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# SYNTHESIS OF DERIVATIVES OF 3-CYANO-6-METHYL-5-PHENYLCARBAMOYLPYRIDINE-2(1H)-THIONE AND 3-CYANO-6-METHYL-5-PHENYL-CARBAMOYLPYRIDINE-2(1H)-SELENONE

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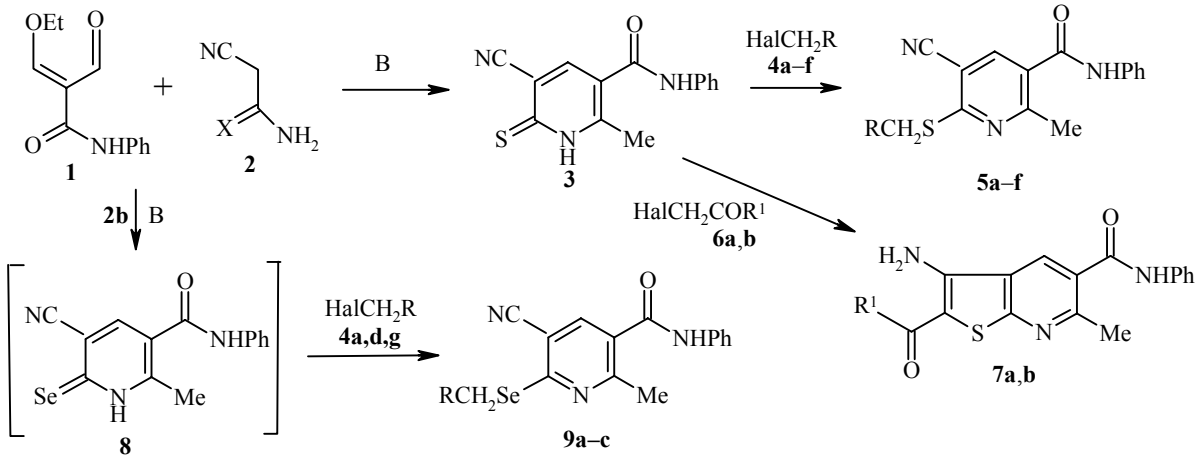
*The reaction of ethoxymethylenacetylacetanilide with cyanothioacetamide or cyanoselenoacetamide in the presence of N-methylmorpholine and alkylating agents gave substituted 2-alkylthio- and 2-alkylselenopyridines and thieno[2,3-b]pyridines.*

**Keywords:** 2-alkylthiopyridines, 2-alkylselenopyridines, thieno[2,3-*b*]pyridines.

4-R-3-Cyano-6-methyl-5-phenylcarbamoylpyridine-2(1H)-thiones have been synthesized through the condensation of aldehydes, the anilide of acetoacetic acid, and cyanothioacetamide. Depending on the nature of the aldehyde used, 4-alkyl- [1, 2], 4-aryl- [3,4], 4-hetaryl- [5-8], or 4-cyclohexanespiropyridinethiones [9] were obtained. Interest in these pyridinethione derivatives is related to their liver protection activity [10]. Since the 4-unsubstituted analogs of these compounds have not been reported, we developed a method for the synthesis of derivatives of 3-cyano-6-methyl-5-phenylcarbamoylpyridine-2(1H)-thiones and 3-cyano-6-methyl-5-phenylcarbamoylpyridine-2(1H)-selenones.




**2 a** X = S, **b** X = Se; **4, 5 a** R = H, Hal = I; **b** R = Et, Hal = Br; **c** R = $H_2C$=CH, Hal = Br; **d** R = Ph, Hal = Cl; **e** R = $H_2NC(O)$, Hal = I; **f** R = 3-cyano-6-methyl-2-methylthiopyridin-5-yl, Hal = Br; **g** R = Me, Hal = I; **6, 7 a** $R^1$= 4-$BrC_6H_4$, Hal= Br, **b** $R^1$= 3-cyano-6-methyl-2-methylthiopyridin-5-yl, Hal = Br; **9 a** R = H, **b** R = Me, **c** R = Ph; B = N-methylmorpholine

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TABLE 1. Characteristics of Compounds **3, 5a-f, 7a,b,** and **9a-c**

| Compound | Empirical formula | Found, % / Calculated, % | | | | mp, °C* | IR spectrum, $cm^{-1}$ | | $^1$H NMR spectrum, δ, ppm, *J* (Hz) | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | S | | C=N $NH_2$ | C=O NH | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| **3** | $C_{14}H_{11}N_3OS$ | 62.54 / 62.43 | 4.22 / 4.13 | 15.60 / 15.59 | 11.91 / 11.92 | 250-252 | 2220 | 1640, 3200, 3320 | 2.53 (3H, s, $CH_3$); 7.34-7.64 (5H, m, Ph); 8.30 (1H, s, C(4)H); 10.30 (1H, br. s, NHCO); 14.27 (1H, br. s, NH) | 86 |
| **5a** | $C_{15}H_{13}N_3OS$ | 63.68 / 63.56 | 4.52 / 4.63 | 14.73 / 14.84 | 11.32 / 11.32 | 190-192 | 2220 | 1640, 3270 | 2.66 (6H, br. s, $CH_3$ and $SCH_3$); 7.22-7.72 (5H, m, Ph); 8.38 (1H, s, C(4)H) | 80 |
| **5b** | $C_{17}H_{17}N_3OS$ | 65.67 / 65.58 | 5.50 / 5.58 | 13.49 / 13.49 | 10.40 / 10.31 | 160-162 | 2220 | 1640, 3250 | 1.00 (3H, t, *J* = 6.4, $CH_3CH_2$); 1.71 (2H, m, $CH_3CH_2$); 3.31 (2H, t, *J* = 5.9, $SCH_2$); 7.10-7.72 (5H, m, Ph); 8.36 (1H, s, C(4)H); 10.45 (1H, br. s, NH) | 92 |
| **5c** | $C_{17}H_{15}N_3OS$ | 66.10 / 66.02 | 4.99 / 4.88 | 13.48 / 13.58 | 10.39 / 10.35 | 157-159 | 2210 | 1640, 3290 | 2.65 (3H, s, $CH_3$); 3.99 (2H, d, *J* = 6.4, $SCH_2$); 5.13 (d, *J* = 9.1) and 5.34 (d, *J* = 15.9), (for 1H, $CH_2$=); 5.93 (1H, m, CH=); 7.08-7.70 (5H, m, Ph); 8.36 (1H, s, C(4)H); 10.42 (1H, br. s, NH) | 88 |
| **5d** | $C_{21}H_{17}N_3OS$ | 70.17 / 70.15 | 4.67 / 4.76 | 11.79 / 11.70 | 8.82 / 8.94 | 161-163 | 2220 | 1640, 3250 | 2.69 (3H, s, $CH_3$); 4.58 (2H, s, $SCH_2$); 7.20-7.70 (10H, m, $CH_2$Ph and HNPh); 8.37 (1H, s, C(4)H); 10.46 (1H, br. s, NH) | 85 |
| **5e** | $C_{16}H_{14}N_4O_2S$ | 58.88 / 58.87 | 4.42 / 4.30 | 17.27 / 17.19 | 9.72 / 9.83 | 208-210 | 2220, 3400 | 1640, 1660, 3290 | 2.71 (3H, s, $CH_3$); 4.02 (2H, s, $SCH_2$); 6.98 br. s and 7.467 br. s (for 1H, $NH_2$); 7.07-7.79 (5H, m, Ph); 8.23 (1H, s, C(4)H); 10.30 (1H, br. s, NH) | 87 |

TABLE 1 (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|
| **5f** | $C_{24}H_{19}N_5O_2S_2$ | 60.97<br>60.86 | 4.04<br>4.05 | 14.89<br>14.78 | 13.64<br>13.55 | 218 subl. | 2225 | 1650,<br>1710,<br>3270 | 2.67 (6H, s, $SCH_3$ and 6-$CH_3$ methylthiopyridin-5-yl); 4.74 (2H, s, $SCH_2$); 7.07-7.79 (5H, m, Ph); 8.25 s and 8.86 s (for 1H, C(4)H pyridine); 10.29 (1H, br. s, NH) | 60 |
| **7a** | $C_{22}H_{16}BrN_3O_2S$ | 56.56<br>56.65 | 3.66<br>3.47 | 9.01<br>9.00 | 6.78<br>6.89 | 302-305 | 3400 | 1650,<br>1660,<br>3270 | 2.27 (3H, s, $CH_3$); 7.09-7.92 (9H, m, Ph and $C_6H_4$); 8.43 (2H, br. s, $NH_2$); 8.80 (1H, s, C(4)H); 10.45 (1H, br. s, NH) | 89 |
| **7b** | $C_{24}H_{19}N_5O_2S_2$ | 60.77<br>60.85 | 4.04<br>4.05 | 14.65<br>14.76 | 13.44<br>13.54 | 279-281 | 2210,<br>3400 | 1650,<br>3270 | 2.59 s, 2.61 s and 2.69 s (for 3H, $CH_3$); 7.07-7.74 (5H, m, Ph); 8.14 br. s and 8.81 br. s (for 1H, C(4)H pyridine); 8.45 (2H, br. s, $NH_2$); 10.44 (1H, br. s, NH) | 78 |
| **9a** | $C_{15}H_{13}N_3OSe$ | 54.45<br>54.56 | 3.87<br>3.96 | 12.72<br>12.73 | 23.81<br>23.90 | 202-204 | 2220 | 1640,<br>3290 | 2.57 (3H, s, $SeCH_3$); 2.66 (3H, s, $CH_3$); 7.09-7.72 (5H, m, Ph); 8.33 (1H, s, C(4)H); 10.43 (1H, br. s, NH) | 83 |
| **9b** | $C_{16}H_{15}N_3OSe$ | 55.92<br>55.80 | 4.39<br>4.40 | 12.11<br>12.23 | 22.84<br>22.93 | 135-137 | 2230 | 1660,<br>3290 | 1.50 (3H, t, $J$ = 6.9, $\underline{CH_3}CH_2$); 2.66 (3H, s, $CH_3$); 3.30 (2H, s, $CH_3\underline{CH_2}$); 7.12-7.72 (5H, m, Ph); 8.33 (1H, s, C(4)H); 10.43 (1H, br. s, NH) | 75 |
| **9c** | $C_{21}H_{17}N_3OSe$ | 62.07<br>62.06 | 4.12<br>4.23 | 11.34<br>11.33 | 19.53<br>19.44 | 184-186 | 2220 | 1680,<br>3300 | 2.73 (3H, s, $CH_3$); 4.62 (2H, s, $CH_2$); 7.02-7.79 (10H, m, $CH_2Ph$ and HNPh); 8.31 (1H, s, C(4)H); 10.42 (1H, br. s, NH) | 82 |

* EtOH for crystallization of **3**, DMF for other products.

The reaction of ethoxymethylenacetylacetanilide (**1**) with cyanothioacetamide (**2a**) in the presence of N-methylmorpholine in absolute ethanol at 25°C gave 3-cyano-6-methyl-5-phenylcarbamoylpyridine-2(1H)-thione (**3**) as indicated by the spectral data. The IR spectra of thione **3** has bands for stretching vibrations of a conjugated nitrile group in the vicinity of 2220 $cm^{-1}$, imino groups at 3200-3320 $cm^{-1}$, and carbonyl group in the vicinity of 1640 $cm^{-1}$. The $^1H$ NMR spectra show characteristic signals for protons of the methyl group at 2.54 ppm, phenyl group and pyridine C(4)H at 7.34-7.64 and 8.30 ppm, and NH protons of the carbamoyl fragment and pyridine ring at 10.30 and 14.27 ppm, respectively.

Alkylation of thione **3** by halides **4a-f** in DMF in the presence of an equimolar amount of KOH proceeds regioselectively, leading to the corresponding alkylthiopyridines **5a-f**. The use of aroylmethyl halides (**6a**) and hetaroylmethyl halides (**6b**) in the alkylation of thione **3** in the presence of a two-fold excess of KOH leads to 3-amino-2-aroyl- (**7a**) and 3-amino-2-hetaroyl-6-methyl-5-phenylcarbamoylthieno[2,3-*b*]pyridines (**7b**).

The reaction of **1** with cyanoselenoacetamide **2b** in the presence of base in absolute ethanol in an argon atmosphere did not yield 3-cyano-6-methyl-5-phenylcarbamoylpyridine-2(1H)-selenone (**8**) as a pure compound, probably due to the strong tendency of selenone **8** to undergo oxidation [11]. However, 2-alkylselenopyridines **9a-c** were obtained upon introducing alkyl halides **4a,d,f** into the reaction mixture. The structure of these products suggests the intermediate formation of selenone **8**.

The structures of **3, 5a-f, 7a,b,** and **9a-c** are in accord with their physico-chemical characteristics (Table 1).

## EXPERIMENTAL

The IR spectra were taken on an IKS-29 spectrometer for vaseline mulls. The $^1H$ NMR spectra were registered on a Bruker WP-100SY spectrometer at 100 MHz, Bruker AM-300 spectrometer for **5e** at 300.13 MHz, and Gemini-200 spectrometer for **5f, 7a,b** at 199.975 MHz for solutions in DMSO-$d_6$ with TMS as the internal standard. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol-254 plates with 3:5 acetone–heptane as the eluent and iodine vapor as the developer.

**3-Cyano-6-methyl-5-phenylcarbamoylpyridine-2(1H)-thione (3).** A mixture of ethoxyethylene **1** (10 g, 42.9 mmol), cyanothioacetamide **2a** (4.29 g, 42.9 mmol), and N-methylmorpholine (4.8 ml, 42.9 mmol) was stirred in absolute ethanol at 25°C for 2 h. The precipitate formed was filtered off and washed with absolute ethanol and hexane to give thione **3** (Table 1).

**2-Alkylthio-3-cyano-6-methyl-5-phenylcarbamoylpyridines (5a-f).** A sample of 10% aqueous KOH (2 ml, 3.7 mmol) was added with stirring to a suspension of thione **3** (1 g, 3.7 mmol) in DMF (10 ml). After 5 min, the corresponding alkyl halide **4a-f** (3.7 mmol) was added, and the mixture was stirred for 4 h. The precipitate formed was filtered off and washed with ethanol and hexane to give **5a-f** (Table 1)

**3-Amino-2-aroyl- (7a) and 3-amino-2-hetaroyl-6-methyl-5-phenylcarbamoylthieno[2,3-*b*]pyridines (7b).** A sample of 10% aqueous KOH (2 ml, 3.7 mmol) was added with stirring to a suspension of thione **3** (1 g, 3.7 mmol) in DMF (10 ml). After 5 min, the corresponding aroyl halide (**6a**) or hetaroyl halide (**6b**) (3.7 mmol) was added. After 0.5 h, another 10% aqueous KOH (2 ml) was added and the mixture was stirred for an additional 4 h. The precipitate formed was filtered off and washed with ethanol and hexane (Table 1).

**4-Alkylseleno-3-cyano-6-methyl-5-phenylcarbamoylpyridines (9a-c).** A mixture of ethoxyethylene **1** (2 g, 8.57 mmol), cyanoselenacetamide **2b** (1.3 g, 8.57 mmol), and N-methylmorpholine (0.96 ml, 8.57 mmol) in absolute ethanol was stirred for 2 h in an argon atmosphere at 25°C. Then, the corresponding alkyl halide **4a,d,f** (8.57 mmol) was added and the mixture was stirred for 4 h. The precipitate formed was separated and washed with ethanol and hexane to give **9a-c** (Table 1).

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