Studies on the reactivity pattern of \textit{in situ} generated tetraethylammonium superoxide with 2-oxazolin-5-ones

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A variety of 2-oxazolin-5-ones have been allowed to react under the mild reaction conditions of potassium superoxide and tetraethylammonium bromide in dry dimethylformamide at room temperature. Different products are obtained depending on the substituents attached to the C-4 position.

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The chemistry of 2-oxazolin-5-ones or 5(4\textit{H})-oxazolones has attracted a great deal of attention due to their usefulness as synthons and/or as biologically active compounds\textsuperscript{1,2}. 2-Oxazolin-5-ones undergo a variety of reactions and are amenable to various manipulations to afford diverse compounds\textsuperscript{3-8}. The oxygenation of 2-oxazolin-5-ones is quite interesting and results in ring opening\textsuperscript{9}. In the presence of triethylamine, oxygen reacts with 4-alkylidene-2-phenyl-2-oxazolin-5-one to give the corresponding imide arising through a hydroperoxy intermediate\textsuperscript{10}. 4-Isopropyl-2-phenyl-2-oxazolin-5-one and 4-benzyl-2-phenyl-2-oxazolin-5-one, in the presence of oxygen, are readily converted to N-isobutyrylbenzimide and N-(phenylacetyl)benzamide respectively\textsuperscript{11}. Rose Bengal-sensitised photo-oxygenation of 2-oxazolin-5-one is observed to afford imide in moderate yield\textsuperscript{12}. 4-Benzylidene-2-oxazolin-5-one is also cleaved under similar conditions. Oxygen induces oxidation of 2,4-disubstituted oxazolones to dehydrodimers via mesoionic form of oxazolone\textsuperscript{13}. The reaction of 2-oxazolin-5-ones and bioxazolinones with potassium has also been investigated\textsuperscript{14}. There exists only one report on the reaction of potassium superoxide with 2-phenyl-4,4-dimethyl-2-oxazolin-5-one and 2-phenyl-4-ethyl-2-oxazolin-5-one using tetrahydrofuran and freon in a UV cell\textsuperscript{15}. In view of the importance of \textit{O}_2\textsuperscript{-} and as a part of our ongoing research\textsuperscript{18} on superoxide chemistry, the reaction of \textit{in situ} generated tetraethylammonium superoxide (Et\textsubscript{4}NO\textsubscript{2}) with various 2-oxazolin-5-ones, particularly 4-arylidene-2-oxazolin-5-ones, is deemed of interest to understand the reaction pathways and product formation (Scheme I). Et\textsubscript{4}NO\textsubscript{2} was generated \textit{in situ} by the phase transfer reaction of KO\textsubscript{2} with Et\textsubscript{4}NBr in DMF under inert atmosphere at room temperature.

Various oxazolones viz., 2,4,4-triphenyl-2-oxazolin-5-one \textbf{1a}, 2,4-diphenyl-2-oxazolin-5-one \textbf{1b}, 2-phenyl-4-benzylidene-2-oxazolin-5-one \textbf{1c}, 2-phenyl-4-(3-nitrobenzylidene)-2-oxazolin-5-one \textbf{1d}, 2-phenyl-4-(cinnamylidene)-2-oxazolin-5-one \textbf{1e}, 2-phenyl-4-(vanillidene)-2-oxazolin-5-one \textbf{1f}, 2-phenyl-4-(2-furylidene)-2-oxazolin-5-one \textbf{1g}, 2-phenyl-4-(2-thienylidene)-2-oxazolin-5-one \textbf{1h} and 2-methyl-4-benzylidene-2-oxazolin-5-one \textbf{1i} were prepared by the Erlenmeyer’s method and subjected to the reaction with Et\textsubscript{4}NO\textsubscript{2}. Results of the investigation are shown in Table I. A perusal of the Table I indicates that under the mild reaction conditions of superoxide, different products are obtained depending on the substituents attached to the C-4 position. In the absence of an acidic hydrogen at C-4 position i.e. when the 4\textsuperscript{th}-position is disubstituted either by alkyl or aryl groups, for example, 2,4,4-triphenyl-2-oxazolin-5-one \textbf{1a} on reaction with Et\textsubscript{4}NO\textsubscript{2} gives N-benzoyl-C, C-diphenylglycine \textbf{2a}. However, when an acidic hydrogen is present at C-4 position, as in 2,4-diphenyl-2-oxazolin-5-one \textbf{1b}, the formation of dibenzamide \textbf{3b} along with N-benzoyl-C-phenylglycine \textbf{2a} is observed. In case of 4-arylidene-2-oxazolin-5-ones \textbf{1c-i}, however, 2-acylamino-2-alkenoic acids \textbf{2c-i} along with aryl carboxylic acids \textbf{3c-i} have been obtained under similar conditions.

A 4-fold molar excess of KO\textsubscript{2} and 2-fold molar excess of Et\textsubscript{4}NBr with respect to the substrate, were employed for achieving the transformations. Each
\[ \text{KO}_2 / \text{Et}_4 \text{NBr} \]

DMF, RT

\[ \begin{align*}
\text{1a} - \text{b} & \rightarrow \text{R}^1 \text{C} = \text{R}^2 \text{CO} + \text{2a} - \text{b} \\
\text{1c} - \text{i} & \rightarrow \text{R}^1 \text{C} = \text{R}^2 \text{CO} + \text{2c} - \text{i}
\end{align*} \]

**Scheme I**

**Table I** — Reaction of *in situ* generated Et$_4$NO$_2$ with various 2-oxazolin-5-ones 1a-i

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield* (%)</th>
<th>Product</th>
<th>Yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>( \text{C}_6\text{H}_5\text{C} = \text{C} = \text{COOH} )</td>
<td>78</td>
<td>( \text{C}_6\text{H}_5\text{C} = \text{C} = \text{COOH} )</td>
<td>48</td>
</tr>
<tr>
<td>1b</td>
<td>( \text{C}_6\text{H}_5\text{C} = \text{NH} = \text{COOH} )</td>
<td>26</td>
<td>( \text{C}_6\text{H}_5\text{C} = \text{NH} = \text{COOH} )</td>
<td>33</td>
</tr>
<tr>
<td>1c</td>
<td>( \text{C}_6\text{H}_5\text{COOH} )</td>
<td></td>
<td>( \text{C}_6\text{H}_5\text{COOH} )</td>
<td></td>
</tr>
</tbody>
</table>

*Isolated mass yields are based on oxazolones

--- **Contd**
### Table I — Reaction of *in situ* generated Et<sub>4</sub>NO<sub>2</sub> with various 2-oxazolin-5-ones 1a–i — contd

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield* (%)</th>
<th>Yield* (%)</th>
</tr>
</thead>
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<td>39</td>
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<td><img src="image3i" alt="Image of product 3i" /></td>
</tr>
</tbody>
</table>

*Isolated mass yields are based on oxazolones*
reaction was monitored by TLC for its completion and subsequently quenched with aqueous brine. The reaction mixture was worked-up to afford the products which were separated by column chromatography over silica gel. The products were identified by their m.p., mixed m.p. and spectral data which were in full agreement with the values described in the literature. Based on product isolation and existing chemistry of $O_2^-$, the following plausible mechanisms may be envisaged for the transformations observed. In the absence of an acidic hydrogen at C-4 position of the substrate 1a, the reaction proceeds by nucleophilic attack of $O_2^-$ at the carbonyl carbon, followed by ring opening to yield the product 2a (Scheme II).

The formation of 2b and 2c may be visualised in terms of the steps given in Scheme III.

The formation of 2-acylamino-2-alkenoic acids 2c-i and aryl carboxylic acids 3c-i may be envisaged by the pathways shown in Scheme IV.

**Experimental Section**

Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. $^1$H NMR spectra were run on a JEOL FT-NMR spectrometer FX-90Q relative to TMS as internal standard (chemical shifts in $\delta$, ppm). Potassium superoxide and tetraethylammonium bromide were procured from E. Merck, Germany and were used as received. Dry DMF of Aldrich, USA was stored over molecular sieves (4A$^\circ$) prior to use. The other reagents and solvents were of A. R. grade. Substrates used in the present investigation were prepared by Erlenmeyer azlactone method$^{19,20}$. $\alpha$-Amino acids were benzoylated by Schotten-Baumann method and the resulting product was treated with acetic anhydride under nitrogen atmosphere to afford the oxazolones 1a and 1b (Ref. 19). Acetyl-and benzoyl-glycine were prepared adopting established method$^{21}$ and subsequently subjected to react with ethyl chloroformate and carbonyl compound in the presence of triethylamine in benzene to provide oxazolones 1c-i. All the products 1a-i exhibited physical and spectral data consistent with their structures.

Reaction of in situ generated tetraethylammonium superoxide with 2-oxazolin-5-ones 1a-i: General procedure. Potassium superoxide (0.56 g;...
0.008 mole) and tetraethylammonium bromide (0.84 g; 0.04 mole) were weighed under nitrogen atmosphere using an atmosbag and transferred into a three-necked round bottom flask equipped with a magnetic stirrer, nitrogen inlet and a Leibig condenser protected by calcium chloride drying tube. Dry dimethylformamide (40 mL) was added to it and the mixture was agitated magnetically for 15 min to facilitate the formation of tetraethylammonium superoxide. Finally, the substrate 1 (0.002 mole) was admitted to it and the stirring continued at room temperature till the complete loss of the substrate was indicated by TLC. The nitrogen gas was bubbled throughout to avoid atmospheric moisture.

After the reaction was over, mixture was treated with saturated aqueous sodium chloride solution (25 mL) to decompose the unreacted potassium superoxide. Saturated sodium hydrogen carbonate solution (15 mL) was added to it and the solution was extracted with diethyl ether (2 × 25 mL) to remove the unreacted substrate. The aqueous layer was acidified with hydrochloric acid and extracted with diethyl ether-ethyl acetate (3 × 25 mL). The organic layers were combined, washed with water (2 × 15 mL) and dried over anhydrous sodium sulfate. The solution was filtered and evaporated to yield a mixture of products which was finally separated by column chromatography, recrystallised and identified.

Acknowledgement

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References