BCl3-Mediated C–N, C–S, and C–O Bond Formation of Imidazo[1,2-a]pyridine Benzylic Ethers

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ABSTRACT: An efficient BCl3-mediated reaction of imidazo[1,2-a]pyridines has been developed for the C–N, C–S, and C–O bond formation. The salient features of this method correspond to the substitution of different nucleophiles via in situ unconventional debenzylation. The developed process is applicable for the synthesis of a wide variety of ((3-amino/thio/alkoxy)-methyl)-imidazo[1,2-a]pyridines.

INTRODUCTION

Substituted imidazopyridines represent an important class of fused heterocyclic compounds owing various pharmacological properties.1 Their analogues have been successfully used for pharmaceutical chemistry as well as in materials science.2 Marketed drugs like alpidem3, zolpidem,4 nicopidem and saripidem,5 minodronic acid,6 and optically active GSK812397 drug7 are derived from the imidazo[1,2-a]pyridine scaffold (Figure 1).8

Figure 1. Imidazo[1,2-a]pyridine-derived drugs.

The construction of new C–N,9 C–S,10 and C–O11 bonds into organic molecules is highly appreciable in modern chemistry. Although in recent times a variety of substitutions on imidazopyridines have been made, there are no reports pertaining to a general approach for the synthesis of different C–X bonds at the C-3 methylene position of imidazo[1,2-a]pyridines. Recently, Hajra and group have presented the aminomethylation of imidazo-heterocycles with morpholine using (diacetoxyiodo)benzene, and Kumar et al. approached the synthesis by using N-methyl-morpholine oxide, which acts as a coupling partner as well as the oxidant.12 Both of these strategies, however, suffer from limitations in the context of (a) use of morpholine as only amine, (b) not a general C–X bond approach, (c) requirement of halo-substituted imidazopyridines as starting materials, (d) harsh reaction conditions, and (e) low atom economy. In this context, we developed a BCl3-mediated general C–X bond formation method around imidazopyridines that involve nucleophilic substitution reactions with a diverse array of amines, thiols, and alcohols at the C-3 methylene position (Scheme 1).

Figure 1. Imidazo[1,2-a]pyridine-derived drugs.

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N/S/O nucleophiles that helped to generate different valuable carbon heterobonds.

**RESULTS AND DISCUSSION**

We commenced our study with 3-((benzyloxy)methyl)-2-phenylimidazo[1,2-a]pyridine 1 (1.0 equiv) as the model substrate to find out the optimized reaction conditions as summarized in Table 1. Initially, the reaction was performed using BCl₃ (1 equiv) and piperidine (1 equiv) in dry dichloromethane (DCM) at −78 °C under a nitrogen atmosphere for 2 h. Under these conditions, 2a was isolated in 12% yield (Table 1, entry 1). Considering the gradual decrease in molarity of BCl₃ solution over time due to high volatility of BCl₃, 1.4 equiv of BCl₃ was used, an improvement in yield (32%) of the desired product 2a (entry 2) was noticed.¹⁶

Following improvised yield of 2a, the reaction conditions particularly the change in the concentration of amine and variation in temperature were explored (entries 3–12). Primarily, screening of our reaction at different concentrations of amine against 1 was performed (entry 3 and 4), and the best result was observed with 3 equiv of amine (entry 4). In continuation, various reactions were conducted at different temperatures (entries 5–6). The reaction executed at 0 °C produced better yield as compared to reaction at 20 °C, indicating that 0 °C is an optimal temperature for this transformation. Further, in the absence of Lewis acid, no reaction was observed (entry 7). Subsequently, boron catalysts BF₃·O(C₂H₅)₂ and BB₃ were also investigated in the presence of 3 equiv of piperidine (entries 8–10) at −78 °C and 0 °C, but BCl₃ was found most appropriate in terms of yield (entry 5). Also, no product was observed in the case of AlCl₃ (entry 12). Finally, the use of BCl₃ (1.4 equiv) and amine (3 equiv) at 0 °C to room temperature (rt) under nitrogen was found to be the optimized reaction condition (entry 3).

With these optimized reaction conditions in hand, the scope of the C3-methylene amination was demonstrated by testing a wide variety of cyclic, acyclic, and aromatic amines. We were pleased to find that in all tested reactions, the desired C3-aminomethylated-imidazo[1,2-a]pyridines (Table 2, entries 2a–2x) were produced in good yields (68–88%). 3-((Benzoyloxy)methyl)-2-phenylimidazo[1,2-a]pyridine 1 reacted efficiently with piperidine and morpholine, giving the corresponding product 2a and 2c in 80 and 74% yields, respectively, and pyrrolidine yielded product 2e with comparable yield (70%). The presence of the electron-donating methyl group on imidazo[1,2-a]pyridines improved the yield to 82% (entries 2b and 2d). Reaction with aniline furnished product 2f in excellent yield (86%). Besides C2-phenyl substitution, the scope and generality of the reaction was also investigated on C2 alkenylated and alkynated imidazo[1,2-a]pyridines further for amination, and these groups were well tolerated and afforded the products (entries 2g–2j) in good yield (68–79%). In addition, different experiments were performed between 2-iodo-imidazo[1,2-a]pyridines and various amines to afford the desired products (entries 2h–2x). In this case, yields were also good for all the reactions conducted irrespective of the nature of amine (Table 2). Reaction with piperidine (entry 2m, 83% yield) and morpholine (entry 2o, 76%) proceeded very smoothly and comparatively more reactive than pyrrolidine (entry 2l, 75% yield). The presence of the methyl group on imidazo[1,2-a]pyridines further enhanced the yield up to 87% (entry 2n) and chloro-substitution slightly decreased the yield (entry 2x, 72%). Aniline and benzylamine were also checked and afforded products 2s and 2t in excellent yields (80 and 88%, respectively). The use of alkyne as a triazole precursor encouraged us to perform reaction with propargyl amine and furnished the desired product 2u in 87% yield without any difficulties. The reaction was also compatible with the secondary amine diethylamine (entries 2q and 2r) as well as the primary amine n-propyl amine (entry 2w, 82% yield), while in the case of hexamethylene diamine (2v), an inseparable mixture was obtained. In general, we observed that irrespective of the nature of imidazopyridines and amines, all of the tested

Table 1. Optimization of the Reaction Conditions

| entry | Lewis acid (equiv) | amine (equiv) | T [°C] | yields* of 2a [%] |
|-------|------------------|--------------|-------|------------------|
| 1     | BCl₃ (1)         | 1            | −78   | 12               |
| 2     | BCl₃ (1.4)       | 1            | −78   | 32               |
| 3     | BCl₃ (1.4)       | 2            | −78   | 54               |
| 4     | BCl₃ (1.4)       | 3            | −78   | 77               |
| 5     | BCl₃ (1.4)       | 3            | 0     | 80               |
| 6     | BCl₃ (1.4)       | 3            | 20    | 43               |
| 7     | BCl₃ (1.4)       | 3            | 0     | 0                |
| 8     | BF₃·O(C₂H₅)₂ (1.4) | 3            | −78   | 28               |
| 9     | BF₃·O(C₂H₅)₂ (1.4) | 3            | 0     | 40               |
| 10    | BB₃ (1.4)        | 3            | −78   | 0                |
| 11    | BB₃ (1.4)        | 3            | 0     | 18               |
| 12    | AlCl₃ (1.4)      | 3            | 0     | 0                |

*General conditions: 1 (0.3 mmol), Lewis acid (0.3 mmol), and piperidine (0.3 mmol), in DCM at −78 °C under N₂ for 2 h. ‡Isolated yield.
reactions were efficiently transformed to desired products within 2 h.

To investigate the practicability of this method, another set of experiments were performed between imidazopyridine 1 and thiols under the optimized reaction conditions and yields were generally good for all tested reactions (entries 3a–3l) (Table 3). Various substituted aromatic and aliphatic thiols proceeded well in this process. 2-Mercaptopyridine smoothly underwent reaction with 1, affording the desired product 3a in 68% yield. Additionally, the electron-donating group on the aromatic ring of thiophenol enhances the yield of the desired product (entries 3b–3c). Reaction with n-octyl mercaptan (entry 3d) afforded the desired compound in good yield (64%). Moreover, 2-alkenyl (entry 3e) and alkynyl (entry 3f) substitution on 1 dropped the yield to 68 and 63%, respectively. Importantly, mono- and dihalogen-substituted thiophenols (entry 3i and 3j) worked well, thus providing an opportunity for additional modifications of products. Notably, 2-iodo-substituted imidazo[1,2-a]pyridine 1 was also a good substrate for this reaction system (entries 3g–3l).

Next, we extended the method for the generation of different C–O bonds by treating different imidazo[1,2-a]pyridine 1 with different aliphatic alcohols as per the earlier optimal conditions and successfully isolated different products (entries 4a–4j) in good yield (60–80%, Table 4). As evident, despite change in the substitutions of 1, we isolated the desired products in moderate to good yield (60–80%). However, reactions with 2-iodo substitutions (entries 4e–4i) produced slightly better yields (68–80%). Furthermore, in these set of reactions, the change in the aliphatic alcohols as the coupling partner did not show a predominant effect in the reaction competence. We successfully isolated the desired products with

Table 2. C3-Methylene Amination of Imidazo[1,2-a]pyridines

| Reaction conditions: 1 (0.3 mmol), BCl3 (0.42 mmol), and R3R3NH (0.9 mmol), in DCM at 0 °C to rt under N2 for 2 h. | b Isolated yield. |

| Reaction number | Structure | Yield (%) |
|----------------|----------|-----------|
| 2a             | ![Structure](image1) | 80%       |
| 2b             | ![Structure](image2) | 82%       |
| 2c             | ![Structure](image3) | 74%       |
| 2d             | ![Structure](image4) | 78%       |
| 2e             | ![Structure](image5) | 70%       |
| 2f             | ![Structure](image6) | 85%       |
| 2g             | ![Structure](image7) | 71%       |
| 2h             | ![Structure](image8) | 76%       |
| 2i             | ![Structure](image9) | 68%       |
| 2j             | ![Structure](image10) | 79%       |
| 2k             | ![Structure](image11) | 72%       |
| 2l             | ![Structure](image12) | 75%       |
| 2m             | ![Structure](image13) | 83%       |
| 2n             | ![Structure](image14) | 87%       |
| 2o             | ![Structure](image15) | 76%       |
| 2p             | ![Structure](image16) | 81%       |
| 2q             | ![Structure](image17) | 68%       |
| 2r             | ![Structure](image18) | 75%       |
| 2s             | ![Structure](image19) | 80%       |
| 2t             | ![Structure](image20) | 88%       |
| 2u             | ![Structure](image21) | 72%       |

"Reaction conditions: 1 (0.3 mmol), BCl3 (0.42 mmol), and R3R3NH (0.9 mmol), in DCM at 0 °C to rt under N2 for 2 h. b Isolated yield."
most of the alcohols tested. However, we observed the best yields when reactions were conducted with methanol (entries 4a, 4b, 4e, 4f, and 4j) and also found that increase in alkyl chain length of alcohol (entries 4g, 4h, and 4i) and C-5 bromo substitution slightly decreased the yield.

On the basis of our observation and previous reports,18 a plausible mechanism is proposed in Scheme 2. Probably, at the first step, 3-((benzyloxy)methyl)-2-phenylimidazo[1,2-a]pyridine 1 forms a complex with BCl₃. This complex converts into intermediate A (supported by mass spectra) through aza-directed electronic delocalization. Subsequently, the intermediate A is readily coupled with nucleophiles to afford the desired compounds 2/3/4.

**CONCLUSIONS**

In summary, BCl₃-mediated methodologies around imidazo[1,2-a]pyridines for the generation of different C−N, C−S, and C−O bonds through an in situ debenzylation are presented. The reaction demonstrated a broad substrate scope and excellent functional group tolerance at mild reaction conditions. These methods furnished a wide variety of 3-amino/thio/alkoxy 2-iodo-imidazo[1,2-a]pyridines in good yields and are perhaps ascertained because of aza-directed unusual coupling with different nucleophiles.

**EXPERIMENTAL SECTION**

**General Information.** All reactions and purity of the synthesized compounds were monitored by Merck thin-layer chromatography (TLC) using silica gel 60 F254 aluminum plates (20 × 20 cm). Visualization was accomplished by UV spectrometry at 254 nm light and exposure to iodine vapors. Buchi rotavapor was used for concentration of organic solvents. Column chromatographic purifications were performed on silica gel (100−200 mesh) for compound purification. ¹H and ¹³C NMR spectra in CDCl₃ were recorded with 400 and 500 MHz NMR instruments, respectively, using (CH₃)₄Si as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm, scale) referenced to the residual solvent (i.e., ¹H 7.24 ppm and ¹³C 77.1 ppm for CDCl₃). MestReNova software was used to process NMR spectra. Signal multiplicity is expressed as follows: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), and m.
General Procedure for C3-Methylene C–N Bond Formation of Imidazo[1,2-a]pyridine (2a). In a round-bottom flask, 3-((benzylxoy)methyl)-2-phenylimidazo[1,2-a]pyridine 1 (0.3 mmol) was dissolved in dry DCM (2 mL) at 0 °C under a nitrogen atmosphere. A BCl3 solution (1.0 M in methylene chloride) (0.42 mmol) was slowly added, and complex formation was confirmed by TLC. After that, temperature of reaction was increased up to rt and an amine (0.9 mmol) was added and stirred for 2 h (reaction progress was monitored by TLC). After completion, the reaction was quenched by water to stop the reaction. The aqueous solution was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na2SO4, and evaporated in vacuum. The residue was purified by a column (silica gel, 80/20 n-hexane/ethyl acetate) to give the desired product.

2-Phenyl-3-(piperidin-1-ylmethyl)imidazo[1,2-a]pyridine (2a). Yield: (70 mg, 80%); 1H NMR (400 MHz, CDCl3): δ 8.56 (d, J = 6.8 Hz, 1H), 7.83 (d, J = 7.2 Hz, 2H), 7.67 (d, J = 9.0 Hz, 1H), 7.50–7.47 (m, 2H), 7.41–7.38 (m, 1H), 7.29–7.23 (m, 1H), 6.87–6.84 (m, 1H), 4.02 (s, 2H), 2.48 (br s, 4H), 1.59 (dt, J = 10.7, 5.4 Hz, 4H), 1.47 (d, J = 4.6 Hz, 2H); 13C NMR (126 MHz, CDCl3): δ 145.08 (C), 134.51 (C), 128.93 (CH), 128.48 (CH), 127.75 (CH), 125.71 (CH), 124.72 (CH), 117.12 (CH), 111.91 (CH), 54.07 (CH2), 52.06 (CH2), 18.54 (CH3). ESI-HRMS (m/z): calcd for C18H20N3O [M + H]+, 294.1605; found, 294.1606.

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(400 MHz, CDCl₃): δ 8.02 (s, 1H), 7.58 (dd, J = 6.5, 3.1 Hz, 2H), 7.47 (d, J = 9.3 Hz, 2H), 7.36 (dd, J = 5.1, 1.8 Hz, 2H), 7.09 (dd, J = 9.2, 1.1 Hz, 1H), 3.92 (s, 2H), 3.71–3.68 (m, 4H), 2.54–2.52 (m, 4H), 2.37 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 144.39 (C), 132.17 (C), 132.07 (C), 131.90 (C), 131.63 (CH), 128.53 (CD), 128.44 (CD), 128.37 (CD), 123.03 (C), 122.28 (CH), 116.83 (CH), 92.77 (C), 82.66 (C), 66.92 (CH₃), 53.50 (CH₂), 52.00 (CH₂), 18.43 (CH₃). ESI-HRMS (m/z): calcd for C₂₁H₂₃N₃O [M + H]⁺, 332.1763; found, 332.1755.

6-Methyl-2-(phenylethyl)-3-(piperidin-1-ylmethyl)imidazo[1,2-alpyridine (2j). Yield: (78 mg, 76%); ¹³C NMR (400 MHz, CDCl₃): δ 8.81 (s, 1H), 7.84 (dd, J = 9.2 Hz, 1H), 7.36 (dd, J = 5.1, 1.8 Hz, 2H); ³¹P NMR (400 MHz, CDCl₃): δ 8.64 (d, J = 2.5 Hz, 1H), 7.04 (d, J = 3.1 Hz, 1H), 3.89 (s, 2H), 2.47 (br s, 2H), 2.37 (s, 3H), 1.70 (m, 4H), 1.50 (br s, 2H); ¹¹B NMR (200 MHz, CDCl₃): δ 8.44 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 9.1 Hz, 1H), 7.20–7.14 (m, 1H), 6.78 (t, J = 6.8 Hz, 1H), 3.89 (s, 2H), 2.55 (q, J = 6.9 Hz, 4H), 1.05 (t, J = 7.1 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 147.29 (C), 128.40 (C), 127.75 (CH), 116.54 (CH), 112.01 (CH), 95.29 (C), 48.35 (CH₂), 46.34 (CH₃), 11.50 (CH₃). ESI-HRMS (m/z): calcd for C₂₂H₂₄B₁N₂ [M + H]⁺, 385.0416; found, 385.0403.

N-Ethyl-(2-idoanilidemidazo[1,2-alpyridine (2k). Yield: (87 mg, 80%); ¹³C NMR (400 MHz, CDCl₃): δ 8.81 (s, 1H), 7.48–7.45 (m, 4H), 7.28–7.25 (m, 2H), 7.04 (d, J = 9.2 Hz, 1H), 3.87 (s, 2H), 2.61–2.56 (m, 4H), 2.35 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H); ¹³C NMR (10 MHz, CDCl₃): δ 146.59 (C), 128.10 (CH), 122.10 (CH), 121.99 (C), 121.04 (C), 116.12 (CH), 95.56 (CH), 53.26 (CH), 53.05 (CH₂), 18.35 (CH₃). ESI-HRMS (m/z): calcd for C₂₃H₂₂IN₂O [M + H]⁺, 398.0462; found, 398.0461.

N-(2-idoanilidemidazo[1,2-alpyridine (2l). Yield: (93 mg, 80%); ¹³C NMR (400 MHz, CDCl₃): δ 8.81 (s, 1H), 7.44–7.41 (m, 4H), 7.28–7.25 (m, 2H), 7.04 (d, J = 9.1 Hz, 1H), 3.87 (s, 2H), 2.61–2.56 (m, 4H), 2.35 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H); ¹³C NMR (10 MHz, CDCl₃): δ 146.59 (C), 128.10 (CH), 122.10 (CH), 121.99 (C), 121.04 (C), 116.12 (CH), 95.56 (CH), 53.26 (CH), 53.05 (CH₂), 18.35 (CH₃). ESI-HRMS (m/z): calcd for C₂₃H₂₂IN₂O [M + H]⁺, 398.0462; found, 398.0461.
N-((2-Phenylimidazo[1,2-a]pyridin-3-yl)methyl)propan-1-amine (2w). Yield: (65 mg, 82%); 1H NMR (400 MHz, CDCl3): δ 8.43 (d, J = 6.8 Hz, 1H), 7.76 (d, J = 7.4 Hz, 2H), 7.65 (d, J = 9.0 Hz, 1H), 7.50–7.47 (m, 2H), 7.41 (d, J = 7.2 Hz, 1H), 7.26–7.22 (m, 1H), 6.88–6.85 (m, 1H), 4.30 (s, 2H), 2.69 (t, J = 7.1 Hz, 2H), 1.58–1.53 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); 13C NMR (101 MHz, CDCl3): δ 144.38 (C), 134.40 (C), 128.80 (CH), 128.62 (CH2), 128.55 (C), 127.87 (C), 124.98 (CH), 124.81 (CH), 117.29 (CH), 112.15 (CH), 111.80 (CH), 51.03 (CH2), 46.32 (CH3), 22.60 (CH3), 11.68 (CH3). ESI-HRMS (m/z): calc for C19H16N4 [M + H]+, 306.1657; found, 306.1643.

6-Chloro-2-ido-3-(piperidin-1-yl)methylimidazo[1,2-a]pyridine (2x). Yield: (81 mg, 72%); 1H NMR (400 MHz, CDCl3): δ 8.37 (s, 1H), 7.78 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 9.5 Hz, 1H), 7.53–7.49 (m, 2H), 7.45 (d, J = 6.8 Hz, 1H), 7.34 (d, J = 9.5 Hz, 1H), 4.88 (s, 2H), 3.47 (s, 3H); 13C NMR (126 MHz, CDCl3): δ 145.66 (C), 126.13 (CH), 123.08 (C), 122.61 (CH), 120.47 (C), 116.91 (CH), 96.06 (C), 54.25 (CH2), 53.52 (CH2), 25.88 (CH2), 24.29 (CH2). ESI-HRMS (m/z): calc for C19H15ClN3 [M + H]+, 327.0767; found, 327.0763.

General Procedure for C3-Methylene C–S Bond Formation of Imidazo[1,2-a]pyridine (3). A solution of 3-(benzoxyl) methyl)-2-phenylimidazo[1,2-a]pyridine (0.3 mmol) in dry DCM (2 mL) was stirred at 0 °C under a nitrogen atmosphere. BCl3 solution (1.0 M in methylene chloride) (0.42 mmol) was slowly added, and complex formation was confirmed by TLC. Then, reaction was transferred to rt and a solution of an organosulfur in DCM (0.9 mmol) was added, and reaction was continuously stirred for 2 h (reaction progress was monitored by TLC). After completion, the reaction was quenched by water to stop the reaction. The aqueous solution was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine, dried over anhydrous Na2SO4, and evaporated in vacuum. The residue was purified by a column (silica gel, 80/20 n-hexane/ethyl acetate) to give the desired product 3.

2-Phenyl-3-(piperidin-2-ylthio)methylimidazo[1,2-a]pyridine (3a). Yield: (65 mg, 68%); 1H NMR (400 MHz, CDCl3): δ 8.37 (s, 1H), 7.78 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 9.5 Hz, 1H), 7.53–7.49 (m, 2H), 7.45 (d, J = 6.8 Hz, 1H), 7.34 (d, J = 9.5 Hz, 1H), 4.88 (s, 2H), 3.47 (s, 3H); 13C NMR (126 MHz, CDCl3): δ 145.66 (C), 126.13 (CH), 123.08 (C), 122.61 (CH), 120.47 (C), 116.91 (CH), 96.06 (C), 54.25 (CH2), 53.52 (CH2), 25.88 (CH2), 24.29 (CH2). ESI-HRMS (m/z): calc for C19H15ClN3 [M + H]+, 327.0767; found, 327.0763.

6-Methyl-2-styryl-3-(p-tolylthio)methyl)imidazo[1,2-a]pyridine (3e). Yield: (56 mg, 64%); 1H NMR (400 MHz, CDCl3): δ 7.74 (s, 1H), 7.49 (d, J = 9.1 Hz, 1H), 7.44–7.37 (m, 3H), 7.34–7.30 (m, 2H), 7.24 (d, J = 7.2 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.08 (dd, J = 9.2, 1.4 Hz, 1H), 7.01 (d, J = 7.9 Hz, 2H), 6.55 (d, J = 15.8 Hz, 1H), 4.34 (s, 3H), 2.36 (s, 3H), 2.13 (s, 3H); 13C NMR (101 MHz, CDCl3): δ 144.61 (C), 142.27 (C), 138.71 (C), 137.43 (C), 130.07 (CH), 130.35 (CH), 130.30 (C), 129.88 (CH), 128.48 (CH), 128.26 (CH), 127.45 (CH), 126.55 (CH), 121.67 (C), 121.34 (CH), 117.82 (CH), 116.95 (C), 116.50 (CH), 29.80 (CH3), 20.90 (CH3), 18.37 (CH3). ESI-HRMS (m/z): calc for C24H23N2S [M + H]+, 371.1582; found, 371.1583.

6-Methyl-2-(phenylthiethyl)-3-(p-tolylthio)methyl)imidazo[1,2-a]pyridine (3f). Yield: (56 mg, 63%); 1H NMR (400 MHz, CDCl3): δ 7.80 (s, 1H), 7.48–7.45 (m, 3H), 7.35–7.33 (m, 3H), 7.21 (d, J = 8.1 Hz, 2H), 7.09 (dd, J = 9.2, 1.3 Hz, 1H), 6.99 (d, J = 7.9 Hz, 2H), 4.43 (s, 3H), 2.36 (s, 3H), 2.20 (s, 3H); 13C NMR (101 MHz, CDCl3): δ 145.54 (C), 138.02 (C), 132.97 (CH), 132.17 (C), 131.62 (CH), 130.15 (C), 129.81 (CH), 128.39 (C), 128.33 (CH), 128.24 (CH), 125.58 (C), 123.02 (C), 122.51 (CH), 121.61 (CH), 117.04 (CH), 95.42 (C), 92.53 (C), 29.53 (CH3), 20.99 (CH3), 18.40 (CH3), 14.06 (CH2). ESI-HRMS (m/z): calc for C24H23N2S [M + H]+, 371.1582; found, 371.1583.
2-Iodo-6-methyl-3-((p-tolylthio)methyl)imidazo[1,2-alpyridine (3h). Yield: (92 mg, 78%); 1H NMR (400 MHz, CDCl3): δ 7.78 (s, 1H), 7.44 (d, J = 9.2 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 7.9 Hz, 3H), 4.27 (s, 2H), 2.33 (s, 3H), 2.30 (s, 3H); 13C NMR (101 MHz, CDCl3): δ 146.30, 138.39, 133.71, 129.83, 126.89, 127.82, 122.35, 121.52, 121.39, 116.34, 95.50 (C), 30.81 (CH2), 21.15 (CH3), 18.31 (CH3). ESI-HRMS (m/z): calcd for C14H13N3S[M + H]+, 398.0079; found, 395.9911.

3-((2,6-Dichlorophenyl)thio)methyl)-2-iodo-6-methylimidazo[1,2-alpyridine (3i). Yield: (107 mg, 80%); 1H NMR (400 MHz, CDCl3): δ 7.94 (s, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.31 (d, J = 7.8 Hz, 2H), 7.21 (dd, J = 8.7, 7.3 Hz, 1H), 7.07 (dd, J = 9.2, 1.5 Hz, 1H), 4.33 (s, 2H), 2.40 (s, 3H); 13C NMR (101 MHz, CDCl3): δ 146.49 (C), 142.67 (C), 130.98 (CH), 128.68 (CH), 128.04 (CH), 122.52 (C), 121.61 (CH), 120.73 (C), 116.31 (CH), 95.06 (C), 29.25 (CH2), 18.38 (CH3). ESI-HRMS (m/z): calcd for C14H13ClIN5S[M + H]+, 448.9143; found, 448.9142.

3-((3-Fluorophenyl)thio)methyl)-2-iodo-6-methylimidazo[1,2-alpyridine (3j). Yield: (87 mg, 73%); 1H NMR (400 MHz, CDCl3): δ 6.79 (s, 1H), 7.45 (d, J = 9.2 Hz, 1H), 7.18 (dd, J = 7.9, 5.5 Hz, 2H), 7.05 (d, J = 9.2 Hz, 1H), 6.90 (t, J = 8.4 Hz, 2H), 4.24 (s, 2H), 2.36 (s, 3H); 13C NMR (101 MHz, CDCl3): δ 164.43 (C), 146.35 (C), 136.45 (CH), 136.37 (CH), 127.96 (CH), 122.55 (C), 121.33 (CH), 121.03 (C), 116.44 (CH), 116.29 (CH), 116.07 (CH), 97.53 (C), 31.10 (CH2), 18.32 (CH3). ESI-HRMS (m/z): calcd for C14H12F3IN4S[M + H]+, 398.9828; found, 398.9932.

3-(Hexylthio)methyl)-2-iodo-6-methylimidazo[1,2-alpyridine (3k). Yield: (86 mg, 74%); 1H NMR (400 MHz, CDCl3): δ 7.88 (s, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.04 (dd, J = 9.2, 1.4 Hz, 1H), 4.00 (s, 2H), 2.40–2.35 (m, 5H), 1.58–1.50 (m, 2H), 1.34–1.20 (m, 6H), 0.84 (t, J = 6.9 Hz, 3H); 13C NMR (101 MHz, CDCl3): δ 146.50 (C), 127.90 (CH), 122.32 (C), 121.67 (CH), 116.36 (CH), 94.83 (C), 31.39 (CH2), 31.29 (CH2), 29.68 (CH2), 28.52 (CH2), 25.66 (CH2), 22.51 (CH2), 18.35 (CH2), 14.00 (CH3). ESI-HRMS (m/z): calcd for C14H15IN4S[M + H]+, 369.0548; found, 381.0539.

2-Iodo-6-methyl-3-((pyridin-2-ylthio)methyl)imidazo[1,2-alpyridine (3l). Yield: (87 mg, 76%); 1H NMR (400 MHz, CDCl3): δ 8.52 (d, J = 4.9 Hz, 1H), 8.05 (s, 1H), 7.51–7.49 (m, 1H), 7.42 (d, J = 9.2 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 7.04 (dd, J = 7.2, 5.1 Hz, 1H), 6.99 (d, J = 9.2 Hz, 1H), 4.82 (s, 2H), 2.28 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 157.67 (C), 149.32 (CH), 146.33 (C), 136.31 (CH), 127.82 (CH), 122.85 (CH), 122.32 (C), 122.12 (CH), 121.69 (C), 120.14 (CH), 116.24 (CH), 95.16 (C), 24.73 (CH3), 18.32 (CH3). ESI-HRMS (m/z): calcd for C14H13IN3S[M + H]+, 381.9875; found, 381.9863.

General Procedure for C3-Methylene C–O Bond Formation of Imidazo[1,2-alpyridine (4). A solution of 3-(benzoxyl)methyl)-2-phenylimidazo[1,2-alpyridine (0.3 mmol) in dry DCM (2 mL) was stirred at 0 °C under a nitrogen atmosphere. BCl3 solution (1.0 M in methylene chloride) (4.0 mmol) was slowly added, and the mixture was stirred at ambient temperature for 2 h. The mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography over silica gel, and the product was further purified by recrystallization. The purified product was characterized by 1H and 13C NMR, MS, and elemental analysis. Yield: (58 mg, 70%); 1H NMR (400 MHz, CDCl3): δ 7.92 (s, 1H), 7.58 (dd, J = 6.5, 3.1 Hz, 2H), 7.48 (d, J = 9.2 Hz, 1H), 7.36–7.34 (m, 3H), 7.11 (dd, J = 9.2, 1.5 Hz, 1H), 4.89 (s, 2H), 3.36 (s, 3H), 2.35 (s, 3H); 13C NMR (101 MHz, CDCl3): δ 144.60 (C), 131.69 (CH), 128.97 (CH), 128.82 (C), 128.52 (CH), 128.36 (CH), 122.91 (C), 122.82 (C), 121.97 (CH), 116.93 (CH), 92.72 (C), 82.33 (C), 62.98 (CH3), 57.43 (CH3), 18.28 (CH3). ESI-HRMS (m/z): calcd for C18H17N3O[M + H]+, 277.1341; found, 277.1326.

Yield: (72 mg, 80%); 1H NMR (400 MHz, CDCl3): δ 7.92 (s, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.06 (dd, J = 9.2, 1.4 Hz, 1H), 4.73 (s, 2H), 3.31 (s, 3H), 2.34 (s, 3H); 13C NMR (101 MHz, CDCl3): δ 144.60 (C), 131.69 (CH), 128.97 (CH), 128.82 (C), 128.52 (CH), 128.36 (CH), 122.91 (C), 122.82 (C), 121.97 (CH), 116.93 (CH), 92.72 (C), 82.33 (C), 62.98 (CH3), 57.43 (CH3), 18.28 (CH3). ESI-HRMS (m/z): calcd for C18H17N3O[M + H]+, 277.1341; found, 277.1326.
NMR (101 MHz, CDCl3): δ 146.75 (C), 128.51 (CH), 122.70 (C), 121.86 (C), 121.72 (CH), 116.29 (CH), 95.87 (CH), 64.14 (CH2), 57.35 (CH2), 18.22 (CH3). ESI-HRMS (m/z): calcd for C13H18INO[M + H]+, 345.0464; found, 345.0465.

3-(Ethoxymethyl)-2-ido-6-methylimidazo[1,2-alpyridine (4g). Yield: (65 mg, 69%); 1H NMR (400 MHz, CDCl3): δ 7.96 (s, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.06 (dd, J = 9.2, 1.6 Hz, 1H), 4.78 (s, 2H), 3.53–3.47 (m, 2H), 2.35 (s, 3H), 1.20 (t, J = 7.0 Hz, 3H); 13C NMR (101 MHz, CDCl3): δ 146.55 (C), 128.40 (CH), 122.60 (C), 122.33 (C), 121.73 (CH), 116.28 (CH), 95.48 (CH), 65.05 (CH2), 62.34 (CH2), 18.22 (CH3), 15.07 (CH3). ESI-HRMS (m/z): calcd for C10H12IN2O[M + H]+, 302.9994; found, 302.9953.

Notes

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