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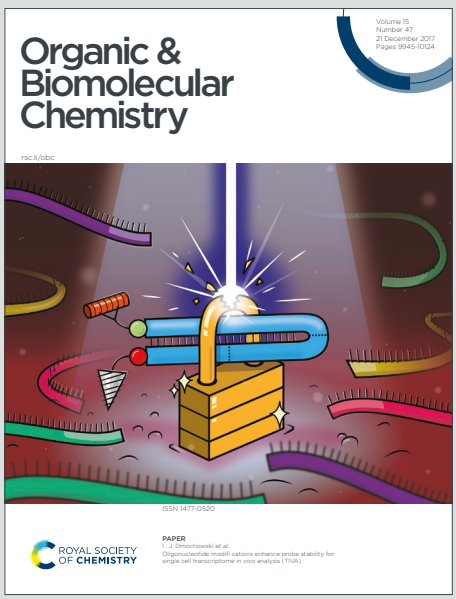

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ARTICLE

Copper(I)-Catalyzed Benzylation of Triazolopyridine Through Direct C-H Functionalization

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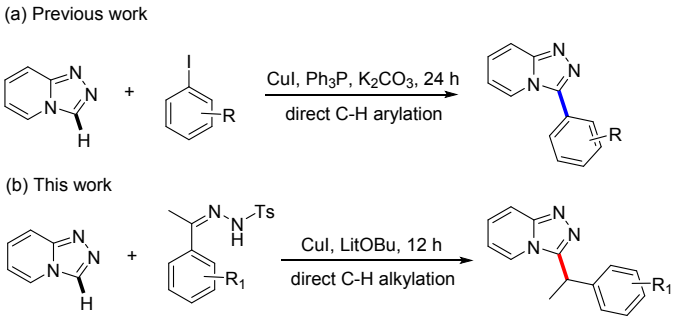
A general and efficient copper-catalyzed benzylation reaction of triazolopyridine with *N*-tosylhydrazones was developed. This reaction forms C(sp^2)-C(sp^3) bond through cross-coupling, and represents an exceedingly practical method to afford 3-benzylated triazolopyridines in moderate to good yields,. A proposed mechanistic pathway underlying this reaction was outlined. This catalytic transformation should enable borad synthetic applications in functionalization chemistry, allowing the synthesis of new pharmaceutically relevant trizaolopyridine derivatives.

Introduction

Cross-coupling reactions mediated by transition metals have been widely regarded as direct and excellent methods to construct C–C bonds.[1] A range of metal catalysts such as ruthenium, rhodium and palladium have been extensively applied in these reactions to furnish diverse molecular structures.[2] Among them, copper catalyst has attracted particular interest for being significantly active, notably inexpensive, and commercially available.[3]

N-tosylhydrazones, readily prepared from carbonyl compounds, are useful synthetic intermediates that have been employed in organic chemistry for almost 65 years. Recently, the synergistic merger of *N*-tosylhydrazones and copper catalyst has been reported to enable the direct C-H functionalization of arenes and heteroarenes.[4] Zhou *et. al.,* reported reductive coupling of *N*-tosylhydrazones with H-phosphorus oxides in the presence of copper catalyst.[5] Wang and co-workers used Cu(I) catalyst in the coupling of terminal alkynes,[6] 1,3-azoles,[7] N-iminopyridinium ylides[8] and polyfluoroarenes[9] with *N*-tosylhydrazones, respectively. In addition, Das and colleagues developed copper-catalyzed direct cross-coupling of oxadiazoles with *N*-tosylhydrazones.[10]

Triazolopyridines are ubiquitous nitrogen-containing fused heterocycles[11] with broad applications in coordination chemistry.[12] They process a privileged 1,2,4-triazolo[4,3-a]pyridine skeleton that is widely found in bioactive molecules[13] as well as in herbicidal agents[14]. Triazolopyridines often exhibit interesting biological effects, through their antibacterial, anti-inflammatory, antifungal, and antiproliferative activities.[15] Thus, the development of straightforward access to functionalized triazolopyridine has become an attractive area of research. In 2015, You and co-workers utilized copper catalyst to achieve successful arylation of triazolopyridine (Scheme 1a).[16]



Scheme 1 Copper-catalyzed C(sp^2)-C(sp^3) cross-coupling

However, the direct cross-coupling of triazolopyridine with sp^3 carbon centers remains challenging. Inspired by the previous findings, we asked whether N-tosylhydrazones could react with triazolopyridines through C(sp^2)-C(sp^3) bond formation via copper catalysis. Based on the confirmative results of our investigation, we herein report the highly efficient copper-catalyzed direct benzylation reaction of triazolopyridine with *N*-tosylhydrazones in good yields (Scheme 1b).

Results and discussion

To optimize the reaction conditions, [1,2,4]triazolo[4,3-a]pyridine **1** and *N*-tosylhydrazone **2a** was initially treated with the similar previously reported reaction condition for the copper-catalyzed direct benzylation of 1,3,4-oxadiazoles,[10a]

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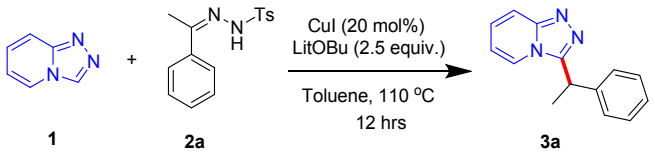
with the presence of CuI as a catalyst and LitOBu as a base in toluene. For the first 3 hours, no reaction was detected (entry 1, Table 1). However, the desired product started to form as the process continued. The product yield reached a maximum of 80% at the 12th hour (entry 3), and gradually decreased hereafter (entry 4). Raising or lowering the reaction temperature from 110 °C would both attenuate the product yield (entries 5 and 6). Next, we examined the various forms of Cu-containing catalysts and found that neither CuBr nor $Cu(OAc)_2.H_2O$ gave desired product **3a** (entries 7 and 8), validating the crucial role of CuI in the reaction. A survey of base and solvent was then conducted. Various base substituents failed the reaction (entries 9–11), necessitating the usage of LitOBu. Switching the solvent to dioxane also diminished the reactivity (entry 12), confirming the judicious choice of toluene. Finally, reducing the loading of the catalyst or the base led to a slight decrease of the yield (entries 13 and 14).

Table 1. Optimization of reaction conditions[a]



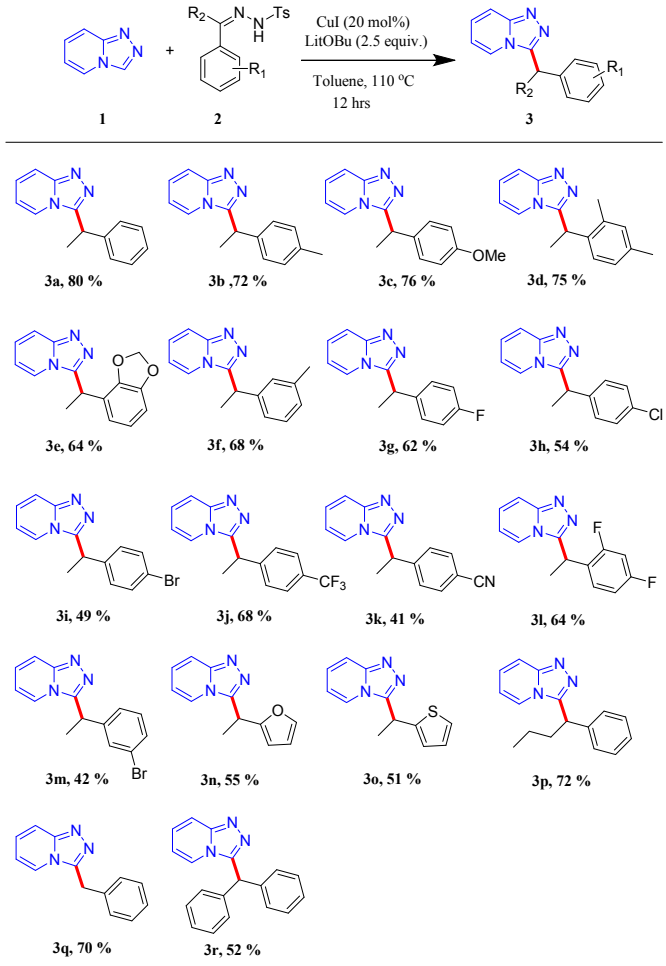
1 2a 3a

Entry	Catalyst (mol%)	Base (equiv.)	Temp (°C)	Time (hrs)	Yield (%)[b]
1	CuI	LitOBu	110	3	N.R[c]
2	CuI	LitOBu	110	6	Trace
3	**CuI**	**LitOBu**	**110**	**12**	**80**
4	CuI	LitOBu	110	24	76
5	CuI	LitOBu	130	12	60
6	CuI	LitOBu	80	12	35
7	$Cu(OAc)_2.H_2O$	LitOBu	110	12	N.R
8	CuBr	LitOBu	110	12	N.R
9	CuI	Cs_2CO_3	110	12	N.R
10	CuI	K_2CO_3	110	12	N.R
11	CuI	KtOBu	110	12	N.R
12	CuI	LitOBu	110	12	N.R[d]
13	CuI	LitOBu	110	12	65[e]
14	CuI	LitOBu	110	12	70[f]

[a]Reaction conditions: [1,2,4]triazolo[4,3-a]pyridine **1** (1.0 mmol), *N*-tosylhydrazone **2a** (1.5 mmol), catalyst (20 mol%.), base (2.5 equiv.) at 110 °C over 12 h in toluene (2 mL). [b]Isolated yield of **3a** after column chromatography. [c]No reaction. [d]Solvent changed to dioxane. [e]Catalyst (10 mol%.), [f] Base (1.5 equiv.).

With the optimized reaction conditions in hand (entry 3, Table 1), we then carried out direct benzylation of [1,2,4]triazolo[4,3-a]pyridine **1** to investigate the scope of *N*-tosylhydrazones. As shown in Table 2, a wide range of *N*-tosylhydrazones undergo the reaction successfully, affording the desired products (**3a–r**) in moderate to good yields. *N*-Tosylhydrazone, derived from acetophenone, smoothly coupled with **1** to afford **3a** in a yield of 80%. *N*-tosylhydrazones with electron-donating alkyl and alkoxy groups were well-tolerated, as evidenced by the formation of **3b–f** in good yields, ranging from 68% to 76%. Halogen-substituted *N*-tosylhydrazones led to slightly lowered turnovers of products (**3g–i**, **3l** and **3m**), a trend being identified with other electrophilic substituents, such as those processing trifluoromethyl and cyano groups (**3j, 3k**). Heterocycle-substituted *N*-tosylhydrazones were also found compatible for this reaction (**3n** and **3o**). Further reaction of **1** with *N*-tosylhydrazone derived from phenylbutanone gave corresponding product **3p** in 72% yield, while the *N*-tosylhydrazone derived from benzaldehyde afforded the benzylated product **3q** in a similar yield. Moreover, *N*-tosylhydrazones derived from diaryl ketone was also proven to be amenable substrate for the reaction, affording **3r** in moderate yield (58%). Conversely, we found that pyridine, nitro and aliphatic group-substituted *N*-tosylhydrazones were not tolerated by this transformation.

Table 2. Substrate scope of *N*-tosylhydrazones[a]



[a]Reaction conditions: [1,2,4]triazolo[4,3-a]pyridine **1** (1 equiv.), **2a–r** (1.5 equiv.), CuI (20 mol%), LitOBu (2.5 equiv.), toluene(2.0 mL), 110 °C for 12 h. All yields refer to the isolated products.

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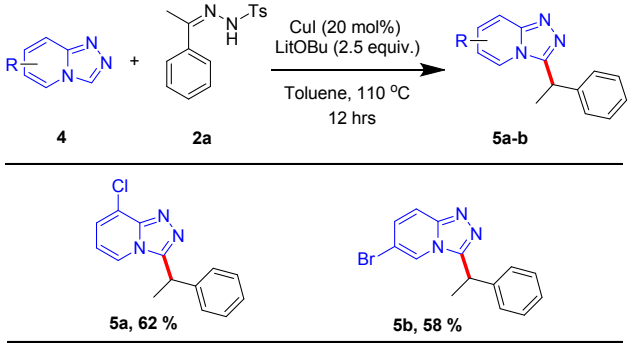
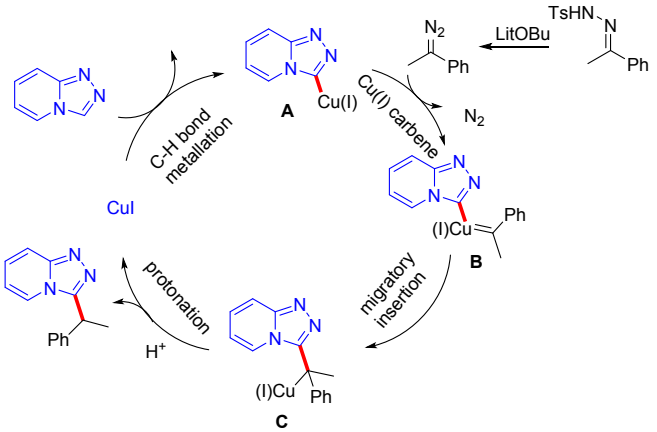
Next, we investigated the scope of substituted [1,2,4]triazolo[4,3-a]pyridines by reaction with *N*-tosylhydrazone **2a** under optimized reaction conditions (Table 3). 8-Chloro[1,2,4]triazolo[4,3-a]pyridine afforded the desired product **5a** in 62% yield and 6-bromo[1,2,4]triazolo[4,3-a]pyridine gave the product **5b** in 58% yield, respectively. We also tried 5-chloro[1,2,4]triazolo[4,3-a]pyridine and no product was observed which might ascribed to the decomposition of the substrate at high temperature. Meanwhile, the protocol we used[12e] to prepare [1,2,4]triazolo[4,3-a]pyridine **1** couldn't afford the electron donating 5-methyl[1,2,4]triazolo[4,3-a]pyridine which might also be due to its instability during the preparation.

Table 3. Substrate scope of [1,2,4]triazolo[4,3-a]pyridines[a]



Reaction conditions[a]: **4** (1 equiv.), **2a** (1.5 equiv.), CuI (20 mol%), LitOBu (2.5 equiv.), toluene(2.0 mL), 110 °C for 12 h. All yields refer to the isolated products.

Based on these experimental observations and previously reported copper-catalyzed C-H activations,[10] we propose a plausible reaction mechanism as delineated in Scheme 2. The copper catalytic cycle commences with deprotonation of the acidic C–H bond of triazolopyridine by LitOBu, followed by transmetalation by the excited Cu(I) state. The resultant metallated triazolopyridinyl species **A** then captures the reactive intermediate derived from tosylhydrazone by LitOBu, to form a Cu(I) carbene species **B**. Subsequent migratory insertion forges the desired C(sp^2)-C(sp^3) bond to furnish intermediate **C**, followed by protonation that ultimately liberates the benzylated product and recovers the copper catalyst.



Scheme 2. Proposed reaction mechanism

Conclusions

In summary, we developed an efficient copper(I)-catalyzed system for the direct benzylation of triazolopyridine with *N*-tosylhydrazones. A variety of benzylated triazolopyridine derivatives have been successfully synthesized in moderate to good yields. Given the operational ease associated with the preparation of *N*-tosylhydrazones from carbonyl compounds and the commercial availability of inexpensive copper(I) catalyst, this reaction represents an exceedingly effective, practical, and economical strategy to access C-H bond functionalization of triazolopyridine by challenging the secondary benzyl group. It broadens the field of cross-coupling chemistry with potential applications to numerous areas of synthetic science.

Experimental Section

General Information:

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. The reactions were monitored by thin-layer chromatography (TLC) with Merck precoated silica gel 60 F254 using UV light as visualizing agent. All the solvents were treated according to general methods. Solvents mixture was understood as volume/ volume. Purifications of reaction products were carried out by chromatography using silica gel (200-300 mesh). ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR at 125 MHz. Tetramethylsilane (TMS) was used as internal standard (δ = 0) for ^{1}H NMR spectra and the values are reported as follows: chemical shift as δ in ppm, and multiplicity as s = singlet, d = doublet, t= triplet, q =quartet, m = multiplet and the coupling constants in Hz. For ^{13}C NMR, $CDCl_3$ (δ = 77.00) was used as internal standard and spectra were obtained with complete proton decoupling.

Typical procedure for the synthesis of [1,2,4]triazolo[4,3-a]pyridine (1):[12e]

A combination of the 2-hydrazino pyridine (1.0 mmol) and formaldehyde (1.0 mmol) in EtOH (10 mL) was heated at reflux for 30 min (TLC indicated that condensation was finished). Then, the solvent was evaporated under reduced pressure, and the resulting crude was redissolved in DCM (10 mL), followed by the addition of K_2CO_3 (3.0 mmol) and iodine (1.2 mmol). The reaction mixture was stirred at room temperature until TLC indicated the total consumption of intermediate. Upon end of the reaction, it was quenched with 5% $Na_2S_2O_3$ (30 mL), and then extracted with DCM (3 x 20 mL). The combined organic layer was washed with brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated. The given residue was purified by column chromatography through silica gel to afford pure product.

light brown oil, 71.6 mg (60% yield); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.86 (s, 1H), 8.20–8.15 (m, 1H), 7.80 (dd, *J* = 9.3, 0.6 Hz, 1H),

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7.31–7.25 (m, 1H), 6.88 (t, *J* = 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 149.13, 135.63, 128.10, 123.69, 116.16, 114.38.

Typical procedure for the synthesis of *N*-Tosylhydrazones (2a–r): [7]

A solution of 4-methylbenzenesulfonohydrazide (5.0 mmol) in methanol (5mL) was stirred and heated to 60 °C until the 4-methylbenzenesulfonohydrazide was completely dissolved. Then carbonyl compound (5.0 mmol) was added to the mixture slowly. After 15–30 mins reaction, the crude product was obtained as precipitate which was washed by petroleum ether and then dried in vacum to afford the pure product.

General procedure for the Cu(I)-catalyzed benzylation of triazolopyridine

A mixture of CuI (10 mol%.), LitOBu (1.25 mmol), *N*-tosylhydrazone **2** (0.75 mmol) and [1,2,4]triazolo[4,3-a]pyridine **1** (0.5 mmol.) was stirred in toluene (2.0 mL) at 110 ^{0}C for 12 h in a sealed Schlenk tube. After cooling to room temperature, the reaction mixture was extracted with EtOAc (2 x 10 mL). The combined organic layer extract was dried over anhydrous Na_2SO_4 and evaporated to remove the solvent. The residue was then purified by flash column chromatography (ethyl acetate) to get benzylated triazolopyridines **3** and **5**.

3-(1-Phenylethyl)-[1,2,4]triazolo[4,3-a]pyridine (3a):

White solid, 89.9 mg (80% yield); mp 125–128 °C; R_f = 0.2 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.75 (d, *J* = 9.3 Hz, 1H), 7.58 (d, *J* = 7.0 Hz, 1H), 7.33–7.29 (m, 2H), 7.27–7.23 (m, 1H), 7.21 (dd, *J* = 5.2, 3.3 Hz, 1H), 7.17 (ddd, *J* = 9.3, 6.5, 1.0 Hz, 1H), 6.67–6.62 (m, 1H), 4.47 (q, *J* = 7.1 Hz, 1H), 1.98 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 150.4, 148.7, 141.3, 129.2, 127.4, 127.1, 126.7, 122.3, 116.5, 113.4, 37.4, 20.9; HRMS calcd. for $C_{14}H_{14}N_3$ $[M+H]^+$ 224.1182, found 228.1186.

3-(1-(*p*-Tolyl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3b):

White solid, 86.0 mg (72% yield); mp 120–122 °C; R_f = 0.2 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.77–7.73 (m, 1H), 7.59 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.17 (ddd, *J* = 9.3, 6.5, 1.1 Hz, 1H), 7.13–7.07 (m, 4H), 6.65 (td, *J* = 7.0, 1.0 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 1H), 2.30 (s, 3H), 1.96 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 150.4, 148.8, 138.2, 137.1, 129.9, 127.0, 126.7, 122.4, 116.5, 113.3, 37.0, 21.0, 20.9; HRMS calcd. for $C_{15}H_{16}N_3$ $[M+H]^+$ 238.1338, found 238.1343.

3-(1-(4-Methoxyphenyl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3c):

White solid, 96.9 mg (76% yield); mp 115–118 °C; R_f = 0.2 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.74 (d, *J* = 9.3 Hz, 1H), 7.59 (dt, *J* = 7.0, 1.2 Hz, 1H), 7.18 (ddd, *J* = 9.3, 6.5, 1.2 Hz, 1H), 7.14–7.09 (m, 2H), 6.86–6.81 (m, 2H), 6.68-6.63 (td, *J* = 6.8, 1.0 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 1H), 3.77 (s, 3H), 1.95 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 158.8, 150.3, 148.9, 133.2, 128.2, 126.8, 122.4, 116.5, 114.5, 113.3, 55.3, 36.6, 20.9; HRMS calcd. for $C_{15}H_{16}N_3O$ $[M+H]^+$ 254.1287, found 254.1291.

3-(1-(2,4-Dimethylphenyl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3d):

White solid, 94.9 mg (75% yield); mp 121–123 °C; R_f = 0.2 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.75 (d, *J* = 9.3 Hz, 1H), 7.36 (d, *J* = 6.9 Hz, 1H), 7.17 (dd, *J* = 8.7, 6.7 Hz, 1H), 7.04 (s, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.62 (t, *J* = 6.7 Hz, 1H), 4.60 (q, *J* = 7.0 Hz, 1H), 2.45 (s, 3H), 2.27 (s, 3H), 1.92 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 136.9, 136.2, 134.7, 131.8, 127.8, 126.7, 122.2, 116.5, 113.3, 33.4, 20.9, 19.5, 19.3; HRMS calcd. for $C_{16}H_{18}N_3$ $[M+H]^+$ 252.1492, found 252.1497.

3-(1-(Benzo[d][1,3]dioxol-4-yl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3e):

White solid, 86.1 mg (64% yield); mp 123–125 °C; R_f = 0.2 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.75 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 6.9 Hz, 1H), 7.19 (dd, *J* = 8.7, 6.8 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.71–6.64 (m, 3H), 5.94–5.90 (m, 2H), 4.39 (q, *J* = 7.1 Hz, 1H), 1.94 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 146.9, 135.1, 126.7, 122.3, 120.3, 116.6, 113.4, 108.7, 107.5, 101.2, 37.1, 21.0; HRMS calcd. for $C_{15}H_{14}N_3O_2$ $[M+H]^+$ 268.1080, found 268.1085.

3-(1-m-Tolyl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3f):

White solid, 81.2 mg (68% yield); mp 130–133 °C; R_f = 0.2 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.74 (d, *J* = 9.3 Hz, 1H), 7.60 (d, *J* = 7.0 Hz, 1H), 7.21–7.14 (m, 2H), 7.05 (d, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 6.1 Hz, 2H), 6.67–6.62 (m, 1H), 4.42 (q, *J* = 7.1 Hz, 1H), 2.28 (s, 3H), 1.96 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 150.3, 148.8, 141.2, 139.0, 129.0, 128.2, 127.8, 126.7, 124.2, 122.3, 116.5, 113.3, 37.3, 21.4, 20.9; HRMS calcd. for $C_{15}H_{16}N_3$ $[M+H]^+$ 238.1338, found 238.1343.

3-(1-(4-Fluorophenyl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3g):

White solid, 75.3 mg (62% yield); mp 135–138 °C; R_f = 0.2 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.76 (d, *J* = 9.3 Hz, 1H), 7.60 (d, *J* = 7.0 Hz, 1H), 7.20 (ddd, *J* = 8.6, 6.7, 1.4 Hz, 3H), 7.02–6.97 (m, 2H), 6.69 (t, *J* = 6.7 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 1H), 1.96 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 162.9 (d, *J* = 246.2 Hz), 136.9 (d, *J* = 3.2 Hz), 128.7 (d, *J* = 8.2 Hz), 126.8, 122.1, 116.6, 116.2 (d, *J* = 21.6 Hz), 113.5, 36.6, 21.0; ^{19}F NMR (471 MHz, $CDCl_3$) *δ* -114.89–-114.96 (m, 1F); HRMS calcd. for $C_{14}H_{13}FN_3$ $[M+H]^+$ 242.1088, found 242.1092.

3-(1-(4-Chlorophenyl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3h):

White solid, 69.9 mg (54% yield); mp 155–157 °C; R_f = 0.2 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.71 (d, *J* = 6.86 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 2H), 7.22 (t, 1H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.70 (t, *J* = 6.7 Hz, 1H), 4.48 (q, *J* = 6.6 Hz, 1H), 1.96 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 139.7, 133.3, 129.4, 128.5, 126.9, 122.2, 116.7,

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113.7, 36.8, 20.9; HRMS calcd. for $C_{14}H_{13}ClN_3$ $[M+H]^+$ 258.0792, found 258.0797.

3-(1-(4-Bromophenyl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3i):

^1H White solid, 74.3 mg (49% yield); mp 160–163 °C; R_f = 0.2 (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 9.3 Hz, 1H), 7.57 (d, J = 7.0 Hz, 1H), 7.45–7.42 (m, 2H), 7.20 (ddd, J = 9.3, 6.5, 1.0 Hz, 1H), 7.11–7.07 (m, 2H), 6.71–6.68 (m, 1H), 4.44 (q, J = 7.1 Hz, 1H), 1.96 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 132.3, 128.9, 126.9, 122.0, 121.3, 116.7, 113.6, 36.8, 20.8; HRMS calcd. for $C_{14}H_{13}BrN_3$ $[M+H]^+$ 302.0287, found 302.0291.

3-(1-(4-(Trifluoromethyl)phenyl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3j):

White solid, 99.7 mg (68% yield); mp 125–128 °C; R_f = 0.2 (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 9.3 Hz, 1H), 7.58 (t, J = 7.3 Hz, 3H), 7.36 (d, J = 8.1 Hz, 2H), 7.22 (dd, J = 8.8, 6.9 Hz, 1H), 6.72 (t, J = 6.7 Hz, 1H), 4.56 (q, J = 7.1 Hz, 1H), 2.00 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 145.3, 129.8 (q, J = 32.6 Hz), 127.6, 127.2, 126.9, 126.2 (q, J = 3.7 Hz), 125.0, 122.8, 121.8, 120.7, 116.7, 113.8, 37.1, 20.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.58 (s, 3F); HRMS calcd. for $C_{15}H_{13}F_3N_3$ $[M+H]^+$ 292.1056, found 292.1061.

4-(1-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)ethyl)benzonitrile (3k):

White solid, 51.2 mg (41% yield); mp 173–175 °C; R_f = 0.2 (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 9.3 Hz, 1H), 7.64–7.60 (m, 2H), 7.58 (d, J = 7.0 Hz, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.24 (ddd, J = 9.2, 6.6, 0.9 Hz, 1H), 6.75 (t, J = 6.6 Hz, 1H), 4.55 (q, J = 7.1 Hz, 1H), 1.99 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 133.0, 128.1, 127.1, 121.6, 118.4, 116.8, 114.0, 111.6, 37.3, 20.7; HRMS calcd. for $C_{15}H_{13}N_4$ $[M+H]^+$ 249.1134, found 249.1139.

3-(1-(2,4-Difluorophenyl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3l):

White solid, 83.5 mg (64% yield); mp 139–142 °C; R_f = 0.2 (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 9.3 Hz, 1H), 7.69 (d, J = 6.9 Hz, 1H), 7.22 (dd, J = 8.8, 6.9 Hz, 1H), 7.07 (td, J = 8.6, 6.5 Hz, 1H), 6.90–6.83 (m, 1H), 6.80–6.73 (m, 2H), 4.81 (q, J = 7.1 Hz, 1H), 1.96 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0 (d, J = 12.1 Hz),160.8 (dd, J = 26.7, 12.0 Hz), 158.9 (d, J = 11.8 Hz), 129.6 (dd, J = 9.7, 5.2 Hz), 126.8, 123.9(d, J = 10.8 Hz),121.7, 116.7, 113.8, 112.4 (dd, J = 21.2, 3.7), 104.0 (t, J = 25.9 Hz), 28.4 (d, J = 3.3 Hz), 19.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ -110.78 (dt, J = 15.0, 7.7 Hz, 1F), -116.03 (dd, J = 17.4, 8.6 Hz, 1F); HRMS calcd. for $C_{14}H_{12}F_2N_3$ $[M+H]^+$ 260.0993, found 260.0998.

3-(1-(3-Bromophenyl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3m):

White solid, 63.7 mg (42% yield); mp 168–171 °C; R_f = 0.2 (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 3.2 Hz, 2H), 7.42–7.36 (m, 2H), 7.22 (s, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.12 (d, J = 7.7 Hz, 1H), 6.71 (t, J = 6.7 Hz, 1H), 4.47 (d, J = 6.8 Hz, 1H), 1.96 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 130.8, 130.6, 130.3, 126.7, 125.8, 123.2, 122.3, 116.8, 113.7, 37.2, 20.8; HRMS calcd. for $C_{14}H_{13}BrN_3$ $[M+H]^+$ 302.0287, found 302.0292.

3-(1-(Furan-2-yl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3n):

White solid, 59.0 mg (55% yield); mp 138–141 °C; R_f = 0.2 (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 7.0 Hz, 1H), 7.76 (d, J = 9.3 Hz, 1H), 7.34–7.31 (m, 1H), 7.22 (ddd, J = 9.3, 6.5, 1.0 Hz, 1H), 6.79–6.74 (m, 1H), 6.32 (dd, J = 3.2, 1.9 Hz, 1H), 6.14 (d, J = 3.3 Hz, 1H), 4.75 (q, J = 7.2 Hz, 1H), 1.95 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 142.1, 126.8, 122.6, 116.6, 113.5, 110.6, 106.3, 31.0, 16.9; HRMS calcd. for $C_{12}H_{12}N_3O$ $[M+H]^+$ 214.0974, found 214.0980.

3-(1-(Thiophen-2-yl)ethyl)-[1,2,4]triazolo[4,3-a]pyridine (3o):
White solid, 58.8 mg (51% yield); mp 145–148 °C; R_f = 0.2 (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 9.3 Hz, 1H), 7.72 (d, J = 6.9 Hz, 1H), 7.21 (dd, J = 7.7, 7.1 Hz, 2H), 6.93 (dd, J = 5.0, 3.6 Hz, 1H), 6.82 (d, J = 3.4 Hz, 1H), 6.71 (t, J = 6.8 Hz, 1H), 4.88 (q, J = 7.1 Hz, 1H), 2.04 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 127.2, 126.8, 124.8, 124.7, 122.4, 116.7, 113.5, 32.6, 21.0; HRMS calcd. for $C_{12}H_{12}N_3S$ $[M+H]^+$ 230.0746, found 230.0751.

3-(1-Phenylbutyl)-[1,2,4]triazolo[4,3-a]pyridine (3p):

White solid, 91.1 mg (72% yield); mp 124–126 °C; R_f = 0.2 (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 9.3 Hz, 1H), 7.66 (d, J = 7.0 Hz, 1H), 7.32–7.26 (m, 2H), 7.26–7.21 (m, 2H), 7.16 (dd, J = 8.8, 6.9 Hz, 1H), 6.65 (t, J = 6.7 Hz, 1H), 4.26 (t, J = 7.5 Hz, 1H), 2.64–2.55 (m, 1H), 2.31 – 2.21 (m, 1H), 1.51–1.33 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 138.0, 129.0, 127.8, 127.3, 126.6, 122.0, 116.6, 113.3, 42.7, 36.7, 20.7, 13.9; HRMS calcd. for $C_{16}H_{18}N_3$ $[M+H]^+$ 252.1492, found 252.1498.

3-Benzyl-[1,2,4]triazolo[4,3-a]pyridine (3q):

White solid, 73.7 mg (70% yield); mp 164–166 °C; R_f = 0.2 (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 9.3 Hz, 1H), 7.71 (d, J = 6.9 Hz, 1H), 7.33–7.28 (m, 2H), 7.24 (dd, J = 7.1, 5.8 Hz, 3H), 7.20 (ddd, J = 9.2, 6.6, 0.9 Hz, 1H), 6.71 (t, J = 6.7 Hz, 1H), 4.56 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.6, 129.1, 128.4, 127.4, 126.7, 122.2, 116.6, 113.6, 31.4; HRMS calcd. for $C_{13}H_{12}N_3$ $[M+H]^+$ 210.1025, found 210.1031.

3-Benzhydryl-[1,2,4]triazolo[4,3-a]pyridine (3r):

White solid, 74.7 mg (52% yield); mp 169–172 °C; R_f = 0.4 (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 9.3, 1H), 7.68 (d, J = 7.0, 1H), 7.34 (dd, J = 11.3, 4.4, 4H), 7.30–7.28 (m, 2H), 7.26 (dd, J = 5.4, 2.9, 4H), 7.22 (dd, J = 9.1, 6.6, 1H,), 6.70 (t, J = 6.7, 1H), 5.89 (s, 1H);.^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 129.0, 128.8, 127.6, 126.8, 122.6, 116.8, 113.75, 48.6; HRMS calcd. for $C_{19}H_{16}N_3$ $[M+H]^+$ 286.1338, found 286.1344.

8-chloro-3-(1-phenyethyl)-[1,2,4]triazolo[4,3-a]pyridine(5a):

White solid, 79.1 mg (62% yield); mp 172–174 °C; R_f = 0.3 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 6.91 1H), 7.33–7.30 (m, 1H), 7.29 (d, J = 2.1, 1H), 7.27–7.22 (m, 2H), 7.20 (dd, J = 5.3, 3.32, 2H), 6.62 (t, J = 7.01, 1H), 4.50 (q, J =7.1, 1H), 1.97 (d, J 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 148.4, 140.8, 129.3, 127.5, 127.1, 125.7, 122.6, 121.1, 113.3, 37.6, 20.7; HRMS calcd. for $C_{14}H_{13}ClN_3$ $[M+H]^+$ 258.0792, found 258.0796.

6-Bromo-3-(1-phenyethyl)-[1,2,4]triazolo[4,3-a]pyridine(5b):

White solid, 87.2 mg (58% yield); mp 146–148 °C; R_f = 0.3 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s,1H,), 7.68 (d, J = 8.8, 1H), 7.33 (t, J = 7.32, 1H), 7.30 – 7.25 (m, 2H), 7.22 (t, J = 7.73, 1H), 4.45 (q, J = 6.91, 1H), 1.97 (d, J = 7.13, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 130.5, 129.3, 127.7, 127.1, 122.3, 117.2, 108.6, 37.4, 20.9. HRMS calcd. for $C_{14}H_{13}BrN_3$ $[M+H]^+$ 302.0287, found 302.0292.

Conflicts of interest

There are no conflicts to declare.

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