Acid Catalyzed α-Alkylation of β-Aminothiophenes with Aldehydes. Synthesis of 2-Alkyl 3-thiophenamines, Bis(3-amino-2-thienyl)-methane Derivatives and Dithieno[3,2-*b*:2',3'-*e*]pyridines

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The acid catalyzed reaction of 3-thiophenamines with aldehydes in the presence of selenophenol as the reducing agent, gives 2-alkyl-3-thiophenamines. Without reduction, bis(3-amino-2-thienyl)methane derivatives have been obtained and transformed into dithieno[3,2-*b*:2',3'-*e*]pyridines by thermal and acidic treatment when the substrates are primary amines. These new tricyclic heterocycles can be synthesized in a one-pot procedure from 3-thiophenamine.

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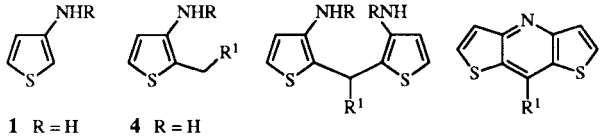
The synthesis of azaheterocycles starting from thiophenamines has been studied in the laboratory for a long time. We have especially focused our interest on the study of 3-thiophenamine and 3,4-thiophenediamine derivatives [1]. In this field, we have shown that secondary and tertiary amines are easily prepared by reduction of amides and carbamates [2].

In a study concerning the *N*-alkylation of 3-thiophenamines **1**, we observed the formation of 2-alkyl-3-thiophenamines **4**, isolated as acetamides, when amine **1** was reacted with an aldehyde in the presence of selenophenol as the reducing agent under acidic conditions. This unexpected α-alkylation reaction was also applied to 3,4-thiophenediamine [2]. The highly enaminic character of these β-aminothiophenes explains the reaction [3].

We decided to extend this work to amines **1**, **2** and **3** using various aldehydes and we have been able to synthesize 2-alkyl-3-thiophenamines **4**, **5** and **6** and bis(3-amino-2-thienyl)methane derivatives **7**, **8** and **9**. Compounds **7** (R = H) can be transformed into dithieno-[3,2-*b*:2',3'-*e*]pyridines **10** (Scheme 1). The first results have been presented in two notes [4,5]. We wish here to describe a more complete study of this reaction between aminothiophenes **1**, **2** and **3** and aldehydes (or acetals) under acidic conditions.

Scheme 1



1 R = H
2 R = Me
3 R = Et

4 R = H
5 R = Me
6 R = Et

7 R = H
8 R = Me
9 R = Et

10

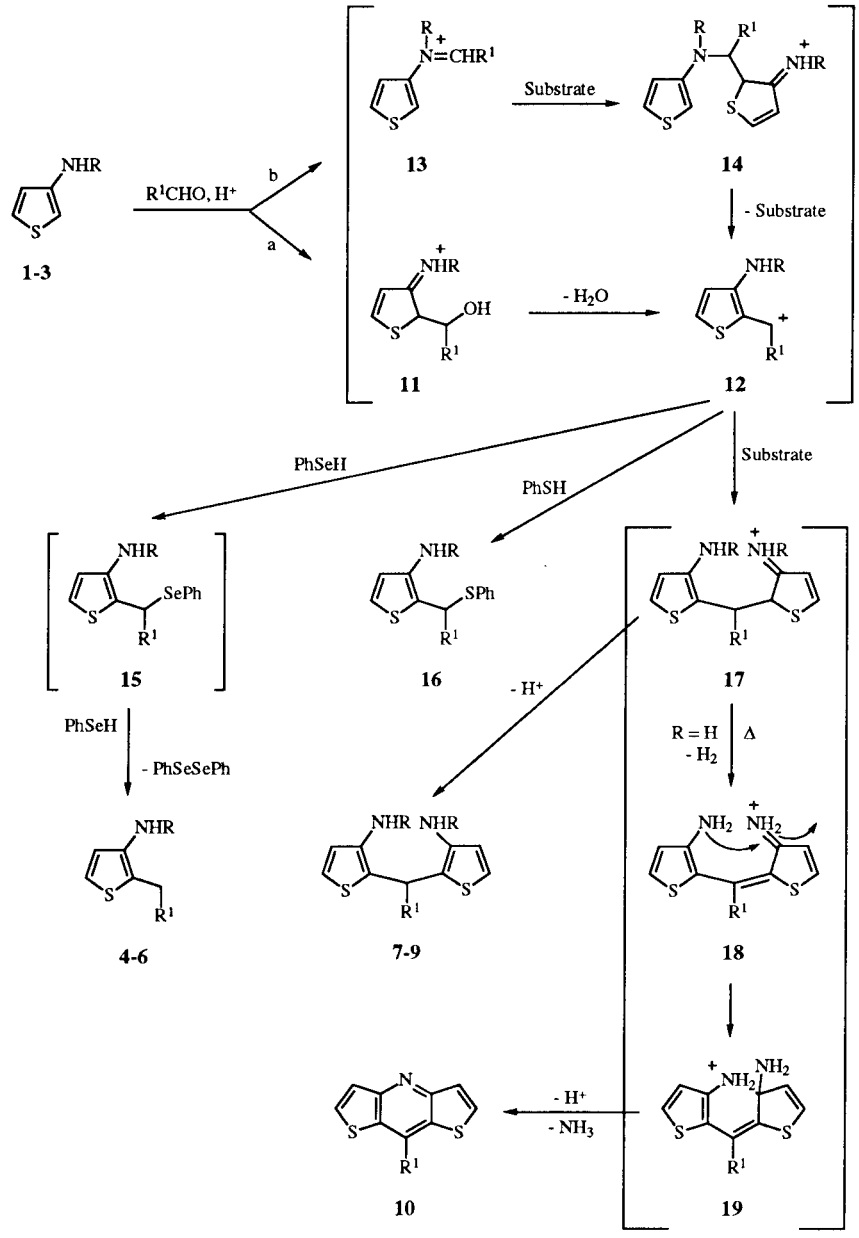
At the beginning of our study on 3-thiophenamine **1**, the goal was to achieve the *N*-alkylation reaction using the classic reductive amination of carbonyl compounds, selenophenol being the reductive agent [6]. This selenol was obtained *in situ* by hypophosphorous acid reduction of diphenyl diselenide. The isolation of *C*-alkylated products was explained by the presence of acid [2]. Under neutral conditions and without a reducing agent, a complex mixture of products was obtained. With these observations in hand, we then verified that amine **1** and propanal in dichloromethane at 0°, with excess of selenophenol and traces of *p*-toluenesulfonic acid, gave 2-propyl-3-thiophenamine **4c** in 78% yield after work-up (Scheme 2, Table 1, entry 2).

The reaction was extended to various aromatic and aliphatic aldehydes and 2-alkyl-3-thiophenamines **4** were isolated in good yields (Table 1). We observed also that with benzaldehyde, *N*-benzyl-3-thiophenamine **20** was formed besides 2-benzyl-3-thiophenamine **4e** (ratio **4e/20**:3/1) (Scheme 3). The same observation was made when an aromatic aldehyde was used and the competitive *N*-alkylation explains the relative low yields for the synthesis of compounds **4** or **5** (Table 1, entries 4, 6, 13).

The examination of Table 1 shows that various aliphatic aldehydes can be used: cyclohexanecarbaldehyde (entry 5), 2-methoxyethanal (entry 7), 3-methylthiopropanal (entry 8), and methyl 5-oxopentanoate (entry 10). The reaction also succeeded with secondary amines **2** and **3**. The yields are lower with α-branched aldehydes (entries 3, 5, 13). A complex mixture is formed with aqueous formaldehyde and 2-methyl-3-thiophenamine **4a** cannot be isolated. We also observed that no reaction occurs on *N,N*-dimethyl-3-thiophenamine **21** and that substitution of selenophenol by thiophenol leads to sulfides **16** (R = H, R^1 = Me or Et) (Scheme 2) when ethanal or propanal reacted with amine **1**. The isolation of 2-alkyl-3-thiophenamines **4-6** results from a PhSeH reduction of intermediates **15** through a selenophilic attack of the PhSe group in a pseudo-benzylic position (Scheme 2).

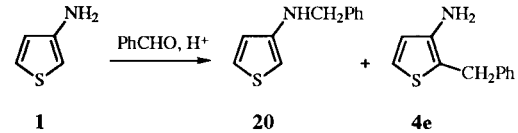
As selenoethers **15** and thioethers **16** arise from the carbonium ions **12**, we first thought that **12** derives from

Scheme 2



the alcohols **11** produced in a direct *C*-alkylation reaction (Scheme 2, path a) [4], but the failure of the reaction with tertiary amine **21** seems to indicate that an initial formation of iminium cations **13**, occurs and that **13** are the true alkylating agents for the substrates (path b). This proposition is in agreement with the mechanism proposed for the formation of *p*-aminobenzyl aryl sulfides and aryl selenides resulting from an acid-catalyzed condensation of aromatic amines with formaldehyde and thiophenol or selenophenol [7]. The ^{1}H nmr data of 2-alkyl-3-thiophenamines **4-6** are gathered together in Table 2.

Scheme 3



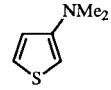


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Table 1

Physical Data of 2-Alkyl-3-thiophenamines **4-6**

Entry	No.	R	R'	Yield %	Formula	Analysis % Calcd./Found C	H	N
1	**4b**	H	Me	84	C_6H_9NS (127.2)	56.65	7.13	11.01
						56.42	7.03	10.65
2	**4c**	H	Et	78	$C_7H_{11}NS$ (141.2)	59.53	7.85	9.92
						59.31	7.78	10.27
3	**4d**	H	iPr	60	$C_8H_{13}NS$ (155.3)	61.89	8.44	9.02
						61.52	8.08	9.18
4	**4e**	H	Ph	56	$C_{11}H_{11}NS$ (189.3)	69.80	5.86	7.40
						69.66	5.67	7.05
5	**4f**	H	*c*-C_6H_{11}	40	$C_{11}H_{17}NS$ (195.3)	67.64	8.77	7.17
						67.87	8.51	7.10
6	**4g**	H	2-Thienyl	60	$C_9H_9NS_2$ (195.3)	55.35	4.65	7.17
						55.51	4.27	7.03
7	**4h**	H	CH_2OMe	50	$C_7H_{11}NOS$ (157.2)	53.47	7.05	8.91
						53.72	6.89	8.68
8	**4i**	H	$(CH_2)_2SMe$	45	$C_8H_{13}NS_2$ (187.3)	51.30	7.00	7.48
						51.14	6.85	7.22
9	**4j**	H	CH_2Ph	45	$C_{12}H_{13}NS$ (203.3)	70.89	6.45	6.89
						70.61	6.19	6.72
10	**4k**	H	$(CH_2)_3COOMe$	65	$C_{10}H_{15}NO_2S$ (213.3)	56.34	7.04	6.57
						56.42	7.13	6.63
11	**5b**	Me	Me	75	$C_7H_{11}NS$ (141.2)	59.53	7.85	9.92
						59.65	7.93	9.72
12	**5c**	Me	Et	60	$C_8H_{13}NS$ (155.3)	61.89	8.44	9.02
						62.13	8.61	8.75
13	**5d**	Me	iPr	42	$C_9H_{15}NS$ (169.3)	63.86	8.93	8.27
						64.32	9.06	8.58
14	**5e**	Me	Ph	62	$C_{12}H_{13}NS$ (203.3)	70.89	6.45	6.89
						70.59	6.72	6.75
15	**6b**	Et	Me	82	$C_8H_{13}NS$ (155.3)	61.89	8.44	9.02
						61.68	8.21	9.24
16	**6c**	Et	Et	77	$C_9H_{15}NS$ (169.3)	63.86	8.93	8.27
						63.91	8.74	8.10

Table 2

^{1}H NMR Data of 2-Alkyl-3-thiophenamines **4-6**

^{1}H NMR, δ ppm ($CDCl_3$), $J_{H4,H5}$ = 5.4 Hz

No.	H_4	H_5	H_{CH2}	H_{R1}	H_R [a]
4b	6.54	6.91	2.60 (q)	1.24 (t)	
4c	6.54	6.91	2.55 (t)	1.78 (m), 0.97 (m)	
4d	6.57	6.95	2.46 (d)	1.85 (m), 0.96 (d)	
4e	6.51	6.92	3.97 (s)	7.20 (s)	
4f	6.55	6.92	2.46 (d)	2.14-2.51 (m)	
4g	6.51	6.91	4.11 (s)	7.12, 7.46, 7.72	
4h	6.54	6.91	2.83 (t)	3.56 (t), 3.35 (s)	
4i	6.51	6.91	2.52 (t)	2.71 (t), 2.07 (s), 1.87 (m)	
4j	6.53	6.91	2.87 (s)	2.87 (s), 7.20 (m)	
4k	6.60	6.88	2.55 (t)	3.62 (s), 2.30 (t), 1.64 (m)	
5b	6.72	7.00	2.60 (q)	1.25 (t)	2.87 (s)
5c	6.73	7.01	2.57 (t)	1.78 (m), 0.98 (t)	2.88 (s)
5d	6.70	7.02	2.44 (d)	1.85 (m), 0.94 (d)	2.84 (s)
5e	6.74	7.04	3.93 (s)	7.24 (s)	2.81 (s)
6b	6.68	6.97	2.55 (q)	1.24 (t)	3.16 (q), 1.20 (t)
6c	6.68	6.97	2.54 (t)	1.77 (m), 0.96 (t)	3.15 (q), 1.19 (t)

[a] The signals of amine protons appear in the range 3-3.5 ppm.

Table 3

Analytical Data of Bis(3-Amino-2-thienyl)methane Derivatives **7-9**

Entry	No.	R	R'	Method	Yield %	Mp (°C)	Formula	Analysis % Calcd./Found C	H	N
1	**7a**	H	H	A	40	105	$C_9H_{10}N_2S_2$ (210.3)	51.40 51.12	4.79 4.62	13.32 13.05
2	**7b**	H	Me	B	80	99	$C_{10}H_{12}N_2S_2$ (224.4)	53.54 53.25	5.39 5.02	12.49 12.05
3	**7c**	H	Et	B	84	70	$C_{11}H_{14}N_2S_2$ (238.4)	55.42 54.99	5.92 5.72	11.75 11.47
4	**7d**	H	CH(Me)Et	A	70	75	$C_{13}H_{18}N_2S_2$ (266.4)	58.61 58.40	6.81 6.59	10.51 10.32
5	**7e**	H	Ph	B	75	102	$C_{15}H_{14}N_2S_2$ (286.4)	62.90 62.72	4.93 4.68	9.78 9.51
6	**7f**	H	CH_2OMe	B	70	—	$C_{11}H_{14}N_2OS_2$ (254.4)	51.94 52.12	5.55 5.32	11.01 10.58
7	**7g**	H	CH_2SePh	A	67	104	$C_{16}H_{16}N_2S_2Se$ (379.4)	50.65 51.08	4.25 4.20	7.38 7.15
8	**7h**	H	$(CH_2)_2SPh$	A	70	—	$C_{17}H_{18}N_2S_3$ (346.5)	58.92 58.63	5.24 5.07	8.08 7.78
9	**7i**	H	$(CH_2)_2SePh$	A	75	—	$C_{17}H_{18}N_2S_2Se$ (393.4)	51.90 51.58	4.61 4.32	7.12 6.89
10	**7j**	H	$CH_2CH(Me)SePh$	A	60	—	$C_{18}H_{20}N_2S_2Se$ (407.5)	53.06 52.85	4.95 4.68	6.88 6.71
11	**8**	Me	Et	A	95	90	$C_{13}H_{18}N_2S_2$ (266.4)	58.61 58.80	6.81 6.82	10.51 10.09
12	**9**	Et	Et	A	78	71	$C_{15}H_{22}N_2S_2$ (294.5)	61.18 61.02	7.53 7.27	9.51 9.33

Table 4

^1H and ^{13}C NMR Data of Bis(3-amino-2-thienyl)methane Derivatives **7-9**

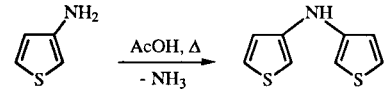
	δ ppm, ($CDCl_3$)								
	(J_{H4H5} = 5.4 Hz)								
No.	H_4	H_5	H_{CH}	$H_{R'}$	H_R	C_α	C_β	C_{CH}	$C_{R'}$
7a	6.51	6.94	4.35 (s)						
7b	6.50	6.94	4.25 (q)	1.65 (d)		121.8	121.3	39.7	33.8
7c	6.48	6.94	3.97 (t)	2.07 (m) 0.98 (t)		121.8	121.5	36.5	27.7, 13.3
7d	6.47	6.95	3.91 (d)	0.81		122.6	121.7	41.6	40.6, 27.9, 17.7, 11.5
7e	6.50	6.94	5.42 (s)	7.28 (m)		122.7	121.9	41.7	128.7, 128.4, 127.3
7f	6.50	6.95	4.42 (t)	3.64 (d) 3.36 (s)		122.1	121.7	36.6	58.9, 32.6
7g	6.50	6.97	4.38 (t)	3.55 (t) 7.23-7.49 (m)		122.1	121.7	36.7	132.8, 129.1, 127.1, 34.5
7h	6.51	6.95	4.49 (t)	3.00 (t) 2.36 (m) 7.23 (s)		121.8	121.1	33.5	129.1, 128.9, 126.1, 34.7, 31.6
7i	6.50	6.95	4.45 (t)	2.99 (t) 2.39 (m) 7.22-7.45 (m)		121.8	121.8	34.6	132.4, 129.1, 126.9, 35.7, 26.1
7j	6.51	6.94	4.62 (t)	3.22 (q) 2.26 (t) 1.44 (d) 7.23-7.47 (m)		122.5	121.6	36.4	135.1, 128.9, 127.6, 43.8, 34.2, 23.5
8	6.68	7.02	3.95 (t)	2.08 (m) 0.98 (t)	2.78 (s)	121.8	118.6	37.5	33.7, 29.7, 12.7
9	6.66	7.00	4.00 (t)	2.07 (m) 0.98 (t)	3.03 (q) 1.06 (t)	122.0	121.1	36.8	34.2, 27.3, 25.7, 11.9

When PhSeH was omitted and with a ratio amine/aldehyde: 2/1, the bis(3-amino-2-thienyl)methane derivatives **7**, **8** or **9** were isolated in good yields (Method A) (Table 3). The same results were observed when a 12*N* hydrochloric acid solution was added to the amine and the aldehyde in dichloromethane (Method B). We must point out that bis(3-amino-2-thienyl)methane **7a** was formed, although in a modest yield, when an aqueous solution of formaldehyde was reacted with amine **1** (Method A). Phenylselenoethanal (entry 7), 3-phenylselenopropanal (entry 9), 3-phenylselenobutanal (entry 10) were used to give the selenides **7g**, **7i** and **7j** respectively in order to prepare the corresponding olefins through an oxidation followed by a *syn*-elimination reaction of the intermediate selenoxides, but **7g** led only to the dithienopyridine **10s** (see below).

Concerning the mechanism of formation of the dithienyl compounds **7**, **8** and **9**, it appears that the carbonium ions **12** are electrophilic toward a molecule of substrate, giving the products *via* **17** after a new *C*-alkylation reaction (Scheme 2). The ^{1}H nmr data of bis(3-amino-2-thienyl)methane derivatives **7-9** are given in Table 4.

On some occasions, we have observed the formation of the corresponding dithienopyridines **10**, as by-products, beside **7** when a greater amount of *p*-toluenesulfonic acid

Scheme 4



1 **22**

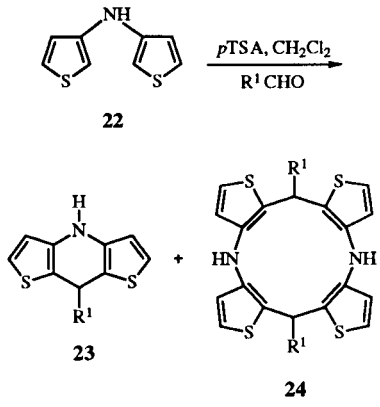
Table 5

Analytical Data of Dithieno[3,2-*b*:2',3'-*e*]pyridines **10**

Entry	No.	R'	Yield %	Mp (°C)	Formula	Analysis % Calcd./Found C	H	N
1	**10a**	H	86	155	[8]			
2	**10b**	Me	81	116	[8]			
3	**10c**	Et	60	102	$C_{11}H_9NS_2$ (219.3)	60.24	4.14	6.39
						60.32	4.22	6.44
4	**10d**	nPr	55	oil	$C_{12}H_{11}NS_2$ (233.4)	61.77	4.75	6.00
						61.51	4.52	5.81
5	**10e**	iPr	65	oil	$C_{12}H_{11}NS_2$ (233.4)	61.77	4.75	6.00
						61.72	4.68	5.91
6	**10f**	Bn	70	120	$C_{16}H_{11}NS_2$ (281.4)	68.29	3.94	4.98
						68.41	3.82	4.75
7	**10g**	Ph	76	174	$C_{15}H_9NS_2$ (267.4)	67.38	3.39	5.24
						67.78	3.26	5.18
8	**10h**	2-Thienyl	50	145	$C_{13}H_7NS_3$ (273.4)	57.11	2.58	5.12
						56.80	2.33	5.06
9	**10i**	$CH{=}CMe_2$	80	125	$C_{14}H_{11}NS_2$ (257.4)	65.33	4.31	5.44
						65.41	4.17	5.28
10	**10j**	COOEt	74	162	$C_{12}H_9NO_2S_2$ (263.4)	54.73	3.45	5.32
						54.40	3.14	5.01
11	**10k**	$(CH_2)_2SMe$	72	100	$C_{12}H_{11}NS_3$ (265.4)	54.30	4.18	5.28
						54.32	4.52	5.33
12	**10l**	$(CH_2)_2SPh$	75	65	$C_{17}H_{13}NS_3$ (237.5)	62.35	4.00	4.28
						62.22	3.88	4.19
13	**10m**	$(CH_2)_2SePh$	70	49	$C_{17}H_{13}NS_2Se$ (274.4)	54.54	3.50	3.74
						54.28	3.37	3.54
14	**10n**	$CH_2CH(Me)SePh$	85	oil	$C_{18}H_{15}NS_2Se$ (288.4)	55.66	3.89	3.61
						55.85	3.96	3.47
15	**10o** [a]	CH_2OMe	55	130	$C_{11}H_9NOS_2$ (235.3)	56.14	3.86	5.95
						56.01	3.75	5.71
16	**10p** [a]	CH_2NHMe	60	oil	$C_{11}H_{10}N_2S_2$ (274.4)	56.38	4.30	11.95
						56.19	4.25	11.83
17	**10q** [b]	$CH{=}CH_2$	77	103	$C_{11}H_7NS_2$ (217.3)	60.80	3.25	6.45
						60.81	3.42	6.12
18	**10r** [c]	CH=CHMe	70	105	$C_{12}H_9NS_2$ (231.3)	62.30	3.92	6.06
						62.41	3.98	5.92
19	**10s**	CH_2SePh	60	120	$C_{16}H_{11}NS_2Se$ (360.4)	53.33	3.08	3.89
						53.73	2.91	4.09
20	**10t** [d]	$CH_2Se(O)Ph$	65	125	$C_{16}H_{11}NOS_2Se$ (376.4)	51.06	2.95	3.72
						50.85	2.83	3.57

[a] From the corresponding dimethylacetal. [b] Oxidation of **10m**. [c] Oxidation of **10n**. [d] Oxidation of **10s**.

Scheme 5



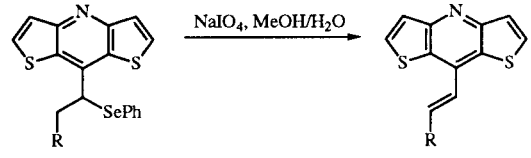
is added (trifluoroacetic acid gave the same result). Two steps are involved in the mechanism of formation of the tricyclic pyridines **10** involving dehydrogenation and transamination reactions (Scheme 2). Some years ago, this last reaction was studied on 3-thiophenamine **1** itself [2b] (Scheme 4).

Taking into account this observation, we were able to synthesize the dithienopyridines **10** in good yields, on heating bis(3-amino-2-thienyl)methane derivatives **7** in dichloromethane in the presence of trifluoroacetic acid (one equivalent) [5]. The question was to determine the order of the two sequences: loss of hydrogen and transamination. When the alkylation reaction leading to **7**, was applied to the bis(3-thienyl)amine **22**, the dihydrodithienopyridines **23** were isolated beside the corresponding dimers **24** as minor products (Scheme 5). The dimers became the major components when a greater amount of *p*TSA was used with a longer reaction time [4].

We were not able to oxidize the dihydropyridines **23** into the corresponding dithienopyridines **10**. With these observations, we assume that the dehydrogenation reaction precedes the transamination-cyclization step (Scheme 2).

All the reactions **1** → **12** → **17** → **18** → **10** are acid-catalyzed or allowed in acidic media. We then verified that the dithienopyridines **10** can be prepared in good yield in a one-pot reaction from 3-thiophenamine **1** (Tables 5 and 6). The inspection of Table 5 shows that aliphatic aldehydes (entries 1-6) aromatic aldehydes (entries 7, 8), conjugated enal (entry 9), ethyl glyoxylate (entry 10), β-methylthio-, β-phenylthio-, β-phenylselenoaldehydes (entries 11-14) phenylselenoethanal (entry

Scheme 6



10m R = H
10n R = Me

10q
10r

Table 6

^1H and ^{13}C NMR Data of Dithieno[3,2-*b*:2',3'-*e*]pyridines **10**

No.	H_α	H_β	$J_{H\alpha H\beta}$ = 5.6 Hz $H_{R'}$	C_α	C_β	$C_{R'}$
			δ ppm, ($CDCl_3$)			
10a	7.73	7.55	8.60 (s)	131.3	124.5	124.3
10b	7.72	7.55	2.76 (s)	130.3	125.2	16.9
10c	7.74	7.56	3.16 (q), 1.44 (t)	130.3	125.2	27.6, 12.3
10d	7.72	7.55	3.10 (t), 1.87 (m), 1.00 (t)	130.3	125.1	36.2, 21.3, 14.2
10e	7.73	7.56	3.54 (m), 1.57 (d)	130.2	125.0	35.1, 20.3
10f	7.73	7.54	4.50 (s), 7.6-7.8 (m)	130.7	125.1	129.1, 128.6, 127.1, 40.0
10g	7.73	7.59	7.5-7.9 (m)	131.6	125.0	129.6, 129.2, 126.6
10h	7.71	7.53	7.77 (q), 7.51 (q), 7.19 (q)	127.9	125.1	131.4, 129.1, 127.9
10i	7.72	7.56	6.46 (m), 2.03 (d), 1.63 (d)	130.9	124.6	119.0, 25.8, 20.9
10j	7.72	7.53	4.60 (q), 1.53 (t)	133.4	124.1	62.8, 14.3
10k	7.73	7.54	3.41 (m), 2.91 (s)	130.3	125.2	34.2, 31.7, 15.7
10l	7.71	7.55	3.38 (m), 7.1-7.5 (m)	130.4	125.2	129.8, 129.0, 126.6, 34.5, 31.4
10m	7.70	7.55	3.27-3.46 (m), 7.2-7.5 (m)	132.9	125.2	130.4, 129.1, 127.1, 35.4, 24.0
10n	7.67	7.57	4.07 (d), 3.40 (m), 1.36 (d), 7.2-7.5 (m)	130.5	125.0	135.1, 128.9, 127.9, 42.9, 36.4, 21.6
10o	7.76	7.57	5.00 (s), 3.46 (s)	131.4	124.5	71.8, 58.1
10p	7.75	7.57	4.32 (s), 2.46 (s)	131.4	124.5	53.5, 36.3
10q	7.74	7.58	7.15 (dd), 6.37 (d, J = 17.4 Hz), 5.97 (d, J = 11.3 Hz)	130.5	124.9	132.0, 123.0
10r	7.74	7.58	7.21 (m), 6.88 (m), 2.11 (d)	131.4	125.0	127.4, 118.3, 19.5
10s	7.68	7.53	4.47 (s), 7.10-7.45 (m)	130.6	124.9	135.1, 129.0, 128.3, 29.1
10t	7.71	7.54	4.85 (d), 4.29 (d, J = 11.6 Hz), 7.24-7.40 (m)	131.6	125.1	131.0, 129.3, 125.7, 62.8

19) can be used in this reaction. The access to the methoxymethyl pyridine **10o** (entry 15) and to the *N*-methylaminomethylpyridine **10p** (entry 16), was allowed when the corresponding dimethyl acetals were employed.

We were also able to synthesize the vinylic dithienopyridines **10q** (entry 17) and **10r** (entry 18) through a sodium periodate oxidation of selenides **10m** and **10n**, respectively, into selenoxides which immediately undergo a syn-elimination reaction (Scheme 6). With the same treatment, the phenylselenomethyldithienopyridine **10s** has given the stable selenoxide **10t** (entry 20, Table 5).

The two first dithienopyridines **10a** and **10b** are already known and obtained, in low yields, by hot aqueous acidic treatment of 3-acetylamino-2-thiophenecarbaldehyde and 3-acetylamino-2-thienylethanone respectively [8]. The ^1H and ^{13}C nmr data of dithienopyridines **10** are assembled in Table 6.

This work has shown that the enaminic 3-thiophenamine **1**, known as unstable, and its *N*-methyl and *N*-ethyl derivatives **2** and **3** undergo an *C*-α-alkylation leading to 2-alkyl-3-thiophenamines **4-6** when they are treated with aliphatic or aromatic aldehydes under acid catalysis, in the presence of selenophenol as a reducing agent. Without reduction and a ratio amine/aldehyde:2/1, the bis(3-amino-2-thienyl)methane derivatives **7-9** are formed. With more forcing conditions (acidity, temperature), the dithienopyridines **10** are prepared in good yields, in a one-pot procedure from 3-thiophenamine **1**.

EXPERIMENTAL

3-Thiophenamine **1** was prepared by the method proposed by Reinecke [9]. The synthesis of *N*-methyl-3-thiophenamine **2**, *N*-ethyl-3-thiophenamine **3**, *N*-benzyl-3-thiophenamine **20**, *N,N*-dimethyl-3-thiophenamine **21** has been previously described [2a]. Phenylselenoethanal, was prepared from ethyl vinyl ether and benzeneselenenyl chloride [10]. 3-Phenylselenopropanal [11] and 3-phenylselenobutanal [11] were synthesized from acrolein and crotonaldehyde respectively by reaction with selenophenol in the presence of triethylamine according to a general method applied to the synthesis of the corresponding phenylthio ethers [12]. Ethyl glyoxylate was obtained through the reaction of ozone on diethyl maleate [13]. The ^1H and ^{13}C nmr spectra were recorded on a Bruker AC 200 spectrometer with tetramethylsilane as an internal reference. Elemental analysis were performed on a Carlo-Erba CHNS-O 1106 automatic analyzer. The chromatographic purifications were carried out on Acros 0.060-0.200 mm silica gel (pore diameter *ca.* 4 nm) or on Aldrich basic activated aluminium oxide (Brockmann I, standard grade).

General Procedure for the Synthesis of 2-Alkyl-3-thiophenamines **4-6**.

A cold solution (0°) of 3-thiophenamine **1** (or **2** or **3**) (2 mmoles) in dichloromethane (20 ml) was added quickly to the aldehyde (2 mmoles) in dichloromethane (10 ml) containing selenophenol (0.785 g, 5 mmoles) and stirred over an ice-bath. A solution of *p*-toluenesulfonic acid (*p*TSA) (20 mg) in the same solvent (dissolution on heating) is then added dropwise. The mixture is stirred 3 hours at room temperature and extracted twice with a 1*N* hydrochloric acid solution (25 ml). The aqueous phase is washed by ether and then basified by a 4*N* sodium hydroxide solution in the presence of ether (30 ml). The aqueous solution is extracted three times with ether (10 ml) and the organic layers are dried and concentrated. The residual oil is chromatographed on basic alumina (elution hexane-chloroform 60/40).

Preparation of 2-(1-Phenylthioalkyl)-3-thiophenamines **16**.

The experimental procedure is the same as that described for the synthesis of 2-alkyl-3-thiophenamines **4-6** except that selenophenol is replaced by thiophenol (0.330 g, 2.5 mmoles). The crude products contain 5-10% of the corresponding dithienopyridines **10**. They are purified by chromatography on basic alumina (elution hexane/chloroform 95/5).

2-(1-Phenylthioethyl)-3-thiophenamine **16a**.

The product was obtained in 65% yield as an oil; ^1H nmr (deuteriochloroform): δ 1.65 (d, CH_3), 4.48 (q, CH), 6.49 (d, H_4, J = 5.4 Hz), 6.95 (d, H_5, J = 5.4 Hz), 7.23-7.30 (m, C_6H_5).

Anal. Calcd. for $C_{12}H_{13}NS_2$ (235.4): C, 61.24; H, 5.57; N, 5.95. Found: C, 61.47; H, 5.68; N, 5.77.

2-(1-Phenylthiopropyl)-3-thiophenamine **16b**.

The product was obtained in 55% yield as an oil; ^1H nmr (deuteriochloroform): δ 1.00 (t, CH_3), 1.98 (m, CH_2), 4.21 (t, CH), 6.45 (d, H_4, J = 5.4 Hz), 6.94 (d, H_5, J = 5.4 Hz), 7.23-7.30 (m, C_6H_5).

Anal. Calcd. for $C_{13}H_{15}NS_2$ (249.4): C, 62.61; H, 6.06; N, 5.62. Found: C, 62.37; H, 5.91; N, 5.47.

General Procedure for the Synthesis of Bis(3-amino-2-thienyl)-methane Derivatives **7-9**.

Method A.

A solution of the aldehyde (1.1 mmoles) in dichloromethane (10 ml) containing *p*TSA (15 mg), previously dissolved as above, is added dropwise to the aminothiophene (2 mmoles) in the same solvent (20 ml) at -5°. The mixture is stirred for 1.5 hours at room temperature. The solution is washed with 1*N* sodium hydroxide solution (10 ml), then with water. The organic phase is dried, concentrated *in vacuo* and the oily residue is chromatographed on basic alumina (elution hexane/dichloromethane 60/40). The solid thienylamines **6-8** are recrystallized in a mixture hexane/chloroform (95/5).

Method B.

The aldehyde (1.1 mmoles) is added to a solution of aminothiophene (2 mmoles) in dichloromethane (20 ml). A 12*N* aqueous hydrochloric acid solution (0.5 ml) is then introduced dropwise. A precipitate appears after two minutes. The suspension is stirred for 40 minutes at room temperature and the solid is isolated, washed with dichloromethane (30 ml), dissolved in water (20 ml). In the presence of dichloromethane (30 ml), treatment with a 1*N* aqueous sodium hydroxide solution allows the transfer of the product to the organic layer which is then separated. The basic aqueous solution is extracted with the same solvent (25 ml). The organic fractions are dried and concentrated under reduced pressure. The thienylamines **6-8** are purified as in method A.

Synthesis of Dithieno[3,2-*b*:2',3'-*e*]pyridines **10**.

A. Direct Preparation Using an Aldehyde.

A cold solution of the aldehyde (1.1 mmoles) in dichloromethane (15 ml) containing trifluoroacetic acid (10 mg) is added dropwise to 3-thiophenamine **1** (0.198 g, 2 mmoles) in the same solvent (15 ml) at -5°. After stirring for 1.5 hours at room temperature, trifluoroacetic acid (0.228 g, 2 mmoles) is again added. The solution is heated for 3 hours under reflux and the solvent is then evaporated. The oily residue is dissolved in ether (20 ml) and treated with a 0.5*N* aqueous sodium hydroxide solution (10 ml). Water is added (10 ml), the organic phase separated and the aqueous layer extracted with ether (20 ml). The organic fractions are dried and concentrated. The solid dithienopyridines are recrystallized from a hexane/chloroform mixture (95/5). The oily dithienopyridines are purified by chromatography on silica gel (elution hexane/dichloromethane 90/10).

B. Direct Preparation of **10o** and **10p** Using an Acetal.

A solution of 3-thiophenamine **1** (0.198 g, 2 mmoles) and methoxyacetaldehyde dimethylacetal (0.132 g, 1.1 mmoles) (for the preparation of **10o**) or *N*-methylaminoacetaldehyde dimethylacetal (0.131 g, 1.1 mmoles) (for **10p**) in dichloromethane (20 ml) is treated with a 12*N* aqueous hydrochloric acid solution (0.5 ml). The mixture is stirred for 2 hours at room temperature, and then basified with a 4*N* aqueous sodium hydroxide solution. The two layers are separated and the aqueous layer is extracted with dichloromethane (20 ml). The organic fractions are dried and concentrated. The oily dithienopyridine is purified by chromatography on silica gel (elution hexane/ethyl acetate 90/10).

C. Synthesis from the Bis(3-amino-2-thienyl)methane Derivatives **7**.

A solution of substrate **6** (2 mmoles) and trifluoroacetic acid (0.228 g, 2 mmoles) in dichloromethane (30 ml) is heated for 3 hours under reflux. The preceeding procedure is then followed.

D. Synthesis of 8-Vinyl and 8-(1-Propenyl)dithieno[3,2-*b*:2',3'-*e*]pyridines **10q** and **10r**.

According to a known method [14], the phenylselenoalkyldithienopyridine **10m** (or **10n**) (1 mmole) in a mixture methanol/water 3/2 (30 ml) containing triethylamine (0.070 g) is treated with sodium periodate (0.220 g) in small portions. The reaction is stirred for 1 hour at room temperature and the product extracted with dichloromethane (2 x 20 ml). The organic layer is washed, dried and concentrated under reduced pressure. The dithienopyridines **10q** and **10r** are recrystallized in hexane.

E. Synthesis of 8-Phenylseleninyldithieno[3,2-*b*:2',3'-*e*]pyridine **10t**.

Following the same procedure [14], the selenide **10s** was oxidized. The *syn*-elimination reaction gives the stable selenoxide **10t**. The appearance of a selenium asymmetric center causes the non-equivalence of the two methylenic protons and two doublets appear in the ^{1}H nmr spectra (J = 11.6 Hz) (Table 6).

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