### Table 18-5: Methods of Preparation of Carboxylic Acids

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hydrolysis of amides</td>
<td>Acid or base catalyzed amide is (mixed base, then hydrolyzed) to the acid, a useful laboratory synthesis if the amide is accessible as by S-N reaction of RX (Section 9-7F).</td>
</tr>
<tr>
<td>2. Hydrolysis of esters and amides</td>
<td>Useful when the starting material can be prepared by a reaction of 3-butyrolactone or propionolactone esters and ethyl acetate.</td>
</tr>
<tr>
<td>3. Carboxylation of organometallic compounds</td>
<td>Usually carried out by boiling solution of organometallic compound over phosgene Dry ice and stirring efficiently as important and versatile reaction (see Section 14-12).</td>
</tr>
<tr>
<td>4. Methyl ester synthesis</td>
<td>An important reaction for synthesis of allyl and dialkyl acetic acid, RX and RX are primary or secondary alkyl halides, (methyl) acetic acid (R = methyl), unsaturated acids (R = an unsaturated hydrocarbon, isopropylidene allylic alcohols, azlactone of, see Sections 18-6C and 18-6D.</td>
</tr>
<tr>
<td>5. Acetylation of esters synthesis</td>
<td>No particular advantage over 4. In fact, ketones may be formed in competition with acids (in acetic anhydride) ester synthesis (see Section 18-6E).</td>
</tr>
<tr>
<td>6. Aminolysis reaction</td>
<td>Useful method of preparing neopentyl amide from acyl chloride (see Section 16-14A and 216-47).</td>
</tr>
<tr>
<td>7. Oxidation of primary alcohols and aldehydes</td>
<td>Oxidizing agents are KMnO₄, H₂O₂ or (OH)₂, CrO₃, HNO₂, and Ag₂O. (Ag₂O only works for aldehydes.)</td>
</tr>
<tr>
<td>8. Oxidation of alcohols</td>
<td>Oxidizing agents are KMnO₄, H₂O₂ or (OH)₂, CrO₃, and HNO₂; used mainly for structure determination; further degradation may occur.</td>
</tr>
<tr>
<td>9. Oxidation of methyl ketones (halogenation reaction)</td>
<td>Hypochlorites may be used in place of Br₂ and NaOH; limited by possible substitution of halogen in R radical (see Section 17-3B).</td>
</tr>
<tr>
<td>10. Clemmensen reduction</td>
<td>Useful only when alicycle has no a hydrogen and cannot undergo an aldol condensation (see Section 16-4E).</td>
</tr>
<tr>
<td>11. Becker-Vilner oxidation of esters with peracids</td>
<td>Generally used method for aliphatic and cyclic ketones without double bonds; oxidizing agents commonly used are peroxyacetic acid (CH₃COOOH), peroxyacetic acid (CH₂COOCA₃), and trifluoroacetic acid (CF₃COOH); the last is prepared from trifluoroacetic anhydride and H₂O₂, and used in the presence of Na₂PO₄ as a buffering agent (Section 16-7).</td>
</tr>
</tbody>
</table>

*aMethods specific for the preparation of aromatic acids are discussed in Chapter 20.*
Table 18-6: Methods of Preparation of Carboxylic Esters

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. From carboxylic acid and primary alcohol</td>
<td>Generally limited to primary alcohols; acidic catalysts include H₂SO₄, HCl, BF₃; for details and mechanism see Sections 18.40 and 18.3A</td>
</tr>
<tr>
<td>( RCOOH + R'OH \xrightarrow{H^+} RCOOR' + H₂O )</td>
<td></td>
</tr>
<tr>
<td>2. From acid chlorides and alcohols</td>
<td>Versatile reaction; works well with primary, sec., and tert. alcohols; a base may be necessary to remove HCl, because HCl phthalic acid; may give ethers and free phthalic acid.</td>
</tr>
<tr>
<td>( RCOCl + R'OH \rightarrow RCOOR' + HCl )</td>
<td></td>
</tr>
<tr>
<td>3. From anhydrides and alcohols</td>
<td>Widely applicable; acid catalyzed;</td>
</tr>
<tr>
<td>( \text{RCO}_2\text{O} + \text{R'OH} \xrightarrow{\text{H}^+} \text{RCO}_2\text{R'} + \text{RCO}_2\text{H} )</td>
<td></td>
</tr>
<tr>
<td>( \text{RCO}_2\text{H} + \text{R'OH} \xrightarrow{\text{H}^+} \text{RCO}_2\text{R'} + \text{H}_2\text{O} )</td>
<td></td>
</tr>
<tr>
<td>4. Ester interchange</td>
<td>Acid- and base-catalyzed; generally limited to primary alcohols (for discussion, see Section 18.7A)</td>
</tr>
<tr>
<td>( \text{RCO}_2\text{R'} + \text{R''OH} \xrightarrow{\text{H}^+ \text{ or CH}^3} \text{RCO}_2\text{R''} + \text{R'}\text{OH} )</td>
<td></td>
</tr>
<tr>
<td>5. From carbonate salt, thionyl chloride, and alcohol</td>
<td>Limited to primary alcohols; it amounts to an S₂ displacement of chloromethane group by carboxylate ion; steric hindrance in the carbonate salt seems unimportant.</td>
</tr>
<tr>
<td>( \text{RCH} + \text{SOCl}_2 \rightarrow \text{R'}\text{SOCl} + \text{HCl} )</td>
<td></td>
</tr>
<tr>
<td>( \text{RCO}_2\text{Na} + \text{R'}\text{SOCl} \rightarrow \text{RCO}_2\text{R'} + \text{SO}_2 + \text{NaCl} )</td>
<td></td>
</tr>
<tr>
<td>6. From carbonate salt and allyl halides</td>
<td>Restricted to primary halides with high S₂ reactivity.</td>
</tr>
<tr>
<td>( \text{RCO}_2\text{Na} + \text{RX} \rightarrow \text{RCO}_2\text{R} + \text{NaX} )</td>
<td></td>
</tr>
<tr>
<td>7. Alkylation of esters</td>
<td>Analogue to hydrolysis of esters, Method 1, Table 18-5.</td>
</tr>
<tr>
<td>( \text{RCO}_2\text{R'} + \text{RCH} \xrightarrow{\text{H}_2\text{O}} \text{RCO}_2\text{R} + \text{NH}_2^\beta )</td>
<td></td>
</tr>
<tr>
<td>8. Diazomethane and carboxylic acids</td>
<td>High yield, clean reaction, but diazomethane is a reactive, explosive, and toxic compound; useful for methyl esters of rare or acid-sensitive carboxylic acids.</td>
</tr>
<tr>
<td>( \text{RCO}_2\text{H} + \text{CH}_2\text{N}_2 \rightarrow \text{RCO}_2\text{N}_2 + \text{N}_2 )</td>
<td></td>
</tr>
</tbody>
</table>

Table 18-7: Methods of Preparation of Acyl Halides, Anhydrides, Amides, and Related Compounds
### ACYL HALIDES

1. From thionyl chloride and carboxylic acids
   
   $$\text{RCOOH} + 5\text{SOCl}_2 \rightarrow 5\text{RCOCl} + \text{HCl} + 5\text{SO}_2$$

   Most acyl chlorides are prepared by this method; anhydride formation is sometimes an objectionable side-reaction.

2. From phosphorus halides and carboxylic acids
   
   $$3\text{HCO}_2\text{H} + \text{PBr}_3 \rightarrow 3\text{HCO}_2\text{Br} + \text{HPO}_3$$

   $$\text{RCOOH} + \text{POCl}_3 \rightarrow \text{RCOOCl} + \text{POCl}_3 + \text{HCl}$$

   Separation difficulty from $\text{HPO}_3$ and $\text{POCl}_3$ sometimes occur.

3. From thionyl chloride and anhydrides

   Useful only when anhydride is more accessible than the parent acid.

4. Acyl fluorides, bromides, and iodides from chlorides

   $$\text{RCOCl} + \text{HX} \rightarrow \text{RCOX} + \text{HCl}$$

   in which $\text{HX} = \text{HF}$, $\text{HBr}$, or $\text{HI}$

5. From ethanedioyl dichloride

   $$\text{RCO}_2\text{Cl} + \text{CO}_2 \rightarrow \text{RCO}_2\text{O} + \text{CO}_2 + \text{HCl}$$

   Usually an excellent method.

### ANHYDRIDES

1. From acid halides and carboxylic acids

   $$\text{RCO}_2\text{H} + \text{R'}\text{COCl} \rightarrow \text{RCO}_2\text{O} + \text{R'O} + \text{HCl}$$

   The most frequently used method; simple or mixed anhydrides can be prepared.

2. From acid halides and carboxylic salts

   $$\text{RCO}_2\text{H} + \text{R'}\text{COOH} \rightarrow \text{RCO}_2\text{O} + \text{R'O} + \text{NaCl}$$

3. From ketones and carboxylic acids

   $$\text{CH}_3\text{C} = \text{O} + \text{RCOOH} \rightarrow \text{RCO}_2\text{O} + \text{CH}_3\text{CHOH}$$

   Commercial preparation of ethanolic anhydride (Section 17.46).
AMIDES

1. From carboxylic acids and ammonia or amines
   \[ \text{RCOOH} + \text{NH}_3 \rightarrow \text{RCONH}_2 + \text{H}_2\text{O} \]
   \[ \text{RCOOH} + 2\text{NH}_3 \rightarrow \text{RCON} = \text{NH} + \text{H}_2\text{O} \]

2. From carboxylic acids and ammonia or amines
   \[ \text{RCOOH} + \text{NH}_3 \rightarrow \text{RCONH}_2 \text{H}_2\text{O} \]
   \[ \text{RCOOH} + \text{R} \text{NH}_2 \rightarrow \text{RCONH} = \text{R} + \text{H}_2\text{O} \]

3. From anhydrides and ammonia or amines
   \[ \text{RC(O)}_2\text{O} + \text{NH}_3 \rightarrow \text{RCONH}_2 + \text{H}_2\text{O} \]

4. Hydrolysis of amides
   \[ \text{RCNH}_2 \rightarrow \text{RCOOH} + \text{H}_2\text{O} \]

5. Alkymination of amides (Kraus reaction)
   \[ \text{RC(=O)CH}_2 + \text{R'} \text{NH}_2 \rightarrow \text{RC(=O)R'} + \text{CH}_2\text{NH}_2 \]

6. Aromatic amides
   \[ \text{RC(O)}_2\text{N}_2 \rightarrow \text{RCONH}_2 + \text{C}_2\text{H}_4\text{OH} \]

7. Hydrolytic aldehydes (acyl azides)
   \[ \text{RC(O)}_2\text{N}_2 \rightarrow \text{RCONH} = \text{O} + \text{C}_2\text{H}_4\text{OH} + \text{H}_2\text{O} \]

8. Acyl azides
   \[ \text{RCOOH} + \text{NaN}_3 \rightarrow \text{RCON} = \text{O} + \text{N}_2 \]

Most amides are prepared by this method. Use base to convert R-NH₂ to R-NH₂⁺ (Sections 23-8A and 24-3).

Requires relatively high temperatures.

Important method for preparation of cyclic amines from cyclic anhydrides.

Hydrolysis stops at amide stage if R is a long chain group; H₂O accelerates the hydrolysis reaction in alkaline solution (Section 24-3).

Gives N,N-diacylamides (good only for alkali; if alkaline, the form relatively stable carbonium ions; useful for preparation of amines with N=\text{N} and groups by hydrolysis of amides (Section 24-3)).