



AN EFFICIENT COPPER CATALYZED SYNTHESIS OF 2-METHOXY-3-(1H-1,2,3-TRIAZOL-1-YL) METHYL)QUINOXALINES UNDER CLICK CONDITIONS

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ABSTRACT

In order to synthesize a novel heterocyclic compound with quinoxaline and 1,2,3 triazole moieties containing potential biological activities, we carried out Huisgen type of 1,3 dipolar cycloaddition where 2-azido methyl quinoxaline and trimethyl silyl acetylene are used as dipole and dipolarophile respectively. To make the reaction more feasible, CuSO₄.5H₂O is used as a catalyst and sodium ascorbate was used as a reducing agent. Targeted products were characterized by IR, NMR, and Mass spectroscopic methods.

KEYWORDS: Click chemistry, 1,2,3 triazoles, quinoxalines, cycloaddition, dipole, dipolarophile.

INTRODUCTION

Copper-catalyzed cycloaddition reaction between azide and alkyne is a very good example of 'Click chemistry, which Sharpless et al. developed. The resulting 1,2,3 triazoles have a wide range of applications in pharmaceutical, agrochemical, and material science fields. Cefatrizine (BL-S640) containing 1,2,3 triazole moiety has antibiotic and anti-proliferative activity and is used for treating breast cancers^[1]. They act as ligands for ruthenium in dye-sensitized solar cells.

The advantage of using a copper catalyst is instead of forming regio isomers only one product is formed. It won't be possible to get the product in a single step without a copper catalyst. Other benefits are high yielding, faster reaction, and can be performed at room temperature. Click reactions are particularly suitable for reactions where there is a problem of isolating the product. These reactions are mostly influenced by steric and electronic effects.

Huisgen Cycloaddition is a reaction between dipolarophile and 1,3 dipolar compounds (a compound containing delocalized electrons and charge separation over three atoms) leading to five-membered heterocyclic rings.

Properties such as high chemical stability, aromatic nature, high dipole moment, and ability to form hydrogen bonding of 1,2,3 triazoles make the synthesis easy and therefore increase their importance in click synthesis. The reaction is favored by the presence of electron-withdrawing groups on dipolarophile which in turn favors interaction between HOMO and LUMO of dipolarophile and dipole respectively, leading to the formation of new bonds. From the literature, it was known that copper-catalyzed click reaction (CuAAC) is used for the synthesis of fused pyridine-triazole compounds. Lu Yong Wu *et al.* achieved the synthesis of 1-substituted 1,2,3 triazoles through click reaction from azides and acetylene gas using a catalyst CuI/Et₃N in DMSO^[iii]. The nature of the solvent influences the progress of the reaction and the yield of the product. D. Khalili and others synthesized a high yield of 1,4 disubstituted 1,2,3 triazoles from sodium azide with terminal aromatic and aliphatic alkynes using CuAl₂O₄ as catalyst and water as solvent^[3]. 1,4 disubstituted 1,2,3 triazoles were also synthesized in the presence of highly efficient CuSO₄·5H₂O in sodium ascorbate/DABCO/AcOH catalytic system^[iv]. A wide range of copper catalysts such as CuI, aqueous CuSO₄, Copper chloride, Copper carboxylates, Copper aluminate spinel, and Cu/Fe bimetallic systems were used to achieve click reaction^[v-xi]. Herein we report the synthesis of fused quinoxaline-1,2,3 triazole compounds using Huisgen type of [3+2] azide-alkyne cycloaddition and CuSO₄ in water as a catalyst at room temperature.

RESULTS AND DISCUSSION

The synthesis of triazolo quinoxaline was illustrated in Scheme 1. Intermediate **2** 2-(azidomethyl)-3-methoxyquinoxaline was prepared from starting material (3-methoxyquinoxalin-2-yl)methanol **1** upon reacting with diphenyl phosphorylazide (DPPA) and triethanolamine (TEA) in the presence of dimethyl formamide (DMF) at 80°C for 4 h. Then compound **2** was treated with CuSO₄, under the click conditions for 12 h. to afford pure target compound **3**. In the ¹H NMR of compound **3**, three methoxy protons appeared at 3.80, methylene -CH₂ protons were observed at 5.03, and remaining all aromatic triazole and quinoxaline protons were observed at 8.11 to 7.72 confirming the product.

EXPERIMENTAL

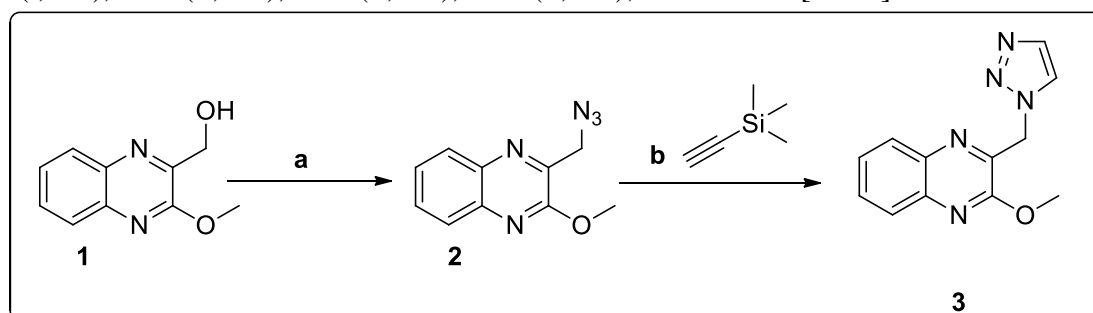
Research-grade chemicals were purchased for the synthesis of targeted compounds. TLC silica gel 60 F254 aluminum plates were used to achieve thin-layer chromatography and the spots were examined under UV light in the UV chamber. Varian 400 MHz spectrometer was used for recording ¹H NMR spectra. DMSO was used as a solvent for dissolving samples. Chemical shift (δ) values were recorded in ppm downfield from tetramethyl silane (TMS), an internal standard. PE SCIEX API 3000 mass spectrometer was used for recording mass spectra.

Synthesis of 2-(Azidomethyl)-3-methoxyquinoxaline (2): To a solution of (2-methoxyquinoxalin-3-yl)methanol (**1**) (1 eq.) in 5 vol. of DMF, 1.5 eq. of DPPA and 3 eq. of TEA were added and the reaction mixture was stirred at 80°C for 4 h. The status of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was poured into ice-cold water and extracted with Ethyl acetate (EtOAc). The attained extract was washed with water followed by a brine solution. It was then dried over anhydrous Na₂SO₄ and the solvent was removed by distillation. The crude product was purified by column chromatography; the desired solid was then eluted with 20% EtOAc in Pet ether to afford an 83% yield of off-white solid, 2-(azidomethyl)-3-methoxyquinoxaline (**2**). IR (KBr): 1491, 1532,

2868, 3046 cm^{-1} ; $^1\text{H NMR}$ (DMSO-d_6), 400 MHz: δ = 8.10 (d, 2H, J = 7.8 Hz), 7.90 (t, 2H), 3.81 (s, 3H), 2.82 (s, 2H); Mass = 216.1 $[\text{M}+\text{H}]^+$

Synthesis of 2-Methoxy-3-(1*H*-1,2,3-triazol-1-yl)methyl)quinoxaline (3):

Trimethylsilylacetylene (1.5 eq.), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.2 eq.), and sodium ascorbate (0.4 eq.) were added to a solution 2-(azidomethyl)-3-methoxyquinoxaline (2) (1 eq.) in MeOH/water (1:1 ratio, 5 Vol) at room temperature with continuous stirring for 12 h. After the addition of aqueous ammonium chloride solution, the mixture was extracted with EtOAc (30 mL). The combined organic phase was washed with water, and brine solution, and dried over anhydrous Na_2SO_4 and then distilled to remove the solvent. The obtained solid product was purified by column chromatography using 50% EtOAc in Pet ether as eluent to afford 2-methoxy-3-(1*H*-1,2,3-triazol-1-yl)methyl)quinoxaline (3) as off-white solid with 84% yield. M.p. 140-142°C. IR (KBr): 1452, 2862, 3028 cm^{-1} ; $^1\text{H NMR}$ (DMSO-d_6), 400 MHz: δ = 8.11 (d, 2H, J = 8.0 Hz), 7.89 (t, 2H), 7.72 (s, 2H), 5.03 (s, 2H), 3.80 (s, 3H); Mass = 242 $[\text{M}+\text{H}]^+$



Scheme 1 Synthesis of 2-Methoxy-3-(1*H*-1,2,3-triazol-1-yl) methyl) quinoxalines

Reagents and conditions: **a.** DPPA, DMF, TEA, 80°C, 4 h;

b. DMF, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, Sodium ascorbate, 70°C, 12 h.

CONCLUSION

Huisgen type of 1,3 dipolar cyclo addition was used to synthesize 2-Methoxy-3-(1*H*-1,2,3-triazol-1-yl) methyl)quinoxalines from 2-azidomethyl quinoxaline (dipole) and trimethyl silyl acetylene (dipolarophile), where $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ is used as a catalyst and sodium ascorbate was used as reducing agent. Achieved products were characterized by IR, NMR, and Mass spectroscopic methods.

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