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Fast and Efficient Mechanosynthesis of Aldonamides by Aminolysis of Unprotected Sugar Lactones

Abed Bil, Bemba Abdellahi, Gwladys Pourceau * and Anne Wadouachi *

Laboratoire de Glycochimie, des Antimicrobiens et des Agroressources (LG2A) UMR CNRS 7378, Institut de Chimie de Picardie CNRS FR 3085, Université de Picardie Jules Verne, 33 Rue Saint Leu, FR-80039 Amiens, France; abed.bil@u-picardie.fr (A.B.); bemba.abdellahi@una.mr (B.A.)
* Correspondence: gwladys.pourceau@u-picardie.fr (G.P.); anne.wadouachi@u-picardie.fr (A.W.)

Abstract: Sugar amides, such as aldonamides, are interesting, sugar-based molecules used in various fields, from detergency to medicine. Nevertheless, their valorization, especially as alternatives to petroleum-based substances, can be slowed down by their synthetic pathway, which is generally not in accordance with green chemistry principles, and is also not economically competitive. We propose herein a fast procedure for the synthesis of aldonamide-derived glycoconjugates with mechanochemistry. The conditions were first optimized with galactonolactone, used as a model lactone, and dodecylamine. After only 5 min of grinding of stoechiometric amounts of amine and lactone, in the presence of water used as a Liquid Assisted Grinding (LAG) agent, the corresponding galactonamide was isolated with a high yield (90%) after a simple aqueous work-up. The optimized conditions were then applied to a wide variety of amines and sugar lactones, showing the versatility of the methodology. Gluco- and ribono-lactone exhibited similarly excellent reactivity, showing that the procedure is not sugar-dependent. Furthermore, the procedure was shown to be compatible with various functional groups such as alkene, alkyne, thiol, ester and hydroxyl.

Keywords: carbohydrates; aldonamides; mechanosynthesis; solvent-free synthesis

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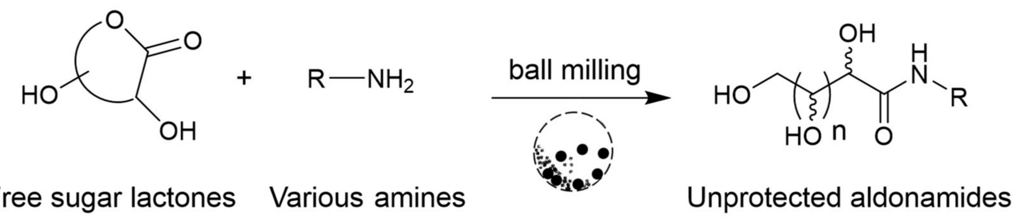
1. Introduction

Thanks to their renewability and abundance, the use of carbohydrates as biomass feedstock, and their eco-friendly conversion into glycoconjugates, are becoming increasingly attractive as potential alternatives to petroleum-based chemicals [1]. In particular, aldonamides, defined as the amides of aldonic acids, were demonstrated to show various properties according to the nature of the amide moiety. The presence of lipophilic alkyl chains linked to hydrophilic sugar heads, leading to *N*-alkyl-aldonamides, confers them amphiphilic properties, making them potential alternatives to petroleum-based surfactants [2]. For example, a composition comprising *N*-alkyl-*D*-gluconamide molecules was very recently patented as a hair conditioning agent by the Henkel group [3]. Otherwise, *N*-alkyl-aldonamides have been reported as good stabilizing agents for microemulsions [4,5] and as hydrogelators [6]. Foamability properties have also been observed for derivatives such as *N*-alkyl-*N*-(2-hydroxyethyl) and *N*-cycloalkylaldonamides [7,8]. Properties of some aldonamides are also interesting for biological applications: abilities to protect hematopoietic stem and progenitor cells against cryoinjury (i.e., ice recrystallization inhibitory properties) [9,10] or bacteriostatic properties on some gram-positive bacteria [11,12] were reported, among others. In addition, aldonamides have been described as intermediates for the synthesis of glycoconjugates, evaluated as glucose-sensing materials [13], or for the synthesis of neo-glycoconjugates [14–17]. For several years, our group has been involved in the design of *N*-alkylaldonamides and their derivatives as sugar-based surfactants [18–20].

Overall, *N*-alkyl-aldonamides can be obtained either by (1) the oxidative amidation of aldoses or by (2) the aminolysis of aldonolactones. Metal-free one-pot procedures have been described for the first strategy. Nevertheless, starting materials need to be at least partially protected, which leads to multistep protocols including protection/deprotection steps and, thus, to poor atom efficiency [21,22]. A direct method was described in 2009, but an excess of amines (4 eq) was necessary and the obtained glyconamides needed to be protected (e.g., peracetylation) to be purified [23]. The second strategy is the reaction of the alkylamine with either an aldonic acid or its cyclic derivative (lactone), but the use of large quantities of hazardous solvents, such as pyridine [24], DMF [25] or DMSO [26], and long reaction times under reflux, are often necessary. Thus, the development of a more eco-friendly procedure, allowing for the modification of non-protected sugars respecting green chemistry principles, represents a challenge for the aldonamide synthesis and, thus, for their valorization.

In recent years, mechanochemical techniques have appeared as an efficient method to reduce or eliminate the use of solvents and to enhance the efficiency of several organic reactions [27–29]. Moreover, it is possible to reduce the environmental footprint of the synthesis by decreasing the reaction time and the number of steps. This technique is particularly appropriate to compounds with opposite polarities, which cannot react in conventional solvent media. Mechanochemical transformations, which have been reported over the three last decades, are conducted in automated ball mills for a wide range of organic transformations [30–35]. They fulfill a similar function to grinding with a mortar and pestle, but in a reproducible manner. Different types of grinding equipment are commercially available, in particular vibrational and planetary ball mills. In a previous study, we successfully used a ball mill to synthesize a broad range of glycosylamines and glycamines from free sugars [36,37]. Furthermore, a very recent article dealing with the direct amidation of esters in a ball mill highlighted (during the course of our study) the requirement for more eco-friendly approaches for the synthesis of amide groups [38].

Herein, we report a fast and efficient synthesis of aldonamides by the aminolysis of unprotected lactones in solvent-free conditions (Scheme 1). This reaction is ecofriendly: (1) it is performed on renewable feedstocks, (2) all of the atoms of the reagents are involved in the final product, in respect with atom economy principle, (3) solventless conditions allow for a reduction in waste and toxicity, etc. The aminolysis procedure was firstly optimized on two model molecules (γ-galactonolactone and dodecylamine) before being applied to a variety of lactones and amines, allowing us to show both the versatility and the limits of the method. As described below, the nature of the amine particularly influences the success of this procedure.



Scheme 1. General procedure for the mechanosynthesis of aldonamides proposed in this work.

2. Materials and Methods

2.1. General

All chemicals were purchased from Fluka, Acros Organics and Sigma Aldrich, and were used as received. Reactions were conducted in a high-speed vibrational ball mill (Spex 8000M) in a stainless steel jar (volume: 60 mL) with stainless steel balls (diameter: 13 mm, 6 mm and 4 mm). Syntheses were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 plates (Merck) and detection was conducted by charring with ninhydrine reagent.

Electrospray high-resolution mass spectrometry experiments (ESI-HRMS) were performed on a SYNAPT G2-Si-Q-TOF hybrid quadrupole time-of-flight instrument (Waters, Manchester, UK). NMR analyses were performed on a BRUKER DRX spectrometer (Bruker, Wissembourg, France), operating at 400 MHz for ^{1}H analysis and 100 MHz ^{13}C analysis. Samples were prepared in DMSO-d_6. Assignments for ^{1}H and ^{13}C signals were performed using correlated spectroscopy (COSY) and heteronuclear single quantum correlation (HSQC).

2.2. General Optimized Procedure

Lactone (500 mg), amine (1 eq.) and H_2O used as a LAG (0.25 mL) were introduced into a stainless steel jar containing the stainless steel balls. The jar was placed in the vibrational ball-mill and was shaken at 18 Hz. After milling, the reaction mixture was scratched off the vessel in a minimum of water. Depending on the amine, the product could be soluble in water; in this case, it was recovered by evaporation. If the as-obtained amide was not soluble in water, it was recovered by filtration.

2.3. Crudes Characterization Data

N-dodecyl-D-galactonamide **1a**. Characterization data in accordance with the literature [39].

N-dodecyl-D-ribonamide **3a**. Characterization data in accordance with the literature [40].

N-dodecyl-D-gluconamide **4a.** Characterization data in accordance with the literature [41].

N-tetradecyl-D-gluconamide **4b**. White powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (t, J = 5.8 Hz, 1H, NH), 5.33 (d, J = 5.0 Hz, 1H, OH-2), 4.52 (d, J = 4.6 Hz, 1H, OH-3), 4.45 (d, J = 4.9 Hz, 1H, OH-4), 4.37 (d, J = 7.2 Hz, 1H, OH-5), 4.32 (t, J = 5.6 Hz, 1H, OH-6), 3.96 (t, J = 4.2 Hz, 1H, H-2), 3.92–3.86 (m, 1H, H-5), 3.61–3.52 (m, 1H, H-6), 3.52–3.41 (m, 2H, H-3, H-4), 3.37 (dd, J = 10.9, 5.5 Hz, 1H, H-6′), 3.12–2.99 (m, 2H, CH_2-N), 1.45–1.35 (m, 2H, C$\underline{H}_2$-CH_2-N), 1.31–1.17 (s, 20H, -CH_2- alkyl), 0.85 (t, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.2 (C=O), 73.6 (C-2), 72.4 (C-3), 71.5 (C-4), 70.1 (C-5), 63.4 (C-6), 38.3 (CH_2-N), 31.3, 29.2, 29.1 (2s), 29.0, 28.8, 28.7, 26.4, 22.1 (CH_2 alkyl), 14.0 (CH_3). HRMS (ESI) *m/z* calcd for $C_{20}H_{41}NO_6Na$ $[M + Na]^+$ 414.2832, found 414.2829. FT-IR ν (cm^{-1}) 3296.4, 2918.3, 2805.8, 1624.1, 1548.8, 1085.9, 1030.0.

N-butyl-D-gluconamide **4c.** Characterization data in accordance with the literature [24].

N-allyl-D-gluconamide **4e.** Characterization data in accordance with the literature [25].

N-propargyl-D-gluconamide **4f.** Characterization data in accordance with the literature [42].

N-benzyl-D-gluconamide **4h**. Characterization data in accordance with the literature [24].

N,N′-1,3-butanediylbis-D-gluconamide **4i′**. White powder. Isolated yield 39%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (br s, 2H, NH), 5.34 (br s, 2H, OH-2), 4.55 (br s, 8H, OH-3, OH-4, OH-5, OH-6), 3.97 (d, J = 2.5 Hz, 2H, H-2), 3.90 (s, 2H, H-5), 3.57 (d J = 10.7 Hz, 2H, H-6), 3.47 (s, 4H, H-3, H-4), 3.42–3.28 (m, 2H, H-6′), 3.08 (s, 4H, CH_2-N), 1.40 (s, 4H, C$\underline{H}_2$-CH_2-N). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.3 (C=O), 73.7 (C-2), 72.4 (C-3), 71.5 (C-4), 70.1 (C-5), 63.4 (C-6), 38.0 (CH_2-N), 26.4 (-$\underline{C}H_2$-CH_2-N). HRMS (ESI) *m/z* calcd for $C_{16}H_{32}N_2O_{12}Na$ $[M + Na]^+$ 467.1853, found 467.1850. FT-IR ν (cm^{-1}) 3300.2, 2935.7, 1624.1, 1546.9, 1469.76, 1446.6, 1085.9, 1030.0.

N,N′-1,3-butanediylbis-D-gluconamide **4i′**. White powder. Isolated yield 39%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (br s, 2H, NH), 5.34 (br s, 2H, OH-2), 4.55 (br s, 8H, OH-3, OH-4, OH-5, OH-6), 3.97 (d, J = 2.5 Hz, 2H, H-2), 3.90 (s, 2H, H-5), 3.57 (d J = 10.7 Hz, 2H, H-6), 3.47 (s, 4H, H-3, H-4), 3.42–3.28 (m, 2H, H-6′), 3.08 (s, 4H, CH_2-N), 1.40 (s, 4H, C$\underline{H}_2$-CH_2-N). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.3 (C=O), 73.7 (C-2), 72.4 (C-3), 71.5 (C-4), 70.1 (C-5), 63.4 (C-6), 38.0 (CH_2-N), 26.4 (-$\underline{C}H_2$-CH_2-N). HRMS (ESI) *m/z* calcd for $C_{16}H_{32}N_2O_{12}Na$ $[M + Na]^+$ 467.1853, found 467.1850. FT-IR ν (cm^{-1}) 3300.2, 2935.7, 1624.1, 1546.9, 1469.76, 1446.6, 1085.9, 1030.0.

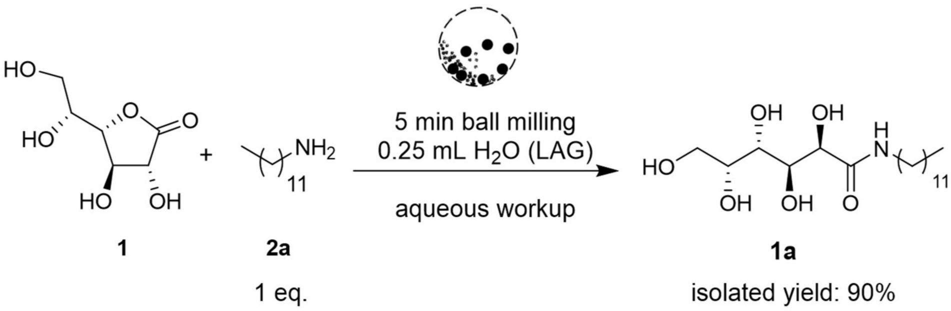
N-(3-hydroxypropyl)-D-gluconamide **4j**. White powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (t, J = 5.8 Hz, 1H, NH), 5.36(d, J = 4.7 Hz, 1H, OH-2), 4.53 (d, J = 2.2 Hz, 1H, OH-3), 4.49–4.41 (m, 2H, OH-4, OH alk), 4.39 (d, J = 7.1 Hz, 1H, OH-5), 4.32 (t, J = 5.3 Hz, 1H, OH-6), 3.97 (t, J = 3.7 Hz, 1H, H-2), 3.90 (d, J = 3.6 Hz, 1H, H-5), 3.63–3.53 (m, 1H, H-6), 3.47 (s, 2H, H-3, H-4), 3.43–3.35 (m, 3H, H-6′, -C$\underline{H}_2$-OH alk), 3.23–3.07 (m, 2H, CH_2-N), 1.56 (p, J = 6.3 Hz, 2H, C$\underline{H}_2$-CH_2-N). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5 (C=O), 73.6 (C-2), 72.4 (C-3), 71.5 (C-4), 70.1 (C-5), 63.4 (C-6), 58.6 (-CH_2-OH alk), 37.5 (CH_2-N), 32.2 (-$\underline{C}H_2$-CH_2-N). HRMS (ESI) *m/z* calcd for $C_9H_{19}NO_7Na$ $[M + Na]^+$ 276.1059, found 276.1067. FT-IR ν (cm^{-1}) 3404.4, 3348.4, 3240.4, 2976.1, 2947.2, 2897.1, 1651.1, 1539.2, 1249.9, 1114.9, 1072.4, 1024.2.

N-(2-thioethyl)-D-gluconamide **4k**. Characterization data in accordance with the literature [43].

N-gluconylglycine methyl ester **4l**. Characterization data in accordance with the literature [23].

3. Results and Discussion

The operating conditions were first optimized on the aminolysis of γ-galactonolactone **1** with dodecylamine **2a** (Scheme 2) in a vibrational ball-mill, and compared to the conventional procedure conducted in MeOH and to manual grinding. The results are reported in Table 1.



Scheme 2. Optimized synthesis of *N*-dodecyl-galactonamide **1a**.

Table 1. Comparative conditions for the synthesis of *N*-dodecyl-D-galactonamide **1a**.

Entry	Conditions	LAG [b]	t (min)	Isolated Yield (%)
1	MeOH [a]	-	30	62
2	SPEX ball mill	-	30	69
3		-	10	34
4		H_2O	10	86
5		H_2O	5	84
6		H_2O	15	83
7	Mortar	H_2O	10	83

Reaction conditions: γ-galactonolactone (2.8 mmol), dodecylamine (2.8 mmol). [a] 10 mL of MeOH. [b] 0.75 mL.

All reactions were performed using stoechiometric amounts of free sugar lactone and amine. In the first study where the optimal conditions were sought, methanol, able to solubilize both unreacted galactonolactone and dodecylamine, but not the as-obtained galactonamide, was chosen to quench the reaction and ensure reliable results concerning the conversion. The latter was also checked using TLC analyses of the crude. After filtration and washing, *N*-dodecyl-galactonamide **1a** was isolated as a white powder. NMR analyses (^{1}H and ^{13}C NMR) confirmed that neither residual lactone nor residual amine were present in the as-obtained crudes, *N*-dodecyl-galactonamide **1a** being the only product observed.

Starting from 0.5 g of lactone **1** in the presence of one equivalent of dodecylamine **2a**, a yield of 62 % for compound **1a** was obtained after 30 min of stirring in MeOH (conventional conditions, entry 1). When the same reaction was performed in a ball mill (Spex

8000M) under less solvent conditions, a comparable yield (69%) was obtained for the same time (entry 2), with TLC analyses showing incomplete conversion. A reduction in milling time led to a drop in the production of amide (34% obtained after 10 min milling (entry 3)). However, when water was added as a liquid-assisted grinding agent (LAG), the yield raised to 86% for 10 min milling (entry 4), confirming the enhancement of conversion (confirmed by TLC measurement) which is well described for other transformations. In general, LAG improved reaction kinetics, allowed for the optimization of reactivity to quantitative yields and reduced the problems of product amorphization, which can be observed with neat grinding [44,45]. The parameter η is defined as the ratio of the added liquid (in μL) to the total weight of the solid reactants (in mg). To be considered as a LAG agent and not as a solvent, η must be lower than 2 μL mg^{-1}. In our case, the η value was below 0.75 μL mg^{-1}. The influence of milling time was also evaluated, but no significant change was observed between 5 and 15 min of milling (entries 5, 6). Finally, since ball mills are not available in every organic lab, we were interested in comparing this method with manual grinding, whilst considering that this technique is not as reliable as mechanical milling. By grinding the same quantities of reagents (equimolar ratio of galactonolactone with dodecylamine in the presence of water as a LAG agent) for 10 min in a mortar with a pestle, a high yield (83%) of *N*-dodecyl-galactonamide **1a** was obtained, similarly to those obtained by mechanical milling, but without requiring any expensive equipment.

As illustrated by the results obtained with and without a LAG (Table 1, entry 3 vs. 4), a LAG agent is essential for the efficiency of this condensation reaction. Its nature and amount should influence the conversion and thus the isolated yield of *N*-dodecyl-galactonamide **1a**. To evaluate these parameters, three different eco-friendly solvents, namely EtOAc, EtOH and H_2O, were added in different quantities (from 0.25 mL to 0.75 mL) to the powder mixture before milling.

As reported in Table 2, when using EtOAc, compound **1a** was obtained in a moderate 50% yield (entry 1), in accordance with the TLC analyses showing an incomplete conversion. In contrast, in the same conditions, protic solvents (H_2O, EtOH) led to total conversions and high isolated yields (82 and 86%, respectively, entries 2 and 3). These results seem to suggest that the establishment of H-bounds with lactone may activate the electrophilic center. The adding of larger quantities of a LAG (0.5 or 0.75 mL, entries 4 and 5) does not allow for the enhancement of the isolated yield, for which a maximum of 86–87% was consistently obtained.

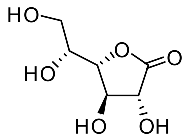
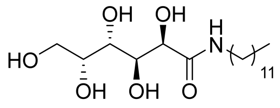
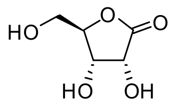
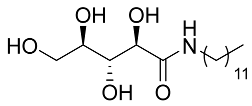
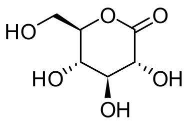
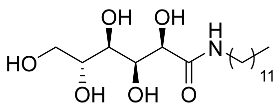
Table 2. Influence of nature and quantity of LAG for the mechanosynthesis of **1a** in the SPEX ball-miller.

Entry	LAG	V (mL)	Yield (%)
1	EtOAc	0.25	50
2	H_2O		82
3	EtOH		86
4	EtOH	0.50	83
5		0.75	84

Reaction conditions: γ-galactonolactone (2.8 mmol), dodecylamine (2.8 mmol), LAG agent, milled during 10 min.

Furthermore, even in the presence of larger amounts of amine (1.05 and 1.1 eq), or by extending the milling time (such as for Table 1, entry 6), no more than 87% of *N*-dodecyl-galactonamide **1a** was ever recovered, suggesting that the ~15% yield loss may occur during the workup (probably due to a slight solubilisation of **1a** in methanol). This hypothesis corroborates the TLC analyses showing a total conversion of lactone. An aqueous workup (i.e., recovering of the white powder as a suspension in water followed by a filtration step) allowed for a slight enhancement of the isolated yield whilst reducing the environmental impact: 90% of *N*-dodecyl-galactonamide **1a** was isolated after 5 min (Table 3, entry 1) of milling vs. 82% when methanol was used for washing. These last conditions of synthesis and workup were chosen as optimized conditions for the subsequent studies.

Table 3. Applications to various sugar lactones [a].

Entry	Sugar Lactone	Product	Isolated Yield (%)
1	 **1**	 **1a**	90
2	 **3**	 **3a**	91
3	 **4**	 **4a**	96

[a] 0.5 g lactone, 1 eq. dodecylamine **2a**, 0.25 mL H_2O (LAG), 5 min milling, aqueous treatment.

The development of a versatile methodology applicable to a wide variety of sugars is not easy in glycochemistry: a procedure, powerful on one series of sugar (i.e., glucose, for example), can lead to erratic results on other sugars (i.e., galactose, mannose and so on). On the other hand, the reactivity of an amine group is directly related to the radical which carries it. To illustrate the proposed methodology and identify its limitations, optimized conditions were applied to a variety of unprotected sugar lactones and amines (Figure 1).

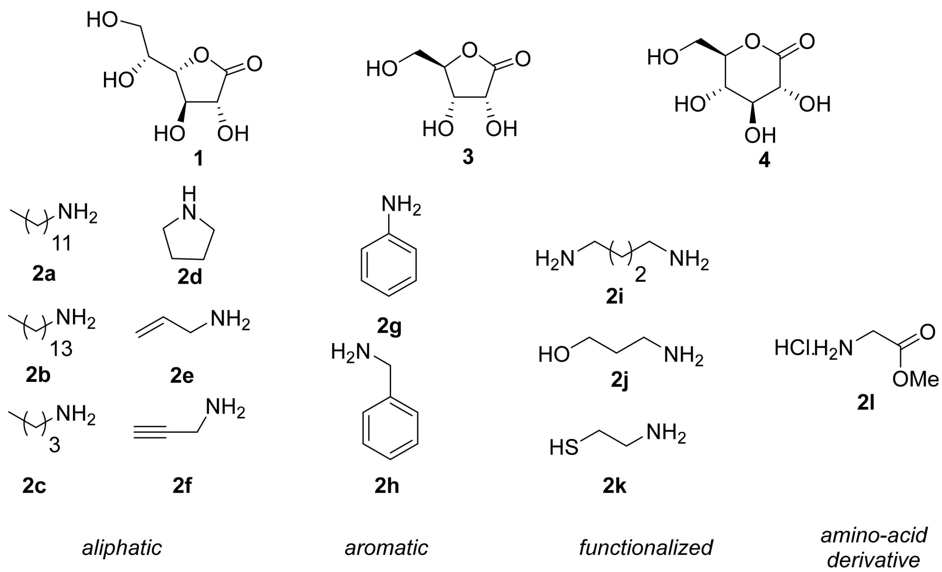


Figure 1. Glyconolactones (**1,3,4**) and amines (**2a**–**2m**) used in this study.

Firstly, in addition to γ-galactonolactone **1**, two commercially available aldonolactones (γ-ribonolactone **3** and δ-gluconolactone **4**) were reacted with dodecylamine **2a** (Table 3). Corresponding *N*-dodecyl-ribonamide **3a** and *N*-dodecyl-gluconamide **4a** were obtained, with high isolated yields (91% and 96% respectively) and excellent purities (>95% determined by NMR), showing that the procedure is not sugar-dependent (entries 2–3).

With the aim to prove the versatility of the procedure on the amines as well, a series of sundry amines (aliphatic, aromatic, unsaturated, functionalized with hydroxyl or thiol group, amino-acids, etc.) were then tested on δ-gluconolactone **4**, this being more reactive, cheaper and abundant (Table 4). Conversion was determined based on ^1H NMR, by comparison between the characteristic signals of the as-obtained amide and of the residual amine or lactone (or its saponified form) when present. All ^{1}H and ^{13}C NMR spectra are displayed in the Supplementary Materials.

Table 4. Applications to various amines [a].

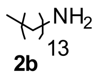
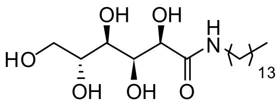
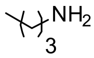
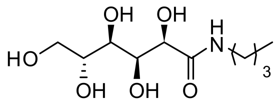
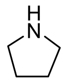
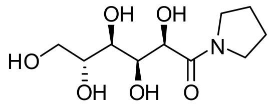
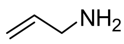
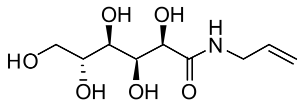
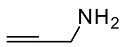
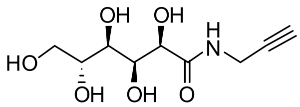
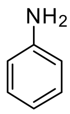
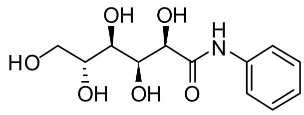
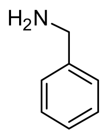
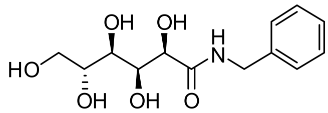
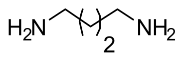
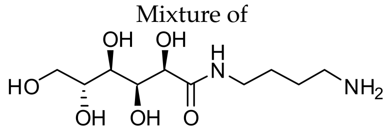
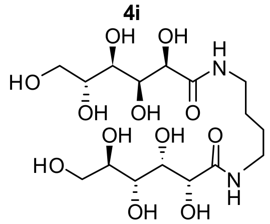
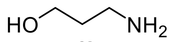
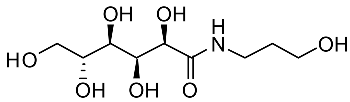
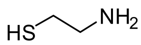
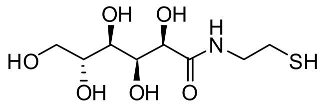
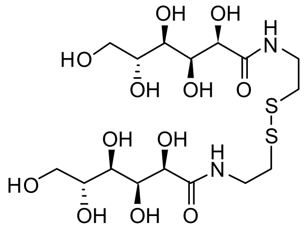
Entry	Amines	Product	Conv. (%)
1	 **2b**	 **4b**	Quant.
2	 **2c**	 **4c**	84
3	 **2d**	 **4d**	24
4	 **2e**	 **4e**	89
5	 **2f**	 **4f**	Quant.
6	 **2g**	 **4g**	-
7	 **2h**	 **4h**	89
8	 **2i**	Mixture of  **4i**  **4i'**	Quant. [b] Isolated yield of **4i′**: 39

Table 4. *Cont.*

Entry	Amines	Product	Conv. (%)
9	 **2j**	 **4j**	80
10	 **2k**	 **4k**  **4k'**	Quant. **4k/4k′**: ~80/20

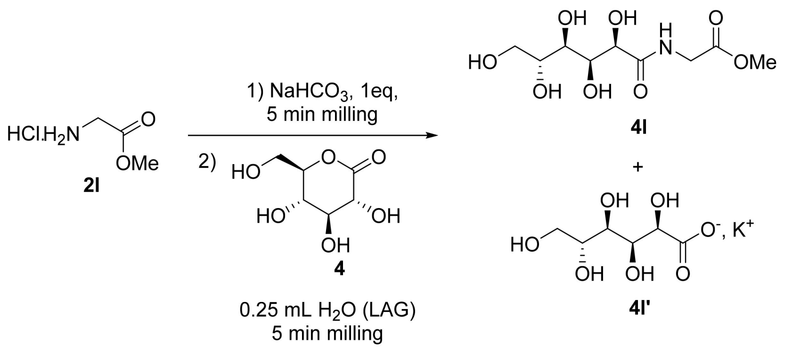
[a] 0.5 g gluconolactone **4**, 1 eq. amine, 0.25 mL H_2O (LAG), 5 min milling, aqueous treatment; [b]: washing with MeOH.

Saturated and unsaturated aliphatic amines (**2b–e**) were used for the synthesis of the corresponding *N*-alkyl-aldonamides **4b–e**. Good (84%) to total conversions (entry 3, Table 3 and entries 1–2, Table 4) were observed using saturated primary alkylamines (**2a–2c**), even for volatile amines such as butylamine, for which milling may cause evaporation. On the other hand, the only secondary amine used in our conditions, pyrrolidine **2d,** logically led to a weaker conversion (24%) because of its steric hindrance, leading to weaker nucleophilicity (entry 3). Nevertheless, this first attempt suggests that, after a new optimization step (by modulating time of milling, quantity of LAG, etc.), this solvent-less procedure may work with secondary amines.

Furthermore, unsaturated volatile amines, such as allylamine **2e** and propargylamine **2f,** gave good to excellent conversions (89% and quantitative, respectively, entries 4-5). Aromatic amines were also studied (entries 6–7). Because of the weak nucleophilicity of the amine group (due to the delocalization of the *N* nucleophilic lone pair into the aromatic moiety), aniline (**2g**) did not react. In contrast, benzylamine (**2h**) led to a good conversion of 89% (entry 7).

In order to study the versatility of the reaction, three functionalized amines (namely diaminobutane **2i**, aminopropanol **2j** and cysteamine **2k**) were used (entries 8–10). Diaminobutane **2i** showed excellent reactivity (quantitative conversion) but low selectivity, despite the use of one equivalent of diamine reagent: a mixture of mono- (**4i**) and di-amide (**4i′**) products was obtained (entry 8). When MeOH was used as a treatment at the end of the milling process, only the di-amide product **4i′** precipitated and was isolated by filtration, with a 39% yield and excellent purity. The reaction was also performed in the presence of 0.5 eq. of diaminobutane **2i**, but a mixture of **4i**/**4i′** was again obtained, leading again to an uncomplete conversion. Furthermore, aminopropanol **2j** showed a weaker reactivity (entry 9), since 80% of the conversion was obtained after 5 min milling. On the other hand, good selectivity was observed when using cysteamine (entry 10), since only the production of *N*-addition was observed. No residual lactone or amine was visualized by NMR, confirming a quantitative conversion. Nevertheless, the disulfide product was detected in the mixture, due to the oxidation of the thiol-free group. A comparison of crude NMR spectra (especially ^{13}C) with the literature [43] with mass spectrometry allows for the confirmation that *N*-(2-thioethyl)-D-gluconamide **4k** was the major product in the crude (~80% determined by NMR).

To complete this work, a protected amino-acid, L-glycine methyl ester **2l**, was used to show the possibility of rapidly and efficiently synthesizing other glycoconjugates, such as glyco-aminoacids, glycopeptids or glycoproteins (Scheme 3). Indeed, for more than 20 years, the glycoscientist community has been interested in this type of glycoconjugates (sugar/amino-acids, peptids and proteins), for the understanding of biological phenomena or the design of new drugs, for instance [46–48]. Since L-glycine methyl ester **2l** is commercially available as hydrochloride salt, the addition of a base is needed to release the free amine. Therefore, one equivalent of $NaHCO_3$ was first milled with amino-ester hydrochloride **2l** for 5 min, then δ-gluconolactone **4** (0.5 g) and LAG (H_2O, 0.25 mL) were added to the jar. The aminolysis step was performed as for the other amines. The preliminary step of alkalinisation is essential for the reactivity of the amine, which is also hazardous: in the second step (the aminolysis of the lactone) the presence of the residual base and water (used as a LAG, but also during the work-up) may cause saponification of the lactone into carboxylate salt, which is unable to react with amine. Consequently, even if the gluconolactone was totally converted, a mixture gluconamide **4l**/gluconate salt **4l′** was obtained (in proportion ~2/1). Two hypotheses can be drawn to explain this degradation: (1) the saponification may take place during the aminolysis when residual base and water (used as a LAG) are present, meaning that the nature and quantity of the base as well as LAG should be optimized, or that the free amine derivative should be isolated prior to aminolysis, or (2) that the conversion is not quantitative and the residual gluconolactone is saponified during the work-up; in this case, an optimization of the aminolysis step in terms of progress of the reaction (milling time, nature of the ball mill, etc.) should be carried out. Nevertheless, this first attempt suggested that the synthesis of such glycoconjugates can be performed by using this simple procedure after optimization. This is under study and will be the subject of a future article.



Scheme 3. Mechanosynthesis of *N*-gluconylglycine methyl ester **4l**.

4. Conclusions

To conclude, we presented herein a fast and simple procedure to obtain a variety of glycoconjugates by the mechanical-assisted aminolysis of sugar lactones using a vibrational ball mill. This methodology is performed on unprotected lactones and is totally free of organic solvents, making it an excellent eco-friendly alternative to conventional procedures for the synthesis of such glycoconjugates. No purification step is needed, avoiding the use of excess solvents. Only a minimum of H_2O as a "liquid-assisted grinding" agent (LAG) is used to activate the reaction, resulting in the corresponding glycoconjugates in less than 5 min. Moreover, it can also be performed in a mortar, which has the advantage of being available in any laboratory. The reaction conditions were first optimized by using dodecylamine and galactonolactone as starting substrates, and the optimal conditions were then applied to a wide variety of substrates (lactones and amines). Gluco-, ribono- and galactonolactone exhibited excellent similar reactivity, showing that the procedure is not sugar-dependent, which is often a lock in glycochemistry. Overall, unfunctionalized primary amines also led to excellent conversions, except for deactivated ones such as aniline. By using pyrrolidine, the proof of concept was also established for secondary amines, which need further optimization to give quantitative conversion. The procedure is compatible with various functional groups, such as alkene, alkyne, thiol, ester, or hydroxyl. Finally, it has been shown that glycoconjugates such as sugar/amino-acid derivatives should be easily obtained (further optimization concerning the nature and quantity of base, milling time, apparatus is currently ongoing), which paves the way to the synthesis of more complex glycoconjugates.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/suschem3030019/s1, ^{1}H and ^{13}C NMR spectra of the **1a**, **3a**, **4a**, **4c-4h**, **4k-l** crudes and characterization (^{1}H, ^{13}C, COSY, HSQC NMR analyses, HRMS and FTIR spectra) of the **4b**, **4i′** and **4j** crudes. Figure S1: ^{1}H NMR spectrum of 1a crude; Figure S2: ^{13}C NMR spectrum of 1a crude; Figure S3: ^{1}H NMR spectrum of 3a crude; Figure S4: ^{13}C NMR spectrum of 3a crude; Figure S5: ^{1}H NMR spectrum of 4a crude; Figure S6: ^{13}C NMR spectrum of 4a crude; Figure S7: ^{1}H NMR spectrum of 4b crude; Figure S8: ^{13}C NMR spectrum of 4b crude; Figure S9: COSY NMR 2D spectrum of 4b crude; Figure S10: HSQC ^{13}C-^{1}H NMR 2D spectrum of 4b crude; Figure S11: HRMS analysis of 4b crude; Figure S12: IR analysis of 4b crude; Figure S13: ^{1}H NMR spectrum of 4c crude; Figure S14: ^{13}C spectrum of 4c crude; Figure S15: ^{1}H NMR spectrum of 4d crude; Figure S16: ^{13}C NMR spectrum of 4d crude; Figure S17: ^{1}H NMR spectrum of 4e crude; Figure S18: ^{13}C NMR spectrum of 4e crude; Figure S19: ^{1}H NMR spectrum of 4f crude; Figure S20: ^{13}C NMR spectrum of 4f crude; Figure S21: ^{1}H NMR spectrum of 4h crude; Figure S22: ^{13}C NMR spectrum of 4h crude; Figure S23: ^{1}H NMR spectrum of 4i′ crude; Figure S24: ^{13}C NMR spectrum of 4i′ crude; Figure S25: COSY NMR 2D spectrum of 4i′ crude; Figure S26: HSQC ^{13}C-^{1}H NMR 2D spectrum of 4i′ crude; Figure S27: HRMS analysis of 4i′ crude; Figure S28: IR analysis of 4i′ crude; Figure S29: ^{1}H NMR spectrum of 4j crude; Figure S30: ^{13}C NMR spectrum of 4j crude; Figure S31: COSY NMR 2D spectrum of 4j crude; Figure S32: HSQC ^{13}C-^{1}H NMR 2D spectrum of 4j crude; Figure S33: HRMS analysis of 4j crude; Figure S34: IR analysis of 4j crude; Figure S35: ^{1}H NMR spectrum of 4k crude; Figure S36: ^{13}C NMR spectrum of 4k crude; Figure S37: ^{1}H NMR spectrum of 4l crude; Figure S38: ^{13}C NMR spectrum of 4l crude.

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