ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 2, pp. 424–427. © Pleiades Publishing, Ltd., 2015.
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To the 80th Anniversary of B.I. Ionin

Synthesis of 5-Acetyl Derivatives of Alkyl 2-Furoates and 3-(2-Furyl)acrylates

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Received October 23, 2014

Abstract—Methyl 5-acetyl-2-furoate has been prepared via oxidation of 5-(1-hydroxyethyl)-2-furoate with the Jones reagent. In turn, the starting compound has been synthesized via sequential chloroethylation of ethyl 2-furoate, substitution of chlorine with acetoxy group, and methanolysis of the acetate in presence of sodium methylate. The vinylog 2-furoate has been obtained as the major product via acetylation of ethyl 3-(2-furyl)-acrylate with acetic anhydride in the presence of magnesium perchlorate.

Keywords: acetylfuran, chloroethylation, oxidation, acetylation, magnesium perchlorate

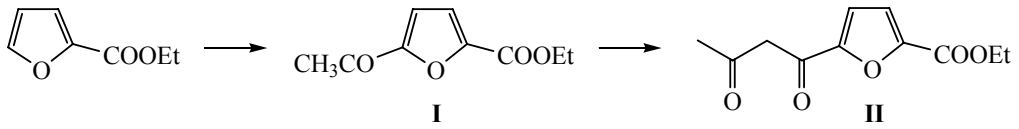
DOI: 10.1134/S1070363215020127

Acetylfurans are valuable starting materials for preparation of various heterocyclic compounds [1–3]. Most acetylfurans known to date have been prepared by acetylation of furan derivatives; however, in the case of alkyl 2-furoates, 5-acetoacetyl-2-furoates (**II**) are the major products [4] (Scheme 1).

It was impossible to find the conditions to prepare acetylfuran **I** in reasonable yield via the reaction with various acylating agents. Therefore, we synthesized compound **I** via oxidation of the corresponding secondary alcohol **III**. In turn, the latter was obtained from ethyl 2-furoate via the following transformations sequence (Scheme 2).

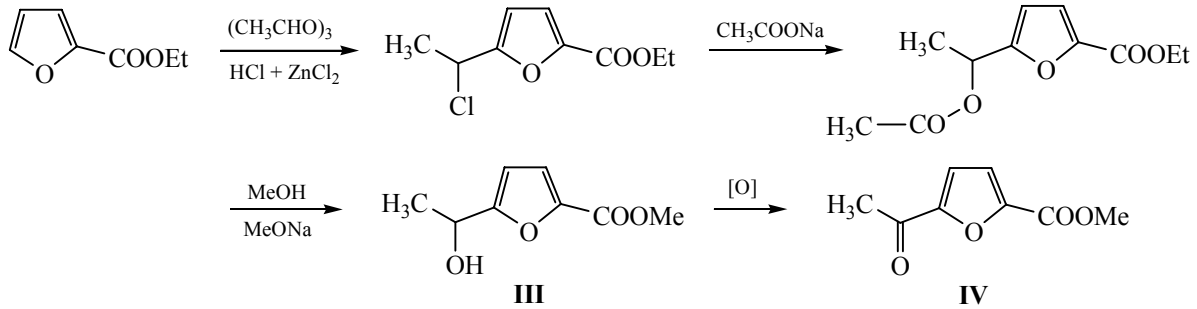
Chloroethylation of ethyl 2-furoate was carried out according to the procedure described elsewhere [5], but we used paraldehyde instead of acetaldehyde for

Scheme 1.



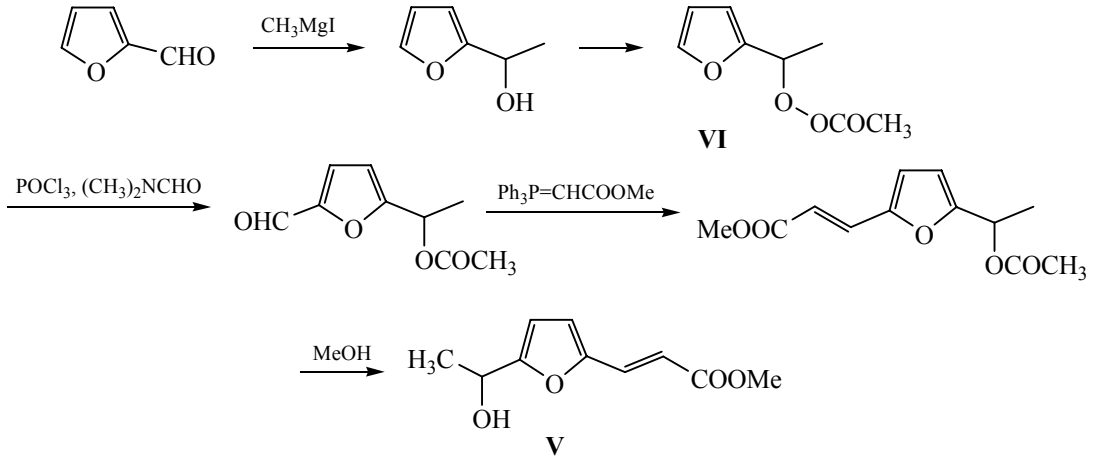
I **II**

Scheme 2.



III **IV**

Scheme 3.



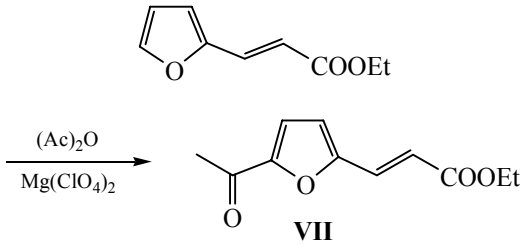
convenience. The reaction mixture temperature was maintained at 25–30°C in the course of the exothermic reaction. Under such conditions, yield of the target product was up to 41%. Substitution of chlorine with acetoxy group was carried out via treatment with sodium acetate in acetic acid. The reaction selectively followed the above-mentioned pathway. No elimination of hydrogen chloride was observed. Methanolysis of the acetate in the presence of catalytic amount of sodium methylate occurred at room temperature involving the both ester groups to give methyl 5-(1-hydroxyethyl)furan-2-carboxylate **III**. According to the spectral data, the target product was pure, and no further purification was required.

Oxidation of the secondary alcohol **III** in aqueous acetone was carried out with a diluted mixture of chromic and sulfuric acids at 10–20°C. However, even under such mild conditions oxidation was not selective, and significant part of the oxidant was consumed in side processes. When the stoichiometric amount of the oxidant was taken, a mixture of the parent alcohol **III** and methyl 5-acetylfuran-2-carboxylate **IV** in the 1 : 1 ratio was obtained. Repeated treatment of that mixture with the oxidant in the 1.3 : 1 molar ratio with respect to the residual alcohol **III**, other conditions being the same, yielded the target acetylfuran **IV** as green crystals. According to ^{1}H NMR spectroscopy data, the so obtained product was pure.

Acetylation of alkyl 3-(2-furyl)acrylates has not been described so far. It has been reported that furylacrylic acid can be acetylated with acetic anhydride under catalysis with phosphoric acid. Besides 3-(5-acetylfur-2-yl)acrylic acid, furfurylidenacetone is formed in this reaction. In view of this, we proposed to use oxidation of alcohol **V** to synthesize alkyl 3-(2-furyl)acrylates. Possible pathway of the process is presented in Scheme 3.

However, in contrast to the case of the esters of furfuryl alcohol, formylation of acetate **VI** under the Vilsmeier reaction conditions was slower than polymerization of the substrate, even in the excess of DMF. Thus, we failed to prepare the target aldehyde.

We further studied acetylation of alkyl 3-(2-furyl)-acrylate with magnesium perchlorate as catalyst. The catalyst has been successively used for acetylation of phenol ethers and naphthalene derivatives [7], but has revealed no advantage as compared to phosphoric acid in acetylation of furan [8]. In the case of alkyl 3-(2-furyl)acrylates, the presence of acidic agents in the reaction mixture might cause polymerization of the unsaturated compounds. Hence, neutral magnesium perchlorate seemed better suitable in that case than the inorganic or Lewis acids. The acetylation was carried out upon boiling; the substrate : anhydride : catalyst molar ratio was of 1 : 1.5 : 0.05. Reaction progress was monitored by TLC. It was found that substitution proceeded exclusively at position 5 of the furan ring. In contrast to the data reported in [5], furfurylideneacetone was not formed.



To conclude, alkyl 5-acetyl-2-furoates could be obtained via oxidation of 2-furylethanol **III**, while its vinylog **VII** was formed as the major product of acetylation of 3-(2-furyl)acrylate with magnesium perchlorate as catalyst.

EXPERIMENTAL

Melting points were measured with a Boetius apparatus. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DPX-400 spectrometer [400.13 MHz (^{1}H) and 100.16 MHz (^{13}C)] in deuterochloroform. Reaction progress was monitored with TLC on Silufol UV-254 plates, developing by UV irradiation or in iodine vapor.

All solvents were purified and dried following the standard procedures.

Ethyl 5-(1-chloroethyl)furan-2-carboxylate. 3.9 g of zinc chloride was added to a solution of 16.0 mL of paraldehyde and 16.9 g of ethyl 2-furoate in 36 mL of chloroform. Hydrogen chloride was passed through the mixture during 5 h at 25–30°C under vigorous stirring. Then, 50 mL of chloroform was added; the reaction mixture was washed with water (2 × 30 mL) and dried over calcium chloride. Solvent was removed under reduced pressure, and the residue was distilled in vacuum to give 10.0 g (41%) of the target product with bp 91°C (1 mmHg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.33 t (3H, CH_3-ethyl, J_{HH} 7.0 Hz), 1.18 d (3H, CH_3-chloroethyl, J_{HH} 7.2 Hz), 4.32 q (2H, CH_2O, J_{HH} 7.0 Hz), 5.09 q (1H, CHCl, J_{HH} 7.2 Hz), 6.41 d (1H, H^4-furan, J_{HH} 3.6 Hz), 7.07 d (1H, H^3-furan, J_{HH} 3.6 Hz).

Ethyl 5-(1-acetoxyethyl)furan-2-carboxylate. 15 g of anhydrous sodium acetate was added to a solution of 25.4 g of ethyl 5-chloroethyl-2-furoate in 125 mL of glacial acetic acid. The reaction mixture was refluxed during 9 h under vigorous stirring, poured in 300 mL of water, and extracted with toluene (3 × 50 mL). The extract was dried over calcium chloride, toluene was removed under reduced pressure, and the residue was distilled in vacuum. Yield 20.3 g, colorless oil, bp 120–121°C (1 mmHg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.36 t (3H, CH_3-ethyl, J_{HH} 7.2 Hz), 1.61 d (3H, CH_3-ethanol, J_{HH} 6.8 Hz), 2.07 s (3H, CH_3-acetate), 4.35 q (2H, CH_2O, J_{HH} 7.2 Hz), 5.94 q (1H, CHO, J_{HH} 6.8 Hz), 6.41 d (H^4-furan, J_{HH} 3.6 Hz) 7.10 d (H^3-furan, J_{HH} 3.6 Hz).

Methyl 5-(1-hydroxyethyl)furan-2-carboxylate (III). 20.3 g of ethyl 5-(1-acetoxyethyl)-2-furoate was added to a solution of sodium methylate prepared from 0.35 g of sodium and 120 mL of methanol. The reaction mixture was incubated at room temperature during 24 h and neutralized with 0.9 mL of acetic acid; the solvent was then removed. The residue was dissolved in 70 mL of dichloromethane, washed with 10 mL of water, and dried over sodium sulfate. After the solvent removal, the residue was kept in vacuum (1 mmHg) during 1 h at room temperature to give 14.9 g (90%) of the target product **III** as light-yellow oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.52 d (3H, CH_3-hydroxyethyl, J_{HH} 6.8 Hz), 3.84 s (3H, CH_3O), 4.89 q (1H, CHOH, J_{HH} 6.8 Hz), 6.33 d (1H, H^4-furan, J_{HH} 3.6 Hz), 7.09 d (1H, H^3-furan, J_{HH} 3.6 Hz). ^{13}C NMR spectrum, ($CDCl_3$), δ_C, ppm: 21.32 (CH_3-hydroxy-ethyl), 51.86 (CH_3O), 63.56 (CHOH), 107.09 (C^4-furan), 118.90 (C^3-furan), 143.33 (C^2-furan), 159.34 (C^5-furan), 162.43 (C=O).

Methyl 5-acetylfuran-2-carboxylate (IV). A solution of 5.7 g of chromium trioxide in a mixture of 40.7 mL of water and 4.4 mL of concentrated sulfuric acid was added dropwise under vigorous stirring at 10–20°C to a solution of 14.9 g of methyl 5-(1-hydroxyethyl)-2-furoate in 100 mL of acetone. The reaction mixture was incubated during 1 h at room temperature. Acetone was then removed on a rotary evaporator. The formed precipitate was filtered off, washed with several portions of water until neutralization, and dried in air. 10.5 g of a mixture of compound **III** and methyl 5-acetylfuran-2-carboxylate in the 1 : 1 ratio (according to the ^{1}H NMR spectroscopy data) was obtained. It was dissolved in 50 mL of acetone and cooled to 10°C; a solution of 2.7 g of chromium oxide and 2.4 mL of concentrated sulfuric acid in 19 mL of water was added dropwise to the mixture upon stirring at 20–26°C. The reaction mixture was incubated during 3 h at room temperature, and acetone was distilled off on a rotary evaporator. The formed precipitate was washed with water until neutralization and dried in air at room temperature. Yield 6.9 g (47%), mp 88°C, light-green crystals. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.57 s (3H, CH_3CO), 3.94 s (3H, CH_3O), 7.20 d (1H, J_{HH} 3.6 Hz), 7.30 d (1H, J_{HH} 3.6 Hz) (H^3,H^4-furan). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 26.31 ($\underline{CH_3}CO$), 52.39 (CH_3O), 116.63 + 118.78 (C^{3,4}-furan), 146.21 (C^2-furan), 154.21 (C^5-furan), 158.55 (C=O-ester), 187.49 (C=O-ketone).

Ethyl 3-(5-acetylfur-3-yl)acrylate (VI). A mixture of 9.5 g of 3-(2-furyl)acrylate, 8.1 mL of acetic

anhydride, and 0.6 g of anhydrous magnesium perchlorate was heated under vigorous stirring during 1.5 h at 127–128°C. The reaction progress was monitored via TLC (Silufol plates, 1 : 1 acetone-chloroform, R_f of the starting substance 0.8). After the reaction was complete, the mixture was poured in 100 mL of water, extracted with toluene (3 × 50 mL), and dried over calcium chloride. After removal of toluene, the residue was distilled under vacuum. Yield of compound **VI** 4.5 g (38%), light-yellow crystals, mp 68°C, bp 125–127°C (1 mmHg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.32 t (3H, CH_3-ethyl, J_{HH} 7.0 Hz), 2.24 s (3H, CH_3-acetyl), 4.34 q (2H, CH_2O, J_{HH} 7.0 Hz), 6.25 d (1H, H^2-acrylic, J_{HH} 14.0 Hz), 6.53 br.s (1H, H^3-furan), 6.96 br.s (H^4-furan), 7.17 d (1H, H^3-acrylic, J_{HH} 14.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.89 (CH_3-ester), 25.33 (CH_3-ketone), 60.40 (CH_2O), 115.49 (C^3-furan), 118.27 (C^4-furan), 119.82 (C^2-acrylic), 129.80 (C^3-acrylic), 152.79 (C^2-furan), 153.27 (C^5-furan), 165.67 (C=O-ester), 186.12 (C=O-ketone).

ACKNOWLEDGMENTS

The work was in scope of the governmental contract; financial support of Ministry of Education and Science of Russian Federation is acknowledged.

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