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Ruthenium-catalyzed 1,3-dipolar cycloaddition of trifluoromethylated propargylic alcohols with azides

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Abstract

The 1,3-dipolar cycloaddition of trifluoromethylated propargylic alcohols **1** with azides in the presence of catalytic $[Cp^*RuCl_2]_n$ afforded exclusively 4-trifluoromethyl-1,4,5-trisubstituted-1,2,3-triazoles **2** in high yields.

Keywords: 1,3-Dipolar cycloaddition; Triazole; Trifluoromethylated compound

The trifluoromethyl-substituted molecules are a class of interesting compounds because of their relevant properties[1] for the pharmaceutical and agrochemical areas.[2] Hence, the development of new synthetic methods and exploration of the utility of such kind of compounds are of great importance.[3] On the other hand, the construction of 1,2,3-triazole derivatives is a matter of current interest.[4] It has been demonstrated that the 1,2,3-triazole derivatives exhibit antimicrobial, antiviral and antitumour activities[5] and have a range of important applications in industries. To obtain these heteroarenes, the most widely used method is Huisgen 1,3-dipolar cycloaddition of azides with alkynes.[6] However, because of the high activation energy, these cycloadditions are often very slow even at elevated temperature (80–120 °C for 12–24 h) and produce a mixture of regioisomers. Recently, new methodologies based on catalysts have been reported for the construction of 1,2,3-triazoles. The 'click' chemistry reported by Sharpless group described that the Cu(I)-catalyzed cycloaddition can be conducted at room temperature and results in 1,4-disubstituted triazoles in high regioselectivity.[7] This type of copper catalysis, however, is restricted to the cycloadditions of terminal alkynes. More recently, the discovery of the ruthenium catalyst $Cp^*RuCl(PPh_3)_2$ allows the use of terminal alkynes and internal alkynes as well. In contrast to the copper-catalyzed 1,3-dipolar cycloaddition, the sole 1,5-disubstituted triazoles were produced in the case of the cycloadditions terminal alkynes and azides under ruthenium catalysis.[8] The regioselectivity of the cycloaddition of azides with unsymmetrical alkynes depends on the nature of the alkynes substituents albeit no rationale was presented.[9] Although efforts have been made to study the scope of the cycloaddition of internal alkynes,[9a] the reactivity of trifluoromethylated internal alkynes and the regioselectivity of the cycloaddition of azides with them have not been investigated so far. Accordingly, we were interested in investigating the feasibility of the synthesis of trifluoromethylated 1,2,3-triazoles and the regioselectivity of 1,3-dipolar cycloaddition of azides with trifluoromethylated alkynols **1**.

Trifluoromethylated propargylic alcohols **1** were easily prepared from 2-bromo-3,3,3-trifluoropropene and ketones (aldedydes) in the presence of 2 equiv of LDA (Scheme 1).[10]

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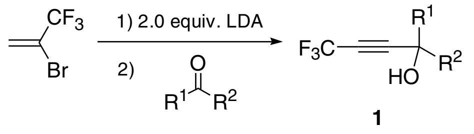
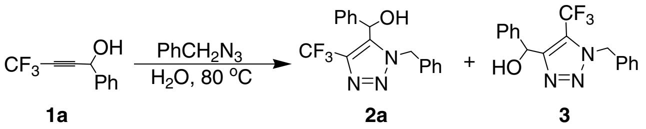


Scheme 1.



Scheme 2. Uncatalyzed cycloaddition of benzyl azide with **1a**.

Recently, Ju et al. reported that the 1,3-dipolar cycloaddition of azides with electron-deficient alkynes proceeded smoothly in water without any catalysts.[11] Accordingly, the thermal (uncatalyzed) cycloaddition of benzyl azide with 4,4,4-trifluoro-1-phenyl-2-butyn-1-ol **1a** in water was investigated. A mixture of benzyl azide and **1a** in water was stirred at 80 °C for 48 h to give a mixture of regioisomers **2a** and **3** in 58% isolated yield. The ratio of **2a**:**3** was 52:48 (Scheme 2). This is different from the previous thermal cycloaddition of electron-deficient internal alkynes with azides, which only results in type **2a** isomer.[11] Structure **3** was determined by the X-ray diffraction analysis (Fig. 1).[12]

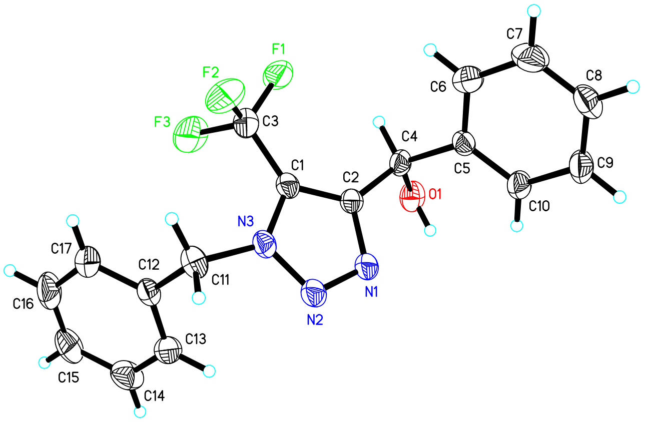


Fig. 1. The crystal structure of **3**.

Table 1

Pd-catalyzed cycloaddition of trifluoromethyl propargylic alcohol **1a** with benzyl azide[a]

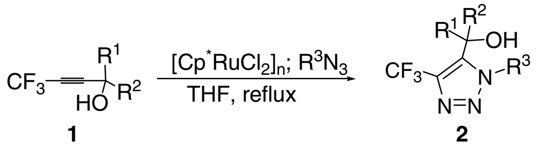
Entry	Catalyst	**2a**:**3**	Isolated yield (%)
1	Pd(OAc)$_2$/PPh$_3$	57:43	81
2	PdCl$_2$(dppf)	54:46	86
3	Pd(PPh$_3$)$_4$	77:23	90

[a] A mixture of **1a**, benzyl azide and 5% palladium catalyst was stirred in reflux benzene for 5 h.

To improve the yield and regioselectivity of this 1,3-dipolar cycloaddition, the cycloaddition of **1a** with benzyl

Table 2

Ruthenium-catalyzed cycloaddition of trifluoromethyl propargylic alcohols and azides[a]



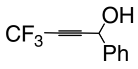
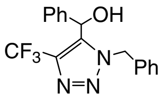
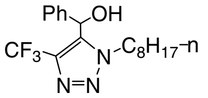
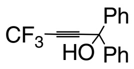
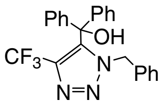
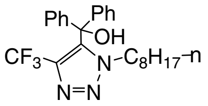
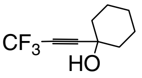
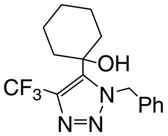
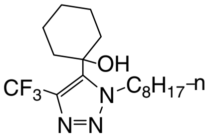
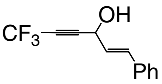
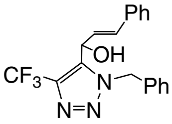
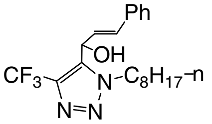
Entry	Alkynol **1**	Azide	1,2,3-Triazole **2**	Isolated yield (%)
1	 **1a**	PhCH$_2$N$_3$	 **2a**	89
		n-C $_8$H$_{17}$N$_3$	 **2a'**	89
2	 **1b**	PhCH$_2$N$_3$	 **2b**	64
		n-C $_8$H$_{17}$N$_3$	 **2b'**	82 (73[b])

Table 2 (*continued*)

Entry	Alkynol **1**	Azide	1,2,3-Triazole **2**	Isolated yield (%)
3	 **1c**	$PhCH_2N_3$	 **2c**	85
		n-$C_8H_{17}N_3$	 **2c'**	92 (66[b])
4	 **1d**	$PhCH_2N_3$	 **2d**	95 (92[b])
		n-$C_8H_{17}N_3$	 **2d'**	86

[a] The reaction was conducted in THF at 66 °C.

[b] The reaction was conducted in benzene at 80 °C.

azide under the palladium catalysis was carried out. As shown in Table 1, the cycloaddition was completed in 5 h and the isolated yields of products (**2a** and **3**) were improved to 81–90%. However, the regioselectivities of the cycloaddition in all the palladium catalysts were still poor (entries 1–3).

To our delight, when the cycloaddition of **1a** and benzyl azide was conducted in the presence of $[Cp^*RuCl_2]n$ (10 mol % base on Ru) in reflux THF for 5 h, the ^{19}F NMR of the reaction mixture showed that only one isomer was formed and product **2a** was isolated in 89% yield (Table 2, entry 1). We then investigated the reaction of various trifluoromethylated propargylic alcohols with benzyl or alkyl azides under these reaction conditions.[13] These results are presented in Table 2. It was noteworthy that all the reactions afforded exclusively 4-trifluoromethyl-1,4,5-trisubstituted-1,2,3-triazoles in high yields. The steric tertiary alcohols **1b**–**c** can also lead to the products in good yields. The yields of cycloaddition reaction in reflux THF were higher than those of in reflux benzene. The regioselectivity of the cycloaddition of trifluoromethylated propargylic alcohols was similar to that of the ruthenium-catalyzed cycloaddition of ussymmetrical disubstituted alkynes bearing a carbonyl group.[9a] These regiochemical results implied that the cycloaddition was presumably controlled by the polarity effect.

In conclusion, we have developed a convenient method for the regioselectivity synthesis of 4-trifluoromethyl-1,4,5-trisubstituted-1,2,3-triazoles [14] by the ruthenium catalyzed cycloaddition of trifluoromethyl alkynols with azides.

Acknowledgement

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12. Crystal data have been deposited at the Cambridge Crystallographic Data Center with reference number CCDC 667050.
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