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Three component, regioselective, one-pot synthesis of β-hydroxytriazoles from epoxides via 'click reactions'

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Abstract—2-Azidoalcohols derived in situ from epoxides and sodium azide undergo smooth coupling with alkynes under neutral conditions by means of 'click reactions' to furnish β-hydroxytriazoles in excellent yields and with high regioselectivity. This reaction proceeds smoothly in water at room temperature without the need for acid catalysis.

1,2,3-Triazoles are potential targets for drug discovery because of their wide range of biological properties such as antibacterial, antiviral, antiepileptic, and anti-allergic behavior.[1,2] They are also used as optical brighteners, light stabilizers, fluorescent whiteners, and corrosion retarding agents.[3] Huisgen's thermal 1,3-dipolar cycloaddition of an alkyne with an azide, sometimes known as a 'click reaction', is one of the most widely used methods for the synthesis of triazoles.[4] The Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC),[5] one of the most reliable 'click reactions',[6] has enabled practical and efficient preparation of 1,4-disubstituted-1,2,3-triazoles, from a wide range of substrates with excellent selectivity, which cannot be prepared via traditional Huisgen uncatalyzed thermal approaches.[4] This powerful and reliable Cu-catalyzed 1,3-dipolar cycloaddition has found widespread applications in combinatorial chemistry for drug discovery,[7] material science,[8] and bioconjugation.[9,10] Since β-hydroxytriazoles have become increasingly useful and important in drugs and pharmaceuticals, the development of a simple and efficient method for their synthesis in a single-step operation is desirable.

In this Letter, we report an efficient approach for the one-pot synthesis of β-hydroxytriazoles from epoxides, sodium azide, and alkynes by way of a three-component reaction, proceeding via the formation of 2-azidoalcohols from epoxides and sodium azide. In a preliminary experiment, styrene oxide (**1**) was treated with sodium azide and phenylacetylene (**2**) in the presence of 10 mol % of $CuSO_4{\cdot}5H_2O$ and 20 mol % of sodium ascorbate in water. The reaction went to completion at room temperature and the product, β-hydroxytriazole **3a** was obtained in 92% yield (Scheme 1).

Various other alkynes such as 1-octyne, 1-hexyne, 3-phenyl-1-propyne, and trimethylsilylacetylene also reacted readily with styrene oxide and sodium azide under these reaction conditions to produce β-hydroxytriazoles in high yields (Table 1, entries b–e). In the case of styrene oxide, product **3** was obtained as a result of the cleavage of the epoxide with sodium azide in a regioselective manner with preferential attack at the benzylic position. Encouraged by the results obtained with styrene oxide, we turned our attention to various other epoxides. Cyclohexene oxide also underwent smooth coupling with sodium azide and phenylacetylene to produce *N*-cyclohexyltriazole **4h** in 84% yield (Scheme 2).

In the case of cyclohexene oxide, the stereochemistry of the ring-opened products was found to be *trans* from the coupling constants of the ring hydrogens as has been observed in most epoxide ring-opening reactions.[11] Next, we examined the reactivity of aliphatic epoxides; propylene oxide, epichlorohydrin, hexene oxide, and 3-aryloxy-1,2-epoxy propane reacted smoothly with sodium azide and alkynes under similar reaction conditions to produce the corresponding β-hydroxytriazoles **5** and **6** in good to excellent yields (entries i–n, Table 1, Scheme 3).

Keywords: Epoxides; 2-Azidoalcohols; Alkynes; Click reaction; Triazoles.
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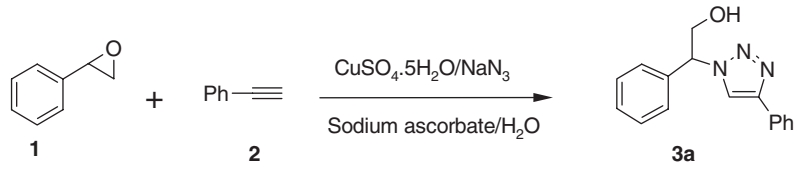


Scheme 1.

Table 1. One-pot synthesis of β-hydroxytriazoles from various epoxides, sodium azide and alkynes

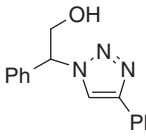
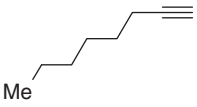
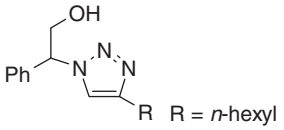
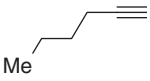
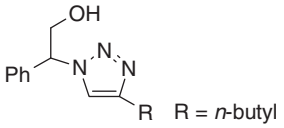
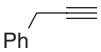
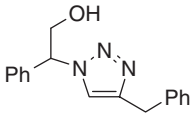
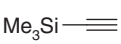
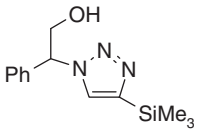
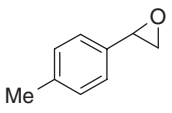
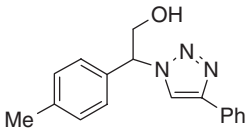
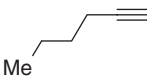
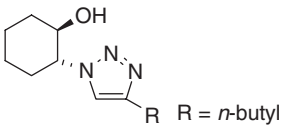
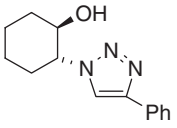
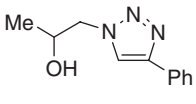
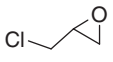
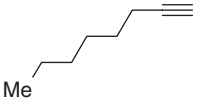
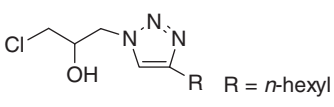
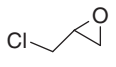
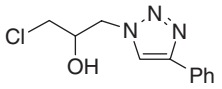
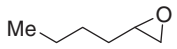
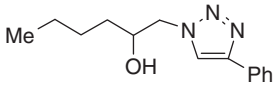
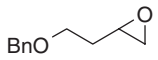
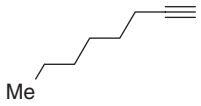
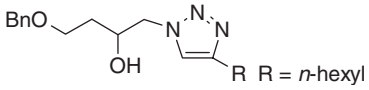
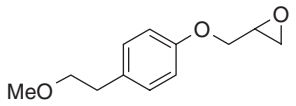
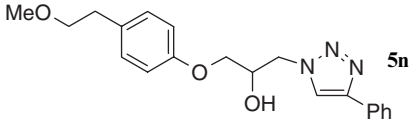
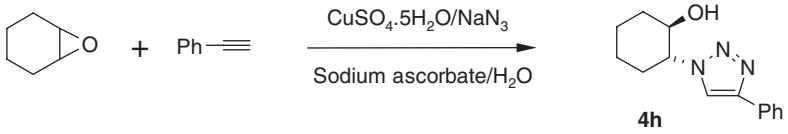
Entry	Epoxide	Alkyne	Product[a]		Time (h)	Yield[b] (%)
a				**3a**	4.0	92
b				**3b**	5.0	90
c				**3c**	5.5	85
d				**3d**	4.5	93
e				**3e**	5.0	83
f				**3f**	3.5	91
g				**4g**	4.5	82
h				**4h**	4.0	84
i				**5i**	4.0	92 (9:1)
j				**5j**	4.5	75 (8:2)

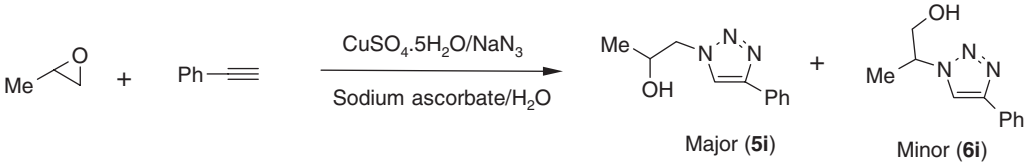
Table 1 (*continued*)

Entry	Epoxide	Alkyne	Product[a]		Time (h)	Yield[b] (%)
k				**5k**	4.0	77 (8:2)
l				**5l**	6.0	87 (9:1)
m				**5m**	5.0	85 (7:3)
n				**5n**	4.5	80 (7:3)

[a] All products were characterized by ^{1}H NMR, IR and mass spectrometry.
[b] Yield refer to pure products after chromatography.



Scheme 2.



Scheme 3.

The product triazoles from aliphatic epoxides were obtained from the terminal attack of the azide nucleophile. Except for the reactions of aliphatic epoxides, which produce a minor amount of the other regioisomer, the reactions of other epoxides were found to be highly regioselective affording a single product in good to excellent yields. The direction of ring opening is that characteristically observed for terminal epoxides under S_N2 conditions, and is probably dictated by steric and electronic factors. However, in the absence of either copper sulfate or sodium ascorbate, the reaction did not give the expected triazole even after long reaction times (8–12 h). Both copper sulfate and sodium ascorbate were essential for the success of the reaction. As a solvent, water gave the best results. The reactions were also conducted in organic solvents such as methanol and acetonitrile, but surprisingly, they took longer time (10–22 h in methanol) and the products were obtained in low yields (55–67%). This is probably due to the high solubility of sodium azide and sodium ascorbate in water. Furthermore, the reactions were clean in water compared to those in organic solvents. For example, treatment of styrene oxide with sodium azide and phenylacetylene in water for 4.0 h gave the corresponding 2-hydroxytriazole in 93% yield. However, the same reaction in refluxing methanol, after 12 h, gave the 2-hydroxytriazole in only 67% yield. The scope and generality of this process are illustrated with respect to various epoxides and acetylenes and the results are presented in Table 1.[12]

In summary, we have described a direct and efficient protocol for the preparation of β-hydroxytriazoles via a three component reaction of an epoxide, sodium azide and an alkyne. In addition to its simplicity and mild reaction conditions, this method provides a wide range of β-hydroxytriazoles in excellent yields with high regioselectivity in a single step operation.

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12. *Experimental procedure*: To a suspension of styrene oxide (120 mg, 0.11 mL, 1.0 mmol) and sodium azide (78 mg, 1.2 mmol) in water (3.0 mL) were added $CuSO_4{\cdot}5H_2O$ (16.0 mg, 0.1 mmol) and sodium ascorbate (39.6 mg, 0.2 mmol). The resulting solution was stirred for 2 h at room temperature. After complete consumption of styrene oxide as indicated by TLC, phenylacetylene (102 mg, 0.11 mL, 1 mmol) was added to the reaction mixture and it was stirred for another 2 h. The reaction mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography (hexane/EtOAc, 3:1) to give the 1,2,3-triazole **3a** as a pale yellow solid, mp 130–132 °C.
Spectral data for selected products:
Compound **3b**: 2-(4-hexyl-1*H*-1,2,3-triazol-1-yl)-2-phenylethanol: Solid, mp 64–66 °C, IR (KBr): $\nu_{(max)}$ 3384, 2925, 2856, 1631, 1455, 1377, 1219, 1067, 770, 699, 533 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.29– 7.39 (m, 3H), 7.11–7.21 (m, 3H), 5.51 (dd, $J = 8.3$, 3.7 Hz, 1H), 4.50–4.60 (m, 1H), 4.04–4.16 (m, 1H), 3.35–3.44 (m, 1H), 2.66 (t, $J = 7.5$ Hz, 2H), 1.58–1.68 (m, 2H), 1.24–1.38 (m, 6H), 0.87 (t, $J = 6.7$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 136.3, 129.0, 128.7, 127.0, 121.4, 66.8, 65.1, 35.4, 29.2, 28.8, 25.6, 22.4, 13.9. LC-MS: *m*/*z*: 274 (M+1). HRMS calcd for $C_{16}H_{23}N_3ONa$: 296.1738; found, 296.1750.
Compound **3d**: 2-(4-benzyl-1*H*-1,2,3-triazol-1-yl)-2-phenylethanol: Solid, mp 110–112 °C; IR (KBr): $\nu_{(max)}$ 3382, 3062, 3030, 2924, 2854, 2361, 1603, 1547, 1494, 1453, 1358, 1221, 1053, 728, 699, 531 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.11–7.34 (m, 11H), 5.49 (dd, $J = 8.3$, 3.0 Hz, 1H), 4.49 (dd, $J = 12.0$, 9.0 Hz, 1H), 3.92–4.08 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 147.5, 130.2, 129.9, 128.8, 128.1, 125.6, 121.3, 114.4, 69.1, 68.9, 53.1, 20.4. LC-MS: *m*/*z*: 280 (M+1). HRMS calcd for $C_{17}H_{17}N_3ONa$: 302.1269; found, 302.1259.
Compound **4h:** 2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)cyclohexan-1-ol: Solid, mp 182–184 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 8.05 (s, 1H), 8.22–8.82 (m, 5H), 4.78 (d, $J = 5.8$ Hz, 1H), 4.12–4.26 (m, 1H), 3.72–3.87 (m, 1H), 1.12–2.26 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.7, 127.9, 125.5, 119.6, 72.6, 67.1, 33.7, 31.5, 29.6,24.7. LC-MS: *m*/*z*: 244 (M+1).
Compound **5k**: 3-Chloro-1-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propan-2-ol: Solid, mp 100–102 °C; IR (KBr): $\nu_{(max)}$ 3446, 2922, 2852, 2364, 1741, 1632, 1461, 1379, 1217, 1020, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.68–7.72 (m, 2H), 7.29–7.40 (m, 3H), 4.63–4.69 (m, 1H), 4.45–4.52 (m, 1H), 4.31–4.38 (m, 1H), 3.56–3.63 (m, 2H). LC-MS: *m*/*z*: 238 (M+1). HRMS calcd for $C_{11}H_{13}N_3OCl(35)$ (M+1): 238.0747; found, 238.0739.