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An enolate-mediated regioselective synthesis of 1,2,3-triazoles via azide-aldehydes or ketones [3+2]-cycloaddition reactions in aqueous phase

Anupam Tripathi, Chandrashekhar V. Rode, Jordi Llop, Subhash P. Chavan, Sameer M. Joshi

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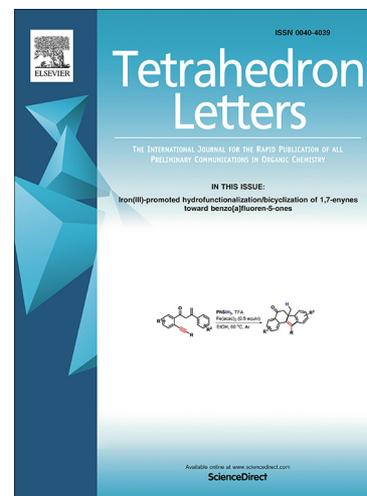
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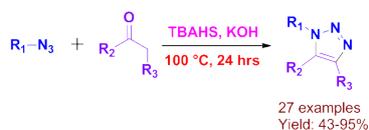
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An enolate-mediated regioselective synthesis of 1,2,3-triazoles via azide-aldehydes or ketones [3+2]-cycloaddition reactions in aqueous phase

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An enolate-mediated regioselective synthesis of 1,2,3-triazoles via azide-aldehydes or ketones [3+2]-cycloaddition reactions in aqueous phase

Anupam Tripathi,^a Chandrashekhar V. Rode,^b Jordi Llop,^c Subhash P. Chavan^{a*} and Sameer M. Joshi^{ad*}

a. Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune 411008, India.

a. Academy of Scientific and Innovative Research (AcSIR), New Delhi 110025, India

b. Chemical Engineering & Process Development Division, National Chemical Laboratory, Dr HomiBhabha Road, Pune 411008, India

c. Radiochemistry and Nuclear Imaging, CIC biomaGUNE, Paseo Miramón 182, 20014 San Sebastián, Spain.

d At present: Department of Oncology, Wayne State University, Detroit, Michigan 48202, United States

**E-mail: Sameer M. Joshi (sameer.joshi3@wayne.edu), Subhash P. Chavan (sp.chavan@ncl.res.in). Electronic Supplementary Information (ESI) available: Characterization details of 1,2,3-triazoles by ¹H and ¹³C NMR. See DOI: 10.1039/x0xx00000x*

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ABSTRACT

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A synthetic route for the direct conversion of arylazides into the corresponding triazoles via phase transfer catalyst-assisted [3+2] cycloaddition reaction under basic conditions in aqueous medium is reported. This synthetic methodology, which offers high yields and excellent regioselectivity for varieties of triazoles at 100 °C for 24 hr- 48 hr and this 'greener' synthesis constitutes an alternative to the previously reported well established click reactions.

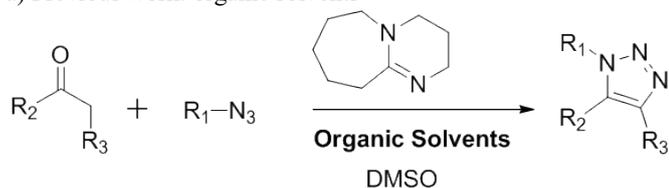
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* Corresponding author.; e-mail: sameer.joshi3@wayne.edu (S. M. Joshi)

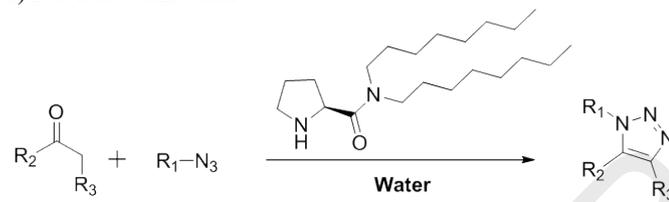
triazoles has been widely used for more than a century^[1,2], and has been extensively applied to the preparation of 1,4- and 1,5-disubstituted 1,2,3-triazoles, which find application in a broad range of industrial and societal sectors^[3]. Early works to achieve regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles was carried out by Meldal and Sharpless' groups using copper catalyzed azide-alkyne [3+2] cycloaddition (CuAAC) reactions^[4], while regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles can be carried out by ruthenium-catalyzed azide alkyne cycloaddition (RuAAC) reactions^[5]. Very recently, nickel-catalyzed azide-alkyne cycloaddition (NiAAC) to yield 1,5-disubstituted 1,2,3-triazoles in aqueous media has been described^[6].

Among triazoles, 1,4-diaryl-5-methyl(alkyl)-1,2,3-triazoles have shown promise in the pharmaceutical sector. However, the development of regioselective synthetic procedures for their preparation has not been thoroughly explored. One alternative involves the reaction of metal acetylide (metal= Li, Mg, Zn or Te) with an organic azide and its subsequent *in situ* reaction with an electrophile to form a metalated triazole with reverse selectivity and high reactivity^[7]. Palladium- or copper-catalyzed reactions^[8], in the presence of arylboronic acid or aryltrifluoroborates^[9], and reaction of aryl azides with active methylenes or symmetrical ketones at high temperature have also been described^[10]. Of note, most of the above mentioned methods employ costly or non-commercial substrates instead of using simple starting materials such as phenylacetaldehyde or arylacetones.

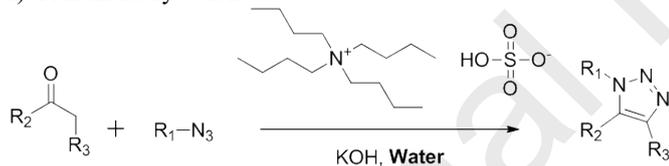
a) Previous work: organic solvents



b) Previous work: water



c) Present study: water



Scheme 1. (a) Reaction reported in previous work^[11]. When $R_1=R_3=Ph$ and $R_2=H$, yield = 5% in water; (b) similar kind of work in water^[12a] and (c) reaction reported in this work, When $R_1=R_3=Ph$ and $R_2=H$, yield = 77% and When $R_2=Ph$, yield = 95%.

Organocatalytic azide-aldehyde^[11] and azide-ketone^[13a,14]

reactions using [3+2] cycloaddition to furnish 1,4-disubstituted 1,2,3-triazoles have been reported. However, their application is limited to organic solvents. Previous attempts to conduct the reaction in aqueous media show limited scope (i.e. simple ketones such as cyclohexanone), and require the use of organocatalysts with long aliphatic chains^[12a]. The outcome becomes more dramatic when translated to cycloaddition reactions involving azides and aldehydes. For example, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)-promoted azide-aldehyde reaction results in less than 5% yields in water (Scheme 1a)^[11]. Still, the use of water as the solvent as reported by Yeung et al^[12a] would be highly desirable to achieve environmental-friendly, easy to scale up synthetic routes. Recently, we have described the preparation of ¹³N-labelled azides^[15], triazoles^[16], and tetrazoles^[17] under catalytic conditions. In continuation of our work, we here present a azide-aldehydes or ketones [3+2]-cycloaddition reactions for the synthesis of triazoles in water as a green solvent (Scheme 1b).

Initially, the reaction between phenyl azide and phenyl acetaldehyde was assayed as a model reaction using different bases, catalysts and reaction conditions, and using water as the only solvent. In the absence of catalyst, the formation of the desired triazole was not observed (Table 1, entries 1 and 3), and identical results were obtained when only TBAHS was added as the catalyst (Table 1, entry 2). Simultaneous addition of KOH and K_2CO_3 resulted in the formation of the corresponding triazole in trace amount (Table 1, entry 4).

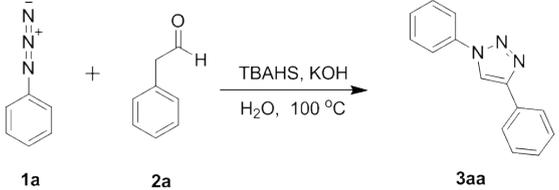
Previous works have shown that phase transfer catalyst (PTC) such as TBAHS can be used under aqueous basic conditions to achieve metal-free reactions of amides with peroxides^[18]. Therefore, we decided to explore the suitability of this catalyst to achieve the desired triazole. In the presence of TBAHS, moderate yields (64%, 61% and 69%) were obtained when potassium, sodium and caesium carbonates, respectively, were used as the base, and the reaction was conducted at 100°C for

respectively (Table 1, Entries 8 and 9). The addition of a stronger base such as NaOH resulted in yields equivalent to those obtained with carbonates (61%; Table 1, entry 10), although this value increased to 77% when KOH was used (Table 1, entry 11). The use of alternative catalysts including tetrabutylammonium bromide (TBAB) and tetrabutylammonium iodide (TBAI) resulted in slightly lower yields (66% and 62%, respectively; Table 1, Entries 12 and 13).

The effect of the concentrations of the catalyst and the base was also investigated. While lowering the concentrations of catalyst and base to 10 mol% and 0.21 mmol, respectively, resulted in moderately lower yields (45%; Table 1, entry 14), an increase in the amount of both the base and the catalyst did not positively affect the yield (Table 1, entry 15). Later, the effect of the temperature was also explored. Our results clearly show that lower reaction temperatures dramatically decrease reaction yields (Table 1, entries 16 and 17).

We next explored the substrate scope of our reaction by reacting a variety of carbonyl compounds with phenyl azide (Table 2). Aliphatic aldehydes did not yield the desired triazoles under our experimental conditions (Table 2, entries 3 and 4), probably due to the lower acidic character of the alpha methylene groups, which hampers the formation of the enolate intermediate. However, the formation of the product was achieved when hydrocinnamaldehyde was used, in spite of the presence of one additional methylene group (59%, Table 2, entry 2). The reaction was also unsuccessful in the case of aliphatic esters (Table 2, entries 5 and 6). Finally, we explored the reactivity of ketones and almost quantitative yields were obtained (Table 2, entries 7 and 8). As in the case of esters, the enolate ion is resonance-stabilised in ketones. However, the negative charge of the conjugate base of the ester is stabilized by the same oxygen atom whose lone pair is involved in the resonance, resulting in a lower effectiveness. Overall, this results in a higher stability of the conjugate base of the ketone, leading to the formation of a more acidic compound which favours the formation of the triazole.

Table 1 Optimization of reaction between arylazide and aldehyde^[a]



Entry	Base ^[b]	Catalyst ^[c]	t/h	T/°C	Yield(%) ^[d]
1	none	none	24	100	0
2	none	TBAHS	24	100	0
3	K ₂ CO ₃	none	24	100	0
4	KOH	K ₂ CO ₃	24	100	10
5	K ₂ CO ₃	TBAHS	24	100	64
6	Na ₂ CO ₃	TBAHS	24	100	61
7	Cs ₂ CO ₃	TBAHS	24	100	69
8	NaHCO ₃	TBAHS	24	100	25
9	KHCO ₃	TBAHS	24	100	42
10	NaOH	TBAHS	24	100	61
11	KOH	TBAHS	24	100	77
12	KOH	TBAB	24	100	66
13	KOH	TBAI	24	100	62
14 ^[e]	KOH	TBAHS	24	100	45
15 ^[f]	KOH	TBAHS	24	100	75
16	KOH	TBAHS	24	50	48
17	KOH	TBAHS	48	RT	21

[a] All reactions were carried out with 1a (0.21 mmol), 2a (0.21 mmol) in presence of TBAHS (0.042 mmol) and KOH (0.42 mmol) in water (1.0 mL); [b] 0.42 mmol; [c] 0.042 mmol; [d] Isolated yields after column chromatography; [e] catalyst- 10 mol% and KOH- 0.21 mmol; [f] catalyst- 30 mol%; TBAHS: Tetrabutyl ammonium hydrogen sulfate; TBAB: Tetrabutylammonium bromide; TBAI: Tetrabutylammonium iodide.

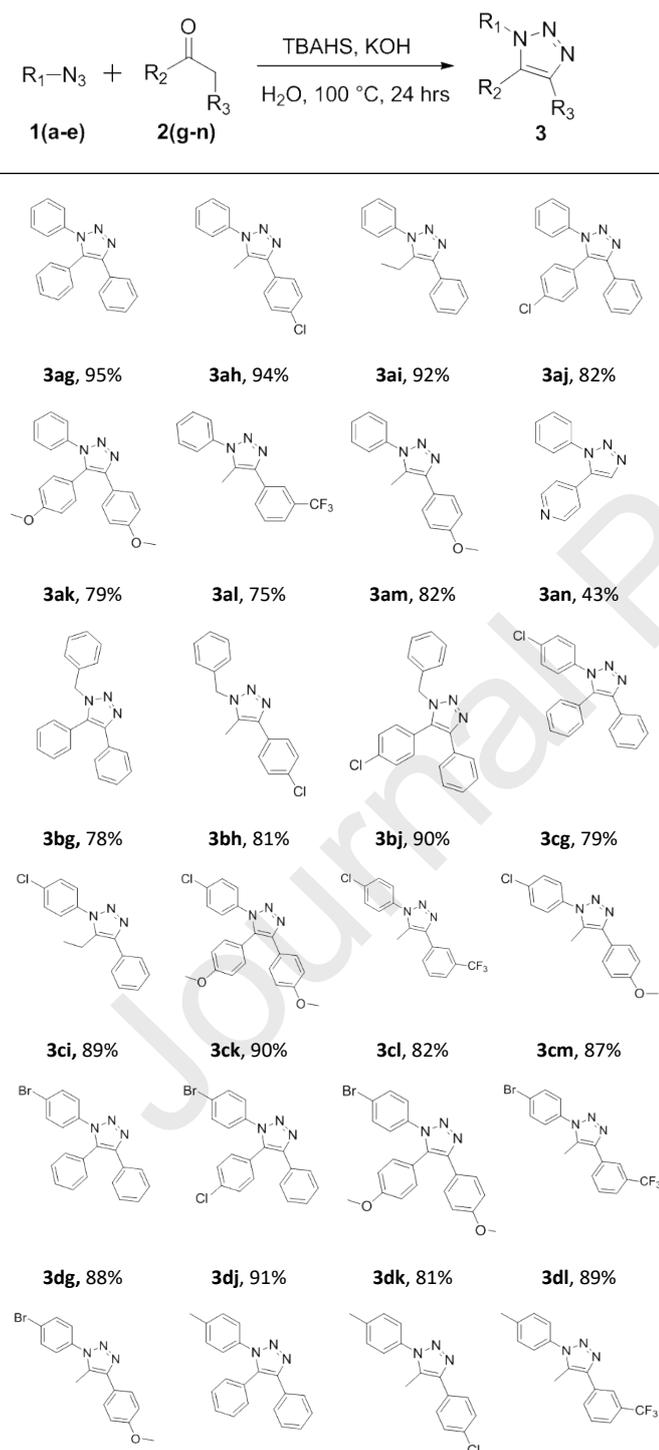
Table 2 Scope of carbonyl compounds^[a]

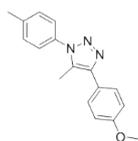


	R ₃	R ₂	compd		(%) ^[b]
1	Ph	H	2a	3aa	77
2 ^[c]	PhCH ₂	H	2b	3ab	59
3	Me(CH ₂) ₂	H	2c	3ac	0
4	Me(CH ₂) ₃	H	2d	3ad	0
5	MeCO	OCH ₂ CH ₃	2e	3ae	0
6	MeCO	OCH ₃	2f	3af	0
7	Ph	Ph	2g	3ag	95
8	4-ClC ₆ H ₄	CH ₃	2h	3ah	94

[a] All reactions were carried out with 1a (0.21 mmol), 2 (0.21 mmol) in presence of TBAHS (0.042 mmol) and KOH (0.42 mmol) in water (1.0 mL) at 100 °C for 24 hr. [b] Isolated yields after column chromatography. [c] Reaction time: 48 hr.

Table 3 Substrate scope^[a]



**3em, 84%**

[a] All reactions were carried out with **1** (0.21 mmol), **2** (0.21 mmol) in presence of TBAHS (0.042 mmol) and KOH (0.42 mmol) in water (100 °C, 24 hr).

Table 4 Substrate that doesn't work^[a]

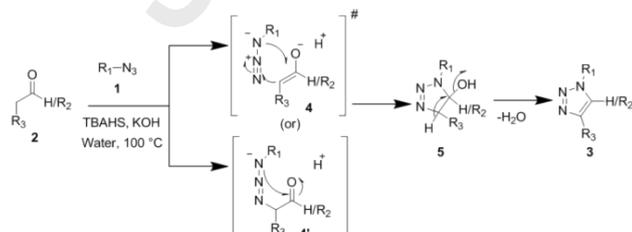
3ao, 0%	3ap, 0%	3fg, 0%

[a] All reactions were carried out with **1** (0.21 mmol), **2** (0.21 mmol) in presence of TBAHS (0.042 mmol) and KOH (0.42 mmol) in water (100 °C, 24 hr).

Encouraged by these results, we investigated the reactivity of different ketones (Table 3, 2g-2n) with different arylazides (Table 3, 1a-1e). Cycloaddition reactions proceeded smoothly, irrespective of the electronic properties of the substituents on the aromatic rings. The presence of both electron withdrawing groups such as chloro and bromo at the *p*- position (Table 3, 3cg-3dm), electron-donating groups like methyl moieties at the *p*- position (Table 3, 3eg-3em), or electron-neutral groups (Table 3, 3ag-3an) on the phenyl azide yielded the corresponding triazoles in very good yields. Notably, high yields were also obtained with benzyl azide (Table 3, 3bg-3bj).

The effect of substituents on the ketone was also explored. When substituted phenyl acetones were used, good yields were obtained irrespective of the substituents on the aromatic rings. The presence of electron withdrawing groups such as chloro and trifluoromethyl at the *p*- and *m*-positions, resulted in 94% and 75% yields, respectively (Table 3, 3ah and 3al). Similar results were obtained with electron donating groups such as methoxy at the *p*- position of the phenyl rings (Table 3, 3am, 3cm, 3dm and 3em) In addition, aromatic ketones containing two methoxy groups also did not affect the reaction rate and which delivers corresponding triazoles in higher yields. (3ak, 3ck and 3dk). 1-Phenyl-2-butanone also resulted in excellent yields (Table 3, 3ai and 3ci). Pleasingly, the best yield was obtained with 2-Phenylacetophenone, which afforded the desired triazole in 95% isolated yield (Table 3, 3ag). However, 4-acetyl pyridine having low reactivity since lack of extra methylene group next to carbonyl group which afforded corresponding triazole only in 43% yield (Table 3, 3an). As expected, alkyl ketones, namely 2-butanone and 2-octanone, did not yield the formation of the triazole (Table 4, 3ao and 3ap), due to the low acidic character of alpha-methylene groups in comparison with aromatic ketones, which hampers the formation of the enolate ion for the subsequent [3+2] cycloaddition reaction. Also reaction was unsuccessful, when it is performed in presence of sulfonylazides (Table 4, 3fg). The results in Table 3 demonstrate the broad scope of this synthetic approach covering a structurally diverse group of aryl azides 1(a-e) and aromatic ketones 2(g-n). It is worth mentioning that, the high yields are even more impressive considering that water was the only solvent. Overall, our methodology has proven robust and demonstrated by the preparation of twenty-seven different triazoles, fourteen of them reported for the first time.

The exact reaction mechanism remains to be explored. However, we hypothesize that the reaction of phase transfer catalyst (PTC) with aldehyde/ketone **2** under basic conditions, forms the enolate ion intermediate **4** or **4'**, which subsequently reacts with R_1-N_3 (**1**) rapidly to yield the 1,2,3-triazoline adduct **5** *via* concerted or stepwise [3+2] cycloaddition amination-cyclization reaction.^[11,13a] Adduct **5** then yields the corresponding 1,2,3-triazole **3** by loss of a water molecule (dehydration) (Scheme 2).

**Scheme 2.** Plausible reaction mechanism.

In conclusion, we have developed a simple, versatile, and green route for enolate-mediated azide-aldehyde or ketone [3+2]-cycloaddition reaction which enables the synthesis of 1,4-disubstituted 1,2,3-triazoles containing a variety of functional

(PTC)-assisted catalytic synthetic approach described here provides a stepping stone towards a greener organic synthesis in pharmaceutical industries.

Experimental:

1, 4-Diphenyl-1H-1, 2, 3-triazole (3aa): Typical procedure

In an ordinary glass tube equipped with a magnetic stirring bar, to phenylacetaldehyde (25.2 mg, 0.21 mmol, 1 equiv.), TBAHS (14 mg, 0.042 mmol, 20 mol %) and potassium hydroxide (23 mg, 0.42 mmol, 2 equiv.) were added successively in Milli-Q water (1.0 mL) at room temperature. Finally, corresponding phenylazide (25mg, 0.21 mmol, 1 equiv.) was added to above reaction mixture. This reaction mixture was stirred at room temperature for 2 minutes which was subsequently heated for 24 hours at 100 °C. The reaction progress was monitored by TLC and after consumption of starting aldehyde, reaction mixture was cooled to room temperature. The crude reaction mixture was extracted with ethyl acetate (3 x 7 mL). These combined mixtures of organic layers were dried over sodium sulfate, filtered and concentrated. Pure product **3aa** was obtained by column chromatography (silica gel, mixture of ethyl acetate/petroleum ether) and was isolated as a white solid. 35 mg, 77% yield. 1,4,5-Triphenyl-1H-1,2,3-triazole (3ag): Typical procedure

In an ordinary glass tube equipped with a magnetic stirring bar, to 2-Phenylacetophenone (41.2 mg, 0.21 mmol, 1 equiv.), TBAHS (14 mg, 0.042 mmol, 20 mol %) and potassium hydroxide (23 mg, 0.42 mmol, 2 equiv.) were added successively in Milli-Q water (1.0 mL) at room temperature. Finally, corresponding phenylazide (25mg, 0.21 mmol, 1 equiv.) was added to above reaction mixture. This reaction mixture was stirred at room temperature for 2 minutes which was subsequently heated for 24 hours at 100 °C. The reaction progress was monitored by TLC and after consumption of starting ketone, reaction mixture was cooled to room temperature. The crude reaction mixture was extracted with ethyl acetate (3 x 7 mL). These combined mixtures of organic layers were dried over sodium sulfate, filtered and concentrated. Pure product **3ag** was obtained by column chromatography (silica gel, mixture of ethyl acetate/petroleum ether) and was isolated as a white solid. 59 mg, 95% yield. This particular reaction was also reproducible in tap water.

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Appendix A. Supplementary data

Supplementary to this article can be found online at <http://dx.doi.org/10.1016/j.tetlet.2019>.

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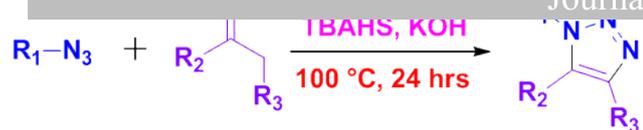
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Declaration of interests

✓ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

✓ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:



27 examples
Yield: 43-95%

- ❖ Click Chemistry: Azide-Aldehyde/Ketone
- ❖ Excellent Regioselectivity
- ❖ High Efficiency
- ❖ Broad Substrate Scope
- ❖ Green Solvent

Highlights

Bullet points

click chemistry

azides + aldehydes or ketones

triazoles

water