Russian Journal of Organic Chemistry, Vol. 37, No. 7, 2001, pp. 1026–1029. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 7, 2001, pp. 1076–1079.

Synthesis of Substituted 2-Aryl- and 2-Hetarylimidazo[4,5-*d*]pyridazines

S. V. Gres'ko, N. N. Smolyar, and Yu. M. Yutilov

Litvinenko Institute of Physical Organic and Coal Chemistry, National Academy of Sciences of Ukraine, ul. R. Luxemburg 70, Donetsk, 83114 Ukraine
e-mail: yutilov@skif.net

Received October 3, 1999

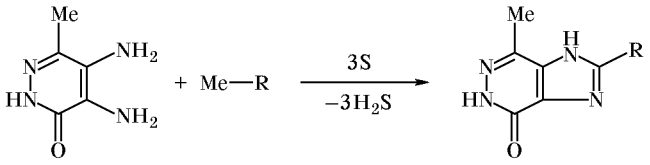
Abstract—Substituted 2-aryl- and 2-hetarylimidazo[4,5-*d*]pyridazines were synthesized by oxidative cyclization in the presence of sulfur of 4,5-diamino-6-methylpyridazin-3-one with substituted arene(hetarene)carbaldehydes or heterocyclic compounds having an activated methyl group.

Imidazo[4,5-*d*]pyridazines are structural analogs of purine and are of interest as biologically active compounds. Antithrombotic, cardiotonic, and antioxidant activity of imidazo[4,5-*d*]pyridazines is well known [1–3]. These data stimulated our studies on the synthesis of 2-aryl- and 2-hetarylimidazo[4,5-*d*]pyridazines. 2-Substituted imidazo[4,5-*d*]pyridazines are usually prepared by cyclization of the corresponding 4,5-diaminopyridazines with formic acid, formamide, or triethyl orthoformate in acetic anhydride [4, 5], as well as by oxidative cyclization of the same diamine with aromatic aldehydes in nitrobenzene [6]. The reaction of 4,5-diaminopyridazines with arenecarboxylic acids in polyphosphoric acid is characterized by poor yields [1, 2]. Imidazo[4,5-*d*]pyridazines are also availavle through cyclization of 2-substituted diethyl imidazole-4,5-dicarboxylates with hydrazine [3].

We now propose a procedure for synthesizing 2-arylimidazo[4,5-*d*]pyridazines via oxidative cyclization of aromatic *ortho*-diamines with compounds having an activated methine, methylene, or methyl group [7–12]. Heating of a mixture of equimolar amounts of 4,5-diaminopyridazine (**I**) and methyl-substituted heterocycles **IIa**–**IId** and 3 equiv of sulfur at 195°C is accompanied by evolution of hydrogen sulfide and leads to formation of 2-hetarylimidazo-[4,5-*d*]pyridazines **IIIa**–**IIId** in good yields (Table 1, Scheme 1).

The structure of compounds **IIIa**–**IIId** was proved by the ^{1}H NMR and IR spectra (Table 2). For instance, the ^{1}H NMR spectrum of **IIIa** contains signals from the methyl group and N^{5}H protons (δ 2.55 and 12.48 ppm, respectively) of the pyridazine moiety and signals from the pyridine fragment: two doublets at δ 8.35 and 8.75 ppm (3′-H, 6′-H) and two triplets at δ 8.07 and 7.60 ppm (4′-H, 5′-H; J = 7 Hz). Compounds **IIIa**–**IIId** characteristically show in the IR spectra carbonyl absorption band at 1665–1670 cm^{-1}.

Scheme 1.



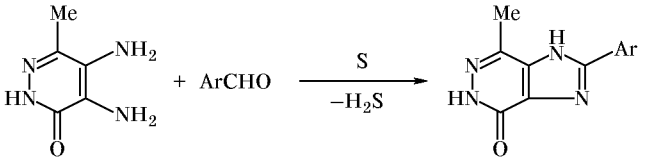
I **IIa–IId** **IIIa–IIId**

II, **III**, R = 2-pyridyl (**a**), 5-ethyl-2-pyridyl (**b**), 4-pyridyl (**c**), 2-quinolyl (**d**).

We previously proposed a simple and convenient procedure for preparation of 2-aryl-substituted imidazo[4,5-*b*]pyridines and imidazo[4,5-*c*]pyridines by oxidative cyclization of the corresponding diaminopyridines and arene(hetarene)carbaldehydes in the presence of sulfur [7, 8]. We made an attempt to apply the same procedure to the synthesis of 2-aryl(hetaryl)-imidazo[4,5-*d*]pyridazines. A mixture of equimolar amounts of 4,5-diamino-6-methylpyridazin-3-one (**I**), aromatic or heteroaromatic aldehyde **IVa**–**IVg** or **Va**, **Vb**, and sulfur was heated at 175–180°C until hydrogen sulfide no longer evolved. The reaction flask contained only the target product, imidazopyridazine **IIIc**, **IVa**–**IVg**, or **VII**, whose yield attained 89% (Scheme 2).

1070-4280/01/3707-1026 $25.00 © 2001 MAIK "Nauka / Interperiodica"

Scheme 2.



I **IVa–IVg** **Va, Vb** **IIIc, VIa–VIg, VII**

IV, **VI**, Ar = C_6H_5 (**a**), 4-$CH_3OC_6H_4$ (**b**), 4-BrC_6H_4 (**c**), 4-$(CH_3)_2NC_6H_4$ (**d**), 2,4-$Cl_2C_6H_3$ (**e**), 1,3-benzodioxol-5-yl (**f**), 2,5-$(CH_3O)_2C_6H_3$ (**g**); **V**, Ar = 2-pyridyl (**a**), 3-pyridyl (**b**); **VII**, Ar = 3-pyridyl.

We also proposed a convenient (from the preparative viewpoint) procedure for the synthesis of initial 4,5-diamino-6-methylpyridazin-3-one (**I**). Amination of 6-methylpyridazin-3-one (**VIII**) [10, 11] with hydrazine hydrate by analogy with the procedure described in [12] gave 4-amino-6-methylpyridazin-3-one (**IX**). The nitration of **IX** afforded 6-methyl-4-nitroaminopyridazin-3-one (**X**) whose rearrangement in concentrated sulfuric acid led to formation of 4-amino-6-methyl-5-nitropyridazin-3-one (**XI**). The latter was reduced to diamine **I** with iron powder in acetic acid (Scheme 3).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Varian Gemini-200 (200 MHz) and Tesla BS-487C (80 MHz) spectrometers in DMSO-d_6 and CF_3COOH, respectively, using hexamethyldisiloxane as internal reference. The IR spectra were measured on a UR-20 instrument in mineral oil.

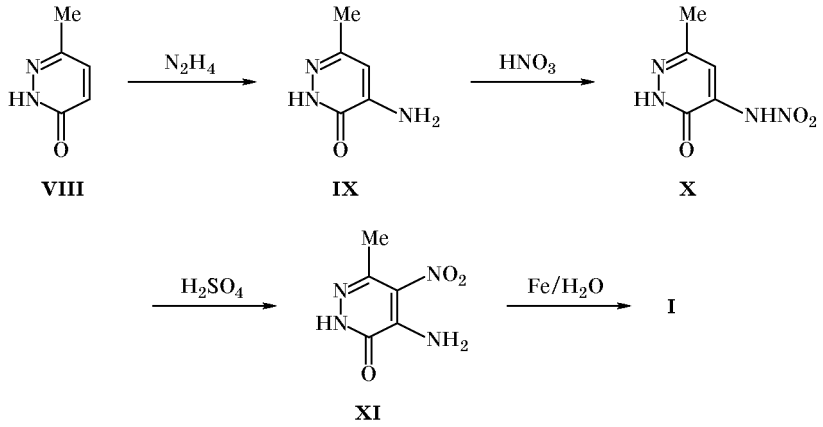
4,5-Diamino-6-methylpyridazin-3(2*H*)-one (I). A mixture of 2 g (11.8 mmol) of 4-amino-6-methyl-5-nitropyridazin-3(2*H*)-one (**XI**) and 2 g of iron powder in 200 ml of 1% aqueous acetic acid was heated to the boiling point and was vigorously stirred for 12–16 h at that temperature. The mixture was then filtered, the filtrate was neutralized with 25% aqueous ammonia, and the precipitate was filtered off and dried. Yield 1.1 g (63%), mp 276–279°C (from water). Found, %: C 42.66; H 5.69; N 39.86. $C_5H_8N_4O$. Calculated, %: C 42.85; H 5.75; N 39.98.

2-Hetaryl-7-methylimidazo[4,5-*d*]pyridazin-4(5*H*)-ones IIIa–IIId. A mixture of 5 mmol of 4,5-diamino-6-methylpyridazin-3(2*H*)-one (**I**), 5.5 mmol of methylpyridine or 2-methylquinoline **IIa**–**IId**, and 15 mmol of sulfur was heated at 185–195°C until hydrogen sulfide no longer evolved. The resulting melt was ground with ether, the precipitate was filtered off and dissolved in 5% hydrochloric acid, the solution was filtered, and the filtrate was neutralized with aqueous ammonia. The precipitate was filtered off and dried. Products **IIIa**–**IIId** were purified by recrystallization from alcohol (Table 1).

2-Aryl(hetaryl)-7-methylimidazo[4,5-*d*]pyridazin-4(5*H*)-ones VIa–VIg and VII. A mixture of 4.3 mmol of compound **I**, 4.5 mmol of arene- or hetarenecarbaldehyde **IVa**–**IVg**, **Va**, or **Vb**, and 4.3 mmol of sulfur was heated at 175–180°C until hydrogen sulfide no longer evolved. The resulting melt was ground with ether, the precipitate was filtered off and dissolved in 5% hydrochloric acid, the solution was filtered, and the filtrate was neutralized with aqueous ammonia. The precipitate was filtered off, dried, and recrystallized from alcohol (Table 1).

4-Amino-6-methylpyridazin-3(2*H*)-one (IX). A mixture of 35 g (0.27 mol) of 6-methylpyridazin-3-one hydrate and 300 ml (6.18 mol) of hydrazine hydrate was heated for 7–10 h at 150–160°C. When the reaction was complete (ammonia no longer

Scheme 3.



VIII **IX** **X** **XI**

Table 1. Yields, melting points, and elemental analyses of 2-aryl- and 2-hetarylimidazo[4,5-*d*]pyridazines **IIIa**–**IIId**, **VIa**–**VIg**, and **VII**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa	53	299–302	57.96	4.01	30.78	$C_{11}H_9N_5O$	58.15	3.96	30.84
IIIa[a]	45	300–302	57.98	3.99	30.73	$C_{11}H_9N_5O$	58.15	3.96	30.84
IIIb	62	276–278	60.98	5.21	27.40	$C_{13}H_{13}N_5O$	61.18	5.10	27.45
IIIc	41	331–332	57.94	3.87	30.69	$C_{11}H_9N_5O$	58.15	3.96	30.84
IIId	78	308–310	64.82	3.89	25.06	$C_{15}H_{11}N_5O$	64.98	3.97	25.27
VIa	78	328–330	63.54	4.38	24.69	$C_{12}H_{10}N_4O$	63.72	4.42	24.78
VIb	82	347–349	60.75	4.65	21.73	$C_{13}H_{12}N_4O_2$	60.94	4.69	21.88
VIc	89	349–351	47.05	2.89	18.25	$C_{12}H_9N_4O$	47.21	2.95	18.37
VId	87	323–325	62.28	5.52	25.93	$C_{14}H_{15}N_5O$	62.45	5.58	26.02
VIe	85	295–297	48.64	2.65	18.91	$C_{12}H_8Cl_2N_4O$	48.81	2.71	18.98
VIf	72	314–316	57.60	3.69	20.61	$C_{13}H_{10}N_4O_3$	57.78	3.73	20.73
VIg	76	279–281	58.56	4.88	19.38	$C_{14}H_{14}N_4O_3$	58.74	4.93	19.57
VII	87	351–353	57.96	3.92	30.68	$C_{11}H_9N_5O$	58.15	3.96	30.84

[a] Synthesized by the same procedure as compounds **VI** and **VII**.

Table 2. IR and ^{1}H NMR spectra of 2-aryl- and 2-hetarylimidazo[4,5-*d*]pyridazines **IIIa**–**IIId**, **VIa**–**VIg**, and **VII**

Comp. no.	IR spectrum, ν(CO), cm^{-1}	^{1}H NMR spectrum (DMSO-d_6), δ, ppm			
		7-CH_3, s	N^5H, br.s	2-Ht (Ar)	^3J, Hz
IIIa	1665	2.55	12.48	7.54 t (1H, 5′-H), 8.07 t (1H, 4′-H), 8.35 d (1H, 3′-H), 8.37 d (1H, 6′-H)	7.0
IIIb	1670	2.53	12.46	1.29 t (3H, CH_3), 2.76 q (2H, CH_2), 7.90 d (1H, 4′-H), 8.26 d (1H, 3′-H), 8.62 s (1H, 6′-H)	8.0
IIIc	1665	2.50	12.47	8.17 d (2H, 3′-H, 5′-H), 8.74 d (2H, 2′-H, 3′-H)	8.0
IIId	1670	2.55	12.53	7.74 d.d (1H, 7′-H), 7.92 d.d (1H, 6′-H), 8.12 d (1H, 8′-H), 8.24 d (1H, 5′-H), 8.47 d (1H, 4′-H), 8.63 d (1H, 3′-H)	7.8
VIa	1665	2.50	12.50	7.54 m (3H, 3′-H, 4′-H, 5′-H), 8.24 d (2H, 2′-H, 6′-H)	8.0
VIb	1670	2.52	12.43	3.85 s (3H, OCH_3), 7.11 d (2H, 3′-H, 5′-H), 8.20 d (2H, 2′-H, 6′-H)	7.8
VIc	1670	2.50	12.53	7.78 d (2H, 2′-H, 6′-H), 8.16 d (2H, 3′-H, 5′-H)	7.8
VId	1650	2.58	12.65	3.08 s [6H, $N(CH_3)_2$], 6.90 d (2H, 3′-H, 5′-H), 8.20 d (2H, 2′-H, 6′-H)	9.0
VIe	1650	2.50	12.55	7.63 d (1H, 6′-H), 7.80 d (1H, 5′-H), 7.86 s (1H, 3′-H)	8.3
VIf	1665	2.49	12.60	6.11 s (2H, CH_2), 7.06 d (1H, 6′-H), 7.71 s (1H, 2′-H), 7.78 d (1H, 5′-H)	8.2
VIg	1670	2.49	12.39	3.78 s (3H, OCH_3), 3.87 s (3H, OCH_3), 7.10 d (1H, 3′-H), 7.13 s (1H, 6′-H), 7.54 d (1H, 4′-H)	2.6
VII	1665	2.52	12.45	7.60 d (1H, 4′-H), 8.56 d.d (1H, 5′-H), 8.70 d (1H, 6′-H), 9.38 s (1H, 2′-H)	8.0

evolved), excess hydrazine hydrate was distilled off, the dry residue was ground with dioxane, and the light yellow precipitate was filtered off and dried. Yield 30 g (87%), mp 257–259°C (from alcohol). ^{1}H NMR spectrum, δ, ppm: 2.55 s (3H, CH_3), 6.88 s (1H, 5-H). Found, %: C 47.79; H 5.70; N 33.56. $C_5H_7N_3O$. Calculated, %: C 47.99; H 5.64; N 33.58.

6-Methyl-4-nitroaminopyridazin-3(2*H*)-one (X). Concentrated nitric acid (d = 1.52), 1 ml (24 mmol), was added dropwise with stirring at 0–5°C to a solution of 2.5 g (20 mmol) of 4-amino-6-methylpyridazin-3-one (**IX**) in 7.5 ml of concentrated sulfuric acid. The mixture was stirred for 0.5–1.0 h at 0–5°C and was then allowed to slowly warm up to room temperature. After 2 h, the mixture was poured onto ice and neutralized with ammonium hydrogen carbonate. The light yellow precipitate was filtered off and washed with alcohol and ether. Yield 3 g (88%), mp 163–165°C. ^{1}H NMR spectrum, δ, ppm: 2.80 s (3H, CH_3), 8.40 s (1H, 5-H). Found, %: C 35.15; H 3.50; N 32.80. $C_5H_6N_4O_3$. Calculated, %: C 35.30; H 3.55; N 32.93.

4-Amino-6-methyl-5-nitropyridazin-3(2*H*)-one (XI). Compound **X**, 2.4 g (14 mmol), was dissolved with stirring and cooling (~0°C) in 14 ml of concentrated sulfuric acid. The solution was heated to 55–60°C and kept for 2.5–3 h at that temperature. It was then cooled, poured onto ice, and neutralized with ammonium hydrogen carbonate. The light yellow precipitate was filtered off, washed with a small amount of ice water, and dried. Yield 2.3 g (95%), mp 268–271°C (from water). ^{1}H NMR spectrum, δ, ppm: 2.95 s (3H, CH_3). Found, %: C 35.20; H 3.51; N 32.86. $C_5H_6N_4O_3$. Calculated, %: C 35.30; H 3.55; N 32.93.

REFERENCES

1. FRG Patent Appl. no. 3347290, 1985; *Ref. Zh., Khim.*, 1986, no. 13O79P.
2. FRG Patent Appl. no. 3445299, 1986; *Ref. Zh., Khim.*, 1987, no. 3O147P.
3. Gerhardt, G.A., Aldous, D.L., and Castle, R.N., *J. Heterocycl. Chem.*, 1965, vol. 2, no. 34, pp. 247–252.
4. Itai, T. and Suzuki, S., *Chem. Pharm. Bull.*, 1960, vol. 8, no. 11, pp. 999–1004.
5. Yanai, M., Kinoshita, T., Takeda, S., Sadaki, H., and Watanabe, H., *Chem. Pharm. Bull.*, 1970, vol. 18, no. 8, pp. 1685–1692.
6. Kenji, K., Hiromu, N., Yusha, O., Keizo, T., and Hirohisa, O., *J. Heterocycl. Chem.*, 1984, vol. 21, no. 5, pp. 1249–1254.
7. Yutilov, Yu.M., Shcherbina, L.I., and Efremenko, A.F., *Khim. Geterotsikl. Soedin.*, 1989, no. 7, pp. 940–947.
8. Yutilov, Yu.M. and Shcherbina, L.I., *Khim. Geterotsikl. Soedin.*, 1987, no. 5, pp. 639–645.
9. Yutilov, Yu.M., Stetsenko, L.V., and Shcherbina, L.I., Abstracts of Papers, *XVII Ukrainskaya konferentsiya po organicheskoi khimii* (XVIIth Ukrainian Conf. on Organic Chemistry), Kharkov, 1995, part 1, p. 91.
10. Lespagnol, A. and Deprey, J., *Bull. Soc. Chim. Fr.*, 1961, no. 3, pp. 606–610.
11. Overend, W.G. and Wiggins, L.F., *J. Chem. Soc.*, 1947, no. 3, pp. 239–244.
12. Singh, B., *Heterocycles*, 1984, vol. 22, no. 8, pp. 1801–1804.