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Sodium trifluoroacetate: an efficient precursor for the trifluoromethylation of aldehydes

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Abstract—In a convenient and efficient procedure, the nucleophilic trifluoromethylation of aldehydes with sodium trifluoroacetate was achieved, using copper(I) halides as the catalyst. © 2005 Elsevier Ltd. All rights reserved.

Due to the peculiar chemical and biological properties of organic compounds containing trifluoromethyl group, considerable efforts have been devoted to develop effective methods for introducing CF₃ group into organic molecules. To date, trifluoromethylation has been mainly based on the five methods: (1) generation of the trifluoromethyl radicals from precursors; 1 (2) use of trifluoromethyl-copper (or -cadmium, -zinc, etc.);² (3) Ruppert reagent CF₃SiMe₃/KF (Me₄NF, *t*-BuOK, etc.) systems; ³ (4) electrochemical methods;⁴ (5) indirect routes, such as halogen exchange of CCl_3 with HF/ SbF_5 .⁵ These methods, however, generally suffer from the use of toxic or expensive reagents, some of which are inconvenient to handle. Therefore, it is still a challenge to develop new efficient precursors of trifluoromethyl group and selectively introduce them into the desired position of organic molecules.

Sodium trifluoroacetate was first reported by Kiyohide et al. as a trifluoromethylating agent for aromatic halides,⁶ and latter Hitomi et al. studied the reaction of sodium trifluoroacetate with nonactivated iodoarenes.⁷ Based on these pioneering work, we further researched the copper(I) iodide catalyzed trifluoromethylation of aromatic halides, and it was shown that the electronwithdrawing substituents, such as nitro group, favored the trifluoromethylation. Besides sodium trifluoroacetate, CF₃TMS is also an effective trifluoromethylating

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agent for aromatic halides and has been reported in numerous papers.⁸

In the recent years, aldehydes are of great interest in the research of trifluoromethylation, and in most cases, CF_3TMS was employed as the trifluoromethylating reagent.⁹ Consideration of the comparable performance of sodium trifluoroacetate with the Ruppert reagents in the reaction with aromatic halides and the high reactivity of Ruppert reagents towards aldehydes, we envisaged that it could be also employed as a trifluoromethylating agent in the reaction with aromatic carbonyl compounds, especially with aldehydes.

In this letter, we would like to describe a novel trifluoromethylation route for aldehydes with sodium trifluoroacetate, using copper(I) halides as the catalyst (Scheme 1). To the best of our knowledge, there is no related report on the trifluoromethylation of aldehydes with sodium trifluoroacetate.

Sodium trifluoroacetate was prepared by treatment of sodium hydroxide with an equivalent of trifluoroacetic



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

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acid and dried in vacuo before storage under nitrogen. All other reagents and solvents were further dried prior to use.

The results reported in Table 1 deserved several comments: benzaldehyde exhibited fairly good reactivity in the trifluoromethylation, and the yield amounted to 99.2%. Reasonably high yields were obtained when tolualdehyde (o-, m-, and p-) and chlorobenzaldehyde (o-, m-, and p-) were employed as substrates, and as could be seen from the results summarized in Table 1 that, the yields of chlorobenzaldehydes were a little higher than that of tolualdehydes. Cyclohexanecarboxaldehyde also showed high reactivity under the experimental conditions and the yield amounted to 95.7%. Although cyclohexanone could be trifluoromethylated to give the corresponding alcohol in 56.7% yield, rather low yield was obtained when acetophenone was used as substrate.

Initiators, such as potassium fluoride and potassium *tert*-butoxide (*t*-BuOK), are generally used with silane trifluoromethylating reagents. In this regards, we were

intrigued by the effects of KF and *t*-BuOK. In an attempt to enhance the reactivity of ketone, both of them were examined in this trifluoromethylation system, respectively. The results, however, were not significantly improved.

The possible reaction mechanism might involve the nucleophilic addition of trifluoromethyl anion or some kinds of its complexes generated in situ. Evolution of CO_2 began at around 140 °C, which was in accordance with the result reported by Kiyohide et al.⁶

Various kinds of copper compounds, such as CuI, CuCl, CuBr, CuBr₂, and Cu, were examined as the copper source in this system (Table 2). The results showed that, the product was obtained in 85.1% when 0.5 equiv CuI was used, and increasing the amount of catalyst led to a higher yield. While copper(I) iodide was found to be the most effective for this purpose, considerable amount of the trifluoromethylated products could be obtained when the other copper compounds were employed as the catalysts. As the results indicated that, there was

Table 1. Trifluoromethylation of aldehydes and ketones with sodium trifluoroacetate

Carbonyl compounds	Product	Conditions (time/h)		Overall	Mass spectra data ^b (m/z)
		Trifluoromethylation	Hydrolysis	yield ^a (%)	
СНО	$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	2	4	99.2	107 (M-69, 100) 176 (M ⁺ , 7.5) 79 (M-96, 60)
СН3	$CH_3 CH - CF_3 2$	2	4	92.4	190 (M ⁺ , 8), 121 (M–69, 90), 91 (M–99, 100), 93 (M–97, 85)
снасно	CH-CH-CF ₃ 3	2	4	82.7	190 (M ⁺ , 38), 121 (M–69, 100), 91 (M–99, 77), 93 (M–97, 85)
СН3-СНО	$CH_3 \rightarrow CH \rightarrow CF_3 4$	2	4	96.0	190 (M ⁺ , 20), 121 (M–69, 100), 91 (M–99, 60), 93 (M–97, 60)
СІ		2	4	96.7	210, 212 (M ⁺ , 13, 5,) 141, 143 (M-69, 100, 40), 113, 115 (M-97, 35, 10), 77 (85), 58 (100)
СІ		2	4	86.8	210, 212 (M ⁺ , 18, 5,) 141, 143 (M-69, 38, 15), 113, 115 (M-97, 25, 8), 77 (35)
СІ—СНО		2	4	98.6	210, 212 (M ⁺ , 32.5, 10), 141, 143 (M-69, 100, 42.5), 113, 115 (M-97, 32.5,12), 77 (80)
СНО		2	4	95.7	182 (M ⁺ , 1), 113 (M-69, 2), 83 (100)
 =0	OH CF ₃ 9	2	4	56.2	168 (M ⁺ , 0.1), 99 (M-69, 100)
C-CH ₃	$ \bigcirc \overset{OH}{\underset{I}{\overset{I}{\underset{CF_{3}}{\overset{OH}{\overset{I}{\underset{CF_{3}}{\overset{I}{\underset{CF_{3}}{\overset{OH}{\overset{I}{\underset{CF_{3}}{\overset{I}{\underset{CF_{3}}{\overset{OH}{\overset{I}{\underset{CF_{3}}{\underset{CF_{3}}{\overset{I}{\underset{CF_{3}}{\overset{I}{\underset{CF_{3}}{\overset{I}{\underset{CF_{3}}{\overset{I}{\underset{CF_{3}}{\overset{I}{\underset{CF_{3}}{\overset{I}{\underset{CF_{3}}}{\underset{CF_{3}}{\underset{CF_{3}}{\underset{CF_{3}}{\underset{CF_{3}}{\underset{CF_{3}}{\underset{CF_{3}}{\underset{CF_{3}}{\underset{CF_{3}}{\underset{CF_{3}}{\underset{CF_{3}}{\underset{1}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}}$	2	6	2.3	190 (M ⁺ , 0.9), 121 (M-69, 100)

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

^b Mass data was obtained on Saturn 2000 GC/MS instrument, only selected data are shown.

Table 2. Trifluoromethylation of benzaldehyde with different catalysts

Entry	Catalyst	x (equiv)	1ª (%)
1		_	59.8
2	CuI	0.5	85.1
3	CuI	1	99.2
4	CuBr	1	98.1
5	CuCl	1	96.9
6	CuBr ₂	1	96.8
7	Cu	1	82.5

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

not much difference between the effects of copper(I) halides and copper(II) bromide, nevertheless, considerable lower yield was obtained when copper powder was used as the catalyst. It should be pointed out that, when benzaldehyde was employed as the substrate, the reaction could go on smoothly in the absence of any catalysts mentioned above, and the yield was 59.8%, though lower than that of the typical procedure.

With these results in hand, we then performed the trifluoromethylation reaction with a more extensive range of carbonyl compounds, and benzoyl chloride was first examined as the substrate (Scheme 2).

When benzoyl chloride was employed as the substrate under the experimental conditions, 2,2,2-trifluorophenylethanol (1, 43.5%) was obtained together with α,α bis(trifluoromethyl)-benzyl alcohol (11, 56.5%) MS: 244 (M⁺, 24), 175 (M⁺-69, 95), 105 (M⁺-138, 100), 77 (M⁺-166, 26).

In summary, the present reaction of sodium trifluoroacetate with aldehydes catalyzed by copper(I) halides was found to be an excellent method for trifluoromethylation. This method has the following attractive characteristic features: (a) the reaction can be carried out without use of special apparatus, such as electrochemical equipments, (b) the reaction gives good to excellent yields, (c) sodium trifluoroacetate is a solid (mp 206 °C) and can be easily handled at ambient temperature, whereas CF₃TMS, a well known trifluoromethylating reagent, is expensive and troublesome to use in laboratories, nevertheless, the technology suffers from the fact that, CF_3TMS is presently prepared from ecotoxic CF_3Br ,¹⁰ (d) copper(I) halides and copper powder, in contrast to other catalysts, such as palladium compounds $Pd(OAc)_2$, $Pd(PPh_3)_4$,¹¹ are easily accessible.

General experimental procedure: To a 100 mL fournecked round bottomed flask equipped with a mechanic stirrer, thermometer, reflux condenser attached to an inlet for maintaining inert nitrogen was quickly added



Scheme 2. Trifluoromethylation of benzoyl chloride with sodium trifluoroacetate.

thoroughly dried CF₃COONa (4.90 g, 36 mmol), *N*,*N*-dimethylformamide (DMF) 30 mL, benzaldehyde (0.9 mL, 9 mmol), copper(I) iodide (1.71 g, 9 mmol). The flask was submerged in an oil bath preheated to 170 °C, and the reaction solution was stirred for 2 h under the protection of nitrogen atmosphere. The flask was then cooled to a lower temperature, aqueous HCl (12 M, 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 products. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography. The prepared compounds were characterized on the basis of analytical and spectroscopic data.¹²

Further studies on examining the reaction mechanism and improving the experimental conditions as well as the scope and applicabilities of this method to esters and sulfur containing compounds, are currently in progress in our group and will be published in due course.

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 Selected data: compound 1: ¹H NMR (300 MHz, CDCl₃): δ 7.45 (m, 5H), 4.9 (q, 1H), 3.1 (OH); IR (KBr): v 3405, 1500, 1460, 1268, 1175, 1130 cm⁻¹. Compound 4: ¹H NMR (300 MHz, CDCl₃): δ 7.0–7.31 (m, 4H), 2.39 (s, 3H), 2.84 (q, 1H), 3.2 (OH); IR (KBr): v 3375, 2870, 1540, 1280, 1185 cm⁻¹. Compound 7: ¹H NMR (300 MHz, CDCl₃): δ 7.5 (m, 4H), 5.0 (q, 1H), 3.1 (OH); IR (KBr): v 3400, 1605, 1500, 1270, 1170, 1135 cm⁻¹. Compound 8: ¹H
 NMR (300 MHz, CDCl₃): δ 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): v 3410, 1445, 1280, 1165, 1130 cm⁻¹. Compound **9**: ¹H NMR (300 MHz, CDCl₃): δ 1.00–1.19 (m, 10H), 1.93 (br s, 1H); IR (KBr): v 3365 (s), 1280 (s), 1140 (s) cm⁻¹. Compound **10**: ¹H NMR (300 MHz, CDCl₃): δ 7.7–7.2 (m, 5H), 3.2 (OH), 1.7 (3H); IR (KBr): v 3445, 1290, 1275, 1170 cm⁻¹.