Pyridines from Azabicyclo[3.2.0]-hept-2-en-4-ones through a Proposed Azacyclopentadienone

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ABSTRACT

Pyridines have been formed by heating azabicyclo[3.2.0]hept-2-en-4-ones in toluene. The generation of a 3-azacyclopentadienone intermediate via a [2+2]-cycloreversion is proposed as the key step. A Diels–Alder reaction of a styrene, extrusion of carbon monoxide, and loss of hydrogen then gives the pyridine. The process parallels the well-known synthesis of benzenes from cyclopentadienones. The azabicyclo[3.2.0]hept-2-en-4-ones were synthesized from the reaction between readily available cyclopropenones and 1-azetines, in which the cyclopropenones behave as all-carbon 1,3-dipolar equivalents.

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unexploited avenue, an absence that is all the more curious given the well-known\(^6\) process by which the corresponding all-carbon diene, cyclopentadienone, is used to access the benzene ring. The absence of azacyclopentadienone based pyridine syntheses is undoubtedly related to the difficulties encountered in accessing this elusive system either in stable form or from readily available suitable precursors. The 2-azacyclopentadienone ring \(1\) (see Figure 1) is rare, but its formation and use are known.\(^5\) Of particular relevance to our work, species \(1\) has been generated from a polymeric 5-sulfonate of 2-oxopyrrolidine and shown to act as a diene toward a polymer supported alkyne, allowing access to one example of a pyridine ring.\(^2\) Work by the same group\(^7\) gave access to a single example of the even more elusive 3-azacyclopentadienone \(2\), generated in similar fashion as an unstable intermediate from a polymeric 1-acyl 3-oxopyrrolidine. A stable 3-thione analogue of azacyclopentadienone \(2\) has also been reported.\(^8\) In view of this scarcity and lack of applicability, there is a requirement for new methods which allow the generation of 3-azacyclopentadienones. We wish to report one such method in this paper and show that such systems can be used to generate pyridines.

Our work started with the synthesis of a range of azabicyclo systems \(3\) which incorporate the 3-oxopyrrolidine moiety. We investigated the azabicyclo[3.2.0]hept-2-en-4-one system \(4\) on the basis that this system might readily yield the desired azacyclopentadienone. Our first example of this system, compound \(4a\) (Table 1), was synthesized as an unstable, but isolable, mixture of diastereoisomers from the reaction of 2-methylthio-4-(4-tolyl)-1-azetine \(5a\) with diphenylcyclopropenone \(6a\), a reaction in which the cyclopropenone acts as an all-carbon 1,3-dipolar equivalent. The chemistry and applications of cyclopropenones\(^9\) and their acetals/ketals\(^10\) have gained momentum in recent years, and there are also other reports of imines reacting with cyclopropenones.\(^11\) The topic of 3-carbon 1,3-dipole equivalents is an area of importance in its own right due to the potential for such processes to provide access to 5-membered rings in \([3+2]\)-cycloaddition reactions.\(^12\)

![Figure 1. Azacyclopentadienones and bicyclic pyrrolinones.](image)

Table 1. Reaction of Cyclopropenones with 1-Azetines

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>Ar</th>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>yield (%)</th>
<th>(diast. ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>4-Tol</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>63</td>
<td>(3:2)</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>Ph</td>
<td>Et</td>
<td>Ph</td>
<td>Ph</td>
<td>63</td>
<td>(5:3)</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td>52</td>
<td>(6:5)</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>2-Tol</td>
<td>Et</td>
<td>Ph</td>
<td>Ph</td>
<td>66</td>
<td>(3:2)</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>2-Naphth</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>51</td>
<td>(3:2)</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>Ph</td>
<td>Et</td>
<td>n-Bu</td>
<td>n-Bu</td>
<td>58</td>
<td>(3:2)</td>
</tr>
</tbody>
</table>

We next found that the treatment of 4a in boiling toluene for < 24 h resulted in the complete consumption of the starting material and the formation of the pyridine 7a (Scheme 1) in good yield. A mechanism for this process is proposed in Scheme 1. An overall [2 + 2]-cycloreversion reaction gives the desired 3-azacyclopentadienone 9a plus styrene 8a. This initial process may be stepwise, polar or free-radical, and we are unable at the moment to discern between these possibilities. Recombination of species 9a and 8a in a regioselective [4 + 2]-cycloaddition would then give the cycloadduct 10a. Extrusion of carbon monoxide and aromatization then give the pyridine 7a. The regiochemistry of the process was established by 2-D NMR studies and by X-ray crystallographic studies on the final pyridine. Based upon this result, we synthesized other azabicyclo[3.2.0]hept-2-en-4-ones 4 to act as pyridine precursors. As shown in Table 1, a series of 1-azetines 5 reacted smoothly with the cyclopropenones 6 to give the azabicyclo[3.2.0]hept-2-en-4-ones 4b–g. Again, these were found to be unstable but isolable mixtures of diastereoisomers, which were used within 24 h. Phenylcyclopropenone gave only the 3-phenyl-1-azabicyclo[3.2.0]hept-2-en-4-one regioisomer 4c, presumably due to the 1-azetine attacking the least hindered cyclopropenone carbon. We have found that other monosubstituted cyclopropenones react in the same manner with 5-, 6-, and 7-membered cyclic imines. Diphenylcyclopropenone was commercially available, phenylcyclopropenone was synthesized by the cyclization of 1-bromo-3-chloro-3-phenyl acetone acetal, and dibutylcyclopropenone was synthesized from the reaction of dichlorocarbene with decyne and subsequent hydrolysis. It is noteworthy that a large range of other di- and monosubstituted cyclopropenones is available by these and other routes. The 1-azetines were readily available by alkylation of the corresponding thio-β-lactam, which was in turn available from the treatment of the β-lactam with Lawesson’s reagent.

Each of the azabicyclo[3.2.0]hept-2-en-4-ones 4b–g gave the desired pyridine 7b–g in good to reasonable yields when heated in boiling toluene (Table 2). It is of note that the presence of the C2-thioalkyl substituent in the pyridines 7a–g offers the potential of Pd-catalyzed functionalization of the type reported by Liebeskind. The handling of the unstable azabicyclo[3.2.0]hept-2-en-4-ones 4 may be improved by telescoping the cyclopropenone addition and heating steps, and we are currently exploring the potential of this process.

To obtain evidence for this mechanism, we have been able to show that the proposed intermediate 3-azacyclopentadienone 9b can be trapped by heating 4b in the

### Scheme 1. Proposed Mechanism for the Formation of Pyridine 7a

```
\begin{center}
\begin{tikzpicture}
\node (a) {4a};
\node (b) [right of=a] {8a};
\node (c) [below right of=a] {9a};
\node (d) [below right of=b] {10a};
\node (e) [below of=d] {7a};

\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (c) -- (d);
\draw[->] (d) -- (e);
\end{tikzpicture}
\end{center}
```

### Table 2. Conversion of Azabicyclo[3.2.0]hept-2-en-4-ones 4 into Pyridines 7

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>Ar</th>
<th>R1</th>
<th>R2</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a</td>
<td>4-Tol</td>
<td>Me</td>
<td>Ph</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>7b</td>
<td>Ph</td>
<td>Et</td>
<td>Ph</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>7c</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>7d</td>
<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>7e</td>
<td>4-Tol</td>
<td>Et</td>
<td>Ph</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>7f</td>
<td>2-Naphth</td>
<td>Me</td>
<td>Ph</td>
<td>69</td>
</tr>
<tr>
<td>7</td>
<td>7g</td>
<td>Ph</td>
<td>Et</td>
<td>n-Bu</td>
<td>n-Bu</td>
</tr>
</tbody>
</table>

### Scheme 2. Evidence for the Proposed Mechanism

```
\begin{center}
\begin{tikzpicture}
\node (a) {4b};
\node (b) [right of=a] {9b};
\node (c) [below of=b] {7b (52%)};
\node (d) [right of=c] {7e (17%)};

\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (c) -- (d);
\end{tikzpicture}
\end{center}
```
presence of a second styrene to give an easily separated mixture of two pyridines, 7b and 7e (Scheme 2). It is also of note that we have previously shown \(^\text{11c}\) that the tetramethyl adduct 11 (Scheme 3) forms the pyrrolylidene-pyrrolone 12 upon heating in dichlorobenzene, a process that is consistent with the formation of intermediate 9b, which then undergoes loss of ethene followed by dimerization with loss of sulfur. Furthermore (Scheme 4), when 2-ethylthio-4-phenyl-1-azetine was reacted with the nitrile oxide derived from 2-azidobenzhydroximoyl chloride,\(^\text{19}\) the resultant cycloadduct 13 also underwent a process consistent with the proposed \([2+2]\)-cycloreversion to give the expectedly stable 1,2,4-oxadiazole 14 as the product,\(^\text{20}\) indicating that such cycloreversions may be a general facet of the chemistry of fused bicyclic azetidines of general type 15, an aspect that we are now exploring more fully. We are currently exploring other reactions that can trap and utilize the proposed intermediate 3-azacyclopentadienones 9, as enophiles, ynophiles, or dienophiles.

In conclusion, a new protocol for the synthesis of pyridines has been developed using the reaction of cyclopropenones with 1-azetines, where the cyclopropenone functions as an all-carbon 1,3-dipole. When heated in toluene, the resulting azabicyclo[3.2.0]hept-2-en-4-ones behave in a manner that is consistent with the generation of an intermediate 3-azacyclopentadienone generated through a \([2+2]\)-cycloreversion. This intermediate undergoes a Diels–Alder reaction with the styrene product of the cycloreversion, followed by extrusion of carbon monoxide and aromatization to generate pyridines. This process parallels the synthesis of benzenes from cyclopentadienones.

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Supporting Information Available. Experimental procedures and characterization data for 4a–g, 5, 6, 7a–g, 13, and 14; copies of \(^1\)H and \(^13\)C spectra of these compounds; X-ray data for 7a. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) We had anticipated that the azide group may trap the styrene, but saw no evidence of such a process.