Chemistry of Heterocyclic Compounds, Vol. 33, No. 8, 1997

STUDY OF UNSATURATED AZOLES. 16* SYNTHESIS AND REACTIONS OF 2-STYRYLBENZIMIDAZOLES

I. I. Popov

Fusion of 1-methyl-2-styrylbenzimidazole with KOH leads to separation of the phenylvinyl or the N-methyl group to give 1-methylbenzimidazol-2-one or 2-styrylbenzimidazole in the ratio 1:1. Decomposition of the perbromides of benzimidazoles by heating in water gives 5(6)-bromobenzimidazoles and, in the presence of KI, to 5(6)-iodobenzimidazoles. Methods are presented for the synthesis of 5(6)-bromo- and 5(6)-iodo-2-styryl- and also 2-α-bromo- and 2-α-iodostyrylbenzimidazoles.

In addition to the known substitution reactions for halogen [2], sulfo groups [3], and hydrogen [4] in position 2 of a benzimidazole ring, there has recently been demonstrated the possibility of nucleophilic substitution of a phenyl or benzyl group by heating 2-phenyl- and 2-benzyl-1-methylbenzimidazole with molten KOH. This leads to fission of the C–C bond, separation of a molecule of benzene or toluene, and formation of 1-methylbenzimidazol-2-one (II) [5, 6]. Similar reactions were expected when fusing 1-methyl-2-styrylbenzimidazole IIIa with KOH. However, in this case we found that along with fission of the C–C bond and formation of II there occurs with equal probability a fission of the C–N bond and separation of a methyl group to give 2-styrylbenzimidazole (IVa) as well. In 1-methyl-2-phenylbenzimidazole, the phenyl group is excluded from conjugation with the heterocyclic ring (dihedral angle between them = 65° [7, 8]). By contrast, in IIIa the effective conjugation between the phenyl group and the benzimidazole ring brings close in activation energy the processes of nucleophilic substitution of the phenylvinyl group and fission of the methyl group using base, hence, this leads to an energetically favorable formation of the mesomeric anion of IVa.

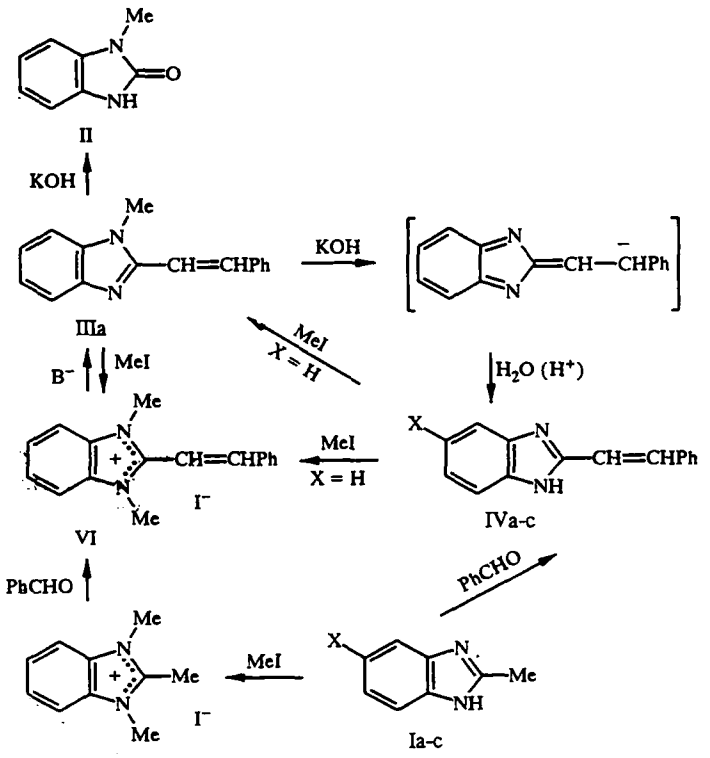
Bearing in mind the literature data on the hydrolytic fission of the multiple bond in different 2-vinyl- and 2-ethynylbenzimidazoles [9-14], the formation of the corresponding 1,2-dimethylbenzimidazoles might also have been expected but this was not observed.

It is known that synthesis of 1-methyl-2-styrylbenzimidazole (IIIa) via condensation of 1,2-dimethylbenzimidazole (V) with benzaldehyde [15] is complicated by the fact that the reaction product is difficult to separate from unreacted starting compound V. Methylation of 2-styrylbenzimidazole (IVa) in alcoholic base solution gives IIIa, which is readily quaternized by methyl iodide to give the slightly soluble iodomethylate VI precipitate. The starting IVa fraction remains in solution and addition of excess methyl iodide gives only an increased yield of the quaternary salt VI. The stability of the latter towards base under these reaction conditions is evidently due to its low solubility. Hence, heating a suspension of salt VI in an aqueous acetone solution of sodium bicarbonate leads to fission of the methyl group for IIIa in high yield without contamination by IVa and V. The quaternary salt VI can be prepared in good yield by refluxing IIIa with methyl iodide in alcohol and also by fusing 1,2,3-trimethylbenzimidazolium iodide with benzaldehyde. Attempts to demethylate 1,3-dimethyl-2-phenyl-benzimidazolium iodide similarly to VI were unsuccessful [8]. The comparatively easy hydrolytic cleavage of the methyl group in salt VI apparently occurs via the same mechanism as in the demethylation of IIIa. Methylation IVa by methyl iodide under phase transfer conditions in aqueous acetone mixture with cooling in ice and also by dimethylsulfate in aqueous alcohol solution without base give rise to IIIa.

*For Communication 15, see [1].

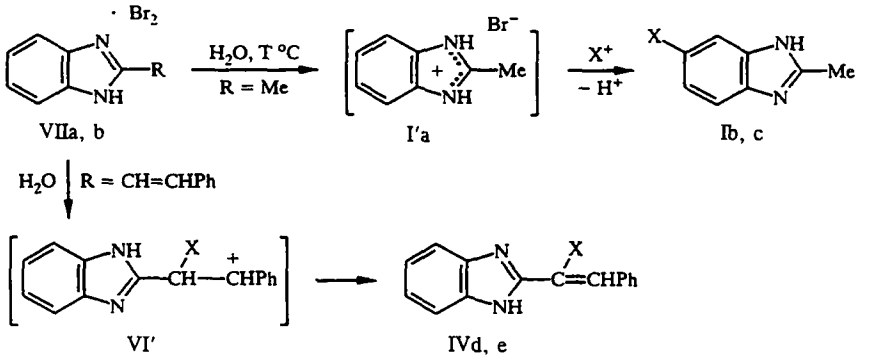
Rostov State University, Rostov-on-Don 344090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1088-1093, August, 1997. Original article submitted August 12, 1996; revision submitted October 11, 1996.

0009-3122/97/3308-0949$18.00



I, IV a X = H, b X = Br, c X = I

It was found that 5(6)-methyl-2-styrylbenzimidazole [16], as 4-styrylpyridine [17], when treated with bromine binds it via participation of the free electron pair of the tertiary nitrogen atom as a stable complex analogous to dioxane dibromide. The complex of bromine with methyl 3-(1-methyl-2-benzimidazolyl)acrylate gradually decomposes in acetic acid solution to give the mono bromo derivative in which (according to UV spectral data) the bromine is bound to the α-C-atom of the unsaturated side chain in the heterocycle [13]. We have shown that 2-methylbenzimidazole perbromide (VIIa), which dissociated on heating to starting Ia and bromine [18], undergoes hydrolytic fission to 5(6)-bromo-2-methylbenzimidazole (Ib) [19]. When heated in the presence of aqueous potassium iodide it gives 5(6)-iodo-2-methylbenzimidazole (Ic) [20], apparently in agreement with the usual route of electrophilic substitution of benzimidazoles [21].



Ib, IV d X = Br; Ic, IVe X = I; VIIa R = Me, ib R = CH=CHPh

It is also known that prolonged standing of 2-methylbenzimidazole (Ia) in acetic acid solution with 1 mole of bromine gives 4(7)-bromo-2-methylbenzimidazole [22]. In the conditions of [19], bromination occurs via the symmetrical benzimidazolium cation Ia and the aromatic ring is attacked by the bromonium cation meta to the ammonium nitrogen atom, and this controls the high reaction selectivity. Addition of sodium acetate or carbonate to the reaction mixture converts salt I'a to base Ia but hypobromous acid in sodium hypobromite leads to both acceleration of the reaction and to lowering of its selectivity. Hydrolysis of 1,2-dimethylbenzimidazole perbromide in similar conditions brominates the unsymmetrical cation, giving a mixture of brominated 1,2-dimethylbenzimidazoles. It has previously been shown [22] that prolonged refluxing of

TABLE 1. Parameters for Newly Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Yield, %
		C	H	Hal	N		
Ib†	$C_8H_7BrN_2$	45.2 45,5	3.6 3,3	38,0 37,9	13,6 13,3	214...215	81
Ic	$C_8H_7IN_2$	37.6 37,2	2.9 2,7	49.0 49,2	11.2 10,9	219...221	80
IVb	$C_{15}H_{11}BrN_2$	59.8 60,2	4.0 3,7	26.4 26,8	9.8 9,4	149...150	86
IVc	$C_{15}H_{11}IN_2$	52.3 52,6	3.0 3,2	36.0 35,6	8.5 8,2	154...156	85
IVd	$C_{15}H_{11}BrN_2$	60.4 60,2	3.8 3,7	26.5 26,8	9.7 9,4	123...125	64
IVe	$C_{15}H_{11}IN_2$	52.8 52,6	3.5 3,2	35.7 36,0	8.6 8,2	95	73
VIa	$C_{17}H_{17}IN_2$	54.0 54,3	4.5 4,5	33.4 33,8	7.6 7,4	235	78

*Solvent for crystallization: IVd dioxane, VIa alcohol, remainder aqueous alcohol.
†As in Russian original; no information is provided — Publisher.

1-alkylbenzimidazoles with bromine in chloroform gives the isomeric 5- and 6-bromo-1-alkylbenzimidazoles mixed with 5,7-dibromo derivatives. Similarly to Ia, 2-styrylbenzimidazole (IVa) gives perbromide VIIb when treated with bromine in chloroform solution, but hydrolytic cleavage in water occurs with substitution of a vinylic hydrogen to give 2-α-bromo- or 2-α-iodostyrylbenzimidazoles IVd, e respectively [19, 20]. Compounds IVd, e differ significantly in physicochemical properties from 5(6)-bromo- and 5(6)-iodo-2-styrylbenzimidazoles (IVb, c) which were synthesized by condensation of benzaldehyde with 5(6)-halo-2-methylbenzimidazoles (Ib, c) (prepared by decomposition of 2-methylbenzimidazole VIIa in aqueous solution according to method [19, 20]).

The position of the halogen in IVb, c was assumed from the work reported in [13, 16]. On the one hand, after dissociation of VIIb to starting materials there can occur addition of bromine to the phenylvinyl group of IVa with formation of the dibromo derivative, dehydrobromination of which leads to IVd in these reaction conditions (see [13]). In addition, IVd, e can evidently be formed through hydrolysis of perbromide VIIb and subsequent reaction of IVa hydrobromide with hydrobromous acid of iodous acid. As an intermediate, it can principally exist as a more stable carbonation IV′.

The PMR spectrum of IVd shows a singlet for a vinyl proton at 4 ppm, but the doublets for the protons of the vinyl group in the spectrum of IVa are in the overall aromatic proton multiplet at 7.0 ppm, as occurs for stilbene. Hence, it is not possible to determine the cis- or trans- structure of IVa from the spin-spin coupling of the vinylic protons. In the PMR spectrum of IIIa there are two doublet protons at 7.7 and 6.6 ppm with spin-spin coupling 16 Hz, hence, they can be assigned to the signals of a transvinylic group. It should be remembered that if 2-styrylbenzimidazole IVa, in contrast to IIIa, had a cis-isomer structure there might occur a sulfur catalyzed cyclocondensation to quinolino[1,2-*a*]benzimidazole. However, fusion of IVa with sulfur at 20°C or prolonged heating of the indicated reagents in DMF, DMSO, or HMPA gave only tarring, due to breakdown of the starting material.

It was not possible to synthesize 2-phenylethynylbenzimidazole via dehydrohalogenation of IVd, e upon heating in superbase (KOH-DMSO at 140°C) or in aniline solution over powdered metallic sodium with a catalytic amount of naphthalene. In all cases, only tarry starting materials were obtained from the reaction mixture.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument for vaseline mulls and PMR spectra on a Tesla BS-487 (80 MHz) instrument with CF_3COOH solvent and HMDS internal standard. Chromatography was carried out on Brockmann grade III alumina. Parameters for the compounds prepared are given in Table 1.

2-Styrylbenzimidazole (IVa). 2-Methylbenzimidazole (Ia, 13.2 g, 0.1 mole) was fused with benzaldehyde (10.7 g, 0.1 mole) and boric acid (0.05 g) at 180-190°C for 2-3 h. The melt was dissolved in DMF (4 ml), held at 150°C for 0.5 h,

cooled, and treated with 10% HCl (50 ml). The precipitated IVa hydrochloride was filtered, washed with water, suspended in water, and neutralized by ammonia to give product (17.8 g, 84%) with mp 201°C (200-201°C [15]).

Compounds IVb, c were obtained similarly.

1-Methyl-2-styrylbenzimidazole (IIIa). A. NaOH (40%, 2 ml) and dimethylsulfate (3 ml, 0.03 mole) were added with stirring and cooling in ice to a solution of IVa (4 g, 0.02 mole) in alcohol (6 ml). The reaction mixture was diluted with an equal volume of water, and the precipitate filtered to give IIIa (1.95 g, 43%).

B. To a solution of NaOH (5 g) in water (10 ml) there were added 2-styrylbenzimidazole (IVa, 22 g, 0.1 mole), acetone (22 ml), and, dropwise with cooling in ice water, methyl iodide (7 ml, 0.12 mole). The product was stirred for 1 h and the precipitated IIIa filtered and washed with water to give IIIa (30.2 g, 96.2%).

C. A mixture of water (30 ml), acetone (20 ml), sodium bicarbonate (1.7 g, 0.02 mole), sodium sulfate (0.1 g), and finely ground, powdered salt VIa (3.76 g, 0.01 mole) was heated until evolution of gas ceased and salt VIa had fully dissolved. The oil which separated after cooling the reaction mixture was extracted with ether. Removal of ether gave IIIa (2.0 g, 90%) with mp 113°C (113-114°C [15]). PMR spectrum ($CDCl_4$): 7.1 (9H, m, arom.), 7.7 (1H, d, =CH), 3.5 ppm (3H, s, $N-CH_3$).

1,3-Dimethyl-2-styrylbenzimidazolium Iodide (VI). A. 1,2,3-Trimethylbenzimidazolium iodide (2.9 g, 0.01 mole) was fused with benzaldehyde (1.1 g, 0.01 mole) for 3 h, DMF (3 ml) added, and the product was heated at gentle reflux for 2 h. After cooling, ethanol (5 ml) was added, the product heated to reflux, and salt VI filtered off and washed with ether to give product (2.8 g, 74.5%) as lettuce green crystals with mp 235°C (from alcohol).

B. A solution of IIIa (5.9 g, 0.025 mole) and ethanol (15 ml) was refluxed with methyl iodide (4.1 g, 0.025 mole) for 15-20 min. The precipitated salt VI was filtered to give product (7.3 g, 78%) with mp 235°C.

Reaction of 1-Methyl-2-styrylbenzimidazole (IIIa) with Potassium Hydroxide. A mixture of IIIa (2.34 g, 10 mole) and fused KOH (1.4 g, 25 mmole) was heated to 220°C and held for 0.5 h. The reaction mixture was cooled, treated with water, neutralized with dilute HCl, extracted with chloroform, and chromatographed on an alumina column to give IVa (0.86 g, 39%) and II (0.62 g, 42%) with mp 190°C (190-192°C, [22]).

5(6)-Bromo-2-methylbenzimidazole (Ib). A. Bromine (8 g, 2.8 ml, 0.05 mole) in chloroform (3 ml) was added dropwise to a solution of 2-methylbenzimidazole (Ia, 6.6 g, 0.05 mole) in chloroform (25 ml) at 0°C, stirred at 20°C for 0.5 h, and the orange precipitate of 2-methylbenzimidazole perbromide filtered off (VII, 14 g, 95%).

The perbromide VII (8.5 g, 0.03 mole) in water (20 ml) was gently heated until the solution was decolorized and sodium carbonate solution (10%, 20 ml) was added. The colorless precipitate of Ib was filtered and dried. Yield 5.6 g.

B. Bromine (8 g, 0.05 mole) was added with cooling and stirring to a suspension of 2-methylbenzimidazole (Ia, 6.6 g, 0.05 mole) in water (30 ml) and ground ice (20 g) and sodium acetate trihydrate (7 g, 0.05 mole) were added. Aqueous ammonia solution (25%) was then added to pH 7-8 and the colorless crystals of product were filtered and dried. Yield 9.2 g.

5(6)-Iodo-2-methylbenzimidazole (Ic). A mixture of 2-methylbenzimidazole perbromide (VIIa, 2.92 g, 0.01 mole), water (10 ml), and KI (1.66 g, 0.01 mole) was heated for 5 min on a water bath at 60-80°C until the solution cleared. Sodium carbonate solution (10%, 10 ml) was added to the dark oily material and the solution on top of it, the product was stirred, the aqueous layer poured off, ether (20 ml) added to the dark oily material and the solution on top of it, the product was stirred, the aqueous layer poured off, ether (20 ml) added to the residue, and allowed to stand overnight. The colorless precipitate was filtered, washed with water, and dried to give Ic (2.1 g).

2-(1-Bromo-2-phenylvinyl)benzimidazole (IVd). Bromine (8 g, 0.05 mole) in chloroform (3 ml) was added dropwise with stirring to a solution of IVa (10.9 g, 0.05 mole) in chloroform (35 ml) at 0°C. The reaction mixture was stirred for 0.5 h at 20°C, and the orange precipitate of the perbromide VIIb filtered and dried (14.5 g, 71%).

Water (15 ml) was added to the obtained perbromide (3 g, 8 mmole) and sodium acetate trihydrate (1.1 g, 8 mmole) added with stirring. The oily substance formed crystallized on cooling to give IVd (2.7 g, 90.3%) with mp 123-124°C (from dioxane).

2-(1-Iodo-2-phenylvinyl)benzimidazole (IVe). A mixture of perbromide VIIb (3 g, 8 mmole), water (15 ml), and KI (1.66 g, 0.01 mole) was heated at 60-80°C until the aqueous layer decolorized. It was then cooled, and sodium carbonate (10%, 5 ml) was added. The yellow oily product crystallized on trituration with ice (IVe, mp 90-95°C).

REFERENCES

1. I. I. Popov and A. A. Zubenko, Khim. Geterotsikl. Soedin., No. 3, 348 (1997).
2. D. Harrison, J. T. Ralph, and A. Smith, J. Chem. Soc., No. 8, 2930 (1963).
3. A. M. Simonov and V. N. Komissarov, Khim. Geterotsikl. Soedin., No. 6, 826 (1975).
4. A. F. Pozharskii and A. M. Simonov, Chichibabin Amination of Heterocycles, Proceedings of the Rostov-on-Don State University (1971).
5. I. I. Popov, P. V. Tkachenko, A. M. Simonov, and A. F. Pozharskii, Zh. Org. Khim., **10**, 1789 (1974).
6. I. I. Popov, Yu. G. Bogachev, P. V. Tkachenko, A. M. Simonov, and B. A. Tertov, Khim. Geterotsikl. Soedin., No. 4, 521 (1976).
7. A. S. Kuzharov, P. V. Tkachenko, I. I. Popov, and V. N. Sheinker, Zh. Fiz. Khim., **52**, 2708 (1978).
8. I. I. Popov, Khim. Geterotsikl. Soedin., No. 6, 781 (1966).
9. W. Wills and J. Whitworth, J. Chem. Soc., No. 6, 2738 (1927).
10. J. B. Wright, Chem. Rev., **48**, 474 (1951).
11. A. A. Zubenko, Dissertations for Candidates in Chemical Sciences, Rostov-on-Don (1977), p. 103.
12. H. Walba, W. L. Murray, G. Knitson, and A. Diaz, J. Am. Chem. Soc., **88**, 1622 (1966).
13. I. I. Popov, A. M. Simonov, V. I. Mikhailov, and N. A. Sil'vanovich, Khim. Geterotsikl. Soedin., No. 3, 408 (1974).
14. A. A. Zubenko, I. I. Popov, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 11, 1539 (1978).
15. L. N. Pushkina, S. A. Mazalov, and I. Ya. Postovskii, Zh. Obsheh. Khim., **32**, 2624 (1962).
16. F. Fichter, J. Pract. Chem., **74**, 320 (1906).
17. J. M. Smith, H. W. Stewart, B. Roht, and E. H. Northey, J. Am. Chem. Soc., **70**, 3997 (1948).
18. P. Linda, Tetrahedron, **25**, 3239 (1969).
19. I. I. Popov, S. L. Boroshko, and A. M. Simonov, Russian Patent 161,912; Byull. Izobret., No. 48 (1990).
20. I. I. Popov, S. L. Boroshko, and A. M. Simonov, Russian Patent 161,911; Byull. Izobret., No. 48 (1990).
21. P. N. Preston, Chem. Rev., **74**, 288 (1974).
22. M. K. A. Khan, M. Amina, and F. Y. Ahmed, Pakistan J. Sci. and Res., **15**, 11, 12 (1972); Russ. Zh. Khim., 7Zh344 (1973).
23. I. S. Kashparov and A. F. Pozharskii, Khim. Geterotsikl. Soedin., No. 1, 124 (1971).