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A remarkable iodine-catalyzed protection of carbonyl compounds

Bimal K. Banik,* Marin Chapa,† Jocabed Marquez† and Magda Cardona†

Department of Chemistry, The University of Texas-Pan American, 1201 West University Drive, Edinburg, TX 78541, USA

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Abstract—We report here a remarkably simple molecular iodine-catalyzed protection method for various carbonyl compounds as ketals in a general reaction. The iodine-catalyzed reaction of mandelic acid and lactic acid with several aldehydes has furnished a highly diastereoselective synthesis of *cis* and *trans* dioxolanones.

Protection of carbonyl groups plays an important role in organic, medicinal, and carbohydrate chemistry as well as the chemistry of drug design.[1] Tremendous efforts have been made to search for a suitable protective group for carbonyl compounds. In spite of these efforts, protection as 1,3-dioxolane remains the most practical choice.[2] The reason for this choice obviously is the simplicity of the protection procedure and ready availability of the starting reagents. In addition, these ketal-type of compounds can be used for the total synthesis of natural products and therefore, serve as valuable intermediates in organic synthesis. In general, the protection method requires protic acids, Lewis acids, or acidic catalysts. The limitations are nonchemoselectivity and incompatibility with the other functional groups present in the molecule. Two of the most important shortcomings of the existing protection methods are the long reaction time and conditions that require a high temperature along with a stoichiometric amount of reagents. Many of the existing methods often use toxic and corrosive reagents, for example, titanium tetrachloride, borontrifluoride etherate, trifluoromethane sulfonic acid, and trifluoromethane sulfonic anhydride.[2g,3–5] Furthermore, lanthanides and other metal catalysts have been found to be excellent in the selective ketalization of carbonyl compounds under mild conditions. Lanthanides are, however, substrate selective, and a general protection method cannot be achieved using these catalysts.[2g,3] Therefore, an alternative method that can overcome these drawbacks and be applied to a number of substrates in a catalytic process is highly desirable.

We have studied iodine-catalyzed organic transformations.[6] Because iodine-catalyzed reaction has considerable promise, our focus has extended to the protection of carbonyl groups. This report gives a preliminary account of our preparation of ketals mediated by molecular iodine. The reaction of mandelic acid and lactic acid with several aldehydes under an identical condition has furnished a highly diastereoselective synthesis of *cis* and *trans* dioxolanones.

Several ketals were prepared using carbonyl compounds and ethylene glycol in the presence of iodine (5 mol%) and the data are shown in Table 1. Aliphatic aldehydes and ketones were extremely good substrates for this purpose. The yields with the aromatic aldehydes and benzylic ketones were satisfactory (Scheme 1).

Realizing the versatility of our method of iodine-catalyzed protection of the carbonyl groups, we envision that this method can provide an easy access to optically active dioxolanones. Notably, many examples of both amino acids and hydroxy carboxylic acids are now available in enantiomeric forms. The scope of this reaction is further increased by the fact that optically active amino acids can be converted to hydroxy acids with retention of configuration. These types of compounds are frequently used as the starting materials for the synthesis of many other natural and nonnatural compounds.[2i,7] In principle, the reaction of optically active hydroxy acids with aldehydes during ketalization can produce two isomeric compounds.

In conformity with this hypothesis, iodine-catalyzed reaction of mandelic acid and lactic acid with several aldehydes produced a highly diastereoselective mixture of *cis* and *trans* dioxolanones (Scheme 2). The isomer

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* Corresponding author. Tel.: +1 956 380 8741; fax: +1 956 384 5006; e-mail: banik@panam.edu

† Undergraduate research participants; contributed equally.

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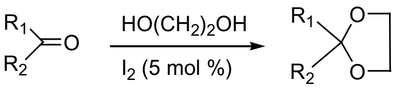
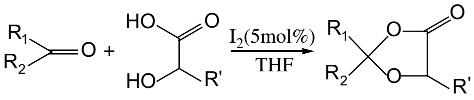
Table 1. Protection of carbonyl compounds as ketal in the presence of iodine

Entry	Carbonyl compounds	Time (h)	Yield (%)[a]
1	Cyclohexanone	16	90
2	2-Methyl-cyclohexanone	16	75
3	4-Methyl-cyclohexanone	16	90
4	3,3,5,5-Tetramethyl-cyclohexanone	16	88
5	4-*tert*-Butyl-cyclohexanone	16	88
6	2-Methyl-cyclopentanone	16	70
7	Acetophenone	16	50
8	4-Methoxy-acetophenone	16	50
9	Benzylacetone	16	40
10	β-Tetralone	16	30
11	2-Heptanone	16	80
12	Benzaldehyde	16	70
13	2-Nitro-benzaldehyde	16	50
14	2-Bromo-benzaldehyde	16	65
15	Cinnamaldehyde	16	65
16	*p*-Anisaldehyde	16	75
17	Decanal	16	88
18	Butanal	16	90
19	Propanal	16	90

[a] The yield was calculated after 16 h reaction in each case.



Scheme 1.



Scheme 2.

ratio was calculated by a comparison of known authentic samples and NMR spectra. Brønsted acid-catalyzed ketalization with azeotropic removal of water and Lewis acid-mediated reaction also produced a similar mixture of isomers. In addition, a recent study showed that scandium trifluoromethanesulfonimide-mediated reactions are believed to be solvent dependent. Moreover, the success in most cases depends on the precise azeotropic removal of water from the reaction media. The ratios of the *cis* and *trans* isomers described above were dependent on the temperature of the reaction. (Table 2) In contrast, our iodine-catalyzed reaction is not dependent on the temperature of the reaction media and proceeds exceedingly well at room to reflux temperature in THF. Interestingly, the stereochemistry of the products remains identical under various reaction conditions. In addition, the solvent does not seem to play a role in the success of the reaction or in dictating the stereochemistry of the products (Scheme 2).

Table 2. Diastereoselective synthesis of ketal

Entry	Carbonyl compounds	R′	Yield (%)	*cis*/*trans*
1	Cyclohexanone	Ph	65	—
2	Pivaldehyde	Ph	90	89/11
3	Pivaldehyde	CH_3	85	84/16
4	Decanal	Ph	50	67/33
5	Decanal	CH_3	40	81/19
6	Hydrocinnamaldehyde	CH_3	50	80/20
7	Butyraldehyde	Ph	86	86/14

The present iodine-catalyzed reaction does not proceed in the absence of iodine. Protection also failed in the presence of iodine (1%) and potassium carbonate mixture (10%). This experiment ruled out the possibility of a complexation role of the molecular iodine to the carbonyl group. This indicates that hydroiodic acid was the actual catalyst in this reaction. However, reaction in the presence of catalytic amounts of hydroiodic acid produced ketals in very low yield. Precise control of the acidity in a small-scale reaction with hydroiodic acid or other strong acids is extremely difficult. Moreover, our method can be applied to a large-scale reaction. Although, a smaller amount of iodine (0.1 mol%) can be used successfully, a higher proportion of iodine (5 mol%) can accelerate the reaction.

In conclusion, our iodine-catalyzed protection of carbonyl groups is general, mild, novel, cost-effective, and convenient from a practical point of view.[8] The asymmetric and diastereoselective version of this method adds significant value. At present, we are exploring other possibilities for this reaction, the results of which will be reported in due course.

Acknowledgements

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8. General ketalization procedure: The carbonyl compound (1 mmol) was dissolved in ethylene glycol (1 mL), and iodine (0.05 mmol) was added to the solution with stirring. After the starting material was consumed as indicated by TLC, diethyl ether (10 mL) was added. The reaction mixture was washed with $Na_2S_2O_3$ (5%, 5 mL), washed with saturated $NaHCO_3$, dried over Na_2SO_4 and the solvent gets evaporated. Finally, the pure products were obtained via purification through basic alumina using ethyl acetate–hexane (10:90) as the solvent.