

Trifluoromethylation of Carbonyl Compounds with Sodium Trifluoroacetate

Ying CHANG, Chun CAI*

School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094

Abstract: In the presence of copper (I) halide as catalyst, a variety of carbonyl compounds could be trifluoromethylated with sodium trifluoroacetate to give the corresponding alcohols in moderate to high yields.

Keywords: Trifluoromethylation, sodium trifluoroacetate, carbonyl compounds, aldehydes.

The trifluoromethyl group is a highly important substituent in the field of organic chemistry. In the past two decades, new organofluorine compounds increased tremendously because of their improved properties compared with nonfluorinated analogues¹. Among them, trifluoromethyl-containing molecules constitute a particular class². The powerful electron-withdrawing ability and relatively small size of trifluoromethyl group can bring remarkable changes in the physical, chemical, and biological properties when this group was incorporated to substrates, making them suitable for diverse applications in the areas of material science, pharmaceutics, agrochemistry, and industry^{3, 4}. Introduction of trifluoromethyl group into molecules leads to profound enhancements of the features of the materials, such as the higher lipophilicity and lower friction⁵. Trifluoromethyl-containing pharmaceutical and agrochemical compounds possess improved transport characteristics *in vivo* and facilitate lower doses rates⁶. Trifluoromethyl-substituted polymers show enhanced stability, resistance to chemicals, and flame retardance. The dyes containing trifluoromethyl group exhibits better properties in light and fastness⁷.

To commitment the wide applications of the trifluoromethyl-containing compounds, numerous trifluoromethylation methods have appeared in literatures, including nucleophilic^{1, 4}, electrophilic^{3, 8}, radical trifluoromethylations⁹, and direct fluorination of methyl or carbonyl group¹⁰. These methods, however, generally suffer from the drawbacks of expensive reagents or harsh conditions, and are troublesome to handle in laboratory. Thus, it is still a challenge to explore new and effective precursors of trifluoromethyl group and introduce selectively into the desired position of a molecule.

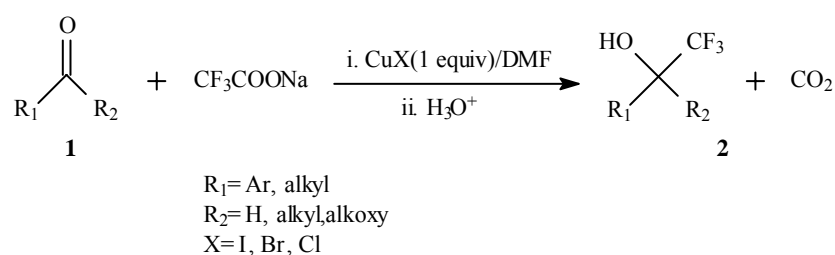
As a part of our research program toward the development of organofluorine compounds, we report herein a novel and efficient nucleophilic trifluoromethylation of

* E-mail: chyingxia@163.com

carbonyl compounds with readily prepared or commercially available sodium trifluoroacetate under the copper halide catalysis (**Scheme 1**).

To determine the suitable reaction conditions for the nucleophilic trifluoromethylation of carbonyl compounds, we employed benzaldehyde as the model compound initially (**Scheme 2**). The results of the trifluoromethylation in various reaction conditions are listed in **Table 1**.

Scheme 1 Trifluoromethylation of carbonyl compounds with sodium trifluoroacetate.



Scheme 2 Trifluoromethylation of benzaldehyde with sodium trifluoroacetate

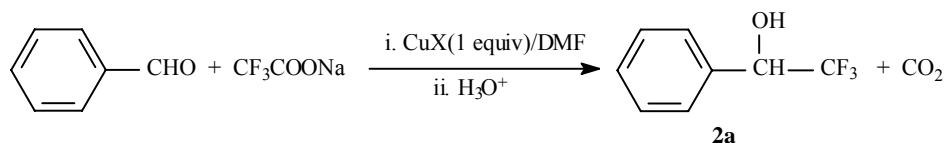


Table 1 Trifluoromethylation of benzaldehyde under different conditions.

Entry	CF ₃ COONa X(equiv.)	Catalyst (1equiv.)	React. temp. (°C)	React. /hydro. time (h)	Yield ^a (%)
1	2	CuI	170	2/4	56.9
2	4	---	170	2/4	59.8
3	4	CuI	170	2/4	99.2
4	4	CuBr	170	2/4	98.1
5	4	CuCl	170	2/4	96.9
6	4	CuI	120	2/4	71.0
7	4	CuI	140	2/4	92.3
8	4	CuI	170	2/4	99.2
9	4	CuI	170	1/1	75.5
10	4	CuI	170	1/2	85.8

^a The yields were calculated from GLC of the reaction mixture by incorporating an internal standard.

As summarized in **Table 1**, sodium trifluoroacetate showed high reactivity toward benzaldehyde, while copper (I) iodide was found to be the most suitable catalyst for the reaction, copper (I) bromide and chloride could also effectively catalyze the trifluoromethylation reaction. It is noteworthy that benzaldehyde could react smoothly with sodium trifluoroacetate to afford product in 59.8% yield in the absence of any catalysts (entry 2, **Table 1**). The trifluoromethylation yields were dependent on temperature.

Good yields could be obtained at about 140 °C, but for achieving maximum yield higher temperature is required.

Having examined the effects of different factors on the trifluoromethylation reaction, we further performed the trifluoromethylation of other carbonyl compounds to extend the application of this method, and the results were shown in **Table 2**. Various carbonyl compounds, including aryl aldehydes, aliphatic aldehydes and ketones, could undergo smooth reaction with sodium trifluoroacetate to give the corresponding trifluoromethylated alcohols in moderate to good yields. When aliphatic ketones were employed as the substrates, the yields declined with the increasing of the carbon chain. This result may be partly caused by the steric hindrance of the alkyl group.

Table 2 Trifluoromethylation of carbonyl compounds with sodium trifluoroacetate.

Entry	R ₁	R ₂	Product	React. temp. (°C)	React./hydro. time (h)	Yield ^a (%)
1	C ₆ H ₅	H	2a	170	2/4	99.2
2	2-Cl C ₆ H ₄	H	2b	170	2/4	96.7
3	4-Cl C ₆ H ₄	H	2c	170	2/4	98.6
4	2-Me C ₆ H ₄	H	2d	170	2/4	92.4
5	4-Me C ₆ H ₄	H	2e	170	2/4	96.0
6	cyclohexane	H	2f	170	2/4	95.7
7	<i>n</i> -Pr	H	2g	170	2/4	85.8
8	CH ₃	CH ₃	2h	160	2/4	73.5 ^b
9	C ₂ H ₅	CH ₃	2i	160	2/4	53.7 ^b
10	C ₃ H ₇	CH ₃	2j	170	2/4	43.9 ^b

^a The yields were calculated from GLC of the reaction mixture by incorporating an internal standard; ^b DMF 20 mL.

In conclusion, a new and efficient nucleophilic trifluoromethylation of carbonyl compounds with sodium trifluoroacetate catalyzed by copper (I) halide was established. Various aldehydes and ketones could be trifluoromethylated in moderate to good yields. The work reported herein enlarges the scope and defines the limitations of nucleophilic trifluoromethylation of carbonyl compounds.

General procedure: To a 100 mL four-necked round bottomed flask equipped with a mechanic stirrer, thermometer, reflux condenser attached to an inlet for maintaining inert nitrogen were quickly added thoroughly dried CF₃COONa (4.9 g, 36 mmol), N,N-dimethylformamide (DMF) 30 mL, benzaldehyde (0.9 mL, 9 mmol) and copper (I) iodide (1.71 g, 9 mmol). The flask was submerged in an oil bath preheated to 170 °C, and the reaction mixture was stirred for 2 h under the protection of nitrogen atmosphere. Aqueous HCl (12 mol/L, 1 mL) was then quickly added, and the mixture was vigorously stirred for a further 4 h at 170 °C. After completion of the reaction, distillation was performed to afford the crude products, which was purified by silica gel column chromatography. The prepared compounds were characterized on the basis of analytical and spectroscopic data¹¹.

References and Notes

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11. Representative data were shown: **2a**: $^1\text{H NMR}$ (CDCl_3 , δ ppm): 7.45 (m, 5H), 4.9 (q, 1H), 3.1 (OH); IR (KBr) ν 3405, 1500, 1460, 1268, 1175, 1130 cm^{-1} ; MS (EI) m/z : 107 (100), 176 (M^+ , 7.5), 79 (60); **2c**: $^1\text{H NMR}$ (CDCl_3 , δ ppm): 7.5 (m, 4H), 5.0 (q, 1H), 3.1 (OH); IR (KBr): ν 3400, 1605, 1500, 1270, 1170, 1135 cm^{-1} ; MS (EI) m/z : 210, 212 (M^+ , 32.5, 10), 141, 143 (100, 42.5), 113, 115 (32.5, 12), 77 (80); **2e**: $^1\text{H NMR}$ (CDCl_3 , δ ppm): 7.0-7.31 (m, 4H), 2.39 (s, 3H), 2.84 (q, 1H), 3.2 (OH); IR (KBr): ν 3375, 2870, 1540, 1280, 1185 cm^{-1} ; MS (EI) m/z : 190 (M^+ , 20), 121 (100), 91 (60); **2f**: $^1\text{H NMR}$ (CDCl_3 , δ ppm): 3.64 (m, 1H), 2.74 (m, 1H), 1.82 (m, 1H), 1.77-1.58 (m, 5H), 1.28-1.03 (m, 5H); IR (KBr): ν 3410, 1445, 1280, 1165, 1130 cm^{-1} ; MS (EI) m/z : 182 (M^+ , 1), 113 (2), 83 (100).

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