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Tandem Acetalation−Acetylation of Sugars and Related Derivatives with Enolacetates under Solvent-Free Conditions

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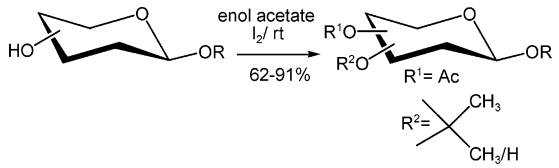

Molecular iodine catalyzes acetalation and acetylation of reducing sugars and sugar glycosides with stoichiometric amounts of enol acetates under solvent-free conditions, thereby facilitating the synthesis of various types of orthogonally protected sugar derivatives in short time and good yields. The outcome of the reaction can be controlled by variation in temperature. Thus at lower temperature, it is possible to obtain the acetonide acetate as a single product whereas peracetate is the major product at higher temperature.

Carbohydrates are useful chiral synthons in natural product synthesis.[1] They contain an abundance of hydroxy groups and it is often necessary to react only one (or some) of these groups at a time. This is generally possible by choosing suitable protecting group/s, which may be manipulated under different reaction conditions.[2] The introduction of such orthogonal protecting groups makes possible the removal of one set of protecting groups, using specific reagents and conditions that do not affect the others. This strategy plays a vital role in the chemical synthesis of biologically active oligosaccharides. Recently Wang et al. have reported a highly regioselective one-pot method that can be used to protect individual hydroxy groups of a monosaccharide unit by using a single catalyst TMSOTf.[3a] However, during the development of such strategies, one has to keep in mind the use of reagents in stoichiometric quantities to maintain atom economy and minimize waste so as to make it environment friendly.[3b,c] Our current efforts have been aimed at meeting the requirements of preparing various orthogonally protected sugars and related building blocks in a fashion that minimizes the reaction steps including the final workup.

Acetonide formation is the most commonly used protection for 1,2 (*cis*)- and 1,3-diols, which has extensively been used in carbohydrate chemistry to selectively mask the hydroxyls of different sugars. These reactions are generally effected either with a free carbonyl[4] (e.g., aldehyde, ketone) or a masked carbonyl (e.g., acetals,[5] ketals,[6] enolethers[7]) in the presence of a variety of catalysts such as mineral acid,[8] formic acid,[9] $CuSO_4$,[10] $ZnCl_2$,[11] *p*-toluenesulfonic acid,[12] camphorsulfonic acid,[13] iodine,[14] etc. The protection of alcohols with an acetyl group is another common transformation in organic synthesis. The process is sluggish in the absence of an appropriate catalyst. Though a number of methods are available, their use in carbohydrate chemistry has limitations. In almost all the cases acetic anhydride is used as the acetylating agent, generally in the presence of pyridine,[15] sodium acetate,[16] $Sc(OTf)_3$,[17] Et_3N-DMAP,[18] I_2,[19] $ZnCl_2$,[20] or $InCl_3$.[21] Perchloric acid[22] and sulfuric acid[23] immobilized on silica have been used as promoters for acetalation and subsequent acetylation of sugar glycosides in good yield, though the acidic conditions during reactions can lead to cleavage of acid-sensitive groups in the sugar ring.

In recent years, molecular iodine has emerged as an inexpensive, nontoxic, nonmetallic, and readily available catalyst for various organic transformations carried out with high selectivity. Molecular iodine-catalyzed acetonide formation[14] and acetylation[19] with acetone and acetic anhydride, respectively, are known in sugar chemistry. The regioselective acetylation

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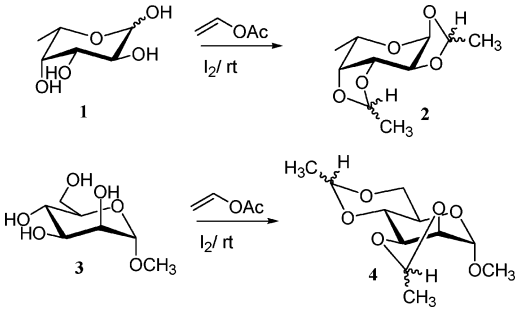
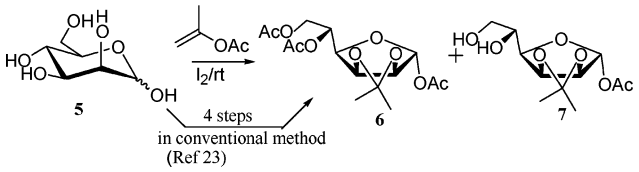
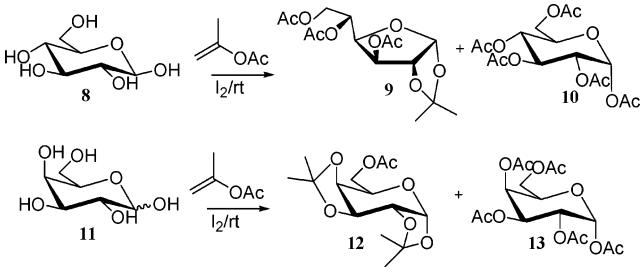
SCHEME 1. Reaction of VA with Sugars



SCHEME 2. Reaction of IPA with Mannose



SCHEME 3. Reaction of IPA with Glucose and Galactose



of alcohols with vinyl esters has also been reported by Bosco et al.[24] They reported that molecular iodine can catalyze the acetylation of primary and secondary alcohols with vinyl acetate (VA), where acetaldehyde is generated as a side product. We therefore envisaged that a combination of molecular iodine and isopropenyl acetate (IPA) or VA in the absence of a solvent would facilitate the formation of per-*O*-acetylated sugars or their acetals/ketals from unprotected sugars or their analogues under mild conditions and in shorter times.

Initially, we effected the reactions of free sugars, sugar glycosides, or pinitol with VA under solvent-free conditions in the presence of a catalytic amount of molecular iodine (10 mol %) and were surprised to observe that L-fucose and methyl α-DL-mannoside afforded diethylidene acetal derivatives in moderate yields (72−74%) at rt, instead of the expected per-*O*-acetylated derivatives (Scheme 1). Use of slightly higher than stoichiometric quantities (2.2 equiv) of VA was enough to bring about the observed transformations. Similar was the case with methyl mannoside. However, formation of diethylidene derivatives resulted in the generation of a new stereogenic center, leading to the formation of a mixture of inseparable diastereomers. Therefore, to avoid the inconvenience of handling diastereomeric mixtures (though inconsequential after deprotection), VA was replaced with IPA, with the anticipation that the resulting acetonide will be devoid of a new stereogenic center. This proved to be the case when a free sugar or unprotected sugar glycoside or pinitol reacted with IPA in the presence of a catalytic amount of molecular iodine, yielding various types of orthogonally protected sugar and pinitol derivatives in good yields. By conventional methods formation of these products would have taken several steps.

Thus, treating the reducing sugar D-mannose (**5**) with IPA and catalytic amounts of iodine led to the synthesis of 1,5,6-tri-*O*-acetyl-2,3-*O*-isopropylidene-α-D-mannofuranose (**6**) (81%) within 1 h, whereas by conventional method it required a four-step-reaction sequence.[25] Besides, a small amount of the side product 1-*O*-acetyl-2,3-*O*-isopropylidene-α-D-mannofuranose (**7**) (5%) was also isolated. Compound **6** was identified as a mannofuranose derivative from the presence of a characteristic one-proton multiplet at δ 5.31−5.34 in the ^{1}H NMR assigned to H-5 of the furanose form, while compound **7** was identified as a 5,6-diol from the upfield shifts of H-5, H-6 signals in the ^{1}H NMR compared to **6**, to which it could be easily converted by acetylation (Scheme 2).

A general procedure involved adding molecular iodine to a stirring suspension of the sugar in a calculated amount of IPA at rt. The reaction is exothermic and total dissolution of the substrate usually indicated the completion of the reaction. When carried out under neat conditions, the reaction completed quickly, but it took a longer time in a solvent such as acetonitrile, THF, or DMF, while solvents like diethylether, toluene, or DCM failed to bring about the conversion. Reaction rates and site of acetonide formation in per-*O*-acetylated products were markedly dependent on the configuration of the sugar ring and the quantity of IPA used. Prolonging the reactions in the presence of an excess of IPA resulted in the formation of higher amounts of peracetylated derivatives (anomeric α-acetate, e.g., compounds **10** and **13**) compared to peracetylated acetal derivatives. Other reducing sugars such as D-glucose (**8**) and D-galactose (**11**) underwent similar kinds of reactions to afford different products, e.g., 3,5,6-tri-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**9**) (69%) and 6-*O*-acetyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**12**) (81%) in good yield together with per-acetylated (anomeric α-acetate) sugar derivatives as minor side products (Scheme 3). On the other hand, it took three- and two-step-reaction sequences respectively to prepare **9** and **12** through a reported method.[26]

The versatility of the reagent system was further demonstrated by the formation of 2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-*β*-D-galactopyranosyl-1,2,3,6-tetra-*O*-acetyl-α-D-glucopyranose (**16**) and 1,2:3,4-di-*O*-isopropylidene-α-L-fucose (**14**) in good yields with lactose and fucose respectively as the substrates. The results of these useful transformations are given in Table 1.

After the successful conversion of the reducing sugars, the applicability of the reagent system was also evaluated in unprotected sugar glycosides and pinitol. Thus treatment of a suspension of methyl α-D-mannopyranoside (**3**) and IPA with a catalytic amount of iodine afforded methyl 4,6-di-*O*-acetyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (**19**) in 82% yield as confirmed by spectral data. It is noteworthy that D-mannose under similar condition yielded the furanose derivative **6**, implying that a free reducing terminus also affects the outcome of the reaction (Scheme 4). Notably, the reported preparation of **19** took three steps by the conventional method (70% yield), starting from methyl α-D-mannopyranoside.[10] Methyl *β*-D-galactopyranoside (**23**) and D-pinitol (**20**) underwent a similar kind of transformation to afford methyl 6-*O*-acetyl-3,4-*O*-isopropylidene-*β*-D-galactopyranoside (**24**) and 6-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-pinitol (**22**), respectively, in very good yields (entries 4 and 5, Table 2).

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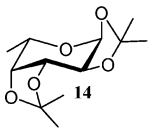
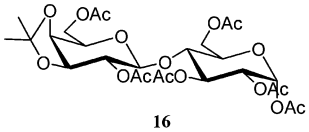
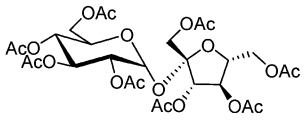
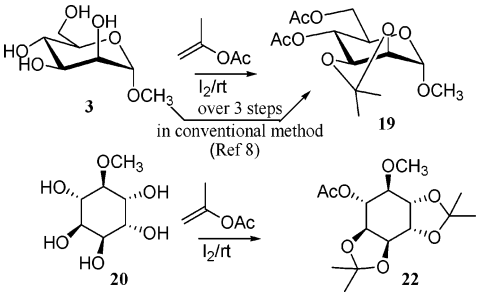
TABLE 1. Iodine-Promoted Ethylidination/Isopropylidination−Acetylation of Different Free Sugars

entry	starting material	reagents	time (h)	product[a]	yield[b] (%)	ref
1.	L-Fucose (**1**)	VA (2 equiv)	2	**2**	72	-
2.	**1**	IPA (2 equiv)	1.5	 **14**	62	27
3.	D-Mannose (**5**)	IPA (4 equiv)	1	**6**	81	25
4.	D-Glucose (**8**)	IPA (4 equiv)	2	**9**	69	28
5.	D-Galactose (**11**)	IPA (3 equiv)	0.7	**12**	81	29
6.	D-Lactose (**15**)	IPA (7 equiv)	0.6	 **16**	79	30
7.	Sucrose (**17**)	IPA (8 equiv)	0.5	 **18**	92	29

[a] All products were characterized by ^{1}H, ^{13}C NMR, and mass spectra. [b] Isolated yields.

SCHEME 4. Reaction of IPA with Methyl Mannoside and Pinitol



3 **19** **20** **22**

The present method also led to the development of a facile experimental protocol wherein a change in the reaction temperature resulted in the formation of differently preferred products. Accordingly, the outcome of a reaction can be predicted ahead of the experiment simply by controlling the temperature. Thus at lower temperature (i.e., −20 °C), it is possible to obtain acetonide acetate as a single product whereas at higher temperature (i.e., ∼80 °C) the peracetate is formed as the major product (Table 3).

These results indicate that the reagent system reacted preferentially with 1,2-*cis* diols to form corresponding acetal/ketals and the remaining hydroxy groups are acetylated (entries 6, 9, 12, and 16 in Table 1 and entries 21, 22, and 24 in Table 2). In the case of 1,3-diol (e.g., 4,6-positions of sugar residue in pyranose form) the initially formed ketal derivative might be hydrolyzed under the acidic condition in the presence of traces of moisture and eventually acetylated (entry 2 Table 2).

Though the mechanism of tandem acetal−acetylation is uncertain, based on our experiments and the earlier proposed mechanism of alcohol acetylation with enol acetate−iodine,[24,38] the acetal/ketal formation may be explained on the basis of activation of enolacetates by iodine to facilitate acetyl transfer (either to sugar hydroxyl or to residual moisture) and concomitant release of aldehyde/ketone to form acetal/ketal with *cis* diols. At elevated temperature (i.e., at ∼80 °C) with IPA, acetone evaporates from the reaction mixture, resulting in the formation of peracetate as the major product. The difference in outcomes with VA and IPA may also be rationalized from the fact that under the specified reaction conditions, VA releases acetaldehyde which can form a six-membered ethylidene ring with 4,6-OH groups of sugars in pyranose form,[31] while IPA generates acetone, which prefers to form a five-membered ring.[29]

The difference in product formation in reducing and nonreducing sugars (glycosides) may be explained as follows. As sugar glycosides are mostly locked in pyranoside conformation (chair form), the reagent system reacts preferentially with 1,2-*cis* diols (or 1,3-*cis* diols) to form the corresponding ketal/acetals.[32,34] In free sugars, on the other hand, contribution (and reactivity) of either of the furanose and pyranose forms and the greater acidity of the anomeric hydroxyl group play a major role.[25]

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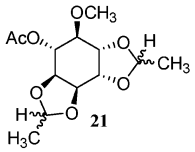
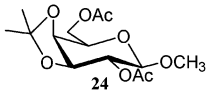
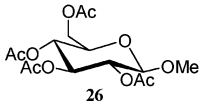
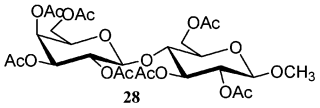
TABLE 2. Iodine-Promoted Ethylidenation/Isopropylidenation−Acetylation of Different Glycosides and Pinitol at RT

entry	starting material	reagents	time (h)	product[a]	yield[b] (%)	ref
1.	**3**	VA (2 equiv)	2	**4**	74	31
2.	**3**	IPA (3 equiv)	1	**19**	82	32
3.	**20**	VA (3 equiv)	2	 **21**	75	-
4.	**20**	IPA (3 equiv)	3	**22**	83	33
5.	Methyl β-D-galactopyranoside (**23**)	IPA (3 equiv)	0.7	 **24**	81	34
6.	Methyl β-D-glucopyranoside (**25**)	IPA (4 equiv)	0.6	 **26**	91	35
7.	Methyl β-D-lactopyranoside (**27**)	IPA (7 equiv)	0.7	 **28**	92	36

[a] All products were characterized by ^{1}H, ^{13}C NMR, and mass spectra. [b] Isolated yield.

TABLE 3. Effect of Temperature on Iodine Promoted Reactions with IPA[a]

		at −20 °C		at +80 °C	
entry	starting material[b]	product	*T* (min)/ yield (%)	product[c]	*T* (min)/ yield (%)
1	**1**	**14**	30/81	**29**[37]	5/75
2	**5**	**6**	25/84	**30**[37]	5/68
3	**8**	**9**	30/75	**10**[37]	5/84
4	**11**	**12**	20/86	**13**[37]	5/78
5	**3**	**19**	25/85	**31**[37]	5/65

[a] Mole proportions of IPA are the same as in Tables 1 and 2. [b] **1** = L-fucose; **5** = D-mannose; **8** = D-glucose; **11** = D-galactose; **3** = methyl mannoside. [c] **29** = 1,2,3,4-tetra-*O*-acetyl-α-L-fucopyranose. **30** = 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose. **10** = 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose. **13** = 1,2,3,4,6-penta-*O*-acetyl-α-D-galactopyranose. **31** = 1,2,3,4,6-penta-*O*-acetyl-α-D-galactopyranose.

In conclusion, a single-step, efficient, fast, and solvent-free catalytic reaction has been demonstrated for the preparation of peracetylated ethylidene acetals or isopropylidene ketals under mild and stoichiometric conditions in moderate to high yields. The major advantage of this reaction is that it does not require or generate any strong acid; as a result, the reaction medium is nearly neutral and free from unwanted byproducts. Additionally, the outcome of the reactions is also predictable as lower temperature leads to generation of acetonide acetate as the major product, whereas at higher temperature peracetate formation dominates.

Experimental Section

Typical Procedure for the Preparation of Peracetylated Isopropylidene Ketal. Molecular iodine (0.1 mmol) was added to a suspension of D-mannose (180 mg, 1 mmol) and IPA (400 mg, 4 mmol) at −20 °C, and the mixture was stirred at room temperature under nitrogen atmosphere. After the reaction was complete (TLC), it was extracted with dichloromethane (20 mL) and washed with saturated sodium thiosulfate solution (4 mL). The organic layer was dried over sodium sulfate, evaporated to dryness, and subjected to column chromatography on silica gel (100−200 mesh) by using petroleum ether (60−80) with increasing proportions of ethyl acetate (1−15%) to afford 1,4,6-tri-*O*-acetyl-2,3-*O*-isopropylidene-α-D-mannopyranose (**6**) (280 mg, 81%) as the major product; $[\alpha]_D^{26}$ +46.9 (*c* 0.7, $CHCl_3$) [lit. $[\alpha]_D^{20}$ +40.0 (*c* 1.4, $CHCl_3$)];[25] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (s, 1H), 5.31−5.34 (m, 1H), 4.82 (dd, 1H, J = 3.8, 5.9 Hz), 4.70 (d, 1H, J = 5.9 Hz, H-2), 4.63 (dd, 1H, J = 12.3, 2.5 Hz), 4.26 (dd, 1H, J = 7.8, 3.7 Hz), 4.19 (dd, 1H, J = 12.3, 5.7 Hz), 2.10, 2.09, 2.08 (3s, 9H), 1.48, 1.36 (2s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.0, 170.0, 169.6, 113.8, 100.9, 85.0, 80.3, 79.5, 78.1, 69.3, 63.4, 26.3, 25.2, 24.5, 21.4, 21.3; ESI MS (*m*/*z*) 369 $[M + Na]^+$. Anal. Calcd for $C_{15}H_{22}O_9$: C, 52.02; H, 6.40. Found: C, 51.93; H, 6.51.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C spectra of all the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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