Communication

Facile Synthesis of Cyclic Vinamidinium p-Toluenesulfonates

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Received October 28, 2003

Key Words: Vinamidinium salts, Cyclohexane-1,3-dione, UV absorber, Enaminone

Recently we have reported on the α-iodination reaction of some cyclic enaminones.1 The required cyclic enaminones have been synthesized by the reaction of cyclohexane-1,3-dione and amines such as aniline in the presence of p-toluenesulfonic acid as the catalyst.2 During the reaction small amounts of cyclic vinamidinium salt was isolated. From the reaction mixture we could not find and isolate any salt-free vinamidine itself. Elimination of p-toluenesulfonic acid from the salt could be carried out by treatment with triethylamine to afford the cyclic vinamidine (vide infra).

The synthesis of vinamidine in a direct method in high yield could not be achieved with excess use of aniline (up to 5 equiv.). The failure might be arised from the basic nature of vinamidine, which trap the acid catalyst and presented as its salt, namely vinamidinium salt. Electronic interactions between p-donor atoms (saturated nitrogen atom in this case) and π-acceptor groups (imino group in this case) through an intervening carbon-carbon double bond make vinamidine as a strong base.3

Vinamidinium salts have been used as versatile three-carbon building blocks in the synthesis of benzenoid, nonbenzenoid, and heterocyclic aromatic rings.4,5 Certain vinamidinium salts can be used as a UV absorber.6 Thus, we intended to develop a facile preparation method of cyclic vinamidinium salt and wish to report herein the results.

As mentioned above the synthesis of vinamidine in a direct method in high yield could not be carried out with excess use of aniline. We envisioned that the problem could be solved by the use of excess amounts of acid catalyst. The acid catalyst might improve the electrophilicity of the carbonyl carbon of enaminone intermediate 3 and also act as a template for the approach of aniline toward the protonated enaminone (Scheme 1).

Thus, we examined the reaction of cyclohexane-1,3-dione (1a) and aniline (2a, 2.0 equiv.) in the presence of p-TsOH (1.0 equiv.). As expected the corresponding vinamidinium salt 4a was isolated in high yield (94%, entry 2).7 The same experiment with 0.1 equiv. of p-TsOH gave trace amounts of 4a (6%) together with the enaminone 3a (66%) as the major product. As shown in Table 1, the reaction of 1a and 4-chloroaniline (2b) or 4-methoxyaniline (2c) showed similar pattern of reaction (entries 2 and 3). The use of dimedone (1b) showed same tendency as those of the cyclohexane-1,3-dione cases (entries 5 and 6). It is interesting to note that the use of picric acid instead of p-TsOH also produced the corresponding vinamidinium salt 4d in moderate yield (entry 4).

As mentioned before synthesis of salt free vinamidine itself (5a and 5b) could be carried out by the use of Et3N or...
Table 1. Synthesis of vinamidinium salts 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>p-TsOH (0.1 eq.), benzene, reflux, 22 h</td>
<td>1a, 2a = 1:2</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>p-TsOH (1 eq.), benzene, reflux, 22 h</td>
<td>1a, 2a = 1:2</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>p-TsOH (1 eq.), benzene, reflux, 10 h</td>
<td>1a, 2a = 1:2</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>p-TsOH (1 eq.), benzene, reflux, 22 h</td>
<td>1a, 2a = 1:2</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>p-TsOH (1 eq.), benzene, reflux, 34 h</td>
<td>1b, 2b = 1:2</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>p-TsOH (1 eq.), benzene, reflux, 22 h</td>
<td>1b, 2b = 1:2</td>
</tr>
</tbody>
</table>

NaOH from the corresponding vinamidinium salts 4a and 4b, for the removal of p-TsOH from 4a could be carried out with Et3N (52%). However, removal of p-TsOH from 4b was not efficient with Et3N, thus we used NaOH in this case (54%).

The UV spectra of some of the prepared compounds (4a, 4b, 4d, 5a) were determined and are shown in Figure 1. Most of the compounds have strong UV absorption in the region of 320-380 nm and have relatively large molar absorptivity (26,000-37,000). Further studies on the sunscreen effects of the vinamidinium salt are under progress.

Acknowledgments. This work was supported by the grant (R05-2003-000-10042-0) from the Basic Research Program of the Korea Science & Engineering Foundation.

References and Notes
7. Typical experimental procedure for the preparation of vinamidinium salt 4a: A stirred mixture of cyclohexane-1,3-dione (112 mg, 1 mmol), aniline (186 mg, 2 mmol), and p-toluenesulfonic acid (190 mg, 1 mmol) in benzene (10 mL) was heated to reflux for 22 h. After cooling to room temperature and removal of solvent the residue was dissolved in CH2Cl2 (3-4 drops of methanol was added in order to dissolve completely). After column chromatographic purification process (CH2Cl2/MeOH, 5:1) pure product 4a was obtained, 408 mg (94%). Other compounds were prepared analogously and the representative spectroscopic data of 4a, 4d, and 5a are summarized below.
8. 4a: 94%, brown solid; mp 182-184 °C; IR (KBr) 3444, 2970, 2927, −1570, 1539 cm−1; 1H NMR (CDCl3) δ 1.77 (br s, 2H), 2.31 (s, 3H), 2.74 (br s, 4H), 7.12-7.40 (m, 10H); 13C NMR (DMSO-d6) δ 21.59, 30.28, 93.86, 121.14, 122.37, 128.80, 145.86, 160.40; UV (MeOH) ε(340 nm) = 26,629.
9. 4d: 57%, yellow solid, mp 52-53 °C; IR (KBr) 3201, 3032, 2943, 2335, 2343, 2342, 262 (M+TsOH, 100). 4d: 57%, yellow solid, mp 52-53 °C; 1H NMR (CDCl3) δ 1.77 (br s, 2H), 2.31 (s, 3H), 2.74 (br s, 4H), 7.12-7.40 (m, 12H), 10.84 (s, 1H); UV (MeOH) λmax 36,725 (M+TsOH, 100). 5a: 52%, brown solid, mp 147-149 °C; IR (KBr) 3016, 2954, 2866, 1570, 1539 cm−1; 1H NMR (CDCl3) δ 1.93 (quintet, J = 6.0 Hz, 2H), 2.45 (t, J = 6.0 Hz, 4H), 4.44 (br s, 1H), 7.54 (s, 1H), 6.89-7.27 (m, 10H); 1H NMR (CDCl3) δ 77 (rel intensity) 77 (40), 130 (21), 143 (22), 233 (43), 234 (42), 262 (M+TsOH, 100). 5a: 52%, brown solid, mp 147-149 °C; IR (KBr) 3016, 2954, 2866, 1570, 1539 cm−1; 1H NMR (CDCl3) δ 1.93 (quintet, J = 6.0 Hz, 2H), 2.45 (t, J = 6.0 Hz, 4H), 4.44 (br s, 1H), 7.54 (s, 1H), 6.89-7.27 (m, 10H); 1H NMR (CDCl3) δ 77 (rel intensity) 77 (40), 130 (21), 143 (22), 233 (43), 234 (42), 262 (M+TsOH, 100).