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Synthesis and Reactions of Substituted 3-amino-2-furyl(aryl)-thieno[2,3-b]pyridines

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Abstract: New substituted thieno[2,3-b]pyridines which contain 4-nitropehnyl and 5-nitro-, carboxy-, methoxycarbonyl-2-furyl groups in the 2 position have been obtained.

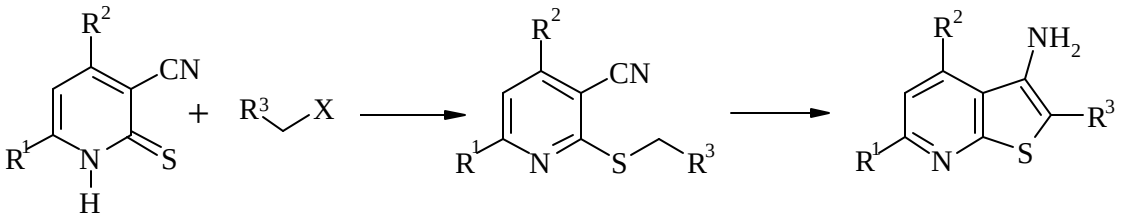
Keywords: Pyridinethione, 3-aminothieno[2,3-b]pyridine, Thorpe-Ziegler cyclization.

Introduction

The alkylation of substituted 3-cyano-2(1H)-pyridinethiones and Thorpe-Ziegler cyclization of the latter in alkali medium to give 3-aminothieno[2,3-b]pyridines have been extensively studied [1-3]. However there is no literature data on the use of 2-halomethyl furan derivatives and 2-furoic acid as alkylating agents or on the synthesis of substituted 3-amino-2-furyl-thieno[2,3-b]pyridines.

Results and Discussion

To further develop our studies on the alkylation of 6-methyl-4-methoxymethyl-3-cyano-2(1H)-pyridinethione (**1a**) and its structural isomer **1b** [4-6], the pyridinethiones 1a,b were reacted with 5-nitro-furylmethyl- and 4-nitrobenzyl bromides and the 5-chloromethyl derivative of methyl 2 furoate (Scheme 1).



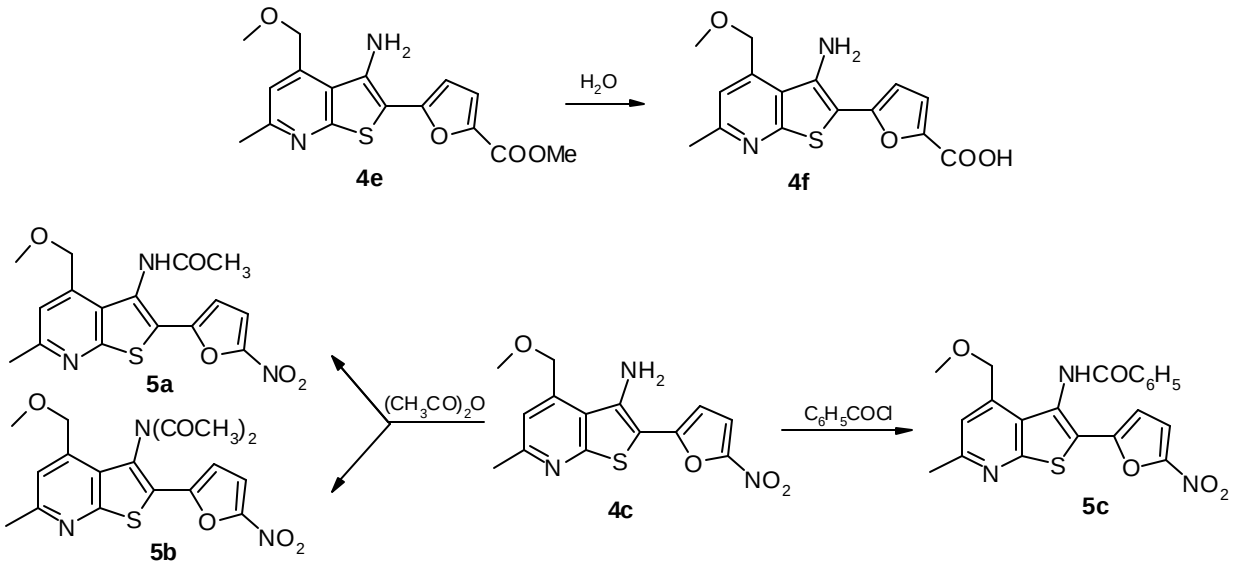
1?,b **3a-e** **4?-e**

1a, 3**?**,**?**, **4?**,**?**,**e** R^1=CH_3; R^2=CH_2OCH_3; **1b**, **3b**,**d**, **4b**,**d** R^1=CH_2OCH_3, R^2=CH_3
3?,**b**, **4?**,**b**, R^3= 4-$NO_2C_6H_4$; **3c**,**d**, **4c**,**d** R^3=5-nitro-2-furyl;
3e, **4e** R^3= 5-methoxycarbonyl-2-furyl; X=Br, Cl

Scheme 1

The reactions of pyridinethiones **1a,b** with 4-nitrobenzyl bromide and methyl 5-chloromethyl-2-furoate were run in dimethylformamide (DMF) in the presence of KOH, and for 5-nitro-2-furylmethyl bromide, in ethanol in the presence of K_2CO_3. The ratio of compounds **1a,b** to alkylating agent to base was 1:1:1. Alkylation was assumed to be regioselective relative to the more nucleophilic centre – the sulphur atom – to give 2-thiopyridines **3** (yields 81-92%) (Table 1). Their structures were confirmed by IR, UV and NMR data (Tables 2, 3). The presence in the structure of compounds **3** of furan and benzene rings containing an electron-withdrawing substituent enhances the acidity of the CH_2 group, thus making Thorpe-Ziegler isomerization of these compounds possible to afford thieno[2,3-b]pyridines **4a-e**, possibly under the action of the base (KOH was used for the syntheses of **4a,b,e** and K_2CO_3 for that of **4c,d**). The acid **4f** was obtained by alkaline hydrolysis of the methyl ester **4e** in aqueous DMF, followed by acidification of the reaction mixture. Aminothieno[2,3-b]pyridines 4a-g are crystalline substances ranging in colour from yellow to dark red. Their IR spectra show no $\nu_{C\equiv N}$ absorption for the nitrile group at 2230-2205 cm^{-1}, as is found in the spectra of the alkylation products, and they also display a broadening of the ν_{NH} bands of the NH_2 group at 3480-3220 cm^{-1} (Table 2), which is characteristic of the 3-amino-thienopyridines [2-4,7].

The reaction of amine 4c and acetic anhydride results in the mono- and diacyl derivatives 5a and 5b, whose formation depended on the reaction conditions (Scheme 2). Acvetylation of compound 4c at room temperature leads to amide 5a. Heating of amine 4c in acetic anhydride gives a mixture of acyl derivatives 5a and 5b, where imide 5b is predominant. Imide 5b was isolated by column chromatography.



Scheme 2

Experimental

General

1H-NMR spectra were recorded on Bruker WM-250 and Tesla BS-487A spectrometers using DMSO-d_6 or $CDCl_3$ as solvents. Chemical shifts (δ) are given in ppm relative to TMS. IR spectra (vaseline oil suspensions) have been measured on a Specord 75-IR spectrophotometer. UV-VIS spectra were recorded on a Specord M-40 spectrophotometer using ethanol as solvent. Thin layer chromatography (TLC) was performed on Silufol UV-254 silica gel plates using hexane-acetone (1-2:1) as the solvent system; plates were visualized with iodine vapour or after spraying with $KMnO_4$ solution. Physical properties and spectral data of the compounds prepared are given in Tables 1-3.

6-Methyl-4-methoxymethyl-3-cyano-2-(4-nitrobenzyl)thiopyridine (***3a*).**

A mixture of pyridinethione **1a** [5] (1.94 g, 10 mmol) in DMF (20-25 mL), 4-nitrobenzyl bromide (2.16g 10 mmol) and a 10% aqueous solution of KOH (5.6 mL, 10 mmol) was kept at r.t for 2h, then diluted with water (10 mL). The precipitate formed was filtered off, washed with water, dried and recrystallized from ethanol to give 3.03 g (92%) of **3a**. Compounds **3b-e** were similarly obtained.

*3-Amino-2-(4-nitrophenyl)-6-methyl-4-methoxymethylthieno[2,3-b]pyridine (**4a**).*

A suspension of thiopyridine **3a** (3.29 g, 10 mmol) in DMF (30 ml) and a 10% aqueous solution of KOH (5.6 mL, 10 mmol) was mixed for 2 h at 45-50°C, then diluted with a two-fold volume

of water. The precipitate formed was separated and recrystallized from ethanol to give 3.06 g (93%) of **4a**. Compounds **4b,e** were obtained in the same manner.

*3-Amino-2-(4-nitrofuran-2-yl)-6-methyl-4-methoxymethylthieno[2,3-b]pyridine (**4c**).*

A mixture of thiopyridine **3c** (3.19 g, 10 mmol) in ethanol (20 mL) and 10% aqueous K_2CO_3 solution (6.9 mL, 5 mmol) was refluxed for 5 hours, then diluted with a two-fold volume of water. The precipitate formed was separated and recrystallized from ethanol to give 2.39 g (75%) of **4c**. Compound **4d** was obtained in the same manner.

*3-Amino-2-(5-carboxylfuran-2-yl)-6-methyl-4-methoxymethylthieno[2,3-b]pyridine (**4f**).*

A mixture of thienopyridine **4e** (3.32 g, 10 mmol) in DMF (20-25 mL) and a 10% aqueous solution of KOH (5.6 mL, 10 mmol) was brought to the boiling point. Then the reaction mixture was diluted with water to twice the volume and acidified with 10% aqueous hydrochloric acid until a precipitate formed. The precipitate was eparated, washed with water, dried and recrystallized from ethanol to yield 1.94g (61%) of **4f**.

*3-N-Acetylamino-2-(5-nitrofuran-2-yl)-6-methyl-4-methoxymethylthieno[2,3-b]-pyridine (**5a**).*

A solution of thienopyridine **4c** (3.19 g, 10 mmol) in acetic anhydride (20 mL) was left to stand at r.t. for 2 h. Then the reaction mixture was diluted with a two-fold volume of water and neutralized with 10% aqueous solution of Na_2CO_3. The solid formed was collected by filtration, washed with water, dried in air and recrystallized from DMF to yield 2.94 g (73%) of **5a**.

*3-N-Acetylamino- and 3-N,N-diacetylamino-2-(5-nitrofuran-2-yl)-6-methyl-4-methoxymethylthieno-[2,3-b]-pyridine (**5a**) and (**5b**).*

A solution of thienopyridine **4c** (3.19 g, 10 mmol) in acetic anhydride (20 mL) was refluxed for 40 minutes. The reaction mixture was then concentrated under vacuum and the residue was washed with 5% aqueous solution of $NaHCO_3$ followed by water, dried in the air and recrystallized from ethanol. The acylation products were separated by column chromatography using hexane-acetone mixture (1:2) as eluent. The yield of **5a** was 0.43 g (12%) and of **5b**, 2.70 g (67%).

*3-N-Benzoylamino-2-(5-nitrofuran-2-yl)-6-methyl-4-methoxymethylthieno[2,3-b]pyridine (**5c**).*

A mixture of thienopyridine 4c (3.19 g, 10 mmol) in chloroform (20 mL) and benzoyl chloride (1.16 mL, 10 mmol) was refluxed for 60 minutes. The solvent was evaporated under vacuum and the residue was washed with 2.5% aqueous solution of $NaHCO_3$ and water, dried in the air and recrystallized from DMF to give 3.89 g (92%) of **5c**.

Table 1 – Characteristics of the compounds obtained

Compound	Empirical formula	Analysis, Found, % Calculated, %				M.p., °C	Yield, %
		C	H	N	S		
3a	$C_{16}H_{15}N_3O_3S$	58.28 58.35	4.48 4.59	12.71 12.76	9.61 9.73	109-110	92
3b	$C_{16}H_{15}N_3O_3S$	58.27 58.35	4.42 4.59	12.69 12.76	9.65 9.73	151-152	90
3c	$C_{14}H_{13}N_3O_4S$	52.49 52.66	4.08 4.10	12.99 13.16	10.00 10.04	117-120	86
3d	$C_{14}H_{13}N_3O_4S$	52.54 52.66	3.98 4.10	13.08 13.16	9.90 10.04	112-114	86
3e	$C_{16}H_{16}N_2O_4S$	57.79 57.82	4.88 4.85	8.50 8.43	9.57 9.65	97-98	81
4a	$C_{16}H_{15}N_3O_3S$	58.29 58.35	4.58 4.59	12.69 12.76	9.72 9.73	204-205	93
4b	$C_{16}H_{15}N_3O_3S$	58.29 58.35	4.58 4.59	12.77 12.76	9.77 9.73	217-218	91
4c	$C_{14}H_{13}N_3O_4S$	52.50 52.66	4.05 4.10	13.02 13.16	9.96 10.04	202-203	75
4d	$C_{14}H_{13}N_3O_4S$	52.57 52.66	4.02 4.10	13.00 13.16	9.95 10.04	199-201	73
4e	$C_{16}H_{16}N_2O_4S$	57.79 57.82	4.82 4.85	8.41 8.43	9.63 9.65	130-131	73
4f	$C_{15}H_{14}N_2O_4S$	56.57 56.59	4.42 4.43	8.76 8.80	10.00 10.07	202-203	61
5a	$C_{16}H_{15}N_3O_5S$	53.10 53.18	4.19 4.18	11.66 11.63	8.85 8.87	238-239	73(12)
5b	$C_{18}H_{17}N_3O_6S$	53.60 53.59	4.20 4.25	10.38 10.42	7.92 7.95	>250 decomposed	67
5c	$C_{21}H_{17}N_3O_5S$	59.54 59.57	4.00 4.05	9.87 9.92	7.55 7.57	108-110	92

- For compounds **3a-d**, **4c**,**d** the eluent was 1:1 hexane -acetone; for compounds **4a**,**b**,**e,f**, and **5a-c**, 2:1 hexane -acetone was used.

Table 2 – IR and UV-VIS spectra of synthesised compounds

Compound	UV-VIS (EtOH) [λ_{max} (nm), log e ($dm^3mol^{-1}cm^{-1}$)]	IR spectra, ν, cm^{-1}					
		C≡N	C–O–C	C=C, C=N	C–H_{Ar}	NO_2	NH_2
3a	218(4.50), 269(4.48)	2205	1095, 1120	1580, 1560, 1530	3170	1495, 1220	–
3b	219(4.39), 268(4.27)	2210	1140, 1110	1598, 1588, 1570	3165	1505, 1240	–
3c	264(4.18), 317(4.23)	2205	1120, 1090	1560	3140	1530, 1220	–
3d	264(4.11), 312(4.17)	2207	1125, 1090	1570	3120	1530, 1220	–
3e	221(4.23), 270(4.38), 308(3.66)	2230	1060 1030 1010	1600 1570	3070 3040	–	–
4a	209(4.29), 226(4.19), 287(4.16), 320(3.94), 423(4.05)	–	1110, 1080	1640, 1570	3070, 3050, 2730	1490, 1240, 1260	3320, 3400
4b	208(4.28), 223(4.22), 255(4.11), 283(4.20), 410(4.00)	–	1105, 1070	1640, 1570	3050, 2720	1490, 1230	3330, 3400
4c	238(4.12), 284(4.13), 347(3.94), 478(4.20)	–	1100, 1090	1610, 1575, 1560	3130	1540, 1230	3220, 3300
4d	235(4.11), 274(4.11), 340(3.99), 464(4.13)	–	1105, 1080	1610, 1570	3130	1570, 1220	3415

4e	220(4.12), 253(3.81), 317(4.13), 393(4.06)	–	1170, 1130, 1080	1640, 1590	3150, 3125	–	3460, 3360, 3220
4f	218(4.32), 247(3.99), 312(4.37), 386(4.17)	–	1110, 1040	1600, 1590	3030, 3010, 3000	–	3480, 3340
5a	214(4.18), 232(4.28), 286(397), 296(3.98), 309(3.97), 388(4.29)	–	1140, 1060, 1050	1580	3150	1570, 1210	3240
5b	214(4.33), 228(4.33), 283(3.97), 293(3.98), 307(3.96), 380(4.23)	–	1110, 1070, 1050	1600	3150, 3120	1580, 1220	3230
5c	211(4.28), 232(4.45), 387(4.25)	–	1130, 1040	1600, 1580	3090	1540, 1210	

Other significant IR spectral bands, cm^{-1}: **3e** 1750 (ν_{CO}), **4f** 1720 (ν_{CO}), **4g** 1720 (ν_{CO}), **5a** 1660 (Amide I), **5b** 1720,1710 (ν_{CO}), **5c** 1650 (Amide I).

Table 3 – ^{1}H NMR – spectral data.

Compound	Signals, δ (ppm)				
	CH_3-Het, s	OCH_3, s	OCH_2, s	SCH_2, s	Other protons (see R)
3a	2.28	3.16	4.39	4.31	7.10 (s, 1H, H_{Het}), 7.63 (d, J=9Hz, 2H, H_{Ar}), 8.21 (d, J=9Hz, 2H, H_{Ar})
3b	2.45	3.45	3.46	3.40	7.11 (s, 1H, H_{Het}), 7.53 (d, J=9Hz, 2H, H_{Ar}), 8.11 (d, J=9Hz, 2H, H_{Ar})

3c	2.24	3.20	4.39	4.32	6.43 (d, J=3.6Hz, 1H, 3-H_{Fur}), 7.11 (d, J=3.6Hz, 1H, 4-H_{Fur}), 7.08 (s, 1H, H_{Het})
3d	2.53	3.42	4.59	4.36	6.45 (d, J=3.6Hz, 1H, 3-H_{Fur}), 7.10 (d, J=3.6Hz, 1H, 4-H_{Fur}), 7.19 (s, 1H, H_{Het})
3e	2.58	3.42 3.88	4.68	4.53	6.38 (d, J=4Hz, 1H, 3-H_{Fur}), 6.95 (d, J=4Hz, 1H, 4-H_{Fur}), 7.01 (s, 1H, H_{Het})
4a	2.63	3.40	4.78	–	6.95 (s, 1H, H_{Het}), 7.72 (d, J=9.5Hz, 2H, H_{Ar}), 8.28 (d, J=9.5Hz, 2H, H_{Ar}), 4.75 (broad s, 1H, NH), 4.98 (broad s, 1H, NH)
4b	2.81	3.46	4.58	–	7.17 (s, 1H, H_{Het}), 7.73 (d, J=9.5Hz, 2H, H_{Ar}), 8.30 (d, J=9.5Hz, 2H, H_{Ar}), 4.45 (broad s, 2H, NH_2).
4c	2.58	3.43	4.86	–	6.28 (broad s, 2H, NH_2), 7.07 (d, J=5.2Hz, 1H, 3-H_{Fur}), 7.26 (s, 1H, H_{Het}), 7.85 (d, J=5.2Hz, 1H, 4-H_{Fur})
4d	2.84	3.41	4.51	–	5.96 (broad s, 2H, NH_2), 6.98 (d, J=6.2Hz, 1H, 3-H_{Fur}), 7.17 (s, 1H, H_{Het}), 7.78 (d, J=5.2Hz, 1H, 4-H_{Fur})
4e	2.10	3.29	4.65	–	3.78 (s, 3H, O-CH_3), 5.85 (broad s, 2H, NH_2), 6.38 (d, J=4.0Hz, 1H, 3-H_{Fur}), 6.88 (s, 1H, H_{Het}), 7.45 (d, J=4.0Hz, 1H, 4-H_{Fur})
4f	2.58	3.42	4.81	–	5.8 (broad s, 2H, NH_2), 6.59 (d, J=4.4Hz, 1H, 3-H_{Fur}), 7.21 (d, J=4.4Hz, 1H, 4-H_{Fur}), 7.15 (s, 1H, H_{Het}),
5a	2.27	2.69 3.42	4.74	–	6.74 (d, J=4.5Hz, 1H, 3-H_{Fur}), 7.16 (s, 1H, H_{Het}), 7.18 (broad s, 1H, NH), 7.44(d, J=4.5Hz, 1H, 4-H_{Fur})
5b	2.12	2.40 2.68 3.37	4.47	–	6.79 (d, J=4.0Hz, 1H, 3-H_{Fur}), 7.22(s, 1H, H_{Het}), 7.25 (d, J=4.0Hz, 1H, 4-H_{Fur})
5c	2.61	3.12	4.73	–	6.68 (d, J=4.0Hz, 1H, 3-H_{Fur}), 7.09 (d, J=4.0Hz, 1H, 4-H_{Fur}), 7.75 (m, 6H, ΣH_{Het}, C_6H_5)

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Sample Availability: Samples are available from the authors.