Microwave-mediated Efficient Protection of Carbonyl Compounds as 1,3-Oxathiolanes in the Presence of Iodine under Solvent Free Condition

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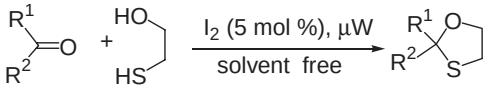
A mild, efficient, and solvent free protocol for conversion of aldehydes and ketones into their corresponding 1,3-oxathiolanes using 2-mercaptoethanol in the presence of catalytic amount of elemental iodine is reported.

Protection and deprotection of reactive functional groups in organic compounds are very important strategies in multistep organic synthesis.[1] Besides choosing the right protecting group with optimum stability, selection of mild, and efficient catalyst to affect these protection and deprotection also plays a pivotal role in dictating the efficiency of a particular reaction protocol. The anonymity in choosing the right catalyst with optimum efficiency is being considered as one of the driving forces for the synthetic chemists in their thrives for better reaction strategies leading to ascending demands for newer discoveries.

Protection of carbonyl compounds as 1,3-oxathiolanes[1] is one of the most important protocols in organic synthesis because of their easy introduction, greater stability towards acidic media as compared to *O*,*O*-acetals and easier deprotection as compared to corresponding *S*,*S*-acetals.[2] Nonetheless, the oxathioacetals find application as important starting materials for stereoselective synthesis of tertiary α-hydroxy aldehydes, α-hydroxy acids and glycols, where they behave as acyl equivalent in the carbon–carbon bond-forming reactions.[3] Although the protection of carbonyls as 1,3-oxathiolanes can be accomplished by using HCl,[4] $HClO_4$,[5] $BF_3 \cdot Et_2O$,[6] TMSCl–NaI,[7] *p*-TsOH,[8] $LiBF_4$,[9] $BF_3 \cdot Et_2O$–$CaCl_2$,[10] Bu_4NBr_3,[11] TMSOTf,[12] *i*-Pr_3SiOTf,[13] SO_2,[14] $ZnCl_2$–Na_2SO_4,[15] $ZrCl_2$,[16] $[(dppb)Pt(m\text{-}OH)]_2(BF_4)_2$–$Mg(ClO_4)_2 \cdot 2H_2O$,[17] polystyryldiphenylphosphonium iodide,[18] natural kaolinitic clay,[19] KSF,[20] Amberlyst-15,[21] PPA on silica,[22] $Yb(OTf)_3$ in ionic liquid,[23] bromodimethylsulphonium bromide,[24] and Fe(III) flouride[25] many of them suffers from the difficulties such as longer reaction time, harsh reaction condition, incompatibility with acid sensitive functional groups, removal of azeotropic mixture, use of dehydrating reagent, involvement of expensive and moisture sensitive catalysts, etc.

Organic reactions under solvent free condition[26] have increasingly become popular from the viewpoint of Green chemistry.[27] In recent times, microwave-accelerated reactions under solvent free conditions are getting increasing attention.[28] Therefore, efforts are being made to find a reagent system that would be environmentally benign and clean and yet mild, efficient, selective, operationally simple, and cost effective. Herein, we wish to report an efficient method for protection of aldehyde and ketones as 1,3-oxathiolanes by reaction with 2-mercaptoethanol in presence of catalytic amount of molecular iodine (Scheme 1). Although the reaction gives almost similar yield on heating with acetonitrile, microwave irradiation at power 100 W, and in the absence of any solvent visibly reduces the reaction time and the amount of iodine required.[29]



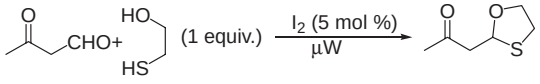
Scheme 1.

The efficiency of our method has been demonstrated through the results documented in the Table 1. It has been observed that both aliphatic and aromatic aldehydes (Entry 1–11) give reasonably good yield of 1,3-oxathiolanes except the citral (Entry 7), in which case, significant amount of an unidentified by-product was formed besides the desired product. Both cyclic and acyclic ketones (Entry 12–20) gave very good yield of the desired 1,3-oxathiolanes except the benzophenone (Entry 18) where in spite of giving 20 min reaction time with 5.0 equivalents of 2-mercaptoethanol could resulted only 30% of its 1,3-oxathiolane derivative. The fact that *m*-acetoxybenzaldehyde (Entry 10) and 2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (Entry 11) generate their corresponding oxathiolanes in very good yields suggest that under this condition acid-sensitive functional groups remain unaffected. Shi's Ketone (Entry 21) was recovered intact even after 8 h of reaction.

The substrate catalyst ratio was determined by studying the extent of conversion, when *p*-chlorobenzaldehyde was treated with 2-mercaptoethanol in the presence of different[30] amount of iodine. In order to study the chemoselectivity of our method, 3-oxobutanal was treated with 2-mercaptoethanol (1 equiv.) under similar reaction condition for 1 h. It was observed that the aldehyde group was protected as 1,3-oxathiolane in preference to the ketonic functionality (Scheme 2).

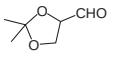
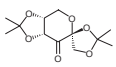
Typically, a mixture of methyl acetoacetate (0.232 g, 2 mmol), 2-mercaptoethanol (0.234 g, 3 mmol), and iodine (0.026 g, 0.1 mmol) was taken in a 50 mL oven-dried Erlen-Meyer flask and irradiated with microwave at 100 W. After 4 min, the reaction was quenched by adding 5% aqueous $Na_2S_2O_3$ solution (5 mL) and extracted with diethyl ether (3×25 mL). The ethereal layer was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (2% ethyl acetate in hexane) to get the pure product in 80% (0.282 g, 1.6 mmol) yield (Entry 19). IR (neat, cm^{-1}): 1045, 1735; ^1H NMR (400 MHz, $CDCl_3$): δ 1.78 (s, 3H), 2.92 (s, 2H), 3.07 (t, $J = 5$ Hz, 2H), 3.67 (s, 3H), 4.18 (t, $J = 5$ Hz, 2H); MS: m/z 176, 161, 117, 103, 85, 69, 59.

In contrast to the previous methods, which required stoichiometric amount of the catalyst,[10,14,15,18] in our method only 5 mol % is enough for completion of the reaction. Moreover,



Scheme 2.

Table 1. Iodine-catalyzed formation of 1,3-oxathiolanes

Entry	Substrate	Reaction time /min[a]	Yield /%[b]
1	PhCHO	3	83
2	*p*-$CH_3C_6H_4CHO$	3	81
3	*p*-ClC_6H_4CHO	3	84
4	*p*-$NO_2C_6H_4CHO$	3	87
5	*p*-OH C_6H_4CHO	5	73
6	*p*-$OMeC_6H_4CHO$	3	89
7	Citral	5	59[c]
8	*n*-Octanal	5	82
9	*m*-$(CO_2Me)C_6H_4CHO$	3	86
10	*m*-AcO C_6H_4CHO	3	91
11		4	80
12	*p*-Bromoacetophenone	4	92
13	Acetophenone	5	81
14	Cyclohexanone	3	95
15	Cyclopentanone	3	92
16	Menthone	3	86
17	Carvone	4	76
18	Benzophenone	20	30[d]
19	Methyl acetoacetate	4	80
20	Cholestanone	5	78
21		10	NR[e]

[a]Microwave irradiation was done with Samsung microwave, Model-1630N keeping the power at 100 W. [b]Yield of the pure isolated product. [c]Another unidentified product was observed. [d]5.0 equiv. of 2-mercaptoethanol was used. [e]NR = No reaction.

neither the azeotropic removal of water[4a,8a–8c,14] nor the use of dehydrating agent[10,15,17] is necessary in our methodology.

In conclusion, we have reported an efficient, simple straightforward, and chemoselective protocol for the synthesis of 1,3-oxathiolanes from carbonyl compounds using iodine. Non-requirement of solvent, dehydrating agent, anhydrous atmosphere, and tedious removal of water during the reaction and the compatibility of the catalyst with acid sensitive fuctional groups such as acetyl, nitro, methoxy, carbomethoxy, 1,3-dioxolane, etc. may work wonder in multistep synthesis.

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29 When *p*-chlorobenzaldehyde in acetonitrile was treated with 2-mercaptoethanol in the presence of 2 mol % I_2 at room temperature, reaction did not complete even after 24 h and gave only 46% yield, while use of 5 mol % I_2 gave 75% yield after 8 h. Use of 10 mol % of I_2 gave 85% of the desired product within half an hour.
30 2 mol % iodine could not complete the reaction even after 10 min and gave only 52% yield, while 10 mol % iodine does not reduce the reaction time than the use of 5 mol % iodine, where the conversion was complete within 3 min to give 84% of the desired product.

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