Comparison between acetic acid and propanoic acid as a solvent/catalyst in the indolenines synthesis: an approach without any indole by-product

S. Sajjadifar1, M. A. Zolfigol2, N. Javaherneshan1, G. Chehardoli3*

1Department of Chemistry, Payame Noor University, Tehran, Iran
2Faculty of Chemistry, Bu-Ali Sina University, Hamedan, 6517838683, Iran
3Department of Medicinal Chemistry, School of Pharmacy, Hamadan University of Medical Sciences, Zip Code 65178, Hamadan, Iran

Received May 24, 2015; Revised June 7, 2016

Some indolenines (3H-indoles) were prepared via reaction of phenylhydrazine derivatives, isopropyl methyl ketone, 2-methyl cyclohexanone and diisopropyl ketone in the presence of propanoic acid or acetic acid as a catalyst/solvent under reflux conditions. We compared the obtained results with propanoic acid to those with acetic acid. In most cases, the results were similar. In some cases, however, propanoic acid provided slightly better results with respect to reaction time and yields. Under these reaction conditions, we did not observe any indole output as by-product.

Keywords: Indolenine, 3H-indole, Phenylhydrazine derivatives, Aliphatic ketones, Propanoic acid, Acetic acid

INTRODUCTION

Indolenine derivatives are a very important class of nitrogen-containing compounds and have been widely used in dyes and antimigraine drugs of the triptan class [1]. The first report of indolenine synthesis was announced by Fischer in 1883 [2]. Some of the Brønsted acids such as HCl, H2SO4, polyphosphoric acid and p-toluenesulfonic acid, and also Lewis acids such as boron trifluoride, zinc chloride, iron chloride, and aluminum chloride have been successfully used as catalysts [2, 3].

Robinson suggested the mechanism of Fischer indole synthetic reaction [4-6]. The methodologies for the synthesis of 3H-indole derivatives are very limited [7]. Therefore, a general and efficient method for the synthesis of 3H-indole derivatives is an attractive and formidable challenge in synthetic chemistry [8].

Miller and Neal Schinske have examined the effects of acid catalysts and temperature in the Fischer indole synthesis. Higher acidity or higher temperature during the thermal process cause cyclization toward the less substituted position. The observations are considered in terms of a refined version of the first two stages of the mechanism of the reaction [9].

A perplexing aspect of the Fischer indole synthesis has been reported in the cyclization of phenylhydrazones of unsymmetrical ketones to form two possible indoles. The early generalizations of Plancher [5] suggesting that the course of the reaction depends only on the structure of the ketone moiety of the phenylhydrazone, have not been sustained by more recent investigations [10-12] in which the ratio of the products has been found to vary with the nature of the acid used as the catalyst, its concentration, or its nature in a thermal cyclization.

Recently, we used citric acid as an organocatalyst for the preparation of some new indolenine derivatives under reflux of ethanol [13].

In continuation of the studies on the preparation and functionalization of heterocyclic compounds [14-17], herein we report that propanoic acid can be used as a catalyst/solvent for the preparation of some indolenine derivatives without any indole output as a by-product and that the results are comparable with those using acetic acid.

EXPERIMENTAL

General

All chemicals were purchased from Merck or Fluka Chemical Companies. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. The 1H NMR (300 MHz) and 13C NMR (75 MHz) spectra were run on a Bruker Avance DPX spectrometer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General procedure for the indolenine synthesis

Phenylhydrazines derivatives (1 mmol) and three aliphatic ketones [isopropyl methyl ketone, 2-methyl cyclohexanone and diisopropyl ketone] (1 mmol) were added to propanoic acid (3 mL) under reflux conditions. The mixture was refluxed for the

* To whom all correspondence should be sent:
E-mail: chehardoli@umsha.ac.ir, cheh1002@gmail.com

© 2017 Bulgarian Academy of Sciences, Union of Chemists in Bulgaria
appropriate time (see the table) under stirring. Progress of the reactions was monitored by TLC (using n-hexane:ethylacetate 3:1 as an eluent). The mixture was cooled and neutralized with 1 M NaOH, then diluted with water (100 mL) and extracted with CHCl$_3$ (3×50 mL). The organic layer was extracted and dried with Na$_2$SO$_4$, the solvent was evaporated and the residue was passed through a short silica gel column for further purification. A light brown viscous oil of indolenines was obtained in high yield.

RESULTS AND DISCUSSION

A range of indolenines derivatives was synthesized from a combination of phenylhydrazines and three aliphatic ketones in the presence of propanoic acid as a solvent/catalyst under reflux conditions. For comparing the results of propanoic acid with those of acetic acid, these reactions were also performed in the presence of acetic acid as a solvent/catalyst. In most cases, the results were similar. In some cases, however, propanoic acid provided slightly better results as regards reaction time and yields.

As mentioned in the introduction, higher temperature during the thermal process causes cyclization toward the less substituted position, i.e. indoles. Although 2-methyl cyclohexyl ketone and isopropyl methyl ketone can generate both indole and indolenine, under the present reaction conditions, no indole did not was obtained (Scheme 1). The results are summarized in the table.

Phenylhydrazine derivatives reacted with isopropyl methyl ketone and produced the corresponding indolenines (see the table, entries: 1, 4, 7, 10, 13, 16) in high yield (92-95%). In the $^1$H NMR spectrum of these indolenines a singlet signal of two methyl groups at $\delta$=1.1 ppm, and a singlet signal of a methyl group C-2 at $\delta$=2.05 were noticed. The IR spectrum indicated a stretching vibration C=N at 1690 cm$^{-1}$.

Also, phenylhydrazine derivatives reacted with 2-methyl cyclohexanone producing indolenines (see the table, entries: 2, 5, 8, 11, 14, 17) in high yield (86-95%). The $^1$H NMR spectrum of 5,6,7,8-tetrahydro-1,4b-dimethyl-4bH-carbazole (see the table, entry 2) as a model for these indolenines showed 0.80 (t, J=11.74 Hz, 1H) 0.94 (s, 3H, CH$_3$) 1.10 (t, J=13.2 Hz, 1H) 1.25-1.46 (m, 2H) 1.86 (t, J=13.74 Hz, 2H) 2.19-2.30 (m,1H) 2.36 (s, 3H, CH$_3$) 2.63 (d, J=12.74 Hz, 1H) 6.79 (s, 3H, Ar-H (Figure 1 as a model shows the $^1$H NMR spectrum of the aliphatic cyclic region). The IR spectrum indicated a stretching vibration C=N at 1706-1716 cm$^{-1}$.

This reaction was carried out with diisopropyl ketone producing indolenines (see the table, entries: 3, 6, 9, 12, 15, 18) in good yield (71-83%). In the $^1$H NMR spectrum of these products a doublet signal of two methyl groups at $\delta$=1.52, a singlet signal of two methyl groups at $\delta$=1.64 and a multiplet signal of CH at $\delta$=2.17-2.39 ppm were noticed. The IR spectrum indicated a stretching vibration C=N at 1706-1716 cm$^{-1}$.

![Scheme 1](image-url)  
**Scheme 1.** Preparation of indolenines by the reaction of substituted phenylhydrazines with isopropyl methyl ketone, 2- methyl cyclohexanone and diisopropyl ketone.
Table. Indolenines synthesis using propanoic acid or acetic acid as a solvent/catalyst under reflux conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Propanoic acid</th>
<th>Acetic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time (h:min)</td>
<td>Isolated yield (%)</td>
</tr>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>00:15</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>00:15</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>24:00</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure 4" /></td>
<td>1:00</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Structure 5" /></td>
<td>00:45</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Structure 6" /></td>
<td>48:00</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Structure 7" /></td>
<td>00:45</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8" alt="Structure 8" /></td>
<td>00:30</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9" alt="Structure 9" /></td>
<td>32:00</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td><img src="image10" alt="Structure 10" /></td>
<td>00:30</td>
<td>94</td>
</tr>
<tr>
<td>11</td>
<td><img src="image11" alt="Structure 11" /></td>
<td>00:15</td>
<td>92</td>
</tr>
<tr>
<td>12</td>
<td><img src="image12" alt="Structure 12" /></td>
<td>48:00</td>
<td>75</td>
</tr>
<tr>
<td>13</td>
<td><img src="image13" alt="Structure 13" /></td>
<td>00:30</td>
<td>94</td>
</tr>
<tr>
<td>14</td>
<td><img src="image14" alt="Structure 14" /></td>
<td>00:15</td>
<td>95</td>
</tr>
<tr>
<td>15</td>
<td><img src="image15" alt="Structure 15" /></td>
<td>24:00</td>
<td>72</td>
</tr>
<tr>
<td>16</td>
<td><img src="image16" alt="Structure 16" /></td>
<td>00:30</td>
<td>95</td>
</tr>
<tr>
<td>17</td>
<td><img src="image17" alt="Structure 17" /></td>
<td>00:30</td>
<td>94</td>
</tr>
<tr>
<td>18</td>
<td><img src="image18" alt="Structure 18" /></td>
<td>18:00</td>
<td>83</td>
</tr>
<tr>
<td>19</td>
<td><img src="image19" alt="Structure 19" /></td>
<td>90:00</td>
<td>10</td>
</tr>
</tbody>
</table>
CONCLUSION

As a weak organic acid, propanoic acid can act as a solvent/catalyst for the efficient indolenines (3H-indoles) synthesis in good to excellent yields. We compared the obtained results with propanoic acid to those with acetic acid. In most cases, the results were similar. In some cases, however, propanoic acid provided slightly better results as regards reaction time and yields. Under the present reaction conditions, we did not observe any indole output as a by-product.

Acknowledgements: The authors gratefully acknowledge partial support for this work by deputy of research, Hamadan University of Medical Sciences (Grant number 9308203950), and Center of Excellence in Development of Chemical Methods (CEDCM), Bu-ali Sina University, Hamedan, I.R. Iran.

REFERENCES
S. Sajjadifar et al.: Comparison between acetic acid and propanoic acid as a solvent/catalyst in the indolenines synthesis: an ...