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Cleavage of Acid-Labile Protective Groups by Tris (*p*-bromophenyl) aminium Hexachloroantimonate

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Selective cleavage of protective groups in polyhydroxy compounds are very useful in organic synthesis, especially in the field of carbohydrate and nucleoside chemistry. Recently we reported new methods for the selective cleavage of acetals and ketals.^{1,2}

In this paper, we report the cleavage of acid-labile protective groups by a stable cation radical, namely tris (*p*-bromophenyl)aminium hexachloroantimonate,³ (*p*-BrC₆H₄)₃N⁺ SbCl₆⁻. This cation radical has been used for the cleavage of the *p*-methoxybenzyl ether in moist acetonitrile^{4,5}. It has been suggested that *p*-methoxybenzyl ether radical is involved as an essential intermediate in that cleavage reaction. We initially hoped that (*p*-BrC₆H₄)₃N⁺ SbCl₆⁻ might selectively cleave acetals but not ketals. Since acetal has a acetal proton, a transformation shown in Scheme 1 might be possible whereas the ketal does not have a that kind of hydrogen. However, (*p*-BrC₆H₄)₃N⁺ SbCl₆⁻ in this work nonselectively cleaved not only acetals and ketals but also other acid-labile protective groups.

Table 1 shows the results of the cleavage. A benzylidene acetal **1** (0.041g, 0.20 mmol) was treated with (*p*-BrC₆H₄)₃N⁺ SbCl₆⁻ (0.092g, 0.20 mmol) in acetonitrile (10ml) at room temperature. The reaction was monitored by gas chromatography. After 30 min, the reaction was quenched by saturated aqueous sodium bicarbonate (2ml). Cyclohexanediol and benzaldehyde were produced in 95% yield. Ketals were also cleaved under the same condition as that for the acetal to give rise to ketones and diols. This result indicates that cyclic carboxonium ion as shown in Scheme 1 is not the intermediate of this cleavage reaction. In dried DME, CH₂Cl₂, or CH₃CN, the cleavage was very slow but the products were also carbonyl compounds and diols which are the usual hydrolysis products of acetals and ketals.

We, therefore, examined the possibility of the involvement of protic acid which might be produced from the radical cation. At first, we hoped to neutralize the protic acid by addition of a base such as pyridine, 2,6-lutidine, triethylamine, or solid sodium bicarbonate. However, those bases readily

destroyed the cation radical. Then, we prepared other hexachloroantimonate salts, namely benzyltriethylammonium hexachloroantimonate(PhCH₂Et₃N⁺ SbCl₆⁻) and tetraethylammonium hexachloroantimonate(Et₄N⁺ SbCl₆⁻).⁶ Neither of them could cleave acetals and ketals in acetonitrile or in methylene chloride. When two or three equivalents of water were added to the reaction mixture, acetals and ketals were hydrolyzed to give carbonyl compounds and diols in poor yields (see Table 2).

Other acid-labile protective groups such as trityl, tetrahydropyranyl, and *tert*-butyldimethylsilyl groups were also cleaved by (*p*-BrC₆H₄)₃N⁺ SbCl₆⁻ in acetonitrile at room temperature as shown in Table 1.

A few further experiments were performed in order to gain more insight into these cleavage reactions. Less than one equivalents of (*p*-BrC₆H₄)₃N⁺ SbCl₆⁻ could cleave the protective groups although a larger amount of the reagent enhanced the reaction rate. Dried solvents substantially decreased the reaction rates but in the usual distilled solvents, the reaction proceeded rapidly.

Based on these results, we could speculate that the reaction would be initiated by the cation radical but the cleavage should be the result of the hydrolysis catalyzed by the proton produced in the initial reaction. A very small amount of water contained in the solvents might be enough for this hydrolysis. Thus, as shown in Scheme 1 and Scheme 2, (*p*-BrC₆H₄)₃N⁺ SbCl₆⁻ generate the cation radical of acetal or ketal at first and then a proton is eliminated from the cation radical of the acetal or the ketal. The next step is the protonation of the acetal or the ketal by the proton eliminated in the earlier step. In the presence of water, then a usual hydrolysis occurs.

Although (*p*-BrC₆H₄)₃N⁺ SbCl₆⁻ did not show selectivities, it efficiently and cleanly cleaved acid-labile protective groups in the organic solvents. The suggested reason for the cleavage would promote further systematic studies on this interesting hydrolysis induced by cation radical.

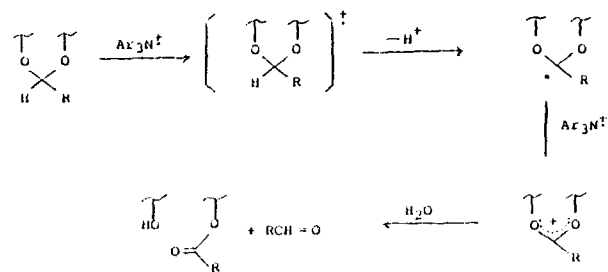
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Table 1. Cleavage of Acid-Labile Protective Groups with (p-BrC₆H₄)₃N⁺ SbCl₆^{-a}

Compound	Time, h	Product	Yield, % ^b
	0.5		95
	0.5	2	99
	0.5	5 (C ₆ H ₅ CHO)	95
	1		100
	1		100
	1		100
	1		100
	0.5	12 (H ₃ C(CH ₂) ₆ CH ₂ OH)	99
	1		100
	0.5		80

^a The reaction was carried out in acetonitrile at room temperature.

^b The yields were determined by GLC.



Scheme 1

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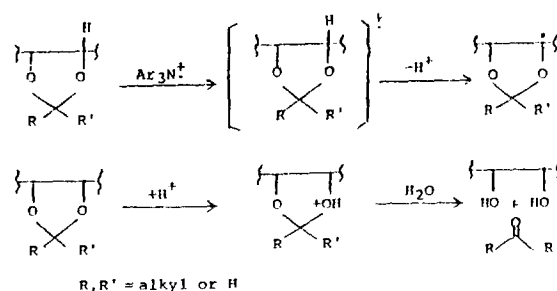
Table 2. Cleavage of Acid-Labile Protective Groups with PhCH₂N⁺Et₃SbCl₆⁻(A) or Et₄N⁺SbCl₆⁻(B)^a

Compound	Reagent	Time, h	Product	Yield, %
4	A	8	5	0
4	B	8	5	0
4	A + H₂O(3 equiv.)	8	5	45
4	B + H₂O(3 equiv.)	8	5	40
5	A	48	7	5
5	B	48	7	5
5	A + H₂O(3 equiv.)	16	7	40
11	A	48	12	5
11	B + H₂O(3 equiv.)	16	12	60

	13	48		14	5
13	A + H₂O(3 equiv.)	72	14	14	65

^a The reaction was carried out in acetonitrile at room temperature.

^b The yields were determined by GLC.



Scheme 2

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