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COMMUNICATION

HMF derivatives as platform molecules: aqueous Baylis–Hillman reaction of glucosyloxymethyl-furfural towards new biobased acrylates†

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A new type of biobased acrylates has been synthesized by a Baylis–Hillman reaction of alkylacrylates with α -D-glucosyloxymethyl-furfural (α -GMF), available in one step from isomaltulose. The reaction, performed in aqueous medium, was extended to other α,β -unsaturated substrates. The use of dimethylisorbide as co-solvent was investigated.

Introduction

Carbohydrates are interesting resources for making new bio-based chemicals, most popular targets being surfactants and monomers, as these two kinds of molecules have obvious wide industrial interest, either in low-added value compounds or in specialty chemicals.¹ Carbohydrates acrylates and methacrylates are, among vinylsaccharides, very attractive functional molecules, notably as building blocks for the synthesis of carbohydrates-based polymers.^{2,3} A lot of effort has thus been devoted to the synthesis of carbohydrate based acrylates and methacrylates, the common strategy consisting of anchoring a sugar to a polymerizable acrylate or methacrylate derivatives through esterification, etherification or C–C bond forming reactions, including chemical or enzymatic transformations.^{2,4}

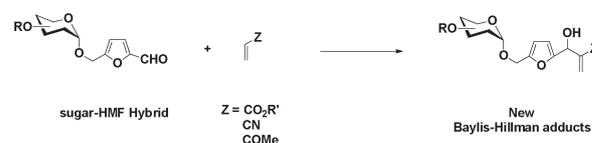
However due to the structural complexity of carbohydrates, the control of selectivity, in terms of degree of substitution and in terms of regioselectivity, remains challenging. With regards to surfactant or polymer properties of the sugar derivatives, monofunctional or multifunctional compounds exhibit very different characteristics.

In order to get purely monofunctional carbohydrate-based acrylates, it therefore necessary to isolate one specific functional group on the starting material for elaborating the sugar backbone only once. With this aim, we have investigated how the aldehyde group present in α -D-glucosyloxymethylfurfural **2a** (α -GMF) could

be used in a Baylis–Hillman (BH) reaction towards new mono-substituted sugar acrylates (Scheme 1).

α -GMF is available in one step from the commercially available disaccharide isomaltulose **1a** (Scheme 2).^{5,8} Isomaltulose (palatinose) is a disaccharide produced by enzymatic conversion of sucrose, whereby the 1,2-glycosidic linkage between glucose and fructose is rearranged into a 1,6-glycosidic linkage by action of an immobilized α -glucosyl transferase.⁶ Isomaltulose is a key molecule for the synthesis of new intermediates and functional materials.⁷ The triple dehydration of the fructosyl moiety of isomaltulose under careful acidic allows formation of α -GMF. Acidic resins which prevent undesired cleavage of the inter-saccharidic linkage allow simple work-up in this reaction.⁸ Lichtenthaler *et al.* reported efficient protocols for the conversion of α -GMF into N-heterocycles of pyrrole, pyridazine, thiophene, and benzodiazepine,⁹ and also various types of bio-based building blocks.¹⁰ To our best knowledge, there has not been any report of using α -GMF in a Baylis–Hillman reaction.

The Baylis–Hillman (or Morita–Baylis–Hillman) reaction¹¹ is an important carbon-carbon bond-forming process that affords densely functionalized products, which are generally referred to as Baylis–Hillman adducts, and found to exhibit numerous applications.¹² This reaction, generally catalyzed by tertiary amines and alkyl (or aryl) phosphines, is formally an addition reaction, as every atom present in the structure of the reaction partners is found in the products, therefore exhibiting a very favorable atom-economical character. Furthermore, the Baylis–Hillman reaction has been shown to be compatible with aqueous media bringing even more attractiveness to this reaction with regards to the field of sustainable chemistry.¹³

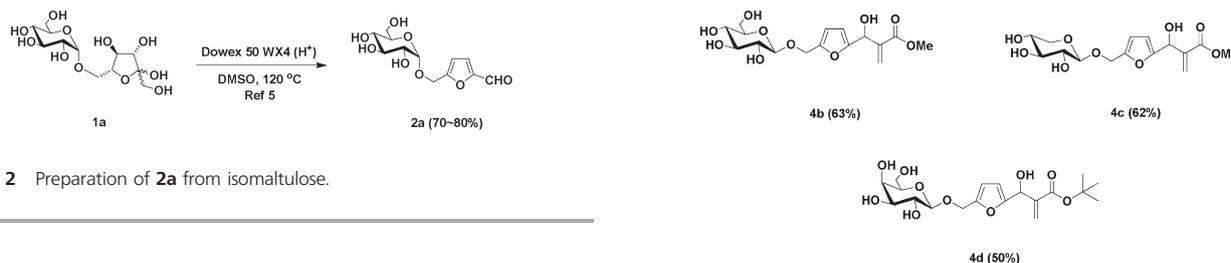


Scheme 1 New route for the synthesis of carbohydrates acrylates.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra43369b



Scheme 2 Preparation of **2a** from isomaltulose.

Hereafter, we wish to report our preliminary investigations on the Baylis–Hillman reaction of the isomaltulose-derived aldehyde α -GMF (**2**) and analogous compounds with α,β -unsaturated ketones and esters. This investigation aimed at providing some preliminary insights on this reaction with respect to the nature of the alkene and the possibility to use aqueous media and dimethylisorbide (DMI) as a co-solvent.

Results and discussion

The reaction of α -GMF with methyl acrylate was studied in different conditions of temperature, solvent, time and basic catalyst and the results are reported in Table 1. The BH adduct methyl 2-[hydroxy-(5-(α -D-glucopyranosyloxymethyl)-furan-2-yl)-methyl]-acrylate (**4a**) was obtained and clearly identified by NMR and mass spectroscopy. Notably, the proton of the newly formed CHOH appears in the ^1H NMR spectrum at δ 5.43 ppm, with interactions with the acrylic methylene and the ester carbonyl group at δ 125.4, 165.8 ppm, respectively, observed in the HMBC spectrum (see in ESI†). The newly formed carbon-carbon bond was thus demonstrated unambiguously. Though the aldehyde is chiral, no diastereoselectivity of the reaction was observed, all products were found to be 1 : 1 mixtures of the two possible

Table 1 Baylis–Hillman reaction of α -GMF with methyl acrylate^a

Entry	Catalyst	Solvent	$T/^\circ\text{C}$	Time (h)	Yield (%) ^b
1 ^c	DABCO	water	25	120	33(47) ^c
2	$\text{P}(m\text{-C}_6\text{H}_4\text{-SO}_3\text{Na})_3$	H_2O	25	120	0
3	DABCO	Dioxane	25	36	0
4	DABCO	DMI	25	36	<5
5	DABCO	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	25	36	31
6	DABCO	Dioxane/ H_2O	25	36	35
7	DABCO	DMI/ H_2O	25	36	56
8 ^d	DABCO	DMI/ H_2O	25	36	17
9 ^e	DABCO	DMI/ H_2O	25	36	42
10	DABCO	DMI/ H_2O	25	18	40
11	DABCO	DMI/ H_2O	0~4	36	47
12	DABCO	DMI/ H_2O	45	36	28
13	PPh_3	DMI/ H_2O	25	36	0
14	$\text{P}(m\text{-C}_6\text{H}_4\text{-SO}_3\text{Na})_3$	DMI/ H_2O	25	36	0
15	DMAP	DMI/ H_2O	25	36	0

^a all reactions were conducted using 3 : 1 molar ratio of methyl acrylate and **2a**, with one equimolar amount of catalyst. ^b yield of isolated product. ^c 47% yield based on starting material recovery.

^d 50 mol% of DABCO has been used. ^e the ratio of **2a/3a** was 1 : 1.

Scheme 3 Substrate generality on the sugar side.†

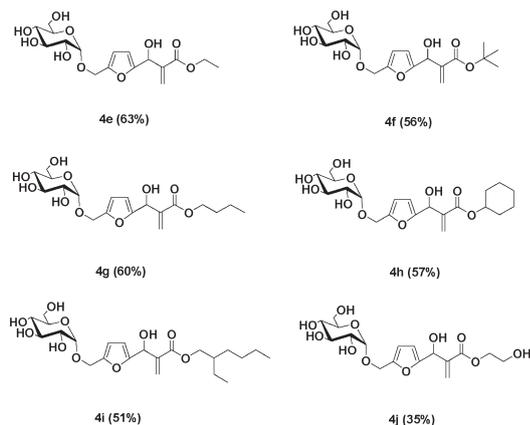
diastereoisomers (as seen when the signals of the two epimers differ slightly for some of the H or C atoms and show equivalent integration).

The reaction was found to proceed quite slowly, as it is often observed for BH reactions. At this stage of our investigations, the best yields were found when a 1 : 1 (v/v) ratio of DMI and water was used (entry 6) leading to a 56% yield of the desired BH adducts. DMI has been reported to find applications in pharmaceutical and cosmetic industries, and as a substitute for DMSO and DMF in some reactions.¹⁴ In pure water in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), a 33% isolated yield of adduct **4a** was obtained (entry 1), along with of 30% of starting aldehyde **2a** thus giving a 47% yield based on starting material recovery. The binary medium DMI/ H_2O was proved to be preferable compared to other tested solvents, such as dioxane or DMI alone, or other binary media such as dioxane/ H_2O or $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, all of them leading to lower yields (entries 3 to 6). DMI is thus shown to substitute efficiently dioxane or THF which are often used for the reaction.

In these solvent conditions, we found that an equimolar amount of DABCO was essential to the reaction, as when the amount of base was reduced to half, the yield dropped to 17% (entry 8). Other tertiary amines like DMAP or aryl phosphines PPh_3 did not allow to obtain the desired adducts even when a water soluble aryl phosphine such as $\text{P}(m\text{-C}_6\text{H}_4\text{-SO}_3\text{Na})_3$ was used (entries 2, 13, 14 and 15). As expected the reaction was also affected by temperature and reaction time (entries 10 to 12), confirming that in BH reactions, increasing temperature does not lead to any rate acceleration.

Having these results in hand, we then investigated the substrate scope of the DABCO-promoted Baylis–Hillman reactions of other hydroxymethyl furfural (HMF) glycosides derivatives with methyl acrylate in binary medium of (DMI/ H_2O). Glycosylation of hydroxymethylfurfural was performed following a reported method in order to obtain the new β -gluco, β -xylo and β -galacto glycosides (see in ESI†).¹⁵ As shown in Scheme 3, in all cases, Baylis–Hillman adducts were obtained with similar yields as observed for α -GMF. The reaction of α -GMF was then investigated with various acrylates differing in their ester group and the results are listed in Scheme 4, with yields in the same range.

† All reactions were conducted under the optimized conditions of Table 1.



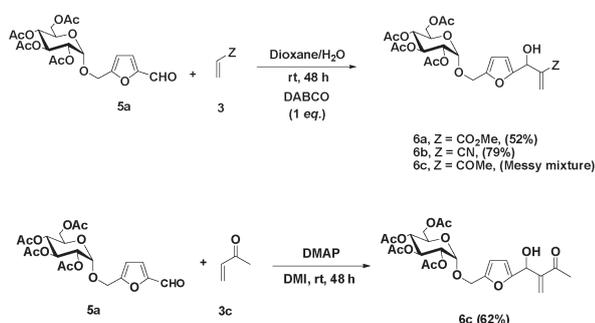
Scheme 4 Substrate generality on the ester side[†].

Hydroxymethyl acrylate was also applicable in this reaction (adduct **4e**).

The reactivity of α -GMF tetraacetate **5a** was also investigated. Using the DMI-water-DABCO conditions did not allow to observe the desired products within acceptable time, but the corresponding BH adducts could be obtained by using Hu's aqueous conditions (DABCO, 1,4-dioxane and water 1 : 1 v/v).^{13b,e} Both methyl acrylate and acrylonitrile gave the desired Baylis-Hillman adducts in fair to good yields (Scheme 5). The reaction using methyl vinyl ketone (MVK) was unsuccessful under these conditions, however, using a less reactive promoter such as DMAP and DMI as solvent, the Baylis-Hillman adduct **7a** was exclusively formed in good yield as well.

All BH reactions conducted on α -GMF **3a** and α -GMF tetraacetate **5a** could easily be performed on a 10 mmol scale making the method applicable for practical synthesis of these new sugar-based acrylates.

Finally, it was found that pure water or the water-DMI mixture could be used for the BH reaction of hydroxymethylfurfural **7** (HMF) itself with methyl acrylate (Table 2), leading to adduct **8** which was found identical to the product reported by Hu *et al.*^{13b,e} Together with Hu's work, our results confirm the very interesting possibility to use aqueous media for such BH reaction on biobased aldehydes.



Scheme 5 Reaction of α -GMF tetraacetate.

Table 2 Baylis-Hillman reaction of **7** with methyl acrylate^a

Entry	Catalyst	Solvent	$T/^\circ\text{C}$	Time (h)	Yield (%) ^b
1 ^c	DABCO	water	25	120	31(51) ^c
2	DABCO	Dioxane	25	36	0
3	DABCO	DMI	25	36	5
4	DABCO	Dioxane/H ₂ O	25	36	62 ^d
5	DABCO	DMI/H ₂ O	25	36	63

^a all reactions were conducted using 3 : 1 molar ratio of methyl acrylate and **7**, with one equimolar amount of catalyst. ^b yield of isolated product. ^c 51% yield based on starting material recovery. ^d Lit. ref. 13b.

Conclusion

The aqueous Baylis-Hillman reaction of α -GMF with acrylic building blocks has been explored. New carbohydrate containing α -hydroxyacrylates have been obtained in fair yields.

It has been found that pure water can be used for this reaction, yet leading to rather slow reactions. Mixtures of water and DMI, or pure DMI in some cases, have also been shown to be possibly used, allowing replacement of dioxane or DMF compared to previous methods. The acrylic esters being also available from biomass (from glycerol or lactic acid),¹⁶ such new acrylates appear as possibly 100% biobased, and obtained *via* a reaction that offers excellent atom economy and solvent conditions. More studies are under way to elucidate all mechanistic details of this reaction, to develop alternative methods towards the starting α -GMF, to study properties of the new acrylates, and extend the strategy to other types of carbohydrate containing compounds including in the field of sugar based surfactants.

Experimental section

Reactions were performed without the protection of an inert atmosphere. Solvents were either ACS reagent grade or HPLC grade. DMSO and DMI were distilled and dried (calcium hydride) before use. Organic solutions were dried over anhydrous sodium sulfate. The reactions were monitored by TLC on Silica Gel 60 F254 (Merck). Silica gel (Merck) was employed for column chromatography.

All reactions were conducted in a 10 mL flask equipped with magnetic stirring. In a typical reaction, α -GMF (289 mg, 1.0 mmol) was mixed with DABCO (112 mg, 1.0 mmol), methyl acrylate (258 mg, 3.0 mmol) in 2 mL of DMI/H₂O (1/1, v/v) under air. The reaction progress was monitored by TLC. Upon completion, remove the solvent in vacuum. The crude product was purified by flash column chromatography on silica gel. Procedures for the other reactions and physicochemical data of the new products are available in (ESI[†]).

Spectroscopic data of the BH adducts 4a and 6a

Methyl 2-[hydroxy-(5-(α -D-glucopyranosyloxymethyl)-furan-2-yl)-methyl]-acrylate (4a, mixture of two epimers at C-7). 56%; Pale-yellow oil; $^1\text{H-NMR}$ (400 MHz, DMSO): 6.33 and 6.34 (2s, 1H, H-4), 6.29 (s, 1H, H-9), 6.07 (2d, 1H, $J = 2.4$ Hz, H-3), 6.03 (2s, 1H, H-9'), 5.92 and 5.93 (2d, 1H, $J = 1.6$ Hz, OH), 5.43 and 5.44 (2s, 1H, H-7), 4.90 and 4.91 (2s, 1H, OH), 4.70~4.80 (m, 3H, H-1' + 2OH), 4.49~4.55 (m, 2H, H-6 + OH), 4.35 and 4.38 (2d, 1H, $J = 2.4$ Hz, H-6), 3.60~3.70 (m, 4H, OCH₃ + H-6'), 3.45 and 3.48 (2d, 1H, $J = 6.0$ Hz, H-6'), 3.35~3.41 (m, 3H, H-3', H-5', OH), 3.17~3.25 (m, 1H, H-2'), 3.04~3.12 (m, 1H, H-4'); $^{13}\text{C-NMR}$ (100 MHz, DMSO): 51.9 (CO₂CH₃), 60.3 (C-6), 60.9 (C-6'), 64.2 and 64.2 (C-7), 70.3 (C-4'), 71.9 (C-2'), 72.9 (C-5'), 73.3 (C-3'), 97.8 and 97.8 (C-1'), 107.5 and 107.5 (C-3), 110.3 (C-4), 125.4 (C-9), 141.1 (C-8), 150.8 and 150.9 (C-5), 155.6 and 155.7 (C-2), 165.8 (C-10); IR (cm⁻¹): 3885, 2918, 1716, 1654, 1636, 1438, 1406, 1340, 1274, 1199, 1147, 1105, 1010, 953, 819, 708; $[\alpha]_{\text{D}} = +53$ (c 1.0, CH₃OH); HRMS m/z (ESI⁺) calculated for C₁₆H₂₂NaO₁₀, $[\text{M} + \text{Na}]^+$ 397.1112; found 397.1105.

Methyl 2-[hydroxy-(5-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyloxymethyl)-furan-2-yl)-methyl]-acrylate (6a, mixture of two epimers at C-7). 52%, Pale-yellow oil; $^1\text{H NMR}$ (400 MHz, CDCl₃): 6.40 and 6.41 (2d, 1H, $J = 2.4$ Hz, H-9); 6.28 and 6.29 (2d, 1H, $J = 3.2$ Hz, H-4); 6.19 and 6.20 (2d, 1H, $J = 3.2$ Hz, H-3); 6.03 and 6.05 (2dd, 1H, $J_{\text{a}} = 1.2$ Hz, $J_{\text{b}} = 2.0$ Hz H-9'); 5.55 and 5.57 (2d_{br}, 1H, $J = 6.0$ Hz, H-7); 5.46 and 5.47 (2dd, 1H, $J_{\text{a}} = 1.2$ Hz, $J_{\text{b}} = 10.4$ Hz, H-3'); 5.24 and 5.28 (2d, 1H, $J = 3.6$ Hz, H-1'); 5.06 (2dd, 1H, $J_{\text{a}} = 2.0$ Hz, $J_{\text{b}} = 10.4$ Hz, H-4'); 4.78 and 4.79 (2dd, 1H, $J_{\text{a}} = 3.6$ Hz, $J_{\text{b}} = 10.4$ Hz, H-2'); 4.53, 4.57 and 4.54, 4.58 (2d + 2d, 1H each, $J = 13.2$ Hz, H-6); 4.23 and 4.26 (2dd, 1H, $J_{\text{a}} = 4.4$ Hz, $J_{\text{b}} = 11.6$ Hz, H-6'); 4.09~4.02 (m, 2H, H-5' + H-6'); 3.75 and 3.76 (2s, 3H, O-CH₃); 3.39 and 3.49 (2d, 1H, $J = 6.0$ Hz, OH). 2.09, 2.02, 2.01, 2.00 (s, 4 Ac-CH₃). $^{13}\text{C NMR}$ (100 MHz, CDCl₃): 20.7, 20.7, 20.8, 20.8 (4 OAc, CH₃), 52.2 and 52.2 (CO₂CH₃), 61.9 (C-6), 61.9 (C-6'), 67.0 and 67.0 (C-7), 67.5 and 67.5 (C-5'), 68.5 and 68.6 (C-4'), 70.1 (C-3'), 71.1 and 71.2 (C-2'), 94.4 and 94.6 (C-1'), 108.1 and 108.1 (C-3), 111.3 and 111.5 (C-4), 126.9 and 127.0 (C-9), 139.3 and 139.3 (C-8), 150.2 and 150.4 (C-5), 155.4 (C-2), 166.4 and 166.4 (C-10), 169.8, 170.2, 170.7 and 170.8 170.9 and 170.9 (CO, 4OAc); IR (cm⁻¹): 3471, 2960, 1751, 1676, 1434, 1369, 1228, 1136, 1043, 801, 601; $[\alpha]_{\text{D}} = +100$ (c 1.0, CH₃OH); HRMS m/z (ESI⁺) calculated for C₂₄H₃₀NaO₁₃, $[\text{M} + \text{Na}]^+$ 565.1528; found 565.1497.

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