Studies on the Synthesis of Some Styryl-3-cyano-2(1*H*)-pyridinethiones and Polyfunctionally Substituted 3-Aminothieno[2,3-*b*]-pyridine Derivatives

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The 3-cyano-4,6-dimethyl-2(1*H*)-pyridinethione was condensed with benzaldehyde in basic solution leads to styryl-3-cyano-2(1*H*)-pyridinethiones. Treatment of cinnamicaldehyde with cyanothioacetamide to give cinnamylidencyanothioacetamide, which can be cyclized with the appropriate ketones to afford the 3-cyano-5,6-polymethylene-4-styryl-2(1*H*)-pyridinethione derivatives. The polyfunctionally substituted 3-aminothieno[2,3-*b*]pyridine derivatives were obtained in good yield by cyclization of 3-cyano-2(1*H*)-pyridinethione derivatives with appropriate α-halogeno carbonyl compounds and nitrile, respectively.

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The various derivatives of 3-cyano-2(1*H*)-pyridinethione are of some interest as intermediates in fine organic synthesis for the production of physiologically active substance, for the protection of plants, and for dyes [1-4], 3-aminothieno[2,3-*b*]pyridines are in connection with the problem of bioisosterism, and other important compounds [5]. In view of this we become interested in the syntheses of new 3-cyano-2(1*H*)-pyridinethiones and 3-aminothieno[2,3-*b*]pyridine derivatives. There are several known methods for the synthesis of 2-mercaptopyridines or 2-pyridothiones. These methods include the usage of other pyridine derivatives such as 2-halopyridines [6,7] or 2-hydroxypyridines [8-10] or the usage of an isothiocyanate and an unsaturated aldehyde [11] or 1,3-diketones [12] as the starting materials.

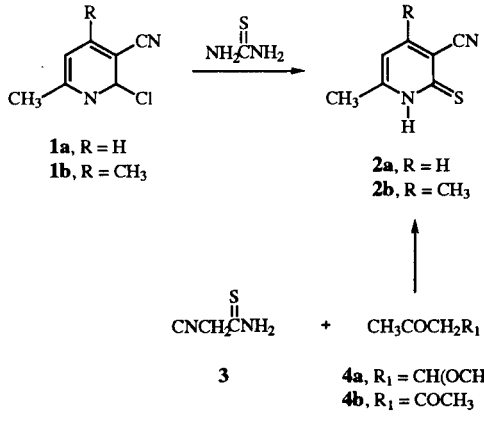
On the other hand, the synthesis of different kinds of pyridones through the reaction of active methylene compounds with α,β-unsaturated ketones, esters or nitriles has been reported [13-17]. Shestopalov and Promonenkov [18] have recently described the synthesis of 3-cyano-4,6-diaryl-2(1*H*)-pyridinethiones from chalcones with cyanothioacetamide and the thiolation of 1,5-ketonitriles with element sulfur. 4-Aryl-3-cyano-5,6-polymethylene-2(1*H*)-pyridinethiones also has been prepared from gem-dithiols with arylidenemalononitriles [19].

Although a number of papers have been published concerning the synthesis of 2(1*H*)-pyridinethione derivatives, those containing a styryl group have not yet been reported. Now we wish to report in this paper the synthesis of some new 3-cyano-2(1*H*)-pyridinethiones containing styryl group and the corresponding polyfunctionally substituted 3-aminothieno[2,3-*b*]pyridine derivatives.

Results and Discussion.

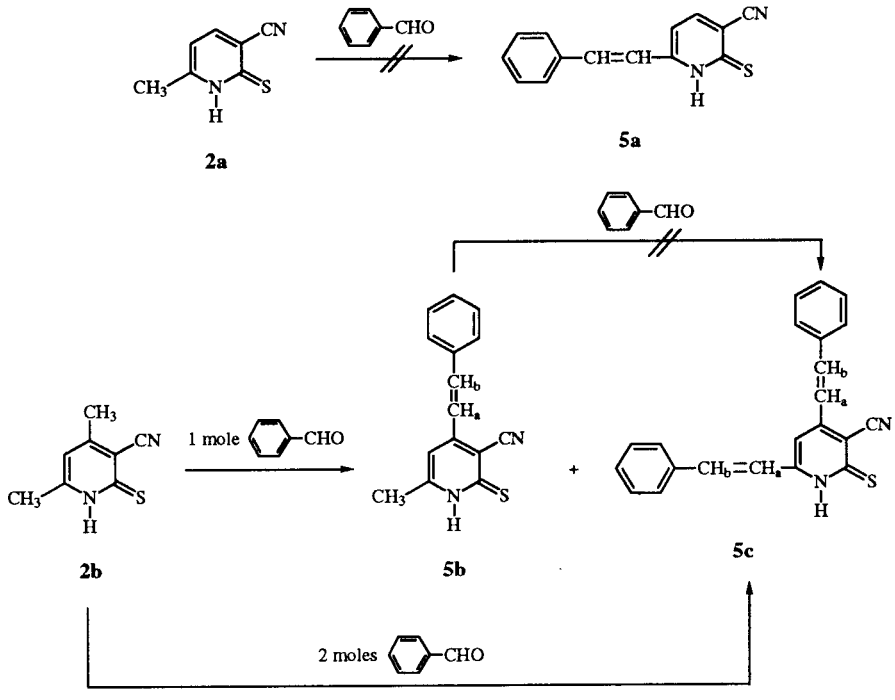
The required compounds **2a** and **2b** were prepared by treating **1a** or **1b** with thiourea in refluxing ethanol (Scheme 1). The reactant **1a** and **1b** were prepared according to the procedures reported previously [20]. Previously **2a** and **2b** were obtained from treating **3** with **4a** and **4b** [21].

Scheme 1



Reaction of compound **2a** with benzaldehyde in refluxing dioxane in the presence of catalytic amounts of piperidine did not produce the desired 3-cyano-6-styryl-2(1*H*)-pyridinethione **5a**, but led only to the recovery of starting material **2a**. When 3-cyano-4,6-dimethyl-2(1*H*)-pyridinethione **2b** was condensed with equimolar amounts of benzaldehyde under similar condition, work up of the reaction mixture yielded a mixture of two products **5b** and **5c** (Scheme 2) which were separated. The structures of **5b** and **5c** were established on the basis of microanalysis and spectra data as well as comparison (ir, mixed mp, tlc). Both the infrared spectra of **5b** and **5c** showed absorption band at 2235-2218 cm^{-1} for the C≡N group, at 3400 cm^{-1} for the NH group, at 1214-1205 cm^{-1} for the thiocarbonyl group (C=S) and at 975-965 cm^{-1} for the *trans*-olefinic configuration group (-CH=CH-). In addition, the structure was supported by the ^1H nmr (DMSO-d_6) spectrum, which showed the presence of the expected protons signal in agreement with the proposed structures. The compound **5b** showed the disappearance of a methyl signal at the 4-position of the **2b** and a styryl signal at δ 7.83-7.20 (7H, m) attributed to 4-position of compound **5b** and a sharp

Scheme 2



three protons singlet at δ 2.38 assigned to 6-CH_3, the mass spectrum was at m/z 252. Compound **5c** showed the disappearance of two methyl signals at the 4- and 6-positron of the **2b** and the appearance of two styryl signals at δ 7.98-7.22 (14H, m), the mass spectrum was at m/z 340. Compound **5b** and **5c** were identified as 3-cyano-6-methyl-4-styryl-2(1*H*)-pyridinethione and 3-cyano-4,6-distyryl-2(1*H*)-pyridinethione. Complete information about the nmr, ir and uv spectra is presented in the Experimental.

An investigation of the yield of **5b** and **5c**, showed that the yield of **5c** increased with the reaction time, while the yield of **5b** stayed unchanged at about 53% (Table 1). The best yield of **5b** and **5c** was obtained by refluxing **2b** and benzaldehyde in dioxane for 36 hours. When **2b** was treated with benzaldehyde in a molar ratio of 1:2 it resulted in the formation of single product, which was identified as **5c** by elemental analyses and spectral data. However, attempting to react compound **5b** with benzaldehyde at refluxing dioxane in the presence of piperidine did not give the expected **5c**; it led only to the recovery of starting material **5b**.

Table 1

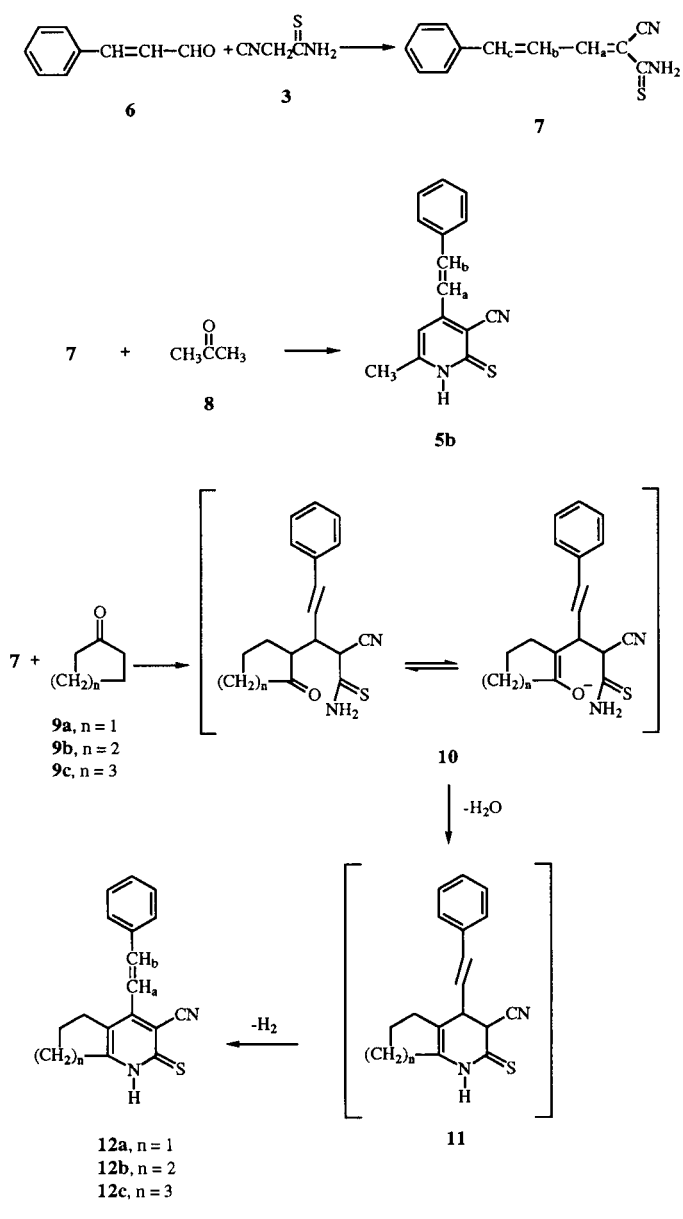
Yield of Compounds **5b** and **5c**

	yield (%) reaction time (hours)			
	9	18	27	36
5b	50	53.8	53.5	53
5c	12.3	16.8	22.7	30

Elgemeie *et al.* [22] and Elnagdi *et al.* [23] have already reported the synthesis of 4-aryl-3-cyano-6-methyl-2(1*H*)-pyridinethiones and 4-aryl-1,2,5,6,7,8-hexahydro-2-thioxo-quinolin-3-carbonitriles by using arylmethylenecyanothioacetamide as the starting material. In this paper, the synthesis of 3-cyano-2(1*H*)-pyridinethiones **12a-12c** having a styryl group at the 4-position are outlined in Scheme 3 and were synthesized from the key intermediate, cinnamylidencyanothioacetamide **7**, which was obtained in good yield from the treatment of cinnamaldehyde **6** with cyanothioacetamide **3** in ethanol in the presence of catalytic amounts of triethylamine.

The structure of the products were established *via* inspection of their spectral data. The ir spectra of the cinnamylidencyanothioacetamide **7** is characterized by the presence of strong absorption band of the nitrile group (C≡N) at 2224 cm^{-1} and a strong absorption band of the amino group (NH_2) at 3379, 3358 cm^{-1}, the thiocarbonyl group (C=S) stretching frequency at 1288-1180 cm^{-1} and the *trans*-olefinic configuration group (-CH=CH-) stretching frequency at 978, 973 cm^{-1}. The ^1H nmr spectra showed signals at δ 7.15 (1H, dd), 7.34 (1H, d) and 7.95 (1H, d), which were readily assigned to the proton H_b, H_a and H_c of cinnamylidene moiety, respectively. The signal at δ 7.68-7.46 (5H, m) was assigned to the phenyl protons of the cinnamylidene moiety, two broad singlet at δ 9.42 (1H) and 9.93 (1H) assigned to the amino group. Brunskill and De [24] assigned the analogous signal of

Scheme 3



the amino group in their products.

The 3-cyano-4-styryl-2(1*H*)-pyridinethione derivative **5b** was also obtained when the reaction of the cinnamylidencyanothioacetamide **7** and acetone in boiling ethanol containing catalytic amounts of piperidine were employed. The structure was shown by microanalysis and spectral data. A similar cyclocondensation of **7** with the appropriate cycloketones **9a-9c** such as cyclopentanone, cyclohexanone and cycloheptanone in refluxing dioxane in the presence of catalytic amounts of piperidine afforded the corresponding 3-cyano-5,6-polymethylene-4-styryl-2(1*H*)-pyridinethiones **12a-12c** (Scheme 3). The structures of **12a-12c** were established and confirmed on the basis of their elemental analysis and spectral data. The ^{1}H nmr spectra of compounds **12a-12c** revealed a low field multiplet at δ 7.70-7.00 (7H, m) for the 4-styryl protons and a broad signal at δ 14.20-13.73 assignable to NH group where it was always detected. The compounds of **12a-12c** showed a multiplet at δ 2.99-2.07 (6H, m), 2.72-1.69 (8H, m) and 2.98-1.53 (10H, m) assigned for the cyclopentyl protons of compound **12a**, cyclohexyl protons of compound **12b** and cycloheptyl protons of compound **12c**, respectively. The proposed structures **12a-12c** were also confirmed by the ir spectra where the nitrile group (C≡N) absorptions at 2221-2217 cm^{-1}, thiocarbonyl absorptions (C=S) at 1225-1203 cm^{-1}, and *trans*-olefinic configuration group (-CH=CH-) at 976-970 cm^{-1} were readily apparent.

The formation of 3-cyano-5,6-polymethylene-4-styryl-2(1*H*)-pyridinethiones **12a-12c** may be explained by the reaction pathway depicted in Scheme 3. Cinnamylidencyanothioacetamide **7** with selected cycloketones can be assumed to proceed *via* addition of the double bond in **7** to yield the nonisolable intermediate Michael adduct **10**. This then cyclized *via* addition of the nitrogen nucleophile at the carbonyl group yielding the intermediate pyridine **11** which then lost water and readily oxidized into the final isolable stable compounds **12a-12c** under the reaction conditions. An analogous Michael reaction was observed [23] to provide some 4-aryl-3-cyano-6-methyl-2(1*H*)-pyridinethiones.

The 3-cyano-2(1*H*)-pyridinethione derivatives **2a-2b**, **5a-5b** and **12a-12c** obtained were used in the synthesis of polyfunctionally substituted 3-aminothieno[2,3-*b*]pyridine derivatives. 3-Cyano-2(1*H*)-pyridinethione derivatives **2a-2b**, **5a-5b** and **12a-12c** were cyclized with alkylating agent **13a-13c** such as chloroacetonitrile, chloroacetone, and ethyl chloroacetate in DMF in the presence of excess anhydrous potassium carbonate at room temperature to form the nonisolable *S*-alkylated intermediate **14**, which *via* nucleophilic substitution and intramolecular cyclo-condensation gave the corresponding polyfunctionally substituted 3-aminothieno[2,3-*b*]pyridine derivatives **15-35** in good yield (Scheme 4). Elgemeie *et al.* [22] and Shestopalov *et al.* [18] have reported an analogous alkylation in their papers.

The structure of the new compounds **15-35** were established on the basis of their elemental analysis and spectral data. The ir spectra of the amino group of compounds **15-35** appears at 3459-3330 cm^{-1} in the form of two bands due to intramolecular association between the amine and the ester carbonyl group, and the nitrile group, as observed in other cyclienamino esters [25]. The ir spectra of the compounds **17**, **20** and **23** revealed the absence of a C≡N band and contain the characteristic absorption band at 1680-1657 cm^{-1} due to the carbonyl group. The ^{1}H nmr spectra of the compounds **17**, **20** and **23** measured in DMSO-d$_6$ showed a triplet at δ 1.28-1.27 (3H, t) and a quartet at δ 4.27-4.24 (2H, q) assigned

to the ethyl group ($-CH_2CH_3$), and a three proton singlet at δ 2.69-2.56 assigned to the 6-methyl group. Compound **17** showed two doublets at δ 7.28 and 8.38 assigned to the 5-H and 4-H protons. Compound **20**

Scheme 4

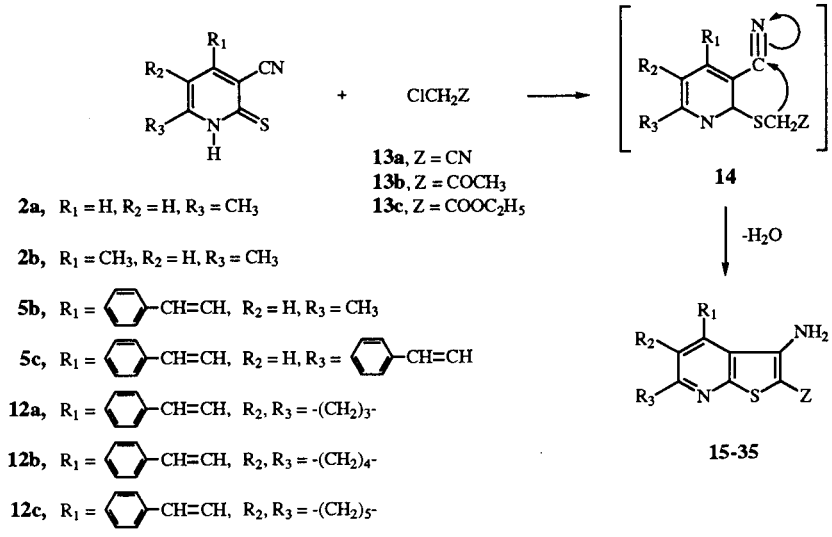
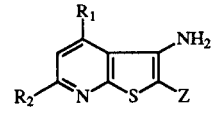


Table 2

4,6-Disubstituted 3-Amino-2-Z-thieno[2,3-*b*]pyridine Derivatives **15-26**



Compound No.	R_1	R_2	Z	MP °C	% Yield	Recrystallization Solvent [a]	Molecular Formula	Mol Wt.	Microanalysis Cacld./Found %C	%H	%N
15	H	CH_3	CN	242-245	74	EA	$C_9H_7N_3S$	189.24	57.13	3.73	22.22
									57.23	3.65	22.19
16	H	CH_3	$COCH_3$	179-180	87	EA	$C_{10}H_{10}N_2OS$	206.27	58.23	4.85	13.59
									58.01	4.96	13.88
17	H	CH_3	$COOC_2H_5$	199-201	79	EA	$C_{11}H_{12}N_2O_2S$	236.29	55.91	5.08	11.86
									55.98	5.08	11.86
18	CH_3	CH_3	CN	242-243	99	EA	$C_{10}H_9N_3S$	203.27	59.11	4.43	20.68
									59.31	4.44	20.54
19	CH_3	CH_3	$COCH_3$	206-207	92	EA	$C_{11}H_{12}N_2OS$	220.29	60.00	5.45	12.72
									59.91	5.42	12.43
20	CH_3	CH_3	$COOC_2H_5$	159-161	98	EA	$C_{12}H_{14}N_2O_2S$	250.32	57.60	5.60	11.20
									57.65	5.56	11.06
21	styryl [b]	CH_3	CN	270-272	90	EA	$C_{17}H_{13}N_3S$	291.14	70.10	4.46	14.43
									70.13	4.61	14.48
22	styryl	CH_3	$COCH_3$	204-205	88	EA	$C_{18}H_{16}N_2OS$	308.40	70.10	5.19	9.09
									70.02	5.27	9.23
23	styryl	CH_3	$COOC_2H_5$	220-223	75	EA	$C_{19}H_{18}N_2O_2S$	338.43	67.45	5.33	8.28
									67.17	5.49	8.42
24	styryl	styryl	CN	155-158	76	EA	$C_{24}H_{17}N_3S$	379.48	75.99	4.48	11.08
									75.81	4.41	11.14
25	styryl	styryl	$COCH_3$	227-229	82	EA	$C_{25}H_{20}N_2OS$	396.51	75.76	5.05	7.07
									75.51	5.23	7.26
26	styryl	styryl	$COOC_2H_5$	157-159	85	EA	$C_{26}H_{22}N_2O_2S$	426.54 [c]	73.24	5.16	6.57
									73.60	5.32	6.43

[a] EA = ethyl acetate. [b] Styryl = C_6H_5-CH_b=CH_a-. [c] Molecular weight determined by mass spectra.

Table 3

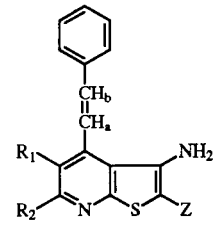
Spectral Data

Compound No.	IR cm^{-1} (Potassium Bromide)	^1H NMR ($DMSO-d_6$) δ ppm [a]
15	3386, 3335 (NH_2), 2194 (C≡N)	2.56 (3H, s, 6-CH_3), 7.22 (2H, br, NH_2), 7.35 (1H, d, 5-H), 8.35 (1H, d, 4-H)
16	3347, 3333 (NH_2), 1607 (C=O)	2.31 (3H, s, $COCH_3$), 2.56 (3H, s, 6-CH_3), 7.28 (1H, d, 5-H), 7.91 (2H, br, NH_2), 8.39 (1H, d, 4-H)
17	3427, 3296 (NH_2), 1674 (C=O)	1.28 (3H, t, CH_3), 2.56 (3H, s, 6-CH_3), 4.24 (2H, q, OCH_2), 7.21 (2H, br, NH_2), 7.28 (1H, d, 5-H), 8.38 (1H, d, 4-H)
18	3433, 3296 (NH_2), 2220 (C≡N)	2.49 (3H, s, 4-CH_3), 2.69 (3H, s, 6-CH_3), 6.46 (2H, br, NH_2), 7.08 (1H, s, 5-H)
19	3435, 3325 (NH_2), 1620 (C=O)	2.32 (3H, s, $COCH_3$), 2.50 (3H, s, 4-CH_3), 2.70 (3H, s, 6-CH_3), 7.05 (1H, s, 5-H), 7.60 (2H, br, NH_2)
20	3440, 3296 (NH_2), 1680 (C=O)	1.27 (3H, t, CH_3), 2.49 (3H, s, 4-CH_3), 2.69 (3H, s, 6-CH_3), 4.24 (2H, q, OCH_2), 6.75 (2H, br, NH_2), 7.03 (1H, s, 5-H)
21	3380, 3318 (NH_2), 2200 (C≡N), 970 (CH=CH, *trans*)	2.49 (3H, s, 6-CH_3), 6.50 (2H, br, NH_2), 7.72-7.33 (5H, m, phenyl-H), 7.55 (1H, s, 5-H), 7.73 (1H, d, H_b), 7.93 (1H, d, H_a)
22	3437, 3321 (NH_2), 1626 (C=O), 975 (CH=CH, *trans*)	2.37 (3H, s, $COCH_3$), 2.60 (3H, s, 6-CH_3), 7.74-7.37 (5H, m, phenyl-H), 7.51 (1H, s, 5-H), 7.59 (2H, br, NH_2), 7.75 (1H, d, H_b), 7.83 (1H, d, H_a)
23	3421, 3331 (NH_2), 1657 (C=O), 981 (CH=CH, *trans*)	1.28 (3H, t, CH_3), 2.58 (3H, s, 6-CH_3), 4.27 (q, OCH_2), 6.78 (2H, br, NH_2), 7.72-7.34 (5H, m, phenyl-H), 7.50 (1H, s, 5-H), 7.73 (1H, d, H_b), 7.91 (1H, d, H_a)
24	3459, 3372 (NH_2), 2195 (C≡N), 970 (CH=CH, *trans*)	7.48 (1H, s, 5-H), 7.47-7.37 (7H, m, 4-styryl-H), 8.00-7.69 (7H, m, 6-styryl-H)
25	3481, 3313 (NH_2), 1627 (C=O), 975 (CH=CH, *trans*)	2.38 (3H, s, $COCH_3$), 7.52 (1H, s, 5-H), 7.50-7.35 (7H, m, 4-styryl-H), 7.94-7.71 (7H, m, 6-styryl-H)
26	3456, 3342 (NH_2), 1673 (C=O), 980 (CH=CH, *trans*)	1.29 (3H, t, CH_3), 4.27 (2H, q, OCH_2), 6.79 (2H, br, NH_2), 7.50 (1H, s, 5-H), 7.47-7.34 (7H, m, 4-styryl-H), 7.96-7.69 (7H, m, 6-styryl-H)

[a] Line shapes: *s* = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Table 4

3-Amino-5,6-polymethylene-2-substituted-4-styryl-thieno[2,3-*b*]pyridine **27-35**



Compound No.	R_1, R_2	Z	MP °C	% Yield	Recrystallization Solvent [a]	Molecular Formula	Mol Wt. [b]	Microanalysis Calcd./Found %C	%H	%N
27	-$(CH_2)_3$-	CN	189-191	70	EA	$C_{19}H_{15}N_3S$	317.41	71.90	4.76	13.24
								71.79	4.90	13.11
28	-$(CH_2)_3$-	$COCH_3$	206-210	74	EA	$C_{20}H_{18}N_2OS$	334.56	71.80	5.42	8.41
								71.54	5.49	8.35
29	-$(CH_2)_3$-	$COOC_2H_5$	158-161	88	EA	$C_{21}H_{20}N_2O_2S$	364.59	69.18	5.53	7.72
								69.11	5.51	7.68
30	-$(CH_2)_4$-	CN	178-179	90	EA	$C_{20}H_{17}N_3S$	331.62	72.44	5.17	12.73
								72.04	5.08	12.43
31	-$(CH_2)_4$-	$COCH_3$	128-131	86	EA	$C_{21}H_{20}N_2OS$	348.59	72.36	5.78	8.07
								72.23	5.83	8.02
32	-$(CH_2)_4$-	$COOC_2H_5$	138-139	96	EA	$C_{22}H_{22}N_2O_2S$	378.61	69.79	5.86	7.43
								69.83	5.63	7.39
33	-$(CH_2)_5$-	CN	220-222	97	EA	$C_{21}H_{19}N_3S$	345.65	72.97	5.54	12.21
								73.24	5.49	12.33
34	-$(CH_2)_5$-	$COCH_3$	216-218	98	EA	$C_{22}H_{22}N_2OS$	362.61	72.87	6.12	7.76
								72.97	5.97	7.84
35	-$(CH_2)_5$-	$COOC_2H_5$	196-197	95	EA	$C_{23}H_{24}N_2O_2S$	392.64	70.36	6.16	7.16
								70.28	5.97	7.21

[a] EA = ethyl acetate. [b] Molecular weight determined by mass spectra.

Table 5

Spectral Data

Compound No.	IR cm^{-1} (Potassium Bromide)	^1H NMR (DMSO-d_6) δ ppm [a]
27	3420, 3330 (NH_2), 2221 (C≡N), 975 (CH=CH, *trans*)	2.14-2.04, 3.31-2.98 (6H, m, cyclopentyl-H), 6.25 (2H, br, NH_2), 6.94 (1H, d, H_b), 7.67-7.35 (5H, m, phenyl-H), 7.70 (1H, d, H_a)
28	3421, 3333 (NH_2), 1635 (C=O), 973 (CH=CH, *trans*)	2.14-2.06, 3.06-2.99 (6H, m, cyclopentyl-H), 2.33 (3H, s, $COCH_3$), 6.99 (1H, d, H_b) 7.32 (2H, br, NH_2), 7.67-7.33 (5H, m, phenyl-H), 7.70 (1H, d, H_a)
29	3420, 3331 (NH_2), 1658 (C=O), 975 (CH=CH, *trans*)	1.28 (3H, t, CH_3), 2.10-2.05, 3.09-2.90 (6H, m, cyclopentyl-H), 4.24 (2H, q, OCH_2), 6.54 (2H, br, NH_2), 6.98 (1H, d, H_b), 7.67-7.35 (5H, m, phenyl-H), 7.70 (1H, d, H_a)
30	3421, 3329 (NH_2), 2220 (C≡N), 975 (CH=CH, *trans*)	1.87, 2.79, 3.03 (8H, m, cyclohexyl-H), 5.08 (2H, br, NH_2), 7.15 (1H, d, H_b) 7.52-7.34 (5H, m, phenyl-H), 7.55 (1H, d, H_a)
31	3420, 3331 (NH_2), 1635 (C=O), 970 (CH=CH, *trans*)	1.76, 2.96-2.69 (8H, m, cyclohexyl-H), 2.30 (3H, s, $COCH_3$), 4.13 (2H, br, NH_2), 7.24 (1H, d, H_b), 7.68-7.24 (5H, m, phenyl-H), 7.70 (1H, d, H_a)
32	3420, 3330 (NH_2), 1659 (C=O), 975 (CH=CH, *trans*)	1.20 (3H, t, CH_3), 1.75, 2.94-2.68 (8H, m, cyclohexyl-H), 4.12 (2H, q, OCH_2), 6.50 (2H, br, NH_2), 7.24 (1H, d, H_b), 7.64-7.24 (5H, m, phenyl-H), 7.67 (1H, d, H_a)
33	3425, 3329 (NH_2), 2220 (C≡N), 970 (CH=CH, *trans*)	1.80-1.58, 3.10-2.88 (10H, m, cycloheptyl-H), 6.25 (2H, br, NH_2), 6.66 (1H, d, H_b) 7.64-7.36 (5H, m, phenyl-H), 7.68 (1H, d, H_a)
34	3420, 3320 (NH_2), 1635 (C=O), 975 (CH=CH, *trans*)	1.78-1.49, 3.09-2.73 (10H, m, cycloheptyl-H), 2.49 (3H, s, $COCH_3$), 6.67 (1H, d, H_b) 7.33-7.16 (5H, m, phenyl-H), 7.42 (1H, d, H_a)
35	3395, 3325 (NH_2), 1660 (C=O), 975 (CH=CH, *trans*)	1.26 (3H, t, CH_3), 1.87-1.57, 3.00-2.80 (10H, m, cycloheptyl-H), 4.80 (2H, q, OCH_2) 7.00 (1H, d, H_b), 7.41-7.29 (5H, m, phenyl-H), 7.62 (1H, d, H_a)

[a] Line shapes: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

showed a three proton singlet at δ 2.49 assigned to the 6-methyl group and the 4-styryl proton signal in compound **23** appear at δ 7.94-7.34 (7H, m). The physical constants and spectral data of polyfunctionally substituted 3-aminothieno[2,3-*b*]pyridine derivatives **15-35** are recorded in Tables 2-5.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on potassium bromide disks on a JASCO FTIR-3 spectrometer. The ^1H nmr spectra were obtained on a Bruker AM-300 WB FT-NMR spectrometer and chemical shifts are expressed in δ ppm using TMS as an internal standard. Electron impact mass spectra were obtained at 70 eV using a Finingan Mat TSQ-46C spectrometer. Microanalyses for C, H, and N were performed on a Perkin-Elmer 240 elemental analyzer.

3-Cyano-6-methyl-2(1*H*)-pyridinethione (**2a**).

To a solution of **1a** (1.53 g, 0.01 mole) and thiourea (1.52 g, 0.02 mole) in ethanol (20 ml) was refluxed for 5 hours. After cooling, the precipitate was filtered and recrystallized from acetic acid to obtain **2a** (1.38 g, 92%), mp 292°; ir: ν 3320 (NH), 2250 (C≡N), 1311, 1195 (C=S) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.37 (3H, s, CH_3), 6.70 (1H, d, 5-H), 7.96 (1H, d, 4-H), 14.06 (1H, br, NH); ms: M^+ 150.

Anal. Calcd. for $C_7H_6N_2S$: C, 55.98; H, 4.0; N, 18.67. Found: C, 55.87; H, 3.97; N, 18.69.

3-Cyano-4,6-dimethyl-2-(1*H*)-pyridinethione (**2b**).

The same procedure as described for **2a** was applied except **1b** was used in place of **1a**. The product recrystallized from acetic acid to yield **2b** (1.28 g, 78%), mp 264°; ir: ν 3352 (NH), 2230 (C≡N), 2225, 1210 (C=S) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.29 (3H, s, 4-CH_3), 2.32 (3H, s, 6-CH_3), 6.67 (1H, s, 5-H), 13.80 (1H, br, NH); ms: M^+ 164.

Anal. Calcd. for $C_8H_8N_2S$: C, 58.54; H, 4.88; N, 17.07. Found: C, 58.66; H, 4.90; N, 17.25.

3-Cyano-6-methyl-4-styryl-2(1*H*)-pyridinethione (**5b**).

To a solution of **2b** (1.64 g, 0.01 mole) in dioxane (20 ml), benzaldehyde (1.16 g, 0.11 mole) and a catalytic amount of piperidine were added. The reaction mixture was refluxed for 36 hours. After cooling, the precipitate was filtered and recrystallized from DMF/acetic acid to yield **5b** (1.34 g, 53%), mp 304-305°; ir: ν 3408 (NH), 2235 (C≡N), 1214 (C=S), 975 (CH=CH, *trans*) cm^{-1}; uv (acetone): λ_{max} 434 nm, log ε 3.54; ^1H nmr (DMSO-d_6): δ 2.38 (3H, s, CH_3), 7.15 (1H, s, 5-H), 7.20 (1H, d, H_b), 7.68-7.47 (5H, m, phenyl-H), 7.8 (1H, d, H_a), 13.75 (1H, br, NH); ms: M^+ 252.

Anal. Calcd. for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10. Found: C, 71.38; H, 4.86; N, 11.06.

3-Cyano-4,6-distyryl-2(1*H*)-pyridinethione (**5c**).

Method A.

The filtrate from the above reaction **5b** was poured into cold water (60 ml) and stirred for 0.5 hours. The resulting precipitate was collected by filtration and washed with ether, the crude product recrystallized from dioxane to yield 4,6-distyryl-3-cyano-2-(1*H*)-pyridinethione **5c** (1.02 g, 30%), mp 177°; uv (acetone): λ_{max} 476 nm, log ε 3.52; ir: ν 3405 (NH), 2218 (C≡N), 1205 (C=S), 965 (CH=CH, *trans*) cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.19 (1H, s, 5-H), 7.98-7.22 (14H, m, 4,6-styryl-H), 13.71 (1H, br, NH); ms: M^+ 340.

Anal. Calcd. for $C_{22}H_{16}N_2S$: C, 77.65; H, 4.70; N, 8.24. Found: C, 77.42; H, 4.83; N, 8.26.

Method B.

To a solution of **2b** (1.64 g, 0.01 mole) in dioxane (20 ml), benzaldehyde (2.32 g, 0.022 mole) and piperidine (1 ml) were added. The reaction mixture was refluxed for 36 hours. After cooling, the reaction mixture was poured into cold water (60 ml)

and stirred for 0.5 hours and acidified with 10% hydrochloric acid. The resulting precipitate was collected by filtration and recystallized to obtain **5c** (3.22 g, 95%).

Cinnamylidencyanothioacetamide (**7**).

To a solution of cinnamaldehyde **6** (1.32 g, 0.01 mole) in ethanol (10 ml), cyanothioacetamide **3** (1.0 g, 0.01 mole) and a few drops of triethylamine were added. The reaction mixture was stirred at 30-40° for 0.5 hours. The resulting solid product was collected by filtration and washed with ether, and recrystallized from ethanol to obtain **7** (1.46 g, 98%), mp 149°; ir: ν 3379, 3358 (NH_2), 2224 (C≡N), 1288, 1180 (C=S), 978, 973 (CH=CH, *trans*) cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.15 (1H, q, H_b), 7.34 (1H, d, H_a), 7.68-7.46 (5H, m, phenyl-H), 7.95 (1H, d, H_c), 9.42 (1H, br, NH), 9.93 (1H, br, NH), ms: M^+ 214.

Anal. Calcd. for $C_{12}H_{10}N_2S$: C, 67.29; H, 4.76; N, 13.08. Found: C, 67.20; H, 4.78; N, 13.05.

3-Cyano-5,6-cyclopenteno-4-styryl-2(1*H*)-pyridinethione (**12a**).

To a mixture of cinnamylidencyanothioacetamide **7** (2.14 g, 0.01 mole) and cyclopentanone **9a** (1.26 g, 0.015 mole) in dioxane (5 ml), a few drops of piperidine was added. The mixture was refluxed for 4 hours, and then allowed to stand overnight. The resulting solid product was collected by filtration and recrystallized from DMF/acetic acid to obtain **12a** (1.48 g, 53%), mp 320°; ir: ν 3427 (NH), 2220 (C≡N), 1225 (C=S), 970 (CH=CH, *trans*) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.92-2.11 (6H, m, cyclopentyl-H), 7.22 (1H, d, H_b), 7.67-7.42 (5H, m, phenyl-H), 7.69 (1H, d, H_a), 14.2 (1H, br, NH); ms: M^+ 278.

Anal. Calcd. for $C_{17}H_{14}N_2S$: C, 73.38; H, 5.04; N, 10.07. Found: C, 73.14; H, 5.24; N, 10.16.

3-Cyano-5,6-cyclohexeno-4-styryl-2(1*H*)-pyridinethione (**12b**).

This compound (1.46 g, 0.005 mole) was synthesized in 50% yield from cinnamylidencyanothioacetamide **7** (2.14 g, 0.01 mole) and cyclohexanone **9b** (1.47 g, 0.015 mole) in a similar way to that described for the preparation of **12a**. An analytical sample was recrystallized from DMF/acetic acid to give yellow needles of **12b**, mp 279-277°; ir: ν 3300 (NH), 2221 (C≡N), 1255, 1204 (C=S), 970 (CH=CH, *trans*) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.72-1.69 (8H, m, cyclohexyl-H), 7.19 (1H, d, H_b), 7.65-7.25 (5H, m, phenyl-H), 7.66 (1H, d, H_a), 13.73 (1H, br, NH); ms: M^+ 292.

Anal. Calcd. for $C_{18}H_{16}N_2S$: C, 73.97; H, 5.48; N, 9.59. Found: C, 73.53; H, 5.57; N, 9.68.

3-Cyano-5,6-cyclohepteno-4-styryl-2(1*H*)-pyridinethione (**12c**).

This compound (0.77 g, 0.0025 moles) was synthesized in 25% yield from cinnamylidencyanothioacetamide **7** (2.14 g, 0.01 mole) and cycloheptanone **9c** (1.68 g, 0.015 moles) in a manner similar to that described for the preparation of **12a**. An analytical sample was recrystallized from DMF/acetic acid to give **12c**, mp 274°; ir: ν 3388 (NH), 2217 (C≡N), 1252, 1203 (C=S), 976 (CH=CH, *trans*) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.76-1.53, 2.98-2.68 (10H, m, cycloheptyl-H), 7.25 (1H, d, H_b), 7.65-7.24 (5H, m, phenyl-H), 7.67 (1H, d, H_a), 13.8 (1H, br, NH); ms: M^+ 306.

Anal. Calcd. for $C_{19}N_{18}N_2S$: C, 74.51; H, 5.88; N, 9.15. Found: C, 74.24; H, 5.93; N, 9.21.

General Procedure of Polyfunctionally Substituted 3-Amino-2-substituted-thieno[2,3-*b*]pyridines **15-35**.

To a solution of pyridine-2(1*H*)-thione (**2a-2b**, **5b-5c**, **12-35**) (0.01 mole) in DMF (50 ml), potassium carbonate anhydrous (2.76 g, 0.02 mole) and chloroacetonitrile (substituted chloroacetone, ethyl chloroacetate) (0.01 mole) were added. The reaction mixture was stirred at room temperature for 4 hours and then diluted with cold water (50 ml). The resulting solid product was collected by filtration, washed with water, to obtain the 3-aminothieno[2,3-*b*]pyridine derivatives **12-35**. The physical constants and spectral data of 3-aminothieno[2,3-*b*]pyridines derivatives **12-35** are shown in Tables 2, 3, 4 and 5.

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