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Synthesis of 2-Aminobenzo[*b*]thiophenes from 4-(2-Haloaryl)-1,2,3-thiadiazoles

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Abstract—A new approach to the synthesis of 2-aminobenzo[*b*]thiophenes was developed on the basis of reaction of 4-aryl-1,2,3-thiadiazoles with amines in the presence of potassium carbonate. The effect of the nature of substituent in the benzene ring of the starting 4-aryl-1,2,3-thiadiazoles on the structure of the final product was studied.

Keywords: acetophenone, hydrazone, thiadiazole, thioamide, 2-aminobenzothiophene

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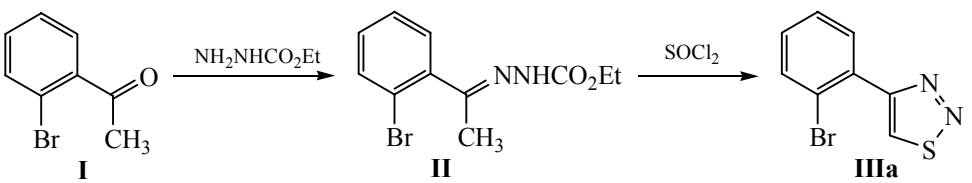
2-Aminobenzo[*b*]thiophene derivatives are intermediates in the synthesis of raloxifene, a selective estrogen receptor modulator, and its analogs [1, 2]. However 2-aminobenzo[*b*]thiophenes are insufficiently explored compounds. To date, only one method for the preparation of 2-aminobenzo[*b*]thiophene from thiosalicylic acid has been described [3]. 2-Morfolinobenzo[*b*]thiophene has been obtained by attaching morpholine at the C^2–C^3 bond of benzo[*b*]thiophene followed by aromatization with sulfur [4]. 2-Piperidinobenzo[*b*]thiophene has been prepared by reacting 2-bromobenzo[*b*]thiophene with piperidine [5]. Another well-known representative of this class of compounds, 2-dimethylamino-6-benzyloxybenzo[*b*]thiophene, was synthesizes by treating a mixture of 4-benzyloxybenzaldehyde and *N*,*N*-dimethylthioformamide with lithium diisopropylamide followed by cycloaromatization under the action of $MeSO_3H$ [6].

In this work we developed a new method for preparing 2-aminobenzo[*b*]thiophenes from readily available 4-(2-chlorophenyl)-1,2,3-thiadiazole **IIIa**, 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole **IIIb** [7], and 4-(2-bromophenyl)-1,2,3-thiadiazole [8]. The latter was prepared from 2-bromoacetophenone **I** via cyclization of the intermediate 2-bromoacetophenone ethoxycarbonylhydrazone **II** under the action of thionyl chloride (Scheme 1).

4-[2-Chloro(bromo)phenyl]-1,2,3-thiadiazoles **IIIa** and **IIIc** undergo decomposition under the action of K_2CO_3 and excess morpholine in DMF to form potassium 2-[2-chloro(bromo)phenyl]ethynylthiolates **IVa** and **IVc** with the release of nitrogen. Further reaction of thiolates **IV** with morpholine led to the formation of potassium 2-[2-chloro(bromo)phenyl]-1-morpholinoethenylthiolates **Va** and **Vb**. However, irrespective of the nature of the halogen, further intramolecular cyclization involving halogen and potassium thiolate did not occur. The acidification of thiolates **Va** and **Vb** led to the formation of morpholinamides of 2-[2-chloro(bromo)phenyl]thioacetic acids **VIa** and **VIb** (Scheme 2).

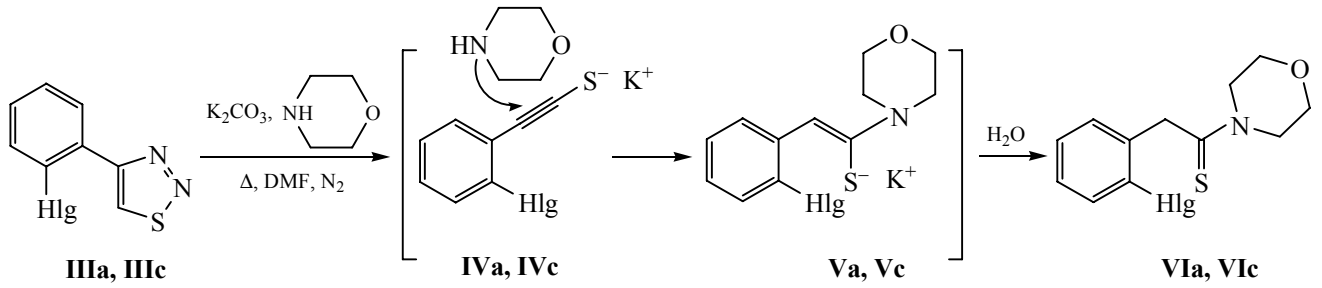
In the case of 4-(2-chloro-5-nitrophenyl)-1,2,3-thiadiazole **IIIb** introduction of the nitro group into the

Scheme 1.



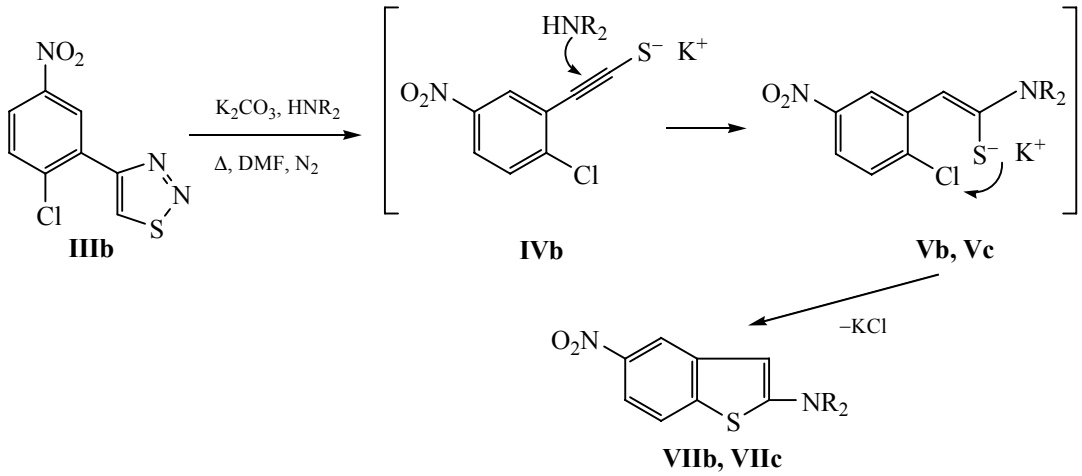
I **II** **IIIa**

Scheme 2.



Hlg = Cl (**a**), Br (**c**).

Scheme 3.



R_2 = $(CH_2CH_2)_2O$ (**b**), $(CH_2)_5$ (**c**).

para-position relative to the chlorine atom allowed successful preparation of the corresponding 2-di-alkylaminobenzo[*b*]thiophenes. 4-(2-Chloro-5-nitrophenyl)-1,2,3-thiadiazole **IIIb** under the action of K_2CO_3 in the presence of excess secondary amine in DMF decomposed with the release of nitrogen and the formation of potassium 2-(5-nitro-2-chlorophenyl)ethynylthiolate **IVb**. Reaction of ethynylthiolate **IVb** with the secondary amines also afforded potassium 2-(2-chlorophenyl)-1-dialkylaminoethenylthiolates **Vb** and **Vd**. Further intramolecular cyclization involving the chlorine atom led to the formation of 2-dialkylaminobenzo[*b*]thiophenes **VIIb** and **VIId** (Scheme 3).

The structure of the compounds obtained was confirmed by ^1H and ^{13}C NMR spectroscopy, mass spectrometry and by comparison with the literature data [9].

EXPERIMENTAL

Melting points were measured on a Boëtius apparatus. ^1H and ^{13}C NMR spectra of the solutions in $CDCl_3$ were recorded on a Bruker DPX-400 spectrometer [400.13 (^1H), 100.16 MHz (^{13}C)]. Mass spectra were taken on a Finnigan INCOS MAT 95 mass spectrometer (70 eV, ionization chamber temperature 200°C). High-resolution mass spectra (HRMS-ESI) were registered on a Micromass 70-VSE spectrometer. The reaction progress was monitored by TLC on Silica Gel 60 F_{254} plates detecting with UV light and iodine vapor. Purification of the obtained compounds was performed by column chromatography using silica gel L 100/160.

2-Bromoacetophenone ethoxycarbonylhydrazone (II). A mixture of 29.38 g (0.15 mol) of 2-bromoacetophenone **I**, 15.35 g (0.15 mol) of ethoxycarbonylhydrazine, 50 mL of ethanol, and 3 drops of conc. sulfuric acid was refluxed for 2 h, then cooled and kept overnight. The formed precipitate was filtered off, washed successively with water and alcohol, and dried. Yield 36.23 g (86%), white crystals, mp 139–140°C, R_f 0.42 (hexane–ethyl acetate, 2 : 1). ^1H NMR

spectrum, δ, ppm: 1.36 t (3H, $\underline{CH_3}CH_2$, *J* 6.8 Hz), 4.34 q (2H, CH_2, *J* 6.8 Hz), 2.24 s (3H, CH_3), 7.17–7.57 m (4H, H_{Ph}), 7.94 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.6, 17.1, 62.2, 121.6, 127.5, 130.0, 130.6, 132.9, 140.8, 150.5, 154. Mass spectrum, *m*/*z* (I_{rel}, %): 286(4) $[M + 1]^+$, 284(4) $[M - 1]^+$, 211(2.5) $[M - Br]^+$, 205(15), 161(27), 133(71), 132(43), 131(27), 103(25), 77(30), 29(100). Found, %: C 46.52; H 4.29; N 9.71. $C_{11}H_{13}BrN_2O_2$. Calculated, %: C 46.34; H 4.60; N 9.82. *M* 285.14.

4-(2-Bromophenyl)-1,2,3-thiadiazole (IIIc). To 5.0 g (17.6 mmol) of hydrazone **II** was added 10 mL of pre-cooled thionyl chloride at 5°C. When cooling was stopped, the reaction start was observed accompanied by evolution of gaseous HCl. The reaction mixture was heated at 60°C for 2 h, then cooled and poured into water. The formed precipitate was filtered off, washed with water until neutral reaction, and recrystallized from ethanol. Yield 3.58 g (84%), white crystals, mp 41.5–42.5°C, R_f 0.61 (hexane–ethyl acetate, 2 : 1). ^1H NMR spectrum, δ, ppm: 7.27–7.35 m (1H, H_{Ph}), 7.42–7.50 m (1H, H_{Ph}), 7.73 d (1H, H_{Ph}, *J* 8.1 Hz), 7.94 d (1H, H_{Ph}, *J* 8.0 Hz), 9.01 s (H^5_{Ht}). ^{13}C NMR spectrum, δ_C, ppm: 122.3, 127.9, 130.6, 131.7, 132.2, 133.9, 134.7, 160.5. Mass spectrum, *m*/*z* (I_{rel}, %): 242(2.5) $[M + 1]^+$, 240(2) $[M - 1]^+$, 214(51) $[M + 1 - N_2]^+$, 212(52) $[M - 1 - N_2]^+$, 171(1), 155(1), 135 (2), 134(5), 133(52), 93(21), 89(100), 63(28), 50(24), 40(24). Found, %: C 39.73; H 2.35; N 11.43. $C_8H_5BrN_2S$. Calculated, %: C 39.85; H 2.09; N 11.62. *M* 241.105.

(2-Chlorophenyl)thioacetic acid morpholinamide (VIa). A mixture of 1 g (5.1 mmol) of 4-(2-chlorophenyl)-1,2,3-thiadiazole **IIIa** [7], 2.2 mL (22.4 mmol) of morpholine, 2.26 g (15.3 mmol) of freshly calcined potassium carbonate, and 50 mL of freshly distilled DMF was heated with stirring for 1 h. The solvent was distilled off in a vacuum, and the residue was extracted with 10 mL of chloroform. The extract was washed with water, dried over Na_2SO_4, and concentrated. The residue was recrystallized from a mixture hexane–petroleum ether–chloroform (50 : 5 : 3). Yield 0.88 g (68%), white crystals, mp 119–120°C (mp 115.5–116°C [9]), R_f 0.25 (ethyl acetate–hexane, 1 : 2). ^1H NMR spectrum, δ, ppm: 3.45 m and 3.53 m (4H, $CSNCH_2\underline{CH_2}$), 3.75 m and 4.37 m (4H, $CSNCH_2$), 4.35 s (2H, CH_2CS), 7.18–7.26 m (2H, H_{Ph}), 7.36 d (1H, H_{Ph}, *J* 8.0 Hz), 7.41 d (1H, H_{Ph}, *J* 6.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 47.1, 50.0, 50.7, 66.1, 66.3, 127.2, 128.5, 129.1, 129.5, 133.1, 133.7, 199.4. Mass spectrum, *m*/*z* (I_{rel}, %): 220(100) $[M - Cl]^+$, 134(25), 125(42), 89 (37), 86(44), 45(37). Found, %: C 56.21; H 5.34; N 5.73. $C_{12}H_{14}ClNOS$. Calculated, %: C 56.35; H 5.52; N 5.48. *M* 255.761.

(2-Bromophenyl)thioacetic acid morpholinamide (VIb) was prepared similarly from 1 g (4.15 mmol) of 4-(2-bromophenyl)-1,2,3-thiadiazole **IIIc**, 1.8 mL (20.7 mmol) of morpholine, 1.74 g (12.6 mmol) of freshly calcined potassium carbonate, and 5 mL of freshly distilled DMF. Yield 1.03 g (82.7%), white crystals, mp 115–117°C (diethyl ether), R_f 0.45 (ethyl acetate–hexane, 1 : 2). ^1H NMR spectrum, δ, ppm: 3.56 m and 3.70 m (4H, $CSNCH_2\underline{CH_2}$), 3.72 m and 4.28 m (4H, $CSNCH_2$), 4.22 s (2H, CH_2CS), 7.19–7.27 m (2H, H_{Ph}), 7.37 m (1H, H_{Ph}), 7.62 d (1H, H_{Ph}, *J* 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 49.2, 50.2, 50.9, 66.2, 66.24, 124.6, 128.3, 129.2, 130.6, 132.9, 136.9, 198.3. Mass spectrum, *m*/*z* (I_{rel}, %): 301(1) $[M + 1]^+$, 220(100) $[M - Br]^+$, 204(2), 169(6), 147(6), 134(20), 89(16), 63(8), 45(12). Found, %: C 47.82; H 4.55; N 4.47. $C_{12}H_{14}BrNOS$. Calculated, %: C 48.01; H 4.70; N 4.67. *M* 300.212.

2-Morpholino-5-nitrobenzo[*b*]thiophene (VIIb). A suspension of 0.57 g (4.13 mmol) of K_2CO_3, 0.9 mL (10 mmol) of morpholine, and 0.5 g (2.07 mmol) of 1,2,3-thiadiazole **IIIb** in 10 mL of DMF was stirred at 90°C for 12 h under argon. After the solvent removal, the residue was chromatographed on silica gel (chloroform–hexane, 1 : 2). Yield 0.27 g (49%), yellow crystals, mp 153–154°C. ^1H NMR spectrum, δ, ppm: 3.28–3.31 m (4H, NCH_2), 3.87–3.90 m (4H, $2CH_2$), 6.28 s (H^3_{Ht}), 7.67 d (H^7_{Ht}, *J* 9.0 Hz), 7.94 d. d (H^6_{Ht}, *J* 9, 2.1 Hz,), 8.30 d (H^4_{Ht}, *J* 2.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 50.4 (NCH_2), 66.1 (OCH_2), 98.5 (C^3), 115.76 (C^6), 115.80 (C^4), 121.8 (C^7), 138.6 (C^9), 140.7 (C^8), 145.9 (C^2), 160.2 (C^5). Mass spectrum, *m*/*z* (I_{rel}, %): 264(100) $[M]^+$, 218(20) $[M - NO_2]^+$, 254(63), 206(48), 160(25), 133(23). Mass spectrum (HRMS-ESI), *m*/*z* (I_{rel}, %): 265.0647 $[M + H]^+$ (calculated for $C_{12}H_{13}N_2O_3S$: *m*/*z* 265.0636).

2-Piperidino-5-nitrobenzo[*b*]thiophene (VIIc) was prepared similarly from 0.57 g (4.13 mmol) of K_2CO_3, 1 mL (10 mmol) of piperidine and 0.5 g (2.07 mmol) of 1,2,3-thiadiazole **IIIb** in 10 mL of DMF. Yield 0.092 g (17%), red crystals, mp 139–140°C. ^1H NMR spectrum, δ, ppm: 1.58–1.76 m (6H, $CH_2CH_2CH_2$), 3.28–3.31 m [4H, $N(CH_2)_2$], 6.18 s (H^3_{Ht}), 7.62 d (H^7_{Ht}, *J* 8.7 Hz), 7.87 d. d (H^6_{Ht}, *J* 8.7, 2.4 Hz), 8.23 d (H^4_{Ht}, *J* 2.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 23.7 [$\underline{CH_2}(CH_2CH_2)_2$], 25.1 [$CH_2(\underline{CH_2}CH_2)_2$], 51.5 ($NCH_2$),

97.3 (C^7), 115.0 (C^4), 115.1 (C^6), 121.5 (C^7), 138.3 (C^9), 145.8 (C^8), 146.2 (C^2), 160.7 (C^5). Mass spectrum (HRMS-ESI), m/z (I_{rel}, %): 263.0854 $[M + H]^+$ (calculated for $C_{13}H_{15}N_2O_3S$: m/z 263.0858).

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REFERENCES

1. Grese, T.A., Pennington, L.D., Sluka, J.P., Adrian, M.D., Cole, H.W., Fuson, T.R., Magee, D.E., Phillips, D.L., Rowley, E.R., Shetler, P.K., Short, L.L., Venugopalan, M., Yang, N.N., Sato, M., Glasebrook, A.L., and Bryant, H.U., *J. Med. Chem*., 1998, vol. 41, no. 8, p. 1272. DOI: 10.1021/jm970688z.
2. Lee, K.C., Moon, B.C., Lee, J.H., Chung, K.-H., Katzenellenbogen, J.A., and Chi, D.Y., *Bioorg. Med. Chem*., 2003, vol. 11, no. 17, p. 3649. DOI: 10.1016/S0968-0896(03)00362-6.
3. Stacy, G.W., Villaescusa, F.W., and Wollner, T.E., *J. Org. Chem*., 1965, vol. 30, no. 12, p. 4074. DOI: 10.1021/jo01023a021.
4. Grandclaudon, P. and Lablache-Combier, A., *J. Org. Chem*., 1978, vol. 43, no. 22, p. 4379. DOI: 10.1021/jo00416a032.
5. Brower, K.R. and Amstutz, E.D., *J. Org. Chem*., 1954, vol. 19, no. 3, p. 411. DOI: 10.1021/jo01368a019.
6. Ablenas, F.J., George, B.E., Maleki, M., Jain, R., Hopkinson, A.C., and Lee-Ruff, E., *Canad. J. Chem*., 1987, vol. 65, no. 8, p. 1800. DOI: 10.1139/v87-302.
7. Androsov, D.A. and Neckers, D.C., *J. Org. Chem*., 2007, vol. 72, no. 8, p. 5368. DOI: 10.1021/jo0707784.
8. Hu, Y., Baudart, S., and Porco, J.A., *J. Org. Chem*., 1999, vol. 64, no. 3, p. 1049. DOI: 10.1021/jo981874v.
9. King, J.A. and McMillan, F.H., *J. Am. Chem. Soc*., 1946, vol. 68, no. 11, p. 2335. DOI: 10.1021/ja01215a058.