Iron(III) Chloride in Ethanol–Water: Highly Efficient Catalytic System for the Synthesis of Garcia Gonzalez Polyhydroxyalkyl- and *C*-Glycosylfurans

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Abstract: An efficient method has been developed for the synthesis of Garcia Gonzalez polyhydroxyalkyl- and *C*-glycosylfurans in excellent yields from unprotected sugar aldoses with β-keto esters by Knoevenagel condensation in the presence of anhydrous iron(III) chloride.

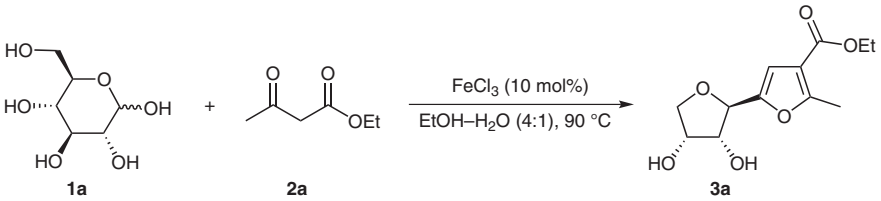
Key words: D-glucose, β-keto esters, Knoevenagel reaction, furans, carbohydrates

Syntheses of polyhydroxyalkyl- and *C*-glycosylfuran derivatives occupy an important place in the realm of natural and synthetic organic chemistry due to the therapeutic and pharmacological properties of these compounds. They have emerged as integral backbones of over 100 natural products isolated from plants and microorganisms.[1] The *C*-glycosylfuran ring system is also an integral part of various types of natural products such as palytoxin, brevetoxin, and polyether antibiotics.[2] They are also useful building blocks in heterocyclic chemistry[3] and in the synthesis of carbohydrates,[4] which, in turn, are of enormous importance in chemical, biological, and medicinal science as well as in the preparation of pharmaceuticals and agrochemicals.[5] Among the various classes of heterocycles, furan derivatives exhibit a wide spectrum of biological activities including cytotoxic,[6] antifungal, antitrypanosomal, gastrointestinal motility, and phosphodiesterase inhibitory activity,[7] and, recently, these compounds have also been used as potential enzyme inhibitors and to construct mimics of peptidoglycans.[4c,8] In view of their biological significance, the synthesis of these heterocycles is of current importance.

The synthesis of *C*-glycosylfuran derivatives in about 32% yield by the condensation of unprotected sugars with β-dicarbonyl compounds in the presence of zinc chloride in methanol under relatively harsh reaction conditions was first reported by Garcia Gonzalez et al. in the 1950s.[9] More recently, the syntheses of these furan derivatives were reported to be carried out by the condensation of unprotected sugar aldoses with β-dicarbonyl compounds in the presence of Lewis acids or protic acids involving acetic acid,[10] ytterbium(III) trifluoromethanesulfonate,[11] cerium(III) chloride heptahydrate,[12] phosphoryl chloride,[6] silicon dioxide–cerium(III) chloride heptahydrate/sodium iodide,[13] and indium(III) chloride.[14] However, these methods suffer from disadvantages such as low yields, harsh reaction conditions, long reaction times, and the use of expensive, toxic, and moisture-sensitive reagents, which limit their practical utility in organic synthesis. Therefore, the development of a more practical and economical method for the one-pot synthesis of polyhydroxyalkyl- and *C*-glycosyl furans is highly desirable.

In recent years, iron(III) chloride has emerged as a powerful Lewis acid catalyst, and performs many useful organic transformations under mild reaction conditions. Moreover, iron salts are inexpensive, easy to handle, and environmentally friendly.[15] In continuation of our program on the development of novel methodologies in organic synthesis,[16] a general and practical method for the synthesis of Garcia Gonzalez furan derivatives from unprotected sugar aldoses and β-keto esters in the presence of anhydrous iron(III) chloride in an ethanol–water (4:1) solvent system under mild conditions has been developed and is reported herein.

Initially, the condensation of D-glucose (**1a**) with ethyl acetoacetate (**2a**) (Scheme 1) was attempted under various reaction conditions in the presence of different acid catalysts such as $K_5CoW_{12}O_{40}\cdot 3H_2O$, bismuth(III) chloride, tin(II) chloride, iodine, silica gel, IR-120 H^+, Dowex-50 H^+, and iron(III) chloride in water, ethanol, methanol, isopropyl alcohol, 1,4-dioxane, or combinations of these. Of



Scheme 1

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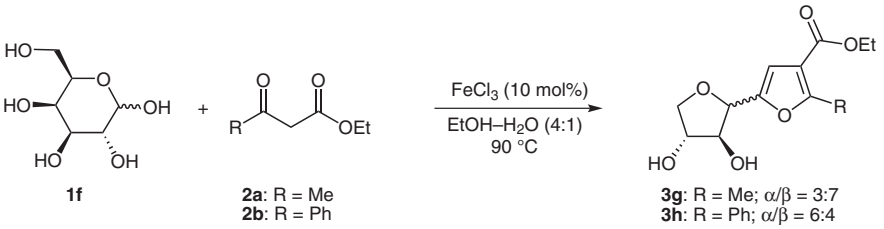
all the various permutations, the reaction in ethanol–water (4:1) in the presence of iron(III) chloride (10%) afforded the *C*-glycosyl 3,4-dihydroxy-2,3,4,5-tetrahydro-2,2′-bifuran **3a** in 95% yield (Scheme 1). All the other tested catalysts afforded only 0–11% yield, and in the absence of catalyst the reaction product **3a** could not be isolated, even after a long reaction time (72 h) at 90 °C.

To improve the yields, we performed the reaction with different quantities of reagents. The best results were obtained with an iron(III) chloride/unprotected sugar aldose/β-keto ester ratio of 0.1:1:1.2. In a typical experimental procedure, a mixture of ethyl acetoacetate (**2a**) or ethyl benzoylacetate (**2b**) and one of sugar aldoses **1a–f** in ethanol–water (4:1) in the presence of a catalytic amount of iron(III) chloride (10 mol%) was heated at 90 °C (Table 1); after completion of the reaction as indicated by thin-layer chromatography, the reaction mixture was concentrated and purified by flash column chromatography over silica gel. Under these conditions, D-ribose (**1c**),

Table 1 Synthesis of Polyhydroxylated Furans **3** Catalyzed by Iron(III) Chloride in Ethanol–Water (4:1)[a]

Entry	Aldose **1**	R	**2**	Furan **3**	Time (h)	Yield[b] (%)
1	**1a**	Me	**2a**	**3a**	5.0	95
2	**1b**	Me	**2a**	**3a**	6.0	88
3	**1c**	Me	**2a**	**3b**	4.5	90
4	**1d**	Me	**2a**	**3b**	5.0	82
5	**1e**	Me	**2a**	**3c**	6.0	82
6	**1a**	Ph	**2b**	**3d**	5.0	87
7	**1b**	Ph	**2b**	**3d**	5.5	82
8	**1c**	Ph	**2b**	**3e**	4.5	86
9	**1d**	Ph	**2b**	**3e**	5.0	80
10	**1e**	Ph	**2b**	**3f**	4.5	85

[a] Reaction conditions: **1** (1 equiv), **2** (1.2 equiv), EtOH–H_2O (4:1), anhyd $FeCl_3$ (10 mol%), 90 °C.
[b] Isolated yield.



Scheme 2

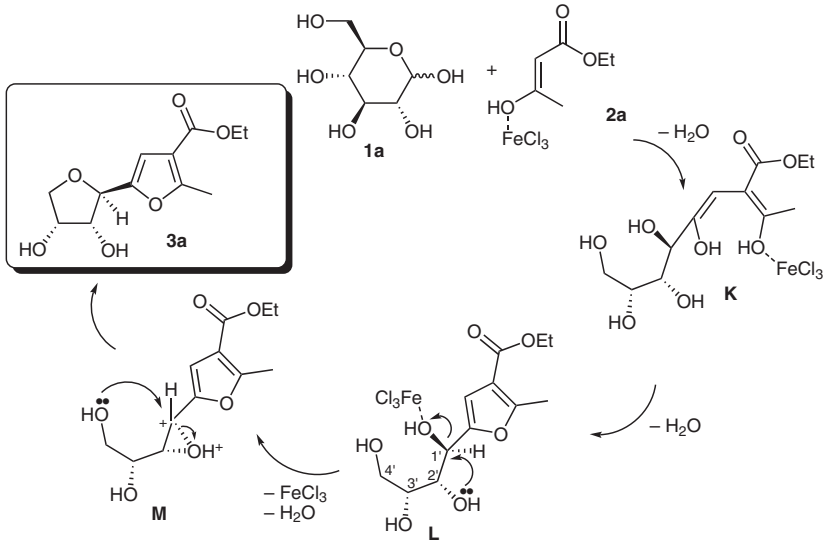
D-arabinose (**1d**), and D-lyxose (**1e**) produced furan derivatives **3b**, **3c**, **3e**, and **3f** with polyhydroxyalkyl side chains (entries 3–5 and 8–10), whereas in the case of D-glucose (**1a**) and D-mannose (**1b**), further cyclization occurred to furnish β-linked hydroxylated 2,3,4,5-tetrahydro-2,2′-bifuran derivatives **3a** and **3d** in excellent yields (entries 1,2, 6, and 7). The reactions of several combinations were studied, to investigate the generality of the process, and the novelty of this process for the synthesis of polyhydroxyalkyl- and *C*-glycosyl furans is illustrated in Table 1.

Many of the pharmacologically relevant substitution patterns on the furan ring could be introduced efficiently with a variety of β-keto ester compounds, such as ethyl acetoacetate and ethyl benzoylacetate, which worked well, without the formation of any side products. The use of just ten mol% of iron(III) chloride is sufficient to push the reaction forward. Larger amounts of iron(III) chloride did not improve the results to a great extent. No additive or protic/Lewis acid is necessary in the procedure, and the products obtained are of high purity (>95% by ^{1}H NMR spectroscopy).

The products obtained from the reactions of D-galactose (**1f**) with ethyl acetoacetate (**2a**) or ethyl benzoylacetate (**2b**) were, however, mixtures of the α- and β-linked 2,3,4,5-tetrahydro-2,2′-bifurans **3g** or **3h**, respectively, in α/β ratios of 3:7 and 6:4, respectively (determined by ^{1}H NMR integration) (Scheme 2).

Mechanistically, the reaction may proceed by Knoevenagel condensation of, for example, D-glucose (**1a**) with the enolate of, for example, β-keto ester **2a** in the presence of iron(III) chloride, to form a stable tetraol **L** via **K** (Scheme 3). Further cyclodehydration of compound **L** predominantly follows an S_N1 mechanism. That is to say, the easily formed carbocation at C1′ is stabilized by the neighboring *trans*-hydroxy group of C2′ to give the intermediate **M**, which undergoes in-plane attack of the hydroxy group on C4′ in a stereoselective process to give the β-isomer of 3,4-dihydroxy-2,3,4,5-tetrahydro-2,2′-bifuran **3a** exclusively and in excellent yield. In contrast, in the case of D-galactose (**1f**), the intermediate carbocation is not stabilized by the neighboring *cis*-hydroxy group of C2′, and the attack of the nucleophile may proceed on either side of the plane, thus resulting in a mixture of α- and β-isomers **3g** in a 3:7 ratio.[6,17]

In conclusion, a series of (hydroxyalkyl)furans **3b**, **3c**, **3e**, and **3f** and β-linked 3,4-dihydroxy-2,3,4,5-tetrahydro-2,2′-bifurans **3a** and **3d** were synthesized by one-pot condensation of one of the unprotected sugar pentoses **1c**–**e**, or hexoses **1a**,**b**, respectively, with one of the β-keto esters **2a** or **2b** in the presence of a catalytic amount of iron(III) chloride (10 mol%) in ethanol–water (4:1) as a solvent system. The remarkable catalytic activity exhibited by iron(III) chloride is convincingly superior to the other recently reported catalytic systems with respect to reaction time and amount of catalyst used. Due to easy workup and the use of an inexpensive, readily available



Scheme 3

catalyst, the procedure is superior to existing methods. Furthermore, the protocol reported here is readily amenable to parallel synthesis and combinatorial generation of substituted furan libraries.

All the commercially obtained reagents and solvents were used without further purification unless stated otherwise. Melting points were recorded on a Buchi 535 melting-point apparatus and are uncorrected. All the reactions were monitored by TLC performed on precoated silica gel $60F_{254}$ plates (Merck). Compounds were visualized with UV light at 254 nm and 365 nm, I_2, and heating plates after dipping the plates in 2% phosphomolybdic acid in 15% aq H_2SO_4. IR spectra of samples prepared as KBr pellets were recorded on Perkin-Elmer 683 or 1310 FT-IR spectrometers. NMR spectra were recorded on Varian Unity 400 MHz and Bruker AMX 300 spectrometers; TMS was used as an internal standard. Mass spectra were recorded on an LCMSD-Trap mass spectrometer.

3,4-Dihydroxy-2,3,4,5-tetrahydro-2,2′-bifuran 3a (Table 1, Entry 1); Typical Procedure

Anhyd $FeCl_3$ (0.162 g, 1 mmol) was added to a stirred soln of D-glucose (**1a**; 1.80 g, 10 mmol) and ethyl acetoacetate (**2a**; 2.56 g, 12 mmol) in an EtOH–H_2O mixture (4:1; 10 mL). The reaction mixture was refluxed for 5 h until completion of the reaction (TLC monitoring) and concentrated under reduced pressure, before the residue was purified by flash column chromatography (silica gel, EtOAc–PE, 3:7) to afford **3a** as a thick syrup.

Yield: 2.432 g (95%).

IR (KBr): 3414, 1711 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.1 Hz, 3 H), 2.55 (s, 3 H), 3.81 (dd, *J* = 4.2, 9.8 Hz, 1 H), 4.11–4.45 (m, 5 H), 4.59 (d, *J* = 6.3 Hz, 1 H), 6.59 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.81, 29.20, 59.97, 70.60, 72.54, 74.28, 76.45, 109.25, 113.65, 149.58, 159.31, 163.76.

MS–FAB: *m*/*z* [M + 1] calcd for $C_{12}H_{16}O_6$: 257; found: 257.

Compound 3b (Table 1, Entry 3)

IR (KBr): 3435, 1714 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 6.9 Hz, 3 H), 2.55 (s, 3 H), 3.25–3.95 (m, 6 H), 4.25 (m, 2 H), 6.61 (d, *J* = 6.3 Hz, 1 H).

MS–FAB: *m*/*z* [M + 1] calcd for $C_{11}H_{16}O_6$: 245; found: 245.

Compound 3c (Table 1, Entry 5)

IR (KBr): 3435, 1714 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.2 Hz, 3 H), 2.55 (s, 3 H), 3.25–3.99 (m, 4 H), 4.25 (m, 2 H), 6.60 (d, *J* = 6.2 Hz, 1 H).

MS–FAB: *m*/*z* [M + 1] calcd for $C_{11}H_{16}O_6$: 245; found: 245.

Compound 3d (Table 1, Entry 7)

IR (KBr): 3416, 1714 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.5 Hz, 3 H), 4.15–4.45 (m, 5 H), 6.79 (s, 1 H), 7.39 (m, 3 H), 7.90 (d, *J* = 10.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.72, 29.31, 60.42, 70.81, 72.67, 74.69, 76.58, 111.27, 113.95, 127.68, 128.11, 129.09, 129.18, 150.87, 157.33, 163.31.

MS–FAB: *m*/*z* [M + 1] calcd for $C_{17}H_{18}O_6$: 319; found: 319.

Compound 3e (Table 1, Entry 8)

IR (KBr): 3423, 1716 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 7.8 Hz, 3 H), 3.35–4.05 (m, 2 H), 4.20–4.50 (m, 4 H), 6.75 (d, *J* = 6.3 Hz, 1 H), 7.40 (m, 3 H), 8.00 (d, *J* = 10.3 Hz, 2 H).

MS–FAB: *m*/*z* [M + 1] calcd for $C_{16}H_{18}O_6$: 307; found: 307.

Compound 3f (Table 1, Entry 10)

IR (KBr): 3424, 1715 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (m, 3 H), 3.38–4.01 (m, 4 H), 4.21–4.45 (m, 2 H), 6.78 (d, *J* = 6.7 Hz, 1 H), 7.40 (m, 3 H), 7.98 (d, *J* = 9.3 Hz, 2 H).

MS–FAB: *m*/*z* [M + 1] calcd for $C_{16}H_{18}O_6$: 307; found: 307.

Compound 3g (Scheme 2)

Mixture of stereoisomers.

IR (KBr): 3419, 1695 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (m, 3 H), 2.52 (2 s, α/β = 3:7, 3 H), 3.66–4.35 (m, 6 H), 4.52 (d, *J* = 3.9 Hz, 1 H), 6.60 (2 s, α/β = 3:7, 1 H).

MS–FAB: *m*/*z* [M + 1] calcd for $C_{12}H_{16}O_6$: 257; found: 257.

Compound 3h (Scheme 2)

Mixture of stereoisomers.

IR (KBr): 3416, 1720 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (m, 3 H), 4.10–4.32 (m, 7 H), 6.75 (2 s, α/β = 6:4, 1 H), 7.35 (m, 3 H), 8.00 (m, 2 H).

MS–FAB: *m*/*z* [M + 1] calcd for $C_{17}H_{18}O_6$: 319; found: 319.

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