PEG MEDIATED SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF ONE POT 1, 4 DISUBSTITUTED 1, 2, 3-TRIAZOLE DERIVATIVES

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ABSTRACT

The regioselective synthesis of 1, 4-disubstituted 1, 2, 3-triazoles derivatives from substituted alkynes and organic halides with sodium azide was done by using CuI catalyst in polyethyleneglycol-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. All the synthesized compounds were characterized by IR, ^{1}H NMR, C^{13} NMR, Mass spectroscopy and were evaluated for in vitro antibacterial activity. Compounds 4a, 4c, 4d, 4h, 4j and 4n showed maximum zone of inhibition against *S. aureus*, *S. epidermidis*, *Pseudomonas spp.* and *Bacillus spp. as* compared with standard *Penicillin*.

KEYWORDS: 1, 2, 3-Triazoles, CuI, PEG-400, Antibacterial activity

INTRODUCTION

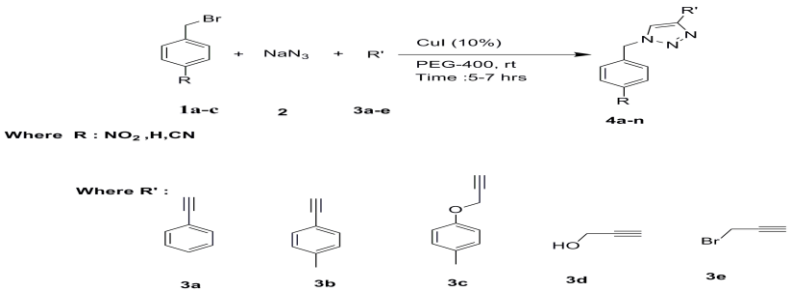
'Click chemistry' has emerged as a fast and efficient approach for synthesis of novel heterocyclic compounds (Kolb *et al.*, 2001). The Huisgen 1,3- dipolar cycloaddition of azides and alkynes resulting in 1,2,3-triazoles is one of the most powerful click reactions 1,2,3-Triazole synthesis has been intensively studied and triazoles are widely used in pharmaceuticals, agrochemicals, dyes, photographic materials, and in corrosion inhibitory materials (Meldal *et al*., 2008). In addition, they possess anti-HIV (Velazquez *et al*., 1998) antimicrobial activities and selective β_3 adrenergic receptor agonism. 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 cyclo additions at room temperature in organic medium (Rostovtsev *et al*., 2002). Recently, Sharpless and co-workers have reported a high yielding synthesis of triazoles using a Cu(I) catalyst with an excellent 1,4-regioselectivity (Wang *et al.*, 2003). 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 (Scriven *et al.*, 1988). Nitrogen heterocycles have received special attention in pharmaceutical chemistry due to their diverse medicinal potential. The availability of therapeutically important drugs such as itavastatin, cerivastatin, streptonigrin, sumatriptan, avitriptan, almotriptan, sumatriptan, pravodoline, remosetron, terconazole, itraconazole, fluconazole and voriconazole (Bringmann *et al.*, 2004) are a few examples which contain nitrogen heterocyclic nucleus. Recently, polyethylene glycols (PEG) as a reaction medium has received considerable attention in synthetic organic chemistry and emerged as alternative green reaction media with unique properties such as thermal stability, commercial availability, nonvolatility, recyclable, non-halogenated, easily degradable, and possess low toxicity (Jadhav *et al.*, 2013; Jadhav *et al.*, 2015). A few reports are available on PEG-400 (Jorapur *et al.*, 2008) for the synthesis of triazoles with limited and narrow application scope for different substrates. . The reaction went to completion at room temperature and the product 1, 4 disubstiuted 1, 2, 3 triazole was obtained in average 88% yields (Scheme 1)

EXPERIMENTAL

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

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 reaction mixture was stirred for 5-7 h at RT. After completion of the reaction (monitored by TLC), the product was extracted with EtOAc (3*15 mL) and the organic extract was dried with sodium sulphate. The crude product was subjected to column chromatography to afford pure products.



Scheme 1: One pot synthesis of 1, 2, 3-triazole derivatives

Characterization data

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.

1-(4-nitrobenzyl)-4-phenyl-1H-1, 2, 3 triazole (4a)

White powder, Yield, 85%; mp, 198-200^{0}C; IR (KBr): m (max) 2925, 2856, 1631, 1455, 1377, 1219, 1067, 770, 699, 533 cm^{-1}. 1H, NMR (400 MHz, $CDCl_3$) : 8.156 (2H,d,Ar-H),7.106 (2H,d,Ar-H) ,3.53 (2H,s,-CH2-), **8.16(1H,s,triazole) ,** 7.82 (2H,d,Ar-H), 6.87(2H,d, Ar-H), 6.74(1H,t,Ar-H); m/z:280

1-(4-nitrobenzyl)-4-p-tolyl-1H-1, 2, 3 triazole (4b)

Pale white powder , Yield, 87% ; mp,190-192^{0}C ; IR (KBr): m(max) 3062, 3030, 2924, 2854, 1547, 1453, 1358, 1221, 1053, 728, 699, 531 cm^{-1}; 1H NMR (400 MHz, CDCl3): 8.156(2H,d,Ar-H),7.106(2H,d,Ar-H),3.53(2H,s,-CH2-), 8.26 (1H,s,triazole), 4.73 (2H,s,O-CH2-), 7.82(2H,d,Ar-H), 6.87 (2H,d,Ar-H),6.74(1H,t,Ar-H) ,2.23(3H,s,Ar-CH3); m/z : 294

(1-(4-nitrobenzyl)-1H-1, 2, 3 –triazol-4-yl) methanol (4d)

White powder ; Yield, 82% ; mp,139-141^{0}C ; IR (KBr): m(max) 3446,3033, 2926, 1547, 1453, 1358, 1221, 1053, 728, 699, 531 cm^{-1}; 1H NMR (400 MHz,DMSO):8.249(2H,d,Ar-H),7.841(2H,d,Ar-H),3.501(2H,s,-CH2-), **8.46 (1H,s,triazole) ,** 4.38 (2H,s,-CH2-O),4.53 (1H,s,-OH) ;m/z: 234

1-benzyl-4-phenyl-1H-1, 2, 3-triazole (4f)

White powder; Yield, 81%; mp, 148-150^{0}C; IR (KBr): m (max) 2925, 2856, 1631, 1455, 1377, 1219, 1067, 770, 699, 533cm^{-1}. 1H, NMR (400 MHz, $CDCl_3$): 8.076(2H,d,Ar-H), 7.106(2H,d,Ar-H), 7.40(1H,t(dd), Ar-H), 3.53 (2H,s,-CH2-),**8.26(1H,s,triazole),** 7.82(2H,d,Ar-H),6.87 (2H,d,Ar-H) 7.50 (1H,t(dd),Ar-H) ; m/z:235

1-benzyl-4-p-tolyl-1H-1, 2, 3-triazole (4g)

White powder ; Yield, 89% ; mp,160-162^{0}C ; IR (KBr): m(max) 3062, 3030, 2924, 2854, 1547, 1453, 1358, 1221, 1053, 728, 699, 531 cm^{-1}; 1H NMR (400 MHz, CDCl3): 8.076(2H,d,Ar-H),7.106(2H,d,Ar-H),6.85(1H,t(dd),Ar-H), 3.53 (2H,s,-CH2-), **8.168(1H,s,triazole),** 4.73(2H,s,CH2-),7.82 (2H,d,Ar-H),6.87 (2H,d,Ar-H),2.43 (3H,s,Ar-CH3) ; m/z : 249

1-benzyl-1H-1, 2, 3-triazol-4-yl) methanol (4i)

White powder; Yield, 85% ; mp,150-152^{0}C ; IR (KBr): m(max) 3556,3033, 2926, 1547, 1453, 1358, 1221, 1053, 728, 699, 531 cm^{-1}; 1H NMR (400 MHz, DMSO): 8.249 (2H,d,Ar-H) , 7.841 (2H,d,Ar-H), 6.84 (1H, t (dd), Ar-H) 3.501(2H,s,-CH2-),8.46(1H,s,triazole),4.38(2H,s,-CH2-O),4.53 (1H,s,-OH);m/z: 189

4-(4-phenyl-1H-1, 2, 3-triazol-1-yl) methyl) benzonitrile (4k)

Pale white powder; Yield, 87%; mp, 133-135^{0}C; IR (KBr): m (max) 2930, 2850, 1641, 1450, 1377, 1217, 1060, 780, 689,533cm^{-1}. 1H,NMR (400MHz,$CDCl_3$): 8.156 (2H,d,Ar-H), 7.106(2H,d,Ar-H),3.53(2H,s,-CH2-),**8.16(1H,s,triazole) ,**7.82 (2H,d,Ar-H), 6.87(2H,d, Ar-H), 6.85(1h,t(dd), Ar-H); m/z:260

4-(4-p-tolyl-1H -1, 2, 3-triazol-1-yl) methylbenzonitrile (4l)

White powder ; Yield, 78% ; mp,144-146^{0}C ; IR (KBr): m(max) 3060, 3030, 2924, 2856, 1547, 1453, 1358, 1221, 1053, 728, 699, 531 cm^{-1}; 1H NMR (400 MHz, CDCl3): 8.056(2H,d,Ar-H),7.206(2H,d,Ar-H),4.53(2H,s,-CH2-), **8.26 (1H,s,triazole),** 7.82 (2H,d,Ar-H), 6.87 (2H,d,Ar-H) ,2.23 (3H,s,Ar-CH3); m/z : 274

4-((4-(hydroxymethyl)-1H-1, 2, 3-triazol-1-yl) methyl) benzonitrile (4n)

White Powder; Yield, 76 % ; mp,155-157^{0}C ; IR (KBr) : m(max) 3446,3033, 2926,1547, 1453, 1358, 1221, 1053, 728, 699,531 cm^{-1} , 1H,NMR (400MHz,DMSO):8.049 (2H,d,Ar-H) , 7.841 (2H,d,Ar-H),3.501 (2H,s,-CH2-),8.46 (1H,s,triazole) ,4.38 (2H ,s, -CH2-O), 4.53 (1H,s,-OH); m/z: 215.

Antibacterial activity

The antibacterial activity was tested through agar diffusion method (Vadlapudi *et al.*, 2009) against human pathogenic bacteria viz. *S.aureus* , *S.epidermidis* , *Serratia*, *Pseudomonas spp.* and *Bacillus spp.*. All the synthesized compounds were dissolved in DMSO to prepare a stock solution of 1 mg/ mL. Stock solution was suitably diluted to have solutions of concentration ranging from 10 to 50 µg /mL. The test organism was incubated on nutrient agar plates and spread uniformly using a sterile glass spreader. Well of 6 mm in diameter were made on the nutrient agar using a sterile cork borer. In each wells the test compound solution (50 µg) was added. The plates were incubated at 37 ^{O}C for 24 hrs bacteria. Each test was performed in duplicate and the results were shown in (table-1). The zone of inhibition was measured in mm, while antibacterial standard *Penicillin* were used as reference. The DMSO alone was used as control.

RESULTS AND DISCUSSION

Chemistry

To begin our study, we carried out the reaction of 1.0 equiv organic halides with 1.4 equiv of sodium azide, 1.6 equiv of triethylamine and 1.10 equiv of alkynes in the presence of 10 mol % CuI in tBuOH. However, the reaction did not proceed at all. Our attempts to carry out the reactions with different solvents such as H_2O, CH_3CN, EtOH or mixture of solvents such as CH_3CN/H_2O (1:1v/v) did not yield fruitful results. However, the use of a mixture of $EtOH/H_2O$ (1:1v/v) at room temperature drove the reaction to form the desired 1, 2, 3-triazole product in 40% yield in 8 h. Surprisingly, when the same reaction was carried out in PEG-400 the desired product was obtained in 88% yield at 6 hrs. This may be due to the hydrophilic and hydrophobic character of the PEG- 400. The reaction took place regioselectively moiety to produce the corresponding 1, 4-disubstituted-1, 2, 3-triazole. The generality of this solvent system (PEG-400) was tested with various alkynes (3a–e) and organic halides (1a–c). Under this condition, triazoles (4a–n**)** were obtained in good to excellent yields (Scheme 1) entries (4a–n). The results revealed that the reaction was highly dependent on the nature of substituent on the aromatic ring of the organic halide and alkynes. All the compounds were confirmed by ^{1}H NMR in $CDCl_3$ which showed the characteristic singlet due to the triazole proton in the region of 8.16–8.66 ppm.

Antibacterial activity

All the synthesized compounds (4a-n) were evaluated for antimicrobial activity against various bacterial strains such as *S. aureus, S. epidermidis, Serratia, Pseudomonas* and *Bacillus.* Antibacterial activity was determined by measuring the diameter of inhibition zone. Antibacterial activity of each compound was compared with *Penicillin as* standard drug and the results are summarized in (Table 1). Compounds 4a, 4c, 4d, 4h, 4j and 4n showed potent antibacterial activity against all the selected strains as compared to the standard drug *penicillin* and other compounds showed moderate activity.

Table 1: Antibacterial activity of one pot synthesis of 1, 2, 3-triazole derivatives (4a-n)

Sr.No.	Compounds	*S .aureus*	*S. epidermidis*	*Serratia*	*Pseudomonas*	*Bacillius*
1	4a	13	-	20	12	15
2	4c	23	16	-	14	-
3	4d	10	15	17	21	-
4	4f	16	-	10	15	10
5	4h	15	10	18	-	22
6	4j	28	12	09	15	23
7	4k	15	10	12	15	10
8	4n	-	22	10	16	15
Penicillin	-	20	20	20	20	20

a. Bold values indicated better result. b. (-) indicated not found result.

CONCLUSION

A safe and efficient method for the generation of 1, 4-disubstituted 1, 2, 3-triazole in a complete region selective manner has been developed. This method avoids isolation and handling of potentially unstable organic azide and provides triazole product in pure form. In addition to its simplicity due to the PEG-400 as a green solvent and mild reaction conditions, this method provides a wide range of 1, 2, 3 triazoles in excellent yields with high regios electivity in a single step operation. Among the synthesized compounds 4a, 4c, 4d, 4h, 4j and 4n were found to be shown potent antibacterial activity against selected strains as compared to the standard drug *penicillin and* other compounds shown moderate activity. The importance of such work lies in the possibility that the compounds might be more efficacious drugs against bacteria and fungi, which could be helpful in designing more potent antibacterial and antifungal agents for therapeutic use.

ACKNOWLEDGEMENT

The authors thank to the Prof. R. B. Bhosale, I/c Director and Head, School of Chemical Sciences, Solapur University, Solapur for his moral support, guidance and providing necessary laboratory facilities.

REFERENCES

Bringmann G., Reichert Y., Kane V. V. (2004). The total synthesis of streptonigrin and related antitumor antibiotic natural products. *Tetrahedron.* 60, 3539

Jadhav S.Y., Shirame S.P., Kulkarni S.D., Patil S.B., Pasale S.K. and Bhosale R.B. (2013). PEG mediated synthesis and pharmacological evaluation of some fluoro substituted pyrazoline derivatives as anti-inflammatory and analgesic agents. *Bioorg. Med Chem Lett*. 23, 2575-2578

Shravan Y. Jadhav, Bhosale, R.B., Shirame, S.P., Sonawane, V.D., Hublikar, M.G., Sonawane, K.D. and Shaikh, R.U. (2013). Synthesis and biological evaluation of fluorohydroxy substituted pyrazole chalcones as anti-inflammatory, antioxidant and antibacterial agents. *Int. J. Pharm. Bio. Sci.* 4, 390–397

Jorapur Y. R., Rajagopal G., Saikia P. J. and Pal R. R. (2008). Poly (ethylene glycol) (PEG) as an efficient and recyclable reaction medium for the synthesis of dibenz[b,f]-1,4-oxazepine. *Tetrahedron Lett.* 49, 1495

Kolb H. C., Finn M. G. and Sharpless K. B. (2001). Click Chemistry: diverse chemical function from a few good reaction. *Angew. Chem., Int. Ed.* 40.

Kolb H. C. and Sharpless K. B., (2003). The growing impact of Click Chemistry on drug discovery. *Drug Discovery Today*. 8, *1128*

Meldal M. and Tornøe C. (2008). Copper catalysed azide alkyne cycloaddition. *Chem. Rev.* 108, 2952

Praveen C., Sagayaraj Y. and Perumal P. (2009). Gold (I)-catalyzed sequential cycloisomerization/bis-addition of o-ethynylanilines: An efficient access to bis (indolyl) ethanes and di (indolyl) indolin-2-ones. *Tetrahedron Lett*. 50, 644

Raghunath B. Bhosale, Sachin P. Shirame, Sandeep B. Patil and Suresh D. Kulkarni. (2015). PEG Mediated Synthesis and Biological Evaluation of Asymmetrical Pyrazole Curcumin Analogues as Potential Analgesic, Anti-Inflammatory and Antioxidant Agents. *Chem Biol Drug Des*. 85, 377–384

Reischer R. J., Ford C. W., Zurenko G. E., Hamel J. C., Schaadt R. D., Stapert D. and Yagi, B. H. (2000). Substituent effects on the antibacterial activity of nitrogen-carbon-linked (azolylphenyl)oxazolidinones with expanded activity against the fastidious gram-negative organisms *Haemophilus influenzae* and *Moraxella catarrhalis. J.Med.Chem.* 43, 953.

Rostovtsev V., Green L., Fokin V. and Sharpless K. (2002). *Angew. Chem.*, Int. Ed. 41, 2596.

Scriven E. and Turnbull K. (1988). Azides: their preparation and synthetic uses. *Chem. Rev*. 88, 297.

Velazquez S., Alvarez R., Perez C., Gago F., De C., Balzarini J. and Camarasa M. (1998). Regiospecific synthesis and anti-human immunodeficiency virus activity of novel 5 substituted N-alkylcarbamoyl and N,N-dialkylcarbamoyl 1,2,3-triazole-TSAO analogues. *Antiviral Chem. Chemother*. 9, 481.

Vadlapudi V., Bobbarala V., Penumajji S. and Naidu K. (2009). Excoecaria agallocha L. antimicrobial properties against important pathogenic microorganisms. *Int. J. Pharm.Tech. Res.* 4, 865-867.

Wang Q., Chan T., Hilgraf R., Fokin V., Sharpless K. and Finn M. (2003). Bioconjugation by copper (I) catalysed azide-alkyne [3+2]cycloaddition. *J.Am.Chem. Soc.* 125: 3192.

Wyvratt M. J., Fisher, M. H. and Weber A. E. (2000). Human β3-Adrenergic Receptor Agonists Containing 1,2,3-Triazolesubstituted Benzenesulfonamides. *Bioorg. Med. Chem. Lett.* 10, 2111.