Article

Synthesis of Triazolo[4′,5′:4,5]furo[2,3-c]pyridine via Post Modification of an Unusual Groebke−Blackburn−Bienaymé Multicomponent Reaction

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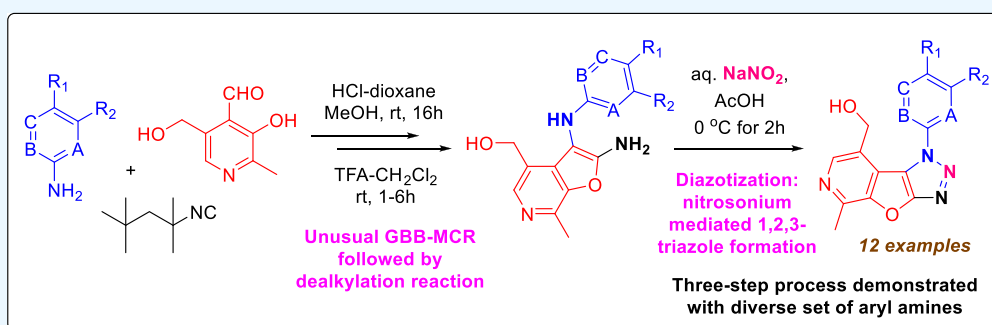
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ABSTRACT: The Groebke−Blackburn−Bienaymé (GBB) reaction is a well-established three-component reaction for synthesizing imidazofused scaffolds from heterocyclic amidines, aldehydes, and isonitriles. However, the replacement of pyridoxal as an aldehyde component in this reaction results in the formation of the furo[2,3-c]pyridine skeleton as an "unusual GBB product". Despite the interesting nature of this unusual reaction, not much work was further reported. The present research investigates the optimization strategy for the synthesis of novel tricyclic triazolo[4′,5′:4,5]furo[2,3-c]pyridines via diazotization of 2,3-diamino-furo[2,3-c]pyridines specifically synthesized utilizing the chemistry of tert-alkyl isocyanide.

INTRODUCTION

Groebke−Blackburn−Bienaymé reaction (GBB reaction) is one of the isocyanide-based multicomponent reactions (MCRs) involving acid-catalyzed condensation of 2-aminoazines, aldehydes, and isonitriles, first reported in 1998.[1−3] The 25 golden years of GBB reaction produced over 250 research articles and numerous patents demonstrating wonderful results not only in the field of chemistry but also in the area of biological and material sciences.[4−7] The GBB three-component chemistry was very much used by medicinal chemists in their quest to design novel ligands due to its easy and one-pot synthetic strategy and potential to easily diversify the scaffold with multiple functionalities, resulting in success with multiple FDA approvals. Recently, we demonstrated an undergraduate laboratory experiment wherein GBB-MCR-derived products were synthesized via in situ generated isocyanides from N-formylamines.[8] The diverse fused heterocycles generated via GBB reaction include bicyclic imidazo[1,2-a]pyridine, imidazo-[1,2-a]pyrimidine, imidazo[1,2-a]pyrazine, imidazo[2,1-b]-thiazole, imidazo[2,1-b][1,3,4]thiadiazole, imidazo[1,2-b]-[1,2,4]triazole, imidazo[1,2-b]pyrazol, and imidazo[2,1-b]-oxazole.[9−14] Various polycyclic scaffolds (1−11, Figure 1) are also synthesized via post modification of the GBB-derived

products.[3,15] Recently, we demonstrated that the one-pot-derived GBB products can be elaborated to fused polycyclic heterocycles (12−14) involving Pictet−Spengler cyclization (Figure 1).[16]

In recent past, on replacement of pyridoxal as an aldehyde component in the GBB reaction, Salunke et al. accidently observed the formation of 2,3-diamino-furo[2,3-c]pyridine as an unusual GBB product (Figure 2).[17] It was predicted that the reaction of pyridoxal and 2-aminopyridine furnished the Schiff base, which underwent cyclization involving a phenolic hydroxyl group instead of the desired pyridine nitrogen, resulting in furo[2,3-c]pyridines.
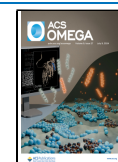
Morkovnik and co-workers also reported the synthesis of the furo[2,3-c]pyridine scaffold but via base-catalyzed cyclization of pyridoxal with acylmethyl halides and halomethylheteroarenes. The 2-acyl- and 2-heteroarylfuro[2,3-c]pyridines[18] synthesized
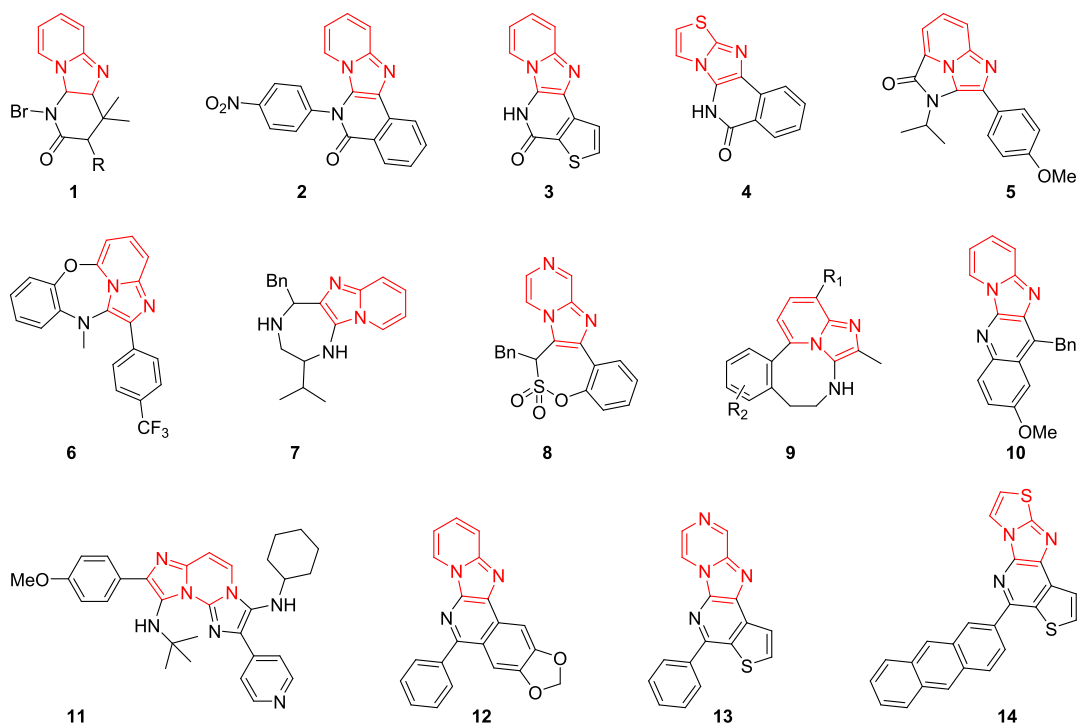
Figure 1. Polycyclic fused heterocycles synthesized via a post-GBB cyclization strategy.
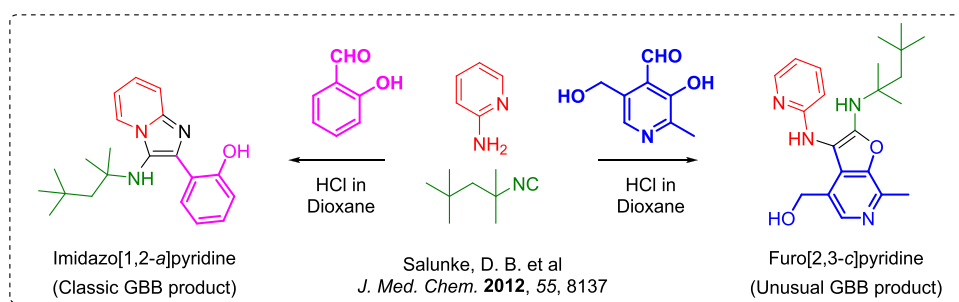

Figure 2. Classic and unusual GBB products.

in this reaction were further elaborated to 4-aminomethyl-2-heteroaryl[2,3-c]pyridines.[19] It is noteworthy to mention that the "unusual GBB-MCR" is the first and the only report that generates 2,3-diamine-substituted furo[2,3-c]pyridines. Encouraged by the structural diversity obtained in the products generated via post modification of classic GBB reaction, we envisioned that the 2,3-diamino-furo[2,3-c]pyridines synthesized via unusual GBB-MCR is amenable for 1,2,3-triazole construction to generate a library of tricyclic heterocycles utilizing nitrosonium-mediated diazotization.[20−22]

■ RESULTS AND DISCUSSION

Very recently, we demonstrated the synthesis of a library of polycyclic imidazo[4,5-b]pyridine-based heterocycles via GBB-MCR coupled with Pictet−Spengler cyclization.[16] The *tert*-octyl isocyanide was used as a convertible reagent in this process, which facilitated the effective removal of the *tert*-octyl group from the imidazo-fused heterocycles at room temperature.[16,23,24] Based on the synthetic utility of *tert*-octyl isocyanide as an effective convertible reagent, in the present investigation, an acid-catalyzed (HCl in dioxane) three-component condensation was carried out using 2-amino-pyridine, pyridoxal, and *tert*-octyl isocyanide in anhydrous

methanol under microwave irradiation for 2 min resulting in the formation of desired (7-methyl-3-(pyridin-2-ylamino)-2-((2,4,4-trimethylpentan-2-yl)amino)furo[2,3-c]pyridin-4-yl)-methanol as an unusual GBB product (**18**, Scheme 1). As expected, a highly fluorescent spot was observed on TLC under

Scheme 1. Synthesis of Triazolo[4′,5′:4,5]furo[2,3-c]pyridine
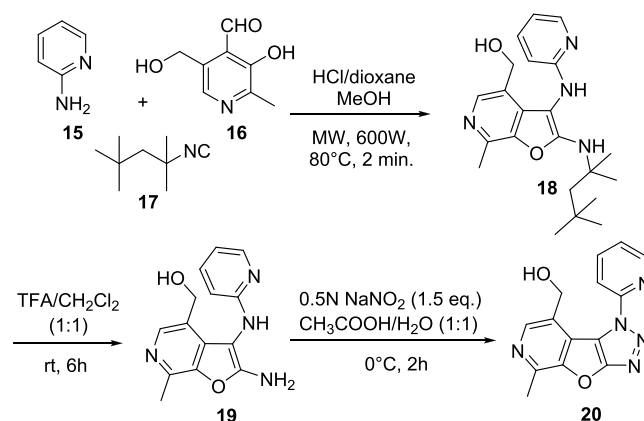
long-wave UV irradiation, which was isolated through flash column chromatography. The product obtained was further treated with trifluoroacetic acid in CH_2Cl_2 (1:1) at room temperature for 6 h to obtain (2-amino-7-methyl-3-(pyridin-2-ylamino)furo[2,3-c]pyridin-4-yl)methanol (**19**), which can be further cyclized utilizing nitrosonium-mediated diazotization.

The 1,2,3-triazole formation *via* diazotization of ortho-diamines on six-membered rings is reported in the literature,[22,25−28] but no report was observed wherein an *ortho*-diamine installed on a five-membered heterocycle was utilized for the synthesis of 1,2,3-triazoles. Our attempt for the diazotization of compound **19** using 5 M HCl and 0.5N $NaNO_2$ (2.0 equiv) solution in water resulted in the formation of desired product **20** in low (30%) yield. A pronounced improvement in the yield (70%) was obtained by employing the reaction in CH_3COOH/H_2O (1:1) with 0.5 N $NaNO_2$ (1.5 equiv) solution in water (Scheme 1). The tricyclic product formed in this reaction was confirmed by using ^{1}H and ^{13}C NMR as well as high-resolution mass spectrometry. Good-quality crystals were also obtained by slow evaporation of the solution of compound **20** in 5% MeOH:CH_2Cl_2, and the single-crystal X-ray diffraction additionally confirmed the formation of a triazolo[4′,5′:4,5]furo[2,3-c]pyridine scaffold in this reaction. Molecule **20** crystallized in the P21/c space group of the monoclinic system. The unit cell contains four independent molecules ($Z = 4$) where each molecule formed a flat structure. The triazole and the furan moieties sit on the middle, while the two pyridyl groups attached sidewise resulted in a V-shaped arrangement (Figure 3).
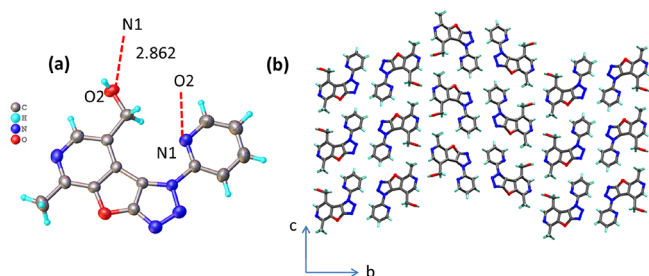
Figure 3. (a) ORTEP diagram of **20** with thermal ellipsoids at 40% probability along with H-bond interactions. (b) Lattice arrangement of **20** along the *bc*-plane.

The details of crystal data, bond lengths, and bond angles are listed in Tables S1−S3. There is a strong H-bond O−H·····N between the hydroxyl (OH) and substituted pyridyl (N) groups of 2.862 (Å). In the lattice arrangement, the only H-bond further helped to form a head-to-head arrangement along the *C*-axis and further an extended sheet-like arrangement along the *bc*-plane.

After the successful demonstration of the strategy to build novel tricyclic triazolo[4′,5′:4,5]furo[2,3-c]pyridine, the possible one-point modification in the process was planned using a diverse set of aromatic amines. Eleven different amines including substituted 2-aminopyridine, aniline, mono- and disubstituted anilines, heteroaryl (pyrazine- and pyrmidine-based) amines, and bicyclic aromatic amine, i.e., quinoline-5-amine, were selected to produce a small focused library of tricyclic compounds (Scheme 2).

During the library synthesis, the first step of microwave-mediated unusual GBB-MCR resulted in poor yields for many reactions, suggesting the need for further reaction optimization. It is noteworthy to mention that the first step of the

condensation reaction carried out by simply stirring the three components in methanol at room temperature instead of a microwave-mediated heating in the presence of a catalytic amount of HCl in dioxane for 12 h resulted in improved yields without the need of column chromatographic purification. Interestingly, the overnight stirring of the reaction mixture for many reactions resulted in the precipitation of the desired intermediates (**22a−22k**), which were used as it is for further dealkylation and diazotization as described earlier to furnish the final products (**24a−24k**). This improved three-step process also resulted in the crystallization of many of the final triazoles with high purity. The earlier synthesized compound **20** was also resynthesized using this improved process, and the products formed were analyzed using ^{1}H and ^{13}C NMR spectroscopy as well as high-resolution mass spectrometry. After the successful optimization and synthesis of novel tricyclic triazole scaffolds using 12 different aryl amines, the synthesis was also attempted using alkyl amines, terminal amides, and carbamates. However, no desired products were obtained in these attempts, which may be attributed to the nonformation or instability of the intermediate Schiff base. No reactivity was observed between benzamide, acetamide, or benzyl carbamate with pyridoxal, and therefore, no desired products were obtained even when the reactions were performed using *tert*-octyl isocyanide in the presence of HCl in dioxane as a catalyst. We did observe the formation of highly fluorescent product in the reaction (Scheme S1 and Figure S45) involving *n*-butylamine, pyridoxal, and *tert*-octyl isocyanide but could not isolate the intermediate as well as the desired tricyclic product confirming that the optimized strategy can be best utilized for the preparation of the triazolo[4′,5′:4,5]furo[2,3-c]pyridine scaffold using only the aromatic amines and amidines.

■ CONCLUSIONS

A novel triazolo[4′,5′:4,5]furo[2,3-c]pyridine scaffold was designed and synthesized using the unusual Groebke−Blackburn−Bienaymé (GBB) MCR coupled with nitrosonium-mediated diazotization. A library of diverse tricyclic compounds utilizing 2-aminopyridine, aniline, mono- and disubstituted anilines, heteroaryl amines, and bicyclic aromatic amines was prepared in a three-step process. The need of microwave-mediated heating was avoided in the first step, and the reaction was optimized to be carried out at room temperature. The improvement in the yield for the diazotization using 0.5 N $NaNO_2$ was observed by replacing aqueous HCl with aqueous acetic acid solution. The green aspect of the synthesis was further improved by optimizing the process without the need for tedious column chromatography.

■ EXPERIMENTAL SECTION

Materials and Methods. All the chemicals, reagents, and solvents were procured commercially. Methanol was dried over magnesium turnings and iodine using the standard procedure, and HCl/dioxane was also prepared in the laboratory by purging HCl gas obtained from NaCl and H_2SO_4 standard setup into 1,4-dioxane. The bulk solvents (hexane and CH_2Cl_2) were distilled before use. The reaction under microwave irradiation was carried out using a Synthos 3000 MW reactor by Anton Paar. All the reactions were monitored by thin layer chromatography (TLC) carried out on Merck silica gel F254 aluminum sheets and visualized under UV light at 254 and/or 360 nm. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker

Scheme 2. Synthesis of Triazolo[4′,5′:4,5]furo[2,3-c]pyridine Utilizing a Variety of Arylamines
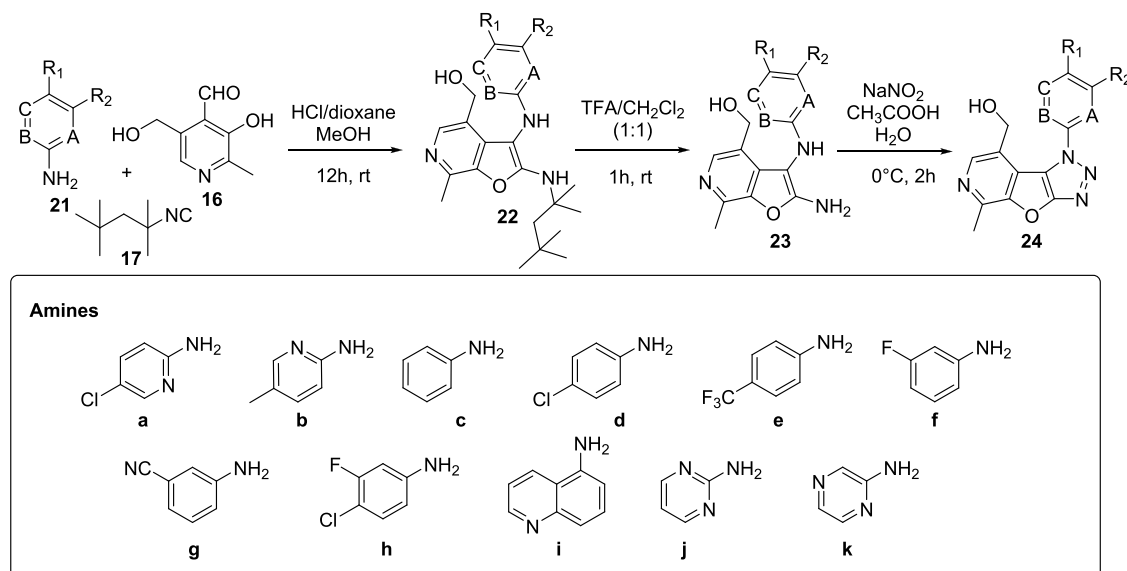
Avance II 500 MHz after dissolving the samples in CDCl$_3$ or DMSO-d_6. ^{1}H NMR chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard and δ = 7.26 for CDCl$_3$ and δ = 2.50 and 3.33 for DMSO-d_6. ^{13}C NMR chemical shifts are also expressed in ppm (δ) relative to δ = 77.16 and 39.50 for CDCl$_3$ or DMSO-d_6, respectively. Mass spectrometric analysis of intermediates was performed utilizing an Agilent (1290 LC/MSD) single quad system, and HRMS (m/z) of final compounds were recorded using a Waters Micromass Q-Tof (ESI-MS) spectrometer. For single-crystal X-ray structure determination of compound **20**, the crystal of compound **20** was mounted on Hampton CryoLoops. All geometric and intensity data for the crystals were collected using a SuperNova (MΘ) X-ray diffractometer equipped with a microfocus-sealed X-ray tube Mo Kα (λ = 0.71073 Å) X-ray source and a HyPix-3000 (CCD Plate) detector with increasing ω (width of 0.3 per frame) at a scan speed of either 5 or 10 s/frame. CrysAlisPro software was used for data acquisition and data extraction. Using Olex2, the structure was solved with the SIR2004[2] structure solution program using direct methods and refined with the ShelXL refinement package using Least Squares minimization. All non-hydrogen atoms were refined with anisotropic thermal parameters. Detailed crystallographic data and structural refinement parameters are summarized in Tables S1−S3.

General Procedure and Analytical Data. *Synthesis of (5-Methyl-1-(pyridin-2-yl)-1H-[1,2,3]triazolo[4′,5′:4,5]furo[2,3-c]pyridin-8-yl)methanol (20).* To a solution of 2-aminopyridine (100 mg, 1.06 mmol, 1.00 equiv) in anhydrous methanol (3.0 mL), pyridoxal hydrochloride (240.3 mg, 1.17 mmol, 1.10 equiv), HCl/dioxane (50 μL), and 1,1,3,3-tetramethylbutyl isocyanide (203.7 μL, 1.17 mmol, 1.10 equiv) were added at room temperature in a 5 mL screwable microwave glass vial, and the vial was sealed. The reaction mixture was then allowed to react under microwave irradiation at 80 °C for 2 min using a 64MG5 rotor. After the completion of reaction (monitored by TLC), the reaction mixture was evaporated under reduced pressure to obtain the crude, which was purified by silica gel (230−400 mesh) column chromatography, and the final product (7-methyl-3-(pyridin-2-ylamino)-2-((2,4,4-trimethyl-pentan-2-yl)amino)furo[2,3-c]pyridin-4-yl)methanol, i.e., **18**

(210 mg, 52%), was obtained. The solution of compound **18** (50 mg, 0.13 mmol) in 50% TFA/CH$_2$Cl$_2$ (2 mL) was stirred at room temperature for 6 h. The solvent was evaporated under reduced pressure after the completion of reaction (monitored by TLC) to give the product (2-amino-7-methyl-3-(pyridin-2-ylamino)furo[2,3-c]pyridin-4-yl)methanol, i.e., **19**. Without any purification, compound **19** was dissolved in 0.5N NaNO$_2$ solution (15 mg in 0.5 mL H$_2$O, 1.50 equiv) and 50% aqueous acetic acid solution (1.5 mL) at room temperature in a 5 mL glass vial. The vial was then stirred at 0 °C for 2 h. After the completion of the reaction, the reaction mixture was quenched using saturated sodium bicarbonate solution (20 mL) followed by the extraction of product in dichloromethane (20 mL × 3). The combined organic layers were washed with water dried over Na$_2$SO$_4$ and evaporated under reduced pressure to obtain the crude solid, which was then purified using silica gel (230−400 mesh) column chromatography (5% MeOH:CH$_2$Cl$_2$) to afford the final product **20** as white powder (26 mg, 70% yield, mp 162−165 °C, R_f 0.65 (9:1 CH$_2$Cl$_2$:MeOH)). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.73 (d, J = 3.9 Hz, 1H), 8.52 (s, 1H), 8.23 (td, J = 7.9, 1.7 Hz, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.71 (td, J = 6.8, 5.0 Hz, 1H), 5.13 (t, J = 5.7 Hz, 1H), 4.93 (d, J = 5.6 Hz, 2H), 2.75 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ 166.6, 155.7, 149.7, 147.9, 144.9, 142.5, 140.8, 128.7, 125.2, 121.5, 120.3, 116.8, 60.9, 17.8. MS (ESI-TOF) (m/z): calcd for C$_{14}$H$_{15}$N$_4$O$_2$$^+$ [M + H]$^+$ 282.0986, found 282.1.

Improved Process for the Synthesis of 1H-1,2,3-Triazolo-[4′,5′:4,5]furo[2,3-c]pyridines (24a−24k). To a solution of respective amines (**21a−21k**, Scheme 2) (50 mg, 1.00 equiv) in anhydrous methanol (2.5 mL) in a 25 mL single-neck round-bottom flask, pyridoxal hydrochloride (1.10 equiv) was added followed by the addition of prepared HCl/dioxane (50 μL). 1,1,3,3-Tetramethylbutyl isocyanide (1.10 equiv) was added and the reaction mixture was stirred at room temperature overnight. After the completion of reaction (monitored by TLC), the reaction mixture was evaporated under reduced pressure to obtain the desired products **22a−22k**, which were used as is for further reaction. The respective furo[2,3-c]pyridines (**22a−22k**) were reacted with trifluoroacetic acid (2 mL) and CH$_2$Cl$_2$ (2 mL) at room temperature for 1−6 h. After the completion of the reaction (monitored by TLC), the

reaction mixture was evaporated under reduced pressure to obtain crude products 2-amino-furo[2,3-*c*]pyridines (**23a–23k**), which were used for further diazotization without any further purification. Compounds **23a–23k** were reacted with a 0.5 N NaNO$_2$ solution (2 mL) in the presence of an aqueous acetic acid solution (2 mL) (AcOH:H$_2$O = 1:1) at 0 °C for 2 h. After the completion of reaction (monitored by TLC), saturated sodium bicarbonate solution (20 mL) was added followed by the extraction of the product in dichloromethane (20 mL × 3). The combined organic layers were washed with water, dried over Na$_2$SO$_4$, and evaporated under reduced pressure to obtain the crude solid, which was then either purified using silica gel (230–400 mesh) column chromatography (5% MeOH:CH$_2$Cl$_2$) or the products were crystallized from the saturated solution of CH$_2$Cl$_2$ to obtain the final products, i.e., 1*H*-[1,2,3]triazolo-[4′,5′:4,5]furo[2,3-*c*]pyridines (**24a–24k**).

(1-(5-Chloropyridin-2-yl)-5-methyl-1H-[1,2,3]triazolo-[4′,5′:4,5]furo[2,3-c]pyridin-8-yl)methanol (24a). Pale-yellow powder (9.1 mg, 10% yield, R_f 0.72 (9:1 CH$_2$Cl$_2$:MeOH)) ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 8.81 (d, *J* = 2.3 Hz, 1H), 8.51 (s, 1H), 8.35 (dd, *J* = 8.6, 2.5 Hz, 1H), 8.16 (d, *J* = 8.6 Hz, 1H), 5.03 (t, *J* = 5.2 Hz, 1H), 4.91 (d, *J* = 5.2 Hz, 2H), 2.76 (s, 3H).^{13}C NMR (126 MHz, DMSO-*d$_6$*) δ 165.1, 154.9, 147.6, 147.1, 143.3, 142.2, 139.8, 131.9, 128.7, 120.9, 119.4, 118.4, 59.8, 18.3. HRMS (*m/z*): calcd for C$_{14}$H$_{11}$^{35}ClN$_5$O$_2$$^+$ [M + H]$^+$ 316.0596, found 316.0671.

(5-Methyl-1-(5-methylpyridin-2-yl)-1H-[1,2,3]triazolo-[4′,5′:4,5]furo[2,3-c]pyridin-8-yl)methanol (24b). Gray powder (40.3 mg, 30% yield, mp 215–219 °C, R_f 0.70 (9:1 CH$_2$Cl$_2$:MeOH)). ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 8.56 (d, *J* = 4.4 Hz, 1H), 8.51 (s, 1H), 7.98 (s, 1H), 7.54 (d, *J* = 3.8 Hz, 1H), 4.91 (s, 2H), 2.75 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d$_6$*) δ 165.2, 154.8, 151.6, 149.2, 148.0, 143.1, 142.2, 128.8, 126.2, 120.8, 119.4, 117.39, 59.8, 39.5, 20.6, 18.2.HRMS (*m/z*): calcd for C$_{15}$H$_{14}$N$_5$O$_2$$^+$ [M + H]$^+$ 296.1142, found 296.1253.

(5-Methyl-1-phenyl-1H-[1,2,3]triazolo[4′,5′:4,5]furo[2,3-c]pyridin-8-yl)methanol (24c). Red powder (14 mg, 10% yield, R_f 0.57 (9:1 CH$_2$Cl$_2$:MeOH)). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.42 (s, 1H), 7.77–7.73 (m, 2H), 7.65 (dd, *J* = 6.8, 3.7 Hz, 3H), 4.61 (s, 2H), 2.85 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ: 155.6, 145.4, 142.8, 137.5, 130.6, 129.6, 125.7, 125.1, 122.5, 120.2, 61.4, 29.7, 22.7, 18.6. MS (ESI-TOF) (*m/z*): calcd for C$_{14}$H$_{13}$N$_4$O$_2$$^+$ [M + H]$^+$ 281.1033, found 281.4.

(1-(4-Chlorophenyl)-5-methyl-1H-[1,2,3]triazolo-[4′,5′:4,5]furo[2,3-c]pyridin-8-yl)methanol (24d). Yellow powder (10.2 mg, 11.2% yield, R_f 0.63 (9:1 CH$_2$Cl$_2$:MeOH)).^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 8.45 (s, 1H), 7.94–7.89 (m, 2H), 7.78–7.73 (m, 2H), 4.44 (s, 2H), 2.75 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d$_6$*) δ: 165.0, 154.7, 143.1, 142.1, 135.9, 135.0, 129.5, 127.9, 127.1, 122.8, 119.3, 59.6, 18.2. HRMS (*m/z*): calcd for C$_{15}$H$_{12}$^{35}ClN$_4$O$_2$$^+$ [M + H]$^+$ 315.0643, found 315.0807.

(5-Methyl-1-(4-(trifluoromethyl)phenyl)-1H-[1,2,3]-triazolo[4′,5′:4,5]furo[2,3-c]pyridin-8-yl)methanol (24e). Bright-yellow powder (7.1 mg, 8% yield, R_f 0.52 (9:1 CH$_2$Cl$_2$:MeOH)). ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 8.45 (s, 1H), 8.10 (dd, *J* = 36.5, 8.3 Hz, 4H), 5.17 (t, *J* = 5.2 Hz, 1H), 4.49 (d, *J* = 5.0 Hz, 2H), 2.76 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d$_6$*) δ 165.1, 154.8, 143.2, 142.3, 140.3, 130.5, 127.9, 126.7 (q, J_{CF} = 11.34 Hz), 125.9, 122.7, 119.5, 59.6, 54.9, 18.2. ^{19}F NMR (470 MHz, DMSO-*d$_6$*): δ −61.03 (s, CF$_3$); HRMS (*m/z*): calcd for C$_{16}$H$_{12}$F$_3$N$_4$O$_2$$^+$ [M + H]$^+$ 349.0907, found 349.1046.

(1-(3-Fluorophenyl)-5-methyl-1H-[1,2,3]triazolo[4′,5′:4,5]-furo[2,3-c]pyridin-8-yl)methanol (24f). Pale-yellow powder (9.5 mg, 10% yield, mp 202–205 °C, R_f 0.60 (9:1 CH$_2$Cl$_2$:MeOH)). ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 8.45 (s, 1H), 7.92–7.85 (m, 1H), 7.79–7.69 (m, 2H), 7.62–7.53 (m, 1H), 4.45 (s, 2H), 2.76 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d$_6$*): δ 164.9, 161.8 (d, $^1J_{CF}$ = 246.96 Hz), 154.8, 143.1, 142.1, 138.2 (d, $^3J_{CF}$ = 11.34 Hz), 131.3 (d, $^3J_{CF}$ = 8.82 Hz), 128.0, 122.8, 121.7 (d, $^4J_{CF}$ = 2.52 Hz), 119.3, 117.5 (d, $^2J_{CF}$ = 45.36 Hz) 113.0 (d, $^2J_{CF}$ = 25.06 Hz), 59.6, 18.2. ^{19}F NMR (470 MHz, DMSO-*d$_6$*) δ −110.87 (s, arC-F); HRMS (*m/z*) calcd for C$_{15}$H$_{12}$FN$_4$O$_2$$^+$ [M + H]$^+$ 299.0939, found 299.1019.

3-(8-(Hydroxymethyl)-5-methyl-1H-[1,2,3]triazolo-[4′,5′:4,5]furo[2,3-c]pyridin-1-yl)benzonitrile (24g). Red powder (9.0 mg,13% yield, mp 195–198 °C, R_f 0.57 (9:1 CH$_2$Cl$_2$:MeOH)). ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 8.48 (s, 1H), 8.43 (s, 1H), 8.23 (dd, *J* = 8.1, 1.0 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.89 (t, *J* = 8.0 Hz, 1H), 5.15 (t, *J* = 5.3 Hz, 1H), 4.44 (d, *J* = 5.3 Hz, 2H), 2.75 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d$_6$*) δ: 165.0, 154.8, 143.2, 142.2, 137.7, 134.2, 130.9, 130.2, 128.9, 128.0, 122.9, 119.5, 117.6, 112.4, 59.5, 18.2. HRMS (*m/z*): calcd for C$_{16}$H$_{12}$N$_5$O$_2$$^+$ [M + H]$^+$ 306.0986, found 306.1072.

(1-(3-Chloro-4-fluorophenyl)-5-methyl-1H-[1,2,3]triazolo-[4′,5′:4,5]furo[2,3-c]pyridin-8-yl)methanol (24h). White powder (17.2 mg, 17% yield, R_f 0.65 (9:1 CH$_2$Cl$_2$:MeOH)). ^{1}H NMR (500 MHz, CDCl3) δ 8.42 (s, 1H), 7.91 (dd, *J* = 6.2, 2.6 Hz, 1H), 7.71 (ddd, *J* = 8.7, 3.9, 2.8 Hz, 1H), 7.41 (t, *J* = 8.5 Hz, 1H), 4.65 (s, 2H), 2.86 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 145.8, 143.1, 127.4, 125.4, 125.0 (d, $^2J_{CF}$ = 22.68 Hz), 124.8, 122.4, 122.3, 120.1, 117.5 (d, $^3J_{CF}$ = 8.82 Hz), 61.3, 18.6. ^{19}F NMR (470 MHz, DMSO-*d$_6$*) δ −110.87 (s, arC-F); MS (ESI-TOF) (*m/z*): calcd for C$_{15}$H$_{12}$^{35}ClFN$_4$O$_2$$^+$ [M + H]$^+$ 333.0549, found 333.4.

(5-Methyl-1-(quinolin-5-yl)-1H-[1,2,3]triazolo[4′,5′:4,5]-furo[2,3-c]pyridin-8-yl)methanol (24i). Light-green powder (6.2 mg, 8% yield, mp 190–193 °C, R_f 0.68 (9:1 CH$_2$Cl$_2$:MeOH)). ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 9.06 (d, *J* = 2.9 Hz, 1H), 8.39 (d, *J* = 8.5 Hz, 1H), 8.34 (s, 1H), 8.13 (d, *J* = 7.2 Hz, 1H), 8.03 (t, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.58 (dd, *J* = 8.5, 4.1 Hz, 1H), 3.91 (s, 2H), 2.77 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d$_6$*) δ: 164.9, 154.9, 151.8, 147.5, 143.0, 141.5, 133.0, 132.2, 130.8, 128.8, 127.8, 125.8, 124.7, 124.5, 123.2, 119.0, 59.1, 18.2. HRMS (*m/z*): calcd for C$_{18}$H$_{14}$N$_5$O$_2$$^+$ [M + H]$^+$ 332.1142, found 332.1273.

(5-Methyl-1-(pyrimidin-2-yl)-1H-[1,2,3]triazolo[4′,5′:4,5]-furo[2,3-c]pyridin-8-yl)methanol (24j). White powder (21 mg, 18% yield, R_f 0.48 (9:1 CH$_2$Cl$_2$:MeOH)). ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 9.14 (d, *J* = 4.9 Hz, 2H), 8.49 (s, 1H), 7.84 (t, *J* = 4.9 Hz, 1H), 4.98 (t, *J* = 5.5 Hz, 1H), 4.90 (d, *J* = 5.6 Hz, 2H), 2.77 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d$_6$*) δ: 159.8, 155.0, 154.6, 143.4, 142.2, 142.0, 129.0, 122.5, 121.5, 119.6, 59.7, 39.5, 18.3. MS (ESI-TOF) (*m/z*): calcd for C$_{13}$H$_{12}$N$_6$O$_2$$^+$ [M + H]$^+$ 283.0938, found 282.7.

(5-Methyl-1-(pyrazin-2-yl)-1H-[1,2,3]triazolo[4′,5′:4,5]-furo[2,3-c]pyridin-8-yl)methanol (24k). Pale-yellow powder (9.2 mg, 7% yield, mp 182–185 °C, R_f 0.47 (9:1 CH$_2$Cl$_2$:MeOH)) ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 9.40 (s, 1H), 8.96 (d, *J* = 2.1 Hz, 1H), 8.83 (s, 1H), 8.48 (s, 1H), 4.84 (s, 2H), 2.75 (s, 3H).^{13}C NMR (126 MHz, DMSO-*d$_6$*) δ 165.1, 155.0, 145.8, 145.7, 143.3, 142.9, 142.1, 138.9, 128.7, 121.4,

119.2, 59.6, 18.2. HRMS (*m/z*): calcd for $C_{13}H_{12}N_6O_2^+$ [M + H]$^+$ 283.0938, found 283.1075.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c01359.

> CCDC-2297235 (20) contains supplementary crystallographic data for the structures (CIF)
> ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and HRMS analyses of compounds 20 and 24a−24k (Figures S7−S44); and ^{1}H NMR analysis of 22c, 22d, 22h, 22i, 22j, and 22k (Figures S1−S6) and single-crystal X-ray diffraction spectrometry details, which includes crystal data and structure refinement, bond lengths, and bond angles of compound 20 (Tables S1−S3) (PDF)

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Notes

The authors report that there are no competing interests to declare.
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