Deprotection of thioacetal using 1-butyl-4-aza-1-azoniabicyclo[2.2.2] octane dichromate (BABOD) in the presence of $AlCl_3$

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A variety of thioacetal (**2**) are deprotected to parent carbonyl compounds (3) using 1-butyl-4-aza-1-azoniabicyclo[2.2.2] octane dichromate (BABOD) (**1**) in the presence of $AlCl_3$ in refluxing CH_3CN.

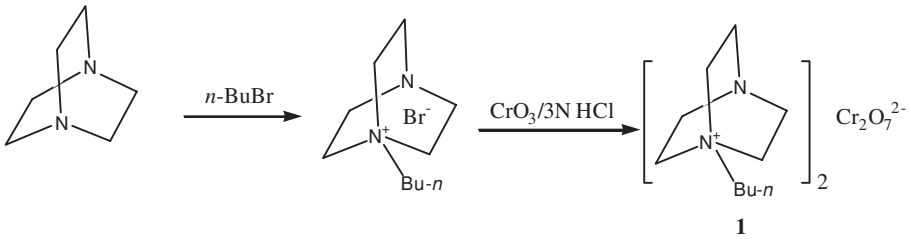
Keywords: deprotection, thioacetal, $AlCl_3$, BABOD

Protection and deprotection of reactive functional groups are essential steps in the synthesis of polyfunctional compounds. Thioacetalisation is well-known as a reaction that protects carbonyl groups of aldehydes and ketones.[1] Thioacetals are frequently encountered in synthetic steps for the preparation of many important organic compounds including natural products.[2] Their stability under acidic and basic conditions make them versatile carbonyl protecting groups.[3,4]

For this reason, the protection and deprotection of the carbonyl functional group remain crucial challenges to organic chemists. Experience shows that the critical parameters are generally the stability and the cleavage of the protecting group rather than its introduction. Therefore regeneration of the parent carbonyl group from a masked form seems to be a useful synthetic process. There are several methods for the deprotection of thioacetals and thioketals.[5]

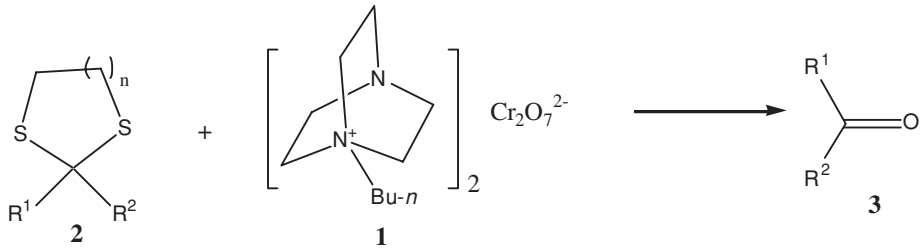
Cr (VI) is an inexpensive, water-soluble and stable oxidising reagent that is commercially available, but this reagent is insoluble in organic solvents. In continuation of to our previous work to develop new reagent and methods[6] we report here 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate (**1**) as an efficient reagent for the deprotection of thioacetal (**2**) (1,3-dithioacetallanes and 1,3-dithianes) to the corresponding carbonyl compounds (**3**) in refluxing acetonitrile. This new reagent has been readily prepared by reaction of an aqueous solution of 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane bromide with CrO_3 in 3 N solution of HCl at room temperature as shown in Scheme 1. The resulting orangepowder, which can be stored for months without losing its activity, is soluble in acetonitrile, acetone and *N,N*-dimethylformamide and slightly soluble in chloroform, ethylacetate and dichloromethane, but is not soluble in carbon tetrachloride, *n*-hexane and diethyl ether.

Deprotection of thioacetal with reagent (**1**) proceeds in acetonitrile under refluxing conditions. Initially, we decided to deprotect 2-methyl-2-(4-chlorophenyl)-1,3-dithioacetallane as a model compound with reagent (**1**) under refluxing conditions. Since deprotection of model 2-methyl-2-(4-chlorophenyl)-1,3-dithioacetallane with this reagent failed in the absence of Lewis acid, the effect of several Lewis acid $ZnCl_2$, $FeCl_3$, $FeBr_3$, $SnCl_2$, $SnCl_4$, $CuCl_2$, $BiCl_3$, $AlBr_3$ and $AlCl_3$ were examined in refluxing acetonitrile. Surprisingly, only $AlCl_3$ was shown to be an effective catalyst for this purpose (Table 1). The reaction in the presence of $ZnCl_2$, $FeCl_3$, $FeBr_3$, $SnCl_2$, $SnCl_4$, $CuCl_2$, $BiCl_3$ and $AlBr_3$ (0.5 mmol) proceeds with lower efficiency even with a higher molar ratio of the oxidant (1.5 mmol) in comparison with the amount of oxidant used in the presence of $AlCl_3$ (0.3 mmol). This could be the effect of hardness and more solubility of $AlCl_3$ in comparison with the other Lewis acids, that have been used in these experiments. The optimum molar ratio of thioacetal, to $AlCl_3$ to oxidant (**1**) (1:0.3:1) was determined for complete deprotection of thioacetal (**2**) to carbonyl compounds (**3**).



1

Scheme 1



2 **1** **3**

n = 1 or 2, R^1, R^2 = Alkyl, aryl, allyl and H

Scheme 2

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Table 1 Oxidative coupling of thiols **4** to disulfides **5** with reagent **1** in refluxing acetonitrile

Thiols (**4**)	Product (**5**)[a,b]	Reaction time/h	Yields/%[e]	M.p. or B.p./mmHg °C (Lit.)[13-18]
C_6H_5SH	$C_6H_5SSC_6H_5$	0.5	92	56–60 (59–60)
4-MeC_6H_4SH	4-$MeC_6H_4SSC_6H_4Me$-4	0.8	98	47–48 (46–48)
4-$MeOC_6H_4SH$	4-$MeOC_6H_4SSC_6H_4OMe$-4	0.9	93	44–45 (43.8)
4-$NH_2C_6H_4SH$	4- $NH_2C_6H_4SSC_6H_4$ NH_2-4	1.1	95	75–77 (76–77)
3-MeC_6H_4SH	3-$MeC_6H_4SSC_6H_4Me$-3	0.8	98	–21 (–21)
4-ClC_6H_4SH	4-$ClC_6H_4SSC_6H_4Cl$-4	0.9	98	72–73 (72–73)
2-$MeOOCC_6H_4SH$	2-$MeOOCC_6H_4SSC_6H_4COOMe$-2	0.8	96	198–191 (193)
$C_6H_5CH_2SH$	C_6H_5 CH_2SS $CH_2C_6H_5$	1.1	95	69–70 (69–70)
4-$NO_2C_6H_4SH$	4- $NO_2C_6H_4SSC_6H_4$ NO_2-4	0.75	88	182–184 (182)
2-PyridylSH	2-PyridylSS-pyridyl-2	0.8	92	52–53 (52–53)
4-PyridylSH	4-PyridylSS-pyridyl-4	1.1	91	76–77 (76–77)
CyclopentylSH	CyclopentylSSCyclopentyl	1.0	93	105–106 (107–108)
CyclohexylSH	CyclohexylSSCyclohexyl	1.2	87	124 129 (125–130)
HO-CH_2CH_2SH	HO-$CH_2CH_2SSCH_2CH_2OH$	1.2	80	156–148/2(158–163/3.5)
$HOOCCH_2CH_2SH$	$HOOCCH_2CH_2SSCH_2CH_2COOH$	1.0	86	157–159 (1157–159)
$HOOCCH_2SH$	$HOOCCH_2SSCH_2COOH$	1.1	91	138–139 (140)
$CH_3(CH_2)_3SH$	$CH_3(CH_2)_3SS(CH_2)_3CH_3$	1.2	92	94–96/6 (86/3.5)
$CH_3(CH_2)_4SH$	$CH_3(CH_2)_4SS(CH_2)_4CH_3$	1.1	87	117–119/6 (90–92/1)
$CH_3(CH_2)_6SH$	$CH_3(CH_2)_6SS(CH_2)_6CH_3$	1.2	90	152–154/6 (143–147/5)
$CH_3(CH_2)_7SH$	$CH_3(CH_2)_7SS(CH_2)_7CH_3$	1.0	96	152–154/6 (143–147/5)
1-$HSCH_2C_6H_4CH_2SH$-4	Linear polymer[c]	1.2	98	–
$SH(CH_2)_3SH$	1,5-Cyclopentanedisulfide	2.0	70	45–47/6 (–)
	+ (-S $(CH_2)_3$S-)$_n$[d]		(30 Polymer)	65–70 (71–73)
$SH(CH_2)_4SH$	1,6-Cyclohexanedisulfide	1.2	98	30–32 (32–33)

[a]Confirmed by comparison with authentic samples (IR, TLC, and NMR). [b]Oxidant/Thiol (1.0:1.0). [c]$HSCH_2C_6H_4CH_2S$——($SCH_2C_6H_4CH_2S$——)*n* $SCH_2C_6H_4CH_2SH$, [d]$HS(CH_2)_3S$——($SCH_2CH_{24}CH_2S$——)*n* $S(CH_2)_3SH$, [e]Yield of isolated pure product after chromatography or distillation.

In this method, deprotection of thioacetals are achieved by refluxing a mixture of a thioacetals (**2**), $AlCl_3$ and reagent (**1**) in acetonitrile. The reaction time is usually between 30-90 minutes (Table 2 and Scheme 2). The carbonyl compounds (**3**) were obtained in excellent yield in refluxing acetonitrile. This method offers a simple, mild, efficient route for converting thioacetals to the corresponding carbonyl compounds. As evident from the results presented in Table 2, functional groups such as NO_2 and MeO increase the duration of reaction. This could be the effect of producing complexes between these functional groups with $AlCl_3$. Notably, aldehydes did not undergo further oxidation to their carboxylic acids under the reaction conditions.

In conclusion, we have reported a new and efficient methodology for the deprotection of thioacetal using 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate (BABOD) in the presence of $AlCl_3$. The stability, easy preparation of the reagent and straightforward purification of products makes this method a useful procedure relative to the present methodologies for regeneration of carbonyl compounds from their thioacetal derivatives.[5]

Experimental

All yields refer to isolated products after purification. All of the products were characterised by comparison of their spectral (IR, ^{1}H NMR and TLC) and physical data (melting and boiling points) with those of authentic samples.[1-6, 7] All ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ relative to TMS as an internal standard and IR spectra were recorded on Shimadzu 435 IR spectrometer.

1-Butyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate: A solution of 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane bromide (12.45 g, 50 mmol) in 50 ml of water was prepared, and then CrO_3 (5.0 g, 50 mmol) in HCl 3 N (50 ml) was added dropwise to the above solution and stirred for 10 min at room temperature. The resulting orange precipitate was filtered and washed with cooled distilled water (2×50 ml), and dried in a desiccator under vacuum over calcium chloride to afford an orange powder (13.09 g, 23.5 mmol, 94% yield), which decomposed at 117–118 °C to a dark-brown material.^{1}H NMR (d_6-DMSO, 500 MHz): δ = 3.84–3.53 (m, 24 H), 1.65–0.91 (m, 18 H). ^{13}C NMR (d_6-DMSO, 125 MHz) δ = 64.74, 51.86, 44.93, 41.45, 41.29, 41.12, 40.95, 40.79, 40.62, 40.46, 24.69, 20.42, 14.83;. Anal. Calcd. For $C_{20}H_{42}N_4Cr_2O_7$: C, 43.32; H, 7.58; N, 10.11. Found: C, 43.15; H, 7.68; N, 10.30.

Typical procedure for solid phase deprotection of 2-Methyl-2-(4-chlorophenyl)-1,3 dithioacetallane 2k with reagent (**1**): In a round-bottom flask equipped with a condenser and a magnetic stirrer, 2-methyl-2-(4-chlorophenyl)-1,3-dithioacetallane (0.231 g, 1 mmol) and aluminum chloride (0.04 g, 0.3 mmol) in dry acetonitrile (5 ml) was added 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate (1) (0.55 g, 1 mmol). The reaction mixture was stirred under reflux conditions for the time specified in Table 1. After disappearance of starting material monitored by TLC, the mixture was cooled to room temperature and filtered under vacuum and the filtrate was evaporated under reduced pressure. The crude product was purified by flash chromatography on SiO_2 (eluent: cyclohexane:EtOAc, 90:10) affording the desired carbonyl compound (**3**).

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