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A practical and efficient procedure for the cleavage of acylals to aldehydes catalyzed by indium tribromide in water

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Abstract—Indium tribromide (10 mol %) is an efficient catalyst for chemoselective cleavage of aryl acylals in refluxing water. A variety of acylals have been deprotected to give the corresponding parent aldehydes in high yield. The procedure presented is operationally simple, practical, and compatible with other sensitive functionalities such as methoxy, methyleneioxy, and benzyloxy groups present in the substrates.

The toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons and benzene, which are widely used in organic synthetic procedures, has posed a serious threat to the environment. There has been considerable research recently into replacing the use of these volatile organic solvents with clean ones as reaction media.[1] Performing organic reactions in aqueous media has attracted much attention, because water would be considerably safe, non-toxic, environmentally friendly and cheap compared to organic solvents.[2] Moreover, when a water-soluble catalyst is used, most products can be separated by simple decantation and the catalyst solution can be recycled. Therefore, development of a catalyst system that is not only stable toward water but also completely soluble in this solvent seems highly desirable.

The protection–deprotection of aldehyde functionalities is important in synthetic organic chemistry, and a plethora of reagents and methods have been developed to this end. In recent years, acylals have been introduced as a suitable protection group for this purpose[3] because of their stability in mildly acidic and basic medium and ease of chemoselective preparation in the presence of ketone.[4] In addition, they can be converted into other useful functional groups by reaction with appropriate nucleophiles[5] and used as carbonyl surrogates for asymmetric synthesis.[6]

However, the final stages of chemical manipulation require their cleavage so as to regenerate the parent aldehydes. Although the conventional deprotection of acylals is achieved under basic conditions by using either sodium hydroxide or potassium carbonate in aqueous THF,[7] the strong basic conditions make them inappropriate for base-sensitive substrates. A variety of reagents for the removal of acylals have been developed to solve this problem. These include the use of boron triiodide-*N*,*N*-diethylaniline complex,[8] ceric ammonium nitrate coated on silica gel,[9] neutral alumina under microwave irradiation,[10] $CeCl_3{\cdot}7H_2O/NaI$,[11] CBr_4,[12] [$NO^+{\cdot}$Crown $H(NO_3)_2^-$],[13]$AlCl_3$,[14] zirconium(IV) chloride,[4e] $BiCl_3$,[15] $Sc(OTf)_3$,[16] 2,6-dicarboxypyridinium chlorochromate[17] and heterogeneous catalyst[18] such as montmorillonite clays,[19] expansive graphite,[20] zeolite,[21] layered zirconium sulfophenyl phosphonate,[22] Envirocat EPZG®.[23] Many of these methods suffer one or more drawbacks, such as the use of harmful volatile organic solvents, unsatisfactory yields, expensive reagents, longer reaction times, tedious work-up procedure or the use of an additional microwave oven. In this context there is a need to devise a mild, efficient method with environmental benign using water as a green solvent for the selective cleavage of acylals in the presence of acid-sensitive protecting groups. Scanning the literature, we have discovered an unique use of water as solvent with β-cyclodextrin for this conversion.[24]

Keywords: Acylals; Aldehydes; Deprotection; Indium tribromide; Protecting groups; Water.

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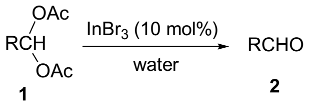


Scheme 1.

Recently, indium tribromide has been discovered to be a new type of water-soluble green Lewis acid imparting high regio-, chemo- and stereoselectivity in various chemical transformations.[25] As a continuation of these studies[26] and in an effort to investigate on organic reactions in water, we first report in this letter a selective and convenient procedure for the deprotection of acylals using a catalytic amount of $InBr_3$ in aqueous media (Scheme 1).

The catalytic activity of indium tribromide was first tested for the deprotection of acylals in water. Initially, the cleavage of α,α-diacetoxytoluene in the presence of 1 equiv $InBr_3$ in water was first investigated at room temperature, no deprotected product was obtained even the mixture was stirred for 24 h. To our satisfaction, rapid conversion was observed when the reaction was carried out with reflux at 100 °C in water. In these cases, lower temperature could also be applied but to result in a longer reaction period (Table 1, entry 5). We have also investigated the efficiency of the catalyst in less than stoichiometric amount. The deprotected benzaldehyde was obtained using 10 mol % of the $InBr_3$ in high yield. Lower catalyst loading could be used with only a marginal drop in reaction rate (Table 1, entries 3 and 4).

Table 1. Cleavage of α,α-diacetoxytoluene using $InBr_3$ in water

Entry	Catalyst load (mol %)	Temp (°C)	Time	Yield[a] (%)
1	100	rt	24 h	—
2	100	100	10 min	96
3	1	100	80 min	95
4	5	100	30 min	96
5	10	60	60 min	93
6	10	100	20 min	96

[a] Isolated yield.

Having established the preferred reaction conditions, the deprotection of several representative acylals was performed to demonstrate the versatility and uniqueness of the present reaction conditions (Table 2). Aromatic acylals were converted to the parent aldehydes in impressive yield. 2-Furanylmethanediol diacetate (entry 15) also was converted to its corresponding aldehydes without polymerization in the presence of $InBr_3$. α,β-

Table 2. Cleavage results of acylals using $InBr_3$ in refluxing water

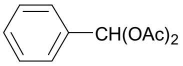
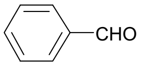
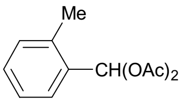
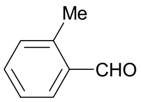
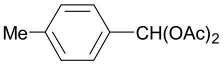
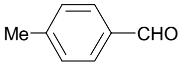
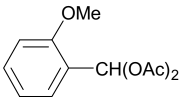
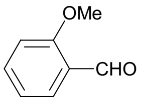
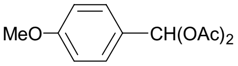
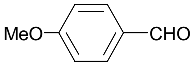
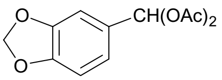
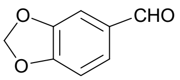
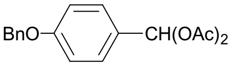
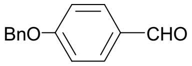
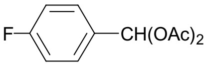
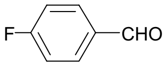
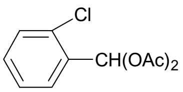
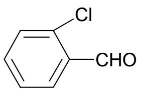
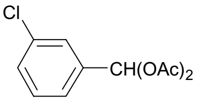
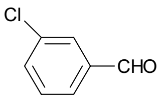
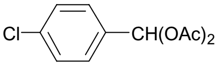
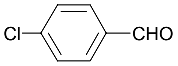
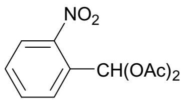
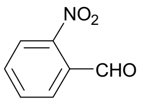
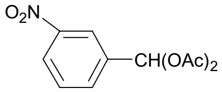
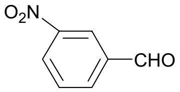
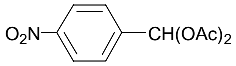
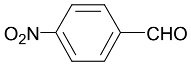
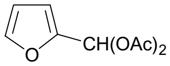
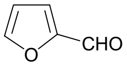
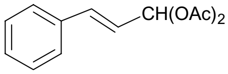
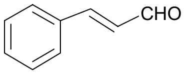
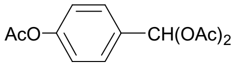
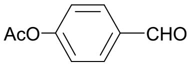
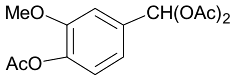
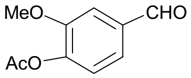
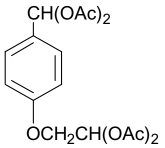
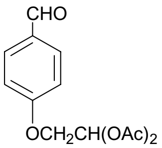
Entry	Substrate	Product	Time (min)	Yield[a,b] (%)
1			20	96
2			20	94
3			18	93
4			15	92
5			15	94
6			30	95
7			18	94
8			20	94
9			35	92
10			35	86
11			50	95

Table 2 (*continued*)

Entry	Substrate	Product	Time (min)	Yield[a,b] (%)
12			180	95
13			200	93
14			240	90[c]
15			25	90
16			40	89
17			15	93 (96[d])
18			20	95 (98[d])
19	$CH_3(CH_2)_8CH(OAc)_2$	$CH_3(CH_2)_8CHO$	5 h	Trace
20			4 h	90

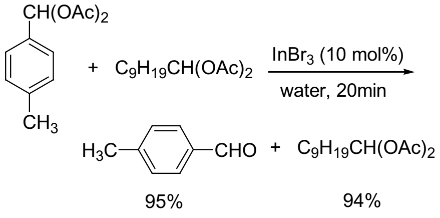
[a] Yield refers to pure isolated products.

[b] All products are known, and spectral data identical with authentic samples.

[c] Two milliliters of methanol was added.

[d] Based on GC analysis.

Unsaturated acylals (entry 16) were also proved amicable to this methodology. The presence of electron-donating and electron-withdrawing groups on the aromatic ring made obvious difference for the deprotection of acylals according to the reaction rates. The substitution of the electron-withdrawing group onto the aromatic ring severely retards the deprotection. The reaction with (4-methylphenyl)methanediol diacetate (entry 3) was completed within 18 min whereas with 2-, 3- and 4-nitrobenzylidene diacetates (entries 12–14) the reaction time was extended to 3–4 h. We have also tried the reaction of 1,1-diacetoxydecane (entry 19) as an example of an aliphatic aldehyde acylal in refluxing water for 5 h in the presence of the catalyst. Only trace of decanal was obtained. Removal of an aromatic acylal group from double protected aldehydes was achieved with high selectivity (entry 20). To stress the selectivity of this method, we have also performed a competitive reaction between 4-methylphenylmethanediol diacetate and 1,1-diacetoxydecane in the presence of 0.1 molar ratio of $InBr_3$ and observed the following conversion (Scheme 2). Such selectivity can be applied in synthetic sequences in which two acylal groups must be deprotected at different stages of the synthesis.



Scheme 2.

It should be noted that the treatment of (4-acetoxyphenyl) methanediol (entry 17) and (4-acetoxy-3-methoxyphenyl) methanediol (entry 18) with $InBr_3$ gave only the cleavage product of acylals in more than 90% yield in short reaction time. These results have demonstrated that such reaction conditions allow for selective cleavage of aryl aldehyde acylals in the presence of phenolic acetate. Moreover, the reaction conditions are sufficiently mild not to affect the methyl (entries 2 and 3), methoxy (entries 4 and 5), methyleneioxy (entry 6), benzyloxy (entry 7) and chloro (entries 9–11) functionalities.

After removal of the reaction product by ethyl acetate extraction of the aqueous reaction mixture, the mother liquor could be reused and subjected to a second run of the cleavage process by charging with the same substrate. The results of the first experiment and four subsequent runs were almost consistent in yield (96%, 95%, 93%, 94%) for the cleavage of α,α-diacetoxytoluene, but the complete conversion of substrate required a longer reaction time (35 min, 60 min, 80 min, 100 min).

Regarding the mechanism, the hydrolysis of benzylidene diacetates in aqueous hydrochloric acid has been proposed,[27] the detailed mechanistic studies of this conversion were not investigated, but a few points merit comment. No deprotected product was obtained when the reaction was processed in water at 100 °C in the absence of catalyst, suggesting that the presence of indium tribromide was necessary. A solution of indium tribromide in water was acidic. The aqueous layer from the workup was also found to be very acidic (pH 3). Thus it appeared that $H^+[InBr_4]^-$, which could be formed by the hydrolysis of indium tribromide in water, presumedly promoted the deprotection. Since the indium(III) salts are commonly identified as chelating Lewis acids,[25j] it is also possible that indium tribromide could coordinate with the oxygen of the acetoxy group to form a complex. Water would facilitate easily the deprotection by attacking the intermediate and yielding the parent aldehydes and acetic acid.

In conclusion, we have developed a practical and efficient protocol for the cleavage of acylals using indium tribromide in aqueous media. The advantage of the present protocol is the simplicity in operation, low cost of the reagent, high yields of deprotected products and the recyclability of the catalyst. Moreover, its compatibility with sensitive functionalities such as OMe, OBn, OAc, and double bonds with regard to economic and ecological consideration allows us to believe that this method may represent a valuable alternative to the existing reagents reported in the literature.

General procedure for cleavage of acylals is as follows: A mixture of acylal (**1**, 1 mmol) and $InBr_3$ (36 mg, 0.1 mmol, 10 mol %) in water (5 mL) was refluxed in air for a specified time as required to complete the reaction (Table 1). After completion as indicated by TLC or GC, the reaction mixture was cooled, extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate) to afford pure aldehyde **2**. The remaining mother liquor containing $InBr_3$ was recovered and recycled in subsequent reaction. The products were characterized by their melting points or boiling points, IR, ^{1}HNMR spectra, TLC and by comparison with their authentic samples.

Acknowledgements

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