



Copper-mediated trifluoromethylation of 5-iodotriazole with (trifluoromethyl)trimethylsilane promoted by silver carbonate



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ABSTRACT

A novel and mild method for copper-mediated trifluoromethylation of 5-iodotriazole using (trifluoromethyl)trimethylsilane (Me_3SiCF_3) as trifluoromethylating reagent with the assistance of Ag_2CO_3 was developed.

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1. Introduction

Compounds containing trifluoromethyl groups have received considerable attention due to their important applications in the pharmaceutical, agrochemical and polymer industry [1]. Up to now, various methods have been developed for trifluoromethylation of diverse molecules such as arenes [2], aryl halides [3], carbonyl compounds [4], arylboronic acids [5] and terminal alkynes [6]. However, the incorporation of the trifluoromethyl group into heteroarenes still remains a great challenge for the chemical community [7].

1,2,3-Triazoles derivatives have occupied a unique position in heterocyclic chemistry due to their wide range of biological activities [8]. However, the method of the introduction of trifluoromethyl group to triazole ring is very scarce [9]. For example, Bakulev reported the regioselective synthesis of 5-trifluoromethyl-1,2,3-triazoles via cyclization of 1-trifluoromethyl-1,3-dicarbonyl compounds with azides [10]. In 2011, Wang et al. synthesized two trifluoromethyl-containing 1,4,5-trisubstituted 1,2,3-triazoles by treatment of phenyl azide with ethyl 4,4,4-trifluoroacetoacetate and 4,4,4-trifluoro-1-phenylbutane-1,3-dione in presence of organocatalytic acyclic diethyl amine [11]. More recently, we reported a facile and practical

method for the synthesis of CF_3 (or CF_2H)-containing 1-aryl-1,4,5-trisubstituted 1,2,3-triazole derivatives via a one-pot three-component reaction of boronic acids, sodium azide, and active methylene ketones, such as ethyl 4,4-difluoroacetoacetate or ethyl 4,4,4-trifluoroacetoacetate in the presence of $\text{Cu}(\text{OAc})_2$ and piperidine [12]. To the best of our knowledge, up to now, there is no report on the direct trifluoromethylation of triazole ring with trifluoromethylating reagent. In continuation of our interest in the synthesis of novel functionalized 1,2,3-triazoles [13], in this paper, we report Cu-mediated trifluoromethylation of 5-iodotriazole by the combination of $\text{Me}_3\text{SiCF}_3/\text{CuI}/\text{KF}/\text{phen}$ (1,10-phenanthroline) using Ag_2CO_3 as a promoter (Scheme 1).

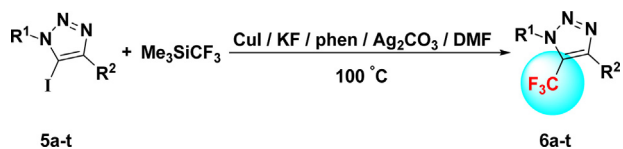
2. Results and discussion

5-Iodo-1,4-disubstituted triazoles are versatile synthetic intermediates and can be used for the further construction of diverse 1,4,5-trisubstituted-1,2,3-triazoles [14]. However, a practical drawback of this building block is that the carbon iodine bond in this triazole ring is easily cleaved and undergo reductive dehalogenation in the presence of copper salt, and can generate the corresponding 5-prototriazole in considerable yields during the course of preparation and functionalization of 5-iodotriazoles [15]. Therefore, an intricate synthetic challenge of trifluoromethylation of 5-iodotriazoles is to inhibit this side reaction (protodehalogenation).

Generally, the most important method for trifluoromethylation of aryl iodides involves the use of Me_3SiCF_3 as trifluoromethylating reagent in presence of a stoichiometric amount of CuI and KF [16a]

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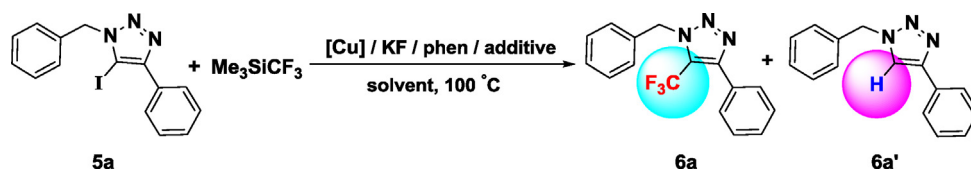
Scheme 1. Trifluoromethylation of 5-iodotriazoles with Me_3SiCF_3 .

or a catalytic amount of CuI and KF along with 10 mol% phen [16b]. Thus, we chose the coupling of 1-benzyl-5-iodo-4-phenyl-1*H*-1,2,3-triazole **5a** with Me_3SiCF_3 in presence of copper salt, KF and phen as a model reaction to determine the optimal reaction conditions (Table 1). Initially, we investigated the influence of solvent on the reaction (entries 1–6). The choice of solvents proved crucial for the formation of trifluoromethylated product **6a**. When toluene, CH_3CN were used as solvents, no desired product **6a** was observed and gave a significant amount of 5-prototriazole **6a'** along with the recovered starting material **5a**. Running the reaction in THF only afforded 5-prototriazole **6a'** as the exclusive product. Fortunately, when the reaction was carried out in CH_3NO_2 , DMSO or DMF, the trifluoromethylation took place and generated the mixture of trifluoromethylated product **6a** and 5-prototriazole **6a'** (entries 4–6). The aprotic polar solvent, DMF, proved to be a more suitable solvent for this transformation and could afford **6a** in 68% yield. However, the yield is unsatisfactory. Therefore, it was necessary to optimize the reaction conditions or develop a practical method for the trifluoromethylation of 5-iodotriazole.

Attempts to improve the yield of **6a** by using other trifluoromethylating reagents were unsuccessful. No product was observed and large amounts of starting material **5a** were recovered when we employed sodium trifluoromethanesulfonate ($\text{CF}_3\text{SO}_2\text{Na}$, Langlois reagent) as the trifluoromethyl source in the presence of *tert*-butylhydroperoxide (TBHP) [17]. Trifluoromethylation of **5a** with Togni reagent or Umemoto reagent in the presence of Cu catalyst afforded the mixture of **6a** and **6a'** [18]. The yield of **6a** was around 55%.

Next, we turned our efforts to improve the yield of trifluoromethylated product **6a** using $\text{Me}_3\text{SiCF}_3/\text{CuI}/\text{KF}/\text{DMF}$ system. According to literatures, oxidants exhibit a strong effect on the copper-mediated or catalyzed oxidative trifluoromethylation of terminal alkynes [19], aryl boronic acids [20] indoles [21] and heteroarenes [22] with Me_3SiCF_3 . However, it is reported that trifluoromethylation of aryl iodides with Me_3SiCF_3 could proceed smoothly in absence of oxidant [23]. Considering that the carbon–iodine bond of the triazole easily undergoes reductive dehalogenation, we envisaged that the competing protodehalogenation reaction might be suppressed by addition of some oxidants to the reaction system. Thus, firstly, reaction of 5-iodo-1,2,3-triazole **5a** with Me_3SiCF_3 was carried out under argon or oxygen atmosphere (Table 1, entries 7 and 8). The results indicated that there are no apparent differences in the yields of **6a** when the reactions were performed under ambient atmosphere of air, argon and oxygen. To improve the transformation, other oxidants such as $\text{K}_2\text{S}_2\text{O}_8$, DDQ, $\text{Cu}(\text{OAc})_2$ and 1,4-benzoquinone were further tested (entries 9–12). When 2,3-dichlorobutane was applied as oxidant, the yield of the desired product **6a** increased to 80% and the side

Table 1
Optimization of the trifluoromethylation of **5a** with Me_3SiCF_3 .^a



Entry	[Cu] (equiv.)	Solvent	Additive (equiv.)	Yields (%) ^b 6a (6a')
1	CuI (1.0)	Toluene	None	0 (58) ^c
2	CuI (1.0)	CH_3CN	None	0 (20) ^c
3	CuI (1.0)	THF	None	0 (98)
4	CuI (1.0)	CH_3NO_2	None	46 (50)
5	CuI (1.0)	DMSO	None	63 (32)
6	CuI (1.0)	DMF	None	68 (28)
7	CuI (1.0)	DMF	Ar	56 (43)
8	CuI (1.0)	DMF	O_2	65 (7)
9	CuI (1.0)	DMF	$\text{K}_2\text{S}_2\text{O}_8$ (3.0)	0 ^c
10	CuI (1.0)	DMF	DDQ (3.0)	5 (72)
11	CuI (1.0)	DMF	$\text{Cu}(\text{OAc})_2$ (3.0)	17 (82)
12	CuI (1.0)	DMF	1,4-Benzoquinone (3.0)	31 (57)
13	CuI (1.0)	DMF	2,3-Dichlorobutane (3.0)	80 (20)
14	CuI (1.0)	DMF	Ag_2CO_3 (5.0)	99
15	CuI (1.0)	DMF	Ag_2CO_3 (4.0)	99
16	CuI (1.0)	DMF	Ag_2CO_3 (3.0)	98
17	CuI (1.0)	DMF	Ag_2CO_3 (2.0)	98
18	CuI (1.0)	DMF	Ag_2CO_3 (1.5)	89 (8)
19	CuI (1.0)	DMF	$\text{CH}_3\text{CO}_2\text{Ag}$ (3.0)	0 (75) ^c
20	CuI (1.0)	DMF	AgNO_3 (3.0)	0 (51) ^c
21	CuI (0.5)	DMF	Ag_2CO_3 (2.0)	39 (60)
22	CuI (0.1)	DMF	Ag_2CO_3 (2.0)	3 (92)
23	Cu (1.0)	DMF	Ag_2CO_3 (2.0)	7 (63) ^c
24	CuCl (1.0)	DMF	Ag_2CO_3 (2.0)	31 (39)
25	$\text{Cu}(\text{OAc})_2$ (1.0)	DMF	Ag_2CO_3 (2.0)	0 (70) ^c
26	CuBr (1.0)	DMF	Ag_2CO_3 (2.0)	89

^a Reagents and conditions: **5a** (1.0 mmol), Me_3SiCF_3 (3.0 mmol), phen (1.0 mmol), KF (3.0 mmol), DMF (15–20 mL), 100 °C, 2–3 h, under air atmosphere.

^b Yields were based on GC analysis.

^c Starting material was incompletely converted.

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