Organic reactions in aqueous media: I_2-in-water-catalysed rapid and chemoselective oxathioacetalisation of aldehydes under mild conditions

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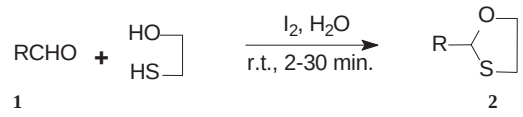
I_2 in water is found to be an efficient catalyst for the chemoselective protection of both aliphatic and aromatic aldehydes as 1,3-oxathioacetals under mild conditions. Fast reactions and excellent yields of pure products using an inexpensive and easily available catalyst and solvent are important features of this method.

Keywords: I_2 in water, oxathioacetalisation, organic reactions in aqueous media, aldehydes, chemoselectivity

Acetals, dithioacetals and oxathioacetals are the most commonly used protecting groups for aldehydes and ketones in the multi-step synthesis of many natural products.[1] Among these various protecting groups, oxathioacetals and also dithioacetals are versatile[2] because of their ease of formation / removal and also their stability under a variety of reaction conditions. In addition to carbonyl protection, they behave as masked acyl anions[3] or masked methylene functions[4] in carbon–carbon bond-forming reactions. Generally oxathioacetals are prepared by condensation of carbonyl compounds with 2-mercaptoethanol using strong protic[5] or Lewis acids[6] as catalysts, but these procedures are often accompanied by long reaction times, unsatisfactory yields and the use of stoichiometric amounts of catalysts. Even though silicon reagents such as trimethylsilyl triflate,[7a] and triisopropylsilyl triflate[7b] are found to be efficient catalysts for this conversion, there are still some limitations including expensive catalysts, strongly acidic conditions and moderate yields of products. Furthermore, very few methods have been reported for the chemoselective protection of aldehydes in the presence of ketones.

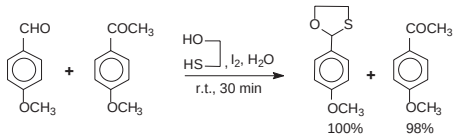
The problem can be somewhat circumvented by using recently reported catalysts such as perchloric acid,[8] $LiBF_4$,[9] organic ammonium tribromide[10] and zirconium tetrachloride.[11] Lack of chemoselectivity, strongly acidic conditions and moderate yields in case of aliphatic aldehydes and aromatic aldehydes with electron-withdrawing substituents are limitations associated with perchloric acid catalyst. Though $LiBF_4$ and tetrabutyl ammonium tribromide are mild and neutral catalysts for oxathiacetalisation, the former catalyst is expensive whereas the latter is not chemoselective for the protection of aldehydes in the presence of ketones. In the case of both catalysts, aldehydes containing electron-withdrawing groups in the aromatic ring take longer reaction times giving low yields as compared with electron-rich counterparts. Zirconium tetrachloride is also an efficient and chemoselective catalyst for the conversion of carbonyl compounds into 1,3-oxathiolanes. However, an excess of reagent, 2-mercaptoethanol (> 3 equivalents), is required for complete conversion of substrates into the corresponding oxathioacetals. Consequently, what is needed is a methodology that is mild, often environmentally benign and yet efficient, chemoselective, operationally simple and cost effective.

In an endeavour gradually to change current working practices to greener alternatives and satisfy environmental demands,[12] an environmentally favourable protocol for the preparation of organic compounds is required. Where a solvent must be used, water is the most acceptable in terms of cost and environmental impact. However, despite its large liquid range and extremely high specific heat capacity, it is frequently overlooked as a solvent for organic reactions.[13] Efforts to carry out organic reactions in water[13] pose an important challenge in the area of reaction design. Literature reports reveal that no catalyst is reported for the oxathioacetalisation of carbonyl compounds in aqueous media. We now report I_2 in water as an efficient chemoselective catalyst for highly rapid oxathioacetalisation of aldehydes in the presence of ketones in quantitative yields under mild conditions (Scheme 1). The results summarised in Table 1 show the scope and generality of the reaction. The reaction of *p*-anisaldehyde with 2-mercaptoethanol in the presence of 10% I_2 in water gave the 1,3-oxathiolane derivative in 100% yield. Similarly various aliphatic, aromatic, heterocyclic and α-β-unsaturated aldehydes were selectively converted into the corresponding oxathioacetals in quantitative yields. The reactions completed smoothly within a short time at room temperature under mild conditions. The procedure is highly chemoselective and provides selective protection of aldehydes in the presence of ketones (equation (1))



1 2

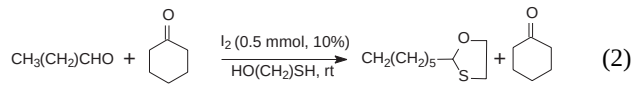
Scheme 1



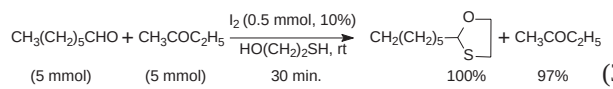
(1)

When a mixture of *p*-anisaldehyde (5 mmol) and *p*-methoxyacetophenone (5 mmol) was allowed to react with 2-mercaptoethanol (5 mmol) in the presence of I_2 (0.5 mmol, 10%) in water, *p*-anisaldehyde was selectively converted into the corresponding oxathioacetal derivative in quantitative yield whereas *p*-methoxyacetophenone was recovered.

Similarly the following examples illustrate the chemoselective oxathioacetalisation of aldehydes in the presence of ketones (equations (2–4)).



(2)



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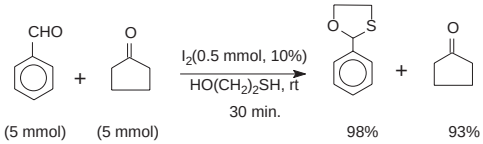

(4)

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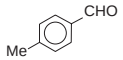
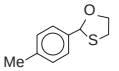
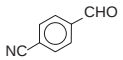
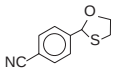
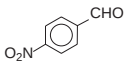
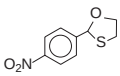
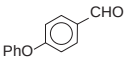
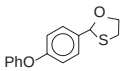
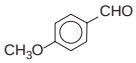
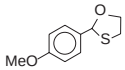
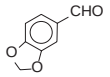
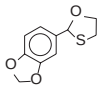
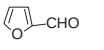
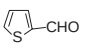
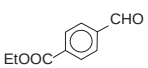
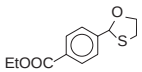
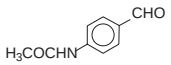
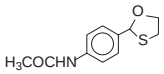
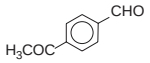
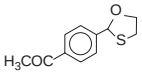
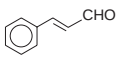
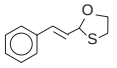
Table 1 I_2 in water catalysed oxathioacetolization of aldehydes

Entry	Substrate	Product	Reaction time/min	Yields/%[a,b]
a	$CH_3(CH_2)_2CHO$	$CH_3(CH_2)_2CH$	3	99
b	$CH_3(CH_2)_4CHO$	$CH_3(CH_2)_4CH$	2	98
c			15	98
d			10	90
e			25	98
f			25	99
g			10	99
h			10	100
i			10	99
j			30	98
k			20	99
l			15	98
m			20	97
n			15	99
o			5	99

[a]Yields of pure isolated products [b]Products are characterised by IR, ^{1}H NMR, elemental analysis and comparison with authentic samples.

Furthermore, the chemoselectivity of the present method was also observed in the case of ester aldehydes, amide aldehydes and keto aldehydes (Table 1, entries 12–14). Acid sensitive substrates like furfural (Table 1, entry 10) are also protected as 1,3-oxathiolanes in excellent yield (98%) without the formation of the side products which are normally encountered under acidic conditions. The tolerance of various functional groups under the present conditions have been examined by reacting substrates bearing ester, amide, OH, CN, OMe, OPh, methylenedioxy, nitro and olefinic groups and it was found that reaction conditions are compatible with these functional groups.

The superiority of this procedure as compared to recently reported ones[9,10] is clearly illustrated by the oxathioacetalisation of aldehydes containing electron-withdrawing groups in an aromatic ring which required a very short time to afford excellent yields of products. The presence of electron-donating and electron-withdrawing groups on the aromatic ring of aldehydes does not make any difference in this oxathioacetalisation. However aliphatic *e.g.* 2-butanone, cyclic e.g. cyclopentanone and aromatic ketones, *e.g.* 4-chloroacetophenone did not yield a trace amount of corresponding oxathioacetal even after stirring the mixture for a longer time (12 h) under the present reaction conditions. This gives the selectivity to protect the carbonyl group of an aldehyde, leaving the carbonyl group of a ketone free for further manipulation.

In conclusion, the present procedure for oxathioacetalisation of aldehydes is an attractive and alternative to the existing one due to its greater selectivity, operational simplicity, excellent yields in a very short reaction time, easy work-up and mild reaction conditions involving an inexpensive and easily available catalyst and solvent.

Experimental

*General procedure***:** A mixture of iodine (0.5 mmol) in water (10 ml), 2-mercaptoethanol (5 mmol) and aldehyde (5 mmol) was stirred for 10 min. at room temperature. After completion of reaction (TLC, petroleum ether : ethyl acetate = 8:2) , the mixture was filtered and the solid product was washed with water and aqueous sodium thiosulfate. The dried product was in almost pure form. If necessary it was further purified by recrystallisation from petroleum ether. Pure liquid products are obtained by usual extraction with ethyl acetate followed by column chromatography (petroleum ether : ethyl acetate = 8:2).

2a: IR ($CHCl_3$), 2958, 2873,1462, 1377,1103,1018,726 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.72 (t, 1 H, CH), 4.36 (m, 1 H), 3.71 (m, 1 H), 2.89 (m, 1 H), 2.80 (m, 1 H), 1.3–1.5 (m, 4 H), 0.9 (t, 3 H, CH_3). Anal.calc for : $C_6H_{12}OS$; C, 54.50 %; H, 9.14 % ; S, 24.25 %. Found : C, 54.34 % ; H, 9.09 %; S, 24.20 %.

2b: IR ($CHCl_3$), 2958, 2928,1614, 1444,1377,1280,1176, 1115, 1018, 836, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.55 (t, 1 H, CH), 3.81 (m, 1 H), 3.71 (m, 1 H), 3.64 (m, 1 H), 2.82 (m, 1 H), 1.1–1.7 (m, 8 H, CH_2), 0.71 (t, 3 H, CH_3). Anal.calc for : $C_8H_{16}OS$; C, 59.94 %; H, 10.06 % ; S, 20.00 %. Found : C, 59.76 % ; H, 9.98 %; S, 24.11 %

2c: Spectroscopic data are in agreement with previously reported.[14]

2d: IR ($CHCl_3$), 3420 (-OH), 2970, 2934, 1608,1511,1468,1261, 1097, 848, 763, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.96 (s, 1 H, OH), 7.31–7.42 (m, 4 H, Ar–H), 5.97 (s, 1 H, CH), 4.40 (m, 1 H), 3.61 (m, 1 H), 3.17 (m, 1H), 2.98 (m, 1 H). Anal.calc for : $C_9H_{10}O2S$; C, 59.31 %; H, 5.53 % ; S, 17.59 %. Found : C, 59.18 % ; H, 5.48 %; S, 17.71 %.

2e: IR ($CHCl_3$), 2988, 2964, 2861, 2228 (-CN),1614,1462,1377, 1231, 1158, 1024, 824, 763 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.34 (d, 2 H, *J*=8.2 Hz, Ar–H), 7.21 (d, 2 H, *J*=8.2 Hz, Ar–H), 6.15 (s, 1 H, CH), 4.51 (m, 1 H), 4.12 (m, 1 H), 3.81 (m, 1 H), 3.52 (m, 1 H). Anal.calc for : $C_{10}H_9NOS$; C, 62.8 %; H, 4.74 % ; N, 7.32 % ; S, 16.76 %. Found : C, 62.69 % ; H, 4.70 %; N, 7.34 % ; S, 16.69 %.

2f: IR ($CHCl_3$), 3001, 2928, 1602, 1505, 1413, 1270, 1158, 1091, 842, 744, 684 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.35 (d, 2 H, *J*=8.4 Hz, Ar–H), 7.22 (d, 2 H, *J*=8.4 Hz, Ar–H), 6.10 (s, 1 H, CH), 4.45 (m, 1 H), 3.90 (m, 1 H), 3.8 (m, 1H), 3.62 (m, 1 H). Anal.calc for : $C_9H_9NO_3S$; C,51.17 %; H, 4.28 % ; N, 6.63 % ; S, 15.17 %. Found : C, 51.00 % ; H, 4.18 %; N, 6.70 % ; S, 15.08 %.

2g: IR ($CHCl_3$), 3011, 2924, 1608, 1602, 1578, 1324, 1234, 1126, 1042, 744, 684 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.8–8.1 (m, 5 H, Ar–H), 7.72 (d, 2 H, *J*=8.3 Hz, Ar–H), 7.61 (d, 2 H, *J*=8.3 Hz, Ar–H), 6.12 (s, 1 H, CH), 4.51–4.72 (m, 4 H). Anal.calc for : $C_{15}H_{14}O_2S$; C ,69.73 %; H, 5.46 % ; S, 12.41 %. Found : C, 69.52 % ; H, 5.40 % ; S, 12.38 %.

2h: IR ($CHCl_3$), 3104, 3019, 2922, 1681, 1614, 1493, 1249, 1219, 1109, 1036, 921, 884 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.2 (d, 2 H, *J*=7.8 Hz, Ar–H), 6.8 (d, 2 H, *J*=7.8 Hz, Ar–H), 6.00 (s, 1 H, CH), 4.40 (m, 1 H), 3.8 (m, 1 H), 3.76 (s, 3 H, OCH_3), 3.68–3.73 (m, 2 H). Anal.calc for : $C_{10}H_{12}O_2S$; C,61.19 %; H, 6.16 % ; S, 16.33 %. Found : C, 61.04 % ; H, 6.21 %; S, 16.33 %.

2i: Spectroscopic data are in agreement with previously reported.[16]

2j: IR ($CHCl_3$), 3055, 2964, 1687, 1578, 1505, 1456, 1280, 1128, 1018, 775, 647 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.40 (d, 1 H, *J*=1.7 Hz, Ar–H), 6.40 (d, 1 H, *J*=3.6 Hz, Ar–H), 6.25 (dd, 1 H, *J*=1.7 Hz, *J*=3.6 Hz, Ar–H.), 6.02 (s, 1 H, CH), 4.21 (m, 1 H), 4.10 (m, 1 H), 3.05–3.12 (m, 2 H). Anal.calc for : $C_7H_8O_2S$; C,53.82 %; H, 5.16 % ; S, 20.52 %. Found : C, 53.91 % ; H, 5.08 %; S, 20.71 %.

2k: Spectroscopic data are in agreement with previously reported.[15]

2l: IR ($CHCl_3$), 3043, 2922, 1742 (C=O), 1614, 1608, 1450, 1273, 1176, 1018, 842, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.10 (d, 2 H, *J*=8.1 Hz, Ar–H), 7.91 (d, 2 H, *J*=8.1 Hz, Ar–H), 6.71 (s, 1 H, CH), 4.61 (q, 2 H, CH_2), 4.48 (t, 3 H, CH_3), 3.6–3.9 (m, 4 H). Anal.calc for : $C_{12}H_{14}O_3S$; C,75.33; H, 7.37 ; S, 16.76 %. Found : C, 75.28 ; H, 7.25; S, 16.64 %.

2m: IR ($CHCl_3$), 3402 (NH), 3143, 2925, 1680 (C=O), 1611, 1608, 1424, 1263, 1173, 1018, 842, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.2–7.3

(m, 4 H, Ar–H), 6.10 (s, 1 H, CH), 5.6 (s, 1 H, NH), 4.40 (m, 1 H.), 4.00 (m, 1 H), 3.68–3.80 (m, 2 H), 2.81 (s, 3 H, $COCH_3$). Anal.calc for : $C_{10}H_{13}NO_2S$; C, 56.84 %; H, 6.20 % ; N, 6.62 % ; S, 15.17 %. Found : C, 56.88 % ; H, 6.15 %; N, 6.59 % ; S, 15.00 %.

2n: IR ($CHCl_3$), 3043, 2928, 1734 (C=O), 1610, 1602, 1421, 1261, 1162, 1018, 842, 728 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.8 (d, 1 H, *J*=7.9 Hz, Ar–H), 7.51 (d, 1 H, *J*=7.9 Hz, Ar–H), 6.8 (s, 1 H, CH), 3.70–3.8 (m, 4 H.), 2.6 (s, 3 H, $COCH_3$). Anal.calc for : $C_{11}H_{12}O_2S$; C, 63.17 %; H, 6.19 %; S, 23.04 %. Found : C, 63.01 % ; H, 6.04 %; S, 22.81 %.

2o: Spectroscopic data are in agreement with previously reported.[16]

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