Synthetic Applications of Dealkoxycarbonylations of Malonate Esters, β-Keto Esters, α-Cyano Esters and Related Compounds in Dipolar Aprotic Media – Part II

A. Paul KRAPCHO

Department of Chemistry, The University of Vermont, Burlington, Vermont 05405, U.S.A.

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5. β-Keto Esters

In our original publication it was reported that the β-keto esters 180, 181 (mixture of methyl and ethyl esters), and 182 (mixture of methyl and ethyl esters) underwent dealkoxycarbonylations on being heated in wet DMSO containing sodium chloride (130–150 °C, 2–4 h) to yield the respective ketones in excellent yields°.

\[
\begin{align*}
&\text{180} \\
&\text{181} \\
&\text{182}
\end{align*}
\]

It was then shown that some β-keto esters undergo dealkoxycarbonylations on being heated in aqueous DMSO without added salts°.°.°.°.°. On the other hand, β-keto esters with no α-hydrogens require the presence of a salt to effect dealkoxycarbonylations.

5.1. Monosubstituted Substrates

5.1.1. Mono-dealkoxycarbonylations

The acyclic substrates 180, 183, 184a, and 184b undergo deethoxy carbonylations to the respective ketones (70–80% yields) on being heated in aqueous DMSO°.°.°.°.°.

\[
\begin{align*}
&\text{180} \\
&\text{183} \\
&\text{184a} \\
&\text{184b}
\end{align*}
\]

\[
\begin{align*}
&\text{184a} \\
&\text{184b}
\end{align*}
\]

6-Methyl-2-tridecanone (186)°.°

The keto ester 185 (980 mg, 3.4 mmol) is heated in DMSO (10 ml) containing water (1 g, 56 mmol) for 6 h. After cooling, the mixture is poured into water (40 ml) and the product extracted with pentane (4 x 10 ml). Evaporation of the pentane and distillation under reduced pressure give the ketone 186; yield: 550 mg (75%); b.p. 110°C/13 torr (bath temperature).

Deethoxy carbonylations of the β-keto esters 187 and 188 can readily be accomplished by heating in wet DMSO (155 °C for 4 h) to give 189 (95%) and 190 (96%), respectively°.°.

\[
\begin{align*}
&\text{187} \\
&\text{188} \\
&\text{189} \\
&\text{190}
\end{align*}
\]

2-Heptanone°.°.°

Ethyl 2-acetylhexanoate (184b: 6.12 g, 0.03 mol) and water (1.08 g, 0.06 mol) are dissolved in DMSO (25 ml) in a 2-necked round bottom flask fitted with a condenser and magnetic stirrer. The reaction vessel is placed in a pre-heated oil bath at 210 °C and the mixture heated for 4 h. The reaction mixture is cooled and the product distilled; yield: 3.62 g (1H-N.M.R. analysis shows the presence of ~33% ethanol; overall yield of ketone: 70%); b.p. 150–153 °C.

The β-keto ester 185 on heating in DMSO containing a little water (165 °C for 6 h) yields ketone 186 (75%)°.°.
cis-Bicyclo[4.3.0]-3-nonen-8-one (189)\textsuperscript{114}.

The cis-\(\beta\)-keto ester 187 (10.4 g, 50 mmol) is heated at 155 °C for 4 h with water (2 g, 111 mmol) in DMSO (45 ml) under an argon atmosphere. After cooling, the mixture is poured into water (150 ml), extracted with light petroleum (4 x 25 ml), the extracts are dried, and concentrated. The product is obtained by distillation under reduced pressure; yield: 6.2 g (95%); b.p. 50–53 °C/0.3 torr.

In a similar manner, cis-191a on heating in wet DMSO yields cis-193a (49%), based on keto ester 187 which was methylated to prepare 191a. This product was contaminated with 189 (12%), trans-192a reacts similarly to yield 194a [50%, contaminated with 190 (4%)]. The deethoxy carbonylation of cis-191b gives 193b (50%), containing 190 (12%) from unmethyalted 188. trans-192b reacts to give 193b (79%)\textsuperscript{115}.

Heating 195 in aqueous DMSO yields ketone 196 (74%, based on acid chloride derived from 195)\textsuperscript{116}.

The deethoxy carbonylation of 197 on heating with DMSO containing water (170 °C, reflux, 4 h) and quenching with water gives the isocoumarin 198 (58%)\textsuperscript{117}. This is the enol lactone of the keto acid formed on deethoxy carbonylation.

Demethoxy carbonylation of 199 (DMF/water/sodium chloride, reflux, 4 h) yields 200 (~70%)\textsuperscript{59}.

Treatment of the \(\beta\)-keto ester 201 with sodium chloride in wet DMSO (160 °C, 9 h) yields 202 (56%)\textsuperscript{118}.

The ethoxy carbonyl group in 203 can readily be removed by heating in wet DMSO containing some sodium chloride (170 °C, 8 h) to yield 204 (70%)\textsuperscript{119}. In a similar manner, 205 can be converted into 206 (60%)\textsuperscript{200}.\textsuperscript{200}

Treatment of 207 with wet DMSO containing sodium cyanide (160–165 °C, 3 h) not only effects the deethoxy carbonylation but displaces bromide to yield the cyano ketone 208 (28%)\textsuperscript{121}.

The deethoxy carbonylation of 209 (prepared from methyl oleate by condensation in the presence of sodium hydride) with sodium chloride in wet DMSO (145 °C, 8 h) leads to 210 (95%). Intermediate 210 was utilized in the preparation of civetone (as a mixture of Z- and E-isomers)\textsuperscript{122}.

18-Oxopentriaconta-8,26-diene (210)\textsuperscript{122}.

The crude \(\beta\)-keto ester 209 (22.3 g, 40 mmol) is added to a solution of sodium chloride (2.3 g, 40 mmol) and water (2.1 g, 116 mmol) in DMSO (30 ml). The solution is heated at 145 °C under an inert atmosphere for 8 h and then cooled. Workup by quenching and extraction gives the ketone 210; yield: 19 g (95%); homogeneous by T.L.C.
Treatment of diketo ester 211 with sodium chloride in DMSO (no water added, 160 °C, 20 h) led to 212 (88%)\(^\text{123}\).

The deethoxy carbonylation of 213 to yield 214 (92%) can be accomplished by heating in wet DMSO containing sodium chloride\(^\text{124}\).

4-(1-Cyclohexenyl)-2-butane (214)\(^\text{124}\):
A mixture of 213 (44.8 g, 0.2 mol), sodium chloride (14.6 g, 0.25 mol), water (11 g, 0.6 mol), and DMSO (150 ml) is heated with stirring for 10 h at 140–150 °C. The mixture is cooled, poured into water (500 ml), and the product extracted into pentane (5 x 100 ml). The pentane extract is washed with saturated aqueous sodium hydrogen carbonate and sodium chloride solutions. Concentration and distillation under reduced pressure gives 214; yield: 28 g (92%); b.p. 81–83 °C/6 torr.

The methoxy ketone 215 on treatment with DMSO containing water and sodium chloride (6 h at reflux) led to 216 in a poor yield\(^\text{125}\).

The deethoxy carbonylation of β-keto ester 217 (wet DMSO/sodium chloride) gives 218 (no yield listed) and 219 (from a retro-Michael reaction)\(^\text{126}\).

Demethoxy carbonylation of 220 with lithium chloride in wet DMSO gives the cyclopentanone 221 (70%)\(^\text{127}\).

3-(6-Methyl-2-oxoheptyl)-cyclopentanone (221)\(^\text{127}\):
The crude 2-methoxy carbonylcyclopentanone 220 (118 mg, 0.46 mmol) is dissolved in DMSO (2 ml) containing water (10 µl) and lithium chloride (58 mg, 1.4 mmol). The mixture is placed in a preheated oil bath at 120 °C for 1.5 h, cooled, and ether and water added. The ether phase is washed with water, and dried with magnesium sulfate, and the solvent removed by distillation through a 15-cm glass-packed column. The product is Kugelrohr distilled; yield: 64 mg (70%); b.p. 60–64 °C/0.3 torr (bath temperature).

The demethoxy carbonylations of the β-keto esters 222a\(^\text{128}\) and 222b\(^\text{129}\) on heating in DMSO and lithium iodide yield the cyclopentanones 223a (76%) and 223b (61%), respectively.

Deethoxy carbonylations of 224a, b, and c with sodium chloride in DMSO (120 °C, 1.5–2.5 h) lead to the ketones 225a, b, and c in 90%, 70%, and 90% yields, respectively\(^\text{130}\).

Intramolecular Michael addition of 226 (sodium methoxide in methanol) leads to 227 which can be demethoxy carbonylated (sodium chloride in wet DMSO) to give the cis-2,6-indandione 228 (~45% overall yield)\(^\text{131}\).
The \( \beta \)-keto ester 229 was deethoxycarbonylated by refluxing with a mixture of wet DMSO and sodium chloride to yield 230 (40\%)\(^{132} \).

![Chemical structures](image)

Demethoxycarbonylation of 231 can readily be accomplished by heating with sodium chloride in DMF/water (10:1, 120 °C, 3 h) to yield 232 (94\%)\(^{133} \).

![Chemical structures](image)

Deethoxycarbonylation of 233a with wet DMSO containing some sodium chloride yields ketone 234a (72\%). In a similar experimental manner, 233b was converted to 234b (19\%)\(^{25} \).

![Chemical structures](image)

2-Amino-3-cyano-5-(2-ethoxycarbonyl)ethyl) pyrazine (234a)\(^{14} \):
The \( \beta \)-keto ester 233a (10.2 g, 0.039 mol), sodium chloride (2.8 g, 0.048 mol), and water (2.8 g, 0.156 mol) in DMSO (~300 mL) are placed in a three-necked 50-mL round bottom flask fitted with a thermometer, condenser, and magnetic stirrer. The mixture is heated at 155–170 °C for 6 h, cooled, and poured into water (50 mL). The aqueous solution is extracted with chloroform (4×30 mL). The extracts are dried with sodium sulfate, filtered, and evaporated. Crystallization from benzene gives a white crystalline solid; yield: 5.3 g (72\%); m.p. 130–131 °C.

![Chemical structures](image)

Demethoxycarbonylation of 235 with sodium chloride in hot, wet DMSO gives 236 (74\%)\(^{134} \). Treatment of 237 with lithium diphenylcuprate gives 238 which on being subjected to deethoxycarbonylation (sodium chloride, hot, wet DMSO) gives 239 (65\% overall conversion). Reaction of 237 with diethylaluminum cyanide in toluene gives 240 which on deethoxycarbonylation as above gives 241 (69\%)\(^{134} \).

![Chemical structures](image)

Treatment of 242 (unspecified regio- and stereochemistry) with sodium chloride in wet DMSO gives 243 (85\%)\(^{135} \).

![Chemical structures](image)

The deethoxycarbonylation of the steroid \( \beta \)-keto ester 244 has been effected by heating in wet DMSO containing sodium chloride to give 245 (unspecified yield)\(^{136} \).

![Chemical structures](image)

Reaction of 246 with wet DMSO containing sodium chloride (180–185 °C, 3.5 h) leads to (3\( R \))-2,2-dimethyl-3-deuteriocyclohexane (247) in ~50% yield\(^{137} \).

![Chemical structures](image)

In a synthesis leading to chiral 3-substituted cyclopentanones and cyclohexanones following a cyclization
route, the dealkoxycarbonylation of $\beta$-ketosteres was
effectected with sodium chloride in wet DMSO. The
demethoxycarbonylation of chiral 248 in this manner led
to crude 249 which was converted into acetal 250 (67% yield
from 248). In a similar fashion chiral 251 was
converted into 252.\(^{138}\)

```
  \[
  \begin{align*}
    &\text{COOR}^* \quad \text{DMSO/H$_2$O/}
    \\
    &\text{NaCl, } \uparrow \quad \text{H$_2$C=CH$_2$}
    \\
    &\quad \rightarrow \quad \text{H$_2$C=CH$_2$}
    \\
    &\text{COOR}^* \quad \text{DMSO/H$_2$O/}
    \\
    &\text{NaCl, } \uparrow \quad \text{H$_3$C}
    \\
    &\quad \rightarrow \quad \text{H$_3$C}
    \\
    &\text{COOC$_2$H$_5$} \quad \text{DMSO/H$_2$O/}
    \\
    &\text{NaCl, } \uparrow \quad \text{H$_2$C}
    \\
    &\quad \rightarrow \quad \text{H$_2$C}
  \end{align*}
\]
```

The demethoxycarbonylation of 253 (wet DMSO with
sodium chloride present) yields 254 (68%). This
compound was converted into 255 which was used in a
photochemical study.\(^{139}\)

**4-Cyano-4-phenylcyclohexanone (254)**\(^{140}\):
A solution of 253 (85.5 g, 0.333 mol), water (18.5 g, 1.02 mol), and so-
dium chloride (20.97 g, 0.36 mol) in DMSO (300 ml) is heated to
130 °C in an oil bath at 160 °C for 2 h. The cooled reaction mixture
is poured into water (500 ml) and extracted with benzene (5 \times 100 ml).
The combined extracts are washed with water (100 ml) and saturated
sodium chloride solution (100 ml) and dried with calcium sulfate. The
solvent is removed in vacuo and the ketone recrystallized from ethanol;
yield: 45.2 g (68%); m.p. 115-117 °C.

```
  \[
  \begin{align*}
    &\text{COOC$_2$H$_5$} \quad \text{DMSO/H$_2$O/}
    \\
    &\text{NaCl, } \uparrow \quad \text{H$_3$C}
    \\
    &\quad \rightarrow \quad \text{H$_3$C}
  \end{align*}
\]
```

Compound 256 can be deethoxycarbonylated with so-
dium chloride in wet DMSO to yield cyclohexanone
257 (95%)\(^{140}\).

```
  \[
  \begin{align*}
    &\text{COOC$_2$H$_5$} \quad \text{DMSO/H$_2$O/}
    \\
    &\text{NaCl, } \uparrow \quad \text{H$_3$C}
    \\
    &\quad \rightarrow \quad \text{H$_3$C}
  \end{align*}
\]
```

Treatment of 258 with sodium chloride in wet DMSO
at 165 °C yields diketone 259 (no yield listed).\(^{141}\)

```
\begin{align*}
  \text{258} & \quad \text{COOC$_2$H$_5$} \quad \text{DMSO/H$_2$O/}
  \\
  & \quad \text{NaCl, } \uparrow \quad \text{H$_3$C}
  \\
  \end{align*}
```

The Dieckmann cyclization of 260 to 261 can be
accomplished by use of sodium hydride in DMSO and
the resulting sodium salt of the $\beta$-keto ester 261 was
neutralized with concentrated hydrochloric acid. The
DMSO reaction mixture was degassed with nitrogen
and heated at 150 °C for 3-6 h. After workup, 65-88% yields of 262 could be obtained.\(^{142}\) The addition of potas-
sium cyanide also effected demethoxycarbonylation
while other inorganic salts (lithium chloride or sodium
acetate) had a deleterious effect on the demethoxycar-
bonylation. In DMF, however, lower yields were ob-
tained. Similarly, the one-pot procedure to 264 from
263, via intermediate 264, was also reported.\(^{142}\)

```
\begin{align*}
  \text{260} & \quad \text{COOCH$_3$} \quad \text{[CH$_2$]$_n$-COOCH$_3$} \quad \text{NaH/}
  \\
  & \quad \text{DMSO} \quad \text{[CH$_2$]$_m$}
  \\
  \text{261} & \quad \text{(m = 1)} \quad \text{264} \quad \text{(m = 2)}
\end{align*}
```

The $\beta$-keto ester 265 on refluxing with DMSO contain-
ing a little water (170-180 °C for 6 h) and sodium chlor-
ide undergoes a smooth deethoxycarbonylation to give
266 (85%)\(^{143}\).

```
\begin{align*}
  \text{265} & \quad \text{COOC$_2$H$_5$} \quad \text{DMSO/H$_2$O/}
  \\
  & \quad \text{NaCl, } \uparrow \quad \text{H$_3$C}
  \\
  \end{align*}
```

Treatment of 267 with sodium hydride in dimethoxy-
ethane leads to the annelled product 268. This latter
compound on heating with sodium chloride in wet
DMSO yields a crude product which consists of 269,
270, and 271 in 56%, 23%, and 21% yields, respective-
ly.\(^{144}\)
The demethoxycarbonylation of \(272\) with dry sodium cyanide in dry DMSO (107 °C, 40 h) leads to \(273\) (58%)\(^{145}\).

Treatment of \(274\) with sodium chloride in wet DMSO (160 °C) affords \(275\) (no yield given)\(^{146}\).

In the preparation of deuterated cycloheptanones, dealkoxycarbonylations have played a significant role. The \(\beta\)-keto ester \(276\) on heating in wet DMSO containing sodium chloride leads to \(277\) (85%)\(^{147}\). The 3,3,6,6-\(^2\)H\(_4\) system corresponding to \(277\) could be prepared in a similar manner in 75% yield.

5.1.3. Vinylogous \(\beta\)-Keto Esters

The deethoxycarbonylation of Hagemann’s ester (\(288\)) can be effected with lithium chloride in wet DMSO to prepare 3-methyl-2-cyclohexenone (\(289\), 70%)\(^{151}\).

Reaction of \(290\) with wet DMSO containing sodium chloride at 150 °C until the evolution of carbon dioxide stops leads to \(291\) (36%)\(^{152}\).
5.1.4. Heterocyclic Substrates

Compound 292 can be quantitatively converted into 293 by heating in DMF containing some water and sodium chloride\(^{153}\).

\[
\text{H}_2\text{O}/\text{DMF/NaCl} \quad \text{H}_2\text{O}/\text{DMF/NaCl} \quad \text{H}_2\text{O}/\text{DMF/NaCl}
\]

\[
\text{292} \quad \text{293} \quad \text{294 a} R^1 = \text{COOCH}_3, R^2 = \text{H} \\
\text{294 b} R^1 = \text{H}, R^2 = \text{COOCH}_3
\]

Treatment of a mixture of the methoxycarbonylpyrrolidones 294 with sodium chloride in DMSO at 140 °C gives the pyrrolidine 295 (65%)\(^{164}\).

\[
\text{R}^1 \text{CH}_2\text{C} = \text{CH}_2\text{COOCH}_3 \quad \text{NaCl/DMF, 140 °C} \quad \text{R}^1 \text{CH}_2\text{C} = \text{CH}_2\text{COOCH}_3
\]

\[
\text{294 a} \quad \text{295}
\]

\[
\text{R}^1 = \text{COOCH}_3, R^2 = \text{H} \\
\text{R}^1 = \text{H}, R^2 = \text{COOCH}_3
\]

The bis-dimethoxycarbonylation of 296 (sodium chloride/water/DMF) yields ketone 297 (56%)\(^{99}\). The facile synthesis of 296 and the conversion of 297 into two ladybug defensive alkaloids coccinelline and precoccinelline make this an attractive synthetic route.

\[
\text{N} \quad \text{COOCH}_3 \quad \text{H}_2\text{O}/\text{DMF/NaCl} \quad \text{N} \quad \text{COOCH}_3
\]

\[
\text{296} \quad \text{297}
\]

2-Oxopropyno-9b-azaphenalen (297)\(^{99}\):

The keto ester 296 (1 g, 3.23 mmol), sodium chloride (0.2 g, 3.42 mmol), and water (2 ml, 11.1 mmol) are dissolved in DMF (15 ml) and heated at reflux under nitrogen for 4 h. The solvent is removed in vacuo and the residue taken up in dichloromethane (10 ml) and filtered through a short column of neutral alumina. Purification is accomplished by chromatography on neutral alumina by eluting with ethyl acetate/hexane (1:1) to give 297; yield: 0.35 g (65%); m.p. 83 °C.

In syntheses of indoloquinolizines, the deethoxycarbonylations of lactams have been important. Deethoxycarbonylation of 298 (an epimeric mixture) by heating in wet DMSO containing water and lithium chloride leads to 299 (89%)\(^{155}\).

\[
\text{298} \quad \text{H}_2\text{O}/\text{DMF/LiCl} \quad \text{H}_2\text{O}/\text{DMF/LiCl} \quad \text{H}_2\text{O}/\text{DMF/LiCl}
\]

\[
\text{298} \quad \text{299}
\]

Deethoxycarbonylation of 300 occurs on heating in wet DMF to give 301 (95%)\(^{156}\).

\[
\text{Cl} \quad \text{Cl} \quad \text{H}_2\text{O}/\text{DMF} \quad \text{H}_2\text{O}/\text{DMF} \quad \text{H}_2\text{O}/\text{DMF}
\]

\[
\text{300} \quad \text{301}
\]

4-(2,2-Dichloroethyl)-5,5-dimethyltetrahydrofuran-2-one (301)\(^{155}\):

A suspension of lactone 300 (267 g, 1 mol) in dimethylformamide (600 ml) and water (27 ml, 1.5 mol) is heated under reflux for 4–12 h. When the reaction is complete, the water and DMF are removed under reduced pressure. Methanol (300 ml) is added to the residual lactone and then water (100 ml). Cooling induces crystallization to occur. The crystals are filtered and a second crop is collected from the filtrate; yield: 198 g (95%); m.p. 116–119 °C [crystallized from hexane/ethanol (2:1)].

Treatment of butyrolactone 302a (as the methyl ester) with sodium chloride in wet DMSO (170–210 °C, 3 h) gives 303a (87%)\(^{157}\). Deethoxycarbonylations of lactones 302a, 302b, and 302c can also be effected by heating in wet DMSO for 40 h at 140 °C to yield 303a, b, and c (75–90% yields)\(^{152}\). When 302d was heated with sodium chloride and wet DMSO at 170 °C, no 303d could be obtained. However, the use of potassium cyanide in wet HMPT yielded 303d (60%).

\[
\text{H}_2\text{O}/\text{DMF/NaCl} \quad \text{H}_2\text{O}/\text{DMF/NaCl} \quad \text{H}_2\text{O}/\text{DMF/NaCl}
\]

\[
\text{302 a} \quad \text{303}
\]

\[
\text{R} = \text{C}_2\text{H}_5 \quad \text{R} = \text{C}_2\text{H}_5 \quad \text{R} = \text{C}_2\text{H}_5 \quad \text{R} = \text{CH}_2\text{CH}_2
\]

On heating 304 in wet DMSO, the products 305 (63%), 306 (14%), and the unsaturated lactone 307 (17.5%) were isolated\(^{152}\). Treatment of 306 with sodium cyanide in DMSO at room temperature leads to 308 and elimination of the ethoxycarbonyl group by reaction with wet DMSO gives 309 (98%)\(^{154}\).

\[
\text{H}_2\text{O}/\text{DMF} \quad \text{H}_2\text{O}/\text{DMF} \quad \text{H}_2\text{O}/\text{DMF}
\]

\[
\text{304} \quad \text{305} \quad \text{306} \quad \text{307}
\]

\[
\text{308} \quad \text{309}
\]
Deethoxycarbonylations of the α-ethoxycarbonyl-γ-lactones 310a or 310b with sodium chloride in wet DMSO (170 °C, 6 h) lead to 311a and 311b, respectively, in 30-40% yields.\textsuperscript{158}

\[
\begin{array}{c}
\text{C}_2\text{H}_5\text{OCOC}_2\text{H}_5 \\
\text{H} \\
\text{H}
\end{array}
\xrightarrow{\text{DMSO/H}_2\text{O/NaCl}}
\begin{array}{c}
\text{O} \\
\text{R} \\
\text{H}
\end{array}
\]

310 a \text{ R = α-H} \\
310 b \text{ R = β-H}

Reaction of the heterocyclic lactone 312 with sodium cyanide in DMSO (80 °C, 48 h) leads to the deethoxycarbonylated lactone 313 (80%)\textsuperscript{159}.

\[
\begin{array}{c}
\text{H}_2\text{COCOC}_2\text{H}_5 \\
\text{N} \\
\text{CH}_3 \\
\text{CH}_3
\end{array}
\xrightarrow{\text{NaCN/DMSO}}
\begin{array}{c}
\text{O} \\
\text{R} \\
\text{H}
\end{array}
\]

312

313

5.2. Disubstituted Substrates

In order to effect dealkoxycarbonylations of disubstituted β-keto esters the use of a salt such as lithium chloride or sodium cyanide is necessary in the dipolar aprotic media.

The deethoxycarbonylation of 314 with sodium cyanide in HMPT (110 °C, 4 h) yields 315 (56%). Under similar experimental conditions 316 can be converted into 317 (43%)\textsuperscript{160}.

\[
\begin{array}{c}
\text{H}_3\text{C} = \text{COCOC}_2\text{H}_5 \\
\text{H} \\
\text{H}
\end{array}
\xrightarrow{\text{NaCN/HMPT}}
\begin{array}{c}
\text{O} \\
\text{R} \\
\text{H}
\end{array}
\]

314

315

316

On heating 318 with sodium cyanide in DMSO (160 °C, 4 h) a mixture of products was formed which consisted of the deethoxycarbonylated product 319 (80%) and the decacylated product 320 (20%). The mixture can be separated by G.L.C. to give pure 319 (70%)\textsuperscript{162}.

\[
\begin{array}{c}
\text{C}_2\text{H}_5\text{OCOC}_2\text{H}_5 \\
\text{H} \\
\text{CH}_3 \\
\text{H}
\end{array}
\xrightarrow{\text{NaCN/HMPT}}
\begin{array}{c}
\text{O} \\
\text{R} \\
\text{H}
\end{array}
\]

318

319

320

The deethoxycarbonylation of 321 has been effected by lithium iodide dihydrate in dry 2,4,6-collidine (reflux 19 h) to yield 322 (72-76%)\textsuperscript{161}.

\[
\begin{array}{c}
\text{COOCH}_3 \\
\text{C}_2\text{H}_5\text{C}_2\text{H}_5 \\
\text{H}
\end{array}
\xrightarrow{\text{N}}
\begin{array}{c}
\text{O} \\
\text{CH}_2\text{C}_2\text{H}_5 \\
\text{H}
\end{array}
\]

321

322

It was then shown that treatment of 321 with lithium chloride (2-fold excess) in HMPT (75 °C, 24 h) leads to 322 (90%). With sodium cyanide (2 fold excess) in HMPT (75 °C, 1 h), 322 could be obtained in an 80% yield\textsuperscript{162}.

In an experiment in which 2-methyl-2-methoxycarbonylcyclopentanone was treated with sodium cyanide in HMPT, acetonitrile was isolated (70% yield). In HMPT, it was shown that the reactivity of the sodium cyanide, lithium chloride, or lithium bromide towards 321 are 65, 2.45 and 1.0, respectively. Sodium cyanide in DMF is about 1/30 as reactive as sodium cyanide in HMPT towards 321. The methyl ester 321 is about 72 times more reactive than the corresponding ethyl ester (sodium cyanide/HMPT)\textsuperscript{165}.

The substituted cyclopentanone 323 on being heated in a sealed tube with sodium chloride in wet DMSO at 180 °C for 3 h leads to 2-n-pentyl-1-cyclopentanone (324, 35%)\textsuperscript{163}.

\[
\begin{array}{c}
\text{C}_6\text{H}_{11} \sim \text{n} \\
\text{COOCH}_3 \\
\text{NaCl}
\end{array}
\xrightarrow{\text{DMSO/H}_2\text{O/NaCl}}
\begin{array}{c}
\text{O} \\
\text{C}_6\text{H}_{11} \sim \text{n}
\end{array}
\]

323

324

Attempts to deethoxycarbonylate 325 in acidic media lead to extensive decomposition. However, on heating a solution of 325 in HMPT with tetramethylammonium acetate (2 equivalents) at 100 °C (12 h), the deethoxycarbonylated product 326 can be obtained in a 72% yield\textsuperscript{164}.

\[
\begin{array}{c}
\text{O} \\
\text{C}_2\text{H}_5\text{COOC}_2\text{H}_5 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3
\end{array}
\xrightarrow{\text{NaCN/HMPT}}
\begin{array}{c}
\text{O} \\
\text{C}_2\text{H}_5\text{COOC}_2\text{H}_5 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3
\end{array}
\]

325

326

3-Isopropenyl-2-methylcyclopentanone (326)\textsuperscript{164}.

A solution of 325 (1.05 g, 5.37 mmol), tetramethylammonium acetate (2.66 g, 20.0 mmol) and anhydrous HMPT (5 ml) is heated to 100 °C for 12 h. The cooled reaction mixture is exhaustively extracted with ether, the ether extracts are washed with water, saturated aqueous sodium carbonate solution, dried with sodium sulfate, and concentrated by distillation through a 10-cm Vigreux column. The residual oil is distilled at reduced pressure; yield: 0.53 g (72%); b.p. 75-77 °C/7.5 torr.

Deethoxycarbonylation of 327 was effected with sodium cyanide in HMPT (70 °C, 1 h, dry argon) to yield 328 (90%)\textsuperscript{165}. This keto ester is the thermodynamically more stable product and may be the result of equilibration under the experimental conditions.
The demethoxycarbonylation of the β-keto ester 329 was effected in refluxing DMF in the presence of lithium iodide to yield 330 (70%)\textsuperscript{166}.

Demethoxycarbonylation of 331 with sodium iodide in HMPT yields 332 (88%)\textsuperscript{167}.

Reaction of 333 with lithium chloride in HMPT (100 °C, 6 h) yields the demethoxycarbonylated product 334 in a 92% conversion\textsuperscript{168}.

In a study dealing with the structure-activity relationship on rice seedling growth, jasmonic acid and related compounds have been prepared for inhibitory evaluation\textsuperscript{169}. Compounds 335 (a, b, c, or d) on heating in wet DMSO containing sodium chloride (180 °C, 4 h) led to the acids 336 (a, b, c, or d) in yields of 28% to 60% (workup involved a saponification procedure).

Demethoxycarbonylation of 337a with sodium chloride in wet DMSO (180 °C, 3–4 h, sealed tube) yields methyl dihydrojasmonate (338a; 70%)\textsuperscript{169}. In a similar experimental fashion 337b and 338c lead to 338b (36–86%) and 338c (86%), respectively\textsuperscript{169}.

Methyl dl-Dehydrojasmonate (338c)\textsuperscript{169}:
A solution of 337c (24 mg, 0.086 mmol) and sodium chloride (10 mg) is mixed with DMSO (1.5 ml) and water (20 mg) and heated in a sealed tube at 180 °C for 3–4 h. The cooled mixture is poured into ice-cold brine and extracted with hexane. The hexane extracts are washed with saturated sodium chloride solution, dried with sodium sulfate, and the solvent removed under vacuo. The product is distilled; yield: 16.3 mg (86%); b.p. 102–103 °C/3 torr.

The demethoxycarbonylation of 339 in wet DMSO containing sodium chloride in a sealed tube (170–175 °C, 4 h) affords a mixture of 340 and 341 in a 2:1 ratio, respectively, in an overall 46% yield\textsuperscript{170}. Isomerization of the double bond also partially occurs under the demethoxycarbonylation conditions used.

It had previously been reported that 342 on treatment with sodium chloride in wet DMSO at 160 °C leads to 343 (32%)\textsuperscript{170}.

In another synthetic procedure to cis-jasmonate, it has been shown that 344 on being heated in aqueous DMSO containing sodium chloride (180 °C, 8 h, sealed tube) also leads to 343 (33%)\textsuperscript{171}. Catalytic hydrogenation of the triple bond of 343 (palladium on barium carbonate/hydrogen) gives cis-jasmonate (65%).
When 345 was heated in wet DMSO containing sodium chloride an incomplete reaction occurred. This β-keto ester was converted into 346 by heating in a mixture of acetic acid and concentrated hydrochloric acid.\(^{172}\)

![Chemical structure of 345 and 346](image)

The demethoxycarbonylation of 347 can be readily accomplished by heating in DMSO in the presence of sodium cyanide to produce 348 (92%)\(^{173}\). Attempts to effect this transformation under the usual alkaline conditions were unsatisfactory as ring-opening occurred.

![Chemical structure of 347 and 348](image)

The application of the sodium chloride/wet DMSO procedure for the preparation of α-arylcyclohexanones 350 from the readily available α-arylated β-keto esters 349 is suggested but no specific experiments are given.\(^{174}\)

![Chemical structure of 349 and 350](image)

Treatment of 351 with sodium chloride in DMSO and water under nitrogen gives 352 (trans:cis isomeric mixture of 2:1), the product from the chemoselective removal of the methoxycarbonyl group adjacent to the carbonyl group.\(^{175}\)

![Chemical structure of 351 and 352](image)

5.2.1. Heterocyclic Substrates

Demethoxycarbonylation of 353 with lithium iodide in DMF yields 354 (45%)\(^{176}\).

![Chemical structure of 353 and 354](image)

Deethoxycarbonylation of 355 using lithium chloride in wet DMSO (reflux, 4 h) leads to two lactams 356 (major product in 51% yield and a minor lactam)\(^{155}\).

The demethoxycarbonylation of 357 was attempted by heating in DMSO/water at 180–190 °C in the presence of sodium chloride. The products were the aldehyde 358 (~70%, major) and a small amount of (±)-4-oxo-protoemetine (359, ~10%). It was also shown that deacetilation of 357 occurred on heating in DMSO in the absence of water and the salt.\(^{177}\)

Deoxybrevianamide E (361) can be obtained in a 59% yield from 360 by heating at 130–140 °C (2.5 h) in the presence of magnesium chloride hexahydrate in DMSO along with the C-9 epimer 362 (38%)\(^{178}\). It is noted that the use of sodium chloride in wet DMSO was unsatisfactory for this conversion.

5.2.2. Bis-dealkoxycarbonylations

Reaction of 363 with sodium chloride in hot, wet DMSO followed by a methanolic hydrogen chloride workup leads to 364 (no yield listed).\(^{179}\)

![Chemical structure of 357, 358, 359, 360, 361, 362, 363, 364](image)
The bis-deethoxycarbonylation of 365 with sodium chloride in wet DMSO at 165–170 °C for 4 h yields the methyl ketone 366 (50%)\(^\text{180}\).

\[
\begin{align*}
\text{365} & \xrightarrow{\text{DMSO/H}_2\text{O}/\text{NaCl}} \text{366} \\
\end{align*}
\]

It is of interest to note that when 367 was heated for 3 h at reflux with a saturated aqueous solution of sodium chloride, 368 (53%) was produced, the product of a monodeethoxycarbonylation\(^\text{181}\).

\[
\begin{align*}
\text{367} & \xrightarrow{\text{H}_2\text{O}/\text{NaCl}} \text{368} \\
\end{align*}
\]

6. \(\alpha\)-Cyano Esters

The deethoxycarbonylation of ethyl cyanoacetate in DMSO containing a little water (2 molar equivalents) at 135–165 °C leads to acetonitrile (75–80%)\(^\text{9,16}\). It has also been shown that the monosubstituted cyanoacetates 369 a and 369 b on heating in DMSO containing some water (4 h) yield the corresponding nitriles 370 a and 370 b, respectively, in 70–80% yields. In these cases, the presence of a salt such as sodium chloride is unnecessary\(^\text{17}\).

\[
\begin{align*}
\text{369 a} & \xrightarrow{\text{R}\text{CH}_2\text{CN}} \text{370 a} \\
\text{369 b} & \xrightarrow{\text{R}\text{CH}_2\text{CN}} \text{370 b} \\
\end{align*}
\]

On the other hand, 369 c on being refluxed with DMSO containing 2 molar equivalents of water (4 h) leads only to recovered starting material. In the disubstituted substrate, the presence of a salt is necessary to effect a dealkoxycarbonylation.

6.1. Monosubstituted Substrates

The demethoxycarbonylation of 371 by heating in DMSO/water (9:1) at 140–180 °C yields the trans-keto nitrile 372 (80%)\(^\text{182}\).

\[
\begin{align*}
\text{371} & \xrightarrow{\text{DMSO/H}_2\text{O}} \text{372} \\
\end{align*}
\]

The \(\alpha\)-cyano ester 373 on treatment with sodium cyanide in DMSO (145 °C for 1.5 h) leads to the demethoxy carbonylated product 374 (89%)\(^\text{183}\).

\[
\begin{align*}
\text{373} & \xrightarrow{\text{DMC/O/NaCN}} \text{374} \\
\end{align*}
\]

The deethoxycarbonylation of 375 with sodium chloride in aqueous DMSO yields 376 (67%)\(^\text{184}\).

\[
\begin{align*}
\text{375} & \xrightarrow{\text{DMC/O/NaCl}} \text{376} \\
\end{align*}
\]

4,6-Diamino-3,5-dicyano-2-pyridylnitrile(376)\(^\text{184}\):

A solution of 375 (0.081 g, 0.3 mmol), sodium chloride (0.006 g, 0.1 mmol), water (0.011 g, 0.6 mmol), and DMSO (1 ml) is heated at 130–150 °C for 2.5 h. The solution is cooled, poured into water (5 ml), and the solid which precipitates is filtered. Recrystallization from aqueous DMF gives the pure product; yield: 0.04 g (67%); m.p. > 300 °C.

The ethoxycarbonyl group in the \(\alpha\)-cyano ester 377 was removed by heating with wet DMSO containing some sodium chloride (3 h, 160–180 °C) to yield 378 (84%)\(^\text{185}\).

\[
\begin{align*}
\text{377} & \xrightarrow{\text{DMC/O/NaCl}} \text{378} \\
\end{align*}
\]

The deethoxycarbonylation of 379 to yield 380 (63%) can be accomplished in a similar manner\(^\text{186}\).

\[
\begin{align*}
\text{379} & \xrightarrow{\text{DMC/O/NaCl}} \text{380} \\
\end{align*}
\]

The \(\alpha\)-cyano ester 381 can be deethoxycarbonylated by heating with sodium cyanide in DMSO (6 h, 160–170 °C) to give 382 (68%)\(^\text{187}\).

\[
\begin{align*}
\text{381} & \xrightarrow{\text{DMC/O/NaCl}} \text{382} \\
\end{align*}
\]

When 383 is heated under reflux in DMF containing lithium iodide dihydrate for 1.5 h, a mixture of 384 and 385 in a 1:1.6 ratio is produced. Compound 385 arises via methylation by iodomethane which is formed during the dealkoxycarbonylation\(^\text{188}\).

\[
\begin{align*}
\text{383} & \xrightarrow{\text{DMC/O/NaCl}} \text{384, 385} \\
\end{align*}
\]
If a little acetic acid is added to the lithium iodide dihydrate/DMF demethoxy carbonylation medium, 383
gives the desired product 384 in a 75% yield.

6.2. Disubstituted Substrates

The α-cyano ester 386 can be demethoxy carbonylated by
heating with sodium cyanide in DMSO to yield 387
(54%) \cite{187}.

\[ \text{386} \xrightarrow{\text{DMSO} / \text{NaCN}} \text{387} \]

Ethyl 6,11-Dimethyl-7-cyno-dodec-10-enoate (387) \cite{190}:
A mixture of 386 (20 g, 0.057 mol), dry DMSO (25 ml),
and dry sodium cyanide (3.3 g, 0.067 mol) is heated at 160–170 °C in an oil bath
for 6 h. The mixture is cooled, poured into cold water (100 ml),
and extracted with petroleum ether (b.p. 60–80 °C). The extract is washed
with water and 10% aqueous sodium carbonate solution. The product
is distilled under reduced pressure; yield: 12 g (54%); b.p. 160–165 °C/2 torr.

Demethoxy carbonylation of 388 by refluxing in DMSO
containing sodium cyanide gives the nitrile 389
(91%) \cite{190}.

\[ \text{388} \xrightarrow{\text{DMSO} / \text{NaCN}} \text{389} \]

Cyclopentane carbonitrile (391, 75% yield) can be pre-
pared by reaction of 390 with sodium cyanide in
DMSO under reflux (2 h). The use of sodium chloride
in wet DMSO is reported as being unsuccessful in the
attempted conversion of 390 to 391 \cite{190}.

\[ \text{390} \xrightarrow{\text{DMSO} / \text{NaCN}} \text{391} \]

The 2,3-dicyano ester 392 can be deethoxy carbonylated
by heating in wet DMSO containing some sodium chloride
to yield meso- and racemic-393 (55%, based on the
preparation of 392 from ethyl cyanoacetate) \cite{191}.

\[ \text{392} \xrightarrow{\text{DMSO/\text{H}_2\text{O} / \text{NaCl}}} \text{393} \]

Reaction of 394 in wet DMSO containing sodium chloride
(175–200 °C, 0.5 h) gives poor yields of 395 (1–6%)
and many unidentified products \cite{192}. A 6% yield of 395 is
reported upon heating 394 at 175 °C in anhydrous
DMSO for 2 h.

\[ \text{394} \xrightarrow{\text{DMSO/\text{H}_2\text{O} / \text{NaCl}}} \text{395} \]

The demethoxy carbonylation of the cyclopropyl cyano
ester 396 with lithium bromide in undried DMSO (sealed
tube, 24 h, 126 °C) leads to 397 (53%) and lactone 398
(23%) \cite{192}. If the reaction is performed in an open flask
(bromomethane can escape) only 397 and recovered
396 can be isolated. The product 397 probably arises
via an attack of the bromide ion on the methyl group of
ester 396 (B,2) to yield the carboxylate anion which
then decarboxylates (a concerted mechanism is also possible).

\[ \text{396} \xrightarrow{\text{DMF/\text{LiBr}}} \text{397} \]

The ring-opened intermediates such as 399 and 400 are proposed to
rationalize the formation of lactone 398 and also the facile racemiza-
tion of chiral starting materials. The formation of 397 was much faster
in the presence of moisture and much faster relative to racemization of
(+)396 in the absence of moisture.

\[ \text{399} \xrightarrow{\text{400}} \text{398} \]

The dealkoxy carbonylation of α-cyano esters in wet
DMSO in the presence of potassium cyanide has been
adapted to the synthesis of 2,3-disubstituted and 2-sub-
stituted succinonitriles. Using DMSO as the solvent,
the entire synthesis sequence can be performed in a
one-pot reaction as outlined in Scheme E \cite{191}. The yields of six dinitriles
which were prepared by this route are summarized in Table 8.

\[ \text{R}^1\text{-CH}=0 + \text{H}_2\text{C-COO}^2 + \text{KCN} \xrightarrow{\text{DMSO}} \text{R}^1\text{-CH-COO}^2 \]

\[ \text{401} \xrightarrow{\text{402}} \text{403} \]

\[ \text{R}^1\text{-CH}=0 + \text{CN} \xrightarrow{\text{H}_2\text{O}, 145 °C} \text{R}^1\text{-CH-CN} \]

\[ \text{404} \xrightarrow{\text{405}} \text{406} \]

Scheme E
Table 8. Succinodinitriles 405 prepared via Scheme E\textsuperscript{193}

<table>
<thead>
<tr>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2} = X</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H\textsubscript{2}C</td>
<td>H\textsubscript{2}C=J</td>
<td>23\textsuperscript{a}</td>
</tr>
<tr>
<td>C\textsubscript{2}H\textsubscript{5}</td>
<td>C\textsubscript{2}H\textsubscript{5}=J</td>
<td>62\textsuperscript{a}</td>
</tr>
<tr>
<td>i-C\textsubscript{3}H\textsubscript{7}</td>
<td>i-C\textsubscript{3}H\textsubscript{7}=J</td>
<td>51\textsuperscript{c}</td>
</tr>
<tr>
<td>H\textsubscript{2}C</td>
<td>H\textsubscript{2}C=J</td>
<td>17\textsuperscript{a}</td>
</tr>
<tr>
<td>i-C\textsubscript{3}H\textsubscript{7}</td>
<td>(\text{-CH}_{2}\text{-Cl}</td>
<td>53\textsuperscript{a}</td>
</tr>
<tr>
<td>i-C\textsubscript{3}H\textsubscript{7}</td>
<td>HCl</td>
<td>70\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Yields based on ethyl cyanoacetate.
\textsuperscript{b} Mixture of meso and racemic forms.
\textsuperscript{c} Racemate only (m.p. data).
\textsuperscript{d} Mixture of erythro and threo forms.
\textsuperscript{e} Threo form only.

The dealkoxyacaronylations of 2-cyano-2-alkenoates with wet DMSO containing sodium chloride lead to reasonable yields of unsaturated nitriles\textsuperscript{193}. Examples and products are tabulated in Table 9.

Table 9. Deethoxycarbonylations of 2-cyano-2-alkenoates\textsuperscript{193}

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Products\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN COOC\textsubscript{2}H\textsubscript{5}</td>
<td>CN \begin{align*} \text{CN} \ \text{CN} \end{align*}</td>
</tr>
<tr>
<td>H\textsubscript{2}C \begin{align*} \text{COOC\textsubscript{2}H\textsubscript{5}} \ \text{H\textsubscript{2}C} \end{align*}</td>
<td>\begin{align*} \text{H\textsubscript{2}C} \ \text{CN} \end{align*}</td>
</tr>
<tr>
<td>H\textsubscript{2}C \begin{align*} \text{COOC\textsubscript{2}H\textsubscript{5}} \ \text{H\textsubscript{2}C} \end{align*}</td>
<td>\begin{align*} \text{H\textsubscript{2}C} \ \text{CN} \end{align*}</td>
</tr>
<tr>
<td>H\textsubscript{2}C \begin{align*} \text{CN} \ \text{COOC\textsubscript{2}H\textsubscript{5}} \end{align*}</td>
<td>\begin{align*} \text{CN} \ \text{CN} \end{align*}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 55–66% yields excluding 20% of the corresponding carbonyl compounds.
\textsuperscript{b} Ketone detected by formation of 2,4-DNP derivative.
\textsuperscript{c} \(\alpha\beta,\gamma\) ratio of 3:4:1.
\textsuperscript{d} \(\alpha\beta,\gamma\) ratio of 1:2.

It is also noted that in the case of entry 4 (Table 9) the sodium chloride is unnecessary. The conjugate addition of water leads to 406 which deethoxycarbonylates with elimination of hydroxide ion to yield the \(\alpha,\beta\)-unsaturated nitrile or it can undergo a retro-aldol reaction to yield some carbonyl product which is isolated as a by-product.

7. \(\alpha\)-Alkyl- or \(\alpha\)-Arylsulfonyl Esters

Demethoxycarbonylation of 407 (sodium chloride in wet DMSO) yields the sulfone 408 (95%)\textsuperscript{194}. In a similar fashion, 409 can be converted into 410 (48%), the acid being formed by hydrolysis of the crude product with methanolic potassium hydroxide solution.

\begin{align*}
\text{H}_{3}\text{C} & \text{COOC} \\
\text{H}_{3}\text{C}=\text{COOC}\text{CH}_{3} & \text{DMSO/H}_{2}\text{O} \\
\text{NaCl} & \\
\rightarrow & \\
\text{407} & \\
\text{H}_{3}\text{C}=\text{SO}_{2} & \\
\text{408} & \\
\text{H}_{3}\text{C}=\text{COOC}\text{CH}_{3} & \text{OAc} \\
\rightarrow & \\
\text{409} & \\
\text{H}_{3}\text{C}=\text{SO}_{2} & \\
\text{410} & \\
\text{O} & \\
\text{COOC}\text{CH}_{3} & \text{OH} \\
\rightarrow & \\
\text{410} & \\
\end{align*}

Methyl \(\beta\)-Methylsulfonyl-12-acetoxyheptadecanoate (408)\textsuperscript{194}:

A stirred mixture of the ester 407 (36.7 g, 0.077 mol), sodium chloride (4.68 g, 0.08 mol), and DMSO (60 ml containing 1.6% water) is heated under a nitrogen blanket in an oil bath (185 °C) for 5 h. The mixture is concentrated in vacuo at 100 °C to yield an oily mixture which is diluted with water. This is acidified with 6 normal hydrochloric acid and then extracted with ether. The ether extract is washed with water, dried with sodium sulfate, and concentrated in vacuo to give 408: yield: 31 g (95%).

The \(\alpha\)-phenylsulfonyl esters 411 and 412 on treatment with lithium iodide trihydrate or sodium cyanide in DMF at 120 °C for 17 h yield 413 and 414 in 59% and 44% yields, respectively\textsuperscript{125}.

\begin{align*}
\text{H}_{3}\text{C} & \text{COO} \\
\text{H}_{3}\text{C}=\text{H} & \\
\text{H}_{3}\text{C} & \\
\rightarrow & \\
\text{406} & \\
\text{R}^{1}-\text{C}=\text{CH}-\text{COOC}\text{H}_{4} & \text{HO} \\
\r^{2} & \\
\text{CN} & \text{CN} \\
\rightarrow & \\
\text{411} & \\
\text{H}_{3}\text{C} & \text{SO}_{2} \\
\text{H}_{3}\text{C}=\text{CH}-\text{COOC}\text{H}_{3} & \\
\rightarrow & \\
\text{413} & \\
\text{H}_{3}\text{C} & \text{SO}_{2} \\
\text{C}_{6}\text{H}_{5} & \\
\text{H}_{3}\text{C} & \text{CH}_{3} \\
\text{H}_{3}\text{C} & \text{CH}_{3} \\
\rightarrow & \\
\text{413} & \\
\end{align*}
Demethoxycarbonylation of 415 with lithium iodide trihydrate and sodium cyanide in DMF yields 416 (78%)\(^\text{196}\). In a similar procedure 417 can be converted into 418 (78%)\(^\text{197}\).

Demethoxycarbonylation of 421 with tetramethylammonium acetate in HMPT at 95 °C yields 422 (86%)\(^\text{199}\).

Lactone 424 (n = 1) can be prepared by heating 423 (n = 1) with tetramethylammonium acetate in HMPT (90-95 °C, 76%). Similarly, 424 (n = 3) could be prepared from 423 (n = 3, 82%)\(^\text{200}\).

8. Phosphine Oxides

One example of the use of a dealkoxy carbonylation which leads to an optically active phosphine oxide is reported\(^\text{201}\). The demethoxycarbonylation of (−)-ethyl-[(menthoxycarbonylmethyl)-phenyl-phosphine (425; a single diastereoisomer and enantiomeric at both the methyl and phosphorus residues) can be effected by heating with lithium chloride in wet DMSO to give 426 (60%). The reaction proceeds without racemization at phosphorus. Attempted demethoxycarbonylation of 425 using chlorotrimethylsilane and sodium iodide or alumina in dioxan and water were unsuccessful. The use of 48% hydrobromic acid is also effective in bringing about this type of cleavage but in this case has to be avoided since optically active phosphines are known to undergo extensive racemization under acidic conditions.

9. Dealkoxycarbonylations in the Presence of Other Electrophiles

The dealkoxycarbonylations of substrates such as geminal diesters, β-keto esters, and α-cyano esters involve carbanionic intermediates which are protonated by water in aqueous dipolar aprotic media to yield esters, ketones, and nitriles, respectively. In the presence of other electrophiles in anhydrous dipolar aprotic media, the carbanions can be trapped and lead to other products.
9.2. α-Alkylations

9.2.1. Intermolecular Alkylations

In the presence of lithium chloride and benzyl bromide or n-octyl bromide, β-keto esters, geminal diesters, and ethyl cyanoacetate in HMPT react to yield α-alkylated ketones, esters and nitriles, respectively. Diethyl malonate in HMPT in the presence of lithium chloride and benzyl bromide (160 °C, 1 h) yields 427 (51%) and 428 (26%).

The ester 427 arises from C-benzylation of the intermediate carbanionic intermediate 429. The bis-alkylated ester 428 could arise from benzylation of carbanion 430 (formed from alkylation of the anion of diethyl malonate followed by deethoxy carbonylation) of from 431 (bis-benzylation of diethyl malonate) via a dealkoxy carbonylation.

$$\text{H}_2\text{C} = \text{C} \text{CO}_2\text{H}_5$$
$$\text{C}_6\text{H}_5 \text{CH}_2 \text{CH}_2 \text{CO}_2\text{H}_5$$

$$\text{H}_2\text{C} = \text{C} \text{CO}_2\text{H}_5$$
$$\text{C}_6\text{H}_5 \text{CH}_2 \text{CH}_2 \text{CO}_2\text{H}_5$$

$$\text{C}_6\text{H}_5 \text{CH}_2 \text{CH}_2 \text{CO}_2\text{H}_5$$
$$\text{C}_6\text{H}_5 \text{CH}_2 \text{CH}_2 \text{CO}_2\text{H}_5$$

$$\text{H}_2\text{C} = \text{C} \text{CO}_2\text{H}_5$$
$$\text{C}_6\text{H}_5 \text{CH}_2 \text{CH}_2 \text{CO}_2\text{H}_5$$

$$\text{C}_6\text{H}_5 \text{CH}_2 \text{CH}_2 \text{CO}_2\text{H}_5$$
$$\text{C}_6\text{H}_5 \text{CH}_2 \text{CH}_2 \text{CO}_2\text{H}_5$$

It is also noted that use of DMSO or sulfolane as solvents led to decreased deethoxy carbonylation rates. The salts lithium bromide, sodium chloride, potassium chloride, and tetramethylammonium bromide gave poor yields of 427 and 428.

Dimethyl diethylmalonate on reaction with lithium chloride in HMPT in the presence of benzyl bromide (155 °C, 1 h) gives 432 (30%) and 433 (18%). In this case the carboxylate anion (formed from B_{Al2} cleavage of Cl) is trapped before it decarboxylates. Additional examples of the synthetic utility of this alkylation dealkoxy carbonylation procedure are listed in Table 11.

### Table 11. Alkylative Dealkoxy Carbonylations

<table>
<thead>
<tr>
<th>Substrate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Alkyl Halide</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-C₅H₉-CH-CHCO₂H₅&lt;sup&gt;b&lt;/sup&gt;</td>
<td>C₆H₅-CH₂-BR₂</td>
<td>n-C₅H₉-CH₂CHCO₂H₅</td>
<td>71 + 10</td>
</tr>
<tr>
<td>H₃C-C₁N⁺CH₂CO₂H₅</td>
<td>C₆H₅-CH₂-BR</td>
<td>n-C₅H₉-CH₂CHCO₂H₅</td>
<td>52</td>
</tr>
<tr>
<td>H₃C-C≡CH₂CO₂H₅&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n-C₅H₉-Br²</td>
<td>n-C₅H₉-CH₂CHCO₂H₅</td>
<td>22</td>
</tr>
<tr>
<td>H₃C-C=CH₂-CH₂CO₂H₅&lt;sup&gt;b&lt;/sup&gt;</td>
<td>C₆H₅-CH₂-BR</td>
<td>C₆H₅-CH₂CH₂CH₂-CN</td>
<td>24</td>
</tr>
<tr>
<td>CH₂COOH&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C₆H₅-CH₂-BR</td>
<td>CH₂COOH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>47 + 10</td>
</tr>
<tr>
<td>CH₃COOCH₃&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C₆H₅-CH₂-BR</td>
<td>CH₃COOCH₃&lt;sub&gt;2&lt;/sub&gt;</td>
<td>35</td>
</tr>
<tr>
<td>NC-C₅H₉-CH₂CO₂H₅&lt;sup&gt;d&lt;/sup&gt;²</td>
<td>C₆H₅-CH₂-BR</td>
<td>NC-C₅H₉-CH₂CN&lt;sub&gt;2&lt;/sub&gt;</td>
<td>15 + 52</td>
</tr>
<tr>
<td>NC-C₅H₉-CH₂CO₂H₅&lt;sup&gt;e&lt;/sup&gt;²</td>
<td>C₆H₅-CH₂-BR</td>
<td>NC-C₅H₉-CH₂-CN&lt;sub&gt;2&lt;/sub&gt;</td>
<td>30 + 84</td>
</tr>
<tr>
<td>NC-C₅H₉-CH₂CO₂H₅&lt;sup&gt;f&lt;/sup&gt;²</td>
<td>n-C₅H₉-Br²</td>
<td>n-C₅H₉-CH₂-CN&lt;sub&gt;2&lt;/sub&gt;</td>
<td>16 + 4</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mol ratio of ester:alkyl halide:lithium chloride = 1.2:1:1.1 with HMPT as solvent.
<sup>b</sup> 150-160 °C for 1-1.5 h.
<sup>c</sup> 160 °C for 0.3 h.
<sup>d</sup> 140 °C for 2 h.
## 9.1. α-Sulfiylation

The dealkoxyacylative sulfinylation of geminal diesters, β-keto esters, and α-cyano esters in HMPT in the presence of sodium iodide at 150–160 °C yield α-phenylthio esters, α-phenylthio ketones, and α-phenylthio nitriles, respectively. For example, on heating a solution of diethyl malonate, diphenyl disulfide, and sodium iodide in HMPT, ethyl phenylthioacetate and ethyl phenyl sulfide can be isolated in 46% and 40% yields, respectively.

\[
\text{H}_2\text{C} = \text{COOC}_2\text{H}_5 \quad \xrightarrow{\text{HMPT/NaI}} \quad \text{C}_6\text{H}_5\text{S} - \text{S} - \text{CH}_2 - \text{COOC}_2\text{H}_5 + \text{C}_6\text{H}_5\text{S} - \text{C}_2\text{H}_5
\]

A variety of salts and solvents were investigated and the highest yields of α-sulfinylated esters were obtained with molar ratios of diester : disulfide : sodium iodide of 2:1:1:2 (82–84% yields based on diphenyl disulfide). The use of DMSO or sulfolane as solvents with sodium iodide led to poorer yields of the α-sulfinylated esters.

Some ethyl 2-phenylthiobutanoate was also formed as a by-product (8–9%). The formation of this product in those cases was excess diethyl malonate is present has been rationalized by the following mechanistic pathway (Scheme F). Other examples of α-sulfinylations are listed in Table 10.

![Scheme F](image)

### Table 10. Sulfinylation of Geminal Diesters, β-Keto Esters, and Ethyl Cyanoacetate

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-C_6H_5=CH</td>
<td>n-C_6H_5=CH-COOC_2H_5</td>
<td>46</td>
</tr>
<tr>
<td>COOC_2H_5</td>
<td>C_6H_5-S-CH-COOC_2H_5</td>
<td>46</td>
</tr>
<tr>
<td>C_6H_5-C=CH</td>
<td>C_6H_5-C=CH-COOC_2H_5</td>
<td>60</td>
</tr>
<tr>
<td>COOC_2H_5</td>
<td>C_6H_5-C=CH-COOC_2H_5</td>
<td>60</td>
</tr>
<tr>
<td>H_2C=COOC_2H_5</td>
<td>H_2C=COOC_2H_5</td>
<td>71</td>
</tr>
<tr>
<td>H_2C=COOC_2H_5</td>
<td>H_2C=COOC_2H_5</td>
<td>66</td>
</tr>
<tr>
<td>C_6H_5-C=CH</td>
<td>C_6H_5-C=CH-COOC_2H_5</td>
<td>36 + 30</td>
</tr>
<tr>
<td>COOC_2H_5</td>
<td>COOC_2H_5</td>
<td>47 + 5</td>
</tr>
<tr>
<td>COOC_2H_5</td>
<td>COOC_2H_5</td>
<td>49</td>
</tr>
<tr>
<td>NC=CH=COOC_2H_5</td>
<td>NC=CH=COOC_2H_5</td>
<td>23 (\times) 3 (\times) 15</td>
</tr>
</tbody>
</table>

* 2 mmol each of substrate, diphenyl disulfide, and sodium iodide in HMPT (2 ml) heated at 160–170 °C for 1 h.
9.2.2. Intramolecular Alkylations

A synthesis of cyclopropyl ketones 435 has been developed via intramolecular alkylation of α-acyl-γ-butyrolactones effected by halide anions in dipolar aprotic media (434 → 435)\textsuperscript{205}. For example, heating 434a in the presence of one molar equivalent of sodium bromide in DMSO (160 °C for 6 h) leads to ketone 435a (92%). The use of sodium chloride, sodium iodide, potassium chloride, or tetramethylammonium bromide in DMSO gave 435a in 50–76% yields, respectively. In refluxing DMF and in the presence of sodium bromide (6 h), 434a led to 435a in a 73% yield.

\[
\begin{align*}
\text{434a} & \quad R_1^2 = \text{CH}_3, R_2 = \text{H} \\
\text{435} & \\
\text{434b} & \quad R_1 = \text{C}_6\text{H}_5, R_2 = \text{H} \\
\text{434c} & \quad R_1 = \text{CH}_3, R_2 = \text{CH}_3
\end{align*}
\]

The conversion of 434b to 435b can be accomplished by heating at 170 °C for 1.5 h in HMPT (5 ml) in the presence of sodium iodide (10 mmol)\textsuperscript{204}. The product 435b distilled from the reaction mixture in an 86% yield. Using lithium chloride in HMPT at 160–170 °C for 2.5 h, 435b was obtained in a 42% yield. In a similar manner, 434c and sodium iodide in HMPT at 180 °C for 1.5 h gives 435c (81%).

The following mechanism was proposed for the overall reaction:

\[
\begin{align*}
\text{436} & \quad \xrightarrow{\text{C}_6\text{H}_5\text{H}_3} \quad \text{437} \\
& \quad \text{435a} \\
\text{434a} & \quad \xrightarrow{\text{DMSO}, \text{NaCl}} \quad \text{438} \\
& \quad \text{435a}
\end{align*}
\]

Consistent with this mechanism is the observation that on treatment of 434a with sodium cyanide in DMSO, 438 (17%) and a small amount of 435a (3.6%) are formed.

Examples of other substrates which were converted into cyclopropyl ketones are tabulated in Table 12.

Table 12. Conversion\textsuperscript{a} of Lactones 434 to Cyclopropyl Ketones 435\textsuperscript{202, 204}

<table>
<thead>
<tr>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>Yield [%] of 435</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>H</td>
<td>69</td>
</tr>
<tr>
<td>H\textsubscript{2}C\textsubscript{=NC}</td>
<td>H</td>
<td>69</td>
</tr>
<tr>
<td>H\textsubscript{2}C\textsubscript{=NO}</td>
<td>H</td>
<td>74</td>
</tr>
<tr>
<td>CH\textsubscript{3}</td>
<td>CH\textsubscript{3}</td>
<td>82</td>
</tr>
<tr>
<td>H</td>
<td>CH\textsubscript{2}CH\textsubscript{2}</td>
<td>100</td>
</tr>
<tr>
<td>H\textsubscript{2}C\textsubscript{=NC}</td>
<td>H</td>
<td>65</td>
</tr>
<tr>
<td>H\textsubscript{2}C\textsubscript{=NO}</td>
<td>H</td>
<td>65</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>70</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Performed in DMSO (160 °C, 6–12 h) except for the last two entries which were done in DMF (reflux, 55–59 h). The salt was sodium chloride except in the last three entries which used sodium bromide.

The regiospecific intramolecular alkylation of enolates generated by halide-induced dealkoxy-carboxylations of α-halo-β-keto esters is a useful preparative route to spiroycyclic ketones\textsuperscript{205}. Reaction of the cycloalkanone carboxylates 439 (n = 5, m = 1; n = 5–7, 12, m = 3) with lithium chloride in HMPT (125–140 °C, 1–1.5 h) leads to the corresponding ketones 440 in 64–75% yields. The use of N-methyl-2-pyrrolidone as a solvent leads to similar results but DMF was less satisfactory.

In similar procedures, annelation of the β-keto ester 441 leads to the acetylcyclopentane 442 (80%) while the methyl lactone-carboxylate 443 gives the Spirolactone 444 (69%).

Examples of other substrates which were converted into cyclopropyl ketones are tabulated in Table 12.

Cyclopropyl Phenyl Ketone (435a)\textsuperscript{205}:
A mixture of 434a (10 mmol) and alkali metal halide (11 mmol) in DMSO (10 ml) is heated at 160 °C under a nitrogen atmosphere. After cooling the mixture, water is added and the product is extracted into chloroform. The extract is washed with water, dried, and then concentrated. The residues is chromatographed over silica gel to yield pure 435a.
Demethoxycarbonylation of the β-keto ester 445 yields ketone 446 (86%) as a 9:1 epimeric mixture. This ketone can be converted into a mixture of β-vetivone and epiti-β-vetivone, or β-vetispirene (and its epimer).

\[
\begin{align*}
\text{O} \quad \text{COOCH}_3 \quad \text{Cl} & \quad \text{O} \quad \text{COOCH}_3 \\
\text{H}_3C & \quad \text{CH}_3 & \quad \text{H}_3C & \quad \text{CH}_3 \\
\end{align*}
\]

445 \quad \text{446}

The keto ester 447 on treatment with lithium chloride/HMPT leads to the spiroketones 448 (98%, 9:1 epimeric mixture). Ketone 448a can be converted into racemic β-vetivone in an excellent yield.

\[
\begin{align*}
\text{O} \quad \text{COOCH}_3 \quad \text{Cl} & \quad \text{O} \quad \text{COOCH}_3 \\
\text{H}_3C & \quad \text{CH}_3 & \quad \text{H}_3C & \quad \text{CH}_3 \\
\end{align*}
\]

447

448a \quad R' = CH_3, R^2 = -

b \quad R' = H, R^2 = CH_3

9.3. Chlorodemethoxycarbonylations

Dimethyl dichloromethylenemalonate (449) on reaction with potassium fluoride in sulfolane at 150 °C in the presence of dicyclohexyl-18-crown-6 yields 450 (70%) based on 2 mol of 449)\(^{256}\). The use of potassium fluoride in place of potassium fluoride yields the same product.

A mechanistic route to 450 involves a demethoxycarbonylation of 449 to yield the vinyl carbamion 451 which then reacts with Cl\(^{-}\) to give 450.

\[
\begin{align*}
\text{Cl} & \quad \text{C} = \text{C} \quad \text{COOCH}_3 \\
\text{Cl} & \quad \text{C} = \text{C} \quad \text{COOCH}_3 \\
\text{Cl} & \quad \text{C} = \text{C} \quad \text{COOCH}_3 \\
\text{Cl} & \quad \text{C} = \text{C} \quad \text{COOCH}_3 \\
\end{align*}
\]

449 \quad 450

10. Dealkoxycarbonylations of Substrates with β-Elimination

On heating the salt 452 (DMF, 80 °C), the methylene-lactone 453 is produced in high yield\(^{207}\), a deaminodeethoxycarbonylation process.

\[
\begin{align*}
\text{H} & \quad \text{COOCH}_3 \quad \text{Cl} \\
\text{H} & \quad \text{CH}_2 & \quad \text{Cl} \\
\text{452} & \quad \text{453} \\
\end{align*}
\]

In a general synthetic route α-substituted acrylonitriles, the quaternary ammonium salts 454 on being heated in DMF for 48 h at 80 °C yield 455\(^{208}\). The results are tabulated in Table 13.

\[
\begin{align*}
\text{CH}_2 & \quad \text{N(CH}_3)_3 \quad \text{O} \quad \text{COCH}_3 \\
\text{H}_3C & \quad \text{O} = \quad \text{C} \quad \text{CN} \\
\text{454} & \quad \text{455} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Yield [%] of 455</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>41</td>
</tr>
<tr>
<td>α-CH₃C₂H₅</td>
<td>68</td>
</tr>
<tr>
<td>i-CH₃C₂H₅</td>
<td>41</td>
</tr>
<tr>
<td>H₂C≡CH=CH₂</td>
<td>66</td>
</tr>
<tr>
<td>CH=CH-</td>
<td>71</td>
</tr>
</tbody>
</table>

Several heterocyclic substituted malonate esters which were previously discussed have been shown to undergo competitive ring-openings on dealkoxycarbonylations\(^{11}\).

Dechlorodemethoxycarbonylation of 456 on heating in potassium chloride in sulfolane in the presence of dicyclohexyl-18-crown-6 (160 °C, 30 min) yields 457 (7%)\(^{206}\).

\[
\begin{align*}
\text{H}_2\text{COOC} & \quad \text{C}=\text{C} \quad \text{COOCH}_3 \\
\text{Cl} & \quad \text{H}_2\text{COOC} \quad \text{C}=\text{C} \quad \text{COOCH}_3 \\
\text{456} & \quad \text{457} \\
\end{align*}
\]

In a similar fashion, 458 leads to 459 (16%). Several other examples of saturated esters were also reported as, for example, vacuum distillation of 460 in the presence of tetraethylammonium chloride gives 461 (36%, mixture of isomers).

\[
\begin{align*}
\text{NC} & \quad \text{C}=\text{C} \quad \text{COOCH}_3 \\
\text{Cl} & \quad \text{NC} \quad \text{C}=\text{C} \quad \text{COOCH}_3 \\
\text{458} & \quad \text{459} \\
\end{align*}
\]

\[
\begin{align*}
\text{NC} & \quad \text{C}=\text{C} \quad \text{COOCH}_3 \\
\text{Cl} & \quad \text{NC} \quad \text{C}=\text{C} \quad \text{COOCH}_3 \\
\text{460} & \quad \text{461} \\
\end{align*}
\]
A procedure for the preparation of α,β-unsaturated nitriles has been developed which involves a denitrodeethyldeoxycarbonylation effect in hot dipolar aprotic solvents. The sodium salts of ethyl α-alkylcyanoacetates 462 are treated with α-bromonitroalkanes in HMPT at room temperature to give the coupled products 463. The resulting solution is heated at 120 °C for 1 h to effect the denitrodeethyldeoxycarbonylation to yield 464 in good yields (Table 14)\textsuperscript{200}. Other dipolar aprotic solvents such as DMF or DMSO were also used but higher temperatures (150 °C) and longer times (6 h) were needed.

\[
\begin{array}{c}
\text{R}^1\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{R}^2 \quad \text{Na}^+ + \text{R}^3\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{R}^4 \quad \text{Br} \\
\hline
\text{462} \\
\text{463} \\
\text{464}
\end{array}
\]

The conversions of 465a and 465b to 466a and 466b by water in DMSO represent a novel process for hydrolytic cleavage of 1,3-diones. On the other hand, it was also reported that 467 on being heated in wet DMSO (160-170 °C for 4 h) did not yield 468 in the presence or absence of sodium chloride. The use of wet HMPT was also unsuccessful.

\[
\begin{array}{c}
\text{C}_6\text{H}_5-\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{C}^\equiv\text{C}_6\text{H}_5 \\
\hline
\text{467} \\
\text{468}
\end{array}
\]

The cleavages of 465a and 465b are probably due to the strong electron-withdrawing character of the nitroaryl system which stabilizes the intermediate carbanion. Compound 318 on deethyldeoxycarbonylation with sodium cyanide in DMSO yields some decylated product 320 (20%)\textsuperscript{1}.

On heating the lactone 469 with sodium chloride in wet DMF for 3 days, a product identified as gentianine (470, 12%) was isolated\textsuperscript{210}.

\[
\begin{array}{c}
\text{COOC}_2\text{H}_5 \\
\hline
\text{H}_2\text{C}^\equiv\text{C}^\equiv\text{CH}_2 \quad \text{NaCl} \\
\text{469} \\
\text{470}
\end{array}
\]

Treatment of the 4-hydroxy-2-pyridones 471a or 471b with sodium cyanide in DMSO (145-155 °C, 4 h) yields the acids 472a (50%) or 472b (44%), respectively\textsuperscript{211}. Heating these acids to 255 °C leads to decarboxylations to afford the pyridones 473a and 473b, respectively.

\[
\begin{array}{c}
\text{C}_6\text{H}_5\text{OC} \quad \text{DMF/H}_2\text{O}/ \quad \text{NaCl} \\
\quad \text{145-155 °C} \\
\text{471a} \quad \text{R}^1 = \text{C}_6\text{H}_5, \quad \text{R}^2 = \text{H} \\
\text{b} \quad \text{R}^1 = \text{C}_6\text{H}_5\text{CH}_2, \quad \text{R}^2 = \text{C}_6\text{H}_5 \\
\hline
\text{472a, b} \\
\text{473a, b}
\end{array}
\]

The dealkoxycarbonylations of pyrazine N-oxides were investigated as a route to 2-amino-3-cyano-5-substituted pyrazines\textsuperscript{212}. The pyrazine N-oxides 474a and 474b on reaction with sodium chloride in wet DMSO (170-185 °C) lead to loss of carbon dioxide but none of the expected pyrazines 475a or 475b could be detected.

\[
\begin{array}{c}
\text{HOOC} \quad \text{DMSO/NaCl,} \\
\quad \text{145-155 °C} \\
\text{472a, b} \\
\quad \text{255 °C} \\
\text{473a, b}
\end{array}
\]
On the other hand, on heating 474a or 474c with lithium iodide in wet pyridine, the pyrazine N-oxides 475a or 475b could be isolated in yields of up to 21%.

Pyrazine N-oxide 476 on being refluxed with lithium iodide in wet DMF for 1 h gives 477 (82%).

The dealkoxycarbonylations of the pyrazines 478a, b, and c were also studied. Attempted deethoxy carbonylation of 478a to prepare 479a by heating with lithium iodide in wet DMF led only to products of apparent decomposition. However, the reaction of 478b with lithium iodide in wet DMF (22 h) gives 479b. The more sterically hindered ethyl ester 478c required more vigorous conditions and only gave a small amount of 479c (15%).

Treatment of 480, formed in situ at 40 °C in tetrahydrofuran, with lithium chloride/HMPT for 2 h leads to the unstable solid 481. On refluxing the solution of 481 in tetrahydrofuran for 4 h, a quantitative evolution of carbon dioxide occurs. Decomposition of 480 by lithium chloride/HMPT in the presence of 2,2,2-trifluoroethanol yields chlorodifluoromethane. Reaction of 480 with lithium chloride/HMPT in the presence of polyfluoromethyl ketones in tetrahydrofuran results in the formation of tertiary alcohols.

Addition of 480 to a refluxing solution of lithium chloride/HMPT and trifluoromethyl ketones 482 in tetrahydrofuran results in the formation of alcohols 483a and 483b in yields of 63% and 38%, respectively.²¹³

12. Conclusions

The dealkoxycarbonylation procedures detailed here should continue to find new applications in synthetic chemistry. The reactions are easily performed and the isolation of products can readily be accomplished. Many functionalities survive the reaction conditions and isomerizations of multiple bonds generally do not occur. The choice of experimental conditions is dictated by the substrate structure. The use of lithium chloride in DMSO is recommended as an excellent salt-solvent combination for effecting dealkoxycarbonylations. The sodium cyanide/HMPT combination, while perhaps kinetically more rapid, is partially negated by the hazardous nature of these reagents.

It is with pleasure that I acknowledge the contributions of my coworkers who performed research on various projects related to dealkoxycarbonylations. The undergraduate students were B. J. Gremor, G. A. Glynn, J. M. Eldridge, J. Seastrom, and M. Marusa and the graduate students were A. J. Lowery, E. G. E. Jahngren, Jr., W. P. Stephens, and J. F. Weinsmiller. I also wish to acknowledge the financial support of the Humphrey Chemical Company of North Haven, CT. In particular I wish to express my appreciation to Dr. B. J. Humphrey for his interest in this area of research.

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