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Mendeleev Commun., 2023, **33**, 11–13

Mendeleev
Communications

Synthesis of substituted furan-3-carboxylates from alkyl 3-bromo-3-nitroacrylates

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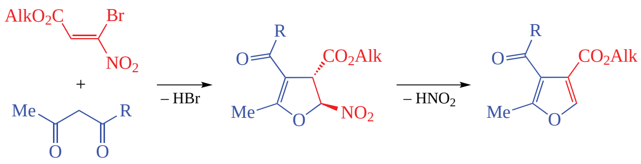
DOI: 10.1016/j.mencom.2023.01.003

Carbonyl-containing furan-3-carboxylates were obtained by the refluxing of alkyl 3-bromo-3-nitroacrylates and acyclic CH-acids, namely, pentane-2,4-dione and alkyl 3-oxobutanoates in methanol in the presence of equimolar amounts of potassium acetate. The products can be prepared by the similar processing of 2-nitro-2,3-dihydrofuran-3-carboxylates being the intermediates in the total transformation.



Keywords: nitroacrylates, 1-halo-1-nitroethenes, CH-acids, acetylacetone, alkyl acetoacetates, 2,3-dihydrofurancarboxylates, furan-carboxylates, heterocyclization.

Substituted furan-3-carboxylates possess various biological activities.[1,2] For example, methyl 4,5-diethyl-2-(3-methoxy-3-oxopropyl)furan-3-carboxylate inhibits insulin secretion[1] while alkyl 5-aryl-2-methyl-4-(2-oxo-2-aryl)furan-3-carboxylates manifest antiparasitic activity.[2]

α-Chloro ketones,[3–6] β-dicarbonyl compounds,[1,7–11] dialkyl acetylenedicarboxylates[12–16] and allene esters[17–19] have been used most often in the syntheses of substituted furan-3-carboxylates.[20] At the same time, it is known that the reaction of *gem*-halonitroalkenes with acyclic CH-acids gives substituted 2-nitro-2,3-dihydrofurans.[21,22] In turn, we have shown that alkyl 3-bromo-3-nitroacrylates[23] containing the *gem*-bromo-nitroethene moiety in the molecule were the convenient starting reagents for the synthesis of fused furan-3-carboxylates in the reactions with cyclic CH-acids.[24,25]

In continuation of studies on the synthetic potential of alkyl 3-bromo-3-nitroacrylates **1a**,**b**, we suggest herein a method for the synthesis of 2-nitro-2,3-dihydrofuran-3-carboxylates **2a–f** and furan-3-carboxylates **3a–f** on their basis (Scheme 1). The reaction of alkyl 3-bromo-3-nitroacrylates **1a**,**b** with pentane-2,4-dione or alkyl 3-oxobutanoates occurs in anhydrous methanol solution at room temperature in the presence of an equimolar amount of potassium acetate to give 2-nitro-2,3-dihydrofuran-3-carboxylates **2a–f** in 67–83% yields.[†] The enolate anion of Michael adduct **A** formed initially undergoes intramolecular O-alkylation with the bromonitromethyl group in the course of the reaction. In turn, the reaction performed by refluxing in anhydrous methanol solution with the ratio bromonitro-acrylate : CH-acid : AcOK = 1 : 1 : 2 gives substituted furan-3-carboxylates **3a–f** in 57–80% yields (see Scheme 1, method A).[‡] At the same time, 2-nitro-2,3-dihydrofuran-3-carboxylates **2d**,**f** eliminate HNO$_2$ on refluxing in the presence of equimolar amounts of potassium acetate in anhydrous methanol to afford furan-3-carboxylates **3d**,**f** in 65% yield (see Scheme 1, method B). Products **2**, **3** appeared mostly as light yellow oils while compound **3a** was obtained as light yellow crystals. It should be noted that furans **3a**,**b**,**d**,**f** were previously obtained by a different method[7,26–28] and compound **3a** was characterized as an oil.[26]

The structures of heterocycles **2**,**3** were confirmed by ^{1}H, ^{13}C–{^{1}H}, ^{1}H–^{1}H dqf-COSY, ^{1}H–^{13}C HMQC, HMBC NMR and IR spectroscopy. In the ^{1}H NMR spectra of compounds **2a–f** the vicinal protons C^{2}H (δ 6.09–6.12, ^3J = 2.0–2.1 Hz) and C^{3}H form an *AMX*-type spin system with methyl group protons at the C^5 carbon atom (δ 2.40–2.41, ^5J = 1.4–1.5 Hz). The signal from the C^{3}H proton, due to long-range spin–spin coupling with methyl protons at the C^5 atom, is manifested in the ^{1}H NMR spectra of compounds **2a**,**b**,**d** as a multiplet in the region of δ 4.31–4.39, and in the spectra of compounds **2c**,**e**,**f** as a doublet of quartets at δ 4.31–4.33 (^3J = 2.1, ^5J = 1.5 Hz). This assignment

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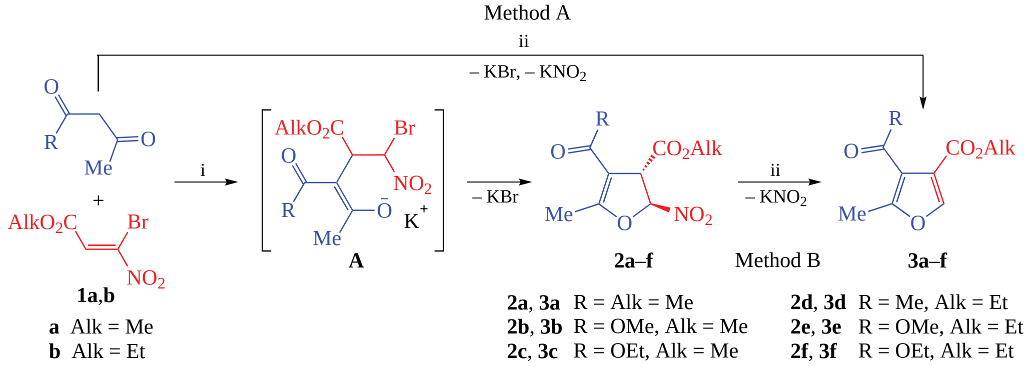
[†] *General procedure for the synthesis of alkyl 4-acetyl(alkoxycarbonyl)-2,3-dihydro-5-methyl-2-nitrofuran-3-carboxylates* **2**. A solution of the corresponding 3-bromo-3-nitroacrylate **1** (1.43 mmol) in anhydrous methanol (5 ml) was added dropwise to a solution of pentane-2,4-dione or alkyl 3-oxobutanoate (1.43 mmol) and fused potassium acetate (140 mg, 1.43 mmol) in anhydrous methanol (5 ml). The resulting mixture was stirred at 18–20 °C for 1 h. The solvent was evaporated and the oily residue was chromatographed on silica gel using CHCl$_3$ as the eluent. Product **2** was isolated as a light-yellow oil.

[‡] *General procedure for the synthesis of alkyl furan-3-carboxylates* **3** *(method A)*. A solution of the corresponding 3-bromo-3-nitroacrylate (0.95 mmol) in anhydrous methanol (4 ml) was added dropwise to a solution of pentane-2,4-dione or alkyl 3-oxobutanoate (0.95 mmol) and fused potassium acetate (187 mg, 1.91 mmol) in anhydrous methanol (4 ml). The mixture was refluxed for 1 h. The solvent was evaporated and the oily residue was chromatographed on silica gel using CHCl$_3$ as the eluent. Product **3** was isolated as a light yellow-oil (or light-yellow crystals of **3a**).

In method B, a solution of compound **2d** or **2f** (0.366 mmol) and fused AcOK (36 mg, 0.366 mmol) in MeOH (4 ml) was refluxed for 2–4 h. The solvent was evaporated and the oily residue was chromatographed on silica gel using CHCl$_3$ as the eluent to afford product **3d** or **3f**.



Scheme 1 *Reagents and conditions*: i, AcOK, MeOH, 18–20 °C, 1 h; ii, AcOK, MeOH, reflux, 1 h (method A) or 2–4 h (method B).

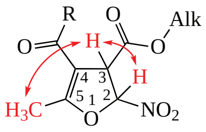


Figure 1 Main correlations in the ^{1}H–^{1}H dqf-COSY spectra of compounds **2d**,**f**.

agrees with the results of ^{1}H–^{1}H dqf-COSY experiments obtained for compounds **2d**,**f** (Figure 1).

The value of spin–spin coupling constant $^3J_{H(2)H(3)}$ being 2.0–2.1 Hz observed in the ^{1}H NMR spectrum of compounds **2a–f** indicates their transoid arrangement, in agreement with literature data.[22,25,29] The carbon atom signals in compounds **2**, **3** were assigned using ^{1}H–^{13}C HMQC and HMBC NMR experiments (the main correlations of non-protonated carbon atoms in the ^{1}H–^{13}C HMBC NMR spectrum of compound **2d** are provided in Online Supplementary Materials). The IR spectra of compounds **2a–f** manifest absorption bands of the non-conjugated nitro group at 1575–1576 cm^{-1} (ν_{as}) and 1366–1370 cm^{-1} (ν_s) with a characteristic difference ($\Delta\nu$ 200–210 cm^{-1}).[30] Moreover, the absorption bands of the ester moiety in the IR spectra of compounds **2**, **3a–f** are observed in the region of 1712–1746 cm^{-1}, while the carbonyl group of the acetyl moiety in the spectra of compounds **2**, **3a**,**d** gives an absorption band at 1679–1689 cm^{-1}.

Crystalline furan-3-carboxylate **3a** was studied by single-crystal X-ray diffraction analysis (Figure 2).[§]

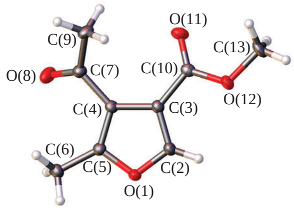


Figure 2 Geometry of methyl 4-acetyl-5-methylfuran-3-carboxylate **3a** molecule in a crystal. The anisotropic displacement ellipsoids are shown at 50% probability level.

As expected, the furan ring including the key substituent atoms is planar. Only a slight rotation of planar moieties of substituents at C(3) and C(4) atoms is observed [the C(3)–C(4)–C(7)–C(9) and C(2)–C(3)–C(10)–O(12) torsion angles are –34.8(2) and –16.0(2)°, respectively]. The bond lengths and bond angles in molecule **3a** have values typical of the furan ring and the acetyl and carboxyl moieties. In the absence of proton-donating substituents in the molecule, the crystal packing of compound **3a** is determined by numerous C–H···O hydrogen bonds and short H···H-type contacts (Figure 3), that is, relatively weak intermolecular interactions. Probably, the difficult crystallization of compound **3a** and the low melting point of the crystals are caused by these weak interactions between the molecules. Due to stronger C–H···O interactions, double layers are formed in the crystal that are bound to each other only by van der Waals dispersion interactions (Figure 3).

In summary, we suggested methods for the synthesis of 2-nitro-2,3-dihydrofuran-3-carboxylates and the corresponding furan-3-carboxylates using the reaction of alkyl 3-bromo-3-nitroacrylates with representatives of acyclic CH-acids. The structure of methyl 4-acetyl-5-methylfuran-3-carboxylate

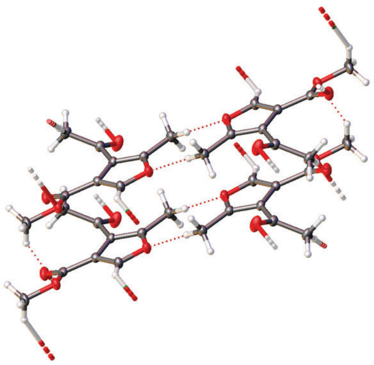


Figure 3 A fragment of **3a** crystal packing. The projection along axis *c*. Short contacts are shown by dotted lines.

[§] *Crystal data for* **3a**. Crystals of **3a**, mp 62–64 °C, $C_9H_{10}O_4$, M = 182.17, were obtained by slow evaporation of a hexane solution; monoclinic. At 105 K: a = 3.7735(5), b = 29.786(4) and c = 7.7343(11) Å, β = 98.255(5)°, V = 860.3(2) Å^3, Z = 4, d_{calc} = 1.406 g cm^{-3}, space group $P2_1/n$, μMo 0.111 mm^{-1}. The data were obtained on a Bruker D8 QUEST diffractometer (graphite monochromator, MoK$_\alpha$ radiation, λ = 0.71073 Å). The intensities of 24393 reflections were measured, 1774 of which were independent (R_{int} = 0.150) and 1278 were observed with $I \geqslant 2\sigma(I)$. The recording ranges were: θ = 2.7–26.5°, reflection indices: h –4: 4; k –37: 37; l –9: 9. Semi-empirical corrections for absorption were performed in the SADABS program.[31] The structure was solved by the direct method using the SHELXT program.[32] Non-hydrogen atoms were refined in isotropic and then in anisotropic approximation using the SHELXL program.[33] Hydrogen atoms were placed in the calculated positions and refined using the riding model. All calculations were performed using the WinGX[34] and APEX2[35] programs. Analysis of intermolecular contacts in the crystal and the drawings were performed using the PLATON[36] and MERCURY[37] programs. The final divergence factors were R = 0.0358, R_w = 0.0917 for the observed reflections with $I \geqslant 2\sigma(I)$, and R = 0.0540, R_w 0.0950 for all the 1774 reflections. The goodness-on-fit was 0.920; the residual electron density extremums were –0.206 and 0.279 e Å^{-3}.

CCDC 2178613 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

isolated in crystalline form was characterized by single crystal X-ray diffraction analysis.

This study was performed as part of a state assignment with financial support from the Ministry of Education of the Russian Federation (project no. FSZN-2020-0026). The X-ray diffraction study was financially supported within the framework of the state assignment for the Federal Research Center ‘Kazan Scientific Center of the Russian Academy of Sciences’.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.01.003.

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Received: 17th June 2022; Com. 22/6930