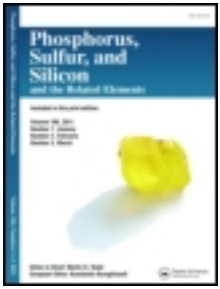

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New Derivatives of 1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione. Synthesis of Thiosemicarbazides and Their Cyclic Analogues

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*A series of 2-(arylthiosemicarbazide)-imidazo[4,5-b]pyridines (**6**–**9**) were prepared by reaction of 2-(carbazoylalkylthio)-imidazo[4,5-b]pyridines (**4** and **5**) with selected arylisothiocyanates. The thiosemicarbazides **6** and **7** were cyclized with 2-bromoacetophenone to give the derivatives of imidazo[4,5-b]pyridine **10** and **11**. Compounds (**2**–**11**) were characterized by elemental analysis as well as IR and ^{s1}H NMR spectroscopy.*

Keywords 1*H*,3*H*-2-Thioxoimidazo[4,5-*b*]pyridine derivatives; hydrazide; structures; synthesis; thiazole; thiosemicarbazide

INTRODUCTION

The thiazole ring is a pharmacophoric group; condensed or substituted with different heterocyclic systems it makes part of many drugs[1] with various pharmacological activities, e.g., Penicillin, Thiamine, Levamisole, Amiphenazole, Mebendazole, and Bleomycin. According to literature data derivatives of various heterocyclic systems as quinazolinones, benzimidazoles, indoles, etc. containing in their structure the thiazole moiety also show pharmacological and biological activities like anti-inflammatory,[2] anti-fungi,[3,4] and anti-microbial as well as anti-viral[5] activity. They are also active antibacterial (*Mycobacterium tuberculosis*),[6] CN depressant,[7] and anticonvulsive[8] agents.

Thiazoles are classically obtained using the Hantzsch reaction,[9] i.e. the condensation of thiourea with an amide acetal to form a thiocarbamoylamidine, followed by base promoted cyclization with a phenacyl halide. Cyclocondensation of thiosemicarbazides[10] or

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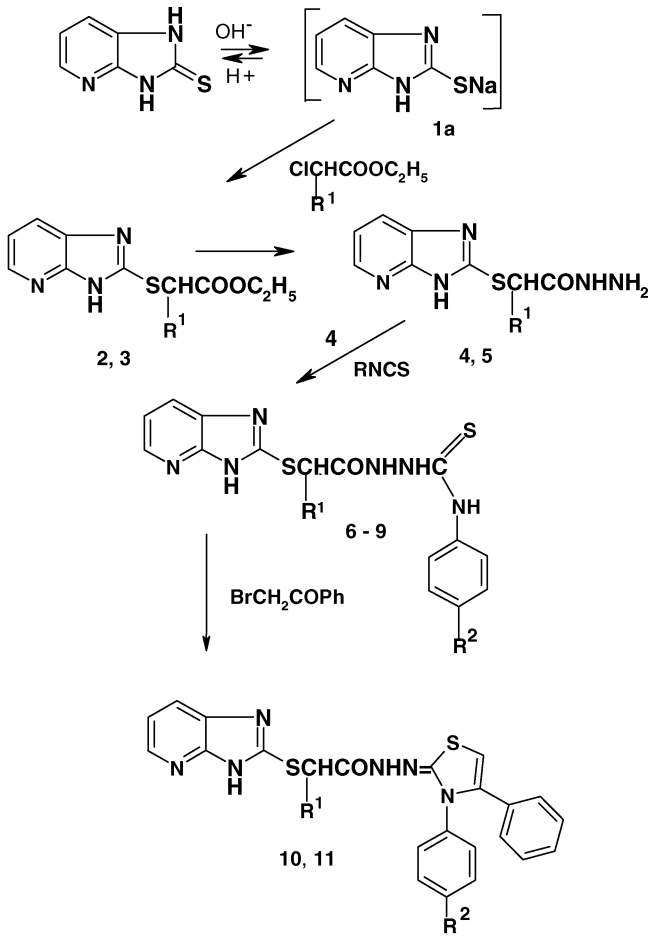
isothiosemicarbazones[4,8] with a phenacyl halide, chloroacetic acid or oxalyl chloride is also possible.

In recent years, the synthesis and biological studies of thiosemicarbazides, thiosemicarbazones and thiazolidine derivatives were described.[4,8,10,13,14] The goal of the present study was to synthesize thiosemicarbazide derivatives of 1*H*-imidazo[4,5-*b*]pyridine-2(3)-thione and of their cyclic analogs in order to use them for biological research, e.g., concerning a possible in vitro antiproliferative activity (Scheme 1). The 1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione is a universal substrate for the synthesis of substituted and condensed compounds containing the 1,3-diamino and the 2-thioxo-thiole group. Synthesis, structure, and in vitro antiproliferative activity of these derivatives were described in our previous paper.[11]

RESULTS AND DISCUSSION

The easily prepared sodium salt of 1*H*-imidazo[4,5-*b*]pyridine-2(3)-thione (**1a**) was used in the alkylation with ethyl bromoacetate or ethyl 2-chloropropionate in ethanol to obtain 2-ethoxycarbonylmethylthio-3*H*-imidazo[4,5-*b*]pyridine (**2**) or 2-(1-ethoxycarbonyl-1-ethylthio)-3*H*-imidazo[4,5-*b*]pyridine (**3**). The esters **2** and **3** were reacted with 80% hydrazine hydrate in ethanol to give 2-carbazoylmethylthioimidazo [4,5-*b*]pyridine (**4**) and 2-(carbazoyl-1-ethylthio)-3*H*-imidazo[4,5-*b*] pyridine (**5**). The hydrazides **4** and **5** were treated with selected substituted arylisothiocyanates to obtain the thiosemicarbazide derivatives **6**–**9**. The thiosemicarbazides **6** and **7** were cyclized with 2-bromoacetophenone to give the corresponding derivatives **10** and **11**. The structures of compounds **2**–**11** were confirmed by elemental analyses as well as by IR and ^{1}H NMR spectroscopy. The IR spectra of the esters **2** and **3** exihibit characteristic C=O bands in the region of 1750–1730 cm^{-1}. The methylene S–C**H**$_2$ protons of compound **2** show in the ^{1}H NMR spectrum a singlet at 4.25 ppm. For compound **3,** a quartet at 4.67 ppm is observed for the S–**CH** proton. The IR spectra of the thiosemicarbazide derivatives **6**–**9** show characteristic **NH** bands in the region of 3320–s3290 cm^{-1}. The **C=O** bands of these compounds are observed at 1690–1665 cm^{-1}. The IR spectra of compounds **10** and **11** exhibited **NH** and **C=O** bands at 3420-3400 cm^{-1} and at 1680–1670 cm^{-1}, respectively, which are attributed to the **CO–NH–N=** group. The ^{1}H NMR spectra display a single CON**H** resonance at 8.85–8.50 ppm. The absence of the ^{1}H NMR signals for the thiosemicarbazide moiety and the appearance of signals for =C**H** at 6.95–6.81 ppm and for –C**H**$_2$– at 4.90–4.55 ppm confirm the presence of the thiazole ring in compounds **10** and **11**. The new compounds prepared are intended for biological



	R^1	R^2
2,4	H	
3,5	CH_3	
6	H	H
7	H	Cl
8	H	Br
9	H	OCH_3
10	H	Cl
11	H	Br

SCHEME 1

research and can be suitable as starting materials for further syntheses, as well.

EXPERIMENTAL

Melting points (uncorrected) were measured with a Boethius melting point apparatus. Analyses of the new compounds were performed on a Perkin Elmer 2400 analyzer and satisfactory results within ±0.4% of the calculated values were obtained. IR spectra (in KBr) were recorded with an IR 75 spectrophotometer. ^{1}H NMR spectra were obtained with a Bruker ARX 300 MHz instrument at room temperature using DMSO-$d_6$or $CDCl_3$ as solvent. Chemical shifts are referred to the residual solvent signal at $\delta = 2.50$ ppm. The course of the reactions and the purity of the products were checked by TLC (Kieselgel G, Merck) using diethyl ether : ethanol = 5:1 as eluent.

1H-Imidazo[4,5-b]pyridine-2(3H)-thione (1)[12]

Yield: 1.15 g (77%); m.p. 318–320°C. IR (KBr), ν (cm^{-1}): 3050 (CH); 1625, 1520 (C═N), 1430, 1250, 1180 (C═S); 920, 840, 780 (Ar); 705 (C═S), ^{1}H NMR (DMSO-d_6): δ = 13.10 (s, 1H, NH); 12.70 (s, 1H, NH); 8.08 (dd, J = 4.8 Hz, J = 1.2 Hz, 1H, H-5); 7.48 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H, H-7); 7.13 (dd, J = 7.8 Hz, J = 4.8 Hz, 1H, H-6). Anal. Calcd. for $C_6H_5N_3S$ (151.19): C, 47.67; H, 3.33; N, 27.79%; Found: C, 47.57; H, 3.30; N, 27.94%.

General Procedure for Compounds 2 and 3

A mixture of 0.01 mol of 1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione (**2**) and 0.01 mol of NaOH in 50 mL of absolute ethanol was refluxed for 0.5 h. After cooling 0.01 mol of ethyl bromoacetate or ethyl 2-chloropropionate was added. The mixture was refluxed for 5 h. The precipitate formed was filtered off, washed with water, dried, and recrystallized from ethanol.

2-Ethoxycarbonylmethylthio-3H-imidazo[4,5-b]pyridine (2)

Yield: 1.77 g (75%); white solid, m.p. 149–150°C. IR (KBr), ν(cm^{-1}): 3400 (CH); 3150 (CH); 1730 ($COOC_2H_5$); 1630, 1570 (CN); 1400 (S─CH); 960, 875, 780 (Ar). ^{1}H NMR (DMSO-d_6): δ = 13.24 (s, 1H, NH); 8.21 (dd, J = 7.9 Hz, J = 5.2 Hz, 1H, H-5); 7.84 (d, J = 7.9 Hz, 1H, H-7), 7.18 (dd, J = 7.9 Hz, J = 5.2 Hz, 1H, H-6); 4.25 (s, 2H, CH_2); 4.09 (q, J = 7.1 Hz, 2H, $\mathbf{CH}_2CH_3$); 1.18 (t, J = 7.1 Hz, 3H, $CH_2\mathbf{CH}_3$). Anal. Calcd. for

$C_{10}H_{11}N_3O_2S$(237.06); C, 50.50; H, 4.64; N, 17.55%; Found: C, 50.62; H, 4.68; N, 17.72%.

2-(1-Ethoxycarbonyl-1-ethylthio)-3H-imidazo[4,5-b]pyridine (3)

Yield: 2,10 g (84%); white solid, m.p. 119–120°C. IR (KBr) ν (cm^{-1}): 3060, 2990 (CH); 1750 ($COOC_2H_5$); 1520 (NH); 1460 (C=N); 1400, 1315, 1280 (C–S); 1170 ($COOC_2H_5$). ^{1}H NMR ($CDCl_3$): $\delta = 12.77$ (s, 1H, NH); 8.44 (d, $J = 5.2$ Hz, 1H, H-5), 8.12 (d, $J = 7.9$ Hz, 1H, H-7), 7.29 (dd, $J = 7.9$ Hz, $J = 5.2$ Hz, 1H, H-6); 4.67 (q, $J = 7.2$ Hz, 1H, S-CH); 4.17 (q, $J = 7.1$ Hz, 2H, $\mathbf{CH_2}$–CH_3); 1.67 (d, $J = 7.2$ Hz, 3H, $\mathbf{CH_3}$–CH); 1.20 (t, $J = 7.1$ Hz, 3H, CH_2–$\mathbf{CH_3}$). Anal. Calcd. for $C_{11}H_{13}N_3O_2S$ (251.30); C, 52.57; H, 5.22; N, 16.73%; Found: C, 53.15; H, 5.31; N, 17.07%.

General Procedure for Preparation of Compounds 4 and 5

A mixture of compound **2** or **3** 0.01 mol and 80% hydrazine hydrate (0.02 mol) in 30 mL of ethanol was refluxed for 20 h. The solvent was evaporated and the resulting residue was crystallized from ethanol.

2-Carbazoylmethylthioimidazo[4,5-b]pyridine (4)

Yield: 1.98 g (88%); m.p. white solid, m.p. 189–190°C. IR (KBr) ν (cm^{-1}): 3350, 3290 (NH_2); 1670 (CONH); 1630, 1590 (NH); 970, 880, 760 (Ar); 700 (C–S). ^{1}H NMR (DMSO-d_6): $\delta = 12.83$ (s, 1H, NH); 9.42 (br, 1H, CONH); 8.20 (dd, $J = 4.8$ Hz, $J = 1.4$ Hz, 1H, H-5); 7.82 (dd, $J = 7.9$ Hz, $J = 1.4$ Hz, 1H, H-7); 7.15 (dd, $J = 7.9$ Hz, $J = 4.8$ Hz, 1H, H-6); 4.33 (br, 2H, NH_2); 4.03 (s, 2H, S–CH_2). Anal. Calcd. for: $C_8H_9N_5OS$(233.25); C, 43.04; H, 4.06; N, 31.37%; Found: C, 43.34; H, 3.68; N, 30.95%.

2-(Carbazoyl-1-ethylthio)-3H-imidazo[4,5-b]pyridine (5)

Yield: 1.3 g (55%); m.p. white solid, m.p. 176–178°C. IR (KBr) ν(cm^{-1}): 3440, 3300 (NH_2); 3080, 3040, 2940 (CH); 1650 (CONH); 1550, 1500 (NH); 1460 (C=N); 1425, 1370, 1275 (C-S); 1120 (NH). ^{1}H NMR (DMSO-d_6): $\delta = 13.00$ (s, 1H, NH); 9.51 (br, 1H, CONH); 8.21 (d, $J = 4.8$ Hz, 1H, H-5); 7.84 (d, $J = 7.9$ Hz, 1H, H-7); 7.16 (dd, $J = 7.9$ Hz, $J = 4.8$ Hz, 1H, H-6); 4.64 (q, $J = 6.9$ Hz, 1H, S–CH); 4.37 (br, 2H, NH_2); 1.53 (d, $J = 6.9$ Hz, 3H, CH–$\mathbf{CH_3}$). Anal. Calcd. for $C_9H_{11}N_5SO$ (237.28); C, 45.56; H, 4.67; N, 29.52%; Found: C, 46.03; H, 4.70; N, 30.01%.

General Procedure for Thiosemicarbazides 6 and 9

A solution of 0.01 mol of hydrazide **4** or **5** in ethanol (50 mL) and 0.01 mol of the appropriate isothiocyanate was refluxed for 6–8 h. The solution

was concentrated at reduced pressure to 20 mL, the solid formed was filtered off and crystallized from *n*-butanol.

2-[4-(Phenylthiosemicarbazide)-carbonylmethylthio]-3H-imidazo[4,5-b]pyridine (6)

Yield: 2.7 g (75%); white solid, m.p. 191–192°C. IR (KBr) $\nu(cm^{-1})$: 3230 (NH); 1665 (CONH); 1570 (NH); 1300, 1245, 1130 (C—S). ^1H NMR (DMSO-d_6): $\delta = 13.28$ (s, 1H, NH); 10.47 (br, 1H, CONH); 9.76 (br, 1H, CONHNH); 9.62 (br, 1H, NH—Ph); 8.15-7.01 (m, 7H, Ar—H); 4.18 (s, 2H, CH_2). Anal. Calcd. for $C_{15}H_{14}N_60_1S_2$ (358.45); C, 50.26; H, 3.94; N, 33.45%; Found: C, 50.42; H, 3.85; N, 33.21%.

2-[4-(p-Chlorophenylthiosemicarbazide)-carbonylmethylthio]-3H-imidazo[4,5-b]-pyridine (7)

Yield: 3.3 g (84%); white solid, m.p. 199–200°C. IR (KBr) ν (cm^{-1}); 3225 (NH); 1420, 1260, 1210 (C—S); 790, 760 (Ar). ^1H NMR (DMSO-d_6): $\delta = 13.30$ (s, 1H, NH); 10.51 (br, 1H, CONH); 9.89 (br, 1H, CONHNH); 9.69 (s, 1H, NH—C_6H_4Cl); 8.17 (d, $J = 4.9$ Hz, 1H, H-5); 7.59 (d, $J = 7.8$ Hz, 1H, H-7); 7.35 (m, 4H, Ar); 7.16 (dd, $J = 7.8$ Hz, $J = 4.9$ Hz, 1H, H-6); 4.19 (s, 2H, CH_2). Anal. Calcd. for: $C_{15}H_{13}N_6Cl_1OS$ (392.88); C, 45.86; H, 3.34; N, 21.39%; Found: C, 45.53; H, 3.16; N, 21.10%.

2-[4-(p-Bromophenylthiosemicarbazide)-carbonylmethylthio]-3H-imidazo[4,5-b]-pyridine (8)

Yield: 3.8 g (86%); white solid, m.p. 204–205°C. IR (KBr) $\nu(cm^{-1})$: 3260 (NH); 1690 (CONH); 1540 (NH); 1260, 1215, 1140 (C—S); 790, 760 (Ar). ^1H NMR (DMSO-d_6): $\delta = 13.28$ (s, 1H, NH); 10.49 (br, 1H, CONH); 9.95 (br, 1H, CONHNH); 9.67 (s, 1H, NH—C_6H_4Br); 8.17 (d, $J = 4.9$ Hz, 1H, H-5); 7.61 (d, $J = 7.9$ Hz, 1H, H-7); 7.41 (m, 4H, Ar); 7.11 (dd, $J = 7.9$ Hz, $J = 4.9$ Hz, 1H, H-6); 4.18 (s, 2H, CH_2). Anal. Calcd. for: $C_{15}H_{13}N_6Br_1OS$ (437.33); C, 41.20; H, 3.00; N, 19.22%; Found: C, 41.10; H, 2.80; N, 18.80%.

2-[4-(p-Anisylthiosemicarbazide)-carbonylmethylthio]-3H-imidazo[4,5-b]pyridine (9)

Yield: 3.21 g (83%); white solid, m.p. 194–195°C. IR (KBr) $\nu(cm^{-1})$: 3320, 3290 (NH); 2975, 2880 (CH); 1680 (CONH); 1600, 1540 (NH); 1425, 1390, 1260, 1230, 1180 (C—S); 840, 800, 760 (Ar). ^1H NMR (DMSO-d_6): $\delta = 13.28$ (s, 1H, NH); 10.45 (br, 1H, CONH); 9.68 (br, 1H, CONHNH); 9.52 (s, 1H, NH—$C_6H_4OCH_3$); 8.16 (d, $J = 4{,}8$ Hz, 1H, H-5); 7.58 (d, $J = 7.9$ Hz, 1H, H-7); 7.70 (m, 5H, Ar—H, H-6); 4.17 (s, 2H, CH_2);

3.74 (s, 3H, OCH_3). Anal. Calcd. for: $C_{16}H_{16}N_6OS$ (388.46); C, 49.47; H, 4.15; N, 21.63%; Found: C, 49.00; H, 3.96; N, 21.31%.

General Procedure for Compounds 10 and 11

A mixture of 0.01 mol of the thiosemicarbazide **10** or **11**, 0.01 mol of 2-bromoacetophenone and 0.04 mol of freshly dehydrated sodium acetate in 80 mL of absolute ethanol was refluxed for 4 h. The solvent from the solution thus obtained was evaporated under reduced pressure, the residue was diluted with H_2O (100 mL) and left overnight. The precipitate obtained was filtered, washed with cold water, dried, and crystallized from *n*-butanol.

2-[3-(p-Chlorophenyl-4-phenyl-3H-thiazol-2-ylidene)-3-carbazoylmethylthio]-3H-imidazo[4,5-b]pyridine (10)

Yield: 2.39 g (47%), m.p. white solid, m.p. 192–194°C. IR (KBr) $\nu(cm^{-1})$: 3060, 2900 (CH); 1670 (CONH); 1600, 1495 (NH); 1395, 1280, 1200, 1160 (C—S); 960, 830, 750 (Ar). ^1H NMR ($CDCl_3$): $\delta = 11.87$ (s, 1H, NH); 8.85 (br, 1H, CONH); 8.25 (d, $J = 5.2$ Hz, 1H, H-5); 8.10 (d, $J = 7.8$ Hz, 1H, H-7); 7.91 (m, 2H, Ar—H); 7.46 (m, 7H, Ar—H); 7.16 (dd, $J = 7.8$ Hz, $J = 5.2$ Hz, 1H, H-6); 6.95 (s, 1H, CH-thiazoline); 4.55 (s, 2H, S—CH_2). Anal. Calcd. for: $C_{23}H_{17}N_6Cl_1O_1S_2$ (492.06): C, 56.09; H, 3.48; N, 17.07%; Found: C, 56.01; H, 3.54; N, 17.54%.

2-[3-(p-Bromophenyl-4-phenyl-3H-thiazol-2-ylidene)-3-carbazoylmethylthio]-3H-imidazo[4,5-b]pyridine (11)

Yield: 2.14 g (39%); m.p. white solid, m.p. 198–200°C. IR (KBr) $\nu(cm^{-1})$: 3060, 2930 (CH); 1680 (CONH); 1600, 1495 (NH); 1330, 1265, 1200, 1170 (C-S); 960, 840, 750 (Ar). ^1H NMR ($CDCl_3$): $\delta = 11.95$ (s, 1H, NH); 8.50 (s, 1H, CONH); 8.28 (d, $J = 4.9$ Hz, 1H, H-5); 7.97 (m, 2H, Ar—H); 7.80 (d, J =7.6 Hz, 1H, H-7); 7.37 (m, 7H, Ar—H); 7.16 (dd, $J =$ 7.6 Hz, $J = 4.9$ Hz, 1H, H-6); 6.81 (s, 1H, CH-thiazoline); 4.90 (s, 2H, S—CH_2). Anal. Calcd. for $C_{23}H_{17}N_6BrOS$(537.45); C, 51.40; H, 3.19; N, 15.64%; Found: C, 50.35; H, 3.05; N, 15.36%.

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