Pergamon

Tetrahedron 55 (1999) 6511–6526

TETRAHEDRON

Convenient Amination of Weakly Activated Thiophenes, Furans and Selenophenes in Aqueous Media

Damien Prim*, Gilbert Kirsch*

Laboratoire de Chimie Organique, Groupe de Synthèse Organique et Hétérocyclique, UFR SciFA, Université de Metz, Ile du Saulcy, 57045 METZ, France.

Received 7 August 1998; accepted 6 April 1999

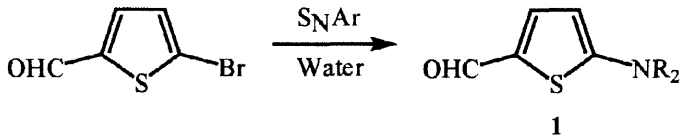
Dedicated to Pr. S. Gronowitz for his contribution to heterocyclic chemistry

Abstract: We describe herein a new amination procedure of weakly activated heterocyclic bromo derivatives in aqueous media. The base catalysed mechanism of this reaction is also confirmed. Moreover, the application of this strategy to the preparation of amino furans and selenophenes is outlined.

INTRODUCTION

The aromatic nucleophilic substitution (S_NAr) is an attractive method for introducing amino groups at the thiophene nucleus[1]. In these S_NAr reactions, the thiophene nucleus is generally substituted by at least one strong electron withdrawing group such as a nitro group[1, 2]. Among the solvents used in S_NAr studies[3], the nucleophilic displacement of an halide by a secondary amine requires polar solvents as acetonitrile, DMF, DMSO or methanol[4]. To our knowledge, only few examples of S_NAr using moderatly activated bromine atoms have been described[2-4]. In these reports, the desired amino derivatives were obtained in modest to good yields.

In a recent paper, we reported a convenient preparation of 5-*N,N*-disubstituted-aminothiophene-2-carboxaldehydes **1** by S_NAr in water from the corresponding bromo derivative[5] (Scheme 1).



1

Scheme 1

We showed that quantitative yields can be obtained in aqueous conditions even when the thiophene ring is weakly activated. This method is a useful alternative to the synthetic methods of aminothiophenes which have been reviewed a few years ago[6].

* Fax: int-3 87 31 53 33; E-mail: prim@sciences.univ-metz.fr; kirsch@sciences.univ-metz.fr

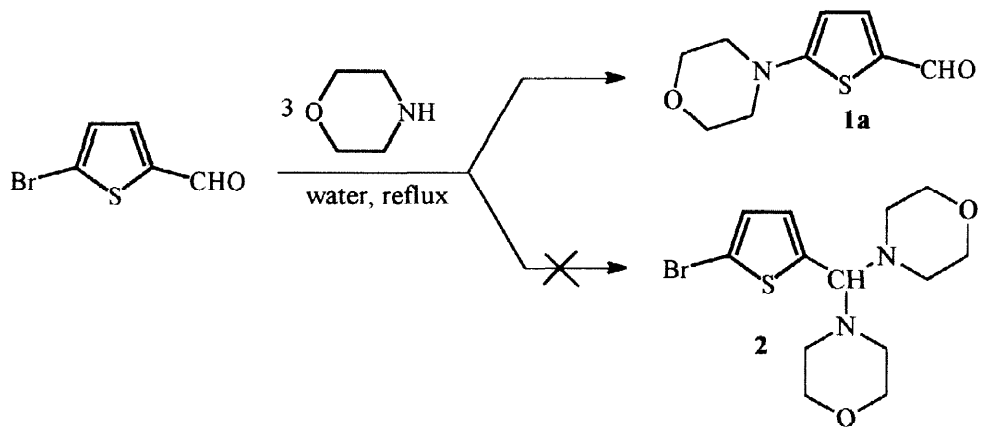
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00318-X

In the present paper, we first wish to discuss the mechanism of aqueous S_NAr with neutral nucleophiles. Secondly, we report the extension of the aqueous amination process to the preparation of 2-acetyl-5-aminothiophenes and various 3-aminothiophenes. We also describe the application of the strategy for the preparation of *N,N*-disubstituted aminofurans and selenophenes.

RESULTS AND DISCUSSION

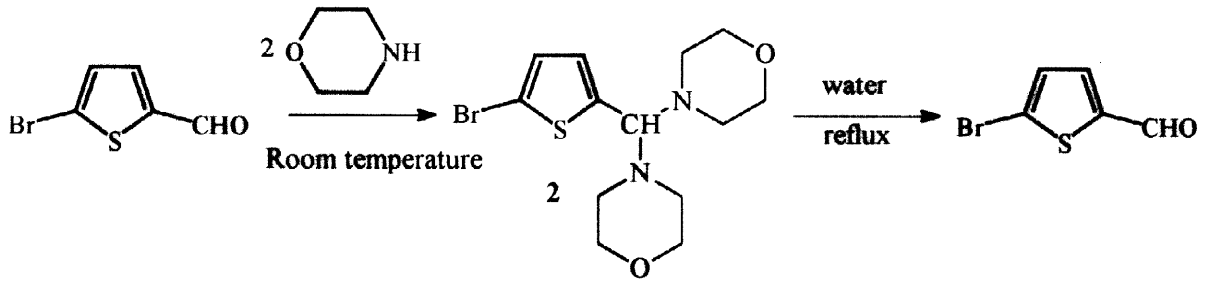
The first part of this paper is dealing with mechanistic aspects of the S_NAr reaction in water. For the following study, we choosed 5-morpholino-thiophene-2-carboxaldehyde **1a** as model compound because morpholine is mildly nucleophilic and basic.

As carboxaldehydes readily react with amines to afford aminals[7], we first wanted to know if this type of reaction occurred in the S_NAr process : 5-bromothiophene-2-carboxaldehyde was refluxed for 12 hours with 3 eq. of morpholine in water but no traces of the aminal **2** could be detected (Scheme 2). In this reaction conditions, only the aminothiophene **1a** was obtained in high yield.



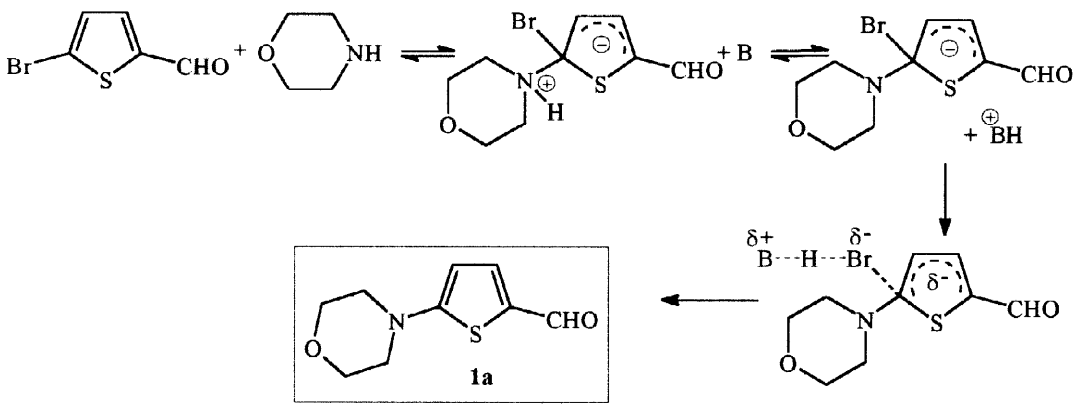
Scheme 2

However, mixing 5-bromothiophene-2-carboxaldehyde and morpholine at room temperature gave the aminal **2** but at least a 2 : 1 aminal / aldehyde ratio was required to ensure completion of the reaction. The crystalline aminal **2** was isolated and characterized. Refluxing **2** in water regenerated the aldehyde in less than 5 minutes (Scheme 3). These two experiences prove that in refluxing water only the S_NAr took place.



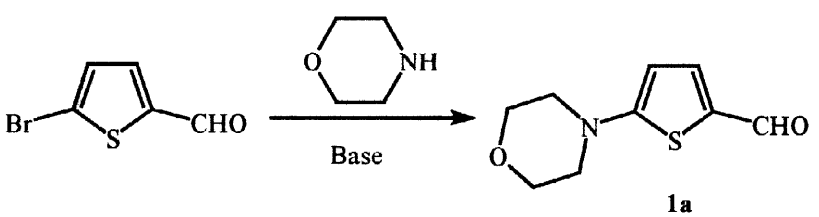
Scheme 3

We showed previously[5], that the S_NAr reaction needs an excess of base to succeed. In fact, the amine plays the role of nucleophile and base. Its role is illustrated in the following mechanism reported earlier by Bunnett[8] (Scheme 4).



Scheme 4

The use of different tertiary amines as base in the reaction of 5-bromo-thiophene-2-carboxaldehyde with 1.1 equivalent of morpholine gave the results shown below in Scheme 5 and Table 1.



Scheme 5

Table 1: Time for the disappearance of 5-bromothiophene-2-carboxaldehyde in the presence of morpholine and a tertiary amine

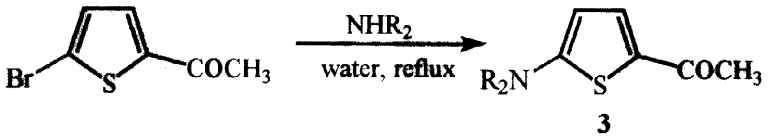
Base	Eq.	pKa	Time (h)
pyridine	2	5.1	48
N-methylmorpholine	2	7.4	14
N-methylpiperidine	2	10.1	12
triethylamine	2	10.7	11
triethylamine	4	10.7	4
DABCO	2	11.1	2

Times for reaction completion have been determined by gas chromatography. They are reduced from 48 hours to 2 hours by going from pyridine to the more basic DABCO. This supports the fact that the deprotonation of the first generated intermediate is rate determining (Scheme 3).
Nevertheless, if Table 1 shows spectacular rate increase by using 4 equivalents of triethylamine or 2 equivalents of DABCO, we recommend to avoid the use of DABCO due to purification problems.

On the other hand, we observed amination rate increase in presence of water as a solvent[5] by comparison with other polar solvents[4]. As recently described by Spinelli[9], it is probable that in S_NAr processes, involving amine nucleophiles, solvation as well as steric and electronic effects come into play. Moreover, when the reaction is carried out in deoxygenated water, in the absence of light and oxygen as suggested by Marquet[10] and others[11, 12], no variations of the reaction rates are observed, suggesting that no radical intermediates are involved.

In a second part, we report the application of the S_NAr in aqueous media to the preparation of 2-acetyl-5(or 3)-aminothiophenes and 3-aminothiophene-2-carboxaldehydes.

Amination of 2-acetyl-5-bromothiophene has been realised by using 3 eq. of the reacting amine in refluxing water (Scheme 6, Table 2). Aminothiophenes **3** were obtained in high yields as indicated in Table 2.

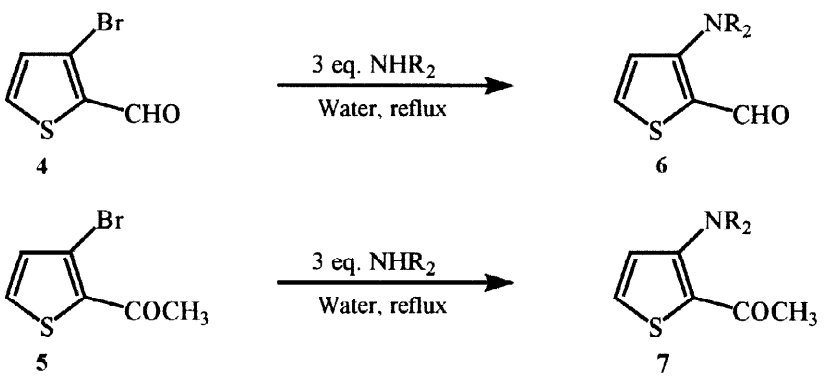


Scheme 6

Table 2: Synthesis of 5-amino-2-acetylthiophenes **3**

Entry	Compound	Amine	Eq.	Time(h)	Yield(%)
1	**3a**	Morpholine	3	12	88
2	**3b**	Piperidine	3	12	85
3	**3c**	Dimethylamine	3	12	90
4	**3d**	Pyrrolidine	3	12	82
5	**3e**	4-hydroxy-piperidine	3	12	79
6	**3f**	diphenylamine	3	24	-

The same strategy was then applied to the 3-bromothiophenes **4** and **5** leading to the corresponding amino derivatives **6** and **7** (Scheme 7, Table 3).



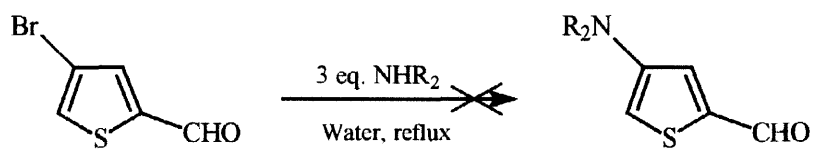
Scheme 7

The reactions were performed in boiling water for the time indicated in Table 3. The yields ranged from 59 to 75%. In both cases, no reaction was observed with the weakly nucleophilic diarylamines even for prolonged heating times, the unchanged starting material being recovered.

Table 3: Synthesis of 3-aminothiophenes **6** and **7**

Entry	Compound	Amine	Eq.	Time(hr)	Yield(%)
1	**6a**	Morpholine	3	18	75
2	**6b**	Piperidine	3	18	73
3	**6c**	Dimethylamine	3	18	69
4	**6d**	Pyrrolidine	3	18	74
5	**6e**	4-hydroxy-Piperidine	3	18	68
6	**6f**	Diphenylamine	3	18	-
7	**7a**	Morpholine	3	24	61
8	**7b**	Piperidine	3	24	65
9	**7c**	Dimethylamine	3	24	66
10	**7d**	Pyrrolidine	3	24	55
11	**7e**	4-hydroxy-Piperidine	3	24	59
12	**7f**	Diphenylamine	3	24	-

In accordance with the experiments of Spinelli, [13] who described that only an activated bromine atom is substituted in S_NAr reactions, the isomeric 4-bromothiophene-2-carboxaldehyde did not give any amination product under these aqueous conditions, even after 72 hours (Scheme 8).

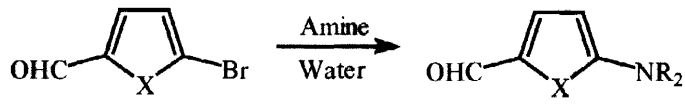


Scheme 8

Finally, we report the application of the aqueous amination procedure to the preparation of aminofurans and selenophenes.

In fact, a few preparations of aminofurans have been described by classical reduction or electroreduction of nitrofurans,[14-15] by reaction of a Grignard reagent to aminocyclobutenone,[16] by conversion of β-aroylpropionic acids with acetic anhydride and a mineral acid[17] or by direct amination of the parent iodo or bromo derivative under various experimental conditions with modest to good yields[18]. To the best of our knowledge, no *N,N*-disubstituted aminoselenophenes have been reported so far.

The results we have obtained, by reacting a secondary amine with 5-bromofuran-2-carboxaldehyde or 5-bromoselenophene-2-carboxaldehyde in aqueous conditions, are shown below (Scheme 9, Table 4).



8 X = O
9 X = Se

Scheme 9

Table 4: Synthesis of aminofurans **8** and -selenophenes **9**

Entry	X	Amine	Eq.	Time	Yield(%)	Product
1	O	morpholine	3	20 min	98	**8a**
2	O	piperidine	3	20 min	96	**8b**
3	O	dimethylamine	3	20 min	98	**8c**
4	Se	morpholine	3	10 hours	95	**9a**
5	Se	dimethylamine	3	12 hours	94	**9c**
6	Se	pyrrolidine	3	12 hours	91	**9d**

If selenophene reacts in 10 to 12 hours as the thiophene ring does, furan affords the corresponding amino derivatives in only 20 minutes with quantitative yields, thus denoting different reactivity for the three heterocycles, with the following order : O> S, Se.

CONCLUSION

In summary, we have developed a new and attractive general method of preparation of some *N,N*-disubstituted aminothiophenes, -furans and -selenophenes. This reaction is particularly adapted to weakly activated heteroaromatic ring systems.

EXPERIMENTAL

M.p.s were determined on a Kofler Bench and are uncorrected. ^{1}H and ^{13}C NMR spectra were respectively recorded on a Bruker AM 250 spectrometer at 250.13 and 62.89 MHz in deuterochloroform solution and chemical shifts (δ) are expressed in ppm relative to internal TMS. Elemental analyses were performed on a Carlo Erba elemental analyser, infrared spectra on a Perkin Elmer FTIR and UV-visible spectra on a Shimadzu 1250 apparatus.

5-bromo-2-(bismorpholino)methyl thiophene **2**:

To 2-bromothiophene-5-carboxaldehyde (176mg, 1mmol) was added morpholine (170mg, 2.1mmol). After cooling the mixture at 0°C, dry ether (10ml) was added. The solid was then filtrated and washed twice with ether (2x10ml).

mp: 128-129°C

IR (KBr) cm^{-1} : 2817, 1117. UV/Vis (MeOH) nm (ε): 243 (10300).

^{1}H NMR ($CDCl_3$) δ 2.46 (m, 8H, $NC\underline{H}_2$), 3.62 (m, 8H, $OC\underline{H}_2$), 3.85 (s, 1H, C<u>H</u>), 6.60 (d, 1H, H_3, J = 3.6 Hz), 6.89 (d, 1H, H_4, J = 3.6 Hz). ^{13}C NMR ($CDCl_3$) δ 140.4 (C_5), 128.9 (C_4), 126.9 (C_3), 112.8 (C_2), 84.7 (<u>C</u>H), 66.9 ($O\underline{C}H_2$), 49.6 ($N\underline{C}H_2$).

Typical procedure for the S_NAr in water: to the bromo derivative (20 mmol) and the secondary reacting amine (60mmol) was added 5ml of water. The resulting mixture was stirred at reflux for the appropriate time. The mixture was allowed to cool to room temperature. The precipitate was filtered off and washed twice with cold water or the reaction mixture was extracted twice with dichloromethane.

In the case of the preparation of 2-acetyl-5-aminothiophenes **3**, the reactants were heated at 120°C in a sealed tube for 18 hours. The same procedure as above can then be applied.

2-acetyl-5-morpholino-thiophene **3a**: mp: 126°C, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1615. UV/Vis (MeOH) nm (ε): 364 (46100).

^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H, $C\underline{H}_3$), 3.28 (t, 4H, $NC\underline{H}_2$, J = 5.8 Hz), 3.84 (t, 4H, $OC\underline{H}_2$, J = 5.8 Hz), 6.05 (d, 1H, H_4, J = 4.4 Hz), 7.46 (d, 1H, H_5, J = 4.5 Hz). ^{13}C NMR ($CDCl_3$) δ 189.1 (<u>C</u>O), 166.8 (C_5), 134.8 (C_3), 126.6 (C_2), 104.2 (C_4), 65.9 ($O\underline{C}H_2$), 49.6 ($N\underline{C}H_2$), 25.25 ($\underline{C}H_3$).

Elemental analysis: Calcd for $C_{10}H_{13}O_2NS$: C: 56.84, H: 6.20, N: 6.63. Found: C: 56.67, H: 6.43, N: 6.83.

2-acetyl-5-piperidino-thiophene **3b**: mp: 112°C, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1619. UV/Vis (MeOH) nm (ε): 372 (36500).

^1H NMR ($CDCl_3$) δ 1.68 (m, 6H, CH_2-C$\underline{H}_2$), 2.40(s, 3H, C$\underline{H}_3$), 3.29 (t, 4H, NC$\underline{H}_2$, J = 4.5 Hz), 5.98 (d, 1H, H_4, J = 3.75 Hz), 7.44 (d, 1H, H_5, J = 3.8 Hz). ^{13}C NMR ($CDCl_3$) δ 188.6 (C=O), 167.5 (C_5), 135.4 (C_3), 127.45 (C_2), 103.5 (C_4), 50.85 (N$\underline{C}H_2$), 24.8 (CH_2-$\underline{C}H_2$), 24.05 (CH_2-$\underline{C}H_2$), 23.5 ($\underline{C}H_3$). Elemental analysis: Calcd for $C_{11}H_{15}ONS$: C: 63.12, H: 6.69, N:7.22. Found: C: 63.28, H: 6.88, N: 7.41.

2-acetyl-5-*N,N*-dimethylamino-thiophene **3c**: mp: 87°C, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1601. UV/Vis (MeOH) nm (ε): 369 (15650).

^1H NMR ($CDCl_3$) δ 2.41 (s, 3H, C$\underline{H}_3$), 3.09 (s, 6H, NC$\underline{H}_3$), 5.85 (d, 1H, H_4, J = 4.1 Hz), 7.45 (d, 1H, H_5, J = 4.5 Hz). ^{13}C NMR ($CDCl_3$) δ 188.3 (C=O), 165.9 (C_5), 134.6 (C_3), 127.1(C_2), 103.2 (C_4), 45.3 (N$\underline{C}H_3$), 23.4 ($\underline{C}H_3$). Elemental analysis: Calcd for $C_8H_{11}ONS$: C: 56.80, H: 6.51, N: 8.28. Found: C: 57.02, H: 6.85, N: 8.12.

2-acetyl-5-pyrrolidino-thiophene **3d**: mp: 116°C, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1600. UV/Vis (MeOH) nm (ε): 375 (31100).

^1H NMR ($CDCl_3$) δ 2.07 (m, 4H, CH_2-C$\underline{H}_2$), 2.39 (s, 3H, C$\underline{H}_3$), 3.34 (m, 4H, NC$\underline{H}_2$), 5.74 (d, 1H, H_4, J = 4.3 Hz), 7.45 (d, 1H, H_5, J = 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ 188.15 (C=O), 163.45 (C_5), 136.05 (C_3), 126.4 (C_2), 101.8 (C_4), 50.5 (N$\underline{C}H_2$), 25.8 (CH_2-$\underline{C}H_2$), 23.6 ($\underline{C}H_3$).

Elemental analysis: Calcd for $C_{10}H_{13}ONS$: C: 61.51, H: 6.69, N: 7.19. Found: C: 61.63, H: 6.41, N: 7.05.

2-acetyl-5-(4-hydroxy)piperidino-thiophene **3e**: mp: 178°C, purification by flash chromatography on silica gel (AcOEt)

IR (KBr) cm^{-1} : 1615. UV/Vis (MeOH) nm (ε): 370 (25200).

^1H NMR ($CDCl_3$) δ 1.60 (brs, 1H, OH), 1.71 (m, 2H, CH_2-C$\underline{H}_2$), 2.04 (m, 2H, CH_2-C$\underline{H}_2$), 2.41 (s, 3H, C$\underline{H}_3$), 3.21 (m, 2H, NC$\underline{H}_2$), 3.61 (m, 2H, NC$\underline{H}_2$), 3.95 (m, 1H, C$\underline{H}$), 6.01(d, 1H, H_4, J = 5.2 Hz), 7.44 (d, 1H, H_5, J = 5.2 Hz). ^{13}C NMR ($CDCl_3$) δ 185.4 (C=O), 166.2 (C_5), 138.2 (C_3), 120.5 (C_2), 102.3 (C_4), 66.2 (C$\underline{H}$OH), 47.9 (N$\underline{C}H_2$), 33.8 (CH_2-$\underline{C}H_2$), 25.1 ($\underline{C}H_3$).

Elemental analysis: Calcd for $C_{11}H_{15}O_2NS$: C: 58.64, H: 6.71, N: 6.22. Found: C: 58.79, H: 6.72, N: 6.04.

3-morpholino-thiophene-2-carboxaldehyde **6a**: oil, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1650. UV/Vis (MeOH) nm (ε): 361 (8000).

^1H NMR ($CDCl_3$) δ 3.28 (t, 4H, NCH_2, J = 4.7 Hz), 3.78 (t, 4H, OCH_2, J = 4.7 Hz), 6.76 (d, 1H, H_4, J = 5.4 Hz), 7.56 (d, 1H, H_5, J = 5.3 Hz), 9.79 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 180.4 (CHO), 157.5 (C_3), 135.4 (C_5), 122.9 (C_2), 120.6 (C_4), 65.3 (OCH_2), 52.7 (NCH_2).

Elemental analysis: Calcd for $C_9H_{11}O_2NS$: C: 54.8, H: 5.62, N: 7.1. Found: C: 54.79, H: 5.71, N: 7.24.

3-piperidino-thiophene-2-carboxaldehyde **6b**: oil, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1630. UV/Vis (MeOH) nm (ε): 373 (12500).

^1H NMR ($CDCl_3$) δ 1.70 (m, 6H, CH_2-CH_2), 3.37 (t, 4H, NCH_2, J = 4.3 Hz), 6.77 (d, 1H, H_4, J = 5.3 Hz), 7.55 (d, 1H, H_5, J = 5.2 Hz), 9.90 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 181.1 (CHO), 158.9 (C_3), 135.4 (C_5), 121.6 (C_2), 121.1 (C_4), 54.4 (NCH_2), 25.8 (CH_2-CH_2), 23.8 (CH_2-CH_2). Elemental analysis: Calcd for $C_{10}H_{13}ONS$: C: 61.51, H: 6.71, N: 7.17. Found: C: 61.58, H: 6.88, N: 7.25.

3-*N,N*-dimethylamino-thiophene-2-carboxaldehyde **6c**: oil, purification by flash chromatography on silica gel ($CHCl_3$)

IR (KBr) cm^{-1} : 1622. UV/Vis (MeOH) nm (ε): 364 (15650).

^1H NMR ($CDCl_3$) δ 3.23 (s, 6H, NCH_3), 6.64 (d, 1H, H_4, J = 5.6 Hz), 7.53 (d, 1H, H_5, J = 5.5 Hz), 9.91 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 180.3 (CHO), 155.9 (C_3), 135.6 (C_5), 118.1 (C_2), 119.2 (C_4), 44.3 (NCH_3). Elemental analysis: Calcd for C_7H_9ONS: C: 54.17, H: 5.84, N: 9.02. Found: C: 54.02, H: 5.85, N: 9.12.

3-pyrrolidino-thiophene-2-carboxaldehyde **6d**: oil, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1611. UV/Vis (MeOH) nm (ε): 369 (12900).

^1H NMR ($CDCl_3$) δ 2.06 (m, 4H, CH_2-CH_2), 3.50 (m, 4H, NCH_2), 6.53 (d, 1H, H_4, J = 5.5 Hz), 7.50 (d, 1H, H_5, J = 5.5 Hz), 9.83 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 180.3 (CHO), 152.7 (C_3), 136.1 (C_5), 117.2 (C_2), 119.3 (C_4), 52.4 (NCH_2), 25.6 (CH_2-CH_2). Elemental analysis: Calcd for $C_9H_{11}ONS$: C: 59.64, H: 6.12, N: 7.73. Found: C: 59.63, H: 6.21, N: 7.75.

3-(4-hydroxy)piperidino-thiophene-2-carboxaldehyde **6e**: oil, purification by flash chromatography on silica gel (AcOEt)

IR (KBr) cm^{-1} : 1620. UV/Vis (MeOH) nm (ε): 367 (5850).

^1H NMR ($CDCl_3$) δ 1.73 (m, 2H, CH_2-$C\underline{H}_2$), 1.95 (brs, 1H, OH), 2.02 (m, 2H, CH_2-$C\underline{H}_2$), 3.21 (m, 2H, $NC\underline{H}_2$), 3.64 (m, 2H, $NC\underline{H}_2$), 3.92 (m, 1H, $C\underline{H}$), 6.78 (d, 1H, H_4, J = 5.6 Hz), 7.54 (d, 1H, H_5, J = 5.6 Hz), 9.86 (s, 1H, $C\underline{H}O$). ^{13}C NMR ($CDCl_3$) δ 180.9 ($\underline{C}HO$), 158.2 (C_3), 135.6 (C_5), 122.2 (C_2), 121.2 (C_4), 66.7 ($\underline{C}HOH$), 50.6 ($N\underline{C}H_2$), 34.1 (CH_2-$\underline{C}H_2$), 23.8 (CH_2-$\underline{C}H_2$).

Elemental analysis: Calcd for $C_{10}H_{13}O_2NS$: C: 56.85, H: 6.20, N: 6.63. Found: C: 56.99, H: 6.22, N: 6.74.

3-*N,N*-dibutylamino-thiophene-2-carboxaldehyde **6f**: oil, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1610. UV/Vis (MeOH) nm (ε): 374 (7950).

^1H NMR ($CDCl_3$) δ 0.90 (m, 6H, $C\underline{H}_3$), 1.20 (m, 4H, CH_2-$C\underline{H}_2$), 1.65 (m, 4H, CH_2-$C\underline{H}_2$), 3.39 (m, 4H, $NC\underline{H}_2$), 6.58 (d, 1H, H_4, J = 5.5 Hz), 7.50 (d, 1H, H_5, J = 5.5 Hz), 9.70 (s, 1H, $C\underline{H}O$).

^{13}C NMR ($CDCl_3$) δ 180.5 ($\underline{C}HO$), 154.3 (C_3), 136.1 (C_5), 117.8 (C_2), 119.7 (C_4), 54.7 ($N\underline{C}H_2$), 29.7 (CH_2-$\underline{C}H_2$), 29.1 ($\underline{C}H_2$-CH_2), 20.1 (CH_2-$\underline{C}H_3$), 11.4 ($\underline{C}H_3$). Elemental analysis: Calcd for $C_{13}H_{21}ONS$: C: 65.23, H: 8.84, N: 5.85. Found: C: 65.27, H: 8.91, N: 6.01.

2-acetyl-3-morpholino-thiophene **7a**: oil , purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1635. UV/Vis (MeOH) nm (ε): 353(11900).

^1H NMR (250 MHz, $CDCl_3$) δ 2.48 (s, 3H, $C\underline{H}_3$), 3.16 (t, 4H, $NC\underline{H}_2$, J = 4.5 Hz), 3.83 (t, 4H, $OC\underline{H}_2$, J = 4.6 Hz), 6.85 (d, 1H, H_4, J = 5.4 Hz), 7.41 (d, 1H, H_5, J = 5.4 Hz). ^{13}C NMR ($CDCl_3$) δ 188.4 ($\underline{C}O$), 156.8 (C_3), 134.7 (C_5), 123.1 (C_2), 121.1 (C_4), 65.7 ($O\underline{C}H_2$), 49.5 ($N\underline{C}H_2$), 29.2 ($\underline{C}H_3$). Elemental analysis: Calcd for $C_{10}H_{13}O_2NS$: C: 56.84, H: 6.20, N: 6.63. Found: C: 56.97, H: 6.03, N: 6.65.

2-acetyl-3-piperidino-thiophene **7b**: oil, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1625. UV/Vis (MeOH) nm (ε): 364 (12600).

^1H NMR ($CDCl_3$) δ 1.60 (m, 6H, CH_2-$C\underline{H}_2$), 2.46 (s, 3H, $C\underline{H}_3$), 3.04 (t, 4H, $NC\underline{H}_2$, J = 4.1 Hz), 6.82 (d, 1H, H_4, J = 5.4 Hz), 7.35 (d, 1H, H_5, J = 5.45 Hz). ^{13}C NMR ($CDCl_3$) δ 188.8 ($\underline{C}O$), 157.3 (C_3), 133.7 (C_5), 123.7 (C_2), 121.6 (C_4), 54.3 ($N\underline{C}H_2$), 25.7 ($\underline{C}H_3$), 24.7 (CH_2-$\underline{C}H_2$), 23.8 (CH_2-$\underline{C}H_2$). Elemental analysis: Calcd for $C_{11}H_{15}ONS$: C: 63.12, H: 6.69, N: 7.22. Found: C: 63.08, H: 6.58, N: 7.04.

2-acetyl-3-*N,N*-dimethylamino-thiophene **7c**: mp: 76°C, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1621. UV/Vis (MeOH) nm (ε): 364 (26500).

^1H NMR ($CDCl_3$) δ 2.45 (s, 3H, $C\underline{H}_3$), 2.95 (s, 6H, $NC\underline{H}_3$), 6.79 (d, 1H, H_4, J = 5.4 Hz), 7.34 (d, 1H, H_5, J = 5.5 Hz). ^{13}C NMR ($CDCl_3$) δ 187.8 ($\underline{C}O$), 157.0 (C_3), 132.8 (C_5), 120.9 (C_2), 118.5 (C_4), 44.5 ($N\underline{C}H_3$), 29.1 ($\underline{C}H_3$). Elemental analysis: Calcd for $C_8H_{11}ONS$: C: 56.80, H: 6.51, N: 8.28. Found: C: 56.82, H: 6.35, N: 8.42.

2-acetyl-3-pyrrolidino-thiophene **7d**: oil, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1620. UV/Vis (MeOH) nm (ε): 363 (32900).

^1H NMR ($CDCl_3$) δ 1.96 (m, 4H, CH_2-$C\underline{H}_2$), 2.43 (s, 3H, $C\underline{H}_3$), 3.37 (m, 4H, $NC\underline{H}_2$), 6.71 (d, 1H, H_4, J = 5.5 Hz), 7.32 (d, 1H, H_5, J = 5.5 Hz). ^{13}C NMR ($CDCl_3$) δ 187.4 ($\underline{C}O$), 152.8 (C_3), 131.4 (C_5), 120.8 (C_2), 119.7 (C_4), 52.5 ($N\underline{C}H_2$), 29.6 ($\underline{C}H_3$), 25.9 (CH_2-$\underline{C}H_2$).

Elemental analysis: Calcd for $C_{10}H_{13}ONS$: C: 61.51, H: 6.69, N: 7.19.Found: C: 61.33, H: 6.61, N: 7.48.

2-acetyl-3-(4-hydroxy)piperidino-thiophene **7e**: oil, purification by flash chromatography on silica gel (AcOEt)

IR (KBr) cm^{-1} : 1634. UV/Vis (MeOH) nm (ε): 362 (8100).

^1H NMR ($CDCl_3$) δ 1.25 (brs, 1H, OH), 1.75 (m, 2H, CH_2-$C\underline{H}_2$), 2.02 (m, 2H, CH_2-$C\underline{H}_2$), 2.51 (s, 3H, $C\underline{H}_3$), 3.01 (m, 2H, $NC\underline{H}_2$), 3.41 (m, 2H, $NC\underline{H}_2$), 3.87 (m, 1H, $C\underline{H}$), 6.88 (d, 1H, H_4, J = 5.4 Hz), 7.42 (d, 1H, H_5, J = 5.4 Hz). ^{13}C NMR ($CDCl_3$) δ 188.9 ($\underline{C}O$), 156.6 (C_3), 130.2 (C_5), 123.5 (C_2), 121.7 (C_4), 67.2 ($\underline{C}HOH$), 50.5 ($N\underline{C}H_2$), 34.4 (CH_2-$\underline{C}H_2$), 28.9 ($\underline{C}H_3$).

Elemental analysis: Calcd for $C_{11}H_{15}O_2NS$: C: 58.64, H: 6.71, N: 6.22. Found: C: 58.79, H: 6.72, N: 6.04.

5-morpholino-furan-2-carboxaldehyde **8a**: oil, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1651. UV/Vis (MeOH) nm (ε): 357 (17300).

^1H NMR ($CDCl_3$) δ 3.25 (t, 4H, $NC\underline{H}_2$, J = 4.8 Hz), 3.62 (t, 4H, $OC\underline{H}_2$, J = 4.8 Hz), 5.22 (d, 1H, H_4, J = 3.9 Hz), 7.08 (d, 1H, H_5, J = 4.0 Hz), 8.91 (s, 1H, $C\underline{H}O$). ^{13}C NMR ($CDCl_3$) δ 172.5 ($\underline{C}HO$), 162.6 (C_5), 144.5 (C_3), 130.9 (C_2), 86.8 (C_4), 65.4 ($O\underline{C}H_2$), 45.6 ($N\underline{C}H_2$).

Elemental analysis: Calcd for $C_9H_{11}O_3N$: C: 59.63, H: 6.08, N: 7.75. Found: C: 59.67, H: 6.33, N: 7.83.

5-piperidino-furan-2-carboxaldehyde **8b**: oil, purification by flash chromatography on silica gel (CH_2Cl_2)
IR (KBr) cm^{-1} : 1652. UV/Vis (MeOH) nm (ε): 364 (46600).
^1H NMR ($CDCl_3$) δ 1.62 (m, 6H, CH_2-C$\underline{H}_2$), 3.39 (m, 4H, NC$\underline{H}_2$), 5.25 (d, 1H, H_4, J = 3.95 Hz), 7.17 (d, 1H, H_5, J = 3.9 Hz), 8.95 (s, 1H, C$\underline{H}$O). ^{13}C NMR ($CDCl_3$) δ 173.6 (C$\underline{O}$), 163.5 (C_5), 142.8 (C_3), 133.4 (C_2), 86.7 (C_4), 47.9 (N$\underline{C}H_2$), 24.95 (CH_2-$\underline{C}H_2$), 23.8 (CH_2-$\underline{C}H_2$).
Elemental analysis: Calcd for $C_{10}H_{13}O_2N$: C: 67.01, H: 7.26, N:7.82. Found: C: 66.88, H: 7.09, N: 7.91.

5-*N,N*-dimethylamino-furan-2-carboxaldehyde **8c**: mp: 82°C, purification by flash chromatography on silica gel (CH_2Cl_2)
IR (KBr) cm^{-1} : 1644. UV/Vis (MeOH) nm (ε): 361 (43900).
^1H NMR ($CDCl_3$) δ 2.97 (s, 6H, NC$\underline{H}_3$), 5.16 (d, 1H, H_4, J = 4.1 Hz), 7.12 (d, 1H, H_5, J = 4.0 Hz), 8.85 (s, 1H, C$\underline{H}$O). ^{13}C NMR ($CDCl_3$) δ 172.5 (C$\underline{H}$O), 163.9 (C_5), 144.25 (C_3), 131.8 (C_2), 86.1 (C_4), 37.8 (N$\underline{C}H_3$). Elemental analysis: Calcd for $C_7H_9O_2N$: C: 60.41, H: 6.46, N: 10.08. Found: C: 60.34, H: 6.25, N: 9.89.

5-morpholino-selenophene-2-carboxaldehyde **9a**: mp: 128°C, purification by flash chromatography on silica gel (CH_2Cl_2)
IR (KBr) cm^{-1} : 1631. UV/Vis (MeOH) nm (ε): 377 (22300).
^1H NMR ($CDCl_3$) δ 3.32 (t, 4H, NC$\underline{H}_2$, J = 5.0 Hz), 3.84 (t, 4H, OC$\underline{H}_2$, J = 5.0 Hz), 6.15 (d, 1H, H_4, J = 4.6 Hz), 7.72 (d, 1H, H_5, J = 4.6 Hz), 9.50 (s, 1H, C$\underline{H}$O). ^{13}C NMR ($CDCl_3$) δ 182.05 (C$\underline{H}$O), 172.7 (C_5), 142.8 (C_3), 132.4 (C_2), 105.25 (C_4), 65.9 (O$\underline{C}H_2$), 50.7 (N$\underline{C}H_2$).
Elemental analysis: Calcd for $C_9H_{11}O_2NSe$: C: 44.41, H: 4.53, N: 5.76. Found: C: 54.22, H: 4.39, N: 5.88.

5-*N,N*-dimethylamino-selenophene-2-carboxaldehyde **9c**: mp: 114°C, purification by flash chromatography on silica gel (CH_2Cl_2)
IR (KBr) cm^{-1} : 1618. UV/Vis (MeOH) nm (ε): 380 (29200).
^1H NMR ($CDCl_3$) δ 3.11 (s, 6H, NC$\underline{H}_3$), 5.91 (d, 1H, H_4, J = 4.7 Hz), 7.68 (d, 1H, H_5, J = 4.7 Hz), 9.42 (s, 1H, C$\underline{H}$O). ^{13}C NMR ($CDCl_3$) δ 181.2 (C$\underline{H}$O), 172.3 (C_5), 143.5 (C_3), 130.7 (C_2), 104.0 (C_4), 43.3 (N$\underline{C}H_3$). Elemental analysis: Calcd for C_7H_9ONSe: C: 41.78, H: 4.46, N: 6.96. Found: C: 41.64, H: 4.25, N: 6.89.

5-pyrrolidino-selenophene-2-carboxaldehyde **9d**: oil, purification by flash chromatography on silica gel (CH_2Cl_2)

IR (KBr) cm^{-1} : 1625. UV/Vis (MeOH) nm (ε): 378 (28700).

^1H NMR ($CDCl_3$) δ 2.12 (m, 4H, CH_2-$C\underline{H}_2$), 3.38 (m, 4H, $NC\underline{H}_2$), 5.85 (d, 1H, H_4, J = 4.6 Hz), 7.68 (d, 1H, H_5, J = 4.6 Hz), 9.40 (s, 1H, $C\underline{H}O$). ^{13}C NMR ($CDCl_3$) δ 181.9 ($\underline{C}HO$), 172.6 (C_5), 141.9 (C_3), 132.5 (C_2), 105.1 (C_4), 50.6 ($N\underline{C}H_2$), 25.7 (CH_2-$\underline{C}H_2$). Elemental analysis: Calcd for $C_9H_{11}ONSe$: C: 47.54, H: 4.85, N: 6.17. Found: C: 47.81, H: 5.09, N: 5.91.

AKNOWLEGMENTS

The authors thank gratefully Prof. Marc Beley and Jean-Michel Adam for helpful discussion.

REFERENCES

1 (a) Steinkopf, W.; Jacob, H. *Justus Liebigs Ann. Chem.* **1934**, *513*, 281-294. (b) Dell'Erba, C.; Novi, M.; Guanti, G.; Spinelli, D. *J. Heterocyl. Chem.* **1975**, *12*, 327-331. (c) Puschmann, I.; Erker, T. *Heterocycles* **1993**, *36*, 1323-1332. (d) Arnone, C.; Consiglio, G.; Frenna, V.; Spinelli, D. *J. Org. Chem.* **1997**, *62*, 3093-3097.

2 (a) Terrier, F.; Chatrousse, A. P.; Paulmier, C. *J. Org. Chem.* **1979**, *44*, 1634-1638. (b) Terrier, F.; Chatrousse, A. P.; Paulmier, C.; Schaal, R. *J. Org. Chem.* **1975**, *40*, 2911-2915. (c) Consiglio, G.; Arnone, C.; Spinelli, D.; Noto, R. *J. Chem. Soc., Perkin Trans. 2* **1981**, 642-644. (d) Spinelli, D.; Consiglio, G.; Noto, R. *J. Org. Chem.* **1978**, *43*, 4038-4041. (e) Spinelli, D.; Consiglio, G.; Noto, R. *J. Heterocylic Chem.* **1977**, *14*, 1325-1329. (f) Dell'Erba, C.; Sancassan, F.; Novi, M.; Spinelli, D.; Consiglio, G.; Arnone, C.; Ferroni, F. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1779-1782.

3 (a) Doddi, G.; Poretti, A.; Stegel, F. *J. Heterocycl. Chem.* **1974**, *11*, 97-98. (b) Hurtel, P.; Delcroix, B.; Morel, J.; Terrier, F. *J. Chem. Res.(S)* **1983**, 58-59; *(M)* **1983**, 725-754. (c) El Kassmi, A.; Heraud, G.; Büchner, W.; Fache, F.; Lemaire, M. *J. Mol. Catal.* **1992**, *72*, 299-305. (d) Kada, R.; Knoppova, V.; Kovac, J.; Balag, M. *Coll. Czech. Chem. Commun.* **1980**, *45*, 2360-2363. (e) Arnone, C.; Consiglio, G.; Frenna, V.; Mezzina, E.; Spinelli, D. *J. Chem. Res.(S)* **1993**, 440-441; *(M)* **1993**, 2949-2963.

4 (a) Shulezhko, A. A.; *Ukr. Khim. Zh.* **1972**, *38*, 68-70; *Chem. Abst.* **1972**, *77*, 7272p. (b) Mikhailenko, F. A.; Sherchuk, L. I. *Khim. Geterotsikl. Soedin* **1974**, **10**, 1325-1326; *Chem. Abst.* **1975**, *82*, 100038e. (c) Cabrera, I.; Althoff, O.; Yoon, H. T. *Adv. Mat.* **1994**, *6*, 43-45. (d)

Serbutoviez, C.; Bosshard, C.; Knöpfle, G.; Wyss, P.; Prêtre, P.; Günter, P.; Schenk, K.; Solari, E.; Chapuis, G. *Chem. Mater.* **1995**, *7*, 1198-1206. (e) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741-776.

5 Prim, D.; Kirsch, G.; Nicoud, J.F. *Synlett* **1998**, *4*, 383-384.

6 (a) Tarasova, O. A.; Klyba, L. V.; Vvendensky, V. Y.; Nedolya, N. A.; Trofimov, B. A.; Brandsma, L.; Verkruijsse, H. D. *Eur. J. Org. Chem.* **1998**, 253-256; (b) Gewald, K.; Schinke, E.; Böttcher, H. *Chem. Ber.* **1966**, *99*, 94-100. (c) Gütschow, M.; Schröter, H.; Kuhnle, G.; Eger, K. *Monats. Chem.* **1996**, *127*, 297-303. (d) Outurquin, F.; Lerouge, P.; Paulmier, C. *Bull. Soc. Chim. F.* **1986**, 259-266; 267-275 and references cited therein. (e) Berkaoui, M.; Outurquin, F.; Paulmier, C. *J. Heterocyclic Chem* **1996**, *33*, 9-16. (f) Prats, M.; Galvez, C. *Heterocyles* **1992**, *36*, 149-156. (g) Hwang, K. J.; Choi, N. K. *Bull. Korean. Chem. Soc.* **1991**, *12*, 121-122. (h) Bedworth, P. V.; Cai, Y.; Jen, A.; Marder, S. R. *J. Org. Chem.* **1996**, *61*, 2242-2246. (i) Takahata, H.; Moriyama, K.; Maruyama, M.; Yamazaki, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1671-1671. (j) De Jong, R. P. L.; Brandsma, L. *Synth. Commun.* **1990**, *20*, 3427-3431. (k) Reinhoudt, D. N.; Trompenaars, W. P.; Geevers, J. *Synthesis* **1978**, 368-370. (l) Norris, R. K. *Heterocyclic Compounds, Thiophene and its derivatives,* part 2; Gronowitz, S. ed.; J. Wiley and Sons: New York;, **1986**, vol. 44, pp. 633-801.

7 Duhamel, L. *The chemistry of amino, nitroso and nitro compounds and its derivatives*, part 2, Patai, S. ed.; J. Wiley and Sons, **1982**, 849.

8 Orvik, J. A.; Bunett, J. F. *J. Am. Chem. Soc.* **1970**, *90*, 2417-2427.

9 Consiglio, G.; Frenna, V.; Mezzina, E.; Pizzolato, A.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1998**, 325-333.

10 (a) Marquet, J.; Casado, F.; Cervera, M.; Espin, M.; Gallardo, I.; Mir, M.; Niat, M. *Pure and Appl. Chem.*. **1995**, *67*, 703-710. (b) Marquet, J. *Personnal communication.*

11 Bunnett, J. F. *Tetrahedron* **1993**, *49*, 4477-4484.

12 Saveant, J. M. *Tetrahedron* **1994**, *50*, 10117-10165.

13 Dell'Erba, C.; Spinelli, D. *Tetrahedron* **1965**, *21*, 1061-1066.

14 Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Heterocyclic Chem.* **1993**, *30*, 113-117.

15 Largeron, M.; Fleury, M. B. *Tetrahedron Lett.* **1991**, *32*, 631-634.

16 Ficini, J.; Claeys, M.; Depezay, J. C. *Tetrahedron Lett.* **1973**, 3353-3355.

17 (a) Aran, V. J.; Soto, J. L. *Synthesis* **1982**, 513-514. (b) Boyd, G. V.; Heatherington, K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2523-2531.

18 (a) Nazarova, Z. N.; Novikov, V. N.; Bukhaeva, V. T. *Zh. Obshch. Khim.* **1964**, *34*, 705-706; C.A. **1964**, *62*, 13209. (b) Nazarova Z. N.; Novikov, V. N. *Byul. Izobret. i Tovarnykh Znakov* **1965**, *9*,

28; C.A. **1965**, *65*, 9915. (c) Nazarova, Z. N.; Babeshkina, L. D. *Metody Poluch. Khim. Reaktiv Prep.* **1969**, *20*, 172-173; C.A. **1972**, *76*, 85770t. (d) Nazarova, Z. N.; Pustovarov, V. S. *Metody Poluch. Khim. Reaktiv Prep.* **1969**, *20*, 78-80; C.A. **1972**, *76*, 85612t. (e) Nazarova, Z. N.; Pustovarov, V. S. *Metody Poluch. Khim. Reaktiv Prep.* **1969**, *20*, 109-110; C.A. **1972**, *76*, 14212b. (f) Nazarova, Z. N.; Pustovarov, V. S.; Belichenko, O. B. *Metody Poluch. Khim. Reaktiv Prep.* **1969**, *20*, 174-175; C.A. **1972**, *76*, 85653g.