Iodoarene-Catalyzed Cyclizations of Unsaturated Amides

Ali Alhalib,† Somaia Kamouka,† and Wesley J. Moran*

Department of Chemistry, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, UK

Supporting Information Placeholder

ABSTRACT: The cyclization of N-alkenylamides catalyzed by iodoarenes under oxidative conditions is presented. Five-, six- and seven-membered rings with a range of substitutions can be prepared by this route. Preliminary data from the use of chiral iodoarenes as precatalysts show that enantiocontrol is feasible.

Research in hypervalent iodine chemistry has gained considerable momentum in recent years. In particular, the emergence of catalytic and enantioselective processes with iodine(III) species is starting to make these competitive with metal-catalysis. Recent examples include the catalytic enantioselective spiro lactonization of phenols,6 dioxygenation of styrenes,7 and intramolecular C-H/C-H cross-coupling.3 This ability to effect “metal-like” synthetic transformations without the toxicity, supply or cost issues of transition metal salts is attractive.

We have previously developed catalytic methods using in situ generated hypervalent iodine species and have reported the oxidative cyclization of β-alkynyl β-ketoesters8 and the enantioselective oxidative cyclization of β-ketoacids.7 We wished to extend this catalytic concept to the formation of useful heterocycles such as oxazolines and dihydrooxazines. Oxazolines are common structural motifs found in natural products with notable biological activities, e.g. the leupyrins, active against fungi and eukaryotic cells,8 and the bistratamides, which possess anticancer properties (Figure 1).9 Dihydrooxazines are useful synthetic intermediates in organic synthesis10 and derivatives possessing fungicidal activity have also been reported.11

In this Communication, we disclose our results on the catalytic cyclization of unsaturated amides to give oxazolines, dihydrooxazines and larger ring analogs. At the beginning of our study, Moon and Harned published the stoichiometric hypervalent iodine mediated cyclization of N-allylamides (Scheme 1).12 Their report was limited to five membered ring formation, the use of terminal alkenes and the products described were all racemic. Herein, we reveal catalytic conditions for the cyclization and expand the scope of the process to include other ring sizes and more substituted alkynes. In addition, we have achieved enantiocontrol in this cyclization using chiral iodoarenes.

![Figure 1. Examples of natural products containing oxazolines.](image-url)
Scheme 1. Cyclization of \(N\)-alkenylamides by iodine(III) species.

\[ \text{R} = \text{O} \quad 1,2 \text{ equiv FN(O)Ac}_2 \]
\[ \text{R} = \text{OAc} \quad 10 \text{ equiv } 
\]

**a) Previous report: stoichiometric process**
- stoichiometric (III)
- only 5-membered ring formation reported
- only substrates with mono-substituted alkenes cyclized
- racemic products

**b) This work: new catalytic paradigm**
- substoichiometric (III)
- 5, 6, 7-membered rings
- mono-, 1,1-dim and 1,2-disubstituted alkene substrates
- preliminary study on enantioselective cyclization

We began our investigation with \(N\)-allylbenzamide 1a and used reaction conditions similar to that used by us in previous reports, namely iodobenzene as the precatalyst with an oxidant, \(m\)-CPBA, an acid, TFA, and a solvent, acetonitrile, at room temperature (Table 1, entry 1). Unfortunately, these conditions led to no conversion of the starting material; not even epoxidation of the alkene occurred. However, changing the oxidant to Selectfluor led to a small amount of the desired product 2a being formed (entry 2). Importantly, a basic workup of the reaction mixture was required in order to isolate the product. Changing the iodoarene catalyst led to surprising variations in yield; 2-iodoanisole led to a 62\% yield (entry 3), whereas 3-iodoanisole, 4-iodoanisole and 5-iodo-\(m\)-xylene provided low yields of isoxazoline (entries 4, 5 and 6). We have demonstrated previously that the presence of a 2-methoxy substituent stabilizes aryliodine(III) species.\(^{14}\) Guilbault and Legault demonstrated that the steric hindrance caused by the introduction of a methyl group ortho to the iodine atom in iodoarene precatalysts led to drastic rate enhancements in the \(\alpha\)-tosyloxylation of ketones.\(^{15}\) Using 2-iodoanisole as catalyst, the oxidant was varied, however the use of \(m\)-CPBA and Oxone both led to no conversion (entries 7 and 8). Finally, running the reaction without the 2-iodoanisole, but with the Selectfluor, led to complete recovery of the starting amide showing that the iodoarene is necessary for this process to proceed (entry 9).

Table 1. Investigation of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArI</th>
<th>Oxidant</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>iodobenzene</td>
<td>(m)-CPBA</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>iodobenzene</td>
<td>Selectfluor</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>2-iodoanisole</td>
<td>Selectfluor</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>3-iodoanisole</td>
<td>Selectfluor</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>4-iodoanisole</td>
<td>Selectfluor</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>5-iodo-(m)-xylene</td>
<td>Selectfluor</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>2-iodoanisole</td>
<td>(m)-CPBA</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>2-iodoanisole</td>
<td>Oxone</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>Selectfluor</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^{a}\) Yields of isolated compounds. Selectfluor: 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

Scheme 2. Scope of cyclization of mono-substituted alkenes

With a desire to increase the scope of the cyclization further, 1,1-disubstituted alkenes 1p and 1q were subjected to the reaction conditions (Scheme 3). Methyl derivative 2p was formed in 81\% yield whereas the phenyl derivative 2q was not isolated. In the latter case, complete conversion of the starting material was observed but several unidentified products were formed.
which could not be separated. 

\textit{Cis}-1,2-Disubstituted alkene 1r cyclized to the bicycle 2r in 56\% yield as one diastereomer. No sign of the other diastereomer was detectable by NMR analysis of the crude reaction mixture. Attempts to cyclize a trisubstituted alkene were unsuccessful as undesired background alkene addition processes occurred.

\textbf{Scheme 3. Scope of cyclization of di-substituted alkenes}

![Scheme 3](image)

The mechanism of this cyclization is proposed to involve oxidation of the iodoarene to the iodine(III) species which activates the alkene to intramolecular attack by the amide oxygen to generate intermediate 3 (Scheme 4). Nucleophilic addition of TFA, or its conjugate base, breaks the alkyl carbon-iodine bond in 3, which regenerates the iodoarene catalyst and releases the cyclized product 4. This compound 4 cannot be isolated as it is unstable, but it is believed to be the trifluoroacetate. Nonetheless, treatment of this with 2 M NaOH solution provides the stable alcohol 2.

\textbf{Scheme 4. Postulated cyclization reaction mechanism}

![Scheme 4](image)

With an effective cyclization process in hand, we turned our attention to the use of chiral iodoarene precatalysts 6-10 in order to develop an enantioselective version of this process.\(^{16}\) Using bisdimethylamide precatalyst 6 a very good yield of 2i was obtained with moderate enantioselectivity of 82:18 er (Table 2, entry 1). Interestingly, the amount of precatalyst could be lowered to 10 mol \% without a drop in yield, compared to the use of 2-idoanisole. To determine the effect of temperature on the cyclization, the reaction was repeated at 50 \(^\circ\) C and at -10 \(^\circ\) C, however selectivity was lower in the former case and about the same in the latter (entries 2 and 3). Conducting the reaction with bistrifluoromethanesulfonamide instead of TFA led to lower yield and lower selectivity (entry 4). Using methanol as solvent instead of acetonitrile led to formation of methyl ether 5 in place of alcohol 2i, but in low yield and with 63:37 er (entry 5). Using a 1:1 or 2:1 acetonitrile/methanol mixture as solvent led to separable mixtures of 2i and 5 being formed (entries 6 and 7). The enantiomeric ratio of ether 5 was up to 81:19, equalling the highest obtained for 2i. We then screened a few other related precatalysts 7-10 but did not see superior selectivity. With disopropylamide precatalyst 7, the conversion in MeCN was very low, however changing to a 1:2 mixture of MeCN and MeOH led to complete conversion to ether 6 with 75:25 er (entry 9). Mesityl amide 8 and ethers 9 and 10 led to moderate yields and enantioselectivities (entries 10-12). However, with the \(t\)-butyl ester precatalyst 10 the major enantiomers of products formed were opposite to the other precatalysts (entry 12).
Table 2. Preliminary chiral precatalyst screening

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>2k yield (%)</th>
<th>5: yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>86</td>
<td>82:18</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>75</td>
<td>67:33</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>10</td>
<td>75:21</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>11</td>
<td>63:37</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>0</td>
<td>63:37</td>
</tr>
<tr>
<td>6</td>
<td>1:1 MeCN:MeOH</td>
<td>37</td>
<td>71:29</td>
</tr>
<tr>
<td>7</td>
<td>1:2 MeCN:MeOH</td>
<td>51</td>
<td>76:24</td>
</tr>
<tr>
<td>8</td>
<td>MeCN</td>
<td>&lt;5</td>
<td>n.d.</td>
</tr>
<tr>
<td>9</td>
<td>1:2 MeCN:MeOH</td>
<td>0</td>
<td>99:5</td>
</tr>
<tr>
<td>10</td>
<td>MeCN</td>
<td>53</td>
<td>75:25</td>
</tr>
<tr>
<td>11</td>
<td>MeCN</td>
<td>23</td>
<td>72:28</td>
</tr>
<tr>
<td>12</td>
<td>1:2 MeCN:MeOH</td>
<td>49</td>
<td>35:65</td>
</tr>
</tbody>
</table>

a Yields of isolated compounds. b Determined by chiral HPLC analysis. c Reaction performed at 50 °C. d Reaction performed at -10 °C. e Bistrifluoromethanesulfonamide used instead of TFA.

Cyclization of amide 1a to generate isoxazoline 2a was also performed using chiral precatalyst 7 and the product was generated in 84.5:15.5 er (Scheme 5).

Scheme 5. Enantioselective formation of isoxazoline 2a

In conclusion, the cyclization of unsaturated amides using catalytic quantities of iodoarenes has been developed. 2-Iodoanisole has proven to be a superior precatalyst than other iodoarenes tested in this process. In addition, chiral iodoarenes have been utilized to impart enantioselectivity, and levels of control up to 81:19 er have been achieved so far. Further work on related cyclizations, and efforts to improve observed enantiomeric excess, is underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information
Characterization data and copies of 1H and 13C NMR spectra for novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
* E-mail: w.j.moran@hud.ac.uk

Author Contributions
† These authors contributed equally.

ACKNOWLEDGMENT

We are grateful to the State of Libya for graduate studentships (AA and SK).

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