Res Chem Intermed
DOI 10.1007/s11164-017-2871-1

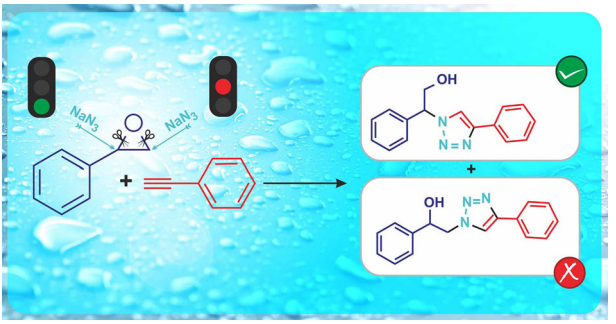
Hydrotrope promoted in situ azidonation followed by copper catalyzed regioselective synthesis of *β*-hydroxytriazoles

Amol Patil[1] · **Rajashri Salunkhe**[1]

Received: 18 May 2016 / Accepted: 17 January 2017

Abstract The rapid method for the synthesis of organic azides was achieved by employing azide acceptors such as halides, epoxides and pseudohalides like diazonium salts and aryl boronic acids in hydrotropic media. In extension, the sequential multi-component reaction of epoxides, azide and alkynes using copper catalysis has been discussed. The reaction proceeds via the in situ generation of azido-alcohol followed by synthesis of chiral *β*-hydroxytriazoles. This [3 + 2] cycloaddition reaction of azide and alkyne using copper catalysis serves as a green and efficient protocol in "Click Chemistry". The nucleophilic addition of azide to epoxide and alkyne-azide cycloaddition is the two simultaneous regioselective click reactions observed in the proposed method.

Graphical Abstract



Keywords Hydrotrope · *β*-Hydroxytriazoles · One-pot synthesis · Click chemistry

✉ Rajashri Salunkhe
rsschem1@gmail.com

[1] Department of Chemistry, Shivaji University, Kolhapur, MS 416004, India

Published online: 31 January 2017

Introduction

The principles of green chemistry include the designing and implementation of novel sustainable methodologies which have minimal impact on the environment. Owing to this, the areas of research have been defined by the scientific community and a myriad of efforts has been undertaken for the same [1–4]. One of such approach is to use water as a reaction medium. The barrier of solubilization of organic reactants in aqueous medium is overcome by using green additives like hydrotropes; which increases the water solubility dramatically up to 200-fold. Hydrotropes are short chain amphiphiles structurally resembling surfactants but the mode of action is based on critical aggregation concentration (cac) of hydrotrope [5–7]. The salient structural characteristic of hydrotropes includes an anionic group and hydrophobic aromatic ring. The amphiphilic molecular structure of the hydrotrope dramatically increases the solubility of sparingly soluble organic molecules in water. Hydrotropic solutions precipitate the solute on dilution with water, which permits the recovery of the hydrotropic solution for re-use.

Azides are the important intermediates in organic chemistry [8, 9]. They serve as one of the most promising ways to introduce a nitrogen substituent of a triazole ring, which is undeniably a crucial part in "Click Chemistry". They give excellent cycloaddition reactions with alkynes due to the presence of a 1,3-dipole in the structure. Several different methodologies have been reported for the synthesis of organic azides; even though they are free from green efforts [10–13]. Therefore, there is a need for environmentally friendly protocols for the synthesis of organic azides and thus, now a day, the strategy of in situ synthesis of azides is employed.

Transition metal-catalysis constitutes a broad spectrum of research in organic transformations. Among them, copper has greatly contributed to the development of C–C, C–N, C–S and C–O bonds in coupling reactions [14–18]. Copper catalyzed azide–alkyne cycloaddition (CuAAC) reactions have extensive applications in triazole chemistry. Very robust, inexpensive, virtually quantitative and orthogonal ligation properties of Cu^{+} made them successful catalytic systems in synthetic chemistry. Cu^{+2} catalysts require a reducing agent like ascorbic acid for activation. Therefore, Cu^{+} catalysts, due to their high activity, found more applications than Cu^{+2} catalysts [19, 20].

The appliance of copper catalysts to other areas of organic chemistry was pursued concurrently with the development of click reactions [21, 22]. The Huisgen 1,3-dipolar cycloaddition of alkynes and azides is regarded as the 'cream of the crop' of concerted reactions [23]. In the realm of 'Click Chemistry', a plethora of methods has been developed a long time ago. Among them transition metals, preferably copper catalysts, were found to be more effective. Depending upon substrates, the azide-alkyne 1,3-dipolar cycloaddition reaction can be successful using copper in solid phase systems, ruthenium, gold catalysis, and nano-catalysis [24, 25]. The immobilization of copper on high surface area supports allows the stability and reactivity as well as recycling purpose of the catalyst [26]. Although a reduced dicopper core showed high reactivity in the synthesis of 1,2,3-triazoles, this left serious drawbacks like the use of hazardous organic solvents, high temperature

and a long reaction time [27]. In order to overcome the shortcomings, the bio-catalytic system was used to synthesize chiral hydroxytriazoles [28]. Most of the supported catalysts [29, 30] failed to give good regioselectivity of the reaction. Several members of the 1,2,3-triazole family have been confirmed to be potent anti-bacterial, anti-HIV and anti-allergic agents [31–35]. The triazole chemistry is widely explored due to its numerous applications in the agrochemicals, dyes, and pharmaceuticals [36, 37]. Moreover, these molecules act as nano-carriers in biological systems [38] as well as having synthetic equivalence in peptides, oligosaccharides and dendrimer synthesis [39–41].

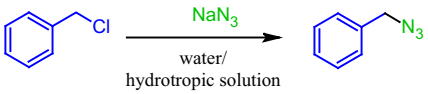
As a part of our interest in the utility of hydrotropic solution for organic transformations [42–44], we planned to design a green methodology for the synthesis of organo-azides. For this purpose, we have used a variety of azide acceptors such as alkyl halides, diazonium salts, boronic acids and epoxides. In extension, one-pot syntheses of β-hydroxytriazoles were carried out from epoxides, sodium azide and alkynes, via the in situ formation of 2-azidoalcohols and further cycloaddition with alkynes.

Results and discussion

In an inception study, we investigated the template reaction of sodium azide and benzyl chloride (**1a**) in aqueous medium. The reaction gave the corresponding product benzyl azide (**5a**) in moderate yield (70%). Inspired by this positive result, we sought to develop methodology by employing an aqueous hydrotropic solution (50% NaPTS) as reaction medium. To our delight, the hydrotropic solution gave good conversion of reactants and offers product **5a** in excellent yield (93%). After this, we screened several hydrotropes like sodium xylene sulphonate, sodium cumene sulphonate, sodium salisylate and sodium *p*-toluene sulphonate (NaPTS); and tried to find out the best suitable reaction medium for the model reaction. We observed that 50% aqueous solution of NaPTS was found to be the best reaction medium among screened hydrotropes and offered good product yield at room temperature (Table 1, entry 2). Decrease in concentration of NaPTS decreases the product yield (Table 1, entries 5–6).

Thereafter, we subjected various substrates susceptible to the azidonation reaction, and the outcomes are listed in Table 2. Alkyl halides (**1**) such as butyl bromide, octyl bromide and ethyl bromide gave good yields (Table 2, entries 2–4). Aryl azides were successfully synthesized by using diazonium salts (**2**) and boronic acids (**3**). It was observed that both activated and deactivated diazonium compounds as well as boronic acids were tolerated well to give azides in good yields (Table 2, entries 5–12). The ring opening reaction of epoxides (**4**) with sodium azide occurs in a regioselective manner. Cyclohexene oxide was treated with sodium azide to give the corresponding *trans*-β-azido alcohol (**7b**) in good yield (Table 2, entry 14). Styrene oxide gave exclusively primary alcohol (**7a**) instead of secondary alcohol (**8**). Here, the nucleophilic attack of azide was observed at sterically crowded benzylic carbon instead of less substituted β-carbon. In this case the electronic factor dominates over the steric factor (Table 2, entry 13). The striking feature of

Table 1 Screening of hydrotropes



Entry	Solvent	Time (min)	Yield[a] (%)
1	Water	60	70
2	Sodium *p*-toluene sulphonate (50% NaPTS)	10	93
3	Sodium *p*-xylene sulphonate (50% NaXS)	10	84
4	Sodium cumene sulphonate (50% NaCS)	10	80
5	Sodium *p*-toluene sulphonate (10% NaPTS)	10	79
6	Sodium *p*-toluene sulphonate (30% NaPTS)	10	86

[a] Yields by GC

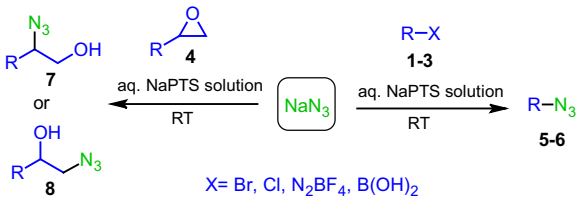
this reaction was the introduction of the chiral center in the product molecule. The azidonation of epichlorohydrin not only displaces chlorine but also opens the epoxide ring offering a *bis*-azido compound (**7c**). Here, the reactivity of azide towards the ring opening reaction and substitution reaction of chlorine remains unchanged (Table 2, entry 15) (CAUTION: Ethyl azide and *bis*-azide are likely to be explosive and dangerous if isolated).

Synthesis of *β*-hydroxy triazoles from epoxides

We next sought to exploit the principle of in situ generation of toxic organo-azides for the synthesis of *β*-hydroxytriazoles from epoxides, sodium azide and alkynes. For this purpose styrene oxide, sodium azide and phenyl acetylene were chosen as reaction partners and the effect of various copper catalysts was examined (Table 3). Initially, the model reaction of styrene oxide with sodium azide was carried out in 50% NaPTS solution for the generation of 1,2-azidol as discussed earlier (Table 2, entry 13). Thereafter, phenyl acetylene was added to the same reaction mixture without catalyst, which does not give product formation. Subsequently, the addition of 10 mol % $CuSO_4$ catalyst gave formation of product **10a** with 40% yield (Table 3, entry 2). Furthermore, $CuSO_4$ + Sodium ascorbate, a classical condition in click chemistry gave 87% product yield (Table 3, entry 3). Encouraged by this positive result, we switched over to screening of different Cu^+ and Cu^{2+} catalysts without use of sodium ascorbate. Among tested copper sources, CuI showed high activity for the cycloaddition reaction (Table 3, entry 10). NMR studies confirm the formation of exclusively the product **10a** instead of product **11** [26]. The calculated atom economy for the model reaction is 92.33%.

With the promising results in hand, we explored the scope of various alkynes for the sequential cycloaddition reaction, and the results are summarized in Table 4.

Table 2 Synthesis of azides from epoxides, halides and *pseudo*-halides[a]



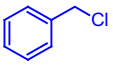
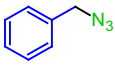
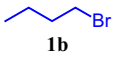
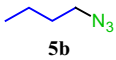
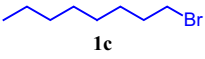
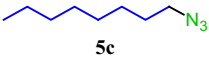
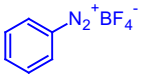
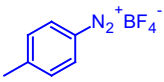
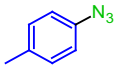
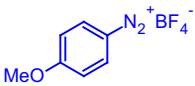
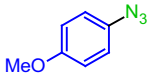
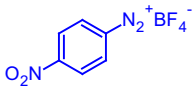
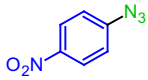
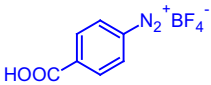
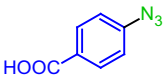
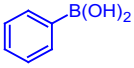
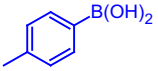
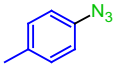
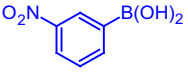
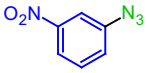
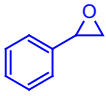
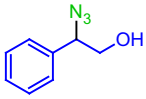
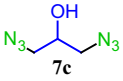
Entry	Reactants	Product	Time (min)	Yield (%)[b]
1	 **1a**	 **5a**	10	93
2	 **1b**	 **5b**	10	90
3	 **1c**	 **5c**	10	89
4	 **1d**	 **5d**	10	90
5	 **2a**	 **6a**	5	94
6	 **2b**	 **6b**	5	93
7	 **2c**	 **6c**	5	94
8	 **2d**	 **6d**	10	91
9	 **2e**	 **6e**	10	94

Table 2 continued

Entry	Reactants	Product	Time (min)	Yield (%)[b]
10	 **3a**	 **6a**	15	86
11	 **3b**	 **6b**	15	83
12	 **3f**	 **6f**	25	80
13	 **4a**	 **7a**	20	91 (96:4)
14	 **4b**	 **7b**	15	95
15[c]	 **4c**	 **7c**	20	93

[a] Reaction conditions: 1 mmol of alkyl halides/diazonium salt/boronic acid/epoxide and 1.2 mmol of NaN_3 in 5 mL 50% NaPTS

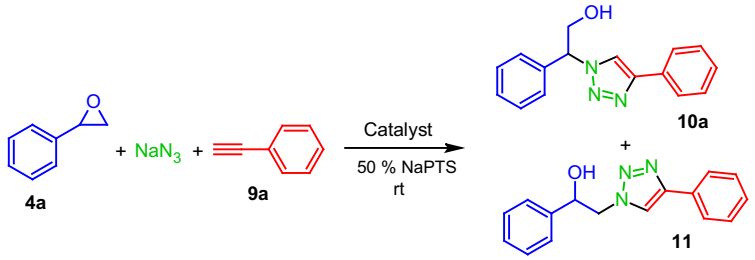
[b] Yields by GC. Value in parenthesis refers to isomers formed determined by GC analysis

[c] Reaction condition: 1 mmol of epichlorohydrin, and 2.4 mmol of NaN_3 in 5 mL 50% NaPTS

Aromatic alkyne like 4-methyl phenylacetylene offers excellent yield of the corresponding *β*-hydroxytriazole (Table 4, entry 2). Moreover, aliphatic alkynes tolerated well and gave corresponding triazoles in high yield. Two simultaneous regioselectivities were observed for the ring opening reaction of epoxide with sodium azide and in the 1,3-cycloaddition reaction of in situ generated azide with alkynes. Among 1,4- and 1,5-disubstituted triazoles, the 1,4-addition product predominates. ^{1}H-NMR spectrum confirmed the formation of chiral product and the methylene protons adjacent to chiral carbon became diastereotopic protons.

In the light of the results obtained, we extended this methodology by subjecting cyclohexene oxide and epichlorohydrin for the azidonation and subsequent cycloaddition reaction with alkynes. Azidonation of cyclohexene oxide follows a S_N^2 path and gave exclusively *trans* isomers, which is confirmed by coupling constant measurement in ^{1}H-NMR spectroscopy. The amount of *trans* isomer formed of product 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)cyclohexanol over *cis*-isomer in the ratio 89:11. D_2O exchange analysis in ^{1}H-NMR confirmed the formation of

Table 3 Optimization of reaction conditions for the synthesis of β-hydroxytriazole[a]



Entry	Catalyst (mol %)	Time (h)	Yield (%)[b]
1	None	24	n r
2	Cu(II) sulfate (10)	4	40
3	$CuSO_4$ + Na-ascorbate	3.5	70
4	Cu(II) bromide (10)	4.5	35
5	Cu(II) chloride (10)	4.5	38
6	Cu(II) iodide (10)	4	41
7	Cu(I) acetate (10)	6	48
8	Cu(I) bromide (10)	4	88
9	Cu(I) chloride (10)	4	80
10	Cu(I) iodide (10)	3	92
11	Cu(I) iodide (5)	3	88
12	Cu(I) iodide (15)	3	92
13	Cu(I) iodide (20)	3	91

[a] All reactions were run with epoxide (1 mmol), sodium azide (1.2 mmol), phenyl acetylene (1 mmol) and catalyst in 5 mL 50% NaPTS solution at room temperature

[b] Isolated yields

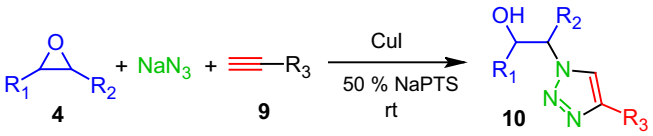
n r: no reaction

the hydroxy derivative. Furthermore, epichlorohydrin gave structurally complex *bis*-triazoles confirming the reactivity of azide towards both nucleophilic displacements of chlorine as well as in ring opening of epoxide. Because of the symmetrical arrangement of the molecule, chirality is not observed for the product which is confirmed by ^{1}H-NMR spectroscopy.

Experimental

Epoxides, alkyl halides, boronic acids, alkynes and sodium *p*-toluene sulphonate were obtained from Alfa Aesar and Sigma Aldrich Company and used as received. Diazonium salts were prepared following the literature procedure [45]. Infrared spectra were obtained on a Perkin Elmer FT-IR spectrometer. NMR spectra were recorded on a Bruker AC (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) spectrometer using $CDCl_3$ and/or DMSO-d_6 as solvent and tetramethylsilane (TMS)

Table 4 CuI catalyzed synthesis of β-hydroxytriazoles from epoxides[a]



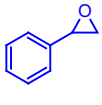
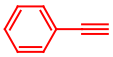
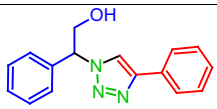
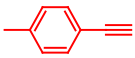
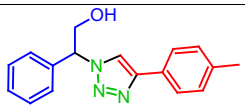
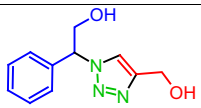
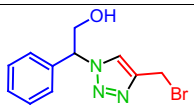
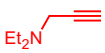
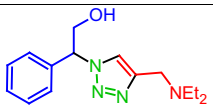
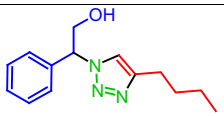
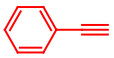
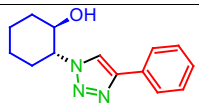
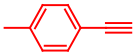
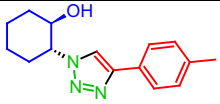
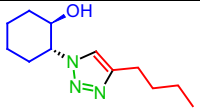
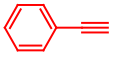
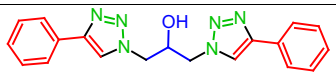
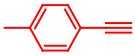
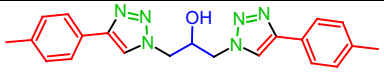
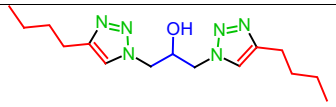
Entry	Epoxide	Alkyne	Product	Time (h)	Yield[b] (%) (Ratio)[c]
1	 **4a**	 **9a**	 **10a**	3	92 (96:4)
2		 **9b**	 **10b**	2.5	93 (96:4)
3		 **9c**	 **10c**	4	83 (94:6)
4		 **9d**	 **10d**	4.5	81 (94:6)
5		 **9e**	 **10e**	4	80 (96:4)
6		 **9f**	 **10f**	3.5	90 (96:4)

Table 4 continued

Entry	Epoxide	Alkyne	Product	Time (h)	Yield[b] (%) (Ratio)[c]
7		 **9a**	 **10g**	2.5	88
8	 **4b**	 **9b**	 **10h**	2.5	90
9		 **9f**	 **10i**	3	86
10		 **9a**	 **10j**	4	82
11	 **4c**	 **9b**	 **10k**	4.5	80
12		 **9f**	 **10l**	4.5	82

[a] All reaction were run with epoxide (1 mmol), sodium azide (1.2 mmol), acetylene (1 mmol) and CuI (10 mol %) in 5 ml 50% NaPTS solution at room temperature

[b] Isolated yields

[c] Ratio of 1,4: 1,5 disubstituted triazole

as an internal standard. Melting points were determined with DBK melting point apparatus and are uncorrected. Elemental analyses were performed on the EURO EA3000 vector model. GC and MS were recorded on a Shimadzu QP2010.

Experimental procedure for the synthesis of organic azides

Sodium azide (1.2 mmol) and alkyl halide/diazonium salt/aryl boronic acid/epoxide (1 mmol) were stirred in 5 mL 50% aq. NaPTS solution at room temperature. The progress of reaction was monitored by gas chromatography until total conversion of starting materials. The reaction mixture was extracted with EtOAc (3 × 5 mL), the organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed in *vacuo* to afford corresponding organic azide.

Experimental procedure for the synthesis of β-hydroxytriazoles

Epoxide (1 mmol), sodium azide (1.2 mmol) and the alkyne (1 mmol) were added to a suspension of CuI (10 mol %) in 50% aq. NaPTS solution. The reaction mixture was stirred at room temperature for an appropriate time, and the progress of the reaction was monitored by TLC until total conversion of starting materials. The reaction mixture was extracted with EtOAc (3 × 5 mL); the organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed in *vacuo*. The resulting residue was purified by column chromatography to afford corresponding *β*-hydroxytriazole.

Spectral data of representative compounds

*1-(Azidomethyl)benzene (**5a**)* Viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.40 (s, 2H), 7.29 (d, $J = 8.7$ Hz, 3H), 7.82 (d, $J = 8.1$ Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 21.5 (*C*H_2), 127.5, 129.8, 139.0, 143.9 (*C*–CH_2); Anal. Calcd for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.26; H, 5.27; N, 31.47. MS (*m/z*): 133 (M+).

*4-Azidobenzoic acid (**6e**)* Pale yellow solid; mp = 182–184 °C; IR (KBr, cm^{-1}): 2404–3412 (br, COOH), 2108 (N_3), 1681 (C=O); ^{1}H NMR (300 MHz, DMSO-*d6*, δ ppm): 7.01 (d, $J = 6.6$ Hz, 2H), 7.93 (d, $J = 8.4$ Hz, 2H), Peak for acidic proton (COOH) was not observed in PMR spectrum; ^{13}C NMR (75 MHz, DMSO-*d6*, δ ppm): 118.8, 127.6, 131.5, 144.2 (*C*–N_3), 167.2 (*C*=O); Anal. Calcd for $C_7H_5N_3O_2$: C, 51.54; H, 3.09; N, 25.76. Found: C, 51.42; H, 3.15; N, 25.67. MS (*m/z*): 163 (M+).

*2-Azidocyclohexanol (**7b**)* White solid, mp = 121–123 °C; IR (KBr, cm^{-1}): 3409 (br, O–H), 2928 (C–H), 2105 (N_3); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 0.92 (t, $J = 7.2$ Hz, 2H), 1.37 (q, $J = 7.2$ Hz, 2H), 1.63 (s, 1H), 2.69 (d, $J = 9.9$ Hz, 1H), 3.41 (d, $J = 7.2$ Hz, 1H), 4.40–4.58 (m, 2H), 7.59 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 13.7, 22.2, 25.1, 31.3, 53.9 (*C*–N_3), 68.5 (*C*–OH); Anal. Calcd for $C_6H_{11}N_3O$: C, 51.05; H, 7.85; N, 29.77. Found: C, 50.96; H, 7.90; N, 29.73. MS (*m/z*): 141 (M+).

*2-Phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanol (**10a**)* White solid, mp = 133–135 °C; IR (KBr, cm^{-1}): 3378 (br, O–H), 3093 (=C–H), 2929 (C–H), 2100 (N=N–N), 1604 (C=C); ^{1}H NMR (300 MHz, DMSO-*d6*, δ ppm): 4.05 (dd, $J = 11.7$, 4.5 Hz,

1H), 4.34 (t, $J = 9.3$ Hz, 1H), 5.80 (q, $J = 4.5$ Hz, 1H), 7.27–7.41 (m, 9H), 7.83 (d, $J = 7.5$ Hz, 2H), 8.65 (s, 1H). ^{13}C NMR (75 MHz, DMSO-*d6*, δ ppm): 68.4 (*C*H_2), 71.5 (*C*H), 125.5, 130.3, 132.0, 132.2, 132.8, 133.2, 133.6, 133.7, 134.0, 135.5, 141.8, 151.6. Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.56; H, 5.75; N, 15.74. MS (*m/z*): 265 (M+).

2-Phenyl-2-(4-p-tolyl-1H-1,2,3-triazol-1-yl)ethanol ***(10b)*** White solid, mp = 151–153 °C; IR (KBr, cm^{-1}): 3404 (br, O–H), 3094 (=C–H), 2930 (C–H), 2100 (N=N–N), 1621 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.38 (s, 3H), 4.24 (d, $J = 11.1$ Hz, 1H), 4.62–4.70 (m, 1H), 5.69 (d, $J = 4.8$ Hz, 1H), 7.21–7.41 (m, 8H), 7.69 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 21.3 (*C*H_3), 65.2 (*C*H_2), 67.3 (*C*H), 125.6, 127.1, 128.7, 128.9, 129.0, 129.2, 129.5, 136.0, 138.2; Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 73.46; H, 5.95; N, 15.18. MS (*m/z*): 279 (M+).

2-(4-Phenyl-1H-1,2,3-triazol-1-yl)cyclohexanol ***(10g)*** Pale yellow solid, mp = 170–172 °C; ^{1}H NMR (300 MHz, DMSO *d6*, δ ppm): 1.37–2.00 (m, 8H), 3.73–3.83 (m, 1H), 4.19–4.28 (m, 1H), 5.02 (d, 1H, $J = 5.7$ Hz, OH exchangeable with D_2O), 7.32 (t, $J = 7.5$ Hz,, 1H), 7.44 (t, $J = 7.5$ Hz, 2H), 7.83–7.86 (m, 2H), 8.59 (s, 1H); ^{13}C NMR (75 MHz, DMSO *d6*, δ ppm): 24.3, 24.9, 32.4, 35.2, 66.4 (*C*H–N), 71.8 (*C*H–OH), 121.0, 125.4, 128.0, 129.3, 131.6, 146.1; Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.26; H, 6.93; N, 17.20. MS (*m/z*): 243 (M+).

1,3-Bis-(4-phenyl-1H-1,2,3-triazol-1-yl)propan-2-ol ***(10j)*** White solid, mp = 231–233 °C; ^{1}H NMR (300 MHz, DMSO-*d6*, δ ppm): 4.44 (s, 3H), 4.60 (s, 2H), 5.81 (s, 1H, OH), 7.30–7.39 (m, 6H), 7.83 (s, 4H), 8.46 (s, 2H). ^{13}C NMR (75 MHz, DMSO-*d6*, δ ppm): 53.4 (*C*H_2), 68.6 (*C*H–OH), 122.3, 125.5, 128.0, 128.9, 130.9, 146.9. Anal. Calcd for $C_{19}H_{18}N_6O$: C, 65.88; H, 5.24; N, 24.26. Found: C, 65.79; H, 5.20; N, 24.32. MS (*m/z*): 346 (M+).

1,3-Bis-(4-p-tolyl-1H-1,2,3-triazol-1-yl)propan-2-ol ***(10k)*** White solid, mp = 242–244 °C; IR (KBr, cm^{-1}): 3348 (br, O–H), 3108 (=C–H), 2920 (C–H), 2100 (N=N–N), 1634 (C=C); ^{1}H NMR (300 MHz, DMSO *d6*, δ ppm): 2.30 (s, 6H), 4.37 (d, $J = 13.2$ Hz, 3H), 4.52 (s, 2H), 4.79 (s, 1H, OH exchangeable with D_2O), 7.15 (d, $J = 6$ Hz, 4H), 7.65 (d, $J = 6$ Hz, 4H), 8.16 (s, 2H); ^{13}C NMR (75 MHz, DMSO *d6*, δ ppm): 21.3 (*C*H_3), 53.3 (*C*H_2), 68.6 (*C*H–OH), 121.7, 125.4, 128.0, 129.5, 137.5, 147.0; Anal. Calcd for $C_{21}H_{22}N_6O$: C, 67.36; H, 5.92; N, 22.44. Found: C, 67.34; H, 5.99; N, 22.38. MS (*m/z*): 374 (M+).

Conclusions

We have developed an efficient method for the synthesis of organic azides using simple starting materials. The method was effectively extended for three component sequential MCR involving epoxides, azide and alkynes leading to the generation of

β-hydroxytriazoles based on the click chemistry approach. The reaction proceeds via the in situ generation of β-hydroxyazide, which undergoes smooth [3 + 2] cycloaddition reaction with terminal alkynes with high atom economy. The additive- and base-free approach follows two simultaneous 'clicks' employing hydrotropic solutions with their green characters. We are privileged to claim that the developed method is a good alternative to the complex catalytic as well as solvent-systems in organic synthesis in the near future.

Acknowledgements The authors thank UGC, New Delhi for financial assistance [F. No. 41-310/2012 (SR)].

References

1. P.T. Anastas, J.C. Warner, *Green Chemistry: Theory and Practice* (Oxford University Press, Oxford, 1998)
2. P.R. Boruah, A.A. Ali, B. Saikia, D. Sarma, Green Chem. **17**, 1442 (2015)
3. A. Kumar, R.D. Shukla, Green Chem. **17**, 848 (2015)
4. G. Lu, C. Cai, B.H. Lipshutz, Green Chem. **15**, 105 (2013)
5. K. Szabo, P. Wang, B. Peles-Lemli, Y. Fang, L. Kollar, S. Kunsagi-Mate, Colloids Surf. A Physicochem. Eng. Asp. **422**, 143 (2013)
6. S. Kumar, N. Parveen, K. Din, J. Surfactants Deterg. **8**, 109 (2005)
7. S.E. Friberg, C. Brancewicz, Langmuir **10**, 2945 (1994)
8. S. Brase, C. Gil, K. Knepper, V. Zimmerman, Angew. Chem. Int. Ed. **44**, 5188 (2005)
9. E.F.V. Scriven, K. Turnbull, Chem. Rev. **88**, 297 (1988)
10. Y. Ju, D. Kumar, R.S. Varma, J. Org. Chem. **71**, 6697 (2006)
11. M. Zarchi, Z. Escandari, J. Appl. Polym. Sci. **121**, 1916 (2011)
12. W. Zhu, D. Ma, Chem. Commun. **7**, 888–889 (2004)
13. G. Sabitha, R. Satheesh Babu, S.M. Rajkumar, J.S. Yadav, Org. Lett. **4**, 343 (2002)
14. Q. Wu, L. Wang, Synthesis **13**, 2007 (2008)
15. Q. Zhang, D. Wang, X. Wang, K. Ding, J. Org. Chem. **74**, 7187 (2009)
16. Y. Zhang, X. Yang, Q. Yao, D. Ma, Org. Lett. **14**, 3056 (2012)
17. A. Sujatha, A.M. Thomas, A.P. Thankachan, G. Anilkumar, ARKIVOC 1 (2015)
18. G. Evano, C. Theunissen, A. Pradal, Nat. Prod. Rep. **30**, 1467 (2013)
19. M. Meldal, C.W. Tornoe, Chem. Rev. **108**, 2952 (2008)
20. J.E. Hein, V.V. Fokin, Chem. Soc. Rev. **39**, 1302 (2010)
21. J.E. Moses, A.D. Moorhouse, Chem. Soc. Rev. **36**, 1249 (2007)
22. H.C. Kolb, M.G. Finn, K.B. Sharpless, Angew. Chem. Int. Ed. **40**, 2004 (2001)
23. S. Lober, P. Rodrigues-Loaiza, P. Gmeiner, Org. Lett. **5**, 1753 (2003)
24. N. Li, P. Zhao, N. Liu, M. Echeverria, S. Moya, L. Salmon, J. Ruiz, D. Astruc, Chem. Eur. J. **20**, 8363 (2014)
25. L. Zhang, X. Chen, P. Xue, H.H.Y. Sun, I.D. Williams, K.B. Sharpless, V.V. Fokin, G. Jia, J. Am. Chem. Soc. **127**, 15998 (2005)
26. F. Alonso, Y. Moglie, G. Radivoy, M. Yus, J. Org. Chem. **76**, 8394 (2011)
27. K. Kamata, Y. Nakagawa, K. Yamaguchi, N. Mizuno, J. Am. Chem. Soc. **130**, 15304 (2008)
28. L.S. Campbell-Verduyn, W. Szymański, C.P. Postema, R.A. Dierckx, P.H. Elsinga, D.B. Janssen, B.L. Feringa, Chem. Commun. **46**, 898 (2010)
29. A.N. Prasad, B. Thirupathi, G. Raju, R. Srinivas, B.M. Reddy, Catal. Sci. Technol. **2**, 1264 (2012)
30. H. Naeimi, V. Nejadshafiee, New J. Chem. **38**, 5429 (2014)
31. P. Thirumurugan, D. Matosiuk, K. Jozwiak, Chem. Rev. **113**, 4905 (2013)
32. R. Alvarez, S. Velazques, A. San-Felix, S. Aquaro, E.D. Clercq, C. Perno, A. Karlsson, J. Balzarini, M.J. Camarasa, J. Med. Chem. **37**, 4185 (1994)
33. D.R. Buckle, C.J.M. Rockell, H. Smith, B.A. Spicer, J. Med. Chem. **29**, 2262 (1986)
34. F. Musumeci, S. Schenone, A. Desogus, E. Nieddu, D. Deodato, L. Botta, Curr. Med. Chem. **22**, 2022 (2015)

35. M.J. Genin, D.A. Allwine, D.J. Anderson, M.R. Barbachyn, D.E. Emmert, S.A. Garmon, D.A. Graber, K.C. Grega, J.B. Hester, D.K. Hutchinson, J. Morris, R.J. Reischer, C.W. Ford, G.E. Zurenko, J.C. Hamel, R.D. Schaadt, D. Stapert, B.H. Yagi, J. Med. Chem. **43**, 953 (2000)
36. A. Brik, J. Alexandratos, Y.C. Lin, J.H. Elder, A.J. Olson, A. Wlodawer, D.S. Goodsell, C.H. Wong, ChemBioChem **6**, 1167 (2005)
37. A.J. Link, D.A. Tirrell, J. Am. Chem. Soc. **125**, 11164 (2003)
38. P.K. Avti, D. Maysinger, A. Kakkar, Molecules **18**, 9531 (2013)
39. D.P. Temelkoff, M. Zeller, P. Norris, Carbohydr. Res. **341**, 1081 (2006)
40. L. Marmuse, S.A. Nepogodiev, R.A. Field, Org. Biomol. Chem. **3**, 2225 (2005)
41. P. Wu, A.K. Feldman, A.K. Nugent, C.J. Hawker, A. Scheel, B. Voit, J. Pyun, J.M.J. Fréchet, K.B. Sharpless, V.V. Fokin, Angew. Chem. Int. Ed. **43**, 3928 (2004)
42. A. Patil, M. Barge, G. Rashinkar, R. Salunkhe, Mol Divers **19**, 435 (2015)
43. S.B. Kamble, A.S. Kumbhar, G.S. Rashinkar, M.S. Barge, R.S. Salunkhe, Ultrason. Sonochem. **19**, 812 (2012)
44. A.S. Kumbhar, S.B. Kamble, M.S. Barge, G.S. Rashinkar, R.S. Salunkhe, Tetrahedron Lett. **53**, 2756 (2012)
45. B. Furnis, A. Hannaford, P. Smith, A. Tatchell, *Vogel's Textbook of Practical Organic Chemistry* (Prentice Hall, Upper Saddle River, 1996), p. 925