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NEW SYNTHESIS OF 3-(2-FURYL)PHTHALIDES

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3-(2-Furyl)phthalides were synthesized for the first time by the reaction of 2-formylbenzoic acids with furan derivatives in the presence of an acidic catalyst. It was found that the reaction of 2-formylbenzoic acids and 2-alkylfurans in aqueous dioxane in the presence of perchloric acid leads to a mixture of 2-carboxyaryldifurylmethanes and 3-furylphthalides, which can be separated easily by preparative column chromatography.

Keywords: 2-alkylfuran, 2-formylbenzoic acid, 3-furylphthalide.

3-(2-Furyl)phthalides are representatives of the 2-carboxybenzylfurans used in the synthesis of naphtho[2,3-*b*]furan-4,9-diones [1, 2]. Many of them were isolated from plants and exhibit cytotoxicity and other types of pharmacological activity [3-5].

As we showed in [6], 2-carboxybenzylfurans can be used in the synthesis of isocoumarin derivatives containing a pharmacophoric fragment and of interest for biological screening.

The most widely used methods for the synthesis of derivatives of 3-(2-furyl)phthalide [7, 8] are based on the procedures of organometallic chemistry, which require special experimental procedures. At the same time it is known that 3-arylphthalides can be obtained with good yields by the condensation of 2-carboxyarylcarbonyl and aromatic compounds in the presence of acidic catalysts [9, 10].

In this paper we present the preliminary results that we obtained in the course of an investigation of the acid-catalyzed condensation of 2-formylbenzoic acids and 2-alkylfurans. Earlier we showed that the reaction of 2-formylbenzoic acids with sylvane or 2-ethylfuran in 1,4-dioxane in the presence of catalytic amounts of perchloric acid leads to high yields of the corresponding 2-carboxyaryl(difuryl)methanes [6].

We have now established that the addition of water to the reaction mixture makes it possible to increase the content of the furylphthalide from trace quantities to 50% or more of the total mass of the reaction products. The optimum amount of water needed to achieve the highest yield of compounds **1a-f** amounts to 12% of the volume of 1,4-dioxane used in the reaction. Decrease in the amount of water leads to an increase in the content of the aryldifurylmethame in the mixture of reaction products, while increase in the amount of water retards the reaction or stops it completely (Scheme 1).

An unexpected feature was the effect of the alkyl substituent on the yield of 3-furylphthalide. With 2-methylfuran in the absence of water 3-furylphthalide is only formed in trace quantities, whereas in the case of 2-*tert*-butylfuran the yield of 3-furylphthalide can reach 36% even without the addition of water to the reaction mixture.

Thus, we have realized for the first time the synthesis of 3-furylphthalides by the reaction of 2-formylbenzoic acids with furan derivatives in the presence of an acidic catalyst. Although the yields of compounds **1** obtained by the method are satisfactory, it can be hoped on the basis of the preliminary results that further optimization of the reaction conditions will make it possible to increase the yields.

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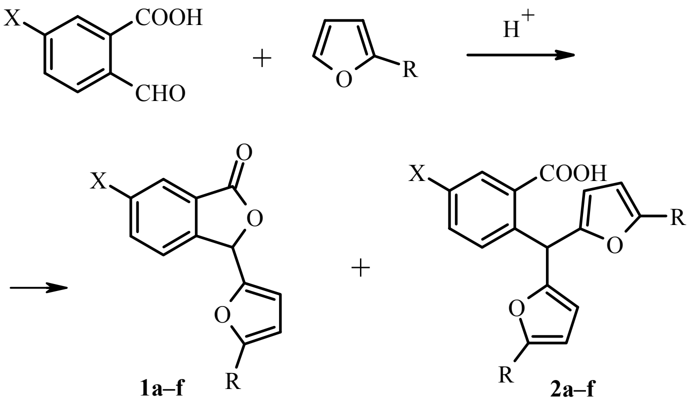
Scheme 1



1a–f **2a–f**

1, 2 a, **d** X = H, **b, e** X = I, **c**, **f** X = NO_2; **a**–**c** R = Me, **d**–**f** R = *t*-Bu

Compound	Yield*, %		Compound	Yield*, %	
	A	B		A	B
1a	Traces	14.0	**2a**	68.5	15.2
1b	Traces	24.4	**2b**	70.2	22.9
1c	Traces	18.8	**2c**	70.0	17.2
1d	21.5	35	**2d**	14.5	13
1e	36.1	42	**2e**	22.7	20
1f	29.2	37	**2f**	16.8	14

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* The yields of the reaction products were calculated on the initial 2-formylbenzoic acid. A) The reaction was carried out in the absence of water; B) The reaction was carried out with the addition of water.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker AM300 instrument (300 MHz) in deuterochloroform (compounds **1a**,**c-f**) and DMSO-d_6 (compound **1b**) with TMS as internal standard.

3-(5-Methylfur-2-yl)-1,3-dihydro-1-isobenzofuranone (1a). To a mixture of 2-formylbenzoic acid (7.0 g, 47 mmol) and 2-methylfuran (7.5 ml, 84 mmol) in 1,4-dioxane (50 ml) we added water (7 ml) and 70% perchloric acid (0.5 ml), and we boiled the mixture for 1.5 h with a reflux condenser. The obtained reaction mass was poured into water and extracted with methylene chloride. The extract was dried with sodium sulfate and evaporated. The obtained oil was separated by column chromatography with a 1:2 mixture of benzene and petroleum ether as eluant. Yield 2.0 g (14%), the product formed colorless crystals; mp 110-111°C (methylene chloride–petroleum ether). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.27 (3H, s, CH_3); 5.96 (1H, d, *J* = 3.2, 4-H_{Fur}); 6.24 (1H, d, *J* = 3.2, 3-H_{Fur}); 6.41 (1H, s, CH); 7.47-7.48 (1H, m, H_{Ar}); 7.56-7.71 (2H, m, H_{Ar}); 7.95-7.96 (1H, m, H_{Ar}). Found %: C 72.97; H 4.65. $C_{13}H_{10}O_3$. Calculated %: C 72.89; H 4.71.

Compounds 1b-f. The compounds were obtained similarly to compound **1a**.

6-Iodo-3-(5-methylfur-2-yl)-1,3-dihydro-1-isobenzofuranone (1b). Yield 24.4%; mp 169-170°C (methylene chloride–petroleum ether). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.25 (3H, s, CH_3); 6.12 (1H, d, *J* = 3.2, 4-H_{Fur}); 6.48 (1H, d, *J* = 3.2, 3-H_{Fur}); 6.72 (1H, s, CH); 7.36 (1H, d, *J* = 8.0, H_{Ar}); 8.14 (1H, dd, *J* = 1.4, *J* = 8.0, H_{Ar}); 8.23 (1H, d, *J* = 1.4, H_{Ar}). Found %: C 46.01; H 2.72. $C_{13}H_9IO_3$. Calculated %: C 45.91; H 2.67.

3-(5-Methylfur-2-yl)-6-nitro-1,3-dihydro-1-isobenzofuranone (1c). Yield 18.8%, the product formed colorless crystals; mp 128-129°C (methylene chloride–petroleum ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (3H, s, CH_3); 6.01 (1H, d, *J* = 3.2, 4-H_{Fur}); 6.37 (1H, d, *J* = 3.2, 3-H_{Fur}); 6.51 (1H, s, CH); 6.64 (1H, d, *J* = 8.4, H_{Ar}); 8.57 (1H, dd, *J* = 2.0, *J* = 8.4, H_{Ar}); 8.78 (1H, d, *J* = 2.0, H_{Ar}). Found %: C 60.29; H 3.45; N 5.49. $C_{13}H_9NO_5$. Calculated %: C 60.24; H 3.50; N 5.40.

3-(5-*tert*-Butylfur-2-yl)-1,3-dihydro-1-isobenzofuran (1d). Yield 35%, the product formed colorless crystals; mp 73-74°C (methylene chloride–petroleum ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz):1.26 (9H, s, *t*-Bu); 5.94 (1H, d, *J* = 3.2, 4-H_{Fur}); 6.16 (1H, d, *J* = 3.2, 3-H_{Fur}); 6.45 (1H, s, CH); 7.47-7.72 (3H, m, H_{Ar}); 7.95-7.99 (1H, m, H_{Ar}). Found %: C 74.90; H 6.32. $C_{16}H_{16}O_3$. Calculated %: C 74.98; H 6.29.

3-(5-*tert*-Butylfur-2-yl)-6-iodo-1,3-dihydro-1-isobenzofuranone (1e). Yield 42%, the product formed colorless crystals; mp 111-112°C (methylene chloride–petroleum ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (9H, s, *t*-Bu); 5.95 (1H, d, *J* = 3.2, 4-H_{Fur}); 6.19 (1H, d, *J* = 3.2, 3-H_{Fur}); 6.39 (1H, s, CH); 7.25 (1H, d, *J* = 8.0, H_{Ar}); 8.01 (1H, dd, *J* = 1.4, H_{Ar}); 8.30 (1H, d, *J* = 1.4, H_{Ar}). Found %: C 50.18; H 3.85. $C_{16}H_{15}IO_3$. Calculated %: C 50.28; H 3.96.

3-(5-*tert*-Butylfur-2-yl)-6-nitro-1,3-dihydro-1-isobenzofuranone (1f). Yield 37%, the product formed colorless crystals; mp 117-118°C (methylene chloride–petroleum ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (9H, s, *t*-Bu); 5.99 (1H, d, *J* = 3.2, 4-H_{Fur}); 6.28 (1H, d, *J* = 3.2, 3-H_{Fur}); 6.55 (1H, s, CH); 7.68 (1H, d, *J* = 8.4, H_{Ar}); 8.57 (1H, dd, *J* = 1.9, *J* = 8.4, H_{Ar}); 8.79 (1H, d, *J* = 1.9, H_{Ar}). Found %: C 63.85; H 5.11; N 4.59. $C_{16}H_{15}NO_5$. Calculated %: C 63.78; H 5.02; N 4.65.

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REFERENCES

1. S. M. Starling, D. S. Raslan, and A. B. De Oliveira, *Synth. Commun.*, **28**, 1013 (1998).
2. S. M. Starling, D. S. Raslan, A. B. De Oliveira, and C. L. Zani, *Synth. Commun.*, **28**, 3567 (1998).
3. M. M. Rao and D. J. I. Kingston, *J. Nat. Prod.*, **45**, 600 (1980).
4. S. V. K. Moideen, P. J. Houghton, P. Rock, S. L. Croft, and F. Aboagye-Nyame, *Planta Med.*, **65**, 536 (1999).
5. D. N. Akunyili and P. J. Houghton, *Phytochemistry*, **32**, 1015 (1993).
6. A. V. Gutnov, V. T. Abaev, A. V. Butin, and A. S. Dmitriev, *J. Org. Chem.*, **66**, 8685 (2001).
7. C. L. Zani, A. B. De Oliveira, and V. Snieckus, *Tetrahedron Lett.*, **28**, 6561 (1987).
8. P. Garibay, P. H. Toy, T. Hoeg-Jensen, and K. D. Janda, *Synlett*, 1438 (1999).
9. V. W. Floutz, *J. Org. Chem.*, **25**, 643 (1960).
10. R. Al-Hamdany, J. M. Al-Rawi, and S. Ibrahim, *J. Prakt. Chem.*, **329**, 126 (1987).