Chapter

PEG-Mediated Green One Pot Synthesis by Using Click Chemistry

Sachin Pandurang Shirame and Raghunath Bhosale

Abstract

The regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles derivatives from substituted alkynes and organic halides with sodium azide by using CuI catalyst in polyethylene glycol-400 as a green reaction media. This process is of considerable synthetic advantages in terms of green principles, high atom economy, low environmental impact, mild reaction condition, high purity and good yields. We find out the use of eco-friendly solvent like mixture of PEG-400 and water for the synthesis of 1,2,3-triazole. The main aim of this research is to found the method which required very short time, cost effective, feasible and a green method as compared to known reported for synthesis of 1,2,3-triazole as a medicinally important scaffold by click chemistry.

Keywords: PEG-400, multicomponent reactions, 1,2,3-triazole, CuI

1. Introduction

'Click chemistry' has emerged as a fast and efficient approach for synthesis of novel heterocyclic compounds [1, 2]. The Huisgen 1,3-dipolar cycloaddition of azides and alkynes resulting in 1,2,3-triazoles is one of the most powerful click reactions [3, 4]. The synthesis of 1,2,3-triazole has been intensively studied, and triazoles are widely used in pharmaceuticals, agrochemicals, dyes, photographic materials, and in corrosion inhibitory materials [5–7]. In addition, they possesses anti-HIV [8, 9] antimicrobial activities [10]. The selective β-3 adrenergic receptor agonism [11]. In the absence of a transition-metal catalyst, these reactions are not regioselective, relatively slow, and require high temperatures to reach acceptable yields. In early 2002, Meldal and co-workers reported that the use of catalytic amounts of copper(I), which can bind to terminal alkynes, leads to fast, highly efficient, and regioselective azide, alkyne cycloadditions at room temperature in organic medium [12–15]. Recently, Sharpless and co-workers have reported a high yielding synthesis of triazoles using a CuI catalyst with an excellent 1,4-regioselectivity [15–18]. The resulting 'clicked' products can even be obtained via in situ generation of the corresponding organic azides from organic halides, NaN_3 in the presence of an alkyne and a copper catalyst, avoiding the need to handle organic azides [19]. Nitrogen heterocycles have received special attention in pharmaceutical chemistry due to their diverse medicinal potential [20–22]. The main aim of our research work is to replace the costly and hazardous organic solvents for the synthesis of 1,2,3-triazoles by using ecofriendly efficient unique properties such as commercial

availability, recyclable, easily degradable, having low toxicity, thermally stability and non-volatility of this PEG-400 solvent [23].

2. Materials and method

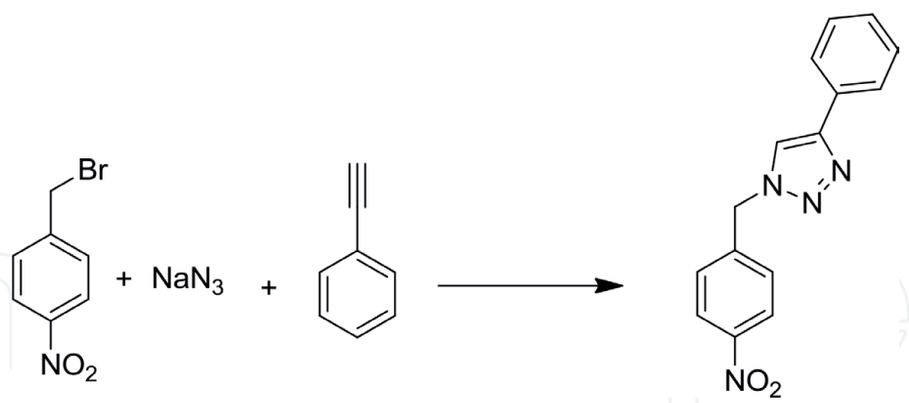
All chemicals were purchased from Merck and Aldrich and used as received. Melting points were recorded in open capillaries.^{1}H NMR were recorded on a Bruker Bio-Spin spectrometer at 400 MHz using TMS as an internal standard (in $CDCl_3$). Mass spectra ESIMS were recorded and IR spectra were recorded on a Shimadzu FTIR spectrometer in KBr pallets.

3. General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazole for compounds (111)

Substituted organic halides (1.0 equiv), sodium azide (1.4 equiv) and substituted alkynes (1.104 equiv) were suspended in polyethylene glycol-400 (5 mL). To this copper iodide (10 mol%) was added and the re action mixture was stirred for 10–45 min at 25–35°C. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc and the organic extract was dried. The crude product was recrystallized from ethanol to yield the desired product.

4. Experimental data

4.1 Synthesis of 1-(4-nitrobenzyl)-4-phenyl-1H-1,2,3-triazole



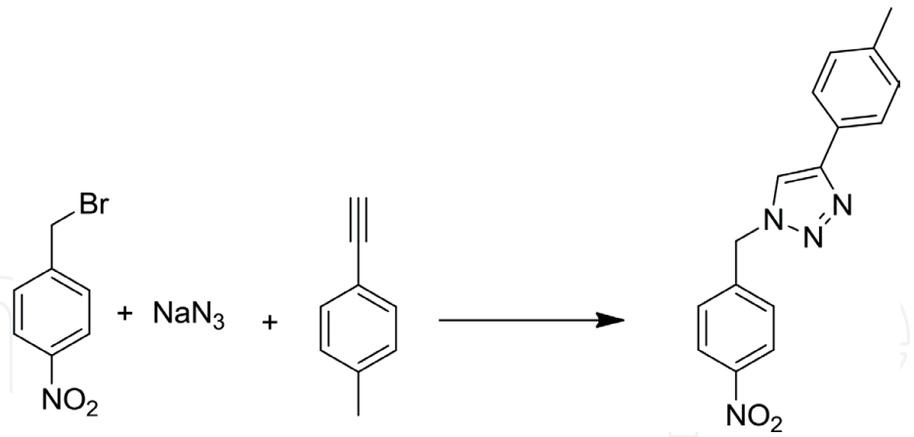
P-Nitrobenzyl bromide 0.216 g (1.0 mmol), sodium azide 0.091 g (1.4 mmol) and phenyl acetelyne 0.112 g (1.1 mmol) were suspended in polyethylene glycol-400 (5 mL). To this reaction mixture in copper iodide (10 mol%) was added and the reaction mixture was stirred for 10 min at 25°C. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc and the organic extract was dried. The crude product was recrystallized from ethanol to yield the desired product.

MF/FWt: $C_{15}H_{12}O_2N_4$/280.10, MP: 198–200°C.

IR (cm^{-1}): 3001, 2988, 2829, 1613, 1209, 876.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.13–8.15 (d,2H), 7.08–7.10 (d,2H),7.80–7.82 (d,2H), 6.85–6.87 (d,2H), 7.10–7.12 (s,1H), 8.39 (s,1H, triazole), 4.73 (s,2H).

4.2 Synthesis of 1-(4-nitrobenzyl)-4-p-tolyl-1H-1,2,3-triazole



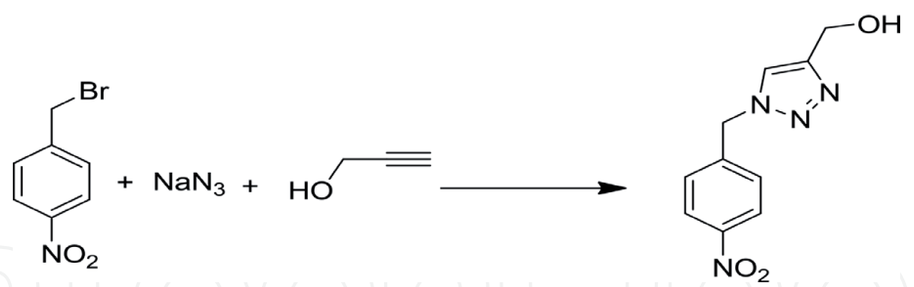
P-Nitrobenzyl bromide 0.216 g (1.0 mmol), sodium azide 0.091 g (1.4 mmol) and 1-ethynyl-4-methylbenzene 0.127 g (1.1 mmol) were suspended in polyethylene glycol-400 (5 mL). To this reaction mixture in copper iodide (10 mol%) was added and the reaction mixture was stirred for 15 min at 30°C. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc and the organic extract was dried. The crude product was recrystallized from ethanol to yield the desired product.

Yield: 87%, MF/FWt: $C_{16}H_{14}N_4O_2$/294.11, MP: 190–192°C.

IR (cm^{-1}): 3123, 2958, 1588, 1430, 1265, 1233, 797.

^1H NMR (300 MHz, $CDCl_3$, δ ppm): 8.13–8.15 (d,2H), 7.08–7.10 (d,2H), 7.80–7.82 (d,2H), 6.85–6.87 (d,2H), 8.39 (s,1H, triazole), 4.73 (s,2H), 2.56 (s,3H).

4.3 Synthesis of (1-(4-nitrobenzyl)-1H-1,2,3-triazole-4-yl) methanol



P-Nitrobenzyl bromide 0.216 g (1.0 mmol), sodium azide 0.091 g (1.4 mmol) was suspended in polyethylene glycol-400 (5 mL). The reaction mixture was stirred for 10 min at 25°C. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc and the organic extract was dried. The crude product was recrystallized from ethanol to yield the desired product.

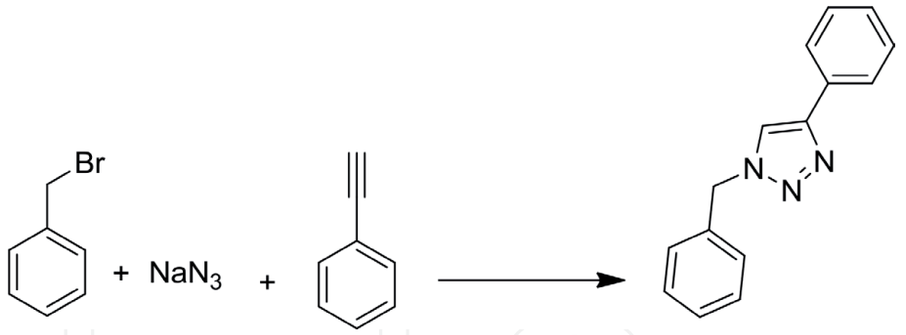
Yield: 72%, MF/FWt: $C_{10}H_{10}N_4O_3$/234.08, MP: 134–136°C.

IR (cm^{-1}): 3643, 2950, 1609, 1508, 1430, 1265, 1233, 867.

^1H NMR (300 MHz, $CDCl_3$, δ ppm): 8.13–8.15 (d,2H), 7.08–7.10 (d,2H), (s,1H, triazole), 4.73 (s,2H), 4.70 (s,2H), 3.65 (s,1H).

4.4 Synthesis of 1-benzyl-4-phenyl-1H-1,2,3-triazole

Benzyl bromide 0.171 g (1.0 mmol), sodium azide 0.091 g (1.4 mmol) and phenyl acetylene 0.112 g (1.1 mmol) were suspended in polyethylene glycol-400 (5 mL).



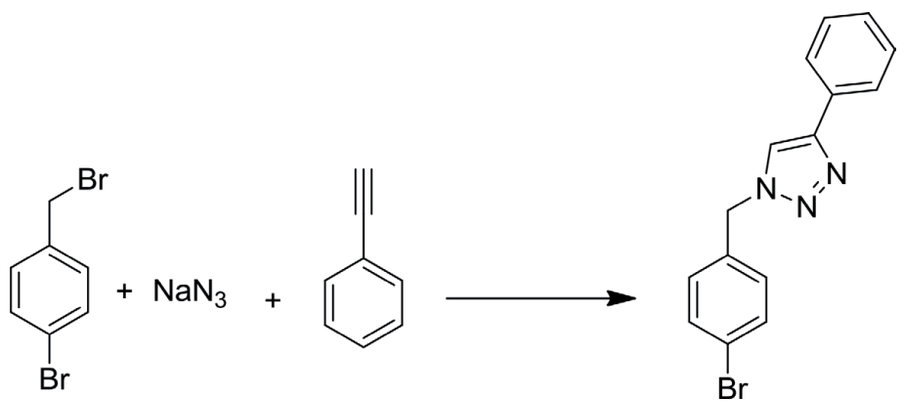
To this reaction mixture in copper iodide (10 mol%) was added and the reaction mixture was stirred for 15 min at 30°C. after completion of the reaction (monotored by TLC), the product was extracted with EtOAc and the organic extract was dried. The crude product was recrystallized from ethanol to yield the desired product.

Yield: 82%, MF/FWt: $C_{15}H_{13}N_3$/235.11, MP: 139–141°C.

IR (cm^{-1}): 2950, 1644, 1578, 1435, 1260, 1223, 876.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 6.87–6.89 (d,2H), 6.64–6.65 (t,1H), 7.12–7.13 (d,2H), 7.53–7.66 (d,2H), 7.39–7.42 (t,2H), 7.30–7.34 (t,1H), 7.66 (s,1H, triazole), 5.53 (s,2H).

4.5 Synthesis of 1,4-bromobenzyl, 4-phenyl-1H-1,2,3-triazole



1-Bromo-4-(bromomethyl) benzene 0.249 g (1.0 mmol), sodium azide 0.091 g (1.4 mmol) and phenyl acetelyne 0.112 g (1.1 mmol) were suspended in polyethylene glycol-400 (5 mL). To this reaction mixture in copper iodide (10 mol%) was added and the reaction mixture was stirred for 20 min at 25°C. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc and the organic extract was dried. The crude product was recrystallized from ethanol to yield the desired product.

Yield: 82%, MF/FWt: $C_{15}H_{12}BrN_3$/313.02, MP: 140–142°C.

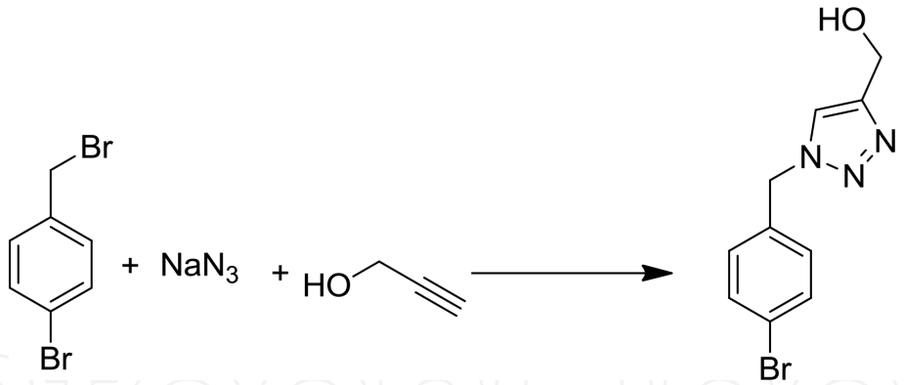
IR (cm^{-1}): 2980, 1601, 1545, 1225, 1157.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.13–8.15 (d,2H), 7.08–7.10 (d,2H), 7.80–7.82 (d,2H), 6.85–6.87 (d,2H),7.81–7.83 (t,1H), 8.39 (s,1H, triazole), 4.73 (s,2H).

^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 53, 113, 114, 118, 133 (carbon triazole), 159, 148, 149, 141.

4.6 Synthesis of 1-4-bromobenzyl-1H-1,2,3-triazol-4-yl)methanol

1-Bromo-4-(bromomethyl) benzene 0.249 g (1.0 mmol), sodium azide 0.091 g (1.4 mmol) were suspended in polyethylene glycol-400 (5 mL). The reaction



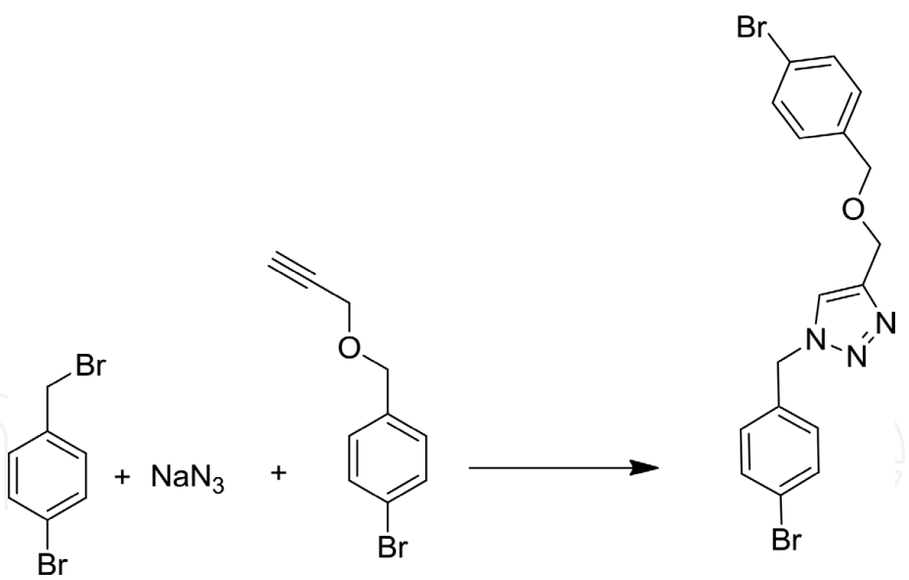
mixture was stirred for 1 h at 40–45°C. Then add propargyl alcohol 0.064 g (1.1 mmol), to this reaction mixture in copper iodide (10 mol%) was added and again reaction mixture was stirred for 10–45 min at 25–35°C. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc and the organic extract was dried. The crude product was recrystallized from ethanol to yield the desired product.

Yield: 81%, MF/FWt: $C_{10}H_{10}BrN_3O$/267.00, MP: 148–150°C.

IR (cm^{-1}): 3660, 2950, 1643, 1578, 1435, 1262, 1222, 879.

^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.51–7.53(d,2H), 7.14–7.16 (d,2H), 7.73 (s,1H, triazole), 5.50 (s,2H), 4.48 (s,2H), 3.50 (s,1H).

4.7 Synthesis of 4-benzyloxy methyl-1-4-bromobenzyl-1H-1,2,3-triazole



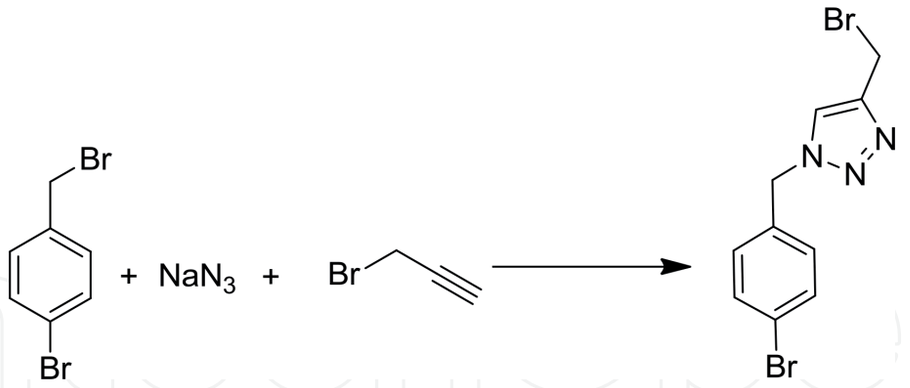
1-Bromo-4-(bromomethyl) benzene 0.249 g (1.0 mmol), sodium azide 0.091 g (1.4 mmol) and 1-bromo-4-((prop-2-ynyloxy)methyl)benzene 0.247 g (1.1 mmol) were suspended in polyethylene glycol-400 (5 mL). To this reaction mixture in copper iodide (10 mol%) was added and the reaction mixture was stirred for 10–45 min at 25–35°C. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc and the organic extract was dried. The crude product was recrystallized from ethanol to yield the desired product.

Yield: 89%, MF/FWt: $C_{17}H_{16}BrN_3O$/357.05, MP: 160–162°C.

IR (cm^{-1}): 2945, 1640, 1588, 1435, 1262, 1222, 867.

^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.49–7.51 (d,2H), 7.19–7.21 (d,2H),7.30–7.32 (d,3H), 7.44–7.46 (d,2H),7.66 (s,1H, triazole), 5.47 (s,2H), 4.53 (s,2H), 4.64 (s,2H).

4.8 Synthesis of 1-(4-bromobenzyl)-4-(bromomethyl)-1H-1,2,3-triazole



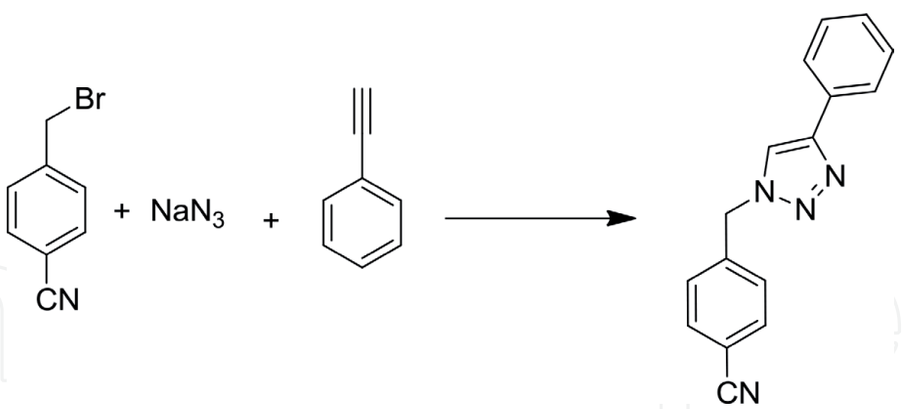
1-Bromo-4-(bromomethyl) benzene 0.249 g (1.0 mmol), sodium azide 0.091 g (1.4 mmol) were suspended in polyethylene glycol-400 (5 mL). The reaction mixture was stirred for 1 h at 40–45°C. Then add propargyl bromide 0.112 g (1.1 mmol), to this reaction mixture in copper iodide (10 mol%) was added and again reaction mixture was stirred for 20 min at 35°C. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc and the organic extract was dried. The crude product was recrystallized from ethanol to yield the desired product.

Yield: 85%, MF/FWt: $C_{10}H_9Br_2N$/328.92, MP: 150–152°C.

IR (cm^{-1}): 2980, 1653, 1568, 1465, 1210, 1222, 889.

^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.14–7.16 (d,2H), 7.03–7.05 (d,2H),7.73 (s,1H, triazole), 5.50 (s,2H), 4.48 (s,2H).

4.9 Synthesis of 4-(4-pheny l-1H-1,2,3-treiazol-1yl) methyl)benzonitrile



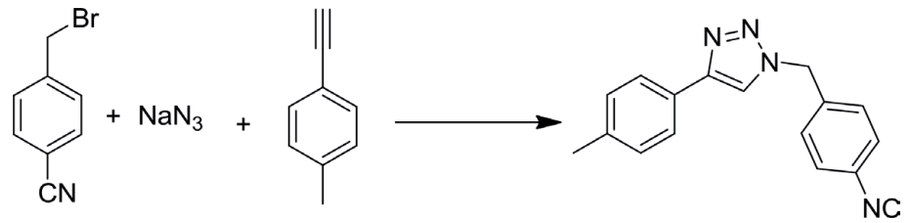
4-(Bromomethyl) benzonitrile 0.196 g (1.0 mmol), sodium azide 0.091 g (1.4 mmol) and phenyl acetelyne 0.112 g (1.1 mmol) were suspended in polyethylene glycol-400 (5 mL). To this reaction mixture in copper iodide (10 mol%) was added and the reaction mixture was stirred for 10 min at 25°C. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc and the organic extract was dried. The crude product was recrystallized from ethanol to yield the desired product.

Yield: 7 8%, MF/FWt: $C_{16}H_{12}N_4$/260.11, MP: 130–132°C.

IR (cm^{-1}): 3088, 2921, 2850, 1607, 1488, 1026.

^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.66–7.68 (d,2H), 7.34–7.36 (t,2H), 7.38–7.43 (t,2H), 7.79–7.81 (d,2H), 7,26–7.32 (t,1H), 7.73 (s,1H, triazole), 5.64 (s,2H); MS: m/e 260 (M^{+1}).

4.10 Synthesis of 1-(4-isocyanobenzy l)-4-p-tolyl-1H-1,2,3-triazole



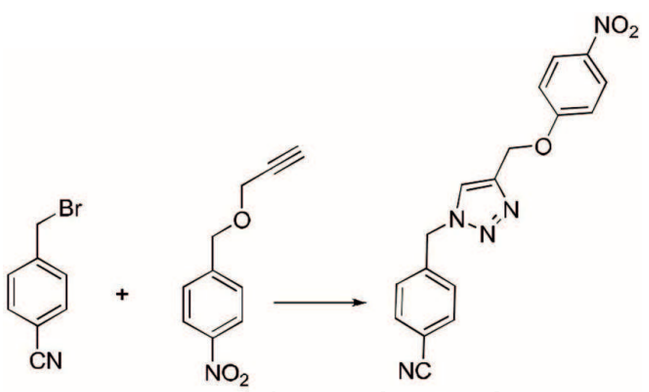
4-(Bromomethyl) benzonitrile 0.196 g (1.0 mmol), sodium azide 0.091 g (1.4 mmol) and 1-ethynyl-4-methylbenzene 0.127 g (1.1 mmol) were suspended in polyethylene glycol-400 (5 mL). To this reaction mixture in copper iodide (10 mol%) was added and the reaction mixture was stirred for 15 min at 30°C. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc and the organic extract was dried. The crude product was recrystallized from ethanol to yield the desired product.

Yield: 87%, MF/FWt: $C_{17}H_{14}N_4$/274.12, MP: 133–135°C.

IR (cm^{-1}): 3081, 2223, 1669, 1470, 1219, 834.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.66–7.68(d,2H), 7.34–7.36 (d,2H), 7.79–7.81 (d,2H), 7.38–7.43 (d,2H), 7.73 (s,1H, triazole), 5.64 (s,2H), 2.58 (s,3H).

4.11 Synthesis of 1-(4-isocyanobenzyl)-4-p-tolyl-1H-1,2,3-triazole



4-(Bromomethyl) benzonitrile 0.196 g (1.0 mmol), sodium azide 0.091 g (1.4 mmol) and 1-methyl-4-(prop-2-ynyloxy) benzene 0.160 g (1.1 mmol) were suspended in polyethylene glycol-400 (5 mL). To this reaction mixture in copper iodide (10 mol%) was added and the reaction mixture was stirred for 40 min at 35°C. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc and the organic extract was dried. The crude product was recrystallized from ethanol to yield the desired product.

Yield: 7 8%, MF/FWt: $C_{18}H_{16}N_4O$/304.13, MP: 144–146°C.

IR (cm^{-1}): 3145, 2227, 1604, 1437, 1154, 857.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.66–7.68 (d,2H), 7.34–7.36 (d,2H), 7.43–7.45 (d,2H), 7.84–7.86 (d,2H), 7.73 (s,1H, triazole), 5.61 (s,2H), 5.37 (s,2H), 2.56 (s,3H).

5. Conclusions

In conclusion a safe and efficient method for the generation of 1,4-disubstituted 1,2,3-triazole in a complete regioselective manner has been developed. Synthesis of

1,2,3-triazole moiety is carried out for the first time by using PEG-400 as a green solvent. This methods are versatile, efficient and convenient. The methods required very short time as compared to reported methods for the synthesis of multicomponent 1,2,3-triazole and their heterocyclic compounds. Avoids the use of expensive volatile organic solvents and laborious work-up. Multicomponent method 1,2,3-triazole derivatives were synthesized. This method avoids isolation and handling of potentially unstable organic azide and provides triazole product in pure form 1,2,3-triazole moiety as a medicinal use.

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List of abbreviations

CuI	copper iodide
NaN_3	sodium azide
EA	ethylacetate
CuAAC	copper-catalyzed azide-alkyne cycloaddition
DCC	*N,N′*-dicyclohexylcarbodiimide
FT-IR	Fourier transformation infra-red
NMR	nuclear magnetic resonance
PEG	poly(ethylene glycol)
RuAAC	ruthenium-catalyzed alky ne azide cycloaddition
THF	tetrahydrofuran
TLC	thin layer chromatography
MCR	multicomponent reaction synthesis
$NaNO_2$	sodium nitrite

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