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$Cu(OTf)_2$/Cu-catalyzed four-component reaction: a facile synthesis of α-alkoxytriazoles via click chemistry

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ABSTRACT

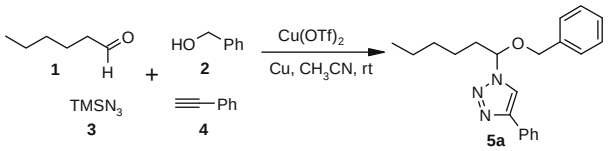
Aldehyde, alcohol, azide, and alkyne undergo smooth coupling by means of acetal formation, azidation, and a subsequent 'click reaction' in the presence of copper(II) triflate and copper metal in acetonitrile to furnish α-alkoxy-1,2,3-triazoles in good yields. The method provides a convenient route to prepare a wide range of triazoles in a one-pot operation via a four-component reaction.

The multi-component reactions are highly important because of their wide range of applications in pharmaceutical chemistry for the production of the diversified structural scaffolds and combinatorial libraries for drug discovery.[1] MCRs are extremely convergent, producing a remarkably high increase of molecular complexity in just one step.[2] Among MCRs, those based on the peculiar reactivity of isocyanides, such as the Doemling and Ugi[3] and the Passerini reactions,[4] have been the most widely used, also in an industrial context.[5] 1,2,3-triazoles are potential targets for drug discovery because of their wide range of biological properties such as anti-bacterial, anti-viral, anti-epileptic, and anti-allergic behavior.[6,7] Huisgen's thermal 1,3-dipolar cycloaddition of an alkyne with an azide, some times known as a 'click reaction', is one of the most widely used methods for the synthesis of triazoles.[8] However, this uncatalyzed cycloaddition results in products with poor regioselectivity and low yields. Subsequently, Cu(I)-catalyzed azide–alkyne cycloadditions (CuAACs), have been reported for the preparation of 1,4-disubstituted-1,2,3-triazoles from a wide range of substrates with excellent selectivity.[9,10] This powerful and reliable Cu(I)-catalyzed 1,3-dipolar cycloaddition has found widespread applications in combinatorial chemistry for drug discovery,[11] material science,[12] and bioconjugation.[13] Since 1,2,3-triazoles have become increasingly useful and important in drugs and pharmaceuticals,[14] the development of a simple and convenient method for their synthesis in a single step operation is desirable.

In this Letter, we report a multi-component, one-pot approach for the synthesis of α-alkoxytriazoles from aldehydes, alcohols, azides, and alkynes via a four-component reaction, proceeding via the formation of hemi-acetal followed by azidation and then 'click reaction.' In a preliminary study, *n*-hexanal (**1**) was treated with benzyl alcohol, trimethylsilyl azide, and phenylacetylene (**2**) in the presence of 5 mol % of $Cu(OTf)_2$ and 1 equiv of metallic copper in acetonitrile (Scheme 1).

The reaction proceeded smoothly at room temperature and the product, 1-[1-(benzyloxy)hexyl]-4-phenyl-1*H*-1,2,3-triazole **5a** was obtained in 75% yield. This result provided the incentive for further study with various other alkynes such as 1-octyne, 1-heptyne, 3,3-dimethyl-1-butyne, and 4-ethynylbiphenyl. These alkynes reacted readily with azides generated in situ from hemiacetals under similar conditions to produce α-alkoxy-1,2,3-triazoles in good yields (Table 1, entries **b**–**l**). Other aldehydes such as propanaldehyde, 2-phenylacetaldehyde, 3-phenylpropanaldehyde, and *n*-butaraldehyde also underwent smooth coupling with various alcohols, trimethylsilyl azide, and alkynes to produce a range of α-alkoxy-1,2,3-triazoles in good yields.

A variety of alcohols such as benzylic, allylic, and primary and cyclic secondary alcohols were reacted effectively in this reaction.



Scheme 1. Preparation of α-alkoxytriazole **5a**.

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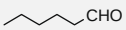
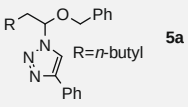
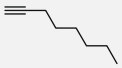
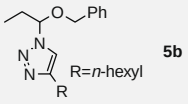
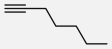
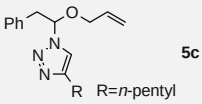
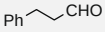
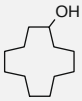
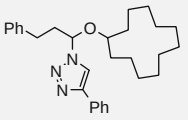
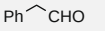
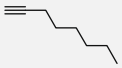
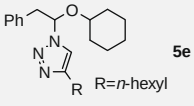
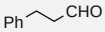
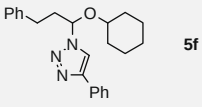
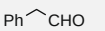
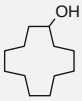
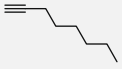
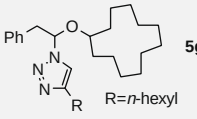
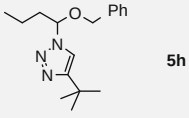
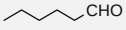
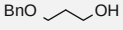
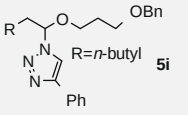
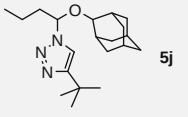
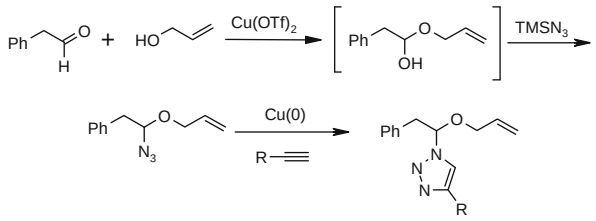
Table 1
Synthesis of α-alkoxytriazoles via the four-component reaction

Entry	Aldehyde	Alcohol	Alkyne	Product[a]	Time (h)	Yield (%)[b]
a				 **5a** R=*n*-butyl	10	75
b				 **5b** R=*n*-hexyl	12	80
c				 **5c** R=*n*-pentyl	14	75
d				 **5d**	13	80
e				 **5e** R=*n*-hexyl	12	75
f				 **5f**	12	80
g				 **5g** R=*n*-hexyl	13	75
h				 **5h**	15	75
i				 **5i** R=*n*-butyl	14	70
J				 **5j**	15	75
k				**5k** R=*n*-pentyl	16	70
l				**5l** R=*n*-pentyl	15	70

[a]The products were characterized by IR, NMR, and mass spectroscopy.
[b]Yield refers to pure products after chromatography.



Scheme 2. A plausible reaction mechanism.

However, in the absence of either copper triflate or copper(0), the reaction did not give the expected triazole even after long reaction times (8–12 h). Both copper triflate and copper metal are essential for the success of the reaction. The effect of various solvents such as THF, 1,2-dimethoxyethane, and acetonitrile was studied in the reaction of *n*-hexanal, benzyl alcohol, $TMSN_3$, and phenylacetylene under identical conditions. The corresponding product **5a** was obtained in 58%, 62%, and 75% yields, respectively. Thus, acetonitrile was found to give the best results. However, this method failed to produce the 1,2,3-triazoles from phenols and aromatic aldehydes. The reaction was successful only with aliphatic aldehydes and alcohols. The scope and generality of this process is illustrated in Table 1.[15] The reaction may proceed via acetal formation followed by azidation and a subsequent [3+2] cycloaddition as depicted in Scheme 2.

In summary, we have developed a novel approach for the preparation of α-alkoxytriazoles via a four-component reaction of aldehyde, alcohol, azide, and alkyne. In addition to its simplicity and mild reaction conditions, this method provides a wide range of α-alkoxytriazoles in good yields in a single-step operation.

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15. *General procedure*: To a mixture of *n*-hexanal (120 mg, 1.2 mmol), benzyl alcohol (108 mg, 1 mmol), and copper(II) triflate (18 mg, 5 mol %) in acetonitrile (5 mL) was added $TMSN_3$ (0.26 mL, 2.0 mmol) at 0 °C under nitrogen atmosphere and allowed to warm to room temperature. The reaction mixture was stirred until the complete consumption of alcohol. Then phenylacetylene (102 mg, 1 mmol) and Cu(0) powder (Aldrich-7440-50-8, 65 mg, 1 mmol) were added to the reaction mixture and stirred for the specified time (Table 1). The reaction mixture was then filtered through Celite and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate-hexane, 3:97) gave the pure triazole, which was characterized by IR, NMR, and mass spectroscopy. Spectral data for selected compounds. Compound **5a**: 1-[1-(Benzyloxy)hexyl]-4-phenyl-1*H*-1,2,3-triazole: Solid, mp 84–86 °C. IR (KBr): ν_{max} 3446, 2923, 2855, 1727, 1635, 1459, 1350, 1219, 1095, 1033, 762, 695 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.80–7.86 (m, 3H), 7.45–7.24 (m, 8H), 5.75 (t, J = 6.2 Hz, 1H), 4.41 (q, J = 19.5 Hz, 2H), 1.89–2.19 (m, 2H), 1.22–1.30 (m, 6H), 0.86 (t, J = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4, 136.2, 130.5, 128.8, 128.5, 128.2, 128.1, 125.7, 116.2, 89.1, 70.8, 35.9, 31.0, 24.2, 22.3, 13.9, 13.8. ESI-MS: m/z: 336 $(M+H)^+$. HRMS calcd for $C_{21}H_{25}N_3ONa$: 358.1895. Found: 358.1913. Compound **5b**: 1-(1-(Benzyloxy)propyl)4-hexyl-1*H*-1,2,3-triazole: Liquid, IR (neat): ν_{max} 3445, 2925, 2856, 1629, 1113 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (s, 1H), 7.22–7.31 (m, 5H), 5.58–5.62 (m, 1H), 4.29–4.39 (q, J = 18.1 Hz, 2H), 2.69 (t, J = 7.5 Hz, 2H), 1.85–2.14 (m, 4H), 1.27–1.67 (m, 6H), 0.89 (t, J = 7.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 141.2, 127.9, 127.2, 127.1, 114.5, 90.6, 72.7, 38.9, 36.1, 31.6, 31.4, 20.4, 19.0, 15.2, 14.2. ESI-MS: m/z: 302 $(M+H)^+$. HRMS calcd for $C_{18}H_{27}N_3ONa$: 324.2052, Found: 324.2078. Compound **5c**: 1-[1-(Allyloxy)-2-phenylethyl]-4-pentyl-1*H*-1,2,3-triazole: Liquid, IR (neat): ν_{max} 3446, 2930, 2858, 2362, 1717, 1646, 1500, 1457, 1372, 1246, 1218, 1035, 756, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.28–7.09 (m, 5H), 5.91–5.98 (m, 1H), 5.58–5.77 (m, 1H), 5.12–5.22 (m, 2H), 3.78–3.99 (m, 2H), 3.17–3.38 (m, 2H), 3.08 (t, J = 7.0 Hz, 2H), 1.68–1.88 (m, 2H), 1.23–1.45 (m, 4H), 1.03 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.0, 134.1, 132.1, 129.5, 128.5, 127.5, 123.0, 118.9, 89.9, 70.3, 42.4, 41.5, 30.9, 29.7, 17.4, 13.8. ESI-MS: m/z: 300 $(M+H)^+$. HRMS calcd for $C_{18}H_{25}N_3ONa$: 322.1895, Found: 322.1927. Compound **5k**: 1-[1-(Adamantanyloxy)hexyl]-4-(4-phenyl)-phenyl-1*H*-1,2,3-triazole: Semi-solid, IR (neat): ν_{max} 3256, 2929, 2853, 1469, 1441, 1342, 1253, 1006, 944, 903, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.87–8.07 (m, 5H), 7.37–7.51 (m, 5H), 5.65–5.70 (m, 1H), 4.00–4.09 (m, 1H), 1.04–1.69 (m, 22H), 0.77–0.83 (t, J = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 130.0, 129.5, 126.6, 125.7, 125.4, 90.4, 75.7, 69.3, 35.2, 32.4, 31.9, 31.4, 31.0, 30.9, 30.1, 29.7, 29.3, 24.5, 24.3, 24.2, 23.9, 23.8, 23.7, 23.6, 23.3, 23.2, 22.9, 22.8, 22.6, 21.0, 20.9, 14.2. ESI-MS: m/z: 456 $(M+H)^+$. HRMS calcd for $C_{30}H_{37}N_3ONa$: 478.2834, Found: 478.2856.