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Acid zeolites as efficient catalysts for *O*- and *S*-glycosylation

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Abstract

We report herein the first regioselective synthesis of β-galactofuranosides by Fischer glycosidation of GalNAc with methanol catalyzed by HY, HZSM-5 and HBEA acid zeolites. The zeolite HY (Si/Al ratio 3.1) was the most efficient catalyst, leading to the highest yield of methyl β-galactofuranoside, isolated as its acetylated or isopropylidene derivatives, indicating that with large pore zeolites, the reaction efficiency depends upon the concentration of the zeolite acid sites and its hydrophilicity. However, the best regioselectivity for β-galactofuranoside versus β-galactopyranoside was obtained with the medium pore zeolite HZSM-5, which also led to the lowest starting material conversion, suggesting that both the zeolite pore size and topology are determinant for the obtained results. Furthermore, these acid zeolites proved to be efficient catalysts to transform 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol (**6**) (3,4,6-tri-*O*-benzyl-D-glucal) exclusively in the 2,3-unsaturated-*O*- and -*S*-α-D-glycosides by Ferrier rearrangement, in moderate yield. For this reaction, the number of acid sites was the key factor for the reaction yield, being HY (Si/Al ratio 3.1) also the most effective zeolite.

Keywords: Acid zeolite; Ferrier rearrangement; Fischer glycosidation; *O*-Glycoside; *S*-Glycoside

1. Introduction

Acid zeolites have been recently used for a variety of transformations with the advantage of being solid catalytic eco-friendly materials, known for their activity, selectivity and reusability [1,2]. Apart from their acidic properties, these materials are shape-selective in reactant, product and transition state, due to the spatial constraints of the pore apertures and zeolite channels and cages, discriminating between molecules with different sizes and forms. Moreover, by strongly adsorbing one or all the reactants, high concentrations are achieved within the zeolite pores with the consequent increase in rate and/or selectivity.

HY zeolites have been reported as catalysts for industrial processes such as the etherification of a benzylic alcohol to give verbutin, a synergist for insecticides and the acetylation of dimethoxyarenes, such as veratrole [2a,3]. Syntheses of industrially relevant fragrances, flavours and aromas were also accomplished using these zeolites, namely aldehydes by isomerization of terpene epoxides [4] and sulphur-containing fragrances [5]. The zeolite pore architecture also enabled lactonization instead of dimerization or polymerization, which are usually the dominant reactions when acid catalysts or amorphous SiO_2–Al_2O_3 are used to mediate the esterification of long chain hydroxy acids [6]. In the carbohydrate field, these zeolites were also described as efficient reaction catalysts of disaccharides isomerization and hydrolysis [7,8], hydrolysis of methyl glucosides [9] and sucrose [10], and stereoselective β-*O*-glucosylation of alcohols with 1,2-anhydro-α-D-glucopyranose derivatives [11]. Chapat et al. [12] have investigated the reaction of D-glucose with *n*-butanol catalyzed by HY zeolites with different Si/Al ratios. The acetonation of various monosaccharides mediated by this solid catalyst was also reported, being the selectivity of the reaction directed away from the thermodynamically most

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feasible route. Hence, the furanose derivatives were obtained as major compounds, when D-galactose and L-arabinose were used as starting materials [13]. Reaction of L-sorbose afforded the first synthesis of 1,2-*O*-isopropylidene-α-L-sorbopyranose [13].

HBEA are also large pore zeolites and were found to be very active for Friedel–Crafts acylation of aromatics, together with the above mentioned HY zeolites, being the most useful zeolite catalysts at industrial and academic level for these reactions [3]. The acetylation of anisole to give a precursor of Parsol as the solo aromatic product, which is used for sun protection, is an industrial process catalyzed by HBEA zeolites [2a]. Etherification of *p*- and *o*-activated benzylic alcohols was accomplished in 100% conversion over HBEA zeolites, but the less expensive HY zeolites have also been used to synthesise various benzylic ethers in high yield, for application in perfumery [2b]. In some cases the steric constrains of the zeolite pores could enable or impede secondary reactions as for the carbon skeleton rearrangement of allyl benzyl ethers over HBEA zeolites [14]. Meerwein–Ponndorf–Verley reduction [15], and the Fischer indole synthesis with restricted transition state selectivity [16] are examples of reactions which selectivity was only found over HBEA zeolites. Moreover, per-*O*-acetylation of mono- and disaccharides [17], preparation of alkyl glucoside surfactants, the new generation of non-ionic detergents [12,18], and the stereoselective synthesis of peracetylated aryl 1,2-*trans*-glycopyranosides and aryl 1,2-*cis*-2-hydroxyglycopyranosides [19] were also catalyzed by HBEA zeolites.

HZSM-5 is a three-dimensional zeolite with medium pores and has also been used to promote C–N, C–C and C–O bond formation, favouring selective reactions due to a more shape-selective environment. This zeolite promoted the cyclisation of a functionalized epoxypolyene to give a single tricyclic derivative, mimicking the activity of polyene cyclases, while the homogeneous catalysis by Lewis acids gives a mixture of isomers [20]. HZSM-5 has also been successfully applied in the hydrolysis of ethers to alcohols, with the advantage of being highly hydrothermal stable over HBEA and HY zeolites, enabling continuous operation over long periods even in the drastic hydrolysis conditions [2c].

The wide variety of organic reactions promoted by these zeolites prompted us to investigate their application to other reactions, in particular to catalyze the Fischer glycosylation of methanol with *N*-acetylgalactosamine (GalNAc). This sugar is a building block of the important glycoprotein family of mucins. Despite their normal cell protecting function, the appearance of mucin molecules with diminished carbohydrate chains has also been correlated with a negative prognosis in the development of tumors. In particular the tumor-associated antigens T, Tn, STn and ST possess GalNAc moieties in their structure [21]. GalNAc is a constituent of dermatan and chondroitin sulphate, polysaccharides found in mammalian tissue and cartilage, which are hardly purified, becoming GalNAc isolation difficult and GalNAc derivatives expensive [22a]. Therefore, novel approaches for the synthesis of GalNAc derivatives using reusable and eco-friendly materials has become a challenge for glycochemists.

Glycals have also been widely used as glycosyl donors, namely for the synthesis of biologically interesting oligosaccharides and glycoconjugates [23], particularly in the field of tumor antigens. Their transformation into 2,3-unsaturated glycosyl derivatives has been reviewed [24]. Typically the reactions are conducted with glycal derivatives possessing acyloxy groups at the allylic positions and Lewis acids, or occasionally protonic acids as catalysts, promoting the departure of these groups, with the formation of delocalised oxycarbenium ions, which react then with *O*-, *S*-, *N*- and *C*-nucleophiles at the anomeric center. A diversity of catalysts have been employed for this reaction leading to *O*-glycosides, such as $BF_3{\cdot}Et_2O$ [25], $SnCl_4$ [26], $InCl_3$ [27], $ZnCl_2$ [28], $Sc(OTf)_3$ [29], $Bi(OTf)_3$ or SiO_2–$Bi(OTf)_3$ [30], $BiCl_3$ [31], $NbCl_5$ [32], $ZrCl_4$ [33], $HClO_4$–SiO_2 [34], trifluoroacetic acid [35], potassium dodecatungstocobaltate trihydrate [36], palladium [37], and montmorillonite K10, which catalyzed a microwave-induced Ferrier rearrangement [38]. Rearrangement catalyzed by $FeCl_3$ based ionic liquid has been described in which the ionic liquid has proved to be an efficient reaction medium, playing a dual role of a catalyst as well as that of a solvent [39]. Recently, $GaCl_3$ was reported as an efficient catalyst for the addition of thiols to glycals under extremely mild conditions, affording 2-deoxy thioglycosides in high yields with a good α-selectivity [40]. Ceric ammonium nitrate was also reported to mediate the synthesis of 2-deoxy-1-thioglycosides, being the 2,3-unsaturated-*S*-glycosides obtained only as minor reaction products [41].

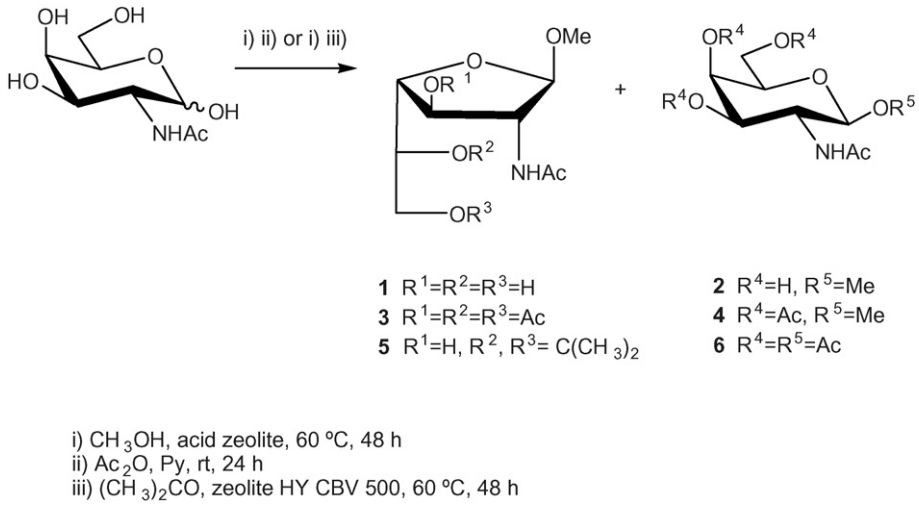
Ferrier rearrangement of glycals exhibiting ether protection at position 3 is only seldom described, although 3-*O*-methyl-D-glucal [42] and 3-*O*-benzyl-D-glucal [43] rearrangement, catalyzed by $BF_3{\cdot}Et_2O$, were reported. Recently, debenzoxylation was described by reaction of a 3-*O*-benzyl glycal with cyclohexanol catalyzed by trifluoroacetic acid, although the corresponding Ferrier product was formed as a minor product [35]. The dominant anomeric effect contributes to the α-stereoselectivity observed in most of the Ferrier rearrangement reactions. However, the α-stereoselective palladium-catalyzed *O*-glycosylation of glycals was controlled by the reagent, rather than by the anomeric or neighbouring group effects [37].

We have previously described the efficacy of the HY zeolite (Si/Al ratio of 2.7) to promote the Ferrier rearrangement of 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol (**6**) (3,4,6-tri-*O*-benzyl-D-glucal), affording only 2,3-unsaturated α-*O*- and α-*S*-glycosides in reasonable yields, by reaction with alcohols and thiols [44]. In this paper we report on the efficiency of various acid zeolites differing in their pore dimensions, hydrophilicity/hydrophobicity characteristics and density of acid sites on the reaction of *O*- and *S*-nucleophiles with **6**.

2. Results and discussion

2.1. Fischer glycosydation of GalNAc with methanol catalyzed by acid zeolites

Reaction of GalNAc with methanol was catalyzed by four different zeolites (Scheme 1, Table 1). Three zeolite topologies



Scheme 1. Fischer glycosidation of *N*-acetylgalactosamine with methanol catalysed by acid zeolites.

were tested: two large pore three-dimensional systems with different pore sizes and structure morphology (HY and HBEA), and a medium pore three-dimensional system (HZSM-5). HY zeolite (FAU structure) is constructed from large supercages with diameters of 13 Å and pore apertures of 7.4 Å diameter (12-membered ring apertures). HBEA zeolite exhibits also 12-membered ring pore apertures with a lower cross-section (5.6 Å and 6.6–6.7 Å). HZSM-5 (MFI structure) possesses straight and sinusoidal channels with 10-membered ring apertures of 5.6 Å × 5.3 Å and 5.5 × 5.1 Å, respectively [45]. The chosen catalysts enable the analysis of the effect of various zeolite characteristics in the catalytic performance. Simultaneously with their different structure, as mentioned above, the chosen samples possess quite different external surface areas (4–178 $m^2\,g^{-1}$), hence different crystal sizes, micro- and mesopore volumes (0.17–0.33 and 0.03–0.038 $cm^3\,g^{-1}$, respectively) and acid sites concentration (74–340 μmol g^{-1} of Lewis acid sites and 315–670 μmol g^{-1} of Brönsted acid sites), being the Brönsted acid sites most likely the active ones. The influence of the Si/Al ratio on the performance of the HY zeolite will also be investigated.

Fischer glycosidation was followed by acetylation of the reaction products with acetic anhydride in pyridine at rt for 24 h, being isolated the derivatives methyl β-galactofuranoside **3** and methyl β-galactopyranoside **4** in different ratios, depending upon the zeolite tested (Table 2). The yields obtained for compound **3** varied from 28 to 67%, while the β-pyranoside derivative **4** was synthesized in 2 to 31% yield. The yield of **3** and **4** seems to be dependent of the concentration of Brönsted acid sites for the large pore zeolites; the zeolite HY (3.1) was the most efficient one, leading to the highest conversion and yield of both diastereoisomers. Due to its upper framework aluminium content, this zeolite has the highest hydrophilicity, which can also play an important role influencing the desorption of the reaction products, which are more lipophilic than the starting material.

A linear relation between yield/zeolite activity and concentration of Brönsted acid sites for both HY and HBEA morphologies shows that any quadratic effect due to the density of Brönsted acid sites or to acid site strength cannot be envisaged. When comparing HY (13.2) and HBEA zeolites, both have a similar Brönsted acidity and lead to an identical starting material conversion, thus indicating that their porous structure does not affect the reaction efficiency. The furanoside/pyranoside forms ratio obtained with the two large pore zeolite catalysts was quite

Table 2
Yield (%) for the Fischer glycosydation of GalNAc with methanol followed by acetylation (compounds 3 and 4), mediated by acid zeolites

Zeolite	Fischer glycosidation yield (%)		
	3	**4**	**6**[a]
HY (3.1)	67	31	2
HY (13.2)	32	14	52
HZSM-5 (13.3)	28	2	69
HBEA (12.5)	33	15	52

[a] Recovered starting material (%).

Table 1
Characteristics of the zeolites HY, HZSM-5 and HBEA

Zeolite	Si/Al ratio	External surface area ($m^2\,g^{-1}$)	Pore volume ($cm^3\,g^{-1}$)[a]		Acid sites concentration (μmol g^{-1})	
			Micropore	Mesopore	Brönsted	Lewis
HY (3.1)	3.1	37	0.30	0.05	670	247
HY (13.2)	13.2	64	0.33	0.11	327	74
HZSM-5 (13.3)	13.3	4	0.17	0.03	469	102
HBEA (12.5)	12.5	178	0.19	0.38	315	340

[a] Micropore (Ø < 2 nm); mesopore (2 nm < Ø < 50 nm).

similar (ca. 2:1). When the medium pore zeolite HZSM-5 was used 69% of starting material was recovered, indicating that the zeolite pore size also plays an important role, being the methyl β-pyranoside derivative **4** obtained only in 2% yield. The regioselectivity **3** versus **4** was the highest obtained, being these compounds isolated in a 14:1 ratio, a result that most probably arises from the zeolite topology and pore size. When observing the data given in Table 1, it can also be suggested that the external surface area of the zeolites does not have any effect on yield/regioselectivity of the reaction, thus indicating that it occurs inside the pores; a direct or indirect participation of Lewis acid sites can be excluded.

The now described procedure catalyzed by these acid zeolites led to the synthesis of the new compound **3**. Its structure was elucidated by means of the ^{1}H NMR and ^{13}C NMR data. The β-anomeric configuration proposed for **3** was expected due to the neighbouring group effect of the 2-acetamide substituent. Moreover, the position of the α/β equilibrium for furanoses lies in favour of the 1,2-*trans*-isomer, because 1,2-*cis*-interactions are destabilizing factors in five-membered rings [22b]. This configuration was confirmed by the resonance of H-1, which appeared as a singlet at δ 4.78, indicating that this proton is *trans* to H-2. For compound **4**, H-1 appeared at δ 4.66 as a doublet presenting $J_{1,2}$ = 8.7 Hz characteristic of its *trans*-diaxial coupling with H-2, indicating that its structure is that of the β-pyranoside anomer. The resonances of C-1 at δ 107.8 and δ 101.7 for **3** and **4**, respectively, are in agreement with the β-furanoside and β-pyranoside structures proposed. The signals of H-3, H-4 and H-5 of **3** show chemical shifts and coupling patterns indicating once again the presence of the five-membered ring. The signal of H-3 is a double doublet at δ 4.72 with $J_{2,3}$ = 2.4 Hz and $J_{3,4}$ = 2.7 Hz, typical of the vicinal protons in position *trans* of a furanose moiety, while H-3 of the pyranose isomer **4** appears at δ 5.32, also as a double doublet with $J_{2,3}$ = 11.1 Hz and $J_{3,4}$ = 3.6 Hz, in accordance to the expected coupling pattern of these protons in a $^{4}C_{1}$ conformation. The resonance of H-4 appears at lower field (δ 5.40) than the corresponding proton of the furanose derivative, which was detected in the multiplet at δ 4.19–4.12, as expected. Since position 5 of the furanose moiety is acetylated, also the signal of H-5 appears at lower field than the corresponding proton of the pyranoside isomer.

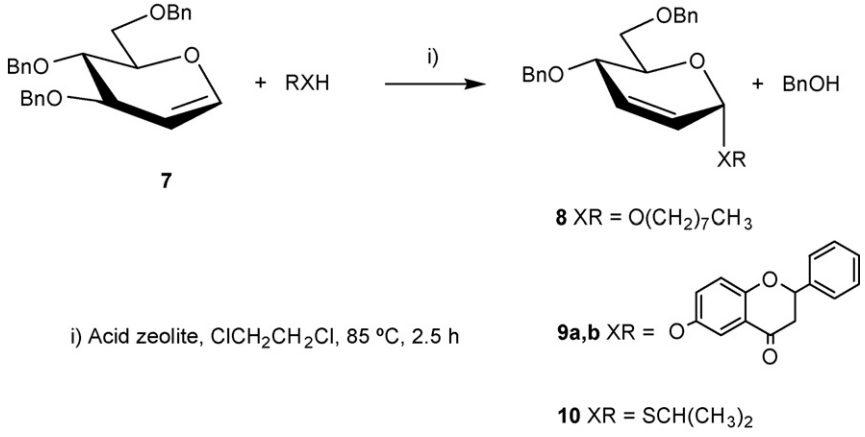
Methyl glycosidation of GalNAc, followed by in situ acetonation, was accomplished using the zeolite HY (Si/Al 3.1) as catalyst, which has proven to be the most effective zeolite (Table 2). The major product formed was methyl 2-acetamide-2-deoxy-5,6-*O*-isopropylidene-β-D-galactofuranoside **5** in 43% yield, confirming the selectivity promoted by the zeolite for the synthesis of a furanoside form, detected by its H-1 signal appearing as a singlet at δ 4.86 and its C-1 resonance at δ 108.1, as expected.

2.2. Reaction of 3,4,6-tri-O-benzyl-D-glucal with nucleophiles catalyzed by acid zeolites

The one-step reaction of 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol (**6**) (trivial name 3,4,6-tri-*O*-benzyl-D-glucal) with octanol, 6-hydroxyflavanone and propane-2-thiol, catalyzed by the above indicated acid zeolites (Table 1), afforded the 2,3-unsaturated α-glycosides **8**, **9a**,**b** and **10** (Scheme 2). The *O*-nucleophiles were chosen in order to obtain potentially bioactive glycosides such as octyl glycosides, which have been reported to present surface active and antimicrobial properties [46] and flavonoid glycosides, known to possess a diversity of bioactivities and to display a remarkable array of biochemical and pharmacological actions, with repercussion on inflammation, heart diseases and cancer. Thus, the condensation of flavonoids with sugars leading to new derivatives for structure/bioactivity relationship studies is a matter of relevance for this type of research.

The structure of the octyl glycoside **8** was easily assigned by NMR experiments. 2,3-Unsaturation was detected by the signal of H-3 appearing at δ 6.06 as a doublet, coupled with H-2 with $J_{2,3}$ 10 Hz, as expected, while H-2 was observed at δ 5.77 as a double triplet, due to the coupling with H-3, H-4 and H-1 with $^{4}J_{2,4} = J_{1,2}$ = 2 Hz. The constant coupling $J_{1,2}$ is of the same order of magnitude of that observed for other anomeric protons equatorially attached to 2,3-unsaturated pyranoid structures [47], thus confirming that compound **8** is the α-anomer.

When the 6-hydroxyflavanone was the nucleophile, a mixture of two diastereoisomers **9a**,**b** was obtained, due to the stereogenic centre at position 2 of the flavanone, indicated by the presence of complex signals for H-2′, H-3′ax and H-3′eq,



Scheme 2. Synthesis of 2,3-unsaturated *O*- and *S*-glycosides by Ferrier rearrangement of a 3-*O*-benzyl glycal catalysed by acid zeolites.

instead of the expected coupling patterns. Both isomers are α-configurated Ferrier products as confirmed by the resonances at δ 6.22 (H-3) and 5.93 (H-2), with $J_{2,3}$ 10.5 Hz, $^4J_{2,4}$ 2.1 Hz, and $J_{1,2}$ 2.7 Hz.

Debenzoxylation at C-3, also detected by the presence of only two benzyl groups in the target molecules, was previously reported when benzyl glycals reacted with glycerol derivatives promoted by boron trifluoroetherate [43], or with ethanethiol in the presence of ceric ammonium nitrate [41], although in the latter reaction the Ferrier products were described as minor compounds. We now report on the reaction of **7** with allyl mercaptan or propane-2-thiol catalyzed by the studied acid zeolites, which affords the corresponding Ferrier product with α-stereoselectivity as the single reaction product, being their NMR data in full agreement with the proposed structure.

Ferrier products are usually obtained when glycals having leaving groups at the allylic sites undergo nucleophilic displacement reactions with allylic rearrangement in the presence of Lewis acids [24]. The results obtained can be rationalized in terms of the HSAB concept. Protonation of the hard C-3 oxygen centre by the zeolite is followed by debenzoxylation with the consequent formation of the delocalized allylic oxycarbenium ion. Its reaction with the *O*- and *S*-nucleophiles at the anomeric center affords only the α-anomers, which stereochemistry arises from the kinetic anomeric effect.

For the three sets of reactions, the best yield (38–50%, Table 3) was again obtained with the zeolite HY (3.1); a lower yield for the Ferrier product was achieved when the reactions were catalyzed by HY (13.2) showing the major role of Brönsted acid sites concentration or framework aluminium content. HBEA zeolite is abnormally inactive for the three sets of reactions; a very low diffusion coefficient of the reaction products should be determinant (despite the smaller crystal size). In all the cases, a large quantity of reactant or product molecules remains adsorbed in the zeolite pores.

All the zeolites are selective to the formation of the showed Ferrier products in spite of the relative low condensation yield. The shape-selectivity of the zeolites towards the exclusive formation of the 2,3-unsaturated glycosides can also be explained by the higher stability of these forms or the transition species involved in their formation in the zeolite microporosity. The mono-esterification of polyols catalyzed by HY is an example of a shape selective reaction inside the pores, which rate and yield depend on the Si/Al ratio [48]. The higher hydrophilicity character of the HY (3.1) in respect to the other samples, assigned to its higher content of aluminium [49], can indeed explain the higher yield observed over this zeolite. The desorption of the products is expected to occur at higher rate over more hydrophilic samples due to the competitive adsorption of the nucleophiles, which are more hydrophilic than the starting material or the Ferrier product.

Table 3
Yield (%) for the Ferrier rearrangement of 6 with octanol, 6-hydroxyflavanone and propane-2-thiol (compounds **8**, **9a**,**b** and **10**), catalyzed by acid zeolites

Zeolite	Yield of the Ferrier products[a]		
	8	**9a**,**b**	**10**
HY (3.1)	46 (3)	38 (10)	50 (2)
HY (13.2)	28 (5)	11 (26)	19 (6)
HZSM-5 (13.3)	37 (7)	18 (29)	44 (10)
HBEA (12.5)	6 (9)	5 (30)	8 (17)

[a] Yield (%) of recovered starting material indicated in parênthesis.

3. Conclusions

The acid zeolites HY, HBEA and HZSM-5 catalyzed Fischer glycosidation of *N*-acetylgalactosamine favouring the formation of the furanoside form, which is the product of kinetic control. The regioselectivity for the furanoside/pyranoside forms depends on the pore size being ca. 2:1 for the large pore zeolites and 14:1 for the medium pore zeolite. However, the most significant starting material conversion occurred with the catalyst HY (3.1), which has the highest Brönsted acid sites concentration and hydrophilicity. This catalyst was also the most efficient one in promoting the Ferrier rearrangement to transform a 3-*O*-benzyl glycal into 2,3-unsaturated-*O*- and *S*-glycosides, key scaffolds for a variety of transformations in carbohydrate chemistry and biochemistry. The methodology developed consists of a simple experimental procedure, leading to an easy recover of the reaction products. Furthermore, the use of zeolites as catalysts provides a cleaner technology, in which the zeolite can be recovered, regenerated and reused, replacing successfully other polluting technologies which use toxic and corrosive acids as catalysts.

4. Experimental

4.1. Zeolite preparation and characterization

All the zeolite samples are commercial forms obtained from Zeolyst International [references: CBV500, CBV720, CBV 3024G and CP 814E for HY (3.1), HY (13.2), HZSM-5 (13.3) and HBEA (12.5), respectively]. The acid form of the samples were prepared by calcination/activation of the parent samples at 500 °C under dry air flow (60 mL min^{-1} g^{-1}, temperature increase rate at 2 °C, steps at 120 °C and 350 °C for 1 h).

The aluminium and silicon bulk content of the samples were determined by elemental analysis. The pore size distribution was obtained from nitrogen adsorption at 77 K. Micropore volume and external surface area were determined by the *t*-plot method using the Harkins–Jura standard isotherm. The mesoporous volume was determined as the difference between the micropore volume and total pore volume (calculated at $p/p_0 = 0.96$). Before measurement, the samples were outgassed in vacuum at 350 °C for 12 h.

The concentration of acid sites was determined by pyridine adsorption. Before IR characterization of adsorbed pyridine molecules (Py), the zeolite samples were pressed into self-supported wafers and activated in situ in the IR cell (heated under dry air flow, 1 mL min^{-1}, at 450 °C for 10 h and evacuated at 10^{-6} Torr) and afterwards exposed to pyridine vapours at a pressure of 2.2 mbar for 10 min at 150 °C. The concentrations of the Brönsted and Lewis acid sites were calculated

from the integrated area of the PyH^+ and PyL bands (at 1545 and 1456 cm^{-1}, respectively), after evacuation at 10^{-6} Torr and 150 °C for 1 h, using the values of the molar extinction coefficients of these bands (1.13 and 1.28 cm μmol^{-1}, respectively). The experimental method used has been previously described [50].

4.2. General methods

All reactions were monitored by TLC (silica gel 60 F_{254}, Merck) with detection by UV light and/or by vanillin in sulphuric acid solution (2.5%) spray, followed by heating at 120 °C. Solutions were concentrated on a rotary evaporator under reduced pressure below 40 °C. Column chromatography (CC) was performed on silica gel 60 G (0.040–0.063 mm, E. Merck) and elution under low pressure. Melting points were determined with an Electrothermal 9100 instrument and are uncorrected. Proton and carbon NMR spectra, DEPT, COSY, NOESY, HMQC and HMBC experiments were recorded using a BRUKER CPX 300 operating at 300.14 MHz for ^{1}H and 75.43 MHz for ^{13}C, or using a BRUKER Avance 400 spectrometer operating at 400.13 MHz for ^{1}H or 100.62 MHz for ^{13}C, both spectrometers operating at a constant temperature of 298 K. The solvent used was $CDCl_3$ (1% v/v Me_4Si or 0.03% v/v Me_4Si, Aldrich). IR spectra were run with a Hitachi 270-50. Optical rotations were registered on a Perkin Elmer 343 polarimeter. Elemental analyses were performed at the Microanalyses Service of Instituto Superior Técnico, Universidade Técnica de Lisboa. High resolution mass spectra were obtained on a Finnigan FT/MS 2001 DT, FT-ICR/MS mass spectrometer equipped with a Nd:YAg laser operating at fundamental wavelength (1064 nm).

4.3. Synthesis of compounds *3*, *4*, *5*, *8*, *9a*,*b* and *10*

4.3.1. Methyl 2-acetamide-3,5,6-tri-O-acetyl-2-deoxy-β-D-galactofuranoside (*3*) and methyl 2-acetamide-3,4,6-tri-O-acetyl-2-deoxy-β-D-galactopyranoside (*4*)

Zeolite (82 mg), previously activated at 140 °C, was added to a solution of *N*-acetylgalactosamine (150 mg, 0.7 mmol) in dry methanol (35 mL). The reaction mixture was refluxed under stirring for 48 h. The zeolite was filtered and the solvent evaporated under reduced pressure to give a residue which was dissolved in pyridine (8 mL). Acetic anhydride was added (42.4 mmol, 4 mL) and the reaction mixture was stirred at rt for 24 h. Pyridine was co-evaporated with toluene and the residue obtained was column cromatographed with EtOAc to give **3** as a colorless solid; HY (3.1), 164 mg, 67%; HY (13.3), 76 mg, 31%; HZSM-5 (13.3), 69 mg, 28%; HBEA (12.5), 81 mg, 33%, and **4** as a colorless solid; HY (3.1), 76 mg, 31%; HY (13.2), 34 mg, 14%; HZSM-5 (13.3), 5 mg, 2%; HBEA (12.5), 37 mg, 15%.

Physical and spectroscopic data for **3**: colorless solid, mp 125–126 °C; R_f 0.47 (EtOAc); $[\alpha]_D^{20} = -0.9$ (*c*1.0, CH_2Cl_2); IR (neat): μ = 1747 cm^{-1} (C=O, OAc); 1635 cm^{-1} (C=O, NAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (d, $J_{2,NH}$ 8 Hz, 1H, NH), 5.29 (ddd, 1H, H-5), 4.78 (s, 1H, H-1), 4.72 (dd, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 2.7 Hz, 1H, H-3), 4.31–4.27 (m, 2H, H-2, H-4), 4.19–4.12 (m, 2H, H-6), 3.30 (s, 3H, OMe), 2.08 (s, 3H, Me, Ac), 2.02 (s, 3H, Me, Ac), 1.99 (s, 3H, Me, Ac), 1.94 (s, 3H, Me, NHAc); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 170.66, 170.57, 170.10, 169.74 (C=O, Ac), 107.81 (C-1), 79.77 (C-4), 77.79 (C-3), 69.95 (C-5), 62.56 (C-2), 60.43 (C-6), 55.07 (OMe), 22.66 (Me, NHAc), 20.90 (Me, Ac), 20.73 (Me, Ac), 20.70 (Me, Ac).

Physical and spectroscopic data for **4**: colorless solid, mp 210–211 °C; R_f 0.23 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, $J_{2,NH}$ 8.7 Hz, 1H, NH), 5.40 (dd, $J_{3,4}$ 3.6 Hz, $J_{4,5}$ 1.2 Hz, 1H, H-4), 5.32 (dd, $J_{2,3}$ 11.1 Hz, $J_{3,4}$ 3.3 Hz, 1H, H-3), 4.66 (d, $J_{1,2}$ 8.4 Hz, 1H, H-1), 4.26–4.14 (m, 2H, H-6), 4.06–3.95 (m, 2H, H-2, H-5), 3.55 (s, 3H, OMe), 2.21 (s, 3H, Me, Ac), 2.09 (s, 3H, Me, Ac), 2.04 (s, 3H, Me, Ac), 2.00 (s, 3H, Me, Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.4 (C=O, Ac), 101.7 (C-1), 70.5–69.9 (C-3, C-4), 66.7 (C-5), 61.4 (C-6), 56.7 (OMe), 51.4 (C-2), 23.4 (Me, NHAc), 20.6 (Me, Ac).

4.3.2. Methyl 2-acetamide-2-deoxy-5,6-O-isopropylidene-β-D-galactofuranoside (*5*)

Zeolite HY CBV 500 (82 mg), previously activated at 140 °C, was added to a solution of *N*-acetylgalactosamine (111 mg, 0.5 mmol) in dry methanol (25 mL). The reaction mixture was refluxed under stirring for 48 h. The zeolite was filtered and the solvent evaporated under reduced pressure to give a residue, which was dissolved in acetone (25 mL). Zeolite HY CBV 500 (76.5 mg), previously activated at 140 °C, was added to this solution and the mixture was refluxed under stirring for 48 h. The zeolite was filtered and the solvent evaporated under reduced pressure to give a syrup, which was column chromatographed with EtOAc to yield **5** (59 mg, 43%) as a colorless oil; R_f 0.24 (EtOAc); $[\alpha]_D^{20} = -27.0$ (*c*1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, $J_{2,NH}$ 8.1 Hz, 1H, NH), 4.86 (s, 1H, H-1), 4.37–4.27 (m, 2H, H-2, H-5), 4.13–3.84 (m, 4H, H-3, H-4, H-6), 3.40 (s, 3H, OMe), 1.97 (s, 3H, Me, Ac), 1.45 (s, 3H, Me, isop), 1.41 (s, 3H, Me, isop); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 109.5 (Cq, isop), 108.1 (C-1), 169.7 (C=O, Ac), 84.5 (C-4), 77.8 (C-3), 75.7 (C-5), 65.6 (C-6), 60.9 (C-2), 55.0 (OMe), 25.9 (Me, isop), 25.5 (Me, isop), 23.0 (Me, NHAc).

4.4. General procedure for the condensation of *7* with octanol, 6-hydroxyflavanone and propane-2-thiol catalyzed by acid zeolites

1,5-Anhydro-3,4,6-tri-*O*-benzyl-2- deoxy-D-*arabino* - hex - 1-enitol (**7**) (417 mg, 1 mmol) and acid zeolite (160 mg) were added to a solution of the nucleophile (2.5 mmol) in dry dichloroethane (4 mL) and the mixture was stirred at 85 °C for 2 h 30 min. Addition of dichloroethane (20 mL) and dichloromethane (20 mL) was followed by filtration and evaporation of the filtrate under reduced pressure. The residue obtained was purified by column chromatography with EtOAc/*n*-hexane mixtures affording the corresponding 2,3-unsaturated enosides.

*4.4.1. Octyl 4,6-di-O-benzyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (**8**)*

Isolated by CC with EtOAc/*n*-hexane 1:15; HY (3.1), 200 mg, 46%, being **7** recovered in 3% yield (13 mg); HY (13.2), 121 mg, 28%, being **7** recovered in 5% yield (20 mg); HZSM-5 (13.3), 160 mg, 37%, being **7** recovered in 7% yield (29 mg); HBEA (12.5), 28 mg, 6%, being **7** recovered in 9% yield (38 mg); R_f 0.54 (EtOAc/*n*-hexane 1:6); $[\alpha]_D^{20} + 33^\circ$ (*c*1.0, CH_2Cl_2); IR (neat) $\nu = 1620\,cm^{-1}$ (C=C); UV (CH_2Cl_2) λ_{max} nm (ε): 245.0 (6090.00); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 10H, Ph), 6.06 (d, $J_{2,3} = 10$ Hz, 1H, H-3), 5.77 (dt, $J_{1,2} = {}^4J_{2,4} = 2.0$ Hz, 1H, H-2), 5.01 (d, 1H, H-1), 4.67–4.42 (m, 4H, 2OCH_2Ph), 4.17 (dd, $J_{4,5} = 9.2$ Hz, 1H, H-4), 3.96 (ddd, $J_{5,6} = 5.4$ Hz, $J_{5,6''} = 2.0$ Hz, 1H, H-5), 3.88–3.68 (m, 3H, H-6, H-1′a), 3.48 (ddd, $J_{1'a,1'b} = 12.8$ Hz, $J_{1'b,2'a} = J_{1'b,2'b} = 6.4$ Hz, 1H, H-1′b), 1.63–1.53 (m, 2H, H-2′), 1.27–1.25 (m, 10H, H-3′-H-7′), 0.87 (t, $J_{7',8'} = 6.8$ Hz, 3H, H-8′); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 138.3, 138.2 (C_q, Ph), 130.9 (C-3), 128.5, 128.4, 127.9, 127.8, 127.7 (CH, Ph), 126.8 (C-2), 94.6 (C-1), 73.3, 71.1 (O*C*H_2Ph), 70.4 (C-4), 69.1 (C-5), 68.9 (C-6), 68.7 (C-1′), 31.9, 29.8, 29.4, 29.3, 26.3, 22.7 (C-2′–C-7′), 14.2 (C-8′); HRMS calcd. for $C_{28}H_{38}O_4$ 438.278552, found 438.277010.

*4.4.2. (2′R)-/(2′S)-Flavanon-6-yl 4,6-di-O-benzyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (**9a**,**b**)*

Isolated by CC with EtOAc/*n*-hexane 1:5; HY (3.1), 207 mg, 38%, being **7** recovered in 10% yield (42 mg); HY (13.2), 61 mg, 11%, being **7** recovered in 26% yield (108 mg); HZSM-5 (13.3), 98 mg, 18%, being **7** recovered in 29% yield (120 mg); HBEA (12.5), 27 mg, 5%, being **7** recovered in 30% yield (125 mg); syrup; R_f 0.43 (EtOAc/*n*-hexane, 1:4); IR (neat) $\nu = 1698\,cm^{-1}$ (C=O); UV λ_{max} nm (ε) 230.0 (276.8); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66–7.65 (m, 2H, H-5′a, H-5′b), 7.50–7.26 (m, 22H, 4Ph, H-7′a, H-7′b), 6.97 (d, $J_{7',8'} = 9$ Hz, 2H, H-8′a, H-8′b), 6.22 (d, $J_{2,3} = 10.5$ Hz, 2H, H-3a, H-3b), 5.93 (ddd, $J_{1,2} = 2.7$ Hz, $J_{2,4} = 2.1$ Hz, 2H, H-2a, H-2b), 5.64 (br s, 2H, H-1a, H-1b), 5.45–5.38 (m, 2H, H-2′a, H-2′b), 4.67–4.47 (m, 8H, 4OCH_2Ph), 4.23 (br d, $^3J_{4,5} = 9.32$ Hz, H-4a, H-4b), 4.11 (ddd, $J_{5,6} = J_{5,6''} = 3$ Hz, 2H, H-5a, H-5b), 3.73–3.72 (m, 4H, H-6a, H-6b), 3.06–2.97 (m, 2H, H-3′ax), 2.89–2.81 (m, $J_{3'ax,3'eq} = 16.8$ Hz, 2H, H-3′eq); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 192.4 (C-4′, C=O), 155.1, 149.3 (C-8′a, C-4′a), 139.5 (C_q, Ph), 132.6 (C-3), 129.5, 129.0, 128.5, 128.2, 126.8 (C-7′, *C*H, Ph), 126.2 (C-2), 119.8 (C-8′), 114.6 (C-5′), 94.8 (C-1), 80.4 (C-2′), 74.0, 72.0 (O*C*H_2), 71.1 (C-4), 70.8 (C-5), 69.4 (C-6), 45.3 (C-3′); HRMS calcd. for $C_{35}H_{32}O_6$ 548.218761, found 548.219890.

*4.4.3. Propan-2-yl 4,6-di-O-benzyl-2,3-dideoxy-1-thio-α-D-erythro-hex-2-enopyranoside (**10**)*

Isolated by CC with the eluent EtOAc/*n*-hexane 1:15; HY (3.1), 194 mg, 50%, being **7** recovered in 2% yield (9 mg); HY (13.2), 72 mg, 19%, being **7** recovered in 6% yield (26 mg); HZSM-5 (13.3), 170 mg, 44%, **7** recovered in 10% yield (41 mg); HBEA (12.5), 32 mg, 8%, being **7** recovered in 17% yield (69 mg); syrup; R_f 0.61 (EtOAc/*n*-hexane 1:6); $[\alpha]_D^{20}$ 14° (*c*1.0, CH_2Cl_2); IR (neat) $\nu = 1620\,cm^{-1}$ (C=C); UV (CH_2Cl_2) λ_{max} nm (ε): 246.5 (12133.79); ^1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.11 (m, 10H, Ph), 5.82 (d, $J_{2,3} = 9.9$ Hz, 1H, H-3), 5.72 (ddd, $J_{1,2} = 3.0$ Hz, $^4J_{2,4} = 1.5$ Hz, 1H, H-2), 5.53 (d, 1H, H-1), 4.58–4.28 (m, 4H, 2OCH_2Ph), 4.13–4.07 (m, 2H, H-4, H-5), 3.67–3.55 (m, 2H, H-6), 3.10–2.99 (qq, $J_{1',2'a} = J_{1',2'b} = 6.9$ Hz, 1H, SC*H*-1′), 1.20–1.18 (m, 6H, CH_3); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 138.3, 138.2 (C_q, Ph), 128.1 (C-3), 128.0 (C-2), 128.5, 128.4, 128.3, 127.8, 127.7 (CH-Ph), 79.8 (C-1), 73.3, 71.1 (O*C*H_2Ph), 70.3 (C-4), 69.02 (C-5), 68.99 (C-6), 36.4 (S*C*H), 24.0, 23.9 (*C*H_3); HRMS calcd. for $C_{23}H_{28}O_3S$ 384.1745635, found 384.175915.

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