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Trifluoromethylation of carbonyl compounds with sodium trifluoroacetate

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Abstract

In the presence of copper(I) iodide as catalyst, a variety of carbonyl compounds, such as aldehydes, ketones and acid anhydrous, could be trifluoromethylated with sodium trifluoroacetate to give the corresponding alcohols in moderate to high yields, and a possible mechanism was proposed to explain the roles of catalyst and solvent in the reaction system.

Keywords: Trifluoromethylation; Sodium trifluoroacetate; Carbonyl compounds; Mechanism

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1. Introduction

Recently, an increasing interest has been focused on the trifluoroemthylation, because the introduction of the trifluoromethyl group into an organic compound can cause remarkable changes in the physical, chemical and biological properties that results in new compounds/materials making them suitable for diverse applications in the areas of material science, agrochemistry and pharmaceuticals [1].

In the previous reports, trifluoromethylation of carbonyl compounds was described on the basis of two methodologies: (1) addition of a trifluoromethyl group to the carbonyl carbon through Ruppert–Prakash reagents [1–2], Barbier procedure [3] and electrochemical methods [4] and (2) substitution of a hydrogen atom or alkyloxy group [1,3]. These methods, however, generally suffer from the use of toxic and expensive reagents or severe experimental conditions requirements. Sodium trifluoroacetate constitutes an ubiquitous and powerful tool for the introduction of a trifluoromethyl moiety into organic substrates [5]. Nevertheless, though the reaction of sodium trifluoroacetate with aromatic halides has been comparably extensively studied, little work has been focused on its reaction with carbonyl functions, despite of the great interest of carbonyl compounds in trifluoromethylation.

In the pioneering paper [6], we have reported our preliminary work on the trifluoromethylation of aldehydes with sodium trifluoroacetate to afford the corresponding trifluoromethylated alcohols in high yields. The ready availability of this cheap and environmental benign reagent led us to consider the further applications its use in the trifluoromethylation of carbonyl compounds. In this paper, we would like to describe the extension of our systematic studies on the reaction of sodium trifluoroacteate with carbonyl compounds, including aldehydes, ketones, acetyl chloride and acid anhydrides. Various kinds of catalysts and solvents were examined to determine the mechanism of the trifluoromethylation reaction, and a possible mechanism was proposed to explain the roles of catalyst and solvent in the reaction system.

2. Results and discussion

To verify the applications of sodium trifluoroacetate as a trifluoromethylating agent for carbonyl compounds (Scheme 1), aromatic and aliphatic aldehydes and ketones were chosen as the substrates, and the results were summarized in Table 1.

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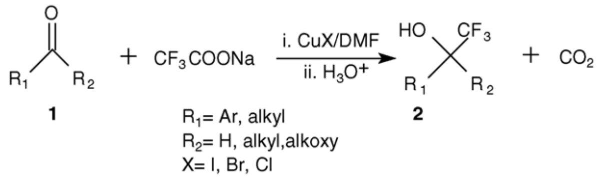


Scheme 1. Trifluoromethylation of aldehydes and ketones with sodium trifluoroacetate.

We can obviously see from Table 1 that a wide range of carbonyl compounds, including aromatic aldehydes and aliphatic ketones, can undergo smooth condensation with sodium trifluoroacetate to give trifluoromethylated alcohols in reasonably high yields. Under these conditions, however, acetophenone was trifluoromethylated to afford the corresponding carbinol in 2.3% yield, and only trace amount of desired product was obtained in the reaction of methyl benzoate with sodium trifluoroacetate. Moreover, improvement of the reaction conditions, such as initiators to the system, the amount of catalyst and the reaction time, did not significantly enhance the yields. The results show that steric hindrance, especially the strongly electron-donating groups adjacent to the carbonyl (alkoxy for example), is a limiting factor in the reactions of sodium trifluoroacetate under these conditions. The reason may lie in the fact that the CF_3 group has an electronegativity similar to that of oxygen [7]. Thus, it appears that the present trifluoromethylation method is not suitable for such compounds possessing strongly electron-donating groups.

According to the literature, there are mainly two different views on the intermediate formed in the trifluoromethylation: one is, the formation of an intermediate trifluoromethyl metal, CF_3Cu or CF_3CuI^- [5,8]; the other is that, the trifluoromethyl anion generated in the reaction was soon trapped in situ by the carbonyl moiety of DMF to form the *gem*-aminoalcoholate [9].

To determine the mechanism of the reaction of sodium trifluoroacetate with carbonyl compounds, different catalysts and solvents were explored and the results were summarized in Table 2.

Table 2
Trifluoromethylation of benzaldehyde with different catalysts and solvents

Entry	Solvent	Catalyst	*x* (equivalent)	Yield[a] (%)
1	DMF	–	–	59.8
2	DMF	CuI	0.5	85.1
3	DMF	CuI	1	99.2
4	DMF	CuBr	1	98.1
5	DMF	CuCl	1	96.9
6	DMF	$CuBr_2$	1	96.8
7	DMF	Cu	1	82.5
8	DMF	Zn	1	82.2
9	THF	CuI	1	Trace
10	Pyridine	CuI	1	Trace
11	NMP	CuI	1	41.9
12	CH_3CN	CuI	1	Trace
13	THF/DMF[b]	CuI	1	42.7

[a] Isolated yields.
[b] THF/DMF = 1:1 (v/v).

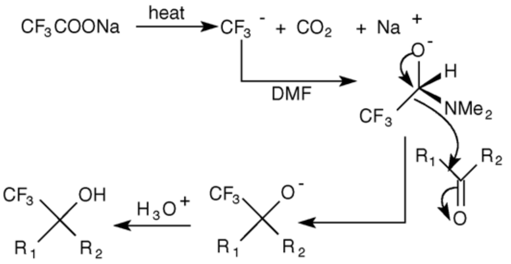
As shown in Table 2, various kinds of copper compounds, including CuI, CuBr, $CuBr_2$ and copper and zinc powder could effectively catalyze the reaction of benzaldehyde and sodium trifluoroacetate to give desired product in good yields. In our experiments, moreover, it was observed that bezaldehyde could smoothly react with sodium trifluoroacetate in the absence of any catalysts to afford reasonably high yield 59.8% (entry 1, Table 2). This result shows that benzaldhyde is sufficient to react with the trifluoro-methyl anion generated from the decarboxylation of sodium trifluoroacetate. The presence of catalyst might promote the reaction through the formation of trifluoromethyl–metal complex as an intermediate, which favors the further decarboxylation of sodium trifluoroacetate and the following addition of trifluoromethyl or its equivalent to substrates.

In our experiments, *N*,*N*-dimethylformamide (DMF) was found to be the most suitable solvent for this reaction. Only trace amounts of trifluoromethyl products, however, were obtained when tetrahydrofuran (THF), pyridine and acetonitrile were employed as solvent instead of DMF. This low yield maybe partly due to the low boiled points of the solvent, but the still poor yield in the case of *N*-methylpyrrolidone (NMP) denied this opinion. Meanwhile,

Table 1
Trifluoromethylation of aldehydes and ketones with sodium trifluoroacetate

Entry	*R*$_1$	*R*$_2$	Product[a]	Reaction temperature (°C)	Reaction/hydrolysis time (h)	Yield[b] (%)
1	C_6H_5	H	**2a**	170	2/4	99.2
2	4-Cl–C_6H_4	H	**2b**	170	2/4	98.6
3	4-Me–C_6H_4	H	**2c**	170	2/4	96.0
4	*n*-Pr	H	**2d**	170	2/4	85.8
5	C_6H_5	CH_3	**2e**	180	2/4	2.3
6	CH_3	CH_3	**2f**	160	2/4	73.5[c]
7	C_2H_5	CH_3	**2g**	160	2/4	53.7[c]
8	C_3H_7	CH_3	**2h**	170	2/4	43.9[c]
9	C_6H_5	OCH_3	**2a**	170	6/–[d]	Trace[c]

[a] All the reaction was catalyzed by CuI.
[b] Isolated yields.
[c] DMF 20 ml.
[d] Without hydrolysis.



Scheme 2. Mechansim for the trifluoromethylation of carbonyl compounds with sodium trifluoroacetate.

when THF/DMF was employed as the solvent, bezaldehyde could react with sodium trifluoroacetate to afford the corresponding trifluoromethyl carbinol in 42.7% yield (entry 13, Table 2). Such results underlined the crucial role of DMF during the trifluoromethylation with sodium trifluoroacetate, and from the mechanistic point of view, it can be reasonably to assume that DMF takes a positive role in the generation of trifluoromethyl anion or transferring it to the carbonyl group, in a way which is similar to Folléas et al. [9] (Scheme 2). This mechanism was supported by the observation that a little amount of *N*,*N*-dimethyltrifluoroacetamide obtained as side product when DMF was used as solvent.

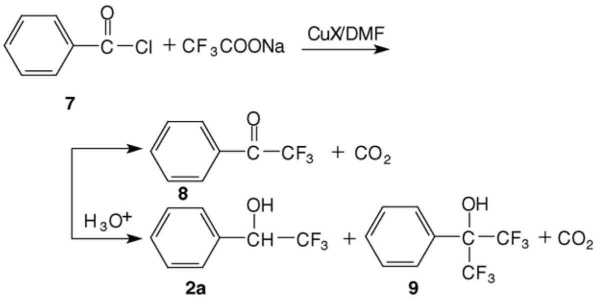
Having established that sodium trifluoroacetate is a versatile reagent to prepare trifluoromethyl-substituted carbinols from aldehydes and ketones, we set out to explore a number of reactions of sodium trifluoroacetate with other substrates containing other carbonyl functional groups. We first examined the acetyl chloride for its reactivity toward sodium trifluoroacetate with copper(I) iodide catalysis in DMF. Indeed, acetyl chloride reacts smoothly with sodium trifluoroacetate under above conditions (Eq. (1)), and the yield (**4**) amounted to 62.9%.

$$\underset{\mathbf{3}}{CH_3COCl} + CF_3COONa \overset{CuX/DMF}{\longrightarrow} \underset{\mathbf{4}}{CH_3COCF_3} + CO_2 \qquad (1)$$

Analogous result was obtained when benzene sulphonyl chloride was employed as substrate, and the yield of the trifluoromethyl sulfone (**6**) was 83.5% (Eq. (2)).

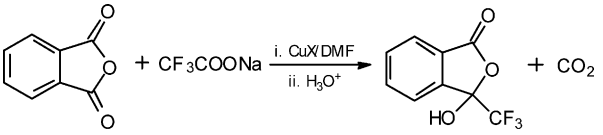
$$\underset{\mathbf{5}}{C_6H_5SO_2Cl} + CF_3COONa \overset{CuX/DMF}{\longrightarrow} \underset{\mathbf{6}}{C_6H_5SO_2CF_3} + CO_2 \qquad (2)$$

Moreover, it was demonstrated that our novel trifluoromethylation of carbonyl compounds by reaction with sodium trifluoroacetate in the presence of copper(I) halides is also applicable for benzoyl chloride, but the products were highly dependent on the treatment of the reaction mixture. The results showed that hydrolysis of the reaction mixture with aqueous HCl leads to the formation of the mixture of trifluoromethyl carbinol (**2a**, 43.5%) and bis-trifluro-methyl carbinol (**9**, 56.5%), while trifluoromethyl ketone was formed exclusively (**8**, 80.3%) without hydrolysis (Scheme 3).



Scheme 3. Trifluoromethylation of benzoyl chloride and benzene sulphonyl chloride.

Acid anhydrous also showed good reactivity via the hydrolysis of reaction mixture, and surprisingly that, only the mono-adducts were obtained in 67.4% yield (Eq. (3)).



(3)

10 **11**

In summary, a concise and convenient method for the trifluoromethylation of carbonyl compounds with easily prepared and commercially available sodium trifluoroacetate has been developed. We believe that this methodology would be widely used in organofluorine chemistry as a novel and efficient trifluoromethylation reaction.

3. Experimental

Sodium trifluoroacetate was prepared by treatment of sodium hydroxide and equivalent trifluoroacetic acid and dried in vacuo before storage under nitrogen. All the other reagents and solvents were further dried prior to use.

IR was recorded on Bumen MB154S infrared analyzer. ^1H NMR spectra were measured on Bruke Advance DMX500. Mass spectra were obtained on Saturn 2000 GC/MS instrument.

3.1. General experimental 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 was quickly added thoroughly dried CF_3COONa (4.9 g and 36 mmol), *N*,*N*-dimethylformamide (DMF) 30 ml, benzaldehyde (0.9 ml and 9 mmol) and copper(I) iodide (1.71 g and 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. The flask was then cooled to a lower temperature, aqueous HCl (12 M and 1 ml) was 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 product. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatograph. Isolated yields are given in Tables 1 and 2. The prepared compounds were characterized on the basis of analytical and spectroscopic data [10], and some analytic data were compared with the published observations [1,11]. Selected data are given below.

Phenyl-2,2,2-trifluoroethanol (**2a**): ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 7.45 (m, 5H), 4.9 (q, 1H), 3.1 (OH); IR (KBr) υ 3405, 1500, 1460, 1268, 1175, 1130 cm^{-1}; MS (EI) m/z: 107 (M-69, 100), 176 (M^+, 7.5), 79 (M-17-69, 60).
2,2,2-Trifluoro-1-(4-chlorophenyl)ethanol (**2b**): ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 7.5 (m, 4H), 5.0 (q, 1H), 3.1 (OH); IR (KBr): υ 3400, 1605, 1500, 1270, 1170, 1135 cm^{-1}; MS (EI) m/z: 210, 212 (M^+, 32.5, 10), 141, 143(M-69, 100, 42.5), 113,115(M-17-69, 32.5,12), 77 (80).
2,2,2-Trifluoro-1-(4-methylphenyl)ethanol (**2c**): ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 7.0–7.31 (m, 4H), 2.39 (s, 3H), 2.84 (q, 1H), 3.2 (OH); IR (KBr): υ 3375, 2870, 1540, 1280, 1185 cm^{-1}; MS (EI) m/z: 190 (M^+, 20), 121 ($M^+ - CF_3$, 100), 91 (60).
1-Methyl-1-phenyl-2,2,2-trifluoroethanol (**2e**): ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 7.7–7.2 (m, 5H), 3.2 (OH), 1.7 (3H); IR (KBr): υ 3440, 1290, 1275, 1170 cm^{-1}; MS (EI) m/z: 190 (M^+, 0.9), 121 (M-69, 100).
3-Hydroxy-3-(trifluoromethyl)phthalide (**11**): ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 8.0–7.5 (m, 4H), 4.4 (OH); IR (KBr): υ 3350, 1765, 1605 cm^{-1}; MS (EI) m/z: 219 ($M^+ + H$, 57), 201 ($M^+ - OH$, 13), 149 ($M^+ - CF_3$, 100), 121 ($M^+ - CF_3$–CO, 22), 93 (15).

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[10] MS (EI) m/z: (2d): 141 ($M^+ - H$, 30), 110 ($M^+ - CH_2OH$, 12), 72 ($M^+ - CF_3$–H, 21), 44 (100); (2f): 127 ($M^+ - H$, 15), 58 ($M^+ - CF_3$–H, 100), 44 (77); (2g): 141 ($M^+ - H$, 52), 110 ($M^+ - CH_2OH$, 3), 72 ($M^+ - CF_3$–H, 100); (2h): 156 (M^+, 3), 87 (10), 70 ($M^+ - CF_3$–OH, 17), 44 (100); (4): 112 (M^+, 35), 43 ($M^+ - CF_3$, 100); (6): 210 (M^+, 8), 141 ($M^+ - CF_3$, 75), 93 (100); (8): 175 ($M^+ + H$, 95), 105 ($M^+ - CF_3$, 100), 77 ($C_6H_5^+$, 35); (9): 244 (M^+, 18), 175 ($M^+ - CF_3$, 100), 105 ($M^+ - CF_3$–CF_3, 97), 77 ($C_6H_5^+$, 30).

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