Synthesis and Alkylation of 5-Benzoyl-3-cyano-6-phenylpyridine-2(1*H*)-thione

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The previously unknown 5-benzoyl-3-cyano-6-phenylpyridine-2(1*H*)-thione was obtained by reaction of cyanothioacetamide with 2-ethoxymethylene-1,3-diphenylpropane-1,3-dione. Depending on the conditions, the thione can be alkylated to give 2-alkylthio-5-benzoyl-3-cyano-6-phenylpyridines and 2-R-3-amino-5-benzoyl-6-phenylthieno[2,3-b]pyridines. The latter also can be obtained by Thorpe-Ziegler cyclization of 2-alkylthio-5-benzoyl-3-cyano-6-phenylpyridines.

Keywords: cyanothioacetamide, vinyl substitution, pyridine-2(1H)-thione, Thorpe-Ziegler reaction, thieno[2,3-b]pyridines.

Introduction

3-Cyanopyridine-2(1*H*)-thiones are a large group of pyridine derivatives with a wide range of practically useful properties (for reviews see [1-6]). Thieno[2,3-b]pyridines, which could be obtained from S-alkylation of 3-cyanopyridine-2(1*H*)-thiones and subsequent Thorpe-Ziegler isomerization of the resulting 2-(alkylthio)pyridine-3-carbonitriles, widely used in the synthesis of polycyclic pyridine derivatives and biologically active compounds, and are also an important class of heterocyclic compounds (for reviews on the chemistry of thienopyridine, see [7-11]).

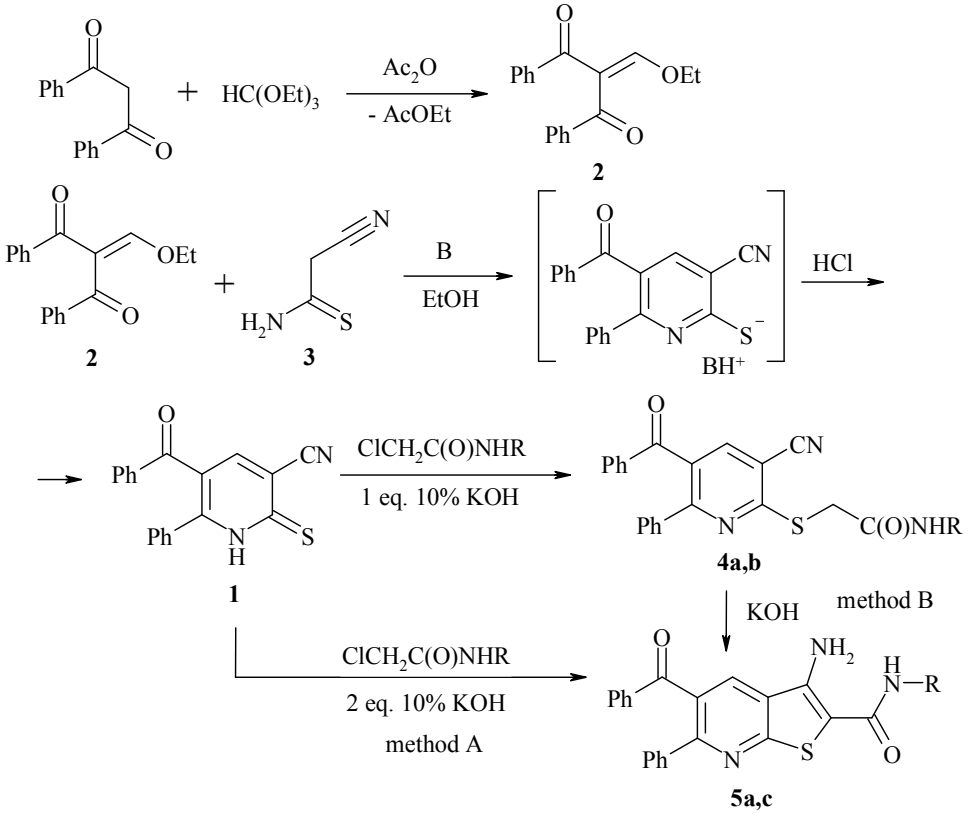
In a continuation of the work on the chemistry cyanothioacetamide and its derivatives – 3-cyanopyridine-2(1*H*)-thiones and thieno[2,3-b]pyridines, we synthesized the previously unknown 5-benzoyl-3-cyano-6-phenylpyridine-2(1*H*)-thione (**1**) by reaction of 2-ethoxymethylene-1,3-diphenylpropane-1,3-dione (**2**) with cyanothioacetamide (**3**) and studied some reactions of thione (**1**) (Scheme 1). It is known that the reaction of C-/N-nucleophiles with β-ethoxy or β-aminoprop-2-enones (S_NVin) is a convenient method to obtain a diversity of heterocyclic compounds [12].

Among these reactions, the reaction of 2-(β-ethoxymethylene)-1,3-diketones and ketoesters with cyanothioacetamide **3** should be mentioned as a promising way to functionally substituted pyridine derivatives [13-17]. Starting β-ethoxymethylene derivatives were obtained by condensation of triethyl orthoformate with 1,3-dicarbonyl compounds [18]. It should be noted, that the the reaction of triethyl orthoformate with dibenzoylmethane has not been described in the literature to the moment. Compound **2** was obtained as a red non-crystallizable oil by reaction of dibenzoylmethane with excessive $HC(OEt)_3$ in Ac_2O, followed by removal of volatile products *in vacuo*.

5-Benzoyl-3-cyano-6-phenylpyridine-2(1*H*)-thione (**1**) was obtained as fine yellow needles in 40% yield by reaction of **2** with cyanothioacetamide **3** in the presence of excessive base, followed by acidification. As expected, thione **1** easily

reacted with alkyl halides to form 2-alkylthio-5-benzoyl-6-phenyl-pyridine-3-carbonitriles **4**. When the alkylation was conducted under harsh conditions (an excess of KOH in hot DMF), thieno[2,3-b]pyridines **5** were isolated in excellent yields (~90%) (Method A). Alternatively, thieno[2,3-b]pyridines **5** can be prepared by treating the compounds **4** with 10% KOH in hot DMF (Method B).

Scheme 1



2 **3** **1** **4a,b** **5a,c**

R = 4-MeC_6H_4 (a); 4-$EtO_2CC_6H_4$ (b); 4-BrC_6H_4 (c).

The structure of compounds **1**, **4**, **5** was confirmed by IR spectrophotometry, ^1H and ^{13}C NMR spectroscopy and CHN analysis. In the ^1H NMR spectrum (500 MHz, DMSO-d_6) of 5-benzoyl-3-cyano-6-phenylpyridine-2(1*H*)-thione **1**, the signals of two phenyls at δ 7.27-7.69 ppm, broadened peak of NH proton at δ 13.92 ppm, and the singlet of C(4)H at δ 8.23 ppm were observed; the spectrum correlates well with literature data [19]. In the ^1H NMR spectra of compounds **4** and **5**, the signals of C(4)H protons shifted predictably to low fields and apperared in the intervals δ 8.45-8.46 ppm and δ 8.77-8.80 ppm, respectively. In the spectrum of 3-aminothieno[2,3-b]pyridine **5** the signals of NH_2 protons appeared at δ 7.33 ppm. In the IR spectra of compounds **1** and **4**, intensive absorption bands in the range 2230-2233 cm^{-1} (conjugated CN groups) were observed.

In the IR spectra of thienopyridines **5** there is no absorption bands of the cyano group, but absorption bands corresponding to the stretching of an amino group were observed.

The compounds obtained were subjected to virtual screening of *in silico* using the PASS program [20]. According to the forecast, the compounds **4** are of interest as potential analgesics and anti-inflammatory agents, whereas for thione **1** and thienopyridines **5** antiviral and anticancer effects should be expected among the most likely types of activity. Furthermore, it should be noted that the

thieno[2,3-b]pyridines **5** appeared to have a bright yellow fluorescence in the near-UV range.

Thus, the reaction of 2-ethoxymethylene-1,3-diphenylpropane-1,3-dione with cyanothioacetamide resulted in formation of 5-benzoyl-3-cyano-6-phenylpyridine-2(1*H*)-thione. Depending on the conditions, alkylation of thione **1** gave 2-alkylthio-5-benzoyl-3-cyano-6-phenylpyridine and 2-R-3-amino-5-benzoyl-6-phenylthieno[2,3-b]pyridines. The latter also can be obtained by Thorpe-Ziegler cyclization of 2-alkylthio-3-cyanopyridines.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DRX (500.13 MHz and 125.77 MHz, respectively) in DMSO-d_6, with TMS as an internal standard. IR spectra were recorded on an IKS-29 spectrophotometer in Nujol mulls. Elemental analysis for C, H, N was performed on Perkin-Elmer C, H, N-analyser. The purity of all obtained compounds was checked by TLC on Silufol® UV 254 plates (sorbent – Silpearl, large-pore silicagel after Pitra with luminiscent indicator for UV 254 on the aluminium foil, binder – starch) in the acetone–hexane (1:1) system; spots were visualized with iodine vapors and UV light. Melting points were determined on Koefler apparatus and are uncorrected.

2-Ethoxymethylene-1,3-diphenyl-propane-1,3-dione (2). A mixture of 10.0 g (44.6 mmol) of dibenzoylmethane, 14.8 mL (89 mmol) of triethyl orthoformate and 12.6 mL (0.134 mol) Ac_2O were heated for 2 days with a constant distillation of alcohol and ethyl acetate. After that, residual solvent was removed *in vacuo* to yield 12.5 g (≈ 100%) of **2** as a non-crystallizable red oil, which was reacted without further purification.

Cyanothioacetamide (3) was obtained by the modified *Brunskill* procedure [21] as follows: the 0.5 L Erlenmeyer flask was charged with 100 g (1.51 mol) of malononitrile and 100 ml of EtOH. Malononitrile was dissolved by stirring at room temperature. Then, 1.0-1.5 ml of a tertiary amine (Et_3N or N-methylmorpholine) were added, the flask was closed with a two-holed rubber stopper fitted with two glass tubes, one of which should be immersed in a solution of malononitrile. The stream of H_2S generated from Al_2S_3 was passed through the tube system. After a short induction period, an exothermic reaction begins, which is accompanied by strong absorption of H_2S by reaction mass. It is important to keep the temperature in the range 15…20 ° C (cooling with ice or snow), to avoid the crystallization of malononitrile – on the one hand, and overheating of the reaction mixture – on the other. After ~30-40 min, cyanothioacetamide begins to crystallize. The reaction mixture should be stirred or shaken periodically to avoid clogging of gas supply pipe by product. Hydrogen sulfide must be passed through a cold solution for at least 6-8 hours to get a good yield of **3**. At the end of the reaction, the mixture was cooled with ice/NaCl, cyanothioacetamide was filtered off, washed several times with cold EtOH to a colorless filtrate, then washed with cold Et_2O and petroleum ether. Cyanothioacetamide was obtained as sand-yellow needles, mp 117-120 °C (Lit. [21]: 121 °C (EtOH)), yield: 130-135 g (86-89%). The product is pure enough for further transformations. Cyanothioacetamide should be kept in a refrigerator at

0...+4 °C. ^{1}H NMR Spectra (δ, ppm, *J*, Hz): 3.96 s (2H, CH_2), 9.43 and 9.77, both br.s (each 1 H, C(S)NH_2). IR spectrum (ν, cm^{-1}): 3270, 3360, 3140 (NH_2); 2258 (C≡N).

5-Benzoyl-3-cyano-6-phenylpyridine-2(1*H*)-thione (1). A mixture of 2-ethoxymethylene-1,3-diphenylpropane-1,3-dione (**2**) (12.5 g, 44.6 mmol), 4.0 g (40 mmol) of cyanothioacetamide **3**, and 7.0 mL (63.6 mol) of N-methylmorpholine in 25-30 mL of EtOH was stirred for 5 h at room temperature, treated with an excess of AcOH and then was allowed to stand for 3 days in a refrigerator at +4 º C. The precipitated crystals were filtered and washed with EtOH. Yield 5.1 g (40%), bright-yellow needles, mp 230-235 °C (dec.). Found,%: C, 73.19, H, 3.77; N, 8.97. $C_{19}H_{12}N_2OS$ (M = 316.38). Calculated, %: C, 72.13, H, 3.82; N, 8.85. ^{1}H NMR Spectrum (δ, ppm, *J*, Hz): 7.27 m (7H, Ar); 7.52 d.d (1H, C (4)H phenyl, ^3J = 7.0, ^3J = 7.0); 7.68 br.d (2H, C(2)H benzoyl and C (6)H benzoyl, ^3J = 7.5); 8.23 s (1H, C(4)H), 13.92 br.s (1H, NH). IR spectrum (ν, cm^{-1}): 3240 (NH); 2233 (C≡N); 1660 (C=O).

2-[(5-Benzoyl-3-cyano-6-phenylpyridin-2-yl)thio]-N-arylacetamides (4a,b). General procedure. To the mixture of 0.5 g (1.58 mmol) of thione **1** in 2 mL of warm DMF, 10% aqueous KOH (0.9 ml, 1.6 mmol) was added dropwise. Thione **1** was dissolved to form a dark red solution of a potassium salt. To the solution formed, 1.6 mmol of the appropriate α-chloroacetanilide was added in one portion. The product precipitated within 5-10 seconds. The mixture was stirred for 2 h at 20 ºC, diluted with an equal volume of EtOH, the precipitate was filtered off, washed with EtOH. Obtained compounds **4a,b** were pure enough for analytical purposes.

2-[(5-Benzoyl-3-cyano-6-phenylpyridin-2-yl)thio]-N-(4-methylphenyl)-acetamide (4a). White crystalline powder, yield 92%, mp. 176-178 °C. Found,%: C, 73.10, H, 4.60; N, 9.20. $C_{28}H_{21}N_3O_2S$ (M = 463.56). Calculated,%: C, 72.55, H, 4.57; N, 9.06. ^{1}H NMR Spectrum (δ, ppm, *J*, Hz): 2.27 s (3H, Me), 4.34 s (2H, SCH_2); 7.12 m (4H, MeC_6H_4) d.d 7.27 (1H, C(4)H phenyl, ^3J = 6.9); 7.42-7.51 m (6H, Ar); 7.58 d.d (1H, C(4)H benzoyl, ^3J = 6.9); 7.70 br.s (2H, C(2)H and C(6)H benzoyl, ^3J = 7.3); 8.47 s (1H, C(4)H); 10.42 c (1H, C(O)NH). ^{13}C NMR Spectrum (δ, ppm): 20.95 (CH_3); 35.68 (SCH_2); 104.42; 115.66; 119.57; 128.80; 129.27; 129.60; 129.75; 129.95; 130.18; 130.47; 132.75; 134.45; 136.31; 137.08; 137.75, 142.93. IR spectrum (ν, cm^{-1}): 3340 (NH); 2231 (C≡N); 1662 (2 C=O).

Ethyl 4-[(5-Benzoyl-3-cyano-6-phenylpyridin-2-yl)thio]acetyl}amino)-benzoate (4b). White crystalline powder, yield 85%, mp. 186-187 °C. Found,%: C, 68.86, H, 4.48; N, 8.17. $C_{30}H_{23}N_3O_4S$ (M = 521.60). Calculated, %: C, 69.08, H, 4.44; N, 8.06. ^{1}H NMR Spectrum (δ, ppm, *J*, Hz): 1.32 t (3H, Et, ^3J = 7.1); 4.30 q (2H, Et, ^3J = 7.1); 4.39 s (2H, SCH_2); 7.05-7.94 m (14H, 3 Ar); 8.46 s (1H, C(4)H); 10.92 c (1H, C(O)NH). ^{13}C NMR Spectrum (δ, ppm): 14.70, 35.84, 60.93, 104.41, 115.61, 118.90, 124.82, 128.73, 129.25, 129.67, 130.02, 130.18, 130.45, 130.72, 134.43, 136.28, 137.69, 137.75, 142.94; 143.88, 159.16, 162.68, 165.80, 166.67, 194.91. IR spectrum (ν, cm^{-1}): 3330 (NH); 2230 (C≡N); 1710, 1675 (3 C=O).

3-Amino-5-benzoyl-6-phenylthieno[2,3-b]pyridine-2-carboxamides 5a,c. Synthesis by direct alkylation of thione 1 (Method A). 10% Aqueous KOH (2.0 ml, 3.93 mmol) was added to the mixture of 1.0 g (3.17 mmol) of thione **1** in 4 ml of DMF. To the solution formed, 3.2 mmol of the appropriate α-chloroacetanilide was added (white precipitate of compounds **4** formed within a few seconds). The mixture was stirred for 10-20 minutes, then brought to a boil under vigorous stirring, and another 2.0 ml of 10% KOH were added dropwise. The mixture was boiled for 1-2 minutes with constant stirring, cooled, diluted with an equal volume of EtOH. The precipitate was filtered off, washed with EtOH to give analytically pure **5a,c**.

Synthesis of 3-amino-5-benzoyl-N-(4-methylphenyl)-6-phenylthieno[2,3-b]pyridine-2-carboxamide (5a) by Thorpe-Ziegler isomerization of 4a по (method B). To a suspension of 0.5 g (1.08 mmol) of **4a** in 3 ml of hot DMF, 10% KOH (0.6 ml) was added dropwise. The starting compound 4a dissolved to give a dark solution, and yellow crystalline precipitate started to form within a few seconds. The mixture was heated with stirring for 1 min, cooled, then diluted with an equal volume of EtOH. The precipitate was filtered off, washed with EtOH, water and petroleum ether to give **5a**.

3-Amino-5-benzoyl-N-(4-methylphenyl)-6-phenylthieno[2,3-b]pyridine-2-carboxamide (5a). The yield was 91% (method A) and 93% (method B), fine bright yellow crystals, mp 235-237 °C. Found, %: C, 72.61, H, 4.60; N, 9.11. $C_{28}H_{21}N_3O_2S$ (M = 463.56). Calculated, %: C, 72.55, H, 4.57; N, 9.06. ^{1}H NMR Spectrum (δ, ppm): 2.29 s (3H, Me); br.s 7.33 (2H, NH_2); 7.16-7.76 m (14H, 3Ar); 8.77 s (1H, C(4)H), 9.52 (1H, NH). ^{13}C NMR Spectrum (δ, ppm): 20.99, 121.77, 124.56, 128.79, 129.34, 129.58, 130.31, 130.80, 132.45, 133.04, 134.21, 136.78, 137.02, 139.22, 147.08, 157.64, 160.17, 164.05, 196.77. IR spectrum (ν, cm^{-1}): 3460, 3325 (NH, NH_2); 1660, 1640 (C=O).

3-Amino-5-benzoyl-N-(4-bromophenyl)-6-phenylthieno[2,3-b]pyridine-2-carboxamide (5c). The yield was 89.5% (method A), bright yellow crystals, mp. 265-266.5 °C. Found, %: C, 61.64, H, 3.48; N, 8.12. $C_{27}H_{18}BrN_3O_2S$ (M = 528.43). Calculated, %: C, 61.37, H, 3.43; N, 7.95. ^{1}H NMR Spectrum (δ, ppm): 7.33 br.s (2H, NH_2); 7.45-7.77 m (14H, 3Ar); 8.80 s (1H, C(4)H), 9.71 s (1H, NH). ^{13}C NMR Spectrum (δ, ppm): 97.79, 115.72, 123.45, 124.45, 128.79, 129.25, 129.59, 130.32, 130.85, 131.73, 132.61, 134.21, 137.01, 138.87, 139.18, 147.64, 157.86, 160.26, 164.19; 196.72. IR spectrum (ν, cm^{-1}): 3465, 3300 (NH, NH_2); 1660, 1645 (C=O).

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