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Note

Tetrabutylammonium tribromide (TBATB): a mild and efficient catalyst for O-isopropylidenation of carbohydrates

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ABSTRACT

A wide range of *O*-isopropylidene derivatives can be prepared from the sugars and their derivatives on reaction with acetone at room temperature by employing 2 mol % of tetrabutylammonium tribromide (TBATB) as a catalyst. Good yields, low catalyst loading, mild reaction conditions, and a non-aqueous workup procedure are some major advantages of this protocol.

The *O*-isopropylidene acetal group is a common protecting group extensively used in carbohydrate chemistry for the preparation of valuable building blocks.[1,2] Especially, acetonation of an aldohexose results in the formation of an *O*-isopropylidene derivative with a selective unmasked hydroxyl group, depending upon the nature of the sugar. For example, D-mannose (**1**) on reaction with acetone in presence of a catalyst provides 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**15**) with an unprotected hydroxyl group at the anomeric position. However, D-glucose (**2**) gives 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**16**) on acetonation, leaving a free OH group at the C-3 position.[3] These compounds serve as glycosyl acceptors,[4] glycosyl donors[5] and valuable starting materials for the synthesis of various natural products.[6] For example, 2,3:4,5-di-*O*-isopropylidene-D-xylose diethyl dithioacetal (**24**) has been utilized for the total synthesis of (+)-phorboxazole A, a potent cytostatic agent.[7] Recently, the *O*-isopropylidene derivative of galactose, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**17**), has been used for conformational studies as well as in theoretical calculations.[8] In addition, some of these isopropylidene derivatives, namely 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**16**), exhibits antipyretic and anti-inflammatory activities with a low toxicity.[9] Therefore, there is a continuous research interest to prepare these important class of compounds in a large quantities.

Conventionally, the *O*-isopropylidene acetal derivatives of sugars are usually prepared from the corresponding sugar on reaction with anhydrous acetone in the presence of a catalytic amount of acid or Lewis acid, for example, concd H_2SO_4[10] or a combination of anhydrous $ZnCl_2$ and H_3PO_4.[11] Literature reports reveal that a number of catalysts have been utilized for acetonation, including anhydrous copper(II) sulfate,[12] $FeCl_3$,[13] pyridinium *p*-toluenesulfonate (PPTS),[14] iodine,[15] ceric ammonium nitrate (CAN),[16] Zeolite HY,[17] and montmorillonite clay.[18] Recently, some methods have also been reported using triphenylphosphine polymer-bound/iodine complex,[19] sulfuric acid immobilized on silica,[20] vanadyl triflate ($VO(OTf)_2{\cdot}xH_2O$)[21], or bromodimethylsulfonium bromide (BDMS).[22] However, many of these procedures have one or more drawbacks such as an excessive amount of catalyst,[18] harsh reaction conditions,[20] and inert atmospheric reaction conditions.[19,21] Although a large number of methods have been developed over the years, there is still a need to find better alternatives by exploring new reagents as catalysts for the preparation of *O*-isopropylidene derivatives.

A few years ago, Chaudhuri et al. reported[23] the environmentally benign synthesis of various organic ammonium tribromides and their application in bromination reactions. Later on, we have shown the efficacy of these solid organic ammonium tribromides for the deprotection of dithioacetals,[24] the interconversion of carbonyl compounds into 1,3-oxathiolanes and vice-versa,[25] as well as the synthesis of α-bromo enones[26] and various naturally occurring flavone derivatives.[27] A wide variety of organic transformations have also been developed by others involving tetrabutylammonium tribromide (TBATB).[28–33] Knowing the unique behavior, properties, and stabilities of these reagents, we conceived the idea that tetrabutylammonium tribromide (TBATB)

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might be a useful catalyst for the preparation of various *O*-isopropylidene derivatives from sugars. In this paper, we report our successful results as depicted in Scheme 1.

For our present study, we prepared TBATB by following the standard literature procedure.[23] Initially, the reaction of D-mannose (**1**) was carried out in anhydrous acetone in presence of 0.5 mol % TBATB. The reaction was incomplete even after 8 h of stirring. Again, the same reaction was performed with 1, 2, and 5 mol % of catalyst, respectively. The best results (see Table 1) were obtained using 2 mol % catalyst with complete conversion within 2 h that furnished the product in 96% yield. The product was obtained as 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**15**), a thermodynamically controlled product, which was characterized by the usual spectroscopic data, melting point, and specific rotation. These data closely matched with the reported data.[19] It is worthwhile to mention that the same transformation was also achieved within 1 h using 5 mol % catalyst.

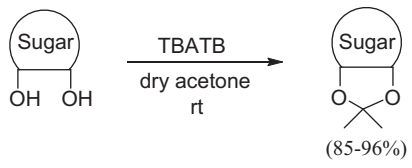
After optimizing the reaction conditions, other aldohexoses such as D-glucose (**2**) and D-galactose (**3**) were tried for isopropylidenation reaction and yielded the products **16** (88%) and **17** (89%) respectively. Next, a range of aldopentoses such as L-arabinose, D-xylose and D-ribose (entries 4–6, Table 2) were smoothly converted into the corresponding *O*-isopropylidene derivatives **18**–**20** in good yields.

To explore further the scope of this reaction, L-rhamnose (**7**) and D-mannitol (**8**) were transformed into the corresponding acetonides **21** and **22** under similar reaction conditions. It is important to mention here that a wide variety of diethyl dithioacetal derivatives of various sugars such as L-arabinose, D-xylose, and L-rhamnose (entries 9–11, Table 2) were also converted into the corresponding products **23**–**25** in good yields without any effect on the dithioacetal group. Further, we have extended our protocol for the O-isopropylidenation of methyl α-glucopyranoside (**12**) and uridine (**13**) and have provided the desired products **26** and **27** in good yields as shown in Table 2. Unfortunately, we did not get the desired product while the reaction was carried out with disaccharide derivative **14** in acetone using TBATB as catalyst under identical reaction reactions. However, we are trying to find out the suitable reaction conditions to obtain the desired *O*-isopropylidenation products from disaccharides, which will be reported in due course.

Interestingly, we note that the conversion of the various free sugars to the respective *O*-isopropylidene derivatives can be achieved on a larger scale (100 mmol) without any difficulty by using only 1 mol % of the catalyst. For example, the reaction of the diethyl dithioacetal of L-arabinose (entry **9**, 25.6 g, 100 mmol) was investigated in dry acetone (400 mL) in the presence of TBATB (1 mmol). The reaction was complete within 2 h, and the desired product **23** was obtained in 91% yield. The above result indicates that a large-scale reaction is also feasible using a lesser amount of catalyst.

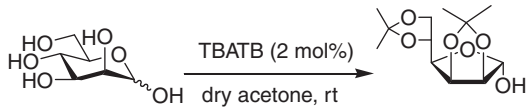
The formation of the product may be explained as follows: It was proposed earlier that benzyltrimethylammonium tribromide can react with alcohol to generate dry HBr in the medium.[34] We thus propose that dry HBr generated in situ catalyzes the O-isopropylidenation reaction of sugars or other sugar derivatives to the corresponding *O*-isopropylidene compounds. The reaction of D-mannose (**1**) and acetone was also examined with aqueous 48% HBr (5 μL) at room temperature. It was found that it requires a longer reaction time and provides a relatively low yield (64%) of product. Furthermore, the efficiency of TBATB in comparison with other catalysts is shown in Table 3. All products were fully characterized by IR, ^{1}H and ^{13}C NMR spectroscopy, specific rotation, and elemental analysis.

In summary, we have demonstrated a simple and efficient method for the preparation of *O*-isopropylidene derivatives from free sugars as well as from acyclic sugar derivatives by employing TBATB as catalyst. The notable advantages of the present protocol are the following: good yields, short reaction times, a stable and easy to handle catalyst, as well as a lower amount of catalyst loading. Due to its operational simplicity, generality, and efficacy, this method is expected to have wider applicability for the preparation of various *O*-isopropylidene derivatives of sugars.



Scheme 1. O-Isopropylidenation of sugars.

Table 1
Screening of amount of TBATB for the O-isopropylidation of D-mannose at room temperature



Entry	Catalyst (mol %)	Time (h)	Conversion[a] (%)	Yield[b] (%)
1	No catalyst	12	0	0
2	0.5	8	50	75
3	1	5	70	80
4	2	2	100	96
5	5	1	100	94

[a] The reactions were performed with 2 mmol scale in 10 mL of dry acetone.
[b] Isolated yield based on starting material recovery.

1. Experimental

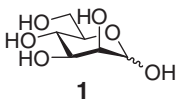
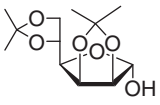
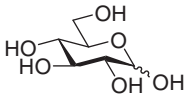
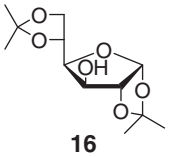
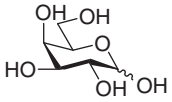
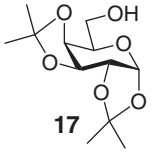
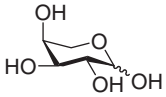
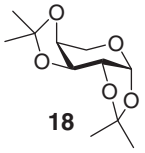
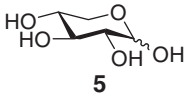
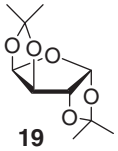
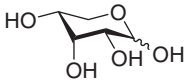
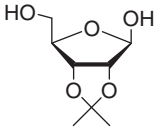
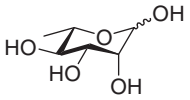
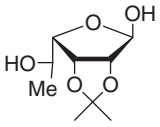
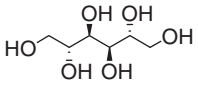
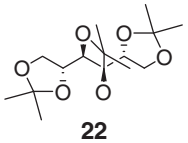
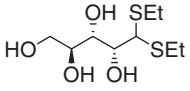
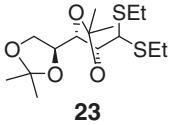
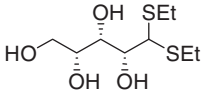
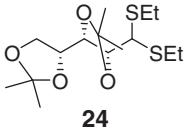
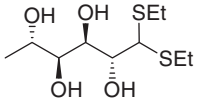
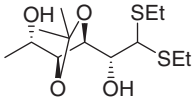
1.1. General methods

Starting materials and reagents used were of commercial grade. The progress of all reactions was monitored by TLC using plastic sheets precoated with Silica Gel 60 F_{254} to a thickness of 0.2 mm (E. Merck). Spots were detected by MOSTAIN solution (by dissolving 20 g ammonium heptamolybdate and 0.4 g cerium(IV) sulfate in 400 mL 10% H_2SO_4 solution). Column chromatography was carried out using silica gel (60–120 mesh, E. Merck, or Qualigen). Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 343 Polarimeter at 25 °C. IR spectra were recorded on a Perkin–Elmer IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian (400 MHz) spectrometer using TMS as the internal standard. Chemical shifts are expressed in parts per million (δ in ppm) in the order of multiplicity, coupling constant (in Hz), no. of protons and signal assignment. Elemental analysis was performed using a Perkin–Elmer CHNS/*O*-2400 Series II elemental analyzer.

1.2. General experimental procedure

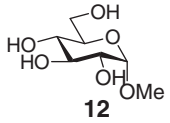
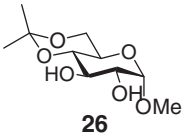
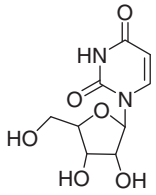
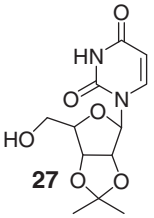
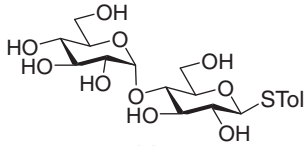
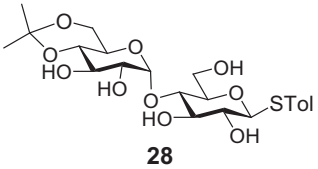
To a stirred solution of the sugar (2 mmol) in dry acetone (10 mL) tetrabutylammonium tribromide (TBATB) (19 mg, 0.04 mmol) was added at room temperature. The reaction was monitored by TLC as mentioned in Table 2. After completion of the reaction, one drop of NEt_3 was added to reaction mixture, and then acetone was removed on a rotary evaporator. Then the

Table 2
Results of the O-isopropylidenation of free sugars and their derivatives using TBATB as catalyst

Entry	Substrate	Product	Time (h)	Yield[a,b] (%)	Reference
1	 **1**	 **15**	2	96	19
2	 **2**	 **16**	8	88[c]	19
3	 **3**	 **17**	8	89[c]	19
4	 **4**	 **18**	5	86	19
5	 **5**	 **19**	3	89	22
6	 **6**	 **20**	1.5	86	19
7	 **7**	 **21**	1	88	22
8	 **8**	 **22**	2	94	22
9	 **9**	 **23**	1.5	91	22
10	 **10**	 **24**	1.5	85	22
11	 **11**	 **25**	1	87	22

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Product	Time (h)	Yield[a,b] (%)	Reference
12	 **12**	 **26**	10	72[c]	34
13	 **13**	 **27**	6	76	35
14	 **14**	 **28**	24	0.0	

[a] All products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and by specific rotation and elemental analysis.
[b] The reaction was carried out with the sugar (2 mmol) in dry acetone (10 mL) using 2 mol % of catalyst TBATB.
[c] A trace amount of sugar remains undissolved.

Table 3
O-Isopropylidenation of D-glucose and D-mannose using various catalysts and their amount of loading

Entry	Substrate	Catalyst	Amount (mol %)	Time (h)	Yield[a] (%)
1	D-Glucose	$FeCl_3$	>10	6	83[13]
		Iodine	>10	4	80[15]
		)–Ph_2P–I_2	200	30 min	95[19]
		$VO(OTf)_2$	5	10	89[21]
		BDMS	5	10	84[22]
		TBATB	2	8	88 (in this work)
2	D-Mannose	$FeCl_3$	>10	1	90[13]
		Iodine	>10	25 min	85[15]
		)–Ph_2P–I_2	200	30 min	95[19]
		$VO(OTf)_2$	5	3	92[21]
		BDMS	5	2	90[22]
		TBATB	2	2	96 (in this work)

[a] Isolated yields.

crude residue was passed through a silica gel column to obtain the desired product in pure form. Compounds **15**, **16**, and **22** were isolated from the crude mixture by direct recrystallization after removing excess acetone. The spectral data of the compounds **15**–**18** and **20** have previously been reported,[19] and the spectral data are in good agreement with our data. Similarly, the spectral data of the compounds **19** and **21**–**25** have recently been reported.[22]

1.2.1. Methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (26)

White solid: mp 112–114 °C (lit.[34] 116 °C); $[\alpha]_D^{25}$ +108.6 (*c* 1.0, H_2O) [lit.[34] $[\alpha]_D^{25}$ +111 (*c* 1.0, H_2O]; IR (KBr): 3436, 2975, 2948, 1371, 1228, 1201, 1068, 974, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.59 (d, J = 2.0 Hz, 1H, OH), 3.41 (s, 3H, CH_3), 3.52 (q, J = 9.6 Hz, 1H, H-5), 3.54–3.64 (m, 2H, H-2, and H-4), 3.73 (t, J = 10.8 Hz, 1H, H-6′), 3.77 (t, J = 10.0 Hz, 1H, H-3), 3.86 (dd, J = 10.8 Hz, J = 5.6 Hz, 1H, H-6), 4.74 (d, J = 3.6 Hz, 1H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 29.3, 55.6, 62.5, 63.5, 72.1, 73.2, 73.7, 99.9, 100.0; Anal. Calcd for $C_{10}H_{18}O_6$ (234.25): C, 51.27; H, 7.75. Found: C, 51.16; H, 7.58.

1.2.2. 2′,3′-*O*-Isopropylideneuridine (27)

White solid: mp 145–146 °C (lit.[35] 146–1147 °C); IR (KBr): 3430, 3316, 2984, 1691, 1586, 1375, 1221, 1031, 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.99 (br s, 1H, NH), 3.81 (br d, J = 11.6 Hz, 1H, H-5′), 3.92 (br d, J = 11.6 Hz, 1H, H-5′), 4.30 (d, J = 3.2 Hz, 1H, H-4′), 4.96 (dd, J = 3.6, 6.4 Hz, 1H, H-2′), 5.04 (dd, J = 2.8, 6.4 Hz, 1H, H-3′), 5.59 (d, J = 1.6 Hz, 1H, H-1′), 5.74 (d, J = 8.0 Hz, 1H, H-5), 7.39 (d, J = 8.0 Hz, 1H, H-6), 9.11 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 27.2, 62.1, 80.6, 84.4, 86.9, 94.2, 102.3, 114.4, 142.4, 150.7, 164.3; Anal. Calcd for $C_{12}H_{16}N_2O_6$ (284.27): C, 50.70; H, 5.67; N, 9.85. Found: C, 50.53; H, 5.51, N, 9.96.

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