Sodium Trifluoroacetate: an Efficient Difluorocarbene Precursor for Alkenes

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A novel and efficient difluorocarbene precursor was achieved. In a convenient procedure, a variety of alkenes could be *gem*-difluorocyclopropanated with sodium trifluoroacetate to give the corresponding products in moderate to high yields, using azobisisobutyronitrile (AIBN) as the catalyst.


Recently, the introduction of the difluoromethyl moiety into organic compounds has attracted increasing attention of chemists due to the improved chemical and biological properties exhibited by *gem*-difluoromethylated compounds as compared to their non-fluorinated analogues.[1] A variety of difluorocarbene precursors have been examined, such as Seyferth's phenyl (trifluoromethyl)mercury,[2] Burton's triphenyl(bromodifluoromethyl)phosphonium bromide,[3] sodium chlorodifluoroacetate,[4] CF_2X_2,[5] and trimethylsilyl fluorosulfonyldifluoroacetate (TFDA).[6] However, most of these methods generally suffer drawbacks either from the difficulties in preparing difluorocarbene reagents or the harsh reaction conditions requirements, and the successes vary in different degrees. Hence, development of new efficient difluorocarbene precursor would be valuable.

As part of our search for versatile fluorine-contaning synthetic building blocks, we have reported in the pioneering paper of our systematic work on sodium trifluoroacetate as an excellent trifluoromethylating agent for carbonyl compounds.[7] The good performance of this environmentally benign reagent has enabled us to focus our attention on its further appilication as the difluorocarbene precursor for alkenes.

This letter describes a simple, facile, and convenient one-step procedure of difluorocarbene generation from readily prepared and commercially available sodium trifluroacetate, and various alkenes, including the electron-deficient alkenes such as acrylonitrile, could be *gem*-difluoropropanated in moderate to high yields (Scheme 1).

In order to determine the suitable reaction conditions for the *gem*-difluorocyclopropanation of alkenes with sodium trifluoroacetate, we initially employed α-methylstyrene as the model substrate (Scheme 2).[8] The results of the difluorocyclopropanation in various reaction conditions were listed in Table 1.

As summarized in Table 1, azobisisobutyronitrile (AIBN) could effectively promote the reaction of α-methylstyrene with sodium trifluoroacetate to give the corresponding difluorocyclopropanated compounds in high yields. The role of AIBN is
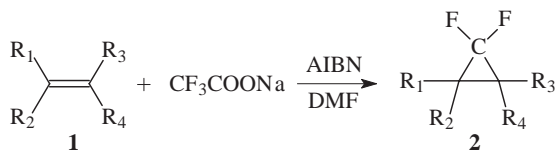
Table 1. *gem*-Difluorocyclopropanation of α-methylstyrene under different conditions

Entry	Catalyst /equiv.	Solvent	Time /h	Yield[a] /%
1	—	DMF	6	53
2	CuI/1	DMF	6	67
3	CuBr/1	DMF	6	60
4	CuCl/1	DMF	6	54
5	Benzoyl peroxide/1	DMF	6	43
6	AIBN/0.5	DMF	6	72
7	AIBN /1	DMF	6	86
8	AIBN /1	DMF	4	71[b]
9	AIBN /1	DMF	8	87
10	AIBN /1	DMF	12	90
11	AIBN /1	DMF	6	53[c]
12	AIBN /1	DMF	6	89[d]
13	AIBN /1	NMP	6	66
14	AIBN /1	THF	6	trace
15	AIBN /1	Pyridine	6	trace

[a]Isolated yields. [b]CF_3COONa 2 equiv. [c]Temperature 150 °C. [d]Temperature 180 °C.

thought to involve its special conjugated structure, which might favor the generation of difluorocarbene. Besides AIBN, the commonly used promoters copper halides in nucleophilic trifluoromethylation also exhibited some contributions to the reaction, and copper iodide worked better than copper bromide and chloride. Nevertheless, benzoyl peroxide failed to catalyze the addition of difluorocarbene to the carbon–carbon double bond. Notably, the reaction could proceed smoothly in the absence of any catalysts mentioned above. Varying the reaction temperature indicated 170 °C is optimal for the reaction and the desired product was afforded in 86% yield (Entry 7, Table 1), though higher temperature seems to be a little advantageous. Lower or trace yields were obtained when 1-methyl-2-pyrrolidone (NMP), tetrahydrofuran (THF), and pyridine were used as solvent instead of *N,N*-dimethylformamide (DMF). The reason is not clear yet, but it is obvious that DMF seems to play an important role in the reaction.

From Table 2, we can see that a wide range of alkenes, including aryl and aliphatic alkenes, could be difluorocyclopropanated in moderate to good yields. Among the aryl alkenes examined, α-methylstyrene showed higher reactivity than styrene and α-methyl-*p*-chlorostyrene gave the highest yield (Entry 3, Table 2), and tetramethylethylene gave better yield than that of tetrachloroethylene. From these results, electron-

R_1, R_2, R_3, R_4 = Ph, Ar, alkyl, halide, or H

Scheme 1.

Table 2. *gem*-Difluorocyclopropanation of alkenes with sodium trifluoroacetate[a]

Entry	R_1	R_2	R_3	R_4	Product	Yield[b] /%
1	Ph	H	H	H	**2a**	68
2	Ph	Me	H	H	**2b**	86
3	*p*-Cl-C$_6$H$_4$	Me	H	H	**2c**	93
4	C$_6$H$_{13}$	H	H	H	**2d**	65
5	C$_{10}$H$_{21}$	H	H	H	**2e**	39
6	CH$_2$CMe$_3$	H	Me	H	**2f**	46
7	Me	Me	Me	Me	**2g**	88
8	Cl	Cl	Cl	Cl	**2h**	48
9	H	H	H	CN	**2i**	57

[a]Reaction was carried out according to the typical procedure.
[b]Isolated yields.

donating substituent methyl attached to the carbon–carbon double bond seems to favor the addition of difluorocarbene to the substrate. Under these experimental conditions, 1-octene gave higher yields than that of 1-dodecene. This result may be partly caused by the steric hindrance, which increased with the carbon chain. Support of this view also comes from the fact that 2,4,4-trimethyl-1-pentene afforded lower yield than that of tetramethylethylene (Entry 6).

We have reported sodium trifluoroacetate in this Letter as a novel and highly reactive difluorocarbene precursor, which has been proved to be effective in *gem*-difluorocyclopropanating various alkenes. Compared with other processes, this procedure used cheap and ready available sodium trifluoroacetate and could be handled conveniently in reasonably high yields. Further detail study on the reaction mechanism is currently underway in our laboratory.

References and Notes
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8   Typical procedure: To a 100 mL four-necked, round bottomed flask equipped with a mechanic maintaining inert nitrogen were quickly added thoroughly dried CF$_3$CO$_2$Na (4.9 g, 24 mmol), *N,N*-dimethylformamide (DMF) 20 mL, α-methylstyrene (0.78 mL, 6 mmol), and azobisisobutyronitrile (AIBN) (0.99 g, 6 mmol). The flask was submerged in an oil bath preheated to 170 °C, and the reaction mixture was stirred for 6 h under nitrogen atmosphere. After completion of the reaction, distillation was performed to afford the crude product, which was diluted with 50 mL of diethyl ether. The solution was washed with water (50 mL × 4) and dried over anhydrous magnesium sulfate, followed by purification on flash chromatography with 10:1 *n*-hexane/ ethyl acetate, provided the pure desired product in a yield of 86%. The cyclopropane adducts were characterized by ^{1}H NMR, ^{19}F NMR, GC/MS, and identified by comparison with authentic samples or with reported. Representative data were shown: compound **2a**: MS (EI) *m/z* 154 (M$^+$, 100), 133 (80), 104 (42), 77 (37), 51 (28); ^{1}H NMR δ 7.41–7.51 (m, 5H), 2.08 (m, 2H), 1.86 (m, 1H). ^{19}F NMR δ −134.4 (dd, $J = 158$ Hz, 1F), −139.7 (dd, $J = 158$ Hz, 1F). **2b**: MS (EI) *m/z* 168 (M$^+$, 33), 153 (100), 133 (58), 118(40), 103 (27), 77 (24); ^{1}H NMR δ 7.25–7.38 (s, 5H), 2.16 (m, 2H), 1.52 (s, 3H). ^{19}F NMR δ −132.8 (dd, $J = 150$ Hz, 1F), −137.8 (dd, $J = 150$ Hz, 1F). Compound **2c**: MS (EI) *m/z* 202 (M$^+$, 15), 187 (100), 189 (37), 152 (21), 137 (53), 77 (45); ^{1}H NMR δ 7.47–7.49 (m, 4H), 2.12 (m, 2H), 1.47 (s, 3H). ^{19}F NMR δ −132.2 (dd, $J = 149$ Hz, 1F), −136.4 (dd, $J = 149$ Hz, 1F). Compound **2e**: MS (EI) *m/z* 218 (M$^+$, 0.1), 141 (100), 77 (43). ^{1}H NMR δ 1.21 (m, 3H), 1.38 (m, 2H), 1.49 (m, 18H), 1.71 (m, 1H). ^{19}F NMR δ −128.9 (d, $J = 154$ Hz, 1F), −137.5 (d, $J = 154$ Hz, 1F).