Chemistry of Heterocyclic Compounds, Vol. 42, No. 8, 2006

SYNTHESIS AND REDUCTION OF 5-HALO- AND 5-NITRO-1-(BENZOFURAN-3-YL)-2-PHENYLETHANONES

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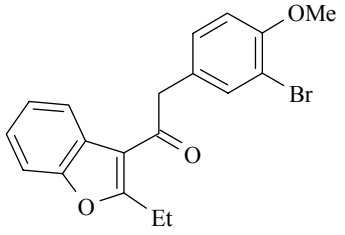
Novel 1-(2-alkylbenzofuran-3-yl)-2-(4-methoxyphenyl)ethanones having a halogen or nitro group in position 5 of the benzofuran ring were synthesized starting with the corresponding 2-(2-formylphenoxy)alkanoic acids. 1-(2-Alkylbenzofuran-3-yl)-2-phenylethanols containing bromine or chlorine atom were prepared in high yields by reduction of the corresponding ethanones with lithium aluminum hydride. Selective catalytic reduction of nitro 1-(2-alkylbenzofuran-3-yl)-2-(4-methoxyphenyl)ethanones to the corresponding amino compounds under Pd/C in room temperature was achieved.

Keywords: amines, benzofurans, ethanols, ethanones, acylation, reduction.

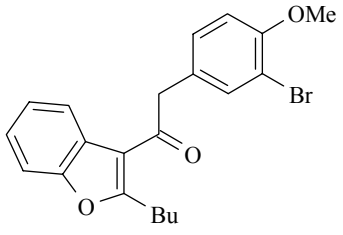
The benzofuran system occurs widely in natural substances and in a variety of synthetic products, which show pharmacological properties. Among synthetic compounds, derivatives of keto benzofurans have a particular importance. These compounds are useful as medicines, such as amiodarone and benziodarone, particulary for the treatment of pathological syndromes of the cardiovascular system, such as arrhythmia [1]. Several aminobenzofuran derivatives likewise exhibited a marked antiarrhythmic activity [2]. Moreover, benzofuranyl methanols have been reported as hypolipidemic agents [3], and a number of halogenated benzofuranylcarbinols have been developed as fungicides [4].

Recently, growing interest in developing synthetic methods for the synthesis of 5-aminobenzofuran derivatives was manifested due to their activity as antagonists of the cysteinyl leukotriene 2-receptor [5] and histamine H_3 receptor [6], and as antitumor agents [7].

As we previously reported (2-alkylbenzofuran-3-yl)-2-phenylethanones (**I** and **II**) having a bromine atom on the phenyl ring showed some fungicidal activity against *Phytophthora infestans* and *Botritis cinera* [8].



I



II

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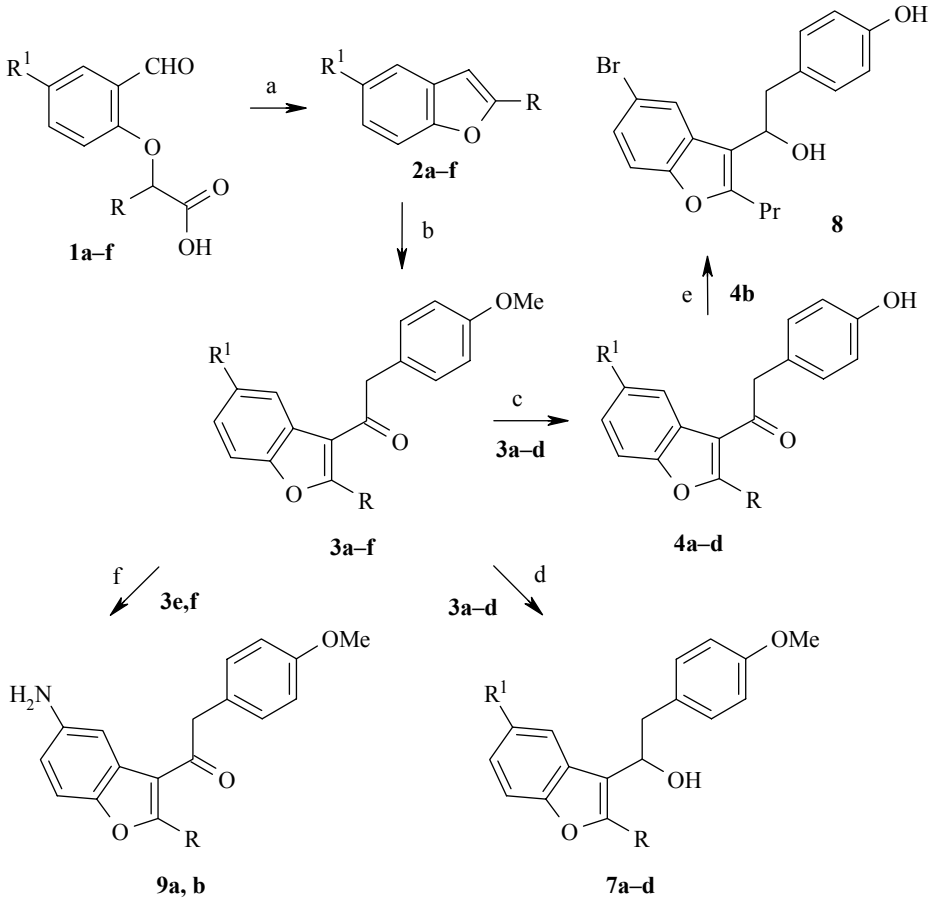
Continuing our research directly for novel phenylacetyl derivatives of benzofuran, herein we report efficient syntheses of the title 5-halo and 5-nitroethanones and their selective reduction to the corresponding halo ethanols and amines, respectively. The ethanols were considered as potential fungicidal agents. However, in view of the above literature reports, it was presumed that N-(2-chloroethyl) and N-acyl derivatives of 1-(5-aminobenzofuran-3-yl)-2-phenylethanones should be antitumor agents.

1-(2-Alkylbenzofuran-3-yl)-2-(4-methoxyphenyl)ethanones **3a-f** were prepared according to the synthetic Scheme 1. The designed compounds **1a-c** and **1e-f** were prepared from the corresponding 2-bromoesters and 5-bromo- or 5-nitrosalicylaldehydes according to the procedures reported by us previously [9, 10]. 2-(4-Chloro-2-formylphenoxy)butanoic acid **1d** was synthesized by the same method starting with 5-chlorosalicylaldehyde and methyl 2-bromobutanoate. Intramolecular cyclization of 2-(2-formyl-5-bromophenoxy)alkanoic acids **1a-c** to the corresponding 5-bromo-2-alkylbenzofurans **2a-c** was performed using an optimized excess of acetic anhydride and acetic acid [9]. Under these conditions 5-chloro-2-ethylbenzofuran **2d** was prepared in 70% yield by 7 h cyclization of 2-(4-chloro-2-formylphenoxy)butanoic acid (Experimental). Cyclization of 2-(2-formylphenoxy)alkanoic acids having a nitro group in position 5 easily afforded 2-alkyl-5-nitrobenzofurans which were obtained in good yield after 3 h reaction [10].

Scheme 1



1-4, 7 a R = Et, R^1 = Br, **b** R = Pr, R^1 = Br, **c** R = Bu, R^1 = Br, **d** R = Et, R^1 = Cl, **e** R = Et, R^1 = NO_2, **f** R = Pr, R^1 = NO_2; **9 a** R =Et, **b** R = Pr

Reagents and conditions: a) AcOH, $(AcO)_2O$, AcONa, reflux; b) $ClCOCH_2C_6H_4$-OMe-*p*, $AlCl_3$, $Cl(CH_2)_2Cl$, 5-15°C, 3-6 h; c) pyridine hydrochloride, reflux, 12 min; d,e) $LiAlH_4$, EtOEt, reflux; f) H_2/Pd/C, MeOH, reflux, 1.5 h

TABLE 1. Reaction of Benzofurans **2a-f** with 4-Methoxyphenacetyl Chloride

Starting benzofuran	Reaction time, h	Reaction temp., °C	Ethanone			
				mp, °C	Appearence	Yield, %
2a	3.0	5	**3a**	54-56	Pale beige needles	78
2b	3.0	5	**3b**	59-61	Pale beige crystals	82
2c	3.0	5	**3c**	62-63	Pale beige crystals	80
2d	3.0	5	**3d**	58-61	Pale beige flakes	76
2e	6.0	15	**3e**	98-100	Yellow needles	74
2f	6.0	15	**3f**	79-82	Yellow needles	76

Further Friedel–Crafts acylation of benzofurans **2a-f** with 4-methoxyphenylacetyl chloride was carried out in 1,2-dichloroethane in the presence of aluminum chloride. The studies to optimize this process were undertaken for each 5-halo- and 5-nitrobenzofuran. The reaction conditions shown in Table 1 (5°C temperature and 3 h reaction time) are sufficient to complete the acylation of benzofurans **2a-d**. In order to attain good yields of ethanones having a nitro group, **3e** and **3f**, a longer time (6 h) and somewhat higher temperature was required.

The structures of the novel ethanones **3a-f** were well characterized by GC/MS and ^{1}H NMR (Tables 2 and 3).

Next, the methoxyethanones **3a-d** were demethylated using an excess of pyridine hydrochloride, which resulted in the formation of the corresponding hydroxy compounds **4a-d** in yields of 60-72%. The optimum reaction time was determined as no longer than 10-12 min.

Reduction of the title ethanones **3a-d** was investigated using sodium boron hydride, lithium aluminum hydride, and H_2 over 10% Pd/C as a reducing agent. When the reduction was carried out with sodium boron hydride in methanol or alkaline aqueous methanol solution, no carbinols were obtained. However, palladium-catalyzed hydrogenation of ethanone **3b** in refluxing methanol resulted in the formation of a mixture of products: carbinol **5** and alkane **6**, both of them without a halogen atom (Scheme 2).

Scheme 2

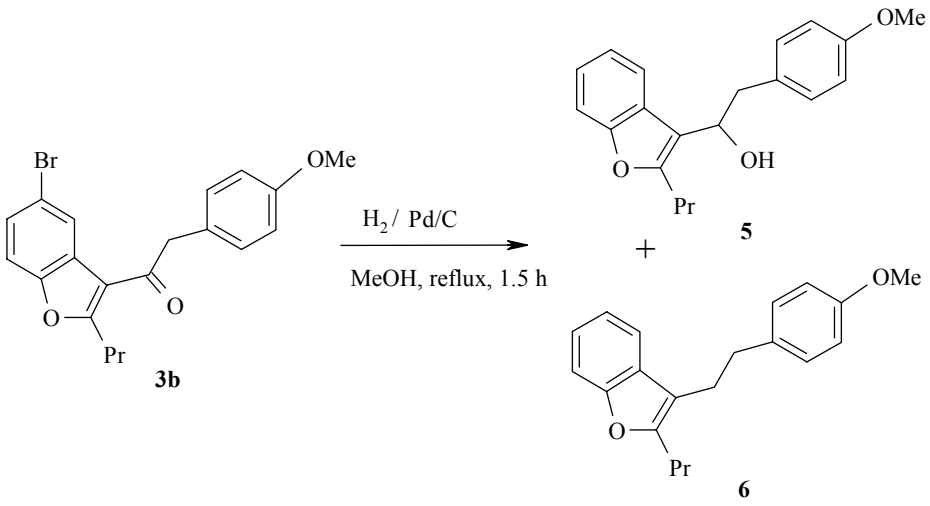


TABLE 2. GC/MS Mass Spectra of Compounds **3a-f, 4a,b, 7a-d, 8**

Com-pound	GC/MS, MS, *m/z* (I_{rel}, %)
3a	374 $[M + 2]^+$ (13), 251 (100), 208 (4), 189 (2), 172 (9), 144 (12), 121 (34), 101 (2), 78 (6), 51 (2)
3b	386 $[M]^+$ (24), 267 (100), 251 (2), 238 (4), 223 (1), 210 (7), 186 (10), 171 (25), 158 (6), 139 (1), 121 (52), 101 (5), 78 (6), 65 (2), 51 (2)
3c	402 $[M+2]^+$ (42), 279 (100), 251 (4), 237 (44), 222 (2), 209 (17), 185 (3), 171 (9), 158 (6), 144 (3), 121 (69), 102 (7), 78 (8), 65 (2), 51 (2)
3d	328 $[M]^+$ (72), 207 (100), 192 (10), 178 (5), 164 (13), 144 (10), 121 (81), 91 (5), 78 (9)
3e	339 $[M]^+$ (11), 218 (61), 202 (2), 188 (5), 172 (20), 121 (100), 91 (5), 77 (5)
3f	353 $[M]^+$ (8), 232 (65), 186 (26), 121 (100), 77 (9)
4a	360 $[M+2]^+$ (11), 281 (2), 251 (100), 236 (2), 222 (1), 208 (4), 187 (1), 173 (5), 157 (1), 144 (11), 129 (1), 115 (11), 101 (25), 77 (5), 64 (1), 51 (1)
4b	374 $[M+2]^+$ (85), 359 (2), 345 (12), 329 (32), 314 (4), 301 (12), 281 (5), 265 (100), 250 (72), 237 (10), 221 (18), 207 (15), 187 (16), 165 (22), 152 (2), 139 (5), 125 (6), 107 (18), 91 (3), 77 (8), 64 (2), 51 (4)
7a	356 $[M–18]^+$ (17), 253 (48), 174 (27), 159 (6), 146 (8), 122 (100), 107 (3), 91 (4), 77 (5)
7b	372 $[M+2–18]^+$ (21), 341 (10), 269 (90), 237 (5), 211 (45), 188 (35), 173 (33), 159 (18), 145 (6), 122 (100) 107 (3), 91 (4), 77 (6)
7c	384 $[M–18]^+$ (8), 341 (4), 281 (4), 253 (5), 239 (7), 202 (9), 173 (30), 159 (10), 144 (4), 122 (100), 77 (4)
7d	312 $[M–18]^+$ (14), 209 (3), 174 (30), 159 (7), 122 (100), 107 (4), 77 (4)
8	374 $[M]^+$ (14), 358 (45), 327 (31), 313 (24), 267 (8), 237 (100), 209 (14), 189 (5), 165 (5), 152 (4), 131 (6), 107 (21), 94 (3), 77 (5)

GC/MS analysis showed a mixture consisting of 1-(2-propylbenzofuran-3-yl)-2-(4-methoxyphenyl)ethanol **5** (43%), 3-(4-methoxystyryl)-2-propylbenzofuran (40%), mass spectrum, *m/z* (I_{rel}, %): 292 $[M]^+$ (100), 263 (51), 249 (12), 231 (35), 218 (11), 202 (8), 189 (7), 165 (4), 146 (35), 131 (65), 115 (30), 101 (2) and 3-(4-methoxyphenethyl)-2-propylbenzofuran **6** (16%), mass spectrum, *m/z* (I_{rel}, %): 294 $[M]^+$ (50), 173 (100), 158 (4), 145 (18), 121 (66), 91 (3), 77 (4). In the ^{1}H NMR spectrum of the product 3-(4-methoxystyryl)-2-propylbenzofuran was not observed; thus it was the result of the dehydration process carried out during the GC/MS analysis. Studies to optimize this process were undertaken, and a variety of quantities of catalyst and reaction temperature was examined, but these conditions did not prove to be effective.

The selective reductions of ethanones **3a-d** were most effective when lithium aluminum hydride in refluxing diethyl ether was used, and the desired ethanols **7a-d** were prepared in practically quantitative yields. No hydrogenolysis of the carbon-halogen bond was observed when a proper excess of lithium aluminum hydride was used. All benzofuranyl ethanols were obtained as analytically pure semisolids without purification. The GC/MS spectrum of the crude product showed one compound, the M^+ ion of which corresponded to an alkene forming by dehydration of carbinol during analysis. The hydroxide proton appeared in the ^{1}H NMR as a broad singlet within the range of δ 1.9-2.2 and the methine proton (CH_2–CH–OH) as a triplet at ~4.9 ppm.

Reduction of 1-(5-bromo-2-propylbenzofuran-3-yl)-2-(4-hydroxyphenyl)ethanone **4b** carried out in the same conditions as the methoxy derivative led to the appropriate carbinol in the form of a yellow semisolid (Scheme 1). The ^{1}H NMR spectrum of the product showed both hydroxy (δ 2.19) and phenol protons (δ 5.88 ppm). After recrystallization from methanol a low melting yellow solid (mp 30°C) was obtained, and its color changed to violet during drying on air. On the other hand, the palladium-catalyzed reduction of nitro ethanones **3e** and **3f** with hydrogen led to the appropriate amines in excellent yields when it was carried out in methanol at room temperature. The novel amines **9a** and **9b** were obtained as analytically pure yellow crystals after recrystalization of the crude product from methanol.

TABLE 3. ^{1}H NMR Spectral Data ($CDCl_3$/TMS) of Compounds **3a-f**, **4a-d**, **7a-d** and **8**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
3a	8.13 (1H, d, *J* = 1.6, Ar); 7.42 (1H, dd, *J* = 8.7, 1.6, Ar); 7.34 (1H, d, *J* = 8.7, Ar); 7.16 (2H, d, *J* = 8.5, Ar); 6.90 (2H, d, *J* = 8.5, Ar); 4.19 (2H, s, CH_2); 3.80 (3H, s, OCH_3); 3.17(2H, q, *J* = 7.5, CH_2); 1.34 (3H, t, *J* = 7.5, CH_3)
3b	8.13 (1H, s, Ar); 7.40 (1H, d, *J* = 8.6, Ar); 7.33 (1H, d, *J* = 8.6, Ar); 7.15 (2H, d, *J* = 8.3, Ar); 6.89 (2H, d, *J* = 8.3, Ar); 4.19 (2H, s, CH_2); 3.80 (3H, s, OCH_3); 3.11 (2H, t, *J* = 7.5, CH_2); 1.82-1.76 (2H, m, CH_2); 0.99 (3H, t, *J* = 7.3, CH_3)
3c	8.12 (1H, d, *J* = 1.8, Ar); 7.39 (1H, dd, *J* = 8.6, 1.8, Ar); 7.32 (1H, d, *J* = 8.6, Ar); 7.15 (2H, d, *J* = 8.6, Ar); 6.88 (2H, d, *J* = 8.6, Ar); 4.18 (2H, s, CH_2); 3.79 (3H, s, OCH_3); 3.13 (2H, t, *J* = 7.6, CH_2); 1.77-1.69 (2H, m, CH_2); 1.44-1.35 (2H, m, CH_2); 0.93 (3H, t, *J* = 7.4, CH_3)
3d	7.97 (1H, d, *J* =2.1, Ar); 7.39 (1H, d, *J* =8.7, Ar); 7.25-7.28 (1H, m, Ar); 7.14-7.17 (2H, m, Ar); 6.87-6.91 (2H, m, Ar); 4.19 (2H, s, CH_2); 3.80 (3H, s, OCH_3); 3.18 (2H, q, *J* = 7.5, CH_2); 1.34 (3H, t, *J* = 7.5, CH_3)
3e	8.83 (1H, s, Ar); 8.13 (1H, d, *J* = 8.8, Ar);7.45 (1H, d, *J* = 8.8, Ar);7.09 (2H, d, *J* = 7.8, Ar); 6.81 (2H, d, *J* = 7.8, Ar); 4.16 (2H, s, CH_2); 3.71 (3H, s, OCH_3); 3.14 (2H, q, *J* = 7.2, CH_2); 1.29 (3H, t, *J* = 7.5, CH_3)
3f	8.92 (1H, d, *J* = 2.2, Ar); 8.24 (1H, m, Ar); 7.55 (1H, m, Ar); 7.18 (2H, d, *J* = 8.6, Ar); 6.90 (2H, m, Ar); 4.26 (2H, s, CH_2); 3.80 (3H, s, OCH_3); 3.71 (2H, t, *J* = 7.6, CH_2); 1.83 (2H, q, *J* = 7.5, CH_2); 1.02 (3H, t, *J* = 7.4, CH_3)
4a	8.12 (1H, d, *J* = 1.6, Ar); 7.42 (1H, dd,*J* = 8.7, 1.6, Ar);7.37 (1H, d, *J* = 8.7, Ar); 7.10 (2H, d, *J* = 8.2, Ar); 6.80 (2H, d, *J* = 8.2, Ar); 5.05 (1H, br. s, OH); 4.18 (2H, s, CH_2); 3.18 (2H, q, *J* = 7.5,CH_2),1.34 (3H, t, *J* = 7.5, CH_3)
4b	8.12 (1H, d, *J* = 1.6, Ar); 7.42 (1H, dd,*J* = 8.6,1.6, Ar); 7.33 (1H, d, *J* = 8.6, Ar); 7.08 (2H, d, *J* = 8.4, Ar); 6.78 (2H, d, *J* = 8.4, Ar); 5.35 (1H, s, OH);4.18 (2H, s, CH_2); 3.12 (2H, t, *J* = 7.5, CH_2); 1.84-1.75 (2H, m, CH_2); 0.99 (3H, t, *J* = 7.5, CH_3)
4c	8.11 (1H, s, Ar); 7.41 (1H, d, *J* = 8.5, Ar); 7.33 (1H, d, *J* = 8.5, Ar); 7.07 (2H, d, *J* = 7.7, Ar); 6.78 (2H, d, *J* = 7.7, Ar); 5.43 (1H, s, OH); 4.18 (2H, s, CH_2); 3.14 (2H, t, *J* = 7.5, CH_2); 1.76-1.70 (2H, m, CH_2); 1.42-1.37 (2H, m, CH_2); 0.93 (3H, t, *J* = 7.3, CH_3)
4d	7.97 (1H, d, *J* = 2.1, Ar); 7.40 (1H, d, *J* = 8.7, Ar); 7.25-7.28 (1H, m, Ar); 7.17-7.14 (2H, m, Ar); 6.91-6.87 (2H, m, Ar); 5.25 (1H, br. s, OH); 4.18 (2H, s, CH_2); 3.18 (2H, q, *J* = 7.5, CH_2); 1.34 (3H, t, *J* = 7.5, CH_3)
7a	7.87 (1H, s, Ar); 7.28 (2H, dd, *J* = 8.5, 8.2, Ar); 6.98 (2H, d, *J* = 7.7, Ar); 6.77 (2H, d, *J* = 7.7, Ar); 4.95 (1H, t, *J* = 6.9, CH); 3.75 (3H, s, OCH_3); 3.19-3.14 (1H, m, CH_2); 3.06-3.01 (1H, m, CH_2); 2.58-2.49 (1H, m, CH_2); 2.47-2.38 (1H, m, CH_2); 2.12 (1H, br. s, OH); 1.03 (3H, t, *J* = 7.4, CH_3)
7b	7.87 (1H, s, Ar); 7.31 (1H, d, *J* = 8.6, Ar); 7.25 (1H, d, *J* = 8.1, Ar); 7.01 (2H, d, *J* = 7.7, Ar);6.79 (2H, d, *J* = 7.7, Ar); 4.95 (1H, t, *J* = 6.8, CH); 3.76 (3H, s, OCH_3); 3.21-3.15 (1H, m, CH_2); 3.06-3.01 (1H, m, CH_2); 2.54-2.39 (2H, m, CH_2); 2.08 (1H, br.s, OH); 1.60-1.51 (1H, m, CH_2); 1.48-1.39 (1H, m, CH_2); 0.85 (3H, t, *J* = 7.2, CH_3)
7c	7.86 (1H, s, Ar); 7.31 (1H, d, *J* = 8.6, Ar); 7.24 (1H, d, *J* = 8.1, Ar); 7.02 (2H, d, *J* = 7.7, Ar); 6.77 (2H, d, *J* = 7.7, Ar); 4.99 (1H, t, *J* = 6.8, CH); 3.78 (3H, s, OCH_3); 3.27-3.25 (1H, m, CH_2); 3.14-3.10 (1H, m, CH_2); 2.55-2.43 (2H, m, CH_2); 1.98 (1H, br.s, OH); 1.50-1.47 (2H, m, CH_2); 1.35-1.21 (1H, m, CH_2); 0.87 (3H, t, *J* = 7.2, CH_3)
7d	7.95 (1H, d, *J* =2.1, Ar); 7.35 (1H, d, *J* = 8.7, Ar); 7.27-7.25 (1H, m, Ar); 7.16-7.14 (2H, m, Ar); 6.90-6.86 (2H, m, Ar); 4.94 (1H, t, *J* = 6.9, CH); 3.78 (3H, s, OCH_3); 3.18-3.13 (1H, m, CH_2); 3.07-3.02 (1H, m, CH_2); 2.56-2.45 (1H, m, CH_2); 2.46-2.39 (1H, m, CH_2); 2.10 (1H, br. s, OH); 1.08 (3H, t, *J* = 7.4, CH_3)
8	7.79-7.75 (1H, m, Ar); 7.19 (2H, dd, *J* = 8.5, 8.2, Ar); 6.85 (2H, d, *J* = 7.6, Ar); 6.60 (2H, d, *J* = 7.7, Ar); 5.88 (1H, s, OH); 4.94-4.83 (1H, m, CH); 3.08 (1H, s, CH_2); 2.97-2.95 (1H, m, CH_2); 2.41-2.34 (2H, m, CH_2); 2.09 (1H, br. s, OH); 1.12 (2H, d, *J* = 6.9, CH_2); 0.82-0.75 (3H, m, CH_3)

Compounds **3a-d** and **4a-d** were tested in the primary laboratory screening for fungicidal, herbicidal, and insecticidal properties. The tests showed that the hydroxy ethanones **4a-d** exhibited fungicidal activity, whereas ketones **3a-c** showed insecticidal activity.

In conclusion, we described the efficient synthesis of novel halo and nitro benzofuranyl ethanones starting with commercially available materials. Selective reduction of halo and nitro ethanones to ethanols and amines, respectively, was achieved. These simple methods should find application as general synthetic routes to the related analogues with biological properties.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a TM Bruker DPX 400 instrument for $CDCl_3$ solution. Chemical shifts are given with TMS as internal standard for ^{1}H NMR, and residual protons of $CDCl_3$ (δ 77.0 ppm) for ^{13}C NMR. Mass spectra were obtained on an Agilent Technologies 6890 N apparatus, equipped with a mass detector 5973 network and 30 m × 0.2 mm capillary column filled with a 0.25 μm film of a 5% Me Ph silicate. IR spectra were recorded on a Specord M 80 Carl Zeiss spectrophotometer (KBr disk). All melting points were determined using a Boetius apparatus and are uncorrected. For all novel compounds satisfactory microanalyses were obtained: C ± 0.31, H ± 0.30, N ± 0.28, and Br or Cl ± 0.40.

5-Chlorosalicylaldehyde (mp 101-103°C) was prepared by chlorination of salicylaldehyde in acetic acid solution, although it is commercially available. Methyl 2-bromoalkanoate, butanoate, pentanoate, and hexanoate were obtained according to the literature data [11]. All other reagents and solvents were commercially available (>98% purity) and used without further purification.

2-(4-Bromo-2-formylphenoxy)butanoic Acid (1a) (mp 108-109°C), **2-(4-Bromo-2-formyl-phenoxy)pentanoic Acid (1b)** (mp 87-89°C), and **2-(4-Bromo-2-formylphenoxy)hexanoic Acid (1c)** (mp 56-58°C) were prepared starting with 5-bromosalicylaldehyde and the corresponding 2-bromo ester according to the procedure reported by us previously [9].

2-(2-Formyl-4-nitrophenoxy)butanoic Acid (1e) (mp 145-146°C) and **2-(2-Formyl-4-nitrophenoxy)pentanoic Acid (1f)** (mp 126-127°C) were prepared according to the procedure reported by us previously [10].

2-(4-Chloro-2-formylphenoxy)butanoic Acid (1d). A mixture of 5-chlorosalicylaldehyde (15.7g, 0.1 mol), methyl 2-bromobutanoate (18.1 g, 0.1 mol), anhydrous potassium carbonate (13.8 g, 0.1 mol), and dry DMF (150 ml) was heated at 92-94°C with stirring for 3.5 h. Then the solution was poured into ice water, and the precipitate was filtered off, washed with water, and dried in air. The crude esters were recrystallized from methanol to give methyl 2-(4-chloro-2-formylphenoxy)butanoate. Yield 21.8 g (85%); mp 28-30°C. ^{1}H NMR, δ, ppm (*J,* Hz): 10.52 (1H, s, CHO); 7.81 (1H, d, *J* = 8.9, Ar); 7.45 (1H, dd, *J* = 8.9, *J* = 2.8, Ar); 6.78 (1H, d, *J* = 8.9, Ar); 4.71 (1H, t, *J* = 5.9, CH); 3.76 (3H, s, OCH_3); 2.05-2.12 (2H, m, CH_2), 1.11 (3H, t, *J* = 7.4, CH_3). The ester (20 g, 0.08 mol) was added to a solution of 5% sodium hydroxide (200 ml), and the mixture was stirred and heated on a steam bath until the oil layer dissolved (2.5 h). Next, the mixture was cooled, 10% hydrochloric acid was added, and the precipitate was separated. The crude acid was purified by converting it into its sodium salt at room temperature with the use of sodium bicarbonate followed by the adsorption of impurities on activated carbon. Yield 15.2 g (80%); mp 98-100°C. ^{1}H NMR, δ, ppm (*J*, Hz): 10.45 (1H, s, CHO); 10.35 (1H, br. s, COOH); 7.80 (1H, d, *J* = 2.7, Ar); 7.47 (1H, dd, *J* = 8.9, *J* = 2.7, Ar); 6.85 (1H, d, *J* = 8.9, Ar); 4.77 (1H, t, *J* = 5.3, CH); 2.05-2.18 (2H, m, CH_2); 1.13 (3H, t, *J* = 7.4, CH_3). ^{13}C NMR, δ, ppm (*J*, Hz): 188.8, 175.6, 158.3, 135.5, 128.8, 127.7, 126.4, 115.0, 25.9, 9.5.

5-Bromo-2-ethylbenzofuran (2a), bp 96-97°C (3 mm Hg), mp 24-25°C, **5-Bromo-2-propylbenzofuran (2b),** bp 131-132°C (7 mm Hg), and **5-Bromo-2-butylbenzofuran (2c),** bp 155-157°C (9 mm Hg), were prepared according to the literature data [9].

2-Ethyl-5-nitrobenzofuran (2e) (mp 86°C) and **5-Nitro-2-propylbenzofuran (2f)** (mp 34-35°C) were prepared according to the procedure reported by us previously [10].

5-Chloro-2-ethylbenzofuran (2d). A mixture of compound **1d** (24.3 g, 0.1 mol), acetic anhydride (170 ml), anhydrous sodium acetate (82 g, 1.0 mol), and glacial acetic acid (150 ml) was heated at reflux for 7 h.

The solution was poured into ice water. The oil layer was extracted with methylene chloride and washed with 5% sodium hydroxide and water. The organic phase was dried and evaporated, and the crude product was distilled *in vacuo* to give **2d**. Yield 13.4 g (70%); bp 68-70°C (8 mm Hg), (bp 128-129°C (15 mm Hg) [11]). ^{1}H NMR, δ, ppm (*J*, Hz): 7.41 (1H, d, *J* = 2.2, Ar); 7.28-7.30 (1H, m, Ar); 7.14 (1H, d, *J* = 2.2, Ar); 6.29 (1H, d, *J* = 2.2, Ar); 2.74-2.79 (2H, m, CH_2); 1.30 (3H, t, *J* = 7.5, CH_3); ^{13}C NMR, δ, ppm (*J*, Hz): 162.6, 153.0, 130.4, 128.4, 123.4, 119.8, 112.4, 100.7, 20.4, 11.6.

Synthesis of 1-(Benzofuran-3-yl)-2-phenylethanones 3a-f (General Procedure). A mixture of the appropriate benzofurans **2a-f** (0.05 mol) and 4-methoxyphenylacetic chloride (0.05 mol) in 1,2-dichloroethane (120 ml) was cooled to 0-15°C (Table 1), and anhydrous aluminum chloride (0.15 mol) was added portionwise for 1.5-3 h. The reaction mixture was stirred at that temperature for 1.5-3 h. Then the mixture was poured into ice water (40 ml) and hydrochloric acid (5 ml). The organic layer was separated, washed with 5% sodium hydroxide (2 × 15 ml), and dried over sodium sulfate. The solvent was removed in *vacuo* to give a yellow solid, which was recrystallized from ethanol to give the expected product **3a-f** (Table 2, 3).

Synthesis of 1-(2-Alkylbenzofuran-3-yl)-2-(4-hydroxyphenyl)ethanones 4a-d (General Procedure). A mixture of methoxyethanone **3a-d** (0.01 mol) and pyridine hydrochloride (11.5 g, 0.1 mol) was shaken and heated under reflux for 10-12 min. The warm solution was poured into 100 ml of ice water, and the mixture was left for 1 h. The precipitate was filtered and dissolved in dichloromethane (30-50 ml). The solution was washed with 5% hydrochloric acid, then with water, and next extracted with 5% sodium hydroxide (3 × 10 ml). Subsequently the alkaline solution was acidified, and the precipitate was filtered. The crude product was recrystallized from ethanol to give **4a-d** (Table 2, 3). **4a** mp 144-146, **4b** mp 136-137, **4c** mp 87-89, **4d** mp 135-137°C. IR spectrum, ν, cm^{-1}: 1670, 3300-3400 (**4c**); 1680, 3350-3400 (**4d**).

Catalytic Reduction of 1-(2-Propylbenzofuran-3-yl)-2-(4-methoxyphenyl)ethanone (3b). A mixture of compound **3b** (1 g, 2.4 mmol) and 10% Pd/C (0.1 g) in methanol (30 ml) was stirred under hydrogen atmosphere and heated in reflux for 1.5 h. The Pd/C was removed and the filtrate concentered *in vacuo*. The crude product was chromatographed on silica gel (dichloromethane–acetone, 10:1, v:v) to afford **1-(2-propylbenzofuran-3-yl)-2-(4-methoxyphenyl)ethanol (5)** as a colorless semisolid. ^{1}H NMR, δ, ppm (*J*, Hz): 7.80-7.75 (1H, m, Ar); 7.40-7.38 (1H, m, Ar); 7.23-7.20 (2H, m, Ar); 7.0 (2H, d, *J* = 8.5, Ar); 6.76 (2H, d, *J* = 8.5, Ar); 4.97 (1H, t, *J* = 7.1, CH); 3.74 (3H, s, OCH_3); 3.25 (1H, d.d, *J* = 7.4, *J* = 6.0, CH_2), 3.09 (1H, dd, *J* = 7.4, *J* = 6.0, CH_2); 2.51-2.46 (2H, m, CH_2); 2.12 (1H, br. s, OH); 1.53-1.52 (1H, m, CH_2); 1.45-1.44 (1H, m, CH_2); 0.85 (3H, t, *J* = 7.4, CH_3). GC/MS, Mass spectrum, *m/z*, (I_{rel}, %): 310 $[M]^+$ (26), 187 (100), 171 (2), 158 (4), 144 (4), 121 (19), 102 (9), 77 (5).

Synthesis of 1-(5-Halo-2-alkylbenzofuran-3-yl)-2-(4-methoxyphenyl)ethanol 7a-d and 8 (General Procedure). To a stirred suspension of lithium aluminum hydride (0.07 g, 0.002 mol) in 30 ml of dry ether a solution of ethanone (0.004 mmol) in 50 ml of ether was added dropwise, and the mixture was heated at reflux for 1.5 h. The mixture was cooled to 0-5°C, and 3 ml of water was added dropwise. After the next 0.5 h, 10% aqueous hydrochloride solution was added. The mixture was warmed to room temperature, and stiring was continued for 0.5 h. The ether layer was separated, dried over sodium sulfate, filtered, and concentrated to dryness under reduced pressure to give the product **7a-d** and **8** (Table 2, 3). Yield: **7a** – 90, **7b** – 85, **7c** – 85, **7d** – 87, **8** – 80%.

Reduction of Nitro Ethanones (3e-f) (General Procedure). A mixture of methanol (25 ml) and 10% palladium-C (0.10 g) was magnetically stirred, and hydrogen was slowly passed at room temperature for 0.5 h. Next, nitroethanone (0.004 mol) in methanol (50 ml) was added, and the reduction was carried out at room temperature for 2 h. The reaction mixture was left overnight and filtered. The filtrate was evaporated to dryness *in vacuo*, and the resulting solid was recrystallized from methanol to give amino ethanone **9a**,**b**.

1-(5-Amino-2-ethylbenzofuran-3-yl)-2-(4-methoxyphenyl)ethanone (9a). Pale orange crystals (0.9 g, 80%); mp 145-147°C. IR, ν, cm^{-1}: 3330-3320, 1680. ^{1}H NMR, δ, ppm (*J*, Hz): 7.25-7.23 (2H, m, Ar); 7.15 (2H, d, *J* = 8.1, Ar); 6.88 (2H, d, *J* = 8.1, Ar); 6.65 (1H, d, *J* = 8.5, Ar); 4.16 (2H, s, CH_2); 3.79 (3H, s, OCH_3); 3.39

(2H, br. s, NH_2); 3.13 (2H, q, J = 7.3, CH_2); 1.31 (3H, t, J = 7.4, CH_3). GC/MS, mass spectrum, m/z (I_{rel}, %): 309 $[M]^+$ (65), 188 (100), 173 (9), 159 (5), 145 (9), 121 (17), 77 (5).

1-(5-Amino-2-propylbenzofuran-3-yl)-2-(4-methoxyphenyl)ethanone (9b). Yellow crystals (1.0 g, 80%); mp 139-141°C. IR, ν, cm^{-1}: 3340, 1680. ^1H NMR, δ, ppm (J, Hz): 7.25-7.23 (2H, m, Ar); 7.16-7.14 (2H, m, Ar); 6.90-6.88 (2H, m, Ar); 6.67-6.65 (1H, d, J = 8.5, Ar); 4.15 (2H, s, CH_2); 3.78 (3H, s, OCH_3); 3.41 (2H, br. s, NH_2); 3.10-3.06 (2H, m, CH_2); 1.89-1.79 (2H, m, CH_2); 1.07 (3H, t, J = 7.4, CH_3). GC/MS, mass spectrum, m/z (I_{rel}, %): 323 $[M]^+$ (70), 202 (100), 187 (6), 173 (4), 159 (4), 121 (15), 77 (4).

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