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.\(^9\)\(^-\)\(^\)\(^1\)\(^3\) There are few reports for the synthesis of tetrazolo[1,5-\(\alpha\)]pyridine derivatives.\(^14\)\(^-\)\(^\)\(^1\)\(^9\) Tetrazolo[1,5-\(\alpha\)]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-\(\alpha\)]pyridine is reaction of pyridine-N-oxide with arenesulfonyl azides\(^2\)\(^0\) and observed yields were poor. Other developed method is treating 2-halopyridines\(^9\)\(^,\)\(^1\)\(^6\)\(^-\)\(^1\)\(^7\) or pyridine N-oxides with sodium azide.\(^1\)\(^5\)\(^,\)\(^1\)\(^8\) Tetrazole diazines can also be prepared from diazine-N-oxides in the presence of tosyl chloride and trimethylsilyl.\(^1\)\(^9\) The synthesis of halopyridines requires the halogenation of pyridine precursors that might lead to low overall yields.\(^2\)\(^1\) 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-\(\alpha\)]pyridine derivatives from easily manageable starting materials.

Results and Discussion

Here, we report a method for the synthesis of tetrazolo[1,5-\(\alpha\)]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.\(^2\)\(^3\) 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-\(\alpha\)]pyridine (2a) was obtained in good yield (80%).

Scheme 1. Synthesis of tetrazolo[1,5-\(\alpha\)]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).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Condition</th>
<th>% Yield of Product (2a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CH(_3)CN, Tf(_2)O (1.5 equiv.), 0 °C to rt, 8h</td>
<td>80% no reaction</td>
</tr>
<tr>
<td>2.</td>
<td>Toluene Tf(_2)O, 0 °C to rt, 10h</td>
<td>no reaction no reaction</td>
</tr>
<tr>
<td>3.</td>
<td>DMSO, Tf(_2)O, 0 °C to rt, 10h</td>
<td>no reaction no reaction</td>
</tr>
<tr>
<td>4.</td>
<td>Et(_2)O, Tf(_2)O, 0 °C to rt, 10h</td>
<td>no reaction no reaction</td>
</tr>
<tr>
<td>5.</td>
<td>THF, Tf(_2)O, 0 °C to rt, 10h</td>
<td>no reaction no reaction</td>
</tr>
<tr>
<td>6.</td>
<td>CH(_2)Cl(_2), Tf(_2)O, 0 °C to rt, 10h</td>
<td>no reaction no reaction</td>
</tr>
</tbody>
</table>

The above utilized reaction conditions were utilized to broaden the scope of the synthesis to substrates bearing electron donating substituents 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).
Scheme 2. Synthesis of tetrazolo fused pyridine derivatives (2b-g)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material (1a-g)</th>
<th>Product (2a-g)</th>
<th>% Yield (2a-g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="1a" /></td>
<td><img src="image2" alt="2a" /></td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="1b" /></td>
<td><img src="image4" alt="2b" /></td>
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<tr>
<td>6</td>
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<td><img src="image12" alt="2f" /></td>
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<td>7</td>
<td><img src="image13" alt="1g" /></td>
<td><img src="image14" alt="2g" /></td>
<td>78</td>
</tr>
</tbody>
</table>

For the mechanistic step, we proposed reaction mechanism and it was shown as in Scheme 3.\textsuperscript{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-\alpha]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$_3$CN (10 mL) was added (Tf)$_2$O (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 CH₂Cl₂ (3 x 50 mL). The combined organic layer was washed by brine (15 mL) and dried over anhydrous Na₂SO₄. The collective organic layer was concentrated and purified by column chromatography on silica gel (60-120 mesh) using mixture of hexane and ethyl acetate as eluent to give pure product (2a-g).

**Tetrazolo[1,5-α]pyridine (2a).** White solid; mp 156-57 °C; Yield: 80% (96 mg); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 148.6, 131.9, 125.5, 116.7, 116.0; m/z [M + Na]⁺ calculated for C₆H₅NaNa: 143.0334; found: 143.0322.

**7-Methoxytetrazolo[1,5-α]pyridine (2b).** Cream color solid; mp 172-73 °C; Yield: 79% (118 mg); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 162.4, 150.4, 125.4, 112.0, 91.8, 56.4; m/z [M + H]⁺ calculated for C₁₆H₁₃N₅O: 223.0620; found: 223.0582.

**Tetrazolo[1,5-α]pyridine-7-carbonitile (2d).** Cream solid; mp 131-32 °C; Yield: 72% (104 mg); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100MHz, CDCl₃) δ 147.6, 127.1, 122.6, 117.0, 116.1, 115.3; m/z [M+Na]⁺ calculated for C₁₆H₁₄N₄: 217.0749; found: 217.0719.

**Tetrazolo[1,5-α]quinoline (2e).** White solid; mp 150-52 °C; Yield: 81% (138 mg); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 147.4, 133.4, 131.2, 130.8, 129.0, 128.0, 123.8, 116.8, 116.2; m/z [M + Na]⁺ calculated for C₁₆H₁₃N₅O: 193.0490; found: 193.0479.

**7-Methoxytetrazolo[1,5-α]quinoline (2f).** White solid; mp 203-05 °C; Yield: 76% (152 mg); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₆H₁₄N₅O Na: 223.0596; found: 223.0582.

**Tetrazolo[5,1-α]isoquinoline (2g).** Cream colour solid; mp 124-26 °C; Yield: 78% (133 mg); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₆H₁₃N₅O: 193.0490; found: 193.0477.

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**Supplementary Material**

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

**References**


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   https://doi.org/10.1039/C9RA10397J

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