Carbohydrate Research 343 (2008) 2819–2821

Contents lists available at ScienceDirect

Carbohydrate Research

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

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Microwave-assisted synthesis of long-chain alkyl glucopyranosides

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ARTICLE INFO

Article history:
Received 25 February 2008
Received in revised form 13 May 2008
Accepted 14 May 2008
Available online 22 May 2008

Keywords:
Glycosylation
Microwave activation
Carbohydrate surfactants
Fatty alcohols

ABSTRACT

Long-chain (C_6 to C_{16}) alkyl glucopyranosides have been synthesized using microwave irradiation. Yields and anomeric ratios can be controlled under precise and short irradiation times (few min). Comparison with classical heating showed a better efficiency of microwaves.

Surfactants are found in a wide range of applications, such as detergents or additives in pharmaceuticals and cosmetics.[1] They are classified, depending on their structure and polarity, as ionic or non-ionic surfactants. Alkyl glycosides are interesting non-ionic surfactants because they show good properties of wetting, foaming, detergency and biodegradability.[1]

A large number of syntheses have already been described. The synthesis of glucosides is usually carried out using two main routes. Enzymatic condensation of a fatty alcohol and D-glucose,[2–4] or a D-glucoside[4–6] allows to obtain a pure anomer. However, reaction time and yield are strongly dependent on the equilibrium of the reaction. An alternative method is chemical synthesis. Fischer glycosylation of fatty alcohols has been employed despite the low solubility of glucose in long-chain fatty alcohols.[7–11] By this methodology, it is usual to obtain a mixture of four isomers: the kinetic furanosides and the thermodynamic pyranosides with the major axial anomeric configuration. A protected glucose is used in the Koenigs–Knorr[12–15] and the Helferich[15–22] glycosylations of fatty alcohols. The two methodologies allow the synthesis of alkyl glucosides in high yield avoiding the formation of furanoside isomers. Anomeric configuration depends on the starting material and conditions. Most often, reaction with acetobromoglucose is performed with mercury salts as promoter and gives exclusively the β anomer.[12–15] On the other hand, glycosylation performed with peracetylated glucose and a Lewis acid may give a mixture of the two anomers. Some Lewis acids favour the synthesis of the kinetic β anomer,[15–17] while others result in the thermodynamic α anomer.[13,14,18–22] However, synthesis of the α anomer as the major isomer or conversion of the β anomer into the α anomer require long reaction times, up to a few days.[18–22]

Compared to conventional methods, reactions under microwaves usually show noticeable improvements such as shorter reaction times, high yields and these can be carried out in solvent-free conditions. Microwave-assisted Fischer glycosylation is feasible for short chain alcohols,[9,10] but in the case of fatty alcohols (octanol[10] and decanol[11]), yields can be diminished due to decomposition of glucosides. Microwave-assisted solvent-free Helferich glycosylation has been reported by Limousin et al. for the preparation of decyl glucosides with good yields.[11] From the literature on microwave-assisted glycosylation,[9–11] we can conclude first that the α anomer is usually the major one; however, little information can be found concerning the control and evolution of the anomeric ratio. Secondly, no information is given about the evolution of yield, which is of importance because of the possible degradation of saccharides.

A part of our work relates to the development of new surfactants based on alkyl glucosides. We needed a high yielding and fast synthetic method, which would offer the possibility to modulate the anomeric ratio and would be applicable to a wide range of fatty alcohols. Microwave-assisted glycosylation seemed to be suitable for our purposes.

In this paper, we extend the studies of Limousin et al. based on solvent-free conditions.[11] We show that this methodology can be applied to the glucosylation of several alcohols from hexanol to hexadecanol (Scheme 1). Variation in yield and anomeric composition depends on the irradiation time and on the length of the carbon chain of the alcohol.

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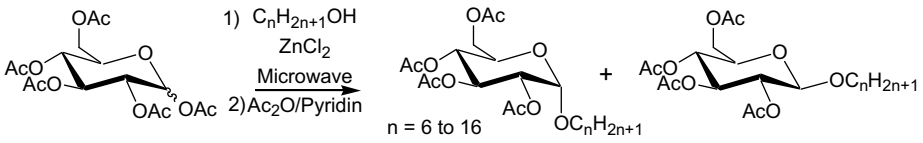
doi:10.1016/j.carres.2008.05.013



Scheme 1. Microwave-assisted glucosylation.

A mixture of peracetylated glucose, fatty alcohol and zinc chloride was irradiated with microwaves in the absence of solvent. We chose to limit the temperature of the reaction at 115 °C and the irradiation level below 60 W to avoid sugar degradation. In these conditions, the glycosylation was effective and gave very good yields of glucosides in a very short time for all the alcohols. The best results obtained with alcohols from hexanol to hexadecanol are summarized in Table 1. Irradiation times and α/β ratios are indicated. As partial 2-O-deacetylation occurred on the α glucoside,[11] after workup, the reaction mixture was re-acetylated before analysis. A similar deacetylation of the 2-*O*-acetyl group has also been observed in a solvent-free reaction using classical heating with a zeolite catalysis.[23]

Yields were determined after flash chromatography, and the anomeric ratio was estimated from the relative intensity of signals corresponding to anomeric carbon atoms in ^{13}C NMR spectra. It is interesting to note the difference between hexadecanol which resulted in the β anomer as the major glucoside (α/β 19/81 after 5 min) and the other alcohols which quickly gave the α anomer as the major one. These interesting results prompted us to vary the reaction conditions in order to modulate the results. A comparison between microwaves vs classical heating has been performed to analyse the differences between the two heating systems. Experiments under classical heating have been conducted using conditions similar to those under microwave irradiation: same quantity of reactants, heating in a thermostatic oil bath at 115 °C. Yields and anomeric ratios were strongly dependent on the alcohol structure and reaction time as shown in Table 2.

Variation in yields: Under microwave activation, yields of about 60–70% were quickly obtained after the beginning of the irradiation. Then after a maximum, the yields were lower a few minutes later due to degradation.

Under classical heating, yields obtained were slightly slower than those obtained under microwave irradiation, and reaction times were a few minutes longer. The study of octanol glucosylation under classical heating showed a maximum (68%) after 10 min while only 1 min was necessary to obtain a similar yield (72%) under microwave heating.

Besides the difference of heating techniques, differences were observed when changing the alcohol, its physical state (solid–liquid) and its polarity. The reaction was much slower for the solid alcohols, dodecanol (mp 23–24 °C) and hexadecanol (mp 49–50 °C), than for the liquid alcohols. In all cases, reactions were unsuccessful before melting of the reaction mixture which required longer time for the two solid alcohols. Furthermore, the smallest alcohols are liquid and are the most polar ones so they could be warmed more efficiently under microwave irradiation. Two additional experiments were conducted in order to analyse the occurrence of a non-thermal microwave effect. When the reaction with octanol was carried out 15 min at 25 °C and 60 W (CoolMate, CEM), no reaction was detected. When it was performed 5 min at 60 °C, only traces of octyl glucosides were obtained. In the latter experiment, we noticed only a slight melting of the reaction mixture during irradiation. From these two experiments, we can conclude that microwave irradiation could not promote reaction without a thermal effect, necessary to have a non-solid state. Therefore, the differences in yields obtained under microwave or classical conditions could be attributed to the heating efficiency. As it is known in the case of microwave irradiation, heating is spread in the whole mass, while in classical heating by conduction it is not the case, as the temperature decreases from the flask shell to the flask centre, especially if the medium is not fluid. This was confirmed by experimental observations. In microwave-assisted experiments, the reaction mixture became black, melted and became quite homogeneous, while under classical heating, it was not the case all the time, as if the classical heating was less effective.

Table 1
Best yields of glycosylation

Alcohols	Irradiation time (min)	Yields (%)	α/β
Hexanol	1	74	71/29
Octanol	3	73	76/24
Decanol	2	80	67/33
Dodecanol	7	77	60/40
Hexadecanol	5	79	19/81

Table 2
Evolution of yield and α/β ratio with time reaction

Alcohols	Microwave heating (115 °C)			Oil bath heating (115 °C)		
	Irradiation time (min)	Yields (%)	α/β	Heating time (min)	Yields[a] (%)	α/β
Hexanol	0.5	67	65/35	0.5	0	
	1	74	71/29	1	0	
	2	69	81/19	2	0	
	3	68	79/21	3	0	
	4	57	82/18	4	16	20/80
				5	27	25/75
				10	46	55/45
Octanol	0.5	42	32/68	0.5	0	
	1	72	56/44	1	0	
	2	72	63/37	2	0	
	3	73	76/24	3	0	
	5	61	82/18	5	0	
	7	35	88/12	7	47	25/75
				10	68	63/37
				15	63	76/24
				360	29	87/13
Decanol	1	75	55/45	1	0	
	2	80	67/33	2	0	
	5	73	70/30	5	25	26/74
	7	53	85/15	7	46	32/68
				10	55	70/30
Dodecanol	3	61	29/71	3	0	
	4	61	31/69	4	0	
	5	63	39/61	5	0	
	7	77	60/40	7	54	26/74
	9	76	80/20	9	67	35/65
				15	43	74/26
Hexadecanol	5	71	17/83	5	0	
	7	79	19/81	7	0	
	9	67	35/65	9	0	
	10	75	74/26	10	0	
	11	47	79/21	11	7.5	17/83
				15	41	63/37
				20	66	66/34

[a] 0% Yield was observed when the reaction mixture was not melted.

Variation in the anomeric ratio: Selectivity of the reactions upon microwave irradiation showed almost the same behaviour than classically heated reactions: the β anomer seemed to be the major one at the beginning of the reaction, and longer reaction times (just a few min) favoured the thermodynamic α anomer. For all the alcohols, the ultimate anomeric ratio was about 4/1, certainly the proportion at the equilibrium. The two studies on the octanol glucosylation showed that the final anomeric ratios were identical and independent of the heating system, but a great difference was observed concerning the rate of anomerisation.

Under microwave irradiation, hexanol reached the equilibrium (α/β about 4/1) very quickly (about 2 min), whereas hexadecanol needed about 11 min to reach the same ratio. Anomer β was the major one only at the beginning of the reaction with the higher alcohols dodecanol and hexadecanol. In all the other cases, shorter alcohols or longer reaction times led to anomer α as the major one. These differences can be ascribed to an improved microwave heating of the most polar alcohol used (hexanol) as compared to the less polar one (hexadecanol).

Under classical heating, for each alcohol, the β anomer was the major one at the beginning of the reaction, then the anomeric ratio increased as in the case of microwave irradiation. The reaction was slow enough to observe the transformation of the major β anomer onto the more stable α anomer.

The conversion rate of the β anomer onto the α anomer was correlated to the efficiency of the heating system. The more efficient microwave heating led to a very fast β to α isomerisation, while in classical conditions the anomerisation was slower.

In summary, we have shown microwave irradiation to be a very efficient tool in glycosylation reactions of fatty alcohols in solvent-free conditions. Yield and selectivity depend on the structure of the alcohol and its polarity. Careful attention must be made to the most polar alcohols which can result in a quick degradation. The glucosylation requires very short reaction times, and glucosides are obtained in high yields. Comparison with classical heating lead to the conclusion that microwave irradiation is the most effective, allowing faster glycosylation and slightly better yields. Furthermore, the two methodologies show to be complementary, microwave irradiation being the best way for the synthesis of α anomers, while classical heating offers the possibility to access to β anomers in higher yields.

1. Experimental

1.1. General methods

All chemicals were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 300 spectrometer. Microwave irradiation was performed in a CEM-Discover® system; the intensity and the temperature selected were, respectively, 60 W and 115 °C (or 60 °C for one experiment), ramp time (time let to the microwave to reach 115 °C), 3 min, power max, off (power is adjusted to maintain 115 °C). Hold times (time of irradiation at 115 °C) are indicated in Tables 1 and 2. Reaction at 25 °C under microwave irradiation was performed in a CEM-Discover® CoolMate.

1.2. General procedure for the microwave-assisted glycosylation

Peracetylated glucose (10 mmol), 2 equiv of fatty alcohol and 1 equiv of $ZnCl_2$ were introduced and mixed in a 100-mL flask under an atmosphere of argon. The flask was stirred under microwave irradiation (CEM Discover). After cooling, the brown oil obtained was filtered through silica with EtOAc. The solvent was then evaporated. The oil was dissolved in 10 mL of EtOAc. Then 4.1 mL of anhyd pyridine and 5 mL of Ac_2O were added. The soln was stirred overnight at room temperature, then 10 mL of methanol was added and the soln was stirred for 10 min. The soln was diluted with EtOAc and washed with water. The organic phase was dried with Na_2SO_4 and filtered. The solvent was eliminated under diminished pressure and the crude product was co-evaporated with toluene. The products were purified by flash chromatography (1:4 to 2:3 EtOAc–cyclohexane).

1.3. General procedure for the glycosylation under classical heating conditions

Peracetylated glucose (10 mmol), 2 equiv of fatty alcohol and 1 equiv of $ZnCl_2$ were introduced and mixed in a 100 mL flask under an atmosphere of argon. The flask was stirred at 115 °C in an oil bath and cooled in a cold water bath after the reaction time. Work-up (acetylation, purification) was identical to the microwave-assisted glycosylation.

All the products obtained are described in the literature and their structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy.[15,16,18–21]

Acknowledgements

The authors thank the Délégation Générale pour l'Armement (fellowship to N.F.), the Centre National de la Recherche Scientifique (CNRS) and the Ministère délégué à l'Enseignement Supérieur et à la Recherche for financial support.

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