Convenient One Pot Conversion of Acetals into Alcohols

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Abstract: Various acetals are conveniently converted into alcohols using a one pot procedure that combines hydrolysis of an acetal by triflouromethanesulfonic acid in tetrahydrofuran and *tert*-butylamine borane reduction of the resulting aldehyde.

Key words: acetals, alcohols, one pot, triflouromethanesulfonic acid, *tert*-butylaminoborane

Selective functionalization of one hydroxyl group in the presence of others can be a challenging problem often requiring additional protection – deprotection steps. Instead, stepwise conversion of various functional groups into a hydroxyl, followed by their subsequent functionalization could be a useful synthetic alternative. In this regard we were particularly interested in the possibility of an efficient conversion of acetals into hydroxyls.

Although both synthetic steps required in this transformation namely, hydrolysis of an acetal[1] and reduction of the resulting aldehyde[2] are well investigated, the isolation of reactive and sometimes unstable aldehydes often presents a problem. We thought that if we would be able to find conditions allowing to combine these steps into a 'one-pot' procedure the conversion of acetals into alcohols would be a useful synthetic tool. Unfortunately, most common conditions used for hydrolyses and reductions are hardly compatible; the former usually requires fairly acidic aqueous media, while the latter transformation is usually conducted in a neutral/basic and anhydrous environment.

After examining various possibilities (*vide infra*) we were able to find an appropriate procedure for the one-pot preparation of alcohols from acetals which is presented in this Letter. We also provide a brief study of the compatibility of this method to other functional groups, and finally demonstrate the utility of this procedure for the synthesis of a prospective anti-viral drug candidate.

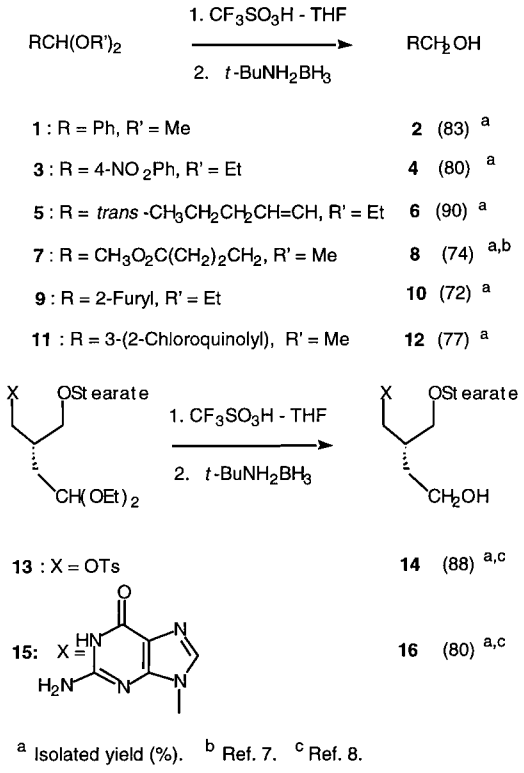
Selection of hydrolytic conditions. Protic or Lewis acids in various solvents have been used to convert acetals into aldehydes.[2] More recently acidic resins (*e.g.* Amberlist-15)[3] and Montmorillonite K-10[4] were introduced as mild deprotecting agents for acetals. These latter reagents seemed particularly suitable for a one-pot procedure as they can be simply filtered-off and the resulting aldehyde solution would be directly used in the reduction. Unfortunately the rate of hydrolysis of many acetals with these reagents is so low that very high loads of clay or resin are required to achieve satisfactory conversions.[3,4] In addition acetals possessing basic groups (e.g. amino or nitrogen containing heterocycles) form salts at the acidic sites of resins and hence are absorbed on its surface resulting in poor recovery of aldehydes. After analysis of other hydrolytic conditions we decided to use aqueous trifluoromethanesulfonic acid as a cleaving agent and tetrahydrofuran as a solvent. We have found that most common acetals and aldehydes are soluble in this system and hydrolysis proceeds smoothly at room temperature in a reasonable amount of time (*vide infra*).

Reduction conditions. It has been well established that aldehydes can be readily reduced to alcohols under variety of conditions.[2] Boron hydrides seemed to be more suitable for the one-pot procedure, *viz.*, aqueous tetrahydrofuran media. However the most common reductant - sodium borohydride could not be used for the following reasons: a) selectivity of the reduction diminished in the presence of water and alcohols (hydrolysis byproducts); b) highly basic reaction media (pH > 10) caused transesterification and ester hydrolysis if these groups were present in the molecule; c) partial decomposition of sodium borohydride required its use in excess.

We found that the readily available but still only occasionally used reagent – *tert*-butylamine borane offered significant advantages.[5,6] Indeed, this compound is stable in water and alcohols and highly selective toward aldehyde reduction. Moreover the pH of the reaction mixture remains between 7 and 8 preventing undesirable side reactions. Under our conditions two hydrogens of the borane were transferred in reductions requiring only 0.67 molar equivalents of the reagent.

Application of the selected conditions to the conversion of dimethoxybenzaldehyde (**1**) into benzyl alcohol (**2**) gave very satisfying results. Hydrolysis using 0.5 molar equivalent of 50% triflic acid was complete in less then 0.5 hour at room temperature. Sodium bicarbonate pH adjustment followed by *tert*-butylamine borane addition at 10 – 20 ºC resulted in immediate and quantitative reduction of the aldehyde (HPLC monitoring). Extractive work up and distillation gave benzyl alcohol in 83% yield.

Scheme 1 provides further examples of one-pot conversions of acetals into alcohols. We have found that the procedure is applicable to aliphatic, aromatic, and heteroaromatic compounds (including basic, nitrogen containing heterocycles e.g. **11** and **15**). It tolerates such functional groups as halogen, tosyl, nitro, ester (examples



Scheme 1

11, **3**, **7**, **13**, **15** respectively) and can be applied to α−β unsaturated aldehyde derivatives as well (compound **5**).

Several additional observations regarding these reactions would be appropriate. Most acetals that we examined were hydrolyzed slower then dimethoxybenzaldehyde and it was found beneficial to use up to 1.5 molar equivalents of 50 % triflic acid to achieve good conversions within 5 hours at room temperature. Competitive ester group hydrolysis was observed in less reactive acetals such as **7**. However it was usually possible to achieve higher then 95 % conversion of the acetal retaining more then 95 % of the ester. Hydrolysis of acetal **15** containing a guanine base in the molecule was so slow that condensation of the resulting aldehyde and competitive hydrolysis of the stearate ester became prevailing reactions. These problems were circumvented when 2.6 equivalents of triflic acid were used – higher then 95% conversion was achieved within 1.5 h at room temperature. It turned out that cleavage of the intermediate borate esters occurred in aqueous media at pH 6-7. However isolation of pure alcohols usually required pH adjustment to 2 - 3 with 2 N hydrochloric acid (see Experimental procedure below).

Preparation of alcohols **14** and **16** - important intermediates in the synthesis of antiviral ABT-606[9] – was particularly challenging as these compounds were very sensitive and underwent intramolecular transesterification under both acidic and basic conditions, or even in polar solvents such as methanol. Nevertheless, using the one-pot procedure alcohol **16** was prepared in 80 % yield further demonstrating utility of the method in the synthesis of complex polyfunctional compounds. This procedure was successfully repeated on a 10 – 20 kg scale at the chemical pilot plant.

We hope that the one-pot conversion of acetals into alcohols will find its place in the growing arsenal of modern synthetic methods.

Typical Procedure for Conversion of Acetals into Alcohols. Preparation of 4-Nitrobenzylalcohol (4)

Trifluoromethanesulfonic acid (4.6 g, 50 % in water, 15 mmol) was added dropwise to a solution of an 4-nitrobenzaldehyde diethylacetal (2.25 g, 10 mmol) in tetrahydrofuran (20 mL) at 17 – 22 ºC under nitrogen. The mixture was stirred at this temperature for 4 - 5 hours until the acetal was consumed. Water (6.6 mL) was added to the reaction mixture followed by sodium bicarbonate (1.7 g). The mixture was cooled to 10 –15 ºC and *t*-butylamine borane (0.52 g, 6 mmol) was added in three portions over 0.5 h. After additional 0.5 h water (20 mL) was added and the mixture was extracted with dichloromethane (2 x 20 mL). Combined organic layer was concentrated under vacuum and water (10 ml) was added to the residue. pH of the mixture was adjusted to 2 – 3 with 2 N HCl and the product was extracted with dichloromethane (2 x 10 mL). Combined organic layer was dried over magnesium sulfate and concentrated under vacuum to give the desired alcohol (1.2 g, 80%). ^{1}H NMR spectrum was identical to the one from the reference sample obtained from Aldrich.

References and Notes

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(8) All new compounds were fully characterized. For alcohol **16**: ^{1}H NMR (DMSO-d_6): 0.9 (t, 3H); 1.25 (m, 24 H); 1.5 (m, 4 H); 2.28 (t, 2 H), 2.41 (m, 1 H); 3.5 (m, 2 H) 3.85 – 4.05 (m, 4H), 4.63 (t, 1 H), 6.68 (s, 2 H); 7.69 (s, 1 H). ^{13}C NMR (DMSO-d_6): 13.9 (CH_3), 22.1 (CH_2), 24.3 (CH_2), 28.5 (CH_2), 28.7 (CH_2), 29.0 (CH_2), 29.1 (9C, CH_2), 31.3 (CH_2), 31.6 (CH_2), 33.3 (CH_2), 34.8 (CH), 44.5 (CH_2), 58.1 (CH_2), 63.8 (CH_2), 116.2 (C), 137.7 (CH), 151.4 (C), 153.7 (C), 156.8 (C), 172.8 (C).
(9) ABT-606 is an antiviral found to be active against Herpes Zoster.