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POLYFURYL(ARYL)ALKANES AND THEIR DERIVATIVES. 11.* OPTIMIZATION OF THE CONDITIONS FOR THE SYNTHESIS OF 2-NITROARYLDIFURYLMETHANES AND THE NATURE OF THE SIDE PRODUCTS

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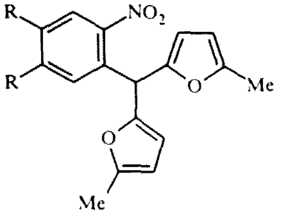
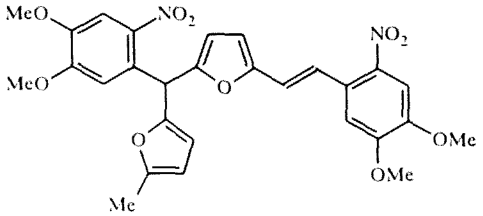
It was found that 2-nitroaryldifurylmethanes can be obtained with high yields as a result of the condensation of derivatives of 2-nitrobenzaldehyde and sylvane in dioxane in the presence of perchloric acid. The reaction of 6-nitroveratraldehyde and sylvane in benzene in the presence of trimethylsilyl chloride leads to the formation of the product from the condensation of the aryldifurylmethane with the initial aldehyde and also a derivative of 3-furyl-2,1-benzisoxazole.

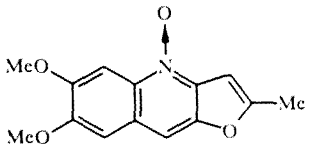
2-Nitroaryldifurylmethanes (I) are used in the synthesis of indole derivatives [2-4]. In spite of the fact that general methods for the production of aryldifurylalkanes have already been fairly well developed [5-7], the yields of compounds (I) are moderate, and the isolation of the final products is quite laborious on account of resin formation. Thus, for example, the condensation of 2-nitrobenzaldehyde with sylvane in glacial acetic acid at 0-5°C in the presence of concentrated sulfuric acid led after purification on a column of aluminum oxide to compound (Ia) with a yield of 50% [3]. As a result of the same reaction in benzene in the presence of perchloric acid [6] after appropriate purification we obtained the product (Ia) with a yield of 60%.



Ia, b



IV*



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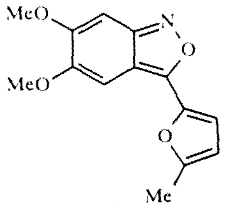

I a R = H, b R = OMe

VI

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*For Communication 10, see [1].

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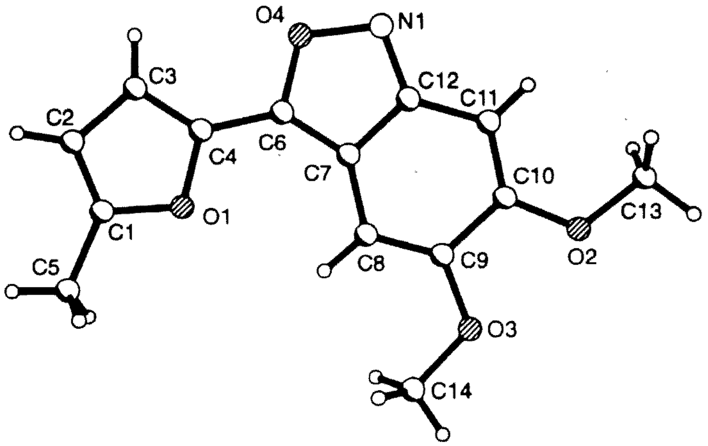
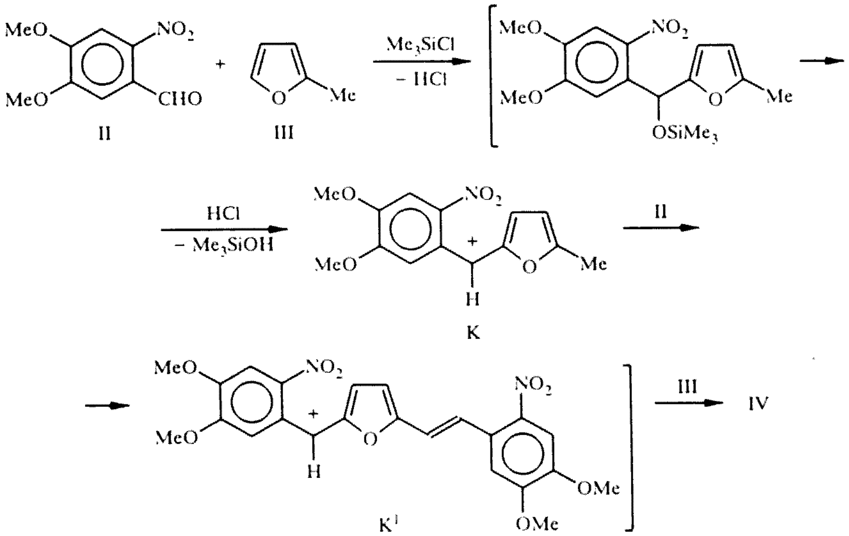


Fig. 1. Projection of the stereochemical model of one of the independent molecules of 3-(5-methyl-2-furyl)-5,6-dimethoxy-2,1-benzisoxazole (VI).

In connection with the foregoing, we set out to optimize the conditions for the synthesis of the 2-nitroaryldifurylmethanes (Ia, b) by the condensation of 2-nitrobenzo- and 6-nitroveratraldehydes (IIa, b) with sylvane (III). We found that the best results were obtained by conducting the reaction at room temperature in dioxane and with perchloric acid as catalyst. In this case the yield of the final reaction product amounted to 70-75%.

While looking for the optimum conditions for the synthesis of compounds (Ia, b) we found that the condensation of 6-nitroveratraldehyde (IIb) with sylvane in benzene in the presence of trimethylsilyl chloride led to a complex mixture, the separation of which by preparative liquid chromatography gave two other products in addition to the desired derivative of phenyldifurylmethane (Ib) and the initial aldehyde.

The structure of one of them was established on the basis of the data from PMR and mass spectrometry (M^+ with m/z = 550). The presence of doublets in the PMR spectrum for the olefinic protons at 6.75 and 7.95 ppm with the characteristic spin–spin coupling constant of 16 Hz for *trans* protons and also a double set of signals for the protons of the aromatic fragments and the β-protons of the furan rings with the absence of a signal for the protons of one of the methyl groups in the furan ring gave reason to suppose that this substance was the product from condensation of the aryldifurylmethane (Ib) with nitroveratraldehyde and had the structure of (IV). The probable mechanism for the formation of compound (IV)* is given below.



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*During the assignment of the signals in the PMR spectrum of compound (IV) (see the Experimental section) the fragments of its molecule were numbered as follows: $Ar^1CH(Fur^1)Fur^2CH^1{=}CH^2Ar^2$.

TABLE 1. Coordinates of the Nonhydrogen Atoms (Å × 10^4) and the Temperature Factors (Å^2 × 10^3) of the Two Independent Molecules of Compound (VI)

Atom	x	y	z	$U(eq)$
$O_{(1)}$	5292(2)	-357(1)	6489(1)	66(1)
$O_{(2)}$	5573(1)	2364(1)	4281(1)	63(1)
$O_{(3)}$	6839(1)	1629(1)	4879(1)	63(1)
$O_{(4)}$	3127(2)	349(1)	5716(1)	73(1)
$N_{(1)}$	3013(2)	911(2)	5246(1)	76(1)
$C_{(1)}$	5354(3)	-921(2)	6925(2)	75(1)
$C_{(2)}$	4462(4)	-1188(2)	7032(2)	86(1)
$C_{(3)}$	3793(3)	-792(2)	6654(2)	77(1)
$C_{(4)}$	4318(2)	-291(2)	6328(2)	62(1)
$C_{(5)}$	6352(4)	-1102(3)	7159(3)	100(2)
$C_{(6)}$	4092(2)	264(2)	5865(2)	56(1)
$C_{(7)}$	4630(2)	746(1)	5511(1)	49(1)
$C_{(8)}$	5647(2)	900(2)	5443(2)	50(1)
$C_{(9)}$	5908(2)	1426(2)	5023(1)	49(1)
$C_{(10)}$	5174(2)	1843(2)	4663(1)	53(1)
$C_{(11)}$	4210(2)	1701(2)	4711(2)	58(1)
$C_{(12)}$	3928(2)	1133(2)	5139(2)	55(1)
$C_{(13)}$	4916(3)	2786(2)	3882(2)	74(1)
$C_{(14)}$	7606(2)	1212(2)	5167(2)	66(1)
$O_{(1A)}$	4944(2)	9103(1)	2313(1)	73(1)
$O_{(2A)}$	5031(1)	6375(1)	4499(1)	74(1)
$O_{(3A)}$	6342(1)	7064(1)	3887(1)	67(1)
$O_{(4A)}$	2692(2)	8314(1)	2901(1)	88(1)
$N_{(1A)}$	2549(2)	7742(2)	3362(2)	88(1)
$C_{(1A)}$	5072(4)	9627(2)	1846(2)	83(1)
$C_{(2A)}$	4198(5)	9808(3)	1594(2)	100(2)
$C_{(3A)}$	3482(4)	9397(3)	1914(2)	96(1)
$C_{(4A)}$	3952(3)	8967(2)	2353(2)	74(1)
$C_{(5A)}$	6092(5)	9844(4)	1726(3)	107(2)
$C_{(6A)}$	3671(2)	8418(2)	2807(2)	68(1)
$C_{(7A)}$	4183(2)	7944(2)	3183(2)	59(1)
$C_{(8A)}$	5194(2)	7798(2)	3291(2)	56(1)
$C_{(9A)}$	5422(2)	7273(2)	3722(2)	54(1)
$C_{(10A)}$	4665(2)	6868(2)	4071(2)	58(1)
$C_{(11A)}$	3706(3)	6995(2)	3969(2)	69(1)
$C_{(12A)}$	3452(2)	7542(2)	3518(2)	65(1)
$C_{(13A)}$	4340(4)	5997(3)	4909(3)	89(1)
$C_{(14A)}$	7133(3)	7485(3)	3625(2)	70(1)

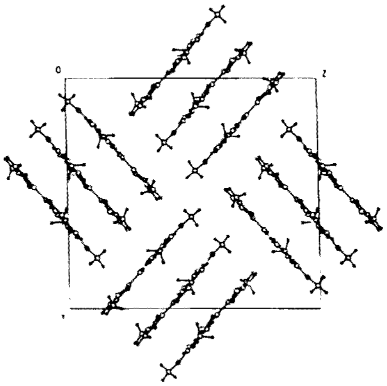


Fig. 2. Packing of the molecules of 3-(5-methyl-2-furyl)-5,6-dimethoxy-2,1-benzisoxazole (VI) in the crystal lattice.

TABLE 2. Bond Lengths in One of the Independent Molecules of Compound (VI)

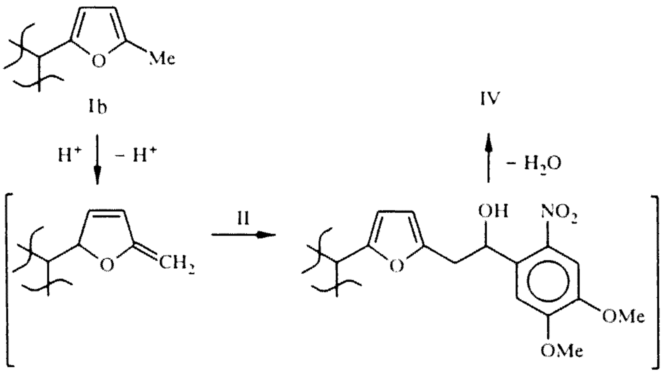
Bond	*l*, Å	Bond	*l*, Å
$O_{(1)}—C_{(4)}$	1,373(4)	$C_{(2)}—C_{(3)}$	1,399(5)
$O_{(1)}—C_{(1)}$	1,373(4)	$C_{(3)}—C_{(4)}$	1,347(4)
$O_{(2)}—C_{(10)}$	1,353(3)	$C_{(4)}—C_{(6)}$	1,426(4)
$O_{(2)}—C_{(13)}$	1,437(4)	$C_{(6)}—C_{(7)}$	1,361(4)
$O_{(3)}—C_{(9)}$	1,356(3)	$C_{(7)}—C_{(12)}$	1,415(4)
$O_{(3)}—C_{(14)}$	1,425(4)	$C_{(7)}—C_{(8)}$	1,422(4)
$O_{(4)}—C_{(6)}$	1,358(3)	$C_{(8)}—C_{(9)}$	1,343(4)
$O_{(4)}—N_{(1)}$	1,421(3)	$C_{(9)}—C_{(10)}$	1,460(4)
$N_{(1)}—C_{(12)}$	1,331(3)	$C_{(10)}—C_{(11)}$	1,343(4)
$C_{(1)}—C_{(2)}$	1,331(5)	$C_{(11)}—C_{(12)}$	1,419(4)
$C_{(1)}—C_{(5)}$	1,479(6)		

TABLE 3. Bond Angles in One of the Independent Molecules of Compound (VI)

Angle	*ω*, deg	Angle	*ω*, deg
$C_{(4)}—O_{(1)}—C_{(1)}$	106,2(3)	$O_{(4)}—C_{(6)}—C_{(4)}$	116,0(3)
$C_{(10)}—O_{(2)}—C_{(13)}$	117,4(3)	$C_{(6)}—C_{(7)}—C_{(12)}$	104,4(2)
$C_{(9)}—O_{(3)}—C_{(14)}$	116,6(2)	$C_{(6)}—C_{(7)}—C_{(8)}$	135,2(3)
$C_{(6)}—O_{(4)}—N_{(1)}$	109,9(2)	$C_{(12)}—C_{(7)}—C_{(8)}$	120,3(3)
$C_{(12)}—N_{(1)}—O_{(4)}$	103,5(2)	$C_{(9)}—C_{(8)}—C_{(7)}$	117,8(3)
$C_{(2)}—C_{(1)}—O_{(1)}$	109,5(4)	$C_{(8)}—C_{(9)}—O_{(3)}$	125,9(3)
$C_{(2)}—C_{(1)}—C_{(5)}$	134,7(4)	$C_{(8)}—C_{(9)}—C_{(10)}$	121,4(3)
$O_{(1)}—C_{(1)}—C_{(5)}$	115,8(4)	$O_{(3)}—C_{(9)}—C_{(10)}$	12,8(3)
$C_{(1)}—C_{(2)}—C_{(3)}$	108,1(4)	$C_{(11)}—C_{(10)}—O_{(2)}$	125,1(3)
$C_{(4)}—C_{(3)}—C_{(2)}$	106,6(4)	$C_{(11)}—C_{(10)}—C_{(9)}$	121,9(3)
$C_{(3)}—C_{(4)}—O_{(1)}$	109,7(3)	$O_{(2)}—C_{(10)}—C_{(9)}$	112,9(2)
$C_{(3)}—C_{(4)}—C_{(6)}$	134,9(4)	$C_{(10)}—C_{(11)}—C_{(12)}$	117,1(3)
$O_{(1)}—C_{(4)}—C_{(6)}$	115,4(3)	$N_{(1)}—C_{(12)}—C_{(7)}$	113,0(3)
$C_{(7)}—C_{(6)}—O_{(4)}$	109,2(3)	$N_{(1)}—C_{(12)}—C_{(11)}$	125,7(3)
$C_{(7)}—C_{(6)}—C_{(4)}$	134,7(3)	$C_{(7)}—C_{(12)}—C_{(11)}$	121,3(3)

In our opinion, the key intermediate in the investigated transformation is the cation K, which reacts at the methyl group of the furan ring with the initial aldehyde by a mechanism of the crotonic condensation type, as has been described many times in the case of pyrylium salts containing a methyl group at position 2 or 4 in relation to the oxygen atom [8, 9]. Further reaction of the newly formed cation K^1 with sylvane leads to the product (IV).

An alternative mechanism for the formation of the latter, similar to the mechanism of the condensation of 2,5-dimethylfuran with carbonyl compounds, is also possible [10-12]. The reaction in this case presumably takes place through the tautomeric form of the initial disubstituted furan (Ib).

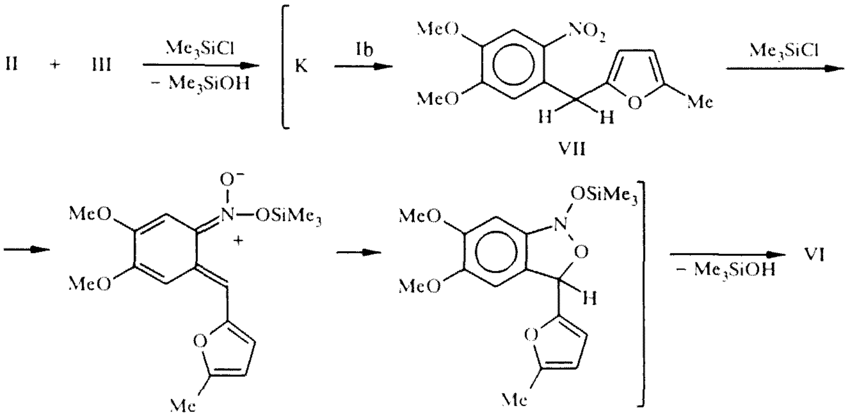


The second unknown product with the molecular formula $C_{14}H_{13}NO_4$ (according to elemental analysis) has a molecular weight of 259 (according to mass spectrometry). In its PMR spectrum, in addition to the singlet signals for the protons of the methyl group and the two methoxyl groups, there are signals for the four chemically nonequivalent aromatic protons. On the basis of these data we previously assigned this product the structure (V) [13].

However, not having found a reasonable explanation for the formation of the N-oxide (V), we doubted accuracy of this assignment. For this reason, in the present work we carried out an x-ray crystallographic analysis of a single crystal of the product. It turned out to be a derivative of 3-furyl-2,1-benzisoxazole (VI), a projection of the stereochemical model of which is shown in Fig. 1. In the crystal the molecules exhibit stereochemical parquet-type packing (Fig. 2). Two independent molecules, the atomic coordinates of which are given in Table 1, coincide in geometric characteristics within ±0.05 Å. The bond lengths and bond angles do not differ from the normal values (Tables 2 and 3) and do not require special comment. We note only that the benzisoxazole $C_{(6)}C_{(7)}C_{(8)}C_{(9)}C_{(10)}C_{(11)}C_{(12)}N_{(1)}O_{(4)}$ and furan $C_{(1)}C_{(2)}C_{(3)}C_{(4)}O_{(1)}$ fragments are planar (the average deviation from the plane is 0.0131 and 0.0013 Å respectively), while the angle between these planes is 3.3°, which is considerably smaller than the angle in the derivatives of 3-furylbenzofuran [14]. We emphasize also that the furan ring, as also in the case of 3-furylbenzofurans [14], is turned with the oxygen atom toward the side of one of the aromatic protons, which may indicate intramolecular interaction of the hydrogen bond type (parameters $O_{(1)}\cdots H_{(8)} = 2.667$ Å, $H_{(8)}O_{(1)}C_{(4)} = 101.4°$, $O_{(1)}H_{(8)}C_{(8)} = 114.5°$). We mentioned the possibility of the formation of a hydrogen bond with the oxygen atom of the furan ring in [1].

The acid-catalyzed condensation of the derivatives of 2-nitrobenzaldehydes with arenes, phenols, or aromatic amines is familiar as the main method for the production of 3-arylanthranils [15]. The intermediate products of such reactions are considered to be derivatives of 2-nitrobenzhydrol. Evidence for this is obtained from the direct production of 3-arylbenzisoxazoles from derivatives of 2-nitrobenzhydrol [16-18]. The further mechanism of the transformation is not entirely clear. It was suggested [15] that this process is an oxidation–reduction reaction and that part of the benzhydrol is converted into benzophenone.

In our case, a derivative of the 2-nitroaryl furyl ketone was not found in the reaction products. We suppose that the source of the electrons in the reduction of the arylfurylcarbinol may be the aryldifurylmethane (Ib).



The transformation of the arylfurylmethane (VII) formed here into compound (VI) probably takes place through the acid form with subsequent intramolecular [3+2]-cycloaddition and aromatization, as was proposed earlier in the case of the transformation of 2-nitrophenylacetic acid into the derivatives of anthranil [19].

EXPERIMENTAL

The PMR spectra were recorded on Tesla BS-467 (60 MHz, internal standard HMDS) and Bruker AMX-44 (400MHz, internal standard TMS) instruments. The mass spectra were obtained on a Varian MAT-112 mass spectrometer with direct injection of the sample into the ion source (energy of ionizing electrons 70 eV, temperature of ionization chamber 100-180°C). The reactions and the individuality of the products were monitored by TLC on Silufol UV-254 plates with the eluants: 6:1:1 hexane–chloroform–acetone [for (Ia)]; 4:1:1 hexane–chloroform–acetone [for (Ib)]; 3:1 hexane–chloroform [for (Ic) and (Id)]. Iodine vapor was used as developer.

X-ray Crystallographic Investigation of Compound (VI). The yellow orthorhombic crystals of compound (VI) with composition $C_{14}H_{13}NO_4$ were grown from a 10:1 mixture of benzene and ether. The unit cell parameters were as follows: $a = 13.629(3)$, $b = 18.595(4)$, $c = 20.203(4)$ Å, V = 5120(2) Å^3. The space group was P_{bca}, z = 16. The unit cell parameters and the intensities of 1457 unique reflections with $I > 2\sigma(I)$ were obtained on a CAD-4 automatic diffractometer without a monochromator (MoKα radiation, $\theta/2\theta$ scan to $2\theta = 45°$). The structure was interpreted by the direct method with the SHELXTL software [20] and was refined in anisotropic approximation (isotropic for the hydrogen atoms) to R = 0.0222 and $R_W = 0.0574$. The coordinates of the hydrogen atoms can be obtained from the authors.

Bis(5-methyl-2-furyl)-4,5-dimethoxy-2-nitrophenylmethane (Ib). A. We dissolved 9.5 g (45 mmole) of 6-nitroveratraldehyde in a mixture of 9.5 g (104 mmole) of sylvane and 50 ml of dioxane. To the solution we added 1 ml of 70% perchloric acid, and we kept the mixture in the dark with periodic shaking for two days. The reaction mixture was then diluted with water (200 ml) and stirred until the separated oil had crystallized. The crystalline precipitate was filtered off, washed with water, and dried in air. After recrystallization from petroleum ether (bp 70-100°C) we obtained 11.1 g of the yellow crystals of compound (Ib). The yield was 69%; mp 98°C (from methanol). PMR spectrum (carbon tetrachloride): 2.18 (6H, s, $2CH_3$); 3.68 (3H, OCH_3); 3.82 (3H, s, OCH_3); 5.66-5.90 (5H, m, CH, $4H_{Fur}$); 6.65 (1H,s, 6-H_{Ar}); 7.48 (1H, s, 3-H_{Ar}). Found %: C 63.89, H 5.40, N 3.91. $C_{19}H_{19}NO_6$. Calculated %: C 63.86, H 5.36, N 3.92.

B. To a solution of 21.1 g (100 mmole) of 6-nitroveratraldehyde in 100 ml of benzene we added over 40 min 20 ml (208 mmole) of sylvane, after which the mixture was stirred for 30 min at 45-50°C and was then left for a further 1 h. The reaction mixture was neutralized with a saturated solution of potassium carbonate until the release of CO_2 had stopped. The organic layer was separated, washed with water, and dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a column of silica gel L 40/100 with a 4:1 mixture of benzene and ether as eluant. The following products were isolated: 5.7 g (16%) of (Ib), 1.7 g (3.1%) of (IV), and 3.9 g (14%) of (VI).

2-[(5-Methyl-2-furyl-4,5-dimethoxy-2-nitrophenyl)methyl]-5-[2-(4,5-dimethoxy-2-nitrophenyl)vinyl]furan (IV). mp 171-172°C (from a mixture of chloroform and petroleum ether). PMR spectrum (deuterochloroform), δ, ppm: 2.26 (3H, bs, CH_3); 3.88 (3H, s, 4-OCH_3–Ar^2); 3.94 (3H, s, OCH_3–Ar^1); 3.95 (3H, s, OCH_3–Ar^1); 4.00 (3H, s, 6-OCH_3–Ar^2); 5.91 (1H, bd, J = 3.2 Hz, 4-H–Fur^1); 6.04 (1H, d, J = 3.2 Hz, 3-H–Fur^1); 6.20 (1H, d, J = 3.2 Hz, 3-H–Fur^2); 6.41 (1H, d, J = 3.2 Hz, 4-H–Fur^2); 6.48 (1H, s, CH); 6.75 (1H, d, J = 16 Hz, CH=$\underline{CH}$); 6.93 (1H, s, 6-H–Ar^1); 7.00 (1H, s, 3-H–Ar^1); 7.58 (1H, s, 6-H–Ar^2); 7.64 (1H, s, 3-H–Ar^2); 7.59 (1H, d, J = 16 Hz, $\underline{CH}$=CH). Mass spectrum (m/z): 550 (M^+). Found %: C 61.07, H 4.79, N 5.11. $C_{28}H_{26}N_2O_{10}$. Calculated %: C 61.09; H 4.76; N 5.09.

3-(5-Methyl-2-furyl)-5,6-dimethoxy-2,1-benzisoxazole (VI). The yield was 3.9 g (14%); mp 145-146°C (from benzene). PMR spectrum (deuterochloroform), δ, ppm: 2.33 (3H, d, J = 0.6 Hz, CH_3); 3.83 (3H, s, OCH_3); 3.84 (3H, s, OCH_3); 6.07 (1H, dq, J = 3.2 Hz, J = 0.6 Hz, 4-H–Fur); 6.58 (1H, s, 4-H); 6.74 (1H, s, 7-H); 6.76 (1H, d, J = 3.2 Hz, 3-H–Fur). Mass spectrum (m/z): 259 (M^+). Found %: C 64.82, H 5.06, N 5.38. Calculated %: C 64.86, H 5.05, N 5.40.

Bis(5-methyl-2-furyl)-2-nitrophenylmethane (Ia). Compound (Ia) was obtained from 2-nitrobenzaldehyde by method A. The yield was 74%; mp 83°C (from hexane). PMR spectrum (deuterochloroform), δ, ppm: 2.18 (6H, s, $2CH_3$); 5.77-5.95 (4H, m, H_{Fur}); 6.17 (1H, bs, CH); 7.18-7.50 (3H, m, 4-, 5-, 6-H_{Ar}); 7.75-7.50 (1H, m, 2-H_{Ar}). Found, %; C 68.71, H 5.12, N 4.69. $C_{17}H_{15}NO_4$. Calculated, %; C 68.68, H 5.09, N 4.71.

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