ONE-POT SYNTHESIS OF 2-ARYLIMINO-2,3-DIHYDROPYRIDO[3,2-e]-1,3-THIAZIN-4-ONES BY THE REACTION OF SECONDARY 2-CHLOROPYRIDINE-3-CARBOXAMIDES WITH ARYL ISOThIOCYANATES

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Abstract – A very facile method for the synthesis of 2-arylimino-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-ones has been developed. Thus, secondary 2-chloropyridine-3-carboxamides undergo addition to aromatic isothiocyanates in the presence of sodium hydride, followed by attack of the sulfur atom of the resulting adducts on the 2-position of the pyridine ring, to give the desired products in fair to good yields.

In a previous paper,¹ we reported a synthesis of 2-(2-imino-2,3-dihydropyrido[3,2-e]-1,3-thiazin-(Z)-4-ylidene)acetamide derivatives by means of a reaction of (Z)-3-amino-3-(2-chloro-6-methylpyridin-3-yl)propenamide derivatives with various isothiocyanates using sodium hydride as a base. As an extension of this work, we now wish to report a new method for the synthesis of 2-arylimino-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-ones (2) by a one-pot addition-cyclization sequence from the reaction of readily available secondary 2-chloropyridine-3-carboxamides (1) with aromatic isothiocyanates in the presence of sodium hydride. Some derivatives having the 2-imino-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-one skeleton have been reported to exhibit biological activity, for example, such as kainic acid neuronotoxicity inhibitory activity.² Their synthesis is based on a reaction of 2-chloropyridine-3-carboxyl chloride with ammonium isothiocyanate, followed by treatment with primary amines and $N_2$-alkylation. This procedure requires multiple steps, making it of limited use. Zawisza and Respond have reported a synthesis of this class of compounds by condensation of ethyl 2-chloropyridine-3-carboxylate with
1,3-dialkyl(aryl)thioureas. However, this method is of limited generality as well.

Four 2-chloropyridine-3-carboxamides (1), the starting materials of the present one-pot synthesis, could be prepared from commercially available 2-chloropyridine-3-carbonyl chloride: the reactions of the acid chloride with primary amines, such as benzylamine, ethylamine, isopropylamine, and aniline, gave the desired amides in almost quantitative yields. These amides could be transformed into 2-arylimino-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-ones (2) as illustrated in Scheme 1. Thus, the carboxamides (1) were treated with an equimolar amount of sodium hydride in DMF at 0 °C, and subsequently allowed to react with aromatic isothiocyanates. After being stirred at room temperature overnight, the aqueous workup followed by purification as described in the Experimental section afforded the desired 2-aryliminopyridothiazinones (2) in generally fair to good yields (Table 1). As can be seen in entry 11, we found that this transformation also works well with 2-chloro-N-phenylpyridine-3-carboxamide (1d) to afford the corresponding product (2k) in a yield equivalent to those using the N-alkylamides (1a-c). These reaction conditions were then applied to aliphatic isothiocyanates to obtain the respective 2-alkylimino derivatives, but similar treatment of 2-chloro-N-ethylpyridine-2-carboxamide (1b) with aliphatic isothiocyanates, such as ethyl isothiocyanate or cyclohexyl isothiocyanate, resulted in the formation of an intractable mixture of products in each case. We have no explicit explanation of the reason for this.

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\text{Scheme 1}
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The cyclization of the intermediate adduct (3) may take place either at the sulfur or at the nitrogen to give 2-iminopyridothiazin-4-one (2) or 2-thioxopyridopyrimidin-4-one (4) structures, respectively, as shown in Scheme 2. The product was, however, found to be an exclusively iminopyridothiazinone (2) and no thioxopyridopyrimidinone (4) was detected. The assignment of the iminopyridothiazinone structure is based on $^{13}$C NMR analyses; the signal assignable to the imino carbon appears at around $\delta$ 159. This excludes the thioxopyridopyrimidinone structure, of which $^{13}$C NMR should reveal a signal due to the thioxo carbon at around $\delta$ 190. The stereochemistry of the arylimino moiety of 2 was tentatively
determined to be Z, as no NOE was observed between the 2-arylimono and the 3-alkyl or aryl protons.

**Table 1. Preparation of Iminopyridothiazinone Derivatives (2)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>Ar</th>
<th>2 (Yield/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>m-Tol</td>
<td>2a (61)</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2-MeOC₆H₄</td>
<td>2b (60)</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>m-Tol</td>
<td>2c (69)</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>2-ClC₆H₄</td>
<td>2d (57)</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>4-BrC₆H₄</td>
<td>2e (68)</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>2-MeOC₆H₄</td>
<td>2f (84)</td>
</tr>
<tr>
<td>7</td>
<td>1c</td>
<td>m-Tol</td>
<td>2g (74)</td>
</tr>
<tr>
<td>8</td>
<td>1c</td>
<td>2-ClC₆H₄</td>
<td>2h (61)</td>
</tr>
<tr>
<td>9</td>
<td>1c</td>
<td>4-BrC₆H₄</td>
<td>2i (72)</td>
</tr>
<tr>
<td>10</td>
<td>1c</td>
<td>2-MeOC₆H₄</td>
<td>2j (62)</td>
</tr>
<tr>
<td>11</td>
<td>1d</td>
<td>Ph</td>
<td>2k (57)</td>
</tr>
</tbody>
</table>

*a*Isolated yields.

![Scheme 2](image)

In summary, we have developed a convenient one-pot method for the synthesis of 2-arylimino-2,3-dihydropyrido[2,3-e]-1,3-thiazin-4-ones under mild conditions. The present method may be of use in organic synthesis, because it has advantages over the previous method in the readily availability of the starting materials and the easiness of operations.

**EXPERIMENTAL**

**General.** All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ¹H NMR spectra were determined in CDCl₃ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. The ¹³C NMR spectra were determined in CDCl₃ using TMS.
as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF₅0₄. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

**Starting Materials.** 2-Chloropyridine-3-carboxamide derivatives 1a, 1b, 1c, and 1d were prepared by treating 2-chloropyridine-3-carbonyl chloride with appropriate primary amines. All other chemicals used in this study were commercially available.

**Typical Procedure for the Preparation of Dihydropyridothiazinones (2).** 2-(3-Methylphenylimino)-3-phenylmethyl-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-one (2a). To a stirred suspension of NaH (60% in oil; 20 mg, 0.50 mmol) in DMF (0.75 mL) at 0 °C was added dropwise a solution of 1a (0.12 g, 0.50 mmol) in DMF (0.75 mL). After the evolution of H₂ gas had ceased, 3-methylphenyl isothiocyanate (75 mg, 0.50 mmol) was added. After stirring at rt overnight, water (20 mL) was added. The precipitate was collected by suction, and recrystallized from hexane to give 2a as a pale-yellow solid; yield: 0.11 g (61%); mp 178–181 °C; IR (KBr) 1690, 1599 cm⁻¹; ¹H NMR δ 2.43 (s, 3H), 5.93 (s, 2H), 7.04–7.06 (m, 2H), 7.23–7.33 (m, 5H), 7.46 (dd, J = 7.8, 7.3 Hz, 1H), 7.55 (d, J = 7.3 Hz, 2H), 8.53 (dd, J = 7.8, 1.8 Hz, 1H), 8.57 (dd, J = 4.6, 1.8 Hz, 1H); ¹³C NMR δ 21.47, 50.94, 112.30, 120.22, 125.95, 127.58, 128.33, 128.60, 129.43, 129.53, 129.69, 136.12, 137.81, 139.74, 140.83, 152.17, 154.75, 159.54, 179.26; MS m/z 359 (100, [M⁺]). Anal. Calcd for C₂₅H₁₇N₃OS: C, 70.17; H, 4.77; N, 11.69. Found: C, 70.02; H, 4.80; N, 11.90.

2-(2-Methoxyphenylimino)-3-phenylmethyl-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-one (2b): a pale-yellow solid; mp 209–212 °C (hexane–CH₂Cl₂); IR (KBr) 1693, 1597 cm⁻¹; ¹H NMR δ 3.76 (s, 3H), 5.95 (d, J = 14.2 Hz, 1H), 5.96 (d, J = 14.2 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.24 (td, J = 7.8, 0.9 Hz, 1H), 7.22–7.27 (m, 3H), 7.31 (t, J = 7.3 Hz, 2H), 7.50 (td, J = 7.3, 1.8 Hz, 1H), 7.53 (d, J = 7.3 Hz, 2H), 8.50 (dd, J = 7.8, 1.8 Hz, 1H), 8.55 (dd, J = 4.6, 1.8 Hz, 1H); MS m/z 375 (24, [M⁺]), 344 (100). Anal. Calcd for C₂₃H₁₇N₃O₃S: C, 67.18; H, 4.56; N, 11.19. Found: C, 67.00; H, 4.67; N, 11.06.

3-Ethyl-2-(3-methylphenylimino)-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-one (2c): a white solid; mp 210–213 °C (hexane–CH₂Cl₂); IR (KBr) 1681, 1596 cm⁻¹; ¹H NMR δ 1.41 (t, J = 7.3 Hz, 3H), 2.44 (s, 3H), 4.73 (q, J = 7.3 Hz, 2H), 7.05–7.07 (m, 2H), 7.25 (dd, J = 7.8, 4.6 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 7.8 Hz, 1H), 8.53 (dd, J = 7.8, 1.8 Hz, 1H), 8.56 (dd, J = 4.6, 1.8 Hz, 1H); MS m/z 297 (89, [M⁺]), 296 (100). Anal. Calcd for C₁₈H₁₅N₃O₃S: C, 64.62; H, 5.08; N, 14.13. Found: C, 63.58; H, 5.15; N, 14.06.

2-(2-Chlorophenylimino)-3-ethyl-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-one (2d): a white solid; mp 222–225 °C (hexane–CH₂Cl₂); IR (KBr) 1686, 1601 cm⁻¹; ¹H NMR δ 1.41 (t, J = 7.3 Hz, 3H), 4.68–4.78 (m, 2H), 7.26–7.29 (m, 1H), 7.33–7.37 (m, 1H), 7.47–7.50 (m, 2H), 7.59–7.62 (m, 1H), 8.53–8.55 (m,
2H); MS m/z 317 (0.7, [M⁺]), 282 (100). Anal. Calcd for C₁₅H₁₂ClN₃OS: C, 56.69; H, 3.81; N, 13.22. Found: C, 56.56; H, 3.76; N, 13.24.

2-(4-Bromophenylimino)-3-ethyl-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-one (2e): a white solid; mp 235–238 °C (hexane–CH₂Cl₂); IR (KBr) 1680, 1595 cm⁻¹; ¹H NMR δ 1.40 (t, J = 6.9 Hz, 3H), 4.71 (q, J = 6.9 Hz, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.27 (dd, J = 7.3, 5.0 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 8.53–8.54 (2H, m); ¹³C NMR δ 11.77, 43.79, 112.39, 120.42, 122.83, 130.83, 133.07, 137.79, 139.70, 151.88, 154.44, 158.91, 178.42; MS m/z 361 (100, [M⁺]). Anal. Calcd for C₁₅H₁₂BrN₃OS: C, 49.73; H, 3.34; N, 11.60. Found: C, 49.36; H, 3.17; N, 11.48.

3-Ethyl-2-(2-methoxyphenylimino)-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-one (2f): a white solid; mp 225–228 °C (hexane–CH₂Cl₂); IR (KBr) 1687, 1597 cm⁻¹; ¹H NMR δ 1.41 (t, J = 6.9 Hz, 3H), 3.75 (s, 3H), 4.68–4.79 (m, 2H), 7.11 (dd, J = 8.2, 1.4 Hz, 1H), 7.15 (dd, J = 7.8, 7.3, 1.4 Hz, 1H), 7.22 (dd, J = 7.8, 1.8 Hz, 1H), 7.24 (dd, J = 7.8, 5.0 Hz, 1H), 7.52 (dd, J = 8.2, 7.3, 1.4 Hz, 1H), 8.52 (dd, J = 7.8, 2.3 Hz, 1H), 8.55 (dd, J = 5.0, 2.3 Hz, 1H); ¹³C NMR δ 11.85, 43.79, 55.93, 112.30, 112.60, 120.12, 121.22, 129.40, 130.04, 130.40, 137.53, 151.81, 154.68, 154.82, 159.28, 178.37; MS m/z 313 (22, [M⁺]). Anal. Calcd for C₁₆H₁₅N₃O₂S: C, 61.32; H, 4.82; N, 13.41. Found: C, 61.00; H, 4.70; N, 13.65.

3-(1-Methylethyl)-2-(3-methylphenylimino)-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-one (2g): a white solid; mp 193–196 °C (hexane–CH₂Cl₂); IR (KBr) 1692, 1599 cm⁻¹; ¹H NMR δ 1.63 (d, J = 6.9 Hz, 6H), 2.44 (s, 3H), 6.28 (sept, J = 6.9 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H), 7.06 (s, 1H), 7.24 (dd, J = 7.8, 4.6 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 8.48 (dd, J = 7.8, 1.8 Hz, 1H), 8.54 (dd, J = 4.6, 1.8 Hz, 1H); ¹³C NMR δ 18.78, 21.48, 55.79, 113.30, 120.21, 125.89, 129.40, 129.45, 129.57, 137.26, 139.71, 141.22, 151.93, 154.32, 159.35, 180.08; MS m/z 311 (100, [M⁺]). Anal. Calcd for C₁₇H₁₇N₃OS: C, 65.57; H, 5.50; N, 13.49. Found: C, 65.72; H, 5.42; N, 13.60.

2-(2-Chlorophenylimino)-3-(1-methylethyl)-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-one (2h): a white solid; mp 189–191 °C (hexane–CH₂Cl₂); IR (KBr) 1684, 1605, 1593 cm⁻¹; ¹H NMR δ 1.64 (d, J = 6.9 Hz, 6H), 6.25 (sept, J = 6.9 Hz, 1H), 7.26 (dd, J = 7.8, 5.0 Hz, 1H), 7.34 (d, J = 6.9, 2.3 Hz, 1H), 7.46–7.49 (m, 2H), 7.60 (dd, J = 6.9, 2.3 Hz, 1H), 8.50 (dd, J = 7.8, 1.8 Hz, 1H), 8.51 (dd, J = 5.0, 1.8 Hz, 1H); MS m/z 331 (0.8, [M⁺]), 296 (100). Anal. Calcd for C₁₆H₁₄ClN₃OS: C, 57.91; H, 5.50; N, 13.49. Found: C, 57.89; H, 3.95; N, 13.26.

2-(4-Bromophenylimino)-3-(1-methylethyl)-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-one (2i): a white solid; mp 241–244 °C (hexane–CH₂Cl₂); IR (KBr) 1693, 1595 cm⁻¹; ¹H NMR δ 1.64 (d, J = 6.9 Hz, 6H), 6.23 (sept, J = 6.9 Hz, 1H), 7.12 (d, J = 8.7 Hz, 2H), 7.26 (dd, J = 7.8, 5.0 Hz, 1H), 7.34 (d, J = 6.9, 2.3 Hz, 1H), 7.46–7.49 (m, 2H), 8.49 (dd, J = 7.8, 1.8 Hz, 1H), 8.52 (dd, J = 5.0, 1.8 Hz, 1H); ¹³C NMR δ 18.77, 55.89, 113.36, 12036, 122.70, 130.75, 133.04, 137.45, 140.24, 151.70, 154.17, 159.17, 179.86; MS m/z 375 (100, [M⁺]). Anal. Calcd for C₁₆H₁₄BrN₃OS: C, 50.82; H, 3.58; N, 11.08.

2-(2-Methoxyphenylimino)-3-(1-methylethyl)-2,3-dihydropyrido[3,2-e]-1,3-thiazin-4-one (2j): a
white solid; mp 218–221 °C (hexane–CH$_2$Cl$_2$); IR (KBr): 1681, 1604, 1593 cm$^{-1}$; $^1$H NMR δ 1.63 (d, $J$ = 6.9 Hz, 3H), 1.64 (d, $J$ = 6.9 Hz, 3H), 3.75 (s, 3H), 6.28 (sept, $J$ = 6.9 Hz, 1H), 7.10 (dd, $J$ = 7.8, 1.4 Hz, 1H), 7.15 (dd, $J$ = 7.8, 7.3, 1.4 Hz, 1H), 7.21 (dd, $J$ = 7.8, 1.8 Hz, 1H), 7.23 (dd, $J$ = 7.8, 5.0 Hz, 1H), 7.51 (ddd, $J$ = 7.8, 7.3, 1.8 Hz, 1H), 8.47 (dd, $J$ = 7.8, 1.8 Hz, 1H), 8.52 (dd, $J$ = 5.0, 1.8 Hz, 1H); MS m/z 327 (27, [M$^+$]), 296 (60), 254 (100).

Anal. Calcd for C$_{17}$H$_{17}$N$_3$O$_2$S: C, 62.36; H, 5.23; N, 12.83. Found: C, 62.36; H, 5.09; N, 12.85.

3-Pheny-2-phenylimino-2,3-dihydropyrido[3,2-e]1,3-thiazin-4-one (2k): a pale-yellow solid; mp 287–289 °C (hexane–CH$_2$Cl$_2$); IR (KBr) 1705, 1599 cm$^{-1}$; $^1$H NMR δ 7.27–7.30 (m, 3H), 7.33 (d, $J$ = 7.3 Hz, 2H), 7.47 (t, $J$ = 7.3 Hz, 1H), 7.51–7.60 (m, 5H), 8.55 (dd, $J$ = 7.8, 1.8 Hz, 1H), 8.60 (dd, $J$ = 4.6, 1.8 Hz, 1H); $^{13}$C NMR δ 112.95, 120.19, 128.35, 128.82, 128.85, 129.05, 129.65, 129.73, 137.97, 139.45, 140.39, 152.60, 154.80, 159.57, 179.63; MS m/z 331 (100, [M$^+$]). Anal. Calcd for C$_{19}$H$_{13}$N$_3$OS: C, 68.86; H, 3.95; N, 12.68. Found: C, 68.82; H, 4.00; N, 12.39.

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REFERENCES