$AgN(CN)_2$/DIPEA/H_2O-EG: A highly efficient catalytic system for synthesis of 1,4-disubstituted-1,2,3 triazoles at room temperature

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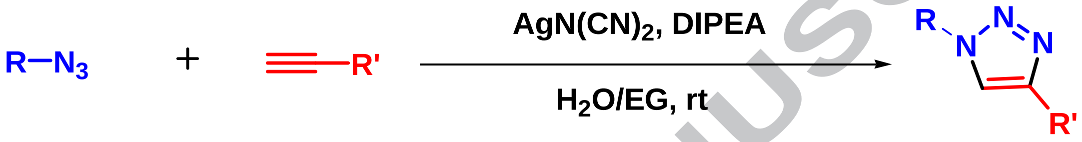

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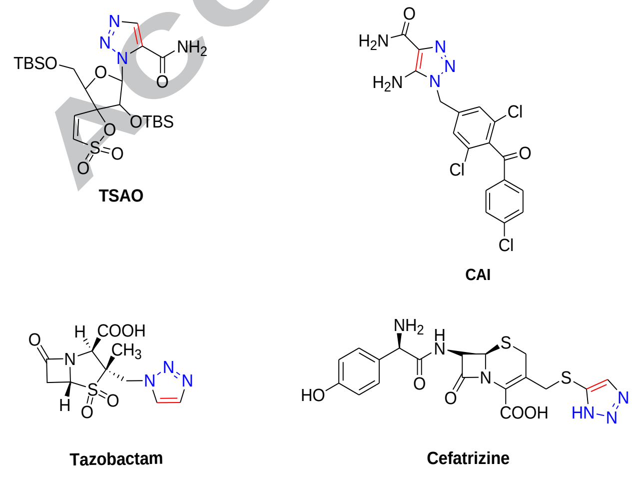
ABSTRACT

A novel, efficient and robust method for silver-catalyzed azide–alkyne cycloaddition (AgAAC) reactions in H$_2$O/Ethylene glycol (EG) at room temperature has been developed. The protocol addresses silver dicyanamide/DIPEA as a highly effective catalyst system for the regioselective formation of 1,4-disubstituted-1,2,3 triazoles under mild conditions.

In recent years, 1,2,3-triazole compounds have received enhanced considerable attention due to their spacious range of applications in organic and medicinal chemistry.[1] Some of these classes of drug molecules, now available in the market or in the final stage of clinical trials, include the anticancer compound carboxyamidotriazole (CAI), the nucleoside derivative non-nucloside reverse transcriptase inhibitor tert-butyldimethylsilylspiroaminooxathioledioxide (known as TSAO), β-lactum antibiotic Tazobactum, the cephalosporine Cefatrizine and so on (**Scheme 1**).[2] Consequently, the development of straightforward and efficient approach for the construction of 1,2,3-triazoles is likely to be enormously demanded.



Scheme1. Potential pharmaceutical based on 1,2,3-triazoles

Perhaps the most useful and powerful procedure for the synthesis of 1,2,3-triazoles is the Huisgen 1,3-dipolar cycloaddition of organic azides with acetylene.[3] However, the conventional thermal conditions normally require high temperature and proceed with limited regioselectivity. The copper-catalyzed version of Huisgen 1,3-dipolar azide-alkyne cycloaddition (CuAAC), reported independently by the groups of Sharpless[4] and Meldal[5] in 2002, is generally recognized as the most prime example of click chemistry. The Cu (I)- catalyzed azide-alkyne cycloaddition (CuAAC) reaction is an important advance in the chemistry of 1,2,3-triazoles because of its 100% atom economy, exclusive regioselectivity (1,4-disubstituted regioisomer), wide substrate scope and mild reaction conditions.[6] Nevertheless, the scope of triazole chemistry is not confined to drug discovery, there are a growing number of applications in numerous other areas of modern chemical sciences, such as biological science, polymer science, and material chemistry.[7] In comparison to copper, silver-based catalysts seemed to be less effective;[8] only recently, several Ag (I)-catalyzed azide-alkyne cycloaddition reactions[9] have been reported for the synthesis of 1,4- disubstituted-1,2,3 triazoles which is still considered a challenge in the silver catalysis. Especially, Cu free catalyst systems that allow for alternative azide-alkyne cycloaddition to take place efficiently are of great value due to cytotoxic[10] nature of redox active copper (I) which prevents the use of CuAAC reaction in living biological systems.[11] The advantage of silver catalysis for the avoidance of the Glaser–Hay coupling commonly encountered with terminal alkynes in CuAAC reaction is also noteworthy. Although, gold (I)[12] and other acetylides[13] were also explored in the azide-alkyne cycloaddition reaction, the addition of copper (I) salts is often required to affect the cycloaddition. The majority of reported silver catalysts are based on the preparation of Ag–ligand complexes by using highly expensive and laborious methods. Likewise, the use of organic solvents, an inert atmosphere and refluxed conditions are required to exploit the catalytic performance. Nowadays,

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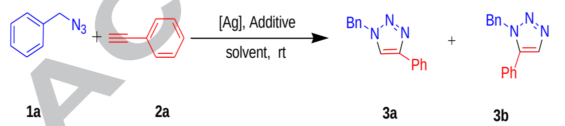
tremendous efforts have been made for the development of catalytic processes to achieve a greener synthesis by reduction of chemical waste and the number of synthetic steps as well as use of environmentally friendly solvent. Water as solvent has received remarkable concern because it is most abundant, non-toxic, non-corrosive, as well as non-flammable and environmentally benign.[14] In several instances, water is the ideal reaction solvent, providing the best yields of the product with the highest rates.[6]

Silver dicyanamide, a coordination polymer has been shown to consist of infinite -Ag-NC-N-CN-Ag- spiral chains ($\mu_{1,5}$-coordination mode)[15] and proved to be excellent, high yielding, simply prepared catalyst.[16] To continue our interest on 'click reactions',[17] we wish to report herein an efficient and preparatively straightforward approach for the generation of diverse 1,2,3-triazoles of high purity and in excellent yields. The reaction is experimentally simple proceeding well in H_2O/ethylene glycol without protection from oxygen, and generating nearly no by-products. The unique aspects of this route are the enormous scope, high selectivity, and nearly quantitative yields of the desired products under mild condition.

Initially, the cycloaddition reaction between benzyl azide and phenyl acetylene was selected to optimize the reaction conditions by using 10 mol % silver dicyanamide as a catalyst (**Table 1**). To our delight, we indeed obtained 1,4-disubstituted triazole regioisomer in moderate yield along with small amount of 1,5-isomer (**Table 1**, entry 1). This exciting transformation to the 1,2,3-triazole encouraged us to further examine the feasibility of this efficient cycloaddition. After many optimization efforts, the use of 5 mol% $AgN(CN)_2$ as the catalyst and DIPEA as a base/ligand in H_2O/ethylene glycol at room temperature turned out to give the optimum result (**Table 1**, entry 18). However, it is apparent that the reaction also proceeded in other solvents, such as dimethyl sulfoxide (DMSO), toluene, N,N-dimethylformamide (DMF) and tetrahydrofuran (THF), but gave the products in inferior yields (**Table 1**, entries 12–16). The necessity of using $AgN(CN)_2$ was confirmed in a control experiment (**Table 1**, entry 21); other silver salts, such as $AgNO_3$ and Ag_2O, were totally ineffective (**Table 1**, entries 10 and 11). Notably, no undesirable byproduct could be detected under optimized condition and gratifyingly, the catalyst loading could be lowered to 1 mol % [Ag] while keeping short reaction times (Table 1, entry 20).

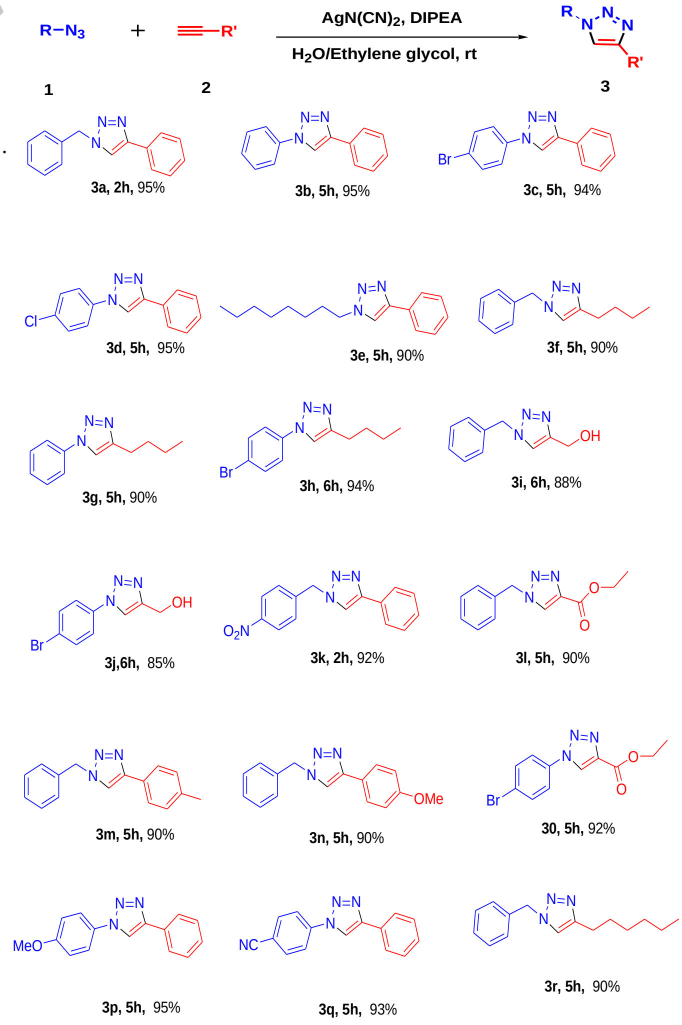
Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst (mol%)	Additive	Solvent	Time	Yield (%)[b]	
					3a	3b
1	$AgN(CN)_2$ (10%)	-	H_2O	24h	40	10
2	$AgN(CN)_2$ (10%)	L-Proline	H_2O	24h	54	0
3	$AgN(CN)_2$ (10%)	Diethyl amine	H_2O	24h	55	0
4	$AgN(CN)_2$ (10%)	NEt_3	H_2O	24h	51	0
5	$AgN(CN)_2$ (10%)	DABCO	H_2O	24h	52	0
6	$AgN(CN)_2$ (10%)	DBU	H_2O	24h	56	0
7	$AgN(CN)_2$ (10%)	DIPEA	H_2O	24h	70	0
8	$AgN(CN)_2$ (10%)	$(DHQD)_2PHAL$	H_2O	24h	45	10
9	$AgN(CN)_2$ (10%)	Pyridine-2-aldehyde	H_2O	24h	43	13
10	$AgNO_3$ (10%)	DIPEA	H_2O	24h	0	0
11	Ag_2O (10%)	DIPEA	H_2O	24h	0	0
12	$AgN(CN)_2$ (10%)	DIPEA	DMSO	24h	50	0
13	$AgN(CN)_2$ (10%)	DIPEA	DMF	24h	48	0
14	$AgN(CN)_2$ (10%)	DIPEA	Toluene	24h	40	0
15	$AgN(CN)_2$ (10%)	DIPEA	H_2O/THF	24h	45	0
16	$AgN(CN)_2$ (10%)	DIPEA	THF	24h	66	0
17	$AgN(CN)_2$ (10%)	DIPEA	EG	12h	78	0
18	$AgN(CN)_2$ (10%)	DIPEA	H_2O/EG	2h	98	0
19	$AgN(CN)_2$ (5%)	DIPEA	H_2O/EG	2h	95	0
20	$AgN(CN)_2$ (1%)	DIPEA	H_2O/EG	2h	80	0
21	-	DIPEA	H_2O/EG	2h	0	0

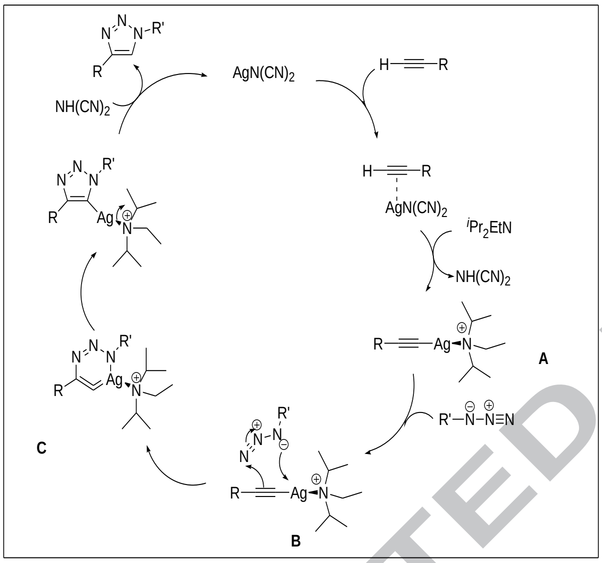
[a] Reactions were performed on a scale of 1 mmol of **1a** and 1.5 mmol of **2a** and additive (1 mmol) in a given solvent was stirred at room temperature in air otherwise stated; [b] Isolated yields.

With these promising results in hand, the scope of the method was investigated with a range of different azides and alkynes. As exemplified in **Scheme 2**, all the reactions proceeded efficiently to completion, and the products were isolated in good to excellent yields with high purity. As expected, the reaction of benzyl, aryl and aliphatic azides with aromatic acetylene afforded the corresponding triazole products in excellent yields (90−97%; **Scheme 2**). In addition to aromatic acetylenes, aliphatic acetylenes are also suitable substrates to produce 1,4-disubstituted 1,2,3-triazoles in 90- 94% (**Scheme 2**, entries 3f-3h, 3r) yields under the same reaction condition. Pleasantly, a variety of reactive functional groups were tolerated, including alcohol, ester functionalized alkyne also delivered the expected product in superior yields under our optimized conditions.



Scheme 2. Silver (I) catalyzed azide–alkyne cycloaddition reaction.

A plausible mechanistic cycle involving $AgN(CN)_2$ as catalyst is depict in **Scheme 3**. Since the tertiary amine functions as both a ligand and a base in CuAAC reactions,[18] here DIPEA contribute a same role in the intermediate step. We propose that the catalytic cycle begins with the formation of silver phenyl acetylide by DIPEA and then DIPEA act as a ligand to give **A**. Nucleophilic attack on **A** by the azide generates **B** and the process proceed through the pathway commonly accepted for this transformation to form a transient silver metallacycle shown as **C**.[9b] Subsequent migration of nitrogen to carbon and protonation leads to the formation of triazole. The observed regioselectivity is due to a probable steric effect where the methyl groups of isopropyl unit of DIPEA efficiently protect one side of the silver metal, thereby blocking the cycloaddition to give up the sterically more crowded 1,5- disubstituted product.



Scheme 3. Proposed catalytic cycle for the Ag(I)-catalyzed AAC reaction.

In summary, a simple and efficient method was effectively developed for synthesizing 1,4-disubstituted 1,2,3-triazoles using $AgN(CN)_2$/DIPEA as catalyst in H_2O/ethylene glycol at room temperature without the exclusion of air. The ease and efficiency of this catalyst system has been successfully demonstrated and we envision that this procedure may release exciting perspectives for use in various synthetic applications.

Acknowledgement

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18. Shao, C.; Wang, X.; Zhang, Q.; Luo, S.; Zhao, J.; Hu, Y. *J. Org. Chem.* **2011**, *76*, 6832-6836.
19. ***Synthesis of Silver Dicyanamide:*** Sodium dicyanamide (1 g, 11.2 mmol) was dissolved in deionized water (20 mL). Silver nitrate (1.9 g, 11.2 mmol) was also dissolved in deionized water (20 mL) and the two solutions were mixed together at room temperature. A white precipitate of silver dicyanamide was formed, filtered and washed with deionized water twice to eliminate the residual sodium nitrate. The resulting material was dried in a vacuum oven at 80 ℃ overnight to remove the trace amount of water. Silver dicyanamide (1.92 g) was obtained as a white powder with a yield of 98 %.
20. ***General procedure for the synthesis of 1,4-disubstituted-1H-1,2,3-triazole:*** To a mixture of azide (1 mmol, 1 equiv.) and acetylene (1.1 mmol, 1.1 equiv.) in H_2O/ethylene glycol (1:1, 2 mL) was added sequentially catalyst $AgN(CN)_2$ (5 mol%) and DIPEA (1mmol.) The mixture was stirred at room temperature for the given time period as mentioned in scheme 2. The progress of the reaction was monitored by TLC. After completion of the reaction it was extracted with EtOAc (2x20 mL), washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified through silica gel column chromatography (10–20% EtOAc/hexanes) to afford the desired product.

Graphical Abstract

$AgN(CN)_2$/DIPEA/H_2O-EG: a highly efficient catalytic system for synthesis of 1,4-disubstituted-1,2,3 triazoles at room temperature

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