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Reductive Heterocyclization of 2-Cyanobenzophenones by the Action of $NaBH_4$. New Efficient Synthesis of 3-Arylphthalides

S. S. Mochalov, A. N. Fedotov,* E. V. Trofimova, and N. S. Zefirov[†]

Faculty of Chemistry, Moscow State University, Leninskie gory 1, Moscow, 119991 Russia
**e-mail: fed@org.chem.msu.ru*

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Abstract—The reduction of 2-cyclopropylcarbonyl-, 2-(thiophen-2-yl)carbonyl-, and 2-arylcarbonylbenzonitriles with sodium tetrahydridoborate afforded 3-cyclopropyl-, 3-(2-thiophen-2-yl)-, and 3-arylphthalides, respectively, in high yields. Under analogous conditions, 3-cyanobenzophenones were converted to the corresponding 3-cyanobenzhydrols.

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We previously described [1] an attempt to synthesize 3-arylpthalimides (practically important heterocyclic compounds) starting from 2-acylbenzonitriles. For this purpose, we planned to accomplish successive transformation of initial nitriles **A** first to amides **B** and then to *o*-carbamoylbenzhydrols **C** and cyclization of the latter to target 3-arylphthalimidines **D** (Scheme 1). However, 2-cyanobenzophenones **A** turned out to behave anomalously even in the hydrolysis stage. Unlike 3-aroylbenzonitriles which were converted in the system $CF_3COOH–H_2SO_4$ to the corresponding benzamides[1] with high yields, and the carbonyl functionality therein remained unchanged, 2-aroylbenzonitriles under the same conditions gave rise to 3-aryl-3-hydroxyphthalimidines **E**. Thus, the aroyl substituent in the *ortho* position with respect to the cyano group in the initial benzonitrile is subject to intramolecular interaction during the hydrolysis process, so that the formation of target benzamides **C** becomes impossible. The failure to convert 2-cyanobenzophenones to 3-arylphthalimidines **D** prompted us to try to obtain the latter from the same benzonitriles but in a different way.

According to the data of [2], 2-cyclopropylbenzonitriles can be converted to 3-ethylphthalimidines by the action of concentrated sulfuric acid. Opening of the cyclopropane ring in the presence of concd. H_2SO_4 generates benzylic cation **G** which is incapable of interacting with the cyano group because of its linear structure. Modification of the cyano group via addition of sulfuric acid thereto gives imidate group (structure **H**), so that the intramolecular interaction between the cationic center and modified cyano group becomes possible. The subsequent closure of five-membered ring and hydrolysis yield final structure **J** (Scheme 2).

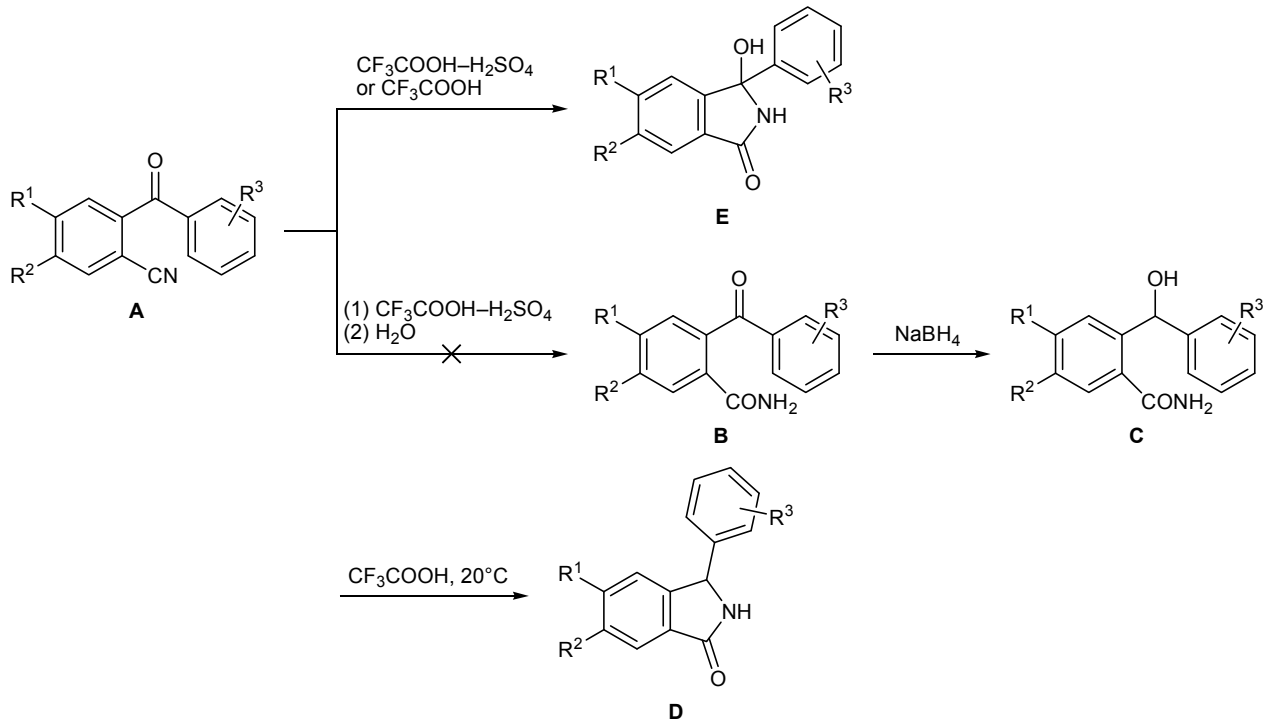
We presumed that analogous scheme of formation of 3-substituted phthalimidines is possible in reactions of benzonitriles with an *ortho*-substituent capable of generating benzylic cation under similar conditions. Taking into account that benzyl alcohols in acidic medium are readily converted to carbenium ions, we made an attempt to synthesize 2-cyanobenzhydrols and study their behavior under the conditions ensuring the transformation of 2-cyclopropylbenzonitriles [2]. We planned to obtain the required 2-cyanobenzhydrols by reduction of the carbonyl group in 2-cyanobenzophenones with $NaBH_4$; it is known that this reducing agent is inactive toward cyano group.

Initial 2-cyanobenzophenones **2a**–**2k** were synthesized by nucleophilic substitution of bromine in 2-bromobenzophenones by the action of copper(I) cyanide in DMF (Rosenmund–von Braun reaction; Scheme 3). Initially, we examined the reduction with $NaBH_4$ of benzophenone **2l** in which the cyano group is located in the *meta* position with respect to the car-

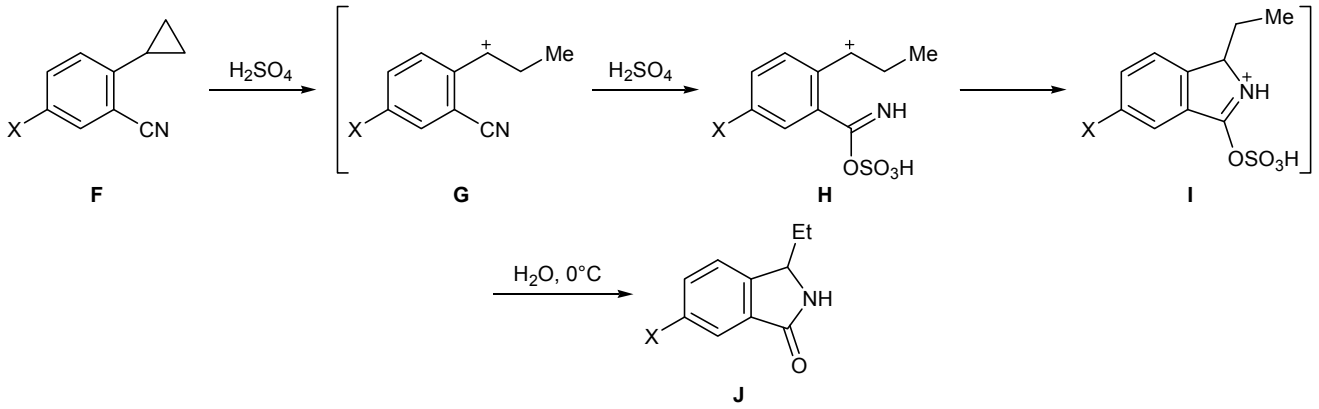
[†] Deceased.

[1] This study was performed specially to compare with the behavior of 2-aroylbenzonitriles under the given hydrolysis conditions.

Scheme 1.

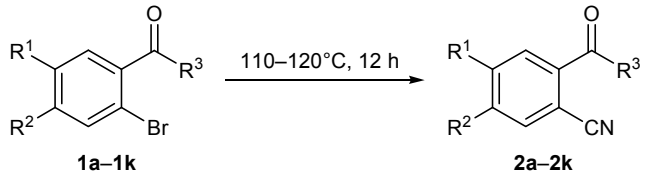


Scheme 2.



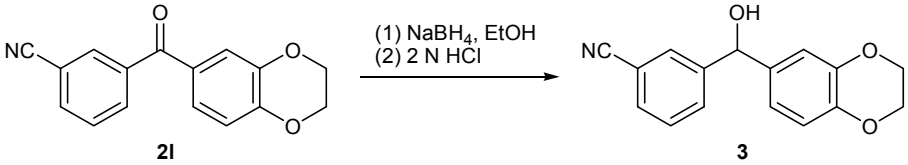
bonyl group. This reaction afforded with high yield benzhydrol **3** with the cyano group being unchanged (Scheme 4). Unlike nitrile **2l**, *ortho*-cyanobenzophenones **2a**–**2k** behaved differently under analogous conditions. The reaction gave 3-arylphthalides **4a**–**4k** rather than the corresponding 2-cyanobenzhydrols **5a**–**5k** (Scheme 5). Thus, the close position of the cyano group to the carbonyl substituent is the crucial factor preventing formation of benzhydrols **5a**–**5k** in the reduction of 2-cyanobenzophenones **2a**–**2k** with $NaBH_4$. Scheme 6 illustrates a probable mechanism of formation of 3-arylphthalides **4a**–**4k** under the given conditions. In the first stage, the addition of tetrahydridoborate ion to the carbonyl group of **2** gives boron alkoxide **K**, which is likely to facilitate intramolecular ring closure via nucleophilic attack on the C≡N carbon atom with formation of intermediate **L**. Treatment of

Scheme 3.

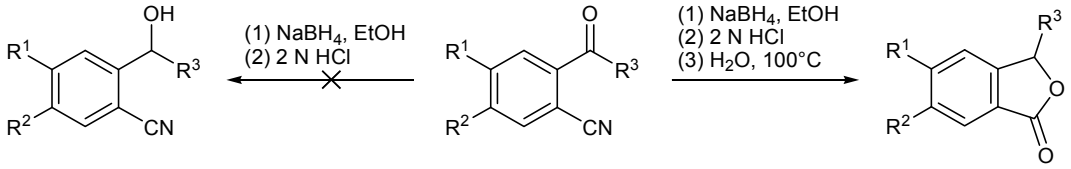


R^1R^2 = OCH_2CH_2O, R^3 = *cyclo*-C_3H_5 (**a**), thiophen-2-yl (**b**), Ph (**c**), 4-MeC_6H_4 (**d**), 2-ClC_6H_4 (**e**); R^1 = R^2 = OMe, R^3 = 4-MeC_6H_4 (**f**); R^1 = R^2 = H, R^3 = Ph (**g**), 4-MeC_6H_4 (**h**), 4-$MeOC_6H_4$ (**i**), 4-BrC_6H_4 (**j**), 1,4-benzodioxan-6-yl (**k**).

Scheme 4.

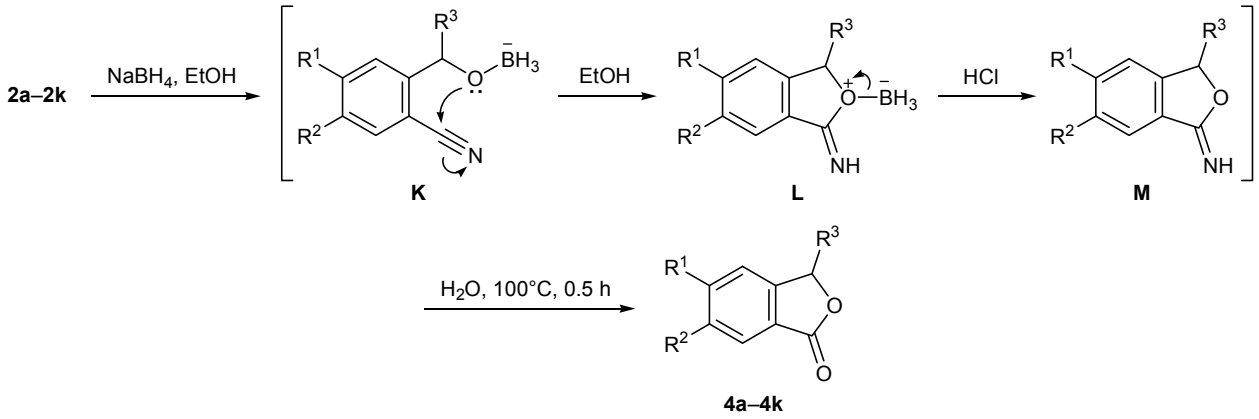


Scheme 5.



R^1R^2 = OCH_2CH_2O, R^3 = *cyclo*-C_3H_5 (**a**), thiophen-2-yl (**b**), Ph (**c**), 4-MeC_6H_4 (**d**), 2-ClC_6H_4 (**e**); R^1 = R^2 = OMe, R^3 = 4-MeC_6H_4 (**f**); R^1 = R^2 = H, R^3 = Ph (**g**), 4-MeC_6H_4 (**h**), 4-$MeOC_6H_4$ (**i**), 4-BrC_6H_4 (**j**), 1,4-benzodioxan-6-yl (**k**).

Scheme 6.



the reaction mixture with 2 N aqueous HCl yields iminofuran structure **M** which is unstable [3] and is readily hydrolyzed further to final products **4a**–**4k**.

Thus, the observed reductive heterocyclization of 2-cyanobenzophenones can be regarded as a novel efficient method of synthesis of 3-substituted phthalides. The synthetic potential of this method is likely to be determined only by the accessibility of initial 2-acylbenzonitriles.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian VXR-400 spectrometer at 400.13 MHz using $CDCl_3$ or DMSO-d_6 as solvent; the chemical shifts were measured relative to the residual proton signal of the solvent ($CHCl_3$) or tetramethylsilane (DMSO-d_6). The mass spectra (electron impact, 70 eV) were recorded on a Finnigan MAT Incos-50 instrument. The elemental analyses were determined with a Vario-11 CHN analyzer. The melting points were determined using an Electrothermal 1A9100 digital melting point apparatus. The products were isolated, and their purity was checked, by chromatography on Al_2O_3 of Brockmann activity grade II using diethyl ether–chloroform–petroleum ether (40–70°C), 1:1:3 or 1:1:2, as eluent.

Aroylbenzonitriles 2a–2l were synthesized from the corresponding 2-bromobenzophenones **1a**–**1k** and 3-bromobenzophenone **1l** according to the procedure described in [1]. Their physical constants and spectral parameters were in agreement with published data [1].

3-[(1,4-Benzodioxan-6-yl)(hydroxy)methyl]-benzonitrile (3). 3-Cyanobenzophenone **2l**, 1 mmol, was added with stirring over a period of 0.5 h to a suspension of 0.04 g (1 mmol) of $NaBH_4$ in 5 mL of ethanol, and the mixture was stirred for 1 h at 40–50°C and was left to stand for 24 h at 20°C. The mixture was treated with 2 N aqueous HCl until weakly acidic reaction, poured into 150 mL of water, and extracted with

diethyl ether. The extract was dried over $CaCl_2$ and evaporated, and the residue was subjected to preparative thin-layer chromatography on Al_2O_3 using diethyl ether–chloroform–petroleum ether (40–70°C), 1:1:2, as eluent. Yield 0.25 g (94%), oily material. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.25 m (4H, OCH_2CH_2O), 5.74 s (1H, C**H**OH), 6.10 s (1H, OH), 6.83 m (3H, H_{arom}), 7.43 m (1H, H_{arom}), 7.54 d (1H, H_{arom}, J = 7.6 Hz), 7.62 d (1H, H_{arom}, J = 7.8 Hz), 7.69 s (1H, H_{arom}). Found, %: C 71.82, 71.98; H 4.68, 4.81; N 5.06, 5.12. $C_{16}H_{13}NO_3$. Calculated, %: C 71.90; H 4.90; N 5.24.

Reductive heterocyclization of 2-acylbenzonitriles 2a–2k by the action of $NaBH_4$ (*general procedure*). Compound **2a**–**2k**, 1 mmol, was added with stirring over a period of 0.5 h to a suspension of 0.04 g (1 mmol) of $NaBH_4$ in 5 mL of ethanol, and the mixture was heated to 40–50°C, kept for 1 h at that temperature, and left to stand for 24 h at 20°C. The mixture was treated with 2 N aqueous HCl, poured into 150 mL of water, refluxed for 0.5 h, and purged with air over a period of 1 h to remove residual ethanol. The precipitate was filtered off and recrystallized from an appropriate solvent or purified by preparative thin-layer chromatography on Al_2O_3. We thus isolated 3-arylphthalides **4a**–**4k**; compounds **4g**, **4h**, and **4j** were described previously [4, 5].

8-Cyclopropyl-2,3-dihydrofuro[3,4-*g*][1,4]benzodioxin-6(8*H*)-one (4a). Yield 69%, mp 142–143°C (purified by chromatography). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.55–0.76 m (4H) and 1.08 m (1H) (C_3H_5), 4.39 m (4H, OCH_2CH_2O), 4.75 d (1H, 8-H, J = 7.3 Hz), 6.98 s (1H, H_{arom}), 7.36 s (1H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 232 (23) $[M]^+$, 204 (10), 191 (25), 176 (20), 163 (91), 148 (9), 135 (9), 107 (15), 103 (15), 77 (22), 74 (12), 69 (21), 63 (25), 53 (14), 50 (53), 39 (100). Found, %: C 67.42, 67.53; H 5.18, 5.31. $C_{13}H_{12}O_4$. Calculated, %: C 67.23; H 5.43. M 232.24.

8-(Thiophen-2-yl)-2,3-dihydrofuro[3,4-*g*][1,4]benzodioxin-6(8*H*)-one (4b). Yield 64%, mp 152–153°C (purified by chromatography). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.32 m (4H, OCH_2CH_2O), 6.54 s (1H, H_{Th}), 6.90 s (1H, H_{arom}), 7.01 m (1H, H_{Th}), 7.14 d (1H, H_{Th}, J = 2.6 Hz), 7.35 d (1H, H_{Th}, J = 4.0 Hz), 7.41 s (1H, H_{arom}). Found, %: C 61.08, 61.21; H 3.29, 3.42. $C_{14}H_{10}O_4S$. Calculated, %: C 61.30; H 3.67.

8-Phenyl-2,3-dihydrofuro[3,4-*g*][1,4]benzodioxin-6(8*H*)-one (4c). Yield 88%, mp 167–168°C (from EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.26–4.31 m (4H, OCH_2CH_2O), 6.26 s (1H, 8-H), 6.75 s (1H, H_{arom}), 7.24–7.28 m (2H, H_{arom}), 7.35–7.38 m (3H, H_{arom}), 7.40 s (1H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 268 (78) $[M]^+$, 239 (23), 191 (26), 168 (32), 163 (100), 152 (10), 139 (90), 134 (31), 127 (12), 105 (32), 89 (12), 77 (84), 74 (24), 69 (18), 63 (36), 50 (90), 39 (19). Found, %: C 71.55, 71.77; H 4.18, 4.26. $C_{16}H_{12}O_4$. Calculated, %: C 71.64; H 4.51. M 268.27.

8-(4-Methylphenyl)-2,3-dihydrofuro[3,4-*g*][1,4]benzodioxin-6(8*H*)-one (4d). Yield 79%, mp 145–147°C (from EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.36 s (3H, CH_3), 4.31 m (4H, OCH_2CH_2O), 6.25 s (1H, 8-H), 6.75 s (1H, H_{arom}), 7.16 d (2H, H_{arom}, J = 8.1 Hz), 7.19 d (2H, H_{arom}, J = 8.1 Hz), 7.42 s (1H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 282 (100) $[M]^+$, 267 (37), 182 (12), 163 (87), 153 (21), 139 (21), 119 (23), 107 (14), 91 (44), 77 (20), 69 (13), 63 (40), 50 (66), 39 (35). Found, %: C 72.11, 72.40; H 4.77, 4.85. $C_{17}H_{14}O_4$. Calculated, %: C 72.33; H 5.00. M 282.30.

8-(2-Chlorophenyl)-2,3-dihydrofuro[3,4-*g*][1,4]benzodioxin-6(8*H*)-one (4e). Yield 73%, mp 143–144°C (from EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.30 m (4H, OCH_2CH_2O), 6.81 s (1H, 8-H), 6.97 s (1H, H_{arom}), 7.13 d.d (1H, H_{arom}, ^3J = 7.8, ^4J = 1.5 Hz), 7.21–7.31 m (2H, H_{arom}), 7.41 s (1H, H_{arom}), 8.16 d.d (1H, H_{arom}, ^3J = 7.9, ^4J = 1.3 Hz). Mass spectrum, m/z (I_{rel}, %): 302 (100) $[M]^+$, 267 (7), 238 (6), 223 (21), 202 (10), 191 (26), 173 (9), 163 (99), 151 (6), 139 (77), 126 (10), 111 (17), 75 (25), 69 (10), 63 (15), 50 (43). Found, %: C 63.28, 63.52; H 3.43, 3.51. $C_{16}H_{11}ClO_4$. Calculated, %: C 63.48; H 3.66. M 302.71.

5,6-Dimethoxy-3-(4-methylphenyl)-2-benzofuran-1(3*H*)-one (4f). Yield 66%, mp 156–157°C (from EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.33 s (3H, CH_3), 3.79 s (3H, OCH_3), 3.87 s (3H, OCH_3), 6.51 s (1H, 3-H), 6.90 s (1H, H_{arom}), 7.17 d (2H, H_{arom}, J = 8.1 Hz), 7.22 d (2H, H_{arom}, J = 8.1 Hz), 7.33 s (1H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 284 (19) $[M]^+$, 269 (6), 182 (6), 165 (100), 152 (7), 139 (6), 119 (15), 91 (12), 77 (6), 63 (7), 50 (6), 39 (6). Found, %: C 71.93, 72.08; H 5.56, 5.74. $C_{17}H_{16}O_4$. Calculated, %: C 71.82; H 5.67. M 284.31.

3-(4-Methoxyphenyl)-2-benzofuran-1(3*H*)-one (4i). Yield 82%, mp 115–117°C (purified by chromatography). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.82 s (3H, OCH_3), 6.39 s (1H, 2-H), 6.91 d.d (2H, H_{arom}, ^3J = 7.2, ^4J = 1.9 Hz), 7.19 d.d (2H, H_{arom}, ^3J = 7.2, ^4J = 1.9 Hz), 7.33 d.d (1H, H_{arom}, ^3J = 7.6, ^4J = 0.9 Hz), 7.57 m (1H, H_{arom}), 7.67 m (1H, H_{arom}), 7.97 d (1H, H_{arom}, J = 7.6 Hz). Mass spectrum, m/z (I_{rel}, %): 240

(86) $[M]^+$, 209 (22), 195 (28), 181 (32), 165 (40), 152 (61), 135 (99), 104 (100), 92 (19), 77 (75), 63 (34), 51 (42), 44 (17), 39 (25). Found, %: C 75.01, 75.21; H 5.02, 5.15. $C_{15}H_{12}O_3$. Calculated, %: C 74.99; H 5.03. *M* 240.26.

3-(2,3-Dihydro-1,4-benzodioxan-6-yl)-2-benzofuran-1(3*H*)-one (4k). Yield 66%, mp 136–137°C (from EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.26 m (4H, OCH_2CH_2O), 6.32 s (1H, 3-H), 6.75–6.79 m (2H, H_{arom}), 6.88 d (1H, H_{arom}, J = 8.2 Hz), 7.35 d (1H, H_{arom}, J = 7.6 Hz), 7.57 m (1H, H_{arom}), 7.67 m (1H, H_{arom}), 7.96 d (1H, H_{arom}, J = 7.7 Hz). Mass spectrum, m/z (I_{rel}, %): 268 (45) $[M]^+$, 168 (32), 163 (29), 152 (6), 139 (40), 133 (14), 128 (16), 113 (7), 104 (100), 87 (12), 77 (86), 63 (44), 51 (92), 43 (12), 39 (26). Found, %: C 71.55, 71.79; H 4.28, 4.37. $C_{16}H_{12}O_4$. Calculated, %: C 71.64; H 4.51. *M* 268.27.

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