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# An efficient method for the oxathioacetalization of carbonyl compounds using *N*-bromosaccharin as a catalyst

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**Abstract**

A mild and highly chemoselective method for the preparation of oxathiolane from aliphatic and aromatic aldehydes and ketones with 2-mercaptoethanol in the presence of catalytic amount of *N*-bromosaccharin at room temperature is reported.


*Keywords:* Protection; Carbonyl compounds; Oxathioacetalization; *N*-Bromosaccharin

Conversion of carbonyl groups to their corresponding oxathioacetals is very important from different aspects [1]. The main reasons for the preparation of 1,3-oxathiolanes are their considerable stability under different reaction conditions, ease of formation and removal and equality to acyl carbanions in C–C bond forming reactions [2].

A number of methods have been reported for the generating of oxathioacetal derivatives by reacting carbonyl compounds with 2-marcaptoethanol using equimolar amount of Lewis acid such as $BF_3{\cdot}OEt_2$ [3], $ZnCl_2$ [4], $LaCl_3$ [5] and $WCl_6$ [6]. Other methods in the literature employ NBS [7], In $(OTf)_3$ [8], $ZrCl_4$ [9], and OTAB [10]. Nevertheless, some of these methods have certain drawbacks such as relatively harsh reaction conditions, long reaction times, reflux condition, expensive reagents, inconvenient procedures, using of stoichiometric amounts of catalyst, unwanted side reaction and poor chemoselectivity. Thus, the development of mild, efficient and chemoselective methodology for this transformation is desirable.

*N*-Bromosaccharin (NBSac) is a strong oxidizing and bromonating agent. This reagent has successfully been used for regioselective cleavage of epoxides [11], oxidative cleavage of oximes [12].

In this communication, we report a mild and highly chemoselective procedure for the conversion of aliphatic and aromatic aldehydes and ketones into 1,3-oxathiolanes using 2-mercaptoethanol and catalytic amount of NBSac in $CH_2Cl_2$ at room temperature (Scheme 1).

## 1. Experimental

Materials were purchased from Merck and Aldrich companies. NBSac was prepared according to the reported procedure [13]. Nuclear magnetic resonance spectra were recorded on a Bruker DRX-400 AVANCE spectrometer in $CDCl_3$ or DMSO as solvent.

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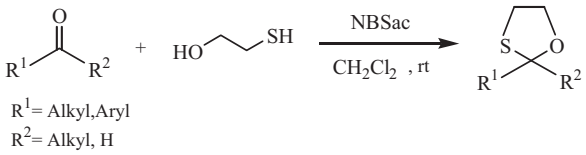


Scheme 1. Protection of carbonyl compounds as oxathiolanes using catalytic amount of NBSac.

Carbonyl compounds (1 mmol), 2-mercaptoethanol (1.2 mmol) and the catalyst (10 mol%) in dichloromethane were stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with aqueous NaOH 10% (10 mL) and it was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic layers were washed with 10% aqueous NaOH (10 mL) and $H_2O$ (2 × 25 mL) and then dried over anhydrous sodium sulfate. The extracts were then concentrated under reduced pressure to afford crude products. Further purification was achieved by chromatography on a silica-gel column to give pure product. Spectroscopic characterization data of some compounds are given in supplementary data.

## 2. Results and discussion

To optimize the reaction conditions, initially we have chosen benzaldehyde as a model compound. Oxathioacetalization of benzaldehyde (1 mmol) with 2-mercaptoethanol (1.2 mmol) was carried out in the presence of catalytic amount of *N*-bromosaccharin at room temperature. We examined the effect of different solvents (THF, $CH_3CN$, $CH_2Cl_2$, EtOH) using NBSac. Dichloromethane was the best solvent (Table 1, entries 1–4). We also found that the amount of catalyst had an effective influence on the reaction course. 10 mol% of catalyst gave the best result (Table 1, entries 5–8). Then we examined the effect of different molar ratio of 2-mercaptoethanol to benzaldehyde in the presence of *N*BSac in dichloromethane at room temperature for this conversion. We found that the optimized molar ratio was 1.2:1 (Table 1, entries 9–11).

To investigate the scope of reaction, a wide variety of carbonyl compounds were protected in the form of 1,3-oxathiolanes using 2-mercaptoethanol as the protecting group and the results are shown in Table 2. As shown in Table 1, the reaction of 2-mercaptoethanol with various aromatic aldehydes and ketone under optimal reaction conditions afforded oxathiolanes in high to excellent yields (Table 2, entries 1–8).

To examine the chemoselectivity of this protocol, we have used the cinnamaldehyde and 4-acetylbenzaldehyde (Table 2, entries 9–10). These reactions were completed without damage of double bond and ketone group in cinnamaldehyde and 4-acetylbenzaldehyde, respectively. Heterocyclic compound such as thiophene-2-carbaldehyde was successfully oxathioacetalized with 84% yield (Table 2, entry 11). The linear chain ketone and aldehyde, *i.e.* 2-heptanone and hexanal were also converted to the corresponding ketal and acetal in moderate yields (Table 2, entries 12–13). Similarly the cyclic ketones such as cyclohexanone and cyclopentanone also worked well (Table 2, entries 14–15).

Table 1
Optimization of the preparation of 2-phenyl-1,3-oxathiolane.

| Entry | Ratio of 2-mercaptoethanol to benzaldehyde (mmol) | Catalyst (mol%) | Solvent | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 1.2: 1 | 10 | $CH_3CN$ | 2 | 70 |
| 2 | 1.2: 1 | 10 | EtOH | 2 | 60 |
| 3 | 1.2: 1 | 10 | THF | 2 | 40 |
| 4 | 1.2: 1 | 10 | $CH_2Cl_2$ | 1.75 | 85 |
| 5 | 1.2: 1 | – | $CH_2Cl_2$ | 1.75 | – |
| 6 | 1.2: 1 | 5 | $CH_2Cl_2$ | 1.75 | 40 |
| 7 | 1.2: 1 | 8 | $CH_2Cl_2$ | 1.75 | 65 |
| 8 | 1.2: 1 | 10 | $CH_2Cl_2$ | 1.75 | 85 |
| 9 | 0.5: 1 | 10 | $CH_2Cl_2$ | 1 | 40 |
| 10 | 1: 1 | 10 | $CH_2Cl_2$ | 1.75 | 70 |
| 11 | 1.2: 1 | 10 | $CH_2Cl_2$ | 1.75 | 85 |

Table 2
Protection of carbonyl compounds as oxathiolanes using catalytic amount of NBSac.[a]

| Entry | Substrate | Product[b] | Time (h) | Yield[c] (%) | Ref. |
|---|---|---|---|---|---|
| 1 | Benzaldehyde | 2-Phenyl-1,3-oxathiolane | 1.25 | 85 | [15] |
| 2 | 4-Nitrobenzaldehyde | 2-(4-Nitrophenyl)-1,3-oxathiolane | 0.25 | 97 | [14] |
| 3 | 4-Chlorobenzaldehyde | 2-(4-Chlorophenyl)-1,3-oxathiolane | 0.5 | 93 | [14] |
| 4 | 4-Bromobenzaldehyde | 2-(4-Bromophenyl)-1,3-oxathiolane | 0.5 | 90 | [19] |
| 5 | 4-Methylbenzaldehyde | 2-(4-Methylphenyl)-1,3-oxathiolane | 0.5 | 87[d] | [14] |
| 6 | 4-Methoxybenzaldehyde | 2-(4-Metoxyphenyl)-1,3-oxathiolane | 0.75 | 83[d] | [14] |
| 7 | 2-Naphthaldehyde | 2-(Naphthalen-6-yl)-1,3-oxathiolane | 0.5 | 80 | [20] |
| 8 | Acetophenone | 2-Methyl-2-phenyl-1,3-oxathiolane | 1.25 | 50[d] | [17] |
| 9 | Cinnamaldehyde | 2-Styryl-1,3-oxathiolane | 1.16 | 90 | [16] |
| 10 | 4-Acetylbenzaldehyde | 1-(4-(1,3-Oxathiolan-2-yl)phenyl)ethanone | 0.25 | 97 | [9] |
| 11 | Thiophene-2-carbaldehyde | 2-(2-Thienyl)-1,3-oxathiolane | 1.83 | 84 | [7] |
| 12 | Hexanal | 2-Pentyl-1,3-oxathiolane | 1 | 80 | [16] |
| 13 | 2-Heptanone | 2-(Heptan-2-yl)-1,3-oxathiolane | 1.5 | 80 | [16] |
| 14 | Cyclohexanone | Spiro[cyclohexane-1,2′-[1,3]oxathiolane] | 1 | 82 | [18] |
| 15 | Cyclopentanone | Spiro[cyclopentane-1,2′-[1,3]oxathiolane] | 1 | 80 | [18] |

[a] Reaction conditions: Benzaldehyde (1 mmol), 2-mercaptoethanol (1.2 mmol), NBSac (10 mol%), room temperature, $CH_2Cl_2$.
[b] The products characterized with $^1H$ and $^{13}C$ NMR.
[c] Yields refer to pure isolated products.
[d] With excess amount of 2-mercaptoethanol.

## 3. Conclusion

A novel and efficient procedure has been developed for synthesis of 1,3-oxathiolane derivatives from carbonyl compounds and 2-mercaptoethanol in the presence of catalytic amount of NBSac. Operational simplicity, low cost of the catalyst, high yield and excellent chemoselectivity reactions are the key features of this methodology.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2012.06.007.

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