Activated Carbon-Promoted Oxidative Aromatization of Hantzsch 1,4-Dihydropyridines and 1,3,5-Trisubstituted Pyrazolines Using Molecular Oxygen

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Abstract: In the presence of activated carbon, Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines were aromatized with molecular oxygen to the corresponding pyridines and pyrazoles in excellent yields.

Key words: activated carbon, aromatization, oxidations, pyridines, pyrazolines, heterocycles

Six- and five-membered heterocycles such as pyridine and pyrazole moieties are important constituents that exist in various bioactive compounds.1 The oxidation of Hantzsch 1,4-dihydropyridines, which can be easily synthesized by the reaction of aldehydes, β-keto esters, and ammonia, provides an efficient access to the corresponding pyridine derivatives. In fact, dihydropyridines have been aromatized to pyridines by various reagents such as HNO3,2 DDQ,3 NaNO2,4 (NH4)2Ce(NO3)6,5 Cu(NO3)2,6 Bi(NO3)⋅5H2O,7 Mn(OAc)3,8 and Zr(NO3)4.9 On the other hand, 1,3,5-trisubstituted pyrazolines have been readily prepared from chalcone derivatives and phenylhydrazine. Therefore, the aromatization of pyrazolines provides an easy access to pyrazole derivatives that also exhibit biological activities, including antipyretic, anticonvulsant, and analgesic properties.10 To oxidize 1,3,5-trisubstituted pyrazolines to the corresponding pyrazoles, several oxidants such as Pb(OAc)4,11 MnO2,12 HgO, 13 KMnO4,14 AgNO3,15 PhI(OAc)2,16 and Zr(NO3)4 have been employed.

Herein, we report a practical and environmentally friendly method for the preparation of pyridines and pyrazoles, which includes the oxidation of dihydropyridines and pyrazolines, respectively, with molecular oxygen in the presence of activated carbon (Darco® KB, Aldrich, Inc. or Shirasagi KL, Japan EnviroChemicals, Ltd.) in acetic acid or xylene (Scheme 1).

In the previous paper, we reported the Pd/C-promoted aerobic oxidative aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines which led to the formation of pyridines and pyrazoles, respectively.17 After that report, we found that the use of xylene as a solvent instead of acetic acid also exhibited high performance.18 The use of xylene as a solvent should be advantageous when acid-labile substituents exist in the substrate.

During the course of a further investigation, we discovered that activated carbon itself promoted the above oxidative aromatization. To promote the aromatization of Hantzsch 1,4-dihydropyridine to pyridine, the presence of activated carbon is crucial but palladium is not necessary.19 That is, the reaction proceeded by using only activated carbon without the palladium source. Treatment of diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (1) with 50% of activated carbon (Darco® KB) under an oxygen atmosphere at 120 °C in acetic acid for 30 min afforded the corresponding pyridine 7 in 84% yield (entry 1 in Table 1). The reaction proved to take place even at 50 °C (entry 4). This transformation proceeds smoothly in xylene20 as well as in acetic acid (120 °C, 3.5 h, 85%; 50 °C, 6 h, 88%; entries 2 and 6). Table 1 exemplifies the conversion of Hantzsch 1,4-dihydropyridines 1–6 possessing a variety of substituents such as H, Me, i-Pr, Ph, p-OH-C6H4, and p-NO2C6H4 at the 4-position to the corresponding pyridine derivatives 7–11. Two types of activated carbon were used in these transformations. One is Darco® KB, and the other is Shirasagi KL. When Hantzsch 1,4-dihydropyridines 1–6 were treated with 50 weight% of activated carbon under an oxygen atmosphere in acetic acid or xylene, the desired pyridines 7–11 were produced in excellent yields. The reactivity of Darco® KB and Shirasagi KL proved to be almost the same. It should be mentioned that among the 1,4-dihydropyridines we examined, substrates 1 and 3 exhibited high reactivity in particular. In each case, the reaction proceeded even without activated carbon (entries 3 and 15). It took less time using acetic acid compared to xylene as a solvent, nevertheless the yields were almost the same in both cases. The reaction of the Hantzsch 1,4-dihydropyridine 3 bearing an isopropyl group at the 4-position provided the de-alkylated...
pyridine 7 (entries 5, 6, 7, and 8). This phenomenon is consistent with that described in the previous reports.\textsuperscript{2,6,17}

Next, we applied the activated carbon–O\textsubscript{2} system to the aromatization of 1,3,5-trisubstituted pyrazolines to the corresponding pyrazoles (Table 2). This system also exhibited high performance in this transformation. That is, 1,3,5-trisubstituted pyrazolines 12–17 bearing a variety of substituents were treated with 50\% of activated carbon (Darco\textsuperscript{®} KB or Shirasagi KL) at 120 °C or 50 °C in acetic acid for 2–12 h to afford the corresponding pyrazoles 18–23 in high yields (77–91\% yield).\textsuperscript{21} It is clear that activated carbon promotes the conversion of pyrazolines to pyrazoles from the results of entries 2 and 3. At present, we assume that activated carbon would adsorb oxygen to accelerate the oxidation.

In conclusion, we have developed an extremely practical and facile method for the aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines with molecular oxygen promoted by activated carbon. This simple process is not only environmentally friendly but also economical and operationally simple. Only oxygen and readily available and inexpensive activated carbon are used. Neither metal oxides nor organic oxidizing agents are necessary. The synthetic application and mechanistic study of the present oxidations are now in progress in our laboratory.

All mps were measured on a Yanaco MP-500D and are uncorrected. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra (400 and 100.6 MHz, respectively), were recorded on a Jeol JNM-LA 400 or a Varian Unity Inova 400 instrument using Me\textsubscript{4}Si as the internal standard in CDCl\textsubscript{3}, IR spectra were measured on a Horiba FT-710 instrument. Elemental analyses were performed on a Yanaco CHN Corder MT-5. Mass spectra were measured on a Shimazu GCMS-QP 2000A instrument. Preparative column chromatography was carried out on foil plates with silica gel 60 F\textsubscript{254} (E. Merck; layer thickness 0.2 mm).

### Table 1 Oxidative Aromatization of Hantzsch 1,4-Dihydropyridines with Molecular Oxygen Promoted by Activated Carbon\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Activated carbon</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image 1" /></td>
<td>Darco\textsuperscript{®} KB</td>
<td>HOAc</td>
<td>120</td>
<td>0.5</td>
<td><img src="image2.png" alt="Image 2" /></td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image 3" /></td>
<td>Darco\textsuperscript{®} KB</td>
<td>xylene</td>
<td>120</td>
<td>3.5</td>
<td><img src="image4.png" alt="Image 4" /></td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Image 5" /></td>
<td>none</td>
<td>xylene</td>
<td>120</td>
<td>4</td>
<td><img src="image6.png" alt="Image 6" /></td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Image 7" /></td>
<td>Darco\textsuperscript{®} KB</td>
<td>HOAc</td>
<td>50</td>
<td>0.5</td>
<td><img src="image8.png" alt="Image 8" /></td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Image 9" /></td>
<td>none</td>
<td>HOAc</td>
<td>50</td>
<td>0.5</td>
<td><img src="image10.png" alt="Image 10" /></td>
<td>57 (42)\textsuperscript{c}</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Image 11" /></td>
<td>Darco\textsuperscript{®} KB</td>
<td>xylene</td>
<td>50</td>
<td>6</td>
<td><img src="image12.png" alt="Image 12" /></td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13.png" alt="Image 13" /></td>
<td>none</td>
<td>xylene</td>
<td>50</td>
<td>6</td>
<td><img src="image14.png" alt="Image 14" /></td>
<td>2 (95)\textsuperscript{c}</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15.png" alt="Image 15" /></td>
<td>Darco\textsuperscript{®} KB</td>
<td>HOAc</td>
<td>120</td>
<td>1</td>
<td><img src="image16.png" alt="Image 16" /></td>
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</tr>
<tr>
<td>9</td>
<td><img src="image17.png" alt="Image 17" /></td>
<td>Darco\textsuperscript{®} KB</td>
<td>xylene</td>
<td>120</td>
<td>4</td>
<td><img src="image18.png" alt="Image 18" /></td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td><img src="image19.png" alt="Image 19" /></td>
<td>none</td>
<td>xylene</td>
<td>120</td>
<td>24</td>
<td><img src="image20.png" alt="Image 20" /></td>
<td>56 (27)</td>
</tr>
<tr>
<td>11</td>
<td><img src="image21.png" alt="Image 21" /></td>
<td>Darco\textsuperscript{®} KB</td>
<td>xylene</td>
<td>50</td>
<td>36</td>
<td><img src="image22.png" alt="Image 22" /></td>
<td>65 (34)\textsuperscript{c}</td>
</tr>
<tr>
<td>12</td>
<td><img src="image23.png" alt="Image 23" /></td>
<td>Darco\textsuperscript{®} KB</td>
<td>HOAc</td>
<td>120</td>
<td>2</td>
<td><img src="image24.png" alt="Image 24" /></td>
<td>93</td>
</tr>
<tr>
<td>13</td>
<td><img src="image25.png" alt="Image 25" /></td>
<td>Shirasagi KL</td>
<td>HOAc</td>
<td>120</td>
<td>2</td>
<td><img src="image26.png" alt="Image 26" /></td>
<td>96</td>
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Aromatization of Hantzsch 1,4-Dihydropyridine in Acetic Acid

**Aromatization of Hantzsch 1,4-Dihydropyridine in Acetic Acid (Entry 1 in Table 1); Typical Procedure**

A mixture of 1,4-dihydropyridine 1 (270 mg, 1.07 mmol) and Darco® KB (135 mg) in HOAc (3.5 mL) was placed in a 100 mL three-necked flask under an oxygen atmosphere and stirred at 120 °C for 30 min. The reaction mixture was then filtered using Celite. The filtrate was then poured into sat. aq NaHCO₃ and extracted with EtOAc. After usual work-up, the obtained residue was column chromatographed (silica gel) to afford the corresponding pyridine 7.

Yield: 225 mg (84%); pale yellow solid.

**Aromatization of Hantzsch 1,4-Dihydropyridine in Xylene (Entry 18 in Table 1); Typical Procedure**

A mixture of 1,4-dihydropyridine 4 (240 mg, 0.80 mmol) and Darco® KB (120 mg) in xylene (3.5 mL) was placed in a 100 mL three-necked flask under an oxygen atmosphere and stirred at 120 °C for 5 h. The reaction mixture was then filtered using Celite. After the filtrate was concentrated, the product was isolated by column chromatography (silica gel) to afford the corresponding pyridine 9.
Yield: 235 mg (98%); pale yellow solid.

**Diethyl 2.6-Dimethyl-3,5-pyridinedicarboxylate (7)**

\( \text{Rf = 0.35 (hexane–EtOAc, 8:1); mp 71–72 °C (Lit.}\ \text{8 71 °C).} \)

**IR (KBr):** 2986, 2978, 2930, 2912, 1718, 1591, 1555, 1548, 1444, 1380, 1368, 1297, 1254, 1223, 1205, 1123, 1109, 1044, 1025, 771 cm\(^{-1}\).

**1H NMR:** \( \delta = 1.41 \) (t, 6 H, \( J = 7.3 \) Hz), 2.84 (s, 6 H), 4.40 (q, 4 H, \( J = 7.3 \) Hz), 8.67 (s, 1 H).

**13C NMR:** \( \delta = 14.3, 25.0, 61.4, 123.0, 140.9, 162.2, 165.9. \)

**MS:** \( m/z \) (relative intensity, %) = 251 (39.8), 206 (100), 195 (19.6), 178 (53.8), 150 (29.0), 106 (21.6).

**Diethyl 2.4,6-Trimethyl-3.5-pyridinedicarboxylate (8)**

\( \text{Rf = 0.24 (hexane–EtOAc, 6:1).} \)

**IR (KBr):** 2982, 2936, 2907, 2875, 1723, 1571, 1447, 1411, 1378, 1285, 1241, 1221, 1173, 1107, 1042, 938, 858, 837, 778, 569 cm\(^{-1}\).

**1H NMR:** \( \delta = 1.39 \) (t, 6 H, \( J = 7.3 \) Hz), 2.27 (s, 3 H), 2.52 (s, 6 H), 4.41 (q, 4 H, \( J = 7.3 \) Hz).

**13C NMR:** \( \delta = 14.0, 16.8, 22.8, 61.4, 127.4, 141.9, 154.7, 168.2. \)

**MS:** \( m/z \) (relative intensity, %) = 265 (31.4), 236 (45.9), 220 (100), 208 (43.2), 192 (25.9), 77 (34.5).

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**Table 2 Oxidative Aromatization of 1,3,5-Trisubstituted Pyrazolines with Molecular Oxygen Promoted by Activated Carbon**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Activated carbon</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
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<tr>
<td>1</td>
<td>Ph</td>
<td>Darco® KB</td>
<td>120</td>
<td>2.5</td>
<td>N.</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td></td>
<td>50</td>
<td>3.5</td>
<td>N.</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>none</td>
<td></td>
<td>50</td>
<td>3.5</td>
<td>13 (38)(^c)</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>Shirasagi KL</td>
<td></td>
<td>120</td>
<td>2</td>
<td>14</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>Darco® KB</td>
<td>120</td>
<td>2</td>
<td>15</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>50</td>
<td>5</td>
<td>78</td>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td>17</td>
<td>Shirasagi KL</td>
<td>120</td>
<td>2</td>
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<td>81</td>
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<td></td>
</tr>
<tr>
<td>11</td>
<td>22</td>
<td>Shirasagi KL</td>
<td>120</td>
<td>2</td>
<td>23</td>
<td>83</td>
</tr>
<tr>
<td>12</td>
<td>23</td>
<td>50</td>
<td>12</td>
<td>82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) All reactions were carried out using 50% of activated carbon in acetic acid under an oxygen atmosphere.

\(^{b}\) Isolated yield by column chromatography.

\(^{c}\) \(^{1}\)H NMR analysis. Value in parenthesis indicates the yield of recovered starting material.

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Diethyl 4-Phenyl-2,6-dimethyl-3,5-pyridinedicarboxylate (9)

RF = 0.24 (hexane–EtOAc, 2:1); mp 174–176 °C (Lit.9 171 °C).

IR (KBr): 2930, 2870, 2360, 1738, 1599, 1519, 1499, 1467, 1377, 1329, 1299, 1259, 1219, 1172, 1099, 1042, 861, 771, 755, 705 cm⁻¹.

1H NMR: δ = 1.00 (t, J = 7.3 Hz), 2.63 (s, 6 H), 4.06 (q, J = 7.3 Hz), 7.59 (br s, 1 H, OH), 7.1–7.3 (m, 4 H).

13C NMR: δ = 13.7, 22.6, 61.5, 115.2, 127.4, 128.0, 129.5, 146.0, 145.1, 155.1, 165.8, 168.2.

MS: m/z (relative intensity, %) = 327 (22.4), 282 (48.1), 254 (42.4), 236 (100), 209 (29.4), 139 (33.8).


Acknowledgment

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References

(18) For example, the aromatization of pyrazoline 12 in MeCN and EtOH produced the corresponding pyrazole 18 only in low yield (1–33% yield). In the case of dihydropyridine, the use of MeCN and EtOH as a solvent was also ineffective.
(19) (a) Recently, we reported that substituted 9,10-dihydroanthracenes were aromatized to anthracenes in xylene under oxygen in the presence of activated carbon: Mashraqui, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* 2003, 68, 8272. (b) We also reported that 2-arylbenzo-oxazoles were directly synthesized from substituted 2-amino-phenols and aldehydes by using activated carbon in xylene under oxygen: Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Chem.* 2003, 21, 3711.
(20) We used a mixture of o-, m-, and p-xylene.
(21) This conversion also proceeds efficiently in xylene instead of HOAc (for example, 81% yield for 7 h at 120 °C, for substrate 12).