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Synthesis, Characterization, Solvent and Temperature effects of 6-(isoxazol-5-yl)furo[3,2-b]pyridine

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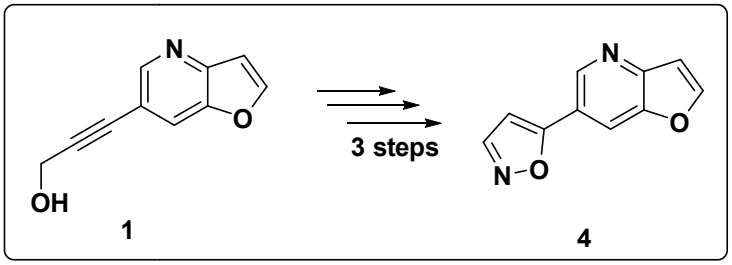
ABSTRACT

Herein, we have depicted the three step synthesis of 6-(isoxazol-5-yl) furo [3,2-b] pyridine under correlation with different solvents, temperatures and different mole percentage of CuCl optimizations shown in Scheme I, tables 1 to 4 and further confirmed by spectral analysis.



Graphical Abstract

KEYWORDS 6-(isoxazol-5-yl) furo [3,2-b]pyridine, DIAD, Hydrazine, *m*-CPBA, TfOH, CuCl

INTRODUCTION

Chemotherapy isbroadly used, mostly against unfeasible cancer [1], as the primary therapy or as an adjunct therapy before and/or after another treatment [2]. Furthermore, chemotherapy use is restricted as it has feeble effectiveness, trifling selectivity alongside target cells, and unwanted side belongings such as alopecia, queasiness, and vomiting [3-4]. Many regular extracts with anti-cancer activity wereestimated in past 15 years [5].

Different types of heterocyclic derivatives such as isoxazole are used extensively as agrochemicals in medicine; indeed, they are efficient in anti-cancer chemotherapy [6-9]. Investigators have found that the isoxazole ring imparts it with anti-proliferative [10-11], hypoglycemic [12], ache killing, bactericidal [13-14], and anti-inflammatory [15] activities.

Pyridine is a precisemutual solvent in organic laboratories, its offshoots have diverse applications in functional nano-materials, as chief ligands for organometallic compounds, and in asymmetric catalysis [16-17]. In organic chemistry, pyridine and its derivatives play dynamic roles [18].Herein, we label thesynthesis of 6-(isoxazol-5-yl) furo [3,2-b]pyridine as shown below.

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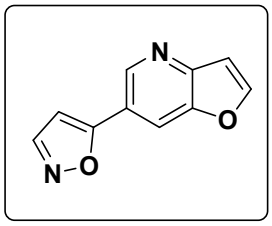
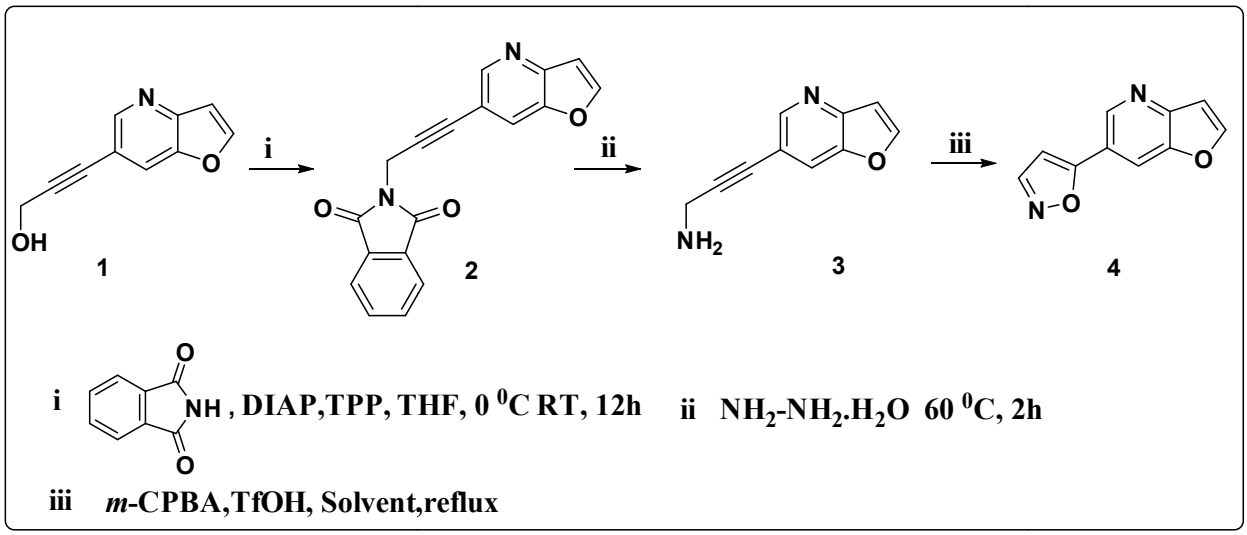


EXPERIMENTAL SECTION



Synthetic Steps:

Step-i: Synthesis of 2-(3-(furo[3,2-b]pyridin-6-yl)prop-2-yn-1-yl)isoindoline-1,3-dione (2)

To a stirred solution of 3-(furo[3,2-b]pyridin-6-yl)prop-2-yn-1-ol**(1)** (1.0 eq), in THF (10 v) was added TPP (1.5 eq) and **DIAD (**2.0 eq**)** at 0 °C then stirred at room Temperature 1h. And added phthalimide (1.2 eq) and stirred at RT for 12 h. The progress of the reaction was monitored by TLC. After completion of the reaction mixture was diluted with sat NH_4Cl solution (10 V), extracted with EtoAc(3x100 mL). The combined organic layer was washed with water (200 mL), brine (200 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by gradient column chromatography (eluted with 20% EtOAc in Hexane) to 2-(3-(furo[3,2-b]pyridin-6-yl)prop-2-yn-1-yl)isoindoline-1,3-dione (**2)** (yield: 55%) as light brownish solid.

Step-ii: Synthesis of 3-(furo[3,2-b]pyridin-6-yl)prop-2-yn-1-amine (3)

To a stirred solution of 2-(3-(furo[3,2-b]pyridin-6-yl)prop-2-yn-1-yl)isoindoline-1,3-dione (**2)**(1.0 eq), in THF (10 v) was added Hydrazine hydrate(5.0 eq)at 0 °C then stirred at 0 °C for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction

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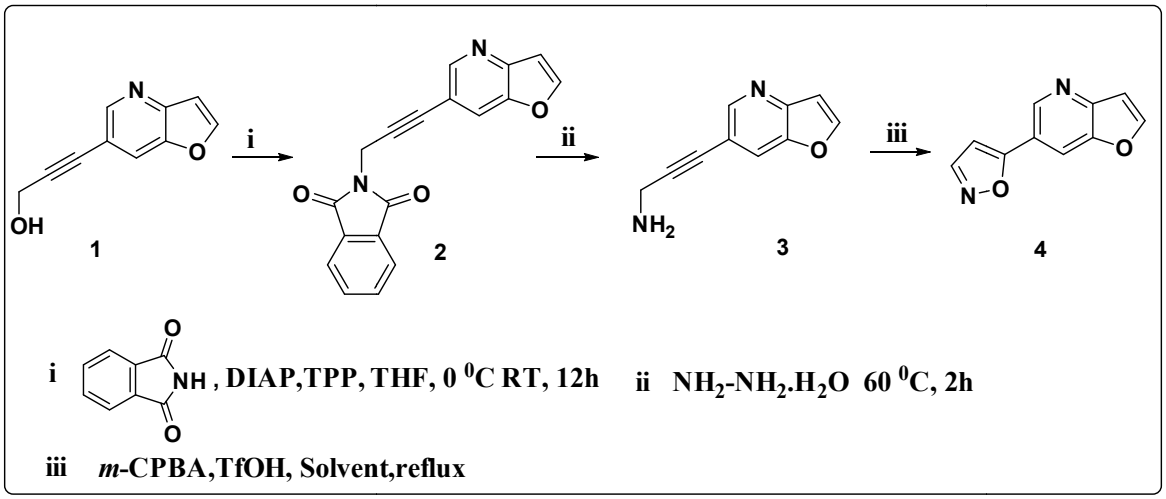
mixture was diluted with water (10 V), extracted with EtoAc(3x100 mL). The combined organic layer was washed with water (200 mL), brine (200 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by gradient column chromatography (eluted with 60 % EtOAc in Hexane) to 3-(furo[3,2-b]pyridin-6-yl)prop-2-yn-1-amine (**3)** (yield: 62%) as pale brown solid.

Step-iii: Synthesis of 6-(isoxazol-5-yl)furo[3,2-b]pyridine(4)

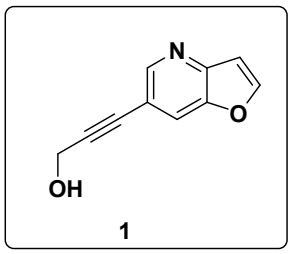
3-(furo[3,2-b]pyridin-6-yl)prop-2-yn-1-amine **(3)**(0.5 mmol, 1.0 equiv.), *m*-CPBA (1.0 mmol, 2.0 equiv.), **Solvent** (5 mL), stir under nitrogen atmosphere at room temperature for 30 minutes, then addtrifluoromethanesulfonic acid (1.0 mmol, 2.0 equiv.), heat at reflux under atmosphere of airfor 2 hr, oxidation of propargylamines to the agreeing oximes monitored by CuCl (0.15 equiv.) intra-molecular cyclization of the end, isoxazole -pyridine bearing light purple colour.



Scheme I Three –Step synthesis of 6-(isoxazol-5-yl) furo [3,2-b] pyridine

RESULTS AND DISCUSSIONS

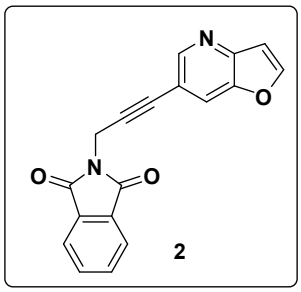
3-(furo[3,2-b]pyridin-6-yl)prop-2-yn-1-ol (1):



MF: $C_{10}H_7NO_2$, **BP:**384-385^{0}C, **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.74 (s, 1H), 8.01 (d, *J* = 30.2 Hz, 2H), 6.99 (d, *J* = 7.5 Hz, 1H), 4.45 (s, 2H), 0.55 (s, 1H),**^{13}C NMR (100 MHz, $CDCl_3$)** δ 154.69, 147.71, 145.26, 117.84 , 116.05, 113.30 , 88.01, 79.41 , 49.44, **ESI m/z:**

173.10,Elemental Analysis: **(Found)**C, 69.48; H, 4.08; N, 8.11; **(Calcd)**C, 69.36; H, 4.07; N, 8.09.

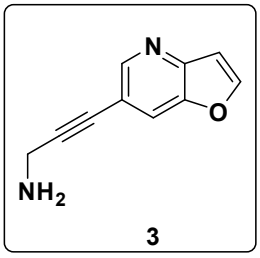
2-(3-(furo[3,2-b]pyridin-6-yl)prop-2-yn-1-yl)isoindoline-1,3-dione (2):



2

MF: $C_{18}H_{10}N_2O_3$, **BP:**673-674^{0}C, **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.41 (s, 1H), 8.12 (s, 1H), 7.82 (d, *J* = 7.3 Hz, 3H), 7.47 (s, 2H), 6.90 (s, 1H), 4.37 (s, 2H), **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.23, 154.69, 147.71, 145.46, 132.21, 125.48, 117.84, 114.67, 94.75 , 90.32 , 32.04,**ESI m/z:** 302.10, Elemental Analysis: **(Found)**C, 71.64; H, 3.34; N, 9.29; **(Calcd)**C, 71.52; H, 3.33; N, 9.27.

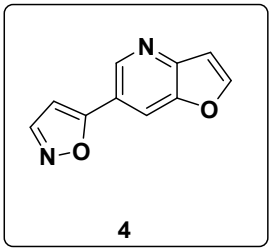
3-(furo[3,2-b]pyridin-6-yl)prop-2-yn-1-amine (3):



3

MF: $C_{10}H_8N_2O$**, BP:** 363-364 ^{0}C, **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.56 (s, 1H), 7.98 (s, 1H), 7.83 (s, 1H), 6.92 (s, 1H), 3.39 (s, 2H), 1.17 (s, 2H), **^{13}C NMR (100 MHz, $CDCl_3$)** δ 154.69, 147.71, 145.26, 117.84, 116.05, 113.30, 91.53, 74.58, 29.49, **ESI m/z:**172.10, Elemental Analysis: **(Found)** C, 69.88; H, 4.69; N, 16.29; **(Calcd)** C, 69.76; H, 4.68; N, 16.27.

6-(isoxazol-5-yl)furo[3,2-b]pyridine(4):



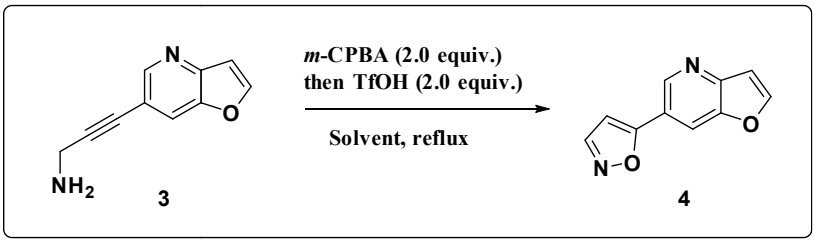
4

MF: $C_{10}H_6N_2O_2$, **BP:**386-387 ^{0}C, **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.84 (s, 1H), 8.23 (s, 1H), 7.88 (s, 1H), 7.67 – 7.44 (m, 2H), 6.97 (s, 1H),**^{13}C NMR (100 MHz, $CDCl_3$)** δ 164.65 , 154.69 ,

154.21 ,147.65, 144.35, 140.08 , 136.17 , 116.05, 113.12, 98.69, **ESI m/z:**186.04, Elemental Analysis: **(Found)**C, 64.64; H, 3.26; N, 15.07; **(Calcd)**C, 64.52; H, 3.25; N, 15.05.

Optimization of reaction conditions

Table 1. Screening of Solvent[a]

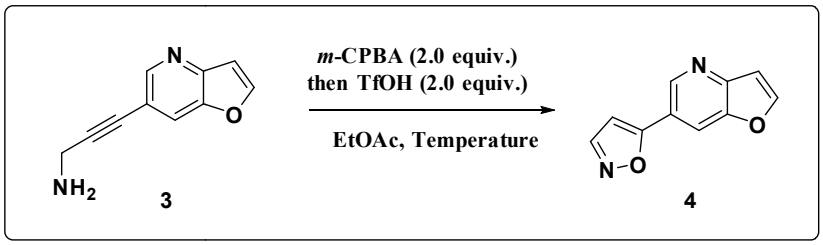


Entry	Solvent	Yield (%) [b]
1	THF	61
2	1,4-dioxane	61
3	DCE	60
4	**EtOAc**	**65**
5	DCM	45[c]
6	CH_3CN	45

[a]Reaction condition: **3**(0.5 mmol, 1.0 equiv.), *m*-CPBA (1.0 mmol, 2.0 equiv.), **Solvent** (5 mL), stir under nitrogen atmosphere at room temperature for 30 minutes, then add trifluoromethanesulfonic acid (1.0 mmol, 2.0 equiv.), heat at reflux under atmosphere of airfor two hours; [b]Isolated yield. [c] Incomplete consumption of oxime intermediate.

After screening, the optimal solvent is **EtOAc**.

Table 2. Screening of Temperature[a]



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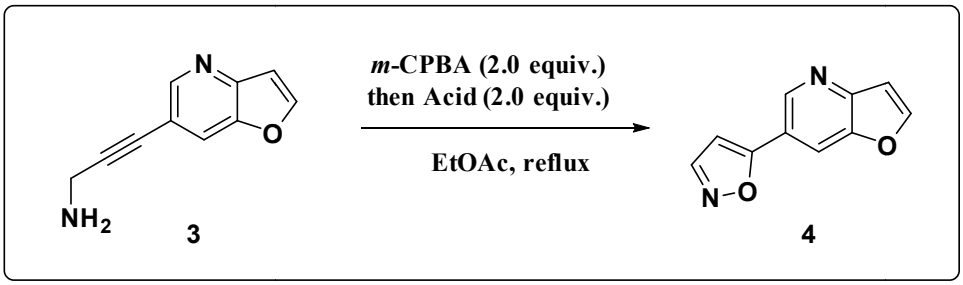
Entry	Temperature (^{0}C)	Yield (%) [b]
1	60	51
2	70	54
3	**reflux**	**65**
4 [c]	90	51

[a]Reaction condition: **3**(0.5 mmol, 1.0 equiv.), *m*-CPBA (1.0 mmol, 2.0 equiv.), EtOAc (5mL), stir under nitrogen atmosphere at room temperature for 30 minutes, then add trifluoromethanesulfonic acid (1.0 mmol, 2.0 equiv.), heat at reflux under atmosphere of airfor two hours; [b]Isolated yield; [c] The reaction was carried out in sealed tube.After screening, the optimal temperature is **reflux**.

Table 3. Screening of Acids[a]



Entry	Acid	Yield (%) [b]
1	H_2SO_4	60
2	CF_3COOH	62
3	CF_3SO_3H	65
4	**CuCl**	**84**
5	CuI	78
6	$CuCl_2$	74
7	$Cu(OAc)_2$	81
8	$EeCl_3$	72
9	$ZnCl_2$	70

[a]Reaction condition: **3** (0.5 mmol, 1.0 equiv.), *m*-CPBA (1.0 mmol, 2.0 equiv.), EtOAc (5mL), stir under nitrogen atmosphere at room temperature for 30 minutes, then add **Acid**(1.0 mmol, 2.0 equiv.), heat at reflux under atmosphere of air for two hours; *b* Isolated yield. After screening, the optimal Lewis acid is **CuCl**.

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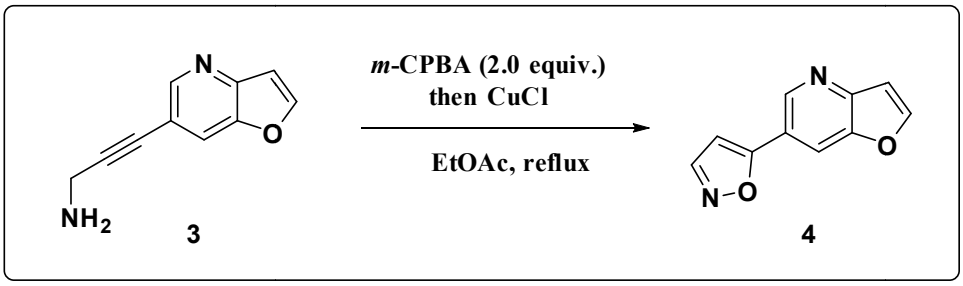
Table 4. Screening the equiv. of CuCl [a]



Entry	CuCl (equiv.)	4 Yield (%) [b]
1	0.1	80
2	**0.15**	**84**
3	0.2	84
4	0.5	84

[a]Reaction condition: **3** (0.5 mmol, 1.0 equiv.), *m*-CPBA (1.0 mmol, 2.0 equiv.), EtOAc (5 mL), stir under nitrogen atmosphere at room temperature for 30 minutes, then add **CuCl**, heat at reflux under atmosphere of air for two hours; [b]Isolated yield. After screening, the optimal equiv. of CuCl is **0.15**.

CONCLUSION

Three –Step synthesis of 6-(isoxazol-5-yl) furo [3,2-b]pyridine has been developed with promising yields, under solvent, temperature and mole percentage of catalyst optimizations were studied and correlated in tabulations.

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