Base-Promoted Reactions of Dichlorocarbene Adducts of Cyclic Enamines: A New Route to Annulated Pyrroles

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ABSTRACT

Treatment of the gem-dihalogenocyclopropanes 1−5 with potassium tert-butoxide or LDA results in the formation of the corresponding and annulated pyrroles 13−17, respectively.

Recently, we reported that the dichlorocarbene adducts of various alkyl enol ethers react with strong base to give furans.1 This process thus provides a method for the three-step furannulation of various enolizable ketones, and we have demonstrated the utility of it in the synthesis of the racemic modification of the furanosesquiterpenoid natural product pallescensin A.1 The relevant reaction sequence is shown in Scheme 1, and the pathway by which the furan-forming step proceeds is the subject of ongoing studies within these laboratories.

In an effort to extend this type of chemistry, we were prompted to examine the base-promoted reactions of the corresponding dihalogenocarbene adducts of enamines. A major motivation for doing so was the expectation that these reactions might lead to pyrroles bearing otherwise difficult to obtain substitution patterns and so provide a useful addition to the repertoire of methods available for preparing these particularly important aromatic heterocycles.2 Although the dichlorocarbene adducts of enamines are known,3 we are not aware of any systematic studies of the base-promoted reactions of such compounds. Herein, therefore, we detail our preliminary studies of this matter and report on the successful generation of a range of unusual pyrrolic systems.4

The adducts 1−10 used in the present study were generally prepared (29−85%) by subjecting the relevant enamine to reaction with chloroform or bromoform and sodium hydroxide in the presence of the phase-transfer catalyst triethyl-
benzylammonium chloride (TEBAC) under conditions first defined by Mąkosza.\(^5\) Despite the propensity of gem-dihalogenocyclopropanes carrying electron-donating substituents to undergo facile electrocyclic ring cleavage,\(^6\) these adducts proved to be rather stable and generally crystalline materials. Indeed, the structures of compounds \(4\) and \(6\) were confirmed by single-crystal X-ray analysis.\(^7\) In contrast, however, no success was had in efforts to isolate the dichlorocarbene adducts of the morpholino-based enamines derived from indan-1-one and cyclopentanone or the same types of adducts from the pyrrolidine-derived enamines of \(\alpha\)-tetralone or cyclohexanone. In each instance only complex mixtures of materials were obtained. Interestingly, attempts to add dichlorocarbene to the double bond of the readily prepared amino-substituted cinnamate \(11\) delivered, as the only isolable material, what is tentatively identified as the dichlorocarbene insertion product \(12\) (11%).

The reaction of substrates \(1\)–\(5\) with base at 0–18 °C for 0.5–5.0 h produced the expected outcomes in that the corresponding pyrroles, \(13\)–\(17\) respectively, were obtained in yields ranging from 28–82% (Table 1, entries 1–7). Such studies also revealed that lithium diisopropylamide (LDA) was a superior base to \(\text{t-BuOK}\). The structures of the products were established by standard spectroscopic methods and confirmed through the single-crystal X-ray analyses of compound \(16\)\(^7\) and a derivative of congener \(17\) (vide infra). The selective and efficient formation of the pyrrolo[2,1-\(\alpha\)]-isoquinoline-type system \(17\) over its pyrrolo[1,2-\(b\)]isoquinoline-based isomer is noteworthy.

\[\begin{align*}
1 & \quad 2 \\
3 & \quad 4 \\
5 & \quad 6
\end{align*}\]

![Diagrams of compounds 1-6.](Image)

**Table 1.** Products Derived from Base-Promoted Reactions of Compounds 1–10\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>base (\text{temp (°C)})</th>
<th>time (\text{(h)})</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1,\text{a,b})</td>
<td>LDA</td>
<td>0</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>(2,\text{a,e})</td>
<td>LDA</td>
<td>0</td>
<td>3</td>
<td>(14^f)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>LDA</td>
<td>0</td>
<td>3</td>
<td>(15^g)</td>
</tr>
<tr>
<td>4</td>
<td>(4,\text{d})</td>
<td>LDA</td>
<td>0</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>(\text{t-BuOK})</td>
<td>0</td>
<td>0.5</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>LDA</td>
<td>0</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>(\text{t-BuOK})</td>
<td>18</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>8</td>
<td>(6,\text{d,h})</td>
<td>(\text{t-BuOK})</td>
<td>18</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>LDA</td>
<td>0</td>
<td>8</td>
<td>NR(^i)</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>LDA</td>
<td>0</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>11</td>
<td>9(^f)</td>
<td>LDA</td>
<td>0</td>
<td>8</td>
<td>NR</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>LDA</td>
<td>0</td>
<td>8</td>
<td>NR</td>
</tr>
</tbody>
</table>

\(^{a}\) All reactions were carried out using THF as solvent, except for entry 5 where 1:1 v/v THF/DMSO was used. \(^{b}\) Reference 3a. \(^{c}\) Reference 3c. \(^{d}\) Reference 3f. \(^{e}\) Reference 3b. \(^{f}\) Reference 8. \(^{g}\) Reference 9. \(^{h}\) Reference 3c. \(^{i}\) NR = no reaction.
There are a number of instances in which pyrrole formation is not observed. For example, subjection of compound 6, the regioisomer of cyclopropane 4, to treatment with t-BuOK failed to give the hoped for pyrrole. Rather, the β-oxygenated cycloheptenone 18 was obtained in 79% yield (Table 1, entry 8). The origin of the divergent behavior of compounds 4 and 6 remains unclear at present. The lack of reaction of the dichlorocarbene adducts 7, 9, and 10 when subjected to the sorts of conditions just mentioned (see entries 9, 11, and 12) was also surprising and prompted an examination of the behavior of the gem-dibromo analogue 8, of compound 7, under the same conditions. Treatment of compound 8 with LDA (entry 10) provided the diquinane 19 in 81% yield. Presumably this compound arises through LDA-promoted lithium-for-bromine exchange at the apical cyclopropyl carbon, and this is followed by loss of the elements of lithium bromide to give the corresponding cyclopropylidene. This last species then undergoes insertion into the remote and syn-orientated benzylic C–H bond to give the observed product.10

On the basis that treatment of the carbene insertion product 12 with base might deliver a pyrrole, this was treated with potassium tert-butoxide. However, the product so formed was the oxazolidinone 20 (62%), the structure of which follows from a single-crystal X-ray analysis.7

At least two distinct reaction pathways can be envisaged for the base-promoted conversion of compounds 1–5 into the corresponding pyroles. Both of these (paths a and b, Scheme 2) would involve dehydrochlorination of the substrate, e.g., 4, to give the corresponding ring-fused cyclopropene 2413 that then engages in ring opening to the

The utility of the pyrrole-forming reaction described above is highlighted by the conversion, using N-bromosuccinimide,


(7) Details of the single-crystal X-ray analyses carried out as part of this study are provided in Supporting Information.


(13) These types of ring-fused cyclopropenes are readily trapped in Diels–Alder cycloaddition reactions. For example, see: Banwell, M. G.; Corbett, M.; Gulbis, J.; Mackay, M. P.; Reum, M. E. J. Chem. Soc., Perkin Trans. 1 1993, 945.
corresponding vinylcarbene 25a/zwitterion 25b. This last species could undergo C–H insertion (path a) to give the chlorinated dihydropyrrole 26 that loses a second equivalent of HCl to deliver the observed and fully aromatic product, e.g., 16. An alternate pathway (path b, Scheme 2) would involve intramolecular proton transfer within intermediate 25 to give the ylide 27. Such a species might then be expected to undergo electrocyclic ring closure2a,16 to give dihydropyrrole 26, the final intermediate in the reaction sequence and one that is common to both paths a and b.

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Supporting Information Available: Full experimental procedures; crystallographic data and atomic displacement ellipsoid plots and CIFs for compounds 4, 6, 16, 18, 20, and 22;17 1H and/or 13C NMR spectra of compounds 1–5, 13–20, and 22. This material is available free of charge via the Internet at http://pubs.acs.org.

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