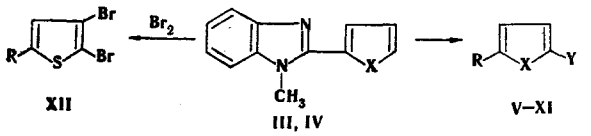
REACTION OF 2-HETEROARYLBENZIMIDAZOLE WITH ELECTROPHILIC REAGENTS

M. M. El'chaninov, L. Ya. Oleinikova, and A. M. Simonov

UDC 547.785.5

An earlier report in the literature [1] has described the direct nitration and acetylation of 1-alkyl substituted 2-(β-furyl-2'-vinyl)benzimidazole which occurs at the furan nucleus. We therefore decided to study the electrophilic substitution in furan and thiophene nuclei which are directly bonded to a benzimidazole ring.

By reacting o-phenylenediamine with furfural and thiophene-2-aldehyde according to the reported method [2], the 2-(furyl-2')- (I) and 2-(thienyl-2')benzimidazoles (II) respectively, were synthesized. Their methylation products (III and IV respectively) were brought into reaction with electrophilic reagents: with acetylnitrate, a mixture of sulfuric and polyphosphoric acids, a solution of bromine in dichloroethane, paraformaldehyde, and concentrated hydrochloric acid.



XII III, IV V–XI

III X=O; IV X=S; V—VIII X=O; IX—XI X=S; V, IX Y=NO_2; VI, X Y=SO_3H; VII, XI Y=CH_2Cl; VIII Y=Br; R=1-methyl-2-benzimidazole

Despite the acidophobic properties of the furan nucleus and the rather rigorous conditions of the conversion, electrophilic substitution in 1-methyl-2-(furyl-2')benzimidazole (III) proceeded smoothly, with quite high yields. 1-Methyl-2-(thienyl-2')benzimidazole (IV) behaved in the same way in these conversions. This is evidently due to the influence of the benzimidazole nucleus, which as a strong electrophilic group stabilizes the heterocyclic ring joined to it. Reaction of compounds III and IV with the electrophilic reagents indicated above resulted in the preparation of 5-substituted 2-heteroarylbenzimidazoles V-XI. Only bromination of 2-thienylbenzimidazole under the same conditions as for bromination of compound III gave a mixture of the 5-bromo- and 4,5-dibromo-substituted compounds. When compound IV and bromine in a molar ratio of 1:2 respectively were brought into reaction the 4,5-derivative XII was formed. The structures of the prepared substances were established by alternative syntheses as well as by IR and PMR spectroscopy.

It is known that 2-furylbenzimidazole (furidazole) [3] and its derivatives [4] exhibit an antifungus action. Study of the effect of compounds V-XII on the growth of a culture of *Triochophyton rubrum* showed that they also possessed fungicidal properties, but the activity is comparatively low. Compound XII showed the greatest activity.

EXPERIMENTAL

IR spectra in chloroform or Vaseline oil were recorded on a UR-20 instrument; PMR spectra were recorded on a Tesla BS-467 instrument using trifluoroacetic acid as solvent and HMDS as internal standard.

2-(Furyl-2')benzimidazole (I) was prepared by the reported method [2]. A mixture of 4.32 g (40 mmoles) o-phenylenediamine in 75 ml of isopropanol, 16 g (80 mmoles) of copper acetate in 200 ml water and 3.84 g (40 mmoles) of furfural was heated at 80-90°C for 2 h. The reaction mixture was cooled, the precipitate of the copper salt was separated and suspended in 150 ml of isopropanol, and hydrogen sulfide then passed through the suspension for an hour. The copper sulfide was filtered off, the filtrate evaporated to half volume, and the residue diluted with 250 ml of water. Yield 7 g (82%). Colorless plates, mp 285-286°C. Literature value mp 286°C [2].

Rostov State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1047-1049, August, 1979. Original article submitted October 20, 1978.

 0009-3122/79/1508-0856$07.50

2-(Thienyl-2')benzimidazole (II) was synthesized in the same way as compound I from 4.32 g (40 mmoles) of o-phenylenediamine, 16 g (80 mmoles) copper acetate, and 4.46 g (40 mmoles) of thiophene-2-aldehyde. Yield 5.8 g (72%), mp 311-312°C (from alcohol). Found, %: C 65.8; H 4.2; N 14.2. $C_{11}H_8N_2S$. Calculated, %: C 66.0; H 4.0; N 13.9.

1-Methyl-2-(furyl-2')benzimidazole (III) was prepared by the reported procedure [5] from 1.84 g (10 mmoles) of 2-(furyl-2')benzimidazole, 1.12 g (20 mmoles) KOH, and 2.84 g (20 mmoles) of methyliodide. Yield quantitative, mp 72-73°C. Literature value, mp 72-73°C [4].

1-Methyl-2-(thienyl-2')benzimidazole (IV) was synthesized in the same way as compound III from 2.0 (10 mmoles) of 2-(thienyl-2')benzimidazole. Yield quantitative, mp 80-81°C (from aqueous alcohol). Found, %: C 67.4; H 4.7; N 13.3. $C_{12}H_{10}N_2S$. Calculated, %: C 67.3; H 4.7; N 13.0.

1-Methyl-2-(5'-nitrofuryl-2')benzimidazole (V). To a solution of 3.96 g (20 mmoles) of compound III in 30 ml of freshly distilled acetic anhydride at 0°C was added dropwise 19 g of nitric acid (d 1.5). The reaction mixture was stirred for 2 h, poured into 150 ml of cold water and carefully treated with aqueous ammonia to pH 7. The precipitated reaction product was separated, carefully washed with water, dried and chromatographed on a column of alumina, eluting with chloroform. Obtained 3.57 g (69%) of bright yellow crystals, mp 213-214°C (from aqueous alcohol). Literature value mp 212-213°C [6]. IR spectrum: 1350 cm^{-1} (NO_2).

1-Methyl-2-(5'-nitrothienyl-2')benzimidazole (VI). A). To 30 g of freshly distilled acetic anhydride was added at 0°C 19 g of nitric acid (d 1.5). Then 4.28 g (20 mmoles) of compound IV was introduced in small portions. The reaction mixture was stirred at 0°C for 6 h, diluted with 100 ml of water, the precipitated product was separated and recrystallized from dimethylformamide. Yield quantitative, mp 267-268°. IR spectrum: 1370 cm^{-1} (NO_2). Found, %: C 55.8; H 3.4; N 16.6. $C_{12}H_9N_3O_2S$. Calculated, %: C 55.6; H 3.5; N 16.2.

B). 3.73 g (10 mmoles) of 1-methyl-2-(5'-bromothienyl-2') benzimidazole was dissolved in 30 ml of acetic acid, 2.07 g (30 mmoles) of sodium nitrate was introduced, the mixture was heated at boiling for 6 h, cooled, and poured into 100 ml H_2O. The precipitated nitro product was dissolved in dimethylformamide, chromatographed on a column of alumina, and eluted with a mixture of isopropanol and diethyl ether (1:2). Obtained 0.7 g (27%) of bright yellow crystals, mp 267-268°C (from dimethylformamide).

1-Methyl-2-(5'-sulfofuryl-2')benzimidazole (VII). A mixture of 1.98 g (10 mmoles) of compound III, 1.47 g (15 mmoles) of sulfuric acid (d 1.84) and 30 g of polyphosphoric acid was heated at 120°C for 1 h. The reaction mixture was cooled, diluted with 100 ml water, the precipitated sulfonic acid was separated and recrystallized from water. Yield 2.4 g (87%), mp 292-293°C. IR spectrum: 1280 cm^{-1} (SO_2). Found, %: C 52.1; H 4.0; N 10.3. $C_{12}H_{10}N_2O_4S$. Calculated, %: C 51.8; H 3.6; N 10.7%.

1-Methyl-2-(5'-sulfothienyl-2')benzimidazone (VIII) was prepared in the same way as compound VII from 2.14 g (10 mmoles) 1-methyl-2-(thienyl-2')benzimidazole. Yield 2.44 g (83%), mp 312-313°C (from water). IR spectrum: 1260 cm^{-1} (SO_2). Found, %: C 49.4; H 3.5; N 9.8. $C_{12}H_{10}N_2O_3S_2$. Calculated, %: C 49.4; H 3.4; N 9.5.

Position of the sulfonic group was established by analogy with other electrophilic substitution reactions.

Hydrochloride of 1-methyl-2-(5'-chloromethylfuryl-2')benzimidazole (IX). To a solution of 3.96 g (20 mmoles) of compound III in 24 ml of hydrochloric acid (d 1.19) was added gradually 2.3 g (26 mmoles) of paraformaldehyde and the mixture heated 5 h at 60-70°C, then concentrated and kept for 12-13 h at 3-5°C. The precipitate was separated, recrystallized from aqueous alcohol to provide 4.5 g (80%) of compound IX, mp 180-181°C. Found, %: N 9.6. $C_{13}H_{11}ClN_2O \cdot HCl$. Calculated, %: N 9.9.

Hydrochloride of 1-methyl-2-(5'-chloromethylthienyl-2')benzimidazole (X) was prepared in the same way as compound (IX) from 4.28 g (20 mmoles) of 1-methyl-2-(thienyl-2')benzimidazole at 60-70°C for 20 h. Towards the end of the reaction compound (X) precipitates out. Yield 3.58 g (60%), mp 214-215°C (from water). Found, %: C 52.0; H 3.8; N 9.6. $C_{13}H_{11}ClN_2S \cdot HCl$. Calculated, %: C 52.2; H 4.0; N 9.4.

The structure of the chloromethylation products was established from the products obtained by oxidizing it with potassium permanganate.

1-Methyl-2-(5'-bromofuryl-2')benzimidazole (XI). To a solution of 1.98 g (10 mmoles) of compound III in 20 ml of dichloroethane at 80°C a solution of 1.6 g (10 mmoles) of bromine in 10 ml of dichloroethane was added gradually and heating continued at the same temperature for 2 h 30 min. The precipitate of the hydrobromide of compound (XI) was separated, recrystallized from water and converted to the base. Yield 1.69 g (61%), mp 123-124°C (from alcohol). Literature value mp 123-124°C [7].

1-Methyl-2-(4',5'-dibromothienyl-2')benzimidazole (XII). A). To a solution of 2.14 g (10 mmoles) of compound IV in 20 ml dichloroethane at 80°C was added gradually a solution of 3.2 g (20 mmoles) bromine in 20 ml dichloroethane and kept at this temperature for 8 h. The reaction mixture was left at 3-5°C for 12 h, the precipitate of the hydrobromide of compound XII was separated, converted to the base, and recrystallized from alcohol. Yield 1.45 g (39%), mp 178-179°C. PMR spectrum: 6.95 ppm (3-H, s). Found, %: 39.0; H 2.5; N 7.2. $C_{12}H_8Br_2N_2S$. Calculated, %: C 38.7; H 2.2; N 7.6.

B). Prepared in the same way as compound I from 4.32 g (40 mmoles) o-phenylenediamine, 6 g (80 mmoles) of copper acetate and 6.8 g (40 mmoles) of 4,5-dibromo-2-thiophenaldehyde with subsequent methylation of the product by the same reaction as for compound III.

LITERATURE CITED

1. F. T. Pozharskii and L. Ya. Bakhmet, Khim. Geterotsikl. Soedin., No. 6, 832 (1970).
2. R. Weidenhagen, Berichte, 69, 2263 (1936).
3. E. M. Andreeva and D. M. Kabakhidze, Zh. V. Kh. O., No. 5, 525 (1973).
4. F. T. Pozharskii, A. M. Simonov, L. Ya. Oleinikova, and M. M. El'chaninov, Khim. Farm. Zh., No. 7, 28 (1977).
5. Z. N. Nazarovoi (ed.), Outlines of Chemistry of the Azoles [in Russian], Rostov-on-Don (1965), p. 17.
6. F. T. Pozharskii, V. Ts. Bukhaeva, A. M. Simonov, and R. A. Savel'eva, Khim. Geterotsikl. Soedin., No. 1, 183 (1969).
7. F. T. Pozharskii, V. Ts. Bukhaeva, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 5, 910 (1967).

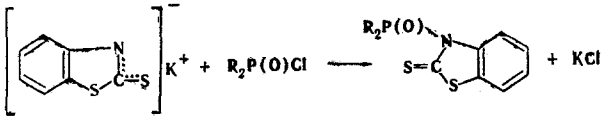
PHOSPHORYLATION OF THE POTASSIUM SALT OF BENZOTHIAZOLINE-2-THIONE BY DIAMIDOCHLOROPHOSPHATES

T. V. Ratnikova, A. I. Ginak, and V. I. Yakovlev

UDC 547.789.6

In order to phosphorylate benzothiazoline-2-thione (I) at the hard donor atom, we have employed diamidochlorophosphates as the phosphorylation agents. The latter, as a result of the negative inductive effect of the chlorine radical and the positive mesomeric effect of the amide groups, which generate an effective positive charge on the phosphorus atom, effect phosphorylation at the hard donor nitrogen atom [7]. This is also facilitated by carrying out the reaction with salts of the thione (I) with a cation of large radius (potassium) in polar aprotic solvents (e.g., acetonitrile) [7].

Phosphorylation of the potassium salt of I by diamidochlorophosphates, using equimolecular amounts of the reactants, results in the preferential formation of the N-derivatives:



I II–VII

Leningrad Lensovet Institute of Technology, Leningrad 198013.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1050-1052, August, 1979. Original article submitted April 4, 1978; revision submitted, December 26, 1978.

0009-3122/79/1508-0858$07.50