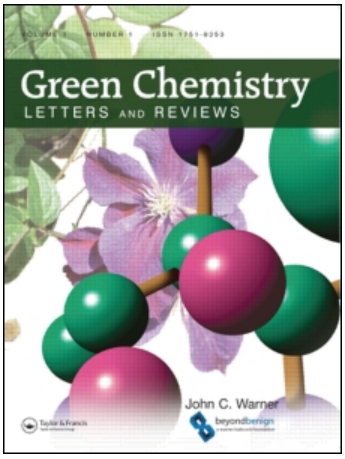

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Reusable polymer-supported copper catalyst for one-pot synthesis of 1-alkyl- and 1-aryl-1,2,3-triazoles: green, simple, and effective

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RESEARCH LETTER

Reusable polymer-supported copper catalyst for one-pot synthesis of 1-alkyl- and 1-aryl-1,2,3-triazoles: green, simple, and effective

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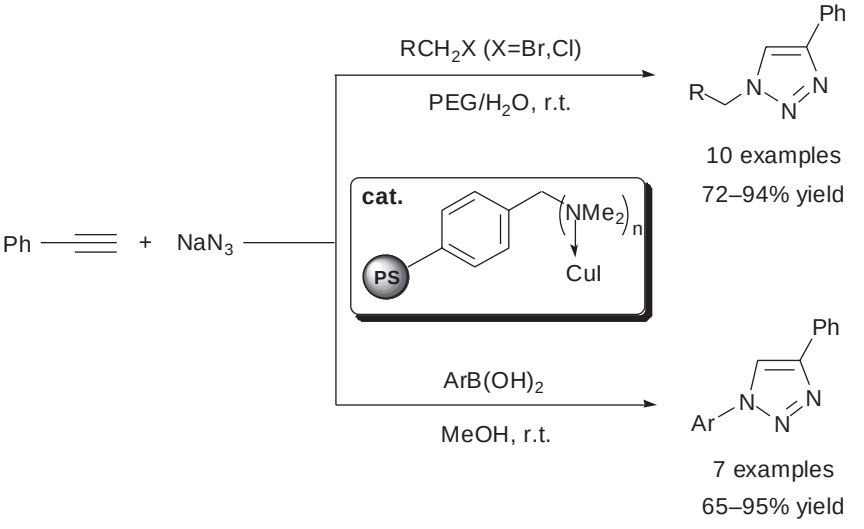
Polymer-supported copper-catalyzed one-pot synthesis of 1,4-disubstituted 1-alkyl- and 1-aryl-1,2,3-triazoles via 1,3-dipolar cycloaddition of alkyl halides or arylboronic acids, sodium azide, and phenylacetylene has been developed. Reactions went smoothly at room temperature using PEG/H_2O or methanol as solvent to afford the corresponding triazoles in good to excellent yields. The catalyst could be recovered by simple filtration and reused several times with slightly decrease in its activity.



Keywords: polymer-supported copper catalyst; 1,2,3-triazoles; alkyl halides; arylboronic acids; click chemistry

Introduction

The Huisgen 1,3-dipolar cycloaddition of azides and alkynes is one of the most powerful reactions to afford the 1,2,3-triazoles (*1*), which have shown interesting biological properties such as anti-allergic (*2–4*), anti-bacterial (*5*), and anti-HIV activity (*6*). An important advance in this field was the recent discovery that cycloadditions of terminal alkynes with organic azides catalyzed by CuI can be conducted at room temperature and are highly regioselective, leading to 4-substituted-1,2,3-triazoles. Consequently, this protocol has received considerable attention and found application in various research fields such as material chemistry (*7–10*), biological science (*11–14*), and medicinal chemistry (*15–19*). Despite these interesting applications, some limitations such as preparation of dangerous organic azides and metal contamination of the products are the problems need to be addressed.

Great efforts in green chemistry have been devoted in recent years to the application of eco-friendly heterogeneous catalysts (*20*) and multicomponent reactions (MCRs) (*21*). Immobilization of catalysts on polymer supports often offers advantages

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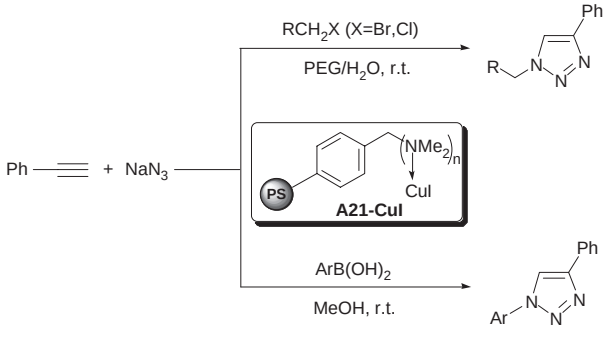
for carrying out organic transformations. Simple work-up, high selectivity, reusability of the catalysts, and low cost often make them more attractive than their homogeneous counterparts. MCRs have also received much attention lately, and have proven to be a very elegant and rapid way to access highly functional molecules from simple building blocks. We envisioned that the combination of heterogeneous catalysis system and the one-pot synthesis of 1,2,3-triazoles via *in situ* formation of organic azides will be advantageous. The azides could be generated in situ from the corresponding alkyl halides or arylboronic acids (*22*) avoiding the isolation step. The catalyst, in addition, could be easily recovered by simple filtration.

In this paper, we disclose a simple (dimethylamino) methyl-polystyrene-supported copper(I) iodide (A21-CuI) as an efficient and environmentally benign heterogeneous catalyst for the one-pot synthesis of 1,2,3-triazoles from alkyl halides or arylboronic acids, sodium azide, and phenylacetylene at ambient temperature (Scheme 1).

Results and discussion

The supported catalyst A21-CuI was prepared according to literature (*23*) and the copper content was found to be 1.31 mmol/g, determined by inductively coupled plasma (ICP) analysis. Initially, we focused on the one-pot synthesis of 1-alkyl substituted 1,2,3-triazoles. In an effort to develop an optimal catalytic system, different reaction parameters including solvent, base, as well as catalyst loading were studied via cycloaddition of benzyl chloride, sodium azide, and phenylacetylene at room temperature. The results are summarized in Table 1. Although the "click" reaction was reported in a wide range of solvent, such as DMSO/H_2O, ^{t}BuOH/H_2O, and CH_2Cl_2/H_2O, only moderate yields were obtained in our cases (Table 1, entries 1–3). Encouraged by recent success in organic reactions with benign solvents, we turned our attention



Scheme 1. Polymer-supported copper catalyst for one-pot synthesis of 1,2,3-triazoles.

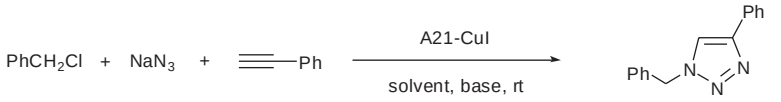
to PEG 400 and H_2O. To our delight, 82% yield was obtained after 12 h when using PEG 400 as solvent. To further improve the solvent system, several combinations of PEG 400 and H_2O were studied and finally PEG 400/H_2O (1:1, v:v) was chosen as the best solvent. We assumed that this result was attributed to the phase-transfer catalytic nature of PEG 400. Water, in another aspect, could increase the solubility of sodium azide. The influences of different bases and catalyst loadings were also evaluated and good yield was obtained when employing Et_3N as base and 10 mol% of catalyst (Table 1, entry 6).

Under the optimized conditions, we carried out the cycloaddition reactions of various alkyl halides, sodium azide, and phenylacetylene (Table 2). It was found that both substituted benzyl halides and allyl halides could be efficiently converted to the desired products in good to excellent yields (72–94%). Among the benzyl halides, substrates bearing electron-withdrawing groups were more active. Other alkyl halides, such as C_2H_5Br and C_4H_9Br were less efficient and a prolonged time was required (Table 2, entries 9 and 10).

Having successfully developed an efficient system for preparation of 1-alkyl substituted triazoles, we considered whether our described procedure could be adapted toward one-pot synthesis of 1-aryl substituted triazoles. However, no reaction occurred at room temperature after 24 h when using iodobenzene as substrate (Table 1, entry 11). It was assumed that the reaction may be problematic with respect to the azidonation of iodobenzene, since the preparation of aryl azides relies upon a limited selection of transformations (*24*). Just recently, Tao et al. (*22*) reported a very interesting method in which copper(II) sulfate was used to promote the azidonation of arylboronic acids at room temperature. We considered that whether our supported CuI catalyst could be helpful in one-pot synthesis of 1-aryl substituted triazoles under mild conditions.

Initially, we tried the azidonation of phenylboronic acid according to the literature (Scheme 2). To our delight, the reaction proceeded fast in 4 h yielding the product in 90%. With this good result, we investigated the application of A21-CuI in one-pot 1,3-dipolar cycloaddition reaction. After consumption of the starting material (monitored by thin-layer chromatography (TLC)), phenylacetylene (1.1 equivalent) was added directly at room temperature to give the triazole in 89% yield. Other arylboronic acids were also employed in this one-pot two-step cycloaddition process. As shown in Table 3, each arylboronic acid could be applied in the reaction and a variety of functional groups on arylboronic acids were fully tolerated. It should be noted that our

Table 1. Screening of reaction parameters for one-pot synthesis of triazoles using benzyl chloride as substrate.[a]



Entry	Solvent	Base	Catalyst loading (mol%)	Time (h)	Yield[b] (%)
1	DMSO/H_2O (2:1)	Et_3N	10	24	56
2	$^tBuOH/H_2O$ (1:1)	Et_3N	10	24	72
3	CH_2Cl_2/H_2O (1:1)	Et_3N	10	24	35
4	PEG 400	Et_3N	10	12	82
5	H_2O	Et_3N	10	24	67
6	PEG 400/H_2O (1:1)	Et_3N	10	8	87
7	PEG 400/H_2O (1:1)	–	10	8	44
8	PEG 400/H_2O (1:1)	Bu_3N	10	8	76
9	PEG 400/H_2O (1:1)	Na_2CO_3	10	8	84
10	PEG 400/H_2O (1:1)	NaOH	10	8	62
11	PEG 400/H_2O (1:1)	Et_3N	5	12	65
12	PEG 400/H_2O (1:1)	Et_3N	–	24	Trace

[a]Reaction conditions: benzyl chloride (1 mmol), NaN_3 (1.2 mmol), phenylacetylene (1 mmol), solvent (4 ml), and room temperature.
[b]Isolated yields.

approach not only provided a simple way to prepare 1-aryl 1,2,3-triazoles in one-pot under mild conditions, the catalyst could also be easily recovered and reused for seven times (Table 3, entry 1).

Experimental

Chemicals were purchased from commercial suppliers and were used without further purification. All ^1H and ^{13}C NMR spectra were recorded with a Bruker Advance RX300 analyzer in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. The Cu content was determined with a Varian AA240 ICP analysis.

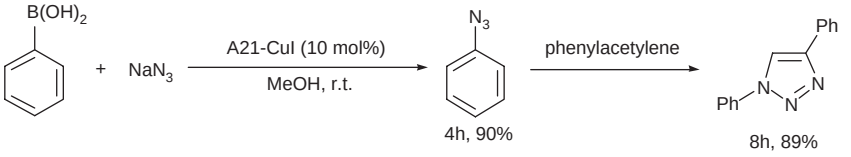
Typical procedure for the one-pot synthesis of 1-alkyl 1,2,3-triazoles

Alkyl halide (1 mmol), NaN_3 (1.2 mmol), and phenylacetylene (1 mmol) were placed in an oven-dried round-bottomed flask. Subsequently, PEG 400/H_2O (4 ml, 1:1), Et_3N (1 mmol), and A21-CuI (77 mg, 10 mol%) were added. The reaction mixture was stirred vigorously at room temperature for a certain time (monitored by TLC). Then EtOAc (20 ml) was added and the catalyst was removed, washed with acetone and water, and dried under vacuum. The extracts were washed with water (2×10 ml), dried over Na_2SO_4, and evaporated under reduced pressure

Table 2. Synthesis of 1,4-disubstituted 1-alkyl-1,2,3-triazoles.[a]

Entry	Substrate	Temperature (°C)	Time (h)	Yield[b] (%)
1	$PhCH_2Cl$	rt	8	87, 87, 85, 85, 67[c]
2	$PhCH_2Br$	rt	8	89
3	*p*-Me- $PhCH_2Cl$	rt	8	85
4	*p*-F- $PhCH_2Cl$	rt	8	90
5	*p*-CN- $PhCH_2Cl$	rt	8	92
6	*p*-NO_2- $PhCH_2Cl$	rt	8	94
7	$CH_2=CHCH_2Cl$	rt	8	72
8	$CH_2=CHCH_2Br$	rt	8	76
9	C_2H_5Br	rt	12	73
10	C_4H_9Br	rt	12	75
11	C_6H_5I	rt	24	–

[a]Reaction conditions: substrate (1 mmol), NaN_3 (1.2 mmol), phenylacetylene (1 mmol), PEG 400/H_2O (4 ml, 1:1), Et_3N (1 mmol), A21-CuI (77 mg, 10 mol%), and room temperature.
[b]Isolated yields.
[c]Catalyst was reused.



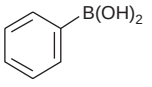
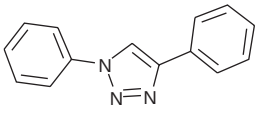
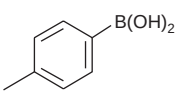
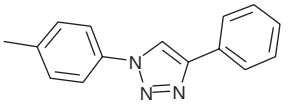
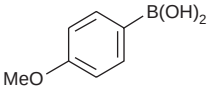
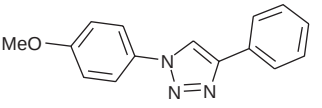
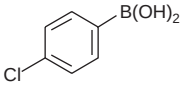
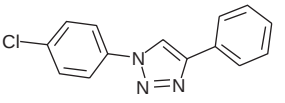
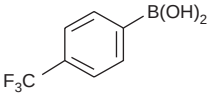
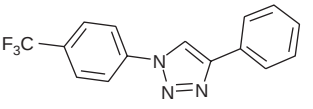
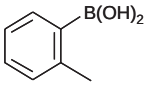
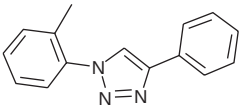
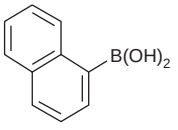
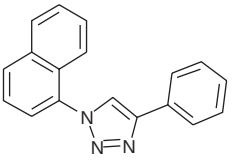
Scheme 2. One-pot two-step synthesis of 1-phenyl triazoles.

to give the crude product which was further purified by column chromatography on silica gel using hexane/ethyl acetate as eluent. Selected data: 1-benzyl-4-phenyl-1*H*-1,2,3-triazole: ^{1}H NMR (300 MHz, $CDCl_3$): $\Delta = 5.46$ (s, 2H), 7.25–7.39 (m, 8H), 7.67 (s, 1H), 7.77 (d, 2H, $J = 7.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\Delta = 53.8$, 119.6, 125.4, 127.7, 127.9, 128.4, 128.6, 128.8, 130.4, 134.6, 147.9.

Typical procedure for the one-pot synthesis of 1-aryl 1,2,3-triazoles

Arylboronic acid (1 mmol) and NaN_3 (1.2 mmol) were placed in an oven-dried round-bottomed flask. Subsequently, methanol (4 ml) and A21-CuI (77 mg, 10 mol%) were added. The reaction mixture was stirred vigorously at room temperature. Then phenylacetylene (1.1 mmol) was added into the flask and the resulting mixture was stirred vigorously for a certain time (monitored by TLC). Then CH_2Cl_2 (20 ml) was added and the catalyst was filtered off, washed with acetone and water, and dried under vacuum. The extracts were washed with water (2×10 ml), dried over Na_2SO_4, and evaporated under reduced pressure to give the crude product which was further purified by column chromatography on silica gel using hexane/ethyl acetate as eluent. Selected data: 1,4-diphenyl-1*H*-1,2,3-triazole: ^{1}H NMR (300 MHz, $CDCl_3$):

Table 3. A21-CuI catalyzed the one-pot synthesis of 1-aryl 1,2,3-triazoles.[a]

Entry	Arylboronic acid	Product	Time (h)	Yield[b] (%)
1			8	89, 89, 87, 88, 85, 82, 74[c]
2			8	91
3			6	95
4			12	73
5			24	65
6			24	76
7			8	92

[a]Reaction conditions: arylboronic acid (1 mmol), NaN_3 (1.2 mmol), phenylacetylene (1.1 mmol), MeOH (4 ml), A21-CuI (77 mg, 10 mol%), and room temperature.
[b]Isolated yields.
[c]Catalyst was reused.

$\delta = 7.37$ (t, $J = 7.2$, 1H), 7.43–7.48 (m, 3H), 7.54 (t, $J = 7.5$, 2H), 7.79 (d, $J = 7.5$, 2H), 7.92 (d, $J = 7.2$, 2H), 8.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 120.7, 126.0, 128.5, 128.9, 129.0, 129.9, 130.4.

Conclusion

In summary, simple and efficient procedures for one-pot synthesis of 1,4-disubstituted-1,2,3-triazoles from corresponding alkyl halides and arylboronic acids have been described. Our protocols are advantageous over the reported procedures not only because of simple operation, high yielding, green reaction system, and mild conditions, but also because they avoided the isolation of the explosive organic azides. Moreover, the supported catalyst can be easily recovered by simple filtration and can be reused for several runs with almost consistent activities.

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