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Metal Free One-Pot Synthesis of \( \alpha \)-Ketoamides from Terminal Alkenes

Sayan Dutta, Surya Srinivas Kotha and Govindasamy Sekar *

A practical approach towards the synthesis of \( \alpha \)-ketoamides from readily available terminal alkenes (styrenes) has been developed. Use of inexpensive I\(_2\)/2-iodoxybenzoic acid (IBX) in dimethyl sulphoxide (DMSO) as oxidant under the metal free one-pot condition makes this methodology versatile.

Very recently, Deshidi et al. reported I\(_2\) mediated \( \alpha \)-ketoamide from terminal alkenes. In addition, they also reported the synthesis of \( \alpha \)-ketoamide using I\(_2\)/TBHP under solvent free conditions. As part of our ongoing research towards developing metal free organic transformation, we here in report the one-pot synthesis of \( \alpha \)-ketoamide from styrenes (Scheme 1). The idea behind in this method to make the use of 2-oxoaldehyde intermediate formed in situ from styrene in presence of IBX in DMSO, for coupling with amines to give hemiaminal type intermediate which then is expected to get further oxidized by IBX to give the desired \( \alpha \)-ketoamides.

To initiate our study, the reaction of styrene 1a with piperidine 1b was chosen as the model reaction in the presence of different iodine sources as additives and different oxidants. It was observed that the reaction of styrene (0.5 mmol) and piperidine (1.5 mmol) with I\(_2\)/IBX (1 mmol / 0.75 mmol) in DMSO at 70 °C for 6 hours afforded the desired \( \alpha \)-ketoamide 2a in 14% yield (Table 1, entry 1). We observed that prolonging the reaction time also did not improve the yield. However, instead of taking the reactants together, styrene and I\(_2\)/IBX were taken and heated at 70 °C in DMSO for 2 hours, with the subsequent addition of piperidine to the mixture and further stirring for 2.5 hours at the same temperature produced the desired product 2a in 31% yield (entry 2).

To improve the yield of \( \alpha \)-ketoamide further, a set of reactions were carried out (entries 3-14). First, the addition of reagent in different time interval of addition was examined. It was observed that the initial stirring of styrene with I\(_2\)/IBX at 70 °C in DMSO for 3.5 hours followed by drop wise addition of piperidine and further stirring for 2 hours gave 38% of 2a (entry 3). Different temperatures were scanned to get the optimum reaction temperature. A better yield of 45% was obtained at 80 °C temperature (entry 4). No further increase in yield was observed at higher temperatures than 80 °C (entry 5). Then different peroxide based oxidants like TBHP, H\(_2\)O\(_2\)
and di tert-butyl peroxide (DTBP) were examined in the presence of molecular iodine and observed that only TBHP gave trace amount of product, whereas none of the other two were able to promote the reaction, resulting in no product formation even after 48 hours (entries 6-8). N-iodosuccinimide (NIS) was also tried as the source of iodine with IBX and gave a moderate yield of 29% (entry 9).

Table 1 Optimization studies for one-pot synthesis of α-ketoamide from styrene

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Additive (mmol)</th>
<th>Oxidant (mmol)</th>
<th>Piperidine (mmol)</th>
<th>Temperature (°C)</th>
<th>Yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂ (0.5)</td>
<td>IBX (0.75)</td>
<td>1.5</td>
<td>70</td>
<td>34↑</td>
</tr>
<tr>
<td>2</td>
<td>I₂ (0.5)</td>
<td>IBX (0.75)</td>
<td>1.5</td>
<td>70</td>
<td>38↑</td>
</tr>
<tr>
<td>3</td>
<td>I₂ (0.5)</td>
<td>IBX (0.75)</td>
<td>1.5</td>
<td>80</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>I₂ (0.5)</td>
<td>IBX (0.75)</td>
<td>1.5</td>
<td>90</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>I₂ (0.5)</td>
<td>TBHP (0.75)</td>
<td>1.5</td>
<td>90</td>
<td>90↑</td>
</tr>
<tr>
<td>6</td>
<td>I₂ (0.5)</td>
<td>H₂C₂ (0.75)</td>
<td>1.5</td>
<td>90</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>I₂ (0.5)</td>
<td>DTBP (0.75)</td>
<td>1.5</td>
<td>90</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>NIS (1.0)</td>
<td>IBX (0.75)</td>
<td>1.5</td>
<td>90</td>
<td>29</td>
</tr>
<tr>
<td>9</td>
<td>I₂ (0.5)</td>
<td>IBX (0.75)</td>
<td>2.0</td>
<td>80</td>
<td>54</td>
</tr>
<tr>
<td>10</td>
<td>I₂ (0.5)</td>
<td>IBX (0.75)</td>
<td>2.0</td>
<td>80</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>I₂ (1.25)</td>
<td>IBX (0.75)</td>
<td>2.0</td>
<td>80</td>
<td>54</td>
</tr>
<tr>
<td>12</td>
<td>I₂ (1.25)</td>
<td>IBX (0.75)</td>
<td>2.0</td>
<td>80</td>
<td>54</td>
</tr>
<tr>
<td>13</td>
<td>I₂ (1.0)</td>
<td>IBX (1.0)</td>
<td>2.0</td>
<td>90</td>
<td>71</td>
</tr>
<tr>
<td>14</td>
<td>I₂ (1.0)</td>
<td>IBX (1.0)</td>
<td>2.0</td>
<td>80</td>
<td>68</td>
</tr>
<tr>
<td>15</td>
<td>I₂ (0.5)</td>
<td>-</td>
<td>2.0</td>
<td>80</td>
<td>47↑</td>
</tr>
<tr>
<td>16</td>
<td>-</td>
<td>IBX (1.25)</td>
<td>2.0</td>
<td>80</td>
<td>43↑</td>
</tr>
<tr>
<td>17</td>
<td>-</td>
<td>-</td>
<td>2.0</td>
<td>80</td>
<td>no↑</td>
</tr>
</tbody>
</table>

*Reaction conditions: Initially, styrene, I₂/IBX mixture was stirred for 2 h and after the addition of amine reaction stirred for 2.5 h. **Reaction condition: reaction was run for 48 h. † Reaction was carried out without IBX. ‡ Reaction was carried out without IBX and I₂.

Further optimization was continued with I₂/IBX, which is the optimal additive-oxidant pair for this transformation. Low solubility of IBX in solvents other than DMSO restricts its reactions in different solvents. The reaction was performed in different solvents like EtOAc, THF, MeCN and solvent mixtures like MeCN:H₂O (1:1), acetonitrile : H₂O (86:14) and DMSO : CH₂Cl₂ (1:1) but no product was obtained in any of the solvents after continuing the reaction for 24 hours. Often to overcome the solubility barrier, different phase transfer catalysts were also used. Other solvents and n-BuNBr is found to be one of the best suited phase transfer catalyst for IBX based reactions. Thus above mentioned solvents were tried in presence of n-BuNBr (0.5 equiv, 0.25 mmol) and 10 equiv. of DMSO (for solvents other than DMSO: CH₂Cl₂) but none resulted in any product formation.

When the reaction was tried with one and two equiv. of piperidine in less yield or incomplete conversion of the phenylglyoxal intermediate was observed.¹⁴ The use of 4 equiv. of piperidine was found to be the best condition for the reaction (entry 10). Subsequently, the amount of I₂ and IBX were also monitored (entries 11-14) and finally the optimal reaction condition for the reaction was turned out to be styrene (0.5 mmol) and piperidine (2 mmol) with I₂/IBX (1.0mmol/1.0mmol) at 80 °C in DMSO solvent (entry 13).

Table 2 Substrate scope of I₂/IBX promoted α-ketoamide formation

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Alkene Product</th>
<th>Time (h)</th>
<th>Yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuC₅H₈</td>
<td>7.5(35+4)</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>n-BuC₅H₈</td>
<td>6.5(35+3)</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>n-BuC₅H₈</td>
<td>8.5(35+5)</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>n-BuC₅H₈</td>
<td>9.5(35+6)</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>n-BuC₅H₈</td>
<td>11.5(35+8)</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>n-BuC₅H₈</td>
<td>16.5(35+13)</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>n-BuC₅H₈</td>
<td>12.5(35+9)</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>n-BuC₅H₈</td>
<td>13.5(35+10)</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>BrBrC₅H₈</td>
<td>11.5(35+8)</td>
<td>59</td>
</tr>
<tr>
<td>10</td>
<td>BrBrC₅H₈</td>
<td>10.5(35+7)</td>
<td>52</td>
</tr>
<tr>
<td>11</td>
<td>BrBrC₅H₈</td>
<td>11.5(35+8)</td>
<td>67</td>
</tr>
<tr>
<td>12</td>
<td>BrBrC₅H₈</td>
<td>6.5(35+3)</td>
<td>62</td>
</tr>
<tr>
<td>13</td>
<td>BrBrC₅H₈</td>
<td>7.5(35+4)</td>
<td>64</td>
</tr>
<tr>
<td>14</td>
<td>BrBrC₅H₈</td>
<td>8.5(35+4)</td>
<td>58</td>
</tr>
</tbody>
</table>

* Isolated yields. General reaction condition: Alkene (0.5 mmol) with I₂/IBX (1.0 mmol/1.0 mmol) were stirred in DMSO at 80 °C for 3 h and then amine (2 mmol) was added dropwise and stirred till completion of reaction.

Following the optimal conditions, different sets of reactions were carried out to investigate the scope as well as the limitations of this methodology and the results are summarized in Table 2. Initially, different styrene derivatives were tested with piperidine under optimized condition. Styrenes with substitution at the phenyl ring
with electron withdrawing as well as electron donating groups such as methyl, methoxy, bromo, and nitro groups were examined and corresponding products were obtained with 56-67% yield (entries 6-14). In addition, several amines were also tried taking styrene as the terminal alkene. Piperidine, pyrrolidine and morpholine as the source of amines gave corresponding products in moderate to good yields (entries 1-3). However, aliphatic primary amine such as N-butyl amine, aromatic primary amine such as aniline and aromatic secondary amines like N,N-diphenylamine and N-methyl aniline were unable to produce the desired products even keeping them for more than 48 hours under optimized reaction conditions. From the above mentioned experimental results it can be concluded that this method is only applicable with aliphatic secondary amines as supported by the Stark enamine reaction which goes via iminium ion intermediate.\textsuperscript{25, 26} On the other hand, non-reactivity of the aromatic secondary amines may be attributed to its decreased nucleophilicity.

To gain insight into the reaction mechanism, control experiments were performed (Scheme 3). When the styrene was treated with optimized amount of I\textsubscript{2} and IBX at 80 °C temperature in DMSO without the addition of amine, it gave phenylglyoxal \textit{via} the intermediates haloaldimin and phenacyl iodide which were isolated and characterised (Eq. 1). This is also supported by previous reports.\textsuperscript{27}

\begin{center}
\begin{tabular}{c}
\hline
\textbf{Scheme 3 Control experiments} \\
\hline
\end{tabular}
\end{center}

When phenylglyoxal was separately treated with the optimized equivalence of piperidine, the reaction was completed within 2 hours in presence of IBX in DMSO at 80 °C (Eq. 2). To emphasize our hypothesis about the role of IBX in the oxidative amidation step, the same reaction was repeated in absence of IBX. Surprisingly, the reaction took place and 83% of the product 2a formed (Eq. 3). This result suggests that DMSO acts as a promoter in the amide C-N bond formation, which is matching with literature reports.\textsuperscript{28} But, this observation does not completely disprove the possibility of IBX acting as an oxidant in C-N bond formation. The reaction was repeated in polar aprotic solvent acetonitrile in presence of IBX and standing on our expectation, reaction completed within 9 hours (Eq. 4). Whereas, in only acetonitrile even after 72 h the conversion was very less (Eq. 5). It suggests that IBX also promotes the reaction, may be by oxidizing the intermediate hemiaminal formed.

On the basis of the control experiments and previous reports, a plausible mechanism is proposed in Scheme 4. In presence of I\textsubscript{2}/IBX, which generates IOH \textit{in situ},\textsuperscript{29} the styrene forms the haloaldimin 1d which in turn is oxidized to phenacyl iodide 1e followed by DMSO mediated oxidation to form phenylglyoxal 1f. It is important to mentioned that we have isolated both 1d and 1e during the course of the reaction. This makes DMSO an integral part of the reaction. Finally, the phenylglyoxal couples with the amine, promoted by DMSO and IBX may be by oxidizing the iminium ion and hemiaminal intermediates respectively, which might exist in equilibrium, to form the desired \(\alpha\)-ketoamides.\textsuperscript{30}

\begin{center}
\begin{tabular}{c}
\hline
\textbf{Scheme 4 Plausible reaction mechanism} \\
\hline
\end{tabular}
\end{center}

\textbf{Conclusions}

In conclusion, we have developed a metal free one-pot strategy for the synthesis of \(\alpha\)-ketoamides from readily available terminal alkenes (styrenes). The uniqueness of the method can be attributed to the use of sterenes, for the synthesis of biologically and functionally important \(\alpha\)-ketoamides. Use of amines and cost effective oxidizing agent IBX under one-pot reaction condition avoiding possibility of metal related contamination makes it suitable for synthesis related to pharmaceuticals.

\textbf{Typical Experimental procedure}

\textbf{General Considerations}

All reactions were carried out in reaction tubes under aerobic atmosphere unless otherwise mentioned. All the solvents were purchased from commercial sources and used without further purification. Wherever necessary, the solvents were dried by standard literature procedures. Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F\textsubscript{254} precoated plates (0.25 mm) and analyzed by UV fluorescence quenching using appropriate mixture of ethyl acetate and hexanes as eluting solvent mixture. Silica gel (particle size 100-200 mesh) purchased from SRL India was used for column chromatography using hexanes and ethyl acetate mixture as eluent. All the chemicals used are purchased from commercially available sources and used without further purification unless otherwise mentioned. IBX was prepared using literature procedure.\textsuperscript{11} Reactions were carried out in temperature controlled IKA magnetic stirrers.\textsuperscript{1H} and \textsuperscript{13}C NMR
spectra were recorded on a Bruker 400 or 500 MHz instrument. 

\(^1\)H NMR spectra were reported relative to Me\(_\text{4}Si\) (δ 0.0 ppm) or residual CHCl\(_3\) (δ 7.26 ppm). \(^{13}\)C NMR were reported relative to CDCl\(_3\) (δ 77.16 ppm). FTIR spectra were recorded on a Nicolet 6700 spectrometer and were reported in frequency of absorption (cm\(^{-1}\)). High resolution mass spectra (HRMS) were recorded on Q-ToF Micro mass spectrometer.

**Typical experimental procedure for α-ketoamides from styrenes**

In a clean reaction tube, I\(_2\) (254 mg, 1.0 mmol) and IBX (280 mg, 1.0 mmol) was taken and dissolved in 2.5 mL of DMSO by stirring for 5 min at rt followed by addition of styrene (1a, 0.05 mL, 0.5 mmol). The mixture was transferred to a 80 °C oil bath and stirred for 3.5 hours. Piperidine (1b, 0.2 mL, 2.0 mmol) was added to the stirring solution slowly and stirred till the reaction was complete. Completion of reaction was monitored using TLC by checking the complete disappearance of the intermediate phenylglyoxal (1f). The reaction was then extracted with ethyl acetate for few times and the combined organic layer was washed with saturated sodium thiosulphate and saturated sodium bicarbonate solutions. It was concentrated under reduced pressure. The crude product was purified using column chromatography (silicagel, petroleum ether:ethyl acetate=85:15) to give the desired tertiary α-Bketoamide (2a).

The data for α-Bketoamides 2a-2c\(^{32}\), 2f-2i\(^{34}\), 2k-2m\(^{35}\), 2n\(^{33}\) and 1e\(^{36}\) are already reported in literature.

**Acknowledgment**

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**Notes and references**

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Electronic Supplementary Information (ESI) available: R\(_f\) values, IR, NMR and MS data for all the products and copy of \(^1\)H and \(^{13}\)C spectra for all the compounds are included in the ESI. See. DOI: 10.1039/c000000x/data.

24. Complete conversion of phenylglyoxal has been the method of monitoring the completion of the last step of reaction after the addition of the amine.


30. The advantage of this report over the literature report is isolating the reaction intermediates 2-iodo-1-phenylethanol and 2-iodo-1-phenylethanone and phenyl glyoxal.


