

SHORT PAPER

Chemoselective dithioacetalisation of carbonyl compounds under solvent-free conditions

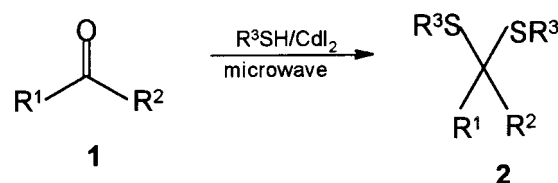
Dhrubojoyti Dey Laskar, Dipak Prajapati* and Jagir S. Sandhu

Division of Organic Chemistry (Drugs), Regional Research laboratory, Jorhat- 785006, Assam, India

Dithioacetalisation of carbonyl compounds in the presence of other structurally different aldehydes and ketones was achieved chemoselectively in the presence of CdI_2 under microwave irradiation in solvent free conditions.

Keywords: dithioacetalisation, carbonyl compounds

Protection and deprotection of functional groups are indispensable ingredients of the synthesis of polyfunctional compounds.¹ The protection of carbonyls as acetals and dithioacetals are important synthetic processes.² Dithioacetals often serve as protecting groups as well as masked acyl anions in organic synthesis³. The importance of dithioacetals is due in part to their stability under the usual acidic or basic conditions as well as the carbanion forming capability of cyclic dithioacetals.³ The sulfur stabilised carbanion generated from cyclic dithioacetals directly reverses the normal pattern of reactivity of the carbonyl group and is thus the equivalent of an acylation.⁴ Although a number of methods have been developed for the protection of aldehydes and ketones as dithioacetals,^{1,2} chemoselective thioacetalisation methods capable of discerning aldehydes from ketones have been rare.⁵ Several types of acid catalysts were introduced previously for this purpose such as LaCl_3 ,⁶ anhydrous $\text{FeCl}_3/\text{SiO}_2$,⁷ $\text{Fe}^{+3}/\text{montmorillonite}$,⁸ LiBr ,⁹ WCl_6 ,¹⁰ AlCl_3 ,¹¹ $\text{ZrCl}_4/\text{SiO}_2$,¹² and SiCl_4 .¹³ Another approach to dithioacetalisation under neutral conditions has been reported very recently involving 5M ethereal solution of LiClO_4 ,¹⁴ but this method works much better with acetals than with the corresponding carbonyl compounds and LiClO_4 is rather expensive. Also mixed reagent systems such as alkylthiosilane/Lewis acid¹⁵ and silica gel supported thionyl chloride,⁵ as well as some sophisticated reagents such as polyphosphoric acid trimethyl silyl ester,¹⁶ 2-chloro-1,3,2-dithiaborolane¹⁷ and LiOTf ¹⁸ have been reported. Major drawbacks involved in many of these reported procedures are low chemoselectivity, the formation of vinyl sulfide from enolizable carbonyl compounds, stoichiometric use of an expensive reagent, the presence of protic acid or strong Lewis acid, an expensive reagent and the necessity of aqueous work-up. In continuation of our studies on cadmium metals¹⁹ we wish to report here that cadmium iodide acts as a highly efficient catalyst for the selective dithioacetalization of various carbonyl compounds under microwave irradiation in the presence of other, structurally different aldehydes and ketones in solvent free conditions.²⁰ The reaction proceeds efficiently in excellent yields at ambient pressure within seconds and in the absence of solvent. The coupling of microwave irradiation with the use of catalysts or mineral supported reagent, under solvent-free conditions, provides chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity and improved ease of manipulation.²¹



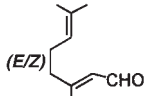
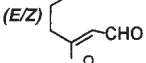
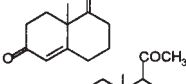
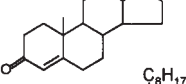
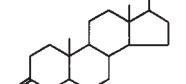
When aldehydes were allowed to react with alkanethiols or alkanedithiols in the presence of cadmium iodide under microwave irradiation, thioacetalisation proceeded smoothly, giving the corresponding dithioacetals in excellent yields (Table 1). Under the same conditions aliphatic ketones are also converted into the corresponding dithioacetals but aromatic ketones were recovered and were almost inert. When the ketoaldehyde (entry **2i**) was reacted with 1,3-propanedithiol under the above conditions, only the aldehyde group was thioacetalised (IR at 1710 cm^{-1} indicates the presence of a $-\text{CO}$ group) in 80% yields which is in contrast to an earlier report¹¹ where reaction with AlCl_3 to give bis-dithioacetals. Also when α,β -unsaturated carbonyl compounds (entry **2f-h**, **2k**, **2l**, and **2m**) were reacted with thiols under the same conditions, the carbonyl group was selectively thioacetalised to give the corresponding thioacetals in 80–86% yields. It is worth noting that thioacetalisation of α,β -unsaturated ketones using $\text{CoBr}_2\text{-SiO}_2$ however gave only complex mixtures and no significant amount of dithioacetals.²² The selectivity of the present method is also demonstrated by competition experiments using structurally differing carbonyl compounds. Thus benzaldehyde and cinnamaldehyde were both cleanly thioacetalised in the presence of acetophenone in excellent yields (entry **2q** and **2r**). To check the efficiency of the microwave energy we have carried out the dithioacetalisation of carbonyl compounds under thermal heating and found that the reaction is less effective and takes about 40–50 mins to give 60–70% yields. An increase in the reaction time had no significant effect on the yield and resulted in a minor amount of decomposition. Moreover, the reaction did not proceed when performed without cadmium iodide under microwave activation. All the compounds obtained were characterised by infrared and ^1H NMR spectroscopy and finally by comparison with an authentic sample.

In conclusion, a wide range of carbonyl compounds could be transformed into the corresponding dithioacetals in good yield by the present method. The striking selectivity of the present procedure can be utilised in the conversion of aromatic and α,β -unsaturated carbonyl compounds into their corresponding thio and dithioacetals in the presence of carbonyl moieties and has the added advantage of proceeding under very mild conditions and solvent-free conditions.

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 Microwave-assisted dithioacetalisation with CdI₂

Products	Aldehydes/ ketones 1	R ³ or R ⁴	M.p. °C found (literature)	Reaction time/min thermal	Yield thermal / %	Reaction time/sec MW ^b	Yield ^a MW / %
2a	PhCHO	-(CH ₂) ₃ -	71-72 (74) ¹⁴	40	65	75	85
2b	PhCHO	-(CH ₂) ₂ -	oil ⁵	30	70	75	90
2c	PhCHO	Ph-	51-52 (51-52) ⁵	35	65	80	90
2d	4-MeC ₆ H ₄ CHO	-(CH ₂) ₃ -	91-92 (91-92) ⁵	45	70	75	85
2e	4-ClC ₆ H ₄ CHO	-(CH ₂) ₃ -	85-86 (85.5-86.5) ⁵	45	65	75	90
2f	PhCH=CHCHO	PhCH ₂ -	oil ⁵	50	60	80	85
2g	PhCH=CHCHO	-(CH ₂) ₂	58-95 (58) ⁵	40	67	80	80
2h	PhCH=CHCHO	Ph-	63-64 (64) ⁵	40	75	85	86
2i	CH ₃ CO(CH ₂) ₄ CHO	-(CH ₂) ₃ -	oil ²³	40	75	80	80
2j	CH ₃ CO(CH ₂) ₄ CHO	-(CH ₂) ₂ -	oil ²³	40	65	80	80
2k		-(CH ₂) ₂ -	oil ²⁴	40	65	80	80
2l		Ph-	oil ²⁴	35	60	80	82
2m		-(CH ₂) ₃ -	106-8 (106-8) ²³	40	69	85	70
2n		-(CH ₂) ₂ -	188-89 (189-190) ²³	40	70	80	72
2o		-(CH ₂) ₃ -	146-7 (146-8) ²³	40	70	80	78
2p	PhCOCH ₃	-(CH ₂) ₂ -		no reaction			
2q^c	$\left\{ \begin{array}{l} \text{PhCOCH}_3 \\ \text{PhCOCH}_3 \\ + \\ \text{PhCH=CHCHO} \end{array} \right\}$	$\left\{ \begin{array}{l} \text{-(CH}_2\text{)}_2\text{-} \\ \text{-(CH}_2\text{)}_2\text{-} \end{array} \right\}$	$\left\{ \begin{array}{l} 58-59 (58)^5 \end{array} \right\}$	50	$\left\{ \begin{array}{l} 0 \\ 75 \end{array} \right\}$	75	$\left\{ \begin{array}{l} 0 \\ 95 \end{array} \right\}$
2r^c	$\left\{ \begin{array}{l} \text{PhCOCH}_3 \\ + \\ \text{PhCHO} \end{array} \right\}$	-(CH ₂) ₃ -	$\left\{ \begin{array}{l} 71-72 (74)^5 \end{array} \right\}$	50	$\left\{ \begin{array}{l} 0 \\ 75 \end{array} \right\}$	75	$\left\{ \begin{array}{l} 0 \\ 98 \end{array} \right\}$

^aYields refer to the isolated pure compounds.^bMW microwave irradiation.^cExperiments with mixtures of ketone and aldehyde.

Experimental

Melting points were determined by using a Buchi melting point apparatus and are uncorrected. IR spectra were obtained KBr disks by using a Perkin-Elmer 237 infrared spectrometers. The 90 MHz NMR spectra were recorded with tetramethylsilane as internal standard (by RSIC, Shillong). All solvents were dried by standard methods before use. The progress of most reactions was monitored by TLC. Chromatographic purification was performed with silica gel 60 (120 mesh). Cadmium iodide used was of commercial grade and procured from Loba Chemie Indoaustran Co., Mumbai. All other chemicals were purified by distillation or crystallisation prior to use.

General procedure: Thioacetalisation and dithioacetalisation of carbonyl compounds under microwave irradiation: A mixture of benzaldehyde (1.06g, 10 mmol), ethanedithiol (0.94g, 10 mmol) and commercial grade cadmium iodide (1.85g, 5 mmol) was mixed thoroughly in an Erlenmeyer flask and placed in a commercial microwave oven operating at 2450 MHz frequency. The whole operation was carried out in a fume-cupboard. After irradiation of the mixture for 75 s (monitored by TLC) it was cooled to room temperature and extracted with dichloromethane. Evaporation of the solvent gave almost pure products. Further purification was achieved by column chromatography on silica gel using 1:5 chloroform:pet.ether as eluent. Similarly other aldehydes were reacted with various dithiols (1,2-ethanedithiol and propanedithiol) and monothiols (thiophenol and benzylmercaptan) under microwave activation, in the presence of CdI₂, and the corresponding dithioacetals and thioacetals were isolated in excellent yields (Table 1). Under this condition aliphatic ketones were also converted into the corresponding dithioacetals but aromatic ketones were recovered almost intact (entry **2p**). The reaction of ketoaldehyde

(entry **2i**) and 9-methyloctalin-1,6-dione with 1,3-propanedithiol were carried out in the same way gave the corresponding dithioacetals in 80 and 75% yields respectively. All the compounds obtained were characterised by IR, ¹H NMR and MS spectra and finally by comparison with an authentic sample.

Thioacetalisation and dithioacetalisation of carbonyl compounds under thermolytic conditions: A mixture of benzaldehyde (1.06g, 10 mmol), ethanedithiol (0.94g, 10 mmol) and commercial grade cadmium iodide (1.85g, 5 mmol) were thoroughly mixed at room temperature. After being stirred for 3 min, the mixture was heated in an oil bath at 75°C for 30 min. It was then stirred and allowed to cool to room temperature, extracted with dichloromethane and dried over anhydrous Na₂SO₄. Evaporation of the solvent gave dithioacetal (entry **2b**) in 90% yield. Further purification was achieved by column chromatography on silica gel using 1:5 chloroform:petroleum.ether as eluent. Similarly other aldehyde were allowed to react with dithiols (1,2-ethanedithiol and propanedithiol) and monothiols (thiophenol and benzylmercaptan) for 30-50 min in the presence of CdI₂, the thioacetalisation proceeded giving the corresponding dithioacetals and thioacetals in good yields (Table 1).

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