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Oxathioacetalization, thioacetalization and transthioacetalization of carbonyl compounds by *N*-bromosuccinimide: selectivity and scope

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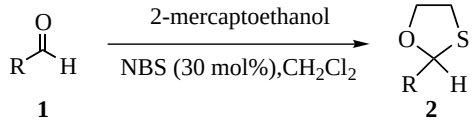
Abstract—Efficient oxathioacetalization, thioacetalization and transthioacetalization of carbonyl compounds have been achieved in high yields employing *N*-bromosuccinimide as a catalyst.

The protection of carbonyl compounds as acetals, dithioacetals and oxathioacetals is an important aspect of the total synthesis of complex natural products.[1] Among these, oxathioacetals and dithioacetals are important because they are considered more stable than the corresponding *O*,*O*-acetals under acidic conditions and are also useful in organic synthesis as acyl carbanion equivalents in C–C bond forming reactions.[2] Moreover, *S*,*S*-acetals can be used as intermediates for the conversion of the carbonyl function to the parent hydrocarbons. In view of the potential applications of 1,3-oxathiolanes and thiolanes, it is important to search for newer and efficient synthetic methodologies for the preparation of these compounds. In general they are prepared by protic or Lewis acid-catalyzed condensation of carbonyl compounds with 2-mercaptoethanol,[3–9] thiols and dithiols.[10] Transthioacetalization of acetals is a useful transformation for the preparation of S,*S*-acetals[11] and in comparison with thioacetalization of carbonyl compounds, it is a faster and cleaner reaction.

However, there are shortcomings in using acidic catalysts in the oxathioacetalization reaction of carbonyl compounds, such as long reaction times, reflux temperature, unwanted side reactions, inert atmosphere and activation of catalyst at high temperature. Although silicon reagents such as trimethylsilyltriflate[12] and triisopropyl silyltriflate[13] are more convenient and milder reagents for the formation of oxathiolanes; however, they are expensive and the yields are usually moderate. Furthermore, most of these methods show poor chemoselectivity with respect to the aldehydes and ketones and in the cases of multifunctional compounds like keto esters both transesterification and ketone protection has been observed. Very recently I_2[14] and $InCl_3$[15] have been described for thioacetalization and transthioacetalization, but these methods involve the use of corrosive reagents and high temperatures, respectively.



1 **2**

R = aryl, alkyl, alkenyl

Scheme 1.

In spite of a number of reports employing conventional catalysts for the protection of carbonyl compounds, the search for new catalysts is still actively pursued to address such problems as harsh reaction conditions and poor chemoselectivity. In addition, environmental and economic considerations have prompted us to redesign these commercially important processes. As a result, there is further scope to explore mild and efficient methods for oxathioacetalization and transthioacetalization. *N*-Bromosuccinimide (NBS) is an important reagent not only for bromination, but also for a range of other reactions.[16] Depending upon the nature of the reactant and reaction conditions in solution, NBS reacts differently with many organic compounds and recently, we have reported dithioacetalization of carbonyl compounds using NBS.[17]

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In this communication, we wish to report a mild and highly chemoselective procedure for the conversion of aldehydes and ketones into 1,3-oxathiolanes and transthioacetalization of acetals using catalytic amount of NBS. The reaction of benzaldehyde with 2-mercaptoethanol in the presence of 30 mol% NBS in dichloromethane gave the corresponding 1,3-oxathiolane derivative in 75% yield.[18] Similarly, various aldehydes selectively produced the corresponding 1,3-oxathiolanes in high yields (Scheme 1).

Table 1. Oxathioacetalization of carbonyl compounds

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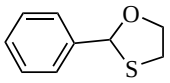
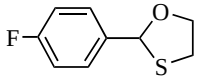
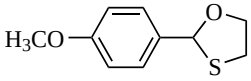
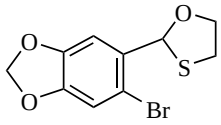
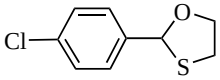
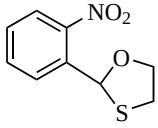
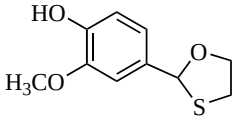
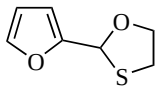
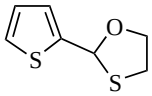
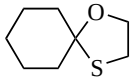
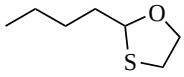
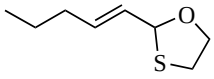
a		2.0	75
b		2.5	80
c		2.0	70
d		2.5	75
e		2.0	76
f		2.0	68
g		2.5	63
h		1.5	73
i		3.0	80
j		2.5	78
k		3.0	58
l		3.0	64

[a] All products were characterised by ^{1}H NMR, IR and mass spectroscopy.

[b] Isolated yields after column chromatography on silica gel.

The reaction proceeds smoothly at ambient temperature. It is observed that both activated and weakly activated aromatic aldehydes form oxathioacetals in good to high yield, whereas in the case of aliphatic aldehydes the yields are good to moderate. The results are summarized in Table 1, which exhibits the scope and the generality of the reaction with respect to different, aromatic, aliphatic and alkenyl aldehydes. Moreover, this procedure is highly chemoselective, providing selective protection of an aldehyde in the presence of a ketone. In a representative example, an equimolar mixture of *p*-chlorobenzaldehyde and acetophenone when allowed to react with 2-mercaptoethanol and a catalytic amount of NBS (30 mol%) in dichloromethane yielded the 1,3-oxathiolane derivative of *p*-chlorobenzaldehyde whilst acetophenone was recovered as its corresponding alcohol after $NaBH_4$ reduction, thus illustrating the chemoselectivity of the present method (Scheme 2).

Further, the usefulness of this methodology has also been extended for the selective protection of an aliphatic ketone (cyclohexanone) in the presence of an aromatic ketone (acetophenone) (Scheme 3). Ketones such as acetophenone and benzophenone, did not produce the oxathioacetals even after prolonged reaction times (4–5 h).

It is interesting to note that by employing NBS we have been able to protect selectively the keto group in keto esters without transesterification (Scheme 4).

In a similar manner an efficient thioacetalization and transthioacetalization of *O*,*O*-acetals using NBS (15 mol%) in dichloromethane has been achieved as shown in Table 2 and Scheme 5.

The high chemoselectivity of the method has also been demonstrated by a competitive reaction between the acetal of an aldehyde and a ketone (Scheme 6).

The role of NBS is not clear but a plausible explanation is that NBS reacts first with the 2-mercaptoethanol and thiol to generate HBr, which may activate the carbonyl group for further reaction. However, the possibility of NBS generating Br_2 cannot be ruled out.

In conclusion, both aromatic and aliphatic aldehydes have been converted to their corresponding oxathioacetals, thioacetals and dithioacetals employing NBS as a catalyst under extremely mild and almost neutral conditions. Moreover, the high chemoselectivity, good to high yields, and short reaction times makes the present method a practical protocol for oxathioacetalization and transthioacetalization processes.

Acknowledgements

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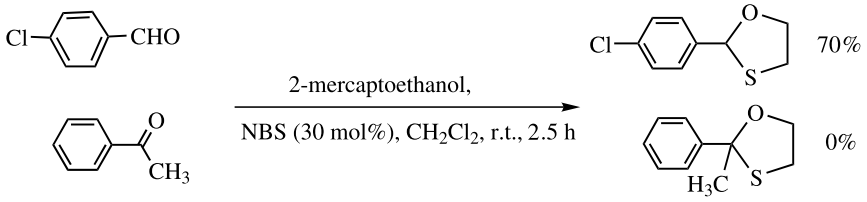
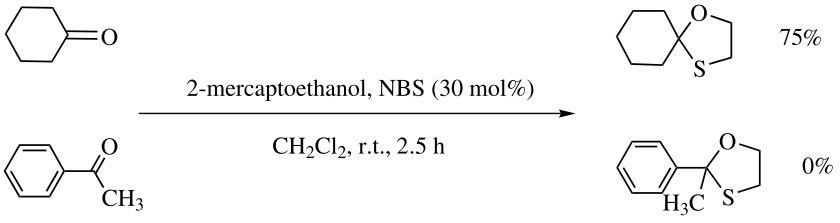
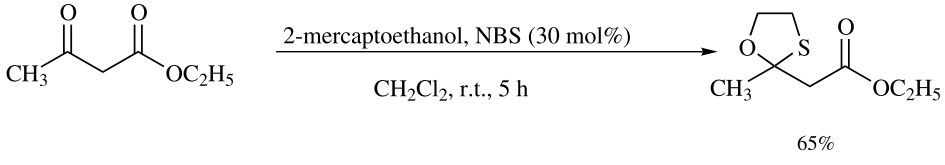


Scheme 2.



Scheme 3.



Scheme 4.

Table 2. Thioacetalization and transthioacetalization of carbonyl compounds

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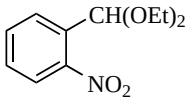
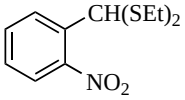
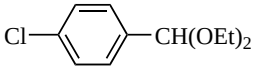
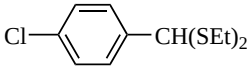
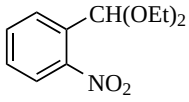
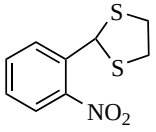
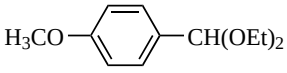
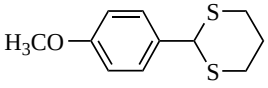
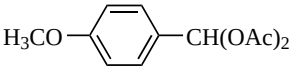
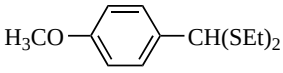
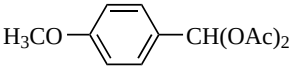
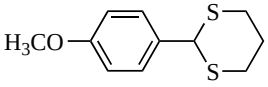
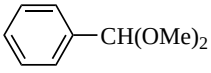
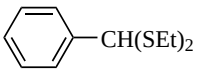
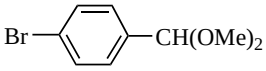
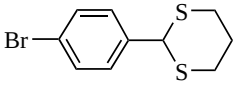
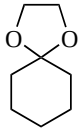
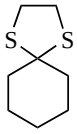
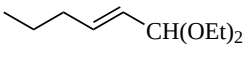
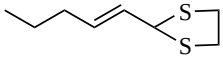
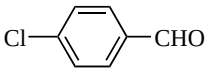
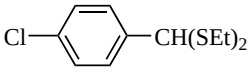
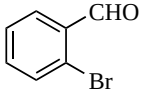
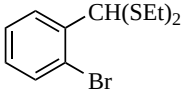
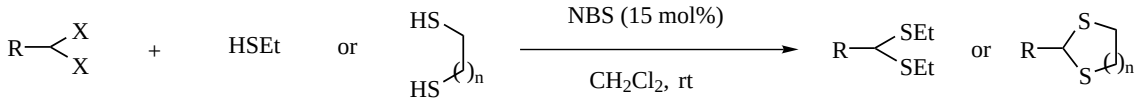
a			10	91
b			12	87
c			15	90
d			10	78
e			10	90
f			20	75
g			20	85
h			20	73
i			15	80
j			25	57
k			20	85
l			25	79

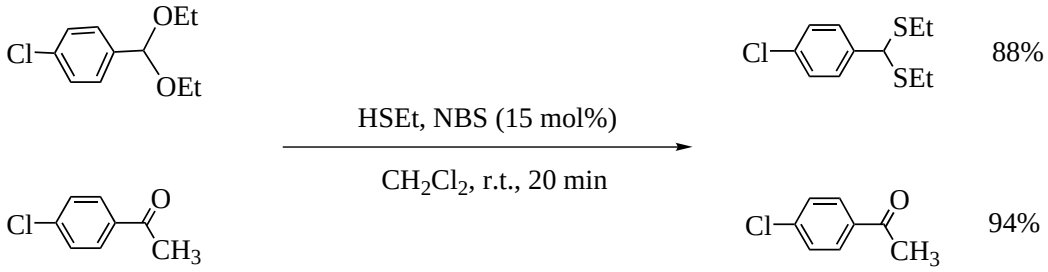
[a]All products were characterised by ^{1}H NMR, IR and mass spectroscopy.

[b]Isolated yields after column chromatography on silica gel.



R = aryl, allyl, cyclohexyl; X = OMe, OEt, OAc ;XX =O; n = 1,2

Scheme 5.



Scheme 6.

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18. **Typical experimental procedure**: To a stirred solution of NBS (30 mol%) and the appropriate aldehyde (1 mmol) in dichloromethane (10 ml) at room temperature was added 2-mercaptoethanol (1.5 mmol). The mixture was stirred at room temperature for the appropriate time (see Table 1). After completion of the reaction as indicated by TLC, the organic solution was washed with aqueous 2N NaOH, extracted with dichloromethane, dried (Na_2SO_4) and concentrated in vacuum and the crude product was purified by silica gel column chromatography to furnish the corresponding 1,3-oxathiolanes. Spectroscopic data for oxathioacetals; Compound **d**: ^{1}H NMR (200 MHz; $CDCl_3$): $\delta=3.16$ (m, 2H), 3.90 (m, 1H), 4.50 (m, 1H), 5.95 (s, 2H), 6.10 (s, 1H), 6.95 (s, 1H), 7.05 (s, 1H). Compound **e**: $\delta=3.20$ (m, 2H), 3.90 (m, 1H), 4.45 (m, 1H), 6.00 (s, 1H), 7.22 (d, 2H, $J=8.2$ Hz), 7.35 (d, 2H, $J=8.2$ Hz). Compound **h**: $\delta=3.05$–3.12 (m, 2H), 4.00 (m, 1H), 4.20 (m, 1H), 6.02 (s, 1H), 6.25 (dd, 1H, $J=3.6$ Hz), 6.40 (d, 1H, $J=3.6$ Hz), 7.40 (d, 1H, $J=1.7$ Hz). Compound **J**: $\delta=1.05$–1.50 (m, 4H), 1.52–1.90 (m, 6H), 2.85 (t, 2H, $J=6.6$ Hz), 4.00 (t, 2H, $J=6.6$ Hz). Spectroscopic data for thioacetals and dithioacetals; Compound **a**: ^{1}H NMR (200 MHz; $CDCl_3$): $\delta=1.20$–1.40 (m, 6H), 2.45–2.80 (m, 4H), 5.65 (s, 1H), 7.25 (dd, 1H, $J=7.4$ Hz), 7.40 (dd, 1H, $J=7.4$ Hz), 7.80 (d, 1H, $J=7.4$ Hz), 7.95 (d, 1H, $J=7.4$ Hz). Compound **d**: $\delta=1.85$–2.00 (m, 1H), 2.10–2.20 (m, 1H), 2.80–3.10 (m, 4H), 3.70 (s, 3H), 5.10 (s, 1H), 6.80 (d, 2H, $J=7.3$ Hz), 7.30 (d, 2H, $J=7.3$ Hz). Compound **i**: $\delta=1.40$ (m, 2H), 1.60 (m, 4H), 2.00 (m, 4H), 3.25 (s, 4H). Compound **k**: $\delta=1.20$–1.30 (t, 6H), 2.45–2.70 (m, 4H), 4.90 (s, 1H), 7.30 (d, 2H, $J=8.1$ Hz), 7.40 (d, 2H, $J=8.1$ Hz).