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Solvent-free, under air selective synthesis of α-glycosides adopting glycosyl chlorides as donors†

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α-Glycosides are highly relevant synthetic targets due to their abundance in natural oligosaccharides involved in many biological processes. Nevertheless their preparation is hampered by several issues, due to both the strictly anhydrous conditions typically required in glycosylation procedures and the non-trivial achievement of high α-stereoselectivity, one of the major challenges in oligosaccharide synthesis. In this paper we report a novel and efficient approach for the highly stereoselective synthesis of α-glycosides. This is based on the unprecedented solvent-free combination of triethylphosphite, tetrabutylammonium bromide and *N*,*N*-diisopropylethylamine for the activation of glycosyl chlorides under air. Despite the relative stability of glycosyl chlorides with respect to more reactive halide donors, the solvent-free procedure allowed a wide set of α-glycosides, including biorelevant fragments, to be obtained in much shorter times compared with similar glycosylation approaches in solution. The presented method features a wide target scope and functional group compatibility, also serving with partially disarmed substrates, and it does not require a high stoichiometric excess of reagents nor the preparation of expensive precursors. The solvent-free glycosylation can be even directly performed from 1-hydroxy sugars without purification of the *in situ* generated chloride, providing an especially useful opportunity in the case of highly reactive and labile glycosyl donors.

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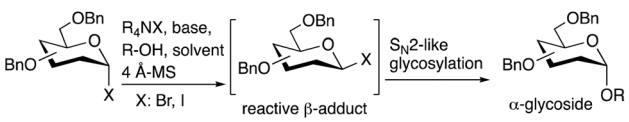
Introduction

Carbohydrates are fundamental molecules involved in many biological processes. This warrants the broad interest of current research towards new carbohydrate-based therapeutics. To this aim, chemical synthesis is routinely exploited to produce substantial amounts of pure oligosaccharides and development of ever more practical synthetic methods in this field is crucial. Indeed, glycosylation reactions are burdened by experimental issues due to the application of demanding procedures and ensuring a rigorously anhydrous atmosphere. In addition, the achievement of high stereoselectivity is highly challenging, especially in the synthesis of 1,2-*cis* glycosides, due to the lack of a reliable strategy providing absolute stereocontrol as the neighbouring group participation is exploited for 1,2-*trans* glycosylations.[1] A large number of approaches have been proposed to address this issue,[2] the most effective one requiring a preliminary functionalization of the donor with suitable groups capable of directing the approach of the incoming nucleophilic acceptor.[3] Installation of these groups entails extra synthetic steps and the use of expensive functionalizing agents. Other strategies have been designed to encourage a S_N2-like glycosylation pathway favoring 1,2-*cis* glycoside generation.[4] Among these methods, S_N2-like α-glycosylations can be achieved through the *in situ* conversion of the donor into a reactive β-adduct promoted by exogeneous nucleophiles. To this aim, nucleophilic modulators such as phosphinoxides, sulfoxides, thioethers and amides,[5] or urea and thiourea organocatalysts in combination with phosphorus additives[6] or a phenanthroline organocatalyst[7] have been used. In this frame, since the introduction of the halide ion catalyzed glycosylation,[8] the synthesis of several α-glycosides was accomplished through the *in situ* anomerization of benzylated glycosyl halides promoted by an external halide source (Scheme 1). When involving a β-bromide intermediate, this strategy



Scheme 1 α-Glycosylation approach based on the *in situ* anomerization of glycosyl halides.

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provides high α-selectivity but its scope is restricted to highly reactive substrates (*e.g.* per-*O*-benzylated fucosyl donors) taking in any case extended reaction times (up to days).[8,9]

A higher efficiency, especially with primary acceptors, could be achieved by adopting more reactive β-iodides[10] although with the use of a highly toxic solvent (dry benzene) and high stoichiometric excess of the donor and the halide promoter. In the arsenal of α-glycosylation methods, one-pot dehydrative strategies are also appreciated since they rely on the *in situ* conversion of 1-hydroxy sugars to reactive halide,[11] oxosulfonium[12] or oxophosphonium[13] donors which are directly coupled with the nucleophilic acceptor. Nevertheless, reagents for the *in situ* anomeric activation are often sensitive, expensive or non-commercially available; in addition, long reaction times, use of toxic or high boiling solvents, a high excess of the acceptor and modest stereoselectivity can be further limitations of these one-pot methods.

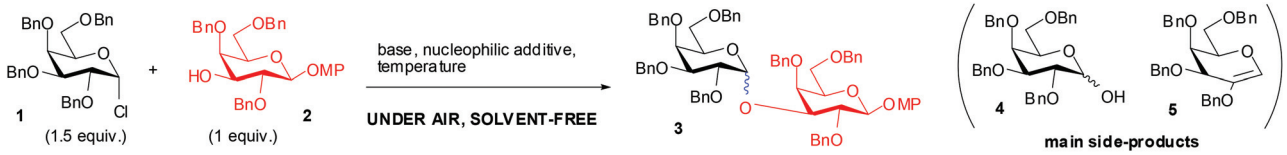
In the last few years, we focused our research on the development of practical protocols for regioselective derivatization of carbohydrates[14] featuring the possibility to perform reactions under air with high efficiency, including multiple one-pot functionalizations, under solvent-free conditions. In this frame, we introduced a solvent-free fast preparation of glycosyl chlorides based on a PPh_3/hexachloroacetone system[14f] which spurred us to consider their use in the development of a practical α-glycosylation procedure. Due to their relatively low reactivity, chlorides are seldom preferred as glycosyl donors, in spite of their easier handling than their iodinated and brominated counterparts. Instead, herein we report a novel α-glycosylation method based on the efficient activation of glycosyl chlorides under air in the absence of any solvent. Reactions are mediated by a small stoichiometric excess of DIPEA as the base and a combination of triethylphosphite and tetrabutylammonium bromide as promoters, affording α-glycosides in short times with high stereoselectivity.

Results and discussion

Initially, the coupling of galactosyl chloride **1** with acceptor **2**, yielding the α-gal epitope disaccharide **3**, was studied as the model reaction (Table 1).

Inspired by previous solvent-free reactions mediated by neat liquid amines,[14] we firstly employed a slight stoichiometric excess of DIPEA as the base, and a sub-stoichiometric amount of TBAB as an exogeneous halide source, obtaining **3** in 4.5 h in 75% isolated yield, with exclusive α-selectivity. In an attempt to minimize the generation of hemiacetal **4** and glycal **5** side-products, we extensively tested alternative bases and nucleophilic additives. In this survey, we also evaluated some liquid bases supposed to be nucleophilic enough to act as mild promoters in place of the exogenous halide ions. Among these, cyclic tertiary amines such as *N*-methylmorpholine and *N*-ethylmorpholine provided dis-

Table 1 Optimization of a solvent-free glycosylation procedure



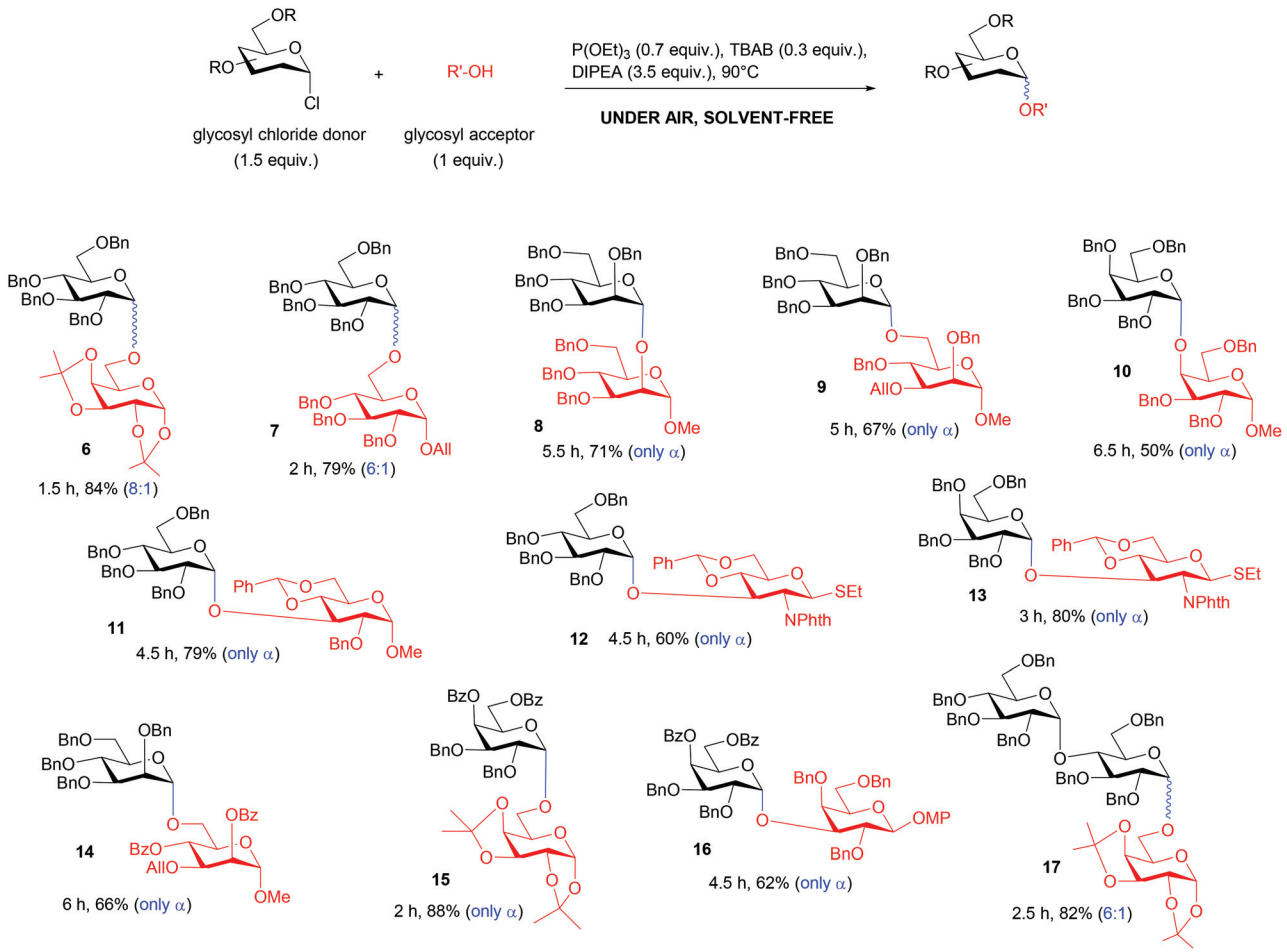
Entry	Base (equiv.)[a]	Additive (equiv.)[a]	Temperature, time	Isolated yield of **3** (α/β)[b]
1	DIPEA (3.5)	TBAB (0.6)	80 °C, 4.5 h	75% (only α)
2	DIPEA (3.5)	TBAB (1.2)	100 °C, 2.5 h	75% (only α)
3	DIPEA (3.5)	TBAI (1.2)	100 °C, 2.5 h	60% (only α)
4	DIPEA (3.5)	LiI (1.5)	100 °C, 1 h	<15% (2.5 : 1)
5	DIPEA (3.5)	LiI (1.5)	60 °C, 3 h	20% (2.5 : 1)
6	DIPEA (3.5)	LiI (0.1)	70 °C, 4 h	49% (2.5 : 1)
7	DIPEA (3.5)	LiI (0.1)	90 °C, 5.5 h	50% (2.5 : 1)
8	TEA (7.5)[c]	—	80 °C, 7 h	52% (3.5 : 1)
9	*N*-Methylmorpholine (7.5)[c]	—	90 to 120 °C, 12 h	62% (3.2 : 1)
10	*N*-Ethylmorpholine (5)	—	120 °C, 5 h	85% (3 : 1)
11	Imidazole (3.5)	—	100 °C, 6 h[d]	—
12	Imidazole (3.5)	TBAB (1.2)	100 to 130 °C, 8 h[d]	—
13	DIPEA (3.5)	HMPA (1)	100 °C, 3 h	53% (4.5 : 1)
14	DIPEA (3.5)	$(PhS)_2$ (1)	90 °C, 5 h	54% (3 : 1)
15	DIPEA (3.5)	$(PhSe)_2$ (1)	90 °C, 5 h	65% (3 : 1)
16	DIPEA (3.5)	PPh_3 (1)	90 °C, 6 h	73% (7.2 : 1)
17	DIPEA (3.5)	PBu_3 (1)	90 °C, 7 h	70% (6.7 : 1)
18	DIPEA (3.5)	PBr_3 (1)	90 °C, 2 h	—
19	DIPEA (3.5)	$P(OEt)_3$ (1)	90 °C, 7 h	87% (7 : 1)
20	DIPEA (3.5)	$P(OEt)_3$ (0.7) + TBAB (0.3)	90 °C, 7.5 h	89% (only α)

[a] Equivalents refer to the glycosyl acceptor. [b] The α/β ratio in parenthesis refers to the isolated product. [c] 3.5 equivalents were initially added, followed by the addition of further 2 equivalent aliquots after 3 h and 5 h, respectively. [d] TLC analysis displayed quantitative consumption of the chloride after 1 h.

crete yields but poor stereoselectivity and required harsher reaction conditions (see Table 1, entries 9 and 10). Therefore, optimization experiments proceeded by evaluating the use of neat DIPEA in combination with nucleophilic additives alternative to halide ions. Hemiacetal **4** was still identified as the main byproduct together with traces of glycal **5** when either oxygenated or chalcogen nucleophiles such as hexamethylphosphoramide, phenyl disulphide and phenyl diselenide (see Table 1, entries 13–15) were used as glycosylation promoters. Phosphorus(III) nucleophiles proved to be particularly efficient promoters in the solvent-free glycosylation mediated by neat DIPEA and an especially good result in terms of yield and stereoselectivity was achieved with triethylphosphite (Table 1, entry 19) which is, to the best of our knowledge, an unprecedented α-glycosylation promoter. Indeed, triethylphosphite had been previously used in glycosylations essentially as a quenching reagent to prevent decomposition of the glycosylation product.[15] An optimized yield of 89% with exclusive α-selectivity could be eventually obtained upon combining $P(OEt)_3$ with a catalytic amount of TBAB (Table 1, entry 20). The scope of this optimized procedure was then assessed to obtain several α-glycosidic bonds (Table 2).

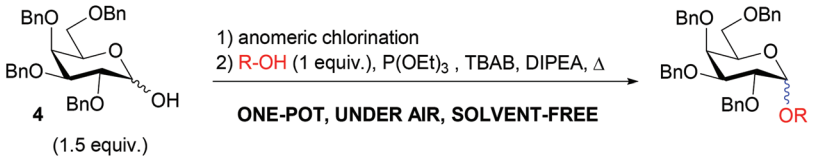
α-1,6-Linked disaccharides **6** and **7** were efficiently accessed from a per-*O*-benzylated glucosyl chloride donor, in both cases with a high stereoselectivity in comparison with typical glycosylations of reactive primary alcohols. Per-*O*-benzylated mannosyl chloride was also efficiently activated in the construction of α-linked di-mannosides **8** and **9**, key structural elements in natural high-mannose glycans. α-1,4-Linked disaccharide **10**, also occurring in highly relevant structures (*e.g.* globo-series glycans), was easily obtained with high α-selectivity albeit in a lower yield, likely due to the poor reactivity of the axial *O*-4 hydroxyl group of galactose acceptors. The method was found to be also compatible with benzylidene protected acceptors, as demonstrated by the synthesis of α-1,3-linked disaccharides **11**, **12** and **13** in high yields. Furthermore, the feasible synthesis of disaccharides **14**, **15** and **16** highlighted that the efficiency of the solvent-free procedure was not affected by the replacement of benzyl ethers with much more disarming protecting groups such as benzoyl esters on either the donor or the acceptor. Another significant result supporting the wide

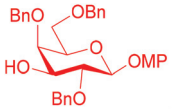
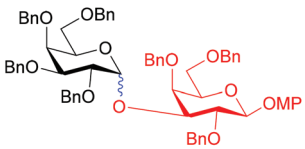
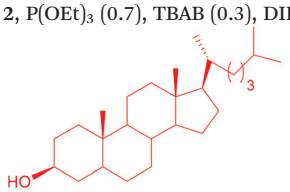
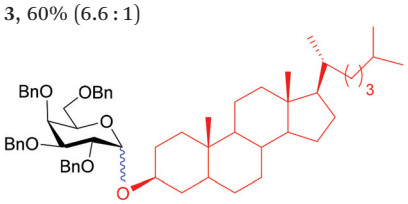
Table 2 Solvent-free synthesis of α-glycosides from glycosyl chlorides promoted by $P(OEt)_3$/TBAB/DIPEA under air[a]



[a] Obtained products, reaction times and isolated yields (the α/β ratio reported in parentheses also refers to the isolated product).

Table 3 Optimization of a one-pot chlorination/glycosylation solvent-free procedure from 1-hydroxy sugars



Entry	1st step conditions (equiv.)[a]	2nd step conditions (equiv.)[b]	Product, isolated yield (α/β)[c]
1	PPh_3 (1.5), $(CCl_3)_2CO$ (1.5), 70 °C, 45 min	 **2**, $P(OEt)_3$ (0.7), TBAB (0.3), DIPEA (3.5), 90 to 100°C, 6 h	No glycosylation reaction
2	PPh_3 (1.5), CCl_4 (1.5), 70 °C, 1 h	**2**, $P(OEt)_3$ (0.7), TBAB (0.3), DIPEA (3.5), 90 °C, 4.5 h	 **3**, 51% (6.6:1)
3	PPh_3 (1.5), CCl_3CN (1.5), 70 °C, 2h	**2**, $P(OEt)_3$ (0.7), TBAB (0.3), DIPEA (3.5), 90 °C, 5 h	**3**, 60% (6.6 : 1)
4	PPh_3 (1.5), CCl_3CN (1.5), 70 °C, 2h	 **18**, $P(OEt)_3$ (0.7), TBAB (0.3), DIPEA (3.5), 90°C, 5 h	 **19**,68% (6:1)
5	PPh_3 (1.5), CCl_3CN (1.5), 70 °C, 2 h	**18**, $P(OEt)_3$ (0.7), TBAB (0.15), DIPEA (3.5), 90 °C, 5 h	**19**, 75% (6 : 1)

[a] Equivalents refer to the hemiacetal substrate. [b] Equivalents refer to the glycosyl acceptor. [c] The α/β ratio in parentheses refers to the isolated product.

applicability of the procedure in oligosaccharide synthesis was the efficient assembly of trisaccharide **17** using per-*O*-benzylated maltosyl chloride as a disaccharide donor.

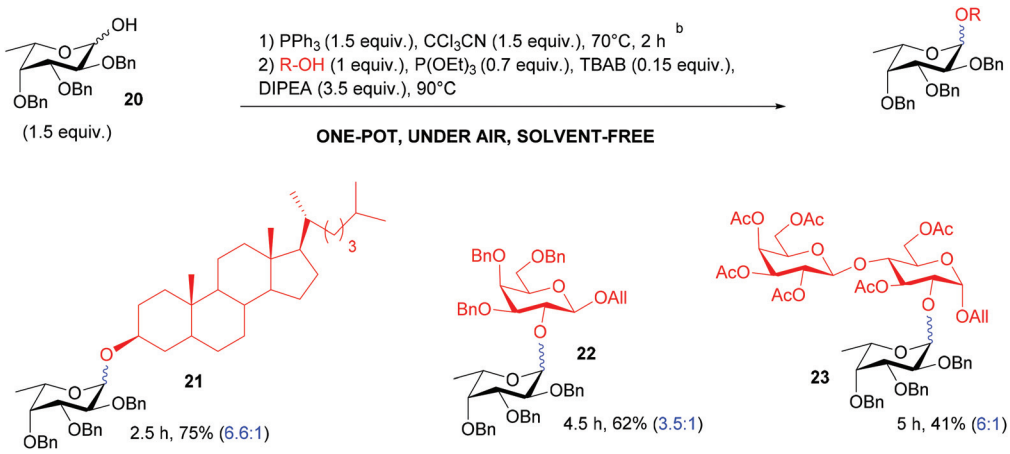
In order to increase further the simplicity of our α-glycosylation approach, we also investigated a one-pot glycosylation protocol entailing *in situ* anomeric chlorination of 1-hydroxy sugars. This variation was initially explored for the synthesis of **3**. To this aim, solvent-free chlorination of commercial hemiacetal **4** was first performed, followed by the addition of acceptor **2**, $P(OEt)_3$, TBAB and DIPEA to the crude chlorination mixture. A screening of chlorinating agents for the first step evidenced the best performance of the PPh_3/CCl_3CN combination (see Table 3).

In the following experiments for the synthesis of glycoside **19**, further optimization was achieved by halving the amount of TBAB, due to minimization of side-product **5** (compare entries 4 and 5 in Table 3). Subsequently we also demonstrated the useful applicability of the optimized one-pot procedure in the synthesis of α-fucosides; these are relevant but challenging targets in oligosaccharide synthesis, due to the high instability of fucosyl donors,[16] often not even purifiable by chromatography. As shown in Table 4, using commercial tri-*O*-benzyl-L-fucose **20** as the hemiacetal precursor, an efficient glycosylation could be achieved with different acceptors.

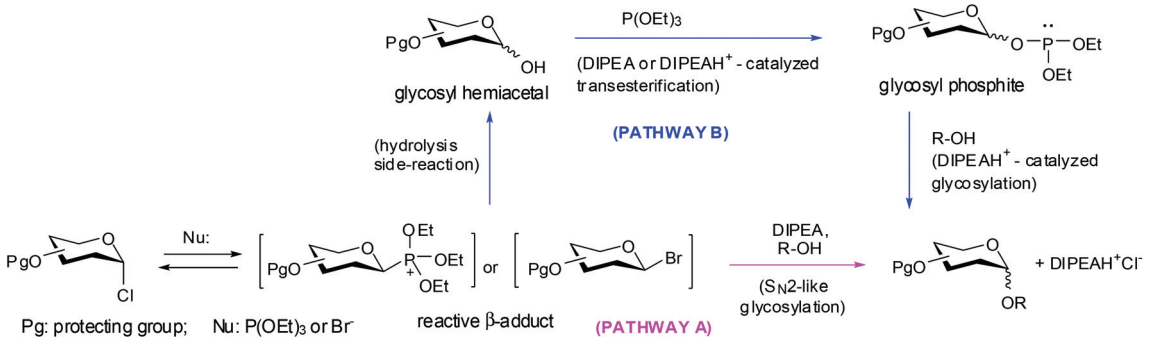
It is worth underlining that glycosylation reactions performed in the absence of solvent have been seldom described in the literature and only in a few cases addressed for the construction of glycosidic linkages connecting saccharide residues. Most of the glycosylation procedures claimed as solvent-free are indeed targeted towards obtaining simple alkyl glycosides and typically involve a large stoichiometric excess of the acceptor and in some cases the assistance of microwave irradiation.[17] Particularly noteworthy in this context are mechanochemical approaches enabling solvent-free glycosylations in a ball mill; such methods have been reported with both glycosyl bromide donors for the synthesis of β-alkyl/aryl glycosides[18] and with armed thioglycoside donors, in this latter case also coupled with some primary saccharide acceptors.[19]

Some mechanistic hypotheses for the α-glycosylation reaction presented here are summarized in Scheme 2. Reasonably, the main reaction pathway involves a glycosyl β-phosphonium (or bromide) intermediate then undergoing S_N2-like glycosylation (Scheme 2, pathway A). However, the appreciable minimization of the hydrolysis side-process (with consequent optimization of the glycosylation yield) observed in the presence of $P(OEt)_3$ as the promoter may suggest its possible involvement in some alternative, minor mechanisms; for example, $P(OEt)_3$

Table 4 α-Fucoside synthesis *via* the one-pot anomeric chlorination/glycosylation procedure[a]



[a] Obtained products, reaction times (of the glycosylation step) and isolated yields (the α/β ratio reported in parentheses also refers to the isolated product). [b] Equivalents of PPh_3 and CCl_3CN refer to the hemiacetal substrate, while equivalents of $P(OEt)_3$, TBAB, DIPEA and the glycosyl hemiacetal refer to the glycosyl acceptor.



Scheme 2 Proposed mechanistic pathways for TBAB/$P(OEt)_3$-promoted glycosylation.

may act as a mild drying agent and/or recycle the hemiacetal side product at high reaction temperature[20] by generation of a transient glycosyl phosphite donor, and then activated[21] to afford the glycoside (Scheme 2, pathway B). These processes could be likely catalyzed by the *in situ* generated $DIPEAH^+$ ions, according to our recent findings on the use of ammonium species in solvent-free acid catalyzed reactions.[14h] In an attempt to support this hypothesis, cholestanol **18** (1 equiv.) and hemiacetal **4** (1.5 equiv.) were reacted for 7 h at 90 °C in a pre-generated mixture of DIPEA and $DIPEAH^+Cl$, obtained by rapid methanolysis of trimethylsilyl chloride in the presence of DIPEA as the base. No reaction was observed in the absence of $P(OEt)_3$; instead, the same experiment performed in the presence of 1.5 equiv. or 4 equiv. of the phosphite, respectively, afforded glycoside **19** in 8% and 15% isolated yields.

Conclusions

In conclusion, we have reported a new method for the synthesis of α-glycosides involving the use of glycosyl chlorides under air and solvent-free conditions. In the presented method, glycosyl chlorides are activated by an unprecedented combination of $P(OEt)_3$ and TBAB in the presence of a slight stoichiometric excess of neat DIPEA at 90 °C. α-Glycosides are thus quickly obtained under air with high yields and stereoselectivity from variously protected donors and acceptors including poorly reactive precursors. The solvent-free strategy is also applicable in a one-pot version, enabling direct glycosylation of 1-hydroxy sugars without isolation of the transient and eventually labile glycosyl chloride. In light of the many advantages in terms of efficiency, experimental simplicity and cheapness with respect to current glycosylation protocols, we expect that the proposed method might have a large impact in streamlining the synthesis of oligosaccharides.

Experimental

General remarks

The whole procedures for glycosylation reactions were performed under air without the use of any drying agent. Solvents eventually used in the glycosylation procedures described

below (*e.g.* for the initial co-evaporation of the donor and acceptor or, where needed, for the *in situ* addition of the acceptor to the reaction flask) were technical grade solvents which were used as supplied, without any drying pre-treatment. Reactions were primarily monitored by TLC analysis. After elution, detection of compounds was performed by soaking the plates in 5% H_2SO_4 in ethanol and subsequent heating at 230 °C. Eventual detection of UV-visible compounds under a UV lamp preceded the acid treatment. NMR spectra were recorded in a 400 MHz device.

General procedure for the solvent-free synthesis of α-glycosides from glycosyl chlorides

The requisite glycosyl acceptor (0.05 mmol, 1 equiv.) and glycosyl chloride donor (0.075 mmol, 1.5 equiv.) were first separately weighted, then dissolved in DCM, combined in a small round-bottom flask and co-evaporated under reduced pressure until complete removal of the solvent. Tetrabutylammonium bromide (4.8 mg, 0.015 mmol, 0.3 equiv.), triethylphosphite (6.1 μL, 0.035 mmol, 0.7 equiv.) and DIPEA (30.5 μL, 0.175 mmol, 3.5 equiv.) were sequentially added and the mixture was heated at 90 °C under vigorous stirring, to ensure the achievement of a homogeneous exposure of all reagents to each other (*e.g.* no residues should be left on the neck or other parts of the flask which fall out of the stirring area). Upon completion of the reaction (see Table 2 for reaction times), the flask was allowed to cool to room temperature and the crude mixture was subjected to silica-gel chromatography to isolate the pure glycosylation product in the yield indicated in Table 2.

It is noteworthy that in order to prove the applicability of the procedure at a larger scale, the synthesis of model disaccharide **3** was also performed with 1 mmol of a glycosyl acceptor with reproducible reaction time, yield and stereoselectivity as reported in Table 1, entry 20.

General procedure for the solvent-free synthesis of α-glycosides from 1-hydroxy sugars

The sugar hemiacetal (0.075 mmol) was weighed in a small round-bottom flask, and then powdered triphenylphosphine (29.5 mg, 0.113 mmol) and trichloroacetonitrile (11.3 μL, 0.113 mmol) were sequentially added. The mixture was heated at 70 °C under vigorous stirring, to ensure achieving a homogeneous exposure of all reagents to each other (*e.g.* no residues should be left on the neck or other parts of the flask which fall out of the stirring area). Upon completion of the chlorination step (2 h), the flask was temporarily brought out of the oil bath and the requisite glycosyl acceptor (0.05 mmol), TBAB (2.4 mg, 0.0075 mmol), $P(OEt)_3$ (6.1 μL, 0.035 mmol) and DIPEA (30.5 μL, 0.175 mmol) were added to the mixture. The flask was placed in an oil bath at 90 °C (temperature required for the glycosylation reaction) and kept under stirring until completion of the second step (reaction times indicated in Tables 3 and 4) (N.B.: the acceptor was weighed in a small tube and directly added to the reaction flask as a powder; only if needed, as in the case of oily compounds, it was added as a solution in a minimal amount of DCM which was readily distilled off as the glycosylation step was performed). The flask was allowed to cool to room temperature and then the crude mixture was concentrated under vacuum and subjected to silica-gel chromatography to isolate the pure glycosylation product (yields of the obtained products are indicated in Tables 3 and 4).

Conflicts of interest

There are no conflicts to declare.

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