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An efficient and mild method for the synthesis of tetrazolo-fused-pyridine derivatives

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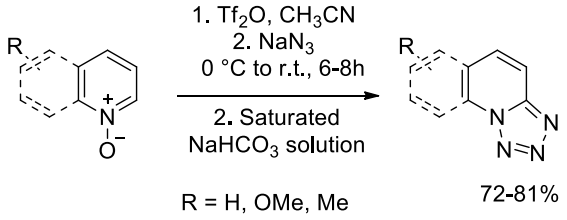
Abstract

An efficient and mild method has been established for the synthesis of tetrazolo-fused-pyridine derivatives from the straightforwardly obtainable starting materials such as pyridine, quinoline, isoquinoline-*N*-oxides, sodium azide, triflic anhydride as activator, and acetonitrile as solvent at 0 °C to room temperature in one pot reaction.



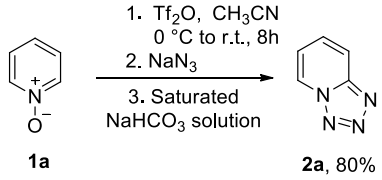
Keywords: Synthesis, tetrazolo-fused-pyridine, Pyridine-N-oxides, triflic anhydride, activator

Introduction

Tetrazoles are very useful scaffolds in the domains of coordination chemistry, material sciences, and medicinal chemistry.[1-4] Tetrazolo-fused pyridines, quinolines and isoquinolines are important classes of heterocycles and act as precursors for the preparation of several biologically important compounds such as 2-aminopyridines, pyrido-2,3-furoxanes,[5,6] substituted 1,3-diazepines,[7] 2-cyanopyrroles[8] and some of these heterocyclic compounds are also utilized for the synthesis of triazoles.[9-13] There are few reports for the synthesis of tetrazolo[1,5-*a*]pyridine derivatives.[14-19] Tetrazolo[1,5-*a*]pyridine derivatives are synthesized by reaction of sulfonyl or phosphoryl azides with pyridine-*N*-oxide[15] and high temperature is required. Another method for the preparation of tetrazolo[1,5-*a*]pyridine is reaction of pyridine-*N*-oxide with arenesulfonyl azides[20] and observed yields were poor. Other developed method is treating 2-halopyridines[9, 16-17] or pyridine *N*-oxides with sodium azide.[15, 18] Tetrazole diazines can also be prepared from diazine-*N*-oxides in the presence of tosyl chloride and trimethylsilyl.[19] The synthesis of halopyridines requires the halogenation of pyridine precursors that might lead to low overall yields..[21] Most of the above discussed methods have some limitations such as harsh reaction conditions, and poor yields. Thus, it is necessary to develop an efficient and mild method for the preparation of tetrazolo[1,5-*a*]pyridine derivatives from easily manageable starting materials.

Results and Discussion

Here, we report a method for the synthesis of tetrazolo[1,5-*a*]pyridine derivatives from the simply obtainable starting materials like pyridine, quinoline and isoquinoline-*N*-oxides by reaction with sodium azide at 0 °C to room temperature in the presence of triflic anhydride as activator and acetonitrile as solvent in one pot reaction (Scheme 1). We began our study utilizing reaction condition of our previous work for the synthesis of 2- and 1-alkyl/aryl/dialkylaminoquinolines and isoquinolines from different amines, quinoline, and isoquinoline-*N*-oxides.[22] We selected pyridine-*N*-oxide (**1a**) as a substrate for reaction and when it was treated with sodium azide in the existence of triflic anhydride as activator in acetonitrile solvent at 0 °C to ambient temperature for 8h as given away in Scheme 1 (entry 1, table 2), tetrazolo[1,5-*a*]pyridine (**2a**) was obtained in good yield (80%).



Scheme 1. Synthesis of tetrazolo[1,5-*a*]pyridine (**2a**)

Spectral data of compound (**2a**) are discussed here. In ^{1}H NMR Spectrum of **2a**, two doublets for two aromatic protons were observed at 8.87 (d, *J* 6.8 Hz, 1H), and 8.14 (d, *J* 9.2 Hz, 1H). Three aromatic protons appeared as multiplets in the range of 7.69-7.73 ppm whereas one more aromatic proton appeared as

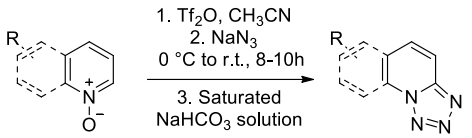
multiplets in the ranges of 7.24-7.28 ppm. The characteristic carbon signals appeared at δ 148.6, 131.9, 125.5, 116.7, 116.0 ppm. Molecular mass of the compound was confirmed by $[M + Na]^+$ at 143.0322 in the mass spectrum.

Further, we tried to see the effect of other solvents such as toluene, DMSO, diethyl ether, THF and dichloromethane and reaction of pyridine-*N*-oxide with sodium azide did not take place except acetonitrile as solvent (Table 1). In our earlier report, we also observed that only acetonitrile as solvent yielded product.[22] This showed that solvent might has some role for synthesis of tetrazolo fused pyridine derivatives.

Table 1. Effect of different solvents for the synthesis of tetrazolo[1,5-*a*]pyridine (**2a**).

Entry	Reaction Condition	% Yield of Product (**2a**)
1.	CH_3CN, Tf_2O (1.5 equiv.), 0 ^{0}C to rt, 8h	80%
2.	Toluene Tf_2O, 0 ^{0}C to rt, 10h	no reaction
3.	DMSO, Tf_2O, 0 ^{0}C to rt, 10h	no reaction
4.	Et_2O, Tf_2O, 0 ^{0}C to rt, 10h	no reaction
5.	THF, Tf_2O, 0 ^{0}C to rt, 10h	no reaction
6.	CH_2Cl_2, Tf_2O, 0 ^{0}C to rt, 10h	no reaction

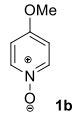
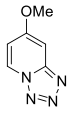
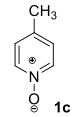
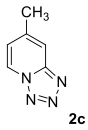
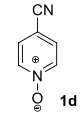
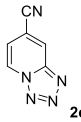
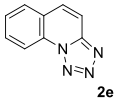
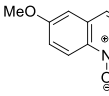
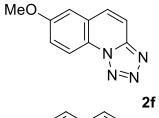
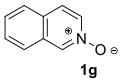
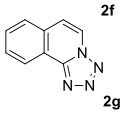
The above utilized reaction conditions were utilized to broaden the scope of the synthesis to substrates bearing electron donating sustituents *i.e.* 4-substituted tetrazolo[1,5-*a*]pyridines. 4-Methoxypyridine-*N*-oxide (**1b**) having an electron-releasing substituent was reacted with sodium azide using above used reaction condition and yielded 7-methoxytetrazolo[1,5-*a*]pyridine (**2b**) in 79% yield (Scheme 2, entry 2, table 2). Another electron releasing substrate *i.e.* 4-methylpyridine-*N*-oxide (**1c**) was also reacted through sodium azide to provide 7-methyltetrazolo[1,5-*a*]pyridine (**2c)**, in 75% yield (Scheme 2, entry 3, table 2). It was observed that electron donating group on pyridine-*N*-oxide did not have an effect on the yield (Table 2, entries 2, 3, 6). This methodology was extended to a substrate having an electron withdrawing group *i.e.* 4-cyanopyridine-*N*-oxide (**1d**) which was treated with sodium azide in the presence of triflic anhydride and acetonitrile as solvent at 0 °C to ambient temperature for 8 h to form tetrazolo[1,5-*a*]pyridine-7-carbonitrile (**2d**) in 72% yield (Scheme 2, entry 4, table 2). Both tetrazolo[1,5-*a*]quinoline (**2e**) and 7-methoxytetrazolo[1,5-*a*]quinoline (**2f**) were synthesized from quinoline-*N*-oxide (**1e**) and 6-methoxyquinoline-*N*-oxide (**1f**) in good yields, respectively (Scheme 2, entries 5-6, table 2). Compound (**2e**) was obtained from quinoline-*N*-oxide (**1e**) in 81% yield whereas compound **2f** was synthesized from 6-methoxy substituted quinoline-*N*-oxide (**1f**) in 76% yield (Scheme 2, entry 6, table 2) by using above used reaction conditions. Further, the method was used to synthesize tetrazolo fused isoquinoline **2g** in 78% when isoquinoline-*N*-oxide (**1g**) was treated with sodium azide in the optimized reaction condition (Scheme 2, entry 7, table 2).



1 **2**

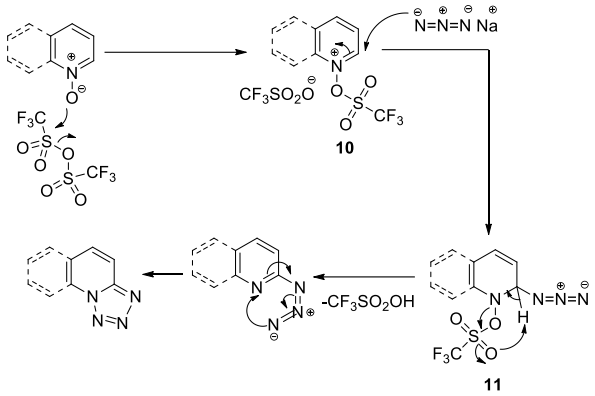
Scheme 2. Synthesis of tetrazolo fused pyridine derivatives (**2b**-**g**)

Table 2. Synthesis of tetrazolo fused pyridine derivatives (**2a**-**g**)

Entry	Starting Material (1a-g)	Product (2a-g)	%Yield (2a-g)
1	 **1a**	 **2a**	80
2	 **1b**	 **2b**	79
3	 **1c**	 **2c**	75
4	 **1d**	 **2d**	72
5	 **1e**	 **2e**	81
6	 1f	 **2f**	76
7	 **1g**	 **2g**	78

For the mechanistic step, we proposed reaction mechanism and it was shown as in Scheme 3.[15, 22] Triflic anhydride reacted with pyridine-*N*-oxide to yield activated pyridine-*N*-oxide intermediate **10**. Further, activated pyridine-*N*-oxide intermediate **10** reacted with azide by nucleophilic addition to give intermediate **11**. The hydrogen at C-2 position of intermediate **11** is abstracted by trifluoromethanesulfonate anion followed by

aromatization to give tetrazolo fused pyridine [1,5-*a*]pyridine (**2**) (Scheme 3). Triflic anhydride improved the CH-acidity and electrophilicity at the C-2 position of *N*-oxide after activation of pyridine-*N*-oxide. Further, detail mechanistic study and effect of substituents are underway in our laboratory.



Scheme 3. Proposed reaction mechanism

Conclusions

In conclusion, we have developed an efficient and mild methodology for preparation of tetrazolo-fused-pyridines from pyridine-*N*-oxide, quinoline-*N*-oxide, and isoquinoline-*N*-oxide, sodium azide, and triflic anhydride as activator in a one pot reaction. Tetrazolo-fused pyridine derivatives (**2a-g**) were synthesized in 72-81% yields. This methodology for the preparation of tetrazolo fused pyridine derivatives displayed a good functional group acceptance and proceeded well for both electron donating and withdrawing substituted pyridine-*N*-oxides derivatives. More mechanistic study details, effect of solvent and substituents effects are ongoing in our laboratory.

Experimental Section

General. Reactions were executed in oven-dried glassware, using solvents, previously dried and distilled. Reactions were done on in a nitrogen atmosphere. Acetonitrile was dried and distilled over CaH_2 and stored over 4 Å molecular sieves. Pyridine/quinoline/isoquinoline-*N*-oxides were used as commercially available. Other commercial reagents were used without further purification, unless otherwise specified. ^{1}H NMR and ^{13}C NMR spectra were taken on 400 MHz, and 100 MHz Bruker spectrometers, respectively, using $CDCl_3$ as solvent and TMS was used as internal standard. Mass was obtained from Agilent 6530 Accurate-Q-TOF mass spectrometer.

General experimental procedure. A solution of pyridine/quinoline/isoquinoline-*N*-oxide (1.0 mmol, 1.0 equiv) (**1a-g**) and sodium azide (1.2 mmol, 1.2 equiv) in dry CH_3CN (10 mL) was added $(Tf)_2O$ (0.25 mL, 1.5 mmol, 1.5 equiv) drop by drop at 0 °C. The reaction mixture was stirred for 8-10 h at room temperature and progress of reaction was observed by TLC. After the end of reaction, reaction was quenched by saturated $NaHCO_3$ solution

(20 mL), and compound was taken out with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed by brine (15 mL) and dried over anhydrous Na_2SO_4. The collective organic layer was concerted and purified by column chromatography on silica gel (60-120 mess) using mixture of hexane and ethyl acetate as eluent to give pure product (**2a-g)**.

Tetrazolo[1,5-*a*]pyridine (2a).[15] White solid; mp 156-57 °C; Yield: 80% (96 mg); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.87 (d, *J* 6.8 Hz, 1H), 8.14 (d, *J* 9.2 Hz, 1H), 7.69-7.73 (m, 1H), 7.24-7.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 131.9, 125.5, 116.7, 116.0; *m/z* $[M + Na]^+$ calculated for $C_5H_4N_4Na$: 143.0334; found: 143.0322.
7-Methoxytetrazolo[1,5-*a*]pyridine (2b).[15] Cream color solid; mp 172-73 °C; Yield: 79% (118 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* 7.6 Hz, 1H), 7.16 (d, *J* 2.0 Hz, 1H), 6.88 (dd, *J* 7.6, 2.4 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 150.4, 125.4, 112.0, 91.8, 56.4; *m/z* $[M + H]^+$ calculated for $C_6H_7N_4O$: 151.0620; found: 151.0611.
7-Methyltetrazolo[1,5-*a*]pyridine (2c).[18] White solid; mp 98-99 °C; Yield: 75% (100 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* 6.8 Hz, 1H), 7.77 (d, *J* 1.2 Hz, 1H), 7.07 (dd, *J* 7.2, 1.6 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 144.1, 124.3, 119.5, 113.4, 21.5; *m/z* $[M+Na]^+$ calculated for $C_6H_6N_4Na$: 157.049; found: 157.048,
Tetrazolo[1,5-*a*]pyridine-7-carbonitrile (2d).[18] Cream solid; mp 131-32 °C; Yield: 72% (104 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (dd, *J* 7.2, 0.8 Hz, 1H), 8.51 (s, 1H), 7.45 (dd, *J* 7.1, 1.3 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 147.6, 127.1, 122.6, 117.0, 116.1, 115.3; *m/z* $[M+H]^+$ calculated for $C_6H_4N_5$: 146.0467; found: 147.0443
Tetrazolo[1,5-*a*]quinoline (2e).[15] White solid; mp 150-52 °C; Yield: 81% (138 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d*, J* 8.4 Hz, 1H), 7.99-8.02 (m, 2H), 7.89-7.98 (m, 2H), 7.75-7.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 133.4, 131.2, 130.8, 129.0, 128.0, 123.8, 116.8, 112.6; *m/z* $[M + Na]^+$ calculated for $C_9H_6N_4Na$: 193.0490; found: 193.0479.
7-Methoxytetrazolo[1,5-*a*]quinoline (2f). White solid; mp 203-05 °C; Yield: 76% (152 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* 8.8 Hz, 1H), 7.86-7.92 (m, 2H), 7.49 (dd, *J* 9.2, 2.8 Hz 1H), 7.35 (d, *J* 2.4 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159, 146.8, 132.8, 125.4, 125.2, 120.7, 118.3, 113.0, 109.6, 55.9; *m/z* $[M + Na]^+$ calculated for $C_{10}H_8N_4ONa$: 223.0596; found: 223.0582.
Tetrazolo[5,1-*a*]isoquinoline (2g).[15] Cream colour solid; mp 124-26 °C; Yield: 78% (133 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78-8.83 (m, 1H), 8.58 (d, *J* 7.6 Hz, 1H), 7.93-7.98 (m, 1H), 7.83-7.90 (m, 2H), 7.46 (d, *J* 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 131.7, 131.6, 129.8, 127.7, 124.9, 121.09, 119.7, 117.7; *m/z* $[M + Na]^+$ calculated for $C_9H_6N_4Na$: 193.0490; found: 193.0477.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra are available in a supplementary material file

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