CHAPTER 1

A SELECT REVIEW OF THE REACTIONS OF o-PHENYLENEDIAMINES
WITH CARBONYL DERIVATIVES AND THEIR EQUIVALENTS.
INTRODUCTION

A variety of diamines have proved to be versatile substrates for heterocyclic synthesis. Among them, o-phenylenediamines (1) and their precursors and derivatives have been extensively used for the synthesis of benzaza-heterocycles in view of the latter's commercial value (Table 1, 2, and 3). Useful summaries of synthetic efforts in this area are available: benzimidazole(1,2) (2), quinoxaline(3,4) (3), benzodiazepine(5,6) (4) and phenanthroline(7) (5). The review presented in this work is an effort to provide an update on this subject incorporating recent data (1975-1992) with emphasis on synthetic approaches based on aromatic 1,2-diamines. In view of the vast literature in this area, any attempt to make a comprehensive survey of the field will be a tall order. The treatment meted out here is therefore a very selective one, highlighting patterns. The narration covers the material from over 300 reports.
<table>
<thead>
<tr>
<th>Sr No</th>
<th>X</th>
<th>R'</th>
<th>R''</th>
<th>Activity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>CH(OH)C₆H₄Cl-p</td>
<td>Neurotropic and Vasodilator.</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>H</td>
<td></td>
<td>Antihelminitic</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H/alkyl</td>
<td></td>
<td>Pesticides</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>H/alkyl</td>
<td>H/Me</td>
<td>CH₂NMeR¹R²</td>
<td>Bactericides</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R¹=H,Me</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R²=C₁₂-₁₈alkyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>H</td>
<td>NHCO₂CH₃</td>
<td>Antihelminitic</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>H₂C-O-Cl</td>
<td>H₂C-N</td>
<td>Antihelminitic</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>H₂C-O-Cl</td>
<td>CH₃</td>
<td>Spasmolytic and antifungal.</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>H</td>
<td>-F HN -(CH₂)₂-</td>
<td>Antihistaminic</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C₆H₄OMe-p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>CONHMe</td>
<td>H</td>
<td>Pesticidal</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>6-C₆H₁₁CO</td>
<td>H</td>
<td>NHCO₂CH₃</td>
<td>Antihelminitic</td>
<td>17</td>
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Table 1A: Continued

<table>
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<th>Ref</th>
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<tr>
<td>11</td>
<td>6-</td>
<td></td>
<td>NHCO₂CH₃</td>
<td>Antihelmintic</td>
<td>17</td>
</tr>
<tr>
<td>12</td>
<td>6-</td>
<td></td>
<td>NHCO₂CH₃</td>
<td>Antihelmintic</td>
<td>17</td>
</tr>
<tr>
<td>13</td>
<td>6-Ph-C-</td>
<td>SO₂CHMe₂</td>
<td>NH₂</td>
<td>Antiviral</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>S-N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>6-Ph₂CH-</td>
<td></td>
<td>CH₂CH₂CH₃</td>
<td>Peripheral vasodilating</td>
<td>19</td>
</tr>
<tr>
<td>15</td>
<td>6-Cl</td>
<td></td>
<td>C₆H₄OCH₂CONHN</td>
<td>Potential antiviral</td>
<td>20</td>
</tr>
<tr>
<td>16</td>
<td>6-H₃C(CH₂)₂O</td>
<td></td>
<td>NHCO₂CH₃</td>
<td>Antihelmintic</td>
<td>21</td>
</tr>
<tr>
<td>17</td>
<td>5-(CH₃)₂CHO-</td>
<td></td>
<td></td>
<td></td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>6-Frs</td>
<td></td>
<td>NHCO₂CH₃</td>
<td>Antihelmintic, agricultural fungicide</td>
<td>23</td>
</tr>
<tr>
<td>19</td>
<td>6-H₃C(CH₂)₃S</td>
<td></td>
<td>NHCO₂CH₃</td>
<td>Antihelmintic</td>
<td>24</td>
</tr>
<tr>
<td>20</td>
<td>6-C₆H₅S</td>
<td></td>
<td>NHCO₂CH₃</td>
<td>Antihelmintic</td>
<td>25</td>
</tr>
<tr>
<td>21</td>
<td>6-C₆H₅S-</td>
<td></td>
<td>NHCO₂CH₃</td>
<td>Antihelmintic</td>
<td>26</td>
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</table>
### Table 1A: Continued

<table>
<thead>
<tr>
<th>Sr No</th>
<th>Compound</th>
<th>Activity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Neoplasm inhibitor</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>R and R' = H, halogen, Me, MeO, NO₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Fungicidal</td>
<td>28</td>
</tr>
</tbody>
</table>

### Table 1B: Biologically active benzimidazole-2-one.

![Chemical Structure](image3)

<table>
<thead>
<tr>
<th>Sr No</th>
<th>X</th>
<th>R</th>
<th>R'</th>
<th>Activity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>-(CH₂)₃-N COPh</td>
<td>Veterinary Sedative</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>H</td>
<td>-(CH₂)₃-N COC₆H₄-F-p</td>
<td>Antipsychotic</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td>-(CH₂)₃-N CHPh₂</td>
<td>Antihistaminic and useful for treatment of asthma</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>6-Cl</td>
<td>(CH₂)₃N(CH₃)₂</td>
<td>C₆H₅</td>
<td>Antidepressant</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>Antiemetic</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sr No</td>
<td>Compound</td>
<td>Activity</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>---------------------</td>
<td>-----</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Hypotensive</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R = Me, Ph, OH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Antimicrobial</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Antiinflammatory</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R&lt;sup&gt;1&lt;/sup&gt; = substituted amino</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R&lt;sup&gt;2&lt;/sup&gt; = H, 6-OMe, 6,7-(OMe)&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>Antiamoebic</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>Atopic eczema urticuria (potentials)</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>X = Cl, NO&lt;sub&gt;2&lt;/sub&gt;; R = Me, Et</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>Insecticide</td>
<td>38</td>
<td></td>
<td></td>
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</table>
Table 2: Continued

<table>
<thead>
<tr>
<th>Sr No</th>
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<th>Activity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td><img src="image" alt="Compound 7" /></td>
<td>Against respiratory infections of poultry</td>
<td>39</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Compound 8" /></td>
<td>&quot;&quot;</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Compound 9" /></td>
<td>Pesticide</td>
<td>41</td>
</tr>
</tbody>
</table>

X = O, S
<table>
<thead>
<tr>
<th>Sr No</th>
<th>Compound</th>
<th>Activity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![ Compound 1 ]</td>
<td>CNS depressant</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>![ Compound 2 ]</td>
<td>Anxiolytic</td>
<td>43, 44</td>
</tr>
<tr>
<td>3</td>
<td>![ Compound 3 ]</td>
<td>Antihypertensive</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>![ Compound 4 ]</td>
<td>&quot;</td>
<td>46a</td>
</tr>
<tr>
<td>5</td>
<td>![ Compound 5 ]</td>
<td>Antiulcer</td>
<td>46b</td>
</tr>
</tbody>
</table>
Scheme 1 (Ref 56a,56b)

1. PhCHO (1 mole), -20°, then at RT. Several days
2. PhCHO (2 mole), 220-230°, 4 hr
Section 1: Reactions of o-PDA with monocarbonyls and their equivalents

Several reports have appeared on the reaction of o-PDA (1) with monocarbonyl compounds. The substrates in this class include carboxylic acids and their derivatives (esters, or haloacids/esters, amides), aldehydes, ketones, α,β-unsaturated carbonyl compounds and lactones. A rich literature has also accumulated on masked carbonyl substrates in the last couple of decades. Heterocycles formed from these reactions are either benzimidazoles (2), quinoxalines (3), benzodiazepines (4) or phenanthrolines (5) depending on the nature of reactants and reaction conditions. Table 4 to 14 highlight the variety of their applications augmented by brief discussions of some of these conversions.

a. with aldehydes:

The reactions of o-PDA with aldehydes have been studied more extensively compared to those with ketones. The nature of the reaction product depends on reaction conditions and the environment of the carbonyl in the substrates.

Aldehydes react with o-PDA in the presence of oxidising agents such as cupric acetate, potassium ferricyanide, nitrobenzene or sulfur to furnish 2-substituted benzimidazoles (Table 4). The general course of this reaction to form benzimidazole may be represented as shown in scheme 1 (Path A, 1→6→7→3). The formation of a mixture of 3 and 15 is observed when the reaction is performed in the absence of oxidants (scheme 1, Table 5). Here the formation of 3 represents oxidation of 2 and the compensating reduction is suggested to be of 6 to 2. The formation of 15 can be either through
Table 4: Benzimidazoles from aldehydes in presence of an oxidising agent.

\[
\text{OHC-}R + \text{NH}_2 \text{NH}_2 \rightarrow \text{R'NHR}
\]

<table>
<thead>
<tr>
<th>Sr No</th>
<th>R</th>
<th>R'</th>
<th>Conditions</th>
<th>Yield %</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>C₆H₄</td>
<td>H</td>
<td>Cu(OAc)₂, 50% aq. MeOH</td>
<td>72-82</td>
<td>47</td>
</tr>
<tr>
<td>2.</td>
<td>p-NO₂C₆H₄</td>
<td>PhCONH</td>
<td>C₆H₅NO₂, reflux, 4hr</td>
<td>76</td>
<td>51</td>
</tr>
<tr>
<td>3.</td>
<td>p-PhC₆H₄</td>
<td>H</td>
<td>Cu(OAc)₂</td>
<td>72-82</td>
<td>51</td>
</tr>
<tr>
<td>4.</td>
<td>N-NH₂</td>
<td>H</td>
<td>C₆H₅NO₂, EtOH, reflux, 4hr</td>
<td>72-82</td>
<td>51</td>
</tr>
<tr>
<td>5.</td>
<td>H</td>
<td>DMF, 110-120º</td>
<td>72-82</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>H</td>
<td>K₂Fe(CN)₆·H₂O, MeOH, reflux, 2hr</td>
<td>72-82</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>H</td>
<td>C₆H₅NO₂, reflux, 1.5-2hr then C₆H₅NO₂, reflux 15 min.</td>
<td>76</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>H</td>
<td>EtOH, reflux, 15 min.</td>
<td>76</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>H</td>
<td>EtOH, reflux, 15 min.</td>
<td>76</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>

# Cu complex of 2-phenylbenzimidazole is obtained.
Table 5: Benzimidazoles from aldehydes in absence of oxidising agent.

![Chemical structures](Ref 59)

**R-CHO + 1 2 \rightarrow 3**

<table>
<thead>
<tr>
<th>Sr NO</th>
<th>R</th>
<th>R'</th>
<th>Mole ratio of 1&amp;2</th>
<th>Conditions</th>
<th>R₂</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>1:1</td>
<td>220-230⁰, 4hr</td>
<td>H</td>
<td>*</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>H</td>
<td>2:1</td>
<td>220-230⁰, 4hr</td>
<td>CH₂Ph</td>
<td>*</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>H</td>
<td>2:1</td>
<td>10% HCl, H₂O MeOH, He 5-6hr</td>
<td>H₂C-F</td>
<td>98</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>NO₂</td>
<td>2:1</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
<td>95</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>o-HOC₆H₄</td>
<td>H</td>
<td>*</td>
<td>EtOH, boil</td>
<td>o-HOC₆H₄CH₂</td>
<td>*</td>
<td>58</td>
</tr>
</tbody>
</table>

* The benzaldehyde and o-PDA used in this reaction was obtained in situ from the reaction of o-nitroaniline and benzylamine.
Scheme 2 (Ref 60)

1. o-PDA, EtOH, 35-40°

Scheme 4 (Ref 63, 64)
the formation and cyclization of the dibenzal derivative 12 or through the imidazoline derivative 7 acting as reducing agent to convert 6→7→15.

Benzimidazoles result from a simple condensation of several furan aldehydes with o-PDA (entries 6, 8, 2, 10, Table 4) to the predictable product. Presence of 5-azido group in 16 changes the course of the reaction to lead to 2-cyanovinyl quinoxaline (20; scheme 2), involving a furan ring rupture in the process.

b. with ketones:

An interesting reaction of ketones such as acetone (21) with substituted 1,2-diaminoethane or o-PDA in presence of chloroform sodium hydroxide and benzyltriethylammonium chloride is reported to give a mixture of the 2-piperazines 23a and 23b, and quinoxaline 23c respectively (scheme 3). Formation of an epoxide intermediate (22) is suggested. In contrast, the reaction of N1,2,2-trisubstituted-1,2-diamine with acetone proceeded with only a mere 12% conversion after 24hr under the same reaction conditions except for the absence of the quaternary salt.

Scheme 3 (61,62)

![Scheme 3 Diagram]

1. H2N(C(n-Pr)2CH2NH(n-Pr), CHCl3, PhCH2NEt3Cl, CH2Cl2, 50% NaOH, 10º, overnight (for 23a and 23b)
2. o-PDA, CHCl3, PhCH2NEt3Cl, CH2Cl2, 50% NaOH, 10º, overnight (for 23c)

The reaction of o-PDA with cyclic ketones (scheme 4) such as cyclohexanone leads to a mixture of the corresponding spiro derivative 25 and isobenzimidazole 26. The former on treatment with MnO2 yields benzimidazole 26 (R=SO2Me, SO2Ph, CN, NO2; R=R'=H)
C. With $\alpha$ and $\beta$-haloketones:

The reactions of o-PDA with $\alpha$-haloketones or with ketones in presence of a halogenating agent furnish quinoxalines. Several recent illustrations are documented in Table 6. Ring-substituted o-PDA's react with $\alpha$-haloketones to generate a mixture of quinoxalines (scheme 6). The major product from the reaction appears to be derived from the condensation of the more basic NH$_2$ group in these derivatives.

Scheme 6 (Ref 66)

![Scheme 6 diagram](image)

Table 6: Quinoxalines from $\alpha$-haloketones

<table>
<thead>
<tr>
<th>Sr No</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>X</th>
<th>Condition</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Me, Et, Pr</td>
<td>NHCOR</td>
<td>Cl/Br</td>
<td>*</td>
<td>52-70</td>
<td>65</td>
</tr>
<tr>
<td>2.</td>
<td>C$_6$H$_5$</td>
<td>H</td>
<td>Br</td>
<td>NaOAC</td>
<td>*</td>
<td>66</td>
</tr>
<tr>
<td>3.</td>
<td>C$_6$H$_5$</td>
<td>CH$_2$CH$_2$C$_6$H$_5$</td>
<td>Br</td>
<td>*</td>
<td>12-40</td>
<td>67</td>
</tr>
<tr>
<td>4.</td>
<td>p-NH$_2$C$_6$H$_4$</td>
<td>H</td>
<td>Cl</td>
<td>DMF, 40-70°C</td>
<td>*</td>
<td>68</td>
</tr>
<tr>
<td>5.</td>
<td>p-NCCH$_2$C$_6$H$_4$</td>
<td>H</td>
<td>Cl</td>
<td>MeOH, reflux 3.5hr</td>
<td>*</td>
<td>69</td>
</tr>
<tr>
<td>6.</td>
<td>2-pyridyl</td>
<td>H</td>
<td>H</td>
<td>Br$_2$, CCl$_4$</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>7.</td>
<td>R-S</td>
<td>H</td>
<td>Br</td>
<td>*</td>
<td>*</td>
<td>71</td>
</tr>
</tbody>
</table>

# [Diagram of quinoxaline]

(Ref 65 66 67 68 69 70 71)
Scheme 7 (Ref 72)

\[
\begin{array}{c}
\text{PhCH–CH–CPh} \\
\text{Br} \quad \text{Br} \quad \text{O} \\
38
\end{array}
\xrightarrow{1}
\begin{array}{c}
\text{Ph} \\
39
\end{array}
\xrightarrow{\text{Acid catalysed}}
\begin{array}{c}
\text{Ph} \\
40
\end{array}
\]

i. o-PDA, MeOH, Et₃N

Scheme 8 (Ref 73)

\[
\begin{array}{c}
\text{Ph} \quad \text{CH} \quad \text{Cl} \\
41
\end{array}
\xrightarrow{1}
\begin{array}{c}
\text{Zn} \\
\text{COMPLEX}
\end{array}
\xrightarrow{\text{i, ii, iii}}
\begin{array}{c}
\text{Ph} \\
42
\end{array}
\]

i. o-PDA HCl, Chloranil, ZnCl₂, 90-100°, 4 hr
ii. MeOH, boil; iii. aq. NaOH

Scheme 9 (Ref 74)

\[
\begin{array}{c}
\text{43}
\end{array}
\xrightarrow{o-PDA}
\begin{array}{c}
\text{44}
\end{array}
\]

Scheme 10

\[
\begin{array}{c}
\text{R–N=CHR} \\
45
\end{array}
\xrightarrow{\text{NH}}
\begin{array}{c}
\text{R–N=CR} \\
46
\end{array}
\xrightarrow{\text{NH₂}}
\begin{array}{c}
\text{R–N=CHR} \\
47
\end{array}
\]

\[
\begin{array}{c}
\text{RHN–C=NR} \\
49
\end{array}
\xrightarrow{\text{NH₂}}
\begin{array}{c}
\text{RHN–C=NR} \\
48
\end{array}
\]
The α,β-dibromoketone 39 reacting in presence of a strong tertiary base gives the aziridoquinoxaline 32 which, under the influence of acid, rearranges to a 2,3-disubstituted quinoxaline (40). Reaction of the β-haloketone 41 with o-PDA in presence of chloranil followed by treatment with methanol and ammonium hydroxide results in formation of 1,10-phenanthroline 42, (scheme 9) obviously resulting from double cyclization. The exact experimental condition for conversion of the hydroxyketone 43 with o-PDA to the benzodiazipine 44 are not available; it would appear rational to consider a prior derivatisation at OH to facilitate aminolysis.

d. with masked isocyanates: (R—N=CXY)

The masked carbonyls in a number of cyanate derivatives react with o-PDA generating 2-aminobenzimidazoles (Table 7). In all these instances, the reaction can be visualised to proceed by way of two vinylic substitutions and a protomeric shift. They may be sequenced in more than one way (scheme 10). In a similar fashion the methine analogs AA react with o-PDA to afford the benzimidazole 50 (scheme 11).

Scheme 11 (Ref 84+)

\[
\begin{align*}
\text{RSO}_2\text{CH} & \equiv \text{C} & \text{Cl} & \text{Cl} & \xrightarrow{o-\text{PDA}} & \text{N} & \text{CH}_2\text{SO}_2\text{R} \\
\text{R} & & \text{Et, Bu, Ph} & & & & 62-84\% \\
\text{AA} & & & & & & 50
\end{align*}
\]
Table 7: Reactions of o-PDA with masked isocyanates

\[
\begin{align*}
R\overset{\equiv}{=}-CXY + & \quad R' \quad \begin{array}{c}
H \\
NH_2 \\
NH_2
\end{array} \quad \rightarrow \quad R \quad \begin{array}{c}
\overset{\equiv}{=} \quad N \\
\quad \quad \quad \quad \mathrm{NHR}
\end{array}
\end{align*}
\]

<table>
<thead>
<tr>
<th>S.No.</th>
<th>X</th>
<th>Y</th>
<th>R</th>
<th>R₁</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>Cl</td>
<td>CO₂Me</td>
<td>H</td>
<td>reflux, 5hr</td>
<td>92</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>OPh</td>
<td>Cl</td>
<td>COCl₂</td>
<td>H</td>
<td>*</td>
<td>*</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>OPh</td>
<td>OPh</td>
<td>CN</td>
<td>H</td>
<td>2-Propanol reflux, 1hr</td>
<td>92</td>
<td>77</td>
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<tr>
<td>4</td>
<td>OPh</td>
<td>OPh</td>
<td>CN</td>
<td>Cl</td>
<td>2-Propanol reflux, 15hr</td>
<td>92</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>OEt</td>
<td>SMe</td>
<td>CO₂Et</td>
<td>H</td>
<td>Toluene, reflux, 6hr</td>
<td>72</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>SMe</td>
<td>SMe</td>
<td>2-benzothiazole</td>
<td>H</td>
<td>DMF, reflux, 10-16 hr</td>
<td>53</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>SMe</td>
<td>SMe</td>
<td>Ph</td>
<td>H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>SMe</td>
<td>NH₂</td>
<td>H</td>
<td>Furyl-CH₂CH₂CO</td>
<td>ClCO₂Me</td>
<td>70</td>
<td>81</td>
</tr>
<tr>
<td>9</td>
<td>SMe</td>
<td>NH₂</td>
<td>H</td>
<td>PhCH₂CH₂CO</td>
<td>ClCO₂Et</td>
<td>50</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>SMe</td>
<td>NHMe</td>
<td>H</td>
<td></td>
<td></td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>SMe</td>
<td>NH₂</td>
<td>CO₂Me</td>
<td>EtNHCONH</td>
<td>MeOH, reflux, 2 hr</td>
<td>92</td>
<td>83</td>
</tr>
</tbody>
</table>
E) With carboxylic acids and derivatives:

Saturated aliphatic and aromatic acids and their derivatives react with o-PDA to give benzimidazole, quinoxaline or benzodiazepinc. The course of the reaction is governed by the nature of reactants as well as reaction conditions. Indeed, bewildering combinations of these parameters have been applied in these syntheses. Benzimidazoles (2) are the sole products obtained when carboxylic acids\(^95-101\) and esters\(^102-112\) are reacted with o-PDA. Heating the carboxylic acids\(^83,89,124\) with o-PDA in presence of hydrochloric acid for varying periods of time appears to be the most common procedure employed for this reaction. We have however noticed, in more recent times that other reagents such as tetraphosphoric acid trimethyl silylether\(^86\), Ti(OBu)\(_4\)\(^91\), PhOPCl\(_2\)\(^94\), TiCl\(_4\)\(^95\), SiCl\(_4\)\(^93\), polyphosphoric acid (PPA)\(^101\) are seen to be preferred. In the case of several esters\(^102,106,112\) and amides\(^136-139\), merely heating the reactants in a neutral solvent in absence of any formal condensing agent provides a general pathway to obtain benzimidazoles. The course of the reaction would involve initial acylation of the amine followed by dehydrative cyclization to give benzimidazoles (scheme 12).

Several examples are collected and classified in Tables 8 (from carboxylic acids) and 9 (from carboxylic ester).

**Scheme 12**

\[
\begin{align*}
\text{RCOX} \quad X=\text{OH, OR, OAr} & \xrightarrow{o-PDA} \begin{bmatrix}
\text{NH}_2 \\
\text{NHCOR}
\end{bmatrix} \xrightarrow{-\text{H}_2\text{O}} \begin{bmatrix}
\text{N} \\
\text{R}
\end{bmatrix}
\end{align*}
\]
Table 8: Benzimidazoles from carboxylic acids

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Sr No</th>
<th>R</th>
<th>X</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>AlCl₃</td>
<td>*</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>H₃C</td>
<td>H</td>
<td>tetraphosphoric acid trimethyl silylether (ClCH₂)₂, 85°C, 20min</td>
<td>65</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>1-Adamantyl</td>
<td>Cl</td>
<td></td>
<td>30-59</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>H₂NCH₂</td>
<td>H</td>
<td>5.5N HCl, reflux 30hr</td>
<td>56</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>MeS(CH₂)ₙ(2,3)</td>
<td>H</td>
<td>Conc HCl, H₂O</td>
<td>*</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>MeCOEtCH</td>
<td>H</td>
<td></td>
<td>55.5</td>
<td>90a</td>
</tr>
<tr>
<td>7</td>
<td>Ph-N=S</td>
<td>H</td>
<td></td>
<td>*</td>
<td>90b</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>H</td>
<td>4N HCl, 2.5hr</td>
<td>*</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>H</td>
<td>190°C, 3hr</td>
<td>87</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>A, X=S</td>
<td>H</td>
<td>190°C, 3hr</td>
<td>84</td>
<td>93</td>
</tr>
</tbody>
</table>
Table 8: Continued

<table>
<thead>
<tr>
<th>Sr</th>
<th>R</th>
<th>X</th>
<th>Conditions</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>PhCH₂</td>
<td>H</td>
<td>PhOPCl₂, Pyridine</td>
<td></td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>110-20°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12a</td>
<td>C₆H₅</td>
<td>H</td>
<td>TiCl₄, xylene, 130°, 3 hr</td>
<td>78</td>
<td>95a</td>
</tr>
<tr>
<td>12b</td>
<td>C₆H₅</td>
<td>SO₃H (only in 3)</td>
<td>96% H₂SO₄, 178° 6 hr</td>
<td>60</td>
<td>95b</td>
</tr>
<tr>
<td>13</td>
<td>p-MeC₆H₄</td>
<td>H</td>
<td>PhOPCl₂, Pyridine</td>
<td></td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>110-120°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>p-ClC₆H₄</td>
<td>H</td>
<td>PhOPCl₂, Pyridine</td>
<td></td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>110-120°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>o-ClC₆H₄</td>
<td>H</td>
<td>Ti(ΟBu)₄, xylene</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>16</td>
<td>3,4-(MeO)₂C₆H₃</td>
<td>H</td>
<td>H₃PO₄, reflux 3-4 hr</td>
<td>78</td>
<td>96</td>
</tr>
<tr>
<td>17</td>
<td>o-N₃C₆H₄</td>
<td>p-NO₂</td>
<td>PPE, 110°, 1 hr</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td>18</td>
<td>o-HOC₆H₄</td>
<td>H</td>
<td>SiCl₄</td>
<td>70-86</td>
<td>98</td>
</tr>
<tr>
<td>19</td>
<td>p-HOC₆H₄</td>
<td>Cl</td>
<td>PTS, 210-20°, 2 hr</td>
<td>70</td>
<td>99</td>
</tr>
<tr>
<td>20</td>
<td>2-furoyl</td>
<td>H</td>
<td>Fusion, 180°, 2 hr</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>21</td>
<td>H₃C</td>
<td>H</td>
<td>EPA, 160°, 4 hr, N₂</td>
<td>86</td>
<td>101</td>
</tr>
</tbody>
</table>
Table 9: Benzimidazoles from carboxylic acid esters

\[
\text{RCO}_2R' + o\text{-PDA} \rightarrow \begin{array}{c}
\text{N} \\
\text{H} \\
\text{N} \\
\text{R}
\end{array}
\]

<table>
<thead>
<tr>
<th>Sr No</th>
<th>( \text{R} )</th>
<th>( \text{R'} )</th>
<th>Condition</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>( \text{C}_6\text{H}_5 )</td>
<td>( \text{C}_6\text{H}_5 )</td>
<td>( 220^\circ ), 1hr</td>
<td>96</td>
<td>102</td>
</tr>
<tr>
<td>2.</td>
<td>( \text{o-HO-C}_6\text{H}_4 )</td>
<td>( \text{C}_6\text{H}_5 )</td>
<td>( 220^\circ ), 1hr</td>
<td>93</td>
<td>102</td>
</tr>
<tr>
<td>3.</td>
<td>( \text{Br CH}_2\text{C(OEt)}_2 )</td>
<td>( \text{p-O}_2\text{NC}_6\text{H}_4 )</td>
<td>DMF, ( 150^\circ ), 3hr then ( \text{HCO}_2\text{H}, 90^\circ )</td>
<td>78*</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.5hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>( \text{NCCH}_2 )</td>
<td>( \text{Me/Et} )</td>
<td>( 140^\circ )</td>
<td>76</td>
<td>104, 105, 106</td>
</tr>
<tr>
<td>5.</td>
<td>( \text{C}_6\text{H}_2\text{O}_2 )</td>
<td>( \text{Et} )</td>
<td>PPA, ( 175-200^\circ ), 2.5hr</td>
<td>90</td>
<td>244</td>
</tr>
<tr>
<td>6.</td>
<td>( \text{Et} )</td>
<td>( \text{Et} )</td>
<td>( 240^\circ )</td>
<td>*</td>
<td>107</td>
</tr>
<tr>
<td>7.</td>
<td>( \text{AllylNHCO} )</td>
<td>( \text{Et} )</td>
<td>DMF, reflux, 4hr</td>
<td>20-30</td>
<td>108</td>
</tr>
<tr>
<td>8.</td>
<td>( \text{C}_6\text{H}_5\text{NHCO} )</td>
<td>( \text{Et} )</td>
<td>DMF, 42-74</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>( \text{p-O}_2\text{NC}_6\text{H}_4\text{NHCO} )</td>
<td>( \text{Et} )</td>
<td>*</td>
<td>*</td>
<td>110</td>
</tr>
<tr>
<td>10.</td>
<td>( \text{EtOOCCCH}_2)_2\text{CH(OH)} )</td>
<td>( \text{Et} )</td>
<td>HCl, reflux, 13hr</td>
<td>*$</td>
<td>111</td>
</tr>
<tr>
<td>11.</td>
<td>( \text{HCl.}_{\text{H}_2}\text{N-CH}_2 )</td>
<td>( \text{Et} )</td>
<td>Fusion, ( \text{N}_2 )</td>
<td>58</td>
<td>112</td>
</tr>
</tbody>
</table>

* The intermediate \( \text{BrCH}_2\text{C(OEt)}_2\text{CONHCH}_2\text{NH}_2\text{-o} \) was isolated and then cyclized to 3.

$ Bisbenzimidazole was obtained \( \left( \begin{array}{c}
\text{N} \\
\text{H} \\
\text{N} \\
\text{CH}_2
\end{array} \right)_2\text{CHOH} \)
The course of the reaction of halocarboxylic acids with o-PDA (Table 10) appears to depend on whether or not the reaction medium is acidic. The expected benzimidazole is formed (1→54\(^{a}\); scheme 13) in acidic medium. Absence of the mineral acid leads to quinoxalines (1→56, scheme 13). The sodium salt of chloroacetic acid on reflux with o-PDA in water gives quinoxaline. The C\(_3\)-chain haloacid reacts with o-PDA to give the corresponding benzimidazole 54\(^b\) in presence of hydrochloric acid but benzodiazepine (57) in its absence\(^{124}\).

**Scheme 13**

\[
\begin{array}{ccc}
\text{54a} & \text{55} & \text{56} \\
R= \text{CH}_2\text{Cl} & \text{R} = \text{OH} & \text{R} = \text{CM}_{\text{Me}}\text{CH}_2\text{F} \\
\text{54b} & \text{o-PDA} & \\
R= \text{CM}_{\text{Me}}\text{CH}_2\text{F} \\
\end{array}
\]

- i) ClCH\(_2\)CO\(_2\)H, 5N HCl, reflux, 45-60 min, then 0\(^{\circ}\), 1-3 days
- ii) ClCH\(_2\)CO\(_2\)Na, H\(_2\)O, reflux, 4hr.
- iii) FCH\(_2\)CM\(_{\text{Me}}\)CO\(_2\)H, HCl, EtOH-H\(_2\)O, 107\(^{\circ}\), 8Kbar, 24hr.
- iv) FCH\(_2\)CM\(_{\text{Me}}\)CO\(_2\)H, EtOH-H\(_2\)O, 110\(^{\circ}\), 8Kbar, 24hr.
- v) BrCH\(_2\)CO\(_2\)Et, pH7-9, then oxidation.
Scheme 15 (Ref 125)

\[ \text{R} = \text{SO}_2\text{C}_6\text{H}_4\text{Me-p} \]

\[ \text{62} \]

\[ \text{63} \]

\[ \text{64} \]

\[ \text{65} \]

\[ \text{66} \]

Scheme 16 (Ref 126)

\[ \text{67} \]

\[ \text{68} \]

\[ \text{69} \]

\[ \text{70} \]

\[ \text{71} \]

\[ \text{72} \]

\[ i. \text{ o-PDA, o-C}_6\text{H}_4\text{Cl}_2. \text{ reflux, 6hr.} \]
A halogen-free bisbenzimidazole 60 is obtained when trichloroacetic acid was reacted\textsuperscript{118} with o-PDA (Scheme 14). The normal product 2-tricloromethyl benzimidazole 61 was not formed. It is interesting to note that benzimidazoles result from \(\alpha\)-hydroxy carboxylic acids and o-PDA\textsuperscript{119,120} (entry 7,8; Table 10), whereas \(\alpha\)-hydroxy ester leads to quinoxaline\textsuperscript{123} (entry 11; Table 10). Several examples of reaction of o-PDA with halocarboxylic acids leading to benzodiazepines are given in Table 11.

**Scheme 14 (Ref 118)**

![Chemical diagram]

1. \(\text{Cl}_3\text{CCO}_2\text{H}, 4\text{N HCl}, \text{reflux}, 3\text{hr};\)
2. \(\Delta \text{at m.p.}\)

Reactions of o-diamines with substrates containing multiple reaction sites can and do become quite varied. The o-substituted methyl benzoate 62 possessing a conglomeration of functional sites reacts\textsuperscript{125} with o-PDA to give the fused hydrobenzimidazole 66 (Scheme 15). In absence of full details, the reaction course can only be guessed to go by initial aminolysis at the ester followed by ring closure at the masked carbonyl. A patent report claims\textsuperscript{126} that treatment of ethyl ester 67 with o-PDA gives 71 (Scheme 16).
Table 10: Reactions of o-PDA with α-halocarboxylic acids/esters and related systems

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>In 1, 3 &amp; 4</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>H H Cl H</td>
<td>5N HCl, reflux, 45-60 min, then 0°, 1-3 days</td>
<td>3</td>
<td>65</td>
<td>112</td>
</tr>
<tr>
<td>2.</td>
<td>H H/Me Cl H</td>
<td>*</td>
<td>3</td>
<td>*</td>
<td>113</td>
</tr>
<tr>
<td>3.</td>
<td>H H Cl H</td>
<td>*</td>
<td>4</td>
<td>*</td>
<td>114,115</td>
</tr>
<tr>
<td>4.</td>
<td>H H Cl H</td>
<td>ammonium carbonate</td>
<td>4</td>
<td>92</td>
<td>116a</td>
</tr>
<tr>
<td>4b.</td>
<td>H H Cl Na+</td>
<td>H2O, reflux, 4 hr</td>
<td>4</td>
<td>*</td>
<td>116b</td>
</tr>
<tr>
<td>5.</td>
<td>F F F H</td>
<td>FeCl3</td>
<td>3</td>
<td>*</td>
<td>85</td>
</tr>
<tr>
<td>6.</td>
<td>H H Br C2H5</td>
<td>EtOH, pH 7-8, oxidation</td>
<td>4</td>
<td>36</td>
<td>117</td>
</tr>
<tr>
<td>7.</td>
<td>H OH H</td>
<td>Fusion</td>
<td>3</td>
<td>*</td>
<td>119</td>
</tr>
<tr>
<td>8.</td>
<td>H p-ClC6H4 OH H</td>
<td>12N HCl, reflux, 7 hr</td>
<td>3</td>
<td>*</td>
<td>120</td>
</tr>
<tr>
<td>9.</td>
<td>H H C10H7O H</td>
<td>boric acid, ethylene glycol, 140°, 1 hr, 200°, 2 hr</td>
<td>3</td>
<td>89</td>
<td>121</td>
</tr>
<tr>
<td>10.</td>
<td>CH3 OH H</td>
<td>Toluene</td>
<td>4</td>
<td>49</td>
<td>122</td>
</tr>
<tr>
<td>11.</td>
<td>(CF2)nH NHAc OR CH3</td>
<td>*</td>
<td>4</td>
<td>*</td>
<td>123</td>
</tr>
</tbody>
</table>

n=1,2,4

$\text{is isolated.}$
Table 11

Benzodiazepines obtained from o-PDA and haloacid derivatives.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Compound</th>
<th>Reaction condition</th>
<th>Product</th>
<th>Yield %</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>R-CH₂CO₂H</td>
<td>2 3 o-PDA R</td>
<td>R²N</td>
<td>3-41</td>
<td>127</td>
</tr>
<tr>
<td>2.</td>
<td>m-XH₄C₆</td>
<td>o-PDA, fusion</td>
<td></td>
<td>80</td>
<td>128</td>
</tr>
<tr>
<td>3.</td>
<td>R-XH₂C₆</td>
<td>o-PDA R= 3-pyrldyl</td>
<td></td>
<td>70</td>
<td>129</td>
</tr>
<tr>
<td>4.</td>
<td>Ph-NH₂C₆</td>
<td>o-PDA 1)EtOH/Et₃N, ii)Na/EtOH</td>
<td></td>
<td>*</td>
<td>130</td>
</tr>
<tr>
<td>5.</td>
<td>OCH₂Cl</td>
<td>o-PDA EtOH/K₂CO₃</td>
<td></td>
<td>35</td>
<td>131</td>
</tr>
<tr>
<td>6.</td>
<td>OCH₂Cl</td>
<td>o-PDA</td>
<td></td>
<td>*</td>
<td>132</td>
</tr>
</tbody>
</table>
Scheme 17 (Ref 135a)

\[
\text{NC-S-SCSMe} + \text{o-PDA} \xrightarrow{\text{dry EtOH, reflux}} \text{dry EtOH, RT, 16hr}
\]

\[
\begin{align*}
&\text{NH-CN} \\
&\text{77} \\
&\text{NH-CN} \\
&\text{78} \\
&\text{NH-CN} \\
&\text{79} \quad (17\%) \\
&\text{NH-CN} \\
&\text{74} \\
&\text{NH-CN} \\
&\text{75} \\
&\text{NH-CN} \\
&\text{76} \quad (41\%)
\end{align*}
\]

Scheme 18 (Ref 135b)

\[
\begin{align*}
&\text{ArNHCS}_2\text{Me} \\
&\text{80} \\
&\text{o-PDA, DMF, HgO, RT} \\
&\text{NH-CN} \\
&\text{81} \\
&\text{H}_2\text{S} \xrightarrow{\text{H}_2\text{S}} \text{H}_2\text{S} \xrightarrow{\text{H}_2\text{S}} \\
&\text{NH-CN} \\
&\text{82} \quad (85\%)
\end{align*}
\]
We are inclined to suggest the alternate structure 72 for the product rather than 71 in view of the greater stability of the former. The plausible reaction path is shown in Scheme 16 (p. 23).

The reaction of alkyl dithioesters with o-PDA gives benzimidazoles (Table 12). Methyl dithiocyanato formate (73) reacts\(^\text{135a}\) with o-PDA in a temperature-sensitive fashion: in refluxing dry ethanol, it affords the bisbenzimidazole and, at room temperature, the quinoxaline 76. The reaction of N-aryldithiocarbamate (90) with o-PDA in presence of mercuric oxide in DMF at room temperature gives 2-arylamino benzimidazole (82) in good yields whereas in absence of mercuric oxide 83 is formed\(^\text{135b}\) (Scheme 19).

Table 12: Benzimidazoles from dithioesters.

<table>
<thead>
<tr>
<th>Sr No</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>Condition</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Me</td>
<td>Et</td>
<td>H</td>
<td>aq. ethanol, pH ca. 8, RT, 49hr</td>
<td>88</td>
<td>133</td>
</tr>
<tr>
<td>2.</td>
<td>C(_6)H(_5)</td>
<td>CH(_2)CO(_2)H</td>
<td>NHCO(_2)Et</td>
<td>EtOH, H(_2)O, pH 9, RT, Overnight then, EtOH, HCl, reflux, 1.5hr</td>
<td>70(^\text{a})</td>
<td>134</td>
</tr>
<tr>
<td>3.</td>
<td>C(_6)H(_5)</td>
<td>CH(_2)CO(_2)H</td>
<td>H</td>
<td>aq. EtOH, pH ca. 8, RT, 74hr</td>
<td>89</td>
<td>133</td>
</tr>
<tr>
<td>4.</td>
<td>NHAr</td>
<td>Me</td>
<td>H</td>
<td>DMF, HgO (Red) RT</td>
<td>85</td>
<td>135b</td>
</tr>
</tbody>
</table>

\(^{135}\) HCl salt of 3 is obtained.
Amides normally react with o-PDA with loss of ammonia or amines to give 2-substituted benzimidazoles. The course of reaction of urea with o-PDA and its tetrachloro derivative warrants a special mention: on treatment of urea with o-PDA, 2-aminobenzimidazole (85) is obtained, which is trapped with ClCO₂Me as 86. However, the role of Me₂SO₄ is not obvious (scheme 12). If the tetrachloro derivative of o-PDA is used, the reaction is claimed to take different course to give 2-oxobenzimidazole (87).

$$\text{Scheme 19 (Ref 139, 140)}$$

$$\begin{align*}
\text{RCONHR}^1 + \text{o-PDA} & \rightarrow \text{2-Benzenimidazole (87)}
\end{align*}$$

**Table 13: Benzimidazoles from amides/acid chlorides**

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>R</th>
<th>R¹</th>
<th>Condition</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>NCCH₂</td>
<td>H</td>
<td>o-C₆H₄Cl₂, 160-190°</td>
<td>60</td>
<td>136</td>
</tr>
<tr>
<td>2.</td>
<td>NCCH₂</td>
<td>H</td>
<td>130-150°</td>
<td>*</td>
<td>137</td>
</tr>
<tr>
<td>3.</td>
<td>o-ClC₆H₄</td>
<td>H</td>
<td>PPA, 250°, 4hr</td>
<td>90</td>
<td>138</td>
</tr>
<tr>
<td>4.</td>
<td>Cl</td>
<td>CO₂Me</td>
<td>benzene, NEt₃, 5°</td>
<td>*#</td>
<td>23</td>
</tr>
</tbody>
</table>

# In 2 R=NHCO₂Me
Scheme 21 (Ref 148)

\[
\begin{align*}
\text{R} & = \text{H, Me} \\
\text{R} & = \text{H} \quad 69\% \\
\text{R} & = \text{Me} \quad 60\%
\end{align*}
\]

1 o-PDA, 85% H\text{3PO}_4, 190-200^\circ, 4\text{hr}

11 o-PDA, PPA, 200-210^\circ, 4\text{hr}

111 o-PDA, 85% H\text{3PO}_4, 190-200^\circ, 4\text{hr}

- H\text{2O}

70%
F) With nitriles:

Trimethylacetonitrile reacts\textsuperscript{142} with o-PDA to give 2-t-butylbenzimidazole (entry 1, Table 14), whereas trichloronacetonitrile gives\textsuperscript{143} 2-aminobenzimidazole (entry 2, Table 14). Cyanogen bromide reacts with o-PDA to give 2-aminobenzimidazole\textsuperscript{144}. In entry 4, it is interesting to note that the lactone moiety is intact (cf: Table 23, p. 63) in the product. Formation of 2-guanidinobenzimidazole (entry 5, Table 9) was accomplished by the reaction of o-PDA with cyanoguanidine. The isoindole \textsuperscript{20} obtained by heating o-phthalonitrile (89) with o-PDA on further heating gives the pyrrolobenzimidazole \textsuperscript{92}, and \textsuperscript{93}. (Scheme 20). The reaction of o-PDA with 3-cyano-6-hydroxy-4-methylpyridone (94) gives\textsuperscript{143} either \textsuperscript{92} or \textsuperscript{100} depending on reaction conditions (Scheme 21). The pyridobenzimidazole \textsuperscript{92} is the only product if the reactants are heated in 85\% H\textsubscript{3}PO\textsubscript{4}. Under these conditions nitrile function in \textsuperscript{94} appears to get lost through hydrolysis followed by decarboxylation. On changing the condensing agent from 85\% H\textsubscript{3}PO\textsubscript{4} to polyphosphoric acid, the reaction affords benzimidazole \textsuperscript{100} indicating the availability of the nitrile function for condensation with o-PDA. The resulting product \textsuperscript{100} on further treatment with an additional mole of o-PDA in 95\% H\textsubscript{3}PO\textsubscript{4} leads to \textsuperscript{101}, imidazoling the other centre. A plausible reaction path is suggested in Scheme 21.

\textbf{Scheme 20 (Ref 145)}

\[ \begin{array}{c}
\text{\textsuperscript{92}} \\
\text{\textsuperscript{93}} + \\
\text{\textsuperscript{94}} \\
\end{array} \]
Table 14: Benzimidazoles from cyano compounds.

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Sr No</th>
<th>R in 1</th>
<th>X in 2</th>
<th>Conditions</th>
<th>R' in 3</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₃C</td>
<td>H</td>
<td>MeOH, 140, 20hr, CMe₃</td>
<td>96.5</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cl₃C</td>
<td>H</td>
<td>EtOH</td>
<td>NH₂</td>
<td>*</td>
<td>142</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>C₆H₄CO</td>
<td>*</td>
<td>NH₂</td>
<td>*</td>
<td>143</td>
</tr>
<tr>
<td>4</td>
<td>R¹=Me, R²=Me, Et</td>
<td></td>
<td>*</td>
<td>MeO₂C₁₀H₁₆</td>
<td>71-95</td>
<td>144</td>
</tr>
<tr>
<td>5</td>
<td>H₂N-C-NH</td>
<td></td>
<td>HCl, EtOH</td>
<td>NHCNHN₂</td>
<td>*</td>
<td>145</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>PPA, 200-210° 4hr</td>
<td>MeO₂C₁₀H₁₆</td>
<td>69</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>AcNMe₂, RuCl₂(PPh₃), 160°, 24 hr</td>
<td>Ph</td>
<td>81</td>
<td>148a</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>H₂N</td>
<td>ClCO₂Me, (HO)₃P</td>
<td>NHCO₂Me</td>
<td>99.2</td>
<td>149b</td>
<td></td>
</tr>
</tbody>
</table>
**Section 2: Reactions of o-PDA with 1,2-dicarbonyls and equivalents.**

1,2-dicarbonyl compounds in their several combinations react with o-PDA to generate quinoxaline and their derivatives (scheme 22). However, the structure of the carbonyl as well as the diamine component and reaction conditions affect the course of the reactions, leading to benzimidazoles.

**Scheme 22**

a) with α-oxoacids/esters:

The reactions of 1,2-dicarbonyl compounds such as 1,2-dicarboxylic acid (oxalic acid), α-keto carboxylic acids and esters with o-PDA afford quinoxalines. Several examples are listed in Table 15.

Ethyl N-substituted oxamate (RNHOCOOC(OEt)) reacts with o-PDA giving 2-(substituted amido)-benzimidazoles, as has already been referred (entry 7, 8, 9; Table 2, p. 21). In these cases, the reaction takes place at only the ester function but not at the amide function.
Table 15: Quinoxalines from 2-oxocarboxylic acids/esters.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Sr No</th>
<th>R</th>
<th>R'</th>
<th>Condition</th>
<th>Yield %</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH</td>
<td>H (diacid)</td>
<td>Aq. HCl</td>
<td>*##</td>
<td>149</td>
</tr>
<tr>
<td>2</td>
<td>PhCH=CH</td>
<td>H (Ketoacid)</td>
<td>AcOH, boil</td>
<td>67</td>
<td>150</td>
</tr>
<tr>
<td>3</td>
<td>H (Ketoacid)</td>
<td>H₂O,100⁰, 30 min</td>
<td>79.75</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>C₂H₅O₂CCHR</td>
<td>C₂H₅ (Ketoester)</td>
<td>*</td>
<td>*</td>
<td>153a</td>
</tr>
<tr>
<td></td>
<td>R=BuS, BuSCH₂CH₂</td>
<td>p-MeC₆H₄S,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td>Ph</td>
<td>C₂H₅ (Ketoester)</td>
<td>EtOH, reflux, 6 hr</td>
<td>53</td>
<td>153b</td>
</tr>
<tr>
<td>5</td>
<td>β-Naphthyl</td>
<td>C₂H₅ (Ketoester)</td>
<td>EtOH, Steam bath, 3 hr</td>
<td>64</td>
<td>154</td>
</tr>
<tr>
<td>6</td>
<td>ArCOCH₂</td>
<td>CH₃ (Ketoester)</td>
<td>*</td>
<td>89-99</td>
<td>155</td>
</tr>
<tr>
<td>7</td>
<td>ArCOCHCl</td>
<td>CH₃ (Ketoester)</td>
<td>*</td>
<td>66-87</td>
<td>156</td>
</tr>
<tr>
<td>8</td>
<td>ArSO₂CH₂</td>
<td>alkyl (Ketoester)</td>
<td>*</td>
<td>57-96</td>
<td>157</td>
</tr>
<tr>
<td>9</td>
<td>MeO₂SCH₂</td>
<td>C₂H₅ (Ketoester)</td>
<td>*</td>
<td>*</td>
<td>152</td>
</tr>
<tr>
<td>10</td>
<td>(CH₃)₂CF</td>
<td>C₂H₅ (Ketoester)</td>
<td>EtOH</td>
<td>70</td>
<td>158</td>
</tr>
<tr>
<td>11</td>
<td>EtO-C-C-OEt</td>
<td>(Imidinoester)</td>
<td>o-PDA, EtOH, reflux</td>
<td>99</td>
<td>159</td>
</tr>
<tr>
<td>12</td>
<td>p-ClC₆H₄C-SMe</td>
<td>(Ketothioester)</td>
<td>EtOH, 30⁰</td>
<td>84.4</td>
<td>160</td>
</tr>
</tbody>
</table>
Scheme 24 (Ref 172)

1. 

\[
\text{EtO}^+ \xrightarrow{\text{a. H, Cl}} \text{Cl} \xrightarrow{\text{b. Me, } \text{MeSO}_2} \xrightarrow{\text{i. o-PDA, anhydrous THF, } 60^\circ} \]

Scheme 25 (Ref 173)

1. 

\[
\text{Ph} \xrightarrow{\text{o-PDA, AcOH, heat, 1hr}} \text{Ph} \xrightarrow{\text{NH}_4\text{OH}} \]

116

118

119
The reaction of cyanoformamide (107) with o-PDA in presence of piperidine affords the diamino quinoxaline 108 (Scheme 23). Benzimidazoles are not among the products.

Scheme 23 (Ref. 164)

Several reactions of o-PDA with 1,2-dicarbonyl equivalents leading to quinoxalines are summarised in Table 16. The methyleneiminium salt (110) reacts with o-PDA to give either quinoxaline 112 or a mixture of 112 and the benzimidazole 115 depending on the nature of R and X as indicated in scheme 24.

The masked carbonyl in the pyrylium perchlorate 116 reacts with o-PDA in presence of acetic acid to give the interesting condensed heterocycle 119 (Scheme 25).

b) With α-oxoaldehyde/ketone and their equivalents:

1,2-dialdehyde (glyoxal), 2-ketoaldehydes, and 1,2-diketones react with o-PDA to give quinoxalines (Table 17, 18). Reaction
Table 16: Reactions of o-PDA with 1,2-dicarbonyl equivalents:
Formation of quinoxaline derivatives.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Substrate</th>
<th>Condition</th>
<th>Product</th>
<th>Yield %</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl[NOH]</td>
<td>o-PDA, Ab. EtOH, RT, 3 hr</td>
<td>![Quinoxaline structure]</td>
<td>71</td>
<td>165</td>
</tr>
<tr>
<td>2</td>
<td>Cl[NOH]</td>
<td>o-PDA, Et(_2)O, Et(_3)N, 5-10°, RT, 4 hr</td>
<td>![Quinoxaline structure]</td>
<td>*</td>
<td>166</td>
</tr>
<tr>
<td>3</td>
<td>Na[NO]</td>
<td>o-PDA</td>
<td>![Quinoxaline structure]</td>
<td>57</td>
<td>167</td>
</tr>
<tr>
<td>4</td>
<td>Ph[N]</td>
<td>o-PDA</td>
<td>![Quinoxaline structure]</td>
<td>75</td>
<td>168</td>
</tr>
<tr>
<td>5</td>
<td>HN[N]</td>
<td>o-PDA</td>
<td>![Quinoxaline structure]</td>
<td>*</td>
<td>169</td>
</tr>
<tr>
<td>6</td>
<td>S[N]</td>
<td>o-PDA, MeOH, heat, 4 hr</td>
<td>![Quinoxaline structure]</td>
<td>31-40</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>R/R(^1) = Me/Me, Me/Ph, Ph/Ph.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>S[N]</td>
<td>o-PDA, EtOH, 48 hr</td>
<td>![Quinoxaline structure]</td>
<td>69</td>
<td>171</td>
</tr>
</tbody>
</table>
of 2-ketoaldehyde (116) with o-PDA affords the expected 2-alkylquinoxaline (117); however, presence of NaHSO₃ leads to formation of 2-amino-3-alkylquinoxaline (120), presumably proceeding via 118 (Scheme 26).

**Scheme 26 (Ref 179, 180)**

Reactions of o-PDA or its nuclear substituted derivatives with 1,2-diketones also afford quinoxalines (182-185). However, reactions involving unsymmetrical o-PDA and unsymmetrical 1,2-diketone generally give mixtures of isomeric quinoxalines (181-183). With unsymmetrical o-PDA, a simplifying generalization can be made, that the more basic amino function reacts with the more electrophilic carbon of the 1,2-diketones.

Thus the C₂-amino group at 4-carboxy-1,2-diaminobenzene (121; Scheme 27) is probably the more basic and thus more reactive than 1-amino group: out of the two carbonyls of 1-(4-bromophenyl)-1,2-propane dione (122), the one adjacent to aromatic ring is likely to be less reactive than the other.

The resultant effect of these factors leads to formation of a mixture where 123 is the major component.
**Table 17**: Reactions of o-PDA with α-oxoaldehydes:

Formation of quinoxalines.

![Quinoxaline Structure](image)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Condition</th>
<th>Product</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>EtOH, Steam bath,</td>
<td>3</td>
<td>52</td>
<td>153b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 hr</td>
<td></td>
<td></td>
<td>175a</td>
</tr>
<tr>
<td>1b</td>
<td>Cl</td>
<td>Cl</td>
<td>Ph</td>
<td>EtOH, reflux, 30 min</td>
<td>3</td>
<td>90</td>
<td>175b</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>Cl</td>
<td>CF₃</td>
<td>aq. MeOH, 23°, 18 hr</td>
<td>3</td>
<td>83</td>
<td>176</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td></td>
<td></td>
<td>3</td>
<td>*</td>
<td>177</td>
</tr>
<tr>
<td>4</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CF₃</td>
<td>aq. MeOH, 23°, 18 hr</td>
<td>3</td>
<td>57</td>
<td>176</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>NO₂</td>
<td></td>
<td>dioxane or 3+4 mix. 3N HCl</td>
<td>55:45</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>CF₃</td>
<td>H</td>
<td>Ph</td>
<td>EtOH, reflux</td>
<td>3+4</td>
<td></td>
<td>183</td>
</tr>
<tr>
<td>7</td>
<td>CF₃</td>
<td>H</td>
<td>Ph</td>
<td>EtOH, reflux, 1 mol. equi.</td>
<td>4</td>
<td>90</td>
<td>183</td>
</tr>
</tbody>
</table>
Table 18: Reactions of symmetrical and unsymmetrical 1,2-diketones with o-PDA: Formation of quinoxalines

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>In 1 &amp; 2</th>
<th>In 2 3 &amp; 4</th>
<th>Condition</th>
<th>Product</th>
<th>YIELD</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>Me C₆H₄Br-p</td>
<td>AcOH, reflux</td>
<td>3</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-Cl</td>
<td>5-Cl</td>
<td>Me C₆H₄Br-p</td>
<td>AcOH, reflux</td>
<td>3</td>
<td>6-Cl</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>5-NO₂</td>
<td>Me C₆H₄Br-p</td>
<td>AcOH, reflux</td>
<td>3</td>
<td>7-NO₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
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<td>Me Me</td>
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</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>3 hr</td>
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<tr>
<td>5</td>
<td>3-CO₂H</td>
<td>H</td>
<td>-(CH₂)₄-</td>
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<td>3</td>
<td>5-CO₂H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3-CO₂H</td>
<td>H</td>
<td>Ph Ph</td>
<td>conc HCl, H₂O, heat, w.b., 1hr</td>
<td>3</td>
<td>5-CO₂H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3-CO₂H</td>
<td>H</td>
<td>Ph Me</td>
<td>AcOH, reflux</td>
<td>3+4</td>
<td>5-CO₂H</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>3 hr or EtOH, reflux, 2 hr</td>
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<tr>
<td>8</td>
<td>4-CO₂H</td>
<td>H</td>
<td>Me Me</td>
<td>conc HCl, H₂O, heat, w.b., 1hr</td>
<td>3</td>
<td>6-CO₂H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4-CO₂H</td>
<td>5-OH</td>
<td>Me n-C₈H₁₇</td>
<td>EtOH, reflux</td>
<td>3+4</td>
<td>6-CO₂H</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2-24 hr</td>
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<tr>
<td>10</td>
<td>4-CF₃</td>
<td>H</td>
<td>Ph Ph</td>
<td>EtOH, reflux</td>
<td>3</td>
<td>6-CF₃</td>
</tr>
</tbody>
</table>

* Yields represent the percentage of the desired product obtained.

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<tr>
<th>Sr. No.</th>
<th>In 1&amp;2</th>
<th>In 2,3 &amp; 4</th>
<th>Condition</th>
<th>Product</th>
<th>In 3&amp;4</th>
<th>Yield</th>
<th>Ref</th>
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</thead>
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<td>R₁</td>
<td>R₂</td>
<td>R³</td>
<td></td>
<td>R</td>
<td>R₁</td>
<td>%</td>
</tr>
<tr>
<td>11.</td>
<td>4-CF₃</td>
<td>H</td>
<td>Me</td>
<td>Ph</td>
<td>EtOH, reflux</td>
<td>3+4</td>
<td>6-CF₃</td>
</tr>
<tr>
<td>12.</td>
<td>4-CF₃</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>EtOH, reflux</td>
<td>3+4</td>
<td>6-CF₃</td>
</tr>
<tr>
<td>13.</td>
<td>4-CF₃</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>EtOH, reflux</td>
<td>4</td>
<td>6-CF₃</td>
</tr>
<tr>
<td>14.</td>
<td>H</td>
<td>H</td>
<td>CF₃</td>
<td>CF₃</td>
<td>DMF, RT, 1.5 hr</td>
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<td>H</td>
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<tr>
<td>15.</td>
<td>C₆H₅CO</td>
<td>H</td>
<td>CF₃</td>
<td>CF₃</td>
<td>DMF, RT, 19 hr</td>
<td>3</td>
<td>C₆H₅CO</td>
</tr>
<tr>
<td>16.</td>
<td>H</td>
<td>H</td>
<td>(CF₃)₂CF</td>
<td>(CF₃)₂CF</td>
<td>*</td>
<td>3</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0(CF₂)₂</td>
<td>0(CF₂)₂</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Scheme 28 (Ref 183)

PhCOCHO, EtOH, reflux

\[
\begin{align*}
F_3C & \quad \begin{array}{c}N \\
\downarrow \quad \downarrow \end{array} \quad \begin{array}{c}\text{Ph} \\
\text{CO} \quad \text{CHO}
\end{array} & \quad \text{N} \quad \text{CHO} & \quad \text{N} \quad \text{H}_2
\end{align*}
\]

126 + 127

(1:1 mixture)

PhCOCHO, EtOH, HCl reflux

\[
\begin{align*}
F_3C & \quad \begin{array}{c}N \\
\downarrow \quad \downarrow \end{array} \quad \begin{array}{c}\text{Ph} \\
\text{CO} \quad \text{CHO}
\end{array} & \quad \text{N} \quad \text{H}_2
\end{align*}
\]

128 + 129

(exclusive)

Scheme 29 (Ref 194)

\[
\begin{align*}
o-PDA & \quad \text{PhCOCH}_2\text{SO}_{\text{Me}}
\end{align*}
\]

132

133 35%

\[
\begin{align*}
\text{N} \quad \text{N} & \quad \text{H} \quad \text{Ph}
\end{align*}
\]

134 30%

\[
\begin{align*}
\text{N} \quad \text{N} & \quad \text{H} \quad \text{Ph}
\end{align*}
\]

135a-b

136

1 Benzene, AcOH, reflux, 2hr.
That relative basicities of the amino groups in o-PDA control their regioactivity is also witnessed in the following case: reaction of 4-trifluoromethyl-1,2-diaminobenzene with PhCHOCHO in refluxing ethanol yields nearly 1:1 mixture of isomeric quinoxalines in spite of the expected difference in the amino group basicities. This lack of regioselectivity under neutral conditions is greatly altered by the presence of 1 mole equivalent of hydrochloric acid (due to preferential protonation of the more basic 2-amino group in 125). Exclusive condensation at the more reactive aldehyde carbonyl occurs with C1-amino function (Scheme 28).

The reaction of 2-ketosulfoxides 132 with o-PDA in presence of acetic acid gave a mixture of 2-phenylquinoxaline (133,35%) and 2-phenylbenzimidazole (134,30%,Scheme 29). The related C-methylsulfinylcyclopentanone (135a,n=3) and the hexanone (135b,n=4) react with o-PDA under comparable conditions to yield only the corresponding quinoxalines though only in poor yields without any competing formation of benzimidazoles. Similarly 137 reacts with o-PDA to give 133.
C. with cyclic 1,2-diketones:

Several examples of the reaction of o-PDA with cyclic 1,2-diketones are collected in Table 19. In these cases, the reactions are straightforward leading to fused quinoxalines. It is worth noting that in the lactone at entry 8 of Table 19, the amine forms the quinoxaline by reacting with the 1,2-dicarbonyl system rather than opening up the lactone ring system.

Reaction of cyclobutene-1,2-diones and benzocyclobutene-1,2-diones with o-PDA appears to be remarkably notorious for their vagaries in affording an array of products with different skeletons. As a result they have formed the subject of several studies (schemes 30,31,32a,32b,32c) 196-202. The various structures obtained from the reaction of cyclobutene-1,2-dione and o-PDA are delicately governed by nature of the substituents on the diketones as well as o-PDA and reaction conditions.

The simplest case in this group happens to be the reaction of o-PDA with bis(diphenylmethylene)-1,2-cyclobutanedione (scheme 30)196. The product ratio for the simple condensation product 138 to the ring expanded diamide 139 remains about the same with minor variations in the conditions.

\[
\text{Scheme 30 (Ref 196)}
\]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yield %</th>
<th>138</th>
<th>139</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  CCl₄, RT, 2 hr</td>
<td></td>
<td>46</td>
<td>53</td>
</tr>
<tr>
<td>11 CCl₄, CBrCl₃ (dark), RT, 40 min</td>
<td>44</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>111 CCl₄, 3% AsOH, RT, 15 min</td>
<td>56</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>
### Table 12: Reactions of o-PDA with cyclic 1,2-diketones

<table>
<thead>
<tr>
<th>S.No</th>
<th>Reactant</th>
<th>Condition</th>
<th>Product</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td>o-PDA, reflux, EtOH</td>
<td><img src="image1.png" alt="Image" /></td>
<td>69</td>
<td>186</td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td>o-PDA, AcOH, reflux</td>
<td><img src="image2.png" alt="Image" /></td>
<td>94</td>
<td>187</td>
</tr>
<tr>
<td>3.</td>
<td>Me, Me</td>
<td>o-PDA, benzene, reflux, heat, 2 hr</td>
<td><img src="image3.png" alt="Image" /></td>
<td>70</td>
<td>188</td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td>o-PDA, HCl, 125°</td>
<td><img src="image4.png" alt="Image" /></td>
<td>29</td>
<td>193</td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td>o-PDA, MeOH, reflux, 3 hr</td>
<td><img src="image5.png" alt="Image" /></td>
<td>34</td>
<td>189</td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td>o-PDA</td>
<td><img src="image6.png" alt="Image" /></td>
<td>75</td>
<td>190</td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td>o-PDA, reflux, 3 hr</td>
<td><img src="image7.png" alt="Image" /></td>
<td>91</td>
<td>191</td>
</tr>
<tr>
<td>8.</td>
<td></td>
<td>o-PDA</td>
<td><img src="image8.png" alt="Image" /></td>
<td>28</td>
<td>192</td>
</tr>
</tbody>
</table>
**Scheme 31** (Ref 197-199)

Ar = C₆H₄NH₂-0

[Images of molecular structures]

<table>
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<tr>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>R⁶</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>R⁶</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>R⁶</th>
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<tbody>
<tr>
<td>a. H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>d. OMe</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>g. benzo</td>
<td>benzo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. H</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>e. H</td>
<td>benzo</td>
<td>H</td>
<td>h. H</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>c. H</td>
<td>Cl</td>
<td>Cl</td>
<td>H</td>
<td>f. H</td>
<td>OMe</td>
<td>H</td>
<td>i. H</td>
<td>Br</td>
<td>Br</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>j. Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. o-PDA, MeOH, AcOH, (141a, 63%)
2. o-PDA, MeOH, AcOH, RT, overnight (141b, 46%)
3. o-PDA MeOH, AcOH, few hours (141c, 66%)
4. o-PDA, MeOH, AcOH, warm, 5 min (141d, 80%; 141e, 68%)
5. o-PDA, (14 equivalents), MeOH, AcOH, overnight (142b, 33%)
6. o-PDA, MeOH, 2NHCl, heat to boiling, 10 min, then RT, 12 hr (143f, 37%)
7. o-PDA, EtOH, AcOH, RT, 24 hr (144r, 37%)
8. o-PDA, EtOH, AcOH, warm, boil, 30 min (144g, 67%)
9. o-PDA, MeOH, AcOH, heat, water bath 30 min, then RT, 3 days (144h, 94%)
10. o-PDA, MeOH, AcOH, RT, 3 days (144i, 22%)
11. o-PDA, phosphoric anhydride, EtOH, boil, 1 hr (145g, 71%).
In the benzocyclobutene-1,2-dione system, the more involved reaction pathways are indicated in scheme 31. Here, we find that in addition to the foregoing skeletons, three additional modes of reactions are also realised. Reaction of o-PDA with 4-hydroxybenzocyclobutene-1,2-dione in a 1.4:1 (the reason for selection of this ratio rather than more logical 2:1 is not clear) is shown to yield the diamine 142b in 33% yield. The presence of mineral acid (HCl) causes a shift in the reaction course involving the opening of cyclobutene ring leading to a 2-aryl-3-quinoxaline-3-one (143j) presumably via an azomethine followed by ring opening. With phenanthrene cyclobutene-1,2-diones, the only product isolated is the pyrrolidone 145g, in 71% yield. The pathway should involve azomethine formation followed by ring expansion and dehydrogenation.

The results of extensive investigations conducted to unravel the course of reaction of o-PDA with substituted cyclobutene-1,2-diones (scheme 32a,32b,32c) offer instances of more deep-seated modifications. The reactions of o-PDA with the phenylthiocyanato-diketone 146a (X=SCN) leads to mixture of quinoxaline 148a and substituted diamine 143b through the common intermediate 147. The reaction of o-PDA with the isothiocyanate diketone 146b (X=-N=C=S) leads to formation of benzimidazole derivative (149)

\[
\text{Scheme 32a (Ref 200)}
\]

\[
\begin{align*}
\text{Ph} \quad \text{X} & \quad \text{Ph} \\
146 & \quad \longrightarrow & \quad \text{Ph-N} & \quad \text{Ph} \\
\text{a,SCN; b,NCS} & \quad \text{X=SCN} & \quad \text{X=NCS} & \quad \text{N} \\
147 & \quad \text{148a (R4)} & \quad \text{149 (2%)} \\
148b (2%) & \quad \text{Ph} \\
\end{align*}
\]

1 o-PDA, anhydrous (PhOCH=CH)(2), RT, 6-9 hr.
11 o-PDA, anhydrous CH$_3$CN, argon, 10-15 min.
by an aminodethiocyanation. With 3,4-diarylcyclobutene-1,2-diones, their reactions with o-PDA leads to an even greater range of products (scheme 32b). This reaction was initially studied by Blomquist and Lauer in 1962 wherein they refer to change of product with a more change of solvent. Thus the reaction of o-PDA with 146b in EtOH alone led to an unidentified product quinoxaline 'B' whereas presence of NaOAc in the ethanolic medium led to 2-phenyl-3-phenylacetyl quinoxaline (150b) as the exclusive product. Change of solvent from EtOH to HOAc caused formation of quinoxaline 'A'. These workers however did not assign any structure to 'A' and 'B'. A later (1976) careful reinvestigation of this reaction resulted in resolving a mixture containing four substances and identifying 'A' as 152b and 'B' as 151c besides 150b and 153. The later work also identified the 4th component formed in 2% yield to be the pyrrolobenzimidazole 153. The critical intermediates required for these transformations are also indicated in scheme 32b.

**Scheme 32b (Ref 201a,b)**

1 o-PDA, EtOH, anhydrous NaOAc, reflux, 1 hr.

11 o-PDA, AcOH, 111, 40 min.
The products formed from the reaction of 2-hydroxyl-1-phenyl-1-cyclobutene-3,4-dione (146c) with o-PDA and its derivatives manifest a still more complex picture (scheme 32c). The reaction of the hydroxyaryldione with o-PDA leads to either 154b or 155 or 156 depending upon the reaction conditions. An inert atmosphere in acetic acid medium promotes formation of the diprotonated bisazomethine 155. Presence of air in the reaction chamber causes formation of either the pyrrolobenzimidazole 154b or the benzo-diazocine 156 depending on the reaction time. Once again the pathway for the reactions is indicated. If the o-PDA employed in the reaction is an N-aryl or N-alkyl derivative, the product obtained is a spirobenzimidazole (157a). With N-acetyl o-PDA, the salt 157b is obtained. The latter can viewed to result from an initial formation of 2-methylbenzimidazole followed by its protonation with the enolic hydrogen.

Scheme 32c (Ref 202)

1 o-PDA (slight excess), AcOH, RT, 12 hr.
2 o-PDA (10 times more than 146c),
3 o-PDA, AcOH, N2, RT, 2 hr.
4 N-(Me/Ph) o-PDA, AcOH, RT, 10 hr.
5 N-acetyl o-PDA, AcOH, 2 hr.
Scheme 32

R' = PhN₂, NO₂, CN, 4-pyridyl

R², R³-benzo, X-NMe₂

1. o-PDA, EtOH/AcOH(10:1)
2. o-PDA, C₆H₆, PTS, reflux.
3. o-PDA, AcOH, reflux.
Section 3: Reactions of o-PDA with 1,3-dicarbonyl compounds and their equivalents.

An amazingly diverse variety of condensation reactions of o-PDA with 1,3-dicarbonyl compounds have been extensively exploited for the synthesis of 3H-benzodiazepines. Comprehensive reviews on the formation of 1,5-benzodiazepines from β-dicarbonyls and o-PDA have appeared. The following report in this section presents the more recent work.

The dialdehyde 158 reacts with o-PDA to afford tetraaza annulenes 162 but not the expected benzodiazepine (Scheme 32). Several groups have focused attention on reactions of formyl chromones (159) with o-PDA. The expected benzopyranbenzodiazepin (160) is the product obtained when 159 was reacted with o-PDA. It would appear that the formyl carbonyl function causes an initial formation of an azomethine followed by Michael addition and isomerisation of azomethine. The ring carbonyl is part of a vinylogous lactone function, justifying its lack of reactivity. A reinvestigation of the same reaction by other groups revealed formation of 162, which can be rationalised (Scheme 32).

Reactions of acetylacetone and its derivatives with o-PDA have also attracted considerable attention. Several examples of simple condensation of 1,3-diketones and o-PDA leading to 1,5-benzodiazepines are summarised in Table 20. The parent compound yields benzodiazepine with o-PDA; its substituted derivatives offer a wide variation in reaction and products. The monosubstituted derivative 164a reacts with o-PDA to give
Table 20: Reactions of o-PDA with 1,3-diketones.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Sr No</th>
<th>R</th>
<th>R'</th>
<th>Condition</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>4-R^2C_6H_4</td>
<td>4-R^3C_6H_4NHCO</td>
<td>115-130°</td>
<td>*</td>
<td>209</td>
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<tr>
<td></td>
<td>R^2=Me,OMe,Br</td>
<td>R^3=Br,OMe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2-HOC_6H_4</td>
<td>C_6H_5</td>
<td>*</td>
<td>*</td>
<td>210</td>
</tr>
<tr>
<td>3</td>
<td>2-R^4C_6H_4</td>
<td>C_6H_5</td>
<td>*</td>
<td>*</td>
<td>212</td>
</tr>
<tr>
<td></td>
<td>R^4=H,Cl</td>
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<tr>
<td>4</td>
<td>2,5-R(HO)C_6H_3</td>
<td>C_6H_5/CH_3</td>
<td>*</td>
<td>*</td>
<td>213</td>
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<tr>
<td>5</td>
<td>3-coumaryl</td>
<td>CH_3</td>
<td>EtOH,30</td>
<td>95</td>
<td>211</td>
</tr>
</tbody>
</table>

![Chemical structure](image)

6. 

![Chemical structure](image)

7. 

![Chemical structure](image)
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield %</th>
<th>Ref</th>
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<td>216</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Substrate 9" /></td>
<td><img src="image" alt="Product 9" /></td>
<td>96</td>
<td>217</td>
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<td><img src="image" alt="Substrate 10" /></td>
<td><img src="image" alt="Product 10" /></td>
<td>*</td>
<td>218a</td>
</tr>
<tr>
<td></td>
<td>R= Ac, CO$_2$Et, 4-MeC$_6$H$_4$SO$_2$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Substrate 11" /></td>
<td><img src="image" alt="Product 11" /></td>
<td>56</td>
<td>219b</td>
</tr>
</tbody>
</table>

*Note: The yield for Substrate 10 is marked with an asterisk (*) indicating a special condition or note.
Scheme 33 (Ref 219)

No reaction

(a) R = Me, R' = H
(b) R = CH₂⁺CH, R' = H
(c) R = CH₂Ph, R = H
(d) R = Cl, R' = H
(e) R = 2,4-(NO₂)₂C₆H₃, R' = H
(f) R = R' = Me
(g) R = Me, R' = CH₂Ph
(h) R = R' = CH₂⁺CH
(i) R = R' = CH₂Cl
(j) R = R' = Cl

1. o-PDA, benzene/MeOH, 43°, 5 hr.
2. o-PDA, EtOH/MeOH, 43°, 18 hr.
1,5-benzodiazepine 165a (Scheme 33). Presence of electron withdrawing substituents such as chloro (164d) and 2,4-dinitrophenyl (164e) changes the course of the reaction. While 164d reacts with o-PDA to afford the monoimine 166, only the starting material is isolated from the reaction of 164e and o-PDA. There appears to be no reaction when 3,3-dialkyl or aralkyl pentane 2,4-diones (164f-i) are treated with o-PDA. However, treatment of 3,3-dichloropentane-2,4-dione with o-PDA gives 168, 169 and 170 (Scheme 33). Prolonged reaction of 164g with o-PDA affords 2-methylbenzimidazoles (170).

Reactions of ethylacetoacetate and its derivatives with o-PDA have been studied extensively by several groups. A mixture of benzodiazepine (174) and benzimidazolone (176) is obtained under neutral conditions, whereas acidic conditions promote formation of 2-methylbenzimidazole\textsuperscript{220,221} (173, Scheme 34). Several additional cases supporting these generalizations are collected in Table 21. Reactions of ethyl acetoacetate with 2,3-diaminopyridine are presented in Table 22.

Scheme 34 (Ref 220)
Table 21: Reaction of o-PDA with ethylacetoacetate and derivatives

<table>
<thead>
<tr>
<th>Sr No</th>
<th>In compound 2,3,4 &amp; 6</th>
<th>Condition</th>
<th>Product</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>R¹</td>
<td>R²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CH₃</td>
<td>H</td>
<td>C₂H₅</td>
<td>xylene</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>C₂H₅</td>
<td>xylene, reflux</td>
<td>3</td>
<td>78-85</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₅</td>
<td>H</td>
<td>C₂H₅</td>
<td>120°</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>C₆H₅</td>
<td>H</td>
<td>C₂H₅</td>
<td>xylene, reflux</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>-CH₂SCH₂</td>
<td>CH₃</td>
<td>Toluene, reflux 2.5hr, Dean-stark</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>CH₃</td>
<td></td>
<td>*</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>CO₂Et</td>
<td>C₂H₅</td>
<td>xylene, reflux</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>Sr. No.</td>
<td>In compound 2, 3, 4 &amp; 6</td>
<td>Condition</td>
<td>Product Yield</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>CH₃ H C₂H₅</td>
<td>PPA, drop of HCl, 120-130°, 2.5 hr</td>
<td>4 48</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CH₃ H C₂H₅</td>
<td>PPA, 150°, 1 hr</td>
<td>4 36</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>R⁵ = CH₂COCH₃</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>CH₃ H C₂H₅</td>
<td>PPA, 85°, 24 hr, then 150°</td>
<td>3 *</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>CH₃ H C₂H₅</td>
<td>orthophosphoric acid, P₂O₅, steam bath</td>
<td>5 *</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>CH₃ H C₂H₅</td>
<td>*</td>
<td>6 70.3</td>
<td>228, 91</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>229</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>CH₃ H CH₃</td>
<td>*</td>
<td>6</td>
<td>230</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>CH₃ H C₂H₅</td>
<td>*</td>
<td>3+6 66+10</td>
<td>231</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>CH₃ Cl C₂H₅</td>
<td>*</td>
<td>6 83</td>
<td>231</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>CH₃ H C₂H₅</td>
<td>CCl₄, HCl</td>
<td>4+6 *</td>
<td>232</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>CH₃ H C₂H₅</td>
<td>MeOH</td>
<td>4 *</td>
<td>232</td>
<td></td>
</tr>
</tbody>
</table>
Table 22: Reactions of 2,3-diaminopyridine with B-ketoesters.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>X</th>
<th>Y</th>
<th>R</th>
<th>R'</th>
<th>Condition</th>
<th>Product</th>
<th>Yield</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃</td>
<td>Br</td>
<td>H</td>
<td>H</td>
<td>Toluene reflux, 3+4+5 4hr</td>
<td>19±28</td>
<td></td>
<td>238</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>Br</td>
<td>H</td>
<td>H</td>
<td>60-65°, 72hr, N₂</td>
<td>83</td>
<td></td>
<td>238</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td>-CH₂CH₂CH₂-</td>
<td>xylene, reflux 6hr (Dean stark)</td>
<td>74</td>
<td></td>
<td>238</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>-CH₂CH₂CH₂-</td>
<td>68-75°, N₂, 20hr</td>
<td>42</td>
<td></td>
<td>238</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>H</td>
<td>-CH₂SCH₂-</td>
<td>Toluene, reflux (Dean-Stark) 3+4</td>
<td>3:1</td>
<td></td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>xylene, reflux, 5 7hr</td>
<td>23</td>
<td></td>
<td>238</td>
</tr>
</tbody>
</table>
**Scheme 35 (Ref 234)**

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{R} = \text{Ph}, 4-\text{MeC}_6\text{H}_4 \\
\text{HO} & \\
\end{align*}
\]

**Scheme 36 (Ref 235, 236)**

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{180} \quad \text{i} \\
\text{N} & \quad \text{183} \\
\text{N} & \\
\end{align*}
\]

1. 25-30°, reduced pressure, over P₂O₅ 2-3 months
2. (C₆H₅)₂O, 228-33°, N₂, 0.5 hr.
3. xylene, H⁺
The course of the reaction of o-PDA and ethylacetoacetate also depends on the solvent used for the reaction\(^{232}\). The reaction when conducted in carbon tetrachloride, benzene or dioxane (containing HCl) yields a mixture of the benzimidazole and enamine (Table 21, entry 15 and 16), whereas in methanol, only benzimidazole is obtained. The ring analogs of 1,3-dicarbonyl derivatives lead to interesting structures when reacted with o-PDA. The hydroxy ketodiester 177 reacts with o-PDA to give the corresponding benzodiazepine 178 either in a single step or two steps, depending upon conditions (Scheme 35).

The reaction of 2-ethoxycarbonylcyclohexanone 180 with o-PDA is reported to yield a phenanthroline (182) or 2-substituted benzimidazole (183) depending on reaction conditions (Scheme 36). The keto-lactone 184, a \(\beta\)-ketoester equivalent reacts with o-PDA in methanol to give 187. The azomethine 185 on pyrolysis give 2-methyl benzimidazole (187) involving the preferential elimination of enol lactone moiety during thermal heterocyclization (Scheme 37).

**Scheme 37 (Ref 237)**
Scheme 38 (Ref 245-248)

\[
\begin{align*}
&\text{193} \quad \text{o-PDA, xylene, } \text{N} \text{,} \\
&\text{191} \quad \text{o-PDA for } e \text{,} \\
&\text{187} \quad \text{o-PDA for } a, b \\
&\text{188} \quad \text{a. } X=\text{Cl, } Y=\text{H, } R=\text{Me} \\
&\text{b. } X=\text{Cl, } Y=\text{H, } R=(\text{CH}_2)_2\text{CH}_3 \\
&\text{c. } X=\text{Cl, } Y=\text{H, } R=\text{CH}_2\text{Cl} \\
&\text{d. } X=\text{Cl, } Y=\text{H, } R=\text{Ph} \\
&\text{e. } X=\text{SMe, } Y=\text{CN, } R=\text{Me} \\
&\text{f. } X=\text{SH, } Y=\text{H, } R=p-\text{C}_6\text{H}_4\text{SMe}_2 \text{H}_4 \\
&\text{g. } X=\text{SH, } Y=\text{H, } R=\text{Ph} \\
&\text{194} \quad \text{195} \\
&\text{189} \quad \text{o-PDA} \\
&\text{190} \quad \text{a-Me} \\
&\text{b-Pr}
\end{align*}
\]

Scheme 40 (Ref 251)

\[
\begin{align*}
&\text{201} \quad \text{o-PDA} \\
&\text{198} \quad \text{o-PDA, xylene} \\
&\text{199} \quad \text{200(10%) + 203(30%) +} \\
&\text{1. o-PDA, BuOH.}
\end{align*}
\]
The reactions of the 1,3-diester diethyl malonate with o-PDA afford benzodiazepine, formed by simple aminolysis of ester carbonyl (Table 21). These results do not warrant any additional comments.

Masked 1,3-dicarbonyl compounds react with o-PDA leading to benzimidazoles or benzodiazepines. Reaction of 187a with o-PDA gives 2-methylbenzimidazole 190a, whereas a mixture of 190a and 190b is obtained when 187b was reacted with o-PDA. The reaction probably proceeds through 188 leading to a mixture of 189 and 190. The former further reacts with o-PDA to give 190a.

The reaction of 187c-e with o-PDA affords 192c-e. This reaction probably goes through the intermediate 191. The formation of benzodiazepine is also reported from 187f-g and o-PDA (Scheme 38). The benzimidazole 197 is formed from the reaction of 196 and o-PDA (Scheme 39). The 1,3-dicarbonyl equivalent 198 (Scheme 40) on treatment with o-PDA in presence of xylene gives mixture of benzodiazepine (200) and benzimidazole (203), whereas the same reaction gives a mixture containing 200,203 and 204 when carried out in presence of butanol. The probable reaction path is shown in Scheme 40.

Scheme 39 (Ref:249,250)
Table 23: Reactions of o-PDA with diethyl malonates.

![Chemical Structure]

<table>
<thead>
<tr>
<th>Sr No</th>
<th>R</th>
<th>R¹ in 1 &amp; 2</th>
<th>Condition</th>
<th>Yield %</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>PPA, 80-90°, 2hr; quantitative</td>
<td>61</td>
<td>241</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>120°, 3hr; 140°, 1hr.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>H</td>
<td>*</td>
<td>61</td>
<td>242</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Me/Et/Bu</td>
<td>*</td>
<td>40-70</td>
<td>243</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>PPA, 175-250°, 2-4 hr</td>
<td>80</td>
<td>244</td>
</tr>
</tbody>
</table>
Scheme 41 (Ref 259)

1. o-PDA, EtOH, AcOH, reflux, 2 hr.

Scheme 42 (Ref 259)

Scheme 43 (Ref 260)
Section 4: Reactions of o-PDA with 1,4 and 1,5-dicarbonyl compounds.

Reactions of 1,4 and 1,5-dicarbonyl compounds with o-PDA are reported to give benzimidazoles, fused benzimidazoles and benzodiazocines. Instances of formation of benzodiazocines from simple cyclization of o-PDA with carbonyl compounds as well as formation of benzimidazoles are listed in Table 24.

Phthalaldehyde 206 reacts with o-PDA to afford fused benzimidazole 210. The plausible reaction pathways are shown in Scheme 41. Similarly the reactions of 1,4-diketone 211 and 1,5-diketone 214 with o-PDA leading to fused heterocycles are shown in Scheme 42 and 43. The loss of t-butyl from 216 appears facile whereas in the related bridgehead trifluoromethyl system 213, the reaction is reported to stop at the imidazoline stage, retaining the bulky groups. The reaction of o-methoxycarbonyl benzoyl chloride (218, Scheme 44) with o-PDA afforded aminolysis at acid chloride leading to 219, which on further heating results in formation of pyrrolobenzimidazole 221.

\[ 206 \rightarrow 210 \]

(Scheme 44 Ref: 261)
Table 24: Reactions of 1,4- and 1,5-dicarbonyl compounds with o-PDA

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Substrate</th>
<th>Condition</th>
<th>Product</th>
<th>Yield %</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Chemical Structure 1" /></td>
<td>o-PDA, PTS, heat</td>
<td><img src="image2" alt="Chemical Structure 2" /></td>
<td>50</td>
<td>253</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Chemical Structure 3" /></td>
<td>o-PDA, NaH, THF</td>
<td><img src="image4" alt="Chemical Structure 4" /></td>
<td>67</td>
<td>254</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Chemical Structure 5" /></td>
<td>o-PDA</td>
<td><img src="image6" alt="Chemical Structure 6" /></td>
<td>55.5-62.5</td>
<td>255</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Chemical Structure 7" /></td>
<td>o-PDA</td>
<td><img src="image8" alt="Chemical Structure 8" /></td>
<td></td>
<td>257</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Chemical Structure 9" /></td>
<td>o-PDA</td>
<td><img src="image10" alt="Chemical Structure 10" /></td>
<td>79-85</td>
<td>252</td>
</tr>
</tbody>
</table>
Scheme 45 (Ref 262)

\[
\text{R-CH=CH-CHO} \xrightarrow{\text{i.o-PDA, EtOH, RT, 3 days}} \text{Ph, Me, 2-furyl, 2-thienyl}
\]

\[
\text{R- Ph, 2-furyl, 2-thienyl}
\]

\[
\text{i. o-PDA, KCN, AcOH(equivalent amount)}
\]

\[
\text{ii. o-PDA, KCN, AcOH(3-5 equivalent)}
\]

Scheme 46 (Ref 263, 264)
Section 5: Reactions of \( \alpha, \beta \)-unsaturated systems and their equivalents.

The reactions of \( \alpha, \beta \)-unsaturated carbonyl compounds and \( \alpha, \beta \)-unsaturated nitriles with o-PDA have received much attention from synthetic chemists. Among the heterocyclic skeletons obtained are benzimidazoles, quinoxalines, and benzodiazepines.

a) with \( \alpha, \beta \)-unsaturated aldehydes:

Crotonaldehyde 222 react\(^{262}\) with o-PDA to afford benzodiazepine derivative 226. It is postulated that the reaction proceeds as indicated in Scheme 45. However, the neutral intermediate 224 and 225 could not be isolated nor the aldimine 223.

The reaction of equivalent amounts of \( \alpha, \beta \)-unsaturated aldehyde 227, potassium cyanide, acetic acid and o-PDA afforded the \( \alpha \)-aminoanilino nitrile 228\(^{263}\), whereas use of excess of acetic acid (3-5 equiv.) gives tetraydrobenzodiazepine 229 (Scheme 46).

b) with \( \alpha, \beta \)-unsaturated ketones:

The reactions of \( \alpha, \beta \)-unsaturated ketones have been studied extensively. In neutral solvent, o-PDA reacts with \( \alpha, \beta \)-unsaturated ketones to give benzodiazepines. 1,10-phenanthroline is obtained in acidic medium and mere fusion of the reactants gives benzimidazoles.
Scheme 47 (Ref 265, 266)

R-CO-CH=CH-R → R

\[ \begin{align*}
1 \quad & R \\
230 \quad & \text{R}
\end{align*} \]

- a. 2-thienyl 3- or 4-pyridyl
- b. 3-pyridyl 3-pyridyl
- c. Ph/tolyl/1-naphthyl/2-naphthyl

1. o-PDA, EtOH, reflux (for a and b);
o-PDA, BuOH, reflux (for c).

ii. Fusion (for a and b); 190-200° (for c)

Scheme 48 (Ref 267)

\[ \begin{align*}
\text{R-CO-CR=CHR}^3 \\
233 \\
\text{R}^1 \quad \text{R}^2 \quad \text{R}^3
\end{align*} \]

- a. Me H H
- b. Me Me H
- c. Me H Me

1. o-PDA, Conc HCl, reflux, 45 min, then 80°, 16 hr.
Thus the ketones 230 reacts with o-PDA on refluxing in ethanol266 or butanol265 to give benzodiazepine 231, whereas their mere fusion affords benzimidazole 232. The $\alpha,\beta$-unsaturated ketones 233 react with o-PDA in presence of concentrated hydrochloric acid to give267 1,10-phenanthroline 236. The probable path of reaction, (a. Michael type addition followed by intramolecular double cyclization and aromatisation) (Scheme 48).
Benzodiazepine 235 also formed in the reaction is suggested to be the possible oxidising agent. The dihydroderivative of 235 has been identified by pmr, corroborating such a possibility.

A few more examples of formation of benzodiazepine from reaction of $\alpha,\beta$-unsaturated ketone and o-PDA are reported (Table 25).

<table>
<thead>
<tr>
<th>Sr No</th>
<th>Compound</th>
<th>Product</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>PhCH=CH-C-Ph</td>
<td>![Image]</td>
<td>268</td>
</tr>
<tr>
<td>2.</td>
<td>![Image]</td>
<td>![Image]</td>
<td>269</td>
</tr>
<tr>
<td>3.</td>
<td>MeCOCH=CH-COEt</td>
<td>![Image]</td>
<td>270</td>
</tr>
<tr>
<td>4.</td>
<td>![Image]</td>
<td>![Image]</td>
<td>271, 272a</td>
</tr>
<tr>
<td>5.</td>
<td>![Image]</td>
<td>![Image]</td>
<td>272b</td>
</tr>
</tbody>
</table>

R=H, Ph; X=CH$_2$,S,0
Scheme 49 (Ref 273, 274)

\[ R-C_6H_4CO-CH=CH-CO-C_6H_4-R \xrightarrow{1 \text{ o-PDA}} \]

\[ R, R = H, Me, Cl, Br, NO_2 \]

Scheme 50 (Ref 280)

1. o-PDA, pyridine, EtOH; ii. o-PDA.2HCl, AcOH.
It is generally observed that $\alpha, \beta$-unsaturated carbonyl compounds having strong electron withdrawing $\beta$-substituent, on reaction with o-PDA affords quinoxaline. Reactions of $\alpha, \beta$-unsaturated ketone 237 reacts with o-PDA leading to quinoxalines 239,273,274. Regiochemistry of these reactions with unsymmetrical diketones should be interesting but unfortunately the details are not available.

c) with $\alpha, \beta$-unsaturated acid/ester/amide.

Crotonic acid reacts275 with o-PDA in presence of hydrochloric acid to give benzodiazepine (entry 1, Table 26), whereas $\alpha$-methyl crotonic acid gives benzimidazole with o-PDA (entry 2, Table 26). The reactions of $\alpha, \beta$-unsaturated esters with o-PDA leading to quinoxalines are also reported (entry 3,4,5; Table 26).

Reaction of $\alpha, \beta$-unsaturated amide 240 with o-PDA (as dihydrochloride) in acetic acid results in the ring transformation product 241a or 241b. The same reactants in presence of pyridine in ethanol give only the transaminolysis product 242 (Scheme 50).280

d) with acetylenic carbonyls:

Reactions281,282 of 243 (Scheme 51; $R^1=H$, $R^2=C_6H_5$, p-MeC_6H_4, pMeOC_6H_4, p-ClC_6H_4, OMe) with o-PDA give Michael-added products 244. Further cyclization may not be possible due to the unfavourable geometry of 244. However 243 ($R^1=R^2=ph$; $R^1 = NM_2/NEt_2$, $R^2 = Me$) reacts with o-PDA to give benzodiazepine 245,283,244 while 243
Table 26: Reactions of o-FDA with \(\alpha,\beta\)-unsaturated acid/esters

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Substrate</th>
<th>Product</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>H$_3$CCH=CHCO$_2$H</td>
<td>$\xrightarrow{4N\text{ HCl, reflux or 160-170°, 4 hr}}$</td>
<td>275a 275b</td>
</tr>
<tr>
<td>2.</td>
<td>H$_3$C(\xrightarrow{\text{acidification}})CH=CHCO$_2$H</td>
<td></td>
<td>276</td>
</tr>
<tr>
<td>3.</td>
<td>O$_2$N(\xrightarrow{\text{NaH, acidification}})C=:CHCO$_2$H</td>
<td></td>
<td>277</td>
</tr>
<tr>
<td>4.</td>
<td>Cl(\xrightarrow{\text{EtOH, 100°, 2 hr}})CN</td>
<td></td>
<td>278</td>
</tr>
<tr>
<td>5.</td>
<td>EtOOC(\xrightarrow{\text{EtOH, 100°, 72 hr}})COOEt</td>
<td></td>
<td>279a 279b</td>
</tr>
<tr>
<td>6.</td>
<td>H$_2$C=CHCO$_2$H</td>
<td>$\xrightarrow{\text{PPA, 100°, 3 hr}}$</td>
<td>279b</td>
</tr>
</tbody>
</table>
Scheme 51

\[ R^1=\text{H}, R^2=\text{Ph}, \text{OH}, \]

(Ref 281, 282)

\[ R^1=\text{R}^2=\text{Ph}, 1 \]

\[ R^1=\text{NHMe}, \text{NMe}_2, 11 \]

\[ R^2=\text{Me} \]

\[ R^1=\text{Ph}, \text{MeO}, (\text{Ref 287}) \]

\[ R^1=\text{Ph}, \text{MeOH}, \text{AcOH} \]

\[ R^1=\text{Ph}, \text{MeOH}, \text{AcOH} \]

\[ R^1=\text{Ph}, \text{MeOH}, \text{AcOH} \]

\[ R^1=\text{COPh}, R^2=\text{OH} \]

(Ref 286)

\[ R^1=\text{COPh}, R^2=\text{OH} \]

(Ref 286)

\[ R^1=\text{Ph}, \text{AcOH}, 3 \text{ hr} \] (Ref 283)

11. \text{o-PDA, THF, 65-70}^\circ \text{C} \] (Ref 284)

Scheme 53, (Ref 299, 290)

\[ \text{MeO}_2\text{C}-\text{C}=\text{C}-\text{CO}_2\text{Me} \]

\[ \xrightarrow{1} \]

\[ \xrightarrow{11} \]

1. \text{o-PDA, H}_2\text{O}, \text{H}^+ \]

11. DAA(25b), distanc, reflux ; 111. Δ or hv

\[ \text{MeO}_2\text{C}-\text{C}=\text{C}-\text{CO}_2\text{Me} \]

\[ \xrightarrow{1} \]

\[ \xrightarrow{11} \]

\[ \text{MeO}_2\text{C}-\text{C}=\text{C}-\text{CO}_2\text{Me} \]

\[ \xrightarrow{111} \]

1. \text{o-PDA, H}_2\text{O}, \text{H}^+ \]

11. DAA(25b), distanc, reflux ; 111. Δ or hv
(R^1-Br, R^2-phen/2- 2-thienyl) reacts with o-PDA to give mixture of 246 and 247. Acetylenic carboxylic acid 243 (R^1=COPh, R^2=OH) carrying an electron withdrawing group at β-carbon reacts with o-PDA to give 249, whereas acetylenic ester 243 (R^1-phen, R^2=OMe, OC_6H_5, OC_6H_4NO_2p) reacts with o-PDA to yield the benzodiazepine 250.

Acetylenic ester 251 reacts with o-PDA to give a mixture of two quinoxalines, 253 and 255 (Scheme 52).

Dimethylacetylene dicarboxylate 256 reacts with o-PDA to yield 257, which on further heating with DMSO gives fused Quinoxaline 258.

**Scheme 52 (Ref 288)**

\[
\begin{align*}
\text{MeO}_2\text{C}-\text{CH}=\text{CH}-\text{C}=\text{C}-\text{CO}_2\text{Me} \\
\text{251} \\
\text{\textdownarrow} \text{\scriptsize i} \\
\text{\textdownarrow} \\
\text{\textdownarrow} \\
\text{\textdownarrow} \\
\text{252} \\
\text{\textdownarrow} \\
\text{253} \\
\text{\textdownarrow} \\
\text{\textdownarrow} \\
\text{254} \\
\text{\textdownarrow} \\
\text{255} \\
\end{align*}
\]

i o-PDA, MeOH, reflux, 30 min, overnight, -14°C.
Acetylenic imidate fluroborate 259 reacts with o-PDA to afford benzimidazole 260. On the other hand, the free imidate base 261 yields the amidine 262, which on further refluxing with ethanol-HCl results in formation of 263. The latter was also prepared directly from reaction of 259 with o-PDA by using hexamethyl phosphoric triamide as the reaction solvent\(^{291,292}\) (259 → 262 → 264 → 263).

Scheme 54 (Ref 291,292)

\[ \text{Ar}=\text{o-ClC}_6\text{H}_4 \]

1. o-PDA, CH\(_2\)Cl\(_2\), reflux, 1 hr; ii 12N HCl, ab EtOH, reflux, 2hr; iii o-PDA, HMPA, steam bath, 3 hr; iv aq. HCl
Reactions of $\alpha, \beta$-unsaturated nitriles such as benzylidenemalononitrile or its equivalents with o-PDA furnish benzimidazoles (Scheme 55, Table 27). In these reactions, the nucleophilic 1,4-addition followed by intramolecular cyclization leads to benzimidazole 269. Mechanistic steps indicated in scheme 55 have been verified, where the oxidation of 268 is compensated by reduction of 265 leading to 270.

\[ \begin{array}{c}
\text{X} = \text{H, 4-Me, 4-OMe} \\
\text{4-NO₂, 4-Cl}
\end{array} \]

\[ \begin{array}{c}
\text{265} \\
\text{266} \\
\text{267} \\
\text{268} \\
\text{269} \\
\text{270}
\end{array} \]

1 o-PDA, EtOH, heat
Table 27: Reactions of \( \alpha, \beta \)-unsaturated nitrile with o-PDA: Formation of 2-alkylbenzimidazole.

\[
\text{Ar-CH}=\text{CR-CN} \xrightarrow{\text{o-PDA}} \text{Ar}
\]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ar</th>
<th>R</th>
<th>Conditions</th>
<th>Yield %</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>4-CH(_3)C(_6)H(_4)</td>
<td>CN</td>
<td>180(^{\circ}), 1 hr</td>
<td>60</td>
<td>293</td>
</tr>
<tr>
<td>2.</td>
<td>3-C(_6)H(_4)</td>
<td>CN</td>
<td>180(^{\circ}), 1 hr</td>
<td>55</td>
<td>293</td>
</tr>
<tr>
<td>3.</td>
<td>4-BrC(_6)H(_4)</td>
<td>CN</td>
<td>180(^{\circ}), 1 hr</td>
<td>60</td>
<td>293</td>
</tr>
<tr>
<td>4.</td>
<td>C(_6)H(_5)</td>
<td>CN</td>
<td>MeOH, boil, 1 hr or RT overnight</td>
<td>70</td>
<td>294</td>
</tr>
<tr>
<td>5.</td>
<td>C(_6)H(_5)</td>
<td>COOC(_2)H(_5)</td>
<td>MeOH, boil, 1 hr or RT overnight</td>
<td>65</td>
<td>294</td>
</tr>
<tr>
<td>6.</td>
<td>C(_6)H(_5)</td>
<td>CONH(_2)</td>
<td>MeOH, boil, 1 hr or RT, overnight</td>
<td>70</td>
<td>294</td>
</tr>
<tr>
<td>7.</td>
<td>C(_6)H(_5)</td>
<td>COOH</td>
<td>MeOH, boil, 1 hr or RT, overnight</td>
<td>55</td>
<td>294</td>
</tr>
<tr>
<td>8.</td>
<td>4-HOC(_{10})H(_6)</td>
<td>CN</td>
<td>MeOH, reflux, 3 hr</td>
<td>65</td>
<td>295</td>
</tr>
<tr>
<td>9.</td>
<td>4-HOC(_{10})H(_6)</td>
<td>COOC(_2)H(_5)</td>
<td>MeOH, reflux, 3 hr</td>
<td>65</td>
<td>295</td>
</tr>
<tr>
<td>10.</td>
<td>4-C(_6)H(<em>5)NHCOOC(</em>{10})H(_6)</td>
<td>CN</td>
<td>MeOH, reflux, 20 min.</td>
<td>65</td>
<td>295</td>
</tr>
<tr>
<td>11.</td>
<td>4-C(_6)H(<em>5)NHCOOC(</em>{10})H(_6)</td>
<td>COOC(_2)H(_5)</td>
<td>MeOH, reflux, 20 min.</td>
<td>65</td>
<td>295</td>
</tr>
</tbody>
</table>
f) with allenes:

The reaction of allenic nitrile 271 with o-PDA under reflux in ethanol gave 272. The latter on further heating at 300° gave the second Michael added intermediate 273. Elimination of acetonitrile from 273 yields 2-alkylbenzimidazole 274 (Scheme 56).

Scheme 56 (Ref 298)

\[
\begin{align*}
R^1 &= \text{Me, Et, Pr} \\
R^2 &= \text{H, Me}
\end{align*}
\]

Dimethyl allene-1,3-dicarboxylate (275) reacts with o-PDA to give 1H-1,5-benzodiazepin rather than the benzimidazole as in the foregoing example. Unsymmetrically substituted dimethyl allene-1,3-dicarboxylate yields a 1:1 mixture of isomeric benzodiazocin (277). A transient enamine intermediate formed by addition of amine to allenic double bond is proposed. Preference for a 7-exo-trig ring closure rather than a 5-exo-trig process is observed (Scheme 57).

Scheme 57 (Ref 299,300)
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(Please note that there are no references corresponding to 161,162,163)


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