Oxidative aromatization of Hantzsch 1,4-dihydropyridines using NaBrO$_3$/NaHSO$_3$

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Abstract
The oxidation of 1,4-dihydropyridines (DHPs) to the corresponding pyridine derivatives constitutes the principle metabolic route in biological systems, as well as a facile access to the corresponding pyridine derivatives. Herein, we report a new method for the oxidative aromatization of 1,4-DHPs using the combination of NaBrO$_3$ and NaHSO$_3$. Again the in situ generated HOBr from the reaction of NaBrO$_3$ and NaHSO$_3$ is expected to induce the dehydrogenation of 1,4-DHPs. © 2009 Trade Science Inc. - INDIA

Introduction
Hantzsch 1,4-dihydropyridine (DHP) structural subunit is contained in a growing number of synthetic and natural products with a wide range of biological properties[1]. For example, the 1,4-DHP derived drugs such as nifedipine (1), amlodipine (1), felodipine (3), nicardipine (4), nimodipine (5) and nitrendipine (6) are frequently used as cardiovascular agents (Ca$^{2+}$ channel blockers) for the treatment of hypertension and angina pectoris diseases[2]. The metabolism of these drugs involves an oxidative aromatization of 1,4-DHP nucleus to corresponding pyridine derivatives, which is catalyzed in the liver by cytochrome P-450[3]. The pyridine derivatives are then further metabolized leading to the cleavage of the ester groups[4]. In this respect, a convenient preparation of pyridines from 1,4-DHPs is important for the identification of metabolites[5].

Results and Discussion
Owing to the great biological and synthetic importance of 1,4-DHP, a plethora of protocols are available in the literature for the oxidative aromatization of 1,4-DHP derivatives. There oxidants are broadly classified into three categories: (a) transition metal based oxidants, (b) halogen derived oxidants, (c) other oxidants. Various transition metal based oxidants[6] reported in the literature includes CrO$_3$, CrO$_2$, Pyridinium chlorochromate (PCC), KMnO$_4$, Mn(OAC)$_3$, MnO$_2$, Mn(TPP)Cl/NaIO$_4$, Mn (III)- salophen/ NaIO$_4$, Fe(ClO$_4$)$_3$/AcOH, RuCl$_3$/O$_2$, Zr(NO$_3$)$_4$, (NH$_4$)$_2$Ce(NO$_3$)$_6$, Cu(NO$_3$)$_2$, Bi(NO$_3$)$_3$.5H$_2$O, Pb(OAc)$_2$, Co(OAc)$_2$.H$_2$O, Pd/C/AcOH. The halogen derived oxidants for the oxidative aromatization of 1,4-DHP are hypervalent iodine (III) reagents and I$_2$/MeOH[7]. The other oxidants are elemental sulfur under microwave conditions[8], HNO$_3$[9], nitric oxide, SeO$_2$[10], N$_2$O$_4$[11], and DDQ[12].

Present work
Oxidative aromatization of Hantzsch 1,4-dihydropyridine to the corresponding pyridine derivative is relevant to the biological NADH redox processes. This fact prompted us to examine this interesting oxidative aromatization of 1,4-DHP. Herein, we wish to report a novel combination of NaBrO$_3$ with NaHSO$_3$ for an efficient oxidative aromatization of Hantzsch 1,4-DHP (SCHEME 1)
TABLE 1: Optimizing the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>(1a)</th>
<th>NaBrO₃</th>
<th>NaHSO₃</th>
<th>Solvent</th>
<th>Reaction time (h)</th>
<th>Yield of (2a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 mmol</td>
<td>1 mmol</td>
<td>-</td>
<td>CH₃CN</td>
<td>10</td>
<td>00</td>
</tr>
<tr>
<td>2</td>
<td>1 mmol</td>
<td>1 mmol</td>
<td>-</td>
<td>CH₃CN-H₂O (3:2)</td>
<td>10</td>
<td>00</td>
</tr>
<tr>
<td>3</td>
<td>1 mmol</td>
<td>3 mmol</td>
<td>-</td>
<td>CH₃CN-H₂O (3:2)</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>1 mmol</td>
<td>1 mmol</td>
<td>1 mmol</td>
<td>CH₃CN-H₂O (3:2)</td>
<td>8</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>1 mmol</td>
<td>3 mmol</td>
<td>3 mmol</td>
<td>CH₃CN-H₂O (3:2)</td>
<td>7</td>
<td>84</td>
</tr>
</tbody>
</table>

*Refluxing conditions, †Isolated yields

TABLE 2: Oxidative aromatization of 1,4-dihydropyridines using NaBrO₃/NaHSO₃ combination in CH₃CN-H₂O system

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
<th>M. p. (°C) obs.</th>
<th>M. p. (°C) lit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C₆H₅</td>
<td>2a</td>
<td>8</td>
<td>83</td>
<td>60-62</td>
<td>63-64</td>
</tr>
<tr>
<td>b</td>
<td>4-MeOC₆H₄</td>
<td>2b</td>
<td>11</td>
<td>81</td>
<td>51-53</td>
<td>51-53</td>
</tr>
<tr>
<td>c</td>
<td>4-MeC₆H₄</td>
<td>2c</td>
<td>10</td>
<td>74</td>
<td>72-73</td>
<td>72-73</td>
</tr>
<tr>
<td>d</td>
<td>3,4-(MeO)₂C₆H₃</td>
<td>2d</td>
<td>13</td>
<td>78</td>
<td>89-91</td>
<td>-</td>
</tr>
<tr>
<td>e</td>
<td>4-ClC₆H₄</td>
<td>2e</td>
<td>10</td>
<td>83</td>
<td>66-68</td>
<td>65-67</td>
</tr>
<tr>
<td>f</td>
<td>3-NO₂C₆H₄</td>
<td>2f</td>
<td>12</td>
<td>80</td>
<td>61-63</td>
<td>62-64</td>
</tr>
<tr>
<td>g</td>
<td>4-NO₂C₆H₄</td>
<td>2g</td>
<td>13</td>
<td>76</td>
<td>112-114</td>
<td>114-115</td>
</tr>
<tr>
<td>h</td>
<td>2- furyl</td>
<td>2h</td>
<td>09</td>
<td>79</td>
<td>40-43</td>
<td>40-42</td>
</tr>
<tr>
<td>i</td>
<td>H</td>
<td>2i</td>
<td>12</td>
<td>71</td>
<td>69-70</td>
<td>69-70</td>
</tr>
<tr>
<td>j</td>
<td>C₆H₄CH₂</td>
<td>2j</td>
<td>10</td>
<td>75</td>
<td>70-71</td>
<td>70-71</td>
</tr>
<tr>
<td>k</td>
<td>n-C₆H₇</td>
<td>2k</td>
<td>11</td>
<td>72</td>
<td>Oil</td>
<td>Oil</td>
</tr>
<tr>
<td>l</td>
<td>n-C₆H₁₃</td>
<td>2l</td>
<td>13</td>
<td>77</td>
<td>Oil</td>
<td>Oil</td>
</tr>
</tbody>
</table>

*Isolated yields after chromatography

The oxidative aromatization of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1a) was chosen as a model substrate. The optimized reaction conditions were investigated by varying the quantity of oxidants as well as the solvents and the results are summarized in TABLE 1.

When 1 equivalent of (1a) was refluxed with 1 equivalent NaBrO₃ in CH₃CN (15 mL), the oxidation of (1a) did not occur and all the starting material was quantitatively recovered. This result is in contrast with the well known oxidizing capacity of NaBrO₃ in various oxidation reactions. The above failure was partially attributed to the complete insolubility of NaBrO₃ in CH₃CN. Therefore, we again examined the oxidation of (1a) (1 mmol) with NaBrO₃ (1 mmol) in CH₃CN-H₂O system in 3:2 v/v proportion. However, the oxidation of (1a) was again failed to produce (2a) in any appreciable yield. Excess of NaBrO₃ (3 equiv. with respect to (1a) also did not influence the outcome of oxidative aromatization of (1a). Thus, NaBrO₃ alone does not induce oxidative aromatization of 1,4-DHP. Based upon the literature report of NaBrO₃ in combination with NaHSO₃ for a variety of oxidative transformations, we then examined the same for oxidation of (1a). It was observed that the addition of NaHSO₃ (1 mmol) to the solution of (1a) (1 mmol) and NaBrO₃ (1 mmol) in CH₃CN-H₂O (3:2 v/v proportion) resulted in the formation of (2a) in 57% yield. However, the addition of excess of NaBrO₃ (3 mmol) and NaHSO₃ (3 mmol) to (1a) (1 mmol) in CH₃CN-H₂O increased the oxidation yield of (1a) to 84%. These experiments proved that NaBrO₃ in combination with NaHSO₃ in CH₃CN-H₂O solvent system transforms 1,4-DHP to the corresponding pyridine derivatives in excellent yields.

The potential scope of this method was investigated by subjecting various alkyl, aryl and heterocyclic Hantzsch 1,4-DHP under the above reaction conditions and the results are summarized in TABLE 2. 1,4-DHP with both aliphatic and aromatic substituents at 4-position underwent smooth oxidative aromatization. The aryl moiety at 4-position having different groups at dif-
different positions did not show much differences in the yields of the products. Heterocyclic moiety such as furan at 4-position of 1,4-DHP also underwent the facile transformation.

**Reaction mechanism**

The tentative mechanism of the reaction is depicted in SCHEME 2. The reaction of NaBrO$_3$ with NaHSO$_3$ will generate hypobromous acid (HOBr) (3) which is an active source of electrophilic bromine. Hantzsch 1,4-DHP (4) will then react with electrophilic hypobromous acid to form the intermediate (5) involving N-Br bond formation. Finally, the concomitant oxidative aromatization of (5) will take place by the elimination of hydrogen at 4-position to form the product (6).

**Spectral analysis**

IR spectra were recorded on a Shimadzu FTIR-1710 spectrophotometer.

The $^1$H NMR spectra were recorded on 400 MHz instrument and the chemical shifts were reported with TMS as an internal standard. The representative spectral analysis for few of the products is given below:

(i) **Diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (2a)**

Yellow solid, M. p. 60-62°C (Lit.$^{12b}$ M. p. 63-64°C); IR (KBr cm$^{-1}$): 3026, 2983, 2937, 1735, 1701, 1685, 1556, 1290, 862, 754, 700; $^1$H NMR (CDCl$_3$): $\delta = 0.82$ (t, J = 7.12 Hz, 6H, 2CH$_3$), 2.53 (s, 6H, 2CH$_3$), 3.92 (q, J = 7.16 Hz, 4H, 2OCH$_2$), 7.18 (m, 2H, ArH), 7.29 (m, 3H, ArH); LCMS (M + 1): m/z = 328.

(ii) **Diethyl 2,6-dimethyl-4-(3,4-dimethoxyphenyl)pyridine-3,5-dicarboxylate (2d)**

Yellow solid, M. p. 89-91°C; IR (KBr, cm$^{-1}$): 3004, 2985, 2902, 2833, 1721, 1560, 1508, 1255, 1143, 1028, 862, 755, 669; $^1$H NMR (CDCl$_3$): $\delta = 1.02$ (t, J = 7.16 Hz, 6H, 2CH$_3$), 2.61 (s, 6H, 2CH$_3$), 3.84 (s, 3H, OCH$_3$), 3.91 (s, 3H, OCH$_3$), 4.05 (q, J = 7.12 Hz, 4H, 2OCH$_2$), 6.81-6.87 (m, 2H, ArH), 7.17 (d, J = 8.44 Hz, 2H, ArH); LCMS (M + 1): m/z = 342.

(iii) **Diethyl 2,6-dimethyl-4-p-tolylpyridine-3,5-dicarboxylate (2c)**

Yellow solid, M. p. 72-73°C (Lit.$^{12b}$ M. p. 72-73°C); IR (KBr, cm$^{-1}$): 3022, 2982, 2872, 1732, 1560, 1236, 1107, 1043, 756, 667; $^1$H NMR (CDCl$_3$): $\delta = 0.96$ (t, J = 7.12 Hz, 6H, 2CH$_3$), 2.17 (s, 3H, ArCH$_3$), 2.60 (s, 6H, 2CH$_3$), 4.03 (q, J = 7.16 Hz, 4H, 2OCH$_2$), 7.13 (d, J = 8.44 Hz, 2H, ArH), 7.17 (d, J = 8.24 Hz, 2H, ArH); LCMS (M + 1): m/z = 342.

(iv) **Diethyl 2,6-dimethyl-4-(4-chlorophenyl)pyridine-3,5-dicarboxylate (2e)**

Yellow solid, M. p. 66-68°C (Lit.$^{12b}$ M. p. 65-67°C); IR (KBr, cm$^{-1}$): 3007, 2983, 2938, 1732, 1643, 1561, 1236, 1107, 758, 669; $^1$H NMR (CDCl$_3$): $\delta = 0.98$ (t, J = 7.12 Hz, 6H, 2CH$_3$), 2.17 (s, 3H, ArCH$_3$), 2.60 (s, 6H, 2CH$_3$), 4.03 (q, J = 7.12 Hz, 4H, 2CH$_2$), 7.13 (d, J = 8.44 Hz, 2H, ArH), 7.31 (d, J = 8.52 Hz, 2H, ArH); LCMS (M + 1): m/z = 364.

(v) **Diethyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate (2f)**

Yellow solid, M. p. 61-63°C (Lit.$^{12b}$ M. p. 62-64°C); IR (KBr, cm$^{-1}$): 3084, 2985, 2935, 1734, 1716, 1558, 1236, 1047, 860, 738; $^1$H NMR (CDCl$_3$): $\delta = 1.01$ (t, J = 8 Hz, 6H, 2CH$_3$), 2.63 (s, 6H, 2CH$_3$), 4.07 (q, J = 7.04 Hz, 4H, 2CH$_2$), 7.61 (m, 2H, ArH), 8.19 (s, 1H, ArH), 8.26 (m, 1H, ArH); LCMS (M + 1): m/z = 373.

**EXPERIMENTAL**

General procedure for the oxidative aromatization of 1,4-DHP using NaBrO$_3$/NaHSO$_3$ reagent:

To a solution of NaBrO$_3$ (6 mmol) in water (12 mL) was added the 1,4-DHP (2 mmol) in acetonitrile (20 mL) followed by the drop wise addition of a solution of NaHSO$_3$ (6 mmol) over a period of about 15-30 min. The mixture was then refluxed for 7-20 hours. The reaction mixture was poured in to 40 mL of CH$_2$Cl$_2$.
After separation of the organic phase, the aqueous layer was extracted twice with CH$_2$Cl$_2$. The combined organic layer was washed with anhydrous Na$_2$SO$_4$ solution and dried over anhydrous sodium sulphate. After filtration, the dichloromethane was removed in vacuum and the residue was purified by column chromatography (silica gel, petroleum ether: ethyl acetate =10:1) to give aromatized pyridine product.

**CONCLUSION**

The oxidative aromatization of 1,4-diarylpyridines using NaBrO$_3$/NaHSO$_3$ reagent offers following notable advantages: (a) a transition-metal free protocol, (b) utilization of aqueous medium in combination with CH$_2$CN, (c) less toxic effect, (d) no dealkylation at 4-position of 1,4-DHP in case of alkyl substituents, (e) good yields of the products, (f) an added entry in the novel applications of NaBrO$_3$/NaHSO$_3$ reagent. In conclusion, a transition metal free oxidative aromatization of Hantzsch 1,4-DHPs was achieved efficiently under almost neutral conditions, by using NaBrO$_3$/NaHSO$_3$ in combination with NaHSO$_3$.

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