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SYNTHESIS OF THIENO[2,3-*b*]PYRAZINES *VIA* AN ACYLATION - DEACYLATION PROCESS OF 3,4-DIHYDRO PRECURSORS[1]

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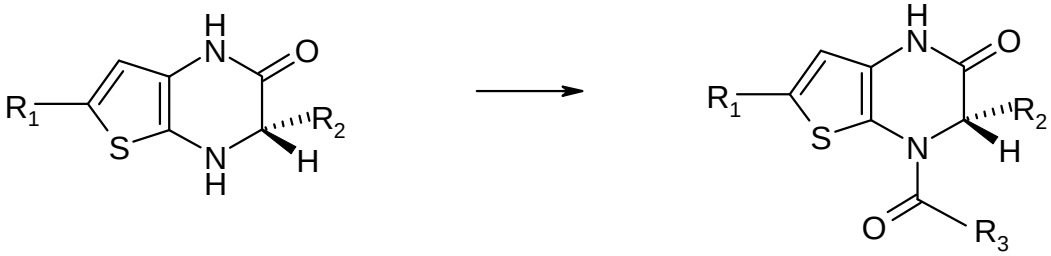
Abstract - In the first step 3, 4-dihydrothieno[2,3-*b*]pyrazines (**1**, **2** and **4**) were *N*-acylated by the acyl chlorides followed by a deacylation process mediated by triethylamine to give thieno[2,3-*b*]pyrazines . In a final rection the excess of the appropriate acyl chlorides react with the free hydroxy residue to afford compounds (**15**, **16** or **17**).

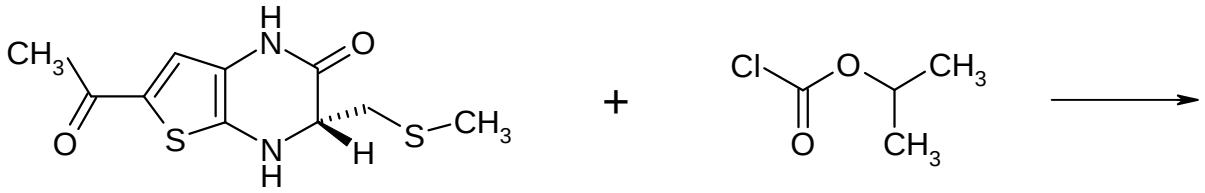
The treatment of arylamines with acyl halides is a very general reaction for the preparation of amides. The *N*-acylation of the bicycles (**1** – **7**)[2] was initially carried out with acyl chlorides in THF in the presence of triethylamine.



1 - 7 **8 - 14**

1, 8 : R_1 = acetyl	R_2 = methyl	R_3 = -OCH=CH_2
2, 9 : R_1 = acetyl	R_2 = benzyl	R_3 = -OCH=CH_2
3, 10 : R_1 = acetyl	R_2 = -CH_2-CH_2-SCH_3	R_3 = -OCH=CH_2
4, **11** : R_1 = acetyl	R_2 = -CH_2-SCH_3	R_3 = -O-isopropyl
5, 12 : R_1 = acetyl	R_2 = H	R_3 = -cyclopropyl
6, 13 : R_1 = benzoyl	R_2 = methyl	R_3 = -OCH=CH_2
7, 14 : R_1 = benzoyl	R_2 = benzyl	R_3 = -OCH=CH_2

By this approach only poor yields (less than 10 %) of the corresponding products (**8 - 14**) were available. But, for compounds (**8 – 10**) and (**12 – 14**) higher yields (38 – 72 %) were obtained when the reactions were conducted without any bases in dry dioxane at 40^0C.[2] Nevertheless under these conditions (in absence of any bases) the acylation of compound (**4**) only afforded 13 % yield of **11**.



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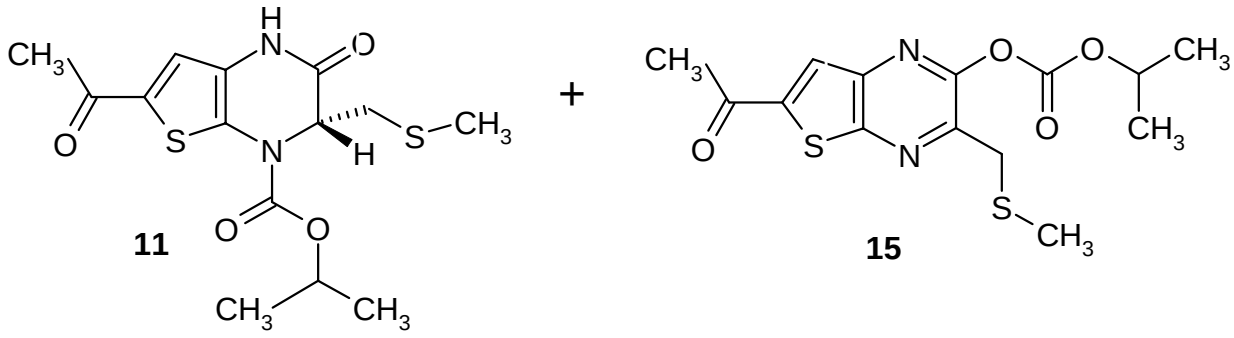
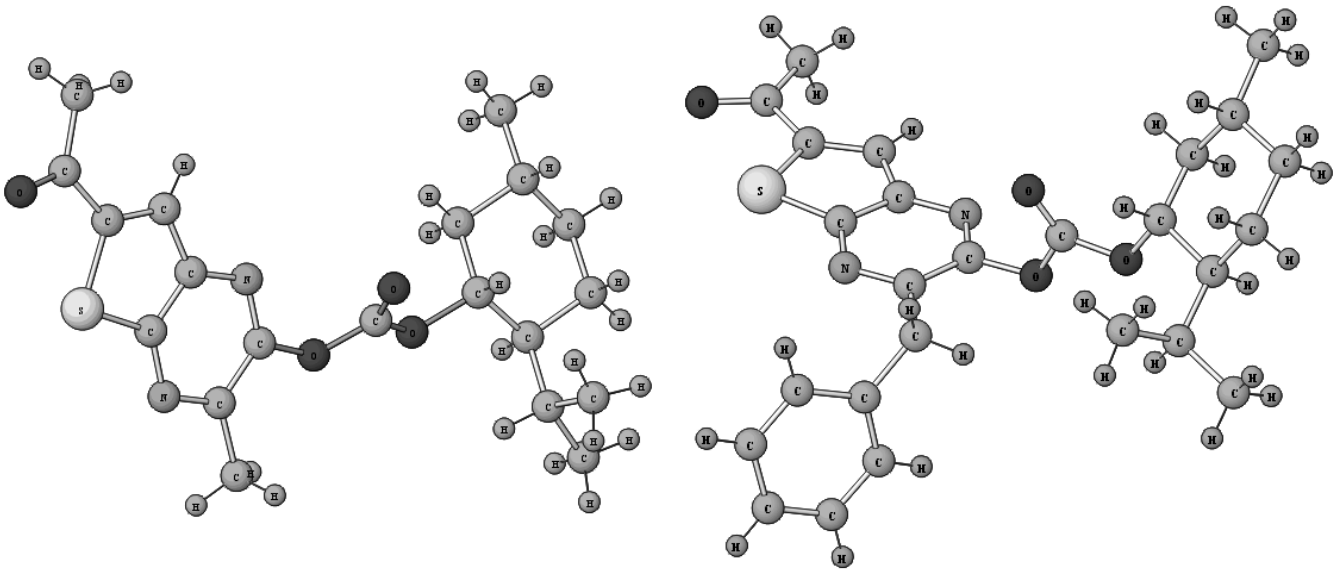


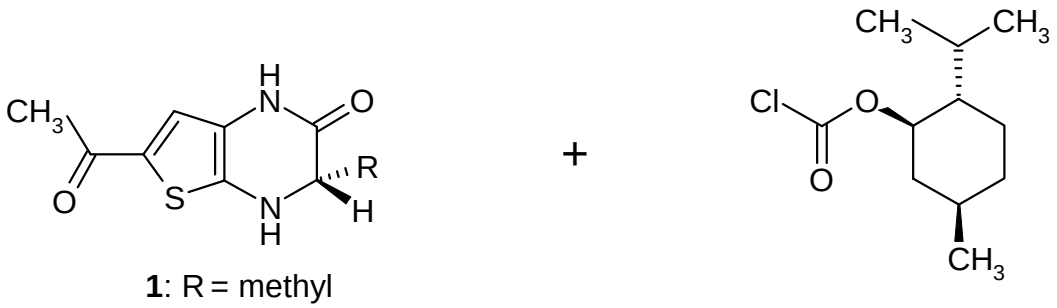
11 **15**

Since we were interested in the causes of this behavior, further investigations on this reaction were done. First trials suggested that elevated temperatures favor the formation of by-products. Indeed when bicycle (**4**) was refluxed with isopropyl chloroformate in dry dioxane no acylated product (**11**) could be detected by TLC analysis. After processing this reaction mixture afforded a new compound (**15**) giving a yield of 12 %. The yield of **15** could be increased up to 48 % by adding molar amounts of triethylamine to the reaction mixture. The molecular ion peak in the MS spectrum and the values received by the elemental analysis suggested a compound structurally similar to **11** with the exception of two mass units due to the loss of two hydrogens. The peaks in the ^{1}H-NMR spectrum exhibited besides the signal due to the thiophene proton (7.99 ppm) and the singlets due to the acetyl group (2.70 ppm) and the methylthio group (2.11 ppm) could be interpreted as a doublet (1.43 ppm) and a septet (5.07 ppm) belonging to the isopropyl unit. Furthermore the spectrum showed an unusual signal as singlet at 3.93 ppm with an intensity of 2 protons. The absence of the broadened singlet due to the lactam proton and the loss of the signal for proton at *C*-3 further indicated a structure quite different from **11**. Instead of three expected peaks the ^{13}C-NMR spectrum showed five signals for quaternary carbons in the range for aromatic atoms. No additional signal for the *C*-3 carbon could be detected as in compound (**4**) at 56.4 ppm or compound (**11**) at 57.4 ppm. Thus, the exact constitution of compond (**15**) could not undoubtedley be confirmed using these spectral data.

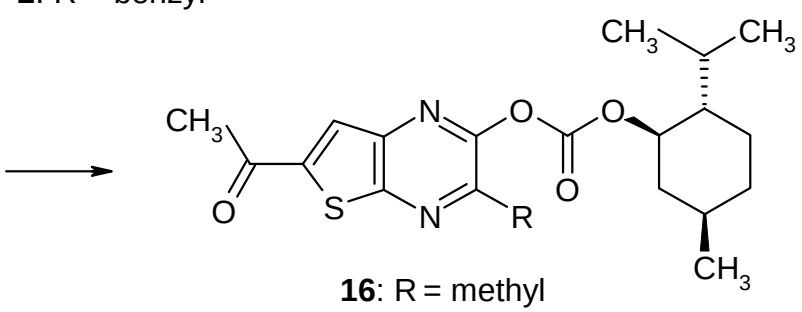
Therefore we decided to study the other reactions shown in the first scheme under the conditiones specified above. We succeeded by reacting the bicycles (**1**) or (**2**) in THF with (1*R*)-(-)-menthyl chloroformate at room temperature in the presence of triethylamine. The reaction mixtures were processed after 27 hours (TLC control), and **16** and **17** were obtained in yields of 45 % and 43 % respectively. Control experiments using other solvents, or reaction without a solvent resulted in lower yields. As for compound (**15**), the spectral data as well as the elemental analysis of **16** and **17** did not allow complete elucidation of the structures of these heterocycles. Therefore the molecular structure of **16** and **17** were unequivocally established by a single crystal X-Ray diffraction structure analysis.[3]



16 **17**

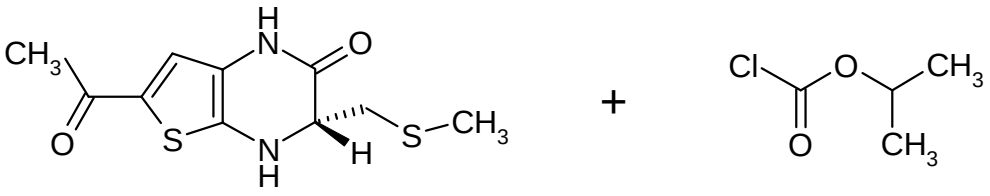


1: R = methyl
2: R = benzyl



16: R = methyl
17: R = benzyl

Based on these results the spectral data for compound (**15**) could be interpreted, too. The singlet at 3.93 ppm with an intensity of 2 protons refers to the methylene protons next to the sulfur atom. The absence of the broadened singlet due to the lactam proton and the loss of the signal for a proton at *C*-3 is a result of a dehydrogenation process. Furthermore the signal for the *C*-3 in the ^{13}C-NMR could be detected as a quaternary carbon in the aromatic range. On basis of this considerations, the elemental analysis and the mass spectrum the shown structure could be definitely assigned to **15**.



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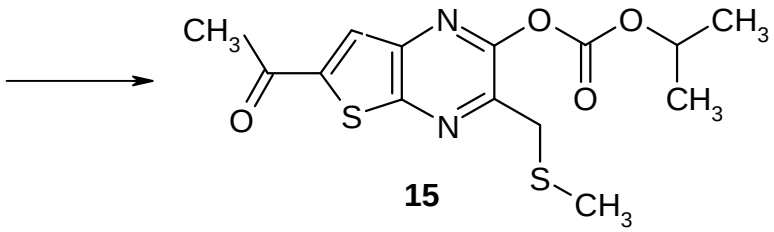
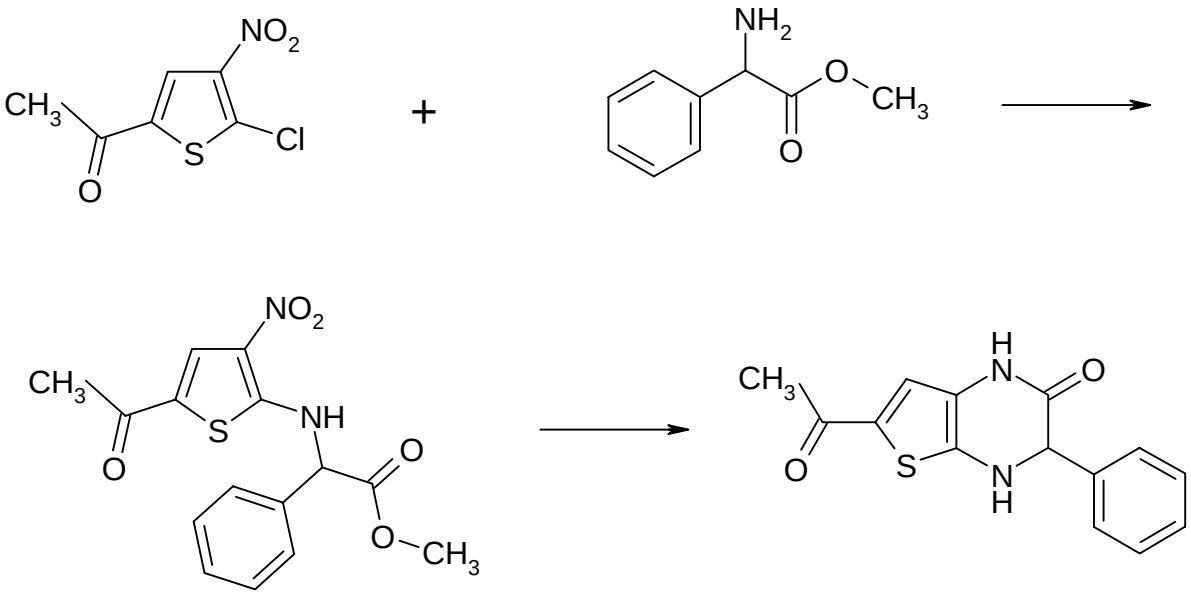


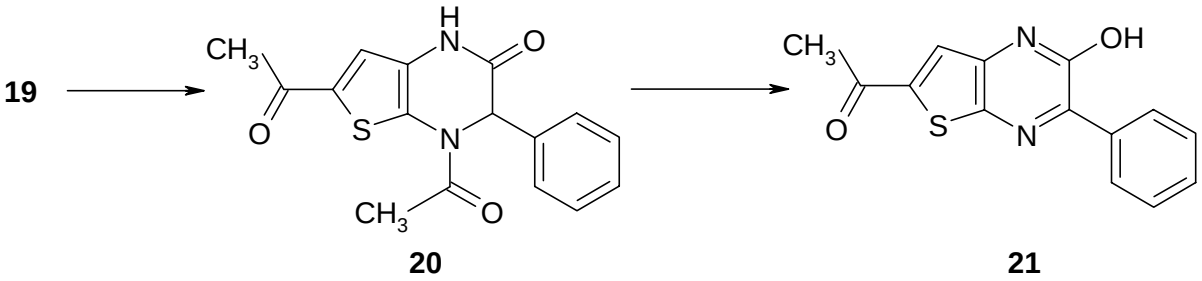
15

Since we were interested in a more general application of this type of reaction, further experiments were done. Activation of the thieno[2,3-*b*]pyrazine bicycle by a phenyl substituent in position 3 should facilitate the elimination of the hydrogen atoms and provide mild reaction conditions. Thus, starting material (**19**) was obtained as shown in the following scheme:



18 **19**

We started from 5-acetyl-2-chloro-3-nitrothiophene,[4] which was reacted with α-phenylglycine methyl ester to compound (**18**). Cyclisation to bicycle (**19**) could be accomplished by using iron powder/ acetic acid.



20 **21**

This lactam (**19**) was subject to a related procedure as mentioned above. In the first step compound (**19**) was treated with acetyl chloride in THF in absence of any base at room temperature. Indeed after processing the acylated heterocycle (**20**) could be isolated in good yield (83 %). The final deacetylation of **20** was accomplished smoothly by reaction with triethylamine in dry dioxane at room temperature to afford bicycle (**21**).

In order to confirm the expectet process by a further experiment we examined the deacetylation step of the acylated bicycle (**11**) with triethylamine. Without processing the resulting product was brought to reaction with isopropyl chloroformate. This sequence afforded the known compound (**15**).

Finally, the following pathway for the formation of compounds (**15**, **16** and **17**) could be assumed: In the first step the starting materials (**1**, **2** and **4**) were *N*-acylated by the acyl chlorides followed by a deacylation process mediated by triethylamine. In a final step the excess of the appropriate acyl chlorides react with the free hydroxy residue to afford **15**, **16** or **17**.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Unity*Plus* 300 spectrometer (using TMS as internal reference, δ values in ppm). MS spectra were obtained by a Shimadzu QP 5000 or a Hewlett Packard 5970 spectrometer. Analytical TLC was performed on silica gel F254 plates. Column chromatography was done on Merck silica gel 60, 0.063- 0.200 mm. Evaporation refers to evaporation under reduced pressure, and drying of solutions refers to the use of anhydrous sodium sulfate. Optical rotations were measured on Perkin-Elmer 241 polarimeter at 20^{0}C.

General procedure for the synthesis of compounds (15-17)

The mixture of the amine (**1**, **2** or **4**) (2.5 mmol), the chloformate (5 mmol)and triethylamine (1.010 g, 10 mmol) in 20 mL of dry THF was stirred at rt for 30 h. Then the organic solvent was removed under reduced pressure and the residue diluted with water and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and after this the solvent was removed under reduced pressure.

6-Acetyl-3-methylsulfanylmethylthieno[2,3-*b*]pyrazine-2-yl isopropyl carbonate (15)

Starting from **4** (0.640 g, 2.5 mmol) and isopropyl chloroformate (0.613 g, 5 mmol) and after purification by column chromatography eluting with toluene:ethyl acetate (4:6) **15** (408 mg, 48 %) as an oil was obtained; MS: m/z (rel. int.) 340 (M^+, 1), 208 (100), 61 (33); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.00 (s, 1H, thiophene-H), 5.07 (sept, 1H, *J* = 6.3 Hz, CH), 3.93 (s, 2H, SCH_2), 2.71 (s, 3H, CH_3), 2.11 (s, 3H, SCH_3), 1.43 (d, 6H, *J* = 6.3 Hz, CH_3); ^{13}C-NMR ($CDCl_3$): δ 191.7, 154.3, 151.3, 151.1, 147.5, 146.6, 145.4, 126.5, 74.4, 35.2, 26.4, 21.5, 15.3; Anal. Calcd for $C_{14}H_{16}N_2O_4S_2$: C, 49.40; H, 4.74; N, 8.23. Found: C, 49.65; H, 4.49; N, 8.01.

6-Acetyl-3-methylthieno[2,3-*b*]pyrazine-2-yl (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl carbonate (16)

Starting from **1** (0.525 g, 2.5 mmol) and (1*R*)-(-)-menthyl chloroformate (1.094 g, 5 mmol) and after crystallization from ethanol **16** (439 mg, 45 %) was obtained; mp 109^{0}C; $[\alpha]_D$ –34.2 ^{0} (c 1.0, toluene); MS: m/z (rel. int.) 390 (M^+, 2), 208 (100), 167 (16), 138 (47), 83 (92); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.96 (s, 1H, thiophene-H), 4.70 (dt, 1H, *J* = 11.1 Hz, *J* = 4.7 Hz, O-CH), 2.70 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.27 – 2.00 (m, 2H, CH_2), 1.87 – 1.66 (m, 2H, CH_2), 1.62 – 1.44 (m, 2H, CH_2), 1.28 – 1.02 (m, 2H, CH), 1.01 – 0.82 (m, 1H, CH), 0.97 (d, 6H, *J* = 6.8 Hz, CH_3), 0.87 (d, 3H, *J* = 7.1 Hz, CH_3); ^{13}C-NMR ($CDCl_3$): δ 191.7, 155.0, 151.7, 151.6, 147.3, 146.8, 144.8, 126.6, 80.8, 46.9, 40.4, 33.9, 31.4, 26.4, 26.2, 23.3, 21.9, 20.6, 19.9, 16.3; Anal. Calcd for $C_{20}H_{26}N_2O_4S$: C, 61.52; H, 6.71; N, 7.17. Found: C, 61.66; H, 6.77; N, 7.11.

6-Acetyl-3-benzylthieno[2,3-*b*]pyrazine-2-yl (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl carbonate (17)

Starting from **2** (0.715 g, 2.5 mmol) and (1*R*)-(-)-menthyl chloroformate (1.094 g, 5 mmol) after crystallization from ethanol **17** (502 mg, 43 %) was obtained; mp 115^{0}C; $[\alpha]_D$ –14.6 ^{0} (c 1.0, toluene); MS: m/z (rel. int.) 466 (M^+, 0.5), 284 (100), 138 (26), 83 (70); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.96 (s, 1H, thiophene-H), 7.35 – 7.09 (m, 5H, phenyl-H), 4.61 (dt, 1H, *J* = 11.0 Hz, *J* = 4.3 Hz, O-CH), 4.29 (s, 2H, CH_2), 2.68 (s, 3H, CH_3), 2.17 – 1.98 (m, 2H, CH_2), 1.78 – 1.63 (m, 2H, CH_2), 1.56 – 1.40 (m, 2H, CH_2),

1.19 – 1.03 (m, 2H, CH), 1.01 – 0.73 (m, 1H, CH), 0.96 (d, 6H, *J* = 6.8 Hz, CH_3), 0.84 (d, 3H, *J* = 6.8 Hz, CH_3); ^{13}C-NMR ($CDCl_3$): δ 191.7, 155.0, 151.6, 151.3, 148.7, 147.3, 145.2, 136.5, 128.9, 128.6, 126.9, 126.5, 80.8, 46.7, 40.3, 39.7, 33.9, 31.3, 26.4, 26.1, 23.2, 21.8, 20.6, 16.2; Anal. Calcd for $C_{26}H_{30}N_2O_4S$: C, 66.92; H, 6.48; N, 6.00. Found: C, 67.16; H, 6.47; N, 5.67.

Methyl 2-[(5-acetyl-3-nitro-2-thienyl)amino]phenylacetate (18)

To a suspension of methyl 2-aminophenylacetate hydrochloride (1.613 g, 8 mmol) and potassium carbonate (2.208 g, 16 mmol) in absolute acetonitrile (15 mL) 5- acetyl-2-chloro-3-nitrothiophene (0.512 g, 2.5 mmol) was added and the mixture was stirred under argon atmosphere at rt. After the reaction was completed (24 h) the organic solvent was removed. Then the residue was diluted with water and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. After crystallization from ethanol **18** (650 mg, 78 %) was obtained; mp 178^{0}C; MS: m/z (rel. int.) 334 (M^+, 6), 275 (51), 107 (58), 77 (36); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 9.62 (d, 1H, *J* = 5.5 Hz, NH), 7.91 (s, 1H, thiophene-H), 7.48 – 7.38 (m, 5H, phenyl-H), 5.08 (d, 1H, *J* = 5.8 Hz, CH), 3.81 (s, 3H, CH_3), 2.43 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 189.6, 168.9, 161.0, 133.1, 129.7, 129.4, 128.1, 127.6, 127.1, 125.3, 63.4, 25.0; Anal. Calcd for $C_{15}H_{14}N_2O_5S$: C, 53.89; H, 4.22; N, 8.38. Found: C, 53.60; H, 4.24; N, 8.12.

6-Acetyl-3-phenyl-3, 4-dihydrothieno[2,3-*b*]pyrazin-2(1*H*)-one (19)

Iron powder (1.562 g) was added in small portions to a suspension of **18** (1.336 g, 4 mmol) in glacial acetic acid (14 mL) and water (1.5 mL). Then the reaction mixture was heated at 70^{0}C for 1.5 h, filtered in hot, washed with water and allowed to cool. The resulting precipitate was filtered off and recrystallized from ethanol to give **19** (793 mg, 73 %); mp 228 - 231^{0}C; MS: m/z (rel. int.) 272 (M^+, 57), 243 (22), 229 (4), 77 (17), 43 (100); ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 10.37 (s, 1H, NH), 7.95 (s, 1H, thiophene-H), 7.14 (s, 5H, phenyl-H), 6.95 (s, 1H, NH), 4.94 (s, 1H, CH), 2.30 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 187.2, 163.5, 142.7, 139.6, 128.6, 128.0, 126.7, 124.0, 122.7, 119.5, 25.0; Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.66; H, 4.23; N, 10.11.

4, 6-Diacetyl-3-phenyl-3, 4-dihydrothieno[2,3-*b*]pyrazin-2(1*H*)-one (20)

To a solution of **19** (1.088 g, 4 mmol) in dry THF (15 mL) acetyl chloride (0.628 g, 8 mmol) was added. Then the reaction mixture was stirred at rt for 24 h. After the reaction was completed (TLC analysis) the organic solvent was removed. Then the residue was diluted with water and extracted with ethyl acetate. The combined organic layers were dried and the solvent was evaporated. After crystallization from ethanol **20** (1.043 g, 83 %) was obtained; mp 212^{0}C; MS: m/z (rel. int.) 314 (M^+, 5), 272 (21), 167 (15), 90 (14), 43 (100); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 9.12 (s, 1H, NH), 7.43 – 7.12 (m, 6H, thiophene-H/

phenyl-H), 5.79 (s, 1H, CH), 2.51 (s, 3H, CH_3), 2.25 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 190.5, 169.0, 164.9, 1354.9, 134.7, 129.5, 129.4, 128.3, 128.1, 125.6, 123.2, 119.1, 63.4, 26.5, 21.3; Anal. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91. Found: C, 61.19; H, 4.72; N, 8.69.

1-(2-Hydroxy-3-phenylthieno[2,3-*b*]pyrazin-6-yl)ethanone (21)

To a solution of **20** (1.256 g, 4 mmol) in dry dioxane (15 mL) triethylamine (1.010 g, 10 mmol) was added. Then the reaction mixture was stirred at rt for 24 h. After the reaction was completed (TLC analysis) the organic solvent was removed. Then the residue was diluted with water and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. After crystallization from methanol **21** (0.571 g, 53 %) was obtained; mp 240^{0}C; MS: m/z (rel. int.) 270 (M^+, 82), 227 (97), 104 (47), 84 (38), 43 (100); ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 12.90 (s, 1H, OH), 8.39 – 8.34 (m, 2H, phenyl-H), 7.52 – 7.39 (m, 4H, thiophene-H/ phenyl-H), 2.62 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 191.7, 155.0, 143.9, 135.4, 133.3, 130.3, 129.1, 128.1, 127.9, 120.4, 26.4; Anal. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36. Found: C, 62.24; H, 3.90; N, 10.08.

REFERENCES AND NOTES

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3. X-Ray data were collected on a Nonius Kappa CCD diffractometer with Mo-Kα Radiation (0.71073 Å). No absorption correction was applied. Structure solutions and full matrix least-squares refinements based on F^2 were performed with SHELXS 93 and SHELXL 93 program packages (Sheldrick, 1993). Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were generated geometrically, assigned appropriate isotropic thermal displacement parameters and allowed to ride on their parent atoms. $C_{20}O_4H_{26}N_2S$: dimensions 0.4 x 0.4 x 0.05 mm^3; monoclinic, space group $P2_1$ (No.4); a = 7.229(1), b = 7.444(1), c = 38.514(4) [Å]; ß = 95.181(5) [^{o}]; V = 2064.07 [Å^3]; Z = 4; μ = 0.18 [mm^{-1}]. Range of data [^{o}]: 4.0 < 2θ < 50.0 with 2θ/ω scan mode. 4443 reflctions collected, 3160 with I>4σ(I). Final conventional R value 0.056 for 3516 reflections [I>4σ(I)]. $C_{26}O_4H_{30}N_2S$: dimensions 0.3 x 0.3x 0.04 mm^3; monoclinic, space group $P2_1$ (No.4); a = 10.057(1), b = 11.810(1), c = 21.644(1) [Å]; ß = 99.01(1) [^{o}]; V = 2539.04 [Å^3]; Z = 4; μ = 0.16 [mm^{-1}]. Range of data [^{o}]: 4.0 < 2θ < 56.6 with 2θ/ω scan mode. 6171 reflctions collected, 3407 with I>4σ(I). Final conventional R value 0.073 for 3407 reflections [I>4σ(I)].References: Sheldrick, G. M. (1993): SHELXS 93 and SHELXL 93 program system. University of Göttingen, Germany. Acknowledgement: Prof. G. Giester, University of Vienna for technical assistance.
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