A New Molecular Iodine-Catalyzed Acetalization of Carbonyl Compounds

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Received 4 October 2001

Abstract: A new and facile molecular iodine-catalyzed acetalization of carbonyl compounds has been developed. Useful selectivity has also been demonstrated.

Key words: acetalization, iodine-catalyzed, carbonyl compounds

The protection of aldehydes and ketones as acetals is one of the most widely used methods. In general, the reaction is usually performed in the presence of acids.[1] There are shortcomings to using acid in the acetalization reaction of carbonyl compounds, namely long reaction time, reflux temperature, unwanted side reactions and nonselectivity. Lanthanides[2] and other metal-catalysts[3] are found to be excellent in the selective acetalization of carbonyl compounds under mild conditions. These expensive reagents are, however, substrate selective and a general method can not be achieved by using these catalysts. Therefore, a method that can overcome the drawbacks of acid catalysis and lanthanide use is desirable.

Recently, we have demonstrated a few molecular iodine-catalyzed organic transformations.[4] In continuation of research on this subject, we report a facile and convenient iodine-catalyzed acetalization method for various carbonyl compounds in high yield. We believe that our method is simple, mild, rapid and new in 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 can be accomplished using the non-protected one with the simultaneous regeneration of the protected one in a single step.

At the beginning of the study, several aldehydes were protected as acetals by using catalytic amounts of iodine and methanol or ethanol. The rate of reaction was found to be extremely fast, and the desired compounds were obtained in excellent yield (Table, entries 1–6).

By following an identical procedure, ketalization was attempted with ketones. Cyclohexanone and 2-tetralone (Table, entries 7 and 8) gave good yields. The time required for the completion of the ketalization with ketones was longer (Table, entries 7 and 8).

Realizing the sharp contrast in the reactivity of aldehydes and ketones, we decided to make selective ketalization our objective. To establish the importance of this selectivity, three reactions were tested. We selected sodium borohydride reduction of carbonyl groups, reductive dimerization of ketones by samarium metal, and reduction of a double bond by samarium metal. The outcome of this procedure was a one-pot reduction of a ketone in the presence of an aldehyde, dimerization of a ketone in the presence of an aldehyde, and reduction of a C-C double bond in an ester in the presence of a C-C double bond in an aldehyde (Scheme 1).

Table Acetalization of Carbonyl Compounds by Catalytic Amounts of Molecular Iodine

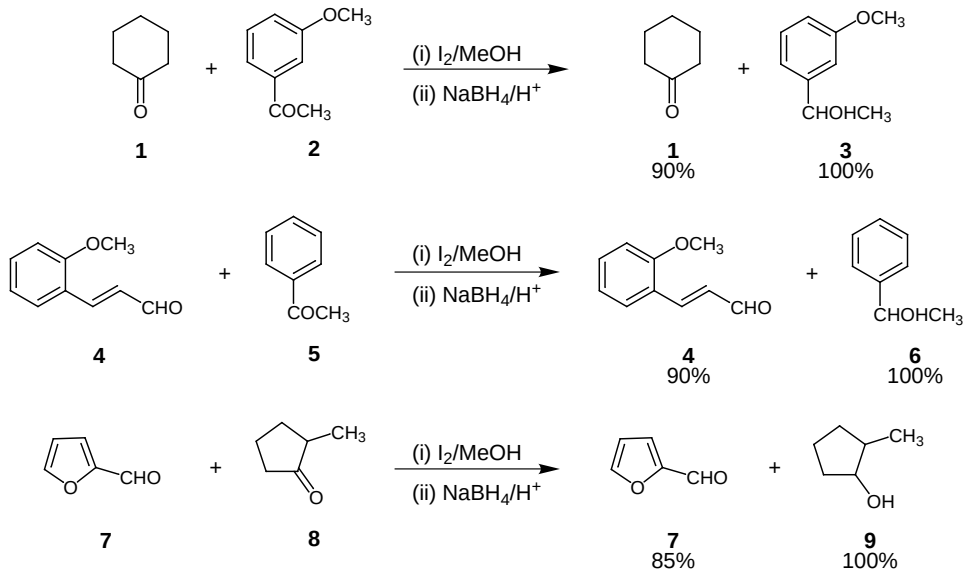
Entry	Carbonyl Compounds	I_2 (mol %)	Reaction Time (h)	Acetal (%)
1	Benzaldehyde	10	1	98
2	2-Furaldehyde	10	1	95
3	2-Methoxy-cinnamaldehyde	10	1	98
4	3-Bromobenzalde-hyde	10	1	99
5	*o*-Nitrobenzaldehyde	10	1	93
6	Decenal	10	2	99
7	Cyclohexanone	10	8	90
8	2-Tetralone	10	8	80

Reaction of a mixture (1:1) of cyclohexanone (**1**) and 3-methoxy acetophenone (**2**) with iodine (10 mol%) in methanol was performed; the reaction was monitored by thin-layer chromatography. When cyclohexanone disappeared from the mixtures, sodium borohydride was added, and after the usual work up, alcohol **3** (100%) from the reduction of 3-methoxy acetophenone (**2**) along with cyclohexanone (**1**) was obtained. By following the same route, acetophenone (**5**) and 2-methyl cyclopentanone (**8**) were reduced in the presence of 2-furfuryl aldehyde (**7**) and 2-methoxy cinnamaldehyde (**4**) in excellent yield (Scheme 1). These results indicated that aldehydes are acetalized much faster than the aliphatic and aromatic ketones.

Having established this type of selectivity, we decided to test the method with other systems as well. We demonstrated a facile dimerization of aromatic ketones in the presence of samarium and alkyl halides.[5] The differences

Synlett 2002, No. 2, 01 02 2002. Article Identifier:
1437-2096,E;2002,0,02,0319,0321,ftx,en;S05301ST.pdf.

ISSN 0936-5214



Scheme 1

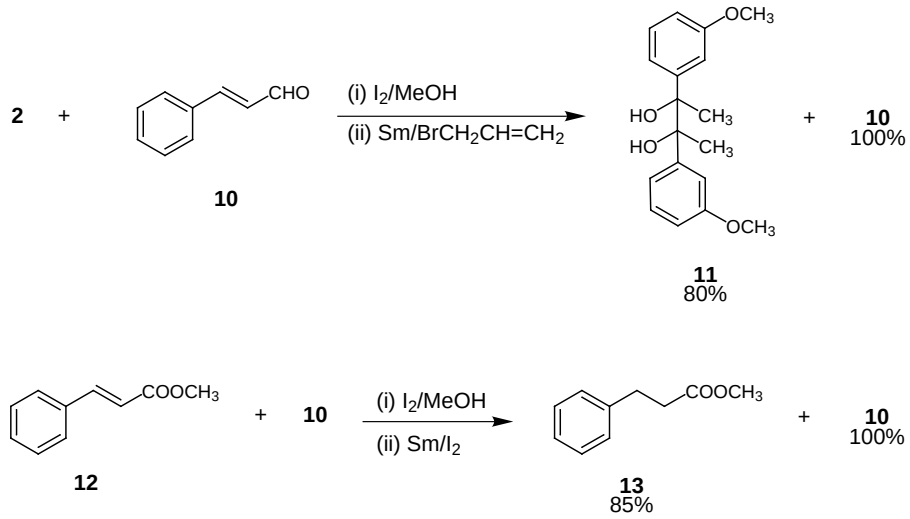
in reactivity of iodine-catalyzed acetalization was then used to effect reductive dimerization of 3-methoxy acetophenone (**2**) in the presence of cinnamaldehyde (**10**). First, selective acetalization was performed by adding iodine in methanol and then to the reaction mixture was added samarium metal and allyl bromide. The net result was the dimerization of 3-methoxy acetophenone (**2**); cinnamaldehyde (**10**) was mostly intact and was regenerated during the work-up.

We also utilized this new iodine-catalyzed reaction for the selective reduction of a C-C unsaturated bond in an ester **12**[6] in the presence of a C-O bond in an aldehyde **10**. As usual, the C-O bond in **10** was ketalized selectively and addition of samarium metal to the mixture produced methyl propionate (**13**) and unchanged cinnamaldehyde (**10**) (Scheme 2).

Finally, the differences of the reactivity of the ketones depending upon their ring size was manifested by a facile protection-reduction of androstane-3,17-dione (**14**). After the iodine-methanol and sodium borohydride treatment, the product was 17-hydroxyandostane-3-one (**16**) in more than 90% yield. In this case, the intermediate acetal **15** was isolated (Scheme 3).

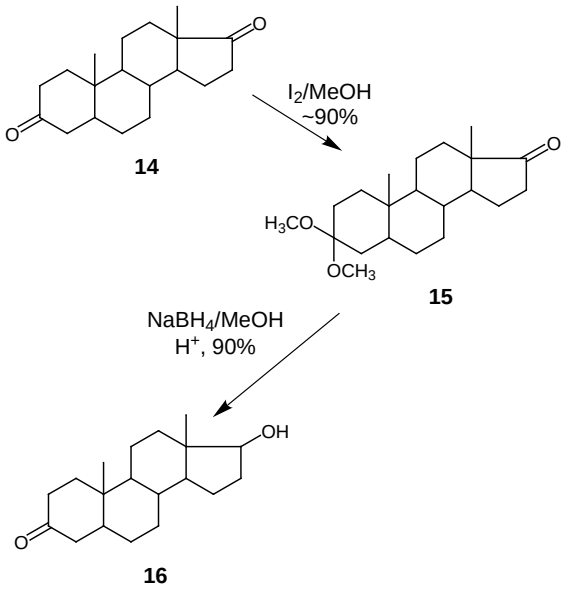
The facile acetalization of carbonyl compounds in the presence of molecular iodine deserves mechanistic investigations. Reaction of aldehydes (Table) with small amounts of hydroiodic acid indicated the formation of the acetals in low yield. This suggests that hydroiodic acid is the catalyst involved in the reaction.

In conclusion, the new, mild and attractive acetalization procedure[7] and the selectivity of acetalization-reduction route described in this paper should prove useful in the



Scheme 2

synthesis of natural products where it is absolutely necessary to have mild conditions, reactivity differences among functional groups, and reagents that are compatible with other acid-sensitive groups.



Scheme 3

Acknowledgement

This work was supported in part by a grant received from the Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation and NIH Cancer Center Support Grant, 5-P30-CA16672-25, in particular the shared resources of the Pharmacology and Analytic Center Facility.

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(7) General Procedure for Acetalization: The carbonyl compound (1 mmol) was dissolved in methanol (4 mL) or ethanol, and iodine (0.1 mmol) was added with stirring. After the starting material was consumed as indicated by TLC, methanol was evaporated. The crude product was extracted with dichloromethane, washed with saturated $NaHCO_3$, and dried over Na_2SO_4 and the solvent was evaporated. Finally the pure products were obtained by purification through basic alumina using ethyl acetate–hexane (10:90) as the solvent.
Procedure for Competitive Reduction of Two Carbonyl Compounds: The two investigated compounds (1 mmol each) were dissolved in dry methanol (4.0 mL), and iodine (12.5 mg) was added. The mixture was then stirred for 1 h. $NaBH_4$ (80.0 mg, 2 equiv) was then added in one portion with stirring. After the vigorous reaction subsided the reaction mixture was refluxed for 0.5 h. The reaction mixture was cooled, acidified (pH 3) by 1 N aqueous HCl, and extracted with dichloromethane. The ratio of the compounds was determined by a comparison study with known authentic samples by NMR.
Procedure for Competitive Reduction of Cinnamaldehyde and Methyl Cinnamate: The two compounds (1 mmol each) were dissolved in dry methanol (4.0 mL) and iodine (13 mg) was added. The mixture was then stirred for 1 h. After this, additional amounts of iodine (25 mg) were added and the mixture was stirred for 5 min. Samarium powder (2.0 mmol) was added under argon atmosphere with stirring. An exothermic reaction with evolution of gas was observed. After 20 min the solution was acidified (pH 3) by 1 N aqueous HCl; saturated NaCl was then added to the reaction mixture and extracted with dichloromethane. Drying of the organic solution over Na_2SO_4 and evaporation of the solvent gave a mixture that was analyzed by NMR.
3,3-Dimethoxyandrostan-17-one(**15**): Androstane-3,17-dione(14, 90 mg, 0.3 mmol) was dissolved in dry methanol (5 mL), and iodine (0.03 mmol) was added. The solution was stirred for 2 h. Methanol was evaporated off and the residue was dissolved in dichloromethane and washed with 5% $NaHCO_3$. After being dried, the organic layer was evaporated, and 101 mg (97%) of a semi-solid mass was obtained. Pure product was obtained by recrystallization from methanol, mp127 °C.
17-β-Hydroxyandrostan-3-one(**16**): Androstane-3,17-dione (90 mg, 0.3 mmol) was dissolved in of dry methanol (5 mL), and iodine (0.03 mmol) was added. The solution was stirred for 2h. When TLC indicated complete disappearance of androstane-3,17-dione, $NaBH_4$ (100 mg) was added and the mixture was stirred for 1 h. Water was then added, and the mixture was extracted with CH_2Cl_2. Drying of organic layer over Na_2SO_4 and removal of solvent under reduced pressure afforded 103 mg of a white solid: mp 171 °C, $[\alpha]_D$ +12.5 in MeOH.[2b] Hydrolysis of this dimethoxy compound (MeOH, 1 N aq. HCl 30 min, room temperature). Crytallization of the crude solid led to 17-β-hydroxyandrostan-3-one (**16**, 76 mg, 83%).