Synthesis of 2-(2-Imino-2,3-dihydropyrido[3,2-e]-1,3-thiazin-(Z)-4-ylidene)acetamide Derivatives

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Abstract: A facile two-step preparation of the title pyridothiazine derivatives starting from commercially available 2-chloro-6-methylpyridine-3-carbonitrile is described. The reaction of this nitrile with magnesium enolates of tertiary acetamides affords (Z)-3-amino-3-(2-chloro-6-methylpyridin-3-yl)propenamide derivatives, which in turn are allowed to react with isothiocyanates in the presence of sodium hydride to give the desired products in satisfactory yields.

Key words: amides, cyclizations, heterocycles, imines, pyridines

We recently reported a convenient method to prepare (Z)-2-(2-oxo-2,3-dihydropyrido[2,3-d]pyrimidin-4(1H)-ylidene)acetamide derivatives.1 This synthesis was based on the reaction of (Z)-3-amino-3-(2-chloro-6-methylpyridin-3-yl)propenamide derivatives 1 with aryl isocyanates to give the dianionic intermediates 2. Attack of nitrogen on the 2-position of the pyridine ring afforded the pyridothiazine derivatives 3, as shown in Scheme 1. Thus, the enaminoo amides 1 were treated with 2 molar amounts of sodium hydride in DMF at 0 °C. The mixture was then allowed to react with a range of isothiocyanates to give the dianionic intermediates 2. Attack of the sulfur atom on the 2-position of the pyridine ring afforded the pyridothiazine derivatives 3, after the usual aqueous workup followed by purification using column chromatography on silica gel, in fair to good yields (Table 1). We were unable to detect the presence any trace amounts of 2-(2-thioxopyrido[2,3-d]pyrimidin-4-ylidene)acetamide derivatives 4, the products arising from the attack of nitrogen on the 2-position of the pyridine ring. The 13C NMR spectra of the products 3 showed signals at about δ = 165, assignable to imine carbons, and no signals at about δ = 200, which would be for thiocarbonyl carbons of the compounds 4. The stereochemistry of the 4-ylidene moiety of the products 3 was assigned to be Z. The Z-preference is ascribed to intramolecular hydrogen bonding between the H-3 of pyridothiazine ring and the amide carbonyl. NOE experiments were carried out to confirm the stereochemistry of compound 3a. Thus, irradiation of

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the signal at δ = 5.68, assignable to the vinyl proton, resulted in an enhancement (9.2%) of the signal at 7.86, assignable to the H-5 of the pyridothiazine ring. Although one of the possible stereoisomers was obtained as a sole product in each reaction, the stereochemistry of the 2-imino moiety was not yet clarified.

The reactions using aliphatic isothiocyanates having δ-hydrogen(s) (entries 4–6, 9, and 10) also successfully proceeded and the desired products were obtained in the yields comparable to those using aromatic isothiocyanates (entries 1–3, 7, 8, and 11). The use of the respective enamino tert-butyl ester in place of the enamino amides 1 resulted in the formation of intractable mixtures of products; however, we have no explanation for this.

The use of two molar amounts of sodium hydride is essential for the satisfactory production of the desired products. For example, the reaction of 1a with phenyl isothiocyanate using an equimolar amount of sodium hydride gave only rather decreased yield (26%) of the product 2a, and a considerable amount of the starting material was recovered. The necessity of two molar amounts of sodium hydride can be explained by the formation of the di-anionic intermediate 2 as stated for the preparation of (Z)-2-(2-oxo-2,3-dihydropyrido[2,3-d]pyrimidin-4(1H)-ylidene)acetamide derivatives in the previous paper.1

In conclusion, we have developed a simple procedure for the preparation of the novel pyridothiazine derivatives. The present method may be valuable for organic synthesis because of the ready availability of the starting materials as well as the ease of operations.

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 or a JEOL LA-400 FT NMR spectrometer operating at 400 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 were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF 254. 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.

3-Amino-3-(2-chloro-6-methylpyridin-3-yl)acetamide derivatives 1a and 1b were prepared according to the procedure previously reported by us.1 All other chemicals used in this study were commercially available.

(Z)-3-Amino-3-(2-chloro-6-methylpyridin-3-yl)-1-(pyrroldin-1-yl)propenone (1c)

This compound was prepared from 2-chloro-6-methylpyridine-3-carbonitrile and 1-acetylpyrrolidine by our previously reported procedure; yield: 64%; yellow oil; Rf = 0.41 (1:2 THF–C6H6).

IR (neat): 3375, 3273, 3184, 1616 cm⁻¹.

1H NMR (500 MHz, CDCl3): δ = 1.84–1.95 (m, 4 H), 2.57 (s, 3 H), 3.37–3.43 (m, 2 H), 3.49–3.56 (m, 2 H), 4.74 (s, 1 H), 6.2–6.9 (br, 2 H), 7.13 (d, J = 7.8 Hz, 1 H), 7.62 (d, J = 7.8 Hz, 1 H).


A,N-Dimethyl-2-[7-methyl-2-(3-methylphenyl)imino-2,3-dihydropyrido[3,2-e]-1,3-thiazin-(Z)-4-ylidene]acetamide (3a); Typical Procedure

To a stirred suspension of NaH (60% in oil; 23 mg, 0.58 mmol) in DMF (2 mL) at 0 °C was added dropwise a solution of 1a (68 mg, 0.29 mmol) in DMF (2 mL). After 15 min, PhNCS (39 mg, 0.29 mmol) was added, and the stirring was continued for an additional 1 h at the same temperature. Sat. aq NH4Cl (10 mL) was added, and the organic materials were extracted with CH2Cl2 (3 × 10 mL). The combined extracts were washed with H2O (3 × 10 mL) and brine (10 mL), and then dried (Na2SO4). Evaporation of solvent gave a residue, which was purified by column chromatography on silica gel (1:2 EtOAc–hexane) to afford 3a.

Yellow solid; yield: 70 mg (72%); mp 221–223 °C (dec.) (hexane–CH2Cl2).

IR (KBr): 3452, 3160, 1605 cm⁻¹.

1H NMR (500 MHz, CDCl3): δ = 2.30 (s, 3 H), 3.06 (br s, 3 H), 3.15 (br s, 3 H), 5.68 (s, 1 H), 6.93 (d, J = 8.2 Hz, 1 H), 7.23 (dd, J = 7.3, 1.4 Hz, 1 H), 7.45 (t, J = 7.3, 1.4 Hz, 1 H), 7.50 (t, J = 7.3 Hz, 2 H), 7.86 (d, J = 8.2 Hz, 1 H), 14.07 (br s, 1 H).

13C NMR (125 MHz, CDCl3): δ = 24.66, 82.01, 109.86, 119.38, 128.17, 128.30, 129.00, 129.46, 131.80, 139.89, 142.28, 149.16, 161.98, 168.50, 175.63.

MS (EL, 70 eV): m/z (%) = 338 (45, [M+]), 292 (100).

Anal. Calcd for C14H14N2O2S: C, 63.88; H, 5.36; N, 16.56; S, 9.47. Found: C, 63.87; H, 5.40; N, 16.77; S, 9.42.

A,N-Dimethyl-2-[7-methyl-2-(3-methylphenyl)imino-2,3-dihydropyrido[3,2-e]-1,3-thiazin-(Z)-4-ylidene]acetamide (3b)

Pale-yellow solid; mp 215 °C (dec.) (hexane–CH2Cl2).

IR (KBr): 3310, 1630, 1605 cm⁻¹.

1H NMR (500 MHz, CDCl3): δ = 2.32 (s, 3 H), 2.41 (s, 3 H), 3.06 (br s, 3 H), 3.15 (br s, 3 H), 5.67 (s, 1 H), 6.92 (d, J = 7.9 Hz, 1 H), 7.03 (d, J = 7.9 Hz, 1 H), 7.04 (s, 1 H), 7.25 (d, J = 7.9 Hz, 1 H), 7.38 (t, J = 7.9 Hz, 1 H), 7.85 (d, J = 7.9 Hz, 1 H), 14.02 (s, 1 H).

Table 1

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<td>1a</td>
<td>3-Tol</td>
<td>3b (71)</td>
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<td>4-BrC6H4</td>
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<td>Bn</td>
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<td>11</td>
<td>1c</td>
<td>Ph</td>
<td>3k (73)</td>
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</table>

a Isolated yield.
2-(1,3-Thiazin-4-ylidene)-5-methyl-2-(2-methylpyridin-4-ylidenemethoxy)methyl-2,3-dihydropyridine (3h)
Pale-yellow solid; mp 262–263 °C (dec.) (hexane–CH2Cl2).

IR (KBr): 3348, 1628, 1605 cm⁻¹.

1H NMR (400 MHz, CDCl3); δ = 2.32 (s, 3 H), 2.75 (s, 3 H), 3.04 (br s, 3 H), 3.11 (br s, 3 H), 4.81 (d, J = 7.3 Hz, 2 H), 5.57 (s, 1 H), 6.93 (d, J = 8.2 Hz, 1 H), 7.73 (d, J = 7.3 Hz, 2 H), 7.82 (d, J = 7.9 Hz, 1 H), 13.81 (br s, 1 H).

MS (EI, 70 eV); m/z (%) = 394 (M⁺, 100). Anal. Calcd for C21H22N4OS: C, 63.94; H, 5.62; N, 14.20; S, 9.60. Found: C, 63.75; H, 5.52; N, 14.08; S, 8.40.

2-(2-Ethyl-1,3-thiazin-4-ylidene)-5-methyl-2-(2-(3-carboxybutyrylamino)pyridin-4-ylidenemethoxy)methyl-2,3-dihydropyridine (3i)
Pale-yellow solid; mp 262–263 °C (dec.) (hexane–CH2Cl2).

IR (KBr): 3348, 1628, 1605 cm⁻¹.

1H NMR (400 MHz, CDCl3); δ = 2.75 (s, 3 H), 2.75–2.77 (m, 1 H), 3.04 (br s, 3 H), 3.10 (br s, 3 H), 5.53 (s, 1 H), 5.93–5.98 (m, 1 H), 6.93 (d, J = 8.2 Hz, 1 H), 7.79 (d, J = 8.2 Hz, 1 H), 13.81 (br s, 1 H).

13C NMR (125 MHz, CDCl3); δ = 34.27, 25.71, 26.64 (2 C), 29.21, 80.76, 111.25, 119.01, 131.94, 142.18, 147.99, 155.50, 160.59, 168.64, 175.79.

MS (EI, 70 eV); m/z (%) = 344 (M⁺, 100). Anal. Calcd for C21H22N4OS: C, 63.94; H, 5.62; N, 14.20; S, 9.60. Found: C, 63.75; H, 5.52; N, 14.08; S, 8.40.
Anal. Calcd for C_{20}H_{20}N_4OS: C, 65.91; H, 5.53; N, 15.37; S, 8.80.  
Found: C, 65.65; H, 5.61; N, 15.14; S, 8.53.

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References


