A convenient, one-step, synthesis of β-*C*-glycosidic ketones in aqueous media

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Condensation of pentane-2,4-dione with different unprotected sugars in alkaline aqueous media gave quantitatively in one step β-*C*-glycosidic ketones.

C-Glycosides are becoming useful as building blocks for the synthesis of various types of natural products and as potential enzyme inhibitors.[1] In addition, they are used as a model in enzymatic and metabolic studies, indeed it has been shown that the conformational differences between the *O*- (or *N*-) glycosides and the *C*-linked analogue are minimal.[2] Moreover, *C*-glycosides are essentially inert to degradation because the natural anomeric centre has been transformed from a hydrolytically labile O or N acetal link to an ether. As a result, significant attention has been focused in the last decade on the development of new routes for their syntheses.

The most common method for C–C bond formation at the anomeric centre involves nucleophilic attack on this naturally electrophilic carbon atom.[3] A wide variety of electrophilic sugars have been employed such as reducing sugars, alkyl glycosides, anomeric esters, anomeric trichloroacetimidates, or glycosyl halides. The carbon nucleophiles that have been used include cyanides, allyl- and propargylsilanes, silyl enol ethers, silyl ketenes, enamines and organometallics such as Grignard reagents, organolithiums, cuprates, or aluminates.[4] In most cases, these procedures require specific, awkward reaction conditions and generally suffer from low yields.

Recently, there have been several advances in C–C bond formation in aqueous media. These milder methods include the coupling of unprotected sugars with malonate-derived nucleophiles such as barbituric derivatives[5] or Meldrum acid,[6] with Wittig-type reagents,[7] or with allyl bromides promoted by tin or indium in Barbier-type reactions.[8] In fact, water is now recognised as an attractive medium for many organic reactions[9] but curiously, for the most part, sugar chemistry stays away from this development of organic synthesis in water. Yet, the use of water-soluble unprotected reducing carbohydrates would allow syntheses without the tedious protection–deprotection protocol.

The Knoevenagel condensation,[10] a century-old reaction, consists of the condensation of aldehydes with active methylene-containing derivatives such as malonic acid or its ester. Despite the Knoevenagel reaction being a net dehydration, this reaction was surprisingly in some cases favoured in aqueous media.[11]

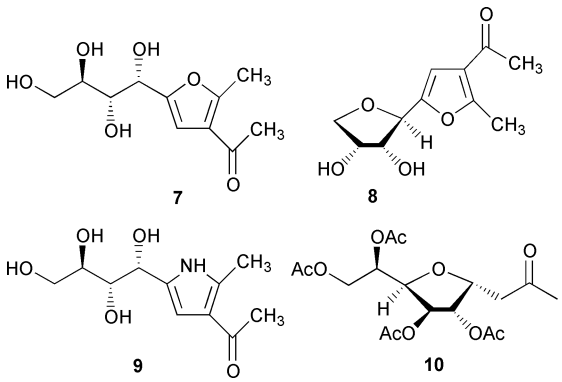
In this communication, we describe the very efficient one-step synthesis of β-*C*-glycosidic ketones in alkaline aqueous media from unprotected carbohydrates *via* the Knoevenagel condensation.

C-Glycosidic ketones are normally prepared in anhydrous conditions from an activated protected sugar by addition of a suitable nucleophile such as silyl enol ether[12] or enamines[13] to give generally the α-*C*-glycoside anomers as the major stereoisomer. Alternatively they can be obtained through multistep chemical transformations of allyl *C*-glycosides or using Wittig-type reaction on reducing sugars.[14]

We describe here the reaction in water of pentane-2,4-dione with D-glucose (**1**), D-mannose **(2)** or D-cellobiose (**3**) in the presence of sodium bicarbonate, which gave quantitatively in one step the β-*C*-glycosidic ketones (**4**–**6**).† The results and conditions are summarised in Table 1.

It is worth pointing out that compound **4** derived from D-glucose and **6** derived from D-cellobiose have been prepared only recently, respectively in six and seven steps in overall low yields from commercial 2,3,4,6-tetrabenzylglucopyranose.[15] In the case of the still unknown compound **5**, the structure and particularly the configuration at the anomeric centre was determined through ^{1}H, ^{13}C and NOESY NMR spectra.‡ Indeed a strong correlation between H-1 with both H-3 and H-5 in the NOESY spectrum along with a small coupling constant $J_{1,2}$ of 1 Hz indicates a β-configuration.

In fact, the reaction of pentane-2,4-dione with reducing sugars had already been studied in acidic medium ($ZnCl_2$, MeOH) and was shown[16] to give in the case of glucose the furan derivative (**7**) which further cyclises to **8** (32% overall yield), or, in aqueous acetone in the presence of sodium carbonate with reducing amino sugars such as glucosamine, the pyrrole derivative (**9**).[17]



In our case, the formation of compounds (**4**–**6**) results from the initial condensation of the carbanion of the β-diketone with the starting sugar (**1**–**3**), β-elimination of water and then cyclisation to the intermediate *C*-glycoside which undergoes a retro-Claisen aldolisation under the basic conditions with concomitant sodium acetate elimination, as shown in Scheme 1.

The exclusive formation of the β-pyranoside stereoisomer in the reaction at 90 °C came from thermodynamic control in the

Table 1 Addition of pentane-2,4-dione onto unprotected carbohydrates in water

Substrates	Conditions	Products and stereoselectivity[b]	Total yields (%)[a]
D-Glucose (**1**)	$NaHCO_3$ (1.5 eq.), 6 h, 90 °C	**4** (100% β)	96
	$Yb(OTf)_3$ (0.1 eq.) 20 h, 60 °C	**7** (58%)[a] + **8** (39%)[a]	97
D-Mannose (**2**)	12 h, 90 °C	**5** (100% β)	95
D-Cellobiose (**3**)	12 h, 90 °C	**6** (100% β)	93

[a] Isolated yields. [b] Determined by ^{1}H and ^{13}C NMR spectroscopy.

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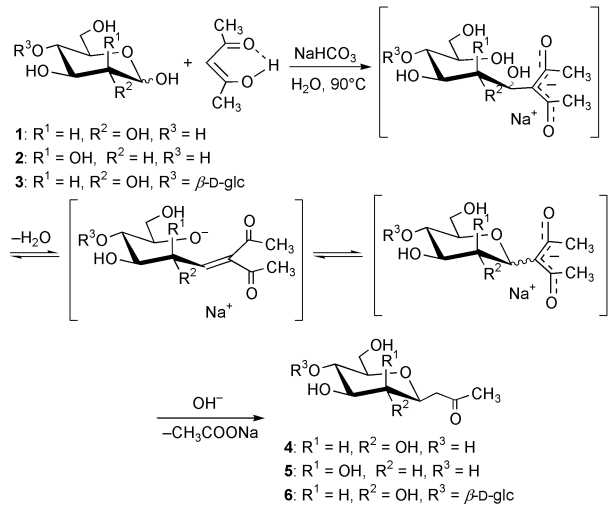

1: R^1 = H, R^2 = OH, R^3 = H
2: R^1 = OH, R^2 = H, R^3 = H
3: R^1 = H, R^2 = OH, R^3 = β-D-glc

4: R^1 = H, R^2 = OH, R^3 = H
5: R^1 = OH, R^2 = H, R^3 = H
6: R^1 = H, R^2 = OH, R^3 = β-D-glc

Scheme 1

presence of sodium bicarbonate. Effectively, at rt after 24 h we get a mixture of the four possible α,β-furanosides and α,β-pyranosides stereoisomers in which the α-furanoside predominates.§ Indeed, it has been shown that equilibration under basic conditions of protected α,β-*C*-glucofuranoside analogues having an activated methylene group adjacent to the anomeric carbon favored the α-anomer through an α,β-unsaturated keto-intermediate.[18] By contrast, in the case of a mixture of α,β-glucopyranosides, equilibration led to the practically exclusive formation of the β-glucopyranoside.[19] In our case, the reaction with D-glucose, including the equilibration towards the pure β-*C*-glucopyranoside, is complete after 6 h at 90 °C whereas for the reaction with D-mannose a longer reaction time is required (12 h at 90 °C) as a result of a slower equilibration process. In the case of cellobiose, pure β-*C*-glycoside was obtained along with a trace of starting cellobiose (< 4%) which still existed after 12 h at 90 °C and which was removed after crystallisation of the β-*C*-glycosidic ketone.

Recently, ytterbium trifluoromethanesulfonate was shown to promote acid-catalysed reactions in water under rather smooth conditions. This encouraged us to try the reaction of pentane-2,4-dione with D-glucose in water in the presence of $Yb(OTf)_3$ at neutral pH. Indeed, after 20 h at 60 °C, we obtained a 1.5 : 1 mixture of compounds **7** and **8**, formerly prepared under rather drastic conditions,[16] in near quantitative yield which could be further separated by flash chromatography into pure **7** (58%) and **8** (39%).

In summary, the Knoevenagel condensation under aqueous conditions presented in this paper represents a very convenient method for the preparation of pure β-*C*-glycosidic ketones in one step directly from the unprotected sugar. Application of this method to other bi-functional compounds as well as the use of these compounds in the preparation of more elaborate *C*-glycosides are at present under investigation in our laboratory.

Notes and references

† *General procedure for the condensation of pentane-2,4-dione with unprotected sugars*: to a solution of D-glucose, D-mannose or D-cellobiose (1 mmol) in water (4 ml) were added sodium bicarbonate (1.5 mmol) and pentane-2,4-dione (1.2 mmol). After stirring at 90 °C for the given time, the reaction mixture was washed with CH_2Cl_2 (5 ml) and treated with Dowex resin (50X8-200, H^+ form). After concentrating the aq. mixture, the residues looked pure by NMR spectroscopy except for **6** which still contained 4% of unreacted cellobiose. Analytical samples were obtained after flash chromatography (AcOEt–iPrOH–H_2O 8 : 1 : 1) or crystallization (MeOH–Et_2O) for **5** and **6**. Compounds **4** and **6** were found identical with those described in literature,[15] except that in our hands **6** crystallized from MeOH–ether mp, 88–89 °C.

‡ (**5**): white powder; mp 125–127 °C (CH_3OH–Et_2O); $[\alpha]_D^{27}$: −10° (*c* 1.2, MeOH); δ_H(200 MHz, D_2O): 2.26 (s, 3H, CH_3), 2.78 (dd, $J_{3a',1}$ 4.4, 1H, H-3a′), 2.98 (dd, $J_{3a',3b'}$ 17.1, $J_{3b',1}$ 8.3, 1H, H-3b′), 3.32–3.41 (ddd, $J_{5,4}$ 9.3, 1H, H-5), 3.55 (t, $J_{4,3}$ 9.3, 1H, H-4), 3.67 (dd, $J_{6a,6b}$ 12.2, $J_{6a,5}$ 6.4, 1H, H-6a), 3.68 (dd, $J_{3,2}$ 3.4, 1H, H-3), 3.85 (dd, $J_{1,2}$ 1.0, 1H, H-2), 3.88 (dd, $J_{6b,5}$ 2.4, 1H, H-6b), 4.05 (ddd, 1H, H-1); δ_C(62.9 MHz, D_2O): 29.8 (C-1′), 44.5 (C-3′), 61.1 (C-6), 66.9, 70.7, 73.7, 74.0, 79.9 (C-1), 212.7 (C-2′); υ_{max}(KBr)/cm^{-1}: 1712 (C=O). Calc. for $C_9H_{16}O_6$: C, 49.09; H, 7.32; O, 43.59. Found: C, 48.88; H, 7.27; O, 43.39%.

§ After 24 h at rt the mixture contained four stereoisomers in a 2 : 1 : 1 : 1 ratio in *ca*. 35% total yield from which the major stereoisomer could be separated by flash chromatography (AcOEt–iPrOH 8 : 2). It was fully characterized after peracetylation (Ac_2O, pyridine, 16 h at rt) and shown to be the α-*C*-glucofuranoside (**10**) by ^{1}H NMR. Indeed, we found H-4 at 4.29 ppm while H-5 moves downfield to 5.17 ppm showing clearly the presence of an acetate at OH-5. Moreover, NOESY experiment shows strong correlations between H-1 and H-5 and between H-1 and H-2 but not between H-1 and H-3, indicating an α configuration.

(**10**): colorless oil; $[\alpha]_D^{25}$: +18° (*c* 1.1, CH_2Cl_2); δ_H(200 MHz, $CDCl_3$): 1.99, 2.08, 2.13, 2.19 (s, 4 CH_3), 2.58 (dd, $J_{3a',1}$ 5.9, 1H, H-3a′), 2.80 (dd, $J_{3a',3b'}$ 17.1, $J_{3b',1}$ 7.3, 1H, H-3b′), 4.10 (dd, $J_{6a,6b}$ 12.2, $J_{6a,5}$ 5.4, 1H, H-6a), 4.29 (dd, $J_{4,5}$ 9.5, $J_{4,3}$ 3.7, 1H, H-4), 4.55 (dd, $J_{6b,5}$ 2.5, 1H, H-6b), 4.69 (ddd, $J_{1,2}$ 3.4, 1H, H-1), 5.17 (ddd, 1H, H-5), 5.21 (dd, $J_{2,3}$ 1.0, 1H, H-2), 5.43 (dd, 1H, H-3); δ_C(62.9 MHz, $CDCl_3$): 20.7 (CH_3CO), 30.4 (C-1′), 42.8 (C-3′), 63.4 (C-6), 67.8, 74.6, 76.2, 76.7, 76.9, 169.1, 169.7, 170.6 (CO), 205.1 (C-2′). Calc. for $C_{17}H_{24}O_{10}$: C, 52.57; H, 6.23; O, 41.20. Found : C, 52.43; H, 6.12; O, 40.93%.

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