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Pyridinium poly(hydrogen fluoride)-assisted cleavage of acetals and ketals

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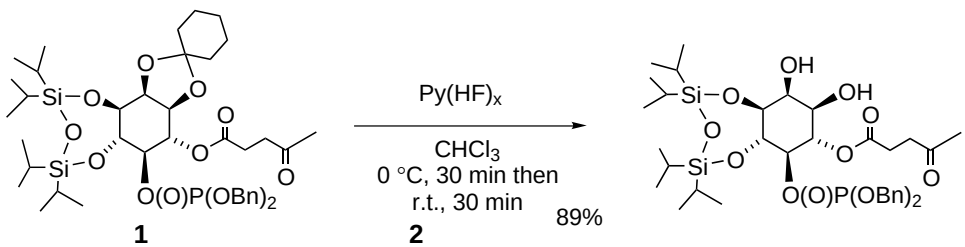
Abstract—Acetals, including ketals, were smoothly cleaved by the action of pyridinium poly(hydrogen fluoride) without addition of water or an alcohol in an anhydrous solvent.

Pyridinium poly(hydrogen fluoride) [PPHF, expressed as $Py(HF)_x$],[1] comprising 30% pyridine and 70% HF by weight, has been used as an HF-equivalent reagent in substitution and addition reactions for various functional groups.[2,3] The reagent was also used for deprotection of tetraisopropyldisiloxanyl ethers[4] as well as other silyl ether derivatives.[5] However, we found that while the same disiloxanyl ether function in the inositol derivative **1** was kept intact, PPHF [14 equiv. as x = ca. 9 in PPHF purchased from Aldrich™] selectively cleaved the cyclohexylidene group in anhydrous $CHCl_3$ to afford 1,2-diol **2**.[6] The result is also contradictory to the fact that acetals[7] and tetrahydropyranyl ethers[8] have been reported to be tolerant toward PPHF. Since the reaction conditions are nearly anhydrous[9] and less acidic than those of ordinary procedures for deprotection of acetals, the PPHF procedure might be promising for cleavage of acetals without decomposition of other acid-sensitive groups in the same molecule. With this expectation, we investigated the generality of the procedure and here propose a new acetal cleavage method using PPHF (Scheme 1).

As a typical example of an acyclic ketal, diethyl ketal of 4-phenyl-2-butanone **3** was cleaved quite smoothly by the action of 0.5 molar equivalent of PPHF in acetonitrile within 30 min at room temperature in a polypropylene vessel, giving the deprotected ketone in 96% yield (Table 1). Anhydrous acetonitrile as a solvent gave the best result in the reaction, while other solvents such as anhydrous benzene, chloroform, and dichloromethane were equally adequate. A limited amount of water (2 equiv.) in acetonitrile enhanced the reaction of **3** (rt, 10 min), resulting in the formation of the ketone in 90%. Its cyclic ketal version **4** needed 21 equiv. of PPHF for satisfactory conversion to the ketone. On the other hand, diethyl and dimethyl acetals **6** and **7** derived from dodecanal required a much larger quantity of PPHF to obtain a high yield of the aldehyde. The reaction of a benzylic acetal **5** proceeded faster than that of acetals **6**



1 2

Scheme 1.

Keywords: acetal; ketal; pyridinium poly(hydrogen fluoride); deprotection; inositol.
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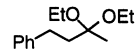
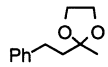
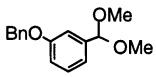
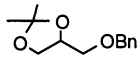
Table 1. Deacetalization using PPHF[a]

Substrate		Py(HF)x, equiv	Time	Additive (equiv)	Yield of carbonyl, %[b]
	**3**	0.5	30 min	-	96*
		3.0	15 min	-	85
		0.5	10 min	H_2O (2.0)	90
	**4**	21	30 min	-	81
	**5**	14	6 h	-	91
$C_{11}H_{23}CH(OMe)_2$	**6**	14	3 h	$Cl_3CCH(OH)_2$ (2.5)	89
		3	1 h		90
$C_{11}H_{23}CH(OEt)_2$	**7**	21	1 h	-	93*
		14	5 h	Cl_3CCHO (2.5)	97
	**8**	14	4 h	-	79[c, d]

[a] In anhydrous CH_3CN at r.t.
[b] Isolated yield except for the case indicated with asterisk where yield was estimated by ^{1}H-NMR analysis of a reaction mixture extracted with ethyl ether.
[c] CH_2Cl_2 as a solvent.
[d] Yield of the corresponding 1,2-diol.
Abbreviation: Bn=benzyl

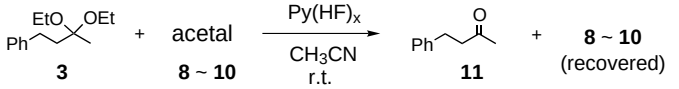
and **7**, as monitored by TLC (almost completion within 1 h), to afford the benzaldehyde in excellent yield though the reaction took longer. In the case of a cyclic ethylene acetal of dodecanal, the reaction was sluggish, even in a large amount of PPHF, to give unacceptable results.

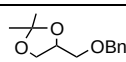
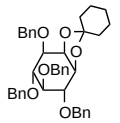
The PPHF-aided cleavage reaction of acetals was reversible, as longer reaction time decreased the yield of dodecanal. In order to shift the equilibrium of the reaction to the left, chloral or chloral hydrate was additionally applied. Thus, 2.5 equiv. of these additives permitted a decrease in the quantity of PPHF and a smooth reaction to afford the aldehyde in excellent yields, as shown in Table 1. The hydrate was slightly more efficient than chloral.

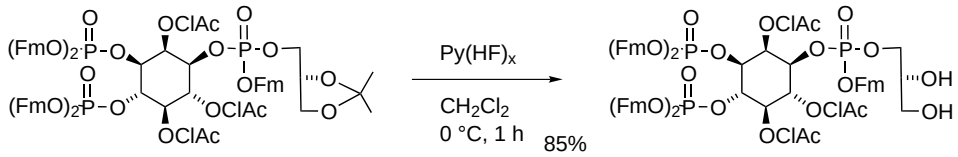
Since the reactivity of acetals toward PPHF depended markedly upon their structure type, selective cleavage of the most reactive acyclic ketal **3** was examined in the presence of other acetals.[10] As shown in Table 2, competition reactions with **8**, MOM ether **9**, and cyclic ketals **10** showed almost complete selectivities. Coexistence of docecanal acetal **7** and tetrahydropyranyl ether[8] of 3-phenylpropanol exhibited fairly good selectivity, but dodecanal and 3-phenylpropanol were generated in about 20 and 30% yields, respectively, as analyzed by NMR. In the latter case, some other unidentified products were also obtained to a slight extent.

The isopropylidene acetal in the inositol derivative **12** was efficiently cleaved with 40 equiv. of PPHF to afford quite unstable diol **13** in 85% yield, suppressing the migration and decomposition of the phosphate function, while employment of ordinary acetal exchange procedures (MeOH–CF_3CO_2H and ethylene glycol–

Table 2. Selective cleavage of **3** in the coexistence of other acetals



Run	Coexistent acetal		Py(HF)x, equiv	Time, min	Yield, % **11**	Yield, % **8 ~ 10**
1		**8**	0.5	20	98	99
2		**9**	7.0	15	90	100
3		**10**	0.5	20	93	99



Scheme 2.

TsOH) for the same purpose gave poorer results (45 and 60% yields, respectively, Scheme 2).

Judging from these results, the present procedure using PPHF is concluded to provide an alternative method for cleavage of acetals.[11]

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11. A typical experimental procedure: To a solution of 4-phenyl-2-butanone diethyl ketal **3** (306 mg, 1.38 mmol) in acetonitrile (1.5 ml) in a polypropylene vessel was added PPHF (118 μl, 4.13 mmol) at room temperature and the mixture was stirred at the same temperature for 15 min. After addition of an adequate quantity of solid $NaHCO_3$ (slightly exothermic) to neutralize briefly, the mixture was stirred for about 5 minutes and transferred into a separatory funnel using ethyl ether. The resultant organic layer was treated successively with a saturated $NaHCO_3$ solution, H_2O, and a saturated NaCl solution, dried over $MgSO_4$, concentrated, and chromatographed on silica gel (AcOEt/hexane, 1:4) to give the ketone **11** (173 mg, 85% yield).