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A new molecular iodine-catalyzed thioketalization of carbonyl compounds: selectivity and scope

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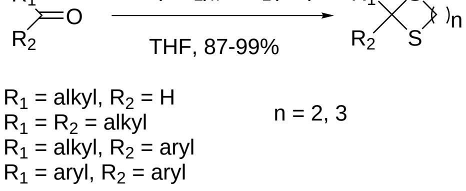
Abstract—A new molecular iodine-catalyzed thioketalization of carbonyl compounds has been developed.

The protection of aldehydes and ketones as thioketals is a widely used method and in general, the reaction is usually performed in the presence of acids.[1] However, there are shortcomings to using acid in the thioketalization reaction of carbonyl compounds, namely long reaction time, reflux temperature, unwanted side reactions and non-selectivity. Many other methods are reported in the literature, such as titanium tetrachloride,[2] magnesium or zinc triflates,[3] lanthanum chloride,[4] and Nafion-H.[5] But, the chemoselectivity between these groups has only been reported with silica-gel–thionyl chloride,[6] Amberlyst-15 catalyst,[7] ceric ammonium nitrate[8] and indium trichloride.[9] Selective protection of a ketone in the presence of another in a complex molecule has never been addressed by the reported methods (Scheme 1).

We now report a facile and convenient iodine-catalyzed thioketalization for various carbonyl compounds in high yield. We believe that our method is very general, simple, mild, rapid and new to the literature. In addition, by using this method, a particular carbonyl group can be selectively blocked in the presence of another in a mixture, and reduction chemistry targeting the non-protected group can then be accomplished with the simultaneous regeneration of the protected one in a single step. Moreover, we report here an excellent intramolecular chemoselectivity between two ketone functionalities.



Scheme 1.

At the inception of this work, we reacted several aromatic aldehydes with ethane thiol (**1**) and 1,3-propane thiol (**2**) in the presence of iodine (10 mol%) in dry THF as the solvent at room temperature. The protected thioketal was obtained in excellent yield within a few minutes (Table 1).

Application of this method was then extended for the protection of ketones of different structures. The thioketals were formed, although time required for the completion of the reaction was found to be longer (Table 1).

The differences of reactivities of the aldehydes and ketones suggest that this method can be used for the selective protection of these groups, and resulted in the successful protection of an aldehyde in the presence of a ketone. This has been shown by a reduction experiment with sodium borohydride (Scheme 2).

We were also able to achieve a selective protection of an aliphatic ketone (2-methyl cyclopentanone) in the presence of an aromatic ketone (acetophenone) by this method and this has been demonstrated by a subsequent reduction reaction (Scheme 3).

This method was then used for selective protection of a six-membered ketone as a thioketal present in

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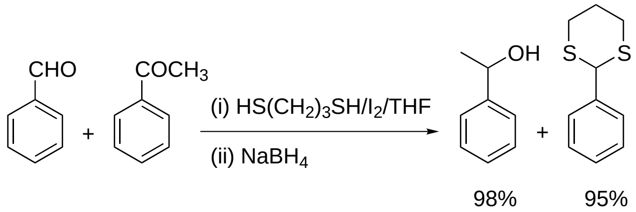
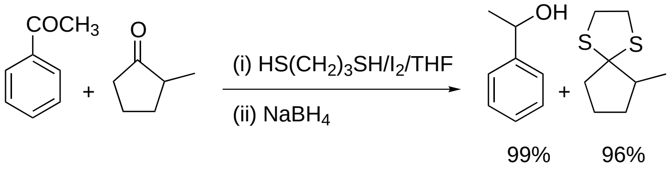
Table 1. Thioketalization of aldehydes and ketones

Entry	Carbonyl compounds	Thiol	Time (h)	Yield (%)
1	Propionaldehyde	**1**, **2**	0.5	98
2	*trans*-Cinnamaldehyde	**2**	0.5	94
3	Benzaldehyde	**1**, **2**	0.5	99
4	2-Bromobenzaldehyde	**2**	0.5	91
5	1-Naphthaldehyde	**2**	0.5	97
6	2-Furaldehyde	**2**	0.5	96
7	3-Methoxy-2-nitrobenzaldehyde	**2**	0.5	89
8	Ferrocenecarboxaldehyde	**2**	0.5	87
9	Hexane-2,5-dione[a]	**2**	3	94
10	Cyclohexanone	**2**	4	97
11	2-Methylcyclopentanone	**1**, **2**	3	98
12	Acetophenone	**1**, **2**	7	92
13	1-Tetralone	**2**	5	90
14	9-Fluorenone	**2**	6	91

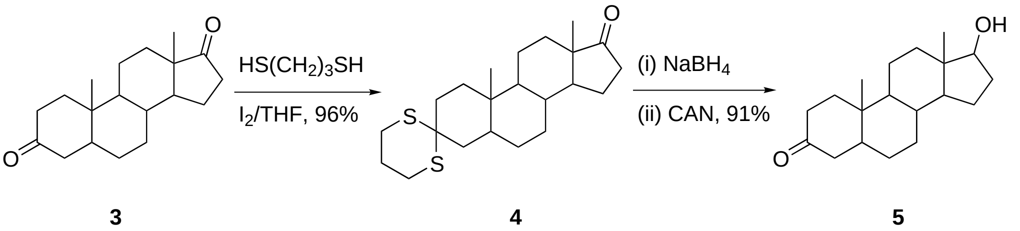
[a] Use of 1 equiv. of thiol gave monothio ketal and 2 equiv. gave dithio ketal.



Scheme 2.



Scheme 3.



Scheme 4.

androstane **3**. Sodium borohydride reduction of the protected androstane **4** and removal of the protective group by oxidation afforded the keto-alcohol **5** in a single step (Scheme 4).

The present iodine-catalyzed thioketalization deserves some special comments. For a successful reaction of this type, one would expect the use of a stoichiometric amount of iodine. But, in the present investigation, we used catalytic amounts of iodine (10 mol%). Moreover, in a large-scale reaction, even a smaller amount of iodine (5 mol%) can be used with success. We suspect that hydroiodic acid is the actual catalyst involved in the reaction.

In summary, our presently reported iodine-catalyzed thioketalization method of carbonyl groups is a novel, generally applicable, chemoselective and convenient one for practical application. The selectivities described herein are not only remarkable, but also they can be applied to a wide range of carbonyl compounds. This method[10] with its mild conditions, sharp selectivity differences between functional groups, should have broad applicability.

Acknowledgements

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10. A representative procedure is as follows: To a stirred solution of carbonyl compound (1 mmol) and thiol (1 mmol) in THF (2 mL) was added iodine (0.1 mmol). After a period specified in Table 1 the solvent was removed under reduced pressure. The crude product was then passed through a short silica-gel column to afford pure thioketal (87–99%).