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New One-Pot Synthesis of Polysubstituted Benzofurans and Benzo-1,4-dioxines

G. N. Sakhabutdinova^{*a*}, G. Z. Raskil'dina^{*a*}, S. S. Zlotskii^{*a*}, and R. M. Sultanova^{*a,b,**}

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Abstract—It has been revealed that the copper(II) triflate catalyzed reaction of ethyl-2-diazo-3-oxobutanoate with phenols followed by cyclization of the intermediate enol in the presence of polyphosphoric acid is a simple and efficient method of synthesis of polysubstituted benzofurans. The use of pyrocatechol leads to the corresponding substituted 1,4-benzodioxine-2-carboxylates as major products.

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Benzofuran and benzo-1,4-dioxine derivatives exhibit diverse biological activity, in particular, antibacterial, antifungal, and anti-inflammatory, and thus attract attention as candidates for use in the synthesis of drugs [1-4].

In this paper, we report a new route of synthesis of polyfunctional benzofurans and benzo-1,4-dioxines through the reaction of substituted phenols **1a–1f** and pyrocatechol **2** with ethyl-2-diazo-3-oxobutanoate **3** in the presence of Cu(OTf)₂, where the key stage is the insertion of a carbene intermediate obtained from α -diazo- β -keto ether into the O–H bond of phenols (Scheme 1). The resulting *O*-arylalkoxycarbonyl ketones were further cyclized to form benzofurans.

In the presence of 2 mol % $Cu(OTf)_2$ in toluene at 110°C, nearly complete conversion of the reagents was observed within 2 h. The subsequent treatment of the reaction mixture with polyphosphoric acid (PPA) under stirring for 8 h led to the formation of benzofurans **4a**-**4e** in 35–70% yields (Table 1).

In the case of *m*-chlorophenol **1f**, the reaction mixture contains both benzofuran isomers **5a** and **5b** (Scheme 2). Judging from their ratio (**5a** : **5b** = 1.5 : 1), the cyclization of the intermediate enol in the *p*-position to the Cl atom is more preferable than in the *o*position. With 4-*tert*-butylpyrocathechol **2**, the reaction involves two hydroxyl groups (Scheme 3), not disturbing the aromatic nucleus, to give a mixture of isomeric ethyl *tert*-butyl-3-methyl-1,4-benzodioxine-2-carboxylates **6a** and **6b**.

It is evident that when treated with PPA, the intermediate enols undergo intramolecular dehydration to give heterocycles **6a** and **6b**.

The *tert*-butyl substituent distant from the hydroxyl groups has no effect on their reaction with alkoxycarbonyl carbene, which explains the formation of the equimolar mixture of benzoheterocycles **6a** and **6b** (Table 1).

The structures of compounds 4a-4e, 5a, 5b, 6a, and 6b were proved by ¹H and ¹³C NMR and chromatography/mass spectrometry.

The signals of substituted benzofurans 4a-4e, 5a, and 5b were assigned by analyzing the chemical shifts and spin coupling constants of the benzoheterocyclic protons.

The ¹H NMR spectrum of a mixture of **5a** and **5b** showed a set of signals characteristic for the ester $-CH_2$ -protons as a quartet at 4.42 ppm and a singlet corresponding to the methyl proton in the range 2.56–2.80 ppm. In the ¹³C NMR spectrum of these compounds, the signals of the C⁴, C⁴ and C⁹, C⁹ carbon atoms of fused nuclei were observed at 141.16 and 127.65 ppm, respectively. The ratio of benzofuran isomers **5a** and **5b** was 1.5 : 1 according to the integrated intensities of methyl protons in the ¹H NMR spectrum.

The ¹H NMR spectrum of the mixture of **6a** and **6b** showed a double set of proton signals. In the ¹³C NMR

^a Ufa State Petroleum Technological University, Ufa, Bashkortostan, 450105 Russia

^b Ufa Institute of Chemistry, Russian Academy of Sciences, Ufa, Bashkortostan, 450054 Russia

^{*}e-mail: sultanova rm@anrb.ru





Scheme 1.







Scheme 3.

spectrum of the mixture of compounds **6a** and **6b**, the chemical shifts of carbon atoms in the 9- and 8'-positions were noticeably different being 147.36 and 148.09 ppm, respectively.

Thus, the reaction of ethyl-2-diazo-3-oxobutanoate with substituted mono- and diphenols is a convenient route of synthesis of polyfunctional benzofurans and 1,4-benzodioxine-2-carboxylates.

EXPERIMENTAL

The NMR spectra of solutions in CDCl₃ were recorded on a Bruker Avance III 500 radiospectrometer operating at 500 (¹H) and 125.76 MHz (¹³C) (TMS as an internal reference). GLC analysis was performed on a Kristall-2000M chromatograph ("Khromatek," Russia, column length 2.0 m, stationary phase SE-30

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Compound (yield, %)	¹ H, ppm	¹³ C, ppm	<i>m/e</i> , (<i>I</i> _{rel} , %)
4a (70)	1.46 (t, 3H, CH ₃ , <i>J</i> 7.2), 2.59 (s, 3H, CH ₃), 4.45 (q, 2H, CH ₂ , <i>J</i> 4.5), 7.29 (t, 1H, CH), 7.42 (t, 1H, CH), 7.53 (d, 1H, CH), 7.62 (d, 1H, CH)	160.38 (C), 154.29 (C), 140.85 (C), 129.02 (C), 127.64 (CH), 125.50 (C), 123.03 (CH), 120.95 (CH), 112.14 (CH), 60.96 (CH ₂), 14.41 (CH ₃), 9.35 (CH ₃)	36 (16), 51 (10), 63 (8), 77 (38), 91 (10), 103 (40), 131 (72), 147 (9), 159 (64), 176 (70), 204 (100)
4b (40)	1.45 (t, 3H, CH ₃ , <i>J</i> 7.1), 2.56 (s, 3H, CH ₃), 2.58 (s, 3H, CH ₃), 4.46 (q, 2H, CH ₂ , <i>J</i> 4.0), 7.20 (t, 1H, CH), 7.25 (t, 1H, CH), 7.43 (d, 1H, CH)	160.70 (C), 153.51(C), 140.77 (C), 128.59 (C), 128.34 (CH), 123.74 (C), 123.09 (CH), 122.41 (C), 118.36 (CH), 60.95 (CH ₂), 15.03 (CH ₃), 14.36 (CH ₃), 9.54 (CH ₃)	39 (8), 51 (8), 65 (9), 77 (8), 91 (28), 115 (64), 145 (54), 173 (48), 189 (74), 218 (100)
4c (40)	1.44 (t, 3H, CH ₃ , <i>J</i> 7.2), 2.47 (s, 3H, CH ₃), 2.57 (s, 3H, CH ₃), 4.42 (q, 2H, CH ₂ , <i>J</i> 4.2), 7.08 (d, 1H, CH), 7.21 (d, 1H, CH), 7.40 (t, 1H, CH)	160.58 (C), 152.80 (C), 140.96 (C), 136.49 (C), 132.63(C), 129.20 (CH), 129.08 (C), 120.56 (CH), 111.66 (CH), 61.00 (CH ₂), 21.30 (CH ₃), 14.38 (CH ₃), 9.34 (CH ₃)	39 (8), 51 (8), 65 (9), 77 (8), 91 (24), 115 (58), 45 (62), 173 (52), 189 (84), 218 (100)
4d (35)	1.32 (t, 9H, 3CH ₃), 1.45 (t, 3H, CH ₃ , <i>J</i> 7.1), 2.60 (s, 3H, CH ₃), 4.45 (q, 2H, CH ₂ , <i>J</i> 7.1), 7.00 (d, 1H, CH), 7.39 (dd, 1H, CH), 7.52 (d, 1H, CH)	160.55 (C), 154.35 (C), 140.90 (C), 130.90 (C), 128.80 (C), 120.80 (CH), 116.70 (CH), 111.53 (CH), 61.02 (CH ₂), 29.68 (C), 31.71 (3CH ₃), 14.30 (CH ₃), 9.20 (CH ₃)	44 (12.5), 57 (5.8), 86 (6.0), 91 (5.0), 115 (8.5), 128 (11.5), 143 (9.0), 172 (7.0), 189 (16.5), 217 (13.5), 245 (100), 260 (5.5)
4e (45)	1.43 (t, 3H, CH ₃ , <i>J</i> 7.1), 2.56 (s, 3H, CH ₃), 4.44 (q, 2H, CH ₂ , <i>J</i> 7.1), 7.18 (t, 1H, CH), 7.23 (t, 1H, CH), 7.45 (t, 1H, CH)	160.59 (C), 153.51 (C), 140.77 (C), 128.61 (C), 128.35 (CH), 125.71 (C), 123.11 (CH), 122.37 (C), 118.35 (CH), 60.87 (CH ₂), 15.08 (CH ₃), 9.56 (CH ₃)	39 (2), 51 (4), 65 (5), 77 (4), 91 (18), 115 (48), 145 (44), 179 (45), 189 (67), 218 (100)
5a + 5b (51)	1.43 (t, 3H, CH ₃ , <i>J</i> 5.5), 2.56 (s, 3H, CH ₃), 4.42 (q, 2H, CH ₂ , <i>J</i> 2.7), 7.26 (t, 1H, CH), 7.40 (d, 1H, CH), 7.50 (d, 1H, CH)	160.08(C), 154.22(C), 141.39(C), 133.65(C), 128.52(C), 125.83(C), 124.20(CH), 124.07 (CH), 112.53 (CH), 61.16 (CH ₂), 14.16 (CH ₃), 9.26 (CH ₃)	44 (12), 51 (6), 75 (12), 102 (28), 136 (20), 165 (42), 193 (52), 210 (84), 238 (100)
	1.43 (t, 3H, CH ₃ , <i>J</i> 5.5), 2.80 (s, 3H, CH ₃), 4.42 (q, 2H, CH ₂ , <i>J</i> 2.7), 7.21 (d, 1H, CH), 7.29 (t, 1H, CH), 7.50 (d, 1H, CH)	160.08 (C), 154.99 (C), 127.84 (CH), 127.65 (C), 126.06 (C), 125.20 (C), 125.20 (C), 121.57 (CH), 110.88 (CH), 61.16 (CH ₂), 14.16 (CH ₃), 10.99 (CH ₃)	
6a + 6b (35)	1.27 (s, 9H, 3CH ₃ , <i>J</i> 7.1), 1.36 (t, 3H, CH ₃), 2.25 (s, 3H, CH ₃), 4.32 (q, 2H, CH ₂ , <i>J</i> 6.9), 6.63 (d, 1H, CH), 6.75 (d, 1H, CH), 7.21(d, 1H, CH)	162.50 (C), 147.29 (C), 148.09 (C), 141.76 (C), 139.97 (C), 125.27 (C), 120.25 (CH), 115.39 (CH), 112.95 (CH), 61.13 (CH ₂), 34.40 (CH ₃), 31.35 (3CH ₃), 16.86 (CH ₃), 14.23 (CH ₃)	43 (8), 55 (6), 67 (4), 77 (7), 91 (10), 105 (6), 115 (12), 131 (6), 159 (5), 187 (12), 233 (24), 261 (100), 276 (58)
		162.50 (C), 148.50 (C), 147.36 (C), 140.42 (C), 138.60 (C), 125.14 (C), 121.48 (CH), 114.91 (CH), 113.55 (CH), 61.13 (CH ₂), 34.40 (CH ₃), 31.35 (3CH ₃), 16.86 (CH ₃), 14.23 (CH ₃)	43 (16), 55 (6), 67 (9), 77 (9), 91 (14), 103 (6), 115 (12), 131 (8), 159 (19), 187 (14), 233 (16), 261 (100), 276 (66)

Table 1. ¹H and ¹³C NMR spectra of products 4a-4e, 5a, 5b, 6a, and 6b

5%), Khromaton N-AW carrier ("Ekolan," Russia, working temperature 50–250°C, carrier gas—helium). Mass spectra were recorded on a ThermoFisher Scientific ThermoFinnigan MAT 95 XP high-resolution chromatograph/mass spectrometer at an ionizing voltage of 70 eV (ionizing chamber temperature 250°C, direct inlet temperature 50–270°C, heating rate 10 K/min). The reaction was monitored by TLC on a Sorbfil silica gel ("IMID," Russia). Silica gel with dispersion 70–230 mesh (Lancaster, Great Britain) was used for column chromatography.

The yields and spectral characteristics of compounds 4a-4e, 5a, 5b, 6a, and 6b are summarized in Table 1. The properties of compound 4a were consistent with the literature data [5].

General procedure of synthesis of benzoheterocycles 4a–4e, 5a, 5b, 6a, and 6b. To a mixture of 1.2 mmol (200 mg) of ethyl-2-diazo-3-oxobutanoate (3) and 1.1 mmol of phenol (1a–1f, 2) in toluene, 2.4×10^{-5} mmol (8 mg) of the Cu(OTf)₂ catalyst was added. The reaction mixture was heated to 110°C for 2 h. Then, the reaction mixture was cooled to room temperature, and the solvent (toluene) was removed under reduced pressure. Polyphosphoric acid (300 mg) was preheated to 85°C and added to the crude reaction mixture. The viscous mixture was stirred at 85°C for 8 h. After the reaction completion, the reaction mixture was extracted with benzene (30 mL × 3).

The organic layer was dried by $MgSO_4$, which was filtered off, and the solvent (benzene) was removed under reduced pressure. The residue was chromatographed on silica gel (elution with petroleum ether : ethyl acetate = 100 : 1).

Quantum-chemical calculations justifying the reaction mechanisms and biological activity of the synthesized compounds will be addressed in our future research.

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