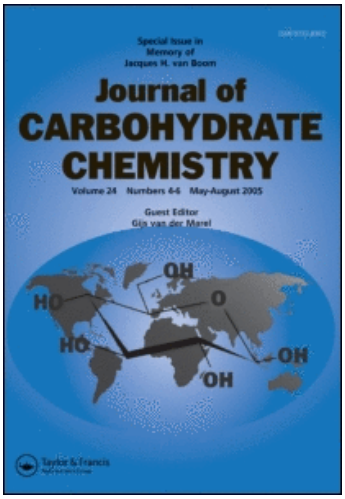

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Efficient Iodine-Catalyzed Preparation of Benzylidene Acetals of Carbohydrate Derivatives

Rajib Panchadhayee[a]; Anup Kumar Misra[a]
[a] Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow, UP, India

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Efficient Iodine-Catalyzed Preparation of Benzylidene Acetals of Carbohydrate Derivatives

Rajib Panchadhayee and Anup Kumar Misra

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow, UP, India

An efficient preparation of benzylidene acetals of carbohydrate derivatives catalyzed by iodine has been developed. Yields were excellent in every case.

Keywords Carbohydrate, Benzylidene acetal, Iodine, Protecting group

INTRODUCTION

Preparation of suitably functionalized monosaccharide derivatives are the basic requirements in the synthesis of oligosaccharides. Benzylidene acetal is one of the frequently used protecting groups in the oligosaccharide synthesis for the temporary protection of C-4/C-6 hydroxyl groups in carbohydrate derivatives.[1] It can be removed easily under acidic hydrolysis[2] or under neutral condition by hydrogenolysis.[3] One of the two C-O bonds of the benzylidene acetal can be regioselectively opened under reductive conditions for its application in oligosaccharide synthesis.[4] For these reasons several methods have appeared in the literature for the introduction of benzylidene acetal moiety in carbohydrates. Most of the methods are based on the original report using benzaldehyde and zinc chloride.[5] As a modification a transacetalation reaction condition has been adopted using benzaldehyde dimethylacetal replacing benzaldehyde in the presence of several Lewis acids (e.g., *p*-toluenesulfonic acid,[6] camphorsulfonic acid,[7] etc.) and heterogeneous catalysts.[8,9] Benzylidene acetal formation has

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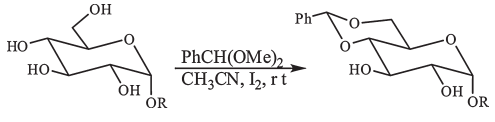
Address correspondence to Anup Kumar Misra, Medicinal and Process Chemistry Division, Central Drug Research Institute, Chattar Manzil Palace, Lucknow 226001, UP, India. E-mail: akmisra69@rediffmail.com

also been carried out under a basic condition using dibromotoluene and pyridine.[10] However, most of these methods are time consuming, often requiring reaction periods in excess of 24 h for completion as well as a large excess of reagent and tedious workup followed by chromatographic purification. Therefore, there is a need for a practical synthetic strategy, which renders the access to the benzylidene acetal-containing carbohydrate derivatives using stoichiometric reagents in a short reaction time. In recent years, molecular iodine has been used as an inexpensive, nonmetallic, nontoxic bench-top catalyst in several functional group transformations in carbohydrate chemistry.[11] It has been applied to activate thioglycosides,[12] glycosyl sulfoxides,[13] and glycosyl halides[14] in the oligosaccharide synthesis. In this communication we describe a rapid preparation of benzylidene acetals of carbohydrate derivatives using benzaldehyde dimethylacetal in the presence of molecular iodine as catalyst (Sch. 1).

RESULTS AND DISCUSSION

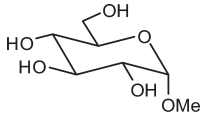
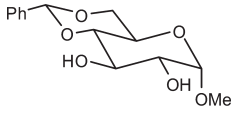
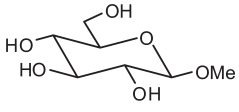
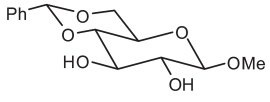
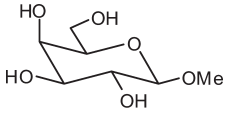
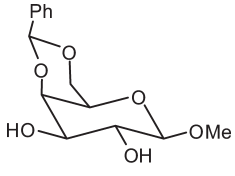
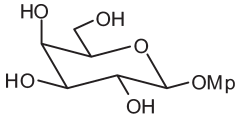
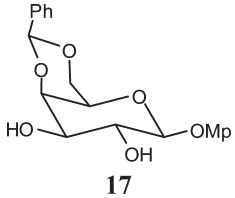
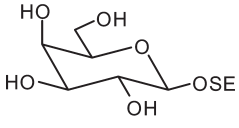
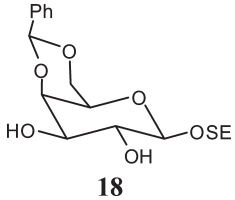
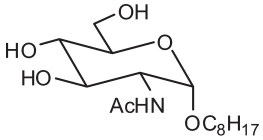
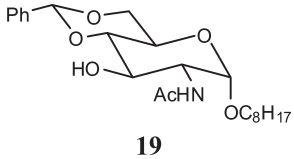
In a set of initial experiments, treatment of methyl α-D-glucopyranoside (**1**) with benzaldehyde dimethylacetal (1.1 mol equiv.) in the presence of molecular iodine (0.5 equiv.) in dry acetonitrile at rt led to the corresponding 4,6-*O*-benzylidene acetal (**3**) within 1 h (TLC; EtOAc-hexane 4:1). After optimization of the reaction conditions it was observed that treatment of compound **1** with benzaldehyde dimethylacetal (1.1 equiv.) in the presence of iodine (0.1 equiv.) could furnish compound **3** in almost quantitative yield in 1 h at rt. Iodine was removed during the removal of solvents under reduced pressure and the compound collected proved to be pure by NMR and mass spectrometry. Following similar reaction conditions, a series of benzylidene acetal-containing carbohydrate derivatives were prepared in excellent yield (Table 1). A 50-mmol scale benzylidenation of methyl α-D-glucopyranoside using the optimized reaction protocol furnished the desired product without affecting the overall yield, indicating that the reagent system is equally viable in a scale-up preparation. The reaction condition has been successfully applied for the preparation of 4-methoxybenzylidene acetal of carbohydrate derivatives (Table 1, entry 13–16). All known products gave acceptable spectral data that matched with the cited references.

In conclusion, an efficient protocol has been demonstrated for the preparation of 4,6-*O*-benzylidene derivatives of carbohydrate derivatives using benzaldehyde



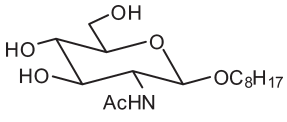
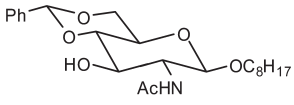
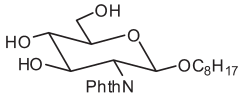
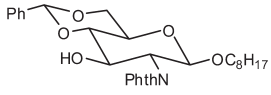
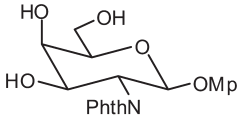
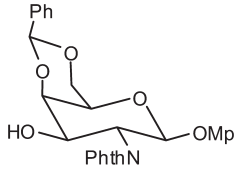
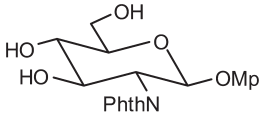
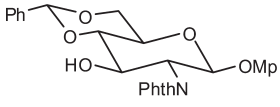
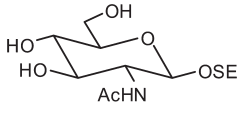
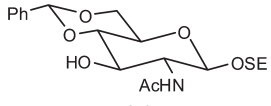
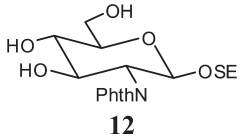
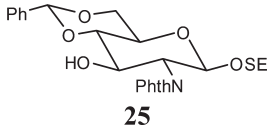
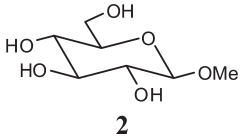
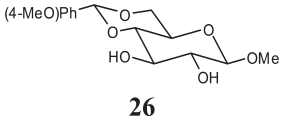
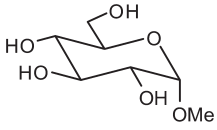
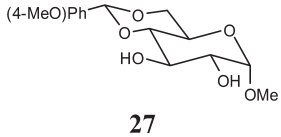
Scheme 1: Molecular iodine-catalyzed benzylidene acetal formation in carbohydrate derivatives.

Table 1: Preparation of benzylidene acetals of carbohydrate derivatives using benzaldehyde dimethylacetal in the presence of iodine[a].

Entry	Substrates	Products	Time (h)	Yield (%)	Ref.
1	 **1**	 **14**	1	90	(6)
2	 **2**	 **15**	1	92	(6)
3	 **3**	 **16**	1	90	(15)
4	 **4**	 **17**	1	88	(8)
5	 **5**	 **18**	1	85	(8)
6	 **6**	 **19**	1.5	85	(8)

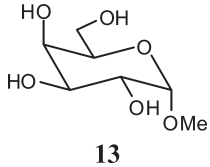
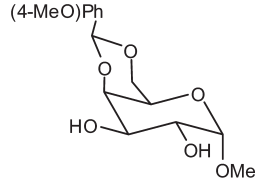
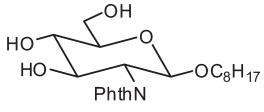
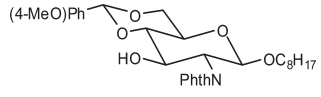
(*continued*)

Table 1: Continued.

Entry	Substrates	Products	Time (h)	Yield (%)	Ref.
7	 **7**	 **20**	1.5	80	(16)
8	 **8**	 **21**	1	90	(17)
9	 **9**	 **22**	1.25	85	—
10	 **10**	 **23**	1	90	(18)
11	 **11**	 **24**	1.5	85	(19)
12	 **12**	 **25**	1	88	(20)
13	 **2**	 **26**	1.25	80	(8)
14	 **1**	 **27**	1.25	82	(21)

(*continued*)

Table 1: Continued.

Entry	Substrates	Products	Time (h)	Yield (%)	Ref.
15	 **13**	 **28**	1.25	80	(22)
16	 **8**	 **29**	1	78	(23)

[a]Reaction condition: substrate (1 mmol), benzaldehyde dimethylacetal (1.1 mmol), CH_3CN, iodine (0.1 mmol), rt.
Mp: 4-methoxyphenyl; SE: 2-trimethylsilylethyl.

dimethyl acetal in the presence of a catalytic amount of molecular iodine. Use of iodine, a cheap bench-top chemical, will certainly attract synthetic carbohydrate chemists as a practical alternative to the currently used hazardous, moisture-sensitive acidic catalysts for the preparation of benzylidene derivatives.

EXPERIMENTAL

General Methods

All the reactions were monitored by thin layer chromatography over silica gel-coated TLC plates. The spots on the TLC were visualized by warming the ceric sulphate [2% $Ce(SO_4)_2$ in 2N H_2SO_4]-sprayed plates on a hot plate. Silica gel 230 to 400 mesh was used for column chromatography. ^1H and ^{13}C NMR were recorded on a Bruker Advance DPX 300 MHz using TMS as internal reference. Chemical shift value is expressed in ppm. Elementary analysis was carried out on a Carlo ERBA-1108 analyzer. Optical rotations were measured at 25°C on a Rudolf Autopol III polarimeter. Commercially available grades of organic solvents of adequate purity were used in all reactions.

General Procedure for the Benzylidenation of Carbohydrate Derivatives

To a solution of the sugar substrate (1 mmol) in dry acetonitrile (2 mL) was added benzaldehyde dimethylacetal (1.1 mmol) followed by iodine (25 mg,

0.1 mmol). The mixture was stirred at rt until TLC revealed complete consumption of the starting material to a faster-moving component (Table 1). Evaporation under reduced pressure to remove the solvents and the catalyst yielded the desired product in >95% purity, which was characterized by spectral analysis.

*4-Methoxyphenyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-β-D-galactopyranoside (**22**)*

Yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08–7.43 (m, 9H, Ar-H), 6.95 (d, $J = 9.0$ Hz, 2H, Ar-H), 6.77 (d, $J = 9.0$ Hz, 2H, Ar-H), 5.85 (d, $J = 9.0$ Hz, 1 H, H-1), 5.65 (s, 1H, PhC*H*), 4.73 (t, $J = 9.0$ Hz, 1H, H-2), 4.62 (dd, $J = 9.6$, 3.0 Hz, 1H, H-3), 4.42 (d, $J = 12.0$ Hz, 1H, H-6_a), 4.36 (d, $J = 3.0$ Hz, 1H, H-4), 4.12 (d, $J = 12$ Hz, 1H, H-6_b), 3.74 (s, 3 H, OCH_3), 3.72–3.70 (m, 1H, H-5); ESI-MS: m/z 526.2 $[M + Na]^+$; Anal. Calcd. for $C_{28}H_{25}NO_8$ (503.16): C, 66.79; H, 5.0; found: C, 66.55; H, 5.22.

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