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SYNTHESIS OF N-ARYL-SUBSTITUTED PYRROLES *via* γ-BROMODYPNONE

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A series of 1-aryl-2,4-diphenylpyrroles were obtained by the reaction of 4-bromo-1,3-diphenyl-2-buten-1-one (γ-bromodypnone) with substituted anilines in the presence of sodium acetate. In the reaction with di- and trimethylenediamines the corresponding 1,2- and 1,3-di(N-pyrryl)alkanes were obtained.

Keywords: γ-bromodypnone, 1,2,4-triarylpyrroles.

In recent years the search for new methods of synthesizing derivatives of the pyrrole series has acquired great significance in connection with the discovery among them of compounds with a high level of biological activity, used as antibiotics, antitumor preparations, and highly effective drugs acting on the central nervous system [1]. Of particular interest are N-substituted diarylpyrroles containing an *o*-substituent in the N-aryl fragment as potential synthetic equivalents of more complex pyrrole-containing heterocyclic systems [2].

In the present investigation we turned to study of the properties of 4-bromo-1,3-diphenyl-2-buten-1-one (γ-bromodypnone) (**1**), which is a synthetic equivalent of the 1,4-dielectrophilic reagents. The use of arylamines in reaction with 1,4-dielectrophiles provides a convenient path to difficultly obtainable N-arylpyrroles [3-5]. Earlier [6, 7] a series of N-substituted 2,4-diphenylpyrroles, which are the products from conjugate nucleophilic substitution and condensation at positions 1 and 4 of the dypnone system, were obtained by using γ-bromodypnone **1** in reaction with primary aliphatic amines. Research into the reaction of γ-bromodypnone with aromatic amines has only previously been carried out on one example, i.e., the reaction with aniline [7]. While studying the reaction of γ-dypnone with amines of the heterocyclic series [8] we found that the reaction with α-aminoazines and α-aminoazoles led to the products (condensed imidazoles) from nucleophilic substitution at position 4 and Michael addition at position 3 of the dypnone system. It was therefore of interest to study the reaction of γ-bromodypnone with other mono- and dinucleophiles of the aromatic and aliphatic series. Of particular interest to us was the reaction of compound (**1**) with *o*-substituted anilines. The production of pyrroles with the use of *o*-phenylenediamine, *o*-aminophenols (and *o*-aminothiophenols), and γ-halo-substituted α,β-unsaturated carbonyl and unsaturated 1,4-dicarbonyl compounds presents a particular problem, since the above-mentioned amines give low yields (~10%) of the pyrroles [4, 9].

We tried various conditions for the reaction of γ-bromodypnone **1** with arylamines, i.e., in solution (benzene, acetone) at various temperatures, with and without the presence of a base (sodium acetate), and with fusion of the reagents. The expected 1-aryl-2,4-diphenyl-1H-pyrroles **2a-k** were obtained in all cases except for the reaction in acetone (where the N-alkylarylammonium salts were obtained). The best result was obtained by fusing the γ-bromodypnone **1** with the aromatic amines in the presence of sodium acetate. The reaction takes place quickly (15 min), and it is not necessary here to use a large excess of the amine, as was suggested in [7]. Anilines containing electron-withdrawing groups lead to the cyclization products with smaller yields (Table 1),

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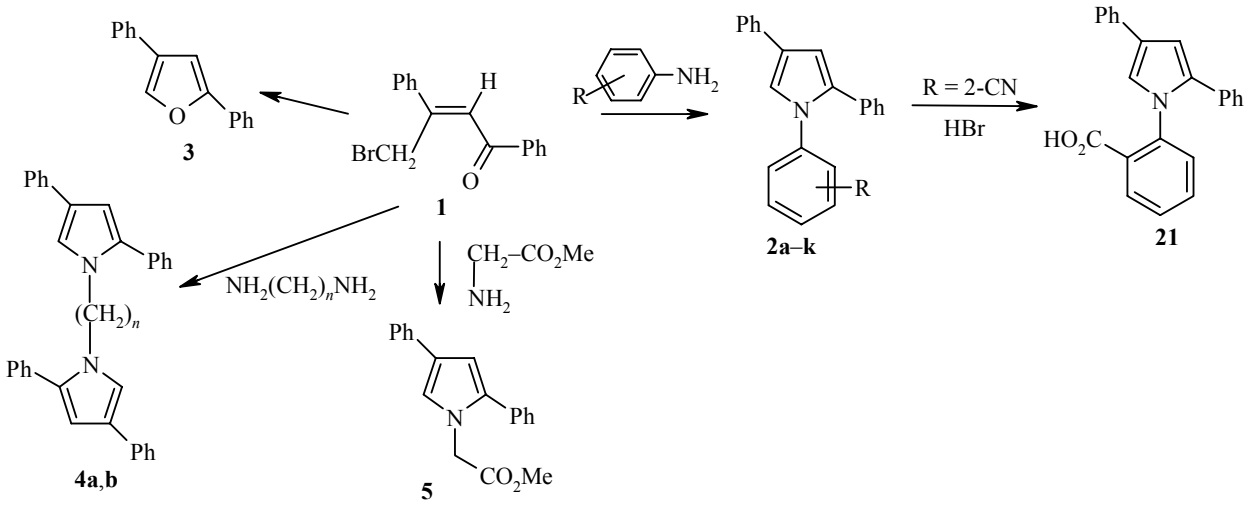

2 a R = 4-OMe, **b** R = 4-Me, **c** R = H, **d** R = 4-Br, **e** R = 4-CO_2Me, **f** R = 2-NH_2, **g** R = 2-OH, **h** R = 2-Me, **i** R = 2-CO_2Me, **j** R = 2-CN, **k** R = 3-CO_2H; **4 a** n = 2, **b** n = 3

TABLE 1. The Physicochemical Characteristics of N-Substituted 2,4-Diphenyl-1H-pyrroles

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent)	Yield, %
		C	H	N		
2a	$C_{23}H_{19}NO$	84.80 / 84.89	5.96 / 5.89	4.31 / 4.30	162 (MeCN)	65
2b	$C_{23}H_{19}N$	89.38 / 89.28	6.25 / 6.19	4.51 / 4.53	121 (MeCN)	64
2c*	$C_{22}H_{17}N$	89.57 / 89.46	5.90 / 5.80	4.63 / 4.74	155 (MeCN)	60
2d*[2]	$C_{22}H_{16}BrN$	70.57 / 70.60	4.30 / 4.31	3.78 / 3.74	135 (MeCN)	55
2e	$C_{24}H_{19}NO_2$	81.50 / 81.56	5.49 / 5.42	3.98 / 3.96	158 (MeCN)	52
2f	$C_{22}H_{18}N_2$	86.00 / 85.13	5.87 / 5.85	9.00 / 9.03	167 (MeCN)	61
2g	$C_{22}H_{17}NO$	84.89 / 84.86	5.49 / 5.50	4.53 / 4.50	97 (*i*-PrOH)	41
2h	$C_{23}H_{19}N$	89.30 / 89.28	6.21 / 6.19	4.54 / 4.53	110 (MeCN)	70
2i	$C_{24}H_{19}NO_2$	81.66 / 81.56	5.52 / 5.42	3.86 / 3.96	101 (*i*-PrOH)	60
2j	$C_{23}H_{16}N_2$	86.20 / 86.22	4.99 / 5.03	8.77 / 8.74	178 (MeCN)	57
2k	$C_{23}H_{17}NO_2$	81.45 / 81.40	5.00 / 5.05	4.14 / 4.13	137 ($MeCO_2H$)	45
2l	$C_{23}H_{17}NO_2$	81.49 / 81.40	5.10 / 5.05	4.15 / 4.13	202 ($MeCO_2H$)	31
4a	$C_{34}H_{28}N_2$	87.97 / 87.96	6.02 / 6.07	6.07 / 6.03	155 (*i*-PrOH)	69
4b	$C_{35}H_{30}N_2$	87.90 / 87.83	6.30 / 6.32	5.88 / 5.85	75 (*n*-$C_6H_{13}OH$)	71
5	$C_{19}H_{17}NO_2$	78.39 / 78.33	5.80 / 5.88	4.84 / 4.81	87 (*i*-PrOH)	42

* Mp of **2c** 153°C [4].

*[2] Found, %: Br 21.38; calculated, %: Br 21.35.

while those with electron-donating groups give larger yields, which correlates fairly well with the series of Hammett σ constants for the *para* and *meta* substituents [10]. The reaction with *o*-substituted anilines also leads to the formation of N-(aryl)-2,4-diphenyl-1H-pyrroles **2f-j** with high yields. The relative decrease in the yield of 1-(2-aminophenyl)pyrrole **2f** and 1-(2-hydroxyphenyl)pyrrole **2g** is undoubtedly explained by the formation of side products from reaction at both nucleophilic centers of the aniline molecules, according to the data presented in [4, 9].

The reaction of γ-bromodypnone **1** with *o*-substituted anilines has another feature due to steric hindrances around the reaction center of the aniline. It is known [11] that the γ-bromodypnone **1** is converted readily into 2,4-diphenylfuran **3** when heated in the presence of bases. A small amount of compound **3** as side product is therefore also formed in the reaction with low-basicity amines in the presence of sodium acetate (2-aminobenzonitrile, methyl anthranilate) (10-20%, according to the ^{1}H NMR spectra of the uncrystallized fusion products). In the case of anthranilic acid and 2-aminobenzenesulfonamide the furan **3** becomes the main reaction product. 2-Pyrrolylbenzoic acid **2l** was obtained during the hydrolysis of the corresponding nitrile **2j** in the presence of hydrobromic acid. This is confirmed by the spectral data, i.e., by the absence of the vibrations of the CN bond and the presence of bands at 3435 (OH) and 1650 cm^{-1} (C=O) in the IR region, and by a broad one-proton signal at 10.85 ppm (OH) in the ^{1}H NMR spectrum (OH).

The structure of the obtained N-arylpyrroles was established on the basis of the data from spectral investigations. The ^{1}H NMR spectra of the 2,4-diphenylpyrroles **2a-l** (Table 2) are characterized by the presence of signals for the protons of the pyrrole ring in the characteristic region [12] of 6.7-6.8 (β-H) and 7.2-7.8 ppm (α-H) in the form of one-proton doublets with spin–spin coupling constant ^mJ = 1.6 Hz. The position of the signals of the pyrrole ring and the aromatic protons of the 2,4-diphenyl substituents depends on the nature and position of the substituents in the N-aryl fragment and also correlates well with the series of Hammett σ constants of the *para* and *meta* substituents [10]. The characteristic pattern of pyrroles is also observed in the IR spectra [12] – bands for the stretching vibrations of the pyrrole ring in the region of 680-750 and 1400-1600 cm^{-1}. The presence of the pyrrole ring in the structure of the reaction products was also confirmed by chemical means – a positive Ehrlich test in the case of compounds **2b**,**h**.

TABLE 2. The Spectral Characteristics of Compounds **2a-l**, **4a**,**b**, and **5**

Com-pound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)*
1	2	3
2a	1600, 1490, 1230 (C–O), 748, 685	7.55 (2H, d, ^3J = 7.2, H-2',6'); 7.30 (3H, m, α-H, H-3',5'); 7.24-7.12 (8H, m, H-4', H-2"–H-6", H-2,6); 6.90 (2H, d, ^3J = 8.0, H-3,5); 6.69 (1H, d, *J* = 1.6, β-H); 3.79 (3H, s, OCH_3)
2b	1602, 1496, 1228, 750, 694	7.57 (2H, d, ^3J = 7.2, H-2',6'); 7.34 (1H, d, *J* = 1.6, α-H); 7.32 (2H, t, ^3J = 8.0, H-3',5'); 7.24-7.12 (10H, m, H-4', H-2"–H-6", H-2–H-6); 6.72 (1H, d, *J* = 1.6, β-H); .36 (3H, s, CH_3)
2c*[2]	1590, 1490, 1395, 1230, 760, 690	7.67 (2H, d, ^3J = 7.2, H-2',6'); 7.57 (1H, d, *J* = 1.6, α-H); 7.45-7.10 (13H, m, Ar-H); 6.85 (1H, d, *J* = 1.6, β-H)
2d	1600, 1480, 1215, 820, 750, 685	7.59 (2H, d, ^3J = 7.2, H-2',6'); 7.42 (1H, d, *J* = 1.6, α-H); 7.33 (2H, t, ^3J = 8.0, H-3',5'); 7.28-7.14 (8H, m, H-4', H-2"–H-6", H-2,6); 7.51 (2H, d, ^3J = 8.0, H-3,5); 6.75 (1H, d, *J* = 1.6, β-H)
2e	1728 (C=O), 1600, 1485, 1260 (C–O), 1225, 750, 690	7.74 (1H, d, ^3J = 7.2, H-3); 7.63 (1H, t, ^3J = 8.0, H-5); 7.58 (2H, d, ^3J = 7.2, H-2',6'); 7.48 (1H, t, ^3J = 8.0, H-4); 7.46 (1H, d, *J* = 1.6, α-H); 7.40 (1H, d, ^3J = 8.0, H-6); 7.35 (2H, t, ^3J = 8.0, H-3',5'); 7.24-7.12 (4H, m, H-4', H-3"–H-5"); 7.05 (2H, d, ^3J = 7.0, H-2",6"); 6.84 (1H, d, *J* = 1.6, β-H); 3.51 (3H, s, OCH_3)

TABLE 2 (continued)

1	2	3
2f	3380 (NH_2), 3460 (NH_2), 1600, 1500, 1220, 745, 685	7.56 (2H, d, ^3J = 7.2, H-2',6'); 7.30 (2H, t, ^3J = 8.0, H-3',5'); 7.22-7.10 (7H, m, H-4', H-2"–H-6", α-H); 7.06 (1H, td, ^3J = 7.2, ^4J = 0.8, H-4); 6.92 (1H, dd, ^3J = 7.6, ^4J = 0.8, H-6); 6.79 (1H, d, ^3J = 7.2, H-3); 6.77 (1H, d, J = 1.6, β-H); 6.53 (1H, t, ^3J = 7.6, H-5); 4.66 (2H, s, NH_2)
2g	3465 (OH), 1603, 1454, 1402, 760, 697	9.73 (1H, s, OH); 7.57 (2H, d, ^3J = 7.2, H-2',6'); 7.32 (2H, t, ^3J = 8.0, H-3',5'); 7.22 (1H, d, J = 2.0, α-H); 7.19-7.12 (7H, m, H-4', H-2"–H-6", H-4); 7.03 (1H, d, ^3J = 8.8, H-6); 6.96 (1H, d, ^3J = 8.2, H-3); 6.77 (1H, t, ^3J = 8.6, H-5); 6.72 (1H, d, J = 2.0, β-H)
2h	1602, 1497, 1228, 754, 694	7.59 (2H, d, ^3J = 7.2, H-2',6'); 7.35-7.25 (6H, m, Ar–H); 7.22 (1H, d, J = 1.6, α-H); 7.18-7.10 (6H, m, Ar–H); 6.80 (1H, d, J = 1.6, β-H); 1.96 (3H, s, CH_3)
2i	1700 (C=O), 1600, 1270 (C–O), 745, 680	7.96 (2H, d, ^3J = 8.0, H-3,5); 7.59 (2H, d, ^3J = 7.2, H-2',6'); 7.52 (1H, d, J = 1.6, α-H); 7.33 (4H, m, H-2,6,3',5'); 7.27-7.13 (6H, m, H-4', H-2"–H-6"); 6.77 (1H, d, J = 1.6, β-H); 3.86 (3H, s, CH_3)
2j	2240 (CN), 1600, 1495, 1230, 755, 694	7.85 (1H, d, ^3J = 7.2, H-3); 7.73 (1H, t, ^3J = 8.0, H-5); 7.61 (2H, d, ^3J = 7.2, H-2',6'); 7.57 (1H, t, ^3J = 8.0, H-4); 7.47 (2H, m, α-H, H-6); 7.35 (2H, t, ^3J = 8.0, H-3',5'); 7.23-7.17 (4H, m, H-4', H-3"–H-5"); 7.09 (2H, d, ^3J = 7.0, H-2",6"); 6.86 (1H, d, J = 1.6, β-H)
2k	3433 (OH), 1670 (C=O), 1602, 1486, 1096, 759, 697	7.93 (2H, m, H-2,4); 7.61 (2H, d, ^3J = 7.6, H-2',6'); 7.61 (1H, d, J = 1.6, α-H); 7.38-7.31 (3H, m, H-6,3',5'); 7.28-7.15 (7H, m, H-4', H-2"–H-6", H-5); 6.76 (1H, d, J = 1.6, β-H); 5.0 (br., OH + H_2O)
2l	3435 (OH), 1650 (C=O), 1600, 1475, 760, 703	10.85 (1H, br. s, OH); 8.38 (2H, m, H-3,5); 7.92 (1H, d, J = 1.6, α-H); 7.62 (2H, d, ^3J = 7.2, H-2',6'); 7.54–7.42 (3H, m, H-4,3',5'); 7.41-7.13 (5H, m, H-4', H-2"–H-6"); 6.95 (1H, d, ^3J = 7.2, H-6); 6.75 (1H, d, J = 1.6, β-H)
4a	3027, 2937, 1600, 1358, 1194, 763, 747, 696	7.43 (4H, d, ^3J = 8.2, H-2',6'); 7.31-7.24 (10H, m, H-3'–H-5', H-3",5"); 7.10 (2H, t, ^3J = 8.0, H-4"); 7.06 (4H, d, ^3J = 8.0, H-2",6"); 7.00 (2H, d, J = 1.6, α-H); 6.35 (2H, d, J = 1.6, β-H); 4.18 (4H, s, CH_2)
4b	3026, 2938, 1600, 1360, 1190, 763, 745, 690	7.47 (4H, d, ^3J = 7.6, H-2',6'); 7.36-7.25 (14H, m, Ar–H); 7.13 (2H, d, J = 1.6, α-H); 7.10 (2H, t, ^3J = 8.0, H-4"); 6.41 (2H, d, J = 1.6, β-H); 3.91 (4H, t, ^3J = 7.0, CH_2); 2.04 (2H, q, ^3J = 7.0, CH_2)
5	1735 (C=O), 1600, 1200 (C–O), 750, 685	7.50 (2H, d, ^3J = 7.2, H-2',6'); 7.42–7.27 (7H, m, Ar–H); 7.24 (1H, d, J = 1.6, α-H); 7.11 (1H, t, ^3J = 7.6, H-4"); 6.47 (1H, d, J = 1.6, β-H); 4.79 (2H, s, CH_2); 3.69 (3H, s, OCH_3)

* Numbering of H atoms: 1-Ar, 2-6; 2-Ar, 2'-6'; 3, β; 4-Ar, 2"-6"; 5, α.
*[2] The spectral data of **2c** correspond to data published in [7].

It was also interesting to obtain functionalized N-alkyl-2,4-diphenylpyrroles. For this purpose ethylenediamine and 1,3-diaminopropane were used in reaction with γ-bromodypnone **1**. The reaction takes place quickly without heat at both amino groups with the formation of 1-[2-(2,4-diphenyl-1H-pyrrol-1-yl)ethyl]- and 1-[2-(2,4-diphenyl-1H-pyrrol-1-yl)propyl]-2,4-diphenyl-1H-pyrroles **4a**,**b**. Attempts to obtain the products from cyclization at one amino group using an excess of the amine or the conditions described in [7] (benzene, without sodium acetate) were unsuccessful.

The reaction of γ-bromodypnone with glycine in the presence of sodium acetate gave the furan **3**, while the reaction with glycine methyl ester gave a mixture of the furan **3** and methyl 2-(2,4-diphenyl-1H-pyrrol-1-yl)acetate **5**, which were purified by fractional crystallization.

EXPERIMENTAL

The melting points of the synthesized compounds were determined on heated Boetius type apparatus and were not corrected. The IR spectra of tablets of the compounds with potassium bromide were recorded on a Pye-Unicam SP3-300 instrument. The ^{1}H NMR spectra were obtained on a Varian Mercury 400 instrument (400 MHz) in DMSO-d_6 with TMS as internal standard. The reactions and the purity of the compounds were monitored by TLC on Silufol UV-254 plates. The 4-bromo-1,3-diphenyl-2-buten-1-one **1** was obtained by the method described in [13].

1-Aryl-2,4-diphenylpyrroles 2a-k. A mixture of (1 g, 3.32 mmol) of γ-bromodypnone, sodium acetate (0.27 g), and aniline (3.32 mmol) was fused on an oil bath at 120-130°C for 15 min. After cooling water (10 ml) was added to the melt, and the mixture was thoroughly rubbed. The solid residue was filtered off, washed thoroughly with water and 2-propanol, and recrystallized. If an oil was formed after treatment with water the aqueous solution was decanted, and 5 ml of 2-propanol was added. The precipitate formed after rubbing was filtered off, washed with alcohol, and recrystallized.

2-(2,4-Diphenylpyrrol-1-yl)benzoic Acid (2l). To a solution of the nitrile **2j** (0.96 g, 3 mmol) in acetic acid (5 ml) we added hydrobromic acid (3 ml). The mixture was boiled for 2 h, and the precipitate that separated after cooling was filtered off and washed with acetic acid and alcohol. The product was recrystallized from acetic acid, and 0.32 g (31%) of 2-pyrrolylbenzoic acid was obtained.

1-[2-(2,4-Diphenylpyrrol-1-yl)ethyl]-2,4-diphenylpyrrole (4a) and 1-[2-(2,4-Diphenylpyrrol-1-yl)propyl]-2,4-diphenylpyrrole (4b). To a mixture of γ-bromodypnone (1 g, 3.32 mmol) and sodium acetate (0.27 g) with stirring we added ethylenediamine or 1,3-diaminopropane (1.66 mmol). The mixture heated up and was left for 1 h, water (10 ml) was added, and the product was rubbed thoroughly. The solid residue was filtered off, washed with water and with 2-propanol, and recrystallized.

Methyl 2-(2,4-Diphenylpyrrol-1-yl)acetate (5). A mixture of γ-bromodypnone (1 g, 3.32 mmol), sodium acetate (0.54 g), and aniline (0.42 g, 3.32 mmol) was fused on an oil bath at 120-130°C for 15 min. After cooling water (10 ml) was added to the melt, and the product was rubbed thoroughly. The solid residue was filtered off, washed thoroughly with water and with 2-propanol, and recrystallized twice from 2-propanol.

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