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Acid Catalyzed α-Alkylation of β-Aminothiophenes Using Aldehydes and Selenophenol Synthesis of Bis(3-amino-2-thienyl)methane Derivatives

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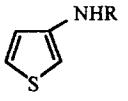
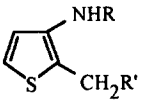
Abstract : *The acid-catalyzed reaction between β-aminothiophenes and aldehydes, in the presence of selenophenol, leads to α-alkyl β-aminothiophenes. The reduction step is not observed with thiophenol. Without selenol, a second alkylation reaction occurs and bis(3-amino-2-thienyl)methane derivatives are isolated.*

In the course of a study concerning the N-alkylation of 3-aminothiophene **1**,[1] we observed the formation of 2-alkyl-3-aminothiophenes **4** isolated as acetamides when **1** was reacted with an aldehyde in the presence of selenophenol generated "in situ" from diphenyldiselenide under acidic conditions.[2] This unexpected reductive C-alkylation reaction succeeded also with 3,4-diaminothiophene[3] leading to α,α'-dialkylated thiophenes,[2] as a consequence of the high enaminic character of these amines.[4]

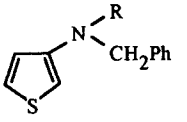
We now wish to present our results concerning the study and the scope of these reaction applied to β-aminothiophenes **1**, **2** and **3**. We present an efficient method for the synthesis of 2-alkyl-3-amino-thiophenes and bis(3-amino-2-thienyl)methane derivatives.



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



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

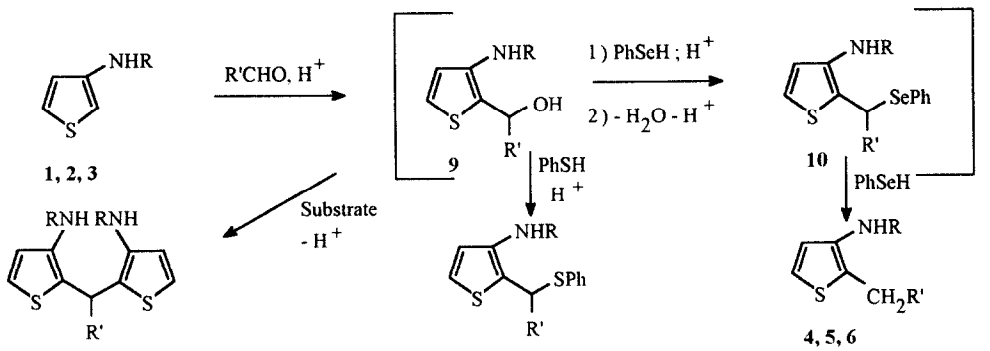


7 R = H
8 R = Me

Without any trace of acid, the reaction of the amine **1** with an aliphatic or aromatic aldehyde in dichloromethane affords a mixture which contains an amino-alcohol **9** as a major product[5] (Scheme). The best conditions for the synthesis of α-alkylated thiophenes **4**, **5** and **6** were then determined. Selenophenol itself is used as reducing agent and a catalytic amount of p-toluenesulfonic acid is added.[6] We presumed that the selenide **10**, formed from the alcohol **9**, is reduced through a selenophile attack of a second molecule of selenophenol (Scheme). The results are summarized in Table 1.

All the α-alkyl β-aminothiophenes **4**, **5** and **6** are oily compounds stable enough to be distilled under reduced pressure or chromotographied. They can be stored in the cold for at least one week without degradation. As seen in the table, the yields lower with the size of the aldehyde and when the nitrogen atom bears an alkyl substituent.[7] With benzaldehyde, the N-benzylated 3-aminothiophenes **7**[1] and **8**[1] were formed in minor amounts beside the C-alkylated thiophenes **4d** and **5d** respectively.

Scheme



12 R = H a) R' = Me b) R' = Et c) R' = Ph **11a** R = H R' = Me
13 R = Me R' = Et **11b** R = H R' = Et
14 R = Et R' = Et

Table 1

2-Alkyl 3-aminothiophenes **4**, **5**, **6**.

N°	R	CH_2R'	Yield %	^{1}H-NMR			
				H_4 (a)	H_5	H_R (b)	$H_{CH_2R'}$
4a (c)	H	Et	84	6.54	6.91	-	1.24 (t), 2.60 (q)
4b (c)	H	nPr	78	6.54	6.92	-	0.97 (t), 1.78 (m), 2.55 (d)
4c	H	iBu	60	6.57	6.95	-	0.96 (d), 1.85 (m), 2.46 (d)
4d	H	Bn	40	6.51	6.92	-	3.97 (s), 7.20 (s)
5a	Me	Et	75	6.72	7.00	2.87	1.25 (t), 2.60 (q)
5b	Me	nPr	60	6.73	7.01	2.88	0.98 (t), 1.78 (m), 2.57 (t)
5c	Me	iBu	42	6.70	7.02	2.84	0.94 (d), 1.85 (m), 2.44 (d)
5d	Me	Bn	36	6.74	7.04	2.81	3.93 (s), 7.24 (s)
6a (c)	Et	Et	82	6.68	6.97	1.20 (t) 3.16 (q)	1.24 (t), 2.55 (q)
6b (c)	Et	nPr	77	6.68	6.97	1.19 (t) 3.15 (q)	0.96 (t), 1.77 (m), 2.54 (t)

(a) $J_{H_4H_5}$=5.37 Hz ; (b) The signal of the aminic proton appear between 3 and 3,5 ppm ; (c) : **4a** ($bp_{0.01}$=38-40°C), **4b** ($bp_{0.01}$=40-44°C), **6a** ($bp_{0.01}$=45-50°C), **6b** ($bp_{0.01}$=45-50°C).

Addition of thiophenol in the media, in the place of selenophenol, gave the phenylthiomethyl derivative **11** when the reaction was carried out on amine **1** with propanal.[8] The last step of reduction does not occur as expected for a thioether.

When the reaction was carried out without selenophenol, with a catalytic amount of p-toluenesulfonic acid and one-half equivalent of aldehyde, the bis (3-amino 2-thienyl) methane derivatives **12, 13 and 14** were isolated.[9] (Table 2) In these conditions, the pseudo-benzylic carbonium ion derived from the alcohol **9** is an electrophile for a second molecule of substrate (Scheme).

Table 2

Bis (3-amino 2-thienyl) methane derivatives **12, 13, 14**.

N°	R	R'	F°C	Yield %	^{1}H-NMR				
					H_4 (b)	H_5	H_R	$H_{\alpha'}$	$H_{R'}$
				(a)					
12a	H	Me	99	80	6.50	6.94	-	4.25 (q)	1.65 (d)
12b	H	Et	70	84	6.48	6.94	-	3.97 (t)	0.98 (t)
									2.07 (m)
12c	H	Ph	45	75	6.50	6.94	-	5.42 (s)	7.28 (m)
13	Me	Et	90	95	6.68	7.02	2.78 (s)	3.95 (t)	0.98 (t)
									2.08 (m)
14	Et	Et	71	78	6.66	7.00	1.06 (t)	4.00 (t)	0.98 (t)
							3.03 (q)		2.07 (m)

(a) Yields are given before recrystallisation.[8] ; (b) $J_{H_4H_5}$=5,37 Hz.

The extension of these work concerning the α-alkylation of 3-aminothiophènes, using functionalized, unsaturated aldehydes, is under investigation. The synthesis of dithieno[3,2-b:2',3'-e]pyridines from bis (3-amino 2-thienyl) methane derivatives **12** was also achieved for the first time.[10]

REFERENCES AND NOTES

1. Outurquin, F.; Lerouge, P.; Paulmier, C. *Bull. Soc. Chim. Fr.*, **1986**, 259-66.
2. Outurquin, F.; Lerouge, P.; Paulmier, C. *Bull. Soc. Chim. Fr.*, **1986**, 267-75.
3. Outurquin, F.; Paulmier, C. *Bull. Soc. Chim. Fr.*, **1983**, II, 153-8.
4. Terrier, F.; Pouet, M.J.; Kizilian, E.; Halle, J.C.; Outurquin, F.; Paulmier, C. Submitted to publication.
5. Amines **1**, **2**, **3**, aldehydes and selenophenol are used freshly distilled. The intermediate **9** (R = H, R' = Et) is characterized by its ^{1}H-NMR spectra ($CDCl_3$) : 1.13 (t, 3H), 1.85 (m, 2H), 3.7 (br.s, NH_2, OH), 5.24 (t, 1H), 6.34 (d, H_4), 6.94 (d, H_5). $J_{4,5}$=6.4 Hz. Without acid catalysis, a mixture of **9**, amine **1**, its corresponding imine and an unidentified compound, is formed. The acid catalysis favors the C-attack.

6. In a typical procedure : A cold CH_2Cl_2 solution (10 ml) of amine **1** (1 mmol) is added to propanal (1.2 mmol) and selenophenol (2.5 mmol) in CH_2Cl_2 containing a catalytic amount of p-toluenesulfonic acid. (Trifluoroacetic acid was also tested but with less good results). After stirring one hour ($0° \rightarrow 20°C$), the alkylated aminothiophene **4b** is extracted with 1N HCl solution. The aqueous phase is washed with ether, treated with 4N NaOH solution to liberate the amine which is extracted with ether. After evaporation of the solvent, the residue is chromatographed (basic alumina, petroleum ether/CH_2Cl_2 80/20) or distilled (Table 1)
7. 3-(Dimethylamino)thiophene, in the same conditions, gave no C-alkylated product.
8. The sulfides **11a** and **11b** were obtained as crude products containing 5-10 % of **12a** and **12b** respectively. ^{1}H-NMR ($CDCl_3$) : **11a** : 1.65 (d, 3H), 3.4 (br. s, NH_2), 4.48 (q, 1H), 6.49 (d, H_4), 6.95 (d, H_5). $J_{H_4H_5}$=5.37 Hz. **11b** : 1.0 (t, 3H), 1.98 (m, 2H), 3.4 (br. s, NH_2), 4.21 (t, 1H), 6.45 (d, H_4), 6.94 (d, H_5). $J_{H_4H_5}$=5.37 Hz.
9. In a typical procedure : A cold solution of aldehyde (1.1 mmol) in CH_2Cl_2 (15 ml) is added dropwise, at -5°C, to the aminothiophene **1**, **2**, or **3** (2 mmol) in the same solvent (15 ml) containing trace amounts of pTSA. After stirring (1.5 h) at room temperature, the solution is washed with aqueous 1M NaOH and with water. The solvent is eliminated and the oily residue crystallises. The dithienylmethane derivatives **12**, **13** and **14** were purified by chromatography (basic alumina, elution hexane/CH_2Cl_2. The recrystallisation was achieved in hexane/$CHCl_3$ 90/10.
10. Outurquin, F.; Paulmier, C. following letter.

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