

MOLECULAR IODINE-CATALYZED PROTECTION OF CARBONYL COMPOUNDS

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Abstract:

Molecular iodine-catalyzed protection method for a variety of carbonyl compounds including acetals, ketals, thioketals, and mixed ketals in high yield at room temperature has been developed. The iodine-catalyzed reaction of lactic acid and maleic acid with aldehydes has provided diastereoselective synthesis of *cis* and *trans* isomers.

Introduction:

Carbonyl groups protection plays an important role in medicinal and organic chemistry. Many efforts have been made to seek out a protective group for carbonyl compounds. Protection such as acetal, 1-3-dioxalane, mixed ketal, and thioacetal are the most practical choices. The simplicity of the procedure is the evident reason behind this choice. The ketal-types of compound serve as valuable intermediates and are used for the total synthesis of natural products. In general, the method requires acidic catalysts. No efficient general method has been developed for the protection of carbonyl groups despite significant achievements in this area. Important shortcomings of the existing methods are the conditions that require high temperature with stoichiometric reagents. We have discovered a novel iodine-catalyzed acetalization and thioacetalization method of aldehydes and ketones in excellent yield and with remarkable chemoselectivity. Our focus has been extended to examine the protection of carbonyl groups broadly, given the fact that the method has considerable promise. This paper exemplifies our full account of several acetals and ketals preparation via our iodine-catalyzed reaction. In comparison with the present method, literature methods are not as versatile, simple and economical.

Results and Discussions:

The protection of aldehydes and ketones as acetals and ketals is one of the important reactions. This reaction is usually performed in the presence of acids using the trialkyl orthoformate or alcohol.¹ Methods that do not require acid-catalysts have been known, and reactions under mild acidic conditions have been developed. In the ketalization of carbonyl compounds, lanthanides and other metal-catalysts are found to be excellent. In the acetalization/ketalization reaction of carbonyl compounds, long reaction time, reflux temperature, unwanted side reactions and nonselectivity are shortcomings to using these methods. Lanthanides reagents are substrate

selective and a general method is not developed using these catalysts. Therefore, a method that overcomes the drawbacks of lanthanides and acid catalysis is desirable. It has been reported, that bismuth triflate-catalyzed method is very versatile in the protection of carbonyl compounds. The application of bismuth compounds as environmentally friendly reagents has been clearly established. A facile and convenient molecular iodine-catalyzed protection for various carbonyl compounds as ketals in high yield is reported herein. Aldehydes were protected as acetals by using catalytic amounts of iodine and methanol or ethanol. The desired compounds were obtained in excellent yield and the rate of reaction was found to be extremely fast. (**Scheme 1**, **Table 1**, entries **1** to **8**). Acetalization was attempted with ketones by following an identical procedure. A similar reaction with ketones was dependent on the nature of the ketones, while a wide range of aldehydes produced the acetals. The time required for the completion of the ketalization with ketones was longer.

Scheme 1

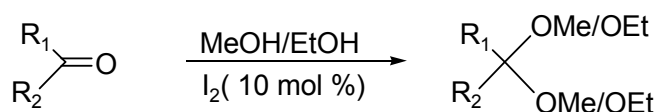
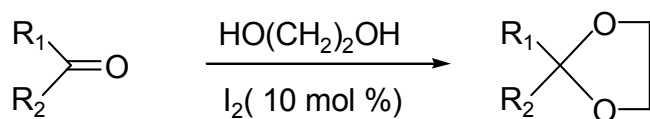


Table 1: Acetalization of carbonyl compounds by catalytic amounts of molecular iodine

Entry	Carbonyl Compounds	Time (hr)	Yield (%)
1	Benzaldehyde	1	98
2	2-Furaldehyde	1	95
3	2-Methoxy cinnamaldehyde	1	98
4	3-Bromo benzaldehyde	1	99
5	o-Nitrobenzaldehyde	1	93
6	2-Tetralone	8	80
7	Decenal	1	99
8	Cyclohexanone	1	90

The advantage of our method is that unlike with the bismuth triflate-catalyzed process it does not require triethyl orthoformate due to the fact that the actual reagent is alcohol. It is remarkable to state that the catalytic activity of bismuth triflate and iodine remain almost identical. Our method was tested for the preparation of 1,3-dioxalane derivatives (**Scheme 2**) and the data is shown in the **Table 2**. Some extremely good substrates for this purpose are aliphatic aldehydes and ketones. Yields with the benzylic ketones and aromatic aldehydes under identical conditions were satisfactory.

Scheme 2**Table 2:** Ketalization of Carbonyl Compounds

Entry	Carbonyl Compounds	Time (h)	Yield (%)
1	Butanal	16	90
2	Decanal	16	88
3	Benzaldehyde	16	45
4	2-Nitro-benzaldehyde	16	5
5	2-Bromo-benzaldehyde	16	65
6	Cinnamaldehyde	16	15
7	5-Chloronitro-benzaldehyde	16	5
8	P-Anisaldehyde	16	40
9	Cyclohexanone	16	90
10	1-Methyl-Cyclohexanone	16	75
11	4-Methyl-Cyclohexanone	16	90
12	3,3,5,5-Tetramethyl-cyclohexanone	16	88
13	4-tert-Butyl-cyclohexanone	16	88
14	2-Methyl-cyclopentanone	16	45
15	Acetophenone	16	15
16	4-Methoxy-acetophenone	16	15
17	Benzylacetone	16	40
18	1-Phenyl-1,4-Pentanonedione	16	40
19	Beta-tetralone	16	30
20	2-Heptanone	16	40

The protection of ketones, and aldehydes as thioketals is usually performed in the presence of acids¹. Other methods are reported in the literature, such as magnesium or zinc triflates² titanium tetrachloride³, Nafion-H⁴ and lanthanum chloride.⁵ But, the chemoselectivity between these

groups has only been reported with, Amberlyst-15 catalyst⁶, silica gel-thionyl chloride⁷ indium trichloride⁸ and ceric ammonium nitrate⁹ Reported methods have never addressed the selective protection of a ketone in the presence of another in a complex molecule. We extended our method for the thioketalization of various carbonyl compounds in high yields. At the inception of this work, we reacted several aromatic aldehydes with 1, 3-propane thiol and ethane thiol in the presence of iodine (10 mol%) in dry THF as the solvent at room temperature (**Scheme 3**). Within a few minutes, the protected thioketal was obtained in excellent yield. (**Table 3**). This method was then extended for the protection of different ketones. Although time required for the completion of the reaction was found to be longer, thioketals were formed.

Scheme: 3

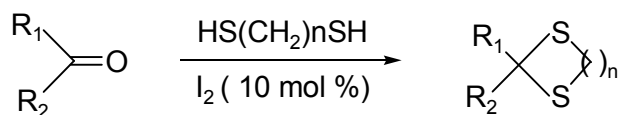
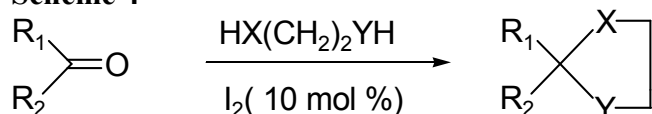


Table 3: Thioketalization of aldehydes and ketones

Entry	Carbonyl Compounds	Thiol n=	Time (hr)	Yield (%)
1	Propion-aldehyde	2,3	.5	98
2	Benzaldehyde	2,3	.5	99
3	2-Bromo-benzaldehyde	3	.5	91
4	Trans-cinnamaldehyde	3	.5	94
5	2-Furaldehyde	3	.5	91
6	3-Methoxy-2-nitrobenzaldehyde	3	.5	89
7	Ferrocenecarboxaldehyde	3	5	87
8	Naphthaldehyde	3	.5	97
9	Hexane-2,5-dione	3	3	94
10	Cyclohexanone	3	4	97
11	2-Methylcyclopentanone	2,3	3	98
12	Acetophenone	2,3	7	92
13	1-Tetralone	2	5	90
14	9-Fluorenone	2	6	91

Abiding by the above method, preparation of a great number of mixed ketals was accomplished in good yield (**Scheme 4**). Most all types of carbonyl compounds can be protected as mixed ketals (Table 4)

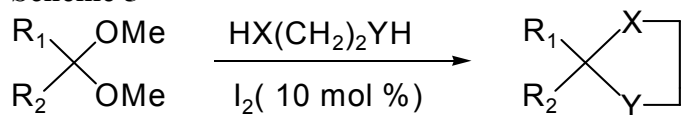
Scheme 4**Table 4:** Mixed Ketalization of Carbonyl Compounds

Entry	Carbonyl compounds	Yield(%)
1	Cyclohexanone	85
2	2-Methyl-cyclohexanone	70
3	4-tert-Butyl-cyclohexanone	85
4	Acetophenone	45
5	Benzaldehyde	70
6	2-Nitro-benzaldehyde	55
7	2-Bromo-benzaldehyde	60
8	<i>p</i> -Anisaldehyde	67
9	Cinnamaldehyde	70

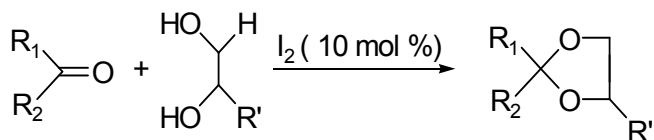
Due to the fact that the present iodine-induced method works so well, this method was then applied to the transketalization reaction with a few substrates; the results were excellent. Transketalization is an important objective from the synthetic chemistry point of view. Acetals were mixed with ethane thiol or ethylene glycol in the presence of iodine and after the indicated time transketalization was observed (**Scheme 5** and **Table 5**).

Realizing the versatilities of our iodine-catalyzed protection of the carbonyl groups, we envision that this method can provide an easy access of optically active dioxolanones. Particularly, many examples of hydroxyl carboxylic acids and amino acids are now available in both enantiomeric forms.

The range is further increased by the fact amino acids that are optically active can be converted to hydroxy acids with retention of configuration. These types of compounds are frequently used as the starting materials for synthesis of many other non-natural and natural compounds. The reaction of aldehydes with optically active hydroxy acids during ketalization, in principle, can produce two isomeric compounds. In conformity of hypothesis, our iodine-catalyzed reaction lactic acid and mandelic acid with several aldehydes produced a highly diastereoselective mixture of *cis* and *trans* dioxolanones. A comparison of known authentic samples and NMR spectrum calculated the ratio of the isomers. Lewis acid-mediated reaction and bronsted acid-catalyzed ketalization with azeotropic removal of water also produced a similar mixture of isomers.

Scheme 5**Table 5:** Transketalization of Carbonyl Compounds

R ₁ = H R ₂ = Phenyl	X=Y= OH	X=Y= SH	X=OH Y= SH
R ₁ = R ₂ = Phenyl	95%	98%	75%
R ₁ =2-Bromophenyl R ₂ =H	99%	95%	75%
R ₁ =3-bromophenyl R ₂ = H	99%	88%	80%

Scheme 6**Table 6:** Diastereoselective synthesis of Ketals

Entries	Carbonyl Compounds	R'	Yields (%)	Cis/Trans
1	Butyraldehyde	Ph	86	86/14
2	Decanal	CH ₃	40	81/19
3	Decanal	Ph	85	84/16
4	Pivaldehyde	CH ₃	50	67/33
5	Pivaldehyde	Ph	40	81/19
6	Hydrocinnam-aldehyhde	CH ₃	50 ^a	80/20
7	Cyclohexanone	Ph	6	86/14

The cis and trans isomer ratios were dependent upon the temperature of the reaction. On the other hand, our iodine-catalyzed reaction is independent of the room temperature of the reaction media and progress remarkably well at room temperature to reflux temperature of THF. Interestingly, under various reaction temperatures, the stereochemistry of the products remains the same. Additionally, neither the success of the reaction nor the dictating of stereochemistry of the products is due to any of the solvents.

Mechanistic considerations: When the carbonyl compounds were kept at room temperature with thiol or alcohol in the absence of iodine, no reaction was observed. The protection also failed in the presence of a mixture of potassium carbonate (10 mol %) and iodine. The possibility of a complexation by molecular iodine to the carbonyl group was ruled out by this experiment. The reaction did not proceed in the presence of a basic reagent. This suggests that hydroiodic acid is the actual catalyst. We used catalytic amounts of iodine (1-10 mol %) in the present investigation. The reaction in the presence of catalytic amounts of hydroiodic acid produced thioketal and ketal in very low yield. In a small-scale reaction with strong acids require precise control of the acidity. A smaller amount of iodine (1 mol %) in a large-scale reaction, can be used with success. A higher proportion of iodine (5 mol %) can make the time shorter.

Maintenance of conditions is absolutely necessary for the success of the reaction. Otherwise, a significant amount of product can revert to the starting compound.

Conclusion:

The present iodine-catalyzed protection of carbonyl groups is very general and mild. In order to establish the versatility of the iodine-catalyzed method, this attempt has been investigated successfully. Methods previously described in the literature do not demonstrate this kind of versatility.

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