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CuBr catalyzed aerobic oxidative coupling of 2-aminopyridines with cinnamaldehydes: Direct access to 3-formyl-2-phenyl-imidazo[1,2-a]pyridines

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Copper bromide catalyzed aerobic oxidative coupling of 2-aminopyridines with cinnamaldehyde, directly produced 3-formyl 2-phenyl-imidazo[1,2-a]pyridines. The quantum chemical calculations were performed to trace the reaction mechanism and get insights on the possible reaction pathway. 2-Aminopyridines on coupling with cinnamaldehyde generates (E)-3-phenyl-3-(pyridin-2-ylamino)acrylaldehyde IV as a key intermediate which undergoes C-N bond formation reaction to produce 3-formyl-2-phenyl-imidazo[1,2-a]pyridines.

Introduction

Nitrogen heterocycles are known to possess diverse range of pharmacological activities.1 Imidazo[1,2-a]pyridine is one of the medicinally important N-heterocycle2 and is a pharmacophore of several drugs including zolpidem, alpidem (anxiolytics),3 and GSK-812397 (anti-HIV) (Figure 1).3 Furthermore, the radiiodinated imidazo[1,2-a]pyridines have been used for in-vivo SPECT imaging of amyloid-β deposition in mice model of Alzheimer’s disease.5

Figure 1. Structures of drugs containing 3-substituted imidazo[1,2-a]pyridine pharmacophore

The synthesis of anxiolytic drugs zolpidem and alpidem requires 3-formyl imidazo[1,2-a]pyridine as one of the key intermediate.

There are several reports on the synthesis of imidazo[1,2-a]pyridines,6 however, the direct access to 3-formyl 2-aryl imidazo[1,2-a]pyridines 3 is somewhat limited. There are only three reports in the literature, which are summarized in Figure 2. These include (a) [Cu(hfacac)]:ηH2O catalyzed cyclization of N-(1-phenylallyl)-2-aminopyridine in DMF,7 (b) two-step approach involving first formation of imidazo[1,2-a]pyridines from 2-aminopyridine and phenacyl bromide, followed by Vilsmeier-Haack formylation,8 (c) Cu-catalyzed selective C-3 formylation of imidazo[1,2-a]pyridine using DMSO.9 Chioya et al.10 reported a silver catalyzed cycloisomerization of N-(prop-2-yn-1-yl) pyridine-2-amines leading to formation of non-aryl substituted 3-formyl imidazo[1,2-a]pyridines 3.

Recently Hajra and coworkers11 have reported synthesis of 3-arylimidazo[1,2-a]pyridines via Cu(OAc)2-catalyzed oxidative coupling of 2-aminopyridines with chalcones. Herein, we have successfully developed a CuBr catalyzed aerobic oxidative coupling of 2-aminopyridines with cinnamaldehydes to produce 3-formyl imidazo[1,2-a]pyridines 3. The major drawbacks of earlier reports are: (a) preparation of starting material is somewhat difficult1 (b) synthesis required more than single step1; (c) high reaction temperature1; and (d) use of expensive silver triflate catalyst.10 The present method utilizes commercially available starting materials 1a and 2a that requires less expensive CuBr catalyst. The plausible reaction mechanism based on the quantum chemical calculations has also been proposed.
Results and discussion

The study was initiated with preliminary reaction of 2-aminopyridine 1a with cinnamaldehyde 2a in the presence of various catalysts in an air atmosphere and under heating condition. The use of acid catalysts such as triflic acid or TFA did not produce desired product (Table 1, entries 1-2). Next, we screened various other catalysts such as molecular iodine (entry 3), Pd(OAc)₂ (entries 4-6), Fe catalysts (entries 7-8), Co catalysts (entries 9-10) and Cu catalysts (entries 11-14). Except copper catalysts (entries 11-14), no other catalyst produced desired product 3a. CuSO₄ and CuCl₂ produced moderate yields (25-30%) of product 3a; however CuBr produced excellent yield (90%) in ethanol as a solvent at 60 °C reaction temperature. This condition (entry 14) was chosen for further experiments. Reaction does not proceed in the case of a control experiment involving CuBr in ethanol under inert atmosphere (in nitrogen atmosphere), indicating the role of air in the reaction.

<table>
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<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>% yield</th>
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<td>1</td>
<td>Triflic acid (100)</td>
<td>EtOH</td>
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<tr>
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<tr>
<td>3</td>
<td>I₂ (10)</td>
<td>Ethanol</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂ (10)</td>
<td>Acetic acid</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂ (10)</td>
<td>Chlorobenzene</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)₂ (10)</td>
<td>Dioxane</td>
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<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Fe(OAc)₂ (10)</td>
<td>Dioxane</td>
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<td>FeCl₃ (10)</td>
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<td>14</td>
<td>CuBr (10)</td>
<td>EtOH</td>
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</table>

With the optimized reaction conditions in hand, the utility of this approach was investigated for coupling of various substituted 2-aminopyridines and cinnamaldehydes. As shown in Scheme 1, various substituted 2-aminopyridines were well tolerated in the reaction. 2-Aminopyridines with electron-donating groups such as 3-methyl, 5-methyl (examples 3c, 3e, 3f, 3h, 3i, 3k, 3l, 3m), as well as electron-withdrawing groups such as Cl (example 3b) participated well in the reaction. The reaction also worked well with cinnamaldehydes substituted with electron-donating groups (e.g. methoxy – examples 3g, 3h, 3i), as well as electron-withdrawing groups (e.g. Br, Cl, NO₂ – examples 3d, 3e, 3f, 3j, 3k, 3l) producing corresponding 3-formyl-2-phenyl-imidazo[1,2-a]pyridines in good yields. Next, we investigated the scope of this reaction for crotonaldehyde (aliphatic enal); however reaction does not proceeded.

On the basis of the results obtained above, we proposed a plausible reaction mechanism for coupling of 2-aminopyridines and cinnamaldehydes as illustrated in Scheme 2, and verified its feasibility using quantum chemical analysis (B3LYP/6-311+G(d,p)). The reaction may undergo the following steps. The first step involves a coupling of a 2-aminopyridine 1a and cinnamaldehyde 2a to produce the Michael addition intermediate I. This step is slightly endoergic with a Gibbs free energy difference (ΔG) of 12.1 kcal/mol. The intermediate I in the presence of copper catalyst loose a hydrogen radical and generate a radical intermediate II with HBr and CuO as side products. This step is highly endoergic and requires free energy of 144.5 kcal/mol. The radical intermediate II further looses one hydrogen radical to give neutral imine intermediate III. Formation of III from II is highly exoergic (109.0 kcal/mol). The imine III then equilibrates to enamine IV, which is more stable by 3.9 kcal/mol. Similarly, H-radical abstraction from intermediate IV in the presence of copper catalyst generates a radical V, which is endoergic by 112.8 kcal/mol. The radical V undergoes 1,3-H shift and cyclize to give an intermediate VI which is stable by 5.1 kcal/mol. Finally, intermediate VI looses one more hydrogen radical to give the product 3a. This step is exoergic by 126.6 kcal/mol.
The formation of Cu₂O as a byproduct in the reaction was also supported by experimental observations. The initial green color of the reaction was changed to red at the completion (after 8 h), indicating the conversion of CuBr (green) to Cu₂O (red).

Scheme 2. Plausible mechanism for the preparation of 3-formyl-2-phenyl-imidazo[1,2-a]pyridine 3a. The Gibbs free energy values at each step are given in kcal/mol.

Conclusions

In conclusion, we have successfully developed a copper (II) catalyzed aerobic oxidative coupling of 2-aminopyridines with cinnamaldehydes for one-pot synthesis of 3-formyl-2-phenyl-imidazo[1,2-a]pyridines. Developed method is operationally simple and could be used efficiently for the preparation of biologically important drugs. This may also serve as an excellent method for C-N bond formation to study its scope in other reactions.

Experimental Section

General. All chemicals were obtained from Sigma-Aldrich Company and used as received. ¹H, ¹³C and DEPT NMR spectra were recorded on Brucker-Avance DPX FT-NMR 500 and 400 MHz instruments. Chemical data for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent (CDCl₃, 7.26 ppm). Carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded at 125 MHz or 100 MHz: chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent (CDCl₃, 77 ppm). ESI-MS and HRMS spectra were recorded on Agilent 1100 LC-Q-TOF and HRMS-6540-UHD machines. IR spectra were recorded on Perkin-Elmer IR spectrophotometer. Melting points were recorded on digital melting point apparatus.

General procedure for synthesis of imidazo[1,2-a]pyridine carbaldehydes (3a-3m). To the mixture of 2-aminopyridine (1.0 equiv.) and cinnamaldehyde (1.2 equiv.) in ethanol was added 10 mol% CuBr and reaction mixture was stirred at 60 °C for 8 h.

After completion of the reaction (monitored by TLC), the reaction mixture was filtered using Whatman paper. The filtrate was dried on rotovapor and was then extracted between water ethyl acetate. EtOAc layer was dried over anhydrous sodium sulphate and evaporated on vacuo rotovaper to get crude product.

The crude product was purified by silica gel (#100-200) column chromatography using n-hexane and EtOAc as an eluent to get pure products 3a-m in 70-90% yield.

2-Phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde (3a).¹² Yellow solid; m.p. 122-123 °C; ¹H NMR (CDCl₃, 400 MHz): δ 10.07 (s, 1H), 9.68 (d, J = 8.0 Hz, 1H), 7.85-7.81 (m, 2H), 7.76 (d, J = 8.0 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 179.7, 158.4, 147.8, 132.3, 130.5, 129.9, 128.9, 128.8, 128.0, 117.5, 115.4; IR (CHCl₃): νmax 2924, 1646, 1634, 1494, 1407, 1326, 1248 cm⁻¹; ESI-MS: m/z 223.00 [M+H⁺]; HR-ESIMS: m/z 223.0878 calc for C₁₃H₁₀N₂O⁺H⁺ (223.0866).

7-Chloro-2-phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde (3b).¹² Yellow solid; m.p. 149-150 °C; ¹H NMR (CDCl₃, 400 MHz): δ 10.07 (s, 1H), 9.75 (s, 1H), 7.85-7.81 (m, 2H), 7.76 (d, J = 12.0 Hz, 1H), 7.56-7.53 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz): δ 179.8, 158.4, 146.0, 131.9, 131.6, 130.1, 129.8, 129.0, 126.8, 123.5, 120.8, 117.7; IR (CHCl₃): νmax 2921, 1641, 1406, 1018 cm⁻¹; ESI-MS: m/z 256.90 [M+H⁺]; HR-ESIMS: m/z 257.0471 calc for C₁₃H₁₁N₂O⁺H⁺ (257.0476).

8-Methyl-2-phenyl-imidazo[1,2-a]pyridine-3-carbaldehyde (3ε).¹² Yellow solid; m.p. 169-170 °C; ¹H NMR (CDCl₃, 400 MHz): δ 10.04 (s, 1H), 9.53 (d, J = 8.0 Hz, 1H), 7.85 (dd, J = 4.0, 8.0 Hz, 2H), 7.53 (m, 3H), 7.39 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 2.73 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 179.6, 158.0, 148.0, 132.7, 130.0, 129.7, 129.4, 128.7, 127.6, 126.5, 121.2, 115.2, 115.3, 17.0; IR (CHCl₃): νmax 2925, 1638, 1409, 1018 cm⁻¹; ESI-MS: m/z 236.90 [M+H⁺]; HR-ESIMS: m/z 237.1005 calc for C₁₃H₁₁N₂O⁺H⁺ (237.1022).

2-(4-Bromophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde (3d).¹² Yellow solid; m.p. 175-176 °C; ¹H NMR (CDCl₃, 400 MHz): δ 10.05 (s, 1H), 9.67 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 12.0 Hz, 1H), 7.73 (dd, J = 8.0, 16.0 Hz, 4H), 7.61 (t, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 178.6, 156.5, 147.3, 131.7, 130.7, 130.1, 128.4, 124.1, 117.0, 115.0; IR (CHCl₃): νmax 2912, 2852, 1730, 1636, 1400, 1257, 1210 cm⁻¹; ESI-MS: m/z 300.90 [M+H⁺]; HR-ESIMS: m/z 300.9980 calc for C₁₃H₁₁BrN₂O⁺H⁺ (300.9971).

2-(4-Bromophenyl)-6-methylimidazo[1,2-a]pyridine-3-carbaldehyde (3ε): Pale yellow solid; m.p. 167-168 °C; ¹H NMR (CDCl₃, 400 MHz): δ 10.01 (s, 1H), 9.48 (s, 1H), 7.72-7.68 (m, 5H), 7.47 (dd, J = 4.0, 8.0 Hz, 1H), 2.46 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 179.0, 156.8, 146.7, 133.6, 132.1, 131.5, 131.2, 126.9, 125.8, 124.4, 120.5, 116.7, 18.4; IR (CHCl₃): νmax 2924, 2843, 1726, 1633, 1420, 1256, 809 cm⁻¹; ESI-MS: m/z 314.80 [M+H⁺]; HR-ESIMS: m/z 315.0130 calc for C₁₃H₁₂BrN₂O⁺H⁺ (315.0128).

2-(4-Chlorophenyl)-6-methylimidazo[1,2-a]pyridine-3-carbaldehyde (3f).³ Yellow solid; m.p. 167-168 °C; ¹H NMR (CDCl₃, 400 MHz): δ 10.01 (s, 1H), 9.48 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 179.1, 156.8, 146.7, 136.1, 133.6, 131.0, 129.2, 126.9, 125.8, 120.5, 116.7, 18.4; IR (CHCl₃): νmax 3436, 1633, 1413, 1020 cm⁻¹; ESI-MS: m/z 271.06 [M+H⁺]; HR-ESIMS: m/z 271.0600 calc for C₁₃H₁₂ClN₂O⁺H⁺ (271.0633).
2-(4-Methoxyphenyl)imidazo[1,2-a]pyridine-3-carbaldehyde (3g). White solid; m.p. 171-172 °C; 1H NMR (CDCl3, 400 MHz): δ 10.06 (s, 1H), 9.67 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 3H), 7.55 (t, J = 8.0 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 3.89 (s, 3H); 13C NMR (CDCl3, 100 MHz): δ 179.6, 161.1, 158.4, 147.8, 131.2, 130.5, 128.9, 124.8, 120.5, 117.2, 115.1, 114.4, 55.5; IR (CHCl3): vmax 3436, 2918, 2850, 1733, 1634, 1409, 1253, 1215 cm⁻¹; ESI-MS: m/z 253.10 [M+H⁺]; HR-ESIMS: m/z 253.1000 calc'd for C13H12N2O2+H⁺ (253.0972).

6-Methyl-2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde (3m): Yellow sticky solid; 1H NMR (CDCl3, 400 MHz): δ 10.70 (s, 1H), 9.48 (s, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.51 (s, 3H), 7.45 (d, J = 8.0 Hz, 1H), 2.44 (s, 3H); 13C NMR (CDCl3, 100 MHz): δ 179.6, 158.1, 146.6, 133.4, 132.3, 129.9, 129.8, 128.9, 126.8, 125.7, 120.5, 116.6, 18.4; IR (CHCl3): vmax 3436, 2924, 1724, 1594, 1442, 1275, 1018 cm⁻¹; ESI-MS: m/z 237.20 [M+H⁺]; HR-ESIMS: m/z 237.2020 calc'd for C12H12N2O+H⁺ (237.2102).

DFT studies. Density functional (DFT) analysis was carried out to explore the reaction mechanism for CuBr catalyzed synthesis of 3-formyl-2-phenylimidazo[1,2-a]pyridines from 2-aminopyridine and cinemaldehyde. The GAUSSIAN09 suite of programs was used to carry out the geometry optimization of all the structures on the possible reaction mechanism pathways and to estimate the Gibbs free energy values at each step. Complete optimizations without any symmetry constraints were carried out using Becke–Lee–Yang–Parr (B3LYP) method with the 6-311+G(d,p) basis set. Same basis set was used to analytically compute frequencies to characterize the stationary points to minima and the transition states. Each transition state is first-order saddle point with only one imaginary vibrational mode on the potential energy surface.

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Notes and Reference