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β-(2-BENZOFURYL)ENAMINES IN THE SYNTHESIS OF DERIVATIVES OF DIBENZOFURAN AND BENZOFURO[3,2-*c*]PYRIDINE

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3-Aroyl-2-(β-dimethylamino-β-methylvinyl)-5-methoxybenzofurans were synthesized by the reaction of the respective 3-aroyl-2-methyl-5-methoxybenzofurans with the diethyl acetal of N,N-dimethylacetamide. They were converted into substituted dibenzofurans and benzofuro[3,2-c]pyridines.

Keywords: acetals, benzofuro[3,2-*c*]pyridines, dibenzofurans, enamines.

Earlier [1-3] we showed that 3-aroyl-2-β-dimethylaminovinyl-5-methoxybenzofurans are suitable starting compounds for the synthesis of various heterocycles and, in particular, benzofuro[3,2-*c*]pyridines. These enamines were obtained by the condensation of DMF diethyl acetal at the CH_3 group of the respective 3-aroyl-2-methyl-5-methoxybenzofurans (**1**). It seemed interesting to realize analogous syntheses based on other enamines, e.g., those obtained by the reaction of the benzofurans **1** with N,N-dimethylacetamide diethyl acetal **2**.

This interest arose from the fact that substances with pronounced biological activity had been found among the derivatives of benzofuro[3,2-*c*]pyridine [4, 5] and also from the fact that the dimethylaminomethylene- and dimethylaminopropylene derivatives can differ considerably in reactivity (e.g., see [6]). Such difference is due primarily to the presence of the β-methyl group in the enamine fragment, which can give rise to unusual chemical transformations uncharacteristic of the demethyl derivatives. In fact, condensation of the benzofurans **1a-e** with the acetal **2** takes place ambiguously – together with the formation of the enamines **3a-e** cyclization takes place with the participation of the methyl group of the enamine fragment and the carbonyl at position 3 with the formation of 1-aryl-3-dimethylamino-8-methoxydibenzofurans **4a-d**. In other words, it is extremely hard to stop the process at the stage of the formation the enamines **3**, and the formation of the dibenzofurans **4** cannot be avoided even with brief heating of compounds **1** and **2**. After strong cooling the almost pure enamines **3** separate from the solutions, while the mother solutions contain mixtures of the enamine **3** and the tricycle **4**, which can only be separated by column chromatography. It is clear that the enamines **3** are an intermediate stage in the formation of the dibenzofurans **4**, i.e., the basicity of the acetal is sufficient for the removal of a proton from the 2-CH_3 group followed by intramolecular cyclization coupled with attack by the carbonyl at the anionic center.

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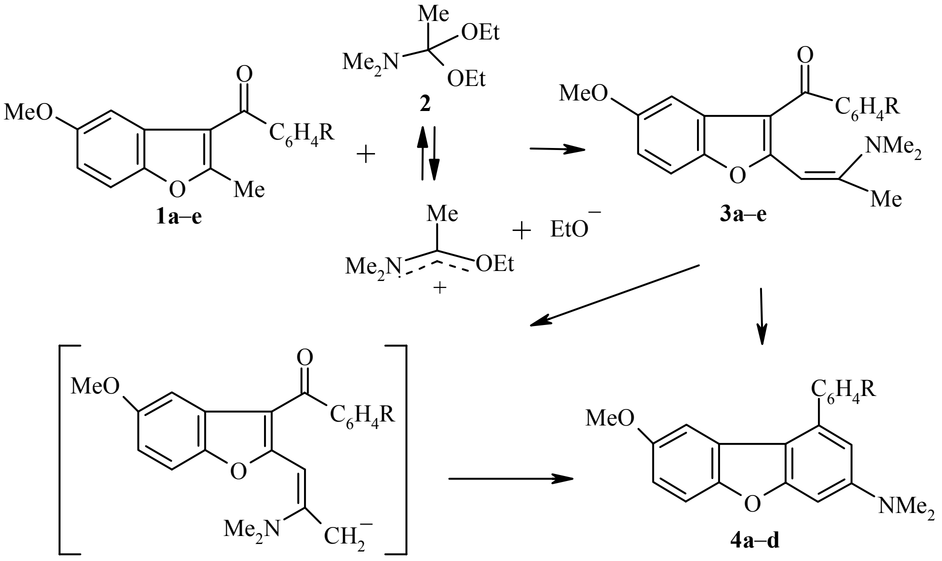
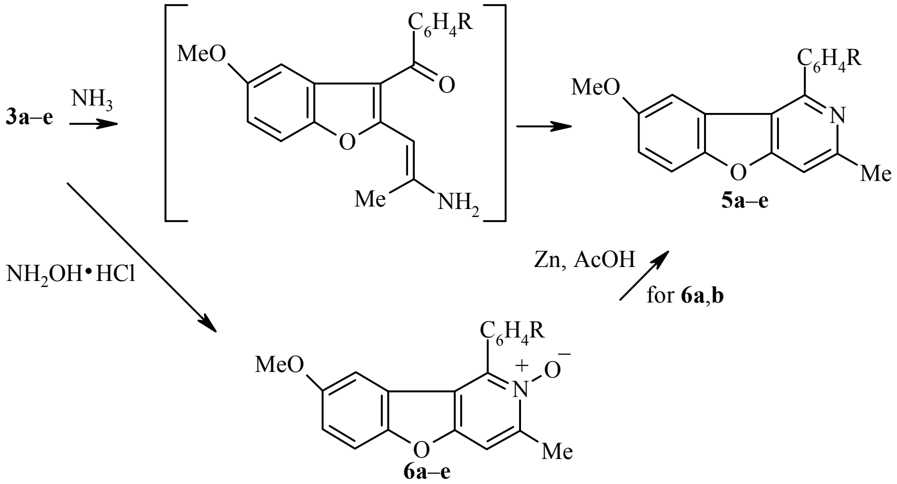


a R = H, **b** R = *p*-Me, **c** R = *p*-Cl, **d** R = *p*-Br, **e** R = *p*-OMe

The dissociation of acetals into an ambident cation and an alkoxy anion was described in [7]. The dibenzofurans **4a-d** can also be obtained directly from the enamines **3a-d**. In fact, the tricycles **4** are formed smoothly when solutions of the enamines in DMF are boiled. The production of the benzofuryleneamines **3** makes it possible also to synthesize the benzofuropyridines **5**. It was proposed to realize this in two stages, i.e., by transamination of the enamines **3a-e** with ammonia followed by cyclization of the obtained primary enamines to the required tricyclic compounds **5**. It was found that the reaction of the benzofurans **3a-e** with ammonia in DMF in the presence of *p*-toluenesulfonic acid takes place successfully at room temperature and results in the formation of 1-aryl-8-methoxybenzofuro[3,2-*c*]pyridines **5a-e** with satisfactory yields.



Compounds **5a**,**b** were also obtained by an alternative method through the corresponding N-oxides **6a-e**. The latter were synthesized by our previously developed method [2, 3] by the reaction of enamines (in the present work the enamines **3a-e**) with hydroxylamine. Reduction of the obtained N-oxides with zinc in acetic acid leads smoothly to benzofuropyridines — in the present work this was demonstrated for the case of the transformation of the N-oxides **6a**,**b** into the tricyclic compounds **5a**,**b**. The N-oxides **6a**,**b** are characterized by

TABLE 1. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % Calculated, %				mp, °C	Mass spectrum	Yield,* %
		C	H	N	Hal			
3a	$C_{21}H_{21}NO_3$	75.12 75.20	6.43 6.31	3.99 4.18		125-128	335	55
3b	$C_{22}H_{23}NO_3$	75.34 75.62	6.48 6.63	4.03 4.01		152-153	349	56
3c	$C_{21}H_{20}ClNO_3$	67.96 68.20	5.29 5.45	3.65 3.79	9.41 9.59	142-144	369	57
3d	$C_{21}H_{20}BrNO_3$	60.96 60.88	5.12 4.87	3.40 3.38		154-155	414	64
3e	$C_{22}H_{23}NO_4$	72.34 72.31	6.27 6.34	4.00 3.83		159-160	365	73
4a	$C_{21}H_{19}NO_2$	79.77 79.47	6.16 6.03	4.15 4.41		122-123	317	60
4b	$C_{22}H_{21}NO_2$	80.07 79.73	6.64 6.39	4.29 4.23		134-135	331	82
4c	$C_{21}H_{18}ClNO_2$	71.53 71.68	5.16 5.16	3.84 3.98	10.08 10.08	138-139	351	70
4d	$C_{21}H_{18}BrNO_2$	63.86 63.64	4.87 4.58	3.46 3.53		136-138	396	67
5a	$C_{19}H_{15}NO_2$	78.82 78.87	5.20 5.23	4.75 4.84		131-132	289	77
5b	$C_{20}H_{17}NO_2$	78.96 79.19	5.69 5.65	4.76 4.62		133-134	303	73
5c	$C_{19}H_{14}ClNO_2$	70.51 70.48	4.40 4.36	4.19 4.33	10.87 10.95	173-174	323	75
5d	$C_{19}H_{14}BrNO_2$	62.34 61.97	3.69 3.83	3.82 3.80		170-172	368	69
5e	$C_{20}H_{17}NO_3$	75.35 75.22	5.40 5.37	4.30 4.39		158-160	319	66
6a	$C_{19}H_{15}NO_3$	74.64 74.74	4.78 4.95	4.37 4.59		232-233	305	96
6b	$C_{20}H_{17}NO_3$	75.22 75.22	5.35 5.37	4.28 4.39		229-232	319	98
6c	$C_{19}H_{14}ClNO_3$	67.08 67.16	4.09 4.15	4.00 4.12	10.57 10.43	208-210	340	96
6d	$C_{19}H_{14}BrNO_3$	60.11 59.39	4.31 3.67	3.75 3.65	20.25 20.8	226-228	383	92
6e	$C_{20}H_{17}NO_4$	71.71 71.63	5.10 5.11	4.11 4.18		188-190	335	98

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* The yields of compounds **4a-d** obtained by method B.

the fact that their ^1H NMR spectra show a significant downfield shift of the signals for the 4-H protons (compared with the signals of the deoxidized derivatives **5a**,**b**) and their mass spectra contain strong peaks for the $[M-H]^+$, $[M-O]^+$, and $[M-OH]^+$ ions in addition to the molecular ion peaks.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker AC-200 instrument (200 MHz) in DMSO-d_6 with TMS as internal standard. The mass spectra were obtained on a Varian ISG-700 chromato-mass spectrometer with direct injection of the samples into the ion source. The individuality of the compounds was checked by TLC on Silufol UV 254 plates with development in UV light.

Benzofurans (1a-e). These compounds were obtained by the previously described method [2]. The physicochemical and spectral data are given in Table 1.

3-Aroyl-2-(β-dimethylamino-β-methylvinyl)-5-methoxybenzofurans (3a-e). A mixture of the benzofuran **1a-e** (0.01 mol), DMF (5 ml), and acetamide diethyl acetal (3 ml) was boiled for 20 min. The reaction mixture was cooled to 0°C, and the crystals that separated were filtered off, washed on the filter with ether, and dried. Compounds **3a-e** were obtained. The solvent and the excess of the acetal were distilled from the mother solution, and the smallest amount of 2-propanol was added to the residue. The precipitate was filtered off and dried. A mixture of compounds **3a-e** and **4a-e** was obtained. ^{1}H NMR spectrum, δ, ppm, J (Hz): **3a** – 2.46 (3H, s, β-CH_3); 2.87 (6H, s, $N(CH_3)_2$), 3.61 (3H, s, 5-OCH_3); 5.58 (1H, s, CH); 6.57 (1H, d, J = 2.5, 4-H); 6.68 (1H, q, J_1 = 2.5, J_2 = 8.7, 6-H); 7.32 (1H, d, J = 8.7, 7-H); 7.54 (5H, m, aromatic protons); **3d** – 2.46 (3H, s, β-CH_3); 2.90 (6H, s, $N(CH_3)_2$); 3.63 (3H, s, 5-OCH_3); 5.59 (1H, s, CH); 6.55 (1H, d, J = 2.8, 4-H); 6.69 (1H, q, J_1 = 2.8, J_2 = 8.5, 6-H); 7.32 (1H, d, J = 8.5, 7-H); 7.58 (4H, A_2B_2 system, aromatic protons).

1-Aryl-3-dimethylamino-8-methoxydibenzofurans (4a-d). A. The mixture of compounds **3** and **4** obtained in the previous experiment was dissolved in benzene and purified by column chromatography on silica gel with benzene as eluant. The solvent was dissolved, and compounds **4a-d** were obtained.

B. A mixture of the enamine **3a-d**, DMF (15 ml), and piperidine (0.6 ml) was boiled for 5 h. The solvent was distilled, and the smallest amount of 2-propanol was added to the residue. The crystals were filtered off and dried. Compounds **4a-d** were obtained. ^{1}H NMR spectrum, δ, ppm, J (Hz): **4a** – 3.04 (6H, s, $N(CH_3)_2$); 3.61 (3H, s, 8-OCH_3); 6.64 (1H, d, J = 2.4, 2-H); 6.73 (1H, d, J = 2.4, 4-H); 6.87 (2H, m, 7- and 9-H); 7.45 (1H, d, J = 8.8, 6-H); 7.5-7.7 (5H, m, aromatic protons); **4b** – 2.42 (3H, s, *p*-CH_3); 3.02 (6H, s, $N(CH_3)_2$); 3.63 (3H, s, 8-OCH_3); 6.60 (1H, d, J = 2.4, 2-H); 6.78 (1H, d, J = 2.4, 4-H); 6.87 (2H, m, 7- and 9-H); 7.44 (1H, d, J = 8.8, 6-H); 7.47 (4H, A_2B_2 system, aromatic protons).

1-Aryl-8-methoxybenzofuro[3,2-*c*]pyridines (5a-e). A. A mixture of the enamine **3a-e** (0.01 mol), *p*-toluenesulfonic acid (1.8 g, 0.01 mol), concentrated ammonia (5 ml), and DMF (20 ml) was stirred at room temperature and left overnight. The crystals that separated were filtered off, washed on the filter with low-boiling petroleum ether, and dried. ^{1}H NMR spectrum, δ, ppm, J (Hz): **5a** – 2.66 (3H, s, 3-CH_3); 3.68 (3H, s, 8-OCH_3); 7.05 (1H, d, J = 2.4, 9-H); 7.11 (1H, q, J_1 = 2.4, J_2 = 8.8, 7-H); 7.55 (1H, s, 4-H); 7.57 (1H, d, J = 8.8, 6-H); 7.59-7.82 (5H, m, aromatic protons); **5d** – 2.64 (3H, s, 3-CH_3); 3.71 (3H, s, 8-OCH_3); 7.04 (1H, d, J = 2.2, 9-H); 7.11 (1H, q, J_1 = 2.2, J_2 = 9.0, 7-H); 7.54 (1H, s, 4-H); 7.63 (1H, d, J = 9.0, 6-H); 7.78 (4H, A_2B_2 system, aromatic protons).

B. To the N-oxide **6a**,**b** (0.01 mol) in glacial acetic acid (20 ml) while boiling we added zinc dust (5 g) in portions over 30 min. The boiling was continued for 2-3 h. The reaction was monitored by chromatography. The reaction mixture was cooled, and the inorganic precipitate was filtered off. The solvent was distilled, water (100 ml) was added to the residue, and the mixture was filtered. The precipitate was washed with water and dried. Compounds **5a**,**b** were obtained.

N-Oxides of 1-Aryl-8-methoxybenzofuro[3,2-*c*]pyridines (6a-e). A mixture of the enamine **3a-e** (0.01 mol), hydroxylamine hydrochloride (0.01 mol), and DMF (5 ml) was boiled for 1 h. The reaction mixture was cooled to 0-5°C, and the precipitate was filtered off, washed on the filter with water, and dried. Compounds **6a-e** were obtained. A further quantity of crystals was obtained after dilution with water. They were filtered off and dried. ^{1}H NMR spectrum, δ, ppm, J (Hz): **6a** – 2.53 (3H, s, 3-CH_3); 3.55 (3H, s, 8-OCH_3); 6.26 (1H, d, J = 2.7, 9-H); 7.10 (1H, q, J_1 = 2.7, J_2 = 9.6, 7-H); 7.62 (5H, m, aromatic protons, 6-H signal masked by the signals of the Ph protons); 7.89 (1H, s, 4-H); **6d** – 2.52 (3H, s, 3-CH_3); 3.62 (3H, s, 8-OCH_3); 6.34 (1H, d, J = 2.4, 9-H); 7.13 (1H, q, J_1 = 2.4, J_2 = 9.6, 7-H); 7.63 (1H, d, J = 9.6, 6-H); 7.70 (4H, A_2B_2 system, aromatic protons).

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