JOC Notes

Highly Efficient Chemoselective Deprotection of *O,O*-Acetals and *O,O*-Ketals Catalyzed by Molecular Iodine in Acetone

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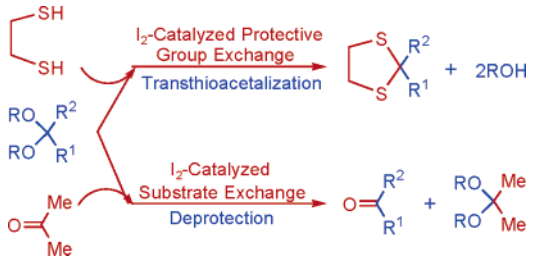
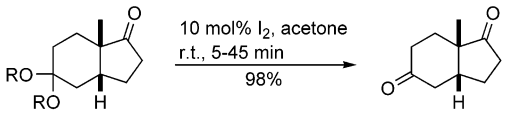
Abstract: An extremely convenient method for deprotection of acetals and ketals catalyzed by molecular iodine (10 mol %) in acetone is reported. The protocol achieved the deprotection of acyclic or cyclic *O,O*-acetals and *O,O*-ketals in excellent yields within a few minutes under neutral conditions. The double bond, hydroxyl group, and acetate group remained unchanged, and the highly acid-sensitive furyl, *tert*-butyl ethers, and ketone-oxime stayed intact under these conditions.

Carbonyl groups are protected frequently as *O,O*-acetals or *O,O*-ketals in the process of multistep organic synthesis. Therefore, deprotection of *O,O*-acetals or *O,O*-ketals is an essential functional group transformation.[1] This transformation is usually accomplished by aqueous acid hydrolysis, which suffers from incompatibility of many other functional groups. Although some weak acidic or nonacidic reagents have been developed and each showed some advantages,[1−10] such as $CeCl_3 \cdot 7H_2O$,[2] $FeCl_3$,[3] $TMSN(SO_2F)_2$,[4] Magtrieve,[5] CAN,[6] $Bi(NO_3)_3 \cdot 5H_2O$,[7] $Ce(OTf)_3$,[8] $Bi(OTf)_3$,[9] and hydrothermal conditions,[10] there remains a great need for a mild, neutral, and chemoselective protocol. Herein, we report a highly chemoselective deprotection procedure of acetals and ketals catalyzed by molecular iodine in acetone, which deprotects acyclic or cyclic acetals and ketals in excellent yields within a few minutes under neutral conditions.

SCHEME 1



SCHEME 2



1a R = -CH_3, 5 min, 98%
1j R = -CH_2CH_2-, 45 min, 98%

2a

Iodine-containing reagents, such as PI_3,[11] P_2I_4,[11] Me_3SiI,[12] $Me_3SiCl-NaI$,[13] and BF_3-NaI,[14] have been employed for the deprotection of acetals and ketals for decades. They have lost their appeal, to a great extent, due to low chemoselectivity, unsatisfactory yields, or the need for anhydrous conditions. Recently, the molecular iodine-catalyzed acetalization,[15] thioacetalization[16] of carbonyl groups, and transthioacetalization of *O,O*-acetals have been reported in excellent yields under neutral conditions. However, no molecular iodine-catalyzed deprotection of acetals and ketals has been reported to date. Realizing iodine-catalyzed transthioacetalization of *O,O*-acetals[16a] results essentially from the exchange between strongly and weakly nucleophilic protective groups, we reasoned that the deprotection of acetals and ketals can be achieved by exchange between substrates in a similar way (Scheme 1).

Thus, acetone was chosen as both the substrate and reaction solvent. Then, (3a*R*,7a*S*)-5,5-dimethoxy-7a-methyloctahydroinden-1-one (**1a**) and (3a*R*,7a*S*)-hexahydro-7a-methylspiro[1,3-dioxolane-2,5′(3*H*)inden]-1′(2*H*)-one (**1j**) were treated with 10 mol % of iodine in acetone at room temperature. To our great surprise, **1a** and **1j** gave the corresponding deprotected ketone (3a*R*,7a*S*)-octahydro-7a-methylinden-1,5-dione (**2a**) in almost quantitative yields within 5 and 45 min, respectively (Scheme 2). The control experiments revealed that no deprotections oc-

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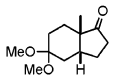
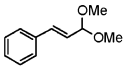
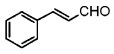
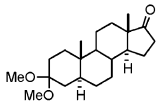
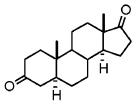
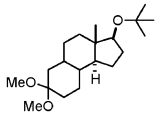
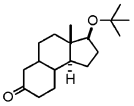
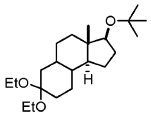
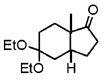
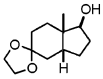
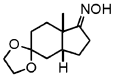
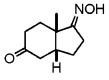
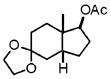
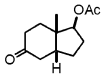
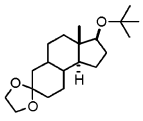
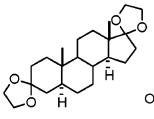
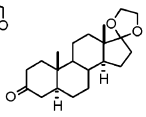
TABLE 1. Molecular Iodine-Catalyzed Deprotection of Acetals and Ketals in Acetone

Entry	Substrate (**1**)	Product (**2**)	Time (m) 25 °C	Yield (%)[a]	Time (m) 56 °C	Yield (%)[a]
a			5	98		
b			5	96		
c			5	96		
d			5	96		
e			5	98		
f			5	97		
g		**2f**	5	97		
h		**2a**	5	95		
i			5	93		
j		**2a**	45	98	5	98
k			5	98		
l			45	94	5	97
m			15	94	5	98
n			40	95	5	97
o		**2f**	20	90	5	97
p			30[b]	94		
q	**1p**	**2e**	25	97	5	98

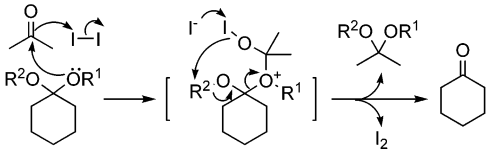
[a] Isolated yields. [b] Low temperature (0−5 °C) was used.

curred for either **1a** or **1j** without iodine or when acetone was replaced with another solvent such as THF, MeCN, or CH_2Cl_2. Although deprotection of acyclic ketal **1a** still occurred with prolonged reaction times (3−5 h) in those nonacetone solvents in the presence of equimolar H_2O, no reaction took place with the cyclic ketal **1j** even in the presence of 20 mol % of iodine.

It was interesting to find that the deprotection of cyclic ketal **1j** was slowed as the concentration of water in acetone increased. By using anhydrous acetone or commercial acetone (reagent ACS, ≤0.5% H_2O), the deprotection finished in 45 min at room temperature. However, it took 4.5 h in the presence of equimolar H_2O. Only a 10% yield of deprotected product was detected when the deprotection was carried out in aqueous acetone (1.0% H_2O) in 4.5 h. These phenomena (including the results from the replacements of solvents studies) are in full agreement with our hypothesis that the molecular iodine-catalyzed deprotection of acetals and ketals goes through a substrate exchange mechanism, rather than a hydrolysis mechanism. We presume that the deprotection initially involves a polarization of carbonyl group in acetone by molecular iodine, and a possible mechanism is proposed as shown in Scheme 3.

We also found that a primary equilibrium of substrate exchange between **1j** and acetone was established very

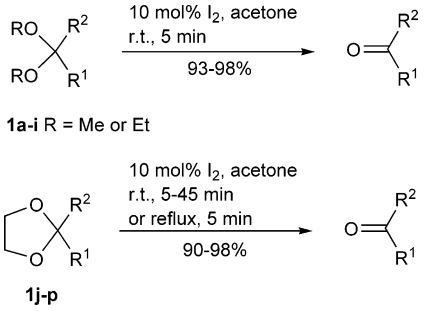
SCHEME 3



fast. Ketal **1j** was deprotected in 91% yield in the first 5 min, and an extra 40 min was required to convert the last 9% of **1j** to **2a**. However, this equilibrium can be shifted easily by elevating the reaction temperature. Thus, compound **1j** was deprotected completely in 30 min at 35 °C or in just 5 min at acetone refluxing temperature (56 °C).

To determine the scope and chemoselectivity of the reaction, different acetals and ketals (**1a**−**p**) were tested. As shown in Table 1, all substrates (entries **1a**−**q**) were deprotected in excellent yields under the mild conditions. The deprotection of dialkyl acetals and ketals (**1a**−**i**) was so fast that no reactivity differences were observed among those structurally diverse aldehydes and ketones. The double bond (**1c**), hydroxyl group (**1k**), and acetate group (**1m**) were tolerated under these conditions. Furthermore, the highly acid-sensitive furyl moiety (**1i**), *tert*-butyl ethers (**1f**, **1g**, **1o**), and ketone-oxime (**1l**) stayed intact. At 0−5 °C, the 3-ketal group in diketal **1p** was depro-

SCHEME 4



tected regioselectively to give **2p** in 94% yield. It is noteworthy that this protocol achieved excellent chemoselectivity and gave extremely clean products at different temperatures (Scheme 4).

In conclusion, a substrate exchange based molecular iodine-catalyzed deprotection of acetals and ketals was developed. The reaction featured convenience, mild and neutral conditions, high chemoselectivity, and excellent yields. It is likely to find use in the manipulation of carbonyl groups in complex natural product synthesis.

Experimental Section

General Procedure for the Molecular Iodine Catalyzed Deprotection of Acetals and Ketals in Acetone. A mixture of acetal or ketal (**1**, 5 mmol) and iodine (125 mg, 0.5 mmol) in acetone (20 mL, reagent ACS, $\leq$0.5% H_2O) was stirred at room temperature for 5 min [for dialkoxyl moieties (**1a**−**i**)] or at refluxing temperature (56 °C) for 5 min [for 1,3-dioxolane moieties (**1j**−**p**)]. Most of the acetone was then removed under vacuum, and the residue was diluted with dichloromethane (50 mL). The mixture was washed successively with 5% aqueous $Na_2S_2O_3$ (10 mL), H_2O (20 mL), and brine (20 mL). The organic layer was separated, dried over Na_2SO_4, and filtered. The solvent was removed to give product **2**, which was purified by short column chromatography (Table 1).

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra of all substrates and products in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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