19}

\[
\begin{array}{c}
\text{Me} \\
\text{CN} \\
\text{CO}_2\text{Et}
\end{array}
\xrightleftharpoons{\text{DMSO, NaCl, water}}
\begin{array}{c}
\text{Me} \\
\text{CN} \\
\text{CO}_2\text{Et}
\end{array}
\]

A number of C-silylated malonate esters have been demethoxycarbonylated using DMSO,
NaCl and water (reflux, 24 h). A typical example is the conversion of a mixture of \textbf{22} [\( \beta \)-Me
(85%) and \( \alpha \)-Me (15%)] into \textbf{23} [\( \beta \)-Me(85%) and \( \alpha \)-Me (15%)] in an overall 81% yield.\textsuperscript{20}

\[
\begin{array}{c}
\text{PhMe}_2\text{Si} \\
\text{Me} \\
\text{CO}_2\text{Me}
\end{array}
\xrightleftharpoons{\text{DMSO, NaCl, water}}
\begin{array}{c}
\text{PhMe}_2\text{Si} \\
\text{Me} \\
\text{CO}_2\text{Me}
\end{array}
\]

The demethoxycarbonylation of \textbf{24HCl} with DMSO, NaCl and water (reflux, 2 h) led to
(S)-3-aminobutyrate \textbf{25} [86% > 95% ee], which was readily converted into the simple chiral \( \beta \)-lactam (95% ee).\textsuperscript{21}

\[
\begin{array}{c}
\text{H} \\
\text{Me} \\
\text{N}{\text{H}_2}
\end{array}
\xrightleftharpoons{\text{HCl}}
\begin{array}{c}
\text{H} \\
\text{Me} \\
\text{N}{\text{H}_2}
\end{array}
\]

Racemic \textbf{26} was converted into racemic \textbf{27} on treatment with tetrabutyl ammonium acetate in
dry DMSO (100°C, heat). This procedure gave better yields than heating in DMSO with NaCl
and water.\textsuperscript{22}
The Michael adducts 28 upon heating in DMSO, NaCl and water (130°C, 24 h) led to the (3S)-substituted tert-butyl butanethioates 29, chiral differentiated glutarate esters. \(^{23}\)

\[
\begin{align*}
\text{t-BuS} & \quad \text{R} \quad \text{CO}_2\text{Me} \\
28 & \quad \text{CO}_2\text{Me} \\
\text{t-BuS} & \quad \text{R} \quad \text{CO}_2\text{Me} \\
29 & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\(\text{R} = \text{Ph, Cyclohexyl, i-Pr, Me (67-86\%)}\)

Treatment of 30 (40%ee) with DMSO and water (150°C, 20 h) led to the thio ester 31 (65%, 64%ee). This could be converted into chiral (R)-methyl 3-(benzoylamino)butanoate. \(^{24}\)

\[
\begin{align*}
\text{t-BuS} & \quad \text{NHCOPh} \\
30 & \quad \text{CO}_2\text{Me} \\
\text{t-BuS} & \quad \text{NHCOPh} \\
31 & \quad \text{CO}_2\text{Me}
\end{align*}
\]

Treatment of 32 with DMSO, LiCl and water (reflux, 5 h) yielded 33 (95%). \(^{25}\)

\[
\begin{align*}
\text{Me} & \quad \text{CH(} \quad \text{CO}_2\text{Et})_2 \\
32 & \quad \text{CO}_2\text{Et} \\
\text{Me} & \quad \text{CH(} \quad \text{CO}_2\text{Et})_2 \\
33 & \quad \text{CO}_2\text{Et}
\end{align*}
\]

The bromo allyl diester 34 on heating in DMSO, NaCl and water (reflux, 8 h) led to the bromo monoester 35 (67%). \(^{26}\)

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{CH} \quad \text{Br} \quad \text{CH(} \quad \text{CO}_2\text{Et})_2 \\
34 & \quad \text{CO}_2\text{Et} \\
\text{H}_2\text{C} & \quad \text{CH} \quad \text{Br} \quad \text{CH(} \quad \text{CO}_2\text{Et})_2 \\
35 & \quad \text{CO}_2\text{Et}
\end{align*}
\]

The decarbomethoxylation of 36 with DMSO, LiCl and water (130-160°C, 6 h) led to the keto ester 37 (65%). \(^{27}\)

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{Me} \\
36 & \quad \text{Me} \\
\text{Me} & \quad \text{CO}_2\text{Me} \\
37 & \quad \text{Me}
\end{align*}
\]

The demethoxycarbonylation of optically active 38 with NaCN and LiI in DMF (128°C, 16 h) led to optically active 39 (64%). \(^{28a,b}\)
The deethoxycarbonylation of 40 with DMSO, NaCl and water (170-180°C, 8 h) led to 41 (60%), which was used in the synthesis of the sex pheromone of the rice green caterpillar.29

Treatment of (R)-42 with a mixture of LiI and NaCN in DMF (120°C, 6 h) or NaCl and water in DMSO (130°C, 8 h) led to demethoxycarbonylation with partial racemization of the allenic axial chirality to afford (R)-43 (82%, 54%ee) or (R)-43 (35%, 69%ee), respectively.30

The deethoxycarbonylation of 44 with DMSO and NaCN (160°C, 4 h) afforded 45 (40%).31

3.1.2.2. From 2-cycloalkyl and 2-cycloalkenyl malonic esters. The racemic starting material 46 on treatment with DMSO, NaCl, water (160°C, 36 h) yielded 47 (40%).32

Treatment of (+) 48 with DMSO, NaCl and water (reflux, 1 h) led to (+)-49 (92%) which was then transformed into the unnatural enantiomer (+)-Δ9(12)-capnellene.33
The demethoxycarbonylation of (-)-(1S,4S) 50 with DMSO, LiCl and water (150°C, 4 h) led to 51(1R,4R). The enantiomer (1R,4R) also led to the corresponding (1S,4S) enantiomer. These esters were used in a synthesis of compounds to assess the bioactive conformations and chiral recognition of a moth sex pheromone.34

Treatment of racemic 52 with DMSO, LiCl and water (178°C, 4.3 h) led to racemic 53 (69%).35

The decarbomethoxylation of (R)-diester 54 using LiI.3H2O in DMSO (25 min, 180°C) led to (R)-55 (52%). This intermediate was subsequently converted into (1R,4S,6S)-6-hydroxybicyclo[2.2.2]octan-one.36

Treatment of enantiomer 56 with DMSO, NaCl and water (150°C, 4 h) led to the decarbomethoxylated enantiomer 57 (92%). This intermediate was converted into the chiral cadinane-sesquiterpene veticadinol.37
The demethoxycarbonylation of R-(+)-58 in DMSO, NaCl and water (160°C, 24 h) led to S-(+)-59 (74%).\textsuperscript{38a} Racemic 58 on treatment with DMSO, LiCl and water (170°C, 24h) gave racemic 59 (61%).\textsuperscript{38b} Similar conditions using DMSO, LiCl, and water had been previously reported (190°C, 6 h) for the conversion to the racemic mono ester 59 (84%).\textsuperscript{38c} Also racemic 58 with DMSO, NaCl and water (170°C, 10 h) led to 59 (88%) which was converted into a substituted alanine analogue.\textsuperscript{38d}

The demethoxycarbonylation of (S)-60 in DMSO, NaCN and water (60°C, 48 h) afforded (R)-61 (80%).\textsuperscript{39}

Treatment of 62 with DMSO, NaCN and water (110°C, 24 h) led to racemic 63 (62%).\textsuperscript{40}

The deethoxycarbonylation of diester 64 with DMSO, NaCl and water (reflux, 22 h) led to racemic 65 (81%).\textsuperscript{41}
The demethoxycarbonylation of 66 in DMSO, LiCl and water (reflux, 45 min) led to 67 (90%), an intermediate useful in studies to evaluate the application of silicon-containing compounds in synthesis.42

Treatment of 68a or 68b with DMSO, NaCN and water (70°C, 36 h) led to 69a (70%) or 69b (60%), respectively. The lower temperature was necessary to avoid extensive rearrangements of the double bonds.43

A mixture of the enantiomer 70 in DMSO, LiCl and water (160°C, 3 h) led to enantiomer 71 (87%).44

The demethoxycarbonylation of optically active 72 using NaCN in DMSO (no experimental details) led to 73 which was used in a total synthesis of optically active sesquiterpenes albolic acid and ceroplastol II, which have been found in the wax secretions of a scale insect.45
In a multi-gram scale up, treatment of 74 with DMSO, NaCl and water (170-180\degree C, 2.5 h) led to 75 (80\%).\textsuperscript{46}

Treatment of enantiomer 76 with DMSO and NaCN (heat, 6 h) led to enantiomer 77 (57\%).\textsuperscript{47}

3.1.2.3. From aryl substituted malonate esters. The enantioselective conjugate addition of diethyl zinc with chiral phosphorus ligands to alkylidene malonates led to 3-ethyl substituted malonate esters. For example, the deethoxycarbonylation of 78 with DMSO, LiCl and water (160\degree C, 15 h) led to (R)-79 (quantitative, 64\% ee).\textsuperscript{48}

The decarbomethoxylation of (R)-80 with DMSO, NaCl and H\textsubscript{2}O (200\degree C, 20 min) in a microwave cavity led to (S)-81 (80\%).\textsuperscript{49}
The demethoxycarbonylation of \( \text{82} \) (no conditions listed) led to \( \text{83} \). Other substituted analogues were also reported.\(^{50}\)

\[
\begin{align*}
\text{82} & \quad \rightarrow \quad \text{83}
\end{align*}
\]

The demethoxycarbonylation of \( \text{84} \) (86\% ee) was accomplished by using DMSO, NaCl and an aqueous phosphate buffer (170°C, 2.75 h) to afford \( \text{85} \) (38\%, with no significant loss of enantiomeric purity), which was used as an intermediate for the preparation of cardiotonic agents.\(^{51}\)

\[
\begin{align*}
\text{84} & \quad \rightarrow \quad \text{85}
\end{align*}
\]

Treatment of \( \text{86} \) with DMSO, NaCl and water (135-170°C, 3 h) led to \( \text{87} \) (84\%). This was converted into a hapten for the radioimmunoassay of bupropion (a non tricyclic antidepressant).\(^{52}\)

\[
\begin{align*}
\text{86} & \quad \rightarrow \quad \text{87}
\end{align*}
\]

The quaternary salt \( \text{88} \) and diethyl malonate (DMF, K\(_2\)CO\(_3\), 156°C, 39 h) led to \( \text{90} \) (70-75\%). Shorter reaction times led to \( \text{89} \), which on demethoxycarbonylation in the presence of KI led to \( \text{90} \). This compound has been isolated from the roots of an endemic Guyana tree.\(^{53}\)
The demethoxycarbonylations of 91a-f on treatment with DMSO, LiCl and H₂O (100°C, 3 h) led to the respective esters 92a-f (56-86%).

The deethoxycarbonylation of 93 with DMSO, NaCl and water (110°C, 3 h) led to the quinone 94 (83%).

3.1.2.4. From 2-heterocyclic substituted malonic esters. The deethoxycarbonylation of 95 using DMSO, NaCl and water led 96 (96%).

Diester (-)-97 (98%ee) on treatment with DMSO, NaCl and water (120°C, 16 h) led to (-)-(R)-98 (58%).
Upon treating the substituted indole 99 with DMF, LiCl, Et₃N.HCl (130°C, 4 h), the demethoxycarbonylated indole 100 was obtained (85%). The N-BOC and benzyl ester functionalities were not affected. This intermediate was subsequentially converted to a tetracyclic ABCE Strychnos alkaloid precursor in an enantioselective manner.  

\[ \text{99} \rightarrow \text{100} \]

The synthesis of a 2-allyl substituted thiophene 102 (80%) was accomplished by treatment of the diester 101 with DMSO, NaCl and water (150-155°C, 8 h).  

\[ \text{101} \rightarrow \text{102} \]

The decarbomethoxylation of racemic 103 with DMSO, NaCN and water (118°C, 3 h) led to monoester 104 (79%).  

\[ \text{racemic 103} \rightarrow \text{104} \]

The decarboethoxylation of the pyrrolidine 105 (2S, 4R) with DMSO, NaCl and water (160°C, 1 h) led to 106 (2S, 4R) [88% for 2 steps which involve a prior Michael addition] in which the protective silyl and BOC groups remained intact. This intermediate was converted into the desired lactam in two steps.  

\[ \text{105 (2S, 4R)} \rightarrow \text{106 (2S, 4R)} \]
The dithioketal 107 on treatment with DMSO, NaCl and water (155-160°C, 4 h) led to corresponding ester 108 with the dithio ketal functionality intact. This intermediate, in a series of subsequent steps, was converted into the δ-dioxo analogues. 62

\[
\begin{align*}
\text{Me} & \quad \text{SS} & \quad \text{Me} \\
\text{CH(CO₂Et)₂} & \quad \rightarrow & \quad \text{Me} & \quad \text{SS} & \quad \text{CO₂Et}
\end{align*}
\]

The demethoxycarbonylations of optically pure diesters 109a,b,c in DMSO, NaCl and water (150°C, 2-3 h) afforded the respective asymmetric succinic semialdehyde derivatives 110a,b,c (63-81%). 63

\[
\begin{align*}
\text{SS} & \quad \text{CO₂Me} & \quad \text{SS} \\
\text{R} & \quad \rightarrow & \quad \text{R} & \quad \text{CO₂Me}
\end{align*}
\]

\(a, R = (\text{CH₂})₂\text{Ph}; b, R = \text{p-NO₂C₆H₄}; c, R = \text{biphenyl}\)

Treatment of diastereoisomers 111 with DMSO, LiCl and water (190°C, 5 h) led to 112a and 112b (65%, ratio 2.2:1) which were separated by chromatography. Compound 112a, in a series of steps, was converted into dolabellane skeleton. 64

The demethoxycarbonylation of diester 113 with DMSO, NaCl and water (160°C, 24 h) led to enantiomer 114 (75%). In a subsequent series of steps this intermediate was converted into the insect sex attractants (-)-anastrephin and (-)-epianastrephin. 65

\[
\begin{align*}
\text{EtO₂C} & \quad \text{CO₂Et} & \quad \text{EtO₂C} \\
\text{O} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]
The Michael addition of the anion to 115 followed by demethoxycarbonylation using DMSO, NaCl and water (no conditions reported) led to enantiomeric 116 (55% for the two steps). This intermediate was used in an enantiospecific synthesis of sesbanimide.66

\[ \text{Me}^+ \text{O} \text{CH}=\text{CHCO}_2\text{Me} \rightarrow \text{Me}^+ \text{O} \text{CH}\left(\text{CH}_2\text{CO}_2\text{Me}\right)_2 \]

The deethoxycarbonylation of 117 using DMSO, LiCl and water (reflux, 2 h) afforded 118 (quantitatively).67

\[ \text{EtO}_2\text{C} \text{CO}_2\text{Et} \rightarrow \text{EtO}_2\text{C} \]

The demethoxycarbonylation of 119 using DMSO, NaCl and water (160°C, 1 h) led to optically active 120 (89%) which was used in a synthesis of (+)-sebanimide and (-)-sebanamide, antitumor alkaloids from the seeds of a leguminous plant.68

\[ \text{BnO} \text{CO}_2\text{Me} \rightarrow \text{BnO} \text{CO}_2\text{Me} \]

The ketal (R)-121 on treatment with DMSO, NaCN and water (160°C, 6 h) led to (R)-122 (72%).69

\[ \text{Me}^+ \text{CO}_2\text{Et} \rightarrow \text{Me}^+ \text{CO}_2\text{Et} \]

The decarbomethoxylation of 123 using DMSO, NaCN and water (115°C, 2 h) led to racemic mono ester 124 (90%), which was then converted into a dihydrofuran analogue of leukotriene A4.70
Treatment of 125 with DMSO, NaCl and water (160°C, 4 h) led to racemic 126 (91%).

Some additional illustrative examples are tabulated in Table 1.

Table 1. Dealkoxycarbonylations of monosubstituted malonate esters

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield(%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(CO2Et)2</td>
<td>DMSO, H2O, 200°C, 5 h</td>
<td>CH(CO2Et)2</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>CH(CO2Et)2</td>
<td>DMSO, LiCl, H2O, 140-170°C, 5 h</td>
<td>CH(CO2Et)2</td>
<td>95</td>
<td>73</td>
</tr>
<tr>
<td>CH(CO2Et)2</td>
<td>DMSO, NaCl, H2O, 160°C, 6 h</td>
<td>CH(CO2Et)2</td>
<td>80</td>
<td>74</td>
</tr>
<tr>
<td>(H3C)3Si-CO2Et</td>
<td>DMSO, LiCl, H2O, 150°C, 15 h</td>
<td>CH(CO2Et)2</td>
<td>55</td>
<td>75</td>
</tr>
<tr>
<td>CH2CH(CO2Et)2</td>
<td>DMSO, NaCl, H2O, 140°C</td>
<td>CH2CH(CO2Et)2</td>
<td>65</td>
<td>76</td>
</tr>
<tr>
<td>CO2Me(123)</td>
<td>DMSO, NaCl, H2O, 160°C</td>
<td>CO2Me(124)</td>
<td>79</td>
<td>77</td>
</tr>
</tbody>
</table>
4. Diesters

4.1. From substrates with two malonate ester functionalities

The substituted 2,2-bipyridine 127 underwent bis-deethoxycarbonylation on heating in DMSO, NaCl and water (reflux, 2.5 h, exclusion of light) to afford the bis-carboethoxyl ethyl substituted 2,2-bipyridine 128 (84%).96
The bis-demethoxycarbonylation of the substituted N-methylphenothiazine 129 on treatment with DMI (1,3-dimethylimidazolidin-2-one), tetramethyl ammonium acetate and water (140°C, 10 h) led to 130 (80%). These molecules were utilized in a synthesis of phenothiazine-bipyridinium cyclophanes.97

In routes to pyrenophanes, the bis-demethoxycarbonylation of 131 was accomplished on heating in DMSO, NaCl and water (160-170°C, 3 h) to yield 132 (59%).98

Treatment of tetra ester 133 with DMSO, LiCl and water (no conditions given) led to diester 134 (35%) which was used in a synthesis of [3.3.1]propellane-2,8-dione.99

Treatment of a mixture of KOH, dimethyl malonate (135) and chloromethallyl chloride (136) in DMF (150°C, 0.5 h) led to dimethyl 4-methyleneiminate (137, 88%), the process involving a bis-demethoxycarbonylation.100
The conversion of the tetra ester 138 to the diester 139 (91%) can be accomplished by treatment with DMSO, LiCl and water (reflux, 4 h).101

\[
\text{CH}_2(\text{CO}_2\text{Me})_2 + \begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \rightarrow \begin{array}{c}
\text{MeO}_2\text{C} \\
\text{MeO}_2\text{C}
\end{array}
\]

\textbf{135} \quad \textbf{136} \quad \textbf{137}

The bis-deethoxycarbonylation of 140 with DMSO, NaCl, water (reflux, 4 h) led to the diester 141 (79%).102

5. Demethoxycarbonylation - rearrangement

Treatment of 142\textit{a} (n = 1) with DMF, NaCl and water (reflux, 6 h) led to the rearranged product 1,2,5,6-tetrahydroindolizine-3,7-dione (143\textit{a}, n = 1, 33%). Under similar conditions 142\textit{b} (n = 2) led to 3,4,6,7,8,9-hexahydro-2H-quinolizine-2,6-dione (143\textit{b}, n = 2, 44%). Additional examples and mechanistic considerations are reported in several later publications.103\textit{a},\textit{b},\textit{c}
6. Aryl methyl substituted benzenes

6.1. From bis-dealkoxycarbonylations

Treatment of 144 with DMSO, water and NaCl (160°C, 5 h) led to a double dealkoxycarbonylation to afford 145.

\[
\text{144} \xrightarrow{\text{DMSO, water, NaCl, 160°C, 5 h}} \text{145}
\]

A number of aryl esters, readily available by S_NAr substitution of 2-fluoro- or -2-chloro nitrobenzene by the anion of diethyl malonate, undergo bis-deethoxycarbonylations to afford 2-methyl nitro benzenes. Treatment of 146 in DMSO, NaCl, water (160-170°C, 12 h) afforded 147 (35%) with a higher yield of 147 (77%) reported when using MgCl_2.6H_2O.

\[
\text{146} \xrightarrow{\text{DMSO, NaCl, water, 160-170°C, 12 h}} \text{147}
\]

The analogue 148 undergoes a tetra-deethoxycarbonylation to afford 149 (60%) on treatment with MgCl_2H_2O in DMA (reflux, 7 h).

\[
\text{148} \xrightarrow{\text{MgCl_2H_2O, DMA, reflux, 7 h}} \text{149}
\]

7. Esters

7.1. From disubstituted malonate esters

The dealkoxycarbonylations are arranged on the basis of the two types of substituents attached to the malonate ester moiety.

7.1.2. Bis-alkyl
The deethoxycarbonylation of diester 150 with DMSO, LiCl and water (reflux, 4 h) led to 151 (73%), a derivative for use in a study of hydrocarbon type dielectric fluids.
The synthesis of the deuterated ester 153 (90-95%) was accomplished by heating 152 in DMSO, LiCl and water (reflux, 12 h).107

The quantitative deethoxycarbonylation of C, C-disubstituted malonates such as 154 supported on polystyrene can be accomplished by heating the polymer with NaI and anhydrous DMSO at 100°C to afford 155. Calcium chloride in DMSO or NaI in nitromethane were also found to be useful for the deethoxycarbonylations.108

Compound 156, on solution in DMSO, LiCl and water (160°C, 4 h), led to the decarbomethoxylated product (S)-157 (66%) with retention of the Cbz and Alloc amino protecting groups.109

7.1.3. Alkyl - benzylic
The diester 158 on heating with DMSO, NaCN (160-170°C, 4.5 h) afforded 159 (85%).110

The β-silylated malonate ester 160 on treatment with DMSO, LiCl and water (reflux, 25 min) led to 161 and 162 (68%) as a 70:30 mixture.111
7.1.4. Dimethylamino-benzyl
Without the benefit of any reactions conditions, it was noted that treatment of 163 with DMSO and NaCN cleanly afforded 164.\(^\text{112}\)

7.1.5. Indanyl-carboethoxymethylene
The triester 165 on heating in DMSO, NaCl and water (178-183°C, 6 h) led to 166 (85%).\(^\text{113}\)

7.1.6. Benzocyclobutane substituted cyclopentane
Treatment of diester 167 in DMSO, NaCN and water (90°C, 19 h) led to mono ester 168 (78%) as an inseparable mixture of isomers.\(^\text{114a}\) Several other related analogues were also dealkoxycarbonylated under similar conditions.\(^\text{114b,c}\)

7.1.7. Alkyl-heterocyclic
The deethoxycarbonylation of 169 with DMSO, LiCl and water (reflux, 3 h) yielded 170 (83%) which was used in a synthesis of an indoloquinolizidine.\(^\text{115}\)
During the decarbomethoxylation of the benzothiazolone 171 in DMSO, KCN and water (reflux, 12 h), the expected product 172 (75%) along with the ring-opened 2-alkylsulfanyl aniline 173 (25%) were isolated.\footnote{116}

Methyl nonactate (+)-175 and 2-epi-methyl nonactate (-)-176 (overall yield 78% in a 1:1 ratio and separated by chromatography) were prepared by heating diester 174 in DMSO with NaCl and water (reflux, 3 h).\footnote{117}

The deethoxycarbonylation of 177 was accomplished using DMSO, LiCl and water (180°C, 4 h) to afford 178 (81%).\footnote{118}

7.1.8. Cycloalkyl-1,1-dicarboxylic esters
The demethoxycarbonylation of the cyclopropane-1,1-dicarboxylic acid methyl ester (179) has been studied under several different conditions. With DMSO, NaCl and water (160°C, 6 h) the three products 180, 181 and 182 were obtained in 73% yield with the trans/cis/ ring opening ratio of 27/21/52. With NaCN in aqueous DMF (120°C, 48 h) total yield was 88% with the ratios of 50/34/16. In the use of tetramethyl ammonium acetate in HMPA (95°C, 4 h, 90% yield) with the ratio being 70/30/0 with no ring opened product.\footnote{119}
The dealkoxycarbonylations of several sulfur- and alkoxy substituted cyclopropane derivatives have been evaluated. The demethoxycarbonylation of alkylthio or aryl thio analogues led to esters as an isomeric mixture with the trans isomers in a large excess, whereas in the sulfonyl analogues the dealkoxycarbonylations were diastereoselective and led exclusively to the trans-derivatives. For example, the sulfonyl analogue 183 on treatment with DMSO, NaCl and water (reflux, 4 h) led to trans-184.120a,b,c

Treatment of 185 with DMSO, NaCl and water (reflux) led to 186 (80%, isomeric mixture).121

In a synthesis leading to 1,2,3-trisubstituted cyclopropanes, the demethoxycarbonylations of several isomeric cyclopropanes have been evaluated. Treatment of 187 with DMSO, LiCl and water (195°C, 2 h) led to 188 (2R,3S,E) and 189 (96%) in a 1:1 product ratio which could be separated by chromatography.122

The diester 190 on treatment with DMSO and NaCN (150°C, 23 h) led to racemic 191 (15%, 9:1 trans:cis) which could be crystallized to obtain pure trans product. This was resolved to give...
enantiomerically pure 191 (1R,3R). This was converted into a cyclopropyl guanidine for evaluation of its activity against the sodium hydrogen exchanger isoform-I.\textsuperscript{123}

![Diagram 190 to 191]

Treatment of 192 with DMSO and NaCN (160°C, 1.5 h) led to the demethoxycarbonylated products 193 and 194 (47%, 1:1 ratio).\textsuperscript{124}

![Diagram 192 to 193 and 194]

Treatment of 195 in DMF, NaCl and water led to methyl caronate 196 (high yield) which could be converted into chrysanthemates.\textsuperscript{125}

![Diagram 195 to 196]

Treatment of 197a or 197b with DMSO, LiCl and water (190°C, overnight) afforded mono ester 198a (80%) or 198b (78%), respectively.\textsuperscript{126}

![Diagram 197 to 198]

In a route to the total synthesis of kempane diterpenes, the intermediate racemic diesters 199a and 199b underwent demethoxycarbonylation on treatment with DMF, NaCN, and water (120°C, 5 h) to afford the mono esters 200a (85%) and 200b (81%), respectively.\textsuperscript{127}
The demethoxycarbonylation of racemate 201 using DMSO, LiCl and water (130°C) led to the product 202, with rearrangement of the double bond (90%).

Treatment of 203 with DMSO and NaCN (160°C) led to 204 (63%) which was converted into azanoradamantyl amine in a subsequent series of steps.

7.1.9. Alkyl–alkenyl
The diester 205 on treatment with DMSO, NaCN and water (170°C, 5 h) led to 206 (82%), an intermediate used in the synthesis of furanoid terpenes.

Treatment of 207 with DMSO, NaCl and water (190°C, 12 h) led to 208 (85%). This intermediate was converted into methyl 2,6,10-trimethyltridecanoate, a male-produced pheromone of several stink bugs.
7.1.10. Alkenyl-bromoalkyl
Treatmen of diester 209 with NaCN in DMSO and water led to decarboethoxylation and displacement of the terminal Br to afford cyano ester 210 (60%).132

7.1.11. Alkenyl-fluoro
The deethoxycarbonylation of the α-fluoro diester 211 to the α-fluoro ester 212 (78%) can be accomplished by heating in DMSO, NaCl, and water (reflux, 4 h).133

7.1.12. Alkenyl-alkenyl
Upon heating diester 213 in anhydrous DMSO and KCN (140°C, 43 h), the pseudo-C2-symmetrical carboxylic acid 214 (3R,1R) (93%) was obtained. These analogues could be desymmetrized and utilized in a target-directed synthesis.134

The decarbalkoxylation of several disubstituted malonates were shown to proceed in good yields when heated with LiCl and water in [bmim]Br to afford the corresponding esters. This ionic liquid functions as an alternative to the use of dipolar aprotic solvents such as DMSO or DMF. Upon heating diester 215 with LiCl and water in the presence of [bmim]br (217) (160°C, 14 h) the mono ester 216 (99%) was obtained.135

Treatment of 218 with DMSO, NaCN and water (95°C, 48 h) afforded 219 (72%).136
Treatment of 220 with DMSO, NaCN and water (95°C, 25 h), with the addition of more NaCN, with stirring for 25 h at 95°C led to the decarbomethoxylated product 221 (88%).

The demethoxycarbonylations of several disubstituted malonate esters with unsaturated side chains have been reported. A typical example is the conversion of 222 on treatment with DMSO, NaCN and water (95°C, 3 h) to yield 223 (81%).

7.1.13. Alkynyl – alkynyl
Treatment of the bis-propargyl substituted diester 224 with DMSO, LiCl and water (reflux, 2 h) led to the deethoxycarbonylated product 225 (82%).

The demethoxycarbonylation of 226 with DMSO, NaCN (100°C) led to 227 (58%).

Treatment of malonate ester 228 in DMSO and NaCN (120°C, 4 h) led to the demethoxycarbonylated product 229 (62%).
7.1.15. Alkenyl-heterocyclic
The substituted imidazole 230 on treatment with DMSO, NaCN and water (120°C, 48 h) led to the deethoxycarbonylation product 231 (45%). Further elaboration of this product led to histamine analogues as potential cardiovascular selective H2 agonists.142

7.1.16. Ethynyl-heterocyclic
The malonate ester 232 (140 g) underwent a deethoxycarbonylation when heated in DMA or DMPU with a large excess of LiBr (85°C, 16 h) to afford the (pyridonyl-1)propargyl acetic ester 233 (87%, 99.5% HPLC purity). This was a key intermediate for the synthesis of a selective inhibitor of a human rhinovirus.143

7.1.17. Cyclopropyl-dichloroalkenyl
A number of halo substituted 4-alkenoic esters have been prepared via the dealkoxycarbonylation procedure. For example, treatment of malonate ester 234 with DMSO, NaBr and water (190°C, 8 h) led to monoester 235 (80%).144

7.1.18. Carbocyclic-1,1-dicarboxylic acid diesters
Treatment of 236 with DMF, LiCl and water (reflux, 48 h) led to 237 (41%) and 238 (29%).145
7.1.19. Heterocyclic-1,1-dicarboxylic acid dialkyl diesters

The deethoxycarbonylations of bis-carbethoxy-\(\beta\)-lactams under microwave irradiation have been studied. As an illustrative example, 239a and 239b using LiCl in DMF under microwave irradiation led to product 240 (50%).

The deethoxycarbonylation of 241 using DMF, LiCl, and water (130°C, 3 h) led to azetidinone 242 (93%, trans:cis 36.3:1), which was subsequently converted into a tryptase inhibitor BMS-262084 (99%ee) for potential treatment of asthma. A study was also performed on the use of other N-protecting groups and the effect of water on the diastereoselectivity of the reaction.

Treatment of azetidin-2-one 243 with DMSO, NaCl and water (reflux, 4 h) afforded predominantly cis-3-phenylthio-4-ethoxycarbonylazetidin-2-one (244) along with small amounts of the trans isomer, cis:trans ratio (12:1).

The deethoxycarbonylations of several N-aryl- and N-aralkyl-4-oxo-azetidine-2,2-dicarboxylates were performed using DMSO, NaCl and water (170-180°C, 5 h). For example,
treatment of 245 led to 246 (94%). Other related dealkoxycarbonylations have been reported.\textsuperscript{149-150a,b,c}

\[
\begin{align*}
\text{245} & \rightarrow \text{246} \\
\end{align*}
\]

The deethoxycarbonylation of diethyl ester 257 using DMSO and LiCl under anhydrous conditions in the presence of molecular sieves and 2,6-di-tert-butyl-4-methylphenol (140°C, 2 h) led to (2S,1’S)-258 and (2R,1’S)-259 (78%) (diastereoisomeric ratio 2.7:1) which could be separated by column chromatography. These isomers were utilized in a synthesis of (S)-azetidine-2-carboxylic acid.\textsuperscript{151}

\[
\begin{align*}
\text{257} & \rightarrow \text{258} + \text{259} \\
\end{align*}
\]

The demethoxycarbonylation of 260 with DMSO, LiCl and water (165-170°C, 70 min) led predominantly to 261 (83%).\textsuperscript{152}

\[
\begin{align*}
\text{260} & \rightarrow \text{261} \\
\end{align*}
\]

Treatment of 262 with DMSO, LiCl and water (140-145°C, 4 h) afforded a mixture of 263 and 264 (80%, ratio cis:trans 89:11), which could be separated.\textsuperscript{153}

\[
\begin{align*}
\text{262} & \rightarrow \text{263} + \text{264} \\
\end{align*}
\]

The diester 265 in DMSO, NaCl and water (reflux, 24 h) led to the demethoxycarbonylation product 266 (69%) with the ketal group intact.\textsuperscript{154a,b}
Upon treatment of the diester rac-267 with DMSO, NaCN and water (110°C, 20 h) a diastereoisomeric mixture of rac-268 (6.7:1) was obtained. These diastereoisomers could be separated by chromatography to afford rac-268 as the major product. Chiral diester 267 (97% ee) led to enantiomer 268.\[155\]

The demethoxycarbonylation of 269 with DMSO, LiCl and water (reflux until no further gas evolution) led to 270a:270b (85%) in a 4:1 ratio which could be separated by chromatography.\[156\]

The pyrrolidinone 271 on treatment with DMSO, NaCl and water led to 272. However it was found that treatment of 271 with LiBr in DMI (1,3-dimethyl-2-imidazolidinone) and water (155°C) led to 272 (64%) as an inseparable mixture of C-5 isomers (ratio 1:1).\[157\]

In routes leading to the preparation of tetrahydro-β-carboline analogues, the deethoxycarbonylation of 273 using DMSO, LiCl and water (180°C, 7 h) led to a diastereoisomeric mixture of 274 (98%) which could be separated by TLC.\[158\]
The deethoxycarbonylation of the silacyclopentane analogue 275 with DMSO, NaCl and water (no conditions reported) led to monoester 276 (90%).

Treatment of 277 with DMSO, LiCl and water (170-180°C, 5 h) to 278 (96%) as a mixture of diastereomeric esters used in a multi-step synthesis of vinblastine analogues.

The deethoxycarbonylations of several 3,4-dihydro-β-carbolines with DMSO, LiCl and water (170°C, 7-9 h) led to the 5,6 and 7-acylamino-β-carbolines. As an illustrative example, analogue 279 led to 280 (30%).

Treatment of racemic 281 with DMSO, NaCl and water (140°C, 20 min) led to racemic 282 (75%) which was utilized in a synthesis of quinocarcinol. In the decarbomethoxylation process, about 10% of the endo-carbomethoxyl analogue was also obtained.
Treatment of 283 with DMSO, NaCl and water (190°C, 25 min) led to the demethoxycarbonylated pyrimidine-5-carboxylate 284 (21%).  

Diester 285 on treatment with DMF, LiCl and water (110°C, 10 h) led to 286a and 286b which were separated by preparative tlc. Several other related systems were also dealkoxycarbonylated.

7.1.20. 2-Acylamino substituted analogues
Treatment of 287 with DMSO and LiCl (120°C, 2 h) led to 288 (88%). On the other hand, the corresponding sulfoxide under similar conditions led to (Z)-ethyl-2-acetylamino-2-butenoate (38%).

Treatment of the diester 289 with DMF, LiBr and water (reflux, 6 h) led to 290 (unspecified yield). It was also noted that the use of LiBr led to dramatic increases in the rate of reaction in comparison to other salts. This intermediate was utilized for the synthesis of several optically active unnatural amino acids.
In pathways leading to 3-deoxy sphingolipids, the diester 291 on treatment with DMSO, NaCl and water (reflux, 18 h) led to intermediate 292 (82%).

Treatment of 293 with DMF, NaCl and water (150°C, 4 h) led to 294 (58%).

The decarboethoxylation of the stannyl substituted derivatives 295a and 295b on treatment with DMF, LiCl and water (reflux, 12 h) led to poor yields of 296a (4.2%) and 296b (5.8%), respectively.

Treatment of 297 with DMSO, NaCl and water (165°C, 8 h) led to the deethoxycarbonylation product 298 (73%).

In synthetic pathways to carbazole-linked cyclic peptoids, treatment of 299 with DMSO, LiCl and water (reflux, 1.75 h) led to intermediate 300 (70%).
Treatment of 301 with DMSO, NaCl and water (200°C, 15 min) led to 302 (53%).

Treatment of the fluorinated analogue 303 with DMF, LiBr and water (reflux, 270 min) led to the deethoxycarbonylation product 304 (73%), which was converted into optically active p-azidotetrafluorophenylalanine and further evaluated as a potential photoaffinity reagent.

Treatment of the substituted isoxazole 305 with DMSO, NaCl and water (160°C, 7 h) led to mono ester 306 (78%). Further elaboration by a α-chymotrypsin resolution led to the corresponding amino acid.

Treatment of 307 with LiCl or LiBr in DMSO and water (120°C, 2 h) led only to the deacylation products along with the acetamido substituted diethyl malonate. If 307 is heated with DMSO and water (2 eq) (reflux, 2 h) 308 (62%) was obtained and a mechanism has been proposed.
7.1.21. Aryl-heteroaryl
The extended malonate system on treatment with DMSO and 3 eq of NaCN (170-180°C, 1-2 h) led to decarbomethoxylation and ester cleavage of the p-CO₂Me group to yield the 2,4-diamino-10-alkyl-8,10-dideazapteric acid.¹⁷⁶,¹⁷⁷ For example, under these conditions, the methyl substituted derivative 309 led to 310 (96%).¹⁷⁶

7.1.22. Bis-cyclic malonic ester
Treatment of the tetra ester 311 under Krapcho’s conditions (not specified) led to cis,cis-3,8-cyclocdecadiene-1,1,6,6-tetracarboxylate (312).¹⁷⁸

7.1.23. Substituted α-difluorobromomethyl malonate
The conversion of malonic esters to esters holding an α-CF₃ group has been accomplished by a dealkoxycarbonylation-fluoridation route. Treatment of α-bromodifluoromethyl substituted malonates 313 with KF in dry DMSO (150°C) led to the α-CF₃ substituted esters 314. Low boiling products were isolated by distillation from the reaction mixture and the higher boiling esters by dilution of the reaction mixture with water and extraction into ether.¹⁷⁹a,b

R = Me, Et, n-Pr, n-Bu (35-61%)
7.1.24. Trimethyl methanetricarboxylate
Treatment of \(\text{315}\) with DMSO and KCN (2 eq) (90°C, 0.5 h) led the monodemethoxycarbonylation product \(\text{316}\) (63%). A similar procedure using the triethyl ester led to the diethyl ester.\(^{180}\)

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{OTHP} & \quad \text{MeO}_2\text{C} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\(\text{315}\) \(\rightarrow\) \(\text{316}\)

Some additional illustrative examples are tabulated in Table 2.

7.1.25. Dealkoxycarbonylation-eliminations
The demethoxycarbonylation of \(\text{317}\) on heating in DMSO (reflux, 2 h) led to the corresponding ethyl-2-benzofuran carboxylate \(\text{318}\) (75-80%), used in the preparation of analogues tested for histamine H\(_2\) receptor antagonist activity.\(^{200}\)

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{OH} & \quad \text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{N(CH}_3\text{)}_2 & \quad \text{O} & \quad \text{N(CH}_3\text{)}_2 & \quad \text{O} \\
\text{317} & \quad \text{318}
\end{align*}
\]

Treatment of \(\text{319}\) with DMSO, LiCl and water (165°C, 1 h) led to the benzofuran derivative \(\text{320}\) (86%).\(^{201a}\) A related example with a different substitution pattern in the aromatic ring has also been reported.\(^{201b}\)

\[
\begin{align*}
\text{OMe} & \quad \text{OH} & \quad \text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{MeO} & \quad \text{Me} & \quad \text{OMe} & \quad \text{Me} \\
\text{319} & \quad \text{320}
\end{align*}
\]
Table 2. Dealkoxycarbonylations of disubstituted malonate esters

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield(%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO2C=CO2Me</td>
<td>DMSO, NaCl, H2O, 150°C, 12 h</td>
<td>MeO2C=H</td>
<td>82</td>
<td>191</td>
</tr>
<tr>
<td></td>
<td>DMSO, LiCl, H2O, reflux, 5 h</td>
<td>MeCO2Et</td>
<td>75</td>
<td>192</td>
</tr>
<tr>
<td></td>
<td>DMSO, LiCl, H2O, reflux, 6 h</td>
<td>HCO2Et</td>
<td>86</td>
<td>193</td>
</tr>
<tr>
<td></td>
<td>DMSO, NaCl, H2O, 180°C</td>
<td>HCO2Me</td>
<td>72</td>
<td>194</td>
</tr>
<tr>
<td></td>
<td>DMSO, NaCl, H2O, 180°C, 12 h</td>
<td>HCO2Et</td>
<td>69</td>
<td>195</td>
</tr>
<tr>
<td></td>
<td>DMSO, NaCN, H2O, 150°C, 5 h</td>
<td>THPO</td>
<td>64</td>
<td>196</td>
</tr>
<tr>
<td></td>
<td>DMSO, KOAc, H2O, 140°C, 5 h</td>
<td>THPO</td>
<td>81</td>
<td>197</td>
</tr>
<tr>
<td></td>
<td>DMF, LiCl, 145-150°C, 7h</td>
<td>CH2Ph</td>
<td>90</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td>DMSO, NaCl, H2O, 150°C, 10 h</td>
<td>cis:trans 56:44</td>
<td>81</td>
<td>199</td>
</tr>
</tbody>
</table>

Treatment of a diastereoisomer mixture of (12R,12S) 321 with DMSO, NaCl and water (110-160°C, 3 h) and 160°C (0.5 h) led to the β-elimination of the acetoxy group to afford 322.
(1R,3R,8R,9R) (47%), along with some recovered starting material, which could be recycled. This derivative was used in a synthetic study of routes to the trichothecene sesquiterpenes.\(^\text{202}\)

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C} \\
\text{O} & \quad \text{O} \\
\text{Ac} & \quad \text{H} \\
\text{H} & \quad \text{O} \\
1 & \quad 9 \\
3 & \quad 8 \\
9 & \quad 1
\end{align*}
\]

The decarbomethoxylation of \(^{323}\) using DMSO, NaCl and water (160°C, 4 h) led to β-elimination of the OH group to form the enantiomerically pure α,β-unsaturated ester \(^{324}\) (80%). This intermediate could not be converted into enantiomerically pure 2-oxospiroalkanes.\(^\text{203}\)

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{HO} & \quad \text{MeO}_2\text{C} \\
\text{O} & \quad \text{MeO}_2\text{C} \\
\end{align*}
\]

A convenient synthesis of 2-alkenoic esters involved treatment of numerous β-substituted derivatives with solvents such as DMSO, DMF or HMPT and salts such as NaBr or LiCl (130°C, 5 h). For example, treatment of \(^{325}\) with HMPT, NaBr at 135-140°C for 5 h gave \(^{326}\) (86%) with an E/Z ratio of 88:12.\(^\text{204,205}\)

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{OH} & \quad \text{MeO}_2\text{C} \\
\text{O} & \quad \text{MeO}_2\text{C} \\
\end{align*}
\]

The demethoxycarbonylation of \(^{327}\) using DMF and LiI (160°C) led to \(^{328}\)-(Z) (14%) and \(^{329}\)-(E) (52%), respectively.\(^\text{206}\)
7.1.26. Substituted heterocyclic system
Treatment of the imidazo[1,2a]pyridine 330 with DMSO, NaCl and water (150°C, 5 h) led regioselectively to the 6-methoxycarbonyl derivative 331 (61%).

\[
\begin{array}{c}
\text{Ph} \quad \text{CO}_2\text{Me} \\
330 \\
\text{Ph} \quad \text{CO}_2\text{Me} \\
331
\end{array}
\]

7.1.27. Cinnamic esters: from arylmethylenepropanedioic acid dimethyl esters
The dealkoxy carbonylations of arylmethylenepropanedioic acid dimethyl esters (332) in DMSO-NaCl-H\(_2\)O (and in DMF with other salts) have been studied. In general, the esters led predominantly to the trans-cinnamic esters (333).

\[
\begin{array}{c}
\text{H} \quad \text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} \\
332 \\
\text{H} \quad \text{CO}_2\text{Me} \\
\text{NaCl, DMSO or DMF} \\
165^\circ\text{C}, 6\text{h} \\
40-50\% \\
333 \quad \text{R} = \text{H, o-Me, o-OMe, o-OCH(CH}_3)_2\text{, p-Me, p-OMe, p-NO}_2
\end{array}
\]

8. Conclusions
The dealkoxy carbonylation procedure is a useful synthetic method for the formal replacement of a CO\(_2\)R moiety with a H atom and should continue to find numerous applications in synthetic strategies.

9. References


Author

A. Paul Krapcho was born in Alden Station, PA on March 6, 1932. He did his undergraduate work at Penn State (B.S. in Chemistry, 1953) and graduate studies at Harvard University (Ph.D. 1957). He then spent the 2-year period of 1957-1959 teaching at Smith College and then held a
post-doctoral position at Penn State from 1959-1960 (with Phil Skell). In 1960 he joined the faculty at the University of Vermont, where he is currently an Emeritus Professor of Chemistry still active in research. He has directed the research of numerous undergraduate and graduate students in projects related to natural product synthesis, solvolytic studies of spiro analogues, reaction mechanism studies of metal-ammonia reductions, chemistry of carbenes (or carbenoids), reactions of α-anions of acids and esters, and the preparation of anticancer heterocyclic analogues. Krapcho has been a Fulbright scholar at the University of Montpellier, France (1968-1969), a research scholar at Stanford University (1976-1977) and an invited lecturer at Addis Ababa University in Ethiopia (1981). He was a research scholar at Duke University (1983-1984), the University research scholar in Physical Sciences (1990), a visiting Professor at the University of Auckland Medical School in Auckland, New Zealand (Spring 1991) and, for a short period, at Humboldt University in Berlin, Germany (1998). He has been involved over the past 15 years in a collaborative anticancer drug development program initially with the Vermont Cancer Center, and then with Novuspharma SpA of Milan, Italy (recently merged with CTI) and the University of Padova, Padova, Italy. These projects deal with the synthesis of telomerase inhibitors. Recently (2005-present) he was awarded a Dreyfus Senior Scientist Mentor grant. Krapcho is a Scientific Editor for ARKIVOC (2000-present) and a Co-Editor-in-Chief of Mini-Reviews in Medicinal Chemistry (2001-present).