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Aluminium Chloride Hexahydrate (AlCl₃ · 6H₂O): An Efficient, Facile, Mild, And Highly Chemoselective Catalytic Deprotection of Tert-Butyldimethylsilyl (TBS) Ethers

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ALUMINIUM CHLORIDE HEXAHYDRATE (AlCl₃· 6H₂O): AN EFFICIENT, FACILE, MILD, AND HIGHLY CHEMOSELECTIVE CATALYTIC DEPROTECTION OF TERT-BUTYLDIMETHYLSILYL (TBS) ETHERS

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GRAPHICAL ABSTRACT
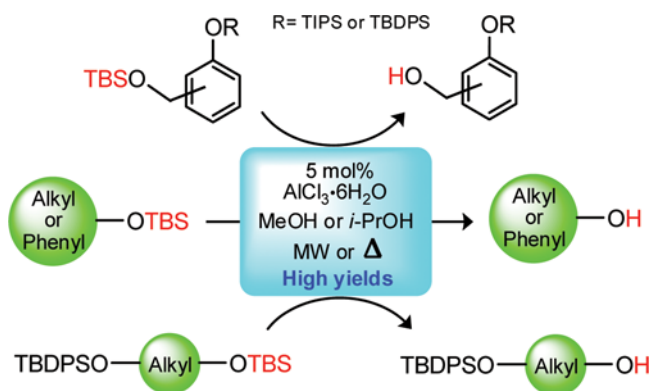
Abstract tert-*Butyldimethylsilyl (TBS) phenyl/alkyl ethers were cleaved to the corresponding efficiently parent hydroxyl compounds in good yields using catalytic amounts of AlCl₃· 6H₂O by conventional or microwave-assisted heating in methanol or isopropanol solution. Intramolecular and competitive experiments demonstrated the chemoselective deprotection of TBS ethers in the presence of triisopropylsilyl and* tert-*butyldiphenylsilyl ethers.*

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INTRODUCTION

Protection and deprotection strategies of functional groups have become very common features used in multistep organic syntheses. In this context, the *tert*-butyldimethylsilyl (TBS), triisopropylsilyl (TIPS), and *tert*-butyldiphenylsilyl (TBDPS) moieties are among the most important hydroxyl protecting groups because they are easily and efficiently installed and are stable to a useful variety of reagents and reaction conditions.[1] A wide variety of protocols for silyl ether removal have been reported. [1,2]

A convenient method for removing silyl ethers should be mild, facile, and selective to approach compounds in good yields by readily available, nontoxic, and preferably catalytic reagents. Unfortunately, many reported methods do not meet these expectations: some protocols require excess amounts[3] or strong[4] reagents and cumbersome experimental procedures.[5] Others procedures are mild,[6] selective,[7] or both[8] for cleavage of silyl ethers, but unfortunately the use of uncommon reagents ($Na_3PO_4 \cdot 12H_2O$,[8f] $TBPA^+ \cdot SbCl_6^-$,[8g] selectfluor,[8h] $Fe(OTs)_3 \cdot 6H_2O$[8i]) hinder their use. However, none of these methods describe in an alternative to conventional or microwave-assisted heating and do not describe *in the same protocol* a selective cleavage of TBS alky ethers in the presence of TIPS aryl ethers as well as a cleavage of TBS-protected alcohols and phenols in the presence of TBDPS aryl and alkyl ethers.

The study of aluminum-based inorganic reagents for deprotection of silyl ethers is highly limited; only the use of alumina has been explored. [9] $AlCl_3/MnO_2$ system[10] has been described for the direct conversion of TBS ethers to their corresponding carbonyl compounds in good yields as well as their *unavailability* in the regeneration of their parent hydroxyl compounds.

RESULTS AND DISCUSSION

During one of our current research programs, we observed that the *bis*-TBS ether **1a** was rapidly cleaved upon microwave heating of a methanol solution containing $AlCl_3 \cdot 6H_2O$. This communication describes our detailed studies of the use of this methodology for the deprotection of silylated alcohols.

Optimization studies for this cleavage process were carried out on compound **1a**. Complete silyl group removal occurred within 15 min, upon microwave heating at 100 °C of methanol or *iso*-propanol solutions containing 5 mol% $AlCl_3 \cdot 6H_2O$ (Table 1). At room temperature silyl group loss was slow, but it occurred at an acceptable rate at 50 °C (conventional heating) and was complete within 12 h. Under microwave conditions, silyl group loss was very inefficient in *tert*-butanol, anhydrous acetonitrile, or aqueous acetone (1:9), and occurred in trace amounts or failed completely in anhydrous THF, 10% aqueous THF, dichloromethane, or anhydrous acetone. Finally, the use of anhydrous $AlCl_3$ in methanol or *iso*-propanol was considerably less efficient (<50% yields) for this deprotection (microwave heating) than that observed for the hexahydrate.

Table 1. Effects of distinct solvents on MW-catalyzed desylation of TBS ether (**1a**)
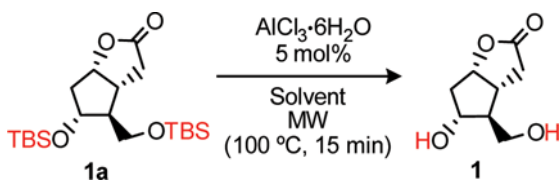
Entry	Solvent	Yield (%)[a,b]
1	MeOH	95
2	i-PrOH	95
3	t-BuOH	35
4	THF anh.	NR
5	THF–H$_2$O (9:1)	Trace
6	DCM	NR
7	MeCN anh.	15
8	Acetone	Trace
9	Acetone–H$_2$O (9:1)	25

[a]Yields refer to chromatographically pure isolated compounds.

[b]In some cases no reaction occurred (NR) or product yields were very poor and ca. 80–98% of starting material was recovered.

The optimized conditions, under microwave and conventional heating conditions (12 h), were then used to study the deprotection of a series compounds containing silylated alcohols and/or phenols, in both methanol and isopropanol solution (Table 2). Both TBS ethers of alcohols (entries 1 and 3) and phenols (entries 13 and 19) are very efficiently cleaved in methanol under microwave or conventional heating conditions. TBS alkyl ethers were also cleaved in very good yields in isopropanol solution (entries 2 and 4), but TBS aryl ethers were less efficiently deprotected in this solvent (entries 14 and 20). The TIPS alkyl and aryl ethers were cleaved in acceptable yields (entries 5, 9, 15, and 21) in methanol. In isopropanol solution, TIPS alkyl ethers were hydrolyzed with poor efficiency (entries 6 and 10) while TIPS aryl ethers were cleaved in trace amounts or not at all (entries 16 and 22). TBDPS alkyl and aryl ethers were essentially inert in both solvents.

These data clearly suggest that selective deprotection of TBS alkyl ethers should be possible by modulating the type of solvent. Table 3 shows the high chemoselective deprotection of TBS alkyl ethers in the presence of TIPS phenyl ethers in isopropanol (entries 1 and 2). Moreover, both methanol and isopropanol allowed chemoselective deprotection of TBS alkyl ethers in the presence of TBDPS phenyl ethers (entries 3 and 4).

Lastly, we have also carried out a series of intra- and intermolecular competition experiments (Table 4), which show that TBS alkyl/aryl ethers are very selectively cleaved in the presence of TBDPS alkyl/aryl ethers in both solvents.
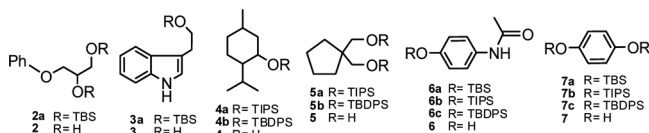
Table 2. Deprotection of silyl ethers using 5 mmol% AlCl3•6H2O by MW-assisted or conventional heating

				Yield (%)[b,c]	
Entry	Silyl ether	Solvent	Alcohol[a]	MW[d]	Δ[e]
1	**2a**	MeOH	**2**	93	95
2	**2a**	i-PrOH	**2**	94	92
3	**3a**	MeOH	**3**	98	96
4	**3a**	i-PrOH	**3**	95	96
5	**4a**	MeOH	**4**	60	67
6	**4a**	i-PrOH	**4**	33	25
7	**4b**	MeOH	**4**	Trace	Trace
8	**4b**	i-PrOH	**4**	NR	NR
9	**5a**	MeOH	**5**	72	75
10	**5a**	i-PrOH	**5**	35	42
11	**5b**	MeOH	**5**	Trace	NR
12	**5b**	i-PrOH	**5**	NR	NR
13	**6a**	MeOH	**6**	90	95
14	**6a**	i-PrOH	**6**	55	66
15	**6b**	MeOH	**6**	60	57
16	**6b**	i-PrOH	**6**	Trace	NR
17	**6c**	MeOH	**6**	NR	Trace
18	**6c**	i-PrOH	**6**	NR	NR
19	**7a**	MeOH	**7**	92	95
20	**7a**	i-PrOH	**7**	64	58
21	**7b**	MeOH	**7**	43	39
22	**7b**	i-PrOH	**7**	Trace	NR
23	**7c**	MeOH	**7**	NR	NR
24	**7c**	i-PrOH	**7**	NR	NR

[a]Confirmed by comparison with MS, ^{1}H NMR, and ^{13}C NMR with authentic samples.

[b]Yields refer to chromatographically pure isolated compounds.

[c]In some cases no reaction occurred (NR) or product yields were very poor and ca. 80–98% of starting material was recovered.
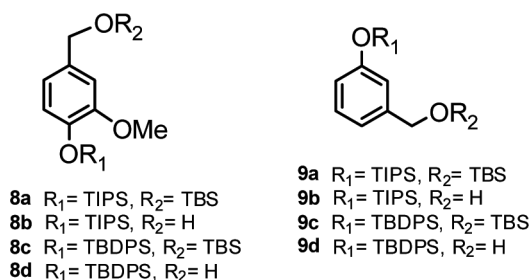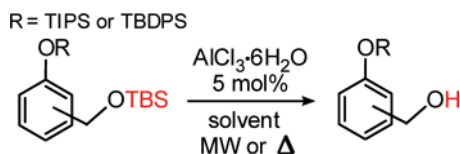
[d]100°C, 15 min.

[e]50°C, 12 h.

8a R$_1$= TIPS, R$_2$= TBS
8b R$_1$= TIPS, R$_2$= H
8c R$_1$= TBDPS, R$_2$= TBS
8d R$_1$= TBDPS, R$_2$= H

9a R$_1$= TIPS, R$_2$= TBS
9b R$_1$= TIPS, R$_2$= H
9c R$_1$= TBDPS, R$_2$= TBS
9d R$_1$= TBDPS, R$_2$= H

Table 3. Intramolecular chemoselectivity deprotection of TBS alkyl ethers in the presence of TIPS and TBDPS phenyl ethers

R = TIPS or TBDPS

Entry	Substrate	Solvent	Product[a]	Yield (%)[b]	
				MW[c]	Δ[d]
1[e]	**8a**	*i*-PrOH	**8b**	90	90
2[e]	**9a**	*i*-PrOH	**9b**	97	94
3	**8c**	MeOH	**8d**	94	96
		i-PrOH	**8d**	93	93
4	**9c**	MeOH	**9d**	93	96
		i-PrOH	**9d**	94	95

[a]Confirmed by comparison with ^{1}H NMR and ^{13}C NMR with authentic sample.
[b]Yields refer to chromatographically pure isolated compounds.
[c]100 °C, 15 min.
[d]50 °C, 12 h.
[e]Clearly the use of methanol is not possible in these cases.

A plausible mechanism for the AlCl$_3$·6H$_2$O-catalyzed deprotection of silyl ethers is shown in Scheme 1. Thus, complexation of the silyl ether oxygen with metal weakens the silyl ether bond while the bond formation between oxygen of the hydration molecule and silicon atom allows the formation of protonated hydroxyl silyl ether. Then, gain and loss of a proton produces the free silanol. The alcohol is produced and the catalytic species is regenerated by rehydration.

CONCLUSION

In conclusion, we report that catalytic AlCl$_3$•6H$_2$O in isopropanol solution selectively cleaves TBS alky ethers in the presence of TIPS aryl ethers. Furthermore, TBS alkyl and aryl ethers are removed in the presence of TBDPS aryl and alkyl ethers in either methanol or isopropanol. In addition to its selectivity, this methodology is
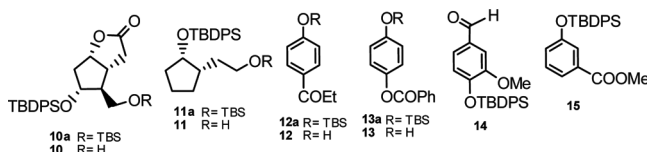
10a R= TBS
10 R= H

11a R= TBS
11 R= H

12a R= TBS
12 R= H

13a R= TBS
13 R= H

14

15

Table 4. Chemoselective deprotection of TBS alkyl and phenyl ethers in the presence of TBDPS alkyl and phenyl ethers by intramolecular and competition experiments

				Yield (%)[b]	
Entry	Substrate	Solvent	Product[a]	Δ[c]	MW[d]
1	**10a**	MeOH	**10**	93	96
		i-PrOH	**10**	88	85
2	**11a**	MeOH	**11**	95	93
		i-PrOH	**11**	93	90

Competition Experiments:

3	**12a+14**	MeOH	**12** (90)+**14**	(94)	**12** (92)+**14** (96)
4	**13a+15**	MeOH	**13** (92)+**15**	(95)	**13** (93)+**15** (93)

[a]Confirmed by comparison with ^{1}H NMR and ^{13}C NMR with authentic samples.
[b]Yields refer to chromatographically pure isolated compounds.
[c]50°C, 12h.
[d]100°C, 15min.
[e]Clearly the use of isopropanol is not possible in these cases.

noteworthy because aluminum chloride hexahydrate is inexpensive, is easily handled, and has very low toxicity.

EXPERIMENTAL

General Microwave Irradiation Procedure

A 10-mL reaction vessel was charged with a magnetic stir bar, 0.4 mmol of TBS ether, and 5 mol% AlCl$_3$·6H$_2$O in 2 mL of MeOH or i-PrOH. A septum cap was affixed; the vessel was placed in the microwave cavity of an Anton-Paar microwave equipment. The stirring reaction mixture was irradiated at 100°C for 15min. After cooling to room temperature, thin-layer chromatography (TLC)
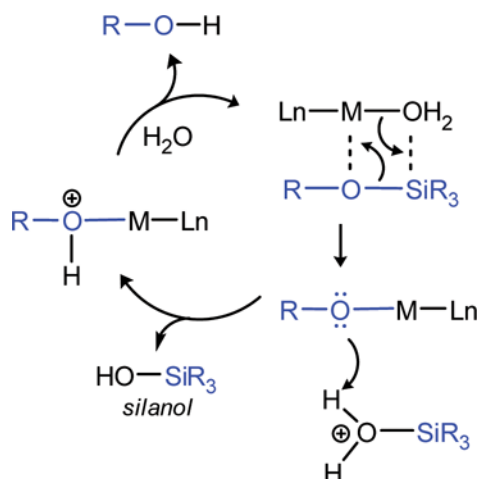
Scheme 1. Proposed plausible mechanism for the cleavage of silyl ethers.

indicated the disappearance of starting material. The solvent was removed under reduced pressure. Column chromatography afforded the pure alcohol. All products were spectrally identical with authentic alcohols.

General Conventional Heating Procedure

A 10-mL round-bottom flask was equipped with a magnetic stir bar and a reflux condenser. Then 0.4 mmol of TBS ether and 5 mol% $AlCl_3 \cdot 6H_2O$ in 2 mL of MeOH or *i*-PrOH were added. The reaction mixture was stirred at 50 °C for 12 h. After cooling to room temperature, TLC indicated the disappearance of starting material. The solvent was removed under reduced pressure. Column chromatography afforded the pure alcohol. All products were spectrally identical with authentic alcohols.

ACKNOWLEDGMENTS

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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