Iodine Catalyzes Efficient and Chemoselective Thioacetalization of Carbonyl Functions, Transthioacetalization of *O,O*- and *S,O*-Acetals and Acylals

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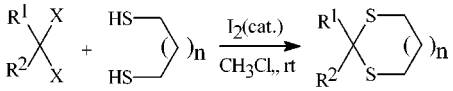
Introduction

Protections of carbonyl groups as thioacetals are quite often a necessary requirement in the synthesis of multifunctional organic molecules.[1] Thioacetals are quite stable toward a wide variety of reagents[2] and are also useful in organic synthesis as acyl carbanion equivalents[2] in C−C bond-forming reactions. Moreover, *S,S*-acetals could be used as intermediates for the conversion of the carbonyl function to the parent hydrocarbons.[3] In general, *S,S*-acetals are prepared by protic or Lewis acid catalyzed condensation of carbonyl compounds with thiols and dithiols.[1,4] Dithioacetalization has also been reported in a 5 M ethereal solution of $LiClO_4$ (LPDE)[5] and some other supported reagents.[6] Transthioacetalization of acetals is a useful transformation for the preparation of *S,S*-acetals[7] and, in comparison with thioacetalization of carbonyl compounds, is a faster and cleaner reaction.

Scheme 1



R^1 = aryl, alkyl,cinnamyl, ferrocenyl, R^2= H, alkyl
X = -OMe, -OEt, -OAc, XX =O, $-O(CH_2)_3O-$,
$-O(CH_2)_2S-$, $-(OCH_2)_2C(CH_2O)_2-$, n= 0, 1

Very recently we have introduced silica chloride as an efficient catalyst for this purpose.[8]

However, some of the reported methods require long reaction times, stoichiometric use of expensive reagents, and harsh reaction conditions and sometimes give poor selectivity when applied to the mixture of aldehydes and ketones.

A literature survey shows that iodine (I_2) has been used for transformation of aldehydes into acylals,[9a] alcoholysis, hydrolysis and acetolysis of epoxides and thiiranes,[9b] deprotection of thioacetals,[9c] and thioketalization of carbonyl compounds.[9d] In this paper, we report that I_2 catalyzes transformation of aromatic and aliphatic aldehydes and ketones, *O,O*-acetals, *O,O*-ketals, *O,S*-acetals, and acylals to their thioacetals in excellent yields at room temperature (Scheme 1, Table 1). The reactions could be performed in different organic solvents such as $CHCl_3$, CH_2Cl_2, benzene, and *n*-hexane efficiently. Due to the more solubility of the substrates and higher rates of the reactions, $CHCl_3$ was chosen as the solvent. It should be pointed out that in the absence of iodine the reactions did not proceed in $CHCl_3$ even after prolonged reaction times.

As shown in Table 1, various types of aromatic aldehydes with electron-donating and electron-withdrawing groups were cleanly and rapidly converted to the corresponding dithianes and dithiolanes in the presence of 10 mol % of I_2 (entries 1a−m). Aliphatic and α,β-unsaturated aldehydes were also thioacetalized in good yields (entries 1n−q). However, aromatic and aliphatic ketones were slowly converted to their corresponding *S,S*-acetals (entries 1hh−ll). Transthioacetalization of *O,O*-acetals, *O,O*-ketals, *O,S*-acetals and acylals was also achieved efficiently with a catalytic amount of I_2 to afford the corresponding *S,S*-acetals in high yields (entries 1r−bb,-ff,gg). Diacetals of 2,2-bis(hydroxymethyl)-1,3-propanediol were also efficiently converted to their dithianes and dithiolanes (entries 1cc−ee). Side product formation was not observed in the reactions we have studied.We have also used supported iodine on polyvinylpyridine (PVP) for this purpose.[9b] Our results showed that the supported iodine works also efficiently as a catalyst for the above functional group interconversions. High chemoselectivity of the method is demonstrated by competetive reactions between an aldehyde and a ketone, a ketal and a ketone,

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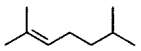
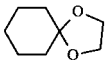
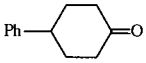
Table 1. Thioacetalization of Carbonyl Functions, Transthioacetalization of *O,O*- and *S,O*-Acetals and Acylals Catalyzed by I_2 in $CHCl_3$ at Room Temperature

Entry	R^1	R^2	X or XX	n	Time (min)	Yield[a] (%)
1a	Ph	H	O	0	10	95
1b	Ph	H	O	1	10	95
1c	4-$(CH_3)C_6H_4$	H	O	0	5	96
1d	4-$(CH_3)C_6H_4$	H	O	1	5	94
1e	4-$(CH_3O)C_6H_4$	H	O	1	5	95
1f	3-$(CH_3)C_6H_4$	H	O	1	5	95
1g	2-$(CH_3O)C_6H_4$	H	O	1	5	94
1h	3-$(CH_3O)C_6H_4$	H	O	1	5	95
1i	2-$(OH)C_6H_4$	H	O	1	5	94[b,7c]
1j	4-$(Br)C_6H_4$	H	O	1	10	95[b]
1k	4-$(Cl)C_6H_4$	H	O	1	10	94
1l	4-$(NO_2)C_6H_4$	H	O	1	30	91
1m	2,4,6-$(CH_3)_3C_6H_2$	H	O	1	10	90[b]
1n	PhCH=CH	H	O	1	10	92
1o	$PhCH_2$	H	O	1	10	90
1p		H	O	1	10	93
1q	CH_3CH=CH	H	O	1	10	91
1r	Ph	H	OCH_3	1	10	94
1s	Ph	H	OCH_2CH_3	1	10	96
1t	CH_3	CH_3	OCH_3	0	15	95
1u	4-$(CH_3)C_6H_4$	H	$O(CH_2)_3O$	1	10	94
1v	4-$(Cl)C_6H_4$	H	$O(CH_2)_3O$	1	10	96
1w	4-$(CH_3O)C_6H_4$	H	$S(CH_2)_2O$	1	10	92
1x	4-$(CH_3)C_6H_4$	H	$S(CH_2)_2O$	0	10	91
1y	$PhCH_2CH_2$	CH_3	$O(CH_2)_3O$	1	120	89
1z	Ph	CH_3	$O(CH_2)_3O$	1	120	88
1aa				1	40	93
1bb				0	120	92[b]
1cc	PhCH=CH	H	$C(CH_2O)_4$	1	15	94[b]
1dd	4-$(CH_3O)C_6H_4$	H	$C(CH_2O)_4$	1	15	96[b]
1ee	4-$(Cl)C_6H_4$	H	$C(CH_2O)_4$	0	20	92
1ff	2-$(CH_3O)C_6H_4$	H	OAc	1	15	93[b]
1gg	4-$(Cl)C_6H_4$	H	OAc	1	30	92
1hh	3,4-$(CH_3O)_3C_6H_3$	CH_3	O	1	420	75
1ii	$PhCH_2$	CH_2CH_3	O	1	300	72
1jj				0	240	70
1kk	acetyl ferrocene			0	300	90

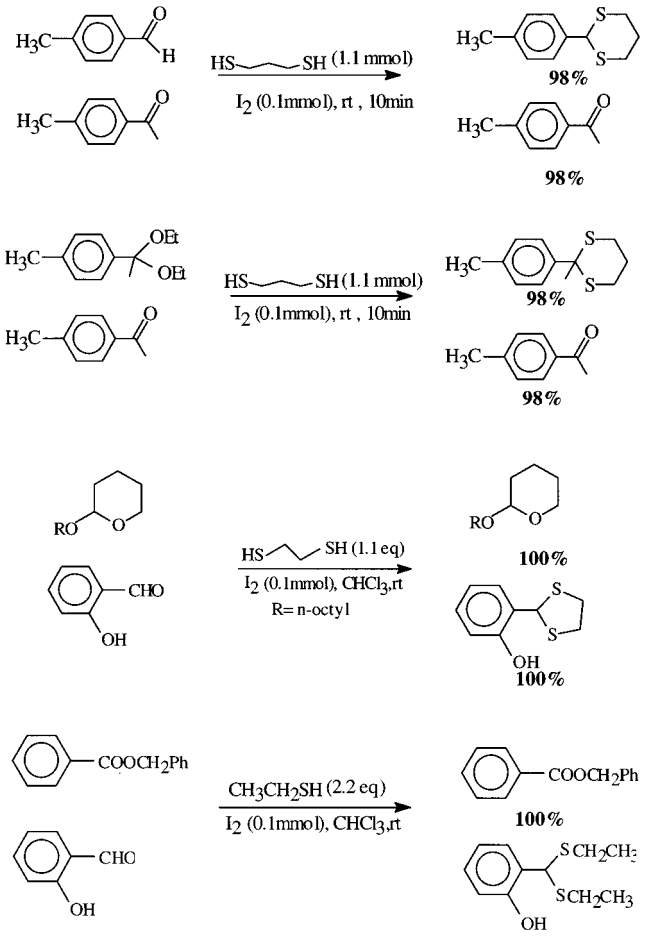
[a] The amount of iodine was 0.1 mmol per 1 mmol of substrate. [b] Spectral data of these compounds are given in ref 10.

an aldehyde and a THP ether and finally between an ester and an aldehyde (Scheme 2).

Conclusions

Aldehydes and ketones were protected as their thioacetals under mild reaction conditions in the presence of catalytic amount of iodine. Transthioacetalization reactions of *O,O*-acetals, *O,O*-ketals, *O,S*-acetals, and acylals were also easily achieved by using this catalyst. In addition, high chemoselectivity observed for functional groups interconversions presents the useful synthetic potentials of the method.

Scheme 2



Experimental Section

General Procedure for Thioacetalization of Aldehydes and Transthioacetalization of Acetals and Acylals Catalyzed by I_2 in $CHCl_3$. To a solution of compounds **1a**−**gg** (5 mmol), 1,3-propanedithiol (0.5−0.6 mL, 5−6 mmol), or 1,2-ethanedithiol(0.5−0.6 mL, 5−6 mmol) in $CHCl_3$ (25 mL) was added iodine (0.13 g, 0.5 mmol), and the resulting mixture was stirred at room temperature. After completion of the reaction (TLC, petreoleum ether/ethyl acetate, 5/2) the reaction was quenched with aqueous solutions of NaS_2O_3 (0.1 M, 25 mL) and NaOH (10%, 25 mL), respectively. Then $CHCl_3$ was added to the resulting reaction mixture. The organic layer was separated and washed with H_2O and decanted. The organic layer was dried over anhydrous $MgSO_4$ and filtered. Evaporation of the solvent in vacuo gave the desired pure product in a high yield (**2a**−**gg**, 88−96%). Further purification was achieved by recrystalization from petroleum ether (bp 60−80 °C). Transdithioacetalization of 2,2-bis(hydroxymethyl)-1,3-propanediol needs 2 equiv of dithiol.

Typical Procedure for Thioacetalization of Ketones Catalyzed by I_2 in $CHCl_3$. To a solution of compound **1kk** (1.14 g, 5 mmol) and 1,3-ethanedithiol (5−6 mmol) in $CHCl_3$ (25 mL) was added iodine (0.13 g, 0.5 mmol), and the resulting mixture was stirred at room temperature. After completion of the reaction (TLC, petreoleum ether/ethyl acetate, 5/1), the reaction was quenched with aqueous solutions of NaS_2O_3 (0.1 M, 25 mL) and NaOH (10%, 25 mL), respectively. Then $CHCl_3$ was added to the resulting reaction mixture. The organic layer was separated and was washed with H_2O. The organic layer was decanted and dried over anhydrous $MgSO_4$ and filtered. Evaporation of the solvent in vacuo gave the crude product. Purification by column chromatography (eleuent, petroleum ether−EtOAc,10/1) gave pure product (**2kk**, 1.36 g, 90%, orange plate crystals (from petroleum benzene, mp 58−60 °C, (uncorrected). ^1H NMR ($CDCl_3$, 250 MHz) δ: 2.14−2.20 (s, 3H), 3.36−3.49 (m,

4H), 4.18−4.69 (m, 9H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 33.83, 40.92, 65.20, 66.94, 68.31, 69.03, 95.18. MS (20 eV) *m/z* (relative intensity): 304 (M^+, 100), 276 ($M^+ - CH_2{=}CH_2$, 22.4), 244 ($M^+ - SC_2H_4$, 32.8), 210 (14.4), 153 (12.9), 121 (37.2), 89 (32.1), 65 (28.8), 56 (86.9). CHN analysis: %C (calcd = 55.26, found = 55.20), %H (calcd = 5.30, found = 5.33).

4-Bromophenyl-1,3-dithiane (2k). White needle crystals from petroleum ether. Mp: 92−4 °C (uncorrected). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.89−2.12 (m, 2H), 2.82−3.03 (t, 4H), 5.04 (s, 1H), 7.33 (d, 2H), 7.46 (d, 2H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 26.80, 32.30, 51.07, 122.73, 129.95, 132.22, 138.51 ppm. MS (20 eV) *m/z* (relative intensity): 276 ($M^+ + 2$, 37.3), 274 (M^+, 35.4), 201 ($M^+ - SC_2H_4$, 32.7), 130 (14.6), 105 (40.2), 74 (45.8), 45 (100). CHN analysis: %C (calcd = 43.64, found = 43.60), %H (calcd = 4.03, found = 4.10).

2,4,6-Trimethylphenyl-1,3-dithiane (2m). White needle crystals from petroleum ether. Mp: 128−130 °C (uncorrected). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.84−2.11 (m, 2H), 2.20 (s, 3H), 2.37 (s, 3H), 2.77 (s, 3H), 2.79−3.06 (m, 4H), 5.58 (s, 1H), 6.78 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 21.21, 21.32, 21.76, 26.12, 33.33, 49.45,129.47, 131.64, 132.61, 135.91, 137.84, 139.12 ppm. MS (20 eV) *m/z* (relative intensity): 238 (M^+, 19.9), 196 ($M^+ - C_3H_6$, 10.6), 163 (100), 91 (20.3), 45 (34.8). CHN analysis: %C (calcd = 65.49, found = 65.48), %H (calcd = 7.60, found = 7.59).

4-Methylphenyl-1,3-dithiolane (2x). White needle crystals from petroleum ether. Mp: 56−8 °C (uncorrected). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 2.38(s, 3H) 3.28−3.45 (m, 2H), 5.60 (s, 1H), 7.11 (d, 2H), 7.40 (d, 2H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 21.09, 40.16, 56.11, 127.79, 129.12, 137.10, 137.78 ppm. MS (20 eV) *m/z* (relative intensity): 196 (M^+, 68.9), 168 ($M^+ - CH_2{=}CH_2$, 25.4), 153 (100), 135 (83.6), 91 (57.5), 45 (99.3). CHN analysis: %C (calcd = 61.17, found = 61.20), %H (calcd = 6.16, found = 6.14).

Cinnamyl-1,3-dithiane (2cc). Yellowish white needle crystals from petroleum ether. Mp: 62−63 °C (lit.[8] mp 63−64 °C). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.76−2.01 (m, 2H), 2.71−2.80 (m, 4H), 4.69 (d, 1H), 6.09−6.19 (d of d, 1H), 6.67 (d, 1H), 7.12−7.28 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 25.60, 30.39, 53.95, 120.05, 127.37, 128.99, 133.78, 136.48, 138.11 ppm.

4-Methoxyphenyl-1,3-dithiane (2dd). White needle crystals from petroleum ether. Mp: 115−117 °C (lit.[8] mp 115−116 °C). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.59−1.86 (m, 2H), 2.72−2.89 (m, 4H), 3.66 (s, 3H), 4.99 (s, 1H), 6.72 (d, 2H), 7.24 (d, 2H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 24.05, 31.16, 49.71, 54.27, 113.05, 127.90, 130.29, 158.53 ppm.

2-Hydroxyphenyl-1,3-dithiane (2i).[7c] White needle crystals from petroleum ether−EtOAc. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.93−2.18 (m, 2H), 2.87−3.08 (m, 4H), 5.42 (s, 1H), 6.42 (s, 1H), 6.84−6.90 (m, 2H), 7.15−7.32 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 25.28, 32.06, 47.58, 117.65, 121.23, 124.14, 129.57, 130.50, 154.73 ppm.

2-Ferrocenyl-2-methyl-1,3-dithiane (2ll). Orange needle crystals from petroleum ether. Mp: 92−4 °C (uncorrected). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.74−1.89 (m, 1H), 2.05−2.07 (m, 1H), 2.12 (s, 3H), 2.63−2.71 (m, 2H), 3.06−3.12 (m, 2H), 4.18−4.59 (m, 9H) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 25.23, 28.32, 28.64, 48.55, 66.43, 67.94, 68.54, 68.95, 93.85 ppm. MS (20 eV) *m/z* (relative intensity): 318 (M^+, 100), 244 ($M^+ - SC_3H_6$, 6.6), 121 (4.1), 91 (7.1), 65 (6.1), 56 (8.9). CHN analysis: %C (calcd = 56.60, found = 56.61), %H (calcd = 5.70, found = 5.65).

1,4-Cyclohexanedione diethylenethioacetal (2bb). Yellowish white needle crystals from petroleum ether/EtOAc (3/2). Mp: 192−194 °C (uncorrected). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 2.29 (s, 8H), 3.29 (s, 8H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 38.49, 42.19, 66.98 ppm. MS (20 eV) *m/z* (relative intensity) 264 (M^+, 73.7), 133 (100), 61 (28.3), 45 (54.1). CHN analysis: %C (calcd = 45.41, found = 45.44), %H (calcd = 6.09, found = 6.08).

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