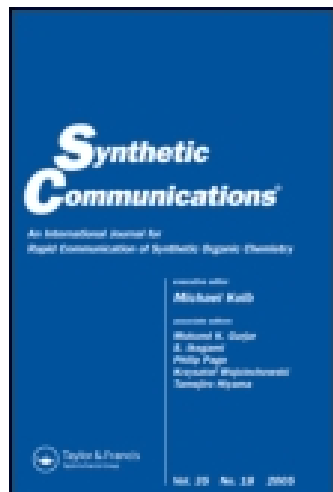


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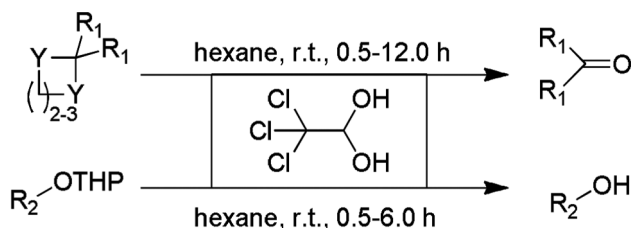
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CHLORAL HYDRATE AS A WATER CARRIER FOR THE EFFICIENT DEPROTECTION OF ACETALS, DITHIOACETALS, AND TETRAHYDROPYRANYL ETHERS IN ORGANIC SOLVENTS

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Bangalore, India

GRAPHICAL ABSTRACT



Y = O, S; R₁ = H, alkyl, aryl, -(CH₂)₄₋₆, etc. and R₂ = alkyl, aryl

Abstract The efficient deprotection of several acetals, dithioacetals, and tetrahydropyranyl (THP) ethers under ambient conditions, using chloral hydrate in hexane, is described. Excellent yields were realized for a wide range of both aliphatic and aromatic substrates. The method is characterized by mild conditions (room temperatures or below), simple workup, and the ready availability of chloral hydrate. High chemoselectivity was also observed in the deprotection, acetones, esters, and amides being unaffected under the reaction conditions. Products were generally purified chromatographically and identified spectrally. These results constitute a novel addition to current methodology involving a widely employed deprotection tactic in organic synthesis. It seems likely that the mechanism of the reaction involves adsorption of the substrate on the surface of the sparingly soluble chloral hydrate.

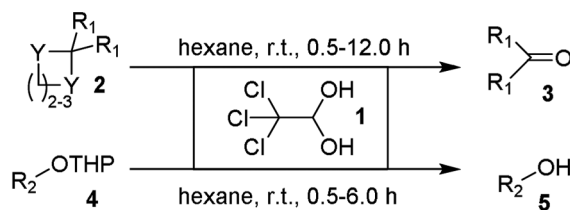
Keywords Acetals; chemoselective; deprotection; hydrolysis; nonaqueous

INTRODUCTION

Acetals, dithioacetals, and tetrahydropyranyl (THP) ethers are widely used as carbonyl protecting groups, often in multistep organic syntheses.^[1–5] Even though many methods have been developed for regenerating the carbonyl functionality from

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Y = O, S; R₁ = H, alkyl, aryl, -(CH₂)₄₋₆-, etc. and R₂ = alkyl, aryl

Scheme 1. Chloral hydrate (**1**) facilitated hydrolysis of acetals and thioacetals (**2**) and of THP ethers (**4**), with the corresponding main products (**3** and **5** respectively).

these acetals, most of them employ aqueous acidic conditions. Thus, acetals can be cleaved by acid-catalyzed exchange dioxolanation, acid-catalyzed hydrolysis, and oxidation;^[2] THP ethers can be removed either by acid hydrolysis to furnish the original alcohol or by oxidative deprotection.^[3] However, most methods employ relatively strong acids in the case of acetals^[2] and THP ethers,^[3] and hazardous mercury salts or expensive silver salts in the case of dithioacetals,^[4] under aqueous conditions.

In protection–deprotection chemistry it is very important that after the step involving the necessary transformation is complete, the protective group be selectively removed, in good yield and under mild conditions. Even when a substrate is protected and deprotected efficiently, the final products must be isolated from the reaction mixture and purified by appropriate methods. Hydrolysis is a straightforward deprotection tactic, in the cases of both base-sensitive and acid-sensitive groups. Therefore, the importance of efficient, mild, and selective deprotection procedures cannot be overstated. We report herein the deprotection of acetals, thioacetals, and THP ethers to corresponding carbonyl compounds and alcohols in hexane, a nonaqueous and nonpolar reaction medium, with chloral hydrate as the reagent (Scheme 1).

Chloral hydrate (**1**) is a colorless crystalline solid, which is inexpensive and readily available. In **1** a molecule of water is covalently bound to chloral in a gem-diol unit. Compound **1** is also weakly acidic with pK_a 9.66.^[6] Essentially, the present method employs **1** as a means to deliver a molecule of water to the substrate molecule.

DISCUSSION

Deprotection of Acetals and Dithioacetals

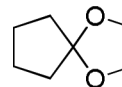
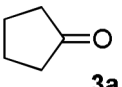
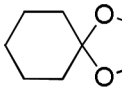
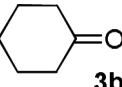
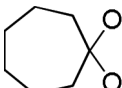
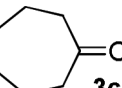
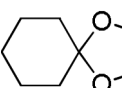
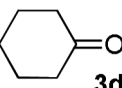
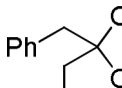
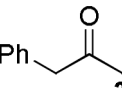
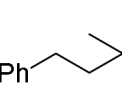
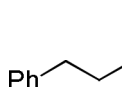
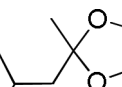
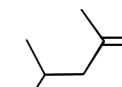
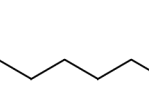
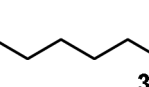
Exploratory and optimization studies were initially carried out with 1,4-dioxaspiro[4.5]decane (**2a**) as a model substrate. The hydrolysis of **2a** was very slow in several polar organic solvents, even when excess **1** (1:3 molar ratio) was employed. In the absence of solvent, the hydrolysis was incomplete (<15%), as even after heating at 70 °C for 12 h only 43% of product ketone was observed.

However, satisfactory results were obtained when the solvent was changed to hexane. It was also observed that any solvent that dissolved **1** decreased the reactivity of **1**. When the nonpolar hexane was used as solvent, **1** did not dissolve completely in the reaction medium, although the acetal hydrolyzed to the extent

of 78% in 1 h. An optimum volume of hexane was also indicated (~1 ml), above which the reaction did not go to completion.

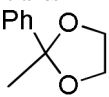

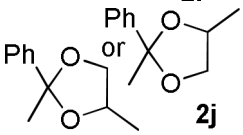

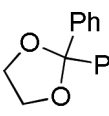
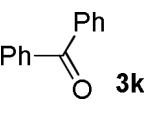
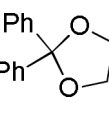
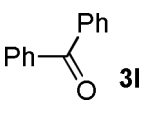
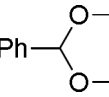

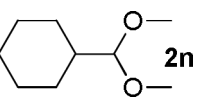
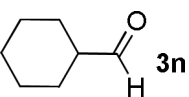
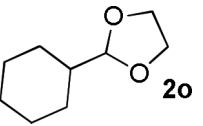
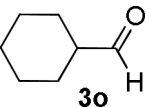
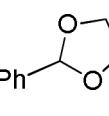
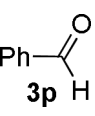
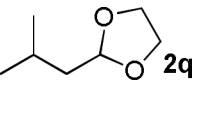
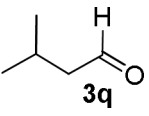
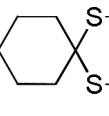
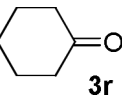
A catalytic amount of **1** in hexane was insufficient to hydrolyze **2a** completely. Stoichiometric quantities of **1** were needed to catalyze the reaction and the rate (in terms of percentage yield at 1 h) increased with the amount of **1** added. Once the ratio of **1** to reactant reached ≥ 4 , there was no effect of **1** concentration on the rate of the reaction.

Table 1. Hydrolysis of acetals and thioacetals

Entry	Substrate (2a–h)	Product (3a–h)	Cl ₃ CCH(OH) ₂ (equiv)	Time (h)	Yield (%)
Alicyclic dioxolanes					
1			1.5	0.5	83
2			3.0	2.0	78
3			1.5	0.5	84
4			3.0	1.0	76
Aliphatic dioxolanes					
5			3.0	5.0	98
6			3.0	3.0	97
7			1.5	0.5	>99
8			1.5	0.5	>99

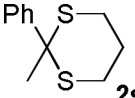
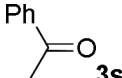
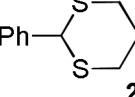
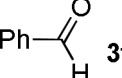
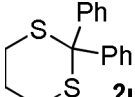
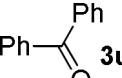
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Table 1. Continued

Entry	Substrate (2i–u)	Product (3i–u)	Cl ₃ CCH(OH) ₂ (equiv)	Time (h)	Yield (%)
Aromatic dioxolanes					
9			1.5	0.5	98
10			3.0	1.0	96
11			1.5	1.0	99
12			1.5	2.0	98
Acyclic acetals					
13			3.0	4.5	82
14			1.5	1.5	83
Cyclic acetals					
15			2.0	3.5	86
16			2.0	4.5	92
17			1.5	1.5	98
Dithioacetals					
18			6.0	12.0	64

(Continued)

Table 1. Continued

Entry	Substrate (2i–u)	Product (3i–u)	Cl ₃ CCH(OH) ₂ (equiv)	Time (h)	Yield (%)
19			6.0	12.0	97
20			6.0	12.0	76
21			6.0	12.0	—

The reaction furnished good yields of product at rt, but at both low and high temperatures the yields were very poor. At low temperature, the reactivity of acetal with **1** would, of course, decrease. At high temperatures, the decomposition of **1** is the likely reason for incomplete hydrolysis.

From these studies, it was apparent that the presence of **1** in the solid state in the reaction medium was important for the hydrolysis reaction to occur. It appeared that the reaction occurs at the surface of **1** and that the solvent should remove the product from the surface efficiently for the reaction to go to completion.

A series of acetals and dithioacetals were subjected to hydrolysis under the optimized reaction conditions, with the results being summarized in Table 1.

The cyclic acetals derived from alicyclic ketones (**2a–d**), aliphatic ketones (**2e–h**), aromatic ketones (**2i–l**), alicyclic acetals (**2m** and **n**), cyclic acetals (**2o–q**), and dithioacetals (**2r–t**) were converted to corresponding ketones or aldehydes often in quantitative yields. Of the ketals **2a–d**, **2b** and **2d** were difficult to hydrolyze as compared to **2a** and **2c**, perhaps because of the greater stability of the cyclohexanone acetal relative to cyclopentanone or cycloheptanone acetals. Dithioacetals (**2r–t**) were less reactive toward **1** and required more equivalents (6 equiv) of **1** for hydrolysis.

Deprotection of Tetrahydropyranyl (THP) Ethers

The reaction conditions employed for the hydrolysis of these substrates also effected the hydrolysis of THP-protected alcohols. When various THP-protected primary and secondary alcohols (aliphatic, aromatic, and heterocyclic) were subjected to hydrolysis using **1** in hexane, quantitative yields of the corresponding alcohols were obtained. The results of these reactions are summarized in Table 2. Note that the nitro alcohol (**5k**) is very sensitive toward aqueous acidic or basic conditions, and hence deprotection of **4k** under the usual aqueous conditions can lead to further degradation of the product. Under such circumstances, **1** can be used for deprotection to yield nearly quantitative yields of the nitro alcohol.

Table 2. Hydrolysis of THP ethers

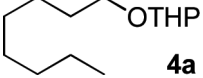
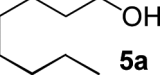
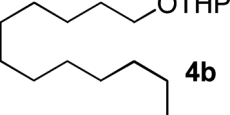
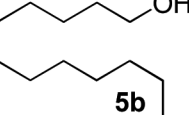
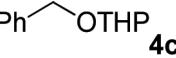
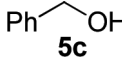
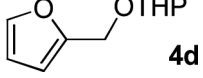
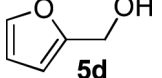
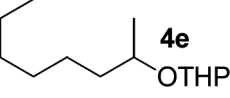
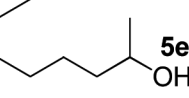
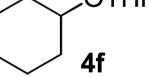
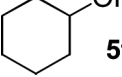
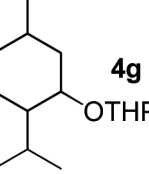
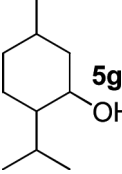
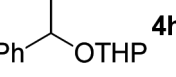
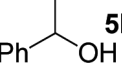
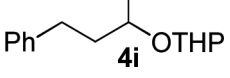
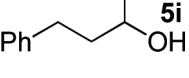
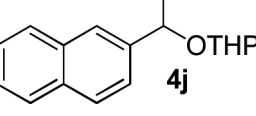
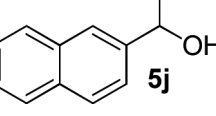
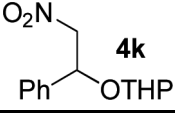
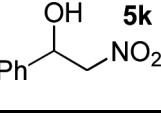
Entry	Substrate (4a-k)	Product (5a-k)	Cl ₃ CCH(OH) ₂ (equiv)	Time (h)	Yield (%)
THP protected 1° alcohols					
1	 4a	 5a	1.5	0.5	95
2	 4b	 5b	1.5	0.5	95
3	 4c	 5c	1.5	0.5	98
4	 4d	 5d	1.5	0.5	98
THP protected 2° alcohols					
5	 4e	 5e	3.0	2.5	93
6	 4f	 5f	3.0	4.0	88
7	 4g	 5g	3.0	6.0	84
8	 4h	 5h	3.0	3.5	98
9	 4i	 5i	3.0	5.0	87
10	 4j	 5j	3.0	2.0	98
THP protected 2-nitro alcohols					
11	 4k	 5k	1.5	1.5	98

Table 3. Chemoselectivity in deprotection

Entry	Substrate (6a–b)	Product (7a–b)	Cl ₃ CCH(OH) ₂ (equiv)	Time (h)	Yield (%)
1			3.0	1.5	99
2			1.5	1.5	92

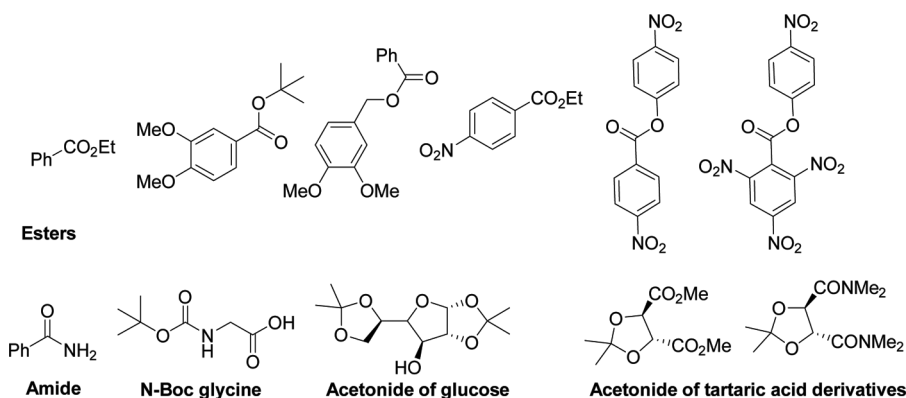
Functional Group Tolerance

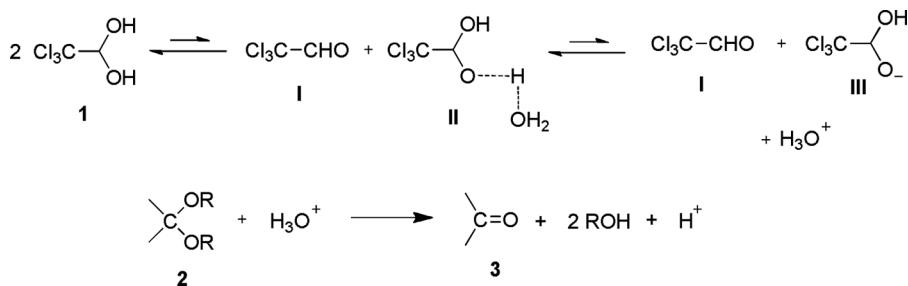
Under the standardized reaction conditions, esters generally remained unreactive (Table 3 and Scheme 2). Heating the reaction mixture and increasing the equivalents of **1** did not hydrolyze the esters studied. Several labile esters such as methyl 4-nitrobenzoate, 4-nitrophenyl 4-nitrobenzoate, and 2,4,6-trinitrophenyl 4-nitrobenzoate also did not react under the reaction conditions. Thus, the reaction may be employed for the selective hydrolysis of acetals and THP ethers in the presence of esters (Table 3).

We have observed that the acid-sensitive protective groups of ketone, alcohol, amine, acid, and amide in the compounds shown in Scheme 2 were also not hydrolyzed by **1**. Therefore, **1** can be used for the selective hydrolysis of acetals or THP ethers in a compound bearing other functional groups shown in Scheme 2.

Possible Mechanism of the Reaction

The fact that the reaction is strongly accelerated in a nonpolar medium (hexane) in which **1** is very sparingly soluble indicates that the reaction likely occurs

Scheme 2. Substrates unreactive toward **1**.



Scheme 3. Possible mechanism of acetal cleavage by chloral hydrate.

at the solid–liquid interface. A pK_a value of 9.66 for **1**^[6] indicates the presence of weakly protic sites on the surface of crystalline **1**. This, combined with dissociated water present nearby, is the likely reason for the observed hydrolysis reaction. A tentative mechanistic scheme for the observed hydrolysis reaction is shown in Scheme 3 (for the case of **2**).

In this, two molecules of **1** lead to the formation of H_3O^+ . This may be envisaged to occur via dissociation of a molecule of **1** to chloral (**I**) and water. The latter is protonated by the acid dissociation of the other chloral hydrate molecule, via the complex **II**, leading to the formation of **III** and H_3O^+ . The H_3O^+ thus generated at the surface of **1** reacts with the acetal (**2**), hydrolyzing it to carbonyl compound (**3**) and the alcohol constituents. Interestingly, the fact that the reaction is incomplete in the absence of solvent indicates that the products need to be removed from the surface sites for the reaction to occur continuously.

CONCLUSIONS

We have developed a novel method for the selective deprotection of acetals, dithioacetals, and THP ethers by chloral hydrate, under mild, nonaqueous, neutral conditions at room temperature. The scope of the methodology is large, involving both aliphatic and aromatic substrates. Reaction apparently occurs at the surface of the solid **1** in hexane, and excellent yields of products were obtained after purification. Furthermore, it is established that chloral hydrate can be used for the selective hydrolysis of acetals, dithioacetals, and THP ethers in the presence of acetamide linkages, esters, and amides.

EXPERIMENTAL

Typical Deprotection Procedure for Acetals and Thioacetals

A stirred solution of the acetal (**2**, 3.5 mmol) in dry hexane (5 ml), under dry nitrogen at 25 °C, was treated with **1** (1.7 g, 10.6 mmol). The mixture was stirred for 2 h, treated with water, and extracted with dichloromethane (10 ml). The extracts were washed with brine solution, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by column chromatography on neutral alumina (50–325 mesh, eluent: 2.5:97.5 ethyl acetate–hexane), to obtain the corresponding

carbonyl compound (**3**). The purity was estimated to be >98% by ^1H and ^{13}C NMR spectroscopic analysis.

In the case of solid acetals, 0.5 ml of dichloromethane along with hexane was added for added solubility; in the case of thioacetals, 21.2 mmol of **1** was used for effective deprotection.

Typical Deprotection Procedure for THP Ethers

To a stirred solution of the THP ether (**4**, 2.6 mmol) in sodium-dried hexane (5 ml) under nitrogen at 0–5 °C was added **1** (0.65 g, 3.9 mmol). The mixture was stirred for 0.5 h and treated with water. The reaction mixture was extracted with dichloromethane (10 ml), and the organic layer was washed with brine solution, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by column chromatography on neutral alumina (50–325 mesh, eluent: 10:90 ethyl acetate–hexane). The purity of the resulting product (**5**) was estimated to be >98% by ^1H and ^{13}C NMR spectroscopic analysis.

FUNDING

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SUPPORTING INFORMATION

Synthetic procedures and spectral characterization data can be accessed on the publisher's website.

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