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Multicomponent reactions in PEG-400:
ruthenium-catalyzed synthesis of substituted pyrroles

Srivari Chandrasekhar*a, Vidyavathi Patro*a, Lahu N. Chavan*a, Rambabu Chegondi*a, René Gréeb

\[
\begin{align*}
&\text{R}^1, \text{R}^2, \text{R}^3, \text{NH}_2 + \text{HO}-
\end{align*}
\]

R\(_1\) - aryl, alkyl; R\(_2\) - alkyl, aryl
R\(_3\) - H, alkyl

\[
\begin{align*}
\text{PEG-400} & \quad \text{[RuCl(diphos)]}_2 \\
(0 \text{ mol\%}) & \\
\text{Tetrabutylammonium chloride} & \quad (20 \text{ mol\%})
\text{130}^\circ \text{C}, 16 - 24 \text{ h} & \\
65 - 85\% & \\
18 \text{ examples}
\end{align*}
\]
Multicomponent reactions in PEG-400: Ruthenium-catalyzed synthesis of substituted pyrroles

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Abstract

An efficient and eco-friendly method for the synthesis of substituted pyrroles has been developed via ruthenium-catalyzed multicomponent reaction of ketone, amine and ethylene glycol in PEG-400 as solvent medium without using any external ligand. The catalytic system and solvent can be recycled with the same, as well as different, ketones with minimum loss of Ru-catalyst activity.

Multicomponent reactions (MCRs),\textsuperscript{1} eco-friendly solvents\textsuperscript{2} and catalysis\textsuperscript{3} have been central themes in green chemistry. Incorporation of these principles into the formation of new C-C and C-X bonds paves the way towards the preparation of new chemicals and products in agrochemicals, pharmaceuticals and materials in an economical fashion. In particular, the use of recyclable and reusable solvents are gaining prominence for organic reactions.\textsuperscript{4} In this direction, we have demonstrated in our early studies that PEG-400 is a preferred solvent medium wherein the expensive metals and their complex could be recovered and reused effectively without loss of activity.

Since the first synthesis of “pyrrole” ring by Knorr way back in 1884, the preparation of pyrroles has come a long way over the past century.\textsuperscript{5} Several approaches, viz., [3+2] cycloadditions,\textsuperscript{6} [4+1] approach,\textsuperscript{7} [2+2+1] approach\textsuperscript{8} and intramolecular versions\textsuperscript{9} have been developed for the synthesis of pyrroles. These approaches are compiled in excellent reviews by Ferreira\textsuperscript{10} and Menendez.\textsuperscript{11} Recently, a novel three-component method for pyrrole synthesis has been reported by the Beller’s group using ruthenium catalysis, assisted by Xantphos as ligand, in a [2+2+1] strategy for pyrrole formation.\textsuperscript{12} This work combined with our experience in using PEG-400 as a solvent medium,\textsuperscript{13} prompted us to look at the recyclability of expensive Ru-catalyst in such a pyrrole synthesis.

The results pertaining to Ru-catalyzed three-component pyrrole synthesis with a recyclable medium (Ru and PEG-400) are reported herein (Scheme 1). Furthermore, a significant advantage of the described method is that the expensive ligand (xantphos) is avoided since the PEG-400 acts as external ligand.\textsuperscript{14}

In the first instance, cyclopentanone 1a, cyclohexylamine 2a and ethylene glycol 3 were chosen as partners in the [2+2+1] condensation process (Table 1, entry 1). The reaction in PEG-400 in the presence of 1 mol% [RuCl$_2$(p-cymene)] and 20 mol% t-BuOK catalytic system was successful and the 1,2,3-trisubstituted pyrrole 4a was isolated in 75% yield, after a routine work-up process.\textsuperscript{15} With this observation on hand, the reaction generality was studied by performing experiments with various substrates. Keeping cyclopentanone 1a and ethylene glycol 3 as the common partners, 4-methoxybenzylamine 2b (Table 1, entry 2) and $n$-butyl amine 2c (Table 1, entry 3) as variable amine counterparts, the pyrroles 4b, 4c were obtained in decent yields. To understand the patterns for aryl ketones, phenylethylketone 1b and ethylene glycol 3 as common partners were treated with benzyl amine 2d, 4-methoxy aniline 2e, (R)-(+)-1-(1-naphthyl)ethyln amine 2f, cyclohexylamine 2a, $n$-butyl amine 2c to give the trisubstituted pyrroles 4d-h respectively in satisfactory yields (Table 1, entries 4-8). In addition, other ketones such as acetophenone 1e with benzyl amine 2d and cyclopentylamine 2g gave disubstituted pyrroles 4i and 4j respectively in acceptable yields (Table 1, entries 9 and 10). The cyclohexanone 1d provided bicyclic fused pyrroles 4k-n with (S)-phenylethylamine 2h, butylamine 2c, benzylamine 2d, aniline 2i consistently well (Table 1, entries 11-14). Another ketone, $\alpha$-tetralone 1e was attempted with butylamine 2c, 4-chlorobenzylamine 2j, benzylamine 2d, cyclopropylamine 2g providing angular tricyclic pyrroles 4o-r respectively in the 75-85% yield range (Table 1, entries 15-18). For direct comparison of present method with Beller’s protocol, the experiments were performed with 2-phenylethylamine (2k) as one of the partners (Table 1, entries 19 and 20). The observations reveal that the yields obtained with the

\begin{center}
\textbf{Scheme 1. Synthesis of substituted pyrroles in PEG-400}
\end{center}

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E-mail address: srivari@iict.res.in (S. Chandrasekhar).
new system are marginally lower, however offers an additional advantage that the external ligand is not required.

**Table 1:** Ruthenium-catalyzed synthesis of substituted pyrroles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Amine</th>
<th>Product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td></td>
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<td></td>
<td></td>
<td>20</td>
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<tr>
<td>3</td>
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<td></td>
<td>16</td>
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<tr>
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<td>8</td>
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<td>9</td>
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<td>16</td>
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<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>

<sup>a</sup> All products were characterized by <sup>1</sup>H, <sup>13</sup>C NMR and Mass spectroscopy.

<sup>b</sup> Isolated yield after column chromatography.

Further, the efficacy of the developed method by recycle and reuse<sup>c</sup> of expensive ruthenium catalyst, has been demonstrated. Towards this, entry 13 (Table 1) has been chosen as representative example. Thus, 1d and 2d were condensed with ethylene glycol 3 in the presence of t-BuOK for over five times using the same PEG-400 and ruthenium catalyst with good yields without significant loss of catalytic activity (Table 2). Also, the cross over experiments performed with three different ketones (Table 3) demonstrated that the products could be completely extracted from PEG and no detectable contaminations were observed. However, due the aqueous work-up process, 20 mol% t-BuOK has to be added after each run. Here also, an addition of 0.2 mol% [RuCl<sub>2</sub>(<i>p</i>-cymene)]<sub>2</sub> allowed us to improve the yields in next runs.

**Table 2:** Recyclability of catalyst in PEG-400

<table>
<thead>
<tr>
<th>Run</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>75</td>
<td>72</td>
<td>70</td>
<td>65 (70)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>63 (70)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>d</sup> Isolated yield after column chromatography.

<sup>e</sup> An additional 0.2 mol% Ru catalyst was added to the reaction.
Based on these findings, it may be inferred that the [2+2+1] condensation for pyrrole synthesis proceeds smoothly in PEG, even in the absence of any added ligand, via imine formation between ketone and amine, followed by dehydrogenation of ethylene glycol to an in situ generated dialdehyde for further condensation to form pyrrole.\(^\text{11}\)

Disappointingly, the substituted vicinal diols viz., 2,3-butanediol, 1,2-diphenylethane-1,2-diol, cyclohexane-1,2-diol and 2-phenylethane-1,2-diol did not participate in the pyrrole condensation to form pyrrole.

**Scheme 2.** Synthesis of α-methyl substituted pyrroles in PEG-400.

These results endorse that the developed methodology follows the major principles of green chemistry wherein catalyst and solvent are recyclable. This MCR is well tolerated in PEG-400, even in the absence of any added ligand, via imine formation between ketone and amine, followed by dehydrogenation of ethylene glycol to an in situ generated dialdehyde for further condensation to form pyrrole.

**Acknowledgments**

This research has been performed as part of the Indo-French "Joint Laboratory for Sustainable Chemistry at Interfaces". We thank CNRS, CSIR, University of Rennes I and CEFIPRA/IFCPAR for support of this research. V.P. & L.N.C thank to CSIR, New Delhi, for research fellowship and R.C. thanks CSIR-SRA for financial assistance. SC thanks CSIR XII plan project ORIGIN (CSC-0108) for funding.

**References and notes**


15. **General experimental procedure:** To a stirred solution of ketone (1.0 mmol) in PEG-400 (4 mL) was added amine (1.5 mmol) at 25 °C in a glass pressure tube. After 5 min, diol (2.2 mmol) was added followed by [Ru(η5-cymene)(Cl)2] (0.01 mmol) and potassium tert-butoxide (0.2 mmol) were added successively. The pressure tube was tightly capped and heated to 130 °C. After completion of the reaction, it was cooled to room temperature. The solution was diluted with ether (10 mL), stirred for 10 min and was allowed to stand in ice-salt bath to solidify PEG-400. The ether layer was decanted, dried over anhydrous Na2SO4 and concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography using 1-5 % ethyl acetate in petroleum ether as eluent to give pure products. The residual PEG-catalyst system was brought to room temperature and reused in next run/experiment.

**Supporting Information**

Supplementary data associated with this article, experimental and characterization data, can be found in the online version.
Run | 1st | 2nd | 3rd | 4th | 5th  
---|-----|-----|-----|-----|------  
Yield (%)<sup>a</sup> | 75  | 72  | 70  | 65 (70)* | 63 (70)*  

<sup>a</sup>Isolated yield after column chromatography  
<sup>*</sup>An additional 0.2 mol% Ru' catalyst was added to the reaction
<table>
<thead>
<tr>
<th>Run</th>
<th>Ketone</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>1d</td>
<td>4m</td>
<td>75</td>
</tr>
<tr>
<td>2nd</td>
<td>1e</td>
<td>4o</td>
<td>70</td>
</tr>
<tr>
<td>3rd</td>
<td>1b</td>
<td>4h</td>
<td>65 (75)*</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after column chromatography

<sup>*</sup>An additional 0.2 mol% 'Ru' catalyst was added to the reaction