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Graphical Abstract

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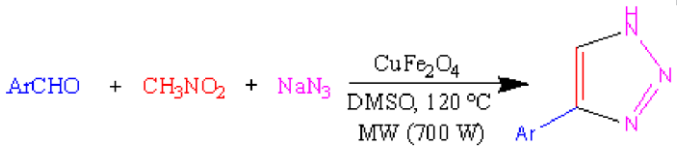

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Magnetically recoverable Copper Ferrite catalyzed cascade synthesis of 4-Aryl-1*H*-1,2,3-triazoles under microwave irradiation

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ABSTRACT

Magnetically active $CuFe_2O_4$ catalyzed cascade synthesis of 4-Aryl-1*H*-1,2,3-triazoles under microwave irradiation starting from aromatic aldehydes, sodium azide and nitromethane has been developed and demonstrated here. The catalyst system needed for the purpose was prepared following a procedure by A. Dandiya et al. with a slight modification and was characterized using FT-IR, XRD, SEM-EDX and TEM analysis. The most notable advantage of the developed methodology is the excellent time economy to carry out the transformation. Other features include simple operating procedure, wide substrate coverage and easy recovery of the catalyst. Reusability of the catalyst has been tested and found to be very satisfactory up to sixth cycle without significant loss in efficiency. All the synthesized compounds have been characterized using FTIR, ^{1}H & ^{13}CNMR spectroscopy, HRMS.

Introduction

1,2,3-triazoles have always been constituting an important class of heterocyclic organic framework due to the immense pharmacological activities associated with them. Features like inertness to acidic and basic hydrolysis as well as to oxidative and reductive conditions, propensity to form hydrogen bonds to increase the solubility as well as to favour bindings with biomolecular targets etc. make the core unit a unique one.[1] Due to the structural resemblance of diversely substituted triazole moieties to amide and thereby to peptide bonds as well as the ability to mimic bioisosteres of acyl phosphonates and the trans-olefinic moieties, this simple architecture has evolved as a lead structure in designing medicinally important organic molecules.[2] Lots of triazole derivatives have been found reported to exhibit activities like anti-cancer,[3] anti-inflammatory,[4] antitubercular,[5] antibacterial,[6] antiviral[7] etc., while a few others have already made their entry in the therapeutic world (Fig. 1).[1c] Consequently, 1,2,3-triazole has become the scaffold to go for many synthetic chemists throughout the globe, and a handful of reports published every year is a mere reflection of it. Majority of these reports have been found to describe the synthesis of diversely substituted 1,2,3-triazoles via reactions of sodium/organic azides with suitably substituted multiple bonds under thermal condition.[8] However, couple of other reports have also been found which demonstrate the suitability of vic- dibromides as substrates for the purpose via reactions with NaN_3.[9]

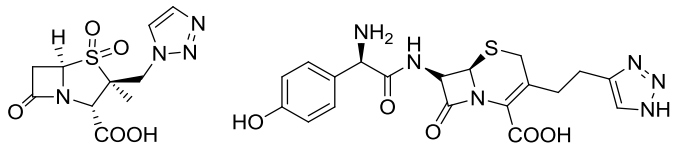

Figure 1. Marketed *β*-lactum antibiotic bearing 1,2,3-triazole moiety.

With the evolvement of 'cascade reactions' as an amazing tool to carry out numerous organic synthesis, many research groups have been putting their effort to develop cascade methodologies for the synthesis of 1,2,3-triazoles too. Cascade methodologies possess advantages over the conventional multistep procedures, of being step-economic by eliminating the need of intermediate isolation. Moreover, cascade methodologies provide the cushion of using commercially available simple compounds as substrates, which interact initially to generate an intermediate that reacts further to furnish the final product. In the year 2016, Q. Hu et al.[10] and L. Wu et al.[11] reported the cascade synthesis of 4-aryl-2*H*-1,2,3-triazoles and 4-aryl-1*H*-1,2,3-triazoles respectively starting from the same set of substrates viz. aromatic aldehydes, nitromethane and NaN_3. J. Thomas et al. disclosed the synthesis of *N*-substituted *and N*-unsubstituted-1,2,3-triazoles in single-step procedures starting from enolizable ketones, organic azides

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and primary amines/ammonium salt in their reports.[12] In their report, A. S. Kumar et al. demonstrated the successful use of magnetically recoverable $CuFe_2O_4$ nanoparticles as catalyst for the synthesis of 1,4-diaryl-1,2,3-triazoles starting from terminal alkynes, aryl boronic acid and NaN_3 in aqueous medium.[13] The reaction proceeds via the initial formation of aryl azide from aryl boronic acid and NaN_3 which reacts further with the third reaction partner to furnish the final product. Despite the elegance of already established methodologies, we have reported herein a cascade methodology for the synthesis of 4-aryl-1*H*-1,2,3-triazoles starting from aromatic aldehydes, nitromethane and NaN_3 under microwave irradiation in presence of magnetically recoverable copper ferrite catalyst. The work of S. Paul et al.[14] which described the use of $CuFe_2O_4$ catalyst for the synthesis of pyrrolo[2,3-*d*]pyrimidines starting from 6-aminouracil, aromatic aldehydes and nitromethane inspired us to use the same catalyst as it revealed the in situ formation of 2-nitrovinylbenzenes in the initial step and the methodology described here was also planned to proceed via the formation of the same intermediate. The thought of testing the reaction protocol under microwave irradiation came to our mind after going through a couple of reports where mircrowave irradiation was used successfully to carry out organic synthesis in general[15] and cascade synnthesis in particular.[16] The current methodology offers significant development in the field of 1,2,3-triazole synthesis by reducing the time requirement in great extent from many hours to a few minutes. It also enjoys additional advantages of easy recovery and reusability of the catalyst along with scope of using cheaper substrates. Fig. 2 summarizes a comparison of reaction conditions, time requirements, substrates used and percentage yields of different reported methods with the current one.

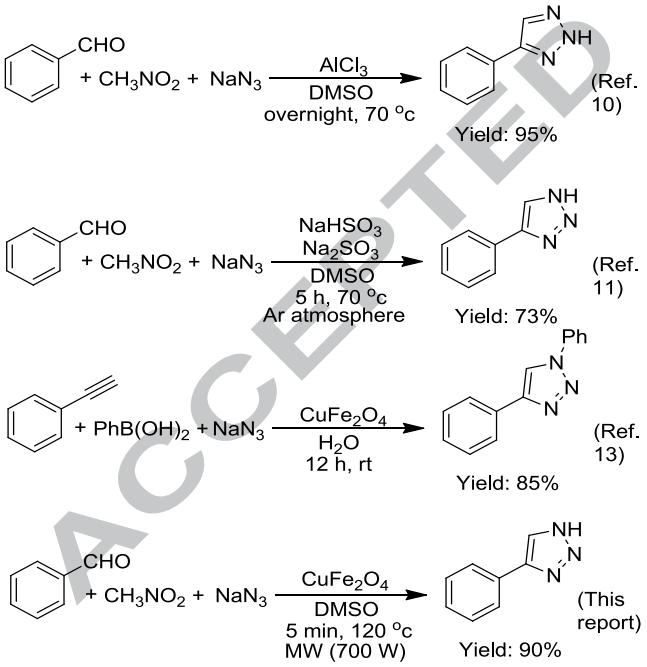
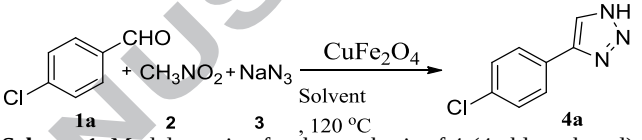


Figure 2. Comparison of reported and present work.

Results and discussion

$CuFe_2O_4$ catalyst system needed for the study was prepared by combined sonochemical and co-precipitation technique as discussed in their report by A. Dandiya et al.[17] with a minor change and was well characterized by using Fourier-transform-infrared spectroscopy (FT-IR), X-ray diffraction (XRD) analysis, scanning electron microscope (SEM) and transmission electron microscope (TEM). The formation of copper ferrite particles was first ascertained by electron dispersive X-ray (EDX) analysis coupled with SEM (Fig. 1, Supplemetary material). The EDX spectrum clearly indicates the elemental presence of Cu, Fe and O in the catalyst system (Fig. 1(c), Supplementary material). In the FT-IR spectrum of the catalyst system (Fig. 2, Supplementary material), an absorption band at 579.43 cm^{-1} was observed which can be attributed to Fe-O stretching vibration.[14] XRD analysis resulted reflection peaks at 2θ values 18.2, 29.8, 35.3, 37.2, 42.8, 52.9, 56.5 and 62.3 degree (Fig. 3, Supplementary material), which are found to be in good agreement with the characteristic peaks of tetragonal $CuFe_2O_4$ with good crystallinity.[13] TEM image reveals the coagulating nature of the particles which may be attributed to the magnetic nature of the particles (Fig. 4, Supplementary material). The size of $CuFe_2O_4$ nanoparticles are calculated to be in the range 13-18 nm. Selected area electron diffraction (SAED) analysis of the sample resulted diffraction spots superimposing on the ring pattern which reveals the polycrystalline nature of the material.



Scheme 1. Model reaction for the synthesis of 4-(4-chlorophenyl)-1*H*-1,2,3-triazole (**4a**).

To evaluate the catalytic activity of the so prepared $CuFe_2O_4$ particles in the cascade synthesis of 4-aryl-1*H*-1,2,3-triazoles, its catalytic activity was screened by carrying out a model reaction (Scheme 1) among *p*-chlorobenzaldehyde, nitromethane and NaN_3 under different reaction conditions and the results are summarized in Table 1. The reactions under microwave heating (700 W) were carried out at 120 ^oC using a monomode microwave synthesizer by Raga's Scientific Microwave Synthesis System. Table 1 clearly reveals the superiority of microwave heating over conventional heating for the purpose and the condition in which the reaction mixtures were exposed to microwave irradiation (700 W) in dimethyl sulfoxide (DMSO) with 10 mol% $CuFe_2O_4$ loading as the most promising reaction condition (Table 1, Entry 26). Decrease in $CuFe_2O_4$ loading to 5 mol% (Table 1, Entry 30) showed little change in isolated yield of 4-(4-chlorophenyl)-1*H*-1,2,3-triazole (**4a**) and so 5 mol% catalyst loading was used to carry out the rest of the study. The reaction was carried out in absence of $CuFe_2O_4$ too (Table 1, Entry 31 & 32) under both conventional and microwave heating which ended up with no and 12% product formation respectively justifying the worth of $CuFe_2O_4$ as catalyst. Among the other solvents tested, DMF also showed its suitability although a little bit inferior than DMSO. The non-suitability of H_2O, CH_3CN, EtOH and $CHCl_3$ as solvent for the purpose may be attributed to the solubility issue: *p*-chlorobenzaldehyde and nitromethane are being insoluble in H_2O while NaN_3 is insoluble in CH_3CN, EtOH and $CHCl_3$.

To have some insight into the way of reaction progress, we carried out some controlled experiments (Scheme 2) under our optimized reaction condition. Initially, we performed the reaction between *p*-chlorobenzaldehyde and nitromethane for 2 min which which resulted the formation of 1-chloro-4-(2-nitrovinyl)benzene (**5a)** almost in quantitative yield (**Reaction 1**). 1-chloro-4-(2-nitrovinyl)benzene (**5a**) thus obtained was then treated with NaN_3, and to our delight it furnished the final product 4-(4-chlorophenyl)-1*H*-1,2,3-triazole (**4a**) (**Reaction 2**) within 2 min suggesting a possibility of the involvement of **5a** as intermediate in our developed reaction protocol. A single pot two step reaction

was also attempted (**Reaction 3**), where NaN_3 was added directly to the product mixture of the first step and the reaction mixture thus obtained was then exposed to microwave irradiation (700 W) for 2 min which concluded with the formation of the final

Table 1. Optimization of reaction condition for **Scheme 1**[a]

Entry	Solvent	$CuFe_2O_4$ loading (mol-%)	Mode of activation	Yield [%][b]
1			Conv. Heating	--[d]
2		10	MW heating	15
3	--[c]		Conv. Heating	--
4		20	MW heating	15
5			Conv. Heating	--
6		10	MW heating	--
7	H_2O		Conv. Heating	--
8		20	MW heating	--
9			Conv. Heating	--
10		10	MW heating	12
11	CH_3CN		Conv. Heating	--
12		20	MW heating	15
13			Conv. Heating	10
14		10	MW heating	15
15	EtOH		Conv. Heating	12
16		20	MW heating	20
17			Conv. Heating	--
18		10	MW heating	--
19	$CHCl_3$		Conv. Heating	--
20		20	MW heating	--
21			Conv. Heating	30
22		10	MW heating	80
23	DMF		Conv. Heating	42
24		20	MW heating	82
25			Conv. Heating	40
26		10	MW heating	96
27			Conv. Heating	50
28		20	MW heating	96
29	DMSO		Conv. Heating	32
30		5	MW heating	95
31			Conv. Heating	--
32		--[e]	MW heating	12

[a]Reaction condition: *p*-chlorobenzaldehyde (1 mmol); nitromethane (1.5 mmol); NaN_3 (1.2 mmol); solvent (3 mL); 8h (conventional heating); 5 min (microwave heating, 700W).

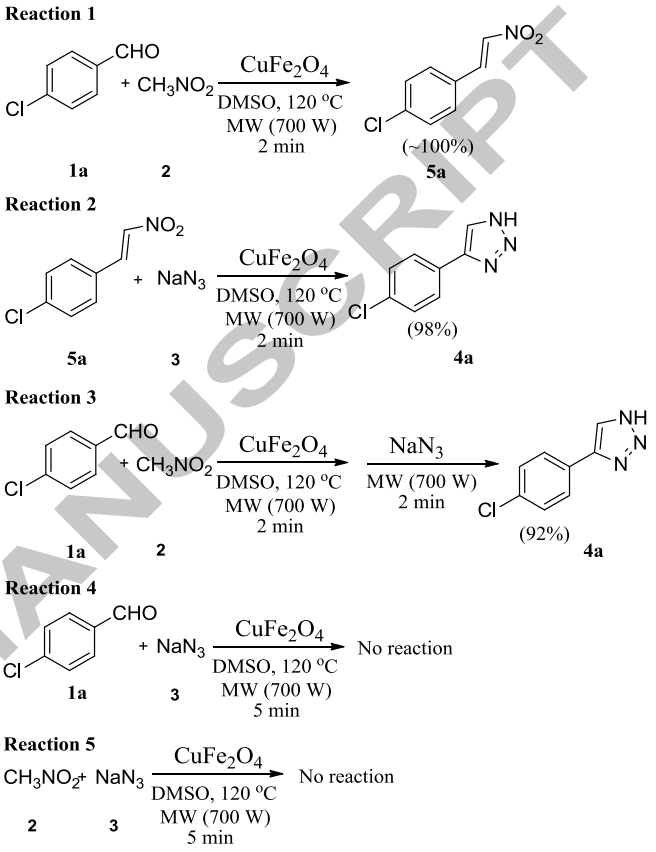
[b]Isolated yield.

[c]No solvent; nitromethane (3 mL) was used.

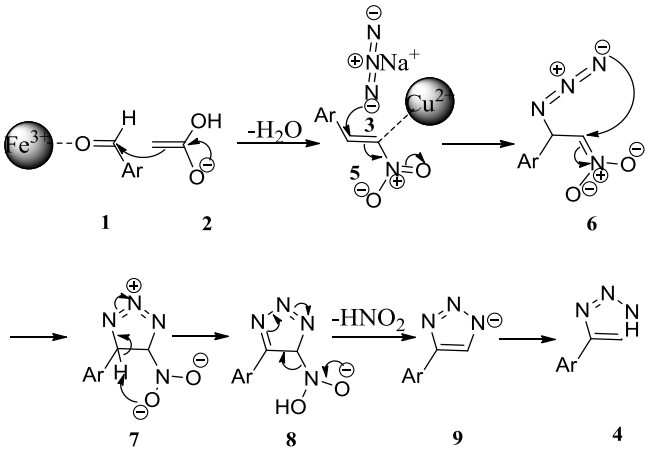
[d]No **4a** formation.

[e]No catalyst.

product (**4a**) in 92 % yield. This is in good agreement with the earlier observation as well as to the fact that **1a** and **2** react first to give **5a** under the reaction condition which reacts further with NaN_3 during the complete course of the reaction to furnish the final product **4a** in a cascade process. We checked the remaining two possibilities for initial product formation (**Reaction 4** & **5**) too which ended up with no reaction at all in each case and thereby left us with a single way of reaction progress, i.e. via the initial formation of **5a**. Although a detailed mechanistic study was not carried out, a plausible mechanism has been suggested based on these observations (Scheme 3).



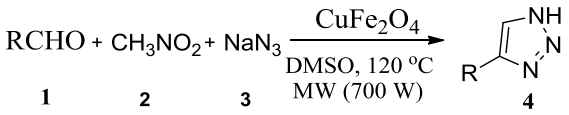
Scheme 2. Controlled experiments for **Scheme 1**.



Scheme 3. Plausible mechanism of **Scheme 1** (Ar is representing aromatic ring).

To access the generality of our developed method for the synthesis of 4-aryl-1*H*-1,2,3-triazoles, a series of aldehydes were screened via Scheme 4 and the results are summarized in Table 2.[18] Table 2 clearly reflects the suitability of the developed methodology for a wide spectrum of aromatic aldehydes bearing substituents with varied electronic nature. However, aldehydes with electron withdrawing groups (Table 2, Entry a, c-d) are

observed to respond the methodology better in comparison to aldehydes with electron releasing groups (Table 2, Entry f-h). Functionalities like -Cl, -NO_2, -OH, -NMe_2, -OMe are found to



Scheme 4. $CuFe_2O_4$ catalyzed cascade synthesis of 4-substituted-1*H*-1,2,3-triazoles.

sustain the reaction condition well while heteroaryl rings also remain undisturbed. In case of terephthaldehyde (Table 2, Entry k), both the aldehyde groups underwent reaction to give **4k** in 80% yield. Attempts were made to extend the reaction protocol for aliphatic aldehydes including α, β-unsaturated aldehydes (Table 2, Entry l-o), but went in vain.

To check the worth of the catalyst further, recovery and reusability study of the catalyst were carried out. For this, the reaction was carried out in comparatively large scale taking 10 mmol of nitrobenzaldehyde (1.51 g), and 12 mmol of NaN_3 (780 mg), 15 mmol of CH_3NO_2 (0.915 g) and 5 mol% of $CuFe_2O_4$. After completion of the reaction, the catalyst was recovered using a bar magnet. The recovered catalyst was then washed thrice with Ethylacetate followed by H_2O and then kept it in an oven at 80 ^{0}C for overnight. The recovered catalyst thus obtained was used for the next batch of reaction. Activity of the reused catalyst was tested and the results have been presented in Fig. 3, which shows only a slight decrease in activity of the catalyst up to the sixth cycle beyond which the reusability was not continued. The reusability test also gave us the opportunity to check applicability of the methodology in gram scale (1.5 g) and it was observed that it works well for 4-nitrobenzaldehye.

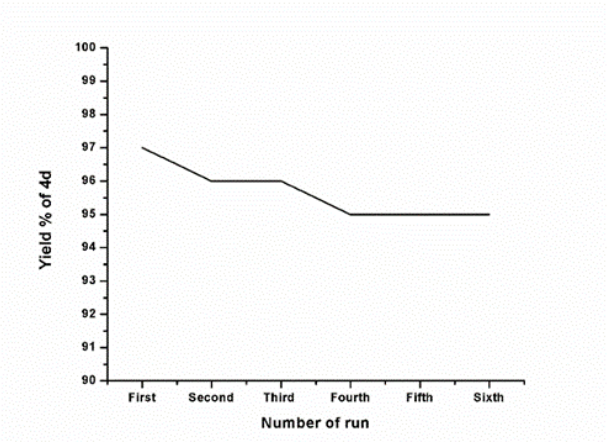


Figure 3. Reusability of $CuFe_2O_4$ for the synthesis of **4d** via Scheme 4.

Conclusions

In conclusion, a microwave assisted $CuFe_2O_4$ catalyzed cascade methodology for the synthesis of 4-aryl-1*H*-1,2,3-triazoles starting from aromatic aldehyde, sodium azide and nitromethane has been developed. The salient feature of the current methodology is the time economy which is found to be superior to that of the already existing methodologies by a huge margin. Other features like simple operating procedure, wide substrate scope, satisfactory to high product yield, high reusability of the catalyst etc. ensure the methodology to be a competitive one to the established methods.

Acknowledgments

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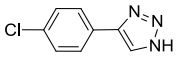
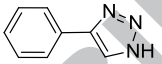
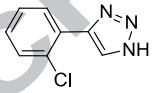
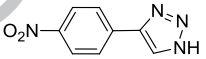
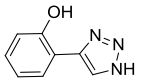
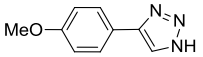
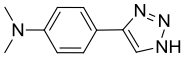
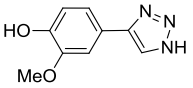
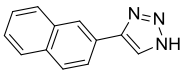
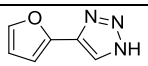
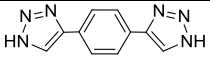
Table 2. Synthesis of **4** via Scheme 4[a]

Entry	RCHO (**1**)	Product (**4**)	Time (min)	Yield [%][b]
a	*p*-Cl-C_6H_4CHO		5	95
b	C_6H_4CHO		5	90
c	*o*-Cl-C_6H_4CHO		5	92
d	*p*-NO_2-C_6H_4CHO		5	97
e	*o*-OH-C_6H_4CHO		8	85
f	*p*-OMe-C_6H_4CHO		8	80
g	*p*-NMe_2-C_6H_4CHO		10	60
h	4-hydroxy-3-methoxybenzaldehyde		10	58
i	2-Naphthaldehyde		5	92
j	2-Furaldehyde		5	92
k	Benzene-1,4-dicarboxaldehyde		5	80[c]
l	*trans*-cinnamaldehyde	--	10	--[d]
m	HCHO	--	10	--
n	CH_3CHO	--	10	--
o	n-Pentanal	--	10	--

[a]Reaction condition: **1** (1 mmol); **2** (1.5 mmol); **3** (1.2 mmol); 5 mol% $CuFe_2O_4$; DMSO (3 mL); microwave heating (700W).

[b]Isolated yield.

[c]**1k** (1 mmol); **2** (3 mmol); **3** (2.4 mmol) were used.

[d]No product formation

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18. **General procedure for the synthesis of 4-Aryl-1*H*-1,2,3-triazoles (Scheme 4):** The aldehyde (1 mmol), NaN_3 (1.2 mmol), CH_3NO_2 (1.5 mmol), $CuFe_2O_4$ (5 mol%) and DMSO (3 mL) were taken in a round bottomed flask fitted with a reflux condenser and exposed to microwave irradiation (700 W) using a monomode microwave synthesizer by Raga's Scientific Microwave Synthesis System for a specified time (Table 2). After the completion of the reaction (monitored by TLC), magnetically active $CuFe_2O_4$ particles were removed using a bar magnet. DMSO was distilled off under vacuum, product was dissolved in Ethyl acetate, washed with water, treated with brine and then the organic layer was dried over anhydrous Na_2SO_4. The crude product was obtained by evaporating the Ethyl acetate and then purified by column chromatography using silica gel (100-200 mesh) as adsorbent and Ethyl acetate-Hexane as eluent.

Supplementary Material

Supplementary data associated with this article can be found in the online version of the manuscript.

- Cascade synthesis
- Excellent time economy
- Microwave assisted
- High reusability of $CuFe_2O_4$