Aromatization of 1,4-dihydropyridines with selenium dioxide

Xiao-hua Cai, Hai-jun Yang, and Guo-lin Zhang

Abstract: 1,4-Dihydropyridines were aromatized to corresponding pyridines using stoichiometric selenium dioxide at ambient temperature in a yield of 87%~98%.

Key words: 1,4-dihydropyridines, aromatization, oxidation, pyridine derivatives, selenium dioxide.

Introduction

1,4-Dihydropyridines are calcium antagonists (1), antitubercular agents (2), and neuro peptide Y Y1 receptor antagonists (3). They possess neuroprotective (4), platelet anti-aggregation (5), and antidiabetic (6) activities. Aromatization of 1,4-dihydropyridines has received considerable attention owing to the fact that 1,4-dihydropyridine-based calcium channel blockers are oxidatively converted to pyridine derivatives by the action of cytochrome P-450 in the liver (7). In addition, the corresponding pyridine derivatives show antihypoxic and antiischemic activities (8). 1,4-Dihydropyridines can easily be synthesized by Hantzsch condensation of aldehydes, β-keto esters, and ammonia or ammonium acetate (7b, 9). 1,4-Dihydropyridines have been aromatized to pyridines by various reagents such as KMnO4 (10), HNO3 (11), DDQ (12), NaNO2 (13), Zr(NO3)4 (14), Cu(NO3) (15), Bi(NO3)·5H2O (16), Mn(OAc)3 (17), (NH4)4Ce(NO3)6 (18), urea nitrate and K2S2O8-Co2+ (19), Pd/C (20), Pt(II) complex – hv (21), GSNO (22), and O2 – activated carbon (23). Despite these intensive efforts, most of the reported oxidation procedures require long reaction time, utilize strong oxidants in large excess, and afford products with only modest yields. In particular, the aromatization reaction with these reagents leads to dealkylation of the 4-position or formation of side products (11, 24). Therefore, the development of more effective methods for aromatization of 1,4-dihydropyridines is still necessary.

Selenium dioxide was widely used for the oxidation of a methylene group activated allylically or benzylically, or by an adjacent carbonyl group (25). Here, we wish to describe a simple and efficient procedure for the aromatization of 1,4-dihydropyridines with selenium dioxide at room temperature (Scheme 1).

Our initial attempts to aromatize 1,4-dihydropyridines (1a) as a test case in EtOH, CH3CN, or THF at ambient or thermal conditions led to corresponding pyridine 2a in very low yield (<40%). But the aromatization of 1a in acetic acid occurred smoothly to give the expected pyridine at room temperature in 96% yield. The success of this reaction prompted us to examine the aromatization of some 4-alkyl, aryl, and alkenyl 1,4-dihydropyridines under the same conditions. All reactions proceeded efficiently within 20~60 min to provide the corresponding pyridines in good yields (87%~98%, Table 1). With respect to the yields of the products, a 1:1 mol ratio of 1,4-dihydropyridines and selenium dioxide in H2OAc was optimal. The salient features for this procedure are milder reaction conditions, shorter reaction...
time, higher yield, avoidance of dealkylation or debenzyl-
ation at C-4, and stoichiometric oxidants used. Moreover,
this is a simple procedure for the separation of the products.

**Conclusion**

An efficient and simple procedure for the aromatization of
1,4-dihydropyridines to pyridine derivatives with stoichiometric selenium dioxide was developed.

**Experimental**

In a typical procedure, a mixture of 1a (165 mg, 0.5 mmol), selenium dioxide (66 mg, 0.5 mmol), and HOAc (4 mL) was stirred at room temperature for 30 min. After completion monitored by TLC, the reaction mixture was
quenched with a satd. aqueous NaHCO₃ solution and the red
solid selenium was filtered off. The filtrate was extracted
over anhydr. MgSO₄, and concentrated to give the pure prod-
uct 2a (156 mg, 96%), mp 63–65 °C (lit. value (14) mp 62
°C). Under similar conditions, various substituted 1,4-
dihydropyridines were converted to corresponding pyridines
(Table 1).

Table 1. Aromatization of 1,4-dihydropyridines to pyridines by SeO₂ at room temperature.

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>C₆H₅</td>
<td>30</td>
<td>96</td>
<td>63–65 (62 to 63 (14))</td>
</tr>
<tr>
<td>2b</td>
<td>H</td>
<td>20</td>
<td>97</td>
<td>71–72 (68 to 69 (14))</td>
</tr>
<tr>
<td>2c</td>
<td>Me</td>
<td>20</td>
<td>97</td>
<td>Yellow oil (liq (17))</td>
</tr>
<tr>
<td>2d</td>
<td>n-Propyl</td>
<td>40</td>
<td>92</td>
<td>Yellow oil (yellow oil (19))</td>
</tr>
<tr>
<td>2e</td>
<td>C₆H₅-CH₂</td>
<td>40</td>
<td>90</td>
<td>Yellow oil (liq (26))</td>
</tr>
<tr>
<td>2f</td>
<td>C₆H₅-CH=CH</td>
<td>50</td>
<td>96</td>
<td>162–164 (162 to 163 (17))</td>
</tr>
<tr>
<td>2g</td>
<td>4-F-C₆H₅</td>
<td>40</td>
<td>94</td>
<td>88–90</td>
</tr>
<tr>
<td>2h</td>
<td>4-Cl-C₆H₅</td>
<td>50</td>
<td>98</td>
<td>63–65 (65 to 66 (14))</td>
</tr>
<tr>
<td>2i</td>
<td>4-MeO-C₆H₅</td>
<td>20</td>
<td>95</td>
<td>55–57 (56–58 (19))</td>
</tr>
<tr>
<td>2j</td>
<td>4-HO-C₆H₅</td>
<td>40</td>
<td>94</td>
<td>172 to 173 (171–173 (17))</td>
</tr>
<tr>
<td>2k</td>
<td>2-NO₂-C₆H₅</td>
<td>60</td>
<td>89</td>
<td>72 to 73 (74–76 (27))</td>
</tr>
<tr>
<td>2l</td>
<td>2-Furyl</td>
<td>60</td>
<td>87</td>
<td>Yellow oil (liq (17))</td>
</tr>
<tr>
<td>2m</td>
<td>4-HO-3-MeO-C₆H₅</td>
<td>50</td>
<td>92</td>
<td>159 to 160</td>
</tr>
<tr>
<td>2n</td>
<td>4-MeO-3-OH-C₆H₅</td>
<td>30</td>
<td>95</td>
<td>140–142</td>
</tr>
<tr>
<td>2o</td>
<td>3,4-Cl₂-C₆H₅</td>
<td>40</td>
<td>94</td>
<td>63–65 (66–68 (28))</td>
</tr>
</tbody>
</table>

*All known compounds were characterized by comparing their spectral data with those reported.*

**Diethyl 2,6-dimethyl-4-(3-hydroxy-4-
methoxyphenyl)pyridine-3,5-dicarboxylate (2n)**

Yellow solid. IR (KBr, cm–1) νₘₐₓ: 3432, 3045, 2984,
2934, 1738, 1724, 1613, 1559, 1507, 1441, 1382, 1267,
1213, 1130, 1045, 1008, 862, 841, 815, 755, 706. ¹H NMR
(CDCl₃, 400 MHz) δₜₜ: 1.01 (t, 6H, J = 7.2 Hz), 2.59 (s, 6H),
3.86 (s, 3H, OCH₃), 4.06 (q, 4H, J = 7.2 Hz), 5.68 (br s, 1H,
OH), 6.74 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 6.77–6.79
(m, 2H). m/z (ESI): 396 (100%, [M + Na⁺]), 374 (100%,

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45, 1215, 1130, 1043, 1008, 866, 836, 757, 691. ¹H NMR
(CDCl₃, 400 MHz) δₜₜ: 1.01 (t, 6H, J = 7.2 Hz), 2.59 (s, 6H),
3.86 (s, 3H, OCH₃), 4.06 (q, 4H, J = 7.2 Hz), 5.68 (br s, 1H,
OH), 6.74 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 6.83–6.87
(m, 2H). m/z (ESI): 374 (100%, [M + 1]⁺).

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