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Regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles via three-component coupling of secondary alcohols, $TMSN_3$ and alkynes

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Abstract—1,4-Disubstituted 1,2,3-triazoles are obtained in excellent yields via a three-component coupling of secondary alcohols, alkynes and trimethylsilyl azide ($TMSN_3$). This one-pot reaction occurs through in situ generation of an azide from the alcohol and $TMSN_3$, followed by 1,3-dipolar cycloaddition of the terminal alkyne to afford the corresponding disubstituted triazoles.

1,2,3-Triazoles are useful synthetic targets in organic synthesis and are associated with biological properties such as antiviral, antibacterial, antiepileptic and anti-allergic.[1,2] They have also found applications as optical brighteners, light stabilizers, fluorescent whiteners and corrosion retarding agents.[3] The well established method for their synthesis is via Huisgen's 1,3-dipolar cycloaddition between an alkyne and an organic azide.[4] However, this uncatalyzed synthetic method results in products with poor regioselectivity and low yields. In recent years, numerous methods have been reported for the synthesis of triazoles, which include Cu(I) catalyzed ligation of azides and alkynes[5] as well as in situ generation of Cu(I) species from copper nanoclusters and nanopowders.[6] Fokin and co-workers have developed the reaction using both conventional and microwave methods.[7] Yamamoto and co-workers reported the synthesis of triazoles via a three-component coupling of carbonates, $TMSN_3$ and alkynes in the presence of Pd–Cu as a bimetallic catalyst.[8]

As part of our research program directed towards the synthesis of triazoles under various reaction conditions,[9] we have studied the reactivity of alcohols in such reactions. Whereas it has been shown that nucleophilic substitution of alcohols with alkali azides generally requires activation of the hydroxyl group of the alcohols by formation of the corresponding tosylates.[10] Herein, we report a one-pot, two-step reaction between secondary alcohols, $TMSN_3$ and terminal alkynes in the presence of a catalytic amount of a $Cu(OTf)_2$ and Cu powder to give 1,4-disubstituted 1,2,3-triazoles (Scheme 1). The products contain various substituents on triazole ring and alkyl side chains on N-1 of the triazole. This three-component coupling reaction proceeds via nucleophilic substitution of the secondary alcohols with $TMSN_3$ to afford the corresponding azides in the presence of $Cu(OTf)_2$ without activation of the hydroxyl group. The azide generated in situ on Cu(I) catalyzed reaction with terminal alkynes gave 1,4-disubstituted 1,2,3-triazoles in excellent yields. The reaction conditions were optimized by varying the catalyst or the solvent.

Primarily, different solvents were screened in the reaction of 1-phenylethanol, **1a** $TMSN_3$ and phenylacetylene **3a** in the presence of 3 mol % of $Cu(OTf)_2$ and Cu-powder at 60 °C, the results are summarized in Table 1. Among the solvents screened, DMSO, methanol and acetonitrile gave the product in moderate to good yields, whereas the reaction in nitromethane gave the desired product in excellent yield. However, when the reaction was carried out in mixed solvent systems, the product was only obtained in trace quantities. Among nitrogen nucleophiles, sodium azide did not result any nucleophilic substitution whereas $TMSN_3$ was very effective for the reaction.

Keywords: 1,4-Disubstituted 1,2,3-triazoles; 1,3-Dipolar cycloaddition; Secondary alcohols; Azide; $Cu(OTf)_2$.
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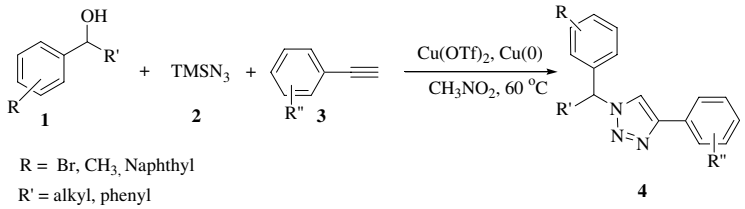


Scheme 1.

Table 1. Effect of solvent on the synthesis of triazoles[a]

Entry	Solvent	Time (h)	Yield[b] (%)
1	DMSO	24	60
2	CH_3OH	24	75
3	CH_3CN	8	80
4	CH_3NO_2	8	95
5	*t*-BuOH/H_2O	24	Trace
6	CH_3CN/H_2O	24	Trace

[a] Reaction conditions as exemplified in the reaction procedure.[11]
[b] Isolated yield.

Further, we investigated the effect of various copper catalysts for the three-component reaction. The presence of either Cu(II) or Cu(0) alone did not afford the desired product, hence a combination of both Cu(II) and Cu(0) catalysts was used to afford **4** in good yields. Initially, the Cu(II) catalyst was responsible for the nucleophilic substitution of the alcohol with the azide, addition of the Cu(0) catalyst facilitates in situ generation of a Cu(I) species which is responsible for the formation of copper acetylide from the terminal alkyne

Table 2. Synthesis of triazoles via the three-component reaction of various secondary alcohols, alkynes and $TMSN_3$[a]

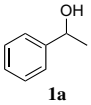
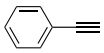
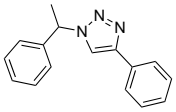
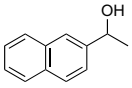
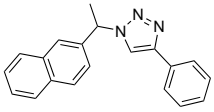
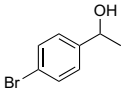
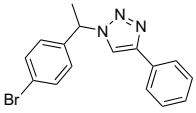
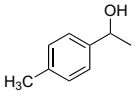
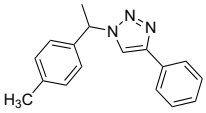
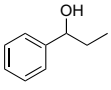
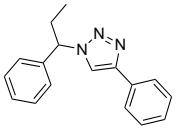
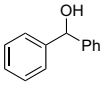
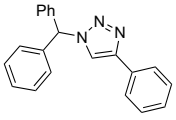
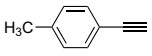
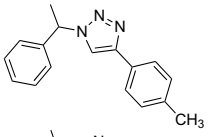
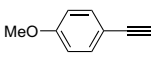
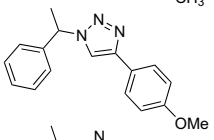
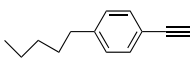
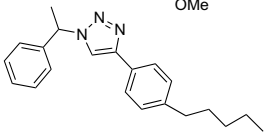
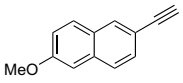
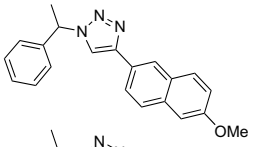
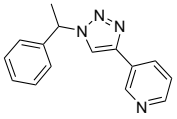
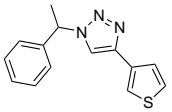
Entry	Alcohol (**1**)	Alkyne (**2**)	Product (**3**)	Yield[b,c] (%)
1	 **1a**	 **2a**		95
2		**2a**		86
3		**2a**		80
4		**2a**		85
5		**2a**		95
6		**2a**		92
7	**1a**			90
8	**1a**			85
9	**1a**			78

Table 2 (*continued*)

Entry	Alcohol (**1**)	Alkyne (**2**)	Product (**3**)	Yield[b,c] (%)
10	**1a**			72
11	**1a**			35
12	**1a**			65

[a] Reaction conditions as exemplified in the typical experimental procedure.[11]
[b] Isolated yields.
[c] All products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy.[12]

resulting in the 1,3-dipolar cycloaddition. Among the various copper(II) salts screened, $CuCl_2$ and $CuSO_4$ were ineffective, whereas $Cu(OTf)_2$ was found to be an efficient catalyst. However, the reaction in the presence of CuI was found to be slow giving low yields.

Under the optimized reaction conditions, various secondary alcohols were subjected to reaction with $TMSN_3$ followed by terminal alkynes and the results are presented in Table 2. It was found that reaction of the secondary alcohols with $TMSN_3$ was fairly general and tolerated a variety of substituted secondary alcohols (Table 2, entries 1–6). In order to extend the scope of the reaction, several terminal alkynes were reacted with the in situ generated azides of 1-phenylethanol. *p*-Methyl- and *p*-methoxy-substituted phenyl acetylenes were found to be more reactive compared to *p*-pentyl-substituted phenyl acetylene and *p*-methoxynaphthyl acetylene (Table 2, entries 7–10). The reaction with heterocyclic terminal alkynes gave the corresponding triazoles in lower yields (Table 2, entries 11 and 12).

In conclusion, an efficient method for the synthesis of 1,4-disubstituted 1,2,3-triazoles from a variety of secondary alcohols, $TMSN_3$ and terminal alkynes has been developed via a simple one-pot, two-step procedure using a combination of both Cu(II) and Cu(0) catalysts ($Cu(OTf)_2$ and Cu-powder).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.069.

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11. *Typical experimental procedure*: A mixture of secondary alcohol (1 mmol), $TMSN_3$ (1.2 mmol) and $Cu(OTf)_2$

(3 mol %) in nitromethane (3 mL) was stirred at 60 °C for 3 h and the extent of reaction was monitored by TLC. Phenylacetylene (1.1 mmol) and Cu-powder (3 mol %) were added and the reaction was stirred at 60 °C for 3 h. After completion of the reaction (as monitored by TLC), the catalyst was filtered through Celite and the product was extracted with ethyl acetate (3 × 10 mL). After drying and removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (hexane–ethyl acetate (12:88)) to afford pure product. All products gave satisfactory spectroscopic and analytical data.

12. Spectroscopic data for representative examples: *4-Phenyl-1-(1-phenyl-ethyl)-1H-(1,2,3)triazole (Table 2, entry 1):* ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.03 (d, 3H, $J = 7.6$ Hz), 5.79–5.86 (q, 1H, $J = 7.6$ Hz), 7.23–7.39 (m, 8H), 7.55 (s, 1H), 7.75 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 21.23, 60.25, 118.20, 125.62, 126.52, 128.0, 128.56, 128.73, 128.99, 130.68, 139.90, 147.76. LC–MS (*m/z*): 250.0 $(M+H)^+$. Anal. Calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.85. Found: C, 77.03; H, 6.12; N, 16.83. *4-(4-Pentyl-phenyl)-1-(1-phenyl-ethyl)-1H-[1,2,3]triazole (Table 2, entry 9):* ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.85 (t, 3H, $J = 6.5$ Hz), 1.24–1.33 (m, 4H), 1.53–1.68 (m, 2H), 2.01 (d, 3H, $J = 7.2$ Hz), 2.55 (t, 2H, $J = 7.9$ Hz), 5.76–5.86 (q, 1H, $J = 7.2$ Hz), 7.12 (d, 2H, $J = 7.9$ Hz), 7.25–7.37 (m, 5H) 7.5 (s, 1H), 7.63 (d, 2H, $J = 7.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 13.96, 21.27, 22.49, 30.98, 31.42, 35.67, 60.19, 118.00, 125.59, 126.06, 128.06, 128.47, 128.76, 128.99, 140.02, 142.96, 147.85. LC–MS (*m/z*): 320.2 $(M+H)^+$. Anal. Calcd for $C_{21}H_{25}N_3$: C, 78.96; H, 7.89; N, 13.15. Found: C, 78.92; H, 7.92; N, 13.15. See Supplementary data for spectral data of all other compounds.