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Synthesis of 1-Benzofuran-2-carboxylates by Reaction of 1-Benzofuran with Halomethanes and Alcohols in the Presence of Iron Compounds

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Abstract—Alkyl 1-benzofuran-2-carboxylates were obtained in quantitative yield by reaction of 1-benzofuran with halomethanes and alcohols in the presence of iron-containing catalysts both in the presence and in the absence of radical initiators.

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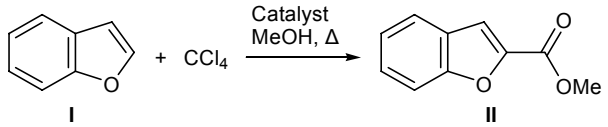
1-Benzofuran-2-carboxylic acid and its derivatives are widely used as starting compounds in the synthesis of pharmaceuticals. For example, alkyl and aryl 1-benzofuran-2-carboxylates are initial compounds for the preparation of inhibitors of leukotriene biosynthesis and are used for the treatment of asthma, allergy, and cardiovascular and skin diseases [1, 2]. 3-Benzofuryl-4-phenyl(allyl)-1,2,4-triazole-5-thiols obtained by cyclization of substituted 1-benzofuran-2-carboxylic acid thiosemicarbazides were found to exhibit antitumor activity [3]. 1-Benzofuran-2-carboxylic acid was used to synthesize cathepsin K inhibitors (azepanone and methylazepanone) [4], neurokinin 2 (NK2) receptor antagonist [5], dopamine (endogenous ligand for dopamine receptors) [6], and chromans [7].

Most known methods for the synthesis of 1-benzofuran-2-carboxylic acid and its derivatives are based on metalation of benzofuran, followed by carbonylation of intermediate metalated derivative [8–13]. The goal of the present work was to obtain 1-benzofuran-2-carboxylic acid esters according to a novel procedure, which was successfully tested with 2-acetylfuran as substrate [14]. Following this procedure, alkoxycarbonyl group is introduced into 2-acetylfuran molecule via conjugate reaction with participation of the heterocyclic substrate, carbon tetrachloride, and methanol in the presence of iron-containing catalyst.

We have found that analogous transformation successfully occurs with benzofuran **I**. Compound **I** reacts with CCl_4 and methanol in the presence of iron catalyst to give methyl 1-benzofuran-2-carboxylate (**II**) (Scheme 1). Among the examined iron-containing compounds, $Fe(acac)_3$, $Fe(C_5H_5)_2$, $FeBr_2$, and $Fe(OAc)_2$ showed the highest catalytic activity. The reactions were carried out at 140–160°C and were complete in 4–6 h (100% conversion of initial benzofuran **I**) with selective formation of ester **II** (Table 1).

Scheme 1.



I **II**

Catalyst = Fc, $Fe(acac)_3$, $FeBr_2$, $Fe(OAc)_2$.

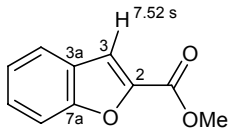
It is known [15] that carbon atoms in the benzene and furan rings of benzofuran molecule are characterized by similar reactivities; therefore, formation of a mixture of regioisomeric benzofurancarboxylic acids may be expected. The examined reaction ensures high regioselectivity, and ester **II** is formed as the only product. Its structure was determined by NMR spectroscopy using one- (^1H, ^{13}C) and two-dimensional homo- (COSY) and heteronuclear correlation techniques (HSQC, HMBC). The position of the ester group in the benzofuran system was identified on the basis of the chemical shift of the quaternary C^2 atom (δ_C 145.37 ppm against δ_C 113.98 ppm for C^3H). The 3-H proton resonated in the ^1H NMR spectrum as

Table 1. Reaction of 1-benzofuran (**I**) with carbon tetrachloride and methanol in the presence of iron-containing catalysts

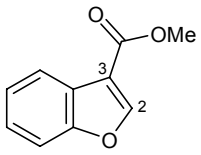
Ratio catalyst–**I**–CCl_4–MeOH	Catalyst	Temperature, °C	Reaction time, h	Conversion, %	Yield of ester **II**,[a] %
1:100:200:800	Fc	140	6	80	93
1:100:200:800	Fc	150	6	90	95
1:100:700:1000	Fc	150	6	98	96
1:100:800:1000	Fc	150	6	98	97
1:100:750:1000	Fc	150	6	98	97
1:100:750:1100	Fc	150	6	100	98
1:100:750:1200	Fc	150	6	100	98
1:100:750:1100	$FeBr_2$	150	6	100	98
1:100:750:1100	Fc	160	4	100	98
1:100:750:1100	$Fe(acac)_3$	160	4	100	99
1:100:750:1100	$FeBr_2$	160	4	100	99
1:100:750:1100	$Fe(OAc)_2$	160	4	100	99

[a] Calculated on the reacted substrate.

a singlet at δ 7.52 ppm, and it showed correlations in the HMBC spectrum with C^{3a} (δ_C 126.90 ppm) and C^2 (δ_C 145.37 ppm), as well as with C^{7a} (δ_C 155.69 ppm). Alternative structure of methyl 1-benzofuran-3-carboxylate (**II′**) should be characterized by upfield signal from the quaternary carbon atom (C^3, δ_C 111.79 ppm) and downfield signal from C^2H (δ_C 152.5 ppm) [16], which are not observed in the experimental ^{13}C NMR spectrum.



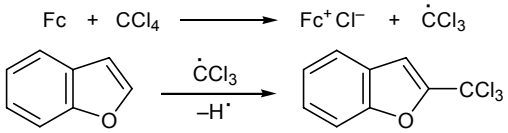
II



II′

It is known that reaction of ferrocene with carbon tetrachloride generates trichloromethyl radical [17] which can attack benzofuran molecule with formation of trichloromethyl derivative (Scheme 2). The latter is then converted into ester **II** via reaction with methanol. This assumption is confirmed by the fact that replacement of methanol by ethanol or propan-1-ol leads to the formation of, respectively, ethyl and propyl esters **III** and **IV** (yield 92 and 95%). At a ferrocene–benzofuran–CCl_4–ROH molar ratio of 1:100:750:1100 (160°C, 8 h), the yields of the corresponding esters ranged from 92 to 98%. Hydrogen chloride and ethers ROR were formed as by-products.

Scheme 2.



With a view to elucidate whether the examined reaction follows a radical mechanism or not, it was carried out in the presence of galvinoxyl which is known as an effective radical scavenger. However, the inhibitory effect of galvinoxyl was insignificant; presumably, it undergoes deactivation at elevated temperature. Replacement of carbon tetrachloride by more active bromine-containing halomethanes, such as CBr_4 and $CBrCl_3$ allowed us to reduce the temperature to 130–140°C, the high yield of ester **II** being retained (Table 2). In the ferrocene-catalyzed reaction of benzofuran **I** with CBr_4 and MeOH in the presence of galvinoxyl (molar ratio Fc–galvinoxyl–**I**–CBr_4–MeOH 1:5:100:200:1100) the conversion of initial compound **I** at 130°C in 4 h was 88%, and the yield of methyl 1-benzofuran-2-carboxylate (**II**) decreased from 95 to 87%. We then examined the effect of such radical initiators as TEMPO, AIBN, $(BzO)_2$, and H_2O_2 (34% aqueous solution) on the process (Table 3). In the presence of radical initiators the optimal temperature decreased to 100°C. Under these conditions, but in the

Table 2. Reaction of 1-benzofuran (**I**) with bromomethanes and methanol in the presence of ferrocene (reaction time 4 h)

Ratio catalyst–**I**–halomethane–MeOH	Halomethane	Temperature, °C	Conversion, %	Yield of ester **II**,[a] %
1:100:200:1100	CBr_4	140	100	98
1:100:750:1100	$CBrCl_3$	140	96	89
1:100:200:1100	CBr_4	130	96	98

[a] Calculated on the reacted substrate.

Table 3. Reaction of 1-benzofuran (**I**) with tetrabromomethane and methanol in the presence of ferrocene and radical initiators (100°C, 9 h)

Ratio catalyst–initiator–**I**–CBr_4–MeOH	Initiator	Conversion of **I**, %	Yield of ester **II**,[a] %
1:5:100:200:1100	TEMPO	98	92
1:5:100:200:1100	AIBN	94	98
1:5:100:200:1100	$(PhCOO)_2$	86	98
1:5:100:200:1100	H_2O_2	88	98
1:10:100:200:1100	H_2O_2	95	99

[a] Calculated on the reacted substrate.

absence of iron catalyst (molar ratio H_2O_2–**I**–CBr_4–ROH 5:100:750:1100), the yield of ester **II** did not exceed 5%.

An additional evidence in support of the radical mechanism of the process is the presence in the reaction mixture of Fe(II)/Fe(III) redox system. The oxidation of Fe(II) to Fe(III) was detected by titration of the reaction mixture with $K_3[Fe(CN)_6]$ and $K_4[Fe(CN)_6]$ solutions. The redox couple Fe(II)/Fe(III) was also formed when $Fe(acac)_3$ was used as catalyst. Methanol is likely to ensure the reduction of Fe(III) to Fe(II). Examples of reduction of Fe(III) to Fe(II) with alcohols have been reported; the latter are thus oxidized to aldehydes [18, 19].

To conclude, we have proposed a procedure for the synthesis of methyl, ethyl, and propyl 1-benzofuran-2-carboxylates in quantitative yield by reaction of 1-benzofuran with halomethanes and the corresponding alcohols in the presence of iron catalysts. Addition of radical initiators makes it possible to reduce the reaction temperature, which suggests radical mechanism of the process.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400.13 and 100.62 MHz, respectively, using $CDCl_3$ as solvent; the chemical shifts were measured relative to tetramethylsilane. The mass spectra were obtained on a Shimadzu GCMS-QP2010Plus instrument (SPB-5 capillary column, 30 m × 0.25 mm; carrier gas helium; oven temperature programming from 40 to 300°C at a rate of 8 deg/min; injector temperature 280°C, ion source temperature 200°C; electron impact, 70 eV). Chromatographic analysis was performed on Shimadzu GC-9A and GC-2014 instruments (2000 × 3-mm column, stationary phase 5% of SE-30 on Chromaton N-AW-HMDS, oven temperature programming from 50 to 270°C at a rate of 8 deg/min; carrier gas helium, flow rate 47 ml/min). The elemental compositions were determined on a Carlo Erba 1106 analyzer.

Commercially available 1-benzofuran, methanol, ethanol, propan-1-ol, carbon tetrachloride, carbon tetrabromide, and bromotrichloromethane were preliminarily purified by distillation or recrystallization. Iron-containing catalysts [$Fe(acac)_3$, $Fe(OAc)_2$, $Fe(C_5H_5)_2$, and $FeBr_2$], radical initiators [TEMPO, AIBN, $(PhCOO)_2$, and H_2O_2], and galvinoxyl (radical scavenger) were commercial products.

The reactions were carried out in a 10-ml glass ampule placed into a 17-ml stainless-steel high-pressure reactor under continuous stirring and controlled heating.

Alkyl 1-benzofuran-2-carboxylates II–IV (*general procedure*). An ampule was charged under argon with 1 mmol of iron-containing catalyst, 0–10 mmol of radical initiator, 100 mmol of 1-benzofuran, 750 mmol of halomethane, and 1100 mmol of alcohol. The ampule was sealed and placed into a high-pressure reactor, and the reactor was sealed and heated for 4–9 h at 100–160°C under continuous stirring. When the reaction was complete, the reactor was cooled to room temperature, the ampule was opened, the reaction mixture was filtered through a layer of silica gel (2 g), and the sorbent was washed with ethyl acetate. The solvent was distilled off, and the residue was recrystallized from aqueous methanol (compound **II**) or distilled under reduced pressure (**III**, **IV**).

The structure of esters **II–IV** was proved by NMR and mass spectrometry, as well as by comparing with authentic samples and reference data.

Methyl 1-benzofuran-2-carboxylate (II). Yield 99%, mp 49.5–50°C; published data: mp 52°C [20], 52–53°C [21]. ^{1}H NMR spectrum, δ, ppm: 3.96 s (3H, OCH_3), 7.30 t (1H, J = 8 Hz), 7.44 t (1H, J = 7.6 Hz), 7.52 s (1H), 7.58 d (1H, J = 8 Hz), 7.67 d (1H, J = 10.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 52.35 (CH_3), 112.32 (C^7), 113.98 (C^3), 122.83 (C^4), 123.8 (C^5), 126.9 (C^{3a}), 127.66 (C^6), 145.37 (C^2), 155.69 (C^{7a}), 159.95 (C=O). Mass spectrum, m/z (I_{rel}, %): 176 (63) $[M]^+$, 145 (100), 118 (11), 89 (41), 63 (15), 44 (2). Found, %: C 68.20; H 4.57; O 27.23. $C_{10}H_8O_3$. Calculated, %: C 68.18; H 4.55; O 27.27. M 176.13.

Ethyl 1-benzofuran-2-carboxylate (III). Yield 92%, bp 106–107°C (2 mm); published data [22]: bp 274°C (720 mm). ^{1}H NMR spectrum, δ, ppm: 1.40 t (3H, $CH_2C\mathbf{H}_3$, J = 7.2 Hz), 4.40 q (2H, OCH_2, J = 7.2 Hz), 7.29 t (1H, J = 7.2 Hz), 7.44 t (1H, J = 7.2 Hz), 7.52 s (1H), 7.59 d (1H, J = 8 Hz), 7.67 d (1H, J = 7.6 Hz) [23, 24]. ^{13}C NMR spectrum, δ_C, ppm: 14.32 (CH_3), 61.48 (CH_2), 112.33 (C^7), 113.76 (C^3), 122.78 (C^4), 123.74 (C^5), 126.96 (C^{3a}), 127.54 (C^6), 145.71 (C^2), 155.68 (C^{7a}), 159.57 (C=O). Found, %: C 69.60; H 5.04; O 25.36. $C_{11}H_{10}O_3$. Calculated, %: C 69.40; H 5.26; O 25.24.

Propyl 1-benzofuran-2-carboxylate (IV). Yield 95%, bp 80–82°C (0.2 mm). ^{1}H NMR spectrum, δ, ppm: 1.05 t (3H, $CH_2C\mathbf{H}_3$, J = 7.6 Hz), 1.70–1.90 m (2H, $C\mathbf{H}_2CH_3$), 4.35 t (2H, OCH_2, J = 6.8 Hz), 7.30 t (1H, J = 7.2 Hz), 7.44 t (1H, J = 7.2 Hz), 7.53 s (1H), 7.61 d (1H, J = 8.4 Hz), 7.68 d (1H, J = 7.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 10.37 (CH_3), 22.08 ($\mathbf{C}H_2CH_3$), 66.97 (OCH_2), 112.34 (C^7), 113.70 (C^3), 122.77 (C^4), 123.74 (C^5), 126.97 (C^{3a}), 127.53 (C^6), 145.71 (C^2), 155.71 (C^{7a}), 159.67 (C=O). Found, %: C 70.50; H 5.92; O 23.58. $C_{12}H_{12}O_3$. Calculated, %: C 70.57; H 5.93; O 23.50.

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