Furazan-containing bromoarenes in the Suzuki—Miyaura reaction*

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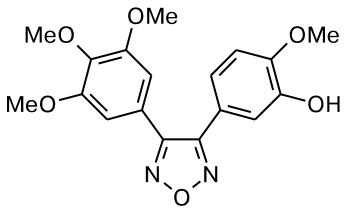
The palladium-catalyzed cross-coupling reactions of 3-[bromo(het)aryl]furazans and bromobenzofurazans with arylboronic acids afford target biaryls in good yields. 3-Bromo-4-phenylfurazan containing a bromine atom in the furazan ring undergoes decomposition under the reaction conditions.

Key words: furazans, benzofurazans, bromoarenes, arylboronic acids, cross-coupling, Suzuki—Miyaura reaction.

Functionalized (het)aryl-substituted derivatives of furazan (1,2,5-oxadiazole) are of interest as anticancer[1] (*e.g.*, combretafurazan **1**) and antiasthmatic[2—4] (*e.g.*, compound **2**) agents.



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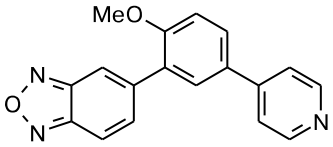

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Despite the fact that the chemistry of furazans has been well developed (see reviews[5]), the synthesis of the above-mentioned structures by conventional methods presents numerous difficulties, and their yield is often low.

It should be noted that methods making halofurazans readily available have been developed only recently.[6] Data on the reactivity of these compounds are scanty.[7] Due to the electron-withdrawing character of the furazan ring, the halogen atom bound to this ring should be highly labile. At the same time, the ability of the furazan ring to be opened under particular conditions can lead to the formation of acyclic products (see, for example, the study[8]). The ability of furazans to form complexes with transition metals is another aspect that should be taken into account when using these compounds.[9] For example, the complexation observed in reactions of the furazan ring with some catalysts interferes with the insertion of carbenes into the C—H bond of monosubstituted furazans.[10]

At present, transition metal-catalyzed cross-coupling reactions are widely used to design molecules containing (hetero)aromatic rings linked together. In particular, the formation of the C—C bond in the Suzuki—Miyaura reaction[11] proceeds through the interaction of halo(het)arenes with (het)arylboronic acids. This cross-coupling was successfully performed with both five- and six-membered heterocycles. As for halogen derivatives of furazan, the scarce data are described in patents and refer only to halobenzofurazan derivatives. The coupling of 4-chloro- and 5-bromobenzofurazans with simple arylboronic acids was documented[3,4,12] (in most cases, the yields of the products were not reported). The Stille coupling of 5-bromobenzofurazan with complicated arylstannanes[2,13] and the catalytic amination of 5-bromobenzofurazan with piperidine and piperazine derivatives[14] were described. It was found[2,3] that 4- and 5-bromobenzofurazans can be transformed into the corresponding benzofurazanylboronic acids (lithiation at −100 °C followed by the treatment with trialkyl borates; the yield of about 30%), which were then coupled with (het)aryl bromides.

In the present study, with the aim to extend the scope of the catalytic cross-coupling in the furazan series, we

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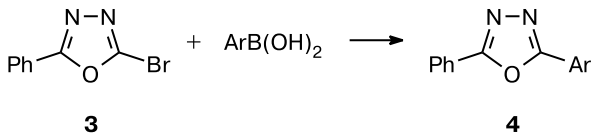
investigated the palladium-catalyzed reaction of bromo derivatives of furazan, which contain a bromine atom both directly in the furazan ring and in other parts of molecules, with (het)arylboronic acids (the Suzuki—Miyaura reaction).

Results and Discussion

It is known[15] that 2-bromo-5-phenyl-1,3,4-oxadiazole (**3**) is readily involved in the Suzuki—Miyaura reaction (Scheme 1) in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 in aqueous DMF to give cross-coupling product **4** in 85—93% yield.

Scheme 1

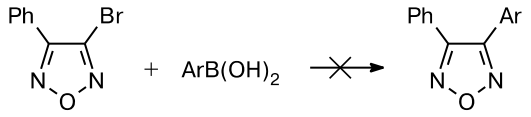


3 **4**

Reagents and conditions: $Pd(PPh_3)_4$, DMF, Na_2CO_3, H_2O, 85 °C.

We made an attempt to perform this reaction with the use of 3-bromo-4-phenylfurazan (3-bromo-4-phenyl-1,2,5-oxadiazole **5**),[16] which is an isomer of compound **3** distinguished by another arrangement of heteroatoms in the ring (Scheme 2). When performing the Suzuki—Miyaura reaction[17] according to the conventional procedure, the starting bromo(het)arene is first stirred with $Pd(PPh_3)_4$ in DMF or 1,2-dimethoxyethane (DME) (~30 min), which provides the oxidative addition of aryl bromide to a Pd^0 complex, followed by the addition of other reagents and heating of the mixture until the reaction is completed. It appeared that the mixture immediately turned black after the addition of $Pd(PPh_3)_4$ to a solution of compound **5** in DME (in DMF, compound **5** decomposes even in the absence of a catalyst!). The subsequent steps of the protocol (see Scheme 2) led to the formation exclusively of resinous products.

Scheme 2



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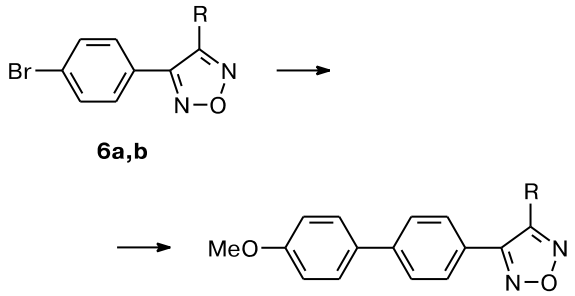
Reagents and conditions: $Pd(PPh_3)_4$, DME, Na_2CO_3, H_2O, 85 °C.

To find out whether the halofurazan or furazan moiety is cleaved in the Suzuki—Miyaura reaction, we studied other compounds containing a bromine atom and the furazan ring, which are not directly bound to each other. It appeared that bromophenyl-substituted furazans **6a**[18] and **6b**[19] are readily cross-coupled with 4-methoxyphenylboronic acid to give the expected products **7a**,**b** (Scheme 3). It should be noted that the presence of the unprotected amino group in compound **6b** does not interfere with the reaction. The yields of both products are high and virtually equal (87% for compound **7a** and 84% for **7b**).

Scheme 3

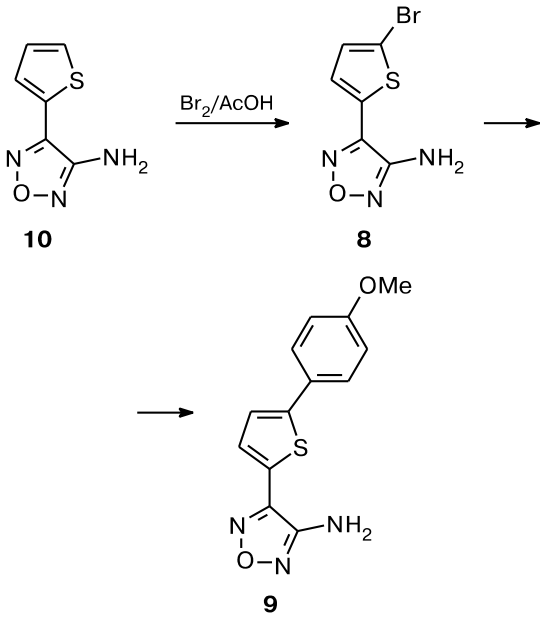


R = Me (**a**), NH_2 (**b**)

Reagents and conditions: 4-$MeOC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, DME, Na_2CO_3, H_2O, Δ.

The cross-coupling of bromothienyl compound **8** affords product **9** in 44% yield (Scheme 4); it should be

Scheme 4



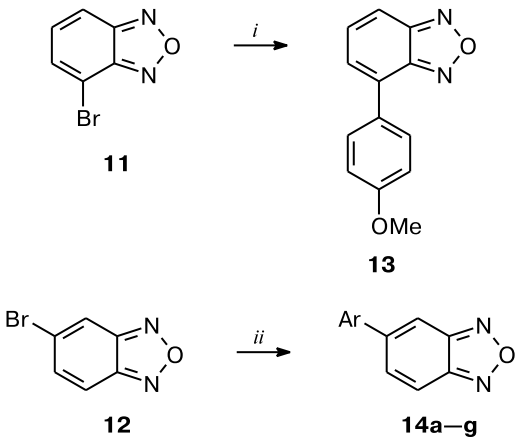
Reagents and conditions: 4-$MeOC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, DME, Na_2CO_3, H_2O, Δ.

noted that the use of 2-bromothiophenes in the Suzuki—Miyaura reaction usually gives good results.[20] The starting compound **8** was prepared by the treatment of thienylfurazan **10**[21] with bromine in acetic acid.

It should be noted that the precipitation of palladium black occurred in the beginning of the preparation of compounds **7a**,**b** and **9** (after the addition of arylboronic acid and an aqueous Na_2CO_3 solution and heating of the mixture to reflux). In the course of the initial stirring of the starting bromo(het)arenes with $Pd(PPh_3)_4$ in DME at room temperature, the mixture remained transparent and only changed the color. Usually, the precipitation of palladium black leads to the removal of the metal from the catalytic cycle and, as a consequence, to retardation of the reaction and even its complete cessation (see the review[22]). Nevertheless, examples of the catalysis of the Suzuki—Miyaura reaction by palladium black are known.[23]

We investigated the behavior of isomeric bromobenzofurazans **11** and **12** in the Suzuki—Miyaura reaction (as mentioned above, the use of isomer **12** in this reaction is described in the patent literature[3,4,13]). In our experiments, the reactions of both compounds with 4-methoxyphenylboronic acid in the presence of $Pd(PPh_3)_4$ in aqueous DME gave cross-coupling products **13** and **14a** (Scheme 5) in high yields (~90%). As in the case of nonfused furazans, the precipitation of palladium black was observed virtually immediately after the temperature of the reaction mixture reached the boiling point.

Scheme 5



14: Ar = 4-$MeOC_6H_4$ (**a**), 3-$MeOC_6H_4$ (**b**), 4-N≡CC_6H_4 (**c**), 3-N≡CC_6H_4 (**d**), 3-$H_2NC_6H_4$ (**e**), 3-pyridyl (**f**), 2,4-$F_2C_6H_3$ (**g**)

Reagents: *i*. 4-$MeOC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3; *ii*. $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3.

Using compound **12** as an example, we showed that a wide range of arylboronic acids containing both electron-donating and -withdrawing substituents can be used.

The structures of products **7a**,**b**, **9**, **13**, and **14a**—**g** were determined by IR spectroscopy, ^1H and ^{13}C NMR spectroscopy, and elemental analysis. Pyridyl-substituted derivative **14f** was studied by X-ray diffraction (Fig. 1).

According to the X-ray diffraction data, the geometric parameters of compound **14f** are typical of this class of compounds. In particular, the C—C bond length alternations in the benzofurazan moiety are observed, with the C(6)—C(7) and C(8)—C(9) bonds being substantially shorter (1.3713(9)—1.3617(10) Å). The pyridine ring is rotated by 39.4°. In the crystal, molecules **14f** form columns through π—π-stacking interactions between the benzofurazan moieties (Fig. 2). The interplanar distance is 3.3 Å, and the shortest C...C and N...C contacts are characterized by the distances of 3.360(1) and 3.357(1) Å, respectively.

To quantify the energy of stacking interactions, we performed the topological analysis of the overall electron density distribution derived from the high-precision X-ray diffraction data for the crystal of **14f** in terms of Bader´s Atoms in Molecules theory.[24] The energy of interactions was evaluated based on the semiquantitative Espinosa—Lecomte correlation,[25] which was developed and successfully used for the description of a wide range of weak, including dispersion, interactions in crystals.[26]

The deformation electron density distribution in the vicinity of the benzofurazan ring is characterized by expected features, such as the accumulation of electrons in the vicinity of the C—C, C—N, and N—O bonds, as well as of lone pairs of the oxygen and nitrogen atoms (Fig. 3).

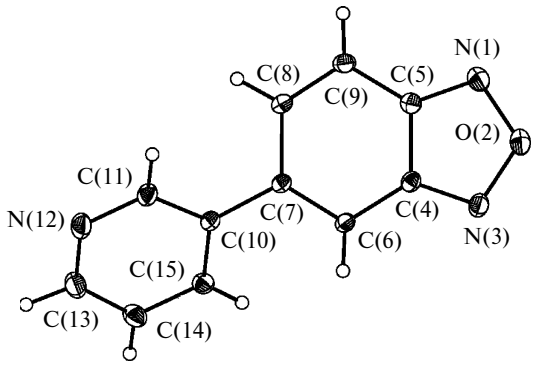


Fig. 1. Molecular structure of compound **14f**; atoms are represented as probability displacement ellipsoids (p = 50%).

Table 1. Selected bond lengths (d) in compound **14f**

Bond	d/Å	Bond	d/Å
N(1)—C(5)	1.3201(10)	C(4)—C(5)	1.4308(10)
N(1)—O(2)	1.3803(10)	C(5)—C(9)	1.4252(11)
O(2)—N(3)	1.3857(9)	C(6)—C(7)	1.3713(9)
N(3)—C(4)	1.3209(9)	C(7)—C(8)	1.4538(9)
C(4)—C(6)	1.4263(9)	C(8)—C(9)	1.3617(10)

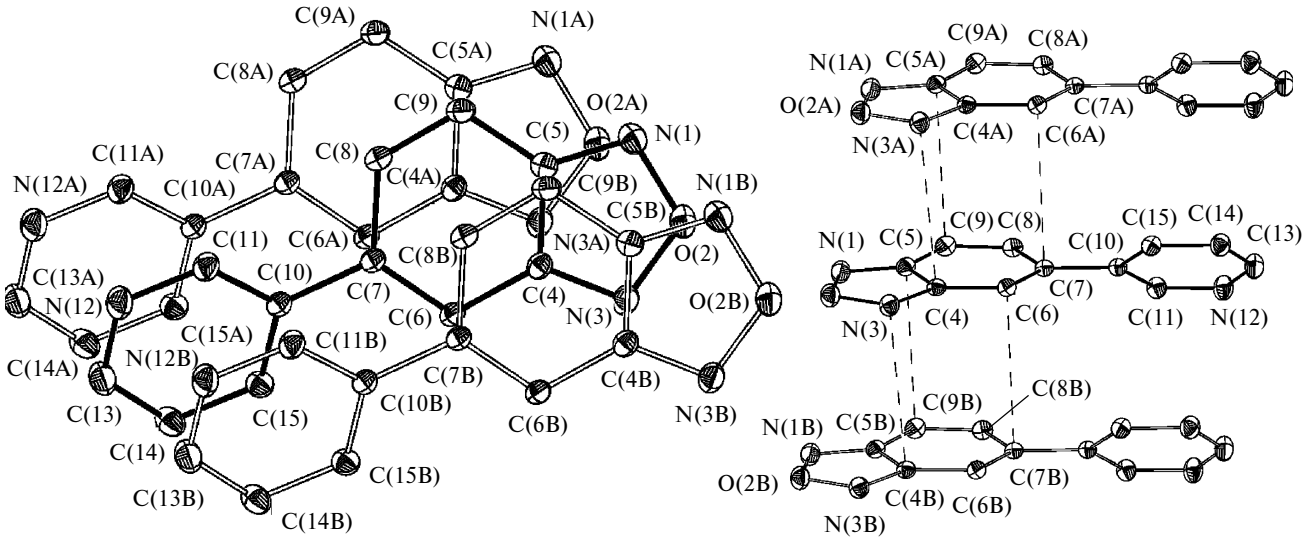


Fig. 2. Fragments of translation-related columns running along the axis *b* as an illustration of the overlap of the benzofurazan rings of compound **14f**.

An analysis of intermolecular interactions showed that there are critical points (3, −1) not only for plausible stacking interactions but also for a number of C—H...O and C—H...N interactions with the participation of both atoms of the benzofurazan ring and the nitrogen atom of pyridine. In addition, the crystal structure is stabilized by weak H...H interactions. Unlike intramolecular interactions, all intermolecular interactions are of the closed-shell type and are characterized by positive values of the Laplacian ($\nabla^2\rho(\mathbf{r})$) and the electron energy density. In particular, the values of $\rho(r)$ and $\nabla^2\rho(r)$ for the stacking interactions are ~0.04 e Å^{-3} and ~0.46 e Å^{-5}; for the shortest C(15)—H(15)...N(12) contact (H...N, 2.45 Å; CHN, 163°), ~0.05 e Å^{-3} and ~0.98 e Å^{-5}, respectively. The energies of intermolecular C...C and N...C interactions estimated with the use of the Espinosa—Lecomte correlation are 0.8—1.0 kcal mol^{-1}, and the energy for the above-mentioned C—H...N interaction is 1.5 kcal mol^{-1}. Therefore, despite a rather short distance between the planes of the molecules in the stack, the total energy of stacking interactions per molecule is small (2.6 kcal mol^{-1}), For comparison, the total crystal lattice energy estimated by the summation of the energies of all binding interactions based on the results of topological analysis of the electron density distribution is 13 kcal mol^{-1}.

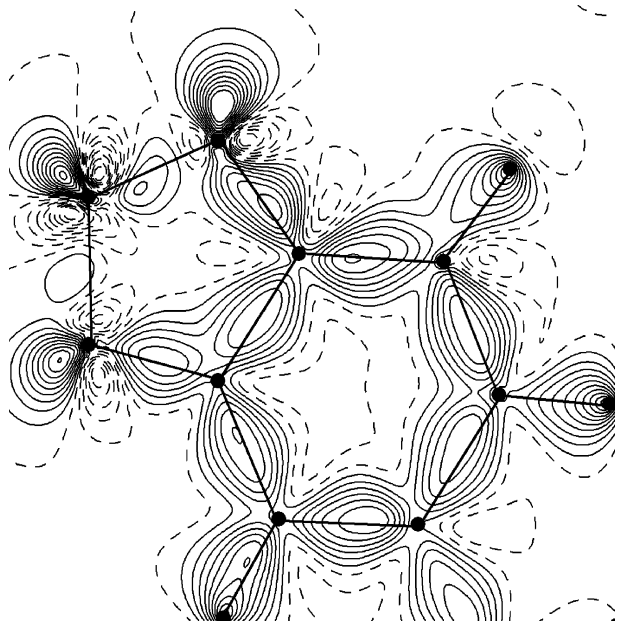
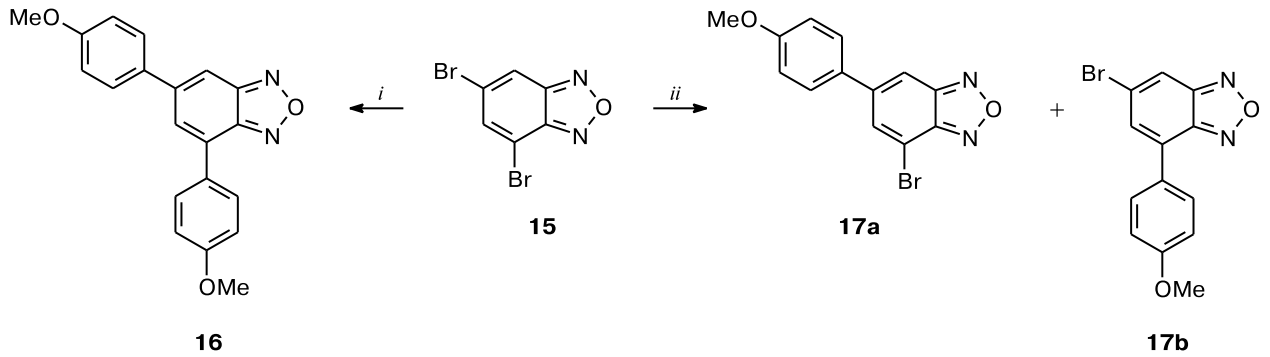


Fig. 3. Deformation electron density distribution in the plane of the benzofurazan ring. The maps are contoured at 0.1 e Å^{-3} intervals. The negative contours are indicated by dashed lines.

The reaction of 4,6-dibromobenzofurazan **15** with two equivalents of 4-methoxyphenylboronic acid (Scheme 6) afforded disubstitution product **16** in 95% yield. The reaction with the use of one equivalent of boronic acid gave a mixture of regioisomeric monosubstitution products **17a** and **17b**, which were separated by column chromatography. It was shown that these products were formed in approximately equal amounts (45 and 50% yields, respectively).

Since we isolated both regioisomers **17a** and **17b** in the individual state, their structures were determined based on substantial differences in the ^{13}C NMR spectra. The spectrum of isomer **17a** shows a high-field signal of the quaternary sp^2-hybridized carbon atom at δ 109.3 due to the simultaneous −β effect of the imino group and the −α effect of the bromine atom. In the spectrum of isomer **17b**, the

Scheme 6



Reagents: 2.2 equiv. (*i*), 1 equiv. (*ii*) 4-$MeOC_6H_4B(OH)_2$.

highest-field signal of the quaternary sp^2-hybridized carbon atom appears at δ 126.2. In addition, the signal of the =CH fragment adjacent to the furazan ring in isomer **17a** is observed at δ 110.2, whereas this signal for isomer **17b** appears at δ 115.6, which is consistent with the fact that the +β effect of bromine is usually 4—5 ppm greater than this for the aryl group.

Therefore, we showed that bromo(het)aryl-substituted furazans and bromobenzofurazans are promising substrates for the Suzuki—Miyaura reaction. The possibility of the use of 3-bromofurazans in the transition metal-catalyzed cross-coupling requires additional investigation.

Experimental

The melting points were determined using a Gallenkamp melting point apparatus and are not corrected. The natural-abundance ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$ or DMSO-d_6 at 300.13 and 75.47 MHz, respectively. The mass spectra were obtained on Varian MAT CH-6 and Varian MAT CH-111 instruments (70 eV). The IR spectra were measured on a Specord M-82 spectrophotometer in KBr pellets. The TLC analysis was performed on Kieselgel 60 F_{254} plates (Merck, Cat. No. 1.05554). Preparative chromatography was carried out with the use of silica gel 40/100 (Merck). Elemental analysis was performed in the Laboratory of Analytical Chemistry of the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences. All solvents for the reactions or column chromatography were pre-distilled. 3-Amino-4-(2-thienyl)furazan,[21] 3-bromo-4-phenylfurazan (**1**),[16] and 3-amino-4-(4-bromophenyl)furazan (**2b**)[19] were synthesized according to procedures described in the literature. Commercially available arylboronic acids were used as received.

3-(4-Bromophenyl)-4-methyl-1,2,5-oxadiazole (6a). A 28% aqueous ammonia solution (8 mL), 1-(4-bromophenyl)-1,2-dihydroxyiminopropane[27] (1.31 g, 5.1 mmol), and urea (0.4 g, 6.7 mmol) were placed in a 30 mL autoclave. The reaction mixture was heated at 150—155 °C for 6.5 h. After cooling, the mixture was extracted with CCl_4 (3×10 mL) and CH_2Cl_2 (10 mL). The combined extracts were washed with water (2×10 mL), dried with $MgSO_4$, and filtered through a thin layer of SiO_2. The filtrate was concentrated to ~3 mL and diluted with an equal volume of pentane. The mixture was kept in a refrigerator for 3 h, and the precipitate was filtered off. A pale cream product was obtained in a yield of 0.64 g (53%), m.p. 66—67 °C (*cf.* lit. data[27]: m.p. 64 °C). IR, ν/cm^{-1}: 2960, 2924, 2852, 1596, 1508, 1444, 1408, 1384, 1264, 1116, 1076, 1052, 1036, 1008, 976, 896, 848, 832, 820, 728. ^1H NMR ($CDCl_3$), δ: 2.58 (s, 3 H, CH_3); 7.69 (m, 4 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 9.6 (CH_3); 124.9 (C—Br and C_{ipso}); 129.4, 132.3 (Ar); 149.4 (C—Ar); 152.9 (C—CH_3). MS, *m/z*: 240, 238 $[M]^+$, 210, 208 $[M - NO]^+$, 199, 197, 183, 181, 169, 167, 157, 155. Found (%): C, 45.27; H, 2.99; N, 11.64. $C_9H_7BrN_2O$. Calculated (%): C, 45.22; H, 2.95; N, 11.72.

3-Amino-4-(5-bromo-2-thienyl)-1,2,5-oxadiazole (8). A solution of Br_2 (0.28 g, 1.75 mmol) in AcOH (3 mL) was added dropwise with stirring to a cold (10 °C) solution of 3-amino-4-(2-thienyl)furazan (**10**)[21] (0.28 g, 1.14 mmol) in glacial acetic acid (5 mL) with maintaining the temperature not higher than 12 °C (cooling bath). Then the reaction mixture was allowed to reach room temperature and was diluted with water (12 mL). The precipitate was filtered off, washed with water (2×5 mL) and hexane (2×5 mL), and dried. The product was obtained in a yield of 0.33 g (80%), m.p. 133—135 °C; chromatorgaphically pure, R_f 0.5 (CH_2Cl_2 : pentane, 1 : 1). The recrystallization from CCl_4 gave pale cream crystals with m.p. 135—136 °C. IR, ν/cm^{-1}: 3448, 3328, 3240, 1632, 1584, 1560, 1496, 1428, 1324, 1288, 1220, 1008, 980, 940, 884, 788, 744, 732. ^1H NMR (DMSO-d_6), δ: 6.34 (s, 2 H, NH_2); 7.41 (d, 1 H, J = 4.0 Hz); 7.62 (d, 1 H, J = 4.0 Hz). ^{13}C NMR (DMSO-d_6), δ: 114.9 (C—Br); 127.5 (C(3)); 129.7, 131.6, 141.6 (C—Th); 154.2 (C—NH_2). Found (%): C, 29.35; H, 1.69; N, 17.00. $C_6H_4BrN_3OS$. Calculated (%): C, 29.29; H, 1.64; N, 17.08.

4-Bromo-2,1,3-benzoxadiazole (11). Sodium azide (1.5 g, 0.023 mol) was added portionwise to a stirred suspension of 2,6-dibromonitrobenzene[28] (5.3 g, 0.02 mol) in DMSO (30 mL) at room temperature, which was accompanied by spontaneous heating of the reaction mixture to 35 °C. Then the mixture was slowly heated to 120—125 °C, avoiding vigorous foaming, and kept at this temperature until the completion of the reaction (~30 min, TLC monitoring). The mixture was diluted with twice the volume of water, and the product was steam-distilled. The precipitate was filtered off from the water distillate and dried in

air. The recrystallization from propan-2-ol gave the product in a yield of 2.63 g (66%), m.p. 107—108°C (*cf.* lit. data[29]: m.p. 107 °C). ^{1}H NMR ($CDCl_3$), δ: 7.30 (dd, 1 H); 7.63 (d, 1 H, J = 7.0 Hz); 7.81 (d, 1 H, J = 8.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 109.4 (C—Br); 115.7, 132.0, 133.8, 149.2, 149.5.

5-Bromo-2,1,3-benzoxadiazole (12). 4-Bromo-2-nitroaniline (7.9 g, 0.036 mol) was stirred in a mixture of water (5 mL) and concentrated hydrochloric acid (15 mL) at 50 °C for 30 min and then cooled to −5 °C. A solution of sodium nitrite (2.76 g, 0.04 mol) in water (10 mL) was added dropwise with maintaining the temperature not higher than 5 °C. The reaction mixture was kept at 0 °C for 1 h, and then a solution of sodium azide (2.8 g, 0.043 mol) in water (10 mL) was added. The precipitate of 4-bromo-2-nitrophenyl azide that formed was filtered off, washed with water, and transferred to a flask containing ethylene glycol (15 mL). The reaction mixture was kept at 100—110 °C until nitrogen evolution ceased (~1 h). After cooling to 60 °C, sodium azide (2.3 g, 0.035 mol) and ethylene glycol (10 mL) were added. The mixture was heated to 120 °C and kept at this temperature for 3 h. Then the mixture was diluted with water (20 mL). The product was steam-distilled and dried in air. The yield of the product was 5.26 g (73%), m.p. 74—75 °C (*cf.* lit. data[30]: m.p. 75 °C). ^{1}H NMR ($CDCl_3$), δ: 7.46 (d, 1 H, J = 8.3 Hz); 7.73 (d, 1 H, J = 8.3 Hz); 8.08 (s, 1 H). ^{13}C NMR ($CDCl_3$), δ: 117.7, 118.4, 126.2 (C—Br); 135.7, 147.6, 149.7.

4,6-Dibromo-2,1,3-benzoxadiazole (15) was synthesized according to a modified procedure.[31] A solution of 4,6-dibromobenzofuroxane (11.84 g, 0.04 mol) in methanol (200 mL) and $P(OMe)_3$ (7.45 g, 0.06 mol) was refluxed for 3 h. Then methanol and unconsumed $P(OMe)_3$ were distilled off, and the residue was diluted with water. The pale yellow precipitate that formed was filtered off, washed with a large amount of water, and recrystallized from ethanol. The yield of the product was 9.0 g (81%), m.p. 70—71 °C (*cf.* lit. data.[32]: 71.5—72 °C). ^{1}H NMR ($CDCl_3$), δ: 7.67 (s, 1 H); 8.00 (s, 1 H). ^{13}C NMR ($CDCl_3$), δ: 110.3 (C—Br); 117.3, 125.7 (C—Br); 137.2, 148.2, 149.2.

Cross-coupling reaction (general procedure). Reactions were carried out in a two-necked flask equipped with a rubber septum and a reflux condenser connected to a vacuum/argon manifold according to procedures reported earlier.[17] Then $Pd(PPh_3)_4$ (35 mg, ~3 mol.%) was added to a deaerated solution of the starting bromo derivative (1 mmol) in 1,2-dimethoxyethane (2 mL), and the reaction mixture was stirred under argon for 30—40 min. Arylboronic acid (1.3 mmol) was added, and the mixture was twice carefully deaerated by evacuating and filling with argon. A freshly prepared deaerated solution of Na_2CO_3 (0.54 g) in water (2.1 mL) was syringed through the septum, and the mixture was heated to reflux, which was accompanied by precipitation of palladium black. The mixture was refluxed for 6 h, cooled, diluted with water, and extracted with CH_2Cl_2. The combined extracts were dried (with $CaCl_2$ or Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography using a mixture of CH_2Cl_2 and petroleum ether as the eluent (the CH_2Cl_2 content was chosen depending on the nature of particular compounds).

4-[4-(4-Methoxyphenyl)phenyl]-3-methyl-1,2,5-oxadiazole (7a), the yield was 87%, white solid, m.p. 139—140 °C. Found (%): C, 72.43; H, 5.47; N, 10.56. $C_{16}H_{14}N_2O_2$. Calculated (%): C, 72.17; H, 5.30; N, 10.52. IR (KBr), ν_{max}/cm^{-1}: 2900, 2936, 2840, 1604, 1508, 1460, 1444, 1292, 1272, 1256, 1204, 1184, 1028, 1012, 980, 892, 828, 816. ^{1}H NMR ($CDCl_3$), δ: 2.61 (s, 3 H); 3.88 (s, 3 H); 7.03 (d, 2 H, J = 8.8 Hz); 7.59 (d, 2 H, J = 8.8 Hz); 7.71 (A part of the AB system, 2 H, J = 8.8 Hz); 7.79 (B part of the AB system, 2 H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 9.8 (CH_3); 55.4 (CH_3); 114.4 (CH); 124.2 (C); 127.2 (CH); 128.2 (CH); 128.4 (CH); 132.3 (C); 142.8 (C); 149.6 (C); 153.6 (C); 159.7 (C).

3-Amino-4-[4-(4-methoxyphenyl)phenyl]-1,2,5-oxadiazole (7b). The yield was 84%, white solid, m.p. 208—210 °C. Found (%): C, 67.33; H, 5.21; N, 15.62. $C_{15}H_{13}N_3O_2$. Calculated (%): C, 67.41; H, 4.90; N, 15.72 IR (KBr), ν_{max}/cm^{-1}: 3460, 3328, 3248, 2956, 2940, 2836, 1636, 1608, 1516, 1484, 1312, 1292, 1256, 1208, 1184, 1036, 1016, 988, 888, 828. ^{1}H NMR (DMSO-d_6), δ: 3.81 (s, 3 H); 6.24 (br.s, 2 H); 7.06 (d, 2 H, J = 8.8 Hz); 7.70 (d, 2 H, J = 8.8 Hz), 7.81 (A part of the AB system, 2 H, J = 8.8 Hz); 7.84 (B part of the AB system, 2 H, J = 8.8 Hz). ^{13}C NMR (DMSO-d_6), δ: 55.1 (CH_3); 114.4 (CH); 123.6 (C); 126.5 (CH); 127.7 (CH); 128.0 (CH); 131.3 (C); 141.4 (C); 146.5 (C); 155.1 (C); 159.3 (C).

3-Amino-4-[5-(4-methoxyphenyl)thiophen-2-yl]-1,2,5-oxadiazole (9). The yield was 44%, greenish solid, m.p. 204—205 °C. Found (%): C, 57.07; H, 4.15; S, 11.53. $C_{13}H_{11}N_3O_2S$. Calculated (%): C, 57.13; H, 4.06; S, 11.73. IR (KBr), ν_{max}/cm^{-1}: 3440, 3320, 3240, 3024, 2972, 2940, 2844, 1636, 1612, 1576, 1556, 1524, 1492, 1448, 1428, 1340, 1308, 1288, 1256, 1180, 1112, 1084, 1032, 1000, 964, 936, 900, 872, 828, 788. ^{1}H NMR (DMSO-d_6), δ: 3.80 (s, 3 H); 6.34 (br.s, 2 H); 7.02 (d, 2 H, J = 8.6 Hz); 7.53 (d, 1 H, J = 3.8 Hz); 7.68 (d, 2 H, J = 8.6 Hz); 7.77 (d, 1 H, J = 3.8 Hz). ^{13}C NMR (DMSO-d_6), δ: 55.5 (CH_3); 114.6 (CH); 123.4 (CH); 123.6 (C); 125.3 (C); 127.0 (CH); 130.0 (CH); 142.3 (C); 146.3 (C); 154.3 (C); 159.6 (C).

4-(4-Methoxyphenyl)-2,1,3-benzoxadiazole (13). The yield was 89%, bright yellow crystals, m.p. 126—127 °C. Found (%): C, 68.35; H, 4.44. $C_{13}H_{10}N_2O_2$. Calculated (%): C, 69.02; H, 4.46. IR (KBr), ν_{max}/cm^{-1}: 3068, 3004, 2968, 2916, 2840, 1612, 1544, 1512, 1444, 1280, 1256, 1184, 1180, 1140, 1120, 1036, 884, 868, 836, 800, 788, 752. ^{1}H NMR ($CDCl_3$), δ: 3.90 (s, 3 H); 7.06 (d, 2 H, J = 8.8 Hz); 7.43—7.53 (m, 2 H); 7.75 (dd, 1 H, J = 7.8 Hz, J = 2.4 Hz); 7.98 (d, 2 H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.4 (CH_3); 114.1 (CH); 114.1 (CH); 126.7 (CH); 127.7 (C); 129.6 (CH); 130.0 (C); 131.9 (CH); 148.7 (C); 149.9 (C); 160.5 (C).

5-(4-Methoxyphenyl)-2,1,3-benzoxadiazole (14a). The yield was 91%, yellow crystals, m.p. 123—124 °C. Found (%): C, 69.12; H, 4.35. $C_{13}H_{10}N_2O_2$. Calculated (%): C, 69.02; H, 4.46. IR (KBr), ν_{max}/cm^{-1}: 3072, 2968, 2936, 2836, 1608, 1572, 1520, 1508, 1468, 1444, 1408, 1380, 1284, 1256, 1244, 1184, 1032, 988, 876, 840, 800. ^{1}H NMR ($CDCl_3$), δ: 3.89 (s, 3 H); 7.04 (d, 2 H, J = 8.8 Hz); 7.61 (d, 2 H, J = 8.8 Hz); 7.71 (d, 1 H, J = 8.1 Hz); 7.88 (d, 1 H, J = 8.1 Hz); 7.88 (s, 1 H). ^{13}C NMR ($CDCl_3$), δ: 55.4 (CH_3); 111.2 (CH); 114.6 (CH); 116.5 (CH); 128.5 (CH); 131.0 (C); 132.8 (CH); 143.7 (C); 148.4 (C); 149.8 (C); 160.5 (C).

5-(3-Methoxyphenyl)-2,1,3-benzoxadiazole (14b). The yield was 86%, white crystals, m.p. 107—108 °C. Found (%): C, 68.91; H, 4.41. $C_{13}H_{10}N_2O_2$. Calculated (%): C, 69.02; H, 4.46. IR (KBr), ν_{max}/cm^{-1}: 3080, 2980, 2940, 2832, 1608, 1580, 1540, 1492, 1464, 1432, 1288, 1204, 1168, 1056, 1000, 876, 860, 816, 780, 768. ^{1}H NMR ($CDCl_3$), δ: 3.89 (s, 3 H); 7.01 (d, 1 H, J = 8.4 Hz); 7.17 (s, 1 H); 7.23 (d, 1 H, J = 7.7 Hz); 7.43 (t, 1 H, J = 8.1 Hz); 7.70 (d, 1 H, J = 9.3 Hz); 7.90 (d, 1 H, J = 9.3 Hz);

7.94 (s, 1 H). ^{13}C NMR ($CDCl_3$), δ: 55.4 (CH_3); 112.7 (CH); 113.2 (CH); 114.3 (CH); 116.6 (CH); 119.7 (CH); 130.2 (CH); 132.9 (CH); 140.2 (C); 141.1 (C); 148.6 (C); 149.6 (C); 160.2 (C).

5-(4-Cyanophenyl)-2,1,3-benzoxadiazole (14c). The yield was 74%, white solid, m.p. 173—174 °C. Found (%): 70.41; H, 3.43; N, 18.83. $C_{13}H_7N_3O$. Calculated (%): C, 70.58; H, 3.19; N, 18.99. IR (KBr), ν_{max}/cm^{-1}: 3108, 3052, 2232, 1628, 1608, 1540, 1524, 1468, 1420, 1404, 1328, 1304, 1184, 1156, 1016, 996, 880, 844, 804, 772. ^{1}H NMR (DMSO-d_6), δ: 7.98 (d, 2 H, J = 8.3 Hz); 7.99 (d, 1 H, J = 9.4 Hz); 8.04 (d, 2 H, J = 8.3 Hz); 8.16 (d, 1 H, J = 9.4 Hz); 8.41 (s, 1 H). ^{13}C NMR (DMSO-d_6), δ: 111.8 (C); 113.9 (CH); 117.0 (CH); 118.5 (C); 128.4 (CH); 132.8 (CH); 133.0 (CH); 142.0 (C); 142.2 (C); 148.4 (C); 149.3 (C).

5-(3-Cyanophenyl)-2,1,3-benzoxadiazole (14d). The yield was 88%, white solid, m.p. 177—178 °C. Found (%): C, 70.71; H, 3.13. $C_{13}H_7N_3O$. Calculated (%): C, 70.58; H, 3.19. IR (KBr), ν_{max}/cm^{-1}: 3064, 2232, 1628, 1580, 1540, 1520, 1468, 1432, 1376, 1316, 1276, 1160, 1036, 1004, 880, 852, 792, 772, 692. ^{1}H NMR (DMSO-d_6), δ: 7.74 (t, 1 H, J = 7.9 Hz); 7.94 (d, 1 H, J = 7.9 Hz); 8.03 (d, 1 H, J = 9.4 Hz); 8.17 (d, 1 H, J = 9.4 Hz); 8.20 (d, 1 H, J = 7.9 Hz); 8.36 (s, 1 H); 8.43 (s, 1 H). ^{13}C NMR (DMSO-d_6), δ: 112.4 (C); 113.5 (CH); 116.9 (CH); 118.5 (C); 130.3 (CH); 131.2 (CH); 132.0 (CH); 132.6 (CH); 134.0 (CH); 138.9 (C); 141.8 (C); 148.4 (C); 149.4 (C).

5-(3-Aminophenyl)-2,1,3-benzoxadiazole (14e). The yield was 78%, yellow solid, m.p. 129—131 °C. Found (%): C, 68.18; H, 4.42. $C_{12}H_9N_3O$. Calculated (%): C, 68.24; H, 4.29. IR (KBr), ν_{max}/cm^{-1}: 3392, 3332, 3240, 1668, 1644, 1604, 1588, 1540, 1496, 1468, 1448, 1328, 1312, 1208, 1160, 1128, 1068, 996, 884, 852, 816, 784, 768. ^{1}H NMR (DMSO-d_6), δ: 5.26 (br.s, 2 H); 6.70 (d, 1 H, J = 7.8 Hz); 6.95 (d, 1 H, J = 7.8 Hz); 7.00 (s, 1 H); 7.18 (t, 1 H, J = 7.8 Hz); 7.87 (d, 1 H, J = 9.8 Hz); 8.08 (s, 1 H); 8.11 (d, 1 H, J = 9.8 Hz). ^{13}C NMR (DMSO-d_6), δ: 111.1 (CH); 112.4 (CH); 114.9 (two overlapping signals of CH), 116.4 (CH); 129.7 (CH); 133.6 (CH); 138.6 (C); 144.7 (C); 148.4 (C); 149.3 (C); 149.6 (C).

5-(3-Pyridyl)-2,1,3-benzoxadiazole (14f). The yield was 83%, beige solid, m.p. 139—140 °C. Found (%): C, 67.06; H, 3.58. $C_{11}H_7N_3O$. Calculated (%): C, 67.00; H, 3.58. IR (KBr), ν_{max}/cm^{-1}: 3028, 1628, 1592, 1512, 1468, 1420, 1408, 1376, 1308, 1264, 1244, 1200, 1160, 1016, 996, 932, 896, 880, 848, 800, 788, 708. ^{1}H NMR ($CDCl_3$), δ: 7.46 (m, 1 H); 7.68 (d, 1 H, J = 9.2 Hz); 7.91—8.05 (m, 3 H); 8.71 (s, 1 H); 8.93 (s, 1 H). ^{13}C NMR ($CDCl_3$), δ: 113.7 (CH); 117.4 (CH); 123.8 (CH); 132.0 (CH); 134.4 (C); 134.5 (CH); 141.1 (C); 148.3 (CH); 148.5 (C); 149.4 (C); 150.2 (CH).

5-(2,4-Difluorophenyl)-2,1,3-benzoxadiazole (14g). The yield was 93%, white solid, m.p. 108—110 °C. Found (%): C, 61.91; H, 2.56. $C_{12}H_6F_2N_2O$. Calculated (%): C, 62.08, H, 2.60. IR (KBr), ν_{max}/cm^{-1}: 3084, 3056, 1620, 1596, 1520, 1496, 1468, 1428, 1324, 1296, 1276, 1224, 1144, 1104, 1020, 1000, 972, 888, 848, 808. ^{1}H NMR ($CDCl_3$), δ: 6.94—7.09 (m, 2 H); 7.50 (q, 1 H, $^3J_{H,H}$ = 8.1 Hz, $^4J_{H,F}$ = 8.1 Hz); 7.59 (d, 1 H, J = 9.2 Hz); 7.90 (d, 1 H, J = 9.2 Hz); 7.92 (s, 1 H). ^{13}C NMR ($CDCl_3$), δ: 104.9 (t, CH, J_{CF} = 26.0 Hz); 112.2 (dd, CH, $J_{C,F}$ = 21.6 Hz, $J_{C,F}$ = 3.9 Hz); 115.5 (d, CH, $J_{C,F}$ = 2.8 Hz); 116.4 (CH); 123.1 (dd, C, $J_{C,F}$ = 13.3 Hz, $J_{C,F}$ = 3.9 Hz); 131.3 (dd, CH, J_{CF} = 9.4 Hz, J_{CF} = 4.4 Hz); 133.5 (d, CH, $J_{C,F}$ = 3.3 Hz); 138.4 (d, C, $J_{C,F}$ = = 1.7 Hz); 148.3 (C); 149.3 (C); 160.0 (dd, CF, $J_{C,F}$ = 252.7 Hz, $J_{C,F}$ = 12.2 Hz); 163.3 (dd, CF, $J_{C,F}$ = 252.1 Hz, $J_{C,F}$ = 11.6 Hz). ^{19}F NMR ($CDCl_3$) δ (relative to $CFCl_3$): −107.6, −111.4.

4,6-Bis(4-methoxyphenyl)-2,1,3-benzoxadiazole (16) was synthesized from dibromide **15** with the use of 2.2 equiv. of 4-methoxyphenylboronic acid. The yield was 95%, bright yellow crystals, m.p. 141—143 °C. Found (%): C, 72.22; H, 5.08; N, 8.39. $C_{20}H_{16}N_2O_3$. Calculated (%): C, 72.28; H, 4.85; N, 8.43. IR (KBr), ν_{max}/cm^{-1}: 3004, 2976, 2940, 2840, 1612, 1508, 1440, 1308, 1292, 1248, 1184, 1172, 1028, 860, 824. ^{1}H NMR ($CDCl_3$), δ: 3.90 (s, 6 H); 7.04 (d, 2 H, J = 8.8 Hz); 7.07 (d, 2 H, J = 8.8 Hz); 7.64 (d, 2 H, J = 8.8 Hz); 7.77 (s, 2 H); 8.01 (d, 2 H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.4 (CH_3); 109.2 (CH); 114.4 (CH); 114.6 (CH); 127.8 (C); 128.3 (CH); 128.5 (CH); 129.7 (CH); 129.9 (C); 131.5 (C); 144.3 (C); 148.2 (C); 150.7 (C); 160.4 (C); 160.5 (C).

Compounds 17a,b were synthesized from dibromide **15** with the use of 1 equiv. of 4-methoxyphenylboronic acid and separated by column chromatography on silica gel (gradient elution to 25% CH_2Cl_2 in petroleum ether), **17b** being eluted first.

4-Bromo-6-(4-methoxyphenyl)-2,1,3-benzoxadiazole (17a). The yield was 50%, white solid, m.p. 131—132 °C. R_f 0.35 (40% CH_2Cl_2 in petroleum ether). Found (%): C, 51.19; H, 2.88; N, 9.09. $C_{13}H_9BrN_2O_2$. Calculated (%): C, 51.17; H, 2.97; N, 9.18. IR (KBr), ν_{max}/cm^{-1}: 3088, 3004, 2920, 2844, 1608, 1508, 1444, 1288, 1260, 1196, 1172, 1064, 1032, 952, 892, 832, 792. ^{1}H NMR ($CDCl_3$), δ: 3.89 (s, 3 H); 7.03 (d, 2 H, J = 8.8 Hz); 7.57 (d, 2 H, J = 8.8 Hz); 7.81 (s, 1 H); 7.92 (s, 1 H). ^{13}C NMR ($CDCl_3$), δ: 55.4 (CH_3); 109.3 (C); 110.2 (CH); 114.7 (CH); 128.5 (CH); 129.8 (C); 135.2 (CH); 144.8 (C); 148.8 (C); 149.8 (C); 160.7 (C).

6-Bromo-4-(4-methoxyphenyl)-2,1,3-benzoxadiazole (17b). The yield was 45%, yellow solid, m.p. 90—91 °C. R_f 0.41 (40% CH_2Cl_2 in petroleum ether). Found (%): C, 51.27; H, 3.06; N, 9.20. $C_{13}H_9BrN_2O_2$. Calculated (%): C, 51.17; H, 2.97; N, 9.18. IR (KBr), ν_{max}/cm^{-1}: 3084, 2928, 2900, 2840, 1608, 1572, 1456, 1288, 1256, 1232, 1180, 1028, 1016, 960, 884, 868, 828. ^{1}H NMR ($CDCl_3$), δ: 3.89 (s, 3 H); 7.05 (d, 2 H, J = 8.8 Hz); 7.57 (s, 1 H); 7.95 (s, 1 H); 7.96 (d, 2 H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 55.4 (CH_3); 114.5 (CH); 115.6 (CH); 126.2 (C); 126.7 (C); 129.8 (CH); 130.5 (CH); 131.2 (C); 147.5 (C); 150.5 (C); 161.0 (C).

X-ray diffraction. Crystals of compound **14f** ($C_{11}H_7N_3O$, M = 197.20) at 100 K are orthorhombic: a = 20.2365(3) Å, b = 3.72030(10) Å, c = 11.9970(2) Å, V = 903.20(3) Å^3, d_{calc} = = 1.450 g cm^{-1}, space group $Pca2_1$, Z = 4. The intensities of 59404 reflections were measured on a Smart APREX2 CCD automated diffractometer at 100 K (Mo-Kα radiation, graphite monochromator, ω-scanning technique, $2\theta_{max}$ = 100°) of which 4848 independent reflections (R_{int} = 0.0381) were used in subsequent calculations. The structure was solved by direct methods and refined by the full-matrix least-squares method with isotropic and anisotropic displacement parameters based on F^2. The hydrogen atoms were located in difference electron density maps and refined isotropically. The final R factors were as follows: wR_2 = 0.1002, GOOF = 0.963 based on all reflections (R_1 = 0.0394 was calculated based on 8064 reflections with $I > 2\sigma(I)$) with the use of the SHELXTL PLUS program package.[33]

The multipole refinement of **14f** was performed in terms of the Hansen—Coppens formalism[34] with the use of the XD program package[35] with the core and valence electron density de-

rived from wavefunctions fitted to a relativistic Dirac—Fock solution. Before the refinement, the C—H bond lengths were normalized to 1.08 Å. The multipole expansion for nitrogen, oxygen, and carbon atoms was taken up to the octupole level and for the hydrogen atoms up to the dipole level. The refinement was performed based on F_{hkl}. All covalently bonded pairs of atoms satisfy the Hirshfeld rigid-bond test.[36] The maximum residual electron density was 0.21 e Å^{-3} (in the vicinity of the N(1) nucleus). Binding interactions were found and the topological characteristics of electron density distribution were calculated with the use of the WINXPRO program.[37] The final R factors were as follows: $R = 0.0262$, $Rw = 0.0259$, GOOF = 0.9882 for 4283 reflections with $I > 3\sigma(I)$.

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