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Ag₂CO₃-catalyzed cycloaddition of organic azides onto terminal alkynes: A green and sustainable protocol accelerated by aqueous micelles of CPyCl

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ABSTRACT

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Using catalytic amount of Ag_2CO_3 a simple, efficient and copper free green protocol has been developed to synthesize 1,4-disubstituted 1,2,3-triazoles regioselectively. Here, the cationic surfactant, cetylpyridinium chloride (CPyCl) in water provides a micellnar media and accelerates the subsequent Ag(1)-catalysed azide-alkyne cycloaddition (AgAAC) reaction by increasing the concentration of reactants in the micellar pseudophase. Our method is found to be environmentally friendly from E-factor measurement. The surfactant, CPyCl is found to be nontoxic.

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Introduction

The increasing awareness towards greener and sustainable technologies has paid tremendous attention on efficient green methodologies for synthesis of chemicals and pharmaceuticals. Therefore, by utilizing the twelve principles of green chemistry, continuous efforts have been made to develop sustainable and effective strategies for organic synthesis. The use of organic solvents for chemical transformation is one of the most important issues in green chemistry because of their harmful effects on health and environment.¹ Considering environmental impact and safety measurement, replacement of these deleterious solvents by environmentally benign solvents such as water, ionic-liquids or supercritical carbon dioxide becomes the foremost aspect of sustainable chemistry. Water is the first choice of green solvent as it is non-destructive, cheap, non-flammable, and abundantly available in pure form.² Water is a polar compound and is called as the "universal solvent" for its ability to dissolve many substances. Molecular structure and capability of forming extensive hydrogen bonding are responsible for its unique physicochemical properties such as high dielectric constant, optimum oxygen solubility, high heat capacity and high cohesive energy density.³ The heterocyclic chemistry becomes a very important field in the organic or pharmaceutical chemistry. As we are totally dependent on the drugs derived from heterocyclic rings, enormous attention has been paid to develop some new advanced methodologies to synthesize heterocycles. After the establishment of copper catalyzed azide-alkyne cycloaddition (CuAAC) by Sharpless and Meldal in 2002,⁴ the 1,2,3-triazole moiety has become one of the most important and well known synthetic nitrogen containing heterocyclic rings having extensive use in different fields including material science, drug discovery, polymer chemistry, chemical synthesis and supramolecular chemistry.⁵ In medicinal chemistry, the importance of triazolic compounds is undeniable as many 1,2,3-triazole containing drugs are used as anti-HIV, anticancer, antitubercular, antifungal, antibacterial, anti-influenza and antiepileptic agents.⁶ Aromatic character, high thermal and chemical stability, participation in hydrogen bonding and strong dipole moment make this moiety widely applicable.

Copper-catalyzed azide-alkyne cycloaddition (CuAAC) for synthesis of 1,4-disubstituted 1,2,3-triazole and rutheniumcatalyzed azide-alkyne cycloaddition (RuAAC)⁸ for synthesis of complementary 1,5-disubstituted 1,2,3-triazole circumvented the problems of high thermal necessity and poor regioselectivity of ordinary Huisgen⁹ 1,3-dipolar cycloaddition reaction. Plenty of works have been done using different copper sources because of CuAAC's high yield in aqueous media, no need of elevated temperature, exclusive regioselectivity and wide substrate scope. Apart from these advantages, the CuAAC reactions have certain limitations also. Cu(I) is cytotoxic in nature and therefore it is incompatible with living cells.¹⁰ Excessive copper intake can cause some side effects like hepatitis, neurological disorders, kidney damage and Alzheimer's disease.¹¹ Another disadvantage of CuAAC reaction is alkyne homocoupling, called Glaser Hay coupling to form dialkynes in presence of copper salts. Therefore, development of alternative methods for AAC reaction is of great demand. Recently, several Ag(I) sources have found to display huge potential towards the synthesis of 1,4-disubstituted 1,2,3triazoles. The indispensable metal, silver has gained growing demand in industries due to its exclusive catalytic, sensing, optical and antimicrobial properties. McNulty et al. identified the first purely silver catalyzed click reaction using P, O-type silver complexes.¹² Further, Ag-graphene nanocomposite,¹³ Ag₂O NPs,¹⁴ combination of AgOTf and Cu(0) catalyst,¹⁵ silver nanoparticle supported on $Al_2O_3@Fe_2O_3^{16}$, $AgN(CN)_2/DIPEA^{17}$ were employed in order to get triazole products. However, in these protocols inert atmospheric condition, toxic organic solvents, elevated temperature, stabilizing ligands, bases and additives and also the formation of silver complexes were

essential. These prominent demerits of the earlier reports strongly demand development of some simple and greener protocols towards AgAAC. Here, we have reported a new strategy for AAC reaction using readily available and relatively inexpensive Ag_2CO_3 catalyst in aqueous micelles of CPyCl.

Absolute solubility of the starting materials, very often, is the crucial factor for better reactivity. For aqueous reactions surfactant incorporation can show growing reactivity by forming micelles. Micelle formation shows a general advancement over the pure aqueous medium by increasing solubility and contact between the starting reagents. TPGS-750-M in water forms recyclable nanomicelles and was used for nitro group reduction and Suzuki-Miyaura coupling reaction reported by Bruce H. Lipshutz.¹⁸ For synthesis of substituted 1,2,3-triazoles only a few number of works have been carried out in micellar media.¹⁹ Here we present a new method using the versatile cationic surfactant, CPyCl in water as the accelerating media for AgAAC.

Results and discussion

To follow the objective, we began our optimization with benzyl azide (1a) and phenyl acetylene (2a) as representative substrates in toluene using Ag_2CO_3 as catalyst at room temperature. After 24 hours, the exhilarating conversion of the starting reagents to the corresponding 1,4-disubstituted 1,2,3-triazole product encouraged us for further analysis (Table 1, entry 1). The search for a green solvent system for this newly synthesized protocol showed that use of both water and ethylene glycol (EG) gives very good results (97%) after 24 hours (Table 1, entries 2 and 3).

Table 1.	Optimization	of reaction	conditions	for Cu	1-free
AgAAC ^a					

\sim	~	=\	- salt additive	Bn _	N ^N N
	^N ³ + <u></u> →			→	\(
\checkmark	<u>v</u>		RT, solvent		3a Ph
1a	2		ou		
Entry	Catalyst (mol%)	Additive	Solvent	Time	Yield ^b
				(h)	(%)
1	Ag ₂ CO ₃ (10 %)	-	MePh	24	50
2	Ag ₂ CO ₃ (10%)	-	EG	24	97
3	Ag ₂ CO ₃ (10%)	-	H_2O	24	97
4	Ag ₂ CO ₃ (10 %)	-	DMF	24	80
5	Ag ₂ CO ₃ (10%)	-	DMSO	24	85
6	Ag ₂ CO ₃ (10%)	-	DCM	24	90
7	Ag ₂ CO ₃ (10%)	-	t-BuOH	24	87
8	Ag ₂ CO ₃ (10 %)	CPyCl	H ₂ O	2	98
9	Ag ₂ CO ₃ (10%)	CTAB	H_2O	2	65
10	Ag ₂ CO ₃ (10%)	SLS	H_2O	2	43
11	Ag ₂ CO ₃ (10%)	SDBS	H_2O	2	81
12	Ag ₂ CO ₃ (10%)	NaDC	H_2O	2	80
13	Ag ₂ CO ₃ (10%)	Triton X-	H_2O	2	20
		100			
14	AgCl (10 %)	CPyC1	H_2O	2	45
15	AgBr (10 %)	CPyC1	H_2O	2	23
16	AgNO ₃ (10 %)	CPyC1	H_2O	2	<10
17	Ag ₂ CO ₃ (5%)	CPyC1	H_2O	2	88
18	Ag ₂ CO ₃ (1%)	CPyCl	H_2O	2	82
19	Ag ₂ CO ₃ (0%)	CPyCl	H_2O	2	0

^a Reagents and conditions: Azide (0.34 mmol, 1.0 equiv), alkyne (0.34 mmol, 1.0 equiv), Ag-catalyst, additive (10 mol%) and solvent (2 mL) were allowed to react at room temperature. ^b Isolated yields of 3a.

Apparently, other organic solvents like DMF, DMSO, DCM and t-BuOH were found to play a suitable role for AgAAC (**Table 1**, **entries 4-7**). Further experiments were conducted in water as it is environment friendly, cheap and easily available. In order to minimize the time requirement we analyzed the reaction

with different types of surface active agents (cationic, anionic and non ionic). The cationic surfactant, cetylpyridinium chloride (CPyCl) accelerated the reaction rate and interestingly an impressive yield was observed after 2 hours (Table 1, entry 8). Cetyltrimethylammonium bromide (CTAB) was used and found to be less effective than that of the previous one (Table 1, entry 9). Besides, the use of anionic surfactants such as sodium lauryl sulphate (SLS), sodium dodecyl benzene sulphonate (SDBS) and sodium deoxycholate (NaDC) showed relatively lower reactivity (Table 1, entries 10-12). A non ionic surfactant, Triton X- 100 was found to be least efficient for our newly developed strategy (Table 1, entry 13). Considering CPyCl as the best promoter and water as the suitable solvent media the reaction was further screened with different silver salts. AgCl, AgBr and AgNO3 were tested and observed to be inferior to Ag₂CO₃, as they afforded lower yields of the desired products (Table 1, entries 14-16). Further investigations were concerned with the catalyst loading. A remarkable change was ascertained while reducing the catalyst loading from 10 mol% to 5 mol% and further to 1 mol% (Table 1, entries 17,18). The reaction did not proceed at all in absence of catalyst (Table 1, entry 19).

Table 2. Screening of surfactant concentration.

1a			2-	Ag ₂ CO ₃ (10 mol%)	20		
	Ia	Ŧ	<u>za</u> -	CPyCl, RT, H ₂ O, 2h	Ja		
Entry		Surfa	octant	Amount (mol%)		Yield (%) ^b	_
1		CPyC	21	0.25		67	_
2		CPyC	C1	0.51		79	
3		CPyC	C1	2		83	
4		CPyC	21	5		89	
5		CPy(Cl	10		98	

^a Reaction conditions: Azide (0.34 mmol, 1.0 equiv), alkyne (0.34 mmol, 1.0 equiv), Ag_2CO_3 (10 mol%) were allowed to react in 2 mL of water at different CPyCl concentrations. [Here, 0.51 mol%= 0.90 mM]. ^b Isolated yields.

The surfactant concentration is a notable factor that substantially affects the rate of a chemical reaction. Considering this, the impact of different CPyCl concentrations on reactivity was also studied and the findings are shown in **Table 2**. Reactivity was found to increase with increase in the amount of CPyCl. We have determined the critical micelle concentration (CMC) of the surfactant in water by conductometric method [**Figure 1**, (a)] and the calculated value (0.90 mM) was found to match with the reported value.²⁰ A lower yield of the product was observed bellow CMC and the yield gradually increased due to increase in aggregation of monomeric species and the size of the colloidal cluster above CMC.

Next, we evaluated the generality and scope of our optimized Cu-free AgAAC system towards synthesis of various 1,4disubstituted 1,2,3-triazoles. In this aspect, a variety of azides (benzyl, aliphatic and aromatic) were allowed to react with different alkynes (both aromatic and aliphatic) under the established conditions. As demonstrated in Table 3, the reactions worked suitably and afforded the corresponding 1,4disubstituted-1H-1,2,3-triazoles in good to excellent yields under our catalytic conditions. The findings indicated that both aromatic and aliphatic alkynes reacted effectively with benzyl azide and provided the corresponding triazoles in excellent yields (Table 3, entries 3a-g). Functional group bearing benzyl azides are also tolerated under our established conditions (Table 3, entries 3h-j). A variety of phenyl azides bearing electron donating or electron withdrawing functional groups were tested and it was noticed that all reactions proceeded efficiently in the direction of click conversion producing the respective triazole products (Table 3, entries 3k-p). Octyl azide and phenethyl azide also showed higher reactivity towards phenyl acetylene under these conditions (Table 3, entries 3q, r). The heterocyclic azide, 2-azidothiophene provided 79% yield of the desired

product by AgAAC with phenylacetylene. 2-azidofuran and 2azidobenzofuran were found to be ineffective for AgAAC.





Figure1. (a) Specific conductivities of CPyCl as a function of concentration at 302.15 K. [CMC of CPyCl in pure water = 0.90 mM]. Optical micrograph of CPyCl in water before (b) and after (c) the addition of reactants. [Scale bar= $1-10 \ \mu$ m]



We have analyzed two samples of CPyCl surfactant in distilled water through an inverted microscope, one is prior to the addition of reactants and the other is after the addition of reactants. Both

the products.

the samples indicated the formation of spherical shaped micelles in water [**Figure 1 (b), (c)**]. It was observed that the size of the spherical shaped micelles became more uniform in presence of reacting substances.

The hydrophobic and electrostatic interactions of organic reagents with the surfactant are believed to enhance the effect of CPyCl micellar solution in water. The high interfacial energy between the polar water molecules and the non polar hydrocarbon chains of surfactant molecule serves as the force governing the association process and leads to the formation of a colloidal sized spherical cluster. As the non polar hydrocarbon chains of the surfactants are pointing towards the interior, the inner part of these spherical droplets behaves as hydrophobic reaction site. Organic reagents are pushed towards the hydrophobic region of the micelles as their solvation is better in the non-polar core of the micelle than in the polar bulk water. Thus, increase in concentration of reagents inside the micelle favours more effective collisions among themselves which act as a driving force for rate enhancement in water. We have suggested a possible mechanism of the reaction on the basis of literature reports (Scheme 1).^{12, 23}

In order to measure the greenness of our AgAAC protocol *Environmental Factor* (E-factor) was determined. The concept of E-factor was introduced by R. Sheldon and it is the weight of raw materials minus the weight of desired product, divided by the weight of the product out.²¹ A comparative study was done with earlier reported methods and the results are illustrated in **Table 4**. E-factors with lower values are preferable. Moreover, the additive CPyCl is found to be non toxic. The cytotoxicity effect of CPyCl (1mg/100µl) is determined in primary hepatocytes by using MTT assay.²² The hepatocyte cells are found to be 51.14% viable from absorption measurement at 750 nm by using a microplate reader. Thus our system will be more environmental friendly in comparison to the previous methods.

Table 3. Substrate scope of azides and alkynes for $AgAAC^{a}$



Table 3. Comparative study of E-factors for measuringenvironmental impact.

Entry	Catalyst	Additive	Solvent	E-	Ref.
	(mol%)			factor	
1	Ag-complex	Caprylic	MePh	22.68	12(a)
	(10 mol%)	acid			
2	Ag-complex (2-	Caprylic	MePh	41.88	12(b)
	2.5 mol%)	acid			
3	Ag_2O	-	MePh	17.99	14
4	AgN(CN) ₂	DIPEA	H ₂ O:EG	5.53	17
	(10 mol%)				
5	Ag ₂ CO ₃	CPyCl	H_2O	0.311	This
	(10 mol%)				work



Scheme 1. Schematic diagram representing the role of CPyCl and the plausible reaction mechanism.

Conclusion

In summary, Ag_2CO_3 in aqueous micelles of CPyCl has been employed for the first time as an efficient and alternative protocol for regioselective synthesis of 1,4-disubstituted-1*H*-1,2,3triazoles at room temperature. From synthetic viewpoint, this versatile method emerges as simple, mild and highly selective for 1,2,3-triazole synthesis and hence it has huge significance in various synthetic applications.

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- Simplest Cu-free protocol for azide-alkyne • cycloaddition reaction reported so far.
- Non toxic cationic surfactant, CPyCl speeded • up the reaction.
- Negligible E-factor as compared to literature • reports.
- Accerbic