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Efficient synthesis of glycosylamines in solventless conditions promoted by mechanical milling

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A mecanosynthesis of glycosylamines under solventless conditions was established. This environmentally friendly approach optimized with L-rhamnose, was investigated using a variety of amines and other carbohydrates. High reaction yields and simple work-up allow the clean and fast synthesis of a variety of glycosylamines and glycosyl-(di)-amines.

Introduction

Green chemistry principles have been established to reduce the use or generation of hazardous substances in synthesis and application of chemicals products.[1,2] Greener procedures for the preparation of synthetic molecules from biomass which are performed in solvent-free conditions are currently more attractive.[3] The use of biomass feedstocks such as carbohydrates or conversion of these products to useful chemicals is particularly interesting, not only to obtain environmentally friendly products but also because it could be an alternative to the limited supply and non-renewability of fossil oil.[4] On the other hand, the solvent-free reactions have gained widespread attention for their ability to significantly reduce solvent waste.[5] As part of our ongoing program,[6] we are interested in the development of efficient and environmentally benign methods in chemical modification of carbohydrates. Herein, we report a solventless, green and efficient mechanosynthesis of glycosylamines derivatives in high yields by condensation of amines or diamines with unprotected carbohydrates.

Glycosylamines derivatives have shown a broad spectrum of biological activities such as antibacterial, anti-inflammatory, antifungal and antiviral activities in agrochemical and pharmacological areas.[7]

Moreover, glycosylamines are known as intermediates for the preparation of various acylated or ammonium compounds of particular interest, useful in the preparation of organogelators[8] or detergent active products as well.[7b,9] Some strategies of synthesis of glycosylamines derivatives have been reported in the literature including Mitsunobu coupling glycosylation with aryl amines and monosaccharide with free anomeric hydroxyl.[10] Generally, glycosylamines are obtained by condensation of carbohydrates and amines in solvent media.[7e,f,11] In most cases, it is noteworthy that the conditions are not mild or environmentally safe either because of the toxicity of solvents and/or catalysts used, or because these published procedures required long reaction times under reflux of the solvent.

High speed ball milling (HSBM) under solvent-free conditions is a scalable experimental technique that has been shown to be an efficient alternative to synthesis with solvent.[12] This technique is well known in material sciences for particule size reduction and preparation of ball-milled powders of metals, minerals and other inorganic solids.[13] Recently, many reports in the literature have shown that mechanosynthesis is effective for various organic transformations such as Wittig,[14] or Horner–Wadsworth–Emmons reaction[15] Michael addition,[16] transesterification,[17] Sonogashira,[18] Tishchenko reactions[19] and others[20]. However, to the best of our knowledge, only few examples of modification of carbohydrates or preparation of

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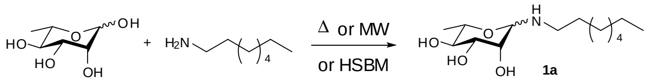
derivatives under solvent-free conditions in a ball mill have been reported. Kartha and coworkers have functionalized sugars using the mechanochemical approach. Most of the time, a protected glycosyl halide is used in this procedure to afford glycosyl azide, alkyl, aryl or thioglycoside derivatives.[21]

In our study, we compared the classical method with a solventless strategy carried out in the ball mill. First, we focused our attention on the synthesis of glycosylamines from L-rhamnose and different primary alkylamines. L-Rhamnose is naturally produced by *Pseudomonas aeruginosa* as rhamnolipids which elicit defense mechanisms in plants.[22] Moreover, some rhamnose derivatives have shown anti-inflammatory and skin soothing properties. Indeed, L-rhamnose has been clinically proven to be an effective anti-aging agent improving collagen production. It may also increase the solubility and the bioavailability of the compounds having potent pharmacological activity.[23]

Results and discussion

The advantage of glycosylamines synthesis lies in the fact that the reaction can be realized in a one-step reaction requiring only a primary amine and a free carbohydrate in a polar solvent such as methanol or ethanol. This reaction avoids protection and deprotection steps of carbohydrate that furnish waste. To prove the feasibility of this reaction in solvent-free conditions, we compared the synthesis of octylrhamnosylamine **1a** in different conditions: classical heating in methanol or solventless, microwave heating in methanol and in a ball mill without solvent (Table 1). L-rhamnose was treated with a slight excess (1.1 eq) of amine in MeOH or solventless at the gram-scale.

Table 1 Comparative conditions for the synthesis of octylrhamnosylamine **1a**



Entry	Conditions^a (technique, solvent)	Temp. (°C)	*t* (h)	Yield(%)
1	Oil bath - solventless	65	6	0
2	Oil bath - MeOH	65	6	83
3	Microwave - MeOH	65	2	72
4	Ball mill - solventless^b	r.t.	1.5	94
5	Oil bath - MeOH^b	65	6	81^c
6	Oil bath - solventless^b	65	48	0

[a] Reaction conditions: Rhamnose (5.5 mmol), octylamine (6 mmol), in MeOH (10 mL) or solventless. [b] 1.5 g SiO_2 was added. [c] Isolated after filtration of crude on silica gel followed by work-up of classical reaction

The heating of the sugar in the presence of alkylamine carried out in solventless conditions with an oil bath failed (entry 1). As expected, compound **1a** was obtained in a shorter reaction time in the case of microwave-assisted synthesis in methanol (entry 3) compared to the classical reaction (entry 2). In the case of ball milling (entry 4), the reaction was conducted in a screw-capped stainless steel jar with stainless steel balls of 7.0 mm or 13.0 mm diameter in a high-energy vibrational apparatus (Spex 8000 M). For liquid amines, such as alkylamines with short chains, the grinding action of the balls may be reduced because of the formation of sticky paste inside the jar. In these cases, the use of an auxiliary agent is necessary to homogenize the mixture, that is why 1.5 g of SiO_2 was added. The reaction was stopped and monitored each 30 min by TLC. We observed that L-rhamnose was totally converted in 1.5h reaction time and the yield was better in the ball mill whereas against all expectations, it reached 2h in a microwave to observe complete conversion of rhamnose at 65°C. In order to verify that SiO_2 only acts as grinding-aid agent, two reactions were carried out in oil bath with SiO_2 (entries 5-6). In solution conditions (entry 5), the same isolated yield was obtained compared to classical conditions (entry 2). Moreover, in solventless conditions (entry 6), no conversion of carbohydrate into glycosylamine was observed, proving that SiO_2 has no promoter side effect.

Others grinding auxiliaries[24] were examined (Table 2). A mixture of the liquid amine with the grinding-aid agent and L-rhamnose was placed into the milling jar with balls. At the end of the experiment, the reaction mixture was scratched off from the vessel and dissolved in a minimum of methanol, then filtered directly through a pad of silica gel without any aqueous workup. The silica gel promotes retention of auxiliary grinding and facilitates the separation of the desired product.

Table 2 Influence of grinding-aid agent on reaction of octylrhamnosyl-amine **1a** in solvent-free conditions^a

Entry	Grinding additive	Weight (g)	*t* (h)	Yield (%)
1	-	-	3	53^b
2	K_2CO_3	3	3	0
3	NaCl	10	1.5	81^c
4	γ-Al_2O_3 (neutral)	3	1.5	86^c
5	SiO_2	1.5	1.5	94^c

[a] Reaction conditions: Rhamnose (5.5 mmol), octylamine (6 mmol). [b] Isolated yields after purification on silica gel by column chromatography (CH_2Cl_2/MeOH). [c] Isolated yields after filtration on silica gel

When the reaction was carried out without grinding auxiliary, the yield was moderate probably because a sticky paste forms during the reaction (entry 1). In this case, the mixture was separated and purified by flash column chromatography. Even at a time twice as long as the other tests reaction, the conversion of rhamnose remained incomplete. Surprisingly, when K_2CO_3 was used as grinding auxiliary, no desired product was detected (entry 2) although basic conditions might promote glycosylamines formation (which are known to be more stable in basic conditions than in other conditions). On the other hand, the use of NaCl (entry 3), Al_2O_3 (entry 4) and SiO_2 (entry 5) led to good to excellent yields respectively. In addition to complete conversion of rhamnose in these conditions (monitored by TLC), yields are excellent when using SiO_2 because the filtration of the crude on silica gel was easier than for the other grinding-aid agents. Furthermore, in the case of NaCl, it was necessary to use a quantity of auxiliary corresponding to about 10 times the total weight of reactants to obtain a powder during the milling. This quantity of NaCl was particularly difficult and tedious to remove at the end of reaction.

Table 3

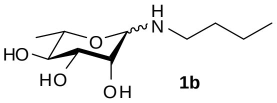
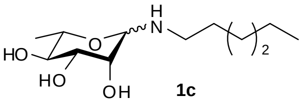
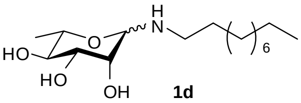
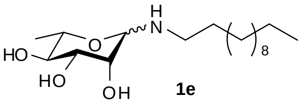
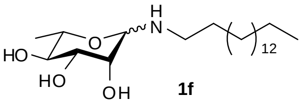
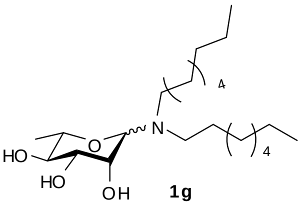
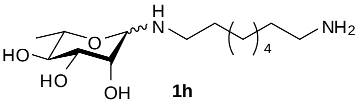
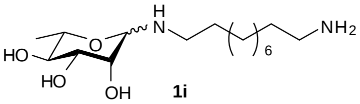
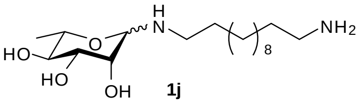
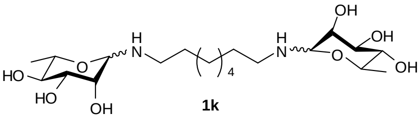
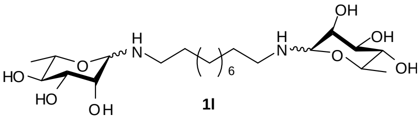
Entry	Sugar	Amine	*t* (h)	Grinding auxiliary	Product	α/β	Yield (%)
1	L-rhamnose	$CH_3(CH_2)_3NH_2$	1.5	SiO_2	 **1b**	93/7	91
2	L-rhamnose	$CH_3(CH_2)_5NH_2$	1.5	SiO_2	 **1c**	89/11	89
3	L-rhamnose	$CH_3(CH_2)_9NH_2$	1.5	SiO_2	 **1d**	93/7	95
4	L-rhamnose	$CH_3(CH_2)_{11}NH_2$	1.5	-	 **1e**	92/8	98
5	L-rhamnose	$CH_3(CH_2)_{15}NH_2$	1.5	-	 **1f**	92/8	99
6	L-rhamnose	$[CH_3(CH_2)_7]_2NH$	7	SiO_2	 **1g**	-	<5
7	L-rhamnose	$H_2N(CH_2)_8NH_2$	1.5	-	 **1h**	87/13	96
8	L-rhamnose	$H_2N(CH_2)_{10}NH_2$	1.5	-	 **1i**	90/10	95
9	L-rhamnose	$H_2N(CH_2)_{12}NH_2$	1.5	-	 **1j**	96/4	96
10	L-rhamnose	$H_2N(CH_2)_8NH_2$	3[a]	-	 **1k**	84/16	95
11	L-rhamnose	$H_2N(CH_2)_{10}NH_2$	3[a]	-	 **1l**	75/25	98

Table 3 *(contd.)*

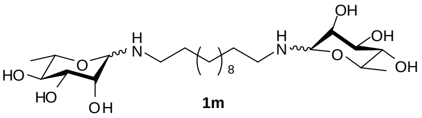
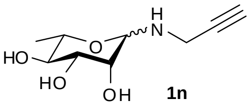
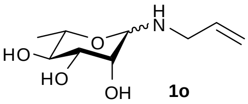
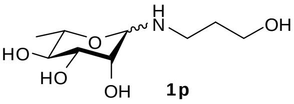
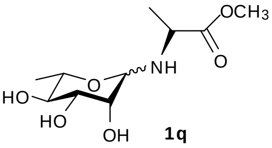
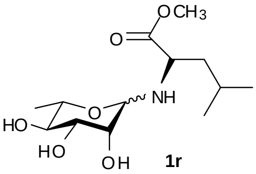
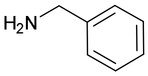
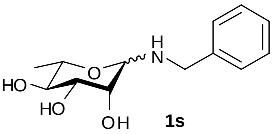
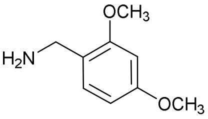
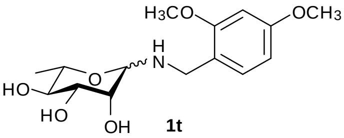
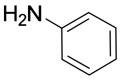
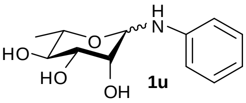
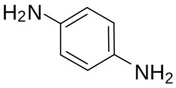
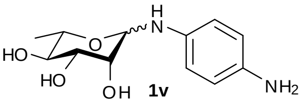
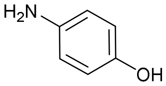
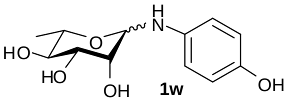
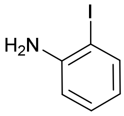
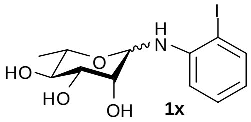
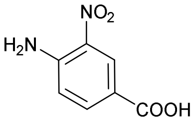
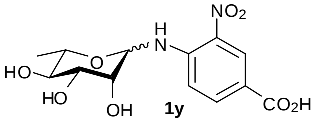
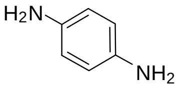
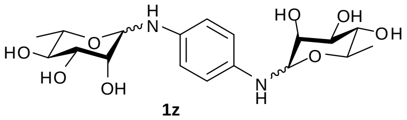
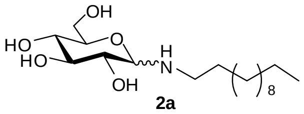
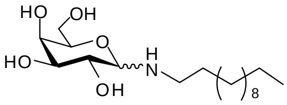
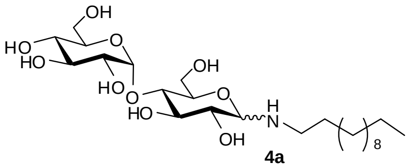
Entry	Sugar	Amine	*t* (h)	Grinding Auxiliary	Product	α/β	Yield (%)
12	L-rhamnose	$H_2N(CH_2)_{12}NH_2$	3[a]	-	 **1m**	96/4	98
13	L-rhamnose	$HC{\equiv}CCH_2NH_2$	1.5	SiO_2	 **1n**	88/12	96
14	L-rhamnose	$H_2C{=}CHCH_2NH_2$	1.5	SiO_2	 **1o**	91/9	91
15	L-rhamnose	$HO(CH_2)_3NH_2$	1.5	SiO_2	 **1p**	91/9	92
16	L-rhamnose	H-Ala-OMe . HCl[b]	1.5	SiO_2	 **1q**	89/11	68
17	L-rhamnose	H-Leu-OMe . HCl[b]	1.5	SiO_2	 **1r**	91/9	70
18	L-rhamnose		1.5	SiO_2	 **1s**	83/17	94
19	L-rhamnose		1.5	SiO_2	 **1t**	c	94
20	L-rhamnose		1.5	SiO_2	 **1u**	c	99
21	L-rhamnose		1.5	-	 **1v**	85/15	95
22	L-rhamnose		1.5	-	 **1w**	c	59

Table 3 *(contd.)*

Entry	Sugar	Amine	*t* (h)	Grinding auxiliary	Product	α/β	Yield (%)
23	L-rhamnose		1.5	-	 **1x**	-	0
24	L-rhamnose		1.5	-	 **1y**	-	0
25	L-rhamnose		3[a]	-	 **1z**	[c]	90
26	D-glucose	$CH_3(CH_2)_{11}NH_2$	1.5	-	 **2a**	[d]	97
27	D-galactose	$CH_3(CH_2)_{11}NH_2$	1.5	-	 **3a**	[d]	94
28	Maltose	$CH_3(CH_2)_{11}NH_2$	1.5	-	 **4a**	20/80	99

[a] 2 eq. of rhamnose were used for 1 eq. of amine

[b] a preliminary treatment with K_2CO_3 in ball mill was realized to obtain the free $–NH_2$ group

[c] the anomeric ratio was not determined, α anomer prevails in this case

[d] the anomeric ratio was not determined, β anomer prevails in all cases

Using these optimised conditions this protocol was extended to other substrates leading to a wide range of glycosylamines. Table 3 summarizes the reactions of several carbohydrates with various amines: alkyl-, arylamines, dialkylamines, aminoesters or aminoalcohols leading to a variety of functionalized glycosylamines. Overall, the reactions of rhamnose with alkylamines led to the corresponding glycosylamines in excellent yields (Table 3, entries 1-5). Besides, we noted that due to the powdery aspect of dodecylamine and hexadecylamine, the reaction of carbohydrates with these amines did not require grinding-aid agent and therefore, rhamnosylamines **1e** and **1f** (Table 3, entries 4 and 5) were isolated with higher yields than **1b**, **1c** and **1d** since purification of the crude was easier. Nevertheless, when using a disubstituted amine such as dioctylamine (entry 6), only traces of desired product were observed, even after 7h of milling, probably due to the weak reactivity of the secondary amine function. Subsequently, we studied the reaction of diamines with rhamnose to obtain monosubstituted (Table 3, entries 7-9) and disubstituted products (Table 3, entries 10-12). To promote monosubstitution of the alkyldiamines, one equivalent of each reactant was used to afford **1h**, **1i**, and **1j** in excellent yields (95-96%). Similarly, to favor disubstituted products, two equivalents of rhamnose were ground with one equivalent of alkyldiamine. Compared to monosubstituted products (**1h**, **1i** and **1j**), a twice longer reaction time was necessary to obtain the corresponding disubstituted products (**1k**, **1l** and **1m**) in high yields (95-98%). It is worth mentioning that the E-factor is minimized by producing only water as waste.

In order to introduce functional groups to the as-obtained glycosylamines, propargylamine, allylamine and aminopropanol were also tested. As for alkylamines, their condensation with rhamnose led to the corresponding products in 91-96% yields (Table 3, entries 13-15). In the other hand, for the extrapolation of this protocol to ester aminoacids (Table 3, entries 16-17), a prior alkaline treatment of the aminoester hydrochloride salt was necessary to activate the -NH_2 group. The deprotection of the amine group was performed with K_2CO_3 followed by the condensation with the carbohydrate using continuous milling. Although, reagents were under powder aspect, a lower conversion of rhamnose was observed and a crude paste had glued on the balls which reduced the efficiency of the mixing as it has been described earlier with liquid alkylamines. Thereby, it was necessary to add an inert additive as SiO_2 in order to keep the crude as a powder during the grinding. This two-step protocol provided the desired rhamnosylamines in appreciable yields (Table 3, entries 16 and 17).

Then, the preparation of glycosylamines was also extended using aromatic amines. The reaction between benzylamine (Table 3, entry 18) or dimethoxybenzylamine (Tables 3, entry 19) and rhamnose afforded the corresponding products (**1s** and **1t**) in high yields. Using aniline derivatives (Table 3, entries 20-24), condensation of aniline and 4-aminoaniline with rhamnose led to the corresponding glycosylamines **1u** and **1v** in high yield (99% and 95% respectively) whereas with *para*-hydroxyaniline, the desired product (**1w**) was obtained with average yield (59%). It is important to note that when sterically hindered and electron-deficient arylamines such as 2-iodoaniline (Table 3, entry 23) and 4-amino-3-nitrobenzoic acid (Table 3, entry 24) were employed, no desired products were observed by TLC after 3h effective milling, the starting material was remained unchanged. Finally, as for alkyldiamines, disubstituted product **1z** was obtained using 4-aminoaniline and 2 equivalents of rhamnose per amine, with high yield (90%).

We applied this methodology to others mono- and disaccharide such as D-glucose, D-galactose and maltose. These carbohydrates were preferentially reacted with dodecylamine without adding any grinding auxiliary in the ball mill for 1.5h in excellent yields (97-99%) (Table 3, entries 26-28). Dodecylamine was chosen because previous studies have indicated that *n*-dodecyl-glycosylamines show better antibacterial and antifungal activities than their analogues with shorter and longer carbon chains.[6a,e,f] In all cases, we observed a complete conversion of carbohydrate and formation of desired products in excellent yields (94-98%).

Conclusion

In conclusion, we have developed a green and efficient method for the synthesis of glycosylamines by mixing unprotected carbohydrates with alkylamines, alkyldiamines, amino-alcohol, amino-esters or arylamines in a ball mill under solventless conditions. Compared with classical conditions, this methodology had several beneficial items: a reduction of the reaction time, the obtaining of desired products from unprotected monosaccharides in good to excellent yields while minimizing waste. This advantageous method which is part of the development of environmentally friendly improved protocols to exploit sustainable resources can be exploited for high-value applications in important area such as pharmaceuticals and agrochemical fields.

General experimental procedure

Amine and sugar were mixed in a mortar with a pestle. For liquid amines and chlorhydrate aminoacids, a prior mixing with SiO_2 was necessary to keep the powder aspect during the reaction. The mixture was then introduced with stainless steel balls into a stainless steel jar, placed in a high-energy vibrational ball-milling and milled at 30 Hz. Finally, the reaction mixture was scratched off the vessel; washed with diethyl ether and filtered or purified by flash chromatography to afford the desired glycosylamines.

More details are available in supporting information.

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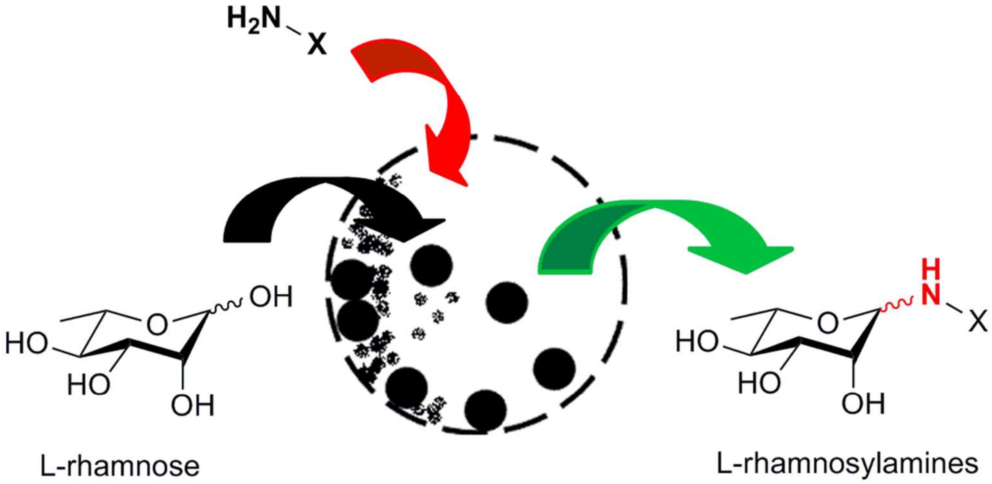

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