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SYNTHESIS AND PROPERTIES OF SUBSTITUTED 2-METHYLENE-HYDRAZONO-2,3-DIHYDRO-3-BENZO[*b*]FURANONES

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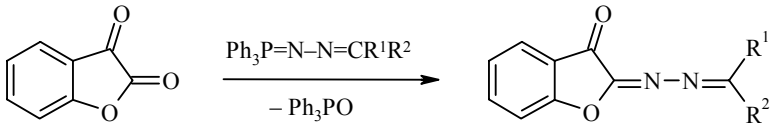
The reaction of 2,3-dihydro-2,3-benzo[b]furandione with the triphenylphosphazines of diazo compounds leads to substituted 2-methylenehydrazono-2,3-dihydro-3-benzo[b]furanones, which are hydrolyzed in an acidic medium to the substituted methylenehydrazides of o-hydroxyphenylglyoxalic acid and react with amines to form the products of addition at the activated CH=N bond of the side chain or 2-hydrazono-2,3-dihydro-3-benzo[b]furanone respectively.

Keywords: substituted 2-methylenehydrazono-2,3-dihydro-3-benzo[b]furanones, aminolysis, hydrolysis.

Earlier we showed that 5-aryl-2,3-dihydrofuran-2,3-diones react with triphenylphosphoranylidenehydrazones (subsequently referred to as triphenylphosphazines), synthesized from various diazo compounds, to form substituted 2-methylenehydrazono-2,3-dihydro-3-furanones [1]. The reaction takes place regioselectively at the lactone carbonyl group [2], but this path is an example of an anomalous Staudinger reaction in the presence of a ketone carbonyl in the heterocycle, which is not typical of triphenylphosphazines [3]. The limits of this reaction can be extended through the benzo[*b*] analog of the studied heterocycles – 2,3-dihydro-2,3-benzo[*b*]furandione. We established that the triphenylphosphazines obtained from diphenyldiazomethane, fluorenyldiazomethane, benzoyldiazomethane, and adamantanoyldiazomethane and (1-methyl-2-oxo-3-indolinylidene)triphenylphosphazine react with 2,3-dihydro-2,3-benzo[*b*]furandione in an inert solvent at room temperature with the formation of substituted 2-methylenehydrazono-2,3-dihydro-3-benzo[*b*]furanones **1a-e** (Table 1) and triphenylphosphine oxide.



1a–e

1a $R^1 = R^2 =$ Ph, **b** $R^1 + R^2 = C_{13}H_8$ (fluorenyl), **c** $R^1 =$ H, $R^2 =$ Bz, **d** $R^1 =$ H, $R^2 =$ AdCO, **e** $R^1 + R^2 = C_{10}H_7NO$ (1-1-methyl-2-oxo-3-indolinylidene)

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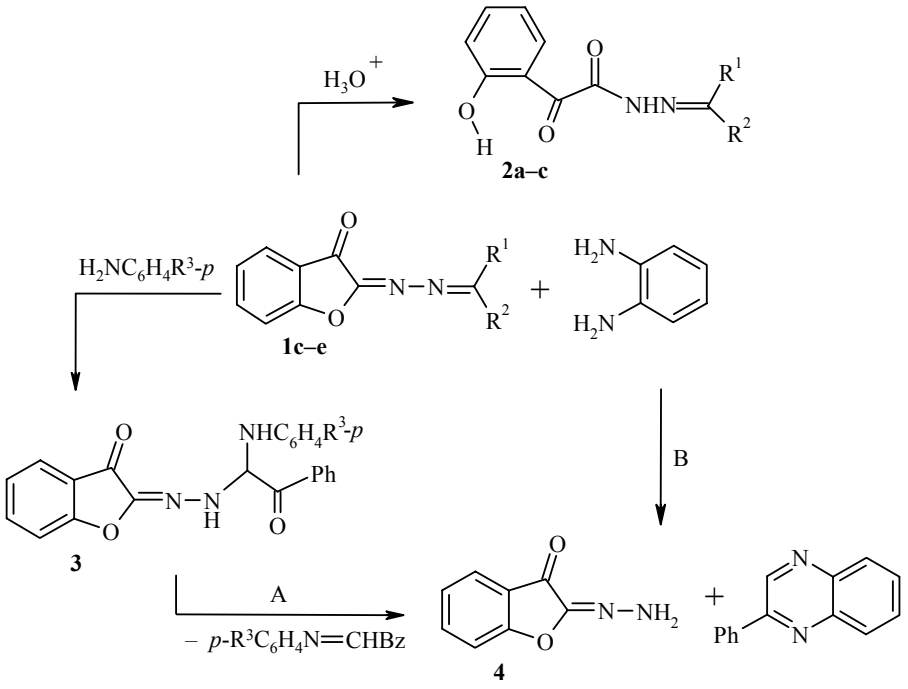
It is known that 2,3-dihydro-2,3-benzo[*b*]furandione is very readily decyclized to form *o*-hydroxyphenylglyoxalic acid [6]. Substitution of the oxygen atom of the lactone carbonyl of the heterocycle by a less electronegative nitrogen atom in compounds **1a-e** changes the distribution of electron density in the molecule and leads to greater stability for the benzofuran ring. Nevertheless, in a water–dioxane medium in the presence of catalytic amounts of hydrochloric acid at room temperature compounds **1c-e** are hydrolyzed to substituted methylenehydrazides of *o*-hydroxyphenylglyoxalic acid **2a-c**. Compounds **1a**,**b**, in which there is no acyl substituent at the C=N bond, are not hydrolyzed under mild conditions.



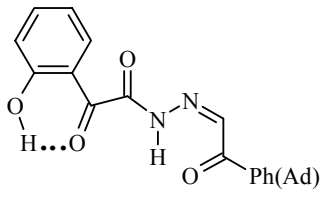
2 a R^1 = H, R^2 = Bz, **b** R^1 = H, R^2 = AdCO, **c** $R^1 + R^2 = C_{10}H_7NO$, **3** R^3 = H

TABLE 1. The Characteristics of the Synthesized Compounds

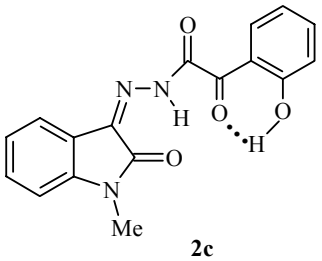
Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1a	$C_{21}H_{14}N_2O_2$	77.20 / 77.29	4.36 / 4.32	8.49 / 8.50	138-139	72
1b	$C_{21}H_{12}N_2O_2$	77.52 / 77.77	3.65 / 3.73	8.66 / 8.63	197-198	89
1c	$C_{16}H_{10}N_2O_3$	73.16 / 73.28	3.67 / 3.84	10.51 / 10.68	146-147	87
1d	$C_{20}H_{20}N_2O_3$	71.55 / 71.41	5.81 / 5.99	8.28 / 8.32	133-134	68
1e	$C_{18}H_{11}N_3O_3$	66.75 / 66.88	3.69 / 3.62	13.70 / 13.76	245-246	76
2a	$C_{16}H_{12}N_2O_4$	64.92 / 64.86	4.12 / 4.08	9.36 / 9.45	160-161	83
2b	$C_{20}H_{22}N_2O_4$	67.89 / 67.78	6.14 / 6.25	7.79 / 7.90	196-197	77
2c	$C_{17}H_{13}N_3O_4$	63.01 / 63.15	4.25 / 4.05	12.83 / 12.99	194-195	89
3	$C_{22}H_{17}N_3O_3$	70.89 / 71.15	4.42 / 4.61	11.38 / 11.37	149-150	92
4	$C_8H_6N_2O_2$	60.12 / 59.26	3.59 / 3.73	17.18 / 17.25	196-197	58 (A), 81 (B)

The IR spectra of compounds **1a-e** (Table 2) contain a band for the stretching vibrations of the ketone carbonyl of the benzofuran ring in the region of 1710-1715 cm^{-1}. The absence of the absorption band of the lactone carbonyl in the region of 1800-1840 cm^{-1} [4, 5] indicates the formation of products from reaction at the carbonyl group at position 2 of the heterocycle.

The low-frequency position of the absorption bands for the carbonyl groups of the acyl fragment of the hydrazides **2a**,**b**, the carbonyl at position 2 of the heterocycle in the hydrazide **2c**, and the ketone carbonyl group (in the region of 1595-1605 cm^{-1}) in the IR spectra of these compounds and the downfield position of the signals for the protons of the N–H and O–H groups in the ^1H NMR spectra indicate that they exist in the form with an intramolecular hydrogen bond, which is possible with the *Z*-configuration along the C=N bond.



2a,b



2c

TABLE 2. The Spectral Characteristics of the Synthesized Compounds

Com-pound	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	^1H NMR spectrum, δ, ppm (*J*, Hz)
1a	1715 ($C_{(3)}$=O); 1595 (C=S, C=N)		6.79-7.83 (14H, m, H_{Ar})
1b	1710 ($C_{(3)}$=O); 1590 (C=S, C=N)	310 (4.03); 385 (4.18)	6.96-8.03 (12H, m, H_{Ar})
1c	1720 ($C_{(3)}$=O); 1660 (PhC=O); 1600 (C=S, C=N)	274 (4.36); 357 (3.72)	7.13-7.76 (9H, m, H_{Ar}); 8.05 (1H, s, CH=N)
1d	1710 ($C_{(3)}$=O); 1650 (AdC=O); 1580 (C=S, C=N)		2.06-1.26 (15H, m, Ad); 7.56-7.10 (4H, m, H_{Ar}); 7.70 (1H, s, CH=N)
1e	1710 ($C_{(3)}$=O); 1715 ($C_{(2)}$=O substituents $R^1 + R^2$); 1600 (C=S, C=N)	312 (4.08); 361 (3.93)	3.11 (3H, s, CH_3); 6.68-7.70 (8H, m, H_{Ar})
2a	3400 (OH); 3230 (NH); 1702 (NHC=O); 1625 (PhC=O); 1540 (amide II)		6.78-7.80 (10H, m, $9H_{Ar}$, CH=N); 10.95 (1H, s, OH); 12.55 (1H, s, NH)
2b	3420 (OH); 3240 (NH); 1698 (NHC=O); 1630 (AdC=O); 1545 (amide II)		1.56-2.18 (15H, m, Ad); 6.99-7.56 (5H, m, $4H_{Ar}$, CH=N); 10.92 (1H, s, OH); 12.58 (1H, s, NH)
2c	3400 (OH); 3225 (NH); 1698 br. (NHC=O, $C_{(2)}$=O substituents R^1R^2); 1550 (amide II)		3.10 (3H, s, CH_3); 6.65-7.76 (8H, m, H_{Ar}); 10.86 (1H, s, OH); 12.65 (1H, s, NH)
3	3373 (NH-Ar); 3245 (NH-CH); 1690 ($C_{(3)}$=O); 1655 (PhC=O)		6.33-8.16 (16H, m, H_{Ar}, CH-NH, NH-Ar); 9.08 (1H, d, *J* = 6.0, NH-CH)
4	3400, 3280, 3215 (NH_2); 1685 ($C_{(3)}$=O)	263 (3.98); 302 (3.97); 382 (3.69)	7.03-7.75 (4H, m, H_{Ar}); 7.90-8.36 (2H, br. s, NH_2)

During study of the chemical behavior of the methylenehydrazones **1** with aromatic amines it was established that the direction of attack by the nucleophile depends on the nature of the substituents R^1 and R^2 in the side chain of the substrate and on the nucleophilicity of the active amine. Thus, the methylenehydrazone **1c** reacts with aniline with the formation of 2-[(2-oxo-2-phenyl-1-phenylamino)ethyl]hydrazono-2,3-dihydro-3-benzo[*b*]furanone (**3**). However, when the reaction of **1c** was carried out with *p*-anisidine (R^3 = OMe) under analogous conditions 2-hydrazono-2,3-dihydro-3-benzo[*b*]furanone (**4**) was isolated instead of the expected product of addition at the activated CH═N bond (method A). Obviously, during the reaction of compound **1c** and an amine with higher nucleophilicity than the formed hydrazone **4** the reaction does not stop at the stage of addition of the amine at the activated CH═N bond in the initial compound, but the hydrazone **4** is displaced by the more nucleophilic reagent with the formation of the products from transimination.

The hydrazone **4** was also obtained in the reaction of compound **1c** with *o*-phenylenediamine (method B). 2-Phenylquinoxaline was isolated from the reaction mixture together with the hydrazone **4**. Here, as in the case with aromatic amines, one amino group of the *o*-phenylenediamine probably adds initially at the CH═N bond of the side chain. However, the addition product formed here is not stable and undergoes intramolecular cyclization through the carbonyl group of the benzoyl fragment and the second amino group of the *o*-phenylenediamine with cleavage of the NH–CH bond. It should be noted that the instability of the benzofuran ring prevents the production of its 2-hydrazono derivative by direct reaction with the hydrazines [7]. Thus, the reaction of methylenehydrazones (**1**) with *o*-phenylenediamine and *p*-anisidine is a convenient method in preparative respects for the synthesis of the unsubstituted hydrazone **4**.

EXPERIMENTAL

The IR spectra were recorded for suspensions in vaseline oil on an FSM-1201 instrument (Russian). The ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 MHz) in DMSO-d_6 with TMS as internal standard. The mass spectra were obtained on a Varian MAT-311 instrument with 70 eV ionizing electrons with direct injection of the sample into the ion source. The UV spectra were recorded on an SF-46 spectrometer for solutions in ethanol. The reactions and the purity of the products were monitored by TLC on Silufol UV-254 in the 10:9:1 ether–benzene–acetone system.

Substituted 2-Methylenehydrazono-2,3-dihydro-3-benzo[*b*]furanones 1a-e (General Method). To a solution of 2,3-dihydro-2,3-benzo[*b*]furandione (1.48 g, 0.01 mol) in anhydrous toluene (10 ml) was added a suspension of triphenylphosphazine (0.01 mol) in the same solvent (15 ml). The mixture was stirred at ~20°C until the reagent had completely dissolved. The obtained solution was cooled to 0°C. The precipitate was filtered off and recrystallized from toluene.

Substituted Methylenehydrazides of *o*-Hydroxyphenylglyoxalic Acid 2a-c (General Method). A suspension of the compound **1c-e** (0.01 mol) was stirred in a 3:1 mixture of dioxane and water (35 ml) in the presence 10% HCl (5 ml) until the reagent had completely dissolved. The solution was kept at ~20°C for 24 h. After removal of the solvent the residue was recrystallized from carbon tetrachloride. Mass spectrum of *o*-hydroxyphenylglyoxalic benzoylmethylenehydrazide (**2a**), *m/z* (I_{rel}, %): 296 $[M]^+$ (55), 191 $[M-C_6H_5CO]^+$ (96), 164 $[M-C_6H_5COCH{=}N]^+$ (17), 147 $[M-OHC_6H_4COCO]^+$ (26), 121 $[OHC_6H_4CO]^+$ (100), 105 $[C_6H_5CO]^+$ (21).

2-[(2-Oxo-2-phenyl-1-phenylamino)ethyl]hydrazono-2,3-dihydro-3-benzo[*b*]furanone (3). To a solution of compound **1c** (2.62 g, 0.01 mol) in anhydrous carbon tetrachloride (30 ml) was added dropwise a solution of aniline (0.93 g, 0.01 mol) in the same solvent (10 ml) with stirring. The reaction mixture was kept at ~20°C for 24 h. The precipitate was filtered off and recrystallized from carbon tetrachloride. Mass spectrum of compound (**3**), *m/z* (I_{rel}, %): 278 $[M-C_6H_5NH_2]^+$ (46), 250 $[M-C_6H_5NH_2-CO]^+$ (100), 173 $[M-C_6H_5NH_2-C_6H_5CO]^+$ (28), 162 $[M\text{-}C_6H_5COCH{=}NC_6H_5]^+$ (44), 105 $[C_6H_5CO]^+$ (25), 93 $[C_6H_5NH_2]$ (38).

2-Hydrazono-2,3-dihydro-3-benzo[*b*]furanone (4). A. To a solution of compound **1c** (2.62 g, 0.01 mol) in anhydrous carbon tetrachloride (30 ml) was added dropwise a solution of of *p*-anisidine (1.22 g, 0.01 mol) in the same solvent (15 ml) with stirring. The reaction mixture was cooled to 0°C, and the precipitate was filtered off and recrystallized from toluene.

B. A solution of compound **1c** (2.62 g, 0.01 mol) and *o*-phenylenediamine (1.08 g, 0.01 mol) in anhydrous toluene (50 ml) was kept at ~20°C for 6 h. After the mixture had been cooled to 0°C the precipitate was filtered off and recrystallized from toluene.

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