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PII: S0040-4039(15)00388-3
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.02.107
Reference: TETL 45977

To appear in: *Tetrahedron Letters*

Received Date: 20 December 2014
Revised Date: 18 February 2015
Accepted Date: 19 February 2015

Please cite this article as: Anil Kumar, B.S.P., Harsha Vardhan Reddy, K., Karnakar, K., Satish, G., Nageswar, Y.V.D., Copper on chitosan: an efficient and easily recoverable heterogeneous catalyst for one pot synthesis of 1,2,3-triazoles from aryl boronic acids in water at room temperature, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.02.107

Graphical Abstract

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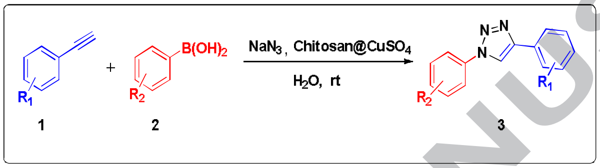

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
copper on chitosan (CS)
recyclability
boronic acids
1,2,3-triazoles
Click reaction

ABSTRACT

A facile, efficient and environmentally-friendly one pot protocol has been developed for the synthesis of 1,4-diaryl-1,2,3-triazoles from boronic acids, sodium azide, and acetylenes using copper sulphate immobilized on chitosan as a recyclable heterogeneous catalyst. This green synthetic three component protocol avoids handling of hazardous and toxic azides involving its *insitu* generation. The use of aqueous medium at room temperature and the easy recovery of the catalyst are other remarkable features of this procedure.

Copper-mediated 1,3-dipolar cycloaddition[1] (click reaction) to give 1,2,3-triazoles has gained prominent attention in green chemistry domain due to the mild reaction conditions and high efficiency involved. These compounds are useful as pharmaceutical agents, agrochemicals, dyes, corrosion inhibitors, photo stabilizers and photographic materials.[2] Efforts have been placed towards the development of novel copper based catalytic systems which minimize pollution in different synthetic protocols.[3] Although Cu(I)-catalyzed click reaction has provided excellent yields and good regioselectivity, thermodynamic instability and initiation of undesired alkyne–alkyne coupling restricted the use of Cu(I) catalysts.[4] Instead Cu(0)/Cu(II) salts with various additives and ligands have been investigated.[5] However, most of them are homogeneous and involved 1,3-dipolar cycloaddition of organic azides with alkynes.[6]

The major limitations of existing protocols can be realized as handling of unstable, toxic organic azides and using homogeneous catalysts which cannot be separated easily from the reaction system. In view of this, it is desirable to use heterogeneous catalysts, which have several advantages, such as faster and simpler isolation of the catalyst from reaction products by filtration, as well as easy recovery and recyclability. For this reason, immobilization of transition metals on various supports such as alumina,[7] Amberlyst[8] and zeolites[9] as well as copper nanoparticles on charcoal[10] have generated remarkable attention because of their green and efficient roles in catalyzed reactions. A number of chitosan-supported (CS) metal complexes such as CS-supported Pd catalyst,[11] CS-supported Cu catalyst,[12] CS-supported Rh catalyst[13] and CS-supported Ti catalyst,[14] have been reported recently.

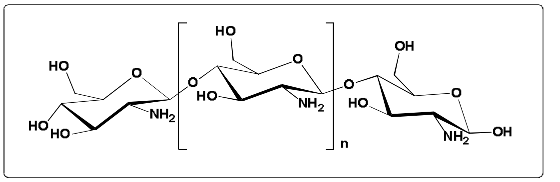
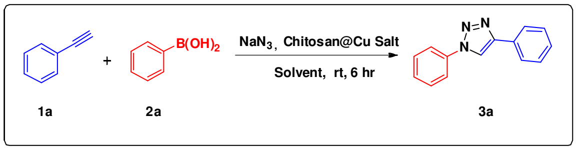


Figure 1: Chitosan

Chitosan (CS) (**Fig 1**) is a biodegradable, non-toxic polymer which can be obtained by deacetylation of chitin from the cell walls of algae.[15] The amino and hydroxyl groups of chitosan form stable complex with Cu metal and the resulting chitosan supported copper complex is recyclable and inexpensive catalyst.[12]

In continuation of our research in the field of novel environ friendly approaches[16, 17] in synthetic organic chemistry, we describe here in a CS- supported copper catalyzed synthesis of 1,2,3 triazoles in aqueous medium from boronic acids, NaN_3 and alkynes in one pot. Initially chitosan supported copper complex was prepared by suspending chitosan in an aqueous solution of $CuSO_4$ or $Cu(OAC)_2$ or CuI for 3 hr under neutral conditions. After the copper adsorption, the copper complex was separated by decantation and washed thoroughly with water several times to remove excess of copper salt, and was dried under vacuum at 60 °C for 12 hr to give the chitosan@copper catalyst (prepared according to the previously reported method[12])

The present protocol offers an improvement over the recent report of R. B. Nasir Baig[18] as we replaced the aryl azides with aryl boronic acids because of their stability, low toxicity and commercial availability. The *insitu* preparation of the organic azide as the main reactant reduces the number of steps and time involved in the reaction strategy. The advantages of the present approach are avoiding the isolation and handling of the hazardous and unstable organic azides, the use of aqueous medium and recyclability of the catalyst.



Scheme 1: Optimisation of reaction conditions for the synthesis of 1,2,3-triazoles

Table 1 Screening of Chitosan@copper salts as catalysts for Phenyl boronicacid and Phenyl acetylene cyclo addition[a]

Entry	Catalyst	Solvent	Yield[b](%)
1	Chit-CuI	MeOH	72
2	Chit-CuI	H_2O	81
3	Chit-Cu(OAc)$_2$	MeOH	63
4	Chit-Cu(OAc)$_2$	H_2O	68
5	Chit-CuSO$_4$	MeOH	84
6	Chit-CuSO$_4$	H_2O	90
7	Chit-CuSO$_4$	DMSO	Trace
8	Chit-CuSO$_4$	DMF	28
9	Chit-CuSO$_4$	CH_3CN	30
10	Chit-CuSO$_4$	EtOH	67
11	Chit-CuSO$_4$	Acetone	29
12	Chit-CuSO$_4$	MeOH:H_2O (1:1)	78
13	Chit-CuSO$_4$	THF	Trace
14	Chit-CuSO$_4$	DCM	Trace

[a]Reaction conditions: Phenyl acetylene (1 mmol), Phenyl boronic acid (1 mmol), NaN$_3$ (1.2 mmol), chitosan@copper salts (10 mol%) in H_2O (2 mL) at rt for 6 hr. [b]Isolated yield

Initially the reaction between phenyl boronic acid with phenyl acetylene was selected as a model reaction for optimizing the reaction conditions such as various copper sources and solvents (**scheme 1**), the results of which were represented in Table 1. The *insitu* generated azide from the reaction mixture of phenyl boronic acid and NaN$_3$ reacted well with phenyl acetylene and desired triazole was obtained in one pot. It was observed that the click reaction occurred smoothly in the presence of several deferent Chitosan supported Cu salts including Cu(OAc)$_2$, CuI and CuSO$_4$. Among the copper salts screened, chitosan@CuSO$_4$ in water was found to be excellent for this tandem reaction giving the desired 1,2,3-triazole (Table 1, entry 6). Other protic solvents such as methanol, ethanol and the mixture of water and methanol are proved to be less suitable for the reaction (Table 1, entries 1, 3, 5, 10 and 12). On the other hand aprotic solvents like DMSO, DMF, acetone, THF and DCM were ineffective (Table 1, entries 7, 8, 11, 13 and 14).

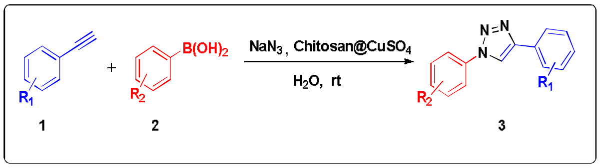
Having identified chitosan@CuSO$_4$ in water as the optimized reaction medium, catalyst loading was next investigated for the representative phenyl boronic acid, sodium azide and phenyl acetylene reaction (Table 2). The highest yield was obtained with 10 mol% of catalyst and 1.2 m.mol of NaN$_3$ (Table 2, entry 3).

Table 2: Copper-catalyzed azide-alkyne cycloaddition with different loadings of NaN$_3$ and chitosan@CuSO$_4$[a]

Entry	Catalyst (mol%)	NaN$_3$ (m.mol)	Yield[b](%)
1	2	1.2	48
2	5	1.2	64
3	10	1.2	90
4	20	1.2	90
5	10	1.0	75
6	10	1.5	90

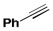
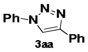
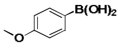
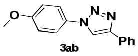
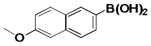
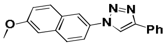
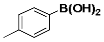
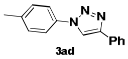
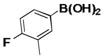
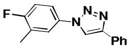
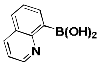
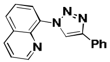
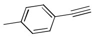
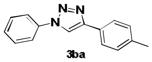
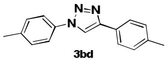
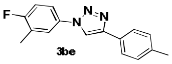
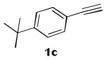
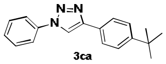
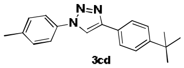
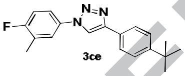
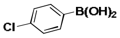
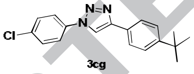
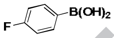
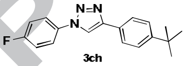
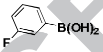
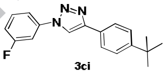
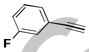
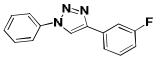
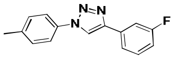
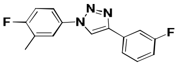
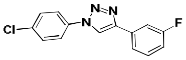
[a]Reaction conditions: Phnyl Acetylene (1 mmol), Phenyl boronic acid (1 mmol), NaN$_3$ (1.0 to 1.2 mmol), chitosan@CuSO$_4$ (2 to 20 mol%) in H_2O (2 mL) at rt for 6 hr. [b]Isolated yield

The scope of this methodology has been extended using a variety of phenyl boronic acids and alkynes (**scheme 2**). As illustrated in Table 3, it was found that both the electron donating substituents (4-methoxyphenyl-boronic acid and 4-methyl phenyl boronic acid) and electron withdrawing substituents (4-chlorophenyl boronic acid and 4-fluoro phenyl boronic acid) could be efficiently converted to the desired products in high yields (Table 3, entries 2, 4, 13 and 14). In the case of para and meta fluoro boronic acids, both have participated well in click cyclisation reaction (Table 3, entries 14 and 15). Furthermore, a disubstituted 4-fluoro-3-methylphenyl boronic acid successfully converted to triazole giving a little low yield (Table 3, entry 5). In addition to the phenyl boronic acids other aromatic substrates such as quinolin-8-ylboronic acid has reacted sluggishly giving rise to the expected triazole in 71% isolated yield (Table 3, entry 6).



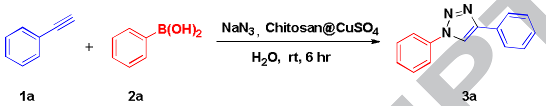
Scheme 2: Synthesis of 1,2,3-triazoles by using chitosan@CuSO$_4$ catalyst

Table 3. Synthesis of 1,4-disubstituted-1,2,3-triazoles using chitosan@$CuSO_4$ as catalyst in water[a]

Entry	Alkyne 1	Boronic acid 2	Triazole 3	t (h)	Yield[b] (%)
1	 1a	 2a	 3aa	6	90
2	1a	 2b	 3ab	5	86
3	1a	 2c	 3ac	8	78
4	1a	 2d	 3ad	5	82
5	1a	 2e	 3ae	8	83
6	1a	 2f	 3af	8	71
7	 1b	2a	 3ba	6	82
8	1b	2d	 3bd	6	84
9	1b	2e	 3be	5	84
10	 1c	2a	 3ca	7	80
11	1c	2d	 3cd	7	85
12	1c	2e	 3ce	7	79
13	1c	 2g	 3cg	6	83
14	1c	 2h	 3ch	6	86
15	1c	 2i	 3ci	6	79
16	 1d	2a	 3da	5	88
17	1d	2d	 3dd	7	86
18	1d	2e	 3de	8	83
19	1d	2g	 3dg	7	84

[a]Reaction conditions: Alkyne (1 mmol), boronic acid (1 mmol), NaN_3 (1.2 mmol), chitosan@copper sulphate (10 mol%) in H_2O (2 mL) at rt. [b]Isolated yield

In the case of substituted alkynes, methyl and tertiary butyl substituents on para position of phenyl acetylenes and meta flouro phenyl acetylene proceeded smoothly and the products were isolated in good yields (Table 3, entries 7-19).



Scheme 3: Model reaction to check the recyclability of the catalyst

Important features of the supported catalysts are reusability, recyclability and selectivity, which make them green catalysts especially considering from an environmental point of view. In this regard, the life time as well as reusability of the catalyst is verified. The recyclability of the CS-$CuSO_4$ catalyst was checked by conducting a model reaction by using phenyl boronic acid, NaN_3, phenyl acetylene (**scheme 3**). After each cycle, the catalyst was recovered by decantation and dried for 3hr at 60 ^{0}C (**Figure 2**).

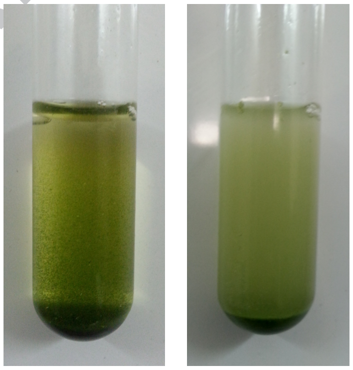


Figure 2: Reaction mixture before and after the reaction

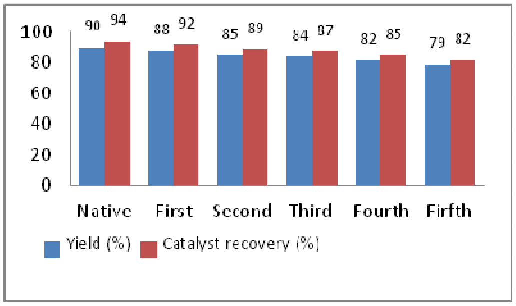


Figure 3. Recyclability of chitosan@$CuSO_4$ catalyst

The recovered catalyst was reused directly in the next cycle. The catalyst was found to be recyclable without significant loss of catalytic activity up to five cycles. (**Figure 3**). SEM analysis showed that the size and shape of catalyst did not change considerably even after fifth cycle. This clearly indicates the unaltered efficiency of the catalyst up to five cycles **(Figure 4)**.

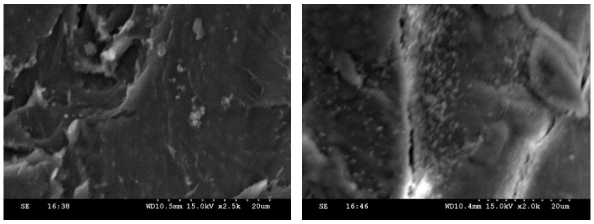


Figure 4. SEM-analysis of **(a)** fresh CS-$CuSO_4$ catalyst. **(b)** reused CS-$CuSO_4$ catalyst after 5th cycle.

In conclusion, the present protocol involves a shorter reaction pathway which helps in the reduction of reaction steps as well as workup and avoids the isolation of unstable azides with the use of recyclable and reusable chitosan@$CuSO_4$ catalyst in water as a green solvent to synthesize 1,4-disubstituted-1,2,3-triazoles with high regioselectivity.

Acknowledgement

The authors thank the Council of Scientific and Industrial Research (CSIR), New Delhi for financial assistance.

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19. ***Preparation of Chitosan@copper catalyst*:**The catalyst was prepared by the method described by Chao shen *et al.*[12] 5 gm of Chitosan was suspended in a 250 ml beaker containing 100 ml of water. 1 gm of copper salt was added to this suspension with stirring. After 3 hr the catalyst was separated by decantation, washed with water several times to remove excess of copper salt, and was dried under vacuum at 60 °C for 12 hr to give the chitosan@copper catalyst.
20. ***Procedure for the synthesis of 1,4-disubstituted 1, 2, 3-triazoles:*** Aryl boronic acid (1 mmol), phenyl acetylene (1 mmol) and NaN_3 (1.2 mmol) in H_2O (2 mL) were placed in a 10 ml RB flask to which 10 mol% chitosan@$CuSO_4$catalyst was added. The reaction mixture was stirred at room temperature and monitored by TLC until total conversion of the starting materials. After completion of the reaction, water (20 mL) was added to the resulting reaction mixture followed by extraction with EtOAc (4x10 mL). Catalyst was separated by simple decantation and dried for 3 hr at 60 °C

temperature. The recovered catalyst was used directly in the next cycle. The organic phase was washed with water and dried with Na_2SO_4. Solvent was removed under vacuum and the crude product was purified by column chromatography to obtain the corresponding triazole compound.

21. ***Data of representative example:*** **1,4-diphenyl-1H-1,2,3-triazole (Table 3, entry 1):** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.62 (m, 6H), 7.73-7.81 (d, *J* = 8.1Hz, 2H), 7.87-7.96 (d, *J* = 6.9Hz, 2H), 8.20 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.39, 117.57, 120.51, 125.84, 128.41, 128.89, 129.75, 137.05, 148.39; ESI-MS: *m/z* 222 $(M+H)^+$. HRMS calctd. For 222.1026 found 222.1024. $C_{14}H_{12}N_3$.