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On the Synthesis of Some 2-Arylhydrazono-3-oxothieno[2,3-*b*]pyridines by Reaction of Nitrilimines with 2-Mercaptonicotinic Acid

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Summary. Nitrilimines prepared from *N*-arylhydrazono chlorides reacted with 2-mercaptonicotinic acid yielding the corresponding addition products, 2-[(2-oxo-1-arylhydrazonopropan-1-yl)mercapto] nicotinic acids, which were treated with 1,1′-carbonyldiimidazole in *THF* affording by cyclocondensation the corresponding hitherto unknown 2-arylhydrazono-3-oxothieno[2,3-*b*]pyridines.

Keywords. Arylacetonitrilimines; 2-Mercaptonicotinic acid; Cyclocondensation; 3-Oxothieno [2,3-*b*]pyridines.

Introduction

Nitrilimines like **2** generated *in situ* from their hydrazonyl chlorides **1** by reaction with triethylamine allow 1,3-additions with a variety of nucleophiles, such as thiols and amines, to form the corresponding acyclic adducts. In preceding papers we have described reactions with α-mercapto alkanoic acids [1] and with 3-aminopropanoic acid [2]. Compound **2** reacted with 2-aminopyridine and yielded a bicyclic product, an imidazo[1,2-*a*]pyridine derivative [3], whereas on the other hand the reaction between **2** and 2-mercaptobenzoic acid yielded 2-arylhydrazono-3-oxobenzothiophenes [4]. These different products prompted us to undertake experiments with a compound containing a pyridine ring and a mercapto group, 2-mercaptonicotinic acid **3**. About the results we report in this paper.

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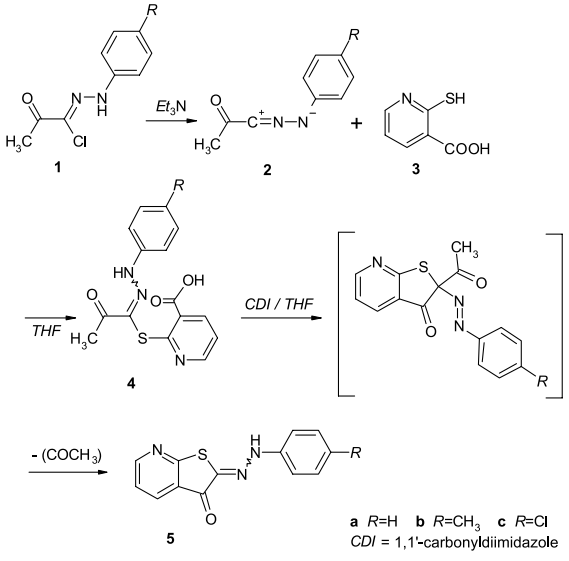
Results and Discussion

2-Mercaptonicotinic acid (**3**) dissolved in a mixture of *Me*OH, H_2O, and Et_3N added easily to the nitrilimines **2a**–**2c** prepared *in situ* from the 1-chloro-1-arylhydrazonopropanones **1a**–**1c** yielding the corresponding 2-[(1-arylhydrazono-2-oxopropane-1-yl)mercapto]nicotinic acids **4a**–**4c** (Scheme 1). This addition established that the sulfur atom as a soft nucleophile in a basic media (Et_3N), is a better electron donator than the harder carboxylate anion and than the pyridine nitrogen. In this respect, 2-mercaptonicotinic acid showed a similar behavior to that of 2-mercaptobenzoic acid towards **2**.

Cyclocondensation of the adducts **4a**–**4c**, in *THF* at 0°C, and promoted by *CDI*, occurred between the activated carboxyl group and the hydrazone carbon (C-1″ anchored to the sulfur atom) with formation of a 2-arylazo intermediate, which was not isolated. Instead, after loss of the acetyl group, it nicely formed the corresponding 2-arylhydrazono-3-oxothieno[2,3-*b*]pyridines **5a**–**5c** (Scheme 1). Here, the adducts **4a**–**4c** showed similar cyclocondensation behavior to the reactions with 2-mercaptobenzoic acid [4], and thus provide another unique example of the azo to hydrazone conversion, the *Japp-Klingemann* reaction [5]. The results presented indicate that the pyridine nitrogen had no influence on the course of the 1,3-nucleophilic addition reaction forming the acyclic adducts **4a**–**4c**, nor on the cyclocondensation pathway of these adducts in providing **5a**–**5c**. This is in clear contrast to the pivotal role played by the ring nitrogen of 2-aminonicotinic acid in its reactions with nitrilimines [3].

All IR, MS, and NMR spectral data and microanalyses of the new compounds **4a**–**4c** and **5a**–**5c** are in accordance with the proposed structures; details are given in the experimental section.



Scheme 1

Experimental

Melting points: Electrothermal Mel. Temp. Apparatus (uncorrected). ^{1}H and ^{13}C NMR spectra: Bruker DPX 300 (300 MHz/75 MHz) at room temp. in *DMSO*-d_6, *TMS* as internal standard, $\delta_{TMS} = 0.00$ ppm. Electron-impact mass spectra were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV; ion source temperature = 200°C. MS-ESI spectral data were obtained with a Bruker Bio TOF III. IR spectra (KBr): Nicolet Impact-400 FT-IR spectrophotometer. Microanalyses were performed at the Microanalytical Laboratory, Inorganic Chemistry Department, Tübingen University, Germany; the results agreed with the calculated values within experimental error. 2-Mercaptonicotinic acid, 3-chloro-2,4-pentanedione, and 1,1′-carbonyldiimidazole (*CDI*) were purchased from Acros. Solvents were purified and dried according to literature procedures. Abbreviations: *Et*OH = ethanol, *Me*OH = methanol, *THF* = tetrahydrofuran. For syntheses of 1-arylhydrazono-1-chloropropanones **1a**–**1c** see Refs. [1, 2].

General Procedure for the Synthesis of ***4***

To a cooled (0°C) and stirred solution of 10 mmol of **1** in 40 cm^3 of *THF* a solution of 1.6 g of 2-mercaptonicotinic acid (10 mmol) in 25 cm^3 of *Me*OH/H_2O (4:1), and 4 cm^3 of Et_3N was added dropwise with stirring. Stirring was continued for 2 h at 5–10°C. Then, the organic solvents were distilled off *in vacuo*, and the remaining aqueous solution was immediately acidified with glacial acetic acid (~4 cm^3). The precipitate was separated, washed with 2×5 cm^3 of water, dried, and crystallized from *Et*OH.

2-[2-Oxo-1-(phenylhydrazono)propylmercapto]pyridine-3-carboxylic acid (**4a**, $C_{15}H_{13}N_3O_3S$)

Yield 2.5 g (79%); mp 180–181°C; IR: $\bar{\nu} = 3380$, 3228 (NH, OH), 3057, 2987 (CH), 1708, 1678 (CO), 1600 (C=N) cm^{-1}; ^{1}H NMR: $\delta = 2.48$ (s, CH_3), 6.96 (t, $J = 7.6$ Hz, 4′-H), 7.19 (dd, $J = 7.7$, 4.7 Hz, 5-H), 7.26 (dd, $J = 7.6$, 8.3 Hz, 3′-H, 5′-H), 7.42 (d, $J = 8.3$ Hz, 2′-H, 6′-H), 8.23 (dd, $J = 7.7$, 1.6 Hz, 4-H), 8.37 (dd, $J = 4.7$, 1.6 Hz, 6-H), 10.68 (s, N–H), 13.62 (br.s, CO_2H) ppm; ^{13}C NMR: $\delta = 26.0$ (CH_3), 115.4 (C-2′, C-6′), 120.5 (C-5), 123.0 (C-4′), 124.6 (C-3), 129.7 (C-3′, C-5′), 131.5 (S–C=N), 139.8 (C-4), 143.5 (C-1′), 152.7 (C-6), 159.0 (C-2), 167.0 (CO_2H), 193.4 (O=C–Me) ppm; HRMS: calcd. $[M + H]^+$ 316.0756, found 316.0750; calcd. $[M + Na]^+$ 338.0575, found 338.0553.

2-[1-(4-Methylphenylhydrazono)-2-oxopropylmercapto]pyridine-3-carboxylic acid (**4b**, $C_{16}H_{15}N_3O_3S$)

Yield 2.5 g (75%); mp 171–172°C; IR: $\bar{\nu} = 3402$, 3236 (NH, OH), 3034, 2923 (CH), 1714, 1682 (CO), 1634 (C=N) cm^{-1}; ^{1}H NMR: $\delta = 2.21$(s, CH_3), 2.46 (s, CH_3), 7.10 (d, $J = 7.3$ Hz, 3′-H, 5′-H), 7.19 (dd, $J = 7.8$, 4.7 Hz, 5-H), 7.32 (d, $J = 7.3$ Hz, 2′-H, 6′-H), 8.22 (dd, $J = 7.8$, 1.7 Hz, 4-H), 8.37 (dd, $J = 4.7$, 1.7 Hz, 6-H), 10.60 (s, N–H), 13.62 (br.s, CO_2H) ppm; ^{13}C NMR: $\delta = 20.9$ (CH_3), 25.9 (CH_3), 115.4 (C-2′, C-6′), 120.4 (C-5), 124.6 (C-3), 130.1 (C-3′, C-5′), 130.7 (S–*C*=N), 132.0 (C-4′), 139.8 (C-4), 141.2 (C-1′), 152.7 (C-6), 159.0 (C-2), 167.0 (CO_2H), 193.2 (O=C–Me) ppm; HRMS: calcd. $[M + H]^+$ 330.0912, found 330.0907; calcd. $[M + Na]^+$ 352.0732, found 352.0726.

2-[1-(4-Chlorophenylhydrazono)-2-oxopropylmercapto]pyridine-3-carboxylic acid (**4c**, $C_{15}H_{12}ClN_3O_3S$)

Yield 2.9 g (83%); mp 166–167°C; IR: $\bar{\nu} = 3408$, 3230 (NH, OH), 3031 (CH), 1704, 1670 (CO) cm^{-1}; ^{1}H NMR: $\delta = 2.46$ (s, CH_3), 7.20 (dd, $J = 7.7$, 4.7 Hz, 5-H), 7.32 (d, $J = 8.9$ Hz, 3′-H, 5′-H), 7.43 (d, $J = 8.9$ Hz, 2′-H, 6′-H), 8.21 (dd, $J = 7.7$, 1.6 Hz, 4-H), 8.36 (dd, $J = 4.7$, 1.6 Hz, 6-H), 10.81 (s, N–H), 13.64 (br.s, CO_2H) ppm; ^{13}C NMR: $\delta = 26.0$ (CH_3), 116.9 (C-2′, C-6′), 120.6 (C-5), 125.1 (C-3), 126.1 (C-4′), 129.6 (C-3′, C-5′), 132.6 (S–C=N), 139.8 (C-4), 142.5 (C-1′), 152.5 (C-6), 158.7 (C-2), 167.1 (CO_2H), 193.4 (O=C–Me) ppm; HRMS: calcd. $[M + H]^+$ 350.0366, found 350.0361; calcd. $[M + Na]^+$ 372.0186, found 372.0180.

General Procedure for the Synthesis of ***5***

1,1′-Carbonyldiimidazole (1.0 g, 6.2 mmol) was added dropwise and with stirring at 0°C to a solution of 5 mmol of **4** (1.6 g) in 40 cm^3 of *THF* and 3 cm^3 of *DMF*. The mixture gradually became red, stirring was continued at 2–5°C for 1–2 h. Then, 60 cm^3 of cold H_2O were added, and the resulting orange precipitate was collected, washed with H_2O, dried, and crystallized from *Et*OH.

3-Oxo-2-(phenylhydrazono)thieno[2,3-b]pyridine (**5a**, $C_{13}H_9N_3OS$)

Yield 0.74 g (58%); mp 237–238°C; IR: $\bar{\nu} = 3221$ (NH), 3174, 3121, 3094 (CH), 1660 (CO), 1583 (C=N) cm^{-1}; ^{1}H NMR: $\delta = 7.01$ (t, $J = 6.5$ Hz, 4′-H), 7.31 (d, $J = 8.3$ Hz, 2′-H, 6′-H), 7.35 (m, 3′-H, 5′-H), 7.42 (dd, 7.5, 4.8 Hz, 5-H), 8.12 (dd, $J = 7.5$, 1.5 Hz, 4-H), 8.71 (dd, $J = 4.8$, 1.5 Hz, 6-H), 11.02 (s, N–H) ppm; ^{13}C NMR: $\delta = 115.4$ (C-2′, C-6′), 122.4 (C-5), 123.5 (C-4′), 125.5 (C-3a), 129.9 (C-3′, C-5′), 130.9 (C-2), 134.4 (C-4), 143.6 (C-1′), 156.3 (C-6), 164.2 (C-7a), 182.3 (CO) ppm; MS-EI: m/z (%) = 255 (M^+, 100), 238 (7), 226 (38), 178 (5), 163 (15), 135 (43), 108 (16), 92 (14); HRMS: calcd. 255.04663, found 255.04842.

2-(4-Methylphenylhydrazono)-3-oxothieno[2,3-b]pyridine (**5b**, $C_{14}H_{11}N_3OS$)

Yield 0.86 g (64%); mp 243–244°C; IR: $\bar{\nu} = 3212$ (NH), 3173, 3106, 3025 (CH), 1656 (CO), 1584 (C=N) cm^{-1}; ^{1}H NMR: $\delta = 2.47$ (s, CH_3), 7.14 (d, $J = 8.3$ Hz, 2′-H, 6′-H), 7.26 (d, $J = 8.3$ Hz, 3′-H, 5′-H), 7.42 (dd, $J = 7.6$, 4.8 Hz, 5-H), 8.12 (dd, $J = 7.6$, 1.7 Hz, 4-H), 8.71 (dd, $J = 4.8$, 1.7 Hz, H-6), 10.99 (s, N–H) ppm; ^{13}C NMR: $\delta = 20.9$ (CH_3), 115.5 (C-2′, C-6′), 122.4 (C-5), 125.7 (C-3a), 130.3 (C-3′, C-5′), 130.4 (C-2), 134.3 (C-4), 141.3 (C-1′), 156.2 (C-6), 164.1 (C-7a), 182.1 (CO) ppm; MS-EI: m/z (%) = 269 (M^+, 100), 252 (7), 240 (14), 178 (2), 163 (10), 135 (38), 106 (35), 91 (30); HRMS: calcd. 269.06228, found 269.06384.

2-(4-Chlorophenylhydrazono)-3-oxothieno[2,3-b]pyridine (**5c**, $C_{13}H_8ClN_3OS$)

Yield 0.94 g (64%); mp 264–265°C; IR: $\bar{\nu} = 3214$ (NH), 3173, 3105, 3030, 2995 (CH), 1660 (CO), 1603 (C=N) cm^{-1}; ^{1}H NMR: $\delta = 7.39$ (m, 2′-H, 6′-H, 3′-H, 5′-H), 7.43 (dd, $J = 7.7$, 4.6 Hz, 5-H), 8.13 (dd, $J = 7.7$, 1.6 Hz, 4-H), 8.73 (dd, $J = 4.6$, 1.6 Hz, 6-H), 11.08 (s, N–H) ppm; ^{13}C NMR: $\delta = 117.0$ (C-2′, C-6′), 122.4 (C-5), 125.6 (C-3a), 127.1 (C-4′), 129.8 (C-3′, C-5′), 131.6 (C-2), 134.4 (C-4), 142.9 (C-1′), 156.3 (C-6), 164.1 (C-7a), 182.0 (CO) ppm; MS-EI: m/z (%) = 289 (M^+, 100), 272 (3), 260 (7), 226 (4), 178 (2), 163 (23), 135 (38), 126 (18), 111 (16); HRMS: calcd. 289.00766, found 289.00595.

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