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FURYL(ARYL)METHANES AND THEIR DERIVATIVES. 23.* SIMPLE SYNTHESIS OF BENZO[*b*]FURAN DERIVATIVES FROM 2-ALKYLFURANS

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New derivatives of benzo[b]furan were obtained during successive bromination and dehydrobromination of alkanones containing a gem-difurylmethyl fragment. A mechanism is proposed for the transformations that occur.

Keywords: 2-alkylfurans, benzo[*b*]furan, intramolecular cyclization.

Benzofuran derivatives exhibit various types of physiological activity and enter into medicinal products [2-4], and this determines the great attention that has been paid to the synthesis of new compounds of this series.

All the known approaches to the synthesis of the benzofuran system can be divided into two main types. The first includes the intramolecular cyclization of benzene derivatives, leading to the formation of an annellated furan ring, while the second leads to the formation of a benzene ring at the heterocycle. The first approach is most familiar and has found widespread use in the construction of benzofuran derivatives [2, 5].

The second type is less widely used. However, several original methods for the synthesis of benzofuran structures are known, e.g., the reaction of α-furfurylidene-γ-aryl-$\Delta^{\beta,\gamma}$-butenolides with anhydrous $AlCl_3$ [6] or the use of 2-vinylfurans as dienes in the Diels–Alder reaction [7].

Comparatively recently papers appeared on the synthesis of benzo[*b*]furans using copper and palladium catalysts for the formation of the C–C bond [8-10]. Katritzky and coworkers used the benzotriazole fragment as a convenient leaving group [11, 12] for the synthesis of benzofurans from benzotriazolylmethylfurans [3]. The latter were converted by addition to α,β-unsaturated ketones into the corresponding γ-benzotriazolyl-γ-furyl-substituted saturated ketones, the cyclization of which followed by dehydration and elimination of benzotriazole led to the desired compounds.

In the present work new derivatives of benzofuran were obtained from alkanones containing a difuryl fragment: 5,5-Di(5-methylfur-2-yl)-2-pentanone (**1a**) and 6,6-di(5-ethylfur-2-yl)-3-hexanone (**1b**), the products from hydrolytic cleavage of the furan ring under the influence of dilute sulfuric acid [13].

* For Communication 22, see [1].

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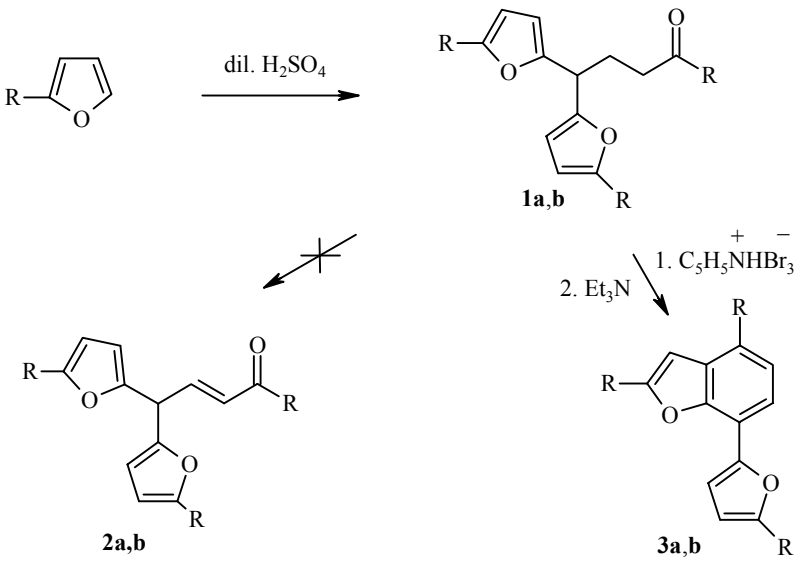
It was proposed to use compounds **1a**,**b** for the synthesis of the unsaturated ketones **2a**,**b** by successive bromination and dehydrobromation. Earlier such a path was used for the synthesis of a series of benzofurylbutenones from the corresponding substituted butanones [14]. However, the bromination of compounds **1a**,**b** with pyridinium perbromide bromide followed by treatment with triethylamine gave the benzofuran derivatives **3a**,**b** instead of the expected ketones **2a**,**b** (Scheme 1).

Scheme 1



The treatment of the ketones **1a**,**b** with pyridinium perbromide bromide was carried out in absolute THF, absolute dioxane, and dioxane containing trace quantities of water. The yields of the benzofurans **3a**,**b** amounted to 17-45% (Table 1).

It should be noted that the reaction in all cases is accompanied by strong resinification of the reaction mixture, particularly with dioxane containing traces of water (Table 1, expts. 3 and 7).

TABLE 1

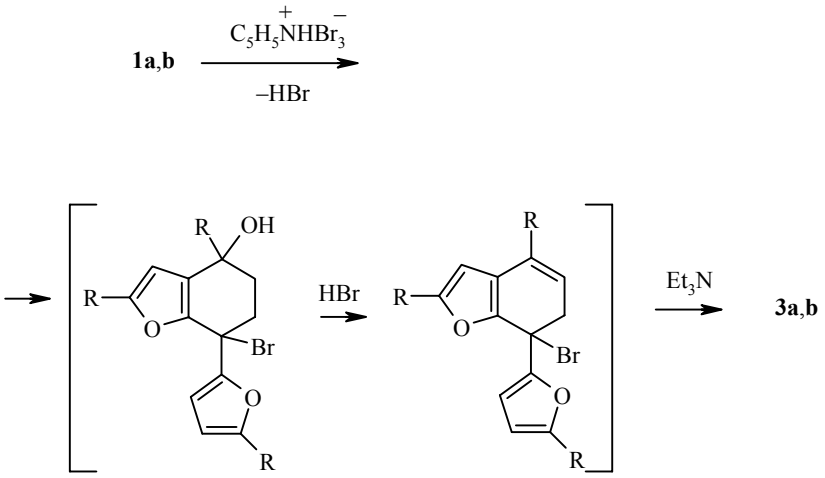
Experiment	R	Procedure*	Solvent	Yield, %
1	CH_3	A	abs. THF	42
2	CH_3	B	abs. dioxane	27
3	CH_3	C	Dioxane*[2]	17
4	CH_3	D	CCl_4	45
5	C_2H_5	A	abs. THF	45
6	C_2H_5	B	abs. dioxane	32
7	C_2H_5	C	Dioxane*[2]	20
8	C_2H_5	D	CCl_4	48

* Brominating agent in procedures A-C, $C_5H_5NHBr_3$; in procedure D, N-bromosuccinimide.

*[2] The commercial reagent was used without drying.

Earlier during study of the bromination of furyl(aryl)methanes we noticed the ease with which the reaction occurs at the methine carbon atom [15]. We therefore supposed that the bromination of compounds **1a**,**b**, containing a difuryl fragment takes place in a similar way. The presence of acid (HBr) in the reaction mixture leads to cyclization at the β position of one of the furan rings, while subsequent treatment with triethylamine leads to dehydrobromination with aromatization of the system and the formation of a benzo[*b*]furan derivative (Scheme 2).

Scheme 2



When the reaction is carried out in dioxane containing traces of water, the direct transformation ketone **1** → benzofuran **3** takes place in the absence of the amine. It is clear that the formation of compounds **3** in this case is promoted by the presence of water, which acts as nucleophile, in the reaction mixture.

Compounds **3a**,**b** were also obtained with yields of 45 and 48% during the bromination of ketones **2a**,**b** with N-bromosuccinimide (NBS) in the presence of benzoyl peroxide or azodiisobutyronitrile (AIBN).

As whole our proposed method for the synthesis of benzo[*b*]furans from derivatives of 2-alkylfurans represents another example of the synthetic potentialities of furan derivatives. A special feature of this approach is the synthesis of benzenoid compounds from alkylfurans – substances produced from furfural, which is a product of the treatment of agricultural waste materials.

EXPERIMENTAL

The IR spectra were recorded in Vaseline oil on a Specord IR-75 instrument. The ^{1}H NMR spectra were recorded on a Tesla BS-467 spectrometer at 60 MHz and a Bruker WM-250 spectrometer at 250 MHz with deuterochloroform as solvent and HMDS as internal standard. The reaction paths and the purity of the products were monitored by TLC on Silufol UV-254 plates with 1:2 methylene chloride–hexane as eluent and iodine vapor, bromine, and 2,4-DNPH as developers. Silufol (μ 5-40) was used for preparative column chromatography.

5,5-Di(5-methylfur-2-yl)-2-pentanone (1a). The compound was obtained by the method described in [13].

6,6-Di(5-ethylfur-2-yl)-3-hexanone (1b). A mixture of 2-ethylfuran (26.3 ml, 0.25 mol), sulfuric acid (*d* 1.84) (21.85 ml, 0.41 mol), and water (125 ml) was kept at 60°C with vigorous stirring for 2-2.5 h. The oily upper layer was separated and distilled under vacuum, and the fraction boiling at 98°C/12 mm Hg was collected. As a result 15.2 g (63.6%) of the oily bright-yellow product (**1b**) was obtained. IR spectrum (thin layer), ν, cm^{-1}: 1720 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.03 (3H, t, *J* = 7.5, CH_3); 1.21 (6H, t, *J* = 7.5, CH_3); 2.23 (2H, q, *J* = 7.5, CH_2); 2.34-2.41 (4H, m, CH_2); 2.59 (4H, q, *J* = 7.5, $2CH_2$); 3.99 (1H, t, *J* = 7.5, CH); 5.87 (2H, d, *J* = 3.2, 4-H_{Fur}); 5.94 (2H, d, *J* = 3.2, 3-H_{Fur}). Found %: C 75.02; H 8.30. $C_{18}H_{24}O_3$. Calculated %: C 74.97; H 8.39.

2,4-R-7-(5-R-Fur-2-yl)benzo[*b*]furans (4a, b). (General Procedures). A. To a solution of ketone **1** (0.01 mol) in absolute THF (15 ml) in small portions while stirring we added pyridinium perbromide bromide (3.84 g, 0.012 mol). After 0.5 h the reaction mixture was separated from the dark oil by decantation, anhydrous triethylamine (5 ml, 0.05 mol) was added, and the mixture was stirred for a further 20 min. The triethylamine hydrobromide was then filtered off, and the precipitate was washed on the filter with a small amount of THF. The solvent was distilled, the oily residue was dissolved by stirring in a mixture of benzene and hexane, and the solution was passed through a small column (15 × 2 cm) of silica gel. The filtrate was evaporated to dryness, and the residue was dissolved in 2-3 ml of hexane and kept in the refrigerator to crystallize.

2,4-Dimethyl-7-(5-methylfur-2-yl)benzo[*b*]furan (3a). The product formed pale-yellow crystals; mp 82°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 2.43 (3H, s, CH_3); 2.49 (3H, s, CH_3); 2.53 (3H, s, CH_3); 6.17 (1H, d, *J* = 3.2, 4-H_{Fur}); 6.42 (1H, s, 3-H); 7.00 (1H, d, *J* = 3.2, 3-H_{Fur}); 7.03 (1H, d, *J* = 8.1, 5-H); 7.55 (1H, d, *J* = 8.1, 5-H). Found %: C 79.75; H 6.20. $C_{15}H_{14}O_2$. Calculated %: C 79.62; H 6.24.

2,4-Diethyl-7-(5-ethylfur-2-yl)benzo[*b*]furan (3b). The product formed beige crystals melting at 21-22°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.31 (6H, t, *J* = 7.5, CH_3); 1.40 (3H, t, *J* = 7.5, $2CH_3$); 2.57 (2H, q, *J* = 7.5, CH_2); 2.88 (4H, q, *J* = 7.5, CH_2); 6.15 (1H, d, *J* = 3.2, 4-H_{Fur}); 6.45 (1H, s, 3-H); 6.99 (1H, d, *J* = 3.2, 3-H_{Fur}); 7.04 (1H, d, *J* = 8.1, 5-H); 7.56 (1H, d, *J* = 8.1, 6-H). Found %: C 80.44; H 7.68. $C_{18}H_{20}O_2$. Calculated %: C 80.56; H 7.51.

B. The reaction was carried out similarly, but anhydrous dioxane (15 ml) was used instead of THF.

C. Commercial dioxane without previous drying was used as solvent.

To a solution of ketone **2** (1.01 mol) in dioxane (15 ml) while stirring we added in portions of $C_5H_5NH^+Br_3^-$ (3.84 g, 0.012 mol) After 0.5 h the reaction mixture was separated from the dark oil that formed by decantation and was passed through a small layer of silica gel, which was washed with dioxane (5-7 ml). The eluate was diluted with water (250 ml) and extracted with methylene chloride. The extract was dried with sodium sulfate, the solvent was distilled, and the residue was purified by column chromatography. After crystallization from hexane compounds **3a**,**b** were obtained with yields of 17 and 20% respectively.

D. To a solution of ketone **1** (0.01 mol) in anhydrous carbon tetrachloride (40 ml) we added NBS (1.96 g, 0.011 mol) and a catalytic amount of AIBN. The mixture was boiled with a reflux condenser until the initial ketone had been completely used up (TLC) and was cooled on an ice bath, and the precipitate was filtered off. A small amount of hexane was added to the filtrate, and the solution was passed through a layer of silica gel. The solvent was evaporated to dryness, and the residue was dissolved in pure hexane and boiled with silica gel. After filtration the solvent was evaporated to ~2 ml, and the product was left to crystallize with cooling. The yield of the benzofuran was 45% for **3a** and 48% for **3b**.

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