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Syntheses of trifluoroethylated unsymmetrical 1,3-diynes by using 1,1-dichloro-2,2,2-trifluoroethane

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ABSTRACT

Copper-mediated reaction of terminal 1,3-diynes with 1,1-dichloro-2,2,2-trifluoroethane (CF_3CHCl_2) using ethanolamine as ligand gave trifluoroethylated unsymmetrical 1,3-diynes in moderate to good yields. The reaction were carried out under mild conditions, and were easy to operate. Aryl groups with weak electron-withdrawing group or electron-donating group, and alkyl substitutents at terminal 1,3-diynes were tolerated. Synthesis of a trifluoroethylated conjugated triyne by using this method was demonstrated. Further transformation of the trifluoroethylated unsymmetrical 1,3-diyne to provide trifluoroethyl-substituted 1,2,3-triazole and isoxazole as application examples were successfully realized.

Introduction

The incorporation of trifluoroethyl moieties into organic molecules has captured the attention of synthetic chemists recently.[1–16] The presence of fluorinated functional groups profoundly modify the physicochemical and biological properties of an organic compounds, and the steric, electronic, lipophilic, and metabolic characteristics of the compounds often changes significantly and commonly positive.[17–22] In recent years, trifluoroethyl-containing aromatic compounds have found an increasing number of applications in the fields of medicinal chemistry and biochemistry.[23] Many trifluoroethyl-containing compounds with biological activities, such as antimalarial activity, hypolipidemic activity, anesthetic property, anti-inflammatory activity and enzyme inhibition ability have been developed (Fig. 1).[24–27] Although fluorinated organic molecules have a great prospect, few natural organic fluorides have been found so far. The development of efficient synthetic methods for fluorinated organic compounds becomes essentially important for building a fluorinated realm as an abundant screening resource of medicinal and biological research.

Unsymmetrical 1,3-diynes have various potential applications in non-linear optical materials, liquid crystal materials and molecular devices.[28] In recent years, they were also found in natural products and some of them have antibacterial, anti-HIV or anticancer ability.[29–32] Simultaneously, unsymmetrical 1,3-diynes are important building blocks for polyynes in organic synthesis,[33] and were more often applied as the synthetic precursor for various heterocyclic compounds.[34] Methods for the syntheses of unsymmetrical diynes, are thus of great importance.

Typical ways of making conjugate diynes include Glaser-Hay coupling and Cadiot–Chodkiewicz coupling.[35] Cu-salt mediated Glaser coupling and related modified methods are still widely applied in the syntheses of conjugated diynes. In addition to the Cu-salt the scientists found that Pd, Ni or Au-catalysis is also effective for syntheses of the unsymmetrical 1,3-diynes.[32,36,37] In 2015, Rao's group[38] realized CuI-catalyzed reaction of 1,1-dibromoalkene and terminal alkynes to provide unsymmetrically substituted 1,3-diynes in a one-pot process. Methods to syntheses of unsymmetrical diynes by using terminal 1,3-diynes are few, because the terminal 1,3-diynes are unstable and easily undergo polymerization.[39] In 2012, Ma's group synthesized unsymmetrical diynes by using trifluoroethyl diazo compound prepared in situ as the trifluoroethylating reagent.[40] But preparation and utilization of explosive trifluoroethyl diazo compound required high caution in operation. In 2015, we developed a copper promoted method to synthesize trifluoroethylated alkynes by using 1,1-dichloro-2,2,2-trifluoroethane (HCFC-123).[41] HCFC-123 is used as refrigerant, centrifugal chiller, blowing agent, fire-extinguishing agent or detergent in industry. However, HCFC-123 is an ozone-depleting

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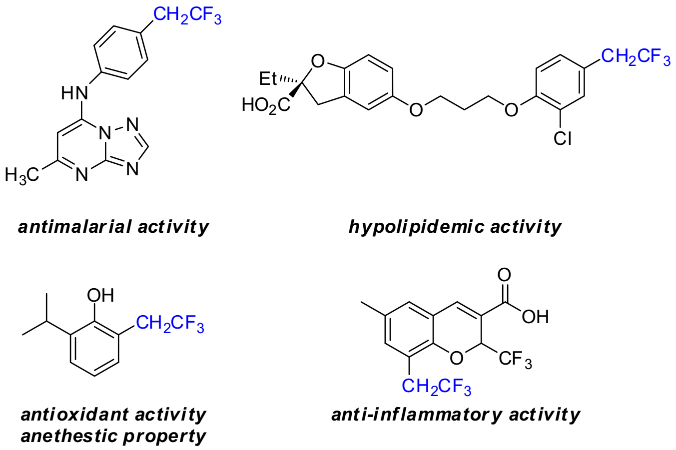


Fig. 1. Some trifluoroethylated compounds with biological activities.

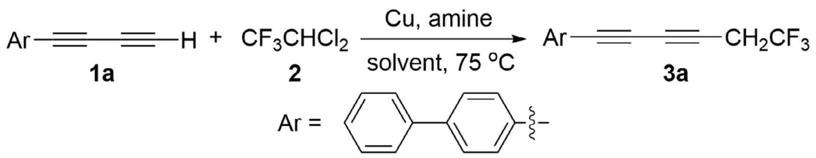
toxic substance, and will cause hepatitis. The research on the conversion of HCFC-123 to valuable materials will definitely important for developing an environmentally benign process for industrial utilization of bulk hydrochlorofluorocarbon. We herein provide this kind of convenient approach for the syntheses of versatile trifluoroethylated unsymmetrical 1,3-diynes by taking the advantage of HCFC-123.

Results and discussion

We began our investigation with biphenyl-1,3-diacetylene (**1a**) as the model substrate. Initially, according to our previous result,[41] a general solvent 1,2-dichloroethane (DCE) was selected as the solvent, and activated copper and diethylamine were used (Table 1, entry 1). To our delight, a new ^{19}F NMR signal at −65.9 ppm (t, $J = 9.4$ Hz) was found in 7% yield. Considering the effect of amines in solvent, different amines were screened in order to improve the yield. A 10% ^{19}F NMR yield of expected product was observed when the secondary amines dipropylamine was added, but no product was found when diisopropylamine was used (Table 1, entries 2 and 3). The desired product was not detected in the presence of tertiary amines, such as triethylamine, and pyridine (Table 1, entries 4 and 5). Then primary amines were examined in order to improve the yield of **3a**. Fortunately, the desired product was obtained in 24% yield when ethylenediamine was added (Table 1, entry 8) although aniline and β-alanine were noneffective (Table 1, entries 6 and 7). The yield was further increased to 45% and 58%, respectively, when benzylamine and *N*-ethylenediamine was used (Table 1, entries 9 and 10). Propylamine and butylamine afforded the desired product in the same yield of 65% (Table 1, entries 11 and 12). The highest yield of the desired product (83%) was achieved when ethanolamine was used as the additive (Table 1, entry 13). Then a series of solvents including CH_3CN, CCl_4, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetone and tetrahydrofuran (THF) were screened and proved to be noneffective. Benzene, toluene and CH_3NO_2 were found to be less effective than DCE (Table 1, entries 14–16).

With the optimized reaction conditions in hand, we next investigated the substrate scope of this reaction (Table 2). We found that various terminal 1,3-diynes (Table 2, entries 1–10) could be transformed to the corresponding products in moderate to good yields. 1,3-Diyne **1** with a methoxy substituent in the *para* position reacted smoothly to give product **3b** in 71% yield (Table 2, entry 2). When the methoxyl group was in the *ortho* and *meta* position, the yield of **3c** and **3d** was slightly decreased to 58% and 50%, respectively (Table 2, entries 3 and 4). Halogen atoms on the aromatic ring of 1,3-diyne including fluoro, chloro and bromo were all well tolerated in the copper-mediated reaction, which provided the possibility for further functionalization (Table 2, entries 8–10). Naphthyl substituted 1,3-diyne was also a good substrate and gave product **3k** in 73% yield (Table 2, entry 11). 1,3-Diynes with aliphatic substituent such as alkyl group and alkenyl group were also suitable substrates for the reaction condition to afford the corresponding trifluoroethylated products **3l**–**3n** in moderated yields (40–58%) (Table 2, entries 12–14).

Table 1
Screening of the optimal reaction conditions.[a]



Entry	Amine	Solvent	Yield (%)[b]
1	Diethylamine	DCE	7
2	Dipropylamine	DCE	10
3	Diisopropylamine	DCE	<5
4	Triethylamine	DCE	<5
5	Pyridine	DCE	<5
6	Aniline	DCE	<5
7	β-Alanine	DCE	<5
8	Ethylenediamine	DCE	24
9	Benzylamine	DCE	45
10	*N*-Ethylethylenediamine	DCE	58
11	Propylamine	DCE	65
12	Butylamine	DCE	65
13	Ethanolamine	DCE	83
14	Ethanolamine	Benzene	35
15	Ethanolamine	Toluene	64
16	Ethanolamine	CH_3NO_2	50

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), Cu (0.4 mmol), amine (0.6 mmol) and solvent (2 mL) at 75 °C in a Schlenk tube under a nitrogen atmosphere for 8 h.
[b] The yields was determined by ^{19}F NMR with benzotrifluoride as an internal standard.