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Aqueous bile salt accelerated cascade synthesis of 1,2,3-triazoles from arylboronic acids

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ABSTRACT

A facile, efficient and mild copper catalyzed strategy for cascade synthesis of various 1,4disubstituted 1,2,3-triazoles from arylboronic acids, sodium azide and alkynes was developed by using aqueous bile salt NaDC solution as an accelerating medium. Low catalyst loading (only 1 mol% Cu source was sufficient for in situ generation of azide followed by azide-alkyne coupling), green solvent, use of bio-surfactant as additive and short reaction time make this protocol highly accessible and environment friendly.

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Introduction

1,2,3-triazoles are nitrogen based five-membered heterocycles and indispensable motif in medicinal chemistry displaying wide array of biological activities.¹ The application of 1,2,3-triazoles is also extended to other areas such as organic synthesis, chemical biology, polymer, and materials science.² The Cu(I) catalyzed azide-alkyne cycloaddition (CuAAC) has emerged as the most reliable way to access 1,4-disubstituted 1,2,3-triazoles.³ Ever since its discovery in 2002, CuAAC has been explored as a tool for bioconjugation,⁴ drug development,⁵ selective modification of enzymes,⁶ construction of simple to complex molecular architecture.⁷ Despite having wide utility, handling of azides especially of lower molecular weight still remains a matter of concern as organic azides are infamous for their instability and explosive nature. Furthermore, preparation of organic azides from their diazonium salts⁸ or the reactions of organometallic aryls with p-tosyl azide9 is not very straightforward. Thus, a three component one pot synthesis of triazoles from in situ generated organic azides from suitable precursor like arylboronic acids allows competent production of complex molecules in a single step. In this context, Guo et al.¹⁰ in 2007 reported such a protocol using CuSO₄/Na-ascorbate catalytic system. Similarly, the Yang group¹¹ showed efficient coupling of arylboronic acid with propiolic acid/calcium carbide as alkyne precursors while Cao and co workers¹² described the use of active methylene ketones in one-pot synthesis of 1,4,5-trisubstituted 1,2,3-triazoles. In the past decade, a number of one-pot multi component synthetic protocols based on different copper catalyst were developed.

These catalysts include Cu(II)-β-cyclodextrin nano complex,¹³ Cu immobilized on various solid support like clay,¹⁴ chitosan,¹⁵ Cu on basic alumina¹⁶ in ball milling apparatus. Most of these strategies require long reaction time, use water along with organic solvents or require high temperature for efficient reactivity. Moreover, the heterogeneous systems lack convenient selectivity, simplicity of homogenous systems.

Considering environmental constrains in the use and disposal of organic solvents in chemical transformations, efforts have been made to perform reaction in aqueous medium.¹⁷ However, poor solubility of organic substrates restricts reaction in purely aqueous media. In order to improve the kinetics reaction is performed at interface of biphasic system or by mere incorporation of surfactants to enhance solubility of immiscible reactants. Few catalytic systems have been developed recently demonstrating micellar solution as excellent promoting media for 1,4-disubstituted triazole synthesis.¹⁸ Although surfactant mediated CuAAC is not new in the era of triazole synthesis however example of bio-surfactant as promoter is scanty. Hence we are interested to use a green alternative bio-surfactant for one pot synthesis of triazole.

Sodium deoxycholate (NaDC), a dihydroxy bile salt, unlike other classical surfactants contains a tetracyclic steroidal nucleus as hydrophilic part while two hydroxyl group and a carboxyl group form the polar hydrophilic part. Bile salts play a crucial role in emulsifying dietary lipids and solubilization of cholesterols and fat-soluble vitamins in intestines.¹⁹ As a representative example of potential bio-surfactant micellar

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properties of NaDC have been widely investigated.²⁰ Raghavan *et al.*²¹ demonstrated NaDC as a gel inducer for organo gelation process while new NaDC-heparin NPs were developed by Lee and coworkers²² for *in vivo* tumour targeting and drug delivery. Interestingly no report has been found accessing NaDC as a potent amphiphile in organic synthesis. In pursuit of greener reaction conditions, we herein presented an efficient, inexpensive and novel protocol with wide applicability in terms of substrates scope with varied functional group tolerance for CuAAC using commercially available sodium deoxycholate solution as promoting micellar media. To the best of our knowledge, this is the first report using aqueous bio-surfactant as green environment friendly micellar medium for one pot synthesis of 1,4-disubstituted triazoles.

Results and discussion

We initiated investigation of cascade synthesis of 1,4disubstituted 1,2,3-triazole with phenyl boronic acid 1a, sodium azide (3 eq.) and phenyl acetylene 2a (Table 1) as model substrate in aqueous medium, using 5 mol% of Cu(OAc)₂ as Cucatalyst (entry 1, Table 1) in air at room temperature. However, the in situ generated phenyl azide from the reaction mixture of phenyl boronic acid and NaN3 did not react well with phenyl acetylene in pure water. Interestingly, employing aqueous NaDC solution the reaction swiftly forms 3a with 95% isolated yield (entry 2, Table 1) within 30 minutes without formation of any by-product. Encouraged by this endeavor, we have screened few more copper catalysts including CuSO₄·5H₂O, Cu(NO₃)₂ and CuBr which give the desired triazole satisfactorily with 89%, 77%, 76% yields (entries 3-5, Table 1) respectively. Cu(I) salts like CuI, CuCN show relatively inferior results (entries 6 and 7, Table 1).

Table 1. Optimization of reaction conditions.^a

		eq) N	=N
	B + NaDC(50	mM)	Ű ()
	1a 2a air, ri		3a
Entry	Change from above condition	Time	Yield
		(h)	[%] ^b
1	H ₂ O	4	40
2	none	30 min	95
3	with 5 mol% CuSO4.5H2O [instead	ad 30 min	89
	of Cu(OAc) ₂]		
4	with 5 mol% Cu(NO ₃) ₂ [instead of	of 1	77
	Cu(OAc) ₂]		
5	with 5 mol% CuBr [instead of	1	76
	Cu(OAc) ₂]		
6	with 5 mol% CuCN [instead of	1	44
	Cu(OAc) ₂]		
7	with 5 mol% CuI [instead of	1	47
	Cu(OAc) ₂]		
8	Methanol	1	38
9	DCM	1	15
10	DMF	1	18
11	With 2 mol% Cu(OAc) ₂	1	94
12	With 1 mol% Cu(OAc) ₂	1	94
13	With 0.5 mol% Cu(OAc) ₂	12	65
14	With 0.2 mol% Cu(OAc) ₂	12	25
15	No Cu(OAc) ₂	24	0
16	With 30 mM NADC	5	82
17	With 10 mM NADC	5	75
18	With 5 mM NADC	5	54

^a Reaction condition: Phenylboronic acid **1a** (1 mmol), NaN₃ (3 eq), phenyl acetylene **2a** (1 mmol) in 2 mL NaDC solution. ^b Isolated yield of product **3a**.

Screening of a series of solvents showed that in both polar and non polar solvents (entries 8-10, Table 1) reaction is little slow indicating better reactivity of the reacting substances under aqueous condition. Decreasing the catalyst loading up to 1 mol% (entries 11-12, Table 1) furnished the triazole product with promising 94% yield within 1 hour. Further decreasing catalytic loading resulted in poor conversion even after increasing reaction time up to 12 hours (entries 13-14, Table 1). Similarly, exclusion of copper catalyst did not form any product (entry 15, Table 1). The concentration of NaDC found to play a crucial role. Reduction in concentration of NaDC solution affected reactivity; even prolonged reaction time fails to produce triazoles satisfactorily. Therefore, we have chosen to proceed further with 50 mM solution of surfactant.

Further, in order to study the role of surfactant four different cationic, anionic as well as neutral surfactants (**Figure 1**)²³ solutions were screened (**Table 2**). It was observed that with cationic surfactants like cetyltrimethylammonium bromide (CTAB) and cetylpyridinium chloride (CPC), poor triazole yields were obtained (**entries 1-2, Table 2**). While with anionic surfactants Triton X-100 triazole product was obtained in good yield (**entries 3 and 5, Table 2**). Remarkably, none of these micellar additives proved superiority to NaDC.



Figure 1: Chemical structures of surfactant used.

Table 2: Screening of different surfactants^a

OH	+ / -	NaN ₃ (3 eq) Cu(OAc) ₂ (1 mol%)	N=N N	
∖/_⊾`он		Surfactant (50 mM)		
1a	2a	aır, rt	3a	
Entry	Surfactant	Time (h)	Yield[%] ^b	
1	CTAB	2	52	
2	CPC	2	47	
3	SDS	2	75	
4	NaDC	1	94	
5	Triton X-100	2	84	

^a Reaction conditions: Phenylboronic acid **1a** (1 mmol), NaN₃ (3 eq), phenyl acetylene **2a** (1 mmol) in 2 mL surfactant (50 mM).

^bIsolated yield of product **3a**.

As 1 mol% of $Cu(OAc)_2$ in NaDC solution standout to be sufficient to afford triazole product in short reaction time with desired efficiency, it was chosen as optimum condition to carry out one pot synthesis of 1,4-disubstituted 1,2,3-triazoles.

With the optimized condition based on Cu(OAc)₂/NaDC catalytic system in hand, an array of aryl boronic acids was subjected to the three-component cascade reaction with different aromatic alkynes and sodium azide in water at room temperature under similar condition. As illustrated in **Table 3**, both the electron-rich and the electron-deficient arylboronic acids showed an excellent

reactivity and furnished the products in high yields (entries 3a-3o, Table 3) at room temperature. It is noteworthy that the catalytic system was tolerant to a wide range of functional groups, such as $-OCH_3$, $-CH_3$, $-NO_2$, -CN, $-CF_3$, and -X and delivered the products under aerobic conditions. However, aliphatic boronic acid like *iso*-butyl boronic acid did not react owing to difficulty in formation of corresponding azide with sterically crowded hydrocarbon chain in aqueous solution.²⁴

The reaction of arylboronic acid with different aliphatic, acid, ether and ester functionalized alkynes were tested, which proceed swiftly with excellent yields (**entries 3p-3t, Table 3**). Furthermore, arylboronic acids showed excellent reactivity with internal alkynes producing 1,4,5-trisubstituted triazoles with excellent yields (**entries 3u,3v, Table 3**).

Table 3: Cascade synthesis of 1,4-disubstituted 1,2,3-triazoles

 from different boronic acids^a





^aReaction conditions: Phenylboronic acid **1a** (1 mmol), NaN₃ (3 eq), phenylacetylene **2a** (1 mmol), Cu(OAc)₂ (1 mol%) in 2 mL NaDC (50 mM) for 1h. (Isolated yields are given).

Catalytic efficiency of our protocol was further tested by employing heteroaryl boronic acids (**entries 3w, 3x, Table 3**) as coupling partners for cycloaddition and found that heterocyclic systems also worked well furnishing desired triazole products with >80% yields.

Reaction rate enhancement by the use of NaDC is typically due to formation of micelle in water which serves as micro reactor vessel allowing close contact between the hydrophobic organic substrates. The organic substrates under influence of electrostatic interaction of anionic surfactant readily move to the hydrophobic region induced by the micelle. In the micellar core, effective collision among the reacting substances in presence of copper catalyst leads to formation of the product. Usually micellization is favoured by combined effect of electrostatic interaction and hydrogen bonding interaction working simultaneously. In case of NaDC micellar aggregates are formed in two distinct stages under different concentrations. At relatively lower concentration (5-15 mM) primary micellization occurs by hydrophobic interactions while much larger polymeric secondary micellization occurs via hydrogen bonding interactions among the primary micelles at relatively higher surfactant concentrations (~50 mM).^{25,26} Concentration of NaDC plays a significant role in reaction kinetics. When reaction was performed at slightly higher concentration than that of primary critical micelle concentration (CMC) of NaDC, conversion into product required longer time with slightly diminished yields (entries 16-18, Table 1). This observation is clearly perceived due to smaller size of primary micelles with very low aggregation number²⁰ allowing smaller interfacial regions for reacting substance to undergo collision. However superior reactivity was observed at concentration near second CMC of NaDC when polymeric micelles with larger aggregation provide sufficient hydrophobicity to organic substrates allowing frequent collision under larger surface.

To draw evidence in support of our observation dynamic light scattering (DLS) and zeta potential measurements were performed. The intensity weighted size distribution showed that average diameter of micellar surfactant (50 mM) is 312.5 nm (**Figure 2a**) with polydispersity index (PDI) of 0.585 likely due to formation of secondary micelles. While performing the same measurement in presence of reacting substances revealed quite larger micellar diameter from 2.67-5.66 μ m with an average of 4.57 μ m having PDI 0.230 indicating trend towards monodispersity and uniform size distribution (**Figure 2b**). This larger micellar size supports encapsulation of reacting substances within hydrophobic region induced by NaDC micelles. Moreover, small negative zeta potential value of the reaction media (-0.483 mV) also indicates decrease in surface charge owing to formation of stable large micellar aggregates.

To further confirm micellar aggregation in aqueous solution we analyzed aliquot of aqueous solution of the bile salt under binocular microscope. The microscopic images showed that prior to addition of reacting substances polymeric micelle of irregular

shapes (**Figure 2c**) were formed spontaneously which is consistent with literature reports.^{20b,26} After addition of reacting substances micellar shapes become larger and more regular which compliments to our earlier observation (**Figure 2d**).



Figure 2: Size of NaDC micelles in absence (a) and presence (b) of reacting substances determination by DLS measurement. Optical microscopic images of NaDC micelles before (c) and after (d) addition of substrates.

Based on literature reports^{15,27} a plausible mechanism for one pot CuAAC has been proposed (**Figure 3**) wherein NaN_3 plays the role of azide precursor and reducing agent as well for generation of active copper(I) catalyst for CuAAC.



Figure 3: Plausible reaction mechanism.

Conclusion

In summary, we have presented a highly efficient one pot cascade synthetic protocol for triazole synthesis under micellar condition. This protocol shows excellent tolerance to various functional groups and can be successfully extended to hetero arylboronic acids as well as internal alkynes with low catalyst loading. Use of bio-surfactant sodium deoxycholate solution as micellar medium to promote CuAAC reaction greatly increases the green credentials of the method and establishes a green alternative to the existing protocols using classical synthetic surfactants.

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- 23. Concentration of surfactants is chosen as 50 mM which is well above critical micelle concentration (CMC) of all the surfactants. Micellar solutions of different surfactants were prepared by dissolving requisite amounts of solid or liquid surfactants in 100 ml deionized water.
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- 28. To a mixture of Cu(OAc)² (0.244 mg, 0.01 mmol) phenylboronic acid (1 mmol) and sodium azide (3 equiv) phenyl acetylene (1mmol) was added in 2 mL aqueous solution of NaDC (50 mM) and stirred at room temperature for 1 h. After completion of the

reaction it was extracted with ethyl acetate (2×10 mL), washed Acctebric with brine, dried over anhydrous sodium sulphate and concentrated under vacuum, which on column chromatography (silica gel, EtOAc: n-Hexane = 1:3) afforded the desired product. The products are characterized by ¹H, ¹³C NMR and ESI-

HIGHLIGHTS

1. Commercially available inexpensive bile salt sodium deoxycholate accelerates the reaction.

Accepter 2. generation of azide and azide-alkyne coupling.

3. The methodology offers broad substrate scope of products with good to excellent yields.