Synthesis of substituted benzoxazinylthieno[2,3-*b*]pyridines by the reaction of (3-cyanopyridin-2-ylthio)acetic acids or their amides with *o*-aminophenyl(diphenyl)carbinol

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A general method for the synthesis of 3-amino-2-(4,4-diphenyl-4*H*-3,1-benzoxazin-2-yl)thieno[2,3-*b*]pyridines was proposed. The method involves reactions of (3-cyanopyridin-2-ylthio)acetic acids or their amides with *o*-aminophenyl(diphenyl)carbinol in nitromethane in the presence of perchloric acid followed by neutralization of the resulting salts.

Key words: (3-cyanopyridin-2-ylthio)acetic acid, (3-cyanopyridin-2-ylthio)acetamide, *o*-aminophenyl(diphenyl)carbinol, 4,4-diphenyl-4*H*-3,1-benzoxazine, 3-amino-2-(4,4-diphenyl-4*H*-3,1-benzoxazin-2-yl)thieno[2,3-*b*]pyridine.

It is known[1,2] that acylation of *o*-aminophenyl(diphenyl)carbinol with organic acids and their halides and anhydrides in the presence of mineral or Lewis acids affords 4,4-diphenyl-4*H*-3,1-benzoxazinium salts. At the same time, 2-alkylthio-3-cyanopyridines with a reactive methylene group at the S atom undergo Thorpe—Ziegler cyclization into the corresponding thieno[2,3-*b*]pyridines in the presence of both acids and bases.[3,4]

We developed a novel method for the synthesis of 3-amino-2-(4,4-diphenyl-4*H*-3,1-benzoxazin-2-yl)thieno[2,3-*b*]pyridines **1a—c** by reactions of *o*-aminophenyl(diphenyl)carbinol (APC, **2**) with (3-cyanopyridin-2-ylthio)acetic acids **3a,b** (procedure *A*) or their amides **3c—e** (procedure *B*) in nitromethane in the presence of $HClO_4$ followed by neutralization of the resulting perchlorates (Scheme 1, Table 1).

Note that the reactions of both acids **3a,b** and the corresponding amides **3c,e** afford the same products **1a,c**. Neither attempts at cyclization of (3-cyanopyridin-2-ylthio)acetic acids **3** into 3-aminothieno[2,3-*b*]pyridine-2-carboxylic acids **4** in nitromethane in the presence of $HClO_4$ nor use of acids **4** in reactions with APC under

Table 1. Physicochemical characteristics of 3-amino-2-(4,4-diphenyl-4*H*-3,1-benzoxazin-2-yl)thieno[2,3-*b*]pyridines (**1a—c**)

Compound	Yield* (%)	M.p. /°C	Found / Calculated (%)			Molecular formula	UV, λ_{max}/nm (log ε)	^{1}H NMR, δ
			C	H	N			
1a	64 (*A*), 65 (*B*), 76 (*C*)	266—267	72.94 / 72.97	5.11 / 5.14	10.18 / 10.21	$C_{25}H_{21}N_3OS$	220 (4.61), 322 (4.26), 418 (4.17)	2.53, 2.75 (both s, 3 H each, 6-Me, 4-Me); 6.63—7.37 (m, 16 H, Σ H_{Ar}, NH_2); 6.84 (s, 1 H, H_{Py})
1b	66 (*B*), 64 (*C*)	269—270	67.32 / 67.33	4.54 / 4.52	9.39 / 9.42	$C_{25}H_{20}ClN_3OS$	220 (4.71), 328 (4.27), 418 (4.16)	2.65, 2.84 (both s, 3 H each, 6-Me, 4-Me); 6.67—7.38 (m, 16 H, Σ H_{Ar}, NH_2)
1c	62 (*A*), 67 (*B*), 78 (*C*)	267—268	70.72 / 70.73	5.25 / 5.25	9.50 / 9.52	$C_{26}H_{23}N_3O_2S$	220 (4.49), 325 (4.34), 418 (4.16)	2.58 (s, 3 H, 6-Me); 3.41 (s, 3 H, OMe); 4.78 (s, 2 H, OCH_2); 6.63—7.35 (m, 15 H, Σ H_{Ar}, H_{Py}); 7.45 (br.s, 2 H, NH_2)

* The procedure used is given in parentheses.

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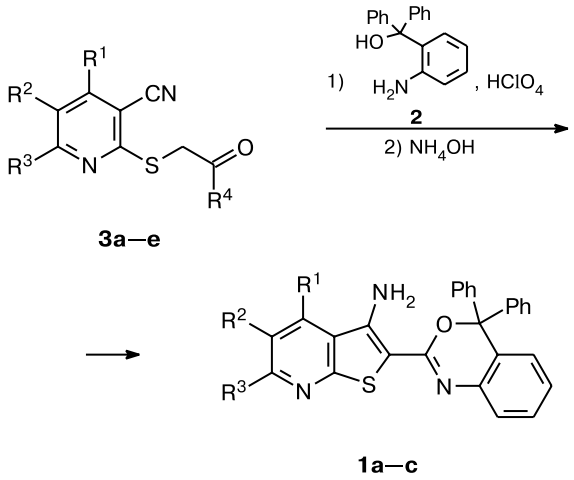
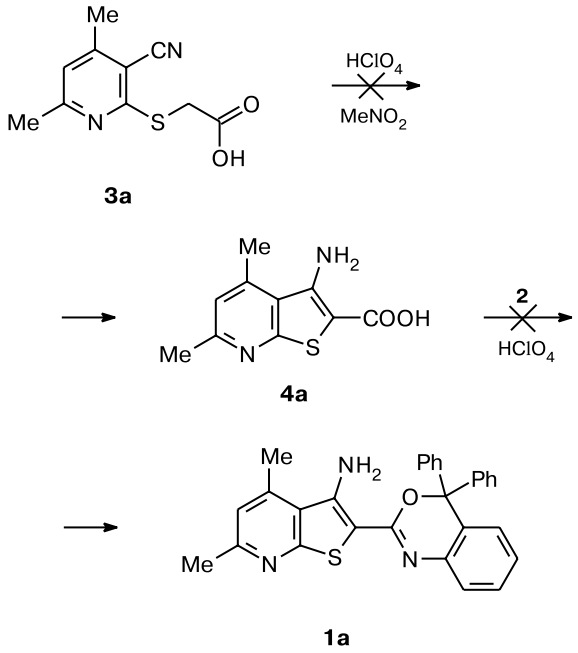
Scheme 1



1a, 3a,c: $R^1 = R^3 = Me$, $R^2 = H$; **1b, 3d:** $R^1 = R^3 = Me$, $R^2 = Cl$; **1c, 3b,e:** $R^1 = CH_2OMe$, $R^2 = H$, $R^3 = Me$; **3a,b:** $R^4 = OH$; **3c—e:** $R^4 = NH_2$

Scheme 2



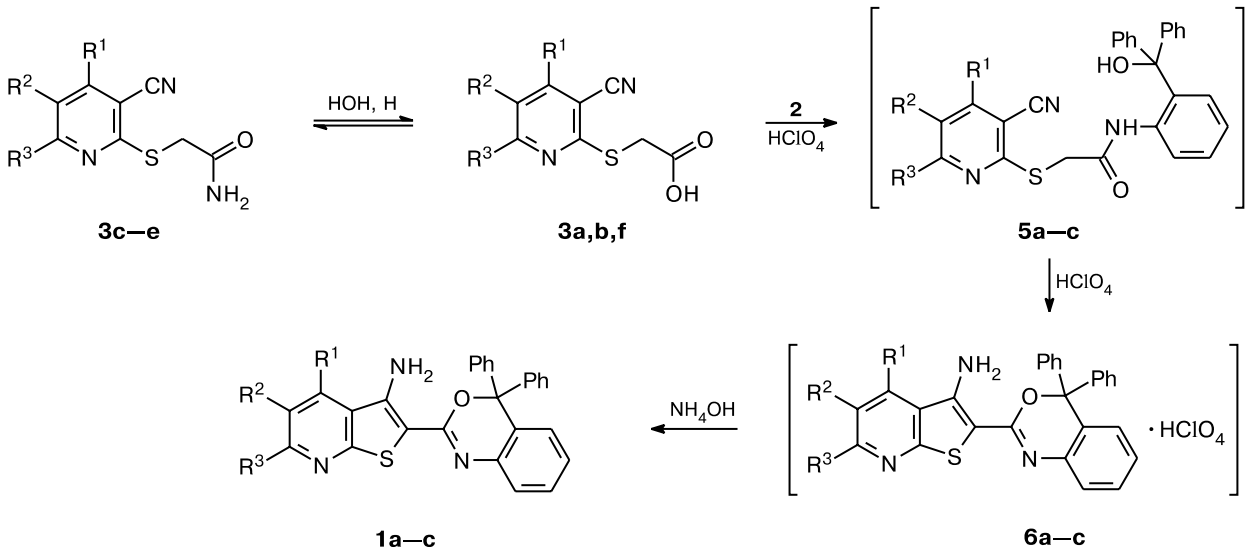
the conditions described above were successful, which was illustrated with compounds **3a** and **4a**, respectively (Scheme 2).

Apparently, the formation of target products **1a—c** includes the following successive reactions: hydrolysis of amides **3c—e** to (3-cyanopyridin-2-ylthio)acetic acids **3a,b,f**, acylation of APC **2** with acids **3**, heterocyclization of *N*-[2-hydroxy(diphenyl)methylphenyl]-(3-cyanopyridin-2-ylthio)acetamides **5a—c**, and neutralization of perchlorates **6a—c** with aqueous ammonia (Scheme 3).

The structures of compounds **1a—c** were confirmed by independent syntheses from the corresponding 3-cyanopyridine-2(1*H*)-thiones **7a—c** and 2-chloromethyl-4,4-diphenyl-4*H*-1,3-benzoxazine (**8**) in the presence of KOH (2 equiv.) (procedure *C*, Scheme 4).

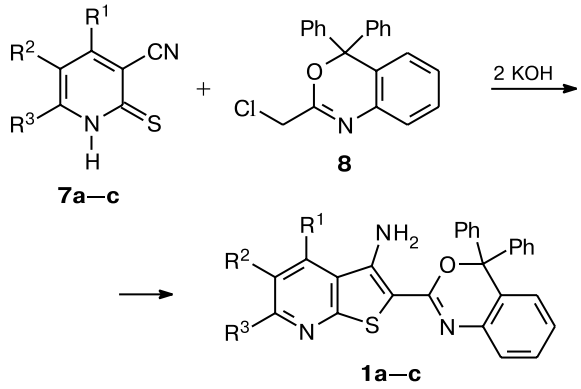
Scheme 4 ensures the higher yields of compounds **1a—c** than procedures *A* and *B* (see Table 1). However,

Scheme 3



5a, **6a:** $R^1 = R^3 = Me$, $R^2 = H$; **3f**, **5b**, **6b**: $R^1 = R^3 = Me$, $R^2 = Cl$; **5c**, **6c:** $R^1 = CH_2OMe$, $R^2 = H$, $R^3 = Me$

Scheme 4



7a: $R^1 = R^3 = Me$, $R^2 = H$; **7b:** $R^1 = R^3 = Me$, $R^2 = Cl$; **7c:** $R^1 = CH_2OMe$, $R^2 = H$, $R^3 = Me$

with the consideration that 2-chloromethyl-4,4-diphenyl-4*H*-1,3-benzoxazine (**8**) is prepared[2] from APC in 75% yield, the yields of products **1a—c** converted to the starting amino alcohol range from 48 to 59%, while their yields attained by procedure *B* with respect to the starting pyridinethiones is higher (60—64%) since the yields of amides **3c—e** from the corresponding pyridinethiones are 92 to 95%.

Compounds **1a—c** are yellow crystalline products; their structures were confirmed by elemental analysis data and ^{1}H NMR and IR spectra (see Table 1).

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 instrument (250.13 MHz) in DMSO-d_6—CCl_4 (1 : 3). IR spectra were recorded on a Specord 75IR instrument (Nujol, NaCl and KBr prisms). UV spectra were recorded on a Specord UV-Vis instrument in ethanol (Nujol).

The syntheses of compounds **3b** and **3e** were described earlier.[5,6] The yield of compound **3b** was 95%, m.p. 112—113 °C. The yield of compound **3e** was 95%, m.p. 168—169 °C. Compounds **3a,c,d** were obtained analogously. The yield of compound **3a** was 86%, m.p. 140—141 °C. Found (%): C, 54.01; H, 4.50; N, 12.64; S, 14.38. $C_{10}H_{10}N_2O_2S$. Calculated (%): C, 54.04; H, 4.53; N, 12.61; S, 14.42. The yield of compound **3c** was 92%, m.p. 192—193 °C. Found (%): C, 54.25; H, 5.03; N, 19.03; S, 14.46. $C_{10}H_{11}N_3OS$. Calculated (%): C, 54.28; H, 5.01; N, 18.99; S, 14.49. The yield of compound **3d** was 95%, m.p. 144—145 °C. Found (%): C, 46.94; H, 3.92; Cl, 13.84; N, 16.39; S, 12.51. $C_{10}H_{10}ClN_3OS$. Calculated (%): C, 46.97; H, 3.94; Cl, 13.86; N, 16.43; S, 12.54. IR, ν/cm^{-1}: **3a**: 3190, 2210, 1700, 1580, 1190, 1030, 920, 870; **3c**: 3390, 3200, 2215, 1655, 1580, 1270, 1230, 1205, 1100, 1040, 1000, 860; **3d**: 3350, 3180, 2225, 1675, 1610, 1570, 1360, 1260, 1180, 1030, 910. ^{1}H NMR, δ: **3a**: 2.50, 2.53 (both s, 3 H each, 4-Me, 6-Me), 3.93 (s, 2 H, CH_2), 6.68 (s, 1 H, H_{Py}), 10.7 (br.s, 1 H, OH); **3c**: 2.40, 2.48 (both s, 3 H each, 4-Me, 6-Me), 3.81 (s, 2 H, CH_2), 7.25 (s, 1 H, H_{Py}), 7.18, 7.25 (both br.s, 1 H each, NH); **3d**: 2.53, 2.65 (both s, 3 H each, 4-Me, 6-Me); 3.97 (s, 2 H, CH_2); 6.89, 7.29 (both br.s, 1 H each, NH).

3-Amino-2-(4,4-diphenyl-4*H*-3,1-benzoxazin-2-yl)-4,6-dimethylthieno[2,3-*b*]pyridine (1a). ***A.*** A suspension of APC (2.75 g, 0.01 mol) in 24 mL of nitromethane was added dropwise for 1.5 h to a boiling solution of nitrile **3a** (2.2 g, 0.01 mol) in 70% $HClO_4$ (0.81 mL, 0.01 mol) and nitromethane (24 mL). The reaction mixture was stirred for an additional 15 min, cooled, and concentrated *in vacuo* to a quarter of its volume. The residue was neutralized with 10% aqueous ammonia to a neutral reaction. The precipitate that formed was filtered off and recrystallized from ethanol—DMF (1 : 10, v/v). The yield of compound **1a** was 2.95 g (64%). Compound **1c** was obtained analogously.

B. Thienopyridine **1a** was synthesized from compound **3c** (2.2 g, 0.01 mol) as described in procedure *A*. The yield of compound **1a** was 3.0 g (65%). Compounds **1b,c** were obtained analogously.

C. A 10% aqueous solution of KOH (5.6 mL, 0.01 mol) and 2-chloromethyl-4,4-diphenyl-4*H*-1,3-benzoxazine (3.33 g, 0.01 mol) were added to a suspension of 3-cyanopyridine-2(1*H*)-thione **7a** (1.64 g, 0.01 mol) in 20 mL of DMF. The reaction mixture was kept at room temperature for 10 to 15 min. Then, an additional portion of 10% aqueous KOH (5.6 mL, 0.01 mol) was added and the mixture was stirred for 2 h. The precipitate that formed was separated, washed with water and ethanol—water (1 : 1), and dried in air. The product was recrystallized from ethanol—DMF (1 : 10, v/v). The yield of compound **1a** was 3.50 g (76%). Compounds **1b,c** were obtained analogously.

IR, ν/cm^{-1}: **1a**: 3480, 3245, 1600, 1550, 1250, 1100, 965, 865; **1b**: 3485, 3310, 1605, 1320, 1250, 1130, 1050, 985; **1c**: 3420, 3245, 1610, 1560, 1245, 1100.

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