Deprotection of Acetals and Ketals in a Colloidal Suspension Generated by Sodium Tetrakis(3,5-trifluoromethylphenyl)borate in Water

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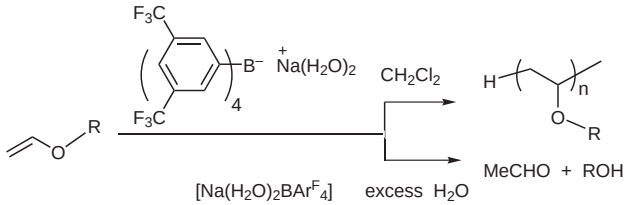
Abstract: Deprotection of acetals and ketals can be achieved by using sodium tetrakis(3,5-trifluoromethylphenyl)borate ($NaBAr^F_4$) as the catalyst in water at 30 °C. For example, a quantitative conversion of 2-phenyl-1,3-dioxolane into benzaldehyde was accomplished within five minutes by using this sodium salt (0.1 mol%) in water.

Key words: acetals, phase-transfer catalysis, hydrolysis, sodium, protecting groups

Protection and deprotection of carbonyl groups are of fundamental importance in the multistep organic synthesis.[1] Although numerous methods for deprotection of acetals are known, chemists are still interested in developing processes of good efficiency under mild conditions.[2] In recent years, deprotection of ketals and acetals under very smooth conditions, such as CAN in neutral or mild conditions,[3] thiourea in EtOH–H_2O,[4] $SmCl_3$–TMSCl,[5] cyclodextrins in H_2O,[6] $Bi(OTf)_3$ in THF–H_2O,[7] $Ce(OTf)_3$ in $MeNO_2$–H_2O,[8a] TESOTf–pyridine–H_2O[8b] and $LiBF_4$ in MeCN–H_2O,[9] have been reported. Quest for a mild and neutral approach particularly in water as reaction medium which may affect the selective hydrolysis of acetals or ketals, is still of interest.[10]

In our previous investigation, we had found that sodium tetrakis(3,5-trifluoromethylphenyl)borate dihydrate ($NaBAr^F_4 \cdot 2H_2O$) was able to render a proton to initiate the polymerization of vinyl ether in anhydrous organic solvents (Scheme 1).[11] This sodium salt could also assist the hydrolysis of vinyl ethers in aqueous solution. Based on our preliminary finding, we have carried out a study on the deprotection of acetals or ketals by using this sodium salt in aqueous medium.



Scheme 1

Hydrolysis of 2-phenyl-1,3-dioxolane was selected as a model reaction to examine the effectiveness of $NaBAr^F_4$ on this reaction. It was surprising to find out that 2-phenyl-1,3-dioxolane was efficiently hydrolyzed into benzaldehyde in water (entry 3, Table 1). Besides water, we also studied the effect of other solvents on the reaction, because a colloidal dispersion of the reaction mixture was formed during the reaction in water. As shown in Table 1, hydrolysis proceeded smoothly in any aqueous/organic mixed solvent except in a pure organic solvent (entries 1 and 2, Table 1). The use of organic/aqueous mixture for hydrolysis of acetals or ketals is a common choice due to solubility. However, the reaction time was directly proportional to the amount of organic solvent used. For example, in aqueous tetrahydrofuran only 84% of the deprotection product was collected after stirring for three hours (entry 4, Table 1), but a 100% conversion was obtained within five minutes in water. Of course, the colloidal dispersion disappeared with the use of a larger amount of organic phase. Nevertheless, the emulsion seemed to accelerate the hydrolysis process, suggesting that the tetrakis(3,5-trifluoromethylphenyl)borate anion might act as a surfactant.[12]

Table 1 Solvent Effect on Hydrolysis of 2-Phenyl-1,3-dioxolane Catalyzed by $NaBAr^F_4$[a]

Entry	Solvent	Time	Yield (%)[b]
1	THF	3 h	0
2	CH_2Cl_2	3 h	0
3	H_2O	5 min	100
4	THF–H_2O (9:1)	3 h	84
5	THF–H_2O (1:1)	30 min	100
6	THF–H_2O (1:9)	10 min	100
7	CH_2Cl_2–H_2O (9:1)	3 h	92
8	CH_2Cl_2–H_2O (1:1)	30 min	99
9	CH_2Cl_2–H_2O (1:9)	10 min	100

[a] Reaction conditions: 2-phenyl-1,3-dioxolane (5 mmol) and $NaBAr^F_4$ (0.005mmol) in solvent (10 mL) at 30 °C for 3 h.
[b] GC yields.

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Table 2 Hydrolysis of Acetals and Ketals[a,13,14]

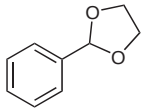
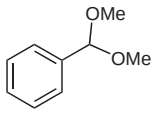
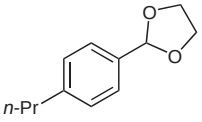
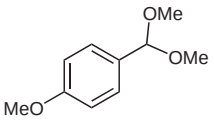
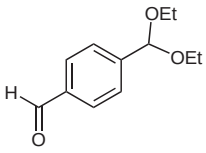
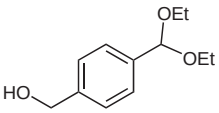
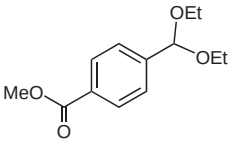
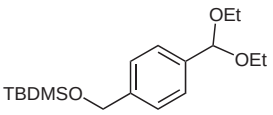
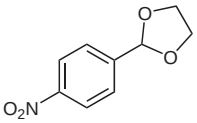
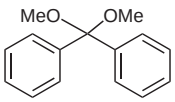
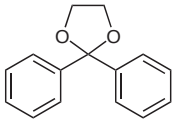
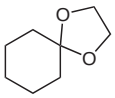
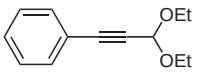
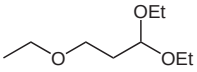
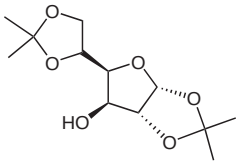
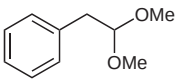
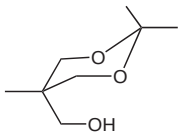
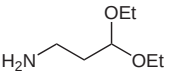
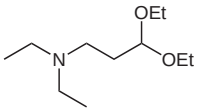
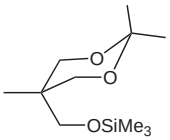
Entry	Substrate[15,16]	Time	Yield (%)
1	 **1**	1 min 5 min	55 100
2	 **2**	1 min 5 min	74 100
3	 **3**	5 min	100
4	 **4**	5 min	100
5	 **5**	5 min	100
6	 **6**	5 min	96
7	 **7**	3 h	100
8	 **8**	5 min	100
9	 **9**	72 h	<5
10	 **10**	30 min	99
11	 **11**	30 min	55

Table 2 Hydrolysis of Acetals and Ketals[a,13,14] (continued)

Entry	Substrate[15,16]	Time	Yield (%)
12	 **12**	30 min	62
13	 **13**	30 min	100
14	 **14**	30 min	100
15	 **15**	24 h	100
16	 **16**	15 h	100
17	 **17**	24 h	100
18	 **18**	72 h	–
19	 **19**	72 h	–
20	 **20**[23]	24 h[c]	100

[a] Reaction conditions: substrate (5 mmol), $NaBAr^F_4$ (0.005 mmol) in H_2O (10 mL) at 30 °C.
[b] Isolated yields.
[c] 1,1,1-Tris(hydroxymethyl)ethane was obtained as the product.

In view of the efficient hydrolysis of benzaldehyde acetal, the deprotection for various dialkyl, ethylene acetals and dioxolanes was investigated and the results are shown in Table 2. The experiment was simply conducted in a water solution of acetals or ketals in the presence of 0.1 mol% of $NaBAr^F_4$ at 30 °C. Acetals of aromatic aldehydes underwent smooth hydrolysis with an extremely fast rate to give the corresponding carbonyls in quantitative yields (entries 1–8, Table 2). In most instances, the reactions

were accomplished within 30 minutes, indicating the efficiency of this approach as compared to other Lewis acid catalyzed methods.[1–8] It is particularly noteworthy that various functional groups, such as ester or *tert*-butyldimethylsilyl (TBDMS) groups, were tolerated under these reaction conditions. However, a competing desilyation reaction was observed alongside the ketone hydrolysis for compound **20**. The process of desilyation appeared to be faster than that of hydrolysis. From ^{1}H NMR integration, it was determined that approximately 50% of **20** was converted into **17** (desilylation) within three hours.

Previous studies showed that the benzaldehyde acetals with electron-withdrawing substituents tended to be slow or resistant to the hydrolysis.[17] Indeed, the deprotection of compound **7** (with an ester substituent) took a longer period for completion, whereas the compound **9** remained almost intact even after three days under the same conditions. Dialkyl aromatic acetals (or ketals) were more reactive toward the reagent than the corresponding cyclic acetals (or ketals) (entries 1 vs. 2, 10 vs. 11, Table 2), whereas the hydrolysis of aromatic acetals seemed to be easier than those of the aliphatic substrates (entries 12, 14, 16 and 17, Table 2).

The beneficial effect of $NaBAr^F_4$ on the deprotection was also applicable to the hydrolysis of acetonide of carbohydrate. When the 1,2:5,6-*O*-isopropylidene-α-D-glucofuranose (**15**) was subjected to these reaction conditions, a quantitative yield of 1,2-*O*-isopropylidene-α-D-glucofuranose was observed; no other hydrolyzed product was isolated even after 24 hours (entry 15, Table 2). Such selectivity was presumably due to a favorable hydrolysis at the less sterically hindered site.[18]

The acetal molecules containing an amino functionality appear to be inert to these reaction conditions as no reaction product was detected even after longer reaction time (72 h). The basicity of amines readily stopped the deprotection of acetals, with all starting material being recovered in both examples (entries 18 and 19, Table 2). Presumably the coordination of amines to the metal centers demolished the activity of the catalyst.

Lipshutz and co-workers have shown that acetals and ketals could be hydrolyzed by $LiBF_4$ in aqueous acetonitrile. It has been demonstrated that this cleavage might involve the participation of HF and boron-containing Lewis acid.[9] However, it is quite unlikely that such a species was generated under the catalytic reaction conditions in our work. Thus the roles of cations and anions in this reaction were examined. Results of the treatment of 2-phenyl-1,3-dioxolane with various salts are summarized in Table 3. Sodium salts of chloride, bromide and tetrafluoroborate, which are soluble in water, did not form colloidal particles in the presence of the organic substrates under the given conditions, thus the deprotection did not proceed or was insignificant. However, the benzaldehyde acetals underwent hydrolysis smoothly on the use of tetrakis(3,5-trifluoromethylphenyl)borate salts (entries 5–7, Table 3), indicating the importance of $^-BAr^F_4$. The reactivity order of the borate salts is $Na^+ > Li^+ > Mg^{2+}$, which was consistent with the order of hydrolysis constant (pK_h).[19] It is noteworthy that the sodium dodecylsulfonate could also act as a catalyst for the deprotection of acetals in water, although with much slower rate. However, hydrolysis of acetals catalyzed by $NaBAr^F_4$ was completely stopped, when 18-crown-6 was added (entry 9, Table 3).

Table 3 Hydrolysis of 2-Phenyl-1,3-dioxolane by Various Salts[a]

Entry	NaX	Time	Yield (%)
1	NaCl	3 h	0
2	NaBr	3 h	0
3	$NaBF_4$	3 h	7
4	$NaBPh_4$[b]	3 h	22
5	$NaBAr^F_4$	5 min	100
6	$LiBAr^F_4$	10 min	100
7	$Mg(BAr^F_4)_2$	20 min	100
8	$CH_3(CH_2)_{11}SO_3Na$[b]	3 h	19
9	$NaBAr^F_4$	24 h	<5[c]

[a] Reaction conditions: NaX (5×10^{-3} mmol), 2-phenyl-1,3-dioxolane (5 mmol) in H_2O (10 mL) at 30 °C.
[b] Obtained from commercial source and used without further purification.
[c] Low yield due to addition of 18-crown-6 (1×10^{-2} mmol).

It has been known that the formation of colloidal particles created by organic substrates, surfactants, or catalysts in water could accelerate chemical reactions.[20] The hydrolysis of acetals/ketals catalyzed by metal salts of tetrakis(3,5-trifluoromethylphenyl)borate makes another example. It is obvious that the trifluoromethyl substituents of the phenyl rings have an influence. In a previous report, we showed the existence of the coordination of Na with F in the crystal structure of $NaBAr^F_4 \cdot 2H_2O$.[11] It is believed that such coordination might partially persist in aqueous environment, and thus increase the Lewis acidity of metal ions. The formation of sodium–crown ether complex, however, hinders the reaction (entry 9, Table 3), showing that the interaction of Na···F is readily interrupted by the addition of the crown ether. Further experiments and theoretical consideration are necessary to confirm such phenomenon. By screening a series of acid-base indicators, we found that the acidity of $[Na(H_2O)_2]BAr^F_4$ in THF–H_2O was estimated to be in the pH range of 3.6–4.5.

In summary, a new and chemoselective method for the cleavage of acetals and ketals in water under mild and neutral reaction conditions has been developed in this work. The advantages of this method are the general applicability in hydrolysis of alkyl and cyclic acetals (ketals) in high yields, the observed selectivity, and very mild reaction conditions such as 0.1 mol% $NaBAr^F_4$ of catalyst

in water at 30 °C. From the anion study, it is quite clear that the property of metal ions changes dramatically by the surrounding anions. At present, the activities of metal salts associated with a tetrakis(3,5-trifluoromethylphenyl)borate anion in other reactions are currently under investigation.

Acknowledgment

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(12) Akiyama, T.; Matsuda, K.; Fuchibe, K. *Synlett* **2005**, 322.
(13) **Typical Procedure for Hydrolysis**: A mixture of $NaBAr^F_4 \times 2H_2O$ (5×10^{-3} mmol)[11] and acetal (5.0 mmol) in H_2O (10 mL) was placed in a 25-mL flask. The resulting suspension was stirred vigorously at 30 °C for a certain period as shown in Table 2. After the completion of the reaction, the reaction mixture was extracted with CH_2Cl_2 (2×5 mL). The extracts were dried and filtered through a short column of silica gel to remove the sodium salt. Upon concentration, the desired carbonyl products were obtained in pure form. For all products reported in Table 2, full ^1H and ^{13}C NMR data were compared with those of the pure sample obtained from commercial sources, or with reported data.[25]
(14) **Spectral Data for the Hydrolyzed Products**:
1,2-*O*-Isopropylidene-α-D-glucofuranose:[18] mp 154–158 °C (dec.).^1H NMR (400 MHz, D_2O): δ = 5.90 (d, *J* = 4 Hz, 1 H), 4.58 (d, *J* = 4 Hz, 1 H), 4.20 (s, 1 H), 3.97 (d, *J* = 8 Hz, 1 H), 3.78 (m, 1 H), 3.68 (d, *J* = 12 Hz, 1 H), 3.97 (d, *J* = 8 Hz, 1 H), 3.52 (dd, *J* = 6 Hz, 1 H), 1.39 (s, 3 H), 1.24 (s, 3 H). ^{13}C NMR (100 MHz, D_2O): δ = 112.5 (C), 104.6 (CH), 84.3 (CH), 79.6 (CH), 78.6 (CH), 68.2 (CH), 63.4 (CH_2), 25.4 (CH_3), 25.0 (CH_3).
4-Propylbenzaldehyde:[21] ^1H NMR (400 MHz, $CDCl_3$): δ = 9.98 (s, 1 H), 7.81 (d, *J* = 6.8 Hz, 2 H), 7.34 (d, *J* = 6.8 Hz, 2 H), 2.68 (t, *J* = 7 Hz, 2 H), 1.68 (m, 2 H), 0.96 (t, *J* = 7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.64 (CH), 150.1 (C), 134.4 (C), 129.9 (CH), 129.2 (CH), 39.0 (CH_2), 26.2 (CH_2), 14.2 (CH_3).
4-(*tert*-Butyldimethylsilyloxymethyl)benzaldehyde:[22] ^1H NMR (300 MHz, $CDCl_3$): δ = 10.01 (s, 1 H), 7.85 (d, *J* = 8 Hz, 2 H), 7.49 (d, *J* = 8 Hz, 2 H), 4.82 (s, 2 H), 0.96 (s, 9 H), 0.13 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.6 (CH), 148.6 (C), 135.3 (C), 129.9 (CH), 126.3 (CH), 65.0 (CH_2), 26.7 (CH_3), 19.3 (C), –4.3 (CH_3).
4-Hydroxymethylbenzaldehyde:[23] ^1H NMR (400 MHz, $CDCl_3$): δ = 9.96 (s, 1 H), 7.84 (d, *J* = 6.8 Hz, 2 H), 7.50 (d, *J* = 6.8 Hz, 2 H), 4.78 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.7 (CH), 147.7 (C), 135.6 (C), 130.1 (CH), 127.0 (CH), 65.1 (CH_2).
3-Ethoxypropionaldehyde:[24] ^1H NMR (400 MHz, $CDCl_3$): δ = 9.78 (t, *J* = 2 Hz, 1 H), 3.76 (t, *J* = 6.4 Hz, 2 H), 3.50 (q, *J* = 6.8 Hz, 2 H), 2.67 (td, *J* = 1.6, 6 Hz, 2 H), 1.20 (t, *J* = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.9 (CH), 67.1 (CH_2), 64.6 (CH_2), 64.6 (CH_2), 44.6 (CH_2), 16.0 (CH_3).
Methyl 4-Formylbenzoate:[25] ^1H NMR (400 MHz, $CDCl_3$): δ = 10.09 (s, 1 H), 8.18 (d, *J* = 8 Hz, 2 H), 7.94 (d, *J* = 8 Hz, 2 H), 3.95 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.6 (CH), 166.0 (C), 139.1 (C), 135.1 (C), 130.2 (CH), 129.5 (CH), 52.6 (CH_3).
(15) Acetals **1**, **6**, **7**, **8**, **9**, **10**, **11**, **15**, **17**, **18** and **19** were synthesized according to the literature methods. Other acetals were obtained from commercial sources:
(a) Compound **1**: Mosca, R.; Fagnoni, M.; Mella, M.; Albini, A. *Tetrahedron* **2001**, *57*, 10319. (b) Compounds **6** and **7**: Barluenga, J.; del Pozo, C.; Olano, B. *Synthesis* **1995**, 1529.
(c) Compound **8**: Eash, K. J.; Pulia, M. S.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2000**, *65*, 8399. (d) Compound **9**: Walton, R.; Lahti, P. M. *Synth. Commun.* **1998**, *28*, 1087.
(e) Compound **10**: Bořkovec, A. B. *J. Org. Chem.* **1961**, *26*, 4866. (f) Compound **11**: Sulzbacher, M.; Bergmann, E.; Pariser, E. R. *J. Am. Chem. Soc.* **1948**, *70*, 2827.
(g) Compound **15**: Goud, P. M.; Venkatachalam, T. K.; Uckun, F. M. *Synth. Commun.* **2003**, *33*, 1185.
(h) Compound **17**: Ouchi, M.; Inoue, Y.; Wada, K.; Iketani, S.; Hakushi, T.; Weber, E. *J. Org. Chem.* **1987**, *52*, 2420.
(i) Compound **18**: Carroll, F. I.; Berrang, B. D.; Linn, C. P. *J. Heterocycl. Chem.* **1981**, *18*, 941. (j) Compound **10**: Lai, J.-Y.; Shi, X.-X.; Dai, L.-X. *J. Org. Chem.* **1992**, *57*, 3485.
(16) **Preparation of 20**: A solution of **17** (0.32 g, 2 mmol) and Et_3N (0.38 mL, 2.8 mmol) in anhyd CH_2Cl_2 (5 mL) was cooled in an ice-water bath under dried nitrogen. Chlorotrimethylsilane (0.31 mL, 2.4 mmol) was slowly added to the above solution with stirring. After the addition, the resulting mixture was heated to reflux for 6 h. The mixture was filtered to remove the ammonium salt and the filtrate was evaporated under reduced pressure to remove the excess amine and chlorotrimethylsilane. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with sat. $NaHCO_3$. The organic extract was dried over $MgSO_4$ and concentrated to give the desired compound **20** (0.46 g, 100%). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.64 (d, *J* = 12 Hz, 2 H), 3.55 (s, 2 H), 3.52 (d, *J* = 12 Hz, 2 H), 1.41 (s, 3 H), 1.37 (s, 3 H), 0.79 (s, 3 H), 0.09 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 97.5 (C), 66.2 (CH_2), 65.2 (CH_2), 35.0 (C), 27.0 (CH_3), 21.2 (CH_3), 18.3 (CH_3), –0.1 (CH_3). Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 56.77; H, 10.21.
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