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FACILE SYNTHESIS OF METHYL 2-FORMYL-5-HYDROXYMETHYL-3-FURANCARBOXYLATE

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Abstract: A short practical synthesis of the title trisubstituted furan is presented. It involves a high yield Knoevenagel condensation of glyceraldehyde and methyl acetoacetate to the furan nucleus and, following a protection of the furyl alcohol, a radical bromination then a Kröhnke reaction of the furyl bromide intermediate.

In the course of our model studies on the total synthesis of chatancin[1] via an extension of the transannular Diels-Alder reaction[2] to furanophanes, methyl 2-formyl-5-hydroxymethyl-3-furan-carboxylate (**1**) was required as a synthetic intermediate. Although this trifunctional furan might suggest a multitude of application, only one synthesis, in conjunction with furanocembranoids, is reported.[3] Now, we offer a more practical access to this compound.

Knoevenagel condensation of aldehydo sugars and active methylene compounds have long been known.[4] These reactions are conducted in dilute aqueous solutions, catalysed with $ZnCl_2$ or piperidine. In particular, in the reaction

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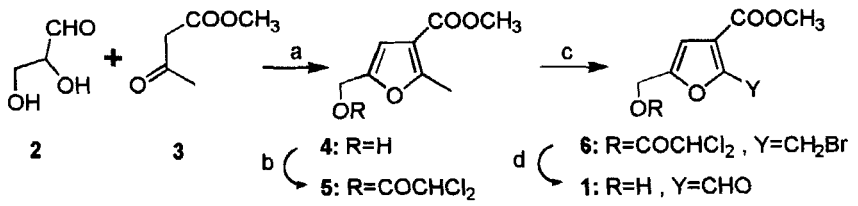

Scheme: (a) DMF, 90°C; (b) Cl_2HCOCl, Pyridine; (c) NBS, Bz_2O_2, CCl_4, reflux; (d) Pyridine then DMNA, NaOMe then H^+.

of glyceraldehyde (**2**) and methyl acetoacetate (**3**), the acetonide of the former was preferred[5] to render the reaction rather impractical. However, we observed a high yield condensation of commercial **2**[6] and **3** to produce furan **4**[7] when the reaction was simply carried out in DMF at 90°C. Following a protection as dichloroacetate **5**,[8] a radical bromination gave entry to the third functional group. Transformation of bromide **6** to aldehyde **1** is best accomplished by Kröhnke reaction.[9] Thus, after pyridinium activation, a basic condensation of pyridinium salt **7** with N,N-dimethylamino-4-nitroso-aniline (DMNA) and acidic hydrolysis of the formed nitrone **9** afforded the title compound **1** as the dichloroacetyl group was also hydrolyzed during the basic condensation.[10]

This communication hopefully opens new applications of these compounds.[11]

Experimental:

The infrared spectra were recorded on KBr (ν-scale in cm^{-1}), on a Perkin-Elmer 1600 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument. Chemical shifts are in ppm δ units, relative to $CHCl_3$ (7.26 ppm for ^1H NMR) and to $CDCl_3$ (77.00 ppm for ^{13}C NMR) as internal standards.

Dichloroacetate 5: A suspension of **2** (5.00 g, 54 mmol) and **3** (7.55 mL, 1.3 eq.) in DMF (15 mL) was stirred for 8 h at 90°C. Upon cooling, the clear solution of **4**[7] was diluted with CH_2Cl_2 (150 mL), dried on $MgSO_4$, added with pyridine

(25 mL) then with $CHCl_2COCl$ (7.8 mL, 1.5 eq.) at -40°C. After 4 h, the reaction was quenched with water, diluted with CH_2Cl_2 (250 mL), washed till neutral with dil. HCl, dried and evaporated. The crude product is filtered through a 5 cm silica plug washed with a mixture of 20% ether in hexane and evaporated to give 13.80 g (84% over 2 steps) **5** as white crystals (mp: 57-58°C), IR: 1764, 1718, 1231. ^1H NMR.[10] ^{13}C NMR: 164.1, 163.9, 160.6, 145.3, 114.4, 112.9, 64.0, 60.3, 51.4, 13.8. EI-MS (*m/z*): 153 (100%), 121 (97%), 280 (30%), 249 (20%). HR-MS, calcd. for $C_{10}H_{10}Cl_2O_5$ $(M)^+$: 279.9905; found: 279.9900 ± 0.0008 .

Bromide 6: Dichloroacetate **5** (11.24 g, 40 mmol), N-bromosuccinimide (8.19 g, 1.15 eq.) and benzoyl peroxide (730 mg, 75 meq.) were refluxed in CCl_4 (200 mL) with vigorous stirring for 15 min. Upon cooling, the mixture was evaporated to 10 mL, hexane (100 mL) was added then the resulting slush was filtered through a 2 cm long and 5 cm wide silica plug. It was washed with a mixture of CH_2Cl_2/hexane (100 mL, 1:4) and ether (250 mL), the filtrate was washed with NaOH (2x50 mL, 0.1 N), HCl (2x50 mL, 0.02 N) and brine (2x50 mL), dried and evaporated to give bromide **6** (14.94 g, 103%, at least 90% pure). ^1H NMR.[10] ^{13}C NMR: 163.8, 162.4, 156.6, 148.1, 116.7, 113.1, 63.8, 60.1, 51.9, 20.2.

Aldehyde 1: A solution of the previous bromide **6** in dry CH_2Cl_2 (50 mL) was added with pyridine (9.71 mL, 3 eq.), stirred for 5 h at 23°C then evaporated to a thick cream. It was dissolved in dry MeOH (100 mL), DMNA (6.01 g, 1 eq.) was added and cooled to 0°C. NaOMe (30 mL, 3.5 eq, 25% in MeOH) was added dropwise then the mixture was stirred for 20 hours at 0°C. MeOH was evaporated, it was diluted with CH_2Cl_2 (20 mL), Et_2O (300 mL) then H_2SO_4 (300 mL, 6 N) was added dropwise with vigorous stirring at -5°C. Following 2 h stirring at 0°C, the organics were washed with H_2SO_4 (2x100 mL, 0.2 N) and brine (100 mL) then dried and evaporated. Chromatography (25-40% ether in hexane), charcoal decolorization in MeOH and crystallization from CH_2Cl_2-Et_2O-hexane afforded 3.19 g (43%) aldehyde **1** as colorless crystals (mp: 76-77°C), IR: 3430 (br), 1726, 1676, 1252. ^1H NMR.[10] ^{13}C NMR: 178.8, 161.9, 159.5, 151.6,

127.1, 109.9, 57.2, 52.5. EI-MS (*m/z*): 184 (100%), 96 (90%), 153 (30%), 124 (60%). HR-MS, calcd. for $C_8H_8O_5$ $(M)^+$: 184.0372; found: 184.0376 ± 0.0005.

References and Notes:

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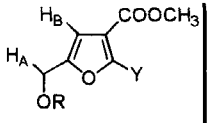
[6] Glyceraldehyde was purchased from Sigma and used without purification. See also: Witzemann, E.J. Evans, W.M.L. and Hass, H. Org. Synth. Coll. Vol. II, **1943** 305.

[7] Isolated furan **4** has a bp: 101-103°C/ 0.1 Hgmm (94-95°C/ 0.1 Hgmm, ref. 5).

[8] Dichloroacetyl group was the hydroxy protection of choice. Neither of THP, TBDMS, trityl, acetyl or pivalate were compatible with bromination. On the other hand, its characteristic base sensitivity is advantageous at the conclusion of the sequence.

[9] Kröhnke, F. Angew. Chem. Int. Ed. **1963**, 2, 380.

[10] Since the intermediates of the last reaction are dyes, the reaction was monitored by ^1H NMR after evaporation of a micro sample of the mixture. Except the aromatics, ^1H NMR shifts ($CDCl_3$, δ, singlets) of the compounds reported herein are as follows:



	R	Y	H_A	H_B	$COOCH_3$	H_Y	$COCHCl_2$
1	H	CHO	4.72(d)	6.80	3.95	10.19	n/a
4	H	CH_3	4.52(d)	6.51	3.80	2.53	n/a
5	$COCHCl_2$	CH_3	5.17	6.75	3.82	2.59	5.95
6	$COCHCl_2$	CH_2Br	5.22	6.80	3.88	4.79	5.97
7	$COCHCl_2$	CH_2Py^+	5.20	6.81	3.89	6.61	6.05
8	H	CH_2Py^+	4.54	6.56	3.87	6.36	n/a
9	H	CHN(O)Ar	4.72	6.53	3.88	8.70	n/a

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