Oxidation of Aromatic Aldehydes with Tetrabutylammonium Fluoride: Competition with the Cannizzaro Reaction

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During the synthesis of 4-fluorobenzaldehyde *via* the S$_N$Ar reaction of 4-nitrobenzaldehyde with TBAF, it was found that an equivalent amount of TBAF could oxidize benzaldehyde to benzoic acid. The reaction of 4-nitrobenzaldehyde with tetrabutylammonium fluoride (TBAF) gave 4-nitrobenzoic acid in high yield. Depending on the reaction conditions, other aromatic aldehydes produced acids with fewer amounts of alcohols. However, this type of oxidation has limited practical applications. Nevertheless, the mechanism is quite different from the Cannizzaro reaction because the amounts of the acid salt and alcohol formed were different.

Key Words : Oxidation, Tetrabutylammonium fluoride, Nucleophilicity of hydride, Cannizzaro reaction, Aromatic aldehyde

Introduction

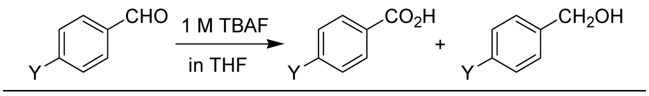
Many oxidants have been developed to oxidize alcohols and aldehydes to their corresponding carboxylic acids. Cr (VI) reagents,[1] Ag$_2$O (selective oxidation of aldehyde),[2] peroxy acids,[3] oxone,[4] and molecular oxygen[5] are the most common oxidants used. In the presence of a base, aromatic aldehydes can undergo a disproportionation reaction, known as the Cannizzaro reaction,[6] to form an equal amount of acid salt and alcohol. As an aldehyde with a proton in the α-carbon can undergo aldol condensations, the Cannizzaro reaction is generally used with aldehydes containing no α-hydrogen.[7]

Tetrabutylammonium fluoride (TBAF) is a nucleophilic fluorination reagent[8] and a typical desilylation agent for breaking oxygen-silicon[9] or carbon-silicon[10] bonds, and plays the role as a base.[11] 4-[^{18}F]Fluorobenzaldehyde is one of the important prosthetic groups in radiopharmaceuticals in positron emission tomography.[12] During the synthesis of 4-fluorobenzaldehyde *via* the S$_N$Ar reaction of 4-nitrobenzaldehyde with TBAF, it was found that an equivalent amount of TBAF could oxidize benzaldehyde to benzoic acid. Herein, we report the characterization of this oxidation reaction. This oxidation process has limited practical applications. However, the mechanism is clearly different from the Cannizzaro reaction because the amounts of acid salt and alcohol formed are different. It will be interesting to figure out the mechanism of this reaction, because the amounts of the formation of acid salt and alcohol are different.

Results and Discussion

The oxidation reactions of five aldehydes using TBAF were performed under two conditions, as shown in Table 1. No attempt was made to optimize the yield but many reactions were carried out in an attempt to understand the reaction mechanism for this oxidation by examining the effect of substituents in benzaldehyde (electronic effect), the reaction time, and reaction temperature. In most cases, both the acid and alcohol were detected. The reaction rate was increased with increasing reaction temperature. The reaction rate decreased when water was added. Electron-withdrawing substituents increased the reaction rate, while electron-donating substituent such as *t*-butyl decreased the reaction rate. The oxidation rate of 4-nitrobenzaldehyde in acetonitrile was faster than in THF (entries 1 and 2), but an acetonitrile-involved side product was detected in the oxidation of other benzaldehydes.[13] Regarding the effects of the solvent on the

Table 1. Oxidations of Various Aromatic Aldehydes with TBAF in THF



entry	Y	time (h)	temp (°C)	yield (%)[a]		
				aldehyde	acid	alcohol
1[b]	NO$_2$	5	rt	–	99 (95)	–
2	NO$_2$	12	rt	26	73 (69)	1
3	NO$_2$	5	50	14	82	4
4	CF$_3$	12	rt	65	28	7
5	CF$_3$	5	50	52	39	9
6	Cl	12	rt	68	19	13
7	Cl	5	50	55	24	21
8	H	12	rt	88	11	1
9	H	5	50	77	21	2
10	*t*-Bu	12	rt	91	9	–
11	*t*-Bu	5	50	88	11	1

[a] All reactions were carried out on a 2.00 mmol reaction scale of benzaldehydes using 2.40 mmol of a 1.0 M solution of TBAF in THF. The relative yields were calculated by integrating the NMR data and the isolated yields were in parenthesis. [b] The reaction was carried out with TBAF·3H$_2$O in CH$_3$CN.

oxidation of aromatic aldehydes with TBAF, cyanomethylation and trichloromethylation were observed with certain aldehydes. It was found that cyanomethylation and trichloromethylation proceeded in competition with oxidation. Therefore, a 1.2 equiv of 1.0 M THF solution of TBAF was used for the oxidation reaction, as shown in Table 1.

As shown in Table 1, the ratio of acid and alcohol were very different. Virtually no alcohol was formed in the case of 4-nitrobenzaldehyde. However, in the case of 4-trifluoromethylbenzaldehyde and 4-chlorobenzaldehyde, the oxidation reaction proceeded slowly and more alcohol was formed (entries 4-7). Benzaldehyde and 4-*t*-butylbenzaldehyde were oxidized much slowly and only trace amounts of their respective alcohols were detected (entries 8-11). There was no oxidation reaction of the alcohol instead of the aldehyde under the same conditions.

The nonsymmetrical formation of acid and alcohol means that the reaction mechanism is somewhat different from the Cannizzaro reaction. Fluoride would attack the carbonyl carbon and form a tetrahedral intermediate alkoxide. The formation of a carbonyl bond by moving the alkoxide anion forces the fluoride (back to starting aldehyde) or the hydride to leave. If the hydride generated attacks the carbonyl carbon of the other aldehyde, the same amount of benzyl alcohol and benzoic acid would be formed, according to the Cannizzaro reaction. As more acid is formed in this oxidation reaction, the hydride would attack another electrophile rather than benzaldehyde itself.

The self-decomposition of TBAF by E2 elimination producing *n*-butene and tributylamine are well known.[8a] It is for this reason why anhydrous TBAF is difficult to be synthesized because the fluoride acts as a base for E2 elimination. Similarly, hydride may attack the β-hydrogen of TBAF to form hydrogen, *n*-butene, and tri-*n*-butylamine. On the other hand, hydride may also attack the α-carbon of TBAF to form *n*-butane and tri-*n*-butylamine. An attempt was made to determine the reaction mechanism of this oxidation. However, there was no evidence for the formation of either hydrogen, *n*-butene, *n*-butane or tri-*n*-butylamine. The benzoyl fluoride generated could be hydrolyzed by H_2O and/or OH^- to give the acid.[14]

The reaction was performed in the presence of NaOH to determine if there was an increase in the reaction rate because the hydroxy anion is a more potent nucleophile than H_2O. As shown in Table 2, 4-nitrobenzaldehyde afforded the corresponding acid in a shorter period of time, as expected (Tables 1 and 2), while the other substituted benzaldehyde gave similar results to the Cannizzaro reaction. This reaction was milder compared with the ordinary Cannizzaro reaction.[6a]

Table 2. Reactions with TBAF in the Presence of NaOH

entry	Y	temp (°C)	time (h)	NaOH (eq)	Yield (%)[a]		
					aldehyde	acid	alcohol
1	NO_2	25	1	1	–	94	–
2	CF_3	25	12	1	–	53	42
3	Cl	25	12	1	–	51	43
4	H	25	12	2	–	48	45
5	*t*-Bu	50	12	2	3	46	44

[a] All reactions were carried out on a 2.00 mmol reaction scale of benzaldehydes using 2.40 mmol of 1.0 M solution of TBAF in THF in the presence of 20% NaOH. The yields were isolated.

Table 3. Reactions with Excess TBAF in THF

entry	Y	TBAF (equiv)	time (h)	temp (°C)	yield (%)[a]		
					aldehyde	acid	alcohol
1[b]	CF_3	2	12	50	–	83	17
2	Cl	3	12	80	–	60	40
3	H	3	12	80	32	50	18
4	*t*-Bu	3	12	80	34	45	21

[a] All reactions were carried out with a 2.00 mmol reaction scale of benzaldehydes using a mixture of 1.0 M TBAF (1.0 equiv) in THF and $TBAF{\cdot}3H_2O$ (2.0 equiv). The relative yields were calculated by integrating the NMR data. [b] The reaction was performed with a mixture of 1.0 M TBAF (1.0 equiv) in THF and $TBAF{\cdot}3H_2O$ (1.0 equiv).

The oxidation reaction was carried out under harsher conditions such as with an excess of TBAF and at higher reaction temperatures (Table 3). Although the reaction with the aldehydes with electron withdrawing groups such as 4-trifluoromethyl- and 4-chlorobenzaldehydes was completed within 12 h, the reaction with benzaldehyde and 4-*t*-butylbenzaldehyde was not completed within this time.

Recently, various facile nucleophilic substitution reactions (halogenation, acetoxylation, nitrilation, alkoxylations, hydroxylation, and pyrrolation of bromo- and mesyloxyalkanes) at the primary or secondary aliphatic position using the corresponding potassium salts as nucleophiles in the presence of ionic liquids were reported.[15] In addition, phenols were regenerated from ethers using ionic liquid halide nucleophilicity.[16] According to the experimental data, ionic liquids should significantly enhance the reactivity of metal salts in the nucleophilic substitution, particularly alkali metal salts, although Welton *et al.* reported that the nucleophilicity of halides is not enhanced in an ionic liquid.[17] In order to provide evidence for the nucleophilic attack of hydride, the oxidation reaction was also attempted in an ionic liquid, [bmim][PF_6] (Table 4).

Despite the fact that the reaction conditions in Table 3 were similar to those shown in Table 2, no alcohols were formed. The reason for this is that the attack of hydride on a

Table 4. The Reactions with Excess TBAF in an Ionic Liquid, [bmim] [PF_6] at 80 °C[a]

entry	Y	TBAF (eq)	time (h)	Yield (%)[b]		
				aldehyde	acid	alcohol
1	CF_3	2	6	–	99 (85)	–
2	Cl	3	12	–	99 (87)	–
3	H	3	12	3	63 (52)	–
4	*t*-Bu	3	12	5	65 (55)	–

[a] All reactions were taken place with a 2.00 mmol reaction scale of benzaldehydes using $TBAF{\cdot}3H_2O$ in [bmim][PF_6] (2.0 mL). [b] The relative yields were calculated by integrations of NMR data and isolated yields were in parenthesis.

tetrabutylammonium salt is much faster than those on aldehydes (Cannizzaro reaction). Boechat and Clark reported that the Hoffmann type elimination of TBAF could occur above 50 ºC through the attack of fluoride.[18] The present study used tetramethylammonium fluoride (TMAF) instead of TBAF to determine if hydride plays a role as either a nucleophile or a base. Similar results were obtained with TMAF and TBAF. Therefore, hydride can attack the α-carbon of TMAF and TBAF. However, Hoffmann type elimination could not be excluded in the case of TBAF. Although there was no direct evidence of hydride attack, these results provide an indirect evidence of hydride attack.

In conclusion, the oxidation mechanism of benzaldehyde in the presence of TBAF is different from that of an ordinary Cannizzaro reaction, even in the presence of NaOH. TBAF might play a role as a fluoride source and an electrophile in an E2 or S_N2 type reaction. To prove this mechanism, many attempts were made to isolate some of the side products such as hydrogen, 1-butene, *n*-butane, and tributylamine. However, no side product was isolated nor was any gas evolution observed, even on the gram-reaction scale. The reactivity increased with increasing electron-withdrawing properties of the substituent. Further studies aimed at determining the mechanism and the role of TBAF in the oxidation reaction of aldehyde are currently underway.

Experimental Section

The chemicals were purchased from Aldrich Chemical Co. and used as received. The ionic liquid, [bmim][PF_6] was purchased from FutureChem Co. Korea. All acids and alcohols were commercially available and were identified by their NMR data.

Typical Procedure for the Oxidation of 4-Nitrobenzaldehyde to 4-Nitrobenzoic Acid. 4-Nitrobenzaldehyde (0.306 g, 2.00 mmol) was added to a 1.0 M solution of TBAF in THF (2.40 mL, 2.40 mmol) at rt. After stirring for 12 h, the pH of the reaction mixture was adjusted to 13 with 1.0 M of NaOH, and extracted with diethyl ether (3 × 30 mL). The ether layer consisted of 4-nitrobenzaldehyde and 4-nitrobenzyl alcohol. The aqueous layer was acidified with concentrated HCl, and extracted with EtOAc (3 × 30 mL). The combined organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give 4-nitrobenzoic acid (0.231 g, 69%). The sample was purified by recrystallization.

Typical Procedure for the Oxidation of Benzaldehydes to Benzoic Acids in an Ionic Liquid, [bmim][PF_6] (Table 4). A mixture of benzaldehyde (0.212 g, 2.00 mmol) and TBAF·$3H_2O$ (1.89 g, 5.99 mmol) in [bmim][PF_6] (2.00 mL) was heated at 80 ºC. After stirring for 12 h, the reaction mixture was extracted with diethyl ether (3 × 40 mL). The ether layer was added to 1.0 M of NaOH (50 mL), separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layer contained the unreacted benzaldehyde and other unknown products. The aqueous layer was acidified with concentrated HCl, and extracted with EtOAc (3 × 30 mL). The combined organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give benzoic acid (0.127 g, 52%).

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