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**Glycerol: a biorenewable solvent for base-free Cu(i)-catalyzed 1,3-dipolar cycloaddition of azides with terminal and 1-iodoalkynes. Highly efficient transformations and catalyst recycling**

Cristian Vidal and Joaquín García-Álvarez*

The catalytic system CuI–glycerol displays a high activity in the CuAAC reaction of azides and terminal or 1-iodoalkynes, at room temperature, under air and in the absence of a base. It is important to note that the desired triazoles were isolated by simple filtration in the absence of organic solvents at any stage of the synthesis. Moreover, the catalyst could be recycled up to six consecutive times in glycerol with only partial deactivation.

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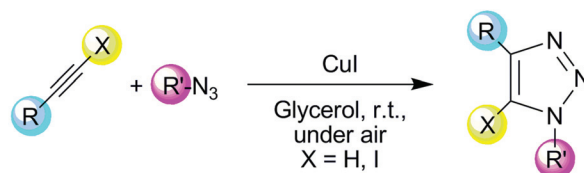
- No *VOCs* used (during reaction and isolation of triazole).
- Large Scale (10 mmol).
- Recyclable (6 consecutive runs).

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Glycerol: a biorenewable solvent for base-free Cu(I)-catalyzed 1,3-dipolar cycloaddition of azides with terminal and 1-iodoalkynes. Highly efficient transformations and catalyst recycling

Cristian Vidal and Joaquín García-Álvarez*

The combination of CuI and glycerol exhibits a versatile and high catalytic activity in the Huisgen cyclo-addition of azides and terminal or 1-iodoalkynes under standard bench experimental techniques (room temperature, under air and in the absence of a base) providing a pivotal contribution to *Green Chemistry*. Since the catalytic reaction: (i) is amenable at low catalyst loading and accessible on a high scale; (ii) tolerates a variety of functionalities (including the presence of a free thio moiety in the substrate); (iii) can be effectively recycled (up to 6 consecutive runs); and (iv) is isolated in a straightforward manner (by simple filtration in the absence of organic solvents at any stage of the synthesis), the practical application of this methodology provides a complementary synthetic tool to the familiar CuAAC reactions.
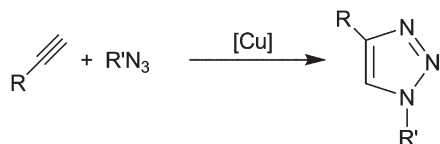
Introduction

Due to both environmental and economic issues, *Chemistry* is driven to reduce waste and re-use materials in order to meet the standards of the *12 Principles of Green Chemistry*.[1] In this sense, one of the largest areas of consumption of petroleum-based chemicals in a conventional chemical transformation is the solvent used as a reaction medium (*i.e.*, solvents account for 80–90% of mass utilization in a typical pharmaceutical/fine chemical operational process).[2] Therefore, there has been a global demand to replace conventional hazardous organic solvents (*VOCs*) by safe, green and biorenewable reaction media that are not based on crude petroleum,[3] like water and super-critical carbon dioxide.[4,5] In this sense, water can be considered as an attractive solvent, because it is non-toxic, cheap and easily available,[6] although limitations arise when: (i) extraction with organic solvents becomes necessary, (ii) the water has to be removed (which is energy consuming), and (iii) waste-water is produced. Supercritical fluids (like $scCO_2$) are beneficial solvents as they are non-toxic, relatively inert, easily removable and recyclable. However, widespread application in research and process chemistry is hampered because: (i) they are poor solvents for many compounds, and (ii) require high-energetic and high-pressure reactors.[7]

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With the ultimate goal of solving these environmental problems, the development of a new generation of greener reaction media is strongly needed. In this regard, biomass-derived solvents are emerging as very promising alternatives (*i.e.* 2-methyl-THF, lactic acid, γ-valerolactone and glycerol).[8] Among them, glycerol is drawing increasing interest as a proto-typical example of a green solvent due to: (i) its unique combination of physicochemical properties (such as high polarity, low toxicity and flammability, high boiling point) and its ability to dissolve both organic and inorganic compounds,[9] (ii) the fast development of the biodiesel industry and new processes for the conversion of cellulose and lignocelluloses into value-added chemicals (in both, glycerol is generated as a by-product),[10] (iii) its capability, in some cases, of enhancing the effectiveness and selectivity,[11,12] and (iv) the previously reported easy product separation and catalyst recycling.[13,14]

Together with the choice of a safe, non-toxic, biorenewable and cheap solvent (like *e.g.* glycerol), some of the crucial points in realizing a *Catalytic Green Chemical* process involve (i) the design of a chemical process with energy efficiency (if possible, synthetic methods should be conducted at ambient temperature), and (ii) atom economy should be maximized.[15] It is also desirable that the catalytic reactions proceed in high yields, as selective and specific processes, under aerobic conditions, in the absence of a co-catalyst and the isolation of the resulting products should be straightforward.[1] In this sense, the copper-catalyzed cycloaddition of azides and terminal alkynes (CuAAC, reported independently in 2002 by Medal[16] and Sharpless,[17] see Scheme 1) in green and biorenewable solvents fulfils the aforementioned principles of *Green Chemistry*,

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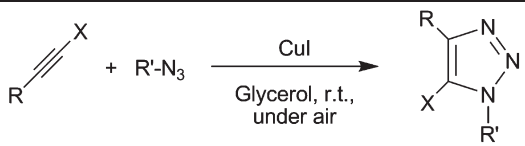**Scheme 1** Copper-catalyzed 1,3-dipolar cycloaddition reaction (CuAAC).

Table 1 Study of the 1,3-dipolar cycloaddition of benzyl azide and phenylacetylene catalyzed by the copper(I) salts **1a–c** in different non-conventional solvents[a]

Entry	Catalyst	Mol% [Cu]	Solvent	Time [h]	Yield[b,c]
1	**1a**	1	Glycerol	1.5	99(94)
2	**1b**	1	Glycerol	3	99(97)
3	**1c**	1	Glycerol	20	99(92)
4	—	—	Glycerol	72	—
5	**1a**	1	1$ChCl$/2Gly	14	99(97)
6	**1a**	1	1$ChCl$/1Gly	20	91(86)
7	**1a**	1	[BMIM][BF$_4$]	24	45(39)
8	**1a**	1	H$_2$O	2	99(97)
9	**1a**	1	CH$_2$Cl$_2$	24	99(97)
10	**1a**	0.5	Glycerol	3	99(93)

[a] Reactions performed under air, at room temperature and using 1 g of the corresponding solvent. 1 mmol of PhC≡CH and PhCH$_2$N$_3$ was always employed. [b] Yields determined by ^{1}H NMR. [c] Isolated yields in brackets (average of two runs).

providing an efficient entry to 1,4-triazoles,[18] under mild and neutral conditions, being the most genuine example of *Click Chemistry*.[19–21] Surprisingly, and despite the previously reported enhanced reactivity and/or selectivity of metal-catalyzed organic reactions performed in pure glycerol,[22] the CuAAC reaction has not been performed in this biorenewable solvent as far as we are aware.[23–25] With these precedents in mind and following our interest in studying the CuAAC reaction in green solvents,[26] herein we report the catalytic activity of the simple copper salt CuI (a cheap and standard bench reagent usually present in almost all laboratories where synthetic chemistry is carried out) in the 1,3-dipolar cycloaddition of both terminal and 1-iodoalkynes with azides, using glycerol as a green and biorenewable solvent. The following features of this catalytic system are remarkable: (i) this is the first example of a CuAAC reaction performed in pure glycerol as a solvent, (ii) the reactions proceed at room temperature, under aerobic conditions, in short reaction times and without the assistance of a base as a co-catalyst, (iii) it is active in the cycloaddition of 1-iodoalkynes with azides to give exclusively 5-iodo-1,2,3-triazoles, (iv) the use of glycerol as a reaction medium allows the catalyst recycling (up to 6 consecutive runs), and (v) the straightforward isolation of triazoles (by simple filtration in the absence of organic solvents at any stage of the synthesis).

Results and discussion

To start this work, we have investigated the catalytic activity of different simple copper salts (CuI (**1a**), CuBr (**1b**) and CuCN (**1c**)) in the 1,3-dipolar cycloaddition of terminal alkynes with organic azides using, as a model reaction, the cycloaddition of benzyl azide (PhCH$_2$N$_3$) and phenylacetylene (PhC≡CH) in neat glycerol. The course of the reaction was monitored by ^{1}H NMR and the results obtained are summarized in Table 1. Firstly, we checked the CuAAC reaction at room temperature, under aerobic conditions and with a catalyst loading of 1 mol% (entries 1–3, Table 1). To our satisfaction, the three copper salts tested (**1a–c**) were found to be active and selective catalysts at room temperature, using only a 1 mol% metal loading and affording the corresponding 1,4-triazole **2a** as the unique reaction product. It is important to note that in no case, the addition of a base to the catalytic system was required, in contrast to most of the known copper catalysts active in this cycloaddition process.[21] At this point, we should mention that a similar rate enhancement, using pure glycerol as a solvent,

was previously observed in a base-free protocol for the microwave-assisted "click" synthesis of tetrazoles.[27,28]

We observed that CuI (**1a**, entry 1, Table 1) displays a higher catalytic activity than CuBr (**1b**) and CuCN (**1c**) (entries 2 and 3, Table 1), leading to quantitative transformation in only 90 minutes. An added advantage of this approach is that the addition of water to the crude reaction mixture allows easy precipitation of the desired triazole without the use of conventional hazardous volatile organic solvents (*VOCs*) at any stage of the synthesis. The presence of catalytic amounts of copper salts was found to be essential for the reaction outcome. Note that in the absence of the metal catalyst the reaction did not generate any product (see entry 4, Table 1). For comparison, we have studied the catalytic activity of CuI in different alternative environmentally friendly solvents (entries 5–8, Table 1) and conventional volatile organic solvents (entry 9, Table 1), finding that the efficiency of the reaction was remarkably lowered when: (i) different glycerol (*Gly*) and choline chloride (*ChCl*) eutectic mixtures (deep eutectic solvents, *DESs*, 1$ChCl$/2Gly, entry 5, Table 1; 1$ChCl$/1Gly, entry 6, Table 1),[29,30] (ii) ionic liquids (*i.e.* [BMIM][BF$_4$], BMIM = 1-butyl-3-methylimidazolium, entry 7, Table 1), or (iii) hazardous and volatile organic solvents (CH$_2$Cl$_2$, entry 9, Table 1)[31] were used as solvents. Also, it is important to note that CuI displays a lower catalytic activity in pure water as a solvent (entry 8, Table 1). Finally, we found that: (i) the use of lower catalytic loadings slowed down the reaction (as an example, by using 0.5 mol% of CuI in glycerol at room temperature, quantitative conversion (99%) was only achieved after 3 hours, entry 10), and (ii) the reaction is accessible on a high scale (10 mmol PhC≡CH and PhCH$_2$N$_3$, 1 mol% CuI, 10 g glycerol) requiring only 1.5 hours to achieve quantitative conversion.

Table 2 CuI-catalyzed synthesis of 1,2,3-triazoles **2a–n** and 5-iodo-1,2,3-triazoles **3a–b** in glycerol[a]

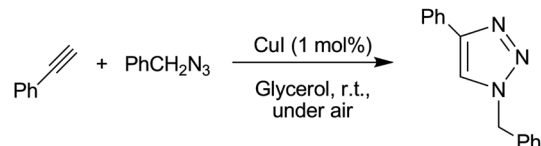| Entry	R	X	R′		Time [h]	Yield[b,c]
1	Ph	H	PhCH$_2$	**2a**	1.5	99(94)
2	Cyclopentyl	H	PhCH$_2$	**2b**	7	99(97)
3	CO$_2$Et	H	PhCH$_2$	**2c**	3	99(93)
4	(OH structure)	H	PhCH$_2$	**2d**	3.5	99(93)
5	PhC(O)N(H)CH$_2$	H	PhCH$_2$	**2e**	2.5	99(96)
6	HO$_2$C(CH$_2$)$_2$	H	PhCH$_2$	**2f**	6.5	99(89)
7	o-I-C$_6$H$_4$-OCH$_2$	H	PhCH$_2$	**2g**	5	99(93)
8	Br(CH$_2$)$_2$	H	PhCH$_2$	**2h**	7	99(93)
9	Ph	H	Ph	**2i**	16	99(91)
10	CO$_2$Et	H	Ph	**2j**	18	99(95)
11	PhC(O)N(H)CH$_2$	H	Ph	**2k**	18.5	99(90)
12	Ph	H	Ph (alkenyl)	**2l**	19	99(95)
13	Ph	H	MeO (alkenyl)	**2m**	13	99(94)
14	Ph	H	PhSCH$_2$	**2n**	6	99(95)
15[d]	Ph	I	PhCH$_2$	**3a**	18	99(97)
16[d]	n-Bu	I	PhCH$_2$	**3b**	24	99(94)

[a] Reactions performed under air, at room temperature, using 1 g of glycerol and with a catalyst loading of 1 mol% in CuI. 1 mmol of the corresponding alkyne and azide was always employed. [b] Yields determined by ^{1}H NMR. [c] Isolated yields in brackets (average of two runs). [d] Catalyst loading of 5 mol%.

Encouraged by these initial findings, which suggest the potential that glycerol has as a green and biorenewable solvent for the CuAAC reaction under standard bench experimental techniques (room temperature, under air and in the absence of a base), we then assessed the scope of this methodology by extending our studies to a range of terminal alkynes using the previously optimized reaction conditions (results are summarized in Table 2). Thus, satisfactory catalytic activities of the system CuI–glycerol have been found with a variety of functional groups in the alkyne, being compatible with the presence of aromatic (entries 1 and 7), alkyl (entry 2), ester (entry 3), alkenyl/hydroxyl (entry 4), amido (entry 5), carboxylic acid (entry 6), ether (entry 7) and halide (entries 7 and 8) substituents. In all cases, the corresponding 1,4-triazoles **2a–h** were obtained in quantitative yields in 1.5–7 hours.

The observed rate of the reaction was strongly dependent on the nature of the azide (as we have previously observed in related CuAAC reactions in water).[26] Thus, for both arylic (PhN$_3$, entries 9–11) and allylic (PhCH=CH–CH$_2$N$_3$ and p-MeOC$_6$H$_4$CH=CH–CH$_2$N$_3$, entries 12–13) azides, longer reaction times (13–19 h) are required to achieve quantitative conversions of the corresponding triazoles. Finally, it is worth noting that the presence of a free thio moiety in the azide (PhSCH$_2$N$_3$, entry 14, Table 2) does not deactivate the catalyst, a fact generally observed in CuAAC reactions with functionalized substrates containing donor atom groups.

The formation of intermediates based on copper(I) alkynyl species is postulated as the first step in CuAAC reactions.[32] In accordance with this proposed mechanistic insight, internal alkynes are not able to undergo the required cycloaddition, a limitation generally observed with conventional copper catalysts.[33,34] In order to overcome this limitation, several CuAAC routes for the synthesis of 5-iodo-1,2,3-triazoles (starting from 1-iodoalkynes) have been devised as alternative synthetic approaches in both organic solvents and water.[26,35,36] 5-Iodo-1,2,3-triazoles, synthesized by application of this click reaction,[37] are versatile synthetic intermediates amenable to further functionalization providing an appealing synthetic approach to different substituted 1,2,3-triazoles.[38] Bearing in mind the efficiency of the catalytic system CuI–glycerol in CuAAC with terminal alkynes and trying to push our methodology to its limits, we decided to focus our attention on the cycloaddition reaction of azides and 1-iodoalkynes in glycerol at room temperature, under air and in the absence of a base. To our delight, this new process was catalyzed by CuI (5 mol%), affording chemoselectively (no by-products or products derived from reductive dehalogenation were observed, i.e. 5-H-1,2,3-triazoles) the corresponding 5-iodo-1,2,3-triazoles **3a–b** in excellent yields (entries 15 and 16, Table 2).

Nowadays it is well-known that one of the major advantages associated with the use of glycerol as a solvent, in metal-catalyzed organic reactions, is the possibility of recycling the catalytic system with the separation of the organic product formed by a simple extraction with organic solvents.[9] In addition, the lifetime of a catalytic system and its level of reusability are very important factors for any catalytic system.[39] Thus, under the catalyst loading previously used for terminal alkynes (1 mol% of CuI), at room temperature, in the absence of a base and employing as a model reaction the CuAAC reaction between benzyl azide and phenylacetylene, we have found that the catalytic system CuI–glycerol could be recycled up to 6 consecutive runs (see Table 3 and the Experimental section for details). Thus, while only partial loss of activity occurs in the glycerol during the first three consecutive runs (1.5–2 h, 97–99%), the

Table 3 CuI-catalyzed 1,3-dipolar cycloaddition of benzyl azide and phenylacetylene in glycerol: catalyst recycling[a]

Cycle	Time [h]	Yield[b]	TON[c]	Cycle	Time [h]	Yield[b]	TON[c]
1	1.5	99	99	4	3	99	393
2	2	97	196	5	5	97	490
3	2	98	294	6	24	98	588

[a] Reactions performed under air, at room temperature, using 1 g of glycerol and with a catalyst loading of 1 mol% in CuI. 1 mmol of PhC≡CH and benzyl azide was always employed. [b] Yields determined by ^{1}H NMR. [c] Cumulative TON values (turnover number = (mol product/mol Cu)).

efficiency of the catalytic system decreases considerably after the fourth cycle, 5 hours being required in the fifth cycle to obtain a quantitative conversion, probably due to both leaching during the workup and decomposition of the catalyst. After the fifth cycle, quantitative conversion was only achieved after longer reaction times (24 hours).

Conclusions

In summary, the present work introduces *Glycerol* as a superior green and biorenewable reaction medium for the Cu-catalyzed 1,3-dipolar cycloaddition of azides and alkynes. As illustrated with both terminal and 1-iodoalkynes, the catalytic system CuI–glycerol is the combination of choice to obtain 1,2,3-triazoles and 5-iodo-1,2,3-triazoles under standard bench experimental techniques (room temperature, under air and in the absence of a base), providing a pivotal contribution to both *Green Chemistry* and CuAAC.

Clearly, and since the reaction: (i) is amenable at low catalyst loading and accessible on a high scale; (ii) takes place under air and in the absence of a base; (iii) tolerates a variety of functionalities (including the presence of a free thio moiety in the substrate); (iii) can be effectively recycled (up to 6 consecutive runs); and (iv) is isolated in a straightforward manner (simple filtration in the absence of organic solvents at any stage of the synthesis), the practical application of this methodology provides a complementary synthetic tool to the familiar CuAAC reactions.

Experimental

General comments

Syntheses were performed under air and at room temperature. All reagents were obtained from commercial suppliers and used without further purification with the exception of: (i) deep eutectic solvents (*DESs*, 1*ChCl*/2*Gly* and 1*ChCl*/1*Gly*),[40] and (ii) 1-iodoalkynes,[41] which were prepared by following the method reported in the literature. NMR spectra were recorded on Bruker DPX-300 or AV-400 instruments.

General procedure for the synthesis of 1,2,3-triazoles 2a–n: synthesis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (2a). CuI (**1a**) (0.0019 g, 1 mol%) was added to 1 g of glycerol under air. Phenylacetylene (0.112 mL, 1 mmol) and benzyl azide (0.132 mL, 1 mmol) were added to the reaction mixture at room temperature. The course of the reaction was monitored by regular sampling and analysis of the aliquots of the mixture by ^{1}H NMR. The mixture was stirred at room temperature for 1.5 hours. Addition of water (5 mL) to the crude reaction mixture allows the easy separation (filtration) of the desired triazole **2a** as a white powder (0.220 g, 94%).

General procedure for the synthesis of 5-iodo-1,2,3-triazoles 3a–b: synthesis of 5-iodo-4-phenyl-1-(phenylmethyl)-1*H*-1,2,3-triazole (3a). CuI (**1a**) (0.0095 g, 5 mol%) was added to 1 g of glycerol under air. 1-Iodo-phenylacetylene (0.228 g, 1 mmol)

and benzyl azide (0.132 mL, 1 mmol) were added to the reaction mixture at room temperature. The course of the reaction was monitored by regular sampling and analysis of the aliquots of the mixture by ^{1}H NMR. The mixture was stirred at room temperature for 18 hours. Addition of water (5 mL) to the crude reaction mixture allows the easy separation (filtration) of the desired 5-iodo-triazole **3a** as a white powder (0.349 g, 97%).

General procedure for the catalyst recycling. The recyclability of our catalytic system was investigated using the CuAAC reaction of phenylacetylene and benzyl azide as a model reaction. Thus, to 1 g of glycerol, CuI (0.0019 g, 1 mol%), phenylacetylene (0.112 mL, 1 mmol) and benzyl azide (0.132 mL, 1 mmol) were added. The resulting mixture was stirred at room temperature and in the presence of air for 90 min (complete consumption of starting materials was observed by ^{1}H NMR). The mixture of the reaction was extracted with 2-methyl-THF (3 × 6 mL). To the glycerol layer, the substrates were again added, and the mixture was stirred under the same conditions for the required time. This procedure was repeated up to six consecutive times.

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