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FULL PAPER

Practical cleavage of acetals using an odorless thiol immobilized on silica

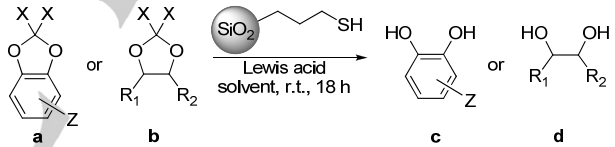
Mylène de Léséleuc,[a] Andrew Kukor,[a] Shaun D. Abbott,[a] and Boulos Zacharie*[a]

Abstract: A practical, efficient and general method was developed for the deprotection of a variety of aromatic and aliphatic acetals to their corresponding catechol or diol derivatives using thiol functionalized on silica gel. This is an application for the well-known commercial solid-supported thiol (Silia*MetS*® Thiol). The procedure is mild and amenable to scale-up. It does not require inert atmosphere and clean conversions were observed. This method is applicable to substituted 1,3-benzodioxole and aliphatic acetals with different functionalities. It offers the advantage of a general route with high yield, which can be undertaken at ambient temperature.

Introduction

Derivatization and modification of silica is extremely important in both pure and applied chemistry.[1] Silica-bound reagents that possess "immobilized" reactive moieties have the capacity to remove a specific contaminant or catalyze only desired reactions.[2] They provide an attractive and practical approach to expedite organic synthesis[3] and facilitate the preparation of libraries of pharmacologically active compounds.[4]

As part of our research, we were interested in the synthesis of catechol derivatives because of their diverse biological activities. During the preparation of these compounds, an isopropylidene protecting group was required to allow other chemical manipulations in the molecules. After protection of our catechol-containing compounds as benzodioxolanes, difficulties were encountered regarding the removal of this acetal from the protected catechol (benzodioxolane) derivatives **a** later in the synthesis. This protecting group was resistant to procedures used for aliphatic acetals, such as cleavage in the presence of strong acids. A literature survey showed cleavage of similar cyclic acetals using a combination of an aliphatic thiol such as 1,2-ethanedithiol and a Lewis acid.[5] This reaction gave a reasonable yield of the corresponding catechol. The drawback of this method is the stench and toxic gases[6] that arise during the reaction and the work-up. The issue remained of how the process could be made friendlier and suitable to large scale reactions. In this context, a solid-supported thiol was selected for this conversion, such as Silia*MetS*® Thiol (Si-Thiol). The advantages of this product are that it is an odorless, stable, thiol-functionalized silica[7] that is commercially available (30 mmol = $CAD115), and insoluble in organic solvent. It is marketed as a scavenger for a variety of metals under a wide range of conditions. It can safely be used without compromising the purity of the material by leaching of the silica-supported product. Although there is published research on the development of low-odor thiol reagents by using high MW thiols;[8] or through using water-soluble derivatives;[9] to the best of our knowledge, no research has been reported concerning the chemical reactions of thiol functionalized silica. In general, silica-supported reagents possess a number of distinct advantages over their polymeric counterparts,[10] and indeed, silica-supported acids have been used successfully to deprotect acyclic acetals.[11] Such reagents are easy to weigh out and handle, the rate of reaction is not controlled by diffusion, they do not partially dissolve in any solvent, are thermally stable and easy to pack into columns. Our goal, therefore, was to develop a new, general and simple procedure for the use of commercial solid-supported thiol for the cleavage of acetals. Our simplified procedure is described in Scheme 1.



Scheme 1. General scheme for the cleavage of a variety of aromatic and aliphatic acetals.

Results and Discussion

Our strategy was based upon reacting Si-Thiol with benzodioxolane derivatives **a** in the presence of a Lewis acid in an organic solvent. The initial experiments were undertaken using 2,2-dimethylbenzo[1,3]dioxolane **1** (i.e., **a**: Z = H, X = CH_3) as a model substrate. The reaction was studied at different molar ratios of the thiol and Lewis acid at room temperature in dichloromethane in order to produce catechol **2** (i.e., **c**: Z = H). The selected Lewis acid was boron trifluoride etherate because it has been successfully used in combination with 1,2-ethanedithiol for the cleavage of ethers and related compounds.[12] The principle of the carbon-oxygen bond cleavage using boron trifluoride etherate combined with a thiol is based on interaction of a hard acid with the oxygen, with the sulfur, being a soft nucleophile, attacking on carbon. The first experiment was carried out using one equivalent of thiol and two equivalents of boron trifluoride etherate at room temperature for 18 h. In this case, catechol **2** was isolated in a reasonable yield (75%; Table 1, entry 1). Changing the ratio to 1:1 produced the catechol **2** in 88% yield.

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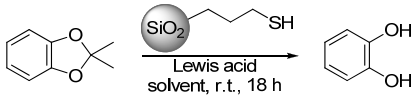
Adding excess (5 equivalents) of the thiol gave high yield (93%) of the expected product **2**. The best result was obtained with the use of a stoichiometric amount (two equivalents) of Si-Thiol and one equivalent of boron trifluoride etherate (entry 4). This procedure provided catechol **2** in quantitative yield. Similar results were obtained by using other Lewis acids (entries 5–8) such as iron(III) chloride, aluminum chloride or zinc chloride. However, *p*-toluene sulfonic acid was less efficient under this condition and gave 85% yield. Also, the effect of the solvent was investigated in this reaction using the best ratio between the thiol and boron trifluoride etherate at room temperature for 18 h. Table 1, entries 9–16 report the yield of catechol **2** with different solvents under optimum conditions.

Table 1. Yield of catechol **2** in different solvents and acid



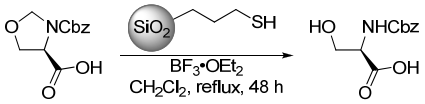
1 **2**

Entry	Si-Thiol (equivalents)	Lewis Acid (equivalents)	Solvent	Yield (%)
1	1.0	$BF_3•Et_2O$ (2.0)	Dichloromethane	75
2	1.0	$BF_3•Et_2O$ (1.0)	Dichloromethane	88
3	5.0	$BF_3•Et_2O$ (1.0)	Dichloromethane	93
4	2.0	$BF_3•Et_2O$ (1.0)	Dichloromethane	>99
5	2.0	$FeCl_3$ (1.0)	Dichloromethane	99
6	2.0	$AlCl_3$ (1.0)	Dichloromethane	99
7	2.0	$ZnCl_2$ (1.0)	Dichloromethane	99
8	2.0	*p*-TsOH (1.0)	Dichloromethane	88
9	2.0	$BF_3•Et_2O$ (1.0)	Acetonitrile	>99
10	2.0	$BF_3•Et_2O$ (1.0)	Dimethoxyethane	90
11	2.0	$BF_3•Et_2O$ (1.0)	*tert*-Butyl methyl ether	90
12	2.0	$BF_3•Et_2O$ (1.0)	Diethyl ether	74
13	2.0	$BF_3•Et_2O$ (1.0)	Acetone	25
14	2.0	$BF_3•Et_2O$ (1.0)	*N*,*N*-Dimethyl-formamide	Mixture of products
15	2.0	$BF_3•Et_2O$ (1.0)	*N*,*N*-Dimethyl-acetamide	Mixture of products
16	2.0	$BF_3•Et_2O$ (1.0)	Methanol	No reaction

Encouraged by these results and having established the optimized procedures, the generality of the method was investigated by examination of an array of structurally diverse acetals. Results are summarized in Table 2.

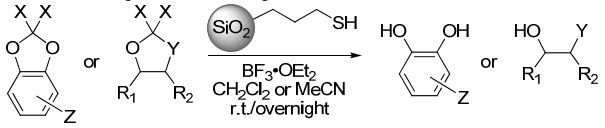
A variety of aromatic and aliphatic cyclic acetals were cleaved efficiently to their corresponding catechol or diol derivatives respectively. The method is general, and several substitutions on the aromatic ring of 1,3-benzodioxole such as fluoro (**3**, entry 2), chloro (**5**, entry 3), bromo (**7**, entry 4), cyano (**9**, entry 5), methoxycarbonyl (**11**, entry 6), *N*-Cbz (**13**, entry 7), *N*-acyl (**15**, entry 8), *N*-Fmoc (**17**, entry 9) and amides (**19**, **21**, **23**, entry 10, 11, 12 respectively) are compatible with this reagent system. Also, functionalities on aliphatic 1,3-dioxolanes such as alcohols **27** and **41** (entries 14, 21 respectively) and methoxycarbonyl **29** and **32** (entries 15, 16 respectively) are stable to these conditions. Other aromatics containing dioxolane rings gave similar results. For example, replacement of the phenyl ring of benzodioxole with a naphthyl gave the desired aromatic diol **34** in a respectable yield (entry 17). Also, aliphatic six-membered ring disubstituted acetals containing 1,3 or 1,4-dioxane gave a good yield of the expected product **36** and **38** (entries 18 and 19 respectively). In addition, deprotection of acetals with Si-Thiol depends on the substituents at C2 on the dioxolane rings. High yields were achieved when the acetal is disubstituted with alkyls at C2 (entries 1–15, 17–18 and 22–24) compared to respectable yield for monosubstituted acetals **40** and **41** (entries 20 and 21 respectively). However, the non-substituted acetal did not give any diol product. The presence of substituents at C2 which can stabilize a carbonium ion increases the reaction rate for the cleavage of acetal products.[13] To confirm this observation, a molecule was synthesized contains both acetals the 2,2-dimethylbenzo[1,3]dioxolane and the benzo[1,3]dioxolane **23** (entry 12). As expected, the disubstituted acetal was cleaved selectively to form the diol, without affecting the non-substituted acetal under the standard condition. Also, we examined the cleavage of 1,3-dioxolane substituted at C5 by methyl acetate **29** (entry 15). The reaction with the Si-Thiol and boron trifluoride etherate gave high yield of a mixture of two compounds: the free diol **30** and cyclic lactone **31** in a ratio of 1:3. The next step was to study the stability of the protected alcohols on the 1,3-dioxolane ring. Both tert-butyldimethylsilyl **43** (TBS, entry 22) and methoxymethyl **44** (MOM, entry 23)[14] protecting groups on the dioxolane ring were quickly cleaved to the corresponding glycerol **42** under the reaction conditions. In contrast, tert-butyldiphenylsilyl **45** (TBDPS, entry 24) was not removed as rapidly as TBS or MOM groups in the presence of the Si-Thiol reagent. After 2 h, the yield of the TBDPS-monoprotected glycerol **46** was 67% (entry 24).

We also studied the deprotection of oxazolidine derivatives. The *N*,*O*-acetal group is the most common protecting group for 1,2- and 1,3 amino alcohols and is more labile than *O*,*O*-acetals.[15] The oxazolidine ring was cleaved to the corresponding substituted ethanolamine under our general condition. As expected, the hydrolyzes of disubstituted *N*,*O*-acetal **32** (entry 16) gave high yield (77%) of the ethanolamine product **33**. However, and contrary to the *O*,*O*-acetal, the cleavage of non-substituted *N,O*-acetal **47** was successful, albeit very slow, affording only 26% yield of the expected product **48** after 48 h (Scheme 2). Heating this reaction under reflux did not improve the yield.



Scheme 2. Cleavage of unsubstituted oxazolidines using Si-Thiol to give 1,2-amino alcohols derivatives.

Table 2. Cleavage of acetals using Si-Thiol



Entry	Substrate	Product	Yield (%)[a]
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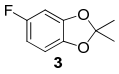
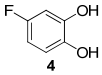
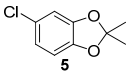
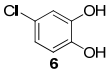
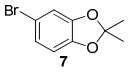
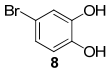
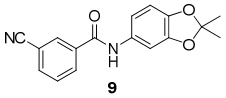
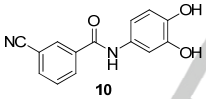
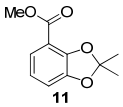
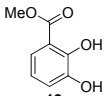
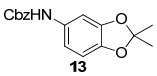
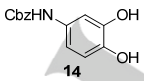
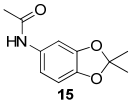
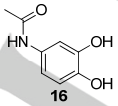
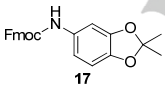
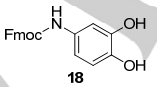
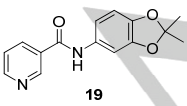
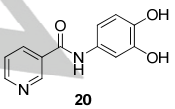
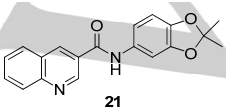
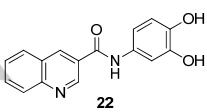
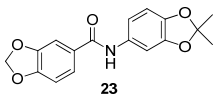
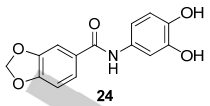
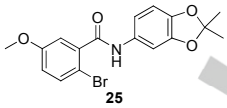
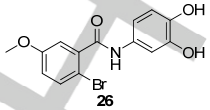
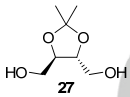
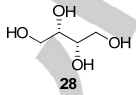
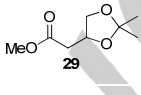
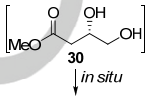
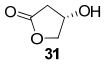
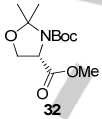
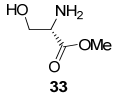
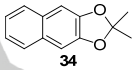
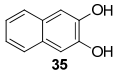
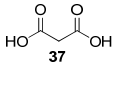
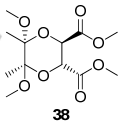
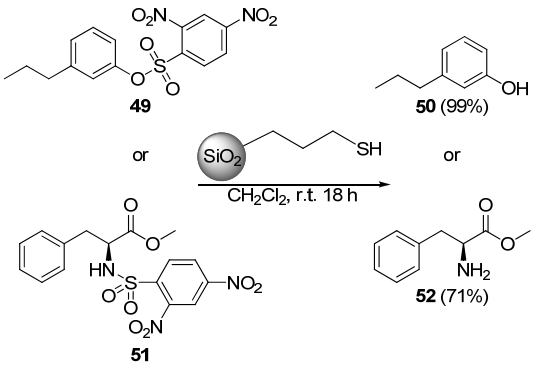
2	 3	 4	90
3	 5	 6	82
4	 7	 8	99
5	 9	 10	75
6	 11	 12	99[c,d]
7	 13	 14	61[d]
8	 15	 16	81[d]
9	 17	 18	74
10	 19	 20	77[d]
11	 21	 22	56[d]
12	 23	 24	76
13	 25	 26	45[d]
14	 27	 28	83[d]
15	 29	 30 *in situ*  31	99[d] (1:3 mixtures)
16	 32	 33	77
17	 34	 35	60[d]
18	 36	 37	60
19	 38	39	77[d]
20	40	2	50[d]
21	41	42	65[d]
22	43	42	87[d]
23	44	42	99[d]
24	45	46	67[d]

[a] Isolated yield. [b] Same yield at 0.33 mmol and 10 mmol scale. [c] Si-Thiol (5 eq.), BF_3•OEt_2 (2.0 eq.). [d] 2 h reaction time.

The method also displays good chemoselectivity. For example, we synthesized a compound containing both benzodioxolane and alkylarylether **25** (entry 13). In the presence of the thiol reagent, disubstituted acetal is cleaved selectively without affecting the alkyl ether bond. In general, alkyl protected phenol are stable under these conditions. However, other protecting groups of phenols or aliphatic amine are removed under our standard procedure. For example, the 2,4-dinitrophenylsulfonyl group has been used to protect the hydroxyl function of phenols (e.g., **49**) or the α-amino function of amino acids (e.g., **51**).[16] This group is labile under our conditions, cleaving the protecting group of **49** and **51**, to give high yield of the corresponding phenol **50**, or amino acid **52** (Scheme 3).



Scheme 3. Cleavage of 2,4-dinitrophenylsulfonyl group of protected phenol or aliphatic amine using Si-Thiol.

Conclusions

In conclusion, a practical, efficient and general method was developed for the deprotection of a variety of aromatic and aliphatic acetals to their corresponding catechol or diol derivatives using thiol functionalized on silica. The method is mild and amenable to scale-up. It does not require an inert atmosphere and clean conversions were observed. It offers the advantage of a general route with high yield which can be undertaken at ambient temperature. The advantages of using thiol bound on silica gels are the following: (i) toxic or difficult to remove reagents and by-products are immobilized and can be separated from the product by a simple filtration; (ii) the reaction is devoid of thiol stench, and (iii) use of solvent independent, thermally stable reagents and easy work up procedure. Furthermore, as in many of our examples purification by chromatography was unnecessary, the amount of solid waste is reduced compared to other methods. Indeed, future work on the regeneration of the thiol groups on silica from the corresponding thioacetals[17] produced by the reaction could allow reuse of the solid-supported thiol.

Experimental Section

Typical Procedure for the deprotection of acetals (**1**)

A mixture of 2,2-dimethyl-1,3-benzodioxole **1** (50 mg, 0.33 mmol) and Si-Thiol (1.37 mmol/g; 0.48 g, 0.664 mmol) in dichloromethane (5 mL) was treated with BF_3•OEt_2 (42 µL, 0.33 mmol). The mixture was stirred at room temperature for 18 h. The mixture was then filtered on celite (washed with ethyl acetate) and the filtrate was washed with hydrochloric acid (1M) and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give then expected product **2** in high yield (99%).

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Keywords: Acetals • *N,O*-acetal • Silia*MetS*® • Thiol solid support • Catechol

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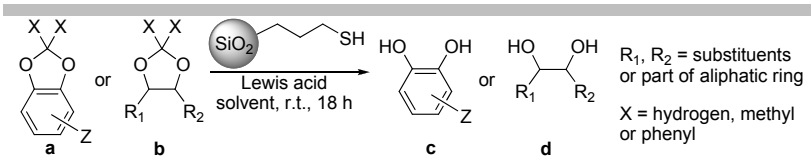
Layout 2:

FULL PAPER



A variety of aromatic and aliphatic acetals were deprotected to their corresponding catechol or diol derivatives using thiol functionalized on silica gels (Silia*MetS*®) in dichloromethane and in the presence of boron trifluoride. The procedure is mild and amenable to scale-up. It does not require heat or inert atmosphere and no side products were observed. It offers the advantage of a general route with high yield, which can be undertaken at ambient temperature and in relatively clean environmental conditions.

Acetals deprotection

Mylène de Léséleuc, Andrew Kukor, Shaun D. Abbott and Boulos Zacharie

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Practical cleavage of acetals using an odorless thiol immobilized on silica