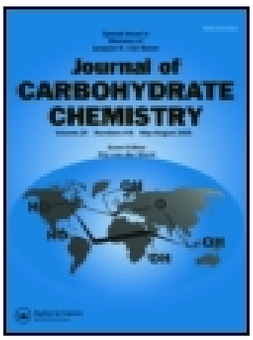

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Practical preparation of mono- and di-*O*-isopropylidene derivatives of monosaccharides and methyl 4,6-*O*-benzylidene glycosides from free sugars in a deep eutectic solvent

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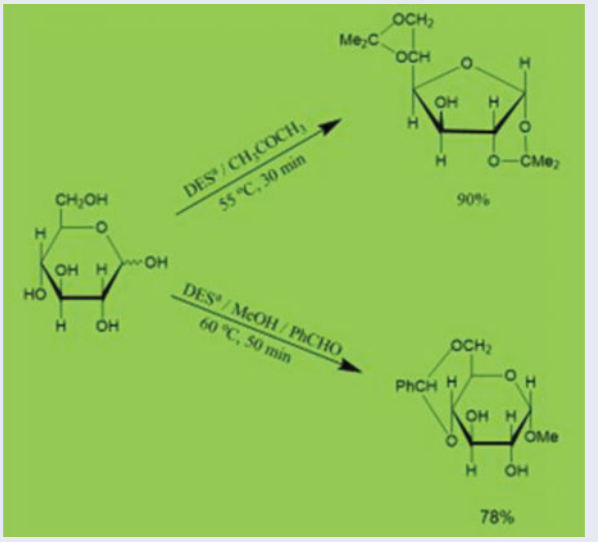
ABSTRACT

Free sugars were rapidly converted into the corresponding di-*O*-isopropylidene derivatives and methyl *O*-benzylidene glycosides in excellent yields and purity in a deep eutectic solvent made from choline chloride and malonic acid (ChCl:MA). Reaction conditions were mild; work-up was easy, and further purification was not necessary. Given the inexpensive, nontoxic, and recyclable nature of ChCl:MA, this protocol is environmental friendly.

GRAPHICAL ABSTRACT

A mild and efficient preparation of *O*-isopropylidene derivatives and methyl 4,6-*O*-benzylidene glycosides from monosaccharides in a deep eutectic solvent.



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Deep eutectic solvents; methyl *O*-benzylidene glycosides; *O*-Isopropylidene sugar derivatives

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Introduction

O-Isopropylidenation, glycosidation, and *O*-benzylidenation of monosaccharides are some basic reactions widely employed in synthetic carbohydrate chemistry.[1–3] The conventional method consists of condensing a sugar with acetone, an alcohol, and benzaldehyde in the presence of a suitable catalyst under anhydrous conditions. Catalysts used include mineral acids,[4] anhydrous zinc chloride along with phosphoric acid,[5] ion exchange resins,[6] anhydrous copper(II) sulfate,[7] iodine,[8] anhydrous ferric chloride,[9] γ-Fe_2O_3,[10] anhydrous aluminum chloride,[11] Zeolite HY,[12] BDMS,[13] and CAN.[14] However, these methods sometimes suffer from low yields[11] and long reaction times.[12,13] In some cases, work-up is tedious and column chromatography becomes necessary for obtaining pure products.[8,10,11,12,13] Hence, there is a clear need for a practical methodology for the preparation of these useful sugar derivatives on a large scale.

A deep eutectic solvent (DES) is a mixture of a quaternary ammonium salt, e.g., choline chloride, with hydrogen bond donating compounds, such as urea, glycerol, malonic acid, etc. These mixtures form eutectics that exhibit melting points much lower than that exhibited by the individual components. DESs possess many beneficial properties, such as non-volatility, non-toxicity, biodegradable nature, and recyclability,[15,16] and have emerged as alternatives to solvents generally used in organic synthesis. A partial list of some reactions conducted in DES includes preparation of nitroaldols,[17] esters,[18] phthalimides,[19] coumarins,[20] xanthenes,[21] formamides,[22] and bisamides.[23] We recently reported a one-pot synthesis of per-*O*-acetylated hemiacetals from free sugars[24] and the Ferrier reaction of glycals in a DES.[25] Described herein is a simple and convenient large scale method for the synthesis of *O*-isopropylidene sugar derivatives and methyl *O*-benzylidene glycosides from free sugars by using a DES prepared from choline chloride and malonic acid (ChCl:MA).

Results and discussion

We initially treated D-glucose (1.0 mmol) with dry acetone (2 mL) in the presence of ChCl:MA (2 g) at room temperature. Thin layer chromatography (TLC) analysis indicated the formation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**1a)** that was isolated in a 78% yield after 4 h. The same reaction when carried out at 55°C was complete within 20 min and afforded **1a** in a 90% yield as a free flowing crystalline material by extraction with ethyl acetate (3 × 20 mL) followed by evaporation of the extract. When DESs prepared from choline chloride:urea and choline chloride:glycerol (entries 2–3, Table 1) were used we obtained lower yields. D-Galactose, D-mannose, D-xylose, L-arabinose, D-fructose, and D-glucal likewise afforded the corresponding *O*-isopropylidene derivatives in 82–93% yields (Table 2).

The reaction could be conveniently carried out on a large scale. Thus, 10 g of D-glucose was converted into 13 g (a 90% yield) of glucose diacetonide within 1 h.

Acetonation of D-lactose by using our protocol was not as successful. While TLC did show the formation of a slightly less polar product, a significant amount of

Table 1. Screening of deep eutectic solvents and optimization of reaction temperature.

Entry	Deep eutectic solvent	Time	Temperature (°C)	Yield (%)
1	ChCl:Malonic acid	4.0 h	rt	78
		3.5 h	40	86
		2.5 h	45	89
		20 min	55	90
2	ChCl:Ethylene glycol	4.0 h	rt	80
		3.5 h	40	72
		2.5 h	45	86
		20 min	55	88
3	ChCl:Urea	4.0 h	rt	75
		3.5 h	40	80
		2.5 h	45	82
		20 min	55	85

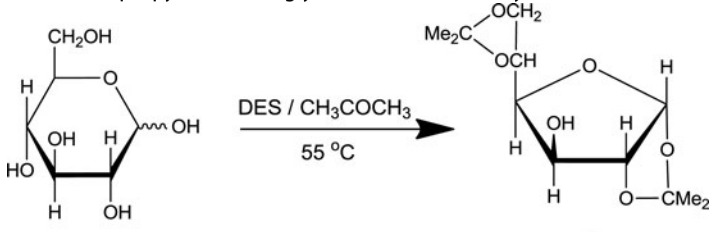
ChCl = Choline chloride

D-lactose remained unreacted even after boiling the DES–acetone–sugar mixture under reflux for 24 h. Furthermore, we were unable to extract the product formed owing to its poor solubility in solvents such as ethyl acetate and dichloromethane. Inability to convert disaccharides to their *O*-isopropylidene derivatives is a limitation of our protocol.

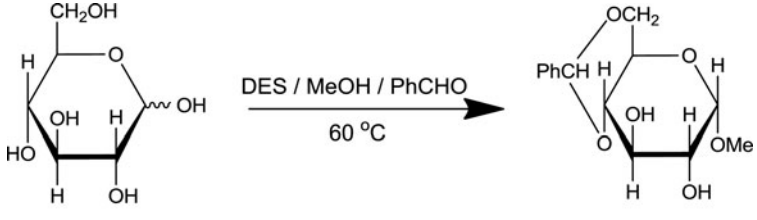
We next attempted the preparation of methyl glycosides in ChCl:MA. We were delighted to observe the formation of methyl α-D-glucopyranoside by stirring a mixture of methanol (8.0 mL), D-glucose (2.5 g, 13.8 mmol), and ChCl:MA (15 g) at 60°C for 30 min. However, we were not able to extract it from its solution in ChCl:MA on account of its poor solubility in solvents such as ethyl acetate and dichloromethane. We then added benzaldehyde (1.4 mL) in order to find out whether it could be converted into a 4,6-*O*-benzylidene derivative and thereby facilitate extraction. TLC indeed indicated the formation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**2a**), which could now be readily extracted with ethyl acetate. We obtained a yield of 78%. We have thus developed a quick and convenient one-pot preparation of this very useful intermediate that does not require (a) large amounts of methanol and benzaldehyde and (b) isolation of methyl α-D-glucopyranoside. D-Mannose and D-galactose likewise afforded the corresponding methyl 4,6-*O*-benzylidene glycosides (see Table 2). The preparation could be readily scaled up and we have prepared 6.2 g of **2a** from 5.0 g of D-glucose in a few hours.

The results showed that ChCl:MA promoted O-isopropylidenation, glycosidation, and O-benzylidenation of free sugars were comparable to or better than conventional methods with respect to yields obtained. These were considerably faster and more convenient as well. The rapid rate of reaction may be explained by the presence of multi-molar quantities of malonic acid resulting in a large Bronsted acid concentration together with the high hydrogen bonding capacity of the eutectic.[35] Free flowing powdery material is obtained in case of derivatives that exist as solids. Although optical rotation, melting point (wherever applicable) and ^{1}H NMR spectra of isolated materials do not indicate absolute analytical purity, we believe that the described derivatives are sufficiently purely based on comparison of ^{1}H NMR spectra recorded by us with those reported (see supporting information), which can be used for further synthetic transformations without additional purification.

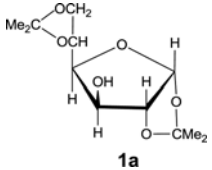
Table 2. Isopropylidenation, glycosidation, and benzylidenation of monosaccharides (2.5 g of starting material used).



1a

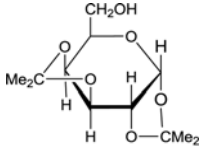
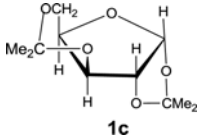
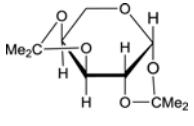
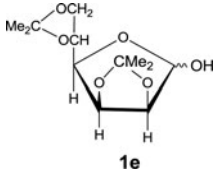
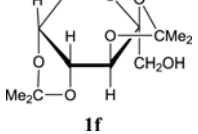


2a

Entry	Starting material	Product	Observed Time (min)	Observed Yield (%)	Observed mp (°C)	Observed $[\alpha]_{25}^{D}$	Reported Time (h)	Reported Yield (%)	Reported mp (°C)	Reported $[\alpha]_{25}^{D}$	Ref.
1	D-Glucose	 **1a**	20	90	107–109	− 18.1	2	90	109–110	− 18.5	[12,13]

(*Continued on next page*)

Table 2. Continued

Entry	Starting material	Product	Observed				Reported				Ref.
			Time (min)	Yield (%)	mp (°C)	$[\alpha]_{25}^{D}$	Time (h)	Yield (%)	mp (°C)	$[\alpha]_{25}^{D}$	
2	D-Galactose	 **1b**	20	92	—	− 59.9	2	93	—	− 59.1	[12,13]
3	D-Xylose	 **1c**	20	89	43–44	+13.2	3	75	41–42	+14.0	[8]
4	L-Arabinose	 **1d**	20	92	41–42	+5.4	2	85	43–44	+6.0	[8]
5	D-Mannose	 **1e**	20	93	123–124	+18.9	0.3	85	121–122	+18.3	[8]
6	D-Fructose	 **1f**	25	89	85–86	− 41.9	22	86	86–87	− 41.0	[26,27]

(*Continued on next page*)

Table 2. Continued

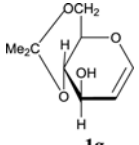
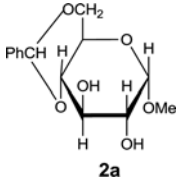
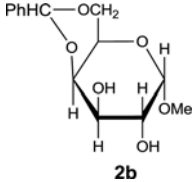
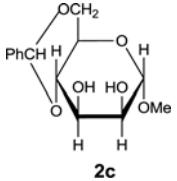
Entry	Starting material	Product	Observed				Reported				Ref.
			Time (min)	Yield (%)	mp (°C)	$[\alpha]_{25}^{D}$	Time (h)	Yield (%)	mp (°C)	$[\alpha]_{25}^{D}$	
7	D-Glucal	 **1g**	25	85	—	−18.2	1	50	—	−19.0	[28]
8	D-Glucose	 **2a**	40	78	142–144	+81.2	48	80.2	144–145	+80.3	[29,30]
9	D-Galactose	 **2b**	40	75	164–166	+138.1	24	78	168–170	+133.9	[31,32]
10	D-Mannose	 **2c**	50	76	147–148	+68.0	26	72	145–146	+68.3	[33,34]

Table 3. Recyclability of DES (ChCl:MA).

Sr. No	Number of runs	Preparation of **1a**		Preparation of **2a**	
		Yield %	Amount of DES obtained (g)	Yield %	Amount of DES obtained (g)
1	Fresh	90	15.00	78	15.00
2	First	90	15.00	78	15.18
3	Second	90	15.11	76	15.22
4	Third	89	15.14	75	15.23
5	Fourth	89	15.18	70	15.42

We chose the preparation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**1a)** and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**2a**) for studying the recyclability of ChCl:MA. Thus, the residual ChCl:MA obtained after extraction of **1a** with ethyl acetate was dehydrated under vacuum on a rotary evaporator for 15 min and directly used for repeating the reaction. In the case of **2a**, the residual ChCl:MA after extraction of the reaction mass with ethyl acetate was treated with (5.0 mL) water and the resulting mass was dehydrated under vacuum on a rotary evaporator at 70°C for 1 h. Table 3 presents data obtained after five such recycles. The results indicate that ChCl:MA can be recycled four times without significant loss in activity in the case of **1a** and three times in the case of **2a**. The slight increases in weight of the recycled ChCl:MA may be on account of non-volatile and highly polar sugar residues.

Conclusion

In conclusion, we have developed a clean, efficient, and high yielding one-pot protocol for the preparation of *O*-isopropylidene derivatives and methyl *O*-benzylidene glycosides from free sugars by using a DES made from choline chloride:malonic acid. These derivatives so prepared can be used for further synthetic transformation without an additional purification step.

Experimental section

General methods

Starting materials and reagents were purchased from commercial suppliers. TLC was performed on aluminum plates pre-coated with Merck silica gel, spots were observed by spraying the plates with a solution of 10% (v/v) aqueous H_2SO_4 with subsequent heating. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 243 polarimeter at 25 ˚C. ^{1}H NMR spectra were recorded on a Varian (500, 400 MHz) spectrometer.

Preparation of deep eutectic solvent[36,37]

Choline chloride (50 g) and malonic acid (75 g) were mixed and heated to 70–80°C for 4 h to obtain a clear transparent solution. In a similar way DESs were prepared

by using choline chloride (50 g) and TsOH (111 g), and choline chloride (50 g) and oxalic acid (70 g).

General procedure for the preparation of O-isopropylidene derivatives

A mixture of the free sugar (2.5 g, 13.8 mmol), dry acetone (15 mL) and a DES (15 g) prepared from choline chloride (6.0 g) and malonic acid (9.0 g) was boiled under reflux for the required time (Table 2). After completion of the reaction as indicated by TLC analysis the resulting mixture was cooled to rt and extracted with ethyl acetate (3 × 20 mL). The combined ethyl acetate layer was evaporated under vacuum to afford the corresponding *O*-isopropylidene derivative. The DES was treated with (5.0 mL) water and dehydrated under vacuum on a rotary evaporator at 70°C for 1 h.

Preparation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (1a)

A mixture of D-glucose (10 g, 55.6 mmol), dry acetone (40 mL), and a DES (30 g) prepared from choline chloride (13 g) and malonic acid (17 g) was boiled under reflux for 30 min. After completion of the reaction as indicated by TLC analysis, the resulting mixture was cooled to rt and extracted with ethyl acetate (3 × 100 mL). The combined ethyl acetate layer was evaporated under vacuum to afford 1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose (**1a**, 13.0 g, 90% yield). The raffinate was treated with (5.0 mL) water and dehydrated under vacuum on a rotary evaporator at 70°C for 1 h to afford DES that could be reused.

General procedure for the preparation of methyl 4,6-O-benzylidene glycosides

A mixture of the free sugar (2.5 g, 13.8 mmol) in dry methanol (8.0 mL) and DES (15.0 g) prepared from choline chloride and malonic acid was boiled under reflux for 30 min and cooled to rt. Benzaldehyde (2.0 mL) was added and the resulting mixture was heated to 60°C and stirred for 20 min. After completion of the reaction as indicated by TLC analysis, it was cooled to rt and extracted with ethyl acetate (3 × 20 mL). The combined ethyl acetate layer was evaporated under vacuum to afford the corresponding methyl 4,6-*O*-benzylidene glycoside. The residual ChCl:MA was treated with water (5.0 mL) and the resulting mass was dehydrated under vacuum on a rotary evaporator at 70°C for 1 h.

Preparation of methyl 4,6-O-benzylidene-α-D-glucopyranoside (2a)

A mixture of D-glucose (5 g, 27.8 mmol) in dry methanol (16 mL) and DES (20.0 g) prepared from choline chloride (8.0 g) and malonic acid (12.0 g) was boiled under reflux for 45 min and cooled to rt. Benzaldehyde (3.53 g, 3.40 mL, 33.3 mmol) was added and the resulting mixture was heated to 60°C and stirred for 30 min. After completion of the reaction as indicated by TLC analysis it was

cooled to rt and extracted with ethyl acetate (30 × 20 mL). The combined ethyl acetate layer was evaporated under vacuum to afford methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**2a**, 6.2 g, 79.1% yield). The raffinate was treated with water (5.0 mL) and the resulting mass was dehydrated under vacuum on a rotary evaporator at 70°C for 1 h to afford DES that could be reused.

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