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COPPER CATALYZED EFFICIENT SYNTHESIS OF 1,2,3-TIAZOLE DERIVATIVES FROM CHALCONE AND BENZYL AZIDE BY 1,3-DIPOLAR CYCLOADDITION REACTION STRATEGY

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ABSTRACT

An efficient copper sulphate catalyzed one pot 1,3-dipolar cycloaddition reaction strategy has been developed for the synthesis of some 1,2,3-triazole derivative from chalcone and benzyl azide by refluxing in toluene. The progress of the reaction was studied in different polar and non polar solvents and the reaction was generalized by using differently substituted chalcones. Yields of all the reactions were excellent and no undesired side products were formed; moreover, the catalyst can be recycled and reused. The structures of the end products were confirmed by IR, ^{1}H, ^{13}C and mass spectrometric analyses.

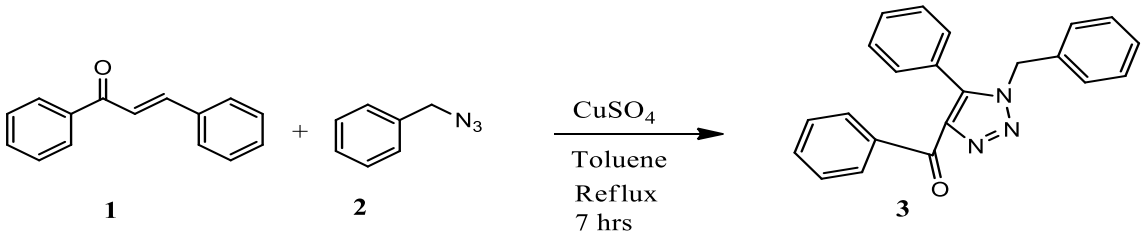
Keywords: 1,2,3-Triazole synthesis, Copper catalyzed, 1,3-dipolar reaction, Chalcone, Azide.

1. INTRODUCTION

Over the last twenty years there has been growing interest in developing new methodologies involving the application of 1,3-dipoles because of their potent synthetic utility [1]. Synthetic worth of these 1,3-dipoles is fully determined by the extent to which regio and stereochemical control could be achieved. This in turn depends on the geometry in the transition state, the nature of dipolarophile and the type of reaction, whether intermolecular or intramolecular. Numerous possibilities for variations are available by changing the structure of both the dipolarophile and 1,3-dipoles. Compounds with carbon-carbon and carbon-nitrogen double and triple bonds as well as many different carbonyl functions are known to react with suitable 1,3-dipoles.

The 1,2,3-triazole and its derivatives are important class of 5-membered nitrogen containing heterocyclic compounds having wide range of important biological properties, such as antibacterial, anticancer, antivirus, antiallergic, anti-HIV and antituberculosis [2]. They also exhibit wide application in the field of medicinal and synthetic organic chemistry. It has been reported that large numbers of 1,2,3-triazole compounds can be employed as candidates or clinical drugs for the therapy of various types of diseases. Moreover, 1,2,3-triazole derivatives have been used as dyes, agrochemicals, corrosion inhibitors, and photostabilizers [3].

Therefore, there has been a growing interest in developing methodologies for the synthesis of these molecules. The 1,2,3-triazole derivatives are generally synthesized by the Huisgen dipolar cycloaddition of alkynes with organic azides [4] which involves prolonged reaction time, and stringent reaction conditions. Again, these cycloadditions afford a mixture of the 1,4- and 1,5-regioisomers. Other important synthetic methodologies in this area involves the copper catalyzed azide-alkyne cycloaddition (CuAAC) to obtain the 1,4-disubstituted isomer and the ruthenium azide-alkyne cycloaddition (RuAAC) and cerium azide-nitroalkene cycloaddition to achieve the 1,5-disubstituted isomer [5-10]. Apart from these synthetic methodologies, in recent years there has been a significant development in the field of 1,2,3- triazole synthesis [11-12]. Although all the reaction methodologies have their own advantages and disadvantages, but most of the available synthetic protocol involves use of hazardous solvent, costly chemicals, tedious reaction condition. As such mild and efficient protocols with readily available chemicals may be considered as a powerful alternative for the 1,2,3-triazole synthesis. In the present study, a highly reusable copper sulphate catalyst is used for the generation 1,2,3-triazole via effective 1,3-dipolar cycloaddition between alkyl azide and a variety of chalcones.



Scheme 1

2. EXPERIMENTAL

2.1. Material and methods

All the commercially available reagents were used as received. Melting points were measured with a Buchi M-560 melting point apparatus and are uncorrected. IR spectra were recorded on a SHIMADZU FTIR-8400 instrument. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on Brucker 500 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given from TMS (0 ppm) and coupling constants are expressed in Hertz (Hz). ^{13}C NMR spectra were recorded on an Brucker 125 MHz FT-NMR spectrometer and Chemical shifts (δ) are given from $CDCl_3$ (77.0 ppm). Mass spectra were recorded on ESQUIRE 3000 Mass spectrometer. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on a pre-coated silica gel plates (Merck). After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by stating $KMnO_4$ and warming in a hot air oven.

2.2. General procedure

Chalcone **1** (1 mmol), benzyl azide **2** (1.5 mmol), copper sulphate (10 mol%) were taken in a round bottom flask and added 15 ml of toluene. The mixture was then refluxed for 7 hrs and filtered. The catalyst recovered by filtration was washed with toluene and dried. It was then used directly for next run. The filtrate was evaporated under reduced pressure and the desired product was recovered by column chromatography using ethylacetate and hexane as eluent.

3. RESULTS AND DISCUSSION

Initially we have carried out a $CuSO_4$ catalyzed reaction between benzoyl azide and chalcone in DMF and the desired 1,2,3-triazole derivative in 15% yield. It was worthwhile to study the progress of the reaction under the influence of organic solvents. But it was observed that the reaction proceed efficiently in toluene (Table 1, entries 5) in solvents. Further, no product formation was observed when water was employed as the reaction medium (Table 1, entry 9). Thus, toluene was used as a solvent for transformation.

The structure of the compound **3a** was confirmed by spectral and elemental analyses. The generality of the reaction was achieved by the synthesis of a series of compounds **3a-j** by using differently substituted chalcones. It was further encouraging to note that no undesired side reaction was detected and desired 1,2,3-triazole was obtained as the sole product. All the products obtained were characterized by IR, NMR and mass spectrometric analyses. Increase in the reaction time did not result in improvement in yield of the reaction, rather, decomposition of the product occurred.

Table 1: Optimization of the reaction in different solvents[a]

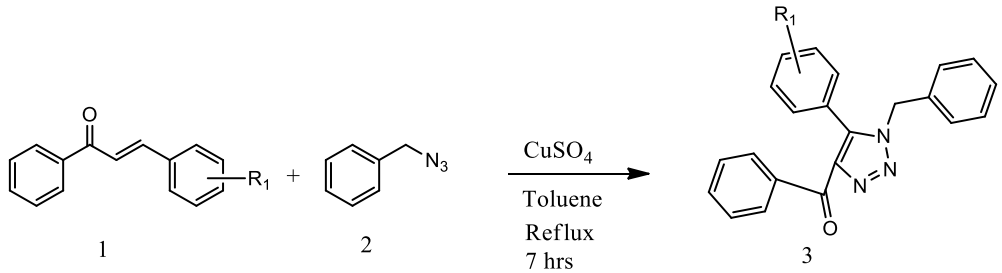
Entry	Solvent	Time (hr)	Yield(%)[b]
1	DMF	7	15
2	Methanol	7	10
3	Acetonitrile	7	12
4	DMSO	7	56
5	Toluene	7	88
6	Nitrobenzene	7	48
7	Tetrahydrofuran	7	05
8	Acetic acid	7	20
9	Chlorobenzene	7	40
10	DCE	7	25

[a]Reaction conditions: Chalcone 1a (1 mmol) and benzoyl azide 2 (1.5mmol) and 10 mol% of $CuSO_4$ were taken in a round bottom flask containg 15 ml of toluene. [b]Isolated yield

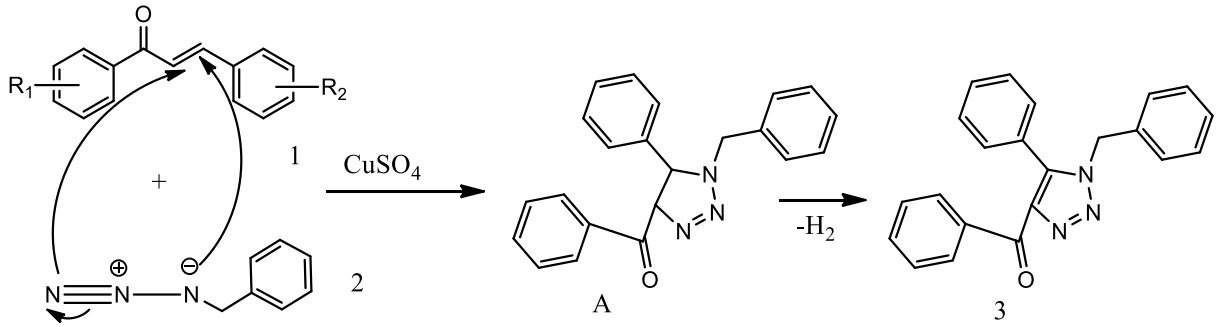
3.1. Mechanism of the reaction

Although the mechanistic studies were not performed, it is likely that dipolarphile chalcone **1** and azide **2** undergoes 1,3-dipolar reaction in presence of $CuSO_4$ to form intermediate **A** which on aromatization results the formation of **3.**

Table 2: Synthesis of 1.2,3-triazole derivatives 3a-3j



Entry	R_1	Product	Yield
1	H	**3a**	82%
2	3-Br	**3b**	75
3	4-OCH_3	**3c**	84
4	4-F	**3d**	81
5	2-CH_3	**3e**	78
6	4-NO_2	**3f**	74
7	4-Cl	**3g**	84
8	2-CH_3	**3h**	80
9	4-Br	**3i**	83
10	2-NO_2	**3j**	73



3.2. Spectral data of the synthesized compounds

3.2.1. (1-Benzyl-5-phenyl-1H-1,2,3-triazol-4-yl)(phenyl)methanone (3a)

Colorless oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.34-8.23 (m, 2H), 7.59-7.54 (m, 1H), 7.50-7.41 (m, 5H), 7.30-7.24 (m, 5H), 7.08-7.04 (m, 2H), 5.47 (s, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.4, 143.8, 141.8, 137.1, 134.7, 133.0, 130.7, 130.1, 129.8, 128.9, 128.7,128.5, 128.2, 127.7, 126.4, 52.1; **IR** ($CHCl_3$, cm^{-1}) 1715, 1605, 1506, 1385, 1228; **MS** (GCMS, m/z) 339.2 $[M]^+$.

3.2.2. (1-Benzyl-5-(3-bromophenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone (3b)

Yellow solid; m.p. 102-104 °C; **^{1}H NMR** (500 MHz, CDCl3): δ 8.30-8.28 (m, 2H), 7.68-7.55 (m, 2H), 7.50-7.47 (m, 2H), 7.35-7.29 (m, 5H), 7.21-7.19 (m, 1H), 7.08-7.07 (m, 2H), 5.46 (s, 2H) ppm; **^{13}C NMR** (125 MHz, CDCl3): δ 186.1, 144.1, 140.3, 136.9, 134.4, 133.2, 133.1, 132.6, 130.7, 130.1, 129.0, 128.7, 128.6, 128.4, 128.3, 127.7, 122.5, 52.4 ppm; **MS (GCMS, m/z)** 418.1 [M+].

3.2.3. (1-Benzyl-5-phenyl-1H-1,2,3-triazol-4-yl)(4-methoxyphenyl)methanone (3c)

Yellow oil; **^{1}H NMR** (500 MHz, CDCl3): δ 8.45-8.31 (m, 2H), 7.53-7.44 (m, 3H), 7.32-7.27 (m, 5H), 7.09 (m, 2H), 7.00-6.96 (m, 2H), 5.49 (s, 2H), 3.90 (s, 3H) ppm; **^{13}C NMR** (125 MHz, CDCl3): δ 184.7, 163.6, 144.1, 141.6, 134.8, 133.2, 130.1, 129.9, 129.8, 128.9, 128.7, 128.4, 127.7, 126.6, 113.5, 55.5, 52.0 ppm; **MS** (GCMS, m/z) 370.2$[M]^+$.

3.2.4. (1-Benzyl-5-phenyl-1H-1,2,3-triazol-4-yl)(4-fluorophenyl)methanone (3d)

Yellow oil; **1H NMR** (500 MHz, CDCl3): δ 8.30-8.27 (m, 2H), 7.60-7.55 (m, 1H), 7.50-7.45 (m, 2H),

7.30-7.27 (m, 3H), 7.25-7.22 (m, 2H), 7.14-7.10 (m, 2H), 7.07-7.03 (m, 2H), 5.46 (s, 2H) ppm; **13C NMR** (125 MHz, CDCl3): δ 186.3, 163.7 144.0, 140.9, 137.0, 134.6, 133.2, 132.0 130.7, 129.0, 128.6, 128.3, 127.6, 122.3 116.0 52.1 ppm; **IR** ($CHCl_3$, cm^{-1}) 1719, 1620, 1506, 1386, 1228, **MS** (GCMS, m/z) 358.1$[M]^+$.

3.2.5. (1-Benzyl-5-o-tolyl-1H-1,2,3-triazol-4-yl)(phenyl)methanone (3e)

Yellow oil; **^{1}H NMR** (500 MHz, CDCl3): δ 8.37-8.32 (m, 2H), 7.59-7.54 (m, 1H), 7.49-7.45 (m, 2H), 7.41-7.38 (m, 1H), 7.29-7.20 (m, 5H), 7.04 (dd, J = 7.6, 1.2 Hz, 1H), 6.99-6.95 (m, 2H), 5.40 (d, J = 14.6 Hz, 1H), 5.31 (d, J = 14.7 Hz, 1H), 1.74 (s, 3H) ppm; **^{13}C NMR** (125 MHz, CDCl3): δ 186.0, 144.6, 141.2, 138.2, 137.0, 134.0, 133.0, 130.7, 130.4, 130.2, 129.2, 128.7, 128.6, 128.3, 128.2, 126.3, 126.0, 52.2, 19.3 ppm; **MS** (GCMS, m/z) 354.1$[M]^+$.

3.2.6. (1-Benzyl-5-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone, 3f

Yellow solid, m.p. 159-162 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.34 (d, J = 7.6 Hz, 2H), 8.28 (d, J = 8.8 Hz, 2H), 7.63-7.60 (m, 1H), 7.52-7.49 (m, 2H), 7.44-7.42 (m, 2H), 7.30-7.27 (m, 3H), 7.04-7.03 (m, 2H), 5.51 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 185.7, 148.5, 144.3, 139.6, 136.4, 133.9, 133.3, 133.1, 130.9, 130.6, 128.9, 128.7, 128.2, 127.3, 123.5, 52.4.

3.2.7. (1-Benzyl-5-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)(phenyl) methanone, (3g)

Yellow solid, m.p. 142-143 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.31 (d, J = 7.6 Hz, 2H), 7.62-7.58 (m, 1H), 7.52-7.48 (m, 2H), 7.44-7.42 (m, 2H), 7.32-7.31 (m, 3H), 7.22-7.20 (m, 2H), 7.09-7.08 (m, 2H), 5.48 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.1, 143.8, 140.6, 136.8, 136.3, 134.3, 133.0, 131.1, 130.6, 128.9, 128.8, 128.5, 128.1, 127.4, 124.6, 52.0.

3.2.8. (1-Benzyl-5-(m-tolyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone, (3h)

Yellow solid, m.p. 93-96 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.31 (d, J = 7.6 Hz, 2H), 7.60-7.57 (m, 1H), 7.51-7.47 (m, 2H), 7.37-7.31 (m, 5H), 7.10 (br, 3H), 7.02 (s, 1H), 5.47 (s, 2H), 2.35 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.3, 143.6, 141.9, 138.3, 137.0, 134.7, 132.9, 130.7, 130.5, 130.2, 128.7, 128.4, 128.3, 128.1, 127.6, 126.7, 126.0, 51.9, 21.2. **MS** (GCMS, m/z) 354.1$[M]^+$.

3.2.9. (1-Benzyl-5-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)(phenyl) methanone, (3i)

White solid, m.p. 137-139 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.32 (d, 2H), 7.62-7.58 (m, 3H), 7.52-7.48 (m, 2H), 7.32-7.31 (m, 3H), 7.15-7.13 (m, 2H), 7.09-7.08 (m, 2H), 5.48 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.0, 143.8, 140.6, 136.8, 134.3, 133.0, 131.8, 131.2, 130.6, 128.8, 128.5, 128.1, 127.4, 125.2, 124.6, 52.0.

3.2.10. (1-benzyl-5-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone4 (3j)

red oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.38-8.30 (m, 2H), 8.23 (dd, J = 8.2, 1.1 Hz, 1H), 7.66-7.45 (m 6H), 7.28-7.19 (m, 3H), 7.05-7.11 (m,3H), 5.57 (d, J = 15.1 Hz, 1H), 5.31 (d, J = 15.1 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, CDCl3): δ 185.8, 148.1, 144.3, 138.7, 136.5, 133.6, 133.4, 133.3, 132.0, 131.2, 130.7, 128.9, 128.8, 128.3, 128.0, 125.2, 122.7, 53.0

4. CONCLUSION

In summary, an efficient reaction strategy has been developed for the construction of some 1,2,3-triazole derivatives via $CuSO_4$ catalyzed reaction between chalcone and benzyl azide by refluxing in toluene. Overall, this is a very simple protocol for obtaining 1,2,3-triazole derivatives in excellent yields within very short time period.

5. ACKNOWLEDGMENT

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6. REFERENCES

1. (a) Baruah B, Deb ML, Bhuyan PJ. *Synlett*, 2007; **12**:1873-1876 (b) Frank E, Wolfing J, Aukszi B, Konig V, Schneider TR, Schneider G. *Tetrahedron*, 2002; **58**:6843-6849. (c) Singh TKM, Wong WF, Ikeno T, Yamada T. *Org. Lett.*, 2007; **9**:207-209.
2. (a) Tron GC, Pirali T, Billington RA, Canonico PL, Sorba G, Genazzani AA. *Med. Res. Rev.*, 2008; **28**:278-308. (b) Thirumurugan P, Matosiuk D, Jozwiak K. *Chem. Rev.*, 2013; **113**:4905-4979.

3. (a) For general reviews on chemistry and applications of 1,2,3- triazoles: Fan W-Q, Katritzky AR. *In Comprehensive Heterocyclic Chemistry II*; Katritzky AR, Rees CW, Scriven EFV. *Eds. Elsevier Science Oxford, U.K.*, 1996; **4**:1-126.
4. Liang L, Astruc D. *Chem. Rev.*, 2011; **255**:2933-2945.
5. Tam A, Arnold U, Soellner MB, Raines RT. *J. Am. Chem. Soc.*, 2007; **129**:12670-12671.
6. Tornøe CW, Christensen C, Meldal M. *J.Org. Chem.*, 2002; **67**:3057-3064.
7. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. *Angew. Chem. Int. Ed.* 2002; **41**:2596-2599.
8. Zhang L, Chen X, Xue P, Sun HHY, Williams ID, Sharpless KB, Fokin VV, Jia G. *J. Am. Chem. Soc.* 2005; **127**:15998-15999.
9. Rasmussen LK, Boren BC, Fokin VV. *Org. Lett.*, 2007, **9**:5337-5339.
10. Boren BC, Narayan S, Rasmussen LK, Zhang L, Zhao H, Lin Z, Jia G, Fokin VV. *J. Am. Chem. Soc.*, 2008; **130**:8923-8930.
11. Johansson JR, Lincoln P, Norden B, Kann N. *J. Org. Chem.*, 2011; **76**:2355-2359.
12. Liu PN, Siyang HX, Zhang L, Tse SKS, Jia GC. *J. Org. Chem.*, 2012; **77**:5844-5849.