Copper(II) Triflate as a Double Catalyst for the One-Pot Click Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from Benzylic Acetates

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Abstract: Copper(II) triflate doubly catalyzed the substitution of benzylic acetates by $TMSN_3$ and the subsequent 1,3-dipolar addition with an alkyne in one pot. This procedure afforded the preparation of 1,4-disubstituted 1,2,3-triazoles in good yields starting from the easily accessible acetates without isolating an organic azide using a single catalyst.

Key words: triazole, copper(II) triflate, click reaction

'Click chemistry' has recently drawn much attention as a powerful and efficient way to synthesize the desired compounds in high yields using a simple and benign procedure.[1] The Huisgen 1,3-dipolar cycloaddition of azide and alkynes is the most intensively studied click reaction which yields 1,2,3-triazoles in high yields by just mixing the starting compounds and Cu(I) catalyst in an aqueous solvent.[2] The starting organic azides are usually prepared and isolated by the substitution reaction of the organic halides by sodium azide. As some organic azides can be explosive and need to be handled with care, a procedure without isolating the azide should be preferable. The improved click syntheses of 1,2,3-triazoles without isolation of organic azides have been reported, in which the three-component reaction of an organic halide, sodium azide, and an alkyne is carried out in one pot.[3] This procedure would be more useful if the starting organic halides could be replaced by more easily accessible compounds, such as alcohols and their derivatives. The one-pot method employs an acetate as the starting compound, but it is first converted into the corresponding halide, then the azide in situ.[4] We now report the $Cu(OTf)_2$ doubly catalyzed one-pot procedure for the synthesis of a 1,4-disubstituted 1,2,3-triazole using the corresponding acetate as a precursor of an azide which undergoes cyloaddition with an alkyne.

We previously reported the substitution of 1-ferrocenylethyl acetate by azidotrimethylsilane ($TMSN_3$) in the presence of a Lewis acid, such as $Cu(OTf)_2$ and $Sc(OTf)_3$, in the synthetic studies of the chiral ferrocenyl diamine.[5] The extension of the reaction to 1-phenylethyl acetate (**1**) successfully produced the corresponding azide in a quantitative amount.[6] We tried the subsequent click reaction of the azide generated in situ from the acetate with phenylacetylene in one pot without isolation of the azides. Table 1 summarizes the results of the one-pot (two-step) click reaction of **1** with phenylacetylene.[7] The preceding displacement reaction was carried out using a 1:1.5 molar ratio of **1** to $TMSN_3$ (1.5 equiv),[8] and a catalytic amount of $Cu(OTf)_2$ (10 mol%) at room temperature in dichloromethane. After the reaction was completed, i.e., disappearance of the acetate **1** (ca. 12 h), then phenylacetylene and the additive (0.1–1.1 equiv) were added to the mixture and the following reaction was carried out for 1 hour. After the usual workup, identification and determination of the product were carried out using GC-MS. The product **2** was fully characterized by a spectroscopic method and confirmed by comparison to the authentic sample separately prepared by Sharpless's click reaction.[2] No additive left the azide unchanged, $Cu(OTf)_2$ itself hardly catalyzing the following 1,3-dipolar cycloaddition (entry 1). When ascorbic acid, sodium ascorbate, or potassium ferrocyanate was added to the mixture in order to reduce the Cu(II) species to the Cu(I) species, which could work as a catalyst for the following cycloaddition reaction, the corresponding 1,4-disubstituted 1,2,3-triazole **2** was obtained in low yields (entries 2 and 3) using the former two additives. The addition of CuI and CuCl as a Cu(I) salt itself resulted in no reaction and a low yield, respectively (entries 5 and 6). The addition of diisopropyl ethyl amine (DIPEA) as an additive remarkably improved the yield of the triazole **2**; compound **2** was obtained in an 81% yield (entry 7) and any unreacted azide was scarcely contained in the final products.[9] The addition of 2,6-lutidine as an tertiary amine was not so effective as DIPEA, producing a low yield of **2** (entry 8).[10]

We separately confirmed that the 1,3-dipolar cycloaddition of the isolated azide with phenylacetylene proceeded to give **2** in the presence of both the amine and a catalytic amount of $Cu(OTf)_2$ (10 mol%), but did not proceed in the absence of either the amine or $Cu(OTf)_2$; the amine itself did not catalyze the cycloaddition. The use of other Cu(I) and Cu(II) salts, such as $CuOTf{\cdot}C_6H_6$ and $CuSO_4{\cdot}5H_2O$, was ineffective for the preceding displacement reaction. While $Sc(OTf)_3$ could catalyze the substitution reaction of **1** with $TMSN_3$, it could not catalyze the cycloaddition: The cycloaddition could not be catalyzed by a Lewis acid, and a copper(II) catalyst should be required for the reaction. Dichloromethane was the choice of solvents; the preceding reaction did not proceed in THF, diethyl ether, DMF, or DMSO, and **2** was hardly obtained in MeCN and

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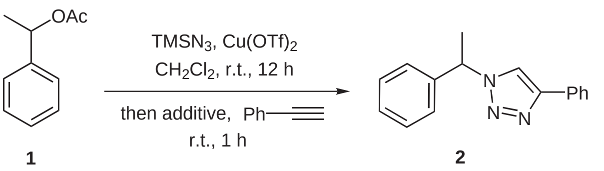
Table 1 The One-Pot Reaction of 1-Phenylethyl Acetate, $TMSN_3$, and Phenylacetylene Catalyzed by $Cu(OTf)_2$[a]

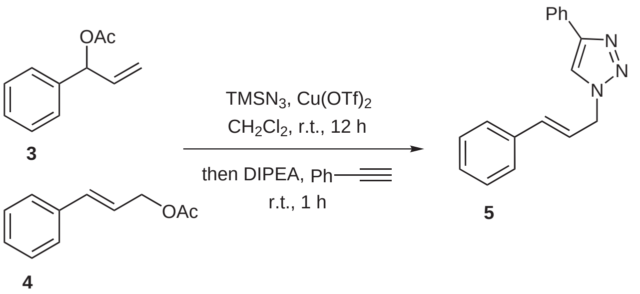


Entry	Additive	Yield of **2** (%)[b]
1	None	0
2	Ascorbic acid	24
3	Sodium ascorbate	26
4	$K_4Fe(CN)_6 \cdot 3H_2O$	0
5	CuI	0
6	CuCl	29
7	DIPEA[c]	81
8	2,6-Lutidine[d]	47

[a] Compound **1** (0.5 mmol), $TMSN_3$ (0.75 mmol), $Cu(OTf)_2$ (0.05 mmol), CH_2Cl_2 (1 mL), r.t., 12 h, then phenylacetylene (0.6 mmol), additive (0.05 mmol), r.t., 1 h.
[b] Determined by GC-MS.
[c] DIPEA (0.55 mmol).
[d] 2,6-Lutidine (0.75 mmol).

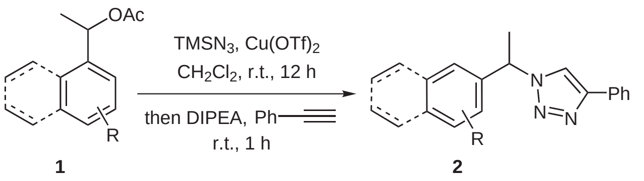
toluene although the production of a small amount of the azide was observed.

This one-pot reaction is interesting and useful because $Cu(OTf)_2$ doubly catalyzed the preceding displacement reaction and the following cycloaddition reaction without any additional metal catalyst. Furthermore, the reaction can completely be carried out at room temperature. Thus, the reaction was applied to the aromatic substituted benzylic acetates, and these results are summarized in Table 2.[11] The sequential reaction with the *o*-, *m*, and *p*-methylphenyl derivatives gave the corresponding 1,4-disubstituted 1,2,3-triazoles in good yields (entries 2–4). For the reaction, the intermediate azide was hardly observed; most of the azide was consumed and transformed into the triazole. The *p*-halogeno-substituted (Cl, F) benzylic triazoles were obtained in good yields (entries 6 and 7), but the reaction with *o*-chlorophenyl derivative gave the corresponding triazole in low yields, the starting acetate being recovered mostly (entry 5). The *p*-nitro-substituted triazoles were not obtained, as no azide was produced in the first reaction (entry 8). The reaction with the 1- and 2-naphthyl derivatives proceeded to give the corresponding **2** in good to excellent yields (entries 9 and 10). This process could be applied to alkynes other than phenylacetylene, such as 1-hexyne and 2-methyl-3-butyn-2-ol with the corresponding 4-alkyl-substituted triazole being obtained in good yields (entries 11 and 12).



Scheme 1

Table 2 The One-Pot Click Synthesis of 1,4-Substituted 1,2,3-Triazoles Doubly Catalyzed by $Cu(OTf)_2$[a]



Entry	R in **1**	Yield of **2** (%)[b]
1	H	81 (71)[c]
2	*o*-Me	85 (81)[c]
3	*m*-Me	75
4	*p*-Me	83 (80)[c]
5	*o*-Cl	11
6	*p*-Cl	61
7	*p*-F	78
8	*p*-NO_2	0
9	1-Naphthyl	94 (84)[c]
10	2-Naphthyl	53
11[d]	H	70[c]
12[e]	H	65[d]

[a] Compound **1** (0.5 mmol), $TMSN_3$ (0.75 mmol), $Cu(OTf)_2$ (0.05 mmol), CH_2Cl_2 (1 mL), r.t., 12 h, then phenylacetylene (0.6 mmol), DIPEA (0.55 mmol), r.t., 1 h.
[b] Determined by GC-MS.
[c] Isolated yield.
[d] 1-Hexyne was used as the alkyne.
[e] 2-Methyl-3-butyn-2-ol was used as the alkyne.

The reaction could not be applied to the benzyl and allyl acetates since the substitution by $TMSN_3$ did not proceed in the presence of $Cu(OTf)_2$. However, the sequential reaction with 1-phenylallyl **3** and cinnamyl acetate **4** proceeded to give the same products, the 1,4-disubstituted cinnamyl triazole **5** in moderate yields (30–50%, Scheme 1).[12]

In conclusion, this procedure allowed the preparation of 1,4-disubstituted 1,2,3-triazoles in good yields starting from easily accessible acetates without isolating the organic azide using $Cu(OTf)_2$ as a double catalyst.

Acknowledgment

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(6) The $Cu(OTf)_2$-catalyzed reaction of (*R*)-1-phenylethyl acetate (95% ee) with $TMSN_3$ under the conditions gave the racemate 1-phenylethyl azide. This result suggests that the substitution reaction proceeds with S_N1-type reaction.

(7) The reaction must be carried out in two steps. Mixing of three components, i.e., compound **1**, phenylacetylene, and $TMSN_3$, in the presence of the Cu catalyst and additive (DIPEA) in CH_2Cl_2 (1 mL) did not afford **2**, along with recovering the starting compounds. A typical experimental procedure is as follows: In a 20 mL Schlenk tube containing a magnetic stirring bar were charged $Cu(OTf)_2$ (18 mg, 0.05 mmol) and dry CH_2Cl_2 (1 mL) under a slight pressure of nitrogen. A mixture of 1-phenylethyl acetate (**1**, 82 mg, 0.5 mmol) and $TMSN_3$ (86 mg, 1.5 mmol) was then added using a syringe through the septum with stirring at r.t. The reaction was monitored by TLC and after the starting acetate had almost disappeared (12 h), phenylacetylene **2** (62 mg, 0.6 mmol) was then added to the mixture followed by DIPEA (95 μL, 0.55 mmol). The mixture was stirred at r.t. for an additional 1 h. The reaction was quenched with H_2O, and extracted with EtOAc (3 × 15 mL). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator that left a yellow residue. The GC-MS analysis revealed the presence of **2** of which the yield was determined by GC using biphenyl as the internal standard. The product **2** was isolated by preparative TLC (hexane–EtOAc, 4:1); yield, 89 mg, 71%. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.00$ (d, 3 H, $J = 7.1$ Hz), 5.86 (q, 1 H, $J = 7.1$ Hz), 7.30–7.50 (m, 8 H), 7.63 (s, 1 H), 7.80 (d, 2 H, $J = 7.3$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 21.2$, 60.1, 118.4, 125.6, 126.4, 128.0, 128.5, 128.7, 128.9, 130.6, 139.8, 147.6. IR (KBr): $\nu = 3092$, 1483, 1459, 1421, 1373, 1349, 1304, 1218, 1175, 1155, 1074, 1038, 1025, 993, 973, 913 cm^{-1}. Anal. Calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.85. Found: C, 76.86; H, 6.14; N, 17.01.

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