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Green synthesis of 1,4-disubstituted 1,2,3-triazoles and their antibacterial activity

Suresh Seeka, Sirassu Narsimha, Vasudeva Reddy N.* and Savithajyostna T.*

Department of Chemistry, Kakatiya University, Warangal, Telangana State, India

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ABSTRACT

A facile and highly efficient green synthesis of 4-((1H-imidazol-1-yl)methyl)-1-phenyl-1H-1,2,3-triazole(1a-1f) and 4-((1H-pyrazol-1-yl)methyl)-1-phenyl-1H-1,2,3-triazole(2a-2f) in good to excellent yields from in-situ-generated alkyne with aryl azides by Cu(I)-catalyzed cycloaddition reaction. The reaction proceeds smoothly in a mixture of [BMIM][PF_6] and water at room temperature without any additive. All the synthesized compounds were characterized by spectral studies and screened for their in vitro antibacterial activity.

Keywords: [BMIM][PF_6]; Imidazole; Pyrazole; 1,2,3-Triazoles; Anti-bacterial.

INTRODUCTION

Heterocyclic chemistry is a branch which inseparable from mankind because human are totally dependent on the drugs derives from heterocyclic rings. Hetrocyclic compounds also have so far been synthhtized meanly due to wide range of biological activities [1, 2]. One such class of compounds like five membered heterocyclic containing two and three nitrogen as hetero atoms in its ring structure i.e. Pyrazoles, imidazole and triazole are an important class of hetero aromatic systems that find extension use in the pharmaceutical industry. Pyrazoles occupy unique positions and they have so far been synthesized mainly due to their higher pharmacological activities. They possess antimicrobial, antiviral, anti-inflammatory and anti-amoebic properties [3-6].

Many drugs contain an imidazole ring, such as certain antifungal drugs, the nitroimidazole series of antibiotics, and the sedative imidazolam [7-11]. Synthetic imidazoles are present in many fungicides and antifungal, antiprotozoal, and antihypertensive medications. Imidazole is part of the theophylline molecule, found in tea leaves and coffee beans, which stimulates the central nervous system. Apart of its use for pharmaceutical purpose it also have varying applications in industries, the imidazole has been used extensively as a corrosion inhibitor on certain transition metals, such as copper. Preventing copper corrosion is important, especially in aqueous systems, where the conductivity of the copper decreases due to corrosion. Many compounds of industrial and technological importance contain imidazole derivatives [12].

1,2,3-triazoles have emerged as an important class of heterocyclic compounds, displaying a vast spectrum of properties and are widely used as pharmaceuticals[13-16]. Many 1,2,3-triazoles have found medicinal applications, such as HIV protease inhibitors[17], anticancer drugs[18], antituberculosis drugs[19], antifungal agents[20],

antibacterial drugs[21], histone deacetylase inhibitors, and bioorthogonal probes, and are also used as corrosion inhibitors, lubricants, dyes, and photostabilizers.

For all the above consideration, biological importance of triazoles, imidazole and pyrazole, we design the new bi-functional mimic heterocyclic compounds consisting the 1,2,3- Triazoles, here we present a highly efficient one pot synthetic method for the synthesis of the new bi-functional mimic heterocyclic compounds containing imidazole, pyrazole and 1,2,3- Triazoles..

MATERIALS AND METHODS

Chemistry

All chemicals were purchased from Aldrich Chemical Co. and solvents were used without further purification. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates. Visualisation of the developed chromatogram was performed by UV light (254 nm). Column chromatography was performed on silica gel 60–120 mesh. Melting points were determined using a Cintex apparatus. Elemental analysis were measured by means of Perkin Elmer 2400 CHN elemental analyzer. ^{1}H nuclear magnetic resonance (NMR) (400 MHz) and ^{13}C NMR (**Compound 2a, 2b**) (100 MHz) spectra were obtained using Bruker DRX-500 Avance at ambient temperature, using tetramethylsilane (TMS) as internal standard. Coupling constant (J) values are presented in Hertz and spin multiples are given as s (singlet), d (doublet), t (triplet), and m (multiplet). Fourier-transform infrared (FT-IR) spectra were obtained as KBr discs on Shimadzu spectrometer. Mass spectra were recorded by using ESI–MS.

Synthesis of 1,4-disubstituted 1,2,3-triazoles.

1-{[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2a): Was carried out by addition of propargyl bromide (1.2 mmol), under stirring, to the 1 ml [bmim][PF6] and 3ml H_2O mixture containing indole (1 mmol) , Cs_2CO_3 (1 mmol) and 1-azido-4-methoxybenzene (1.2 mmol) at room temperature for 8hrs. The reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography (30% Ethyl acetate/Hexane) to give 90% yield of ***2a*** as a white solid. The residue ionic liquid was washed with water and reused for the cyclo addition reaction. m.p. 122–124 ^{o}C; ^{1}H-NMR (400 MHz,$CDCl_3$) δ ^{1}H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.820 (d, *J=8.4 Hz*, Ar, 2H); 7.671 (s, triazole-H, 1H); 7.515 (m, Ar, 4H); 7.310 (m, Ar, 2H); 6.977 (d, *J=8.8 Hz*, Ar, 2H); 5.582 (s, N-CH_2, 2H); 3.832 (s, O-CH_3, 3H); ^{13}C-NMR(100MHz,$CDCl_3$) δ158.9 ,145.6, 136.2, 130.3, 119.1, 60.6, 56.4; IR(KBr,cm^{-1}) 3144, 1594, 1514, 1459, 1400, 1111, 835 ; EI-MS m/z (M+H)-305; Anal. Calcd for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41; found : C, 71.01; H, 5.34; N, 18.45

1-{[1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2b): m.p. 118–120 ^{o}C; ^{1}H-NMR (400 MHz,$CDCl_3$) δ ^{1}H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.713 (d, *J=8 Hz*, Ar, 2H); 7.642 (s, triazole-H, 1H); 7.512 (m, Ar, 3H); 7.320 (m, Ar, 3H); 7.012 (d, *J=8.8 Hz*, Ar, 2H); 5.552 (s, N-CH_2, 2H); 2.441 (s, Ar-CH_3, 3H);^{13}C-NMR(100MHz,$CDCl_3$) δ145.6, 138.4, 136.2, 119.8, 115.2, 58.6, 25.4; IR(KBr, cm^{-1}3142, 1593,1515, 1455,1400,1110,835,EI-MS m/z (M+H)- EI-MS m/z (M+1)-289; Anal. Calcd for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43; found : C, 75.00; H, 5.55; N, 19.45

1-{[1-(3,5-dimethylphenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2c): mp 129-131^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.654 (s, triazole-H, 1H); 7.541 (m, Ar, 3H); 7.512 (m, Ar, 3H); 7.311(m, Ar, 2H), 6.971(s, Ar, 1H), 5.553 (s, N-CH_2, 2H); 2.781 (s, Ar-CH_3, 6H); IR(KBr, cm^{-1}) 3142, 1594,1514, 1459,1400, 1112. EI-MS m/z (M+H)-303; Anal. Calcd for $C_{19}H_{18}N_4$: C, 75.47; H, 6.00; N, 18.53; found : C, 75.50; H, 6.06; N, 18.44

1-{[1-(3,5-dichlorophenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2d): mp 135-137^{o}C; ^{1}H-NMR (400MHz, $CDCl_3$) δ in ppm: 7.8150 (s, Ar, 1H); 7.721 (s, Ar, 2H); 7.651 (s, triazole-H, 1H); 7.508 (m, Ar, 3H); 7.421 (m, 2H); 7.056 (d, *J= 4.8 Hz*, Ar, 1H); 5.503 (s, N-CH_2, 2H); IR(KBr, cm^{-1} 3131, 1594,1511, 1459,1398, 1110, 835, EI-MS m/z(M+H)-345; Anal. Calcd for $C_{17}H_{12}Cl_2N_4$: C, 59.49; H, 3.52; N, 16.32; found : C, 59.50; H, 3.55; N, 16.27

1-{[1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2e): mp 121-123^{o}C, ^{1}H-NMR (400 MHz, CDCl3) δ in ppm: 7.730 (d, *J=8 Hz*, 2H); 7.645 (s, triazole-H, 1H); 7.520 (m, Ar, 3H); 7.310 (m, Ar, 2H); 6.971 (d, *J=8.8 Hz*, Ar, 2H); 5.582 (s, N-CH_2, 2H); IR(KBr, cm^{-1}) 3134, 1594,1514, 1459,1400, 1111, 835;EI-MS m/z(M+Na)-342; Anal. Calcd for $C_{17}H_{13}N_5O_2$ **:** C, 63.94; H, 4.10; N, 21.93; found: C, 63.90; H, 4.13; N, 21.96.

1-{[1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2f): m.p. 118–120 ^{o}C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.632 (s, 1H .triazole-*H*); 7.052 -7.655(m,10H); 5.521 (s, 2H . N-CH_2); IR(KBr, cm^{-1}) 3131, 1590,1514, 1449,1405, 1110, 835, EI-MS m/z(M+1)-309; Anal. Calcd for $C_{17}H_{13}ClN_4$: C, 66.13; H, 4.24; N, 18.15; found: C, 66.08; H, 4.23; N, 18.17

1-{[1-(4-butylphenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2g): Was carried out by addition of propargyl bromide (1.2 mmol), under stirring, to the 1 ml [bmim][PF6] and 3ml H_2O mixture containing indole (1 mmol) , Cs_2CO_3 (2 mmol) and 1-azido-4-butylbenzene (1.5 mmol) at room temperature for 8hrs. The reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography (30% Ethyl acetate/Hexane) to give 70% yield of ***2g*** as a white solid. The residue ionic liquid was washed with water and reused for the cyclo addition reaction. m.p. 125–127 ^{o}C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.878 (s, 1H .triazole-*H*); 6.987-7.654 (m,10H); 5.523 (s, 2H . N-CH_2); 2.701(t, *J*= 6 Hz ,2H),1.3-1.654(m,4H),0.961(t, *J*=8 Hz,3H); IR(KBr, cm^{-1}) 3134, 1593,1511, 1459,1400, 1111, 835 ;EI-MS m/z (M+Na)-331; Anal. Calcd for $C_{21}H_{22}N_4$: C, 76.33; H, 6.71; N, 16.96; found: C, 76.39; H, 6.70; N, 16.91

1-({1-[3-(trifluoromethyl)phenyl]-1*H*-1,2,3-triazol-4-yl}methyl)-1*H*-indole(2h): m.p. 136–138 ^{o}C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.780 (s, 1H .triazole-*H*); 7.032-7.698 (m,10H); 5.523 (s, 2H . N-CH_2); IR(KBr, cm^{-1}) 3144, 1593,1511, 1449, 1390, 1114; EI-MS m/z (M+1)-343; Anal. Calcd for $C_{18}H_{13}F_3N_4$: C, 63.16; H, 3.83; N, 16.37; found: C, 63.18; H, 3.85; N, 16.33

{1-{[1-(naphthalen-1-yl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2i):. m.p. 144–146 ^{o}C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.874 (s, 1H .triazole-*H*); 7.782(m,4H); 7.132-7.608 (m,10H) 5.548 (s, 2H . N-CH_2); IR(KBr, cm^{-1}) 3134, 1593,1511, 1450,1409, 1115: EI-MS m/z(M+1)-325; Anal. Calcd for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27; found: C, 77.68; H, 4.99; N, 17.33

1-{[1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-indole(2j): m.p. 134–136 ^{o}C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.742 (d, *J=8 Hz*, Ar, 2H); 7.632 (s, triazole-H, 1H); 7.523 (m, Ar, 3H); 7.120 (m, Ar, 3H); 7.002 (d, *J=8.8 Hz*, Ar, 2H); 5.535 (s, N-CH_2, 2H); IR(KBr, cm^{-1}) 3141, 1593,1511, 1449, 1411 , 1109;EI-MS m/z(M+1)-354; Anal. Calcd for $C_{17}H_{13}BrN_4$: C, 57.81; H, 3.71; N, 15.86;found: C, 57.76; H, 3.73; N, 15.88

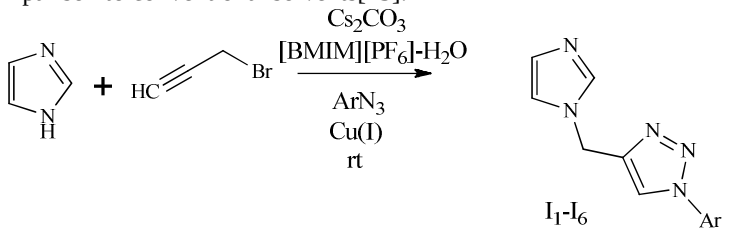
Antibacterial activity

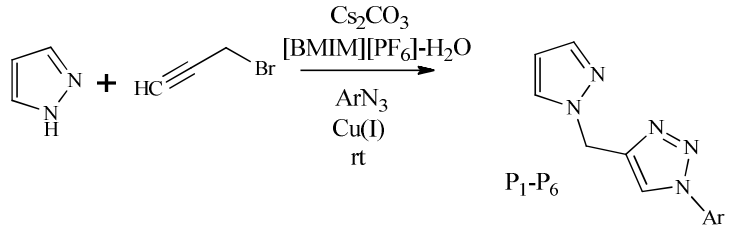
The newly synthesized compounds **(2a-j)** were evaluated for in-vitro antibacterial against various Gram-positive and Gram-negative bacteria [22]. The results are shown in **Tables 2**. Penicillin were used as standard drugs for comparison. The minimum inhibitory concentrations (MIC) of synthesized compounds (**1a-2f)** were tested against three representative Gram-positive organisms such as *E.coli***(MTCC 443)**, *B.subtiles* **(MTCC 441)**, *and S.aureus* **(*MTCC 96),** *and K.pneumoniae* **(MTCC 618**) by broth dilution method recommended by National Committee for Clinical Laboratory (NCCL) standards. The Standard antibacterial agent Penicillin also screened under identical conditions for comparison.The standard pathogenic microbial cultures were procured from the Microbial Type Culture Collection (MTCC), Chandigarh, India and were incubated on sterile nutrient agar at room temperature and inoculated into the fresh nutrient broth of 10 mL, in order to yield bacterial suspension of about 10–100 colony forming units (CFU) per mL. The inoculums size of approximately 106 CFU per plate was spread plated over the surface of the nutrient agar by diluting the initial microbial suspension 10 times with distilled water. 30 mL of Antibacterial suspension of 100 µg mL- 1 concentration was transferred into the 6 mm diameter well made by the sterile cork borer and incubated for about 24 h at 37 oC. Antibacterial screenings were conducted in triplicates by wellplate method in Mueller- Hinton Agar at 100 µg mL-1concentration for the synthesized compounds **(2a-j)** with respect to positive control streptomycin at 30 µg mL-1. Minimum inhibitory concentration (MIC) forthe tested compounds, as well as standards were measured in µg mL-1by micro dilution method. DMSO used as a solvent control and the results are depicted in **Table 2**.

RESULTS AND DISCUSSION

This three-component reaction proceeds via in-situ formation of an N-propargylation from an indole and propargyl bromide. The alkyne then undergoes 1, 3-dipolar cycloaddition reaction with aryl azide to give 1, 4-disubstituted 1,2,3-triazoles [23]. Here we describe a process in which copper iodide efficiently catalyzes azide–alkyne cycloaddition in the presence of [BMIM][PF_6] and H2O mixture (**Scheme 1**)[24]. The [BMIM][PF6] effects can be explained to solvophobic interactions that generate an internal pressure, which promotes the association of the

reactants in a solvent cavity during the activation process and showed an acceleration of the multi-component reactions (MCRs) in comparison to conventional solvents[25].

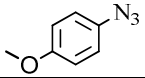
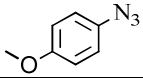
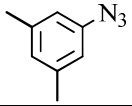
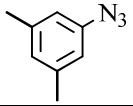
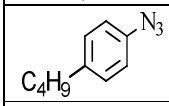
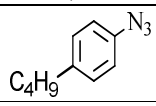
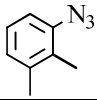
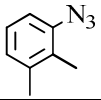
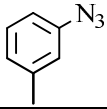
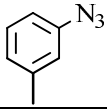
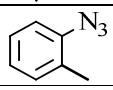
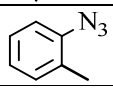




Ar = **1:** 4-methoxy phenyl; **2:** 3,5-dimethyl phenyl
3: 4-butyl phenyl; **4:** 2,3-dimethyl phenyl
5: 3-methyl phenyl; **6:** 2-methyl phenyl

Scheme1. Synthetic route of 1,4-di substituted 1,2,3- triazole derived Indole

Table 1: Synthesis of 1,2,3-triazoles 1a-2f from aryl azides in the presence of [BMIM][PF$_6$]-H$_2$O

Azide	Time(h)	Product	Yield(%)	Azide	Time(h)	Product	Yield(%)
	8	1a	40[a],35[b],50[c],55[d], 90		10	2a	80
	8.5	1b	86		8.5	2b	70
	8.5	1c	82		9	2c	65
	10	1d	75		8.5	2d	85
	10	1e	70		9	2e	80
	10	1f	70		10	2f	74

Reaction conditions: absence of IL yield of product with different solvents, a=CH$_3$CN; b=Acetone; c=THF; d=H$_2$O

Antibacterial activity: All the synthesized compounds were screened for their *in vitro* antibacterial activity against both gram positive bacteria and gram negative bacteria using broth dilution method . The results are shown in **Table 2.** Penicillin was used as standard drugs for comparison**.** The minimum inhibitory concentrations (MIC) of synthesized compounds (**1a-2f**) were tested against Gram-positive and gram negative organisms such as

Staphylococcus aureus, *Bacillus subtilis*, *Escherichia coli*, and *Klebsiella pneumoniae* by broth dilution method recommended by National Committee for Clinical Laboratory (NCCL) standards[26] using broth dilution method was employed for determination of antibacterial activity. Antibacterial activity results (**Table 2**). Evaluation of antibacterial data, compounds **1a** and **2a**, was found to be effective against ***S.aureus*** and ***E.coli***, and compounds **1c, 2d** and **2f** was effective against ***K.pneumoniae*** have shown good antibacterial activity.. A detailed report is tabulated in **Table No. 2**

Table 2: Anti-bacterial activity of 1-((1-aryl-1H-1,2,3-triazol-4-yl)methyl)-1H-indole (1a-2f) against tested bacteria

	MIC(*µg/mL*)			
Analog	***K.pneumoniae***	***S.aureus***	***B.Subtilis***	***E.coli***
1a	>150	**4.548**	>150	**6.548**
1b	>150	>150	>150	>150
1c	**2.253**	>150	>150	>150
1d	>150	>150	>150	>150
1e	>150	>150	>150	>150
1f	>150	>150	>150	>150
2a	>150	**3.401**	>150	**3.441**
2b	>150	>150	>150	>150
2c	>150	>150	>150	>150
2d	**2.150**	>150	>150	>150
2e	>150	>150	>150	>150
2f	**1.546**	>150	>150	>150
Penicillin	**1.562**	**1.562**	**6.25**	**6.25**

CONCLUSION

In conclusion, the present work demonstrated an environmentally benign and a convenient method for the synthesis of biologically active novel 1, 2, 3-triazole derivatives. All the compounds were screened for antimicrobial activity. Among all the synthesized compounds, **1a**, **1c**, **2a**, **2d** and **2f** showed significant antibacterial activity against both gram positive and negative bacterial strains. These results suggest that the synthesized compounds can be good candidates for future investigations.

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