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Synthesis of functionalized 1,2,3-triazoles using Bi_2WO_6 nanoparticles as efficient and reusable heterogeneous catalyst in aqueous medium†

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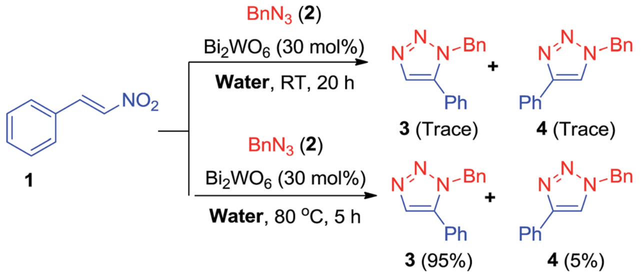
Synthesis of functionalized triazoles is reported *via* Bi_2WO_6 nanoparticle (10 mol%) mediated 1,3-dipolar cycloaddition reactions of β-nitrostyrenes, phenylacetylene and chalcones with azides (80 °C, 2–6 h) in water. The regioselective formation of 1,4-disubstituted triazoles was achieved in 5–20 minutes using azides and alkynes in presence of $CuSO_4 \cdot 5H_2O$ (2 mol%), sodium ascorbate (10 mol%) and Bi_2WO_6 nanoparticles (10 mol%) at room temperature in water. Similarly, regioselective synthesis of 1,4,5-trisubstituted triazoles was achieved from chalcones in aqueous medium.

1,2,3-Triazole is an important scaffold for organic, medicinal and materials chemistry. Huisgen 1,3-dipolar cycloaddition and copper mediated azide-alkyne cycloaddition (CuAAC, Click reaction) have contributed tremendously for the construction of 1,2,3-triazoles.[1,2] Subsequently, many alternative catalysts and conditions such as Cu-based nanomaterials,[3] solid supported copper,[4] Cu-based NHC complexes,[5] organometallic complexes[6] ionic liquids,[7] microwave,[8] solvent free[9] and metal free[10] conditions *etc.* have been developed for the click reaction. Recently, Ramachary *et al.*, developed the [3 + 2] cycloaddition of aldehydes and ketones *via* cascade/push–pull, enamine and enolate mechanisms under organocatalytic conditions.[11a,b] Similar to this Wang[11c,d] Bressy,[11e] and Márcio[11f] groups independently explored the organocatalysis for the synthesis of functionalized 1,2,3-triazoles using ketones (simple and α,β-unsaturated), and alkyledine melanonitriles. Dehaen,[12] Wang and Pan groups[13] reported the 1,3-dipolar cycloaddition reactions of nitro alkanes, β-nitrostyrenes and chalcones using morpholine/PTSA and $Ce(OTf)_3$. However, some of these reports use organic solvent or require prolonged times for completion of the reaction. Considering the importance of 1,2,3-triazoles and in continuation with our interest in heterogeneous catalysis in aqueous medium,[14] here in we report the application of Bi_2WO_6 nanoparticles as heterogeneous catalyst for the 1,3-dipolar cycloadditions of azides with β-nitrostyrenes, chalcones and phenylacetylene.

Thus, β-nitrostyrene (**1**) was reacted with benzylazide (**2**) in presence of Bi_2WO_6 nanoparticles (30 mol%) in water at room temperature (20 h) to give only trace amounts of the desired triazoles **3** and **4.** When the same reaction mixture was heated at 80 °C for 5 h the products **3** and **4** were obtained in 95% and 5% yields (Scheme 1). After confirming the structures of the isomeric products,[15] simultaneous experiments were conducted by varying solvent, reaction temperature and catalyst loading, (entries 1–9) along with the catalyst recyclability studies (entries 10–13) as shown in the Table 1.

Table 1 indicates the success of the reactions with 10 mol% catalyst (entry 8). Thus, different β-nitrostyrenes were treated with benzylazide (**2**) and phenylazide (**5**) using 10 mol% of catalyst to give 1,5-disubstituted triazoles **8–22** (Scheme 2) in good to excellent yields as shown in (Fig. 1). Further, to explore the reactivity of Bi_2WO_6 nanoparticles, different β-nitrostyrenes were reacted with NaN_3 under optimized conditions to give the 1*H*-1,2,3-triazoles **23–28** in 75–90% yields (Scheme 3). To



Scheme 1 Reaction of β-nitrostyrene (**1**) with benzyl azide (**2**) in presence of 30 mol% of catalyst (Bi_2WO_6).

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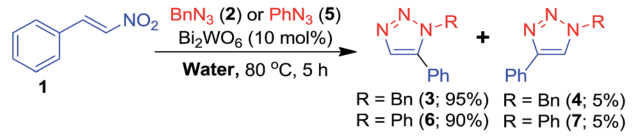
Table 1 Optimization of the reaction conditions (solvent, catalyst loading, temperature) and catalyst recyclability

S. no	Solvent	Temp. (°C)	Reaction time (h)	Catalyst loading (mol%)	Isolated yield[a] (%) ratio of **3** : **4**
1	Water	RT	20	30	Trace
2	DMF	RT	20	30	—
3	DMSO	RT	20	30	—
4	Toluene	50	10	30	50
5	Water	50	10	30	70
6	Water	80	5	30	95 : 5
7	Water	80	5	20	95 : 5
8	**Water**	**80**	**5**	**10**	**95 : 5**
9	Water	80	5	5	85 : 3
10	Water	80	5	10	95 : 5[b]
11	Water	80	5	10	93 : trace[c]
12	Water	80	5	10	90 : trace[d]
13	Water	80	5	10	85 : trace[e]

[a] Total yield of products **3** and **4**. [b] Cycle-1. [c] Cycle-2. [d] Cycle-3. [e] Cycle-4.

confirm the reaction pathway, separate experiments were performed using phenylacetylene (**29**) as coupling partner. Thus, the reaction of benzylazide (**2**) and phenyl acetylene (**29**) in presence of Bi_2WO_6 (10 mol%) at 80 °C for 2.5 h in water gave the triazoles (**3** and **4**) in 25% and 75% yields respectively. In a similar experiment, benzylbromide (**30**) and NaN_3 were treated with phenylacetylene (**29**) to give the desired triazoles (**3** and **4**) in 1 : 3 ratios as shown in Scheme 4. In order to achieve better selectivity, the classical copper-mediated click reaction was attempted in presence of Bi_2WO_6. Thus, different alkynes were treated with benzylazide (**2**) in presence of $CuSO_4 \cdot 5H_2O$ (2 mol%), sodium ascorbate (10 mol%) and Bi_2WO_6 (10 mol%) in aqueous medium at room temperature (Scheme 5). It was observed that the reaction went for completion within 5-20 min giving the 1,4-disubstituted triazoles (**4**, **7**, **33–35**) in 90–99% as single isomers. This remarkable activity of Bi_2WO_6 is due to presence of acidic and basic sites which are helping for the success of the reaction as shown in Fig. 2.

Since the reaction is giving the quantitative yield of triazole (**4**), attempts were made to test the recyclability of entire catalyst system [*i.e.* $Bi_2WO_6 + CuSO_4 \cdot 5H_2O$ + sodium ascorbate in water] by adding organic solvent to the reaction mixture to isolate desired product and leaving the catalyst system in aqueous layer. This recovered catalyst was reused up to 5 cycles for the same reaction without much loss in the catalytic activity (Table 2). This recyclable catalytic activity was also supported by the XRD data of the catalyst which indicate no changes in the morphology even after 5 cycles (see ESI†). Based on the observations, a plausible mechanism is proposed as shown in Fig. 2.



Scheme 2 Reactions of β-nitrostyrene (**1**) with benzyl azide (**2**) and phenylazide (**5**) under optimized conditions.

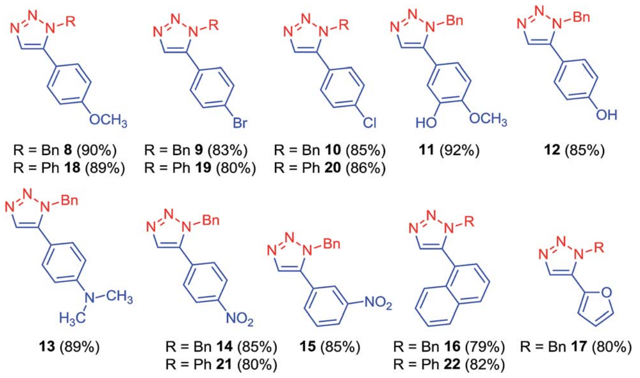
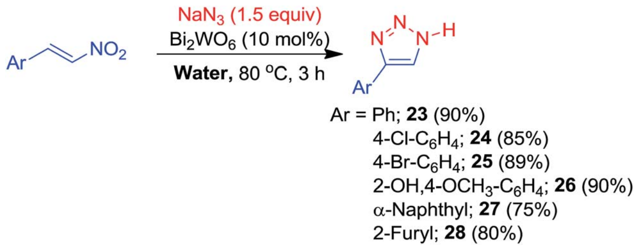
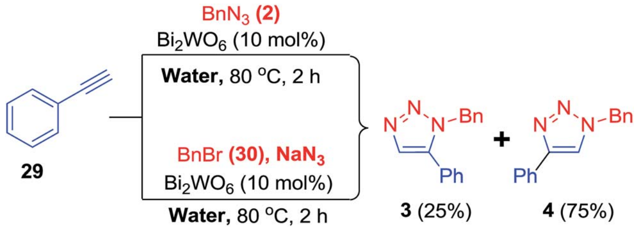


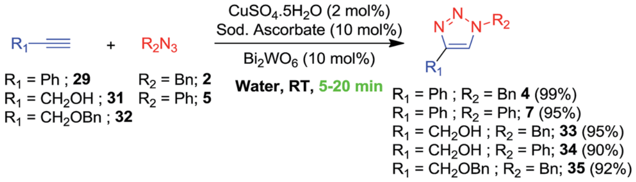
Fig. 1 Different triazole derivatives (**8–22**) prepared from β-nitrostyrenes and azides (**2** and **5**).



Scheme 3 Preparation of unsubstituted triazole using β-nitrostyrene, NaN_3 and Bi_2WO_6 nanoparticle (10 mol%).



Scheme 4 Preparation of disubstituted triazoles **3** and **4** using phenylacetylene (**29**).



Scheme 5 Bi_2WO_6-supported Click reaction (CuAAC) reaction of different alkynes and benzylazide (**2**) and phenylazide (**5**).

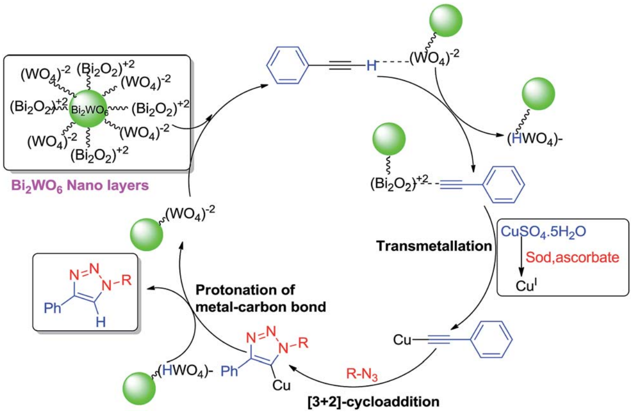


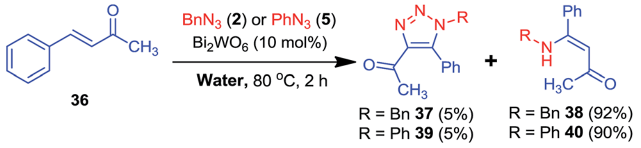
Fig. 2 Plausible reaction mechanism for the Bi_2WO_6 nanoparticles-mediated Click reaction.

From the mechanism we assume that the $(WO_4)^{2-}$ layers of Bi_2WO_6 nanoparticle abstract the terminal proton from phenyl acetylene. The resulting carbanion gets coordinated with $(Bi_2O_2)^{2+}$ layer giving the bismuth-acetylide species which then undergoes transmetallation with Cu^{1+} (generated by sodium ascorbate from Cu^{2+}) to form Cu-acetylide. This can react with the azide *via* [3 + 2]-cyclo addition followed by the protonation of the metal–carbon bond to give the desired 1,2,3-triazole in a regiospecific manner.

Later, attention was focused towards the synthesis of functionalized triazoles using chalcones. Thus, chalcone (**36**) was reacted with azides (**2**) or (**5**) under optimized conditions Scheme 6. However, it was observed that the formation of the desired triazoles (**37**, **39**) as minor products along with the enaminones (**38**, **40**). This type of reactivity is known to involve *cycloaddition-ring cleavage-rearrangement* sequence.[16a] The improved yield of desired triazole **37**, was achieved up to 85% by performing solvent dependent reactions using water and toluene as combination as shown in Table 3. Though the enaminones are forming as by-products, these can be used for the functionalized heterocyclic molecules.[16b] Considering this, different chalcones treated with azides **2** and **5** using water and toluene as reaction medium to obtain functionalized enaminones **41–51** and triazoles **52–62** (Fig. 3). For achieving better selectivity in the cycloaddition of chalcones with azides in water, the classical click conditions were attempted as described earlier. Thus, reaction of chalcones and benzylazide (**2**) in presence of $CuSO_4 \cdot 2H_2O$ (2 mol%), sodium ascorbate (10 mol%) and Bi_2WO_6 (10 mol%) at 80 °C for 6 h gave the trisubstituted triazoles as single isomers in 85–95% yields (Scheme 7). Further applications of these methods on complex examples are in progress in our laboratory.

Table 2 Recyclability of the catalyst system (Bi_2WO_6 + $CuSO_4 \cdot 5H_2O$ + sod. ascorbate in water) for the formation of triazole (**4**)

S. no.	No of cycle	Reaction time	Isolated yield (%) (min)
1	1	5	99
2	2	5	99
3	3	7	96
4	4	10	95
5	5	10	95



Scheme 6 Reaction of chalcone **36** with benzyl and phenyl azides in water.

Table 3 Solvent controlled experiments for the formation of enaminone (**38**) and triazole (**37**)

S. no.	Water (%)	Toluene (%)	Enaminone (%)	Triazole (%)
1	90	10	90	07
2	80	20	85	12
3	70	30	75	22
4	60	40	68	29
5	50	50	50	47
6	25	75	23	75
7	—	**100**	**10**	**85**

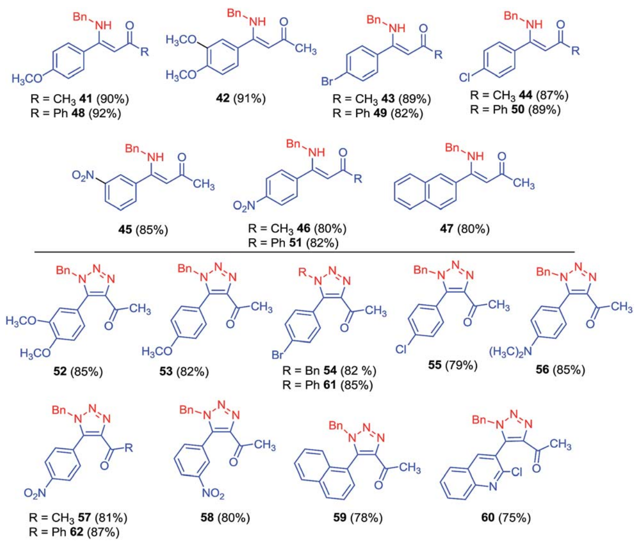
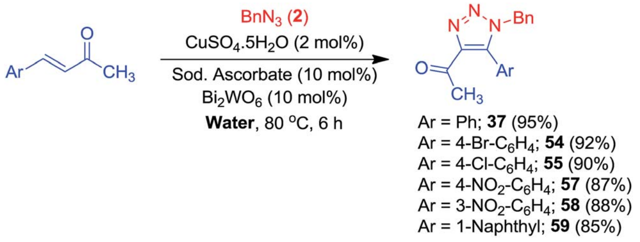


Fig. 3 Different enaminones (**41–51**) and triazole (**52–62**) derivatives.



Scheme 7 Bi_2WO_6-supported cycloaddition reaction of chalcones and benzylazide (**2**).

In conclusion, we have demonstrated the use of Bi_2WO_6 nanoparticles as highly effective and reusable catalyst for the 1,3-dipolar cycloaddition reactions of β-nitrostyrenes, phenylacetylene and chalcones with azides. The regioselective formation of 1,4-disubstituted triazoles was achieved for the first time in very short time (5–20 min) using combination of click reaction (CuAAC) and Bi_2WO_6 nanoparticles at room temperature in water. Similarly functionalized triazoles were prepared from chalcones under similar conditions in aqueous medium.

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