A Convenient Method of Synthesizing 3-Ethoxycarbonylbenzofurans from Salicylaldehydes and Ethyl Diazoacetate

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Abstract: We have developed a convenient one-pot procedure for the synthesis of 3-ethoxycarbonylbenzofurans from commercially available salicylaldehydes and ethyl diazoacetate. The method is high-yielding, efficient, simple and selective.

Key words: benzofurans, salicylaldehyde, ethyl diazoacetate

Benzofuran derivatives are medicinally important compounds.[1a] Several benzofuran-containing compounds are shown in Figure 1; BRL 37959 (**3**) is an analgesic compound with low gastric irritancy,[1b] while compound **4** and natural product **5** are potential anticancer agents.[1c–e] Many of the benzofuran syntheses to date result in the formation of 2-substituted or 2,3-disubstituted benzofurans, although 3-substituted benzofurans are not often reported. Nonetheless, at least two efficient synthetic methods have appeared recently.[2] One involves metal-mediated coupling reactions of relatively expensive benzyl halides,[2a,2b] and the second involves palladium-mediated carbonylative cyclization of complex *o*-alkynylphenols.[2c,2d] Herein, we report a method toward the synthesis of 3-substituted benzofurans using relatively inexpensive and simple salicylaldehydes. So far, we have seen only one report of using salicylaldehyde to prepare 2-ethylsulfonylbenzofurans in low yields (29–48%).[3]

In 2004, we reported a procedure for making 3-hydroxyacrylate **7** from ethyl diazoacetate and benzaldehyde (**6**) in excellent yield using $HBF_4{\cdot}OEt_2$ as a catalyst (Scheme 1).[4] During our studies with substituted benzaldehydes to prepare substituted 3-hydroxyacrylates, we reacted salicylaldehyde (**1a**) with ethyl diazoacetate in the presence of $HBF_4{\cdot}OEt_2$. The reaction did not produce any acrylate **8**, rather 20% of 3-ethoxycarbonylbenzofuran (**2a**) was isolated from the reaction.[4] This result prompted us to investigate the reaction in more detail.

In the initial stage, we undertook a study of this reaction by NMR. We monitored a sample of 0.215 mL of salicylaldehyde (2.04 mmol) with 0.275 mL (2.45 mmol) of ethyl diazoacetate in the presence of $HBF_4{\cdot}OEt_2$ (0.204 mmol) and 0.250 mL of $CDCl_3$ by NMR; we observed no starting materials. Three products were detected in this reaction-mixture sample: 3% of 3-hydroxyacrylate **8**, 5% of 3-ethoxycarbonylbenzofuran (**2a**) and 90% of a hemiacetal, 3-ethoxycarbonyl-2-hydroxy-2,3-dihydrofuran (**9**) (Scheme 2).

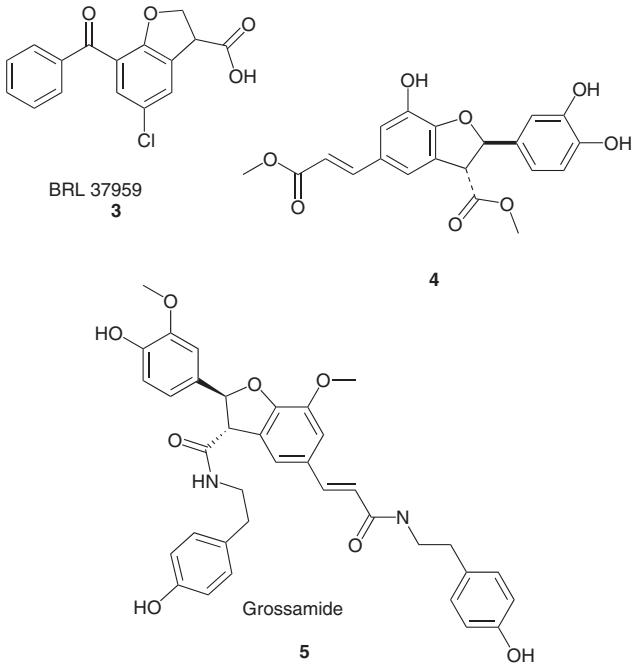
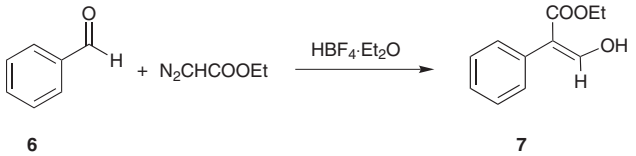


Figure 1 Important biologically active target molecules

The presence of **9** was confirmed using COSY, HSQC, and HMBC spectra (Figure 2). From the HMBC data (Figure 2c), we found that the carbonyl carbon (169.8 ppm) is coupled with neighboring proton H-3 (4.00 ppm). The ^1H–^1H COSY data revealed that the proton H-3 (4.00 ppm) couples with proton H-2 (6.30 ppm), which in turn is coupled with the hydroxyl proton (Figure 2b). This confirms that both H-2 and OH are attached to the same carbon atom, C-2. In the HSQC data (Figure 2b), correlations with H-3 and H-2 gave absorptions for C-3 at 55.0 ppm and C-2 at 102.5 ppm. Interestingly, only one diastereomer of hemiacetal **9** was observed by NMR. The stereochemistry of this diastereomer is under investigation.



Scheme 1

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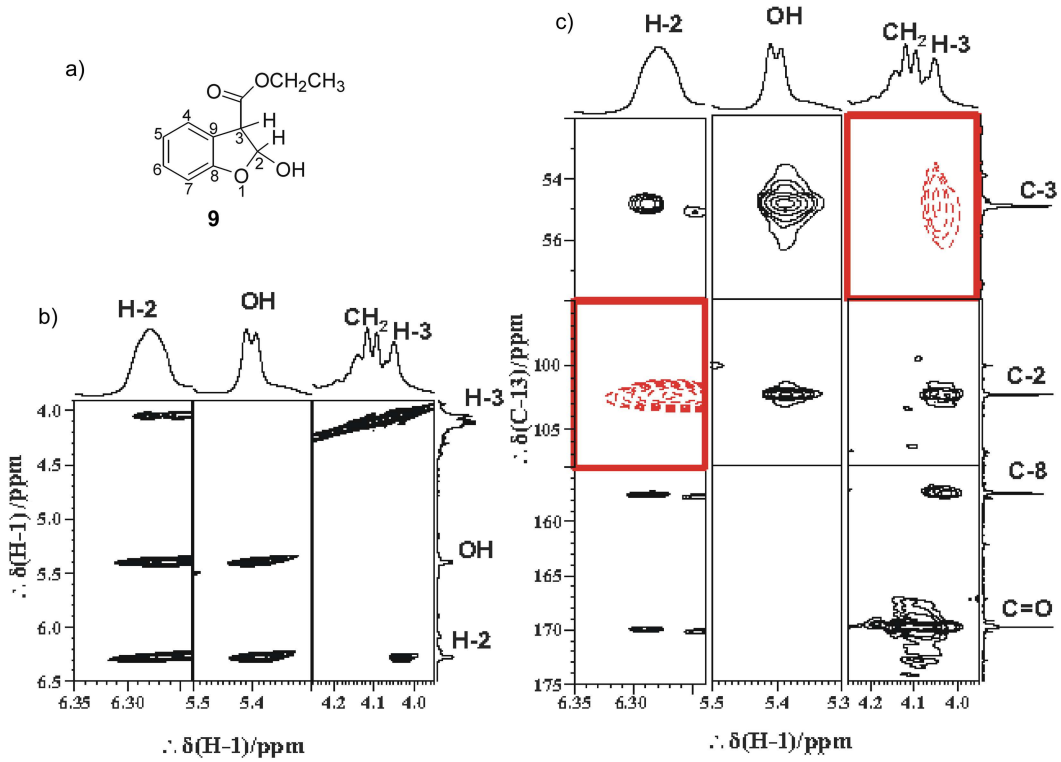


Figure 2 a) Structural assignment of hemiacetal **9**; b) ^{1}H–^{1}H COSY spectrum; c) HMBC (black/solid contour lines) and HSQC (red/dotted contour lines) spectra

Analysis of the structure of hemiacetal **9** indicated that dehydration across C-2 and C-3 might yield the target benzofuran **2a**. Consequently, the synthesis of 3-ethoxycarbonylbenzofuran (**2a**) in 91% yield (Table 1) from salicylaldehyde (**1a**) was performed in one pot, using ethyl diazoacetate in the presence of $HBF_4{\cdot}OEt_2$, followed by dehydration with sulfuric acid (see experimental section). The general scope of the reaction was then investigated using various commercially available substituted salicylaldehydes. The procedure was found to be quite successful, providing the desired products in excellent to quantitative isolated yields (Table 1).

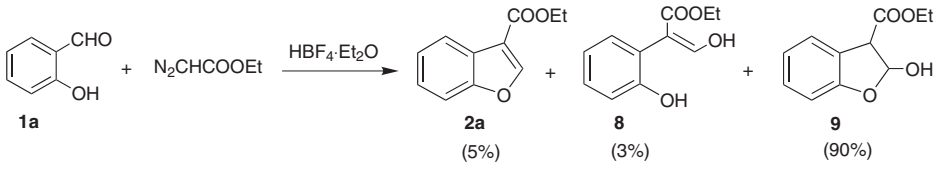
Although the mechanistic details concerning formation of hemiacetal **9** are not fully studied, we propose the mechanism outlined in Scheme 3, based on our experimental data. We believe that upon protonation of the carbonyl oxygen, the aldehyde undergoes an aryl migration after reaction with ethyl diazoacetate to form aryl propanal **10**, which undergoes tautomerization to form the 3-hydroxyacrylate **8**, as proposed earlier by our group.[4] The resulting 3-hydroxyacrylate **8**, then undergoes the acid-catalyzed cyclization to form the hemiacetal **9**. This hemiacetal undergoes dehydration in the presence of concentrated sulfuric acid to form the benzofuran, **2a**.

In conclusion, we have described a simple, high-yielding procedure for producing 3-ethoxycarbonyl benzofurans. Work is underway using our methods to synthesize some important biologically active target molecules containing 3-carbonyl-substituted benzofurans as shown in Figure 1.

NMR data were collected on a Bruker 300 MHz instrument. Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane, and $CDCl_3$ was used as the solvent. Silica gel (40–140 mesh), $HBF_4{\cdot}OEt_2$, HPLC grade CH_2Cl_2, salicylaldehydes and ethyl diazoacetate were used without further purification from Aldrich. On some occasions, ethyl diazoacetate was prepared in the lab according to a literature procedure.[5]

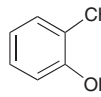
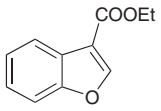
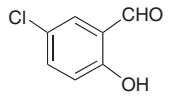
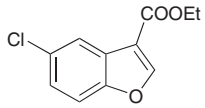
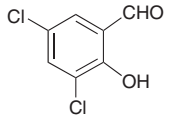
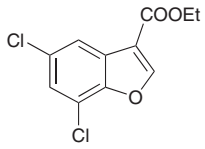
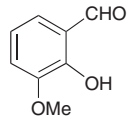
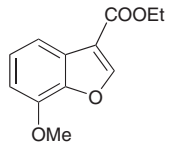
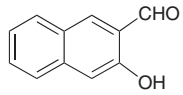
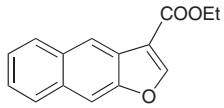
Synthesis of 3-Substituted Benzofurans; General Procedure

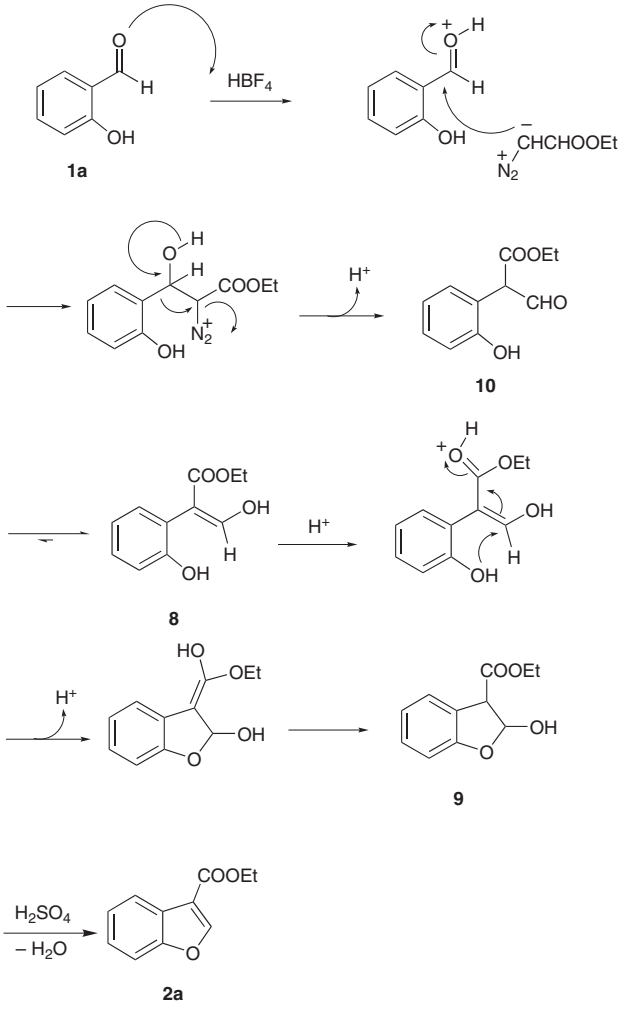
No inert N_2 atmosphere was required. The entire two-step, one-pot reaction can be accomplished in less than 1 h. For each experiment, $HBF_4{\cdot}OEt_2$ was added to the salicylaldehyde (1 g) in CH_2Cl_2 (2 mL). A solution of ethyl diazoacetate in CH_2Cl_2 was introduced into the reaction mixture as the evolution of N_2 gas permitted (ca. 3–6



Scheme 2

Table 1 Isolated Yields of 3-Ethoxycarbonyl Benzofurans

Entry	Aldehyde	Benzofuran	Yield (%)
1	 **1a**	 **2a**	91
2	 **1b**	 **2b**	95
3	 **1c**	 **2c**	>99
4	 **1d**	 **2d**	97
5	 **1e**	 **2e**	>99



Scheme 3

min addition time) and the reaction was not allowed to go above 38 °C. Once gas evolution ceased, the reaction mixture was concentrated by rotary evaporator and H_2SO_4 (0.3 to 0.5 mL) was added to the mixture while stirring. After 5 to 10 min, the mixture was diluted with CH_2Cl_2 (5 to 10 mL) and the H_2SO_4 was quenched with solid $NaHCO_3$. The mixture was then filtered through silica gel (1 g), and concentrated by rotary evaporator to give an oil, which slowly crystallized under high vacuum.

3-Ethoxycarbonylbenzofuran (2a)[1b]

The title compound was isolated in 91% (1.42 g) yield from salicylaldehyde (1.00 g, 8.19 mmol) and ethyl diazoacetate solution (8%; 15.70 mL, 13.1 mmol) in the presence of $HBF_4{\cdot}OEt_2$ (54%; 0.112 mL, 0.819 mmol).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.24 (s, 1 H), 8.06 (m, 1 H), 7.49 (m, 1 H), 7.35 (m, 2 H), 4.40 (q, *J* = 7.14 Hz, 2 H), 1.41 (t, *J* = 7.14 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 163.25, 155.45, 150.80, 125.10, 124.50, 124.00, 121.90, 114.60, 111.50, 60.40, 14.25.

5-Chloro-3-ethoxycarbonylbenzofuran (2b)

The title compound was isolated in 95% (4.21 g) yield from 5-chlorosalicylaldehyde (3.09 g, 19.6 mmol) and ethyl diazoacetate solution (8%; 37.6 mL, 31.4 mmol) in the presence of $HBF_4{\cdot}OEt_2$ (54%; 0.267 mL, 1.96 mmol).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.24 (s, 1 H), 8.00 (d, *J* = 2.01 Hz, 1 H), 7.42 (d, *J* = 8.78 Hz, 1 H), 7.29 (dd, *J* = 8.78, 2.01 Hz, 1 H), 4.41 (q, *J* = 7.14 Hz, 2 H), 1.43 (t, *J* = 7.14 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 162.70, 153.75, 151.85, 129.85, 125.85, 125.50, 121.60, 114.40, 112.50, 60.70, 14.25.

5,7-Dichloro-3-ethoxycarbonylbenzofuran (2c)

The title compound was isolated in quantitative (1.36 g) yield from 3,5-dichlorosalicylaldehyde (1.00 g, 5.24 mmol) and ethyl diazoacetate solution (8%; 10 mL, 8.4 mmol) in the presence of $HBF_4{\cdot}OEt_2$ (54%; 0.071 mL, 0.52 mmol).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.27 (s, 1 H), 7.88 (d, *J* = 2.01 Hz, 1 H), 7.31 (d, *J* = 2.01 Hz, 1 H), 4.40 (q, *J* = 7.14 Hz, 2 H), 1.42 (t, *J* = 7.14 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 162.15, 152.15, 149.75, 130.15, 126.85, 125.45, 120.25, 117.50, 115.00, 60.95, 14.20.

7-Methoxy-3-ethoxycarbonylbenzofuran (2d)

The title compound was isolated in 97% (1.405 g) yield from 3-methoxysalicylaldehyde (*o*-vanillin) (1.007 g, 6.62 mmol) and ethyl diazoacetate solution (8%; 12.25 mL, 10.6 mmol) in the presence of $HBF_4{\cdot}OEt_2$ (54%; 0.088 mL, 0.66 mmol).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.25 (s, 1 H), 7.64 (dd, *J* = 7.87, 0.91 Hz, 1 H), 7.27 (m, 1 H), 6.86 (d, *J* = 7.87 Hz, 1 H), 4.40 (q, *J* = 7.14 Hz, 2 H), 4.01 (s, 3 H), 1.42 (t, *J* = 7.14 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 150.75, 113.92, 124.84, 107.1, 60.50, 14.24.

3-Ethoxycarbonylnaphthofuran (2e)

The title compound was isolated in quantitative (1.41 g) yield from 2-hydroxy-1-naphthaldehyde (1.01 g, 5.87 mmol) and ethyl diazoacetate solution (8%; 11.1 mL, 9.39 mmol) in the presence of $HBF_4{\cdot}OEt_2$ (54%; 0.080 mL, 0.59 mmol).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.52 (d, *J* = 8.42 Hz, 1 H), 8.42 (s, 1 H), 7.96 (d, *J* = 8.05 Hz, 1 H), 7.82 (d, *J* = 8.96 Hz, 1 H), 7.69 (m, 2 H), 7.56 (m, 1 H), 4.48 (q, *J* = 7.14 Hz, 2 H), 1.48 (t, *J* = 7.14 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 163.60, 153.85, 151.05, 131.15, 128.50, 128.05, 127.30, 126.70, 126.60, 125.05, 119.25, 116.70, 112.05, 60.75, 14.30.

NMR Study of Ethyl Diazoacetate with 0.1 equiv $HBF_4{\cdot}OEt_2$ and Salicylaldehyde

Salicylaldehyde (0.215 mL, 2.04 mmol), $HBF_4{\cdot}OEt_2$ (0.015 mL, 0.20 mmol), $CDCl_3$ (0.250 mL), and ethyl diazoacetate (0.275 mL, 2.45 mmol) were cautiously mixed in a 5-mm NMR tube. The mixture was allowed to evolve N_2 overnight in the freezer. After warming to r.t., several NMR spectra (^{1}H, ^{13}C, COSY, HSQC, and HMBC) were recorded. The ^{1}H NMR spectrum revealed the presence of roughly 3% of 3-hydroxyacrylate (**8**), 5% of benzofuran 3-ethyl ester (**2a**) and 90% of the hemiacetal **9**, which was assigned according to the ring numbering in Figure 2a.

3-Ethoxycarbonyl-2-hydroxy-2,3-dihydrobenzofuran (9)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.30 (d, *J* = 7.32 Hz, 1 H, H-4), 7.10 (m, 1 H, H-6), 6.85 (m, 1 H, H-5), 6.80 (d, *J* = 7.87 Hz, 1 H, H-7), 6.30 (s, 1 H, H-2), 5.40 (d, *J* = 4.94 Hz, 1 H, OH), 4.10 (q, *J* = 7.14 Hz, 2 H, CH_2), 4.00 (d, *J* = 7.14 Hz, 1 H, H-3), 1.20 (t, *J* = 2.38 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 169.8 (C=O), 157.6 (C-8), 129.4 (C-6), 125.4 (C-4), 123.0 (C-9), 121.0 (C-5), 109.8 (C-7), 102.5 (C-2), 61.7 (CH_2), 55.0 (C-3), 14.1 (CH_3).

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