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A useful and convenient synthetic protocol for interconversion of carbonyl compounds to the corresponding 1,3-oxathiolanes and vice versa employing organic ammonium tribromide (OATB)†

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Abstract—A wide variety of carbonyl compounds **1** can be easily protected selectively as the corresponding 1,3-oxathiolanes **2** in good yields using a catalytic amount (0.01–0.1 equiv.) of *n*-tetrabutylammonium tribromide in dry CH_2Cl_2 at 0–5 °C. On the other hand, various 1,3-oxathiolanes **2** can be deprotected chemoselectively to the parent carbonyl compounds **1** employing 0.5 equivalents of organic ammonium tribromides under identical conditions in very high yields. Mild conditions, high selectivity and yield, highly efficient, less expensive, and no brominations either at the double bond or allylic position and even α- to the keto position or aromatic ring are some of the major advantages of the protocol. © 2002 Elsevier Science Ltd. All rights reserved.

Protection and deprotection strategies are very commonly used techniques for complex natural and non-natural product synthesis. Among various functional groups, protection of the carbonyl group as a 1,3-oxathiolane is important for the following reasons. Firstly, they can be used as acyl carbanion equivalents[1] for carbon–carbon bond forming reactions. Secondly, the chiral 1,3-oxathiolanes are valuable synthons for enantioselective synthesis of α-hydroxyaldehydes, first demonstrated by Eliel and his co-workers.[2] Later on, these compounds were further utilized by Utimoto et al.[3] for studying diastereoselective reactions. Thirdly, the use of oxathioacetals is more convenient than the corresponding *O*,*O*-acetals or *S*,*S*-acetals because they are comparatively more stable than *O*,*O*-acetals in acidic conditions and much easier to remove than *S*,*S*-acetals. Though a large number of methods have been developed for the protection and deprotection of carbonyl compounds as 1,3-dithiolanes,[4] only a few methods are available for oxathioacetals.[5] The usual procedures for the formation of oxathioacetals from their corresponding carbonyl compounds are as follows: (i) using HCl,[6a] (ii) refluxing with *p*-TSA,[6b] (iii) treating with BF_3-OEt_2,[6c] (iv) using $ZnCl_2$,[6d] and (v) utilizing catalytic amounts of TMSOTf.[6e] All these methods have certain drawbacks such as low yield,[6a] relatively harsh reaction conditions,[6b,c] relatively long reaction times,[6c] and expensive reagents[6e] (TMSOTf) as well as inconvenience of use. Similarly, a few methods are also reported for the deprotection of 1,3-oxathiolanes using (i) isoamyl nitrite[7a] and chloramine-T,[7b] (ii) TMSOTf alone,[6e] or in the presence of *p*-nitrobenzaldehyde,[7c,d] and polymer supported *p*-nitrobenzaldehyde.[7e] Some of these methods have serious drawbacks such as difficult to remove by-product 1,3-oxathiolanes derived from *p*-nitrobenzaldehyde,[7c,d] or the use of expensive polymer supported reagents.[7e] Another important drawback is the deprotection of non-benzylic oxathioacetals which requires much longer reaction times.[6e] Some methods also known in the literature are based on halonium ion sources such as NCS-$AgNO_3$,[8a,b] I_2-$AgNO_2$[8c,d] and NBS in acetone[8e] for the deprotection of a wide variety of oxathioacetals. Unfortunately, these methods suffer from the requirement of a large molar excess of reagents such as expensive silver salts[8a–d] as well as much longer reaction times.[8e] Very recently, another method has appeared[9] for deprotection of various oxathioacetals by using glyoxylic acid in the presence of Amberlyst 15 in a microwave oven, which is relatively expensive. Consequently, what is needed is a methodology that is mild, clean, environ-

Keywords: protection; deprotection; 1,3-oxathiolanes; *n*-tetrabutylammonium tribromide (TBATB); cetyltrimethylammonium tribromide (CetTMATB).

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mentally benign and yet efficient, site selective, operationally simple, and cost effective.

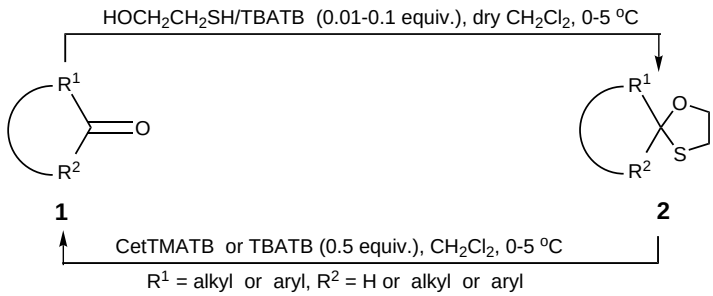
In an endeavor to gradually change the current working practices to greener alternatives and environmental demands,[10] an environmentally favorable protocol for the preparation of various organic ammonium tribromides (OATB) and some of its applications was disclosed recently.[11] We have also shown that these reagents are extremely useful in organic synthesis particularly for deprotection of dithioacetals,[12a] and in natural product synthesis.[12b] Some other valuable applications were also reported recently for deprotection of TBDMS ethers[13a] and protection/deprotection of THP ethers.[13b] Knowing the unique behavior and properties of the reagents and as part of our ongoing research project to develop a newer methodology,[14] we conceived the idea that OATBs might further be applied for interconversion of various carbonyl compounds to 1,3-oxathiolanes and vice versa. We would like to report our successful results in this communication, as depicted in Scheme 1.

We have attempted optimization of the reaction conditions for protection of a wide variety of carbonyl compounds giving the corresponding 1,3-oxathiolanes. The substrate *p*-methoxybenzaldehyde **1a** was converted to the protected compound **2a** using 0.01 equivalents of *n*-tetrabutylammonium tribromide (TBATB) in dichloromethane at ice-bath temperature within 5 min and in 65% yield. Similarly, compound **2a** can also be prepared from compound **1a** using 0.01 equivalents of acetyltrimethylammonium tribromide (CetTMATB) under identical reaction conditions in 30 min. Using TBATB, the reaction is faster in comparison to CetTMATB. Likewise, we have successfully converted various carbonyl compounds **1b**–**1n** to the corresponding 1,3-oxathiolanes **2b**–**2n**, on treating the carbonyl compound with 2-mercaptoethanol in the presence of a catalytic amount of TBATB depending upon the amount of reagent and reaction conditions, as shown in Table 1. The results summarized in Table 1 clearly demonstrate that the method is equally efficient for various substrates.

It is significant that no brominations take place either at the double bond or allylic positions, for instance **1f**, **1g** and **1i**. More interestingly, the TBDMS group is also unaffected under the experimental conditions although TBATB can be used for deprotection of silyl ethers.[13a] All the protected compounds were fully characterized by ^{1}H NMR spectroscopy and elemental analyses.[15] The formation of the products can be explained as follows. It has been shown that OATB such as benzyltrimethyl ammonium tribromide generates HBr and MeOBr in methanol.[16] We suggest that HBr is forming slowly from the reaction of TBATB with 2-mercaptoethanol, which catalyzes the conversion of the carbonyl compounds into the corresponding 1,3-oxathiolanes. We noted that the pH of the solution was ~2–3 while carrying out the reaction.

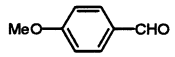
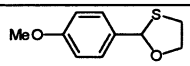
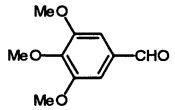
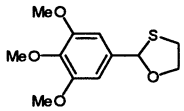
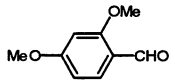
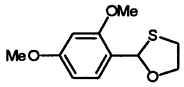
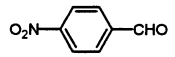
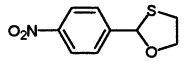
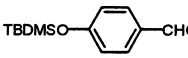
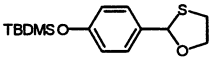
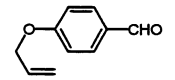
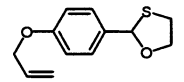
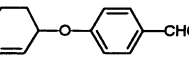
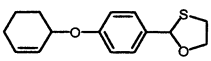
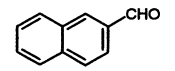
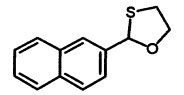
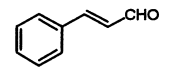
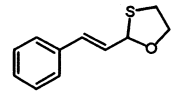
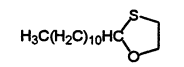
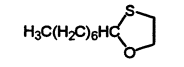
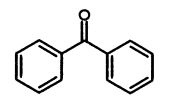
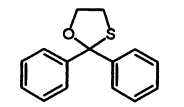
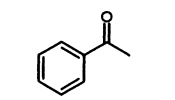
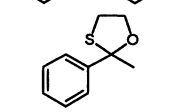
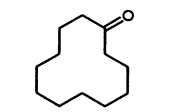
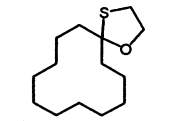
Next, we looked for suitable reaction conditions for deprotection of 1,3-oxathiolanes to the parent carbonyl compounds. The compound 2-(4-methoxyphenyl)-1,3-oxathiolane **2a** was deprotected smoothly to the parent carbonyl compound 4-methoxybenzaldehyde **1a** within 5 min on treatment with 0.5 equivalents of CetTMATB or TBATB in dichloromethane at 0–5 °C. Similarly, we have successfully converted various substituted 1,3-oxathiolanes **2b**–**2n** to the parent compounds **1b**–**1n** employing either CetTMATB or TBATB under identical reaction conditions, respectively. The results are shown in Table 1 and the products were characterized by IR, ^{1}H NMR spectroscopy and elemental analyses as well as by comparison with the authentic compounds.[17] Our protocol is very effective, for instance, oxathioacetal **2d** was deprotected more rapidly than by the earlier reported procedure.[8e] It is pertinent to mention that the substrate **2g** gives an undesired compound instead of expected **1g** at ice-bath temperature reaction conditions. However, the compound **1g** can be obtained from the compound **2g** if the reaction is carried out at a lower temperature (−20°C), implying that the selectivity can be achieved by controlling reaction temperature. The formation of the deprotected compound can be rationalized as follows. TBATB generates Br^+ ions, which react with sulfur to form a bromosulfonium complex, which is finally hydrolyzed to the corresponding carbonyl compound.

In summary, we have devised a simple and convenient method for the protection of various carbonyl compounds as the corresponding 1,3-oxathiolanes as well as deprotection to the parent carbonyl compounds, chemoselectively, using OATBs and by tuning the amount of the reagents, under very mild reaction conditions. In addition, these reagents are environmentally



Scheme 1.

Table 1. Protection of various carbonyl compounds **1** as the corresponding 1,3-oxathiolanes **2** and deprotection of compounds **2** to the parent carbonyl compounds **1** using OATB

Entry	Substrate 1	Time min/ [h]	TBATB used in equiv.	Yield[b] %	Product 2[a]	Method	Time min/ [h]	Product 1[a]	Yield[b] %
a		5	0.01	65		A B	5 5	**1a**	85 95
b		[1]	0.025	70		A B	3 5	**1b**	91 90
c		45	0.025	66		A B	2 2	**1c**	80 86
d		[5]	0.01	64		A B	10 10	**1d**	97 98
e		10	0.01	56			5 5	**1e**	90 89
f		[2]	0.01	68		A B	15 7	**1f**	83 81
g		30	0.01	45		A B	[1.5] [1.5]	**1g**	85[d] 88[d]
h		30	0.05	55		A B	10 12	**1h**	75 83
i		[1]	0.05	58		A B	17 15	**1i**	60 62
j	$CH_3(CH_2)_{10}CHO$	30	0.05	65		A B	5 3	**1j**	87 84
k	$CH_3(CH_2)_6CHO$	[1]	0.05	58		A B	2 2	**1k**	93 92
l		[3]	0.1	85		A B	5 2	**1l**	90 96
m		[4]	0.05	81		A B	10 10	**1m**	60 65
n		[4.5]	0.05	72[c]		A B	45 40	**1n**	70 75

[a] Products **2** were characterized by IR, ^{1}H NMR, elemental analyses and the deprotected compounds **1** were confirmed by comparison with the IR and ^{1}H NMR spectra of the parent carbonyl compounds. [b]Isolated yield. [c]Based on recovered starting material. [d]Reaction carried out at –20 °C. Method A - using CetTMATB and method B - using TBATB.

benign and are easy to handle. It is noteworthy that no brominations take place either at the double bond or allylic position, or in the aromatic rings. Due to its operational simplicity, generality and efficacy, this method is expected to have wider applicability for interconversion of various carbonyl compounds to the corresponding oxathioacetals and vice versa. Other OATBs can also be used for similar transformations, which are under investigation and will be reported in due course.

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15. **Spectroscopic data for compound 2f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.15–3.31 (m, 2H, –SCH_2–), 3.87–3.95 (m, 1H, –OCH_2–), 4.53 (m, 3H, –OCH_2–), 5.28 (d, 1H, $J=10.5$ Hz, =CH_2), 5.40 (d, 1H, $J=17.2$ Hz, =CH_2), 5.99 (s, 1H, –OC*H*–S), 6.01–6.10 (m, 1H, –CH_2=C*H*–), 6.89 (d, 2H, $J=8.5$ Hz, ArH), 7.39 (d, 2H, $J=8.5$ Hz, ArH). Anal. calcd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35. Found: C, 64.67; H, 6.31. **Compound 2g:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85–2.09 (m, 6H, cyclohexyl CH_2–), 3.16–3.32 (m, 2H, –SCH_2–), 3.87–3.95 (m, 1H, –OCH_2–), 4.48–4.54 (m, 1H, –OCH_2–), 4.79–4.91 (m, 1H, OCH_2), 5.83–5.99 (m, 3H, olefinic H, –O–CH–S), 6.89 (d, 2H, $J=8.5$ Hz, ArH), 7.39 (d, 2H, $J=8.5$ Hz, ArH). Anal. calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.91. Found: C, 68.52; H, 6.88.
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17. **Spectroscopic data for compound 1f:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.62 (d, 2H, $J=5.2$ Hz, –OCH_2–), 5.33 (d, 1H, $J=10.5$ Hz, =CH_2), 5.43 (d, 1H, $J=17.2$ Hz, =CH_2), 5.99–6.16 (m, 1H, CH_2=C*H*–), 7.01 (d, 2H, $J=8.6$ Hz, ArH), 7.83 (d, 2H, $J=8.6$ Hz, ArH), 9.88 (s, 1H, –CHO). Anal. calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 73.89; H, 6.19. **Compound 1g:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.87–2.17 (m, 6H, –cyclohexyl CH_2–), 4.92 (bs, 1H, –OC*H*–), 5.84–6.04 (m, 2H, CH=CH), 7.01 (d, 2H, $J=8.5$ Hz, ArH), 7.82 (d, 2H, $J=8.6$ Hz, ArH), 9.87 (s, 1H, –CHO). Anal. calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.01; H, 6.94.