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SYNTHESIS OF THIENO[2,3-*b*]PYRIDINYL-4H-3,1-BENZOXAZIN-4-ONE DERIVATIVES

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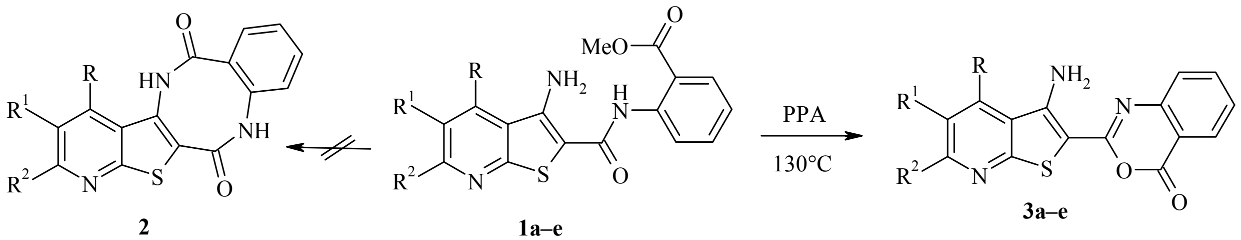
3-Aminothieno[2,3-*b*]pyridine amides have held interest for many years in the study of intramolecular cyclizations and the formation of polycyclic condensed and conjugated systems. Thieno[2,3-*b*]pyridine aminoamides obtained from natural α-amino acids readily undergo intramolecular cyclization upon heating to give condensed pyridothieno[1,4]diazepines [1]. We have shown that the direction of the intramolecular cyclization of α-amino acid derivatives depends on the reaction conditions and may lead to the formation of derivatives of 1,4-diazepine ($H_3PO_4/MeCO_2H$ or PPA), oxazine (PPA), and oxazole (Ac_2O) [3].

3-Amino-N-(2-methoxycarbonyl)phenylthieno[2,3-*b*]pyridinecarboxamides **1** were synthesized in our work using our previously reported method [3] and the transformations of these compounds in PPA were studied.



1–3 a R = R^2 = Me, R^1 = H, **b** R = MeOCH$_2$, R^1 = H, R^2 = Me, **c** R = Me, R^1 = Br, R^2 = Me, **d** R = 5-methylfur-2-yl, R^1 = H, R^2 = Ph, **e** R = 4-BrC$_6$H$_4$, R^1 = H, R^2 = Ph

Heating aminoamides **1a-e** does not lead to conversion into the expected oxazocinediones **2**, which are the products of cyclization involving the ester and amino groups, but rather gives brightly colored benzoxazinones **3a-e** in yields from 52 to 75%. In this case, the indicated tautomeric form of amide **1** likely takes part in the cyclization, while formation of the oxazine ring proceeds similarly to the Erlenmeyer azlactone synthesis.

The ^{1}H NMR spectra were taken on a Bruker DRX500 spectrometer at 500 MHz spectrometer in DMSO-d$_6$ with TMS as the internal standard. The electron impact mass spectra were taken on an MAT-112 mass spectrometer with direct introduction of the sample into the ion source at 70 eV.

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Synthesis of benzoxazinones 3a-e (General Method). Finely ground aminoamide **1a-e** (2 mmol) was added to PPA [4] (5 g) and heated with stirring until foaming of the reaction mixture ceases taking care that the reaction temperature does not exceed 130°C. The cooled mixture was diluted with 150 ml ice water and brought to pH ~7-8 by adding 10% aqueous NaOH. The precipitate formed was filtered off, washed with ice water, dried in the air, and recrystallized from DMF to give **3** as brightly colored crystals.

2-(3-Amino-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)-4H-3,1-benzoxazin-4-one (3a) was obtained in 74% yield as bright-yellow crystals; mp >280°C (dec.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (3H, s, CH_3); 2.75 (3H, s, CH_3), 7.04 (1H, s, H-5 pyridine); 7.43 (1H, dd, *J* = 7.5, *J* = 7.6, H arom); 7.52-7.58 (3H, m, NH_2+H arom); 7.87 (1H, dd, *J* = 7.6, *J* = 7.8, H arom); 8.05 (1H, d, *J* = 7.8, H arom). Mass spectrum, *m/z* (I_{rel}, %): 323 $[M]^+$ (100), 306 (18), 295 (12), 281 (25), 280 (18), 205 (21), 204 (10), 177 (18), 176 (13), 150 (11), 146 (14), 132 (32), 120 (25), 104 (13), 102 (11). Found, %: C 63.19; H 4.00; N 13.03. $C_{17}H_{13}N_3O_2S$. Calculated, %: C 63.14; H 4.05; N 12.99.

2-(3-Amino-4-methoxymethyl-6-methylthieno[2,3-*b*]pyridin-2-yl)-4H-3,1-benzoxazin-4-one (3b) was obtained in 68% yield as yellow crystals; mp 251-253°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.58 (3H, s, CH_3); 3.42 (3H, s, $CH_2OC\underline{H}_3$); 4.87 (2H, s, $C\underline{H}_2OCH_3$); 7.27 (1H, s, H-5 pyridine); 7.45 (1H, dd, *J* = 7.9, *J* = 7.3, H arom); 7.63 (1H, d, *J* = 7.9, H arom); 7.72 (2H, s, NH_2); 7.87 (1H, dd, *J* = 7.3, *J* = 7.8, H arom); 8.05 (1H, d, *J* = 7.8, H arom). Mass spectrum, *m/z* (I_{rel}, %): 353 $[M]^+$ (100), 340 (10), 339 (15), 338 (67), 331 (27), 290 (12), 289 (13), 219 (21), 210 (12), 175 (20), 163 (16), 146 (48), 120 (88), 105 (15), 101 (11). Found, %: C 61.26; H 4.21; N 11.97. $C_{18}H_{15}N_3O_3S$. Calculated, %: C 61.18; H 4.28; N 11.89.

3-(2-Amino-5-bromo-4,6-dimethylthieno[2,3-*b*]pyridin-2-yl)-4H-3,1-benzoxazin-4-one (3c) was obtained in 75% yield as bright-yellow needles; mp 325-326 C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.66 (3H, s, CH_3); 2.86 (3H, s, CH_3); 7.42 (1H, dd, *J* = 7.3, *J* = 7.5, H arom); 7.52-7.59 (3H, m, NH_2+H arom); 7.83 (1H, dd, *J* = 7.5, *J* = 7.8, H arom); 7.99 (1H, d, *J* = 7.8, H arom). Mass spectrum, *m/z* (I_{rel}, %): 402 $[M]^+$ (7.1), 401 (25), 175 (10), 148 (15), 146 (52), 132 (36), 131 (16), 120 (35), 119 (17), 104 (22), 102 (13). Found, %: C 50.68; H 3.06; N 10.50. $C_{17}H_{12}BrN_3O_2S$. Calculated, %: C 50.76; H 3.01; N 10.45.

2-[Amino-4-(2-furyl-5-methyl)-6-phenylthieno[2,3-*b*]pyridin-2-yl]-4H-3,1-benzoxazin-4-one (3d) was obtained in 52% yield as dark-red crystals; mp 275-277°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.52 (3H, s, CH_3); 6.48 (1H, d, *J* = 3.3, H-4 furyl); 7.31 (1H, d, *J* = 3.3, H-3 furyl); 7.46 (1H, dd, *J* = 7.8, *J* = 7.3, H arom); 7.50-7.57 (3H, m, NH_2+H arom); 7.61-7.65 (3H, m, H phenyl); 7.87 (1H, dd, *J* = 7.3, *J* = 7.8, H arom); 8.02 (1H, s, H-5 pyridine); 8.06 (1H, d, *J* = 7.8, H arom); 8.21-8.25 (2H, m, H phenyl). Mass spectrum, *m/z* (I_{rel}, %): 451 $[M]^+$ (6), 305 (15), 290 (12), 289 (14), 263 (13), 262 (24), 261 (57), 260 (19), 233 (11), 229 (15), 218 (12), 217 (15), 216 (17), 204 (11), 203 (14), 191 (10), 190 (30), 165 (12), 164 (15), 152 (13), 146 (100), 132 (17), 120 (54), 119 (14). Found, %: C 69.26; H 3.88; N 9.37. $C_{26}H_{17}N_3O_3S$. Calculated, %: C 69.17; H 3.79; N 9.31.

2-[Amino-4-(4-bromophenyl)-6-phenylthieno[1,2-*b*]pyridin-2-yl]-4H-3,1-benzoxazin-4-one (3e) was obtained in 70% yield as dark-orange crystals; mp >320°C (dec.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.60 (2H, br. s, NH_2); 7.44-7.64 (7H, m, H arom); 7.81-7.85 (4H, m, H-5 pyridine + 3H arom); 8.06 (1H, dd, *J* =7.3, *J* = 7.5, H arom); 8.21-8.26 (2H, m, H arom). Mass spectrum, *m/z* (I_{rel}, %): 526 $[M]^+$ (1.3), 227 (12), 146 (100), 132 (26), 120 (64), 119 (26), 102 (13). Found, %: C 61.68; H 2.98, N 8.06. $C_{27}H_{16}BrN_3O_2S$. Calculated, %: C 61.61; H 3.06; N 7.98.

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