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$CuFe_2O_4$ Nanoparticles Mediated Synthesis of 1,4-Disubstituted 1,2,3-Triazoles

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A one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles *via* three component coupling of secondary alcohol, trimethylsilylazide and terminal alkynes in the presence of a catalytic amount of $CuFe_2O_4$ nanoparticles is reported.

Keywords: 1,2,3-Triazoles, $CuFe_2O_4$ Nanoparticles, Catalyst, Terminal alkynes.

INTRODUCTION

Glaser [1] discoverd the oxidative homo-coupling of terminal acetylenes using these transformations. Baeyer [2], Straus [3], Reppe [4] and Eglinton [5] extended the scope of the reaction in subsequent studies. Castro and Stephens [6] reported a hetero-coupling reactions of copper(I) acetylides without oxygen and Chodkiewicz and Cadiot [7] reported with bromoalkyne. These copper-mediated cross-coupling reactions of alkynes have been reviewed extensively [8].

Huisgen [9] extended his research work on 1,3-dipolar cycloaddition reactions which led to the general concepts of 1,3-dipolar cycloadditions. With the disclosure of Cu-mediated synthesis of β-lactams from nitrones and alkynes by Kinugasa and Hashimoto [10], the paths of copper acetylides and 1,3-dipoles towards organic azides was not discovered until the 21st century [11]. Bertozzi *et al.* [12] exploited their reaction with phosphines in metabolic oligosaccharide engineering studies. At the same time, Kolb *et al.* [13] introduced the concept of "click chemistry" and since its discovery, the Cu-catalyzed azide alkyne 1,3-dipolar cyclo-addition becomes means for the covalent assembly of complex molecules. It leads to the discovery of a many applications in pharmaceutical chemistry, synthesis and materials science [14].

In addition to these advances, it is indeed to broaden the scope of one-pot multicomponent reaction in combination with "click chemistry". As organic azides are safe compounds, but those of low molecular weight can be unstable and difficult to handle [15]. This is commonly true for compounds with several azide functionalities for polyvalent structures generation.

EXPERIMENTAL

All chemicals and reagents were bought from Sigma-Aldrich/S.D Fine Chemicals, India and used. Silica gel (100-200 mesh) was used for column chromatography. Required other chemicals, solvents and reagents were obtained from commercial sources.

Typical experimental procedure: A mixture of alcohol (1 mmol), trimethylsilyl azide (2.0 mmol) and $CuFe_2O_4$ nanoparticles (3 mol %) in toluene (3 mL) was stirred at 60 °C for 3 h. After complete consumption of the alcohol as indicated by TLC, to this add alkyne (1.2 mmol) and water (2 mL) and continued the reaction. After confirmation from TLC that the reaction is completed, the reaction mixture needed to be diluted with H_2O and extracted with ethyl acetate (2 × 10 mL). By using anhydrous Na_2SO_4, the combined organic layers were dried and concentrated *in vacuo* and purified by column chromatography to afford the final product. The product was well characterized by ^{1}H NMR, mass spectroscopic analysis and ^{13}C NMR.

1-[1-(4-Bromo-phenyl)-ethyl]4-phenyl-1*H*-(1,2,3)triazole (Table-1, entry 1): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.01 (d, 3H, *J* = 7.6 Hz) 5.75-5.82 (q, 1H *J* = 7.6 Hz), 7.17 (d, 2H, *J* = 8.309 Hz), 7.27-7.39 (m, 3H), 7.48 (d, 2H, *J* = 8.309 Hz) 7.56 (s, 1 H), 7.74 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.24, 59.70, 118.21, 120.19, 125.71, 127.98, 128.18, 128.65, 128.77, 132.26, 139.80, 147.75. ESI MS (*m/z*): 329 $(M+2)^+$.

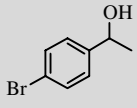
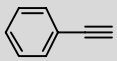
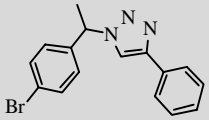
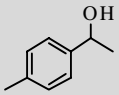
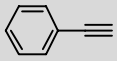
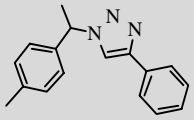
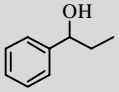
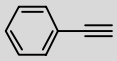
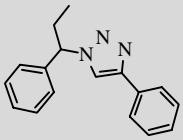
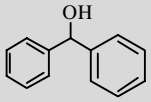
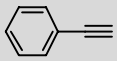
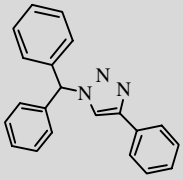
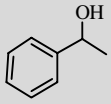
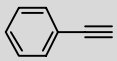
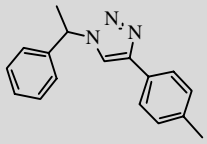
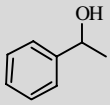
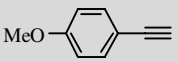
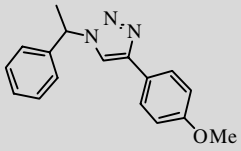
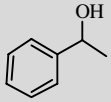
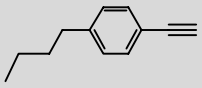
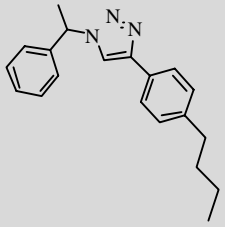
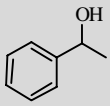
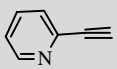
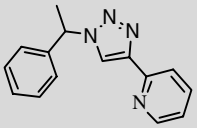
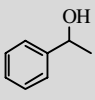
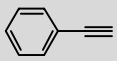
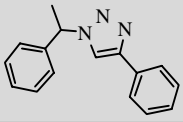
4-Phenyl-1-(1-phenyl-propyl)-1*H*-[1,2,3]triazole (Table-1, entry 4): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.98 (t, 3H, *J* = 7.6 Hz), 2.27-2.42 (m, 1H), 2.48-2.63 (m, 1H), 5.46 (t,

1H, *J* = 6.798 Hz), 7.302-7.38 (m, 8H), 7.59 (s, 1H), 7.75 (d, 2H, *J* = 7.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 11.0, 28.36, 66.85, 118.52, 125.59, 127.02, 128.50, 128.70, 128.94, 130.68, 138.83, 147.64. ESI MS (*m/z*): 264.1 $(M+H)^+$.

4-(4-Pentyl-phenyl)-1-(1-phenyl-ethyl)-1*H*-[1,2,3]triazole (Table-1, entry 7): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.85 (t, 3 H, *J* = 6.5 Hz), 1.24-1.33 (m, 4H, *J* = 3.6 Hz), 1.53-1.68 (m, 2H, *J* = 7.9 Hz), 2.01 (d, 3H, *J* = 7.2 Hz), 2.55 (t, 2H, *J* = 7.9 Hz), 5.76-5.86 (q, 1H, *J* = 7.2 Hz), 7.12 (d, 2H, *J* = 7.9 Hz), 7.25-7.37 (m, 5H) 7.5 (s, 1H), 7.63 (d, 2H, *J* = 7.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 13.96, 21.27, 22.49, 30.98, 31.42, 35.67, 60.19, 118.00, 125.59, 126.06, 128.06, 128.47, 128.76, 128.99, 140.02, 142.96, 147.85. ESI MS (*m/z*): 320.2 $(M+H)^+$.

3-[1-(1-Phenyl-ethyl)-1*H*-[1,2,3]triazol-4-yl]-pyridine (Table-1, entry 8): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.01 (d, 3H, *J* = 7.6 Hz), 5.75-5.79 (q, 1H, *J* = 7.6 Hz), 7.28-7.34 (m, 5H), 7.46 (d, 1H, *J* = 8.4 Hz), 7.57 (s, 1H), 8.09 (d, 1H, *J* = 8.4 Hz), 8.75 (d, 1H *J* = 4.8 Hz), 8. 92 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.19, 60.20, 118.20, 124.2, 125.52,

TABLE-1
ONE-POT SYNTHESIS OF 1,4-DISUBSTITUTED 1,2,3-TRIAZOLES FROM DIFFERENT ALCOHOLS WITH TRIMETHYLSILYLAZIDE ($TMSN_3$) AND PHENYL ACETYLENE*

Entry	Alcohol	Alkyne	Product	Time (h)	Yield (%)
1				4.5	70
2				4.5	76
3				5.0	72
4				4.0	80
5				5.0	78
6				5.0	72
7				4.5	78
8				5.0	60
9				5.0	80

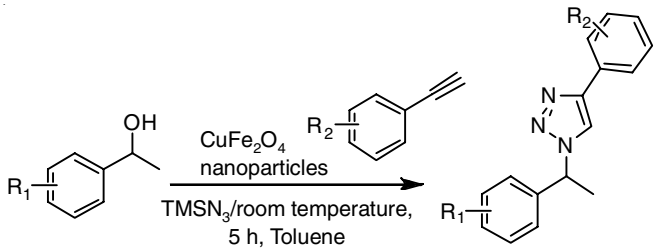
*Reaction conditions: Alcohol (1 mmol), $TMSN_3$ (1.5 equiv), Phenyl acetylene (1.2 mmol) and toluene (3 mL), room temperature.

127.52, 128.01, 133.51, 135.42, 140.26, 147.94, 149.24. ESI MS (*m/z*): 251.1 $(M+H)^+$.

RESULTS AND DISCUSSION

Aliphatic azides can be synthesized from the corresponding halides by nucleophilic displacement or, in cases of vinyl azides and aryl by a $CuFe_2O_4$ nanoparticles catalyzed reaction with sodium azide. When we use activated halides like propargylic, benzylic and allylic, then the substitution is facile.

Herein, we report a $CuFe_2O_4$ nanoparticles mediated one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles by using a three component coupling of trimethylsilylazide ($TMSN_3$), secondary alcohol and terminal alkynes (**Scheme-I**).



Scheme-I

In this paper, we began with the direct conversion of an alcohol with trimethylsilylazide into a alkyl azide intermediate. This intermediate upon treated with phenylacetylene without isolation to get the 1,4-disubstituted-1,2,3-triazole in an one-pot operation *via* 1,3-dipolar cycloaddition product by using $CuFe_2O_4$ nanoparticles as a catalyst. In this reaction, water plays an important role such as (a) quenching of excess trimethylsilylazide; (b) acetylene without any amine base and (c) formation of copper acetylide from $CuFe_2O_4$ nanoparticles. As exemplified in Table-1, the reaction proceeds smoothly to completion and the yields are very good. The reaction of various secondary benzylic alcohols bearing electron-rich and electron-poor substituents underwent the reaction smoothly and gave the products in good yield (Table-1, entries 1-4).

In order to disclose the importance of reaction, different types of terminal alkynes derivatives were reacted with the azides of benzylic alcohols, which were generated *in situ*. In this reaction, it was observed that the reaction with a range of different alkynes, such as substituted phenyl acetylenes, aliphatic and hetero aromatic terminal alkynes, were fruitful and the formed triazoles were obtained in good yields (85-65 %). Among the various terminal alkynes used in this study, 4-methyl-, 4-methoxy-, 4-pentyl- and 3-fluoro-substituted phenyl acetylenes were found to be more reactive when compared to the heteroaromatic alkyne (Table-1, entries 5-9).

Conclusion

The variety of 1,4-disubstituted 1,2,3-triazoles were prepared using benzylic/allylic alcohols, trimethylsilyl azide and terminal alkynes *via* a simple one-pot, two-step procedure involving the azidation of alcohols, followed by 1,3-dipolar cycloaddition with terminal alkynes using $CuFe_2O_4$ nanoparticles as catalyst. 1,4-Disubstituted 1,2,3-triazoles are obtained in good to excellent yields without the need for the reactivation and isolation of the azide intermediates.

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