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BRIEF COMMUNICATIONS

New Procedure for Synthesis Alkyl Esters of 5-Acetyl-2-Furan-Carboxylic Acid Alkyl Ester

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Abstract—The possibility to synthesize alkyl esters of 5-acetyl-2-furan-carboxylic acid by the reaction of 5-acetyl-2-furan with CCl_4 and aliphatic alcohols under the action of iron-containing catalysts was studied.

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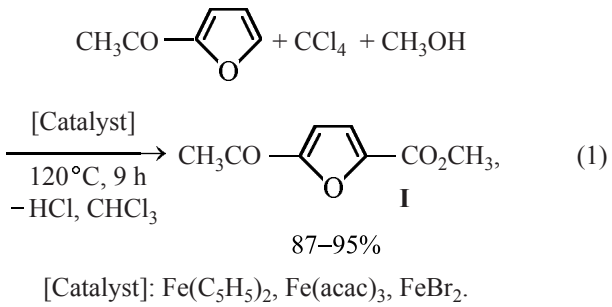
Furan derivatives find wide application as starting compounds in the synthesis of pharmaceuticals. Thus, 2-furan-carboxylic acid and its esters possess anti-tumor activity [1], and methyl ester of 5-acetyl-2-furan-carboxylate (**I**) is used as a starting compound in the synthesis of pharmaceuticals applied to treatment and prophylaxis of mammals' peptide cankers [2].

The majority of known procedures for the preparation of methyl 5-acetyl-2-furan-carboxylate (**I**) are based on a catalytic acylation of 2-furan-carboxylic acid esters by acetic anhydride. When H_2SO_4 is used as the acylation catalyst the yield of **I** is only 0.5% [3], whereas in the presence of fourfould $SnCl_4$ excess it reaches 96% [2].

With the aim to develop a new procedure for the synthesis of methyl 5-acetyl-2-furan-carboxylate (**I**), we studied the possibility of introducing the CO_2CH_3 group in a molecule of 2-acetylfuran (more accessible than the methyl 2-furancarboxylates [4]) by means of a new procedure successfully tested on thiophene and its derivatives [5]. The essence of the procedure consists in the interaction of thiophenes with the system CCl_4–CH_3OH–catalyst: under the action of the catalyst thiophene is alkylated by CCl_4 to form 2-trichloromethylthiophene, which then undergoes alcoholysis to form methyl 2-thiophenecarboxylateic acid. Starting the study of the reaction of 2-acetyl-2-furan with the system CCl_4–CH_3OH–catalyst, it was necessary to take into account the pronounced tendency of the furan cycle to opening, as the attempt to realize the above-mentioned reaction using furfulyl alcohol as an example was unsuccessful and has led to obtaining methyl ester of levulinic acid [6].

It has been shown that methyl 5-acetyl-2-furan-carboxylate (**I**) is the main product of the reaction between 2-acetylfuran and the system CCl_4–CH_3OH–catalyst. As the catalysts we have tested compounds and complexes of Ni, Cu, Mn, Pd, V, and Fe, which have the common ability to labilize the C-Cl bond in the CCl_4 molecule [7, 8].

Among the compounds and complexes, which have shown catalytic activity, iron derivatives form the following series: $Fe(acac)_3$ (95%) > $Fe(C_5H_5)_2$ (90%) > $FeBr_2$ (87%). The reaction proceeds at 120°C and is completed within 9 h by the full conversion of initial 2-acetyl-2-furan:



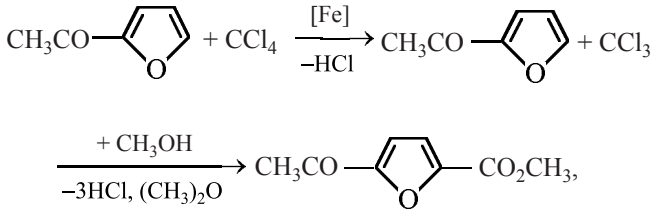
(1)

[Catalyst]: $Fe(C_5H_5)_2$, $Fe(acac)_3$, $FeBr_2$.

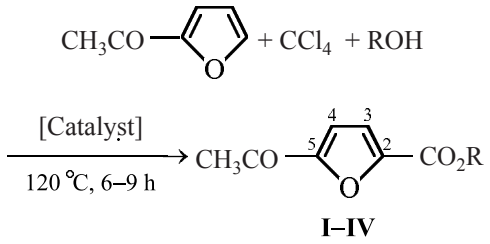
The structure of compound **I** was confirmed by the methods of one-dimensional [^1H, ^{13}C, and APT (Attached proton treatment) NMR spectroscopy] and two-dimensional NMR spectroscopy [HMBC (Hetero Multiple-bond Correlation)]. The 2,5-position of the

substituents is unambiguously determined by the downfield values of chemical shifts (δ C^2 = 145.80 and δ C^5 = 154.26 ppm), the latter signal correlating in the HMBC experiment with protons of the acetyl group which resonate at 2.57 ppm.

We can assume that, similarly to the case of thiophene, the probable reaction scheme includes the successive alkylation of 2-acetyl-2-furan by carbon tetrachloride with the formation of 5 trichloromethyl-2-acetyl-2-furan, which undergoes alcoholysis with the conversion to the corresponding 5-acetyl-2-furancarboxylic acid ester:



This assumption is supported by the fact that when methanol is replaced by ethyl, propyl, and isopropyl alcohols, ethyl (**II**), propyl (**III**), and isopropyl (**IV**) esters, respectively, of 5-acetyl-2-furan-carboxylic acid are formed with fairly high yields. Furthermore HCl and esters of the alcohols taken in the reaction were detected in the reaction mass. A reactively low yield of ethyl 5-acetyl-2-furancarboxylate (**II**) is attributable to the fact that the side reaction of the formation of diethyl ester readily proceeds:



I–IV

[Cat.] - $Fe(C_5H_5)_2$, $Fe(acac)_3$, $FeBr_2$; R = Me (**I**), Et (**II**), *n*-Pr (**III**), *i*-Pr (**IV**).

We have found experimentally that the optimal ratio of the catalyst and reagents is $Fe(acac)_3$: [2-acetyl-2-furan] : [CCl_4] : [ROH] =1 : 100 : 200 : 800.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on Bruker Avance-400 (400.13 and 100.62 MHz) and JEOL FX90Q [90 MHz (^1H), 22.5 MHz (^{13}C)] spectrometers in $CDCl_3$, chemical shifts δ (ppm) were measured relative to TMS. GS-MS data were obtained on a Finnigan MAT-112S chromatography-mass spectrometer (electron impact 70 eV). The chromatographic analysis was carried out on a Chrom-5 instrument [a 1.2 m × 33 mm column, silicon SE-30 (5%) as the istationary, on a Chromaton N-AW-HMDS, a temperature mode from 50 up to 250°C with the heating rate of 8 deg min^{-1} and helium as a gas-carrier (47 ml min^{-1})].

As the initial reagents we used commercially available 2-acetyl-2-furan, methanol, ethanol, propanol, isopropanol, and carbon tetrachloride, which were preminarily distilled. Iron acetylacetonate, ferrocene, and iron bromide ("Acros" made) were recrystallized and dried in a vacuum desiccator before using.

General procedure of obtaining esters of 5-acetyl-2-furancarboxylic acid. In a stainless-steel microreactor (V = 17 ml) or in a glass ampula (V = 20 ml) 0.1 mmol of $Fe(acac)_3$, 10 mmol of 2-acetyl-2-furan, 80 mmol of an aliphatic alcohol, and 20 mmol of CCl_4 were charged under argon; the reactor was hermetically closed (the ampula was sealed) and heated up at 120°C within 6–9 h with permanent stirring. After the reaction termination the reactor (ampule) was cooled to room temperature, opened, and the reaction mixture was filtered through a silica gel layer (eluent–hexane). After distilling off a solvent the residuel was recrystallized or distilled in a vacuum.

Methyl 5-acetyl-2-furancarboxylate (I). Mp 100.5–101°C (according to the published data [9] 101–102°C). Yield 95%. ^1H NMR spectrum, δ, ppm: 2.57 (s, 3H, CH_3CO), 3.95 (s, 3H, OCH_3), 7.15-7.25 (m, 2H, furan, =CH–CH=). ^{13}C NMR, δ, ppm: 26.30 ($CO\underline{C}H_3$), 52.37 (OCH_3), 116.54 (C^4), 118.75 (C^3), 145.80 (C^2), 154.26 (C^5), 158.62 ($COOCH_3$), 187.46 ($\underline{C}OCH_3$). Mass spectrum, *m/e* (I_{rel}, %): 168 $[M]^+$ (42), 43 (30), 59 (10), 69 (12), 79 (5), 95 (21), 125 (4), 137 (20), 153 (100), 154 (10), 169 (18). Found (%): C 57.28, H 5.06, O 37.66. Calculated (%): C 57.14, H 4.80, O 38.06.

Ethyl 5-acetyl-2-furancarboxylate (II). Mp 71–72°C (according to the published data [9] 71–71.5°C). Yield 45 %. ^1H NMR spectrum, δ, ppm: 1.38 (t, $^3J_{HH}$=7.2 Hz, 3H, $C\underline{H}_3CH_2$), 2.55 (s, 3H, $COC\underline{H}_3$), 4.39 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $CH_3C\underline{H}_2$), 7.15–7.25 (m, 2H, furan, =CH-CH=). ^{13}C NMR, δ, ppm: 14.21 ($\underline{C}H_3CH_2$), 26.30 ($CO\underline{C}H_3$), 61.63 (OCH_2), 116.59 (C^4), 118.54 (C^3), 146.53 (C^2), 154.14 (C^5), 158.14 ($\underline{C}OOEt$), 187.51 ($\underline{C}OCH_3$). Found (%): C 60.01, H 5.86, O 34.13. $C_9H_{10}O_4$. Calculated (%): C 59.33, H 5.53, O 35.13.

Propyl 5-acetyl-2-furancarboxylate (II). Mp 90°C/2 mm Hg. Yield 60%. ^{1}H NMR spectrum, δ, ppm: 0.93 (t, 3H, $^3J_{HH}$ = 8.2 Hz, C$\underline{H}_3$CH$_2$CH$_2$), 1.4–2.0 (m, 2H, CH$_3$C$\underline{H}_2$CH$_2$), 2.47 (s, 3H, COCH$_3$), 4.22 (t, $^3J_{HH}$ = 7.4 Hz, 2H, CH$_3$CH$_2$C$\underline{H}_2$), 7.05-7.4 (m, 2H, furan, =CH–CH=). ^{13}C NMR, δ, ppm: 9.76 (C$\underline{H}_3$CH$_2$CH$_2$), 21.48 (CH$_3$C$\underline{H}_2$CH$_2$), 25.68 (CO$\underline{C}$H$_3$), 66.55 (OCH$_2$), 116.43 (C^4), 118.16 (C^3), 146.19 (C^2), 153.78 (C^5), 157.75 (Pr-*n*-COO), 187.51 ($\underline{C}$OCH$_3$). Found (%): C 60.52, H 5.87, O 33.61. $C_{10}H_{12}O_4$. Calculated (%): C 61.21, H 6.17, O 32.62.

Isoropyl 5-acetyl-2-furancarboxylate (II). Mp 96°C/4 mm Hg. Yield 60%. ^{1}H NMR spectrum, δ, ppm: 1.27 [d, $^3J_{HH}$ =7.1 Hz, 6H, (C$\underline{H}_3$)$_2$CH], 2.37 (s, 3H, CH$_3$CO), 4.95–5.5 (m, 1H, [CH$_3$)$_2$C$\underline{H}$], 7.05–7.5 (m, 2H, furan, CH). ^{13}C NMR, δ, ppm: 21.57 [CH$_3$)$_2$$\underline{C}$H], 25.68 (CO$\underline{C}H_3$), 69.35 (OCH$_2$), 116.53 (C^4), 118.19 (C^3), 146.32 (C^2), 153.84 (C^5), 157.30 (*i*-$\underline{C}$OOPr), 186.57 ($\underline{C}$OCH$_3$). Found (%): C 62.40, H 6.32, O 31.28. $C_{10}H_{12}O_4$. Calculated (%): C 61.21, H 6.17, O 32.62.

CONCLUSION

The reactions of 2-acetyl-2-furan with CCl_4 and aliphatic alcohols in the presence of iron complexes result in the formation of 5-acetyl-2-furancarboxylate with 45–95% yields.

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