Chemistry of Heterocyclic Compounds, Vol. 43, No. 8, 2007

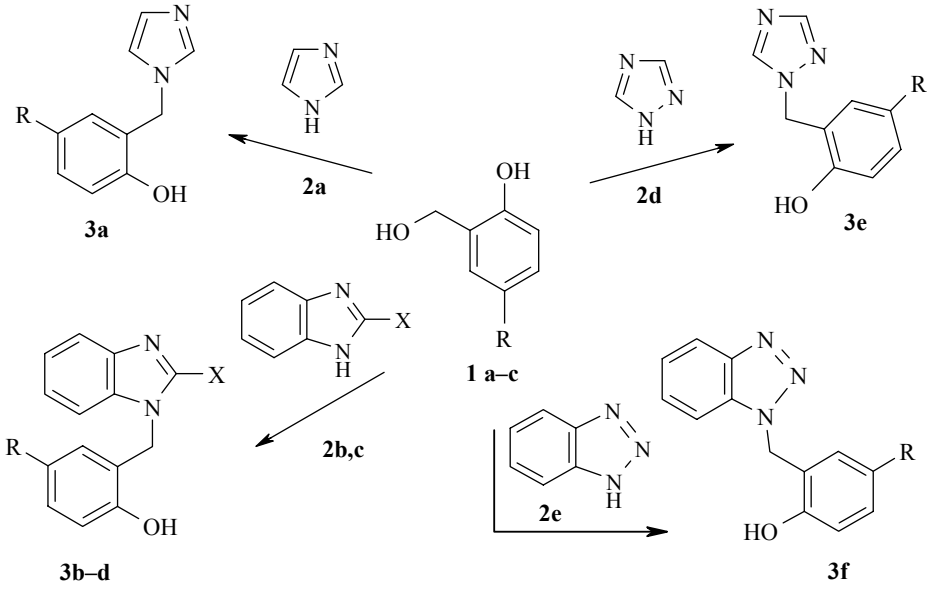
REACTION OF 1H-AZOLES WITH 2-HYDROXYBENZYL ALCOHOLS

N. E. Sidorina[1] and V. A. Osyanin[2]

Condensation of 1H-azoles with 2-hydroxybenzyl alcohols gave a series 2-(1H-azol-1-ylmethyl)phenols. 12H-Benzimidazo[2,1-b][1,3]benzoxazine was synthesized from 2-methylmercaptobenzimidazole and 2-hydroxybenzyl alcohol. The X-ray diffraction data of 7-nitro-2,3-diphenyl-5H-imidazo[2,1-b]-[1,3]benzoxazine are discussed.

Keywords: 1H-azoles, 2-(1H-azol-1-ylmethyl)phenols, (benz)imidazo[2,1-*b*][1,3]benzoxazines, 2-hydroxybenzyl alcohols, *o*-methylenequinones, X-ray diffraction.

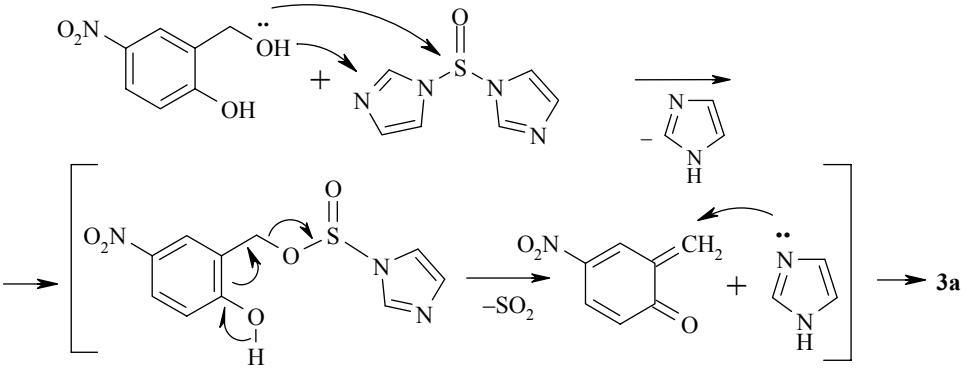
Recently *o*-methylenequinones (*o*-quinone methides) have frequently been used for the design of new oxygen-containing heterocyclic systems [1, 3] and modification of those already known [4, 5]. In a continuation of studies on the interaction of nitrogen-containing heterocycles with *o*-methylenequinones we have investigated the reaction between 2-hydroxybenzyl alcohols and 1H-azoles.



1b, **3c** R = H; **1a**, **3a**,**b**,**f** R = NO_2; **1c**, **3d**,**e** R = Br; **2**,**3 b** X = Me; **c** X = CF_3

[1]Samara State University, Samara 443011, Russia; e-mail: sidorinan@inbox.ru. [2]Samara State Technical University, Samara 443100, Russia; e-mail: vosyanin@mail.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, 1256-1263, August, 2007. Original article submitted March, 21, 2006.

A series of compounds with noticeable difference in basicity were chosen as azoles. The pK_a values varied from 2.20 (for 1,2,4-triazole) to 6.95 (for imidazole) [6]. Despite the considerable difference in the pK_a values, all of the listed heterocycles reacted readily with 2-hydroxybenzyl alcohols. *o*-Methylenequinone was generated thermally *in situ* with an azole molecule acting both as nucleophile by attacking the *o*-methylenequinone and facilitating the dehydration of the alcohol as a base. During the reaction time the azole molecules produced only a small concentration of *o*-methylenequinone which prevented its oligomerization and led to high yields of the products of N-benzylation.

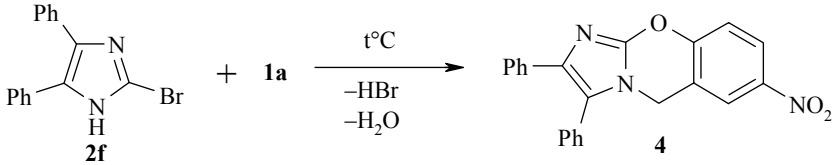


Compound **3a** was also made by counter synthesis from bis(imidazol-1-yl) sulfoxide and 2-hydroxy-5-nitrobenzyl alcohol (**1a**) in THF. This reaction was mentioned elsewhere [7, 8] but the authors did not provide exact experimental details [9]. The process evidently occurs *via* formation of *o*-methylenequinone which is generated at a much lower temperature in this case.

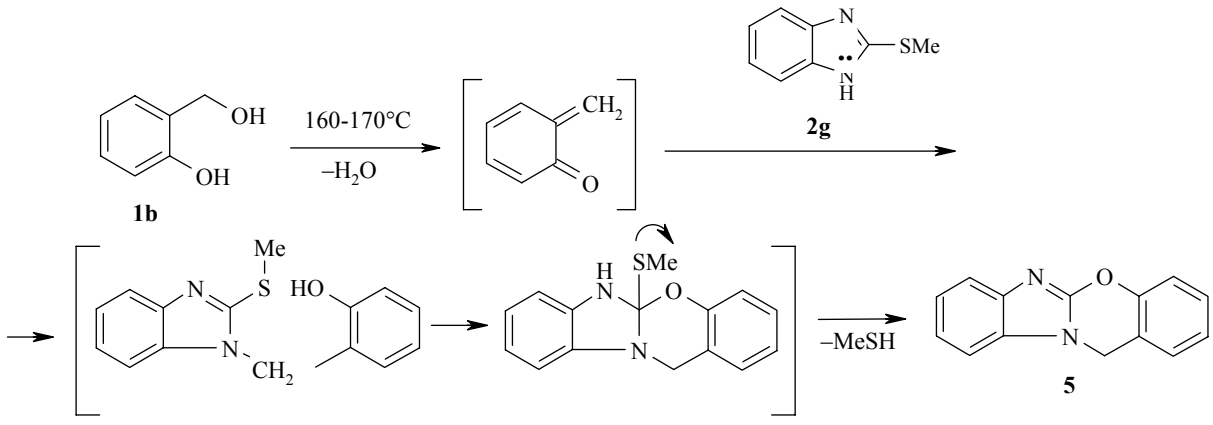
Samples of 2-(1H-imidazol-1-ylmethyl)-4-nitrophenol (**3a**) made by the two methods have identical spectral data and did not give a depression of the melting point.

When a suitable substituent is present in the β-position to the NH group in the azole molecule intramolecular heterocyclization of the 2-(1H-azol-1-ylmethyl)phenol intermediate is possible.

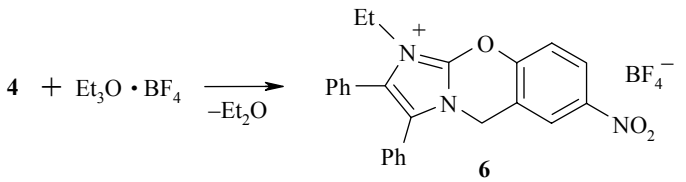
For example, we have shown previously [10] that 7-nitro-2,3-diphenyl-5H-imidazo[2,1-*b*][1,3]benzoxazine (**4**) is formed by reaction of 2-bromo-4,5-diphenylimidazole (**2f**) with 2-hydroxy-5-nitrobenzyl alcohol (**1a**).



Heterocyclic systems may be desighed analogously from 2-methylmercaptobenzimidazole (**2g**). 12H-Benzimidazo[2,1-*b*][1,3]benzoxazine (**5**) is formed from its thermal condensation with salicylic alcohol **1b**.



The monocyclic products **3a-e** are readily alkylated at the basic nitrogen with alkyl and benzyl halides, whereas in the case of the polycyclic compound **4** the process occurs only with powerful alkylating agents, in particular $Et_3O \cdot BF_4$.



It should be noted that in the presence of strong acceptor substituents in the molecules of halo-substituted azoles, alkylation with 2-hydroxybenzyl alcohols does not occur selectively at high temperatures (160-170°C). When 2,4,5-tribromoimidazole, 2-chloro-5,6-dinitrobenzimidazole, or 5(4)-iodo-2-methyl-4(5)-nitroimidazole reacted with salicylic alcohol complex mixture of products were formed from which it was not possible to isolate individual components.

The reactions of 2-(azol-1-ylmethyl)phenols are general in nature, the azole nature has no major influence on the yield of the required product.

The obtained products **3a-f** are crystalline, thermally stable high-melting compounds, which are poorly soluble in water and most organic solvents. In contrast to the monocyclic compounds **3a-f**, the polycyclic imidazo[2,1-*b*]-[1,3]benzoxazines are readily soluble in dichloromethane, dioxane, and acetone. It should be noted that the solubility of 2-(azol-1-ylmethyl)phenol in dilute solutions of acids and alkalis is associated with salt formation. In contrast (benz)imidazo[2,1-*b*][1,3]benzoxazines **4** and **5** are practically insoluble in aqueous solutions of acids, despite the presence of a basic nitrogen atom.

In the ^{1}H NMR spectra of all the compounds synthesized there are signals of the methylene protons in the 5.12-5.95 ppm region. The signals at 8.9-10.4 ppm for compounds **3a-f** are assigned to protons of the OH group.

TABLE 1. Characteristics of the Synthesized Compounds **3a-f**, **4**, and **5**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, % (method)
		C	H	N		
3a	$C_{10}H_9N_3O_3$	54.65 / 54.79	4.16 / 4.11	18.77 / 19.18	248-250	79 (A), 65 (B)
3b	$C_{15}H_{13}N_3O_3$	63.44 / 63.60	4.65 / 4.59	14.53 / 14.84	255-257	71
3c	$C_{15}H_{11}F_3N_2O$	61.48 / 61.64	3.82 / 3.77	9.59 / 9.39	216-217	69
3d	$C_{15}H_{10}BrF_3N_2O$	48.40 / 48.52	2.73 / 2.70	7.39 / 7.55	240-242	73
3e	$C_9H_8BrN_3O$	42.41 / 42.52	3.19 / 3.15	16.19 / 16.54	173-174	75
3f	$C_{13}H_{10}N_4O_3$	57.63 / 57.78	3.74 / 3.70	20.30 / 20.74	241-242	70
4*	$C_{22}H_{15}N_3O_3$	75.35 / 75.54	4.12 / 4.07	11.14 / 11.38	234-235	80
5	$C_{14}H_{10}N_2O$	75.49 / 75.68	4.55 / 4.50	12.34 / 12.61	233-235	65

* Data from [10].

In the IR spectra there are absorption bands at 1600 cm^{-1} corresponding to of C=C/C=N bonds vibrations in the aromatic rings and the CH_{arom} bonds at 760-741 cm^{-1}. In the spectra of compounds **4** and **5** bands of medium intensity are present at 1269-1270 cm^{-1} corresponding to vibrations of the C–O–C unit, and for compounds **3a-f** there are broad absorption bands at 3400-2500 cm^{-1} corresponding to hydroxy group, associated *via* hydrogen bonds. There are characteristic absorption bands of the nitro group in the regions of 1562-1520 and 1342-1327 cm^{-1} in the spectra of compounds **3a,b,f** and **4**.

Decomposition of the molecular ions of the compounds **4** and **5,** formed by electron ionization, occurs nonselectively: the intensity of the molecular ion peak for compound **4** is maximal, while for compound **5** the ion $[M–H]^+$ has maximum intensity due to loss of a hydrogen atom from the oxazine ring, which is explained by the formation of a chain of conjugation.

In the ^1H NMR spectra of compounds **4** and **5** there are no signals in the region ~9.0 ppm and there are no broad intense absorption bands in the IR spectra, which confirms the cyclic structure of the molecules of these compounds (Table 2).

TABLE 2. Spectral Characteristics of Compounds **3a-f**

Com-pound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
3a	3394, 3136-3086, 2372, 1597, 1558, 1477, 1339, 1296, 1145, 1088, 837, 748	5.40 (2H, s, CH_2); 6.93 (1H, d, *J* = 8.0, H_{Az}-4); 7.23 (1H, d, *J* = 7.2, H-6); 7.53 (1H, d, *J* = 8.0, H_{Az}-5); 7.97 (1H, s, H_{Az}-2); 8.05 (1H, d, *J* = 7.2, H-5); 8.20 (1H, s, H-3); 9.25 (1H, s, OH)
3b	3250-2400, 1616, 1593, 1524, 1497, 1427, 1327, 1285, 741	2.49 (3H, s, CH_3); 5.31 (2H, s, CH_2); 7.23 (1H, d, *J* = 8, H-6); 7.27-7.39 (4H, m, H_{Az}-4-7); 7.91 (1H, s, H-3); 7.94 (1H, d, *J* = 8, H-5); 9.51 (1H, s, OH)
3c	3148-3086, 1601, 1520, 1458, 1277, 1180, 1153, 1122, 1095, 744	5.62 (2H, s, CH_2); 6.89 (1H, t, *J* = 7.8, H-4); 6.96-7.01 (2H, m, H-3, 6); 7.28-7.49 (4H, m, H_{Az}-5,6,7, H-5); 7.98 (1H, d, *J* = 8.6, H_{Az}-4); 9.75 (1H, s, OH)
3d	3063-2955, 1593, 1520, 1477, 1423, 1265, 1195, 1138, 1095, 818, 748	5.61 (2H, s, CH_2); 6.91-7.37 (4H, m, H_{Az}-5, H-3,5,6); 7.49 (1H, t, *J* = 7, H_{Az}-6); 7.78 (1H, d, *J* = 8, H_{Az}-7); 7.89 (1H, d, *J* = 8.5, H_{Az}-4); 9.71 (1H, s, OH)
3e	3105-2604, 1589, 1497, 1435, 1346, 1277, 1142, 1107, 1018, 818, 760, 671, 656	5.31 (2H, s, CH_2); 6.82 (1H, d, *J* = 8, H-5); 7.18 (1H, s, H-3); 7.31 (1H, d, *J* = 8, H-6); 7.94 (1H, s, H_{Az}-3); 8.51 (1H, s, H_{Az}-5); 10.08 (1H, s, OH)
3f	3300-2500, 1620, 1593, 1527, 1497, 1447, 1339, 1300, 1273, 1088,748	5.95 (2H, s, CH_2); 7.03 (1H, d, *J* = 8.3, H-6); 7.41 (1H, t, *J* = 8.4, H_{Az}-6); 7.55 (1H, t, *J* = 8.4, H_{Az}-5); 7.83 (2H, m, H_{Az}-7, H-5); 7.92 (1H, s, H-3); 8.02 (1H, d, *J* = 8.2, H_{Az}-4); 11.05 (1H, s, OH)
3g*	3047, 2916, 1597, 1551, 1508, 1485, 1443, 1342, 1296, 1258, 775, 744, 706	5.12 (2H, s, CH_2); 7.15 (2H, t, *J* = 1.2, C_6H_5); 7.21-7.25 (3H, m, C_6H_5); 7.42 (1H, d, *J* = 8, H-9); 7.48-7.56 (5H, m, C_6H_5); 8.24 (1H, d, *J* = 8, H-8); 8.38 (1H, s, H-6)
3h*	3421, 3383, 3047, 2924, 1631, 1547, 1458, 1288, 1188, 756, 736, 439	5.40 (2H, s, CH_2); 7.20-7.26 (5H, m, H-1,2,3,4, 10); 7.42-7.49 (3H, m, H-7,8,9)

* From [10], mass spectra, *m/z* (I_{rel}, %): compound **3g** 369 $[M]^+$ (100), 323 $[M–NO_2]^+$ (29), 165 (23), 89 (33), 77 $[C_6H_5]^+$ (16), 63 (20); compound **3h** 222 $[M]^+$ (94), 221 $[M–H]^+$ (100), 166 (12), 97 (13), 90 (41), 89 (36), 83 (16), 77 $[C_6H_5]^+$ (23), 64 (18), 63 (32), 51 (24).

The structure of compound **4** has also been confirmed by X-ray diffraction. The geometry of the molecule, numbering of the atoms, principal bond lengths, and the principal bond and torsion angles are given in Fig. 1 and Table 3.

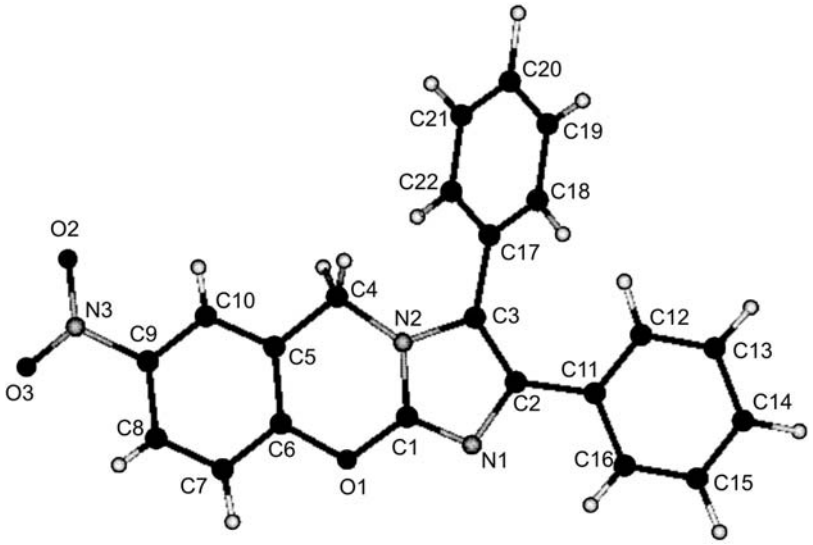


Fig 1. General view of molecule **3g** and numbering of the atoms.

The imidazo[2,1-*b*][1,3]benzoxazine ring has a practically planar cycle, despite the fact that it contains an sp^3-hybridized carbon atom; the maximal distortion of the value of the torsion angles from the ideal planar structure is 3.87°.

The phenyl group $C_{(11)}…C_{(16)}$ is practically coplanar with the imidazo[2,1-*b*][1,3]benzoxazine, with the torsion angle $C_{(3)}C_{(2)}C_{(11)}C_{(16)}$ 178.71°. The plane of the $C_{(17)}…C_{(22)}$ phenyl ring forms a dihedral angle of 112.28° with the plane of the imidazo[2,1-*b*][1,3]benzoxazine ring.

In the crystal molecules of compound **4** form stacks along the crystal direction (0 0 1) with the molecules within the stacks arranged "head to tail".

Thus we have shown 1H-azoles are quite easily alkylated by 2-hydroxybenzyl alcohols under conditions of thermal condensation with formation of 2-(1H-azol-1-ylmethyl)phenols which, with presence at position 2 of 1H-azole of group capable of nucleophilic substitution, may undergo intramolecular heterocyclization with formation of condensed imidazo[2,1-*b*][1,3]benzoxazine system.

TABLE 3. Bond Lengths (*d*), Values of theValence (ω) and Torsion (τ) Angles in the Molecule of 7-nitro-2,3-diphenyl-5H-imidazo[2,1-*b*][1,3]-benzoxazine*

Bond	*d*, Å	Angle	ω, deg	Angle	τ, deg
$N_{(2)}–C_{(1)}$	1.334(3)	$C_{(4)}N_{(2)}C_{(1)}$	126.5(2)	$C_{(4)}N_{(2)}C_{(1)}O_{(1)}$	0.25
$C_{(1)}–O_{(1)}$	1.361(3)	$N_{(2)}C_{(1)}O_{(1)}$	122.4(2)	$N_{(2)}C_{(1)}O_{(1)}C_{(6)}$	-3.54
$O_{(1)}–C_{(6)}$	1.391(3)	$C_{(1)}O_{(1)}C_{(6)}$	117.2(2)	$C_{(1)}O_{(1)}C_{(6)}C_{(5)}$	3.87
$C_{(6)}–C_{(5)}$	1.375(3)	$O_{(1)}C_{(6)}C_{(5)}$	122.2(2)	$O_{(1)}C_{(6)}C_{(5)}C_{(10)}$	178.66
$C_{(5)}–C_{(4)}$	1.493(3)	$C_{(6)}C_{(5)}C_{(4)}$	122.7(2)	$C_{(6)}C_{(5)}C_{(4)}N_{(2)}$	-2.01
$C_{(4)}–N_{(2)}$	1.447(3)	$C_{(5)}C_{(4)}N_{(2)}$	108.9(2)	$C_{(17)}C_{(3)}N_{(2)}C_{(1)}$	-176.31

* Complete listings of atomic coordinates and valence of the temperature parameters may be obtained from the authors.

EXPERIMENTAL

IR spectra of KBr disks were recorded with a Shimadzu FTIR-8400S spectrophotometer. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with a Bruker AM-400 (400 MHz) instrument. Mass spectra were obtained with a JMS-D300 instrument with direct injection and an ionization energy of 70 eV. Purity of products was monitored by TLC (Silufol UV-254, eluent 20:1 chloroform-methanol, development with UV light).

2-Trifluoromethylbenzimidazole (**2c**) was obtained by a method in [11], and 2-bromo-4,5-diphenyl-imidazole (**2f**) and 2-methylmercaptobenzimidazole (**2g**) as in [12].

Synthesis of 2-(1H-Azol-1-ylmethyl)phenols 3a-f. A. An equimolar mixture of the azole **2a-f** and a 2-hydroxybenzyl alcohol **1a-c** was heated at 160-170°C with intense stirring for 20 min. The reaction product was washed with cold dichloromethane and crystallized from ethanol.

B. $SOCl_2$ (1.19 g, 10 mmol) was added to a solution of imidazole **2a** (2.72 g, 40 mmol) in dry THF, the precipitate of imidazole hydrochloride was filtered off, and the solution of bis(imidazol-1-yl) sulfoxide was added rapidly to a solution of benzyl alcohol **1a** (1.69 g, 10 mmol) in THF. The reaction mixture was boiled for 2 h, the solvent was evaporated, and the residue was crystallized from an ethanol-DMF mixture.

12H-Benzimidazo[2,1-*b*][1,3]benzoxazine (5). A mixture of compound **2g** (1.64 g, 10 mmol) and 2-hydroxybenzyl alcohol **1b** (1.30 g, 10.5 mmol) was heated for 30 min at 160-165°C with intense stirring until water vapor evolution ceased. The product crystallized twice from methanol.

1-Ethyl-7-nitro-2,3-diphenyl-5H-imidazo[2,1,*b*][1,3]benzoxazinium Tetrafluoroborate (6) [10]. A solution of triethyloxonium tetrafluoroborate (1.9 g, 10 mmol) in dichloromethane (10 ml) was added to a solution of compound **4** (3.69 g, 10 mmol) in absolute dichloromethane (50 ml) and the reaction mixture was stirred at room temperature for 25 min. The precipitate was filtered off and washed successively with dichloromethane and ethanol to give compound **6** as yellow crystals in a yield of 2.91 g (60%); mp 273-274°C (DMF). IR spectrum, ν, cm^{-1}: 2962, 2854 (CH_{arom}), 1655, 1628, 1585 (C=C/C=N), 1528 (NO_2), 1485 (C=C), 1346 (NO_2), 1092 (B–F), 771, 702 (CH_{arom}).

X-ray Diffraction Study of Compound 4. Crystals were grown from a mixture of DMF-ethanol (1:2) by slow evaporation at room temperature: a monocrystal with linear dimensions 0.2×0.25×0.3 mm was chosen for investigation. The yellow needle crystals belonged to the monoclinic system: a = 19.112(4), b = 11.207(2), c = 8.092(2) Å, β = 94.69(3)°, V = 1727.4(6) Å^3, M = 369.36, d_{calc} = 1.420 g/cm^3, Z = 4, space group $P2_1/n$. Unit parameters and a set of experimental reflexions were measured on an automatic four-cycle diffractometer (KUMA DIFFRACTION, KM-4) with χ-geometry and ω/2θ scanning with monochromatized MoKα radiation (2θ ≤50.1°); segment of the sphere: $-22 \le h \le 22$, $0 \le k \le 13$, $0 \le l \le 9$. A total of 3493 reflexions were measured of which 3071 were symmetrically independent [R(int) = 0.0223, R(σ) = 0.0683]. Since the crystals of the compound studied have small absorption coefficients and small sizes, corrections for absorption were not applied (μ = 0.098 mm^{-1}). The structure was solved by direct method using the programm SIR92 [13] with subsequent calculations using the electron density distribution. All hydrogen atoms were found from electron density difference syntheses and refined in the isotropic approximation. A full matrix anisotropic (non-hydrogen atoms) least squares analysis using the SHELX97 program [14] refined to R_1 = 0.0444, wR_2 = 0.1119 for 1488 reflexions with $I \ge 2\sigma(I)$, GooF 0.856.

REFERENCES

1. C. Botteghi, S. Paganelli, F. Moratti, M. Marchetti, R. Lazzaroni, R. Settambolo, and O. Piccolo, *J. Mol. Catal. A: Chem.,* **200**, 147 (2003).

2. K. Wojciechowski and K. Dolatowska, *Tetrahedron*, **61**, 8419 (2005).
3. C. C. Lindsey and T. R. R. Pettus, *Tetrahedron Lett.*, **47,** 201 (2006).
4. S. L. Crawley and R. L. Funk, *Org. Lett.*, **5**, 3169 (2003).
5. J. E. Ezcurra, K. Karabelas, and H. W. Moore, *Tetrahedron***, 61**, 275 (2005).
6. D. Barton and U. D. Ollis (editors), *General Organic Chemistry* [Russian translation], Khimiya, Moscow, 1985. Vol. 8, p. 437.
7. R. W. Van De Water and T. R. R. Pettus, *Tetrahedron*, **58**, 5367 (2002).
8. M. Ogata, *Ann. N. Y. Acad. Sci.,* **544**, 12 (1988).
9. H. A. Staab, H. Bauer, and K. M. Schneider, *Azolides in Organic Synthesis and Biochemistry,* Wiley-VCH Verlag GmbH and Co., KGaA, 2002, p. 456.
10. V. A. Osyanin and N. E. Sidorina, *Izv. Vuzov. Khimiya I Khim. Tekhnologiya,* **48**, No. 10, 83 (2005).
11. G. Crank and A. Mursyidi, *Aust. J. Chem.,* **35**, 775 (1982).
12. A. F. Pozharskii, V. A. Anisimova, and E. B. Tsupak, *Practical Work on Heterocycle Chemistry* [in Russian], Rostov Univ. Press, Rostov on Don (1988).
13. A. Altomare, G. Cascarano, C. Giacovazzo, and A. Gualardi, *J. Appl. Crystallogr.,* **26**, 343 (1993).
14. G. M. Sheldrick. SHELX-97. *Programs for Crystal Structure Analysis.* Univ. of Göttingen, Göttingen, Germany, 2332 (1998).