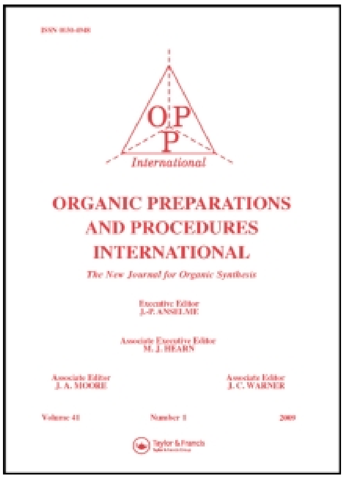

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SOLID STATE DEPROTECTION OF THIOACETALS AND THIOKETALS USING 1-BENZYL-4-AZA-1-AZONIABICYCLO[2.2.2]OCTANE PERIODATE AND ALUMINUM CHLORIDE

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Carbonyl compounds are often protected as thioacetals and thioketals in organic synthesis,[1,2] due to their stability under both acidic and basic conditions. Many procedures are available for the preparation of these derivatives [3-4] and extensive studies on the deprotection of these derivatives to the parent carbonyl compounds have been carried out.[5] However, some of these methods for deprotection require higher temperatures, long reaction times and involve toxic metal ions and solvents which are detrimental to the environment.[5] Therefore, there is need for a simple, less expensive and safer methods for deprotection of thioacetals and thioketals.

In recent years, there has been an increasing interest in reactions that proceed in the absence of solvent due to reduced pollution, low costs and simplicity in process and straightforward work-up.[7] Because of our interest in development of solvent-free reactions,[8] we now report 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane periodate **1** as an efficient and selective reagent for the deprotection of thioacetal **2** or **3** (1,3-dithioacetals and 1,3-dithianes) to the corresponding carbonyl compounds **4**. 1-Benzyl-4-aza-1-azoniabicyclo[2.2.2]octane periodate (**1**) is a mild, efficient, stable and inexpensive reagent; it is a white powder, which is quite soluble in polar organic solvent such as dichloromethane, chloroform, acetone and acetonitrile and insoluble in non-polar solvents such as carbon tetrachloride, *n*-hexane and diethyl ether. This reagent is readily prepared by addition of an aqueous solution of $NaIO_4$ to an aqueous solution of 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride in quantitative yield at room temperature and may be stored for months without losing its potency.[6]

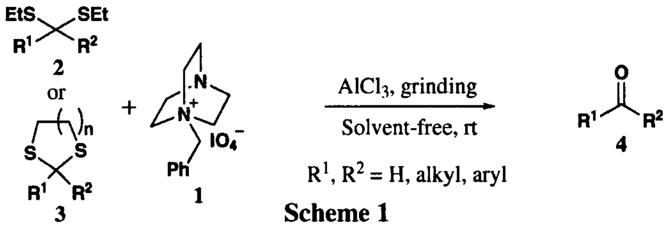
Deprotection of thioacetals and thioketals with reagent **1** proceeds under solid-state conditions. To optimize the reaction conditions, we initially decided to explore the role of the reagent **1** in the presence of Lewis acid in a solventless system for the deprotection of 2-(3-nitrophenyl)-1,3-dithiane as a model compound. Addition of Lewis acid under solid-state condition in the absence of reagent **1** did not effect dethioacetalization of the 2-(3-nitrophenyl)-1,3-dithiane after prolonged reaction times. Since deprotection of model 2-(3-nitrophenyl)-1,3-dithiane with this reagent failed in the absence of Lewis acid, the effect of the acids $ZnCl_2$, $FeCl_3$, $FeBr_3$, $SnCl_2$, $SnCl_4$, $CuCl_2$, $BiCl_3$, $AlBr_3$ and $AlCl_3$ was also examined under solid-state conditions. $AlCl_3$ was shown to be the most 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 greater solubility of $AlCl_3$ in comparison with the other acids used in this study. The optimum molar ratio of thioacetal to $AlCl_3$ to oxidant **1** (1:0.3:1) was found best for complete deprotection of thioacetals **2** or **3** to carbonyl compounds **4**.

Table 1. Deprotection of 2-(3-Nitrophenyl)-1,3-Dithiane By Reagent **1** with Different Lewis Acids Under Solvent-Free Conditions [a, b]

Entry	Lewis acid	Time (min)	Yield (%)
1	$ZnCl_2$[c]	60	30
2	$CuCl_2$	60	40
3	$FeCl_3$[c]	60	50
4	$BiCl_3$[c]	60	60
5	$FeBr_3$[c]	60	40
6	$SnCl_2$[c]	60	30
7	$SnCl_4$[c]	60	40
8	$AlBr_3$	20	75
9	$AlCl_3$	20	95

[a] Monitored by TLC analysis. [b] Oxidant/2-(3-Nitrophenyl)-1,3-dithiane /Lewis acid (1:1:0.3). [c] Oxidant/2-(3-Nitrophenyl)-1,3-dithiane /Lewis acid (1.5:1:0.5).

In this method, deprotection of the substrate was achieved by grinding a mixture of a thioacetal (or thioketal) **2** or **3**, $AlCl_3$ and reagent **1** under solvent-free condition for 5-35 minutes (*Table 2* and *Scheme 1*). The carbonyl compounds **4** were isolated by extracting the reaction



Scheme 1

mixture with a solvent followed by filtration of the mixture. Evaporation of filtrate under vacuum followed by flash chromatography provided pure carbonyl compounds **4** in high yield (*Table 2*). As evident from the results shown in *Table 2*, functional groups such as NO_2 and MeO required longer times.reaction. This could be the formation of complexes between these functional groups with $AlCl_3$. It is to be noted that aldehydes did not undergo further oxidation to carboxylic acids under the reaction conditions. To demonstrate the utility of the procedure, reaction on a ten-fold scale was carried out under solvent-free condition for the deprotection of 2-(3-nitrophenyl)-1,3-dithiane to afford 3-nitrobenzaldehyde in 95% yield. There are no thermal or safety problems during mixing and reaction of starting materials.

Table 2. Deprotection of 1,3-Dithianes And 1,3-Dithioacetals with Reagent **1** in the Presence of $AlCl_3$ in Solventless System [a,b]

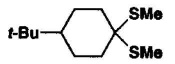
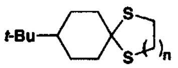
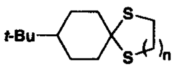
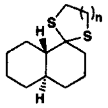
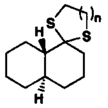
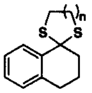
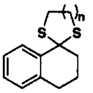
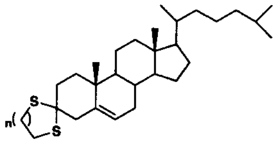
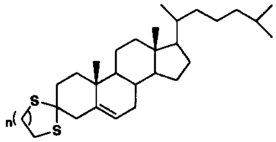
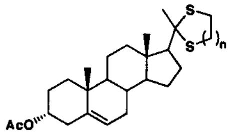
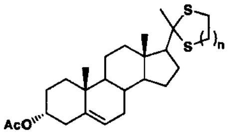
Substrate	R^1	R^2	n	Time (Min)	Yield (%)[c]	mp or bp (°C)/torr (*lit.*[8-9])
2a	$4\text{-}MeOC_6H_4$	H	----	15	94	141-143/50 (141-143/50)
2b	$3,4\text{-}(MeO)_2C_6H_3$	H	----	12	95	81-83 (82)
2c	$4\text{-}O_2NC_6H_4$	H	----	20	98	104-106 (104-106
2d	C_6H_5	CH_3	----	10	91	200-2002/760 (200-2002/760)
2e	C_6H_5	C_6H_5	----	10	93	46-48 (47-49)
2f	$CH_3(CH_2)_9CH_2$	H	----	35	88	239-240/760 (240/760)
2g			----	30	90	170-172/760 (169-171/760)
3a	C_6H_5	Me	1	10	92	201-202/760 (200-202/760)
3b	$4\text{-}BrC_6H_4$	Me	1	12	94	49-52 (49-52)
3c	$2\text{-}O_2NC_6H_4$	H	2	20	91	43-45 (42-43)
3d	$3\text{-}O_2NC_6H_4$	H	2	20	95	54-56 (55-58)
3e	$4\text{-}O_2NC_6H_4$	H	2	20	96	81-83 (82)
3f			1	30	88	170-172/760 (169-171/760)
3g			2	30	85	

Table 2. Continued...

Substrate	R^1	R^2	n	Time (Min)	Yield (%)[c]	mp or bp (°C)/torr (*lit.*[8-9])
3h			1	35	82	57-59 (57-59)
3i			2	30	86	57-59 (57-59)
3j	4-ClC$_6$H$_4$	H	2	10	98	45-48 (45-47)
3k	4-ClC$_6$H$_4$	Me	1	12	95	231-232/760 (232/760)
3l	4-Br-C$_6$H$_4$	CH$_2$Br	2	15	85	107-110 (108-110)
3m			1	12	93	127/13 (127/13)
3n			2	15	94	127/13 (127/13)
3o	Ph	H	2	10	90	176-1178760 (176-1178760)
3p	2-MeOC$_6$H$_4$	H	2	15	93	37-39 (37-39)
3q	MeO$_2$CCH$_2$CH$_2$	Me	1	25	88	192-193/760 (193-195/760)
3r	MeO$_2$CCH$_2$CH$_2$	Me	2	25	90	192-193/760 (193-195/760)
3s			1	35	91	79-81 (79-82)
3t			2	35	95	79-81 (79-82)
3u			1	35	86	148-150 (148-150)
3v			2	35	88	148-150 (148-150)

a) Confirmed by comparison with authentic samples (TLC, IR, ^{1}H-NMR, melting and boiling points). b) Yield of carbonyl compound after purification.

EXPERIMENTAL SECTION

All of the yields refer to isolated products after purification. All of the products were characterized by comparison of their spectral (IR, ^{1}H-NMR and TLC) and physical data (melting and boiling points) with those of authentic samples.[2-5, 8] All 1H-NMR spectra were recorded at 300 MHz in CDCl3 relative to TMS as an internal standard and IR spectra were recorded on Shimadzu 435 IR spectrometer. The reagent **1** was prepared according to our previous reported procedures.[6] All of the reactions were carried out in a hood with strong ventilation. The carbonyl derivatives were prepared from the corresponding carbonyl compounds and 1,2-ethanedithioacetal and 1,3-propanedithioacetal according to the reported procedures.[3, 5]

Typical Procedure for Solvent-Free Deprotection of Thioacetals and Thioketals with Reagent 1.- To a mixture of 2-methyl-2-(4-chlorophenyl)-1,3-dithioketal (**3k**, 0.231 g, 1 mmol) and aluminum chloride (0.04 g, 0.3 mmol)in a mortar was added 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane periodate **1** (0.40 g, 1 mmol). The reaction mixture was ground with pestle at room temperature under solvent-free condition for 12 minutes. After the disappearance of starting material (monitored by TLC, *n*-hexane:EtOAc 80:20), the mixture was extracted with cyclohexane (2 x 10 mL) and filtered. The filtrate was evaporated under reduced pressure and the resulting crude material was purified by flash chromatography on SiO_2 (eluent: dichloromethane) to afford 4-chloroacetophenone (0.14 g, 90%), bp 231-232°C/760 Torr (*lit.*[8] bp 232°C/760 Torr). IR (KBr): 3050 (m), 2890 (m), 1680 (s), 1590 (s), 1400 (m), 1250 (s), 830 (m), 760 (m) cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.6 (s, 3H), 7.4-7.7 (d, 2H, J = 6 Hz), 7.9-8.2 (d, 2H, J = 6 Hz) ppm.

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