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## ARTICLE

# Investigation of the copper(I) catalysed azide-alkyne cycloaddition reactions (CuAAC) in molten PEG$_{2000}$.

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The copper-catalysed azide-alkyne cycloaddition of lipophilic and hydrophilic substrates was investigated in molten PEG2000 using various sources of Cu(I). The reaction proceeded smoothly and afforded the corresponding triazole in good yields. Depending on the solubility of the product, two types of treatment were investigated: precipitation of the polymer-solvent for the compounds soluble in organic solvents, and ultrafiltration for the water-soluble compounds. In the former case, assays demonstrated that most of the copper precipitated together with PEG, thus enabling the efficient recycling of PEG-Cu(I), while for hydrophilic compounds, the treatment led to the precipitation of copper. The electron paramagnetic resonance spectroscopy study showed that in this chelating solvent copper was protected from oxidation to Cu(II), therefore, in PEG the reaction could be carried out under an uncontrolled atmosphere. Upon examination of copper turnings surface by X-ray photoelectron spectroscopy, it was also demonstrated that the nature of the substrates had an influence on the species of copper dissolved in the PEG, which led to different results in terms of reactivity when copper turnings were used as source of Cu(I).

## 1. Introduction

Polyethylene glycol (PEG), a linear polymer available in a wide range of molecular weights, is non-volatile and has low toxicity and high chemical and thermal stability. Such characteristics, combined with a relatively low cost, have promoted the use of this polymer as an alternative solvent in order to develop more environmentally friendly processes.[1] At less than 1000 g mol$^{-1}$ molecular weight, PEG is a viscous liquid, whereas higher molecular weight PEG is a solid with a melting point increasing with molecular weight up to a plateau at 67 °C for MW greater than 8000 g mol$^{-1}$,[2] so that all PEGs can be used as liquid solvents at moderate temperatures. PEGs are soluble in water and in many organic solvents such as toluene, dichloromethane or acetone, and insoluble in hexane, aliphatic hydrocarbons, various ethers, and ethylene glycol. These solubility properties allow to easily isolate the reaction products from the polymeric solvent either by extraction with an ether for instance, or by dissolution of the reaction mixture with e. g. dichloromethane and precipitation of the polymer with a solvent in which it is insoluble in the case of the use of solid PEGs. Alternatively, membranes techniques such as ultrafiltration can be used to separate molecules of low molecular weight, passing the

membrane whose molecular weight cut-off is suitably chosen, from macromolecules that are retained by the membrane.[3]
Another interesting property of PEGs is that they dissolve many organic compounds and forms complexes with metallic cations thanks to its flexible helical conformation.[4] This latter property makes it an alternative solvent of choice for reactions involving metals with the possibility to recycle both the PEG and the catalyst at the end of the reaction.[5] In particular, copper-catalysed reactions were investigated in PEG as the solvent or co-solvent[5] and amongst them, the copper-catalyzed azide-alkyne cycloaddition (CuAAC).[6] This remarkably effective reaction[7] can be performed in a wide range of solvents with several Cu(I) sources and has been largely used in various fields of chemistry.[8]
All studies concerning the CuAAc in PEG or aqueous PEG so far reported in the literature were carried out using a PEG of molecular weight 400 (PEG$_{400}$), therefore liquid at room temperature, and in most cases, the products were separated from the polymeric solvent by extraction with Et$_2$O.[6] One pot processes were developed, the azide function having been introduced by nucleophilic displacement of Baylis-Hillman acetates,[6a] nucleophilic ring-opening of aziridines or epoxides,[6b] nucleophilic substitution of α-halo[6c,6g] or tosyloxy[6d] ketones, or reaction of diaryliodonium salts[6e] with sodium azide. CuI[6a,6b,6d,6e] or CuSO$_4$-sodium ascorbate[6c,6f,6g] were used as

catalysts, and in some cases, catalyst and PEG reuse was carried out for three[6e,6f] or four[6a] recycling runs in which the catalytic activity was maintained. This recycling possibility suggested that the copper partition during Et$_2$O-PEG liquid-liquid extraction was in favour of the PEG phase, however, this has never been proven.

We report herein the study of this reaction in PEG$_{2000}$ with two kinds of treatment to recover lipophilic or hydrophilic products. The recycling of the PEG-Cu system was also investigated by a) measuring the copper concentration in both the polymer used as the solvent and the cycloadducts and b) analyzing the copper surfaces when Cu(0) was used as Cu(I) source.

## 2. Results and discussion

### Synthesis of lipophilic triazoles - Recovery of PEG by precipitation

3-Azidopropanol (**1**)[9] or its acetate derivatives **2**[10] and phenylacetylene (**3a**) were selected as reactants for the model reaction affording lipophilic triazoles **4a**[11] and **5a** respectively (Scheme 1).
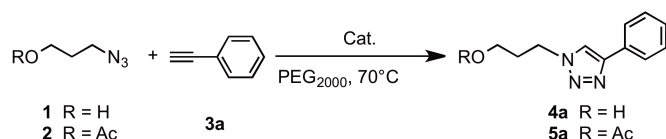


**Scheme 1.** Model reaction affording lipophilic triazoles.

First, we investigated the effect of the concentration and the catalyst (CuI) loading on the reaction between **1** and **3a** under ligand-free conditions. Each reaction was carried out at 70 °C for 0.5 h in PEG$_{2000}$ under open air conditions. Initial experiments were conducted using 0.5 g of PEG per mmol of substrate **3a** in the presence of 5 or 1% of copper(I) iodide. The cycloaddition afforded the 1,4-disubstituted[12] triazole **4a** in 97 or 95% isolated yield (Table 1, entries 1 and 2). The non-catalyzed thermal reaction was tested in PEG$_{2000}$ at 70 °C. The reaction was very slow and afforded a 1:1 mixture of 1,4 and 1,5 regioisomers **4a** and **4'a**[13] (Chart 1) in 64% yield after 72 h.
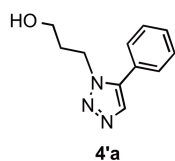


**Chart 1.** Structure of the 1,5 regioisomer obtained in the non-catalyzed thermal reaction.

The cycloadduct was recovered from the reaction mixtures by dilution with dichloromethane, precipitation of PEG with diethyl ether, filtration and evaporation of the solvents. The operation was repeated three times in order to precipitate all the PEG; no column chromatography was necessary to isolate pure (NMR analysis) triazole **4a**. Then, the same cycloaddition was

repeated using 1% of the copper catalyst and reduced amounts of PEG. We obtained complete conversion in 0.5 h in the presence of 1% of CuI, using 0.3, 0.2 or 0.1 g PEG/mmol of **3a**, isolated yields being 97, 94 and 93%, respectively (Table 1, entries 3, 9, 15). Recycling of the PEG and the catalyst was also examined. The isolated yields of 1,4-disubstituted triazole **4a** were almost constant for 5 additional runs when 0.3 g PEG/mmol was used (Table 1, entries 3-8) whereas the conversions fell to 88 and 71% in the 5th and 6th runs, respectively, at higher concentration (0.2 g PEG/mmol) of substrates (Table 1, entries 13 and 14) and even to 20% at the second run when the amount of PEG was 0.1 g/mmol (Table 1, entry 16). Hence, using the optimized conditions (0.3 g PEG/mmol; 1% CuI), the PEG-catalyst system appeared not to be deteriorated throughout six consecutive runs and very likely could be reused in further experiments. Moreover, the reactions were carried out under air atmosphere without the addition of auxiliary ligand generally used for protecting the Cu(I) from oxidation or disproportionation, suggesting that the PEG served as ligands. Such Cu(I)-stabilizing effect of solvent was already reported using nonbasic ionic liquid AMMOENG 100™ bearing short PEG chains.[14]

**Table 1.** Yields and PEG recovery for the CuAAC between **1** and **3a** using CuI as the catalyst in various amount of PEG$_{2000}$ at 70 °C and further recycling.

| Entry | PEG (g/mmol) | CuI (mol%) | Run[a] | **4a** yield[b] (%) | PEG recovery (%)[c] |
|---|---|---|---|---|---|
| 1 | 0.5 | 5% | 1 | 97 | 90 |
| 2 | 0.5 | 1% | 1 | 95 | 91 |
| 3 | 0.3 | 1% | 1 | 97 | 90 |
| 4 | | | 2 | 98 | 93 |
| 5 | | | 3 | 95 | 86 |
| 6 | | | 4 | 95 | 85 |
| 7 | | | 5 | 94 | 87 |
| 8 | | | 6 | 96 | 86 |
| 9 | 0.2 | 1% | 1 | 94 | 93 |
| 10 | | | 2 | 92[d] | 78 |
| 11 | | | 3 | 94[d] | 74 |
| 12 | | | 4 | 93[d] | 82 |
| 13 | | | 5 | 88[d] | 77 |
| 14 | | | 6 | 71[d] | 73 |
| 15 | 0.1 | 1% | 1 | 93 | 96 |
| 16 | | | 2 | 20[d] | 90 |

[a] Reactions were performed for successive runs by reusing the PEG recovered at previous run without additional catalyst. [b] Isolated yield after precipitation of PEG and removal of solvent under reduce pressure. [c] PEG was recovered by precipitation in CH$_2$Cl$_2$/Et$_2$O. [d] Conversion determined by 1H NMR.

We then consider the possibility to use commercially available Cu(0) as Cu(I) sources. Orgueira et al. reported the use of copper powder in the presence of an amine hydrochloride salt to enhance the dissolution of Cu(0) and thus, to facilitate the generation of the catalytic Cu(I) species.[15] Unfortunately, the

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dissolution of the catalyst under reaction conditions ($H_2O/t$BuOH, Cu(0) powder and 1 equiv of $Et_3N.HCl$) prevented any recycling. This prompted us to examine the use of this catalyst in the CuAAC in PEG because we thought that the latter could allow to avoid the use of amine salts, as we have already shown that in the presence of CuI, PEG could act as a ligand. Moreover, we expected that the treatment of the reaction mixture by precipitation of the solvent could allow the reuse of the solvent and the catalyst. Hence, the reaction between **1** and **3a** in $PEG_{2000}$ at 70 °C was carried out in the presence of copper nanopowder (CuNP) or copper turnings (CuT). While the conversion was total in 30 min with 1% Cu(0) nanosize powder, the use of metal turnings with a smaller surface area led to a longer reaction time (6 h) and required a higher catalyst loading (40%). Isolated yields were 90% and 94% respectively (Table 2).

**Table 2.** Yields for the CuAAC between **1** and **3a** using copper nanopowder (CuNP) and copper turnings (CuT) as the catalysts in $PEG_{2000}$ (0.3 g/mmol) at 70 °C and further recycling.

| Entry | Catalyst (wt %) | run[a] | **4a** yield[b] (%) |
|---|---|---|---|
| 1 | CuNP[c] (1%) | 1 | 90 |
| 2 | | 2 | 90 |
| 3 | | 3 | 90 |
| 4 | | 4 | 92 |
| 5 | | 5 | 92 |
| 6 | | 6 | 90 |
| 7 | CuT[d] (40%) | 1 | 94 |
| 8 | | 2 | 94 |
| 9 | | 3 | 94 |
| 10 | | 4 | 96 |
| 11 | | 5 | 94 |
| 12 | | 6 | 91 |
| 13 | CuT[e] (40%) | 1 | 94 |
| 14 | | 2 | 92 |
| 15 | | 3 | 92 |
| 16 | | 4 | 93 |
| 17 | | 5 | 93 |
| 18 | | 6 | 93 |

[a] Successive runs reusing the PEG recovered at previous run, without additional catalyst. [b] Isolated yield after precipitation of PEG and removal of solvent under reduce pressure. [c] CuNP (NanoPowder of copper < 50 nm). [d] Small pieces (2 to 3 $mm^2$) of CuT were added at the first run then removed for next runs. [e] The small pieces of CuT were recovered and added to new PEG for each run.

The two systems were then evaluated for their recycling possibilities. The precipitation procedure described above was applied after removal of the pieces of catalyst in the case of copper turnings. We did not observe a reduction in the rate of the reaction during the 5 recycling since the conversions were complete within 30 min when copper nanopowder was used, and 6 h in the case of copper turnings. The isolated yields were almost constant. Interestingly, when recovered PEG was reused without the pieces of copper turning, the 1,3-dipolar

cycloaddition still occurred for 5 more runs. We also confirmed that the presence of azide and/or triazole was required to observe the leaching of Cu(I) in the reaction mixture as already stated by Kappe and co-workers,[16] since when pieces of copper turning were kept alone in PEG for 6 days at 70 °C and removed before using PEG for CuAAC, incomplete conversion (< 30%) of azide **1** was observed even after 48 h. We also reuse the pieces of copper turning in new PEG and obtained complete conversion for 6 runs suggesting that Cu(I) could be leached from copper turning surfaces at high level. The species of copper recovered in PEG and the copper concentration when copper turnings were used will be discussed below.

The same systems were also used in the cycloaddition between **2** and **3a** and comparable results were obtained in the initial conditions and in the further runs (Table 3). In all cases, triazole **5a** was obtained as pure compound (^{1}H NMR analysis) using the PEG precipitation procedure ($CH_2Cl_2/Et_2O$).

**Table 3.** Isolated yields (%) for the CuAAC between **2** and **3a** using CuI, Cu nanopowder (CuNP), or Cu turnings (CuT) in $PEG_{2000}$ at 70 °C and further recycling.

| Run[a] | CuI (1%) | CuNP[b] (1%) | CuT[c] (40%) |
|---|---|---|---|
| 1 | 95 | 90 | 95 |
| 2 | 93 | 95 | 97 |
| 3 | 98 | 96 | 95 |
| 4 | 93 | 94 | 95 |
| 5 | 90 | 93 | 95 |
| 6 | 94 | 90 | 95 |

[a] Successive runs reusing the PEG recovered at previous run without additional catalyst. [b] CuNP (NanoPowder < 50 nm). [c] Small pieces (2 to 3 $mm^2$) of copper turnings (CuT) were added at the first run then removed for next runs.

Then we applied the protocol based on the use of PEG as the solvent for the CuAAC on the terminal acetylenes **3b–d** (Chart 2) and azides **1** and **2**.
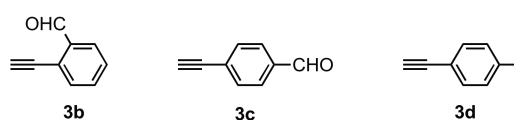


**Chart 2.** Organic solvent soluble terminal acetylene used in the CuAAC with **1** and **2**.

All the substrates tested provided very high yields of the desired 1,4-disubstituted triazoles (Chart 3, see Supporting information).



**4b** R = H
**5b** R = Ac

**4c** R' = CHO R = H
**5c** R' = CHO R = Ac
**4d** R' = $CH_3$ R = H
**5d** R' = $CH_3$ R = Ac

**Chart 3.** Structure of the triazoles obtained from the CuAAC between azides **1** and **2** and alkynes **3b-d**.

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**Table 4:** Copper concentration (ppm) and residual weight copper (%) remaining in cycloadducts **4a** or **5a** and in PEG using precipitation procedure.
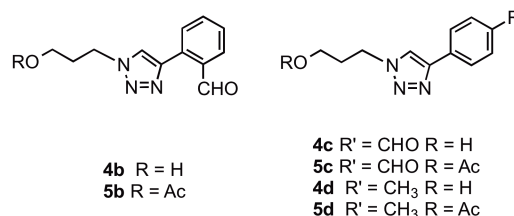
| Entry | Cat. (mol %) | Triazole (yield %) | Run[a] (yield PEG %) | [Cu] ppm[b] in triazoles | % wt Cu[c] in triazoles | [Cu] ppm[b] in PEG | % wt Cu[c] in PEG |
|---|---|---|---|---|---|---|---|
| 1 | CuI (1) | **4a** (97) | 1 (90) | 145 (4.8) | 4 | 1638 | 70 |
| 2 | | **4a** (96) | 6 (46) | 104 | 3 | 734 | 16 |
| 3 | | **5a** (95) | 1 (90) | 219 (4.1) | 8 | 1879 | 80 |
| 4 | | **5a** (94) | 6 (41) | 135 | 5 | 1015 | 20 |
| 5 | CuNP (1) | **4a** (90) | 1 (92) | 158 (2) | 3 | 1989 | 73 |
| 6 | | **4a** (90) | 6 (41) | 98 | 2 | 1308 | 20 |
| 7 | | **5a** (90) | 1 (90) | 152 (2.7) | 4 | 1786 | 60 |
| 8 | | **5a** (90) | 6 (46) | 95 | 2 | 696 | 10 |
| 9 | CuT[d] (40) | **4a** (95) | 1 (90) | 158 (2.7) | 0.1 | 829 | 0.8 |
| 10 | | **4a** (91) | 6 (40) | 68 | 0.05 | 646 | 0.3 |
| 11 | | **4a** (93) | 6[e] (91) | 134 | 0.1 | 962 | 1 |
| 12 | | **5a** (95) | 1 (89) | 172 (3.8) | 0.1 | 995 | 1 |
| 13 | | **5a** (97) | 6[f] (35) | 351 | 0.3 | 4502 | 2 |

[a] Run number, reactions were performed for successive runs reusing the PEG recovered at previous run without addition of catalyst otherwise specified, 1 = first run, 6 = sixth run, the yield of PEG was calculated from the mass of PEG used in the first run. [b] [Cu] in ppm have been measured by atomic absorption spectroscopy after precipitation of PEG. Values in brackets are [Cu] in ppm measured by ICP-MS after treatment of triazoles by the QuadraPureTM IDA resin. Mean value of three measurements, the standard deviations were lower than 4%. [c] Residual weight Cu (%) has been calculated from [Cu] in ppm in products (triazoles or PEG) and the weight of copper in the catalyst introduced in the reaction at the first run. It should be noted that the copper could not be totally recovered because it was lost in part during the workup, i.e. adsorbed onto the glassware or in the PEG not recovered during the filtration step. [d] Small pieces of copper turnings. [e] Sixth run with the same pieces of Cu T in new PEG at each run. [f] CuT and recovered PEG were both reused at each run.

Given the particular procedure used to separate the cycloadducts from PEG solvent, i.e. PEG precipitation and recovery of the products in the mother liquor, the question of the distribution of copper between the two phases, solid (PEG) and liquid (cycloadducts solution in $CH_2Cl_2$-$Et_2O$) was raised. Therefore, the copper concentrations were measured by atomic absorption spectroscopy (AAS) or inductively coupled plasma mass spectrometry (ICP-MS) both in cycloadducts (**4a** and **5a**) and in PEG. Results concerning the first and the sixth runs are shown in Table 4.

Whatever the catalyst used, the concentration of copper was, in average, 10 times higher in PEG than in the triazoles **4a** or **5a**. Most copper was thus driven with PEG during its precipitation, allowing efficient recycling of the solvent-catalyst system.

Interestingly, when CuT was used as the catalyst, the copper concentrations in PEG (Table 4, entries 9 and 12) were lower only by one half compared to the concentrations measured in PEG for the first run with the other catalysts (CuI and CuNP). In this particular case the copper remaining in the PEG represented only the dissolved copper species from copper turning surfaces, since the pieces of copper turning were removed before the precipitation of PEG. The residual weight of copper appeared thus very low and represented no more than 1% of the initial weight of copper turning used.

At the sixth run, copper concentrations were divided by a factor of 1.8 on average compared to the first run but were sufficient to effectively catalyze the reaction, as we have shown above. Although relatively low, the residual copper levels (<135 ppm) required additional treatment to be lowered to less than 15 ppm, the level required for pharmaceutical applications.[17]

Different methods[18] have been applied to remove the metal after CuAAc: washing with EDTA,[16] metal scavenging by iron/iron oxide nanoparticles ($Fe_xO_y$@Fe),[19] thiourea functionalised macroporous polystyrene-based resin beads (QuadraPure[TM] TU)[16,20] activated charcoal (Norite type A)[16] or nanofiltration on solvent-resistant membrane in the case of polymeric compounds obtained by CuAAC.[21] Another strategy relies on the use of materials able to catalyze the reaction and to scavenge copper.[22] For this purpose, we chose to use the commercially available metal scavenger imino diacetate functionalized resin (QuadraPure[TM] IDA, Chart 4).[23]
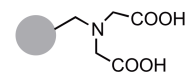


**Chart 4.** Imino diacetate functionalized resin (QuadraPure[TM] IDA) used as copper scavenger.

The copper concentration determined in PEG after the first run using copper turnings was 829 ppm in the case of **4a** and 995 ppm when **5a** was the substrate (Table 4, entries 9 and 12). As the PEG was reused efficiently for the next runs without addition of catalyst, it was clear that the species responsible for the catalysis were dissolved in the solvent. Moreover, the pieces of copper turning could be recycled in new PEG and led to similar copper concentration in PEG even after six reuse (Table 4, entry 11). As a consequence of this continuous leaching, when the copper turnings and the PEG were both recycled for 6 runs, the level of copper in PEG reached 4502 ppm, which led to a high residual copper concentration (350 ppm) in triazole **3b** (Table 4, entry 13). This PEG sample has been used to identify the species of copper dissolved in PEG by X-ray photoelectron spectroscopy (XPS) (see below).

Interestingly, when $PEG_{2000}$ was kept in the presence of copper turning at 70 °C for 6 days (without azides and phenylacetylene), the copper concentration in PEG was below 200 ppm, which is too low for catalysis as we have described above.

**Table 5.** Cu(II) concentration and weight % of Cu(II) in PEG determined by EPR spectroscopy

| Entry | Catalyst | [Cu(II)] (ppm) | [Cu] (ppm)[a] | Cu(II) Wt%[b] |
|-------|----------|----------------|---------------|----------------|
| 1 | CuNP (1st run) | 10 | 1989 | 0.5% |
| 2 | CuT (6 recycling of CuT in new PEG) | 89 | 962 | 9 |
| 3 | CuT (6 recycling of PEG and CuT) | 226 | 4502 | 5 |
| 4 | CuT (6 days , 70 °C no use for CuAAC) | 17 | 114 | 15 |
| 5 | CuI (1st run) | 57 | 1889 | 3 |

[a] Total [Cu] in PEG measured by AAS, [b] relative to total Cu.

In order to better characterize the oxidation state of the total copper in PEG after CuAAC for all catalysts used for the cycloaddition involving organic soluble azides **1** or **2**, electron paramagnetic resonance (EPR) spectroscopy was used to detect and quantify the paramagnetic copper specie (Cu(II)) in different PEG samples recovered by the precipitation procedure. The concentrations of [Cu(II)] have been calculated after double integration of spectra (see Supporting information) followed by calibration against standard solutions in a range between 0.53 and 0.05 mM.[24]

As a rule, the concentrations of Cu(II) (Table 5) in all PEG samples were very low compared to the total [Cu] measured by atomic absorption spectroscopy indicating that the cuprous ion, the less thermodynamically stable of the 3 oxidation states (0, +1 and +2) was preserved for oxidation in PEG even if it was not used in an inert atmosphere.

**Synthesis of water-soluble triazole- Recovery of PEG by ultrafiltration.**

The protocol described above was very efficient to isolate lipophilic triazoles, however it cannot be implemented for the synthesis of hydrophilic compounds. To explore this case, we used 3-azido-1-*C*-(β-D-glucopyranosyl)-propan-2-one (**8**). This compound was obtained by nucleophilic substitution with $NaN_3$ in $PEG_{2000}$ from the corresponding bromo derivatives **7**[25] itself prepared from **6**, easily obtained in one step from D-glucose[26] (Scheme 2).
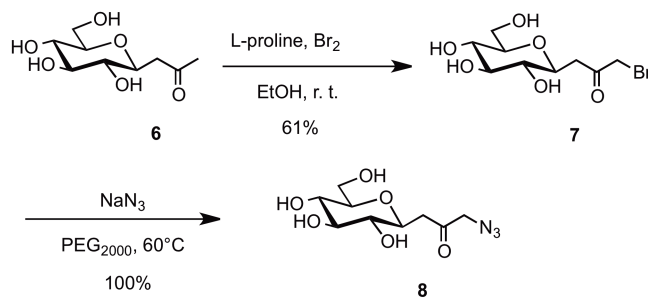


**Scheme 2.** Synthesis of the water-soluble azide **8**.

Although **8** could be isolated in quantitative yield, this compound was relatively unstable and we decided to use a one-pot condensation procedure of the bromo ketone **7**, sodium azide, and phenylacetylene (**3a**) using copper catalysts (Scheme 3). In order to obtain a not too viscous reaction mixture, we carried out the reaction in a mixture $PEG_{2000}$ (0.5 g / mmol of substrate)-$H_2O$ (3.3 / 1) at 60 °C.
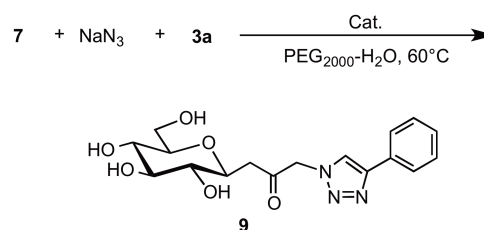


**Scheme 3.** One pot synthesis of hydrophilic triazole **9**.

The same catalysts than those previously used for the preparation of lipophilic triazole were tested (CuI, CuNP and CuT). In addition, as the presence of water in the reaction mixture was not a problem for the recovery of PEG (see below), the $CuSO_4$/Na ascorbate catalytic system was also employed.

As we recently showed that ultrafiltration of aqueous solutions was a valuable tool for the separation of PEG or PEG derivatives from small molecules or salts,[27] we decided to use this technique to recover separately $PEG_{2000}$ and water soluble triazole **9** (Figure 1).
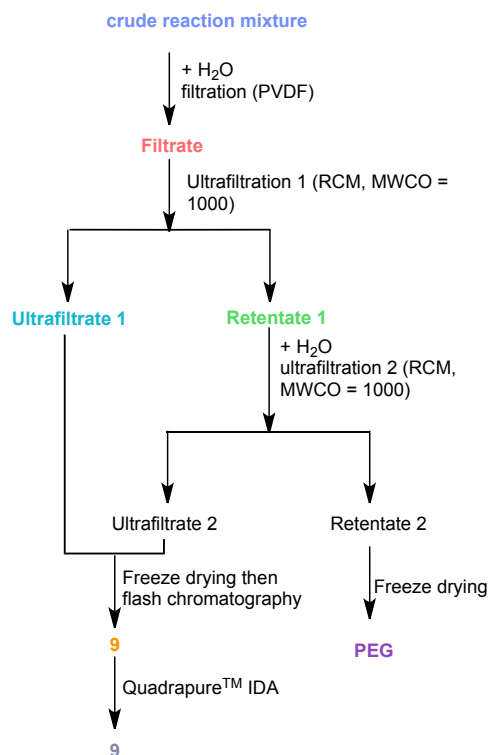
**Figure 1.** Treatment of the reaction mixture affording water soluble triazole **9**. PVDF: polyvinyl difluoride; RCM: regenerated cellulose membrane; MWCO: molecular-size cut-off.

Therefore, at the completion of the cycloaddition, the reaction mixture was diluted with water, filtrated to remove insoluble material through polyvinyl difluoride (PVDF) membrane and ultrafiltrated by forcing the aqueous solution through a regenerated cellulose membrane (RCM) with a molecular-size cut-off (MWCO) of 1000. The retentate containing PEG, and the filtrate, containing the triazole **9** and salts, were both freeze dried. Compound **9** was then purified by flash chromatography. A final treatment with Quadrapure IDA resin was used to isolate **9** with a very low level of residual copper (see below).

While using CuI, CuNP, or CuSO$_4$/NaAsc as catalysts, triazole **9** was isolated in high yields (Table 6, entries 1, 4 and 6), the use of copper turnings gave poor result as 500 mol% of catalyst have had to be used to achieve a 45% yield. In comparison with the results described above with the same catalyst, this behaviour was surprising. Therefore we performed the same experiment in DMF (Table 6, entry 3) and obtained **9** in 68% yield. Meanwhile, the reaction was also carried out in PEG$_{2000}$ as the solvent, using Cu$_2$O (5 mol%) as the catalyst since this oxide on the surface of copper metal is known to be the most active species in catalysis.[16,28] These conditions allowed the isolation of **9** in 92% yield. We have therefore supposed that the Cu(I) (Cu$_2$O) amount dissolved in PEG$_{2000}$ from CuT surfaces was not enough to efficiently catalyzed the 1,3-dipolar cycloaddition while this amount was sufficient in DMF. In order to support this hypothesis, we analysed the CuT surfaces before and after the reaction by X-Ray Photoelectron Spectroscopy (see below).

**Table 6.** Yields and reaction times for the one pot S$_N$-CuAAC between **7** and **3a** using copper nanopowder (CuNP), copper turnings (CuT), CuI, Cu$_2$O and CuSO$_4$/ NaAsc as catalysts in PEG-H$_2$O (3.3 / 1) at 60 °C.

| Entry | Cat. | Cat. mol% | Time (h) | **9** Yield[a] (%) | PEG yield[b] (%) |
|---|---|---|---|---|---|
| 1 | CuNP | 5 | 16 | 93 | 94 |
| 2 | CuT[c] | 500 | 15 | 45 | 99 |
| 3 | CuT[c,d] | 500 | 16 | 68 | - |
| 4 | CuI | 5 | 15 | 94 | 99 |
| 5 | Cu$_2$O | 5 | 4 | 92 | 100 |
| 6 | CuSO$_4$/ NaAsc. | 5/10 | 9 | 100 | 100 |

[a] Isolated yield (%) after ultrafiltration, freeze-drying and flash chromatography. [b] Yield (%) of PEG recovered after ultrafiltration and freeze drying. [c] One piece of copper turning twined the stirred bare. [d] Reaction performed in DMF.

The recovery of PEG by ultrafiltration was as effective as the precipitation since the yields of recovered PEG$_{2000}$ were at least 94%. Unfortunately, reuse of the recovered PEG without additional catalyst in further CuAAC was not possible after the ultrafiltration procedure because the copper concentrations in the recovered PEG were low (Table 7). Nevertheless, with the ultrafiltration procedure, PEG$_{2000}$ used as the solvent in the CuAAC could still be recycled.

The levels of residual copper in the cycloadduct (Table 7) were comparable to those obtained previously for organic solvents soluble compounds (103-144 ppm, Table 4). As the reaction was also carried out in DMF (Table 7, entry 3), we determined the copper content in the triazole prepared in this solvent and we found a higher level (299 ppm) compared with the copper content of the adducts obtained in PEG. For the latter reactions, most of the copper was however not found in the PEG since only 1 to 2% by weight of the initial copper remained in the ultrafiltered polymer. Hence, in order to determine in which step of the treatment most of the copper was eliminated, we undertook its filiation when CuI was used as the catalysts.

The crude reaction mixture contained 3270 ppm of copper, but after dilution of the mixture with water and filtration through PVDF membrane, about 40% of copper was removed (Figure 2). After the first ultrafiltration, only 0.7 and 2.7% of copper used as the catalyst were found in the filtrate and the retentate, respectively, suggesting that a large portion of the catalyst was adsorbed on the surface of the regenerated cellulose membrane. After purification by flash chromatography, the residual copper concentration was 119 ppm. As for the organic solvent soluble compounds, treatment with Quadrapure IDA resin was necessary to decrease the concentration of residual copper. Actually, levels below 4 ppm were reached without any lost of product (Table 7).

**Table 7.** Copper concentration (ppm) and residual weight copper (%) remaining in cycloadduct **9** and in PEG using ultrafiltration procedure.

| Entry | Cat. (mol %) | [Cu] ppm[a] in **9** | % wt Cu[b] in **9** | [Cu] ppm[a] in PEG | % wt Cu[b] in PEG |
|---|---|---|---|---|---|
| 1 | CuI (5) | 119 (1.5) | 1.2 | 131 | 1.1 |
| 2 | CuNP (5) | 103 (1.4) | 1 | 132 | 2 |
| 3 | CuT[c] (500) | 135 (3.7) | 0.01 | 192 | 0.03 |
| 4 | CuT[c,d] (500) | 600[e] 299[f] (3.8) | 0.02 | - | - |
| 5 | CuSO$_4$/ NaAsc. (5/10) | 144 (3.5) | 1.7 | 57 | 0.9 |

[a] [Cu] in ppm have been measured by AAS in **3c** after ultrafiltration and chromatography and in PEG after ultrafiltration. Values in brackets are [Cu] in ppm measured by ICP-MS after treatment of **9** with QuadraPure™ IDA resin. [b] Residual weight Cu (%) have been calculated from [Cu] in ppm in products (triazoles or PEG) and the weight of copper in the catalyst introduced in the reaction at the first run. [c] One piece of copper turning twined the stirred bare. [d] Reaction performed in DMF. [e] In the crude mixture. [f] After chromatography.

Using this procedure, despite the loss of catalyst, the PEG was recovered and could be still recycled for the 1,3-dipolar cycloaddition in the presence of additional catalyst.
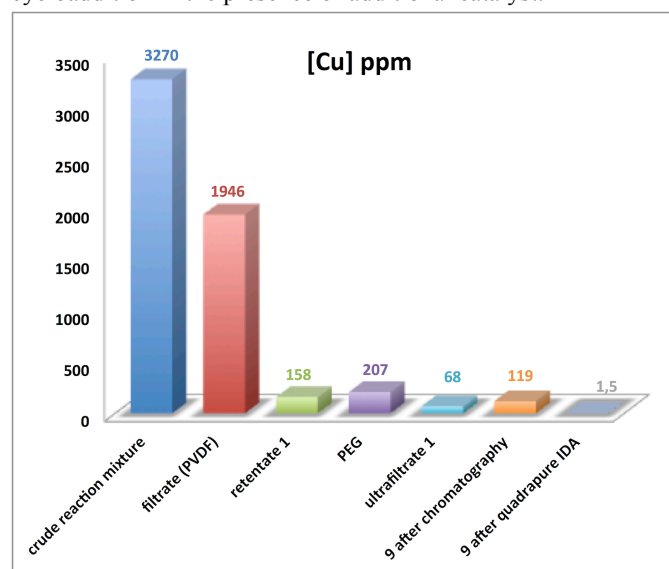


**Figure 2.** Filiation of copper during the purification process of the one pot S$_N$-CuAAC between **7** and **3a** using CuI as the catalyst.

Since the results of the cycloaddition using CuT were different depending on the substrates (greater than 92% yields with **1** or **2** and only 45% with **8** as the substrate), we examined the copper turnings before and after reaction by X-ray photoelectron spectroscopy (XPS). Copper, cuprous oxide (Cu$_2$O) and divalent cupric oxide **(CuO)** could be characterized by their Auger kinetic and binding energies.[29]

Cu$_2$O and Cu(0) could be evidenced from their $2p_{3/2}$ lines but could not be distinguished since their binding energies are similar (932.4 eV). The presence of CuO could be ascertained

by the $2p_{3/2}$ line at 934.0 eV as well as by the satellite peak at 943.7 eV.
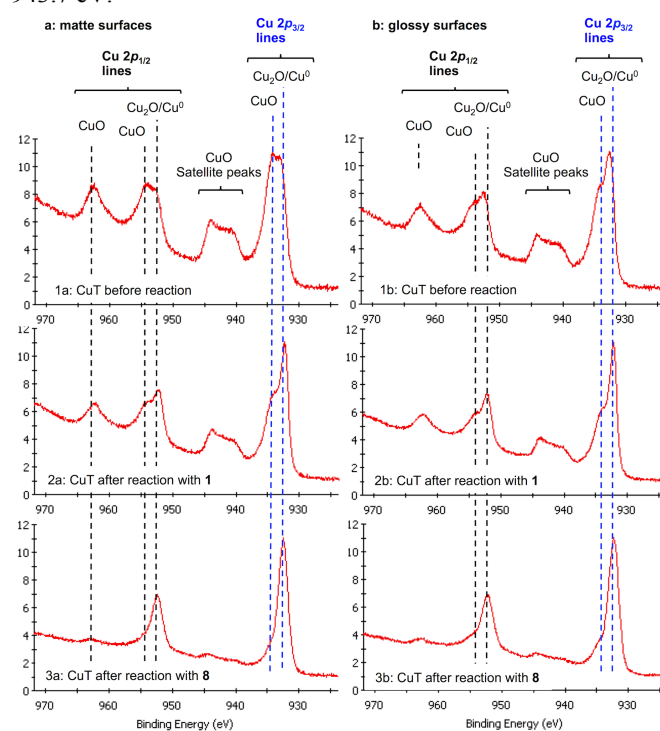


**Figure 3.** XPS spectra for the Cu 2p 3/2 lines for copper turnings: (2a) and (2b) after the six runs for 1,3 dipolar cyclisation with azide 1 in new PEG

As expected, both surfaces of copper turning (the matte and the glossy) contained Cu(0), along with Cu$_2$O and CuO (Figure 3). The two surfaces were different in term of copper oxides composition since the matte surface compared to the glossy one displayed a line CuO much more intense than the line for Cu$_2$O and Cu(0). The CuO layer on the matte face appears thus thicker than the one on the glossy surfaces. Moreover from XP spectra, it could be evidenced that copper surfaces changed after its use as catalyst for the CuAAC since copper surfaces were leached during the reaction causing significant amount of copper dissolved in PEG. As a consequence, for both surfaces the line intensities corresponding to CuO significantly decreased compare to the Cu$_2$O/Cu(0) $2p_{3/2}$ lines when the CuT was used as catalyst for CuAAC from azide **1** and for the six runs in new PEG (Figure 3, spectra 2a and 2b). This demonstrated that at least a part of CuO layer was removed during the reaction. Interestingly, after using the copper turning for the CuAAC with azide **8**, a strongest decreased in intensity of the $2p_{3/2}$ CuO line at both faces could be observed (Figure 3, spectra 3a and 3b). In this specific case, if a large portion of CuO, an ineffective copper specie for CuAAC, was dissolved in the reaction mixture, this could explain the poor catalytic efficacy of the CuT in the 1,3-dipolar cycloaddition. Unfortunately, as both Cu(0) and Cu$_2$O lines have a similar binding energy, it was not possible to evidence the leaching of Cu$_2$O from the surface and quantify directly the leaching of CuO and Cu$_2$O from the XP spectra of copper turning surface.

We assumed that the difference of reactivity between **1** or **2** and **8** was mainly due to the difference of the species solubilised in PEG, as shown by XPS analysis. As azide **8** was rather unstable and the reaction using CuT as the catalyst was slow, it is highly probable that the substrate decomposed before reacting, therefore, the poor concentration of triazole **9** in the reaction mixture led to a weak leaching of Cu(I) from CuT (see above).[16]

## 3. Conclusion

$PEG_{2000}$ is a valuable alternative solvent for the copper-catalysed azide-alkyne cycloaddition of both lipophilic and hydrophilic substrates using various sources of Cu(I) thanks to its unique solvent properties. The metal cation coordination ability of PEG allowed to perform the reaction under an uncontrolled atmosphere without the addition of auxiliary ligand generally used for protecting the cuprous ion from oxidation or disproportionation. In addition, the polymer-cation interaction allowed effectively recycling of the system by precipitation without loss of activity during 6 cycles, and it is likely that other cycles are still possible. In the case of water-soluble compounds, the method used, i.e. ultrafiltration of an aqueous solution, only enabled the recycling of PEG. The mild reaction conditions, the low load of catalyst, the non use of additional ligand and the high substrate concentrations (2-3 mmol / g of solvent) associated with the additional feature of PEG such as low-toxicity, low volatility, and biodegradability and its relatively low cost, make this process really attractive.

## 4. Experimental

Copper nanopowder (CuNP; particles size <50 nm), CuI, $Cu_2O$ and $PEG_{2000}$ were purchased from Sigma Aldrich, copper turning (CuT) from Fabriques de produits chimiques Billault (Aubervilliers, Seine) and $CuSO_4.5H_2O$ from Acros Organic. QuadraPure[TM] IDA resin (macroporous, 350-750 μm particle size) was purchased from Sigma Aldrich. Uptidisc membranes PVDF (47 mm, 0.45 mm) were from Interchim and Amicon Ultracel ultrafiltration disk (cut-off 1kDa) from Millipore. $^1H$ and $^{13}C$-NMR spectra were recorded on Bruker spectrometers (250, 300, 360 or 400 MHz). Chemical shifts (δ) in ppm, are given relative to tetramethylsilane for $^1H$-NMR and relative to the $CD_3OD$ or $CDCl_3$ resonances at 49.00 and 77.00 ppm, respectively for $^{13}C$-NMR. Signals were assigned on the basis of $^1H$-$^1H$ COSY and HSQC or DEPT experiments. Melting points were measured on Leica VMHB system Kofler. HRMS spectra were recorded in positive mode with a microtof-QII spectrometer (Bruker) using electrospray ionization. IR spectra were recorded on FT/IR Jasco 4100 equipped with diamond ATR. Copper concentrations were determined at 324.8 nm on a spectrometer AAS novAA400 with flame $C_2H_2$/air (fuel flow at 50 L/h), equipped with a burner of 10 mm and a lamp M-HCL. A certified soln of Cu in $HNO_3$ (Copper RS NORMEX, Carlo Erba) was diluted in distilled water to give a stock soln at 1000 ppm Cu that was used to prepare standard solns for

calibration. Samples were dissolved in 1% aq. soln of $HNO_3$ at 1 mg/mL. Three replicates were recorded for each sample (SD for all samples were < 4%). ICP-MS measurements were performed at the *Laboratoire d'Analyses Nucleaires Isotopiques et Elémentaires*, CEA-Saclay, France.

XPS experiments were recorded at the *Service de Physique et de Chimie des Surfaces et Interfaces*, CEA-Saclay, France. Spectra were recorded on a KRATOS Axis Ultra DLD spectrometer using monochromatic Al Ka (1486.6 eV) radiation. The binding energy (BE) scale was calibrated from the BE of the Au $4f_{7/2}$ (84 eV). Pressure in the sample chamber was $5.10^{-9}$ kPa. Acquisition parameters were as follow: entry slit 700 x 300 mm and 20 eV pass energy. The instrumental resolution was 0.6 eV (Full Width at half maximum (FWHM) of the Au $4f_{7/2}$ energy level under those conditions. Acquisition time was 65 min for all spectra. The binding energy of the C 1s line due to carbon contamination was at 284.6 +/- 0.1 eV. Curve fitting was performed using the software Avantage. EPR spectra were recorded on frozen solution at liquid nitrogen temperature on a Bruker Elysys 500 spectrometer (9.4 GHz). Samples of PEG (14 mg) were dissolved in DMF (150 mL). A stock solution of $CuSO_4.H_2O$ at 1 mM in HCl (2 mM) and $NaClO_4.5H_2O$ (2 M) in $H_2O$/glycerol mixture (70/30 v/v) was used to prepare standard solutions for calibration between 0.53 and 0.05 mM Cu(II).

Spectrum of the mixture of $H_2O$/glycerol (70/30 v/v), HCl (2 mM) and $NaClO_4.5H_2O$ (2 M) was recorded as blank reference. The concentrations of Cu(II) in PEG samples were determined by double integration of the spectra using the software Xepr.

**3-Azido propanol (1).**[9]

A mixture of 3-bromo-propanol (2.78 g, 20 mmol), sodium azide (1.56 g, 24 mmol) and $PEG_{2000}$ (2 g) was stirred and heated at 70 °C for 24 h. After cooling to room temperature, the mixture was diluted with $CH_2Cl_2$ (5 mL) and insoluble salts were removed by decantation. $Et_2O$ (50 mL) was added over 30 min under vigorous stirring at 0 °C to the $CH_2Cl_2$ phase and PEG was filtered. The organic phase was concentrated and the precipitation procedure was repeated two times. The final filtrate was concentrated to give crude **1** (1.77-1.90 g) as a liquid. From nine experiments, 16.3 g of crude were obtained and purified by distillation under vacuum (bp = 75-77 °C, 18 mm Hg) to afford **1** as a colorless liquid (13.7 g, 75 %).

NMR data were in accordance with those previously reported.[9]

**3-Azidopropyl acetate (2).**[10]

A mixture of **1** (2.02 g, 20 mmol), acetic anhydride (3.06 g, 30 mmol) and $ZnCl_2$ (409 mg, 3 mmol) was stirred and heated at 70 °C for 2 h and then concentrated under reduce pressure. From 3 experiments, 11.87 g were obtained and purified by distillation under vacuum (bp = 82 °C, 18 mm Hg) to afford **2** as a colorless liquid (6.3 g, 73%).

NMR data were in accordance with those previously reported.[10]

**General procedure for CuAAC between 1 or 2 and 3a-d.**

A mixture of the azido derivative **1** or **2** (2 mmol), alkyne (2 mmol), catalyst (CuI or CuNP, 0.02 mmol or CuT, 0.8 mmol) in $PEG_{2000}$ (0.6 g) was stirred and heated at 70 °C for an

appropriate time (0.5 h for CuI or CuNP, 6 h for CuT). After cooling to room temperature, the mixture was diluted with $CH_2Cl_2$ (5 mL), copper turnings were removed when used as catalyst source, and $Et_2O$ (50 mL) was added over 30 min under vigorous stirring at 0 °C. Solid $PEG_{2000}$ was recovered by filtration. The organic phase was concentrated and the precipitation procedure was repeated two times. The final filtrate was concentrated to afford the product.

**1-(3-Hydroxypropyl)-4-phenyl-1,2,3-triazole (4a).**[11]

From **1** and **3a**. White solid; mp 92-93 °C; lit. 90-92 °C.[11a] NMR data were in accordance with those previously reported.[11b]

**1-(3-Acetoxypropyl)-4-phenyl-1,2,3-triazole (5a).**

From **2** and **3a**. White solid; mp 91-93 °C; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = 2.05 (s, 3H), 2.29 (tt, $J$ = 6.0 Hz, $J$ = 7.0 Hz, 2H), 4.13 (t, $J$ = 6.0 Hz, 2H), 4.49 (t, $J$ = 7.0 Hz, 2H), 7.29-7.48 (m, 3H), 7.74-7.91 (m, 3H); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$ = 20.73, 29.33, 47.17, 60.87, 119.79, 125.56, 128.08, 128.75, 130.43, 147.82, 170.74; HR-MS (ESI+) $m/z$ = 268.1050, calcd. for $C_{13}H_{15}N_3O_2Na$ [M+Na]$^+$: 268.1056; IR: $\nu$ (cm$^{-1}$) = 3112, 3089, 2984, 2934,1730, 1608, 1580, 765, 694.

**4-(2-Formylphenyl)-1-(3-hydroxypropyl)-1,2,3-triazole (4b).**

From **1** and **3b**. colorless oil; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = 2.20 (tt, $J$ = 5.8 Hz, $J$ = 6.8 Hz, 2H), 2.28 (s, 1H), 3.70 (t, $J$ = 5.8 Hz, 2H), 4.62 (t, $J$ = 6.8 Hz, 2H), 7.45-7.55 (m, 1H), 7.58-7.74 (m, 2H), 7.96 (s, 1H), 7.97-8.03 (m, 1H), 10.36 (s, 1H); $^{13}C$ NMR (90.6 MHz, $CDCl_3$): $\delta$ = 32.81, 47.48, 58.84, 124.16, 128.86, 129.05, 130.23, 133.22, 134.00, 134.04, 144.79, 192.82; HR-MS (ESI$^+$) $m/z$ = 254.0894, calcd. for $C_{12}H_{13}N_3O_2Na$ [M+Na]$^+$: 254.0900; IR: $\nu$ (cm$^{-1}$)= 3382, 3139, 3111, 3066, 2952-2845, 2763, 1685, 1601, 1573.

**1-(3-Acetoxypropyl)-4-(2-formylphenyl)-1,2,3-triazole (5b).**

From **2** and **3b**. colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 2.07 (s, 3H), 2.35 (tt, $J$ = 6.0 Hz, $J$ = 7.0 Hz, 2H), 4.17 (t, $J$ = 6.0 Hz, 2H), 4.56 (t, $J$ = 7.0 Hz, 2H), 7.45-7.55 (m, 1H), 7.60-7.67 (m, 1H), 7.68-7.73 (m, 1H), 7.95 (s, 1H), 7.97-8.03 (m, 1H), 10.39 (s, 1H); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$ = 20.46, 29.01, 47.11, 60.62, 123.39, 128.21, 128.24, 129.59, 132.67, 133.42, 133.49, 144.44, 170.51, 192.19; HR-MS (ESI$^+$) $m/z$ = 296.0997, calcd. for $C_{14}H_{15}N_3O_2Na$ [M+Na]$^+$: 296.1006; IR: $\nu$ (cm$^{-1}$) = 3101, 3070, 2966-2843, 2766, 1736, 1689, 1600, 1579.

**4-(4-Formylphenyl)-1-(3-hydroxypropyl)-1,2,3-triazole (4c).**

From **1** and **3c**. White solid; mp = 109-110 °C; $^1H$ NMR (360 MHz, $CDCl_3$): $\delta$ = 1.99 (s, 1 H), 2.21 (tt, $J$ = 5.8 Hz, $J$ = 6.8 Hz, 2H), 3.72 (t, $J$ = 5.8 Hz, 2H), 4.62 (t, $J$ = 6.8 Hz, 2H), 7.91-7.96 (m, 2H), 7.95 (s, 1H), 7.98-8.04 (m, 2H), 10.02 (s, 1H); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$ = 32.51, 47.16, 58.72, 121.37, 126.00, 128.24, 130.37, 135.81, 136.35, 146.15, 191.65; HR-MS (ESI$^+$) $m/z$ = 254.0897, calcd. for $C_{12}H_{13}N_3O_2Na$ [M+Na]$^+$: 254.0900; IR: $\nu$ (cm$^{-1}$) = 3391, 3138, 3112, 2951-2839, 2755, 1691, 1608, 1571.

**1-(3-Acetoxypropyl)-4-(4-formylphenyl)-1,2,3-triazole (5c).**

From **2** and **3c**. White solid; mp = 70-71 °C; $^1H$ NMR (360 MHz, $CDCl_3$): $\delta$ = 2.07 (s, 3H), 2.34 (tt, $J$ = 6.0 Hz, $J$ = 7.0 Hz, 2H), 4.17 (t, $J$ = 6.0 Hz, 2H), 4.54 (t, $J$ = 7.0 Hz, 2H), 7.90 (s, 1H), 7.93-7.97 (m, 2H), 7.99-8.04 (m, 2H), 10.39 (s, 1H); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$ = 20.65, 29.27, 47.30, 60.73, 121.10, 125.87, 130.21, 135.65, 136.19, 146.33, 170.69, 191.52; HR-MS (ESI$^+$) $m/z$ = 296.0993, calcd. for $C_{14}H_{15}N_3O_2Na$ [M+Na]$^+$: 296.1006; IR: $\nu$ (cm$^{-1}$) = 3119, 3084, 2979-2817, 2730, 1734, 1698, 1611, 1575.

**1-(3-Hydroxypropyl)-4-(4-methylphenyl)-1,2,3-triazole (4d).**

From **1** and **3d**. White solid; mp = 113-114 °C; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = 2.17 (tt, $J$ = 5.8 Hz, $J$ = 6.7 Hz, 2H), 2.37 (s, 3H), 2.56 (s, 1H), 3.68 (t, $J$ = 5.8 Hz, 2H), 4.56 (t, $J$ = 6.7 Hz, 2H), 7.19-7.28 (m, 2H), 7.66-7.75 (m, 2H), 7.78 (s, 1H); $^{13}C$ NMR (90.6 MHz, $CDCl_3$): $\delta$ = 21.20, 32.62, 47.03, 58.52, 119.95, 125.53, 127.50, 129.47, 138.02, 147.64; HR-MS (ESI$^+$) $m/z$ = 240.1099, calcd. for $C_{12}H_{15}N_3O_2Na$ [M+Na]$^+$: 240.1107; IR: $\nu$ (cm$^{-1}$) = 3261, 3145, 3087, 3020, 2956-2880, 1582, 1560, 811.

**1-(3-Acetoxypropyl)-4-(4-methylphenyl)-1,2,3-triazole (5d).**

From **2** and **3d**. White solid; mp = 95-96 °C; $^1H$ NMR (360 MHz, $CDCl_3$): $\delta$ = 2.06 (s, 3H), 2.30 (tt, $J$ = 6.0 Hz, $J$ = 7.0 Hz, 2H), 2.37 (s, 3H), 4.15 (t, $J$ = 6.0 Hz, 2H), 4.49 (t, $J$ = 7.0 Hz, 2H), 7.20-7.26 (m, 2H), 7.68-7.74 (m, 2H), 7.75 (s, 1H); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$ = 20.65, 21.10, 29.28, 47.08, 60.85, 119.41, 125.44, 127.61, 129.36, 137.84, 147.72, 170.63; HR-MS (ESI$^+$) $m/z$ = 282.1206, calcd. for $C_{14}H_{17}N_3O_2Na$ [M+Na]$^+$: 282.1213; IR: $\nu$ ( cm$^{-1}$) = 3133, 3115, 2982-2899, 1728, 1578, 1563, 817.

**3-Bromo-1-(C-β-D-glucopyranosyl)-propan-2-one (7).**[25]

To a solution of L-proline (1.05 g, 9.08 mmol) and 1-C-(β-D-glucopyranosyl)ethan-2-one **6** (2 g, 9.08 mmol) in ethanol (20 mL), bromine (933 μL, 18.16 mmol) was added at room temperature. After 2.5 hours, the reaction mixture was treated by an aq. soln of $NaHSO_3$ (4 M, 2.25 mL) then an aq. soln of $Na_2CO_3$ (2.7 M, 4 mL) until pH = 6 was reached. The mixture was then concentrated *in vacuo* and purified by flash chromatography (AcOEt:MeOH 9.5:0.5 then 9:1) to give the bromo C-glucoside **7** as a white foam (1.65 g, 61%). NMR data were in accordance with those reported.[25]

**3-Azido-1-(C-β-D-glucopyranosyl)-propan-2-one (8).**

To a solution of bromo C-glucoside **7** (129 mg, 0.43 mmol) in molten $PEG_{2000}$ (216 mg) at 60 °C was added sodium azide (29.3 mg, 0.45 mmol). After 2 h, the reacting mixture was diluted with water (50 mL), filtered through a PVDF membrane (0.45 mm) then subjected to ultrafiltration in an Amicon 8050 stirred cell fitted with Amicon Ultracel Ultrafiltration Disk with a molecular weight cut-off of 1 kDa, under 3.5 bar pressure. After the first ultrafiltration, the retentate (10 mL) was diluted with water (40 mL), and the solution was subjected to ultrafiltration again. Filtrates were combined, concentrated under reduce pressure and the residue was purified by flash chromatography (AcOEt:MeOH 9.5:0.5 then 9:1) to give the azido C-glucoside **8** as a white foam (128 mg, 100%) $[\alpha]_D^{21}$ = - 24.8 (c 1, MeOH); $^1H$ NMR (360 MHz, $D_2O$): $\delta$ = 2.76 (dd, $J$ = 9.0 Hz, $J$ = 16.0 Hz, 1H), 2.99 (dd, $J$ = 3.5 Hz, $J$ = 16.0 Hz, 1H), 3.26 (t, $J$ = 9.5 Hz, 1H), 3.36-3.45 (m, 2H), 3.49 (t, $J$ = 9.0

Hz, 1H), 3.69 (dd, $J = 5.0$ Hz, $J = 12.5$ Hz, 1H), 3.81 (td, $J = 4.0$ Hz, $J = 9.0$ Hz, 1H), 3.86 (dd, $J = 2.0$ Hz, $J = 12.5$ Hz, 1H), 4.31 (d, $J = 19.0$ Hz, 1H), 4.35 (d, $J = 19.0$ Hz, 1H); $^{13}$C NMR (90.6 MHz, CD$_3$OD): $\delta = 43.80$, 59.16, 62.74, 71.66, 75.09, 77.23, 79.47, 81.60, 205.30; (ESI+) $m/z = 284.0847$, calcd. for C$_9$H$_{15}$N$_3$O$_6$Na [M+Na]$^+$: 284.0853; IR: $\nu$ (cm$^{-1}$) = 3349, 2889, 2104, 1720.

**1-(1-($C$-β-D-glucopyranosyl)-2-oxo-propyl)-4-phenyl-1,2,3-triazole (9).**

To a solution of the bromo $C$-glucoside **7** (0.34 to 0.45 mmol) in PEG$_{2000}$ (0.5 g/mmol) at 60 °C was added sodium azide (1.05 eq.) and the mixture was stirred at 60 °C for 1 h. Phenylacetylene (1.05 eq), catalyst (CuI 5 mol%, Cu$_2$O 5 mol%, CuNP 5 mol%; CuSO$_4$ 5 mol%/Na ascorbate 10 mol%; or Cu turning (CuT) 500 mol%) and water (0.15 mL/mmol) were added and the mixture was stirred at 60 °C. At reaction time completion, the mixture was diluted with water (25 mL) then filtered on PVDF membrane (20 mm, 0.45 μm). The membrane was washed with water (25 mL) and the filtrate (50 mL) was subjected to ultrafiltration in an Amicon 8050 stirred cell fitted with Ultracel Ultrafiltration Disk with a molecular weight cut-off of 1 kDa under 3.5 bar pressure. After the first ultrafiltration, the retentate (10 mL) was diluted with water (40 mL), and the solution was subjected to ultrafiltration again. The filtrates were freeze-dried and the residue was purified by flash chromatography (AcOEt:MeOH 9.5:0.5 then 9:1) to give **9** as a white solid (Yields: 93 % (CuI); 92 % (Cu$_2$O); 97 % (CuNP); 100% (CuSO$_4$/Na ascorbate and 45% (CuT)).

Mp 130-132 °C; $[\alpha]_D^{24} = -28.4$ (c 1, MeOH); $^1$H NMR (360 MHz, D$_2$O): $\delta = 2.92$ (dd, $J = 9.0$ Hz, $J = 16.0$ Hz, 1H), 3.15 (dd, $J = 4.0$ Hz, $J = 16.0$ Hz, 1H), 3.31 (t, $J = 9.0$ Hz, 1H), 3.38-3.47 (m, 2H), 3.51 (t, $J = 8.5$ Hz, 1H), 3.72 (dd, $J = 5.0$ Hz, $J = 12.5$ Hz, 1H), 3.86 (td, $J = 4.0$ Hz, $J = 9.5$ Hz, 1H), 3.89 (dd, $J = 2.0$ Hz, $J = 12.5$ Hz, 1H), 5.58 (d, $J = 19.0$ Hz, 1H), 5.60 (d, $J = 19.0$ Hz, 1H), 7.37-7.45 (m, 1H), 7.45-7.53 (m, 2H), 7-73-7.80 (m, 1H), 8.17 (s, 1H); $^{13}$C NMR (90.6 MHz, CD$_3$OD): $\delta = 49.85$, 60.28, 62.85, 71.75, 75.12, 77.40, 79.33, 81.75, 123.95, 126.63, 129.30, 129.93, 131.56, 148.72, 202.84; (ESI+) $m/z = 386.1310$, calcd. for C$_{17}$H$_{21}$N$_3$O$_6$Na [M+Na]$^+$: 386.1323; IR: $\nu$ (cm$^{-1}$) = 3313, 3128, 3096, 2923, 2887,1723, 1651, 1616, 764, 689.

Retentate was freeze-dried to recover PEG$_{2000}$ as a solid (yields: 87 to 100%).

## Notes and references

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