

# Reusable Polymer-Supported Catalyst for the [3+2] Huisgen Cycloaddition in Automation Protocols

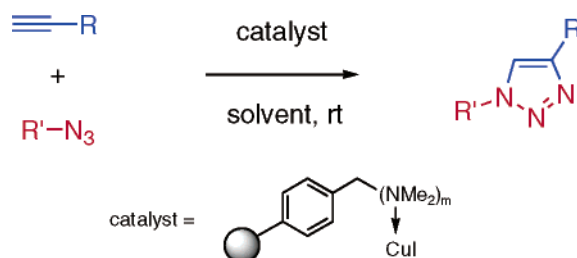
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## ABSTRACT



A polymer-supported catalyst for Huisgen's [3+2] cycloaddition reaction between azides and alkynes was prepared from copper(I) iodide and Amberlyst A-21. This catalyst was then used in an automated synthesis of 1,4-disubstituted 1,2,3-triazoles giving access to these products in good yields. The catalyst has shown good activity, stability, and recycling capabilities.

Modern drug discovery requires the identification and the optimization of specifically acting low molecular weight molecules. That is why simple methods that can quickly and easily generate large libraries of compounds emerge and are more and more used.<sup>1,2</sup> Click chemistry is one of these methods based on reactions which are of wide scope, give high yields, and use highly energetic reactants to form irreversible carbon–carbon or carbon–heteroatom bonds.<sup>3,4</sup> The Huisgen 1,3-dipolar cycloaddition<sup>5</sup> perfectly illustrates

this kind of reaction. It consists of the ligation of azides and terminal alkynes to give triazoles. As has been recently shown,<sup>6</sup> under copper(I) catalysis, the rate of this coupling event is dramatically accelerated and only the corresponding 1,4-disubstituted regioisomer is obtained. The usual procedure for Huisgen's cycloaddition involves the use of a copper salt in conjunction with an added organic or inorganic base. The catalyst can be directly introduced as a Cu(I) salt<sup>7</sup> (CuI, CuBr, ...) or generated in situ by reduction of Cu(II) salts, usually in organoaqueous systems.<sup>8,9</sup>

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**Table 1.** Solubility Tests of Copper(I) Halides in Organic Solvents<sup>a</sup>

salt	EtOH	MeOH	DMSO	DMF	THF	AcOEt	CH <sub>3</sub> CN	CH <sub>2</sub> Cl <sub>2</sub>
CuCl	I	I	I	I	I	I	I	I
CuBr	S	S	S	S	I	I	I	I
CuI	I	I	I	I	I	I	S	I

<sup>a</sup> For 0.1 M solutions (0.5 mmol of CuX/5 mL of solvent); S = soluble, I = insoluble or partially soluble.

We sought to develop a copper catalyst, as a heterogeneous catalytic system for automation protocols, that can have several advantages, such as fast and simple isolation of the reaction products by filtration as well as recovery and recycling of the catalyst.<sup>10</sup> In this article, we report the preparation of a polymer-supported catalyst and its preliminary evaluation in cycloaddition reactions between commercially available terminal alkynes and synthetic azides.

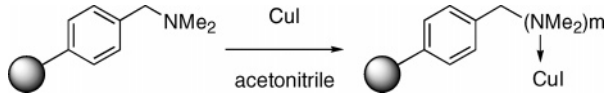
To select our catalytic system, we took into account that the copper salt has to be fixed onto a polymer, possibly by chelation, and has to include a base to be complete. Because of our previous experience with polymeric systems, we selected to test the fixation and activity of copper(I) salts on Amberlyst A-21. This well-known polymer is a dimethyl-aminomethyl-grafted polystyrene and thus bears an amine group that can act as both a chelatatant and a base.

The solubility of simple copper(I) halides in various organic solvents was first tested (Table 1). In usual solvents, cuprous chloride is quite insoluble. Better results were obtained with the corresponding bromide which was soluble in four of them (EtOH, MeOH, DMSO, and DMF). Finally, cuprous iodide was only soluble in acetonitrile. The solvent used to fix the copper salt on the polymer has to be compatible with the hydrophobic polystyrene network and easily removed during the drying process following the incubation and filtration.

The use of CuBr in alcoholic or high boiling point solvents was thus ruled out, and the CuI/CH<sub>3</sub>CN combination was selected as the best alternative.

Fixation tests were conducted using various ratios of A-21 and CuI in the same volume of acetonitrile (Table 2). Increasing the contact time between the CuI solution and the resin (entries 2 and 3) from 1 to 24 h doubled the amount of CuI fixed. Other tests were thus run overnight to ensure a better fixation. Modifications in the amount of A-21 used from 1.2 to 2.4 and 4.8 mmol of amine against 0.5 mmol of CuI (entries 1, 3, and 5) showed that a better fixation was reached for 2.4 mmol of amine/0.5 mmol of CuI. When amounts of CuI were increased to 1.0 mmol for 2.4 and 4.8

**Table 2.** Fixation Tests of Cuprous Iodide on Amberlyst A-21 in Acetonitrile at Room Temperature<sup>a</sup>

					
entry	A-21 <sup>b</sup> mg (mmol)	CuI mg (mmol)	t h	CuI fixed <sup>c</sup> mmol (mg)	catalyst mmol CuI/g
1	250 (1.2)	95 (0.5)	24	0.221 (42)	0.76
2	500 (2.4)	95 (0.5)	1	0.195 (37)	0.36
3	500 (2.4)	95 (0.5)	24	0.368 (70)	0.65
4	500 (2.4)	190 (1.0)	24	0.805 (153)	1.23
5	1000 (4.8)	95 (0.5)	24	0.274 (52)	0.26
6	1000 (4.8)	190 (1.0)	24	0.726 (138)	0.64

<sup>a</sup> Performed in 5 mL of solvent at room temperature for the indicated time under agitation. <sup>b</sup> Dry Amberlyst A-21, 4.8 mmol N/g. <sup>c</sup> After filtration, washings, and drying of the polymer in vacuo.

mmol of amine (entries 4 and 6), higher fixations were observed at 1.0 mmol of CuI. Furthermore, the maximum adsorption for all these experiments was reached for the 2.4 mmol of amine/1.0 mmol of CuI ratio (entry 4, 0.805 mmol of CuI).

From all these experiments, the best fixation protocol was the use of the ratio of 2.4 mmol of amine/1.0 mmol of CuI. This gave a polymer with a final composition of 1.23 mmol of CuI/g of resin. This catalyst was selected over the others for its highest content in copper and a recalculated ratio of 3 amine groups for 1 copper atom, suggesting that at least one amine function was free to act as the required base.

This polymer-supported catalyst was then tested in Huisgen's cycloaddition between various terminal alkynes and organic azides using a synthesis robot (Table 3).<sup>11</sup> We first conducted the experiments in the same solvent as that for the fixation, i.e., acetonitrile (conditions A).

Even if all products were formed, LC-MS analyses showed that they all needed to be purified afterward because of the presence of colored impurities, some residual azide, and traces of copper released from the polymeric catalyst. Quick purifications on short pads of silica afforded the products **9–18** with purified yields ranging from low to good (27–91%, 66% average). Under these conditions, the reaction of benzyl azide (**6**) gave good yields from 74 to 91%, except for the triazole **12** (50%). With propanol azide (**7**), the yields obtained were modest (27–70%) with a good result for **18** (87%).

The reaction was then performed in dichloromethane (conditions B). In this case, all products were isolated as pure, except for a few, after a simple filtration to remove the catalyst and evaporation of the solvent. No traces of starting material or copper were detected on LC-MS analyses. The use of a low polarity and nonchelating solvent such as dichloromethane seems to prevent significant leaking of the

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(11) Reactions performed in 13 mL glass reactors equipped with a plunging filter on a Chemspeed ASW-2000. The reactions can also be done in peptide synthesis glass reactors or in usual round-bottom flasks followed by filtration on fritted glass funnels.

**Table 3.** Automated Synthesis of 1,4-Substituted 1,2,3-Triazoles Using the A-21•CuI Catalyst at Room Temperature<sup>a</sup>

Alkyne	Azide / Product <sup>b</sup> Bn-N <sub>3</sub> 6	Yield <sup>c</sup> (%)	Azide / Product <sup>b</sup> HO-CH <sub>2</sub> -CH <sub>2</sub> -N <sub>3</sub> 7	Yield <sup>c</sup> (%)	Azide / Product <sup>b</sup> EtO <sub>2</sub> C-CH <sub>2</sub> -N <sub>3</sub> 8	Yield <sup>c</sup> (%)
		A: 91 B: 93		A: 27 B: 61 <sup>d</sup>		B: 76
		A: 80 B: 92		A: 62 B: 90		B: 99
		A: 78 B: 97		A: 70 B: 13 <sup>d,e</sup>		B: 99
		A: 50 B: 99		A: 37 B: 99		B: 99
		A: 74 B: 99		A: 87 B: 84 <sup>d</sup>		B: 99

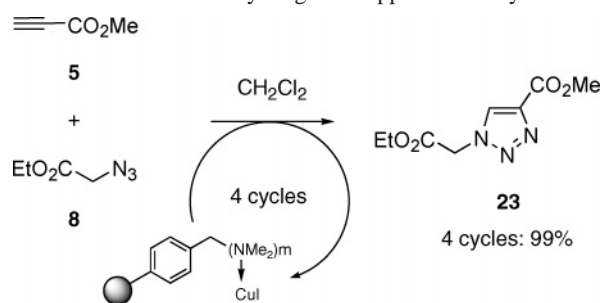
<sup>a</sup> Reaction conditions: 0.5 mmol of alkyne, 0.55 mmol of azide, 31 mg of resin (1.23 mmol of CuI/g, 0.038 mmol of CuI, 8 mol %), 2 mL of solvent.<sup>b</sup> All products gave correct analyses. <sup>c</sup> Conditions A: Yields in CH<sub>3</sub>CN after a needed purification for all products. Conditions B: Unoptimized isolated yields from CH<sub>2</sub>Cl<sub>2</sub>. No purification needed unless otherwise stated. <sup>d</sup> Purified yield. <sup>e</sup> Solubility problems for **16** in CH<sub>2</sub>Cl<sub>2</sub>.

catalyst. Unoptimized isolated yields reached for the triazoles **9–23** were included between 13 and 99% (86% average). The cycloadditions with benzyl azide (**6**) and ethyl azidoacetate (**8**) gave very good yields for all compounds (76–99%). Once again, the use of propanol azide (**7**) gave lower yields. This is mainly due to the purification that had to be done for triazoles **14** (61%) and **18** (84%) and a very low solubility of **16** (13%) in CH<sub>2</sub>Cl<sub>2</sub>, which made its recovery difficult under the automated protocol. The heterocycles **15** and **17** were however obtained with yields of 90 and 99%, respectively, without having to be purified. While looking at the alkynes' reactivities, the propargyl derivatives **2**, **4**, and **5** all gave very good results with the three azides. Alkynes **1** and **3** also gave similar results, with the only lower yields being obtained with propanol azide (**7**).

Finally, the catalyst was tested to evaluate its stability and recycling capabilities. The reaction between propionic acid methyl ester (**5**) and ethyl azidoacetate (**8**) led to the triazole **23** in quantitative yield (Scheme 1).<sup>12</sup> The same polymeric catalyst was then reused to produce **23**, which was obtained without a decrease in yield over four cycles. Furthermore, a

certain stability of this catalyst was observed because during the course of our study samples stored on shelves remained equally active after at least up to four months.

We presented in this communication the preparation of a polymer-supported catalyst containing cuprous iodide and amine functions needed for the Huisgen 1,3-dipolar cycloaddition. The catalyst had a final loading of 1.23 mmol of CuI/g

**Scheme 1.** Recycling the Supported Catalyst

of polymer and was shelf stable without any particular protection. It was used for the preparation of a small library of 1,4-disubstituted 1,2,3-triazoles which were obtained in very good yields for most of them in acetonitrile and dichloromethane. The use of a less polar solvent like dichloromethane led to pure products without the need for purification. Furthermore, the catalyst did not show significant leaching of copper and can be reused for a number of cycles without decreased reaction yields. The advantage of this system is a quick and easy recovery of the reaction

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(12) General procedure for the preparation of triazoles: *Synthesis of methyl 1-(ethoxycarbonylmethyl)triazole-4-carboxylate 23*. The polymer-supported catalyst (Amberlyst A-21•CuI, 1.23 mmol/g, 31 mg, 0.038 mmol, 8 mol %) was placed in the reactor. Ethyl azidoacetate (**8**) (71 mg, 0.55 mmol) dissolved in 1 mL of CH<sub>2</sub>Cl<sub>2</sub> was added dropwise followed by propionic acid methyl ester (**5**) (42 mg, 0.50 mmol) in the same amount of CH<sub>2</sub>Cl<sub>2</sub>. The suspension was orbitally stirred (600 rpm) for 12 h at room temperature. The solution was filtered, and the reactor and the polymer were washed with CH<sub>2</sub>Cl<sub>2</sub> (2 × 2 mL). The extracts were evaporated under reduced pressure, and the product was dried in vacuo. The title compound (**23**) was obtained as a beige powder (105 mg, 99%). Mp 102–104°C. <sup>1</sup>H NMR (300, MHz, CDCl<sub>3</sub>) δ 1.30 (t, *J* = 7.2 Hz, 3H), 3.95 (s, 3H, H-5), 4.28 (q, *J* = 7.2 Hz, 2H), 5.25 (s, 2H), 8.30 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 14.4, 51.4, 52.7, 63.2, 129.4, 161.4, 166.0. LC-MS: *R*<sub>t</sub> = 3.68 min, *m/z* 214 [M + H]<sup>+</sup>. **CAUTION!** Organic azides are potentially explosive. Furthermore, all NaN<sub>3</sub> used for their synthesis should be removed before attempting the reaction in CH<sub>2</sub>Cl<sub>2</sub> because explosive diazomethane could be formed.

products and the catalyst by simple filtration and evaporation. This system can thus be a valuable addition to the existing ones and may find some applications for the synthesis of triazole in organic solvents. Complementary studies on this system are currently en route and will be reported in due course.

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**Supporting Information Available:** Experimental procedures for the formation and use of the polymer-supported catalyst in triazole synthesis, characterizations, and copies of <sup>1</sup>H/<sup>13</sup>C NMR spectra for compounds **9**–**23**. This material is available free of charge via the Internet at <http://pubs.acs.org> OL060283L