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COMMUNICATION

Micellar Promoted Multi-Component Synthesis of 1,2,3-Triazoles in Water at Room Temperature

Cite this: DOI: 10.1039/x0xx00000x

Elena Tasca,[a] Giorgio La Sorella,[a] Laura Sperni,[a] Giorgio Strukul,[a] Alessandro Scarso[a,*]

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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Micellar media in water provide a simple and efficient environment to favor the multi-component synthesis of 1,2,3-triazoles from organic bromides, sodium azide and terminal alkynes in the presence of [Cu(IMes)Cl] 1 catalyst at room temperature within few hours. The micellar medium favors both the *in situ* formation of the organic azide and its metal promoted cycloaddition with the alkyne

1,2,3-Triazoles are important heterocyclic structures that showed interesting biological and pharmaceutical properties,[1] such as anti-allergic,[2] anti-bacterial,[3] and anti-HIV activity,[4] and selective β3-adrenergic receptor agonism.[5] Additionally, 1,2,3-triazoles are found in fungicides, herbicides, and dyes.[6]

The atom efficient 1,3-dipolar Huisgen cycloaddition between alkynes and organic azides (AAC) is certainly the most straightforward method for the synthesis of 1,2,3-triazoles.[7] The reaction can be thermally activated providing a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazoles[8] and is favored by the use of particular substrates like strained cyclooctynes,[9] activated[10] and electron deficient alkynes like propiolates[11] also under microemulsion conditions.[12] Some years ago, Sharpless[13] and Medal[14] introduced the use of Cu(I) catalysts under mild conditions that selectively form 1,4-disubstituted 1,2,3-triazoles in high yields (click reaction), while 1,5-disubstituted 1,2,3 triazoles are selectively obtained with Ruthenium[15] catalysts or, as recently disclosed, using Iridium[16] catalysts when applied to electron rich internal alkynes. Moreover the Cu(I) promoted click reaction is an established approach for the conjugation in biochemical systems as well as for the preparation of supramolecular functional systems.[17]

The most simple catalytically active Cu(I) species for the click triazole synthesis is usually generated from $CuSO_4$ and sodium ascorbate in excess but suffers from high metal loading. Alternatively, preformed stable Cu(I) complexes with phosphines like $Cu(PPh_3)NO_3$[18] and PTA-iminophosphorane Cu(I) complex (3) (PTA = 1,3,5-triaza-7-phosphaadamantane)[19] or nitrogen ligands like polytriazoles and tris(2-aminoethyl)amine derivatives (tren) could be employed usually in the order of 1 mol%. Cu(I) complexes of the type [(NHC)CuX] (NHC=*N*-heterocyclic carbene, X=halogen) developed by Nolan were found to greatly accelerate the reaction[20,21] while subsequent bis-carbenic complexes like the heteroleptic *bis*(*N*-heterocyclic carbene)copper(I) complexes developed by Cazin and collaborators[22] as well as ring-expanded carbene ligands[23] showed interesting catalytic activities. This class of catalysts are highly active and selective and operate well under neat conditions at room temperature leading to high yields with catalyst loadings lower than 1 mol%.

Even though solvent free conditions are desirable in terms of green approaches to catalysis, the use and handling of potentially unstable small organic azides,[24] the high exothermicity of the cycloaddition reaction and the possible presence of solid substrates that can be difficult to solubilize in the reaction mixture led to the development of multicomponent one-pot reactions between terminal alkynes and *in situ* formed organic azides from organic halides and NaN_3 thus avoiding the pre-isolation of organic azides. Recently, alternative multicomponent syntheses from anilines and sodium nitrite under acid catalysis[25] or from epoxides with sodium azide and alkynes,[26] in both cases avoiding organic bromides has been reported.

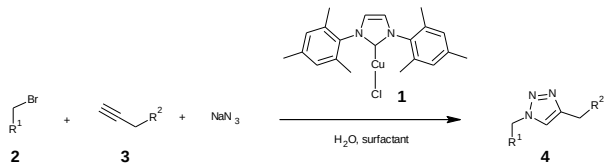
Most of the examples of multicomponent 1,2,3-triazole synthesis are carried out in water or under neat conditions using heterogeneously supported catalysts like $Cu(OAc)_2$ on MCM-41,[27] NHC–Cu(I) complexes on silica[28] as well as magnetically recoverable heterogeneous Cu catalyst[29] or copper nanoparticles on silica coated magnetic nanoparticles (5–30 nm).[30] In the above mentioned cases the reaction is carried out in the range 70-120 °C for few hours in order to achieve high yields. Alternative systems exist like the employment of mechano-chemical conditions in a ball milling apparatus using a copper vial at high temperature for at least 16h or the use of a structurally well-defined copper(I) isonitrile complex,[31] insoluble in the reaction medium, that can be readily

recovered by precipitation and filtration and recycled for at least five runs without significant loss of activity.

Examples of purely homogeneous multicomponent reactions for triazoles synthesis are indeed rare, based on the use of $CuSO_4$ at 100°C in water in the presence of excess of azide that acts as a reducing agent.[32] Alternatively, examples operating at room temperature are based on well defined complexes like the original [Cu(NHC)X] system (X halogen atom) developed by Nolan[20] or the PTA-iminophosphorane Cu(I) complex (PTA = 1,3,5-triaza-7-phosphaadamantane)[33] both in water and mainly focused on the use or terminal aromatic alkynes.

Very recently Astruc reported a supramolecular catalytic approach for the reaction based on well defined dendrimers as nanoreactors for the solubilization of preformed Cu(I) species or *in situ* generated Cu(I) species from Cu(II) and ascorbate. The system operated in water under very mild experimental conditions and very low catalyst loading, enabling recycling.[34]

Herein we report an alternative supramolecular approach that makes use of readily available and economic surfactants in water to promote the formation of spontaneous self-assembled nanometric entities to promote the multicomponent reaction at room temperature in the presence of [Cu(IMes)Cl] **1** (IMes 1,3-*bis*(2,4,6-trimethylphenyl)imidazol-2-ylidene) as catalyst. The latter catalytic system was selected because of its known catalytic activity[20,21] and higher lipophilic character compared to the traditional Cu(II)/ascorbate system. In fact, the addition of surfactants in water provides micellar nano-environments that should favor solubilization and reciprocal contact between apolar organic substrates like organic bromides **2** and alkynes **3** with the neutral catalyst 1 and the ionic sodium azide, in principle allowing the one-pot preparation of 1,4-disubstituted 1,2,3-triazoles **4** with low catalyst loading (Scheme 1). To the best of our knowledge the use of micellar environments has been rarely investigated for the synthesis of triazoles and never for the direct three component synthesis but always directly using organic azides.[35,36]



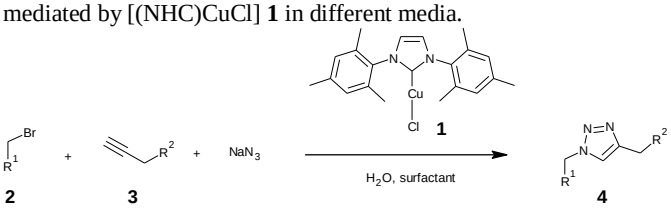
Scheme 1. Multicomponent cycloaddition reaction between organic halides, sodium azide and alkynes mediated by [Cu(IMes)Cl] **1** in water at room temperature under micellar conditions.

The multicomponent synthesis of triazoles consists of two consecutive steps, i) the *in situ* formation of the organic azide between sodium azide and the organic bromide and ii) the click reaction between the organic azide and the alkyne mediated by the Cu(I) catalyst. The most suitable surfactant for the direct reaction should favor both synthetic steps and ensure good solubilization and close contact between the three reagents and the catalyst. We therefore screened several micellar media for the first and second step and for the entire multicomponent reaction.

Initially we investigated the test reaction between pre-synthesized benzyl azide and 1-octyne in the presence of the [Cu(IMes)Cl] catalyst **1** in different media ranging from organic solvents to water with the addition of a wide range of surfactants[37] (Table 1) seeking for the best medium to dissolve all species and favor the cycloaddition reaction.

Catalyst **1** is known to operate efficiently under neat conditions and this is confirmed by observing that both in apolar and polar protic solvents the reaction was sluggish (Table 1, entries 1 and 2). Triazole formation was improved in pure water (Table 1, entry 3) where organic substrates and the catalyst are poorly soluble thereby providing pseudo-neat conditions. Addition of surfactants showed that ionic ones like SDS, CTAB, the zwitterionic surfactant *N*-dodecyl-*N*,*N*-dimethyl-3-amonium-1-propan sulfonate (DDAPS) and Triton X-100 all led to low or negligible yields in triazole product, while TPGS-750-M[35] efficiently promoted the reaction forming the corresponding triazole in high yield (>98%, Table 1, entry 8).

Table 1. Triazole synthesis from benzyl azide and 1-octyne mediated by [(NHC)CuCl] **1** in different media.



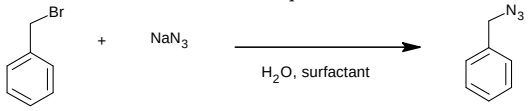
#	Medium	Yield (%)[a]
1	CH_2Cl_2	5
2	CH_3OH	2
3	H_2O	54
4	H_2O/CTAB	2
5	H_2O/SDS	23
6	H_2O/ DDAPS	6
7	H_2O/Triton X-100	3
8	H_2O/ TPGS-750-M	>98
9	H_2O/ SLS	63

Experimental conditions: [benzyl azide]= 250 mM; [1-octyne]= 250 mM; [Cu(IMes)Cl **1**]= 5 mM (2 mol%); [surfactant]= 180 mM, for TPGS-750-M 2 w/w%; solvent 1 mL, rt, 1 h. a) determined by ^{1}H NMR.

Sodium lauryl sulfosuccinate (SLS) even being an anionic surfactant, showed intermediate properties leading to 63% yield in the cycloaddition test reaction (Table 1, entry 9).

The reaction between sodium azide and alkyl bromides in water has been rarely investigated in the presence of surfactants. Examples are known employing cationic phase transfer species[38] or with surfactant pillared clays operating exclusively on α-tosyloxyketones under sonochemistry conditions and at high temperature.[39,40] In order to investigate the first step of the multicomponent click reaction, we compared several surfactants/H_2O micellar media in the reaction between sodium azide and benzyl bromide at room temperature for 1h (Table 2).

Table 2. Benzyl azide synthesis from benzyl bromide and sodium azide in different aqueous media.



#	Medium	Yield (%)[a]
1	H_2O	36
2	H_2O/SDS	74
3	H_2O/CTAB	>98
4	H_2O/DDAPS	>98
5	H_2O/Triton X-100	>98
6	H_2O/ TPGS-750-M	62
7	H_2O/SLS	79

Experimental conditions: [benzyl bromide]= 250 mM; [NaN_3]= 370 mM; [surfactant]= 180 mM, for TPGS-750-M 2 w/w %; water 1 mL, rt, 1 h. a) determined by ^{1}H NMR.

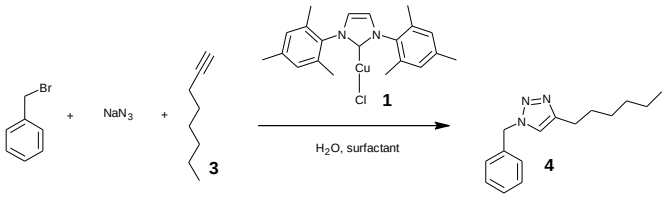
It is clear that the reaction in pure water is not favored because of the poor contact between the poorly soluble organic benzyl bromide and the completely soluble sodium azide (Table 2, entry 1). The use of surfactants showed a general improvement with respect to pure water because of the better contact between the substrates. In particular moderate to good yields were observed with anionic SDS and SLS as well as neutral TPGS-750-M surfactants (Table 2, entries 2, 6 and 7), while excellent yields >98% were found with cationic CTAB, zwitterionic DDAPS and neutral Triton X-100 surfactants (Table 2, entries 3-5).

Consequently, we investigated the direct three component reaction between benzyl bromide, sodium azide and 1-octyne in different micellar media mediated by Cu(I) catalyst **1**. Adding catalyst **1** to the substrate mixture since the very beginning led to the formation of the desired triazole product together with different amounts of a dimeric by-product 3,3'-dibenzyl-5,5'-di-*n*-hexyl-3*H*,3'*H*-4,4'-*bis*-1,2,3-triazole (see scheme in supporting information) In particular with CTAB and DDAPS 11% yield of this atropoisomeric dimer was observed, while the same was formed in 4% yield in SDS and 6% yield in pure water. The formation of this species can be rationalized considering the initial 1-alkyne dimerization mediated by the copper catalyst[41] and subsequent double click reaction with benzyl azide on the conjugated internal alkynes. This side-reaction occurs in the early stages of the reaction when the catalyst gets in contact with the alkyne and the concentration of organic azide is low. In order to limit the formation of such by-product we modified the experimental procedure running the reaction between 1-octyne, benzyl bromide and sodium azide for 1h followed by the addition of the Cu(I) catalyst. This expedient favorably influenced the course of the process leading to a drastic decrease of the side product in all the surfactant/water media considered (Table 3).

As observed for the direct synthesis from benzyl azide above reported (Table 1 entry 1), the use of pure water showed only partial triazole formation in the multicomponent reaction (Table 3, entry 1). Surfactants like SDS, CTAB, Triton X-100 and DDAPS showed very low yields in triazole, in all cases <10% (Table 3, entries 2-5). Better results were observed with the neutral surfactant TPGS-750-M and with SLS observing 68 and 73% yield of the corresponding triazole (Table 3, entries 6 and 7).

Overall the last two surfactants turned out to be the best compromise in order to promote both the organic azide synthesis and the solubilization of the Cu(I) **1** catalyst for the click reaction. When the reaction was repeated running the click reaction for 2h instead of 1h either in pure water, or with TPGS-750-M and (better) SLS, we observed an increase in both organic azide and triazole formation. The use of *in situ* formed Cu(I) species from $CuSO_4$/ascorbate as traditional catalyst for the click triazole synthesis in water and in TPGS-750-M and SLS as selected micellar media showed a substantial decrease of the yield of the corresponding triazole formed in 26% yield at the best (Table 3, entries 1, 6 and 7). This is likely to occur because the *in situ* formed catalytic system is not sufficiently lipophilic to enter the micelles of surfactant where substrates are hosted.

Table 3. Triazole direct synthesis from benzyl bromide, sodium azide and 1-octyne mediated by [Cu(IMes)Cl] **1** in different aqueous media.



#	Medium	Azide Yield (%)[a]	Triazole Yield (%)[a]
1	H_2O	44 54[b] 56[c]	22 37[b] 17[c]
2	H_2O/SDS	86	1
3	H_2O/CTAB	93	7
4	H_2O/DDAPS	88	12
5	H_2O/Triton X-100	87	3
6	H_2O/TPGS-750-M	25 27[b] 56[c]	68 71[b] 25[c]
7	H_2O/SLS	18 10[b] 46[c]	73 88[b] 26[c]

Experimental conditions: [benzyl bromide]= 250 mM; [NaN_3]= 370 mM; [1-octyne]= 370 mM; [Cu(IMes)Cl] **1** 2.5 mM (1 mol%); [surfactant]= 180 mM, for TPGS-750-M 2 w/w %; water 1 mL, rt. [Cu(IMes)Cl] **1** added after 1 h, total reaction time 2 h. a) determined by ^{1}H NMR; b) [Cu(IMes)Cl] **1** added after 1 hr, total reaction time 3 h.; c) $CuSO_4$ 1 mol% and sodium ascorbate 2% added after 1 hr, total reaction time 3 h.

In order to extend the catalytic protocol to the synthesis of different 1,2,3-triazoles, we tested the reaction between a series of organic bromides and alkynes with sodium azide in the presence of **1** comparing the activity observed in pure water with those observed in the presence of TPGS-750-M and SLS as selected surfactants (Table 4). The reaction between a series of different terminal aliphatic alkynes with benzyl bromide and sodium azide greatly benefitted from the presence of SLS or TPGS-750-M as surfactants with respect to the same reaction in pure water. In particular 1-decyne, 1-dodecyne, 4-phenyl-1-butyne all led to good yields of corresponding triazoles in the range 77 - >98% yield (Table 4, entries 1-3).[42] It is noteworthy that the same reaction with propargyl dimethyl malonate

(Table 4, entry 4) turned out to be suppressed in pure water while from moderate to good yields were observed with TPGS-750-M and with SLS. The reaction is known to be highly favored with aromatic alkynes and also in these cases the use of micellar media favored the reaction allowing the formation of the corresponding triazoles in 30 minutes (Table 4, entries 5-9). In particular SLS showed in all cases to ensure much higher yields compared to the use of pure water as reaction medium.

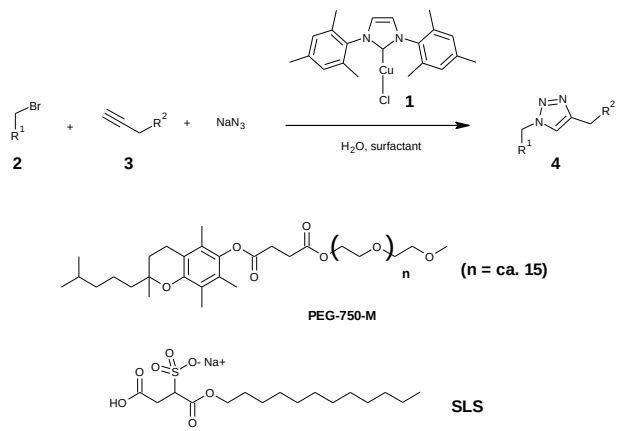
We then analyzed the behavior of different benzyl bromides in the multicomponent reaction. The synthesis with 3-bromo-benzyl bromide and 4-bromo-benzyl bromide showed in all cases a three-fold increase of the catalytic activity comparing the reaction in the presence of surfactants *vs.* pure water even though the solid bromides tested dissolved with difficulty in the micellar medium (Table 4 entries 10 and 11). The reaction did not proceed using purely aliphatic halogenated substrates like butyl bromide or iodide because of the difficult formation of the corresponding organic azide. In fact these products are usually prepared either in polar non-protic solvents like DMSO or DMF[43] at low temperature or in water with acetone under reflux.[44]

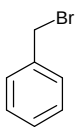
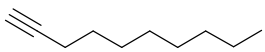
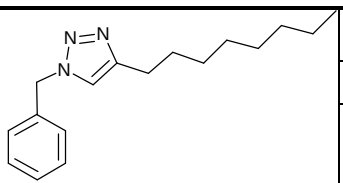
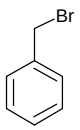
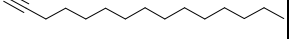
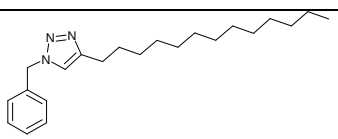
Better results were obtained with allyl bromide that in the presence of aliphatic alkynes smoothly led to the formation of the corresponding organic azide and quantitative formation of the corresponding triazoles while in pure water the yields were in the range 66-77% (Table 4, entries 12-15). Similarly the reaction between allyl bromide, propargyl dimethyl malonate and sodium azide was more efficient with SLS and TPGS-750-M with respect to the use of pure water (Table 4, entry 16). The reaction of allyl bromide with several aromatic alkynes in SLS as well as in TPGS-750-M yielded quantitative formation of the corresponding triazoles in 30 min, while in pure water the reactivity was much lower especially with less substituted aromatic alkynes (Table 4, entries 17-19). For the highly reactive alkynes reported in Table 4 entries 20 and 21 the reaction was carried out with only 0.5 mol% **1** for 15 minutes at rt observing from good to excellent triazole formation in the presence of the selected surfactants while the reaction did not occur in pure water.

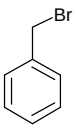
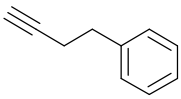
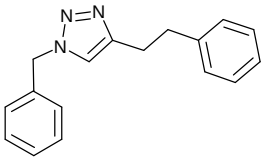
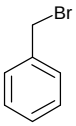
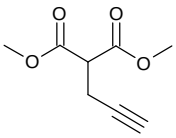
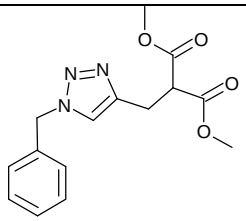
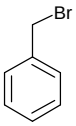
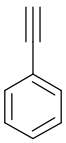
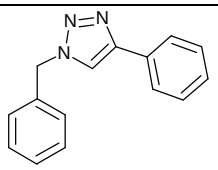
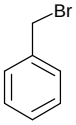
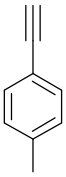
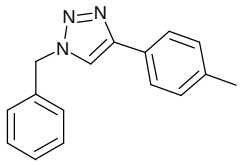
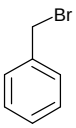
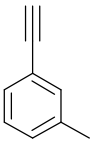
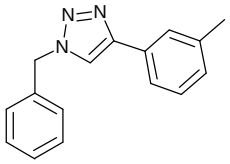
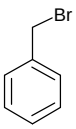
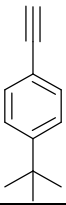
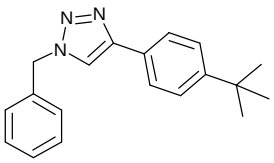
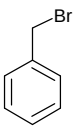
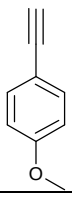
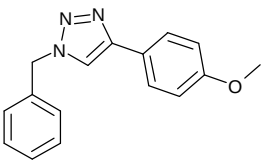
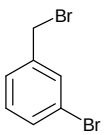
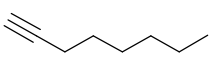
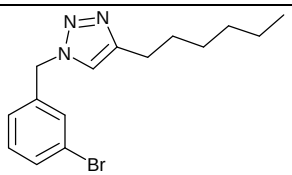
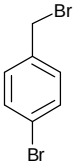
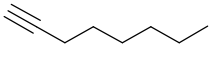
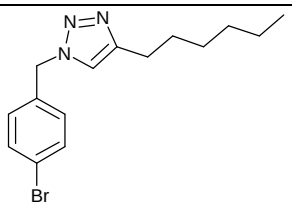
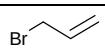
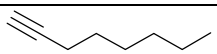
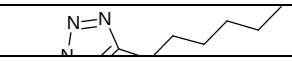
Since in most cases the most effective surfactant turned out to be SLS, this surfactant was chosen to scale up the multicomponent reaction between sodium azide, benzyl bromide and 1-octyne using 2 mmoles of the bromide as limiting reagent. The reaction was carried out under the same experimental conditions as in Table 4 and the corresponding triazole was obtained in 82% isolated yield.

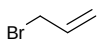
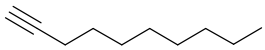
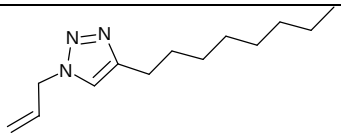
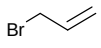
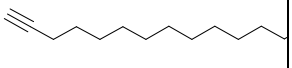
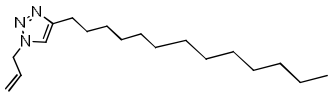
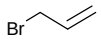
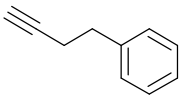
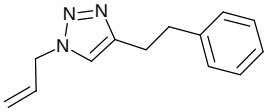
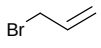
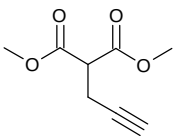
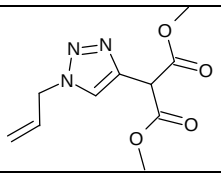
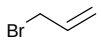
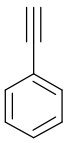
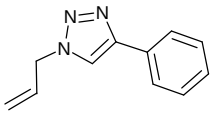
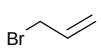
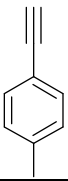
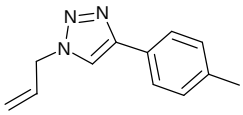
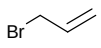
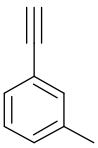
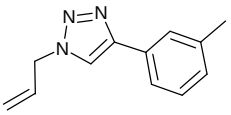
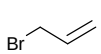
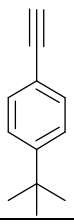
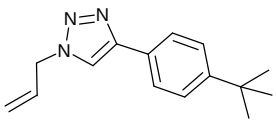
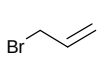
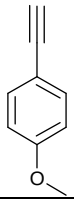
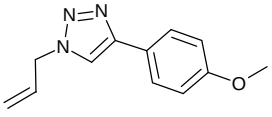
In order to investigate the possible recycling of the Cu(I) catalyst in the reaction between benzyl bromide, sodium azide and dimethyl propargyl malonate in H_2O/SLS, after extraction of the products fresh substrates were added obtaining at the end of the second cycle the corresponding triazole in just 27% yield together with 61% of the benzyl azide.

Table 4. Triazole direct synthesis from different organic bromides, sodium azide and alkynes mediated by [Cu(IMes)Cl] **1** in different aqueous media.



#	Organic bromide	Alkyne	Triazole Product	Medium	Azide Yield (%)[a]	Triazole Yield (%)[a]
1				H_2O	45	45
				H_2O/SLS	0	>98
				H_2O/ TPGS-750-M	58	39
2				H_2O	56	31
				H_2O/SLS	17	77
				H_2O/ TPGS-750-M	26	62

3				H_2O	65	16
				H_2O/SLS	9	87
				H_2O/ TPGS-750-M	5	13
4				H_2O	80	1
				H_2O/SLS	14	86
				H_2O/ TPGS-750-M	26	67
5				H_2O	41[b]	17[b]
				H_2O/SLS	16[b]	51[b]
				H_2O/ TPGS-750-M	19[b]	46[b]
6				H_2O	10[b]	61[b]
				H_2O/SLS	2[b]	76[b]
				H_2O/ TPGS-750-M	21[b]	42[b]
7				H_2O	46[b]	32[b]
				H_2O/SLS	5[b]	79[b]
				H_2O/ TPGS-750-M	15[b]	65[b]
8				H_2O	36[b]	42[b]
				H_2O/SLS	3[b]	83[b]
				H_2O/ TPGS-750-M	34[b]	42[b]
9				H_2O	52[b]	19[b]
				H_2O/SLS	13[b]	54[b]
				H_2O/ TPGS-750-M	50[b]	25[b]
10				H_2O	32	20
				H_2O/SLS	4	55
				H_2O/ TPGS-750-M	18	25
11				H_2O	27	24
				H_2O/SLS	11	72
				H_2O/ TPGS-750-M	13	18
12				H_2O	25	68

				H_2O/SLS	4	93
				H_2O/ TPGS-750-M	2	98
13				H_2O	18	77
				H_2O/SLS	0	>98
				H_2O/ TPGS-750-M	0	>98
14				H_2O	15	75
				H_2O/SLS	0	>98
				H_2O/ TPGS-750-M	0	>98
15				H_2O	0	66
				H_2O/SLS	0	>98
				H_2O/ TPGS-750-M	0	88
16				H_2O	44	56
				H_2O/SLS	8	92
				H_2O/ TPGS-750-M	19	81
17				H_2O	9^b	52^b
				H_2O/SLS	15^b	64^b
				H_2O/ TPGS-750-M	0^b	31^b
18				H_2O	3^b	56^b
				H_2O/SLS	0^b	$>98^b$
				H_2O/ TPGS-750-M	0^b	$>98^b$
19				H_2O	0^b	53^b
				H_2O/SLS	0^b	$>98^b$
				H_2O/ TPGS-750-M	0^b	$>98^b$
20				H_2O	0^c	0^c
				H_2O/SLS	0^c	$>98^c$
				H_2O/ TPGS-750-M	7^c	$>93^c$
21				H_2O	0^c	0^c
				H_2O/SLS	14^c	$>86^c$
				H_2O/ TPGS-750-M	35^c	65^c

Experimental conditions: [organic bromide] 250 mM; [NaN_3] 370 mM; [alkyne] 370 mM; [Cu(IMes)Cl] **1** 2.5 mM (1 mol%); [surfactant]= 180 mM, for TPGS-750-M 2 w/w%; water 1 mL, rt, [Cu(IMes)Cl] **1** added after 1 hr, total reaction time 3 h. a) determined by ^{1}H NMR. b) [Cu(IMes)Cl] **1** added after 1 hr, total reaction time 1.5 h; c) [Cu(IMes)Cl] **1** (0.5 mol %) added after 1 hr, total reaction time 1.25 h.

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Conclusions

In conclusion, herein we reported a room temperature, extremely simple and efficient regioselective multicomponent synthesis of 1,4- disubstituted 1,2,3-triazoles from organic bromides, sodium azide and alkynes mediated by 1 mol% of [Cu(IMes)Cl] **1** catalyst in water and in the presence of surfactants. The key feature of the catalytic system is the micellar medium obtained by simple addition of commercially available SLS or TPG-750-M surfactants in water. The apolar nano-environments thus obtained favor the *in situ* formation of the organic azide, thus avoiding its separate synthesis and storage. The micellar media are responsible also for the consecutive fruitful interaction between the organic azide and the alkyne mediated by the organometallic Cu(I) catalyst. The catalytic system developed can be applied to a wide range of combinations of organic bromides and alkynes obtaining overall more than 20 different 1,2,3-triazoles in 51->98 % yields within a few hours. In one case the reaction was scaled up to 2 mmoles of product, as demonstrated in the reaction between benzyl bromide, sodium azide and 1-octyne. The triazole products could be easily isolated by means of simple extraction with ethyl acetate. The multicomponent reaction can be carried out in a greener way and is competitive in terms of yields and selectivities with respect to the direct synthesis from an isolated organic azide, avoiding the manipulation of these noxious chemicals and with the advantage of carrying out the whole procedure in one pot.

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[a] Dipartimento di Scienze Molecolari e Nanosistemi, Università Ca' Foscari di Venezia, Calle Larga S. Marta 2137, 30123, Venezia (ITALY). Fax: +39-041-2340517; Tel:+39-041-2348569.

Electronic Supplementary Information (ESI) available: experimental procedures and characterization of compounds. See DOI: 10.1039/c000000x/

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Graphical Abstract