Tetrahedron Letters 51 (2010) 1356–1360

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave-assisted synthesis of D-glucuronic acid derivatives using cost-effective solid acid catalysts

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ARTICLE INFO

Article history:
Received 27 October 2009
Revised 8 December 2009
Accepted 11 December 2009
Available online 21 December 2009

ABSTRACT

Monomode microwave-assisted coupling of D-glucuronic acid with alcohols, in the presence of various impregnated acid catalysts, was successfully performed, affording in almost quantitative yields the corresponding monosubstituted β-D-glucofuranosidurono-6,3-lactones in less than 10 min at 85 °C. This study evidences the synergy of microwaves and impregnated acid catalysts as a fast and clean strategy in the field of carbohydrate chemistry.

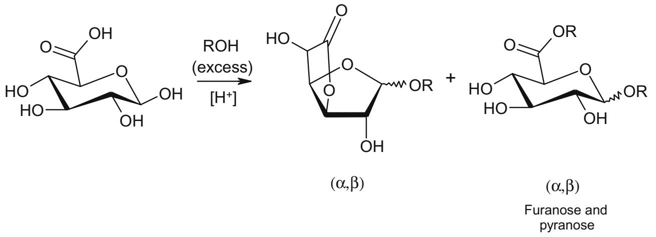
1. Introduction

D-Glucuronic acid (D-GlcA), its mono- and polysaccharide derivatives are important natural compounds, widely distributed in animals and plants.[1] Besides, synthetical D-GlcA derivatives find numerous applications in bioactive molecules development,[2] material sciences,[3] and as surface-active agents.[4] D-Glucuronic acid contains both carboxylic acid and hydroxyl moieties, which are suitable targets for performing synthetical modifications.[5] Nevertheless, the regioselective synthesis of well-defined glucuronic acid-containing compounds is usually fastidious and time-consuming.[6] Indeed, as O-glycosidation and esterification are competitive, unprotected D-GlcA undergoes many transformations when chemically coupled with alcohols under acidic conditions (Scheme 1). As a consequence, implementation of straightforward chemical strategies for the obtention of tautomerically and anomerically pure uronic acid derivatives from O-unprotected acidic sugars remains actually a particularly challenging task.

On the other hand, since the Letters of Gedye et al.[7] and Gigure et al.[8], the application of microwaves (MW) as a non-classical heating technique has gained special attention. In recent years, indeed, a plethora of publications has illustrated the effectiveness of microwave heating in many different types of organic synthesis, largely due to the frequently observed acceleration in reaction rates, improved yields and enhanced selectivities.[9] Nevertheless, to the best of our knowledge, there is only one Letter dealing with chemical modifications of D-GlcA accelerated by microwaves.[10] Thus, Rat and co-workers disclosed on the synthesis, mediated by homogeneous acid catalysts (i.e., H_2SO_4 or Lewis acids), of a range of alkyl GlcA derivatives in less than 10 min at 60–85 °C. This solvent-free approach, relying on esterification and/or glycosydation of D-GlcA or its O-protected 6,1-lactone, illustrates how the nature of the acid promoter can be used to tune the chemoselectivity of the reaction.

We herein evaluate the replacement of these soluble catalysts by recyclable heterogeneous acid systems in order to develop a truly eco-friendly green process.[11,12] In this context, we lay emphasis on acids impregnated on inorganic oxide supports (viz. silica gel or mesoporous silica), including cost-effective sulfuric acid loaded on porous silica (H_2SO_4/SiG_{60})[13,14] and silica-supported Keggin type heteropolyacid.[15] These entities present favourable thermal and mechanical properties and provide good dispersion of active sites, leading generally to improvement in reactivity and reaction selectivity.[16] Moreover, these supported acids usually offer convenient work-up advantages as they can be conveniently removed at the end of the reaction by simple filtration, avoiding the need for neutralisation and resulting salt formation, and thus minimising wastes.[17]

This work is aimed at illustrating for the first time the microwave-assisted 'one-pot' functionalisation of totally unprotected D-GlcA with alkyl alcohols in the presence of various impregnated solid acids. Due to the lack of previous works, our approach was rather exploratory. The scope and limitations of using such heter-



Scheme 1.

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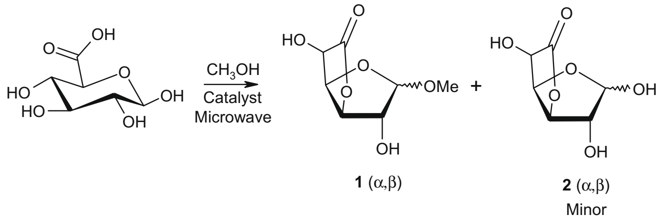
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.12.065



Scheme 2.

ogeneous catalysts are therefore discussed in terms of activity, chemoselectivity and catalyst recycling initiatives.

2. Results and discussion

Optimisation of reaction conditions was achieved, using a CEM Discover reactor, for the benchmark functionalisation of D-glucuronic acid (D-GlcA) by methanol promoted by H_2SO_4/SiG_{60} (35 wt %[†]) (Scheme 2).[10] Our results allowed us to identify that a temperature of 85 °C at a maximum microwave power of 80 W associated with a runtime of 10 min were the most effective reaction conditions for the nearly quantitative transformation of 200 mg of GlcA into **1** in the presence of 50 mg of 35 wt % H_2SO_4/SiG_{60} (see Supplementary data S1). Compared to previous works, this approach gives higher yields (reaching up to 85%) and better anomeric selectivities (α:β ≈ 10:90) can be attained using an impregnated catalyst under microwave conditions.[6c,10]

2.1. Synthesis of methyl D-glucofuranosidurono-6,3-lactone promoted by various solid acid catalysts

These preferred experimental conditions were afterwards used for the microwave-assisted reaction of D-GlcA with methanol catalysed by a diverse set of impregnated catalysts. We anticipated that H_3PO_4 and 12-tungstophosphoric acid (HPWA), impregnated on silica or onto siliceous MCM-41, could likewise be suitable promoters for this microwave-mediated reaction. Indeed, these solid acids present main attractive features, namely their strong acid character combined with the ability of the silica surface to adsorb reactants and to absorb microwave energy,[12b,18] leading to an increase in local concentration and probable reaction rate enhancement.

2.1.1. Catalytic tests under microwave exposure

When using impregnated species (listed in Table 1) as catalysts, the reaction proceeded in most cases rapidly (less than 10 min) to afford the corresponding methyl D-glucofuranosidurono-6,3-lactone **1**, predominantly as the β anomer.[19] However, a noticeable difference in reaction yields was recorded depending on the promoter used. H_2SO_4/SiG_{60} with an acid loading of 35 wt % was found to be one of the most active and efficient catalyst of the series, proving 83% isolated yield of the corresponding methyl D-glucofuranosidurono-6,3-lactone **1**. For the sake of comparison, when phosphoric acid was impregnated in the same way on silica gel, the yield of isolated product **1** was substantially lower and did not exceed 24%. A higher sulfuric acid loading (50 or 70 wt %) on the oxide support did not improve the performance in the reaction. Indeed, a slight unfavourable effect over the yield was recorded. This decrease in yield suggested that, despite increasing H_2SO_4 loadings, fewer catalytic sites are accessible for the reactants if the reaction takes place actually on the surface of the catalyst (or by dissolution in the supported H_2SO_4) rather than by dissolved sulfuric acid.[18] Noteworthy, even if **1**β was the major product formed, unexpected D-glucuronic acid γ-lactone **2** (10%) was detected as a side-product. This by-product was identified unambiguously by comparison with an authentic commercial sample. For comparison, reference reaction performed using only liquid sulfuric acid (0.1 equiv), that is, without oxide carrier, was otherwise sluggish and afforded **1** in 52% yield and in a α:β ratio of 40:60. Herein, D-glucuronic acid γ-lactone **2** was also recovered in more than 10% yield. This finding suggested the superiority (in terms of activity and anomeric selectivity) of silica gel-impregnated sulfuric acid over its homogeneous counterpart. On the other hand, the control experiment without sulfuric acid did not afford a significant conversion of D-GlcA and more than 95% of the initial uronic acid remained after microwave exposure. In the same way, the mesoporous molecular sieve (MCM-41) without H_2SO_4 exhibited practically low catalytic activity.

Table 1
Microwave-assisted reaction of D-glucuronic acid with methanol in the presence of various solid acid catalysts[a]

Catalyst	D-GlcA conversion (%)	**1** Yield (%)[b] (α:β)[c]
None	–	–
SiG_{60}	m	m
MCM-41	17	5 (50:50)
35 wt % H_2SO_4/SiG_{60}[d]	88	83 (10:90)
50 wt % H_2SO_4/SiG_{60}	86	79 (5:95)
70 wt % H_2SO_4/SiG_{60}	74	62 (5:95)
H_2SO_4[e]	67	52 (40:60)
35 wt % H_2SO_4/MCM-41	32	9 (20:80)
35 wt % H_3PO_4/SiG_{60}	27	24 (10:90)
35 wt % HPWA/SiG_{60}	62	50 (15:85)
35 wt % HPWA/MCM-41	70	68 (50:50)

[a] Reaction conditions: GlcA (200 mg, 1.03 mmol), MeOH (0.25 mL, 6 equiv) and the catalyst (50 mg) were introduced in a 10 mL microwave reaction vial and irradiated, under agitation, at 85 °C, during 10 min, and with a maximum power of 80 W.

[b] Isolated yields of pure anomeric mixtures. *m* stands for minute amounts.

[c] Anomeric compositions of reaction mixtures were determined by ^1H NMR spectroscopy.

[d] Corresponding to 0.1 equiv of pure H_2SO_4

[e] GlcA (200 mg, 1.03 mmol), MeOH (0.25 mL, 6 equiv), H_2SO_4 96% aqueous solution (0.1 equiv).

When impregnating the mesoporous MCM-41 with sulfuric acid, the yield of **1** was undoubtedly strongly affected compared to the reaction catalysed under the same conditions by 35 wt % H_2SO_4/SiG_{60}. Indeed, isolated yield of **1** was down to ca. 9% compared with 83% under identical conditions using sulfuric acid impregnated on silica gel. Once again, a significant amount (about 20%) of D-glucuronic acid γ-lactone **2** was detected in the crude mixture. This lowest yield of adduct **1** may probably be correlated to the diffusion-limited process of the reactants and products within the mesopores of the catalyst support. When using a Keggin type heteropolyacid ($H_3PW_{12}O_{40}$) in its supported version, results were quite satisfactory, providing the target methyl D-glucofuranosidurono-6,3-lactone in 50–70% yield. In this case, the recourse to a mesoporous oxide support induced a slight beneficial effect over the yield and afforded the methyl adduct **1** as an anomeric mixture in a 50:50 α:β ratio.

2.1.2. Comparison with conventional heating

In order to appreciate a potential beneficial effect played by the microwave heating, some comparative tests were conducted using a thermostated bath under otherwise identical conditions of concentrations and temperature, except that the reactions were performed in sealed tubes, which were immersed in an oil bath at 85 °C (Table 2).

Again, the control experiments without supported solid acids or only in the presence of silica gel or MCM-41 indicated no trace of expected methyl D-glucofuranosidurono-6,3-lactone **1** and almost

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[†] Expressed as pure H_2SO_4 based on the total catalyst weight.

Table 2
Thermally-driven reaction of D-glucuronic acid with methanol in the presence of various solid acid catalysts[a]

Catalyst	D-GlcA conversion (%)	Isolated yield[b] (%)	
		1[c] (α:β)	**2**[c] (α:β)
None	m	–	–
SiG_{60}	m	–	m
MCM-41	m	m	m
35 wt % H_2SO_4/SiG_{60}	69	m	68 (20:80)
50 wt % H_2SO_4/SiG_{60}	73	m	72 (20:80)
70 wt % H_2SO_4/SiG_{60}	82	m	80 (20:80)
35 wt % H_2SO_4/MCM-41	76	30 (10:90)	45 (20:80)

[a] Reaction conditions: GlcA (200 mg, 1.03 mmol), MeOH (0.25 mL) and the catalyst (50 mg) were heated under agitation at 85 °C for 10 min using a thermostated oil bath. Conversions are based on D-GlcA and were estimated by ^{1}H NMR, directly on crude sample after reaction.

[b] Isolated yields of pure anomeric mixtures. *m* stands for minute amounts.

[c] Anomeric compositions of reaction mixtures were determined by ^{1}H NMR spectroscopy.

all initial D-GlcA was recovered at the end of each experiment. When using sulfuric acid impregnated on silica gel, results were quite the opposite of those obtained previously under microwave heating. Indeed, although D-GlcA conversions were satisfactory and reached up to 70%, formation of the corresponding methyl-D-glucurono-6,3-lactone was negligible. On the other hand, D-glucuronic acid γ-lactone **2** was systematically isolated as the major product with an anomeric ratio (α:β) of 20:80. Furthermore, when using H_2SO_4 trapped onto MCM-41 as the catalyst, the desired adduct **1** (α:β = 10:90) was obtained in 30% yield, together with significant amount (45% yield) of D-GlcA γ-lactone **2** (α:β = 20:80). These results demonstrate how microwaves, in combination with our home-made impregnated catalysts, can be profitably used to tune the chemoselectivity of the transformation of totally O-unprotected D-glucuronic acid in a methanolic solution. Indeed, whilst D-GlcA γ-lactone **2** was the major product isolated after reaction under thermally-driven conditions, methylated glucofuranosidurono-6,3-lactone **1** was the main product detected after microwave exposure.

2.1.3. Stability and reusability of H_2SO_4/SiG_{60} for microwave-assisted reactions in methanol

Even if sulfuric acid trapped on silica gel was claimed to be an efficient promoter for several literature-known catalysed transformations in polar solvents (including alcohols),[14] the stability of this catalyst during processes, and in particular in 'water-generating' reactions, was faintly addressed.

Herein, we decided to launch a systematic study concerning the fate of two distinct catalysts, namely 35 wt % H_2SO_4/SiG_{60} and 35 wt % HPWA/MCM-41, during the microwave-assisted conversion of D-GlcA into its corresponding substituted 6,3-lactone **1** in methanol. Complementarily, we decided to assess the reusability of these solid catalytic species in consecutive batch reaction tests. In this way, each catalyst was carefully recovered at the end of the first microwave-assisted reaction by filtration through a glass frit. The recovered catalyst was then subsequently dried under static air at 120 °C (or 160 °C) before being reused again for a second run as described above (reaction conditions as in Table 1).

Thermogravimetric analyses, achieved under inert atmosphere, of 35 wt % H_2SO_4/SiG_{60} before and after reaction between D-GlcA and MeOH revealed two distinct weight losses (Fig. 1). The first weight change was associated with desorption of water onto silica, whilst the second at about 260 °C matched with the desorption of sulfuric acid.[20] Before reaction, the weight loss associated to the desorption peak at 260 °C represented 34% (based on total sample weight). After a first reaction, the value of the weight loss decreased significantly and reached only 25.9%,[21] evidencing a progressive leaching of H_2SO_4 into the reaction medium. In addition, the activity of the catalyst was, as expected, slightly affected as 67% of methyl D-glucofuranosidurono-6,3-lactone **1** (α:β = 25:75) were isolated after the second run (vs 83% after the first run). In parallel, γ-glucurono-lactone **2** was detected as a minor side-product (see also Supplementary data S2 for the stability and reusability of HPWA/MCM-41).

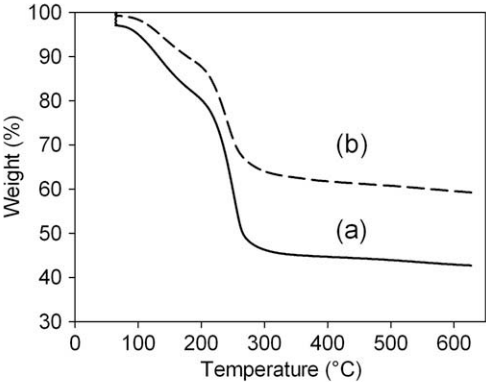


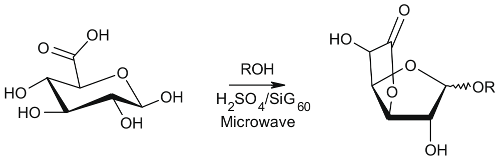
Figure 1. TGA, under flowing argon, of freshly conditioned 35 wt % H_2SO_4/SiG_{60} before (a) and after (b) microwave-assisted reaction between D-GlcA and methanol.

2.2. Reaction between D-glucuronic acid and various alkyl alcohols catalysed by 35 wt % H_2SO_4/SiG_{60}

In order to ascertain the applicability of the microwave-assisted protocol elaborated in our first sets of trials, we decided to extend our investigations to the reaction between D-glucuronic acid and various alkyl alcohols (Scheme 3). Reactions under solventless conditions were achieved in the presence of 35 wt % H_2SO_4/SiG_{60} selected as the solid-phase promoter (Table 3).[22]

Reaction between totally O-unprotected D-glucuronic acid and linear alcohols of the general formula $CH_3(CH_2)_nOH$ ($n = 3, 5, 7$), under microwave conditions, resulted in the almost quantitative and clean formation of the corresponding alkyl D-glucofuranosidurono-6,3-lactones **3**–**5**, obtained with high diastereoselectivities (α:β = 10:90). In each case, the formation of **2** was insignificant. Furthermore, no trace of disubstituted adducts were recovered. For comparison, treatment of D-GlcA with *n*-butanol in the presence of H_2SO_4/SiG_{60}, using a thermostated oil bath as the heating source, led to the isolation of butyl D-glucofurosidurono-6,3-lactone **3** (α:β = 5:95) in only 48% yield after 10 min. When performing thermally-driven reaction with *n*-octanol, conversion of D-GlcA was in this case negligible, glaringly evidencing a real advantage of microwaves over conventional heating method.

When using *n*-dodecanol, the result was somewhat less satisfactory and yield reached only 62% after 10 min. This limitation in yield is mainly due to decomposition, by browning reaction, of the initial D-glucuronic acid in the early stage of the microwave-assisted process. This result is however quite noteworthy when compared with results from previous classical experiments in an oil



1-7 (α,β)

Scheme 3.

Table 3
Microwave-assisted reaction between D-GlcA and various alcohols in the presence of 35 wt % H_2SO_4/SiG_{60}[a]

ROH	Overall yield[b] (%)	Ratio[c] (α:β)
MeOH	83	10:90
$CH_3(CH_2)_3OH$	98	10:90
$CH_3(CH_2)_5OH$	96	10:90
$CH_3(CH_2)_7OH$	97	10:90
$CH_3(CH_2)_{11}OH$	62 (68[d])	10:90 (20:80[d])
$(CH_3)_2CHOH$	87	5:95

[a] Reaction conditions: GlcA (200 mg, 1.03 mmol), ROH (5 equiv) and the catalyst were irradiated under agitation at 85 °C for 10 min, with a maximum power of 80 W.

[b] Isolated yields of pure anomeric mixtures.

[c] Anomeric compositions as determined by ^1H NMR.

[d] Reaction performed in *tert*-butanol used as the solvent.

bath involving harsh reaction conditions (i.e., $BF_3 \cdot OEt_2$ under inert atmosphere) and/or extended reaction time (several days when reaction was catalysed by $FeCl_3$).[6a,c] Complementarily, reaction carried out in the presence of *tert*-butanol as the solvent yielded 68% of the corresponding dodecyl-D-glucofuranosidurono-6,3-lactone **6**, evidencing that the addition of a theoretical well-adapted microwave solvent was not a prerequisite.

When switching from linear alcohols to anhydrous *iso*propanol, the corresponding monosubstituted lactonic compound **7** was obtained in 87% yield. In order to study the stability of the catalyst during this microwave-assisted reaction, thermogravimetric analyses were performed before and after the microwave experiment. The leaching of H_2SO_4 during the microwave test was less pronounced than when the catalyst was immersed in methanol (see Supplementary data S3). In this present case, the weight changes (associated to the desorption of sulfuric acid) estimated before and after microwave-assisted synthesis were not so dissimilar and reached 34.05% and 33.63%, respectively. This observation was quite encouraging and aimed to prove the efficient recovery of our impregnated catalyst when working with anhydrous alcohols.

3. Conclusion

In summary, we have described a detailed optimisation procedure for the microwave-assisted synthesis of various alkyl D-glucofuranosidurono-6,3-lactones. This one-step protocol involves direct coupling between totally O-unprotected D-GlcA and alcohols in the presence of cost-effective impregnated acids as the heterogeneous catalysts. Faced with environmental concerns, this solventless methodology offers attractive features, including short reaction times, high yields, easy set-up and work-up. To our opinion, this simple method could open new vistas for the preparation of high value uronic acid-based compounds that could be expanded to large scale production.

Acknowledgements

This work has been carried out in the framework of the 'Technose' Excellence Programme supported by the 'Région Wallonne' (Belgium). The authors are grateful to the 'Région Wallonne' for its financial support. A.R. thanks Pr. A. Demonceau (Laboratory of Macromolecular Chemistry and Organic Catalysis, University of Liege) for helpful discussions related to microwave experiments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.065.

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19. *Catalysts preparation:* Both silica-based supports, namely Silica Gel 60 (with BET-specific surface area of 500 ± 50 m^2/g and average pore diameter of 60 ± 5 Å) and Si-MCM-41 (with BET-specific surface area of 1000 m^2/g and pore size of 23–27 Å), were predried prior to use at 200 °C overnight. Silica-supported sulfuric acid catalysts were prepared according to Kogelbauer by aqueous incipient wetness impregnation of Silica Gel 60 with appropriated aqueous solutions of H_2SO_4 yielding catalysts with respective loadings of 35% (i.e., 35 g pure H_2SO_4/100 g final catalyst), 50% and 70%. The same procedure was used for the preparation of 35% H_2SO_4/MCM-41, H_3PO_4/SiG_{60} and silica-supported Keggin type heteropolyacid. After preparation, each catalytic system was dried for 24 h in static air at 120 °C and stored in a desiccator under vacuum.
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21. For sake of comparison, the weight loss associated to the desorption of H_2SO_4 reached 33.4% for the catalyst recovered after a blank reaction, where H_2SO_4/SiG_{60} was stirred together with methanol, under microwave heating at 85 °C for 10 min.
22. *General procedure for the microwave-assisted synthesis of compounds* **1**–**7**: D-GlcA (200 mg, 1.03 mmol), alcohol (5–25 equiv) and the acid catalyst were introduced together in a specific 10 mL microwave vial. The vial was next placed in the microwave cavity and irradiated under stirring. Control of the temperature during the experiment was assigned by an infrared detector. For classical thermally driven reactions, the reactions were performed under agitation in a thermostated oil bath. After heating, the crude mixture was filtrated to eliminate solid acid catalyst and then chromatographed on silica

gel. Spectral and physico-chemical data for **1**, **3** and **4**–**6** (α,β) are proposed in Supplementary Data S4. *i-Propyl* D*-glucofuranosidurono-6,3-lactone* **7**: White solid (recrystallised in $CHCl_3$); mp 110–112 °C (decomp.). IR (KBr) ν 3440 cm^{-1}, 2976 cm^{-1}, 1755 cm^{-1}. Compound **7**β: TLC (EtOAc/*n*-hexane 1/1 v/v): R_f 0.11. ^{1}H NMR (600 MHz, D_2O) δ 5.17 (s, 1H, H-1), 4.88 (m, 2H, H-3, H-4), 4.59 (d, 1H, $J_{4,5}$ 6.6 Hz, H-5), 4.21 (s, 1H, H-2), 3.87 (m, 1H, OC*H*(CH_3)$_2$), 1.17 (d, 6H, OCH(C*H*$_3$)$_2$). ^{13}C NMR (D_2O) δ 177.23 (C=O), 107.66 (C-1), 83.79 (C-3), 76.79 (C-4), 76.69 (C-2), 69.03 (C-5), 64.25 (O*C*H(CH_3)$_2$), 23.59 (OCH(*C*H$_3$)$_2$).