Additions of Acetonitrile and Chloroform to Aromatic Aldehydes in the Presence of Tetrabutylammonium Fluoride

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Addition reactions of acetonitrile to aldehydes afford β-hydroxynitriles which can be converted into amino, carboxyl or other functional groups in organic chemistry. Cyanomethylation has been performed by deprotonation of a nitrile compound followed by addition to an aldehyde or a ketone.[1] Depending on the reaction conditions, α,β-unsaturated nitriles are given as in aldol-type condensations.[2] There have been some reports describing various methods of cyanomethylation.[3]

Addition reactions of a trichloromethyl group to aldehydes give trichloromethyl carbinols which can be converted into α-amino, α-hydroxy and α-thio acids.[4] The reaction can be carried out by base-mediated addition of the trichloromethyl group to an aldehyde or ketone as the same manner as in cyanomethylation. Reagents of trichloromethylation are made of a CCl_3^- source such as chloroform, tetrachloromethane and (trimethylsilyl)trichloromethane and bases such as *n*-butyl lithium, potassium *t*-butoxide, potassium hydroxide, and DBU.[5] When strong bases are used, a carbene could be generated in some cases.[6]

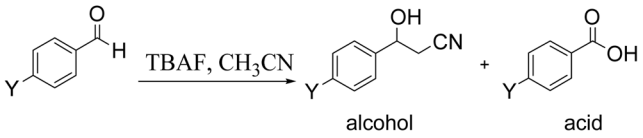
Tetrabutylammonium fluoride (TBAF) is a typical desilylation agent for breaking oxygen-silicon[7] or carbon-silicon[8] bonds and plays a role as a base[9] or a nucleophilic fluorination reagent.[10] Recently, we have found an equivalent of TBAF can oxidize benzaldehyde to benzoic acid.[11] During the studies on solvent effects in the oxidations of aromatic aldehydes with TBAF, we observed cyanomethylation and trichloromethylation with certain aldehydes. In this paper, we described cyanomethylation and trichloromethylation, as well as competition with oxidation.

Results and Discussion

Since the oxidation of *p*-nitrobenzaldehyde with TBAF into *p*-nitrobenzoic acid was faster in acetonitrile than in other solvents, the reaction in CH_3CN was examined with other benzaldehydes. In variation of the electronic effect of the substituents in para position of benzaldehyde, five different benzaldehydes were employed. As shown in Table 1, the oxidation reaction competed with the cyanomethylation. The reaction mechanism of oxidation has been studied in our laboratory, but it was not clear until now.[11] Deprotonation of acetonitrile by TBAF generated cyanomethyl anion which was added into a carbonyl group to give a β-hydroxynitrile (Scheme 1).

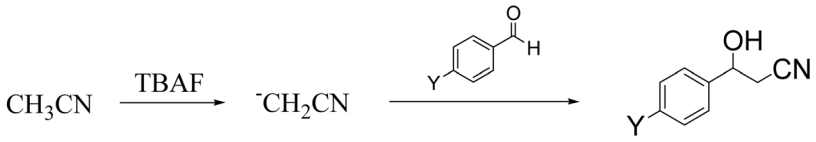
In the case of the *p*-nitro derivative, oxidation took place to give the corresponding acid and no cyanomethylation was observed (Table 1, entries 1 and 2). As the oxidation proceeded, the basicity of TBAF decreased. When excess of TBAF was used in the case of *p*-CF_3, the starting material

Table 1. Cyanomethylation of aromatic aldehydes[a]



entry	Y	TBAF (equiv)	CH_3CN (equiv)	time (h)	yield[b]		
					SM[c]	alcohol	Acid
1	NO_2	1.2	3	12	17	–	83
2	NO_2	3	3	1	–	–	99
3	CF_3	1.2	3	12	42	–	58
4	CF_3	3	3	12	–	63	37
5	Cl	1.2	3	12	–	99(87)	–
6	Cl	3	1.2	3	–	99	–
7	H	1.2	3	12	10	90	–
8	H	3	1.2	3	–	99	–
9	*t*Bu	1.2	3	12	24	76	–
10	*t*Bu	3	1.2	3	–	99(93)	–

[a]The reaction took place with 1.0 M TBAF in THF at 25 °C. [b]The relative yields were calculated by integrations of NMR data and the isolated one was in parenthesis. [c]SM means the starting materials, and the same notation will be applied in the following tables.



Scheme 1. Addition of acetonitrile to aromatic aldehydes (Cyanomethylation).

Table 2. Reactions of *p*-trifluoromethylbenzaldehyde under various conditions[a]

entry	CH_3CN (equiv)	temp (°C)	yield[b]		
			SM	alcohol	acid
1	1.2	25		17	83
2	3	0		31	69
3	3	25		63	37
4	3	50		73	27
5[c]	10	25		74	26

[a]The reaction took place with 1.0 M TBAF in THF for 12 h. [b]The relative yields were calculated by integrations of NMR. [c]The reaction took place with TBAF·$3H_2O$.

disappeared and oxidation competed with cyanomethylation (entry 4). The reactions of the *p*-CF_3 derivative, under various conditions were shown in Table 2. In the cases of *p*-Cl, H, and *t*-Bu, only cyanomethylation proceeded, indicating that the rate of cyanomethylation was much faster than that of oxidation (entries 5-10).

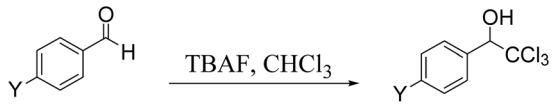
As shown in Table 2, the reaction of *p*-trifluoromethylbenzaldehyde gave a mixture of *p*-trifluoromethylbenzoic acid, the oxidation product and 3-hydroxy-3-(*p*-trifluoromethylphenyl)propanenitrile, the cyanomethylated one. When excess of acetonitrile was used, the rate of cyanomethylation was faster than that of the oxidation. As the reaction temperature increased, cyanomethylation also took place more readily.

In conclusion, cyanomethylation proceeded faster, as the electron withdrawing effect increased, unless the oxidation took place. In the case of *p*-nitro, only oxidation took place. The competition mainly depended upon the electronic effect of the substituents.

When the ^1H nmr spectrum of *p*-nitrobezaldehyde was recorded in $CDCl_3$ in the presence of TBAF, the characteristic peak of a benzyl alcohol was detected. The trichloromethyl group was incorporated in the reaction mixtures, when the oxidation reaction of benzaldehydes with TBAF was carried out in chloroform as a solvent. As shown in Table 3, the trichloromethylation took place without competition of the oxidation. As the electronic withdrawing effect of the substituents increased, the rate of reaction was faster (entries 1, 3, 5, 8, 11). When the reaction temperature went up, the rate also became faster a little (entries 7, 10, 13). The mechanism was the same as that of the cyanomethylation. Deprotonation of $CHCl_3$ by TBAF and the resulting CCl_3 anion was added into the benzaldehydes to give α-trichloromethylbenzyl alchohols. In the cases of *p*-NO_2 and *p*-CF_3, one equivalent of TBAF was enough proceeding the reaction in a short period of time.

To complete the trichloromethylation of other benzaldehydes, various reaction conditions were tested. Higher temperature was needed for *p*-chlorobenzaldehyde, but the amount of chloroform was more crucial, as shown in Table 4. When more than 1 equivalent of TBAF was used, excess of chloroform was enough ending the reaction. The reaction more depended upon the amount of chloroform than that of

Table 3. Trichloromethylation of aromatic aldehydes[a]



entry	Y	TBAF (equiv)	temp (°C)	time (h)	yield[b]	
					SM	alcohol
1	NO_2	1.2	25	1	–	99(94)
2	NO_2	3	25	0.5	–	99
3	CF_3	1.2	25	3	–	99
4[c]	CF_3	3	25	0.5	–	99
5	Cl	1.2	25	12	23	77
6	Cl	3	25	12	16	84
7	Cl	3	50	12	–	99(84)
8	H	1.2	25	12	30	70
9	H	3	25	12	24	76
10	H	3	50	12	22	78
11	*t*Bu	1.2	25	12	41	59
12	*t*Bu	3	25	12	38	62
13	*t*Bu	3	50	12	33	67

[a]The reaction took place with 1.0 M TBAF in THF and 3 equiv of $CHCl_3$. [b]The relative yields were calculated by integrations of NMR data and the isolated one was in parenthesis.

Table 4. Influence of the amount of $CHCl_3$[a]

entry	Y	TBAF (equiv)	$CHCl_3$ (equiv)	yield[b]	
				SM	alcohol
1[c]	Cl	1.2	10	–	99
2	H	1.2	3	30	70
3	H	3	1.2	62	38
4	H	3	3	24	76
5[c]	H	3	10	–	99
6[c]	*t*Bu	3	10	–	99

[a]The reaction took place with 1.0 M TBAF in THF at 25 °C for 12 h, and Y is the same as in Table 3. [b]The relative yields were calculated by integrations of NMR data and the isolated one was in parenthesis. [c]The reaction took place with TBAF·$3H_2O$.

TBAF (entries 2 and 3).

In the case of hexanal, as an aliphatic aldehyde bearing α-protones, the reaction in acetonitrile gave a mixture of compounds, presumably because the cyanomethylation and extensive aldol-type condensations occure,[12] while the reaction in chloroform gave mainly 1,1,1-trichloro-2-heptanol, the trichloromethylated compound at lower temperature.[13] Additions of a cyanomethyl group to ketones bearing α-protones gave complex mixtures like aldehydes, while the trichloromethylation did not take place.

Conclusion

When the reaction of para substituted benzaldehyde with acetonitrile took place in the presence of TBAF, cyanomethylation competed with oxidation depending upon the electronic effect of the substitutent, while the reaction in

chloroform gave only chloromethylated products. Generally, cyanomethylation and trichloromethylation proceeded faster, as the electron withdrawing effect increased, unless the oxidation took place. To complete the reaction, excess of TBAF was needed in case of cyanomethylation, while excess of chloroform was needed in trichloromethylation.

Experimental Section

All reactions were performed in vials. Compounds such as tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran), *p*-nitrobenzaldehyde, *p*-trifluoromethylbenzaldehyde, *p*-chlorobenzaldehyde, benzaldehyde, and *p*-*tert*-butylbenzaldehyde were purchased from Aldrich. Acetonitrile and chloroform were purchased from DC Chemical Co., Ltd. Chromatography was performed with E. Merck silica gel 60 (63-200 μm). ^{1}H spectra were recorded on a Varian Jemini 2000 (200 MHz). ^{13}C spectra were recorded on a Varian Unity Inova 400 (100 MHz). All NMR data were obtained in $CDCl_3$ or DMSO solutions. EA spectra were recorded on a EA-1110 CHNS-O (CE instruments).

Typical procedure for the cyanomethylation of *p*-chlorobenzaldehyde. Acetonitrile (0.032 mL, 0.61 mmol) and 1.0 M tetrabutylammonium fluoride in THF (0.24 mL, 0.24 mmol) were placed in a 5mL vial. After stirring for 0.5 h, *p*-chlorobenzaldehyde (28.1 mg, 0.20 mmol) was added to the reaction mixture that was stirred at 25 °C for 12 h. The reaction mixture was poured into water and extracted three times with ether. The organic layer was dried with anhydrous magnesium sulfate, and then evaporated under reduced pressure to give 3-(4-chlorophenyl)-3-hydroxypropionitrile as a crude product. The product was purified by column chromatography (ethyl acetate : hexane = 2 : 8). The NMR data have been reported.[3f]

3-(4-Trifluoromethylphenyl)-3-hydroxylpropanenitrile. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.67 (d, 2H), 7.59 (d, 2H), 5.13 (t, 1H), 2.73 (d, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.8, 130.9 (q, $J_{C\text{-}F}$ = 38.3 Hz), 125.9, 116.9, 69.3, 28.0. Anal. Calcd for $C_{10}H_8F_3NO$: C, 55.82; H, 3.75; N, 6.51. Found: C, 55.67; N, 6.36; H, 3.90.

3-Phenyl-3-hydroxylpropanenitrile. NMR data have been reported.[3f]

3-(4-*tert*-Butylphenyl)-3-hydroxylpropanenitrile. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.38-7.19 (m, 4H), 4.96 (t, 1H), 2.71 (d, 2H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.0, 318.0, 125.9, 125.3, 117.3, 70.0, 34.6, 31.3, 27.8. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.74; H, 8.67; N, 6.67.

General procedure for the trichloromethylation. The procedure outlined above was followed using chloroform instead of acetonitrile.

2,2,2-Trichloro-1-(4-nitrophenyl)ethanol. NMR data have been reported.[4a]

2,2,2-Trichloro-1-(4-trifluoromethylphenyl)ethanol. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.69 (d, 2H), 7.58 (d, 2H), 5.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 131.5, 129.7, 124.7, 102.5, 83.8. Anal. Calcd for $C_9H_6Cl_3F_3O$: C, 36.83; H, 2.06. Found: C, 37.08; H, 2.05.

2,2,2-Trichloro-1-(4-chlorophenyl)ethanol. NMR data have been reported.[5f]

2,2,2-Trichloro-1-phenylethanol. NMR data have been reported.[4a]

2,2,2-Trichloro-1-(4-*tert*-butylphenyl)ethanol. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.47 (d, 2H), 7.26 (d, 2H), 5.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.6, 131.9, 128.8, 124.8, 94.4, 84.4, 34.7, 31.3. Anal. Calcd for $C_{12}H_{15}Cl_3O$: C, 51.18; H, 5.37. Found: C, 51.29; H, 5.32.

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