

Investigating the Use of Metal Catalysts in Iron Oxide Nano/Microspheres for the Synthesis of 1,2,3-triazoles From Alkynes and Azides

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1. Background and Purpose of Research

Triazoles have found a wide range of applications in the world today. They function as excellent antifungal drugs and plant protection fungicides [1], some examples being fluconazole, isavuconazole, itraconazole, and epoxiconazole. Elsewhere, triazoles are being implemented as antibiotics and for the treatment of cancer due to the effective 1,2,4-triazole moiety pharmacophore [2]. Aside from this, they also serve as useful chemical building blocks for functional materials [3]. As such, this class of compounds has established its value in the agriculture, medical, and chemical industries. The term triazole refers to either chemical species of an isomeric pair of compounds containing the $C_2H_3N_3$ five-membered ring of 2 carbon atoms and 3 nitrogen atoms.

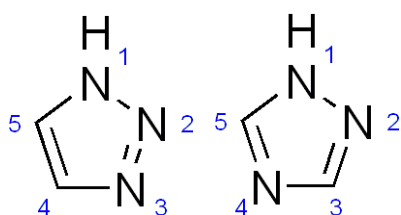


Fig 1.1 Five-membered rings of 1,2,3-triazole (left) and 1,2,4-triazole (right)

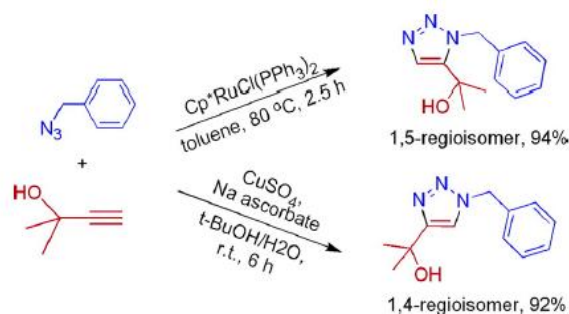


Fig 1.2 Example of Huisgen's dipolar cycloaddition

Importantly, triazoles can be synthesized relatively easily through Huisgen's dipolar cycloaddition of organic azides and alkynes [4], which can be achieved through a one-pot process. This direct route is representative of a branch of chemistry termed as "click chemistry", a collection of reactions giving high chemical yields, is stereospecific, and uses readily available starting materials or reagents.

2. Hypothesis of the Research

However, because the reaction has a high activation energy (25-26kcal/mol) [5], cycloaddition occurs slowly kinetically even at elevated temperatures for unactivated reactants. This energy barrier is overcome through the use of catalysts such as those containing copper and ruthenium, whose catalytic activity have been verified through several

studies [6], [7]. These catalysts are economically costly, hence the goal of this study is to synthesize copper and ruthenium catalysts coated with a magnetic mesoporous Fe₂O₃ layer. We hypothesize that the layer allows for recollection of catalyst and subsequent reuse, preventing wastage and enhancing sustainability as a 'green reaction'. The efficiency of the catalyst will be documented following each reaction cycle so as to access recyclability.

It is anticipated that the additional outer coating would hinder contact of the catalyst with substrate molecules, thus affecting yield. Hence a second goal of this study would be to optimize the catalytic process for nano-coated catalysts. This will be done by varying the physical and chemical environments.

3. Research Method and Materials

A. Equipment:

- 1) Sonicator- uses ultrasound to aid in the even dispersal of Fe₂O₃ particles and impregnation of catalyst molecules
- 2) Multimax Machine- This piece of equipment monitors reaction time, stirring, and temperature conditions for each test tube set-up.
- 3) Gas-chromatography, mass spectrometry (GCMS)- Reaction mixtures containing the desired triazole product were vaporized to analyze yield and regioselectivity. For this purpose, a calibration curve of mesitylene standard/ (compound close to triazole) against amount of triazole (mmol) was plotted. An exponential graph with $f(x) = 0.081871396 * 1.5926545^x$ and R² value 0.9364 was obtained. (Refer to Annex A for graph) Regioselectivity was calculated based on the percentage makeup of total product of each stereoisomer. An example of the obtained graph and percentage report from the GCMS machine can be found in Annex B.
- 4) Transmission electron microscope(TEM)- Nanoparticle grains were analyzed with TEM.

B. Synthesis of mesoporous Fe₂O₃ nanoparticles stock and TEM analysis: 7.5g of NaOAc added to 10mmol Fe (acc)₃, followed by 3g polyacrylic acid, 0.64g NaOH, and then 8ml ethylene glycol. The mixture was stirred for 1h, then refluxed for 2h before being washed with ethanol and water and dried for use. Sample was then scanned using TEM [8].

C. Impregnation of Fe₂O₃ nanoparticles with desired catalyst: The metal species component of the final catalyst constitutes 2% of its entire weight. A corresponding metal precursor was added to introduce the metal species. Ruthenium (III) chloride with reducing agent NaBH₄ for Ruthenium metal catalyst, Ruthenium (III) chloride for Ruthenium (II) catalyst and Copper (II) nitrate for Copper (II) catalyst.

D. Experimental Procedure: 5mg of above-synthesised metal-ion loaded Fe₂O₃ nanoparticles was added to a test tube, followed by 78mg of NaN₃. 0.115ml of Benzyl Chloride and 0.220ml of Phenylacetylene was then added, followed by 2ml of solvent. The mixture was then stirred and heated under reflux for 5 hours. Organic azides undergoing the actual cycloaddition reaction was generated in-situ through S_N2 nucleophilic substitution reaction (Refer to Annex C for pictorial reaction scheme)

E. Temperature of reaction: Reaction yield and regioselectivity were investigated as a function of temperature. Temperature conditions of 40°C, 60°C, 70°C, 80°C, 100°C and 120°C were used for each of the three catalysts. Water was chosen arbitrarily as the solvent, and the reaction left overnight.

F. Solvent combination analysis: The effect of type of solvent used to mediate the reaction was also investigated. Solvent types included protic and aprotic, illustrated below.

Solvent no.	Solvent used	Type
1	Water: MeCN (1ml each)	Polar protic : Polar aprotic
2	Water: Ethanol (1ml each)	Polar protic : Polar protic
3	DMF (2ml)	Polar aprotic
4	DMSO (2ml)	Polar aprotic
5	Water: DMSO (1ml each)	Polar protic : Polar aprotic
6	Water (2ml)	Polar Protic

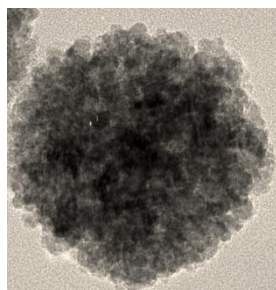
Table 2.1. Panel of solvents used for solvent combination analysis

G. Recyclability: Once the optimum temperature and solvent combination was determined (solvent type 1 and 2, temperature: 100 degrees Celsius), the recyclability of the copper catalyst, which displayed the greatest yield and regioselectivity, was accessed. The click reaction was run 3 times, and yield and regioselectivity were quantified following each trial.

3. Interpretation of Data, Results, and Findings

TEM Imaging:

Fig 3.1. TEM image of synthesized nanosupport. Diameter: Approximately 100nm



This image depicts the mesoporous Fe₂O₃ nano support which was successfully synthesized through the methods listed above.

The catalytic activity of Cu@Fe₂O₃ catalysts was evaluated by the cycloaddition of Benzyl Chloride and Phenylacetylene in the presence of Sodium Azide. All results were analysed via Gas Chromatography Mass Spectrometry with Mesitylene as internal standard.

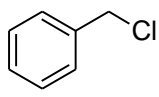
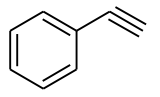
Catalytic Activity for Cu@Fe ₂ O ₃ catalyst:				Yield	
Entry	Substrate 1	Substrate 2	Catalyst	1,5	1,4
1			None	Trace	11%
2	“	“	CuI	Trace	89%
3	“	“	Cu@Fe ₂ O ₃	Trace	84%

Table 3.1. Catalytic activity of Cu(I) ions with without mesoporous Fe₂O₃ nanosupport

In the above data, Cu@Fe₂O₃ catalyst demonstrated similar catalytic activity as standard catalysts for synthesis of 1,4-disubstituted triazoles, Cu(I) ions. This shows that the mesoporous Fe₂O₃ nanoparticle support is non-sterically hindering during the catalytic process of the reaction.

Temperature of reaction: Table 3.2 shows the percentage yield of both 1,4-disubstituted and 1,5-disubstituted triazoles when then reaction is carried out at different temperatures.

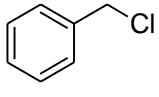
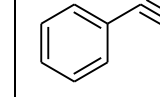
				Yield	
Entry	Substrate 1	Substrate 2	Temperature	1,5	1,4
1			RT	Trace	21%
2	“	“	40°C	Trace	Trace
3	“	“	60°C	Trace	Trace
4	“	“	70°C	16%	21%
5	“	“	80°C	21%	29%
6	“	“	100°C	14%	86%
7	“	“	120°C	Trace	64%

Table 3.2. Cu@ Fe₂O₃ catalysed reactions at different temperatures

Examination of the effect of temperature on yield of the reaction shows that at low temperatures from ambient temperature to 80°C, the reaction exhibited both limited total conversion rate and regioselectivity. The reaction reached optimum performance (100% conversion, 86% yield of 1,5-disubstituted triazoles) when conducted at a temperature of 100°C. At even more elevated temperatures, the total conversion rate of the reaction was compromised, despite maintaining its regioselectivity.

Solvent combination analysis: Table 3.3 shows the percentage yield of both 1,4-disubstituted and 1,5-disubstituted triazoles when the reaction is carried out in a panel of solvents. For entries 1, 2 and 5, the ratios of H₂O to the corresponding solvents are all 1:1.

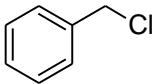
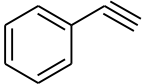
Entry	Substrate 1	Substrate 2	Solvent	Yield	
				1,5	1,4
1			H ₂ O:MeCN	Trace	84%
2	“	“	H ₂ O:EtOH	Trace	74%
3	“	“	DMF	Trace	13%
4	“	“	DMSO	Trace	10%
5	“	“	H ₂ O:DMSO	13%	17%
6	“	“	H ₂ O	11%	80%

Table 3.3. Yield of Cu@Fe₂O₃ catalyst in different solvent combinations

From the above data, it is found that all solvents containing H₂O displayed satisfactory catalytic activity in terms of both total conversion and regioselectivity, other than H₂O:DMSO which only produced 17% of the desired product. This result shows that polar protic solvents used in tandem with aprotic solvents (Solvent combination 1) are most suitable for CuAAC reactions involving a mesoporous Fe₂O₃ nanoparticle support though generally protic solvents like water and H₂O provide good yields too. However, the addition of DMSO as an aprotic solvent to the reaction does not demonstrate the same optimum yield. One possible explanation would be the formation of coordination bonds between DMSO and Cu(I) ions, thus sterically hindering the catalyst from reactants.

C. Recyclability: Table 3.4 depicts performance of Cu@Fe₂O₃ catalysts after each cycle.

Entry	Reaction	Yield	
		1,5	1,4
1	1	12%	83%
2	2	14%	85%
3	3	18%	81%

Table 3.4. Yield of Cu@Fe₂O₃ catalyst with each repeated use

From the above data, it shows that even after multiple batches of reactions, Cu@Fe₂O₃ catalysts showed minuscule deterioration of both catalytic activity and regioselectivity. Additionally, the retrievable characteristic of the synthesized catalyst is highly advantageous in an industrial setting, as it can be readily separated from the desired product through magnetic attraction with little cost. Furthermore, being reusable without compromise in its

catalytic activity and regioselectivity allows our catalyst to help reduce financial costs of the cycloaddition reaction.

Results and discussion: Ru@Fe₂O₃ catalyst

Both Ru(0)@Fe₂O₃ catalysts and Ru(II)@Fe₂O₃ were tested for catalytic activity through cycloaddition of Benzyl Chloride and Phenylacetylene. The yields are displayed

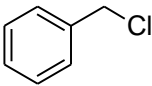
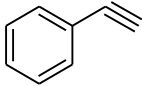
Ru(0)@Fe ₂ O ₃				Yield	
Entry	Substrate 1	Substrate 2	Solvent	1,5	1,4
1			H ₂ O:MeCN	11%	13%
2	“	“	H ₂ O:EtOH	15%	18%
3	“	“	DMF	Trace	10%
4	“	“	DMSO	10%	12%
5	“	“	H ₂ O:DMSO	13%	16%
6	“	“	H ₂ O	14%	15%

Table 3.5. Yield of Ru(0)@Fe₂O₃ catalyst in different solvent combinations

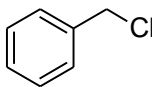
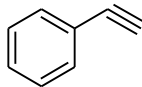
Ru(II)@Fe ₂ O ₃				Yield	
Entry	Substrate 1	Substrate 2	Solvent	1,5	1,4
1			H ₂ O:MeCN	10%	12%
2	“	“	H ₂ O:EtOH	13%	14%
3	“	“	DMF	Trace	Trace
4	“	“	DMSO	Trace	10%
5	“	“	H ₂ O:DMSO	16%	22%
6	“	“	H ₂ O	19%	27%

Table 3.6. Yield of Ru(II)@Fe₂O₃ catalyst in different solvent combinations

Both Ru(0)@Fe₂O₃ and Ru(II)@Fe₂O₃ catalysts displayed insignificant activity regardless of solvent choice. This is due to an absence of ligands that stabilise higher formal oxidation states of Ru metal center during catalysis, because of obstruction by the nanosupport. Stabilisation is usually achieved with η^5 -pentamethylcyclopentadienyl [CP*] ligands.

5. Conclusion and Recommendations

In conclusion, we found that a mesoporous Fe₂O₃ nanoparticle support reduces catalytic activity of Ruthenium ions, but have no detrimental effect on the activity of Cu ions, contrary to our hypothesis. It proves to be a useful addition to the CuAAC process, reducing financial costs and enhancing its green value due to it being easy to retrieve with magnets, as well as

maintaining its catalytic activity in terms of total conversion and regioselectivity with each batch of repeated use. Its optimum temperature is relatively low at 100°C, which deems it safe and easy to conduct industrially. The optimum solvent choices of water, MeCN and ethanol are also significant, since these solvents are readily available, and present versatility in reaction conditions, be it protic or aprotic. Importantly, our study demonstrated the usefulness and ease of employment of this particular click reaction. The simplicity of synthesis of both catalyst and product have been established. Thus, with further work, introducing mesoporous Fe₂O₃ magnetic supports for catalysis proves to be an interesting field with undiscovered potentials.

Our next step in determining the utility of Cu@Fe₂O₃ catalysts would be performing a substrate analysis, where more combinations of organic alkynes and azides can be tested for consistency in yield. Further recyclability can also be conducted to determine after which batch of repeated does the catalyst start to display a decrease in catalytic activity. Finally, gaining insights to each step of CuAAC's reaction mechanism will also be beneficial, as we can then determine if the addition of mesoporous Fe₂O₃ nanoparticle support changes the catalytic process.

6. Bibliography of References

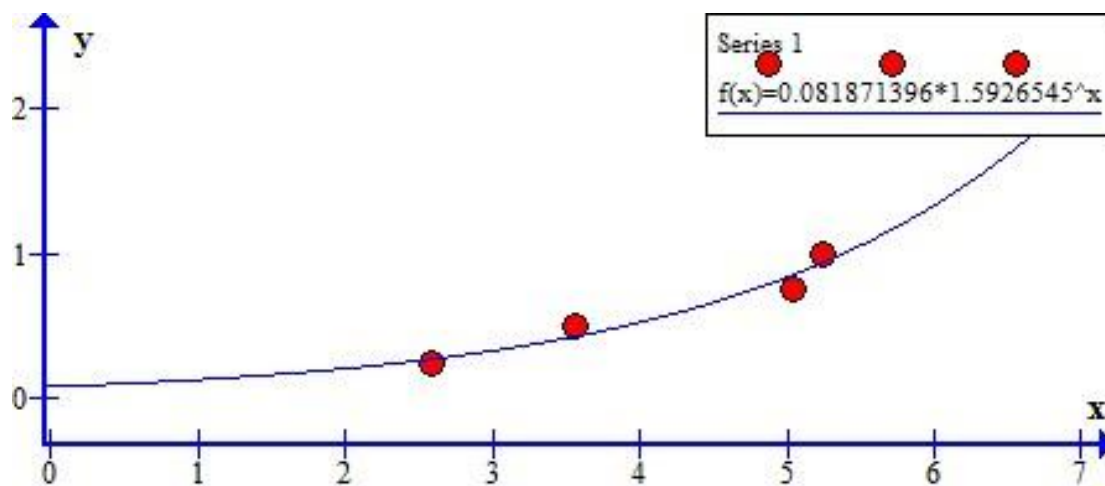
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7. ANNEX A

(Exponential graph used for calculation of triazole yield)

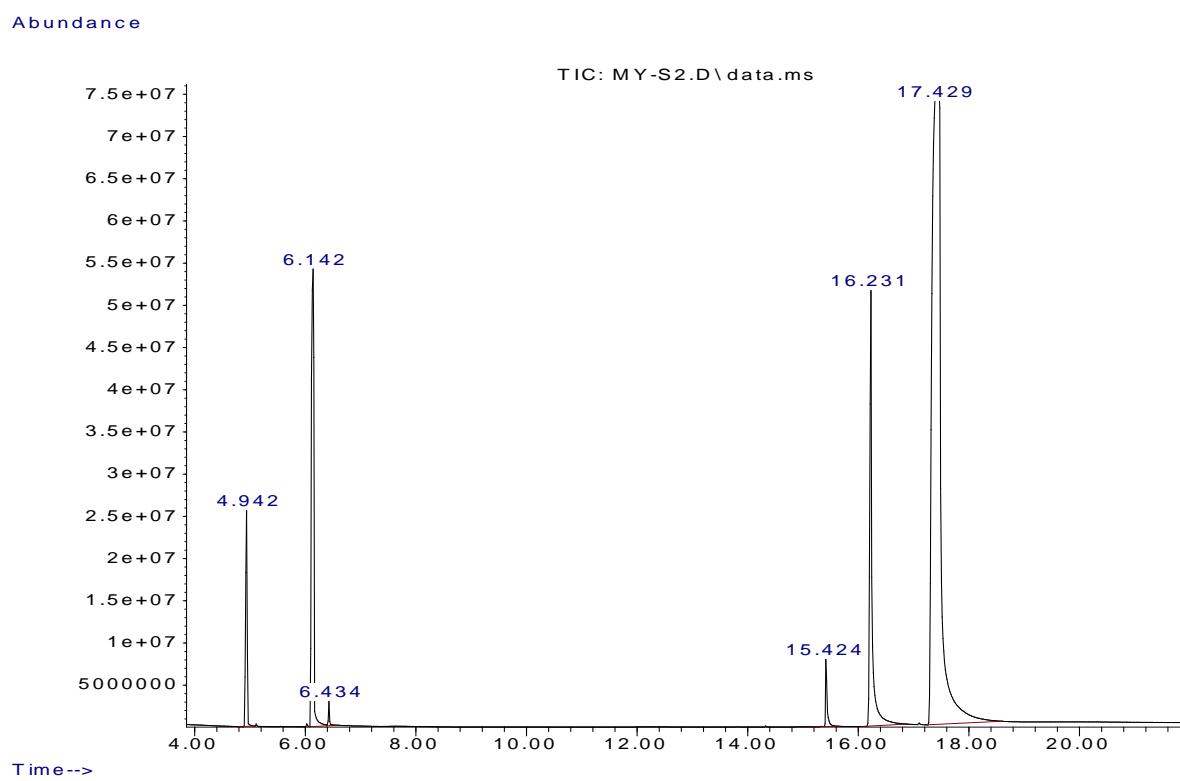


y= Amount of triazole produced (mmol)

$$x = \frac{\text{Area under triazole peak}}{\text{Area under mesitylene peak}}$$

ANNEX B

(Example of GCMS graph and percent report)



The following are compounds with their respective peaks of interest and time value.

Mesitylene – 6.142

1,4-triazole – 17.129

1,5-triazole – 16.231

(Example of Area percent report obtained)

Area Percent Report

Data Path : D:\IMRE-DATA\BAISHIQIANG\28-12-2011\

Data File : MY-S2.D

Acq On : 28 Dec 2011 11:52

Operator :

Sample : sample

Misc :

ALS Vial : 6 Sample Multiplier: 1

Integration Parameters: autoint1.e

Integrator: ChemStation

Method : C:\MSDCHEM\1\METHODS\BAISHIQIANG-atune.M

Title :

Signal : TIC: MY-S2.D\data.ms

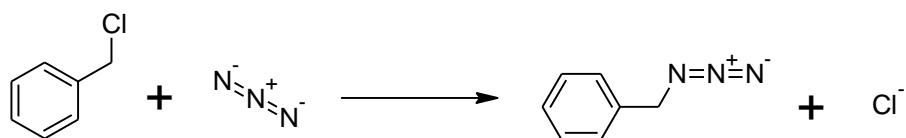
peak #	R.T. min	first scan	max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	4.942	67	77	87	BV	23375004	486399141	5.59%	3.835%
2	6.142	156	161	178	PV	53348648	1788119687	20.57%	14.099%
3	6.434	178	181	193	VB	2280609	40364965	0.46%	0.318%
4	15.424	793	810	825	BB	7466392	156300423	1.80%	1.232%
5	16.231	855	866	911	BB	49062592	1517849731	17.46%	11.968%
6	17.429	937	950	1032	BB 5	75731962	8693729783	100.00%	68.548%

Sum of corrected areas: 12682763730

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Annex C

(Full reaction scheme)



The azide generated then undergoes the actual cycloaddition reaction:

