Furan Ring Recyclization in 2-Furfurylthieno[2,3-*b*]pyridines: An Intramolecular N-alkylation of Pyrrole Ring under Acid Conditions

Darya Yu. Kosulina, Vladimir K. Vasilin, Tatyana A. Stroganova,*
Tatyana Ya. Kaklyugina, and Gennady D. Krapivin

Department of Organic Chemistry, Kuban State University of Technology, Krasnodar 350072, Russian Federation
*E-mail: tatka_s@mail.ru

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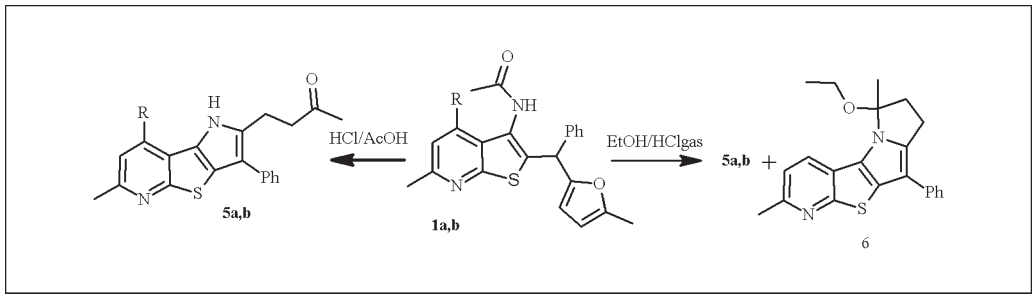

The preparation of new 3-amino-2-furfurylthieno[2,3-*b*]pyridines (**1a,b**, 69–80%) is described. Subsequent acidic rearrangement of **1a,b** afforded two new annulated heterocyclic products, **5a,b**, pyrrolothieno[2,3-*b*]pyridines (45–74%), and **6**, pyridothieno[2,3-*b*]pyrrolizine (22%), depending on reaction conditions.

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INTRODUCTION

Thieno[2,3-*b*]pyridine derivatives are well known to possess varied biological and pharmacological activities, and hence, their synthesis has been of interest to chemists [1–7]. We have successively used different thieno[2,3-*b*]pyridine derivatives as intermediates for synthesis of some interesting conjugated and annulated heterocyclic systems [8–11].

Thus, continuing our investigation along this line, we herein wish to report the synthesis and acid catalyzed transformations of *N*-{2-[(5-methyl-2-furyl)(phenyl)methyl]thieno[2,3-*b*]pyridin-3-yl}acetamides.

RESULTS AND DISCUSSION

The preparation and transformations of 3-amino-2-furfurylthieno[2,3-*b*]pyridines (e.g. 1, Scheme 1) under acid conditions have attracted our attention because these substances could be considered as heteroanalogues of *ortho*-aminobenzylfurans, which were converted into indole derivatives *via* the furan ring recyclization under acid conditions [12–14] (Scheme 1).

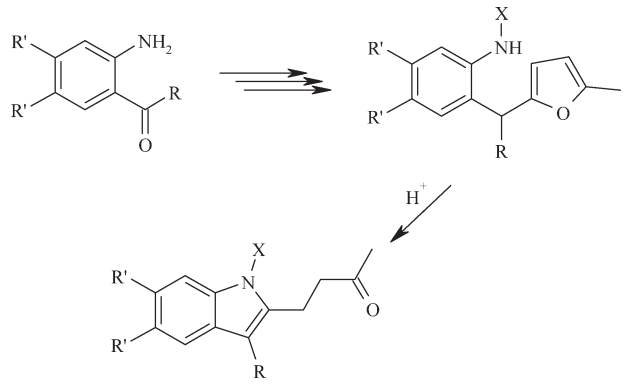
The 3-amino-2-furfurylthieno[2,3-*b*]pyridines **1** were prepared easily from 3-amino-2-benzoylthieno[2,3-*b*]pyridines **2** according to Scheme 2. This approach included an acetylation of aminoketones **2** with acetyl chloride followed by reduction of carbonyl group and alkylation of 2-methylfuran with the alcohols obtained. A mixture of 70% $HClO_4$, acetic anhydride, and acetic acid ($HClO_4$:Ac_2O:AcOH = 5.6:3.3:5.2 mmoles) was used as a catalyst for the last stage. The application of the catalyst allowed to decrease undesired side-transformations of alcohols **4a,b** and 2-methylfuran during the reaction [15].

A new heterocyclic system—pyridothienopyrrole **5**—was made from **1** by successive treatment with concentrated HCl in acetic acid under heating (Scheme 3). A cleavage of the protective acetyl group was observed during the reaction.

An attempt to recyclize **1** on heating in ethanolic HCl solution gave the unusual results: if **1b** (R = Me) was smoothly converted into the corresponding pyridothienopyrrole **5b** (64%), **1a** (R = H) gave two substances. We found that in addition to the expected **5a** (45%) another product—a compound **6** (22%)—was isolated from the reaction mixture (Scheme 3).

The structure of **6** is assigned by X-ray analysis [Fig.(1)] [16]. The crystal was grown from CH_2Cl_2-petroleum ether mixture. Pyrrolidine moiety of the molecule is practically planar: the angle between planes C(7)-N(2)-C(10)-C(6) and C(7)-C(8)-C(9) is 176.1°. H(8b)-C(8)-C(7)-C(19), H(8a)-C(8)-C(7)-H(9a), H(9b)-C(9)-C(8)-H(8b), and H(9a)-C(9)-C(8)-H(8a) torsion

Scheme 1

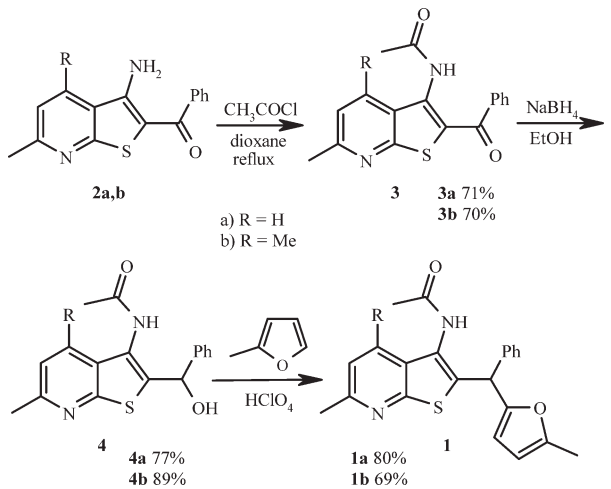


angles equals 4.6, 2.4, 2.1, and 4.7°, correspondingly. Phenyl substituent is located in a plane forming an angle of 3.4° with the heterocyclic core.

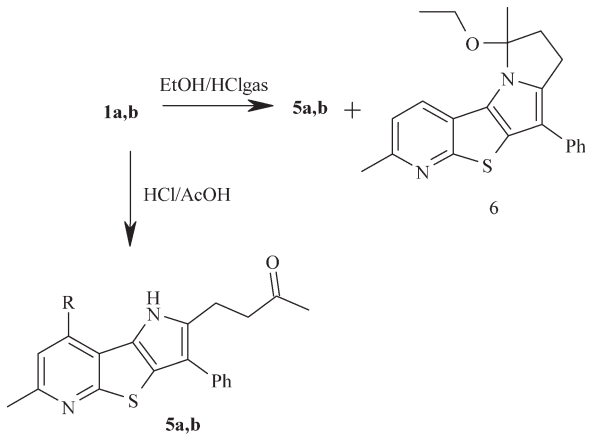
We suppose that the formation of **5a** and **6** proceeds as follows: the furan ring opening leads to a diketone, which in turn reacts with amino group to afford **A** (Scheme 4). The aromatization of **A** leads to pyrrole ring formation as observed earlier for benzylfurans [11–13] to give compound **5a** (Path ***a***). Another route—pyrrolizine **6** formation—is a concurrent process. Probably, compound **6** is provided by ring closure of dihydropyrrolothienopyridine **A** with side chain carbonyl group to produce a cyclic semiaminal **B** (Path ***b***). The interaction between the semiaminal **B** and EtOH molecule allows fixing the pyrrolizine ring as ethoxy derivative which then converts into **6**.

We found that all efforts to furnish the pyrrolizine **6** by heating of the ketone **5a** under identical conditions failed. In our opinion, this result confirms the proposed mechanism: the alkylation occurs before the aromatization of the pyrrole ring. On treating **1a,b** with HCl/

Scheme 2



Scheme 3



AcOH mixture only **5a,b** (74%, 61%) were formed. In this case the Path ***a*** is predominant because of the equilibrium between cyclic seminal **B** and **A**.

As to the recyclization of **1b**, we suppose that the Me-substituent in position 4 of the pyridine ring prevents the pyrrolidine ring closure, probably, due to steric factors. So in this case, the Path ***a*** is the only possible way for the reaction.

In conclusion, acid-catalyzed transformations of 2-furfurylthieno[2,3-*b*]pyridines have been studied, and the unusual intramolecular N-alkylation of pyrrole ring under acid condition has been disclosed. Possible mechanism of the reaction has been proposed.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-NMR spectra were measured in DMSO-d_6 on Bruker AM 300 spectrometer using TMS as an internal standard. Coupling constant (J) values are given in Hz. Mass spectra were recorded on a Kratos MS-30 instrument with 70 eV impact ionization. IR spectra were recorded

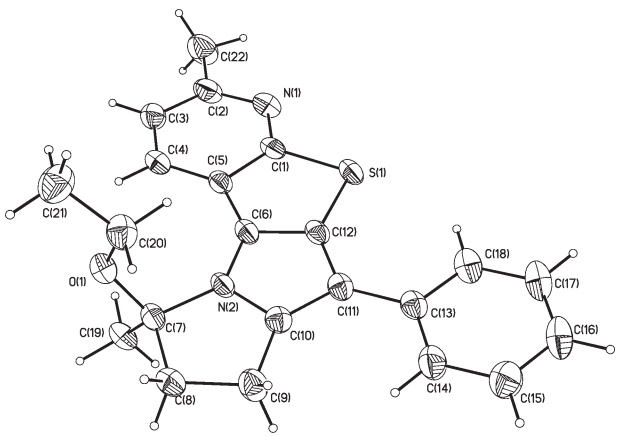
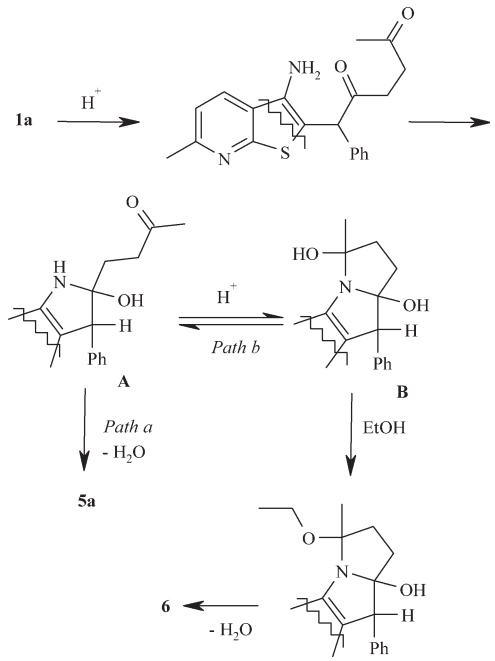


Figure 1. ORTEP of the molecular structure of compound **6.**

Scheme 4



on an InfraLUM FT-02 spectrometer, and absorptions are given in wavenumbers (cm^{-1}). Column chromatography was carried out using KSK silica gel (5–40 μm) manufactured by Sorbpolymer Ltd.

General procedure for acetylation of amines 2a,b. A mixture of amine (**2a,b**) (10 mmoles) and AcCl (20 mmoles) in 1,4-dioxane (60 mL) was refluxed until the complete conversion of the compounds **2** (TLC). To the cooled stirred mixture, water (10–15 mL) was added drop by drop, and the resulted mixture was left at RT for crystallization of a product. The precipitate thus obtained was separated with suction, washed with aq solution of sodium hydrocarbonate, water, and air-dried. Recrystallization of the solid from DMF yielded compounds **3a,b** as colorless crystals.

N-(2-Benzoyl-4,6-dimethylthieno[2,3-b]pyridin-3-yl)acetamide (3a). This compound was obtained as colorless crystals in 71% yield, mp 161–162°C; IR: NH 3245, CO 1662, CO 1645 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.50 (s, 3H, $COCH_3$), 2.57 (s, 3H, 4-CH_3), 2.62 (s, 3H, 6-CH_3), 7.19 (s, 1H, H-5), 7.52 (t, 2H, H_{Ph}, J = 7.3 Hz), 7.62–7.74 (m, 3H, phenyl protons), 9.76 ppm (s, 1H, NH), ms: *m/z* 324 (29), 281 (100), 121 (11), 105 (13), 59 (25), 43 (49). Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.65; H, 4.97; N, 8.64. Found: C, 66.80; H, 5.09; N, 8.70.

N-(2-Benzoyl-6-methylthieno[2,3-b]pyridin-3-yl)acetamide (3b). This compound was obtained as colorless crystals in 70% yield, mp 187–188°C; IR: NH 3213, 3192, CO 1705, CO 1635 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.65 (s, 3H, $COCH_3$), 2.65 (s, 3H, 6-CH_3), 7.42–7.55 (m, 3H, phenyl protons), 7.60–7.67 (m, 2H, phenyl protons), 7.72 (d, 1H, J = 7.3 Hz, H-5), 8.33 (d, 1H, J = 8.1 Hz, H-4), 10.51 ppm (s, 1H, NH); ms: *m/z* 310 (21), 269 (12), 268 (82), 267 (94), 105 (17), 101 (13), 77 (100), 69 (12), 59 (35), 57 (17), 55 (14), 51 (18), 45 (22). Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.91; H, 4.68; N, 8.91.

General procedure for the reduction of acylaminoketones 3a,b. To a vigorously stirred suspension of acylaminoketone (**3a,b**) (5 mmoles) in ethanol (40 mL), $NaBH_4$ (0.23 g, 6 mmoles) was added portion wise, and the mixture was kept at 50–60°C for 2 h. After that the mixture was diluted with water (200 mL) and a precipitate formed was separated by filtration. The solid was recrystallized from ethanol yielding alcohols **4a,b**.

N-{2-[Hydroxy(phenyl)methyl]-4,6-dimethylthieno[2,3-b]pyridin-3-yl}acetamide (4a). This compound was obtained as white powder in 77% yield, mp 178–179 °C; IR: OH 3280, NH 3225, 3120, CO 1652 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.03 (s, 3H, $COCH_3$), 3.35 (s, 6H, 4-,6-CH_3), 5.98 (d, 1H, *CH*—OH, J = 3.7 Hz), 6.36 (d, 1H, CH—*OH*, J = 3.7 Hz), 7.00 (s, 1H, H-5), 7.20–7.41 (m, 5H, phenyl protons), 9.51 ppm (s, 1H, NH), ms: *m/z* 326 (0.7), 308 (20), 293 (40), 267 (100), 265 (98), 251 (12), 105 (21), 101 (10), 80 (38), 76 (17), 59 (24), 43 (59). Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.32; H, 5.60; N, 8.69.

N-{2-[Hydroxy(phenyl)methyl]-6-methylthieno[2,3-b]pyridin-3-yl}acetamide (4b). This compound was obtained as white powder in 89% yield, mp 197–198°C; IR: OH 3259, NH 3230, 3158, CO 1656 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.06 (s, 3H, $COCH_3$), 2.50 (c, 3H, 6-CH_3), 6.12 (d, 1H, *CH*—OH, J = 4.4 Hz), 6.37 (d, 1H, CH—*OH*, J = 4.4 Hz), 7.19–7.43 (m, 6H, phenyl protons, H-5), 7.75 (d, 1H, H-4, J = 8.8 Hz), 9.67 ppm (s, 1H, NH); ms: *m/z* 253 (32), 252 (20), 251 (100), 134 (26), 105 (30), 91 (15), 90 (19), 77 (41), 65 (12), 63 (11), 59 (15), 43 (28). Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.46; H, 5.24; N, 8.89.

Preparation of N-{2-[(5-methyl-2-furyl)(phenyl)methyl]thieno[2,3-b]pyridin-3-yl}acetamide (1a,b). To a solution of **4a,b** (8.3 mmoles) in 1,4-dioxane (20 mL), 2-methylfuran (1.12 mL, 12.5 mmoles) and a catalyst (0.4 mL), which was a mixture of 70% $HClO_4$ (2 mL), Ac_2O (5.3 mL) and AcOH (3 mL), was added [15]. The mixture was refluxed for 5 h until no initial compound remained (TLC control), then it was poured into of cold water (100 mL), neutralized with sodium hydrocarbonate to pH ∼ 6–7. The crude product was filtered with suction and recrystallized from ethanol with charcoal.

N-{6-Methyl-2-[(5-methyl-2-furyl)(phenyl)methyl]thieno[2,3-b]pyridin-3-yl}acetamide (1a). This compound was obtained as white powder in 80% yield, mp 186–187°C; IR: NH 3247, CO 1659 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.05 (s, 3H, $COCH_3$), 2.22 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 5.90 (s, 1H, CH), 6.00 (d, 1H, H_{Fur}, J = 3.2 Hz), 6.08 (d, 1H, H_{Fur}, J = 3.2 Hz), 7.26 (s, 5H, phenyl protons), 7.77 (s, 2H, H-5, H-4), 9.68 ppm (s, 1H, NH). Anal. Calcd. for $C_{22}H_{20}N_2O_2S$: C, 70.19; H, 5.35; N, 7.44. Found: C, 70.21; H, 5.32; N, 7.41.

N-{4,6-Dimethyl-2-[(5-methyl-2-furyl)(phenyl)methyl]thieno[2,3-b]pyridin-3-yl}acetamide (1b). This compound was obtained as colorless crystals in 69% yield, mp 187–188°C; IR: NH 3272, CO 1654 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.04 (s, 6H, 2× CH_3), 2.23 (s, 6H, 2× CH_3), 5.77 (s, 1H, CH), 6.02 (d, 1H, H_{Fur}, J = 3.2 Hz), 6.04 (d, 1H, H_{Fur}, J = 3.2 Hz), 7.03 (s, 1H, H-5), 7.21–7.38 (m, 5H, phenyl protons), 9.57 ppm (s, 1H, NH); ms: *m/z* 390 (82), 374 (12), 332 (88), 305 (49), 303 (18), 291 (28), 289 (18), 271 (11), 265 (19), 229 (12), 184 (17), 178 (20), 171 (37), 165 (11), 155 (12), 141 (32), 127 (15), 105 (25), 101 (16), 76 (14), 59 (21), 44 (29), 43 (54). Anal. Calcd.

for $C_{23}H_{22}N_2O_2S$: C, 70.74; H, 5.68; N, 7.17. Found: C, 70.65; H, 5.78; N, 7.24.

General procedure for the reaction of thieno[2,3-*b*]pyridines 1a,b with HCl/AcOH mixture. A solution of **1a,b** (2 mmoles) in a mixture of glacial acetic acid (20 mL) and hydrochloric acid (5 mL) was refluxed until no initial compounds remained (TLC) and then was poured into cold water (100 mL) and neutralized with sodium hydrocarbonate to pH ~ 6–7. A precipitate was collected, washed with water, and air-dried. A hot solution of the solid in dichloromethane-petroleum ether mixture was filtered through a pad of silica gel to give desired compounds **5a,b**.

4-(6-Methyl-3-phenyl-1H-pyrrolo[2′,3′:4,5]thieno[2,3-b]pyridin-2-yl)butan-2-one (5a). This compound was obtained as white powder in 74% yield; mp 98–99°C; IR: NH 3360, CO 1709 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.12 (s, 3H, $COCH_3$), 2.57 (s, 3H, CH_3), 2.92 (t, 2H, $CH_2CH_2COCH_3$, J = 8.1 Hz), 3.10 (t, 2H, $CH_2CH_2COCH_3$, J = 8.1 Hz), 7.28 (d, 1H, H-5, J = 8.1 Hz), 7.43–7.58 (m, 5H, phenyl protons), 8.04 (d, 1H, H-4 J = 7.3 Hz), 11.87 ppm (s, 1H, NH); ms: *m*/*z* 334 (54), 314 (12), 289 (12), 279 (16), 278 (30), 277 (100), 275 (19), 59 (13), 58 (15), 55 (11), 43 (26), 42 (13), 41 (12). Anal. Calcd for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38. Found: C, 71.86; H, 5.40; N, 8.35.

4-(4,6-Dimethyl-3-phenyl-1H-pyrrolo[2′,3′:4,5]thieno[2,3-b]pyridin-2-yl)butan-2-one (5b). This compound was obtained as white powder in 61% yield; mp 178–179°C; IR: NH 3262, CO 1715 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.11 (s, 3H, $COCH_3$), 2.70 (s, 6H, 2× CH_3), 2.92 (t, 2H, $CH_2CH_2COCH_3$, J = 7.3 Hz), 3.12 (t, 2H, $CH_2CH_2COCH_3$, J = 7.3 Hz), 7.06 (s, 1H, H-5), 7.25–7.29 (m, 2H, phenyl protons), 7.43–7.57 (m, 3H, phenyl protons), 11.46 ppm (s, 1H, NH); ms: *m*/*z* 348 (44), 291 (100), 151 (15), 128 (29), 115 (30), 101 (26), 89 (11), 76 (26), 66 (11), 59 (16), 58 (40), 51 (24), 45 (14). Anal. Calcd for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.79; N, 8.04. Found: C, 72.38; H, 5.91; N, 7.94.

General procedure for the interaction of thieno[2,3-*b*]pyridines 1a,b with EtOH/HCl(gas). A solution of **1a,b** (2 mmoles) in EtOH saturated with dry HCl (gas) (20 mL) was refluxed for 50 min. Then the mixture was poured into cold water (100 mL), and neutralized with sodium hydrocarbonate to pH ~ 6–7. The solid formed was filtered off, washed with water, and air-dried. For **1b**—the precipitate was purified as described above yielding **5b** in 64% yield.

In case of **1a,** the solid was separated by column chromatography (silica gel, petroleum ether : ethyl acetate 1:2) to afford **5a** and **6** as colorless crystals in 45 and 22% yield, respectively.

9-Ethoxy-3,9-dimethyl-6-phenyl-8,9-dihydro-7H-pyrido[3′,2′:4,5]thieno[2,3-b]pyrrolizine (6). This compound was obtained as colorless crystals in 22% yield, mp 166–167°C; IR: 3053, 2984, 2921, 2881, 1603, 1559, 1540, 1453, 1420, 1338, 1212, 1132, 1101, 1065, 976, 813, 761, 723, 688, 510 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.05 (t, 3H, OCH_2CH_3, J = 6.6 Hz), 1.80 (s, 3H, CH_3), 2.60 (c, 3H, CH_3-Py), 2.98 (t, 2H, CH_2, J = 7.3 Hz), 3.35 (q, 2H, OCH_2CH_3, J = 6.6 Hz), 3.59 (t, 2H, CH_2, J = 7.3 Hz), 7.23 (t, 1H, 4-H_{Ph}, J = 7.3 Hz), 7.37 (d, 1H, H_{Py}, J = 8.1 Hz,), 7.48 (t, 2H, J = 7.3 Hz, 3-, 5-H_{Ph}), 7.56 (d, 2H, 2-, 6-H_{Ph}, J = 7.3 Hz), 8.14 ppm (d, 1H, H_{Py}, J = 8.1 Hz); ms: *m*/*z* 362 (37), 317 (12.8), 315 (11), 301 (24), 277 (25), 96 (14), 95 (100), 43 (23). Anal. Calcd for $C_{22}H_{22}N_2OS$: C, 72.89; H, 6.12; N, 7.73. Found: C, 72.91; H, 6.10; N, 7.74.

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[16] CCDC 693220 for **6** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; Available at: deposit@ccdc.cam.ac.uk.