

Synthesis of Some New 5-(1-Phenyl-1*H*-1,2,3-triazol-4-yl)-1*H*-tetrazoles and Evaluation of Their Antimicrobial Activity¹

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Abstract—a series of new tetrazole derivatives were synthesized by a reaction of triazole oxime with sodium azide catalyzed by copper acetate and isolated with high yield under mild conditions. All synthesized compounds were characterized by IR, NMR, and MS data. Evaluation of antimicrobial activity of the products against Gram-positive and Gram-negative bacterial and antifungal strains has been carried out. Among the compounds **3a**, **3c**, **3e**, and **3f** exhibited high antibacterial activity and compounds **3a**, **3c**, **3e** demonstrated high antifungal activity.

Keywords: triazole aldehyde, triazolyl tetrazole, copper acetate, and antibacterial activity

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INTRODUCTION

Tetrazoles found a wide range of applications in materials science [1], as lipophilic spacers and metabolically stable carboxylic acid surrogates [2], nitrogen-containing heterocyclic ligands [3], in information recording systems [4], and medicine [2–7].

RESULTS AND DISCUSSION

Herein we report a simple method of synthesis of 5-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-1*H*-tetrazole via the reaction of organic oxime with NaN₃ in the presence of 25 mol % of Cu(OAc)₂ as a catalyst in DMF solution (Scheme 1). The newly synthesized compounds were characterized by NMR and MS. In ¹H NMR spectrum of compound **3a** the triazole proton was recorded at δ 8.17. In ¹³C NMR spectrum the tetrazole ipso carbon was recorded at 151.9 ppm. Its LC-MS spectrum contained the peak [*M* + *H*]⁺ at *m/z* 214. The above data supported the structure of **3a** to be 5-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-1*H*-tetrazole.

Antibacterial activity. Antibacterial activity of compounds **3a**, **3c**, **3e**, and **3f** demonstrated distinctive zones of inhibition in cases of *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Klebsiella pneumoniae* (compared to Gatifloxacin at

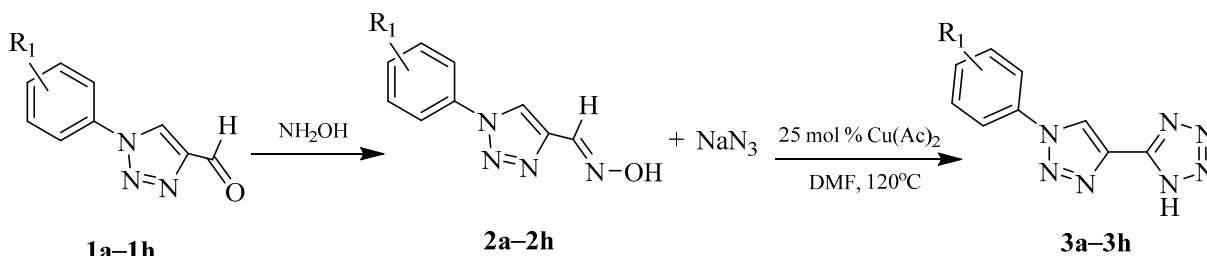
10 µg/mL and 20 µg/mL). Compounds **3b** and **3g** demonstrated zones of inhibition against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Klebsiella pneumoniae* to be almost equal to the standard drug, whereas the other compounds exhibited the moderate activity.

Antifungal activity. Antifungal activity of synthesized compounds **3a–3h** was tested against three pathogenic fungi: *Fusarium oxysporum*, *Aspergillus nigerzeae* and *Aspergillus flavus* at the concentration of 100 µg/mL compared to the standard drug Clotrimazole (100 µg/mL). Compounds **3a**, **3c**, **3e** demonstrated high activity against *Aspergillus nigerzeae*, *Aspergillus flavus* and *Fusarium oxysporum*. The other products exhibited moderate activity against pathogenic fungi.

EXPERIMENTAL

Melting points were determined in open glass capillary tube on a Gallen-Kamp MFB-595 apparatus. Elemental analysis was performed on a Perkin Elmer CHN-2400 analyzer. IR spectra (KBr discs) were recorded on a Perkin-Elmer FT-IR-8400s. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded on a Bruker Avance II 400 spectrometer in CDCl₃ and DMSO-*d*₆ using TMS as the internal standard. MS were recorded on a SHIMADZU LCMS

¹ The text was submitted by the authors in English.

Scheme 1. Synthesis of 5-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-1*H*-tetrazoles (**3a–3h**).

2020 mass spectrometers. Progress of the reactions was monitored by TLC (Silica gel, aluminium sheets 60 F₂₅₄, Merck).

Synthesis of 5-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-1*H*-tetrazole (3a–3h**).** A mixture of an oxime (**2a–2h**) (1 mmol), sodium azide (1.5 mmol), the catalyst (25 mol %) in DMF (3 mL) was heated at 120°C in a 25 mL round bottomed flask for 8 h. Upon completion of the reaction (TLC), the mixture was cooled down to room temperature and 5 mL of water were added followed by 5 mL of 2 N HCl. The mixture was stirred for 10 min and a product was extracted with ethylacetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The products were purified by column chromatography (silica gel) using petroleum ether/ethyl acetate (3 : 1) as the eluent.

5-[1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-1*H*-tetrazole (3a**).** Yield 95%, mp 166–168°C. IR spectrum, ν , cm^{-1} : 2340 (N=N–N–), 1572, 1450 (C=C). ^1H NMR spectrum, δ , ppm: 8.17 s (1H, triazole H), 7.73–7.84 m (2H, Ar-H), 7.41–7.51 m (2H, Ar-H), 6.90–7.02 m (2H, Ar-H). ^{13}C NMR spectrum, δ , ppm: 151.9, 147.4, 129.8, 126.4, 125.4, 122.7, 121.1. M 214 $[M + \text{H}]^+$. Found, %: C 50.58; H 3.22; N 45.78. $\text{C}_9\text{H}_7\text{N}_7$. Calculated, %: C 50.70; H 3.31; N 45.99.

5-[1-(2-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-1*H*-tetrazole (3b**).** Yield 95%, mp 175–177°C. IR spectrum, ν , cm^{-1} : 2338 (N=N–N–), 1570, 1452 (C=C). ^1H NMR spectrum, δ , ppm: 8.07 s (1H, triazole H), 7.94–7.97 m (1H, Ar-H), 7.70–7.72 m (2H, Ar-H), 7.04–7.11 m (2H, Ar-H). ^{13}C NMR spectrum, δ , ppm: 153.3, 147.1, 135.6, 134.2, 130.8, 129.8, 127.8, 127.7, 121.6. M 248 $[M + \text{H}]^+$. Found, %: C 43.65; H 2.44; N 39.59. $\text{C}_9\text{H}_6\text{ClN}_7$. Calculated, %: C 43.65; H 2.44; N 39.59.

5-[1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-1*H*-tetrazole (3c**).** Yield 96%, mp: 158–160°C. IR spectrum, ν , cm^{-1} : 2341 (N=N–N–), 1570, 1453 (C=C). ^1H NMR spectrum, δ , ppm: 8.09 s (1H, triazole H), 7.95–7.97 m (1H, Ar-H), 7.74–7.76 m (2H, Ar-H), 7.05–7.10 m (2H, Ar-H). ^{13}C NMR spectrum, δ , ppm: 152.4, 145.8, 136.9, 129.6, 128.7, 120.4, 119.3. M 248 $[M + \text{H}]^+$. Found, %: C 43.62; H 2.46; N 39.58. $\text{C}_9\text{H}_6\text{ClN}_7$. Calculated, %: C 43.65; H 2.44; N 39.59.

5-[1-(2-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-1*H*-tetrazole (4d**).** Yield 95%, mp 164–166°C. IR, ν , cm^{-1} : 2345 (N=N–N–), 1572, 1453 (C=C). ^1H NMR spectrum, δ , ppm: 8.31 s (1H, triazole H), 7.81–7.85 m (2H, Ar-H), 7.26–7.32 m (1H, Ar-H), 7.10–7.15 m (2H, Ar-H), 3.93 s (1H, OCH₃). ^{13}C NMR spectrum, δ , ppm: 153.3, 147.1, 134.2, 130.8, 129.8, 127.8, 122.7, 121.6, 118.5, 51.0. M 244 $[M + \text{H}]^+$. Found, %: C 49.22; H 3.52; N 40.25. $\text{C}_{10}\text{H}_9\text{N}_7\text{O}$. Calculated, %: C 49.38; H 3.73; N 40.31.

5-[1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-1*H*-tetrazole (3e**).** Yield 95%, mp 168–170°C. IR spectrum, ν , cm^{-1} : 2344 (N=N–N–), 1571, 1452 (C=C); ^1H NMR spectrum, δ , ppm: 8.41 s (1H, triazole H), 7.90–7.95 m (2H, Ar-H), 7.41–7.51 m (4H, Ar-H), 3.79 s (1H, OCH₃). ^{13}C NMR spectrum, δ , ppm: 153.1, 147.1, 137.1, 129.6, 128.5, 120.4, 118.6, 50.9. M 244 $[M + \text{H}]^+$. Found, %: C 49.20; H 3.53; N 40.27. $\text{C}_{10}\text{H}_9\text{N}_7\text{O}$. Calculated, %: C 49.38; H 3.73; N 40.31.

4-[4-(1*H*-Tetrazol-5-yl)-1*H*-1,2,3-triazol-1-yl]phenol (3f**).** Yield 92%, mp 174–177°C. IR spectrum, ν , cm^{-1} : 2343 (N=N–N–), 1570, 1453 (C=C); ^1H NMR spectrum, δ , ppm: 9.89 s (1H, OH), 8.67 s (1H, triazole H), 7.42–7.58 m (5H, Ar-H). ^{13}C NMR spectrum, δ , ppm: 153.6, 145.2, 136.6, 128.9, 128.5, 120.5, 119.5; M 230 $[M + \text{H}]^+$. Found, %: C 47.08; H 3.00; N 42.62. $\text{C}_9\text{H}_7\text{N}_7\text{O}$. Calculated, %: C 47.16; H 3.08; N 42.78.

5-[1-(4-Nitrophenyl)-1H-1,2,3-triazol-4-yl]-1H-tetrazole (3g). Yield 93%, mp 182–184°C. IR spectrum, ν , cm^{-1} : 2340 (N=N–N–), 1571, 1453 (C=C). ^1H NMR spectrum, δ , ppm: 7.83–7.89 m (2H, Ar-H, triazole H), 7.41–7.44 m (1H, Ar-H), 7.05–7.10 m (1H, Ar-H), 6.89–6.98 m (2H, Ar-H). ^{13}C NMR spectrum, δ , ppm: 158.6, 146.2, 128.3, 127.7, 127.6, 123.9, 114.6. M 259 $[M + \text{H}]^+$. Found, %: C 41.72; H 2.28; N 43.33. $\text{C}_9\text{H}_6\text{N}_8\text{O}_2$. Calculated, %: C 41.87; H 2.34; N 43.40.

5-[1-{3-(Trifluoromethyl)phenyl}-1H-1,2,3-triazol-4-yl]-1H-tetrazole (3h). Yield 93%, mp 155–157°C. IR spectrum, ν , cm^{-1} : 2342 (N=N–N–), 1575, 1450 (C=C). ^1H NMR spectrum, δ , ppm: 7.98 (s, 1H, triazole H), 7.82–7.85 m (1H, Ar-H), 7.65–7.68 m (1H, Ar-H), 7.46–7.50 m (1H, Ar-H), 6.90–6.98 m (1H, Ar-H). ^{13}C NMR spectrum, δ , ppm: 152.5, 145.6, 135.7, 129.5, 127.5, 125.6, 121.5, 120.5, 119.8. M 282 $[M + \text{H}]^+$. Found, %: C 42.62; H 2.10; N 34.76. $\text{C}_{10}\text{H}_6\text{N}_7\text{F}_3$. Calculated, %: C 42.71; H 2.15; N 34.87.

CONCLUSIONS

We have synthesized a new series of triazole-tetrazole hybrids (**3a–3h**) and evaluated their antimicrobial activity. The compounds **3a**, **3c**, **3e**, and **3f** demonstrated high antibacterial activity and compounds **3a**, **3c**, and **3e** exhibited some antifungal activity.

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