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SYNTHESIS AND REACTIVITY OF 3-AMINOTHIOPHENES AND 3,4-DIAMINOTHIOPHENES

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CONTENTS

1. INTRODUCTION

Ten years ago, thiophenamines and thiophenediamines, usually called aminothiophenes and diaminothiophenes, were the subject of an important report.[1] 3,4-Diaminothiophenes have also received separate attention.[2] For a long time, *N*-(2-thienyl)acetamide and alkyl 2-thienyl carbamates have been extensively studied, 2-aminothiophene itself being considered as very unstable. However, 2-aminothiophenes with electron-withdrawing substituents or functional groups are the subject of numerous papers.[1]

My aim here is to present the main results concerning the chemistry of 3-aminothiophene **1**, 3,4-diaminothiophene **2** and of their more used derivatives: *N*-(3-thienyl)acetamide **3a**, alkyl 3-thienyl carbamates, **4**, *N,N'*-3,4-thienylenediacetamide **5a** and dialkyl *N,N'*-3,4-thienylenedicarbamates **6**.

The great difficulty of access to β-functionalized thiophenes, added to the particular sensitivity of amines **1** and **2** to acidic media, can explain the lack of interest for these compounds compared to their 2-analogs. Despite these facts, 3-aminothiophenes and 3,4-diaminothiophenes constitute an important field of research in my laboratory since twenty years.

The preparation of 3-aminothiophene **1** and 3,4-diaminothiophene **2** is no obstacle. They can be obtained from thiophene on a multigram scale in two and four steps, respectively.

I will show that the reactions occurring on the thiophene ring are the consequence of a pronounced enaminic character coupled with a good level of aromaticity which facilitate electrophilic substitutions in the α-position of the nucleus.

2. SYNTHESIS OF 3-THIOPHENAMINES AND DERIVATIVES

Preparations of 3-aminothiophenes bearing another functional group in the 2-position which involve thiophene ring formation, including the Fiesselmann and the Gompper synthesis, have been reviewed.[1] I wish first to mention only the known methods allowing access to 3-aminothiophene **1**, *N*-(3-thienyl)amides **3**, and alkyl 3-thienyl carbamates **4** starting from

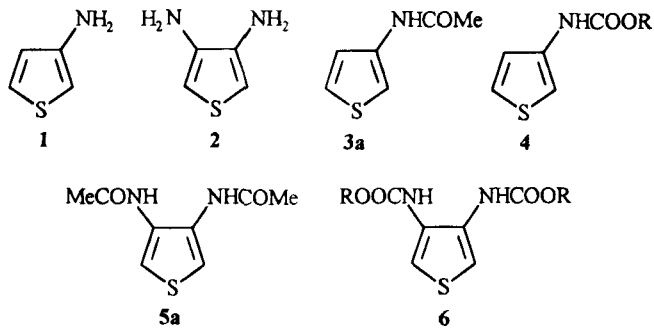
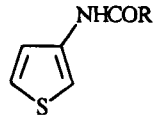
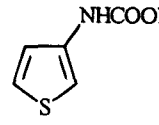


FIGURE 1



3

a R = Me
b R = H
c R = Ph
d R = *t*-Bu
e R = CF_3



4

a R = *t*-Bu (COOR = Boc)
b R = Et
c R = Me
d R = iPr
e R = CH_2Bu-*t*

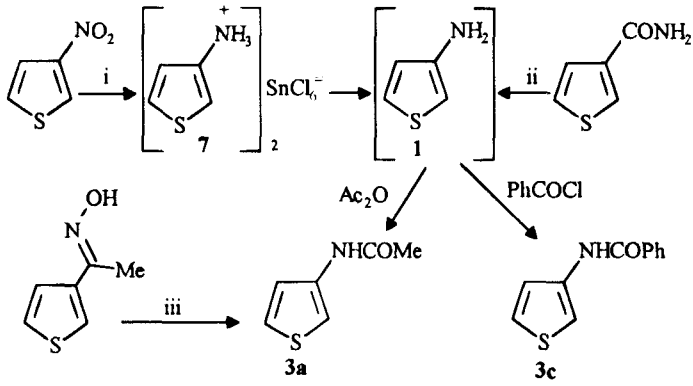
FIGURE 2

monosubstituted thiophenes. The different procedures for N-alkylation are then discussed.

2.1. *3-Thiophenamine 1, N-(3-Thienyl)amides 3 and 3-Thienyl Carbamates 4*

The first method, described fifty years ago, involves reduction of 3-nitrothiophene.[3] The intermediate thienylammonium hexachlorostannate **7** was transformed to the acetamide **3a** after neutralisation and acetylation without isolation of the amine **1** (Scheme 1). The Hofmann hypobromite rearrangement of 3-thiophenecarboxamide was then used.[4] Here also, only the acetamide **3a** was isolated (Scheme 1). Later, 3-aminothiophene **1** was obtained in a pure form by GPC and characterized by ^{1}H NMR.[5] Beckmann rearrangement of 3-acetylthiophene oxime and Schmidt rearrangement of the same ketone were also described for the preparation of the acetamide **3a** in yields close to 70%[6] (Scheme 1).

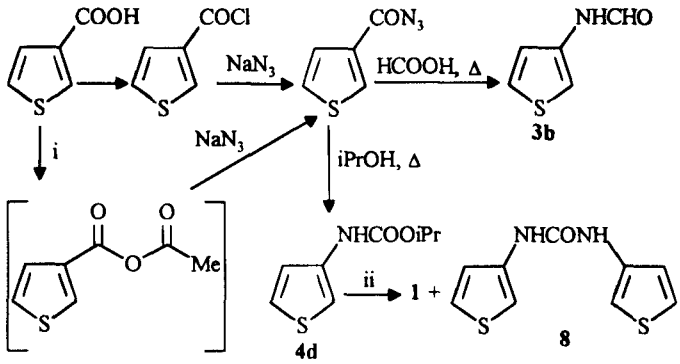
The methyl 3-thienyl carbamate **4c** was formed by Curtius rearrangement of 3-thiophenecarbonyl azide in methanol at reflux[7] (Scheme 2). The t-butyl carbamate **4a** was obtained in the same way.[8] This method was modified by treating 3-thiophenecarboxylic acid with *t*-butanol and diphenylphosphonyl azide (DPPA) in refluxing dioxane in the presence of triethylamine.[9] A modified procedure was proposed.[10] It involves the formation of the carbonyl azide from a carboxylic acid, ethyl chloroformate, triethylamine and sodium azide. The isopropyl carbamate **4d** was prepared in 70% yield by heating of the carbonyl azide in 2-propanol. The amine **1** was isolated (74% yield) after hydrolysis of the carbamate **4d**. The urea **8** was also formed in



i) Sn, HCl, H_2O. ii) Br_2, NaOH, H_2O. iii) PCl_3, ether.

SCHEME 1

small amounts. Decomposition of the carbonyl azide in formic acid under reflux has led to the formamide **3b** (83% yield)[10] (Scheme 2).

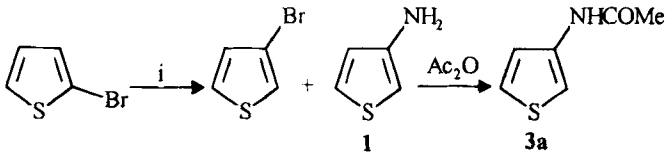


i) ClCOOEt, acetone, Et_3N. ii) NaOH, H_2O, MeOH.

SCHEME 2

From our experience we can say that the best and most efficient method for the preparation of 3-aminothiophene **1**, on a 20–30 g scale, involves the potassium amide treatment of 2-bromothiophene in liquid ammonia.[11,12] 3-Bromothiophene is also formed and becomes the major product when sodium amide is used instead of potassium amide[12] (Scheme 3). Because

of the recognized instability of amine **1**, its solution was directly treated with acetic anhydride to isolate the acetamide **3a**. However, we have found that 3-aminothiophene **1** can be obtained in practically pure form by dissolution in dilute acidic solution and ether extraction after neutralisation.[6] The dried ether solution can be stored two or three months at –15 °C without noticeable degradation (see Section 2.6).



		1	3a
$NaNH_2$ [13]	73 %	-	-
KNH_2 [13]	-	-	74 %
KNH_2 [6]	-	55 %	-

i) MNH_2 (2 eq.), liq. NH_3.

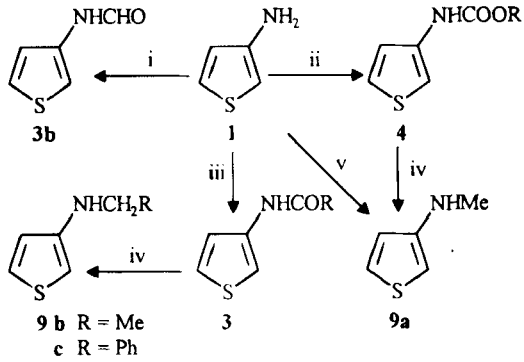
SCHEME 3

An intermolecular transbromination process involving intermediate formation of di- and tribromothiophenes has been proposed. β-Amination was supposed to occur with polybromothiophenes, followed by debromination with thiophene anions, and not through hetaryne intermediate formation.[12]

2.2. *Secondary and Tertiary Alkylamines*

Amides **3** and carbamates **4** were easily prepared in good yields by conventional methods carried out with the amine **1**.[14] The carbamates **4** were reduced to *N*-methylaminothiophene **9a** with $LiAlH_4$ in ether.[15] This same secondary amine **9a** was also prepared by a condensation-reduction procedure using formaldehyde and $NaBH_4$ (70% yield)[14] (Scheme 4).

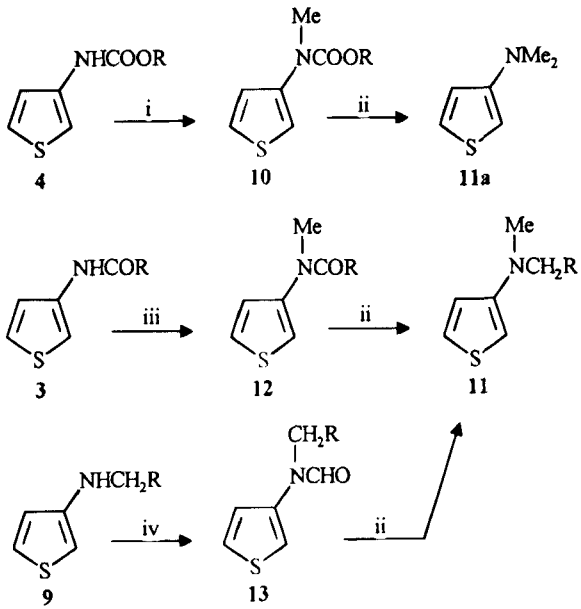
Other secondary amines **9** have been prepared by reduction of the amides **3**.[14] (Scheme 4). The carbamates **4** can be *N*-alkylated under basic conditions.[7,8] Methylation leads, after reduction of the *N*-methyl carbamate **10**, to the stable 3-(dimethylamino)thiophene **11a**[7] (Scheme 5). The formamide **3b** and the acetamide **3a** have been methylated in the presence of an alumina-potassium fluoride mixture. The isolated *N*-methylamides **12** are also easily reduced to the tertiary amines **11**.[14] An alternative route



i) HCOOH, Ac_2O. ii) ClCOOR, base. iii) Ac_2O or RCOCl.
iv) $LiAlH_4$, ether. v) $(CH_2O)_n$, NaOMe, MeOH ; $NaBH_4$, Δ.

SCHEME 4

involves formylation of the secondary amines **9**, followed by reduction of the carbonyl group of the intermediate formamide **13**[14] (Scheme 5).

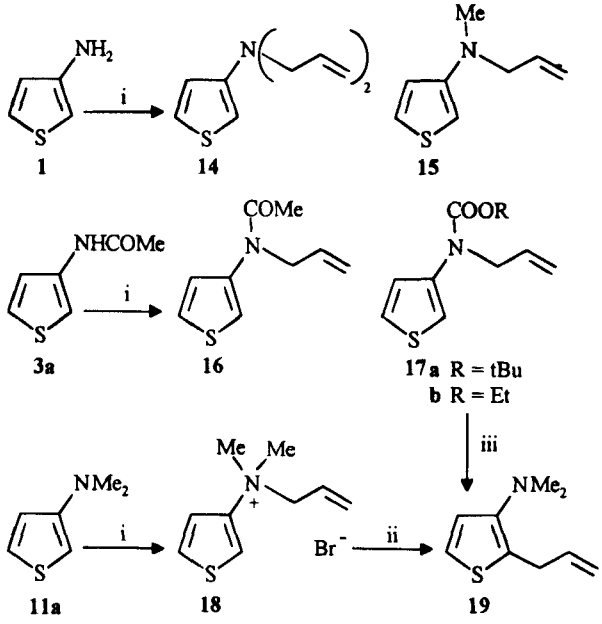


i) NaH, MeI, toluene, Δ. ii) $LiAlH_4$, ether. iii) MeI, KF-Al_2O_3, MeCN. iv) HCOOH, Ac_2O, ether.

SCHEME 5

2.3. *N-Allylamines and Aza-Cope Rearrangement*

With the goal to study reactions involving rearrangement and cyclization of 3-aminothiophenes bearing *N*-unsaturated substituents, we have achieved allylation of the amines **1** and **9a**, the acetamide **3a**, the carbamates **4** and the tertiary amine **11a**, which leads to stable quaternary ammonium salts[15] (Scheme 6). We observed that the amine **1** can be allylated twice, leading to the tertiary amine **14**, with base and allyl bromide. The amine **9a** is in the same way converted to **15**, the acetamide **3a** to **16** and the carbamates **4a** and **4b** to the *N*-allyl carbamates **17a** and **17b**, respectively.[16] The tertiary amine **11a** gives the given ammonium salt **18** which undergoes aza-Cope rearrangement allowing the isolation of 2-allyl-3-(dimethylamino)thiophene **19**. *N*-Methylation of the allyl carbamate **17a** led to the unexpected formation of 2-allylthiophene **19** after the same rearrangement[16] (Scheme 6).

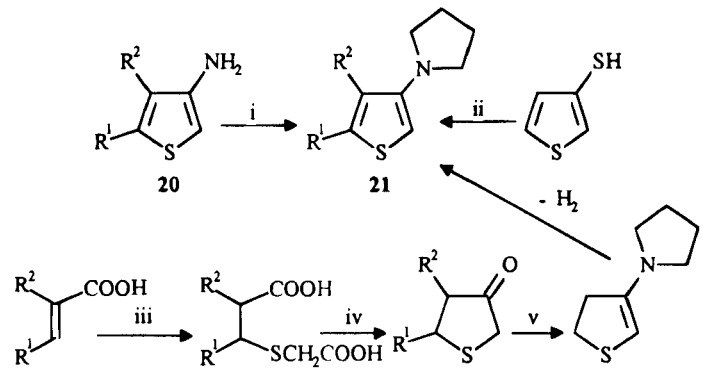


i) NaH, $BrCH_2CH{=}CH_2$, THF. ii) NaOH, H_2O.
iii) MeI (excess); NaOH, H_2O.

SCHEME 6

2.4. *Indirect Synthesis, Special Structures*

Specific methods leading to various 3-aminothiophene derivatives are presented in this section. Tertiary amines in which the nitrogen atom is part of a ring, such as the 3-(1-pyrrolidinyl)thiophenes **21**, have been synthetized from the corresponding primary amines **20** by cyclization with 1,4-dibromobutane,[17] by reaction of cyclic amines with 3-thiophenethiol[18] or by formation of the thiophene nucleus involving cyclization to 3-oxothiolanes, subsequently transformed into cyclic enamines which then undergo aromatization by loss of hydrogen[19] (Scheme 7).

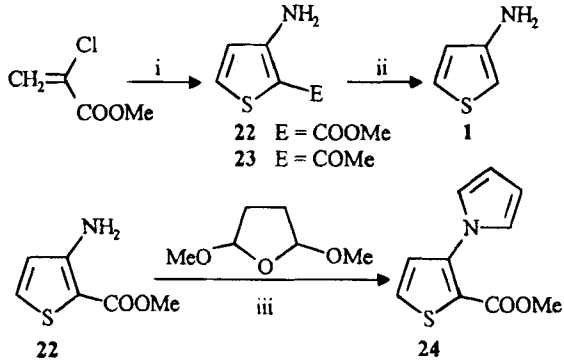


i) $Br(CH_2)_4Br$, $EtN(iPr)_2$. ii) Pyrrolidine, toluene, Δ.
iii) $HSCH_2COOH$, dioxane, Et_3N. iv) Ac_2O, LiOAc.
v) pyrrolidine, *p*-TSA, C_6H_6, Δ.

SCHEME 7

Methyl 3-amino-2-thiophenecarboxylate **22** and 2-acetyl-3-aminothiophene **23** have been prepared efficiently from 2-chloroacrylonitrile by a modified Fiesselmann procedure with methyl thioglycolate and mercaptoacetone, respectively[20] (Scheme 8). 3-Thiophenamine **1** has recently been obtained by decarboxylation of **22**.[21]

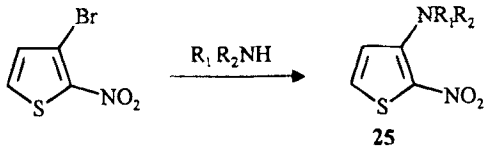
The amino ester **22** was treated under acidic conditions with 2,5-dimethoxytetrahydrofuran (equivalent to succinaldehyde) to give methyl 3-(1-pyrrolyl)-2-thiophenecarboxylate **24**[22,23] (Scheme 8).



i) $HSCH_2E$, MeONa, MeOH. ii) 2 N NaOH; 1-propanol, oxalic acid; NH_4OH, H_2O. iii) AcOH, Δ.

SCHEME 8

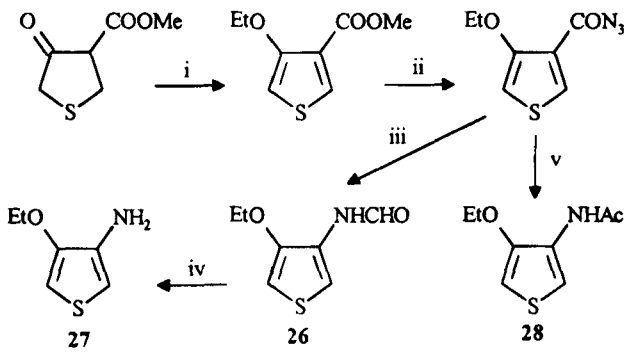
We must also recall that primary and secondary aliphatic and aromatic amines can displace bromide ion from 3-bromo-2-nitrothiophene. Various 3-amino-2-nitrothiophenes **25** have been prepared as already reviewed[1] (Scheme 9).



SCHEME 9

It is surprising that 4-ethoxy-3-aminothiophene **27** could be isolated.[24] Its synthesis started from methyl tetrahydro-4-oxo-3-thiophenecarboxylate transformed successively into the ethoxy ester, the ethoxy carboxylic acid hydrazide, and the ethoxy formamide **26**. The ethoxy acetamide **28** was prepared through decomposition of the same carbonyl azide in acetic anhydride (Scheme 10).

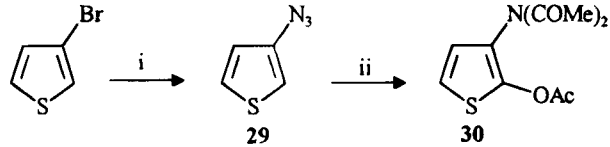
Several methods are available for the preparation of primary amines through reduction of azides, expecially in the aromatic and heteroaromatic



i) CH_2=C(Me)OCOMe, *p*-TSA; SO_2Cl_2; EtOH, *p*-TSA, Δ. ii) N_2H_4, EtOH, Δ; $NaNO_2$, HCl, AcOH. iii) HCOOH, Δ. iv) HCl, EtOH, Δ; 5 N NaOH. v) Ac_2O, Δ.

SCHEME 10

series. 3-Azidothiophene **29** has been synthetized in good yield from 3-lithiothiophene and tosyl azide at low temperature after fragmentation of an intermediate triazene salt.[25] Decomposition of azide **29** in acetic anhydride at reflux led to 3-(diacetylamino)-2-acetoxythiophene **30**[25] (Scheme 11).

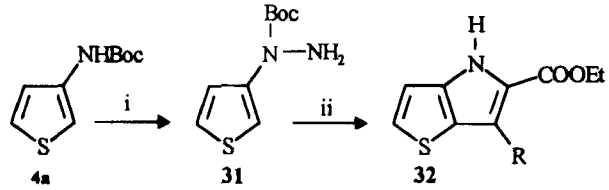


i) BuLi, ether, - 70 °C ; $TosN_3$. ii) Ac_2O, Δ.

SCHEME 11

2.5. *Hydrazone Derivatives*

The amides **3** and the carbamates **4** react under basic conditions with nitrogen electrophilic reagents such as *O*-(2,4-dinitrophenyl) hydroxylamine.[26] For example, the carbazate **31** has been synthetized in good yield from the carbamate **4a**. Treatment of **31** with an α-oxo ester under acidic conditions led to the formation of the thieno[3,2-*b*]pyrroles **32**. The mechanism of this cyclization seems to be reminiscent of the Fischer indole synthesis[27] (Scheme 12).



i) NaH, DMF, Δ ; 2,4-$(NO_2)_2C_6H_3ONH_2$. ii) $RCH_2COCOOEt$, EtOH, HCl, Δ.

SCHEME 12

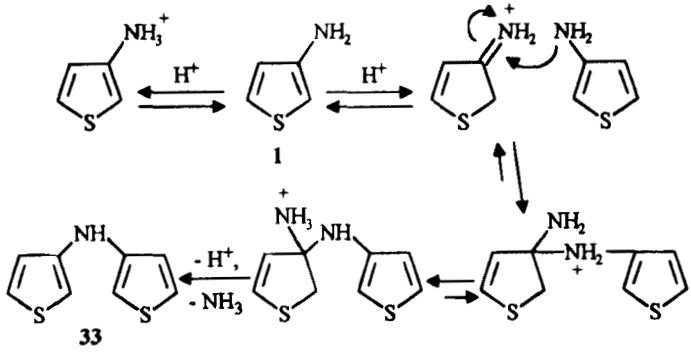
2.6. *Stability, Basicity and Reactivity*

3-Aminothiophene **1** has been considered more unstable than its 2-isomer. As already seen, however, this amine can be stored in ethereal solution for several weeks at −15 °C and distilled under reduced pressure. The secondary amines **9** and especially the tertiary amines **11**, **14** and **15** exhibit good stability. The presence of an alkyl substituent in the 2-position (see Section 3.8) also increases the stability.

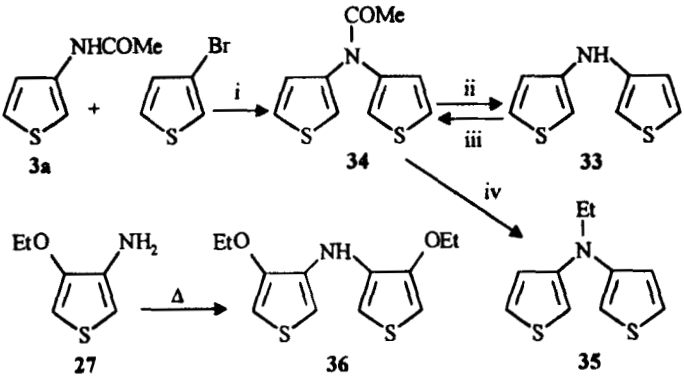
On exposure to air for some days at room temperature, 3-aminothiophene **1** forms slowly a resin. After storage at 0 °C and even in solution after two months, dithienylamine **33** appears progressively. Upon heating at 100 °C, trimers and tetramers are also formed.[10] We have studied this transformation and have concluded that the formation of dithienylamine **33** is a result of an acid-catalyzed reaction between amine **1** and its C-protonated form. In refluxing benzene/acetic acid, di(3-thienyl)amine **33** can be prepared in good yield (75%).[28] A transamination mechanism accounts for this transformation (Scheme 13).

The dithienylamine **33** was also obtained by coupling of 3-bromothiophene with acetamide **3a** and hydrolysis of the intermediate amide **34**.[29] Conversely, the acetamide **34** can be prepared by acetylation of the amine **33**. Its reduction led to *N,N*-di(3-thienyl)ethylamine **35**[16] (Scheme 14). Di(4-ethoxy-3-thienyl)amine **36** was isolated (60% yield) by heating 4-ethoxy-3-aminothiophene **27** at 135–140 °C[24] (Scheme 14).

Amine **1** cannot be diazoted contrary to 3-aminothiophenes bearing an electron-withdrawing group, especially in the 2-position.[1] (cf. Sections 3.3.; 3.4.; 3.6.). Nitrosation probably does not occur at the nitrogen atom because of the acidic conditions. As we will see later, 2-alkyl derivatives can be prepared, but their diazotation has not yet been investigated.



SCHEME 13

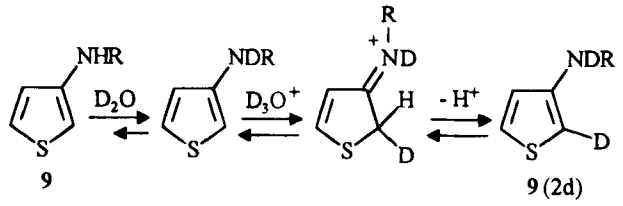


i) Cu, K_2CO_3, $NO_2C_6H_5$, Δ. ii) KOH, EtOH, Δ. iii) Ac_2O, ether. iv) $LiAlH_4$, ether.

SCHEME 14

Deuteration via D_2O exchange appears only in the amino group of the amines **1**, **9a**, and **9b**.[28] With acid catalysis, the same amines and the tertiary amine **11a** are instantaneously deuterated at the α-carbon[28] (Scheme 15).

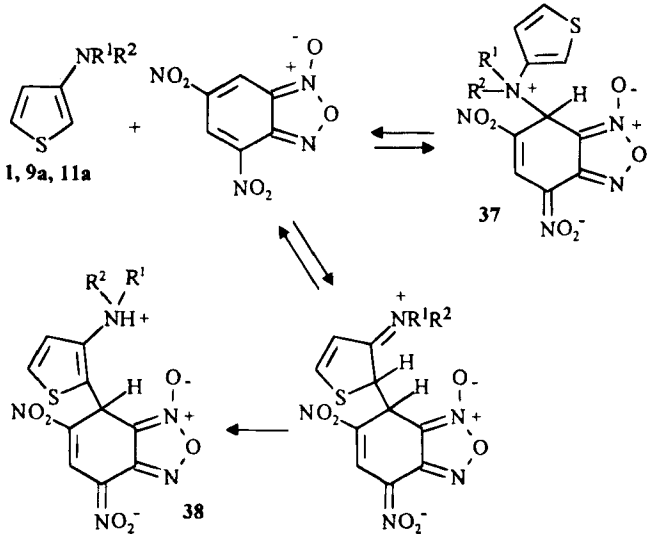
In fact, 3-thienylammonium salts can be isolated, but a rapid exchange occurs in the 2-position. This result is a consequence of the strongly enaminic character of 3-aminothiophenes associated with a sufficient level of aromaticity which is the driving force of the second step of this process. The electrophilic aromatic substitutions presented in the next section also occur in the same way in the 2-position.



SCHEME 15

Potentiometric and NMR measurements have recently allowed the determination of pK_a 3.38, 3.65, and 3.53, respectively, for amine **1**, **9a**, and **11a** in water-DMSO (50/50). These values reveal that the acid-base behaviour of these amines is analogous to that of classical aromatic amines (aniline, pK_a 3.73 in the same medium).[30]

NMR and kinetic studies related to the interaction between these amines and dinitrobenzofuroxane (DNBF), a superelectrophilic reagent, have been undertaken.[30] The *N*-adducts **37** were never seen. *C*-Adducts **38** were characterized and the rate constant of their formation measured. The corresponding anionic adducts were also observed (Scheme 16).



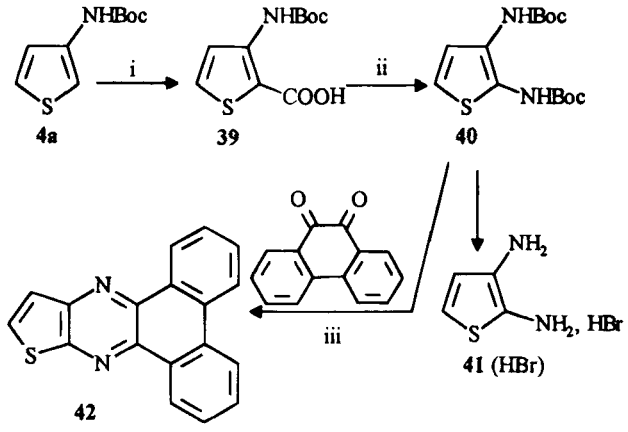
SCHEME 16

3. REACTIONS ON THE NUCLEUS OF 3-THIOPHENAMINES

Before we present the results concerning electrophilic substitutions achieved on the ring, this first paragraph will be devoted to reactions which occur through *C*-metallation of amides and carbamates.

3.1. *C-Metallation of Amides and Carbamates*

The well-known ortho-directed metallation of aromatic amides and carbamates can be achieved with 3-aminothiophene derivatives.[31] The dianion formed by *n*BuLi treatment of the carbamate **4a** gives the acid **39** after reaction with carbon dioxide. This acid was converted to di-*t*-butyl 2,3-thiophenedicarbamate **40** via Curtius rearrangement upon DPPA treatment in *t*-butanol under reflux. Hydrolysis of **40** has allowed isolation of the salt **41**(HBr) derived from 2,3-diaminothiophene. The dicarbamate **40** was also condensed with phenanthraquinone leading to dibenzo[*f,h*]thieno[2,3-*b*]quinoxaline **42**[32] (Scheme 17).

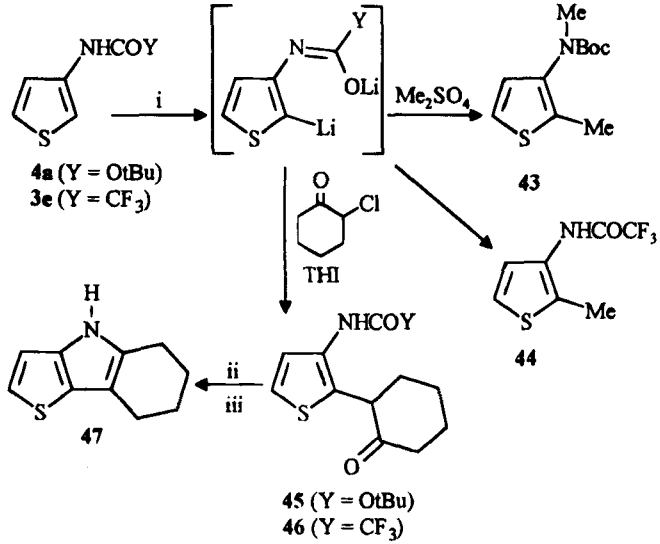


i) BuLi (2 eq.), ether, - 10 °C; CO_2. ii) DPPA, Et_3N, *t*-BuOH, Δ.
iii) AcOH, Δ.

SCHEME 17

The double *N*- and *C*-methylation of the dianion derived from **4a** has led to the *N*-methyl carbamate **43**. Starting from the trifluoroacetamide **3e**, *C*-methy-

lation only occurs and *N*-(2-methyl-3-thienyl)trifluoroacetamide **44** can be isolated.[33] Upon addition of 2-chlorocyclohexanone as electrophile, the ketones **45** and **46** were obtained. Cleavage of the functional group liberates the corresponding amine which cyclizes to thieno[3,2-*b*]pyrrole **47**[33] (Scheme 18).



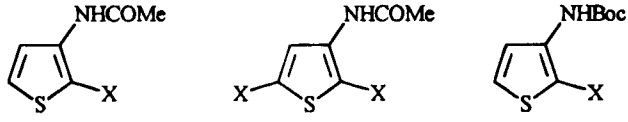
i) BuLi (excess), THF. ii) Me_3SiI; CH_3CN. iii) KOH, MeOH.

SCHEME 18

The preparation of 2-thienyl trialkylstannates has been achieved by trialkylstannyl chloride treatment of 2-lithio-3-thienyl carbamates obtained by deprotonation of 3-thienyl carbamates. However, halogen-metal exchange was preferred for the formation of the lithio derivative.[34]

3.2. *Halogenation*

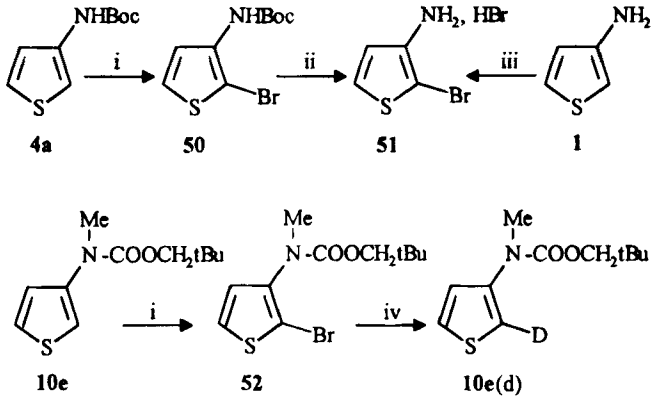
Among the electrophilic substitutions, the halogenation of amides and carbamates was first investigated.[1] In the 3-aminothiophene series, acetamide **3a** was halogenated using conventional methods:[4] sulfuryl chloride or *N*-chlorosuccinimide in chloroform for the preparation of compound **47** (X = Cl) and **48** (X = Cl), *N*-bromosuccinimide in the same solvent for **47** (X = Br), bromine in acetic acid for **48** (X = Br) and iodine monochloride in acetic acid for **47** (X = I) and **48** (X = I).



47 (X = Cl, Br, I) **48** (X = Cl, Br, I) **49** (X = Br, I)

FIGURE 3

The carbamates **4**[5] and the *N*-methyl carbamate **10e**[8] have been subjected to monohalogenation with *N*-halosuccinimides or bromine in methanol (Scheme 19). Hydrolysis of the carbamate **50** has allowed the isolation of the HBr salt **51** derived from the unstable 2-bromo-3-aminothiophene.[36] This salt can be directly obtained by bromination of amine **1** and converted to the bromo acetamide **47** (X = Br).[28]



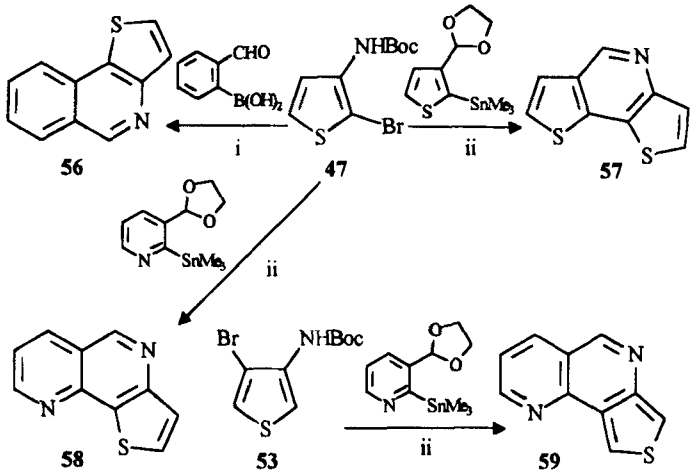
i) Br_2, MeOH. ii) HBr, CH_2Cl_2. iii) Br_2, ether, 0 °C. iv) BuLi, ether, - 78 °C; D_2O.

SCHEME 19

Bromine-lithium exchange has been achieved in the bromo carbamate **52**[8] and the 2-deuterated derivative **10e**(d) was obtained. The iodo carbamate **49** (X = I) has recently been prepared with *N*-iodosuccinimide.[37] The *N*-(4-halo-3-thienyl) carbamates; **53** (X = Br, I) have been synthetized from the corresponding 4-halo-3-thiophenecarboxylic acids by DPPA treatment in the presence of *t*-butanol[38] as previously described (see Section 2.1). The trimethylstannyl derivative **54** was obtained via bromine-metal

exchange from **49** (X = Br). The isomeric stannane **55** was prepared in the same way from **53** (X = Br).[34]

Several Pd(0)-catalyzed coupling reactions with *2*-iodopyridinecarbaldehydes leading to thienonaphthyridines have been achieved with the stannanes **54** and **55**.[34] Conversely, the bromo carbamates **47** (X = Br) and **53** (X = Br) have been used in Pd-catalyzed coupling reactions with formylthiopheneboronic acid[38] and 2-formylbenzeneboronic acid.[39] With this last compound, thieno[3,2-*c*]isoquinoline **56** could be synthesized (Scheme 20). The use of 2-[2-(trimethylstannyl)-3-thienyl]-1,3-dioxolane led, after coupling and hydrolysis, to the dithienopyridine **57**.[40] The thienonaphthyridine **58** was prepared in a similar way.[34] The isomeric heterocycle **59** was obtained from the bromo carbamate **53**[39] (Scheme 20).



i) Na_2CO_3, $MeO(CH_2)_2OMe$, $Pd(PPh_3)_4$; 2N HCl, Δ.
ii) $Pd(PPh_3)_4$, DMF, Δ; 2N HCl, Δ.

SCHEME 20

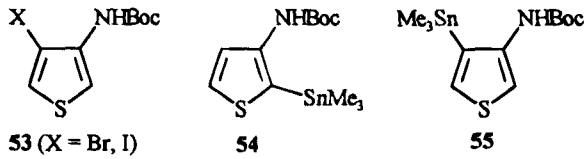
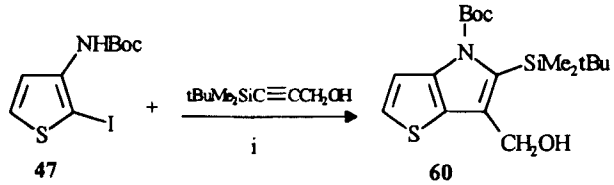


FIGURE 4

Pd-catalyzed condensation of the carbamate **47** (X = I) with 3-(trialkylsilyl)propargylic alcohols has also been achieved. After cyclization, thieno[3,2-*b*]pyrroles, such as **60**, could be isolated[40] (Scheme 21).



47 **60**

i) $Pd(OAc)_2$ cat., DMF, n-Bu_4NCl, Na_2CO_3.

SCHEME 21

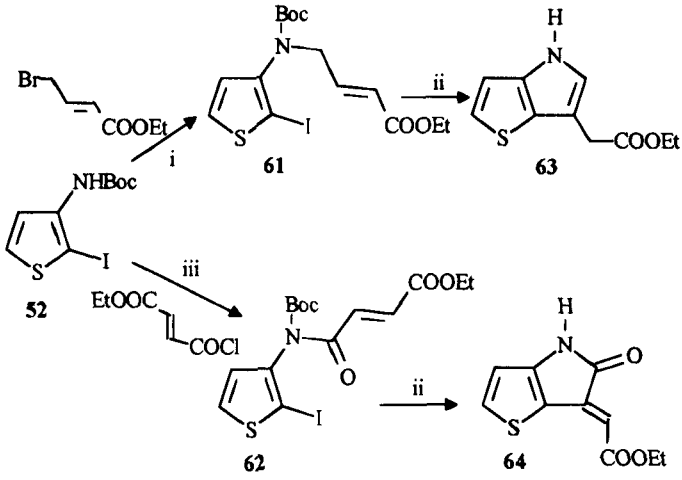
The same iodo carbamate **47** can be *N*-allylated with ethyl 4-bromocrotonate and *N*-acylated with ethoxyfumaroyl chloride. The corresponding unsaturated iodo esters **61** and **62** were subjected to Pd-catalyzed ring closure. Thieno[3,2-*b*]pyrrole **63** and thieno[3,2-*b*]pyrrolidone **64**, respectively, could be isolated[37] (Scheme 22).

3.3. *Nitration*

Nitration was first carried out on acetamide **3a** with nitric acid in acetic anhydride at –5 °C.[4] *N*-(2-Nitro-3-thienyl)acetamide **65** was the only product isolated. This amide was hydrolyzed in a strongly acidic medium and the free amine **67** extracted with ether[6] (Scheme 23). The *N*-methyl carbamate **10e** has been nitrated in the 2-position.[35] Mixtures of isomers were obtained by nitration of acetamides bearing an ester group in the α-position.[1]

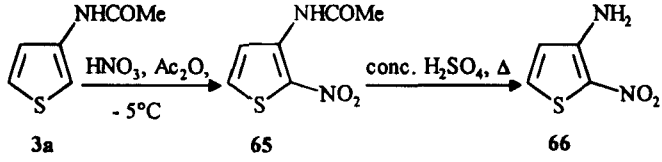
The nitro azide **68** was the result of sodium azide treatment of the diazonium salt **67** derived from amine **66**.[41] Nucleophilic azide substitution carried out on 2-nitro-3-(phenylsulfonyl)thiophene is an alternative synthetic method and reduction of **68** is another way to the nitro amine **66**[42] (Scheme 24).

Thermal decomposition of the nitro azide **68** in acetic acid[41] or benzene[42] leads to mixtures of the isomeric thienofurazane *N*-oxides **69a** and **69b**, **69a** being the major isomer.



i) $CaCO_3$, DMF. ii) $Pd(OAc)_2$, PPh_3, DMF, Δ; SiO_2, Δ, (1 mm Hg).
iii) DMAP, Et_3N, THF.

SCHEME 22



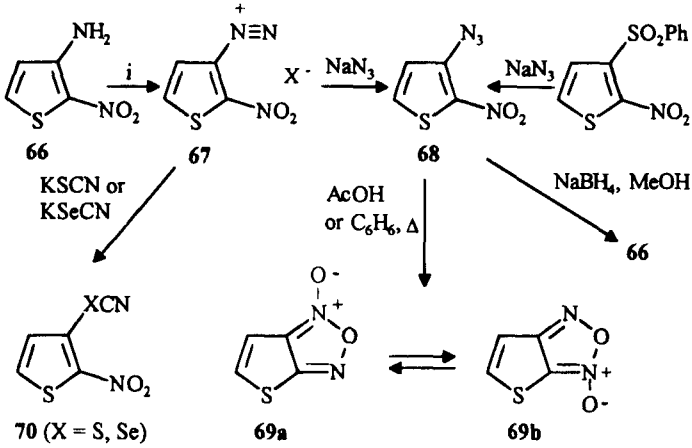
SCHEME 23

Treatment of the diazonium salt **67** with potassium thiocyanate or potassium selenocyanate under controlled acidic conditions permits the isolation of the thiocyanate and selenocyanate, respectively, **70**[43] (Scheme 24). 2,3-Diaminothiophene **41** has been formed by reduction of the nitro-amine **66** and then condensed with diacetyl to give thieno[2,3-*b*]pyrazine **71**.[44]

The carbamate **4e** has been previously subjected to nitration with copper(II) nitrate trihydrate in acetic anhydride giving the nitro carbamate **72**.[35]

3.4. *Reactions with Sulfur and Selenium Electrophilic Reagents*

Benzeneselenenyl bromide reacts with 3-aminothiophene **1** in ether at low temperature. The unstable amine **73** was then transformed to acetamide **74**.[28] The Kaufmann reaction when applied to amine **1** leads to the amino



i) $NaNO_2$, HCl or H_2SO_4, H_2O, - 5 °C.

SCHEME 24

thiocyanate **75**. Sodium sulfide reduction of this thiocyanate, followed by chloroacetic acid treatment, gives the thienothiazinone **76** which can subsequently be reduced to 2,3-dihydrothieno[2,3-*b*]thiazine **77**[45] (Scheme 25). Diazotation of the same intermediate salt has led with a poor yield to thieno-[3,2-*d*][1,2,3]-thiadiazole **78**,[45] and carbon disulfide addition to the thieno[3,2-*d*]thiazolethiol **79**[45] (Scheme 25).

Kaufmann thiocyanation has also been carried out with the acetamide **3a** and the formamide **3b**. The thiocyanates **80** (R = H) and **81** (R = Me) were isolated. A comparable electrophilic selenocyanation gives the selenocyanate **82** (R = Me), albeit in lower yield.[45] Thermal isomerization of the thiocyanate **81** gave the acetylaminothieno[3,2-*b*]thiazole **83**, subsequently hydrolyzed to amine **84**. Diazotation of this amine, followed by reduction of

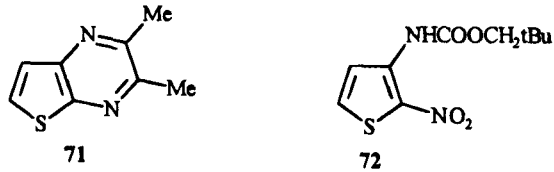
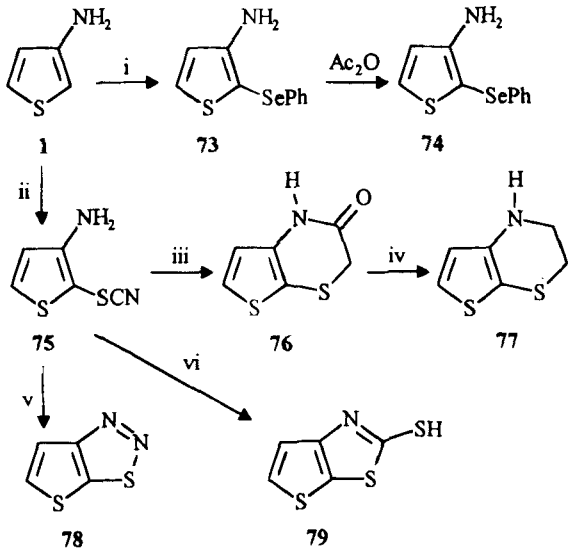


FIGURE 5



i) PhSeBr, ether, - 60 °C. ii) NH_4SCN, Br_2, MeOH, 0 °C. iii) Na_2S, $ClCH_2COOH$; HCl, H_2O. iv) $LiAlH_4$, ether. v) Na_2S, H_2O; $NaNO_2$, H_2SO_4, 0 °C. vi) Na_2S, H_2O; CS_2; HCl, H_2O.

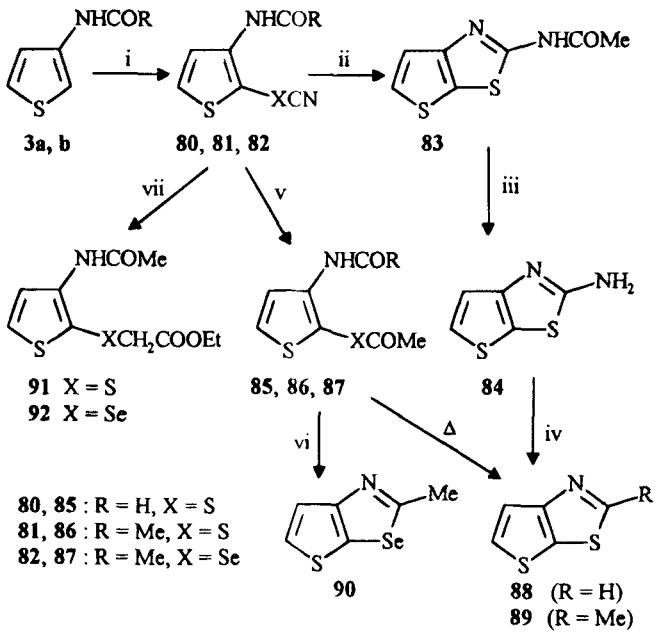
SCHEME 25

the resulting diazonium salt, has allowed the isolation of the thieno[3,2-*d*]thiazole **88**[45] (Scheme 26). Acylation of the sodium salts derived from **80**, **81**, and **82** gave the respectively thioesters **85** and **86** and the selenoester **87**. Thermal decomposition of the thioesters gave, respectively, the thienothiazole **88** and its 2-methyl derivative **89**. In the same way, the *N*-acetyl derivative of selenoester **87** gave 2-methylthieno[3,2-*d*]selenazole **90**.[45] Alkylation of the sodium salts of **81** and **82** with ethyl bromacetate gives the esters **91** and **92**, respectively[45] (Scheme 26).

A short paper has proposed the synthesis of dithieno[2,3-*b*:3′,2′-*e*][1, 4]thiazine **93** by SCl_2 treatment of *N,N*-di(3-thienyl)acetamide **34**[29] (Scheme 27).

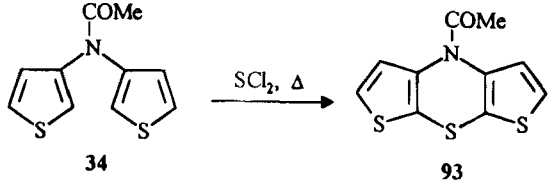
3.5. *Coupling Reactions with Diazonium Salts*

The carbamate **4e** and the acetamide **3a** have been coupled in the 2-position with *p*-nitrobenzenediazonium salts. The azo compounds **94**[35] and **95**[4], respectively, were thus synthetized.

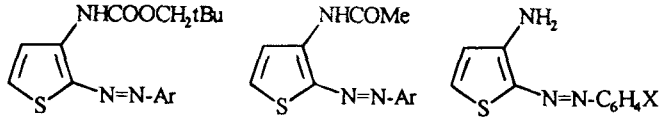


i) NH_4SCN or KSeCN, Br_2, MeOH, 0 °C. ii) PhCOOEt, Δ. iii) HCl, H_2O, dioxane, Δ. iv) H_2SO_4, H_2O, 0 °C; $NaNO_2$; H_3PO_2, H_2O. v) Na_2S, H_2O; Ac_2O. vi) Δ or Ac_2O, Zn, Δ. vii) Na_2S, H_2O, $BrCH_2COOEt$.

SCHEME 26



SCHEME 27



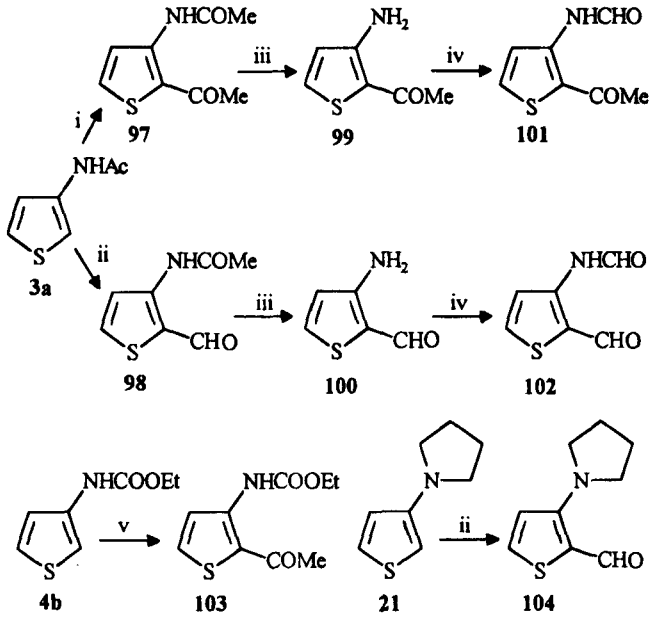
94 (Ar = *p*-$NO_2C_6H_4$) **95** (Ar = *p*-$NO_2C_6H_4$) **96** (X = H, 2-NO_2, 4-OMe)

FIGURE 6

We have recently observed that amine **1** undergoes coupling reactions with various diazonium salts.[16] The azo compounds **96** were isolated in good yields.

3.6. *Acetylation and Formylation*

Friedel-Crafts acetylation of the acetamide **3a** gives *N*-(2-acetyl-3-thienyl)acetamide **97** in good yield. Vilsmeier formylation furnishes the corresponding aldehyde **98** in moderate yield requiring carefully controlled experimental conditions[6] (Scheme 28). As we will see in the next Section, the ratio of reagents is crucial. Secondary reactions leading to thieno[3,2-*b*]pyridines can occur. As was the case with the nitro acetamide **65**, acid hydrolysis of **97** and **98** allowed preparation of the amino ketone **99** and the amino aldehyde **100**,[6] also obtained by hydrogen sulfide reduction of the corresponding formyl azide.[46]

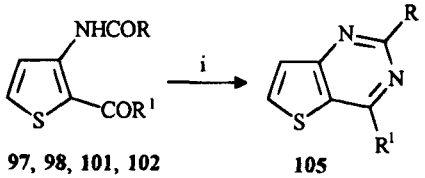


i) $AlCl_3$, AcCl. ii) $POCl_3$, DMF. iii) conc. H_2SO_4, Δ. iv) HCOOH, Ac_2O. v) Ac_2O, AcOH, Δ.

SCHEME 28

The formamide **3b** cannot be acetyled nor formylated, but the corresponding formamides **101** and **102** have been synthetized by acetic formic anhydride treatment of the corresponding amines **99** and **100**[6] (Scheme 28). Ethyl (2-acetyl-3-thienyl)carbamate **103** was easily isolated by simple treatment of the carbamate **4b** with acetic anhydride in acetic acid.[47] Previously, Vilsmeier formylation of amine **21** ($R^1 = R^2 = H$) and of other cyclic amines was used to obtain aldehydes such as **104**.[18]

Upon heating in the presence of ammonium formate and ammonia, the acetamides **97** and **98** and the formamides **101** and **102** cyclize leading to formation of the four thieno[3,2-*d*]pyrimidines **105**[6] (Scheme 29).



97, 98, 101, 102 **105**

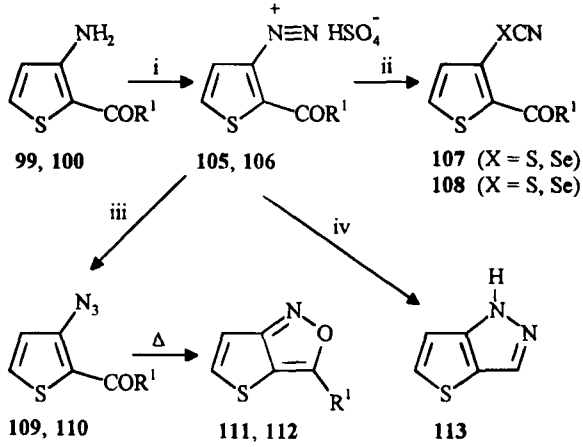
a $R = R^1 = Me$
b $R = Me$ $R^1 = H$
c $R = H$ $R^1 = Me$
d $R = H$ $R^1 = H$

i) $HCOONH_4$, NH_3, Δ.

SCHEME 29

The diazonium salts derived from the amino ketone **99** and the amino aldehyde **100** were easily prepared and then treated with potassium thiocyanate or selenocyanate. The corresponding thiocyanates and selenocyanates **107** and **108** were isolated[43] (Scheme 30). Sodium azide treatment leads to the azido ketone **109** and the azido aldehyde **110**.[48] This latter aldehyde was also prepared by nucleophilic substitution of 3-bromo-2-thiophenecarbaldehyde.[46] Thermal decomposition of the azides **109** and **110** gives the thieno[3,2-*c*]isoxazoles **111** (R^1 = Me)[48] and **112** (R^2 = H).[46] Reduction of the diazonium salt **106** ($R^1 = H$) is followed by cyclization of the intermediate hydrazine giving thieno[3,2-*c*]pyrazole **113**.[49]

The amino aldehyde **100** formed by reduction of the azido aldehyde **110** has been used in Friedländer type reactions without isolation. Cyclization with pyruvic acid under basic conditions gave thieno[3,2-*b*]pyridine-3-carboxylic acid **114** which was smoothly decarboxylated upon heating to form

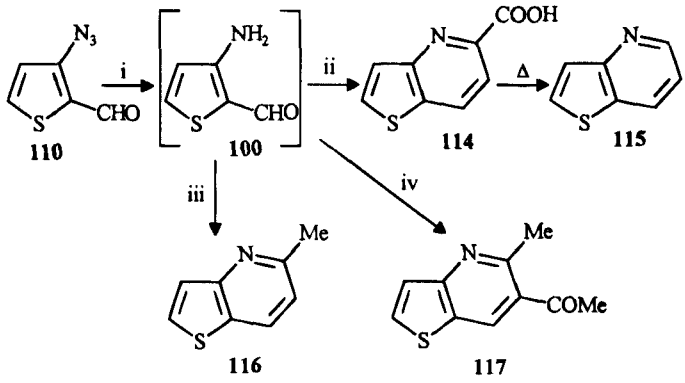


99, 105, 107, 109, 111 (R = Me)
100, 106, 108, 110, 112 (R = H)

i) $NaNO_2$, H_2SO_4, H_2O, O °C. ii) KSCN or KSeCN. iii) NaN_3.
iv) $Na_2S_2O_4$.

SCHEME 30

thieno[3,2-*c*]pyridine **115**. With acetone and acetylacetone the thienopyridines **116** and **117**, respectively, could be synthesized[50] (Scheme 31).



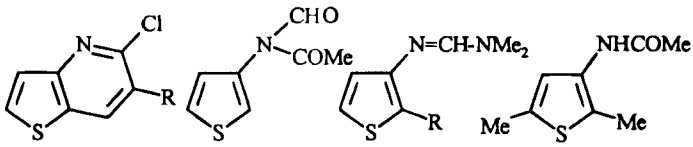
i) H_2S, piperidine, EtOH. ii) $CH_3COCOOH$, NaOH, H_2O.
iii) Acetone. iv) Acetylacetone.

SCHEME 31

3.7. *Conversion of N-(3-Thienyl)acetamide to Thieno[3,2-b]pyridines*

While attempting the formylation of acetamide **3a** via a Vilsmeier reaction we have observed that the aldehyde **98** is obtained in 73% yield when the reaction is carried out in DMF with a stoichiometric amount of $POCl_3$ below 20 °C.[51] On heating with excess of reagents others products were formed.

The thienopyridines **118** and **119**, the *N*-acetyl formamide **120** and the formamidines **121** and **122** were isolated. A mechanism of formation of these various compounds has been proposed. After this work, another group carried out an extensive study of this reaction on *N*-(2-thienyl)acetamide, the acetamides **3a** and **123** and on acetanilides.[52,53] Chlorothienopyridine **118** was isolated in 70% yield with a ratio DMF/$POCl_3$ 1:3 and 1,2-dichloroethane as solvent. The thienopyridinecarbaldehyde **119** was prepared in 72% yield with $POCl_3$/DMF 7:3 at reflux of the solvent.[53] To account for this thienopyridine formation a mechanism was proposed (Scheme 32).



118 R = H
119 R = CHO

120

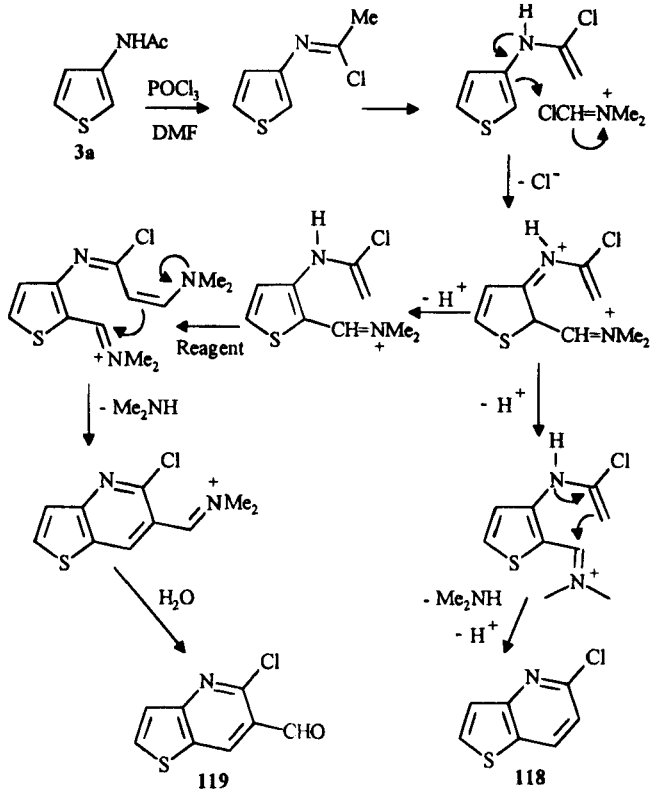
121 R = H
122 R = CHO

123

FIGURE 7

3.8. *Reductive C-Alkylation of 3-Aminothiophenes and Derivatives*

In the course of the preparation of the *N*-benzylamine **9c** by PhSeH reduction of the imine formed from amine **1** and benzaldehyde, we observed that 2-benzyl-3-aminothiophene **124** (R^1 = Ph) was also obtained with acid catalysis.[14] Under these conditions we then prepared in good yields several 2-alkyl-3-aminothiophenes **124** and extended the reaction to the synthesis of the amines **125** from the *N*-alkylamines **9**. Minor amounts of C-alkylation products are formed with tertiary amines **11**.[54,55] We recently observed that the acetamide **3a** and the carbamates **4** can be α-alkylated in an analogous manner leading to the acetamides **126** and the carbamates **127** and **128**, respectively.[55]



SCHEME 32

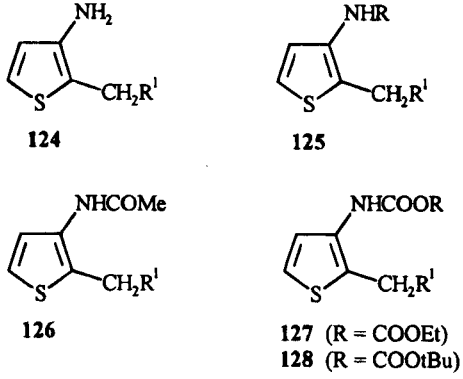
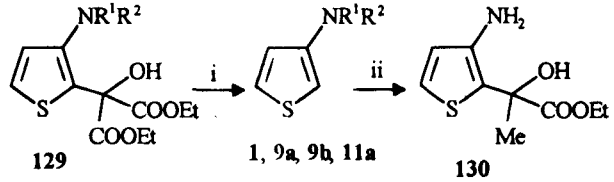


FIGURE 8

The strongly enaminic character of 3-aminothiophenes coupled with the considerable aromaticity of the thiophene nucleus (see Section 2.6) explains this facile α-alkylation reaction. Moreover, the hydroxy esters **129** and **130** have been isolated in good yields from diethyl ketomalonate and ethyl pyruvate, respectively, and the amines **1**, **9a**, and **11a** without acid catalysis[28] (Scheme 33).



129 **1, 9a, 9b, 11a** **130**

i) $(EtOOC)_2C{=}O$, ether. ii) $CH_3COCOOEt$, ether.

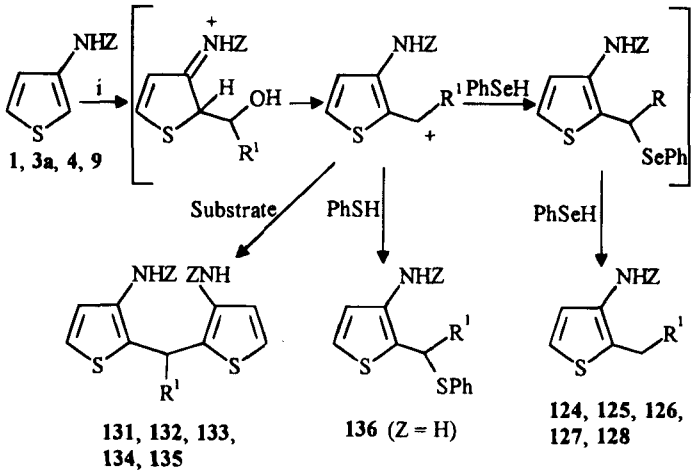
SCHEME 33

When selenophenol was omitted, the acid catalyzed reaction of an aldehyde with two equivalents of the amine **1** led to the bis(aminothienyl)methane derivatives **131**.[54] The amines **9**, the acetamide **3a** and the carbamates **4a** and **4b** have been converted to the C-alkyl derivatives **132**,[54] **133**,[55] **134**, and **135**,[55] respectively. Replacement of selenophenol by thiophenol gives the phenyl sulfides **136**.[54,55] This result shows that intermediately phenyl selenides are reduced by selenophenol. A mechanism which accounts for each step of the process has been proposed (Scheme 34).

The reaction occurs very slowly with ketones. However, amine **1** and acetone in the presence of selenophenol, give 2-isopropyl-3-aminothiophene **137** which was isolated and derivatized to acetamide **138**.[14]

Upon heating under acidic conditions the bis(aminothienyl)methane derivatives **131** undergo a transamination reaction as previously described (see Section 2.6, Scheme 13). Prior to cyclization, however, loss of hydrogen occurs.[55,56] Several dithieno[3,2-*b*:2′,3′-*e*]pyridines **139** have been synthesized in this way and in a one-pot procedure from 3-aminothiophene **1**. With a ketone as reagent, amine **1** forms the dihydrodithienopyridines **140**[16] (Scheme 35).

This acid catalyzed process has also been applied to di(3-thienyl)amine **33**. Dihydrodithienopyridines **141** have been obtained in good yields.[56] (Scheme 36). Various attempts to achieve aromatization failed. This result



124, 131 Z = H **126, 133** Z = COMe **128, 135** Z = COOtBu
125, 132 Z = R **127, 134** Z = COOEt

i) R^1CHO, CH_2Cl_2, *p*-TSA, RT.

SCHEME 34

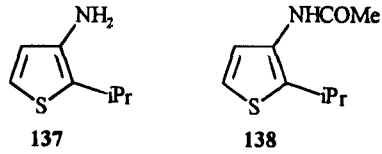
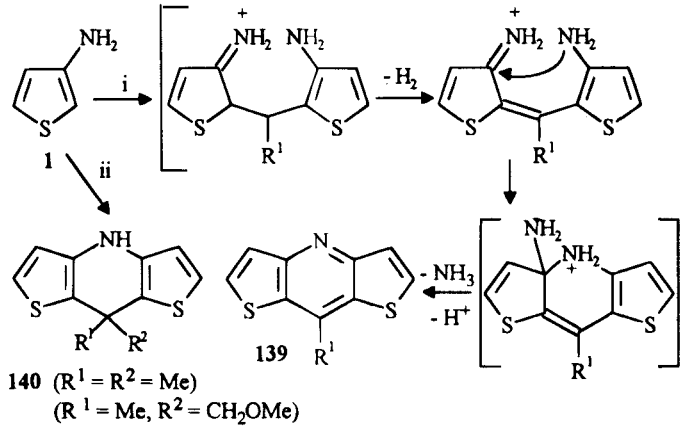


FIGURE 9

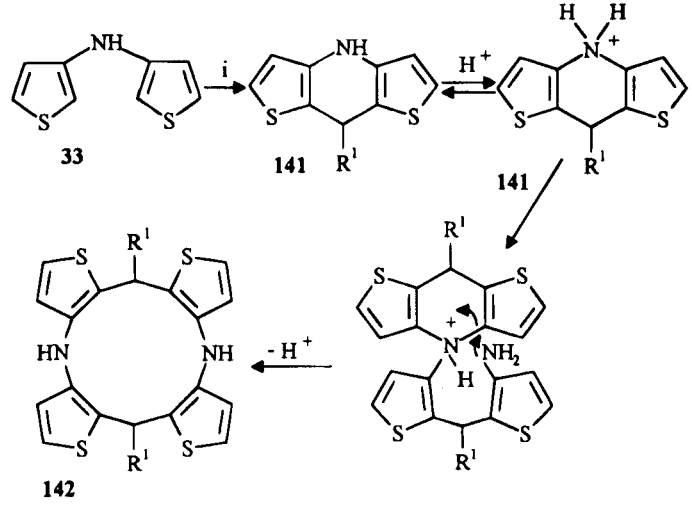
suggests that the dehydrogenation step precedes cyclization during the formation of the dithienopyridines **139**. With longer reaction times the dimers **142** (and also trimers) are formed from **141** via an acid catalyzed dimerization process[56] (Scheme 36).

The formation of a conjugated double bond was observed when a stoichiometric amount of an α-branched aldehyde was allowed to react with amine **1** or a secondary amine **9**, the acetamide **3a**, and the carbamates **4** under acidic conditions. We observed that the deprotonation of the substituent occurs faster than the second electrophilic substitution. The 3-amino-2-vinylthiophene derivatives **143–147** have been prepared in good yields[16] (Scheme 37).



i) R^1CHO (0.5 eq.) CH_2Cl_2, *p*-TSA. ii) R^1COR^2, conc. HCl, CH_2Cl_2.

SCHEME 35

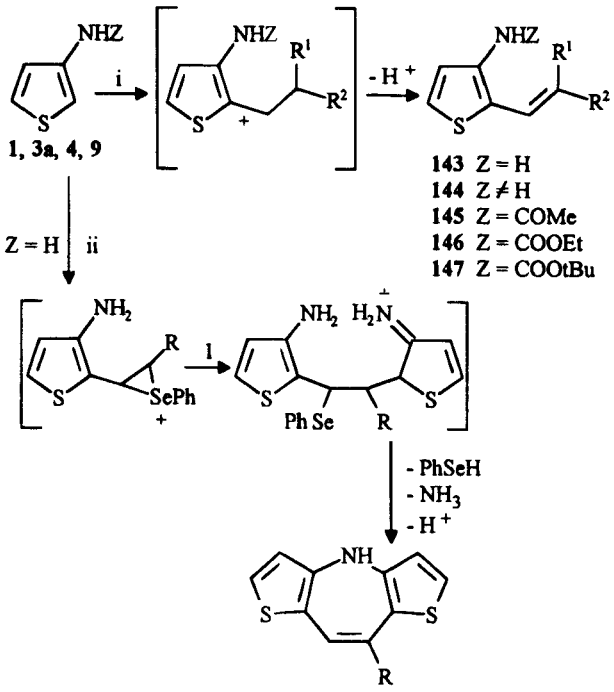


i) R^1CHO, CH_2Cl_2, *p*-TSA, Δ.

SCHEME 36

When this reaction was carried out with amine **1** and an α-phenylseleno aldehyde, the dithieno[3,2-*b*:2′,3′-*f*]azepines **148** were isolated in fair yields.[16] The formation of these tricyclic azaheterocycles involves probably a second electrophilic alkylation with an intermediate seleniranium

cation as electrophile, followed by loss of selenophenol and completed by an internal transamination reaction (Scheme 37).



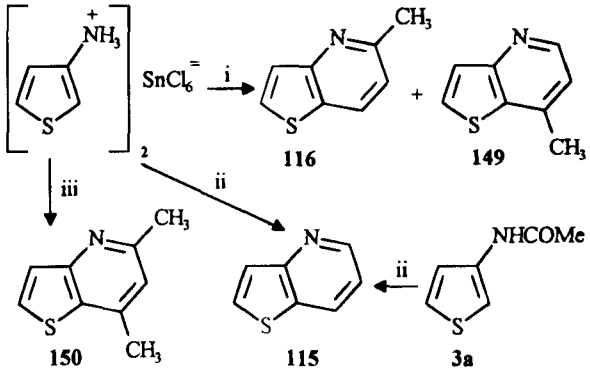
148 (R = Et, Bu)

i) R^1R^2CHCHO, conc. HCl, CH_2Cl_2, RT. ii) RCH(SePh)CHO, conc. HCl, CH_2Cl_2, RT.

SCHEME 37

3.9. *Synthesis of Thieno[3,2-b]pyridines*

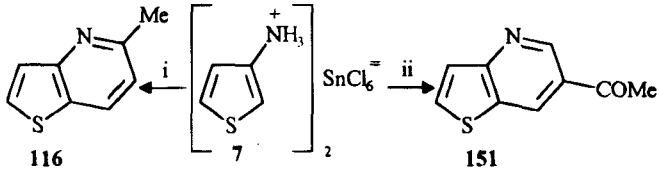
The preparation of thieno[3,2-*b*]pyridine **115** from amine **1** or its hexachlorostannate salt **7** by the well-known Skraup reaction or with conjugated enals has not been investigated. It has only been shown that methyl vinyl ketone and the ammonium salt **7** gave a mixture of the 5-methyl and the 7-methyl pyridine derivatives **116** and **149** in the ratio 1:4[57] (Scheme 38). This result clearly indicates competitive nucleophilic attacks of nitrogen and α-carbon atoms on the carbonyl group.



i) $CH_3COCH{=}CH_2$, $FeCl_3$, $ZnCl_2$, EtOH, Δ. ii) $CH_2[CH(OEt)_2]_2$, EtOH, conc. HCl, $ZnCl_2$, Δ. iii) $CH_3COCH_2COCH_3$, EtOH, conc. HCl, $ZnCl_2$, Δ.

SCHEME 38

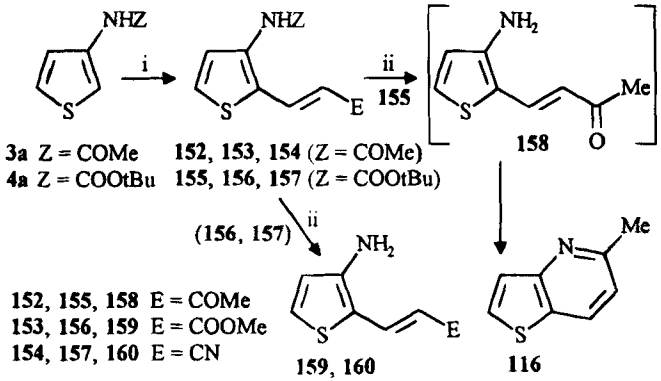
The thieno[3,2-*b*]pyridine **115** has been prepared from the ammonium salt **7**[57] or the acetamide **3a**[58] and malondialdehyde tetraethyl acetal under acidic conditions (Scheme 38). Introduction of acetylacetone as difunctional electrophilic reagent leads to 5,7-dimethylthieno[3,2-*b*]pyridine **150**[59] (Scheme 38). 5-Methylthieno[3,2-*b*]pyridine **116** has been obtained in an analogous way from the ammonium salt **7** and a stoichiometric amount of acetoacetaldehyde dimethyl acetal.[60] However, with large excess of reagent, under the same conditions, 6-acetylthieno[3,2-*b*]pyridine **151** has been isolated[57] (Scheme 39). A mechanism requiring two molecules of electrophilic reagent, as well as formation of an imine, followed by an aldol condensation, has been proposed.[57] As we will see later, the true mechanism has now been elucidated.



i) $CH_3COCH_2CH(OEt)_2$, EtOH, $ZnCl_2$, Δ.
ii) $CH_3COCH_2CH(OMe)_2$, conc. HCl, EtOH, Δ.

SCHEME 39

Continuing our study on the α-vinylation of 3-aminothiophenes and their derivatives (see Section 3.8, Scheme 37), we recently observed that the acetamide **3a** reacts under acidic conditions with α-functionalized acetals $ECH_2CH(OMe)_2$ (E = COMe, COOMe, CN). The corresponding β-(3-amino-2-thienyl) α,β-unsaturated ketone, ester and nitrile **152, 153** and **154** were synthetized in good yields. Analogous results were found with the carbamate **4a** and the ketone **155**, the ester **156** and the nitrile **157** were isolated[56] (Scheme 40).

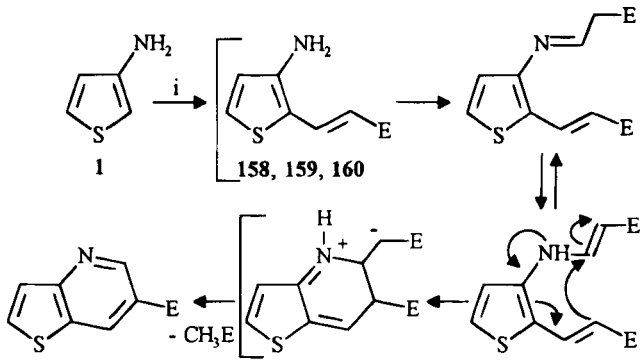


i) $ECH_2CH(OMe)_2$, conc. HCl, CH_2Cl_2, RT. ii) HBr, AcOH, R.T.

SCHEME 40

Acidic cleavage of the carbamate **155** allows cyclization to 5-methylthieno[3,2-*b*]pyridine **116** without isolation of the amino ketone **158**. The same treatment of the carbamates **156** and **157** gives the amino ester **159** and the amino nitrile **160**, respectively[16] (Scheme 40).

When the amino ester **159** and the amino nitrile **160** were subjected to the acidic conditions used for α-vinylation, with one equivalent of functionalized acetal, methyl thieno-[3,2-*b*]pyridine-6-carboxylate **161** and thieno-[3,2-*b*]pyridine-6-carbonitrile **162**, respectively, were obtained in good yields. The nitrile **162** was also isolated from a reaction of acetoacetaldehyde dimethyl acetal with compound **160**.[16] All these results allow us to propose a mechanism for the cyclization to 6-functionalized thieno[3,2-*b*]pyridines which can be prepared in a one-pot procedure from amine **1** (Scheme 41).



151 (E = COMe)
161 (E = COOMe)
162 (E = CN)

i) $ECH_2CH(OMe)_2$ (2.1 eq.), conc. HCl, THF, RT.

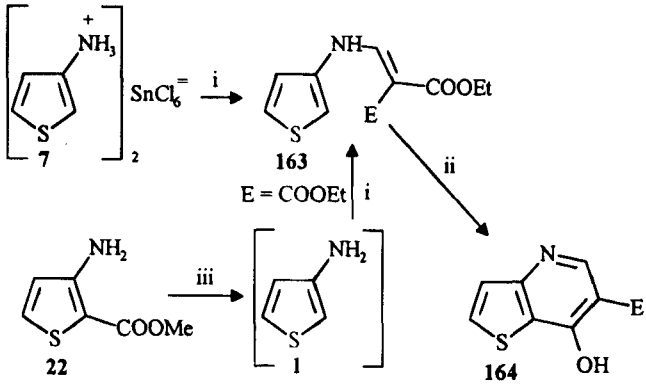
SCHEME 41

This work clearly shows that the formation of the pyridine ring begins with a nucleophilic attack on the carbonyl group by the α-carbon. It can be assumed that the same mechanism is involved with β-dicarbonyl compounds or their acetals under mild acidic and thermal conditions.

Syntheses of 7-hydroxythieno[3,2-*b*]pyridines bearing a functional group in the 6-position have been extensively studied[1] starting with the hexachlorostannate salt **7** and diethyl ethoxymethylenemalonate and analogs (Scheme 42) (E = CN, $COCH_3$). β-(3-Thienylamino)acrylates **163** were isolated. They undergo thermal cyclization and lead to the functionalized hydroxythienopyridines **164**.[61] Recently, improvements have been proposed.[62] The substrate was amine **1**, prepared in solution from the amino ester **22** (see Section 2.4, Scheme 8), and the ring formation achieved under acidic conditions. The 2,7-dichloro derivative was isolated from 5-bromo-3-aminothiophene when the cyclization was carried out in the presence of phosphorus oxychloride.[63]

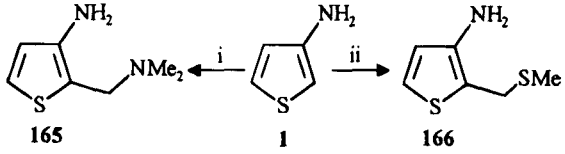
3.10. *Reactions with Other Carbon Electrophiles*

C-Dimethylaminomethylation of amine **1** by reaction with Eschenmoser's salt leads to the diamine **165**. The methylthiomethyl derivative **166** has been prepared by reaction with chloromethyl methyl sulfide and aluminum chloride[16] (Scheme 42).



i) EtOCH=C(E)COOEt, (E = CN, COOEt), pyridine, Δ. ii) PhOPh, Δ or conc. H_2SO_4, Ac_2O, Δ. iii) NaOH, H_2O, Δ; EtOH, AcOH; $EtOCH=C(COOEt)_2$.

SCHEME 42

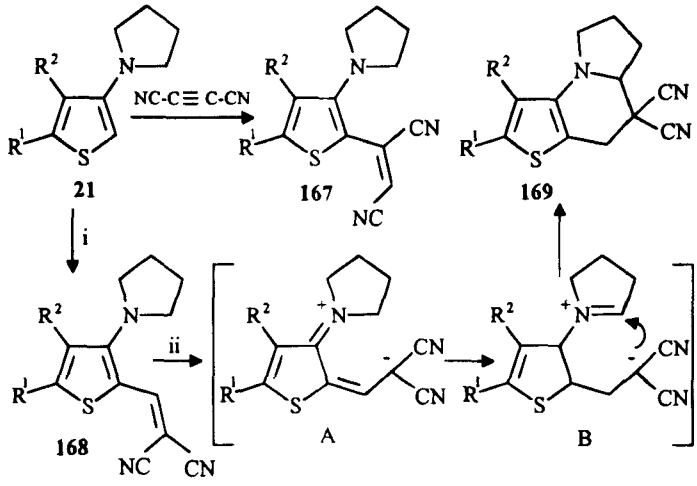


i) $CH_2=\overset{+}{N}Me_2I^-$, CH_3CN. ii) $MeSCH_2Cl$, $AlCl_3$, CH_2Cl_2, 0 °C.

SCHEME 43

3.11. *Reactivity of 3-Pyrrolidinothiophenes and Other Cyclic Amines*

The synthesis of 3-pyrrolidinothiophenes **21** has been mentioned previously (see Section 2.4, Scheme 7). It was first observed that **21** (R^1 = H, R^2 = Me) and butynedinitrile give the unstable adduct **167**.[64] The reaction of the amines **21** with dimethyl acetylenedicarboxylate has also been studied.[17] The strongly enaminic character of these amines allows a facile Michael addition of (methoxymethylene)malonitrile, followed by elimination[65] (Scheme 44). Heating of the adducts **168** in refluxing 1-butanol gave the thieno[3,2-*e*]indolizines **169**. The first step of the ring closure can be assumed to be a thermal 1,5-hydrogen shift producing a zwitterion **B** followed by an intramolecular addition of the carbanion to the iminium double bond as depicted in Scheme 44.



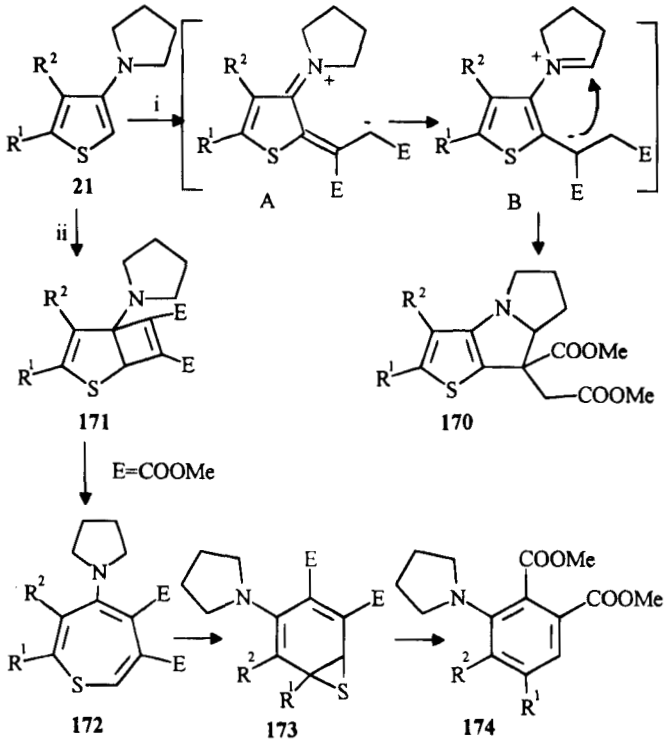
i) $MeOCH{=}C(CN)_2$, THF, R.T. ii) *t*-BuOH, Δ. ii) *t*-BuOH, Δ.

SCHEME 44

In a polar solvent such as methanol or acetonitrile, the formation of a Michael adduct from an amine **21** and dimethyl acetylenedicarboxylate is followed by a [1,6] hydrogen shift (**A** → **B**) (Scheme 45). The isomeric iminium form **B** cyclizes to the tetrahydrothieno[3,2-*b*]pyrrolizines **170**[17,66] A [2 + 2] cycloaddition reaction occurs first when the reaction is carried out in a polar solvent.[66] The thiepins **172** are then formed by internal bond cleavage of the adducts **171**. A rearrangement then follows with formation of dimethyl 3-piperidinophthalates **174** after loss of sulfur from **173** (Scheme 45). The bicyclic bicycloadducts **171** and the thiepins **172** have been characterized at low temperature by ^{1}H NMR spectroscopy.[64]

4. SYNTHESIS OF 3,4-THIOPHENEDIAMINES AND DERIVATIVES

This chapter deals with preparations of 3,4-diaminothiophenes. We will discuss the synthesis of amides and carbamates and the different methods for *N*-alkylation. The reactivity of these diamines will be then discussed.



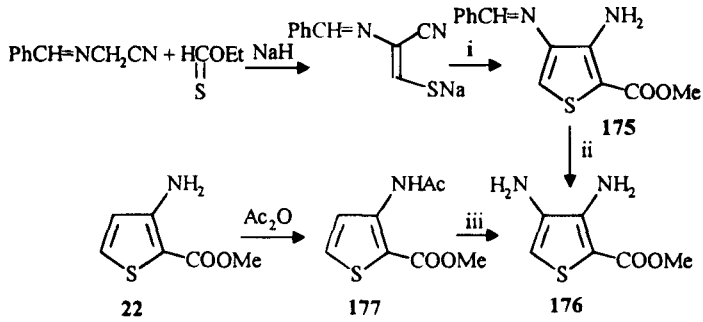
i) E-C≡C-E (E = COOMe), MeOH or CH_3CN. ii) E-C≡C-E, ether or $CHCl_3$.

SCHEME 45

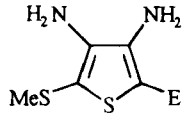
4.1. *3,4-Thiophenediamines*

The methods developed for the synthesis of 3,4-diaminothiophenes bearing an electron withdrawing functional group on the nucleus have been reviewed.[1] One of them involves reaction of an enethiolate with methyl chloroacetate. Hydrolysis of the imino ester **175** (Scheme 46) leads to methyl 3,4-diamino-2-thiophenecarboxylate **176**.[67,68] Another route consists in the nitration of the acetamido ester **177** derived from the amino ester **22**. Hydrogenation of the nitro group leads to the diamine **176**.[68] Following a similar approach, 2,5-disubstituted 3,4-diaminothiophenes **178** have been described[69] (Scheme 46).

A unique and convenient procedure to prepare diamine **2** on a multigram scale involves double nitration of 2,5-dibromothiophene, followed by a



i) $ClCH_2COOMe$, NaOMe. ii) HCl, Et_2O; NaOH, H_2O. iii) HNO_3, H_2SO_4, - 30 °C; NaOH, H_2O; H_2, Pd/C.



178

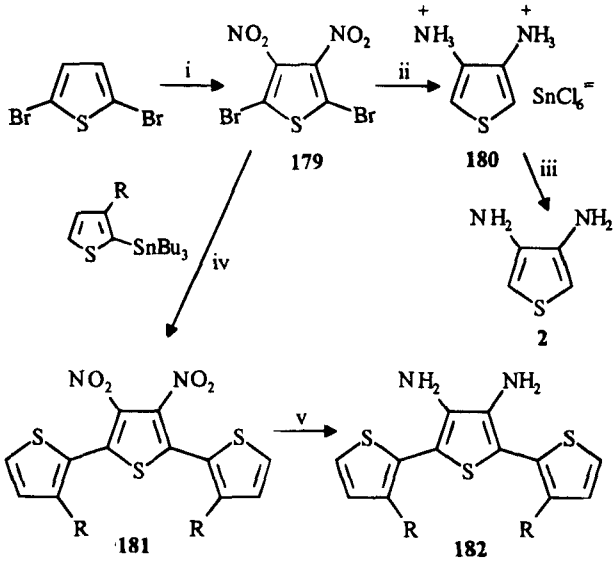
(E = CN, COPh, COOEt...)

SCHEME 46

one-pot reduction of the two C-Br bonds and the two nitro groups.[70,71] This method was originally part of a biotin synthesis (see Section 6.7). 3,4-Diaminothiophene **2**, considered as unstable, was not isolated and transformed in solution to the diacetamide **5a** or the dibenzamide **5b**.[70]

We have particularly studied this method and diamine **2** was isolated as a crystalline compound which can be stored during for several months in the refrigerator, protected from light and moisture. The experimental details of the three steps have been improved[72,73] (Scheme 47). Nitration of 2,5-dibromothiophene can be achieved in 60 % yield to give the dinitro derivative **179** which is then reduced in acidic medium with tin[72] or tin(II) chloride.[73] In fact the hexachlorostannate salt **180** contains some hydrochloride salt. This mixture was treated with dilute sodium hydroxide solution and extracted with ether[72] or methylene chloride.[73] The overall yield of the two last steps is close to 60%.[73] The diamine **2** can be easily prepared on a 20–30 g scale.[74]

A double Pd-catalyzed coupling reaction between dibromo compound **179** and 2-thienyltributylstannane leads to the dinitroterthienyl **181** which can be reduced to the diamine **182**[75] (Scheme 47).



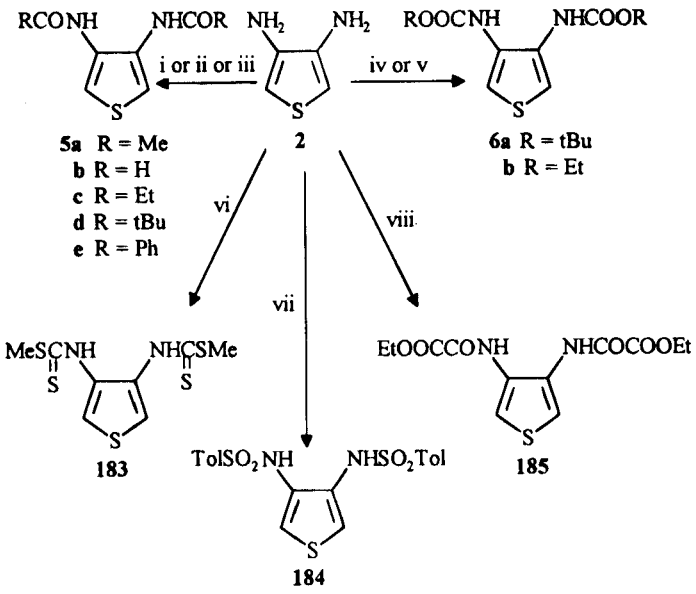
i) Conc. HNO_3, H_2SO_4, SO_3. ii) Sn or $SnCl_2$, HCl, H_2O. iii) NaOH, H_2O, ether. iv) $Pd(PPh_3)_2Cl_2$, THF. v) $SnCl_2$, HCl, EtOH.

SCHEME 47

4.2. *Diamides and Dicarbamates*

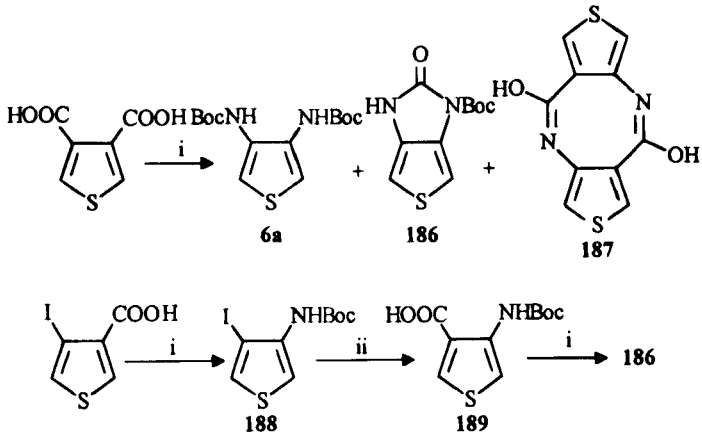
The diformamide **5b**,[14] the diacetamide **5a** and several others diamides **5**[72] have been prepared by acylation of the diamine **2** according to classical methods as indicated in Scheme 48. The di-*t*-butyl dicarbamate **6a** and the diethyl dicarbamate **6b** have been easily obtained[76] as the bis(dithiocarbamate) **183**,[72] the di(*p*-toluenesulfonamide) **184**[72] and the bis(oxamate) **185**[72] (Scheme 48).

A double Curtius rearrangement using 3,4-thiophenedicarboxylic acid, DPPA and *t*-butanol (see Section 2.1) has been used by others[77] as an access to the di-*t*-butyl dicarbamate **6a**. The yield was, however, low owing to secondary reactions occurring after the formation of the first isocyanate group. The thienoimidazolone **186** and the dithienodiazocine **187** were formed (Scheme 49). An indirect pathway was thus followed from 4-iodo-3-thiophenecarboxylic acid. A first carbamate group was introduced by Curtius rearrangement of the corresponding acyl azide. Halogen-metal exchange on **188**, followed by carbonation, led to the introduction of the second carboxyl group. Unfortunately, the second rearrangement of **189** led to the thienoimidazolone **186**.[77]



i) HCOOH, Ac_2O ; ether (**5b**). ii) Ac_2O, ether (**5a**). iii) RCOCl, Et_3N, ether. iv) ClCOOEt, ether, NaOH (**6b**). v) $(Boc)_2O$, CH_2Cl_2 (**6a**). vi) CS_2, DMSO, NaOH, MeI. vii) TsCl, pyridine. viii) ClCOCOOEt, ether, NaOH.

SCHEME 48

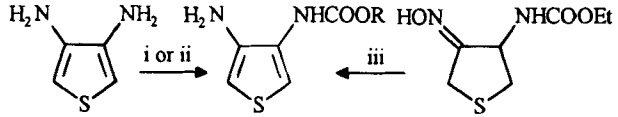


i) DPPA, Et_3N, *t*-BuOH, Δ. ii) BuLi, ether, - 78 °C; CO_2; H_3O^+.

SCHEME 49

4.3. *Monocarbamates*

It will be described later (see Section 6.5) that 3,4-diaminothiophene **2** behaves as a double enamine and reacts also very easily with the two amino groups as illustrated by the preparation of diamides and dicarbamates. It was of interest to differentiate the enaminic reactivity of the two sides of the molecule. With this perspective, we suceeded in the preparation of the monocarbamates **190** (R = *t*-Bu, Et) under appropriate experimental conditions and in yields greater than 60%[76] (Scheme 50). The hydrochloride of the ethyl carbamate **190b** was previously isolated by acid treatment of the oxime **191**.[78]



2 **190a** R = tBu, **b** R = Et **191**

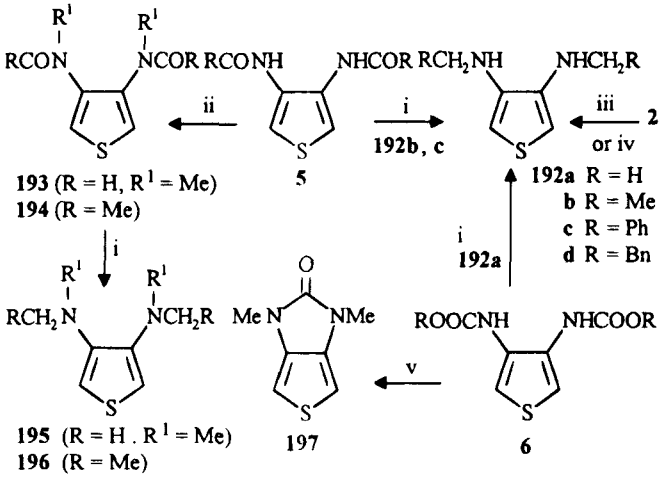
i) ClCOOEt (1.0 eq.); CH_2Cl_2, NaOH, RT, (**190b**). ii) $(Boc)_2O$ (1.1 eq.), petroleum ether/THF, RT (**190a**). iii) HCl, ether.

SCHEME 50

4.4. *Mono- and Poly-N-Alkylated Diaminothiophenes*

Lithium aluminum hydride reduction of diamides **5** is a general method for the synthesis of symmetrical secondary diamines **192** (R ≠ H). The diamides **5** can undergo double *N*-alkylation under basic conditions. The corresponding diamides **193** and **194** have been reduced to the symmetrical tertiary amines **195** and **196**[14] (Scheme 51). 3,4-Bis(methylamino)thiophene **192a** has been synthesized either by direct double methylation of the diamine **2** or by reduction of the dicarbamate **6b**.[14] Double *N*-benzylation of the diamine **2** leading to 3,4-bis(benzylamino)thiophene **192d** was achieved in good yield[76] but double methylation of the dicarbamate **6b** under basic conditions led to *N,N'*-dimethylthieno[3,4-*d*]imidazolone **197**[76] (Scheme 51).

Double methylation of the dicarbamate **6b** to the *N,N'*-dimethyl dicarbamate **198** was achieved by methyl iodide treatment in the presence of KF/Al_2O_3. Reduction of **198** constitutes another route to 3,4-bis(dimethylamino)thiophene **195**[14] (Scheme 52). We were surprised to observe that

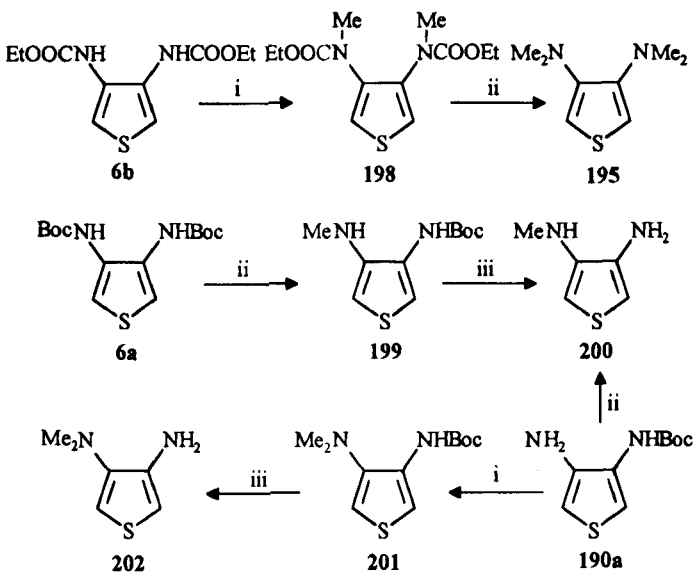


i) $LiAlH_4$, ether, RT (**192 a, b, c**). ii) R^1I, KF-Al_2O_3, MeCN, RT. iii) $(CH_2O)_n$, NaOMe, MeOH, $NaBH_4$, RT (**192a**). iv) $PhCH_2Cl$ (excess), CH_2Cl_2, RT (**192b**). v) NaH, MeI, DMF, Δ.

SCHEME 51

the reduction of the di-*t*-butyl dicarbamate **6a** occurs only on one group, leading to the monocarbamate **199**. Hydrolysis of **199** gave the unsymmetrical diamine **200** also obtained by reduction of the monocarbamate **190a**.[76] The same carbamate **190a** undergoes a double methylation of the free amino group with methyl iodide and KF/Al_2O_3 allowing isolation of the monocarbamate **201** which can be reduced to 3-amino-4-(dimethylamino)thiophene **202**[76] (Scheme 52).

The *N*-alkylation of the amine **2** and its derivatives has also been studied. When treated with allyl bromide under basic conditions, the diamine **2** gives the mono-*N*-allylated diamine **203** as the major product, but the *N,N'*-diallyldiamine **204** and the *N,N,N'*-triallyldiamine **205** are also formed.[76] (Scheme 53). The diallyl derivative **206** was obtained from the dicarbamate **6a** under the same conditions. We observed that *N,N'*-diallylthieno[3,4-*d*]-imidazolone **207** is formed in apreciable amount beside dicarbamate **206** when a large excess of allyl bromide is added. The amino carbamate **190a** was mostly allylated on the carbamic nitrogen atom giving **208**, but the triallyl carbamate derivative **209** was the major product when excess allyl bromide was used[76] (Scheme 53).



i) MeI, KF-Al_2O_3, MeCN, RT. ii) $LiAlH_4$, ether, RT. iii) HBr, AcOH, then Et_2O, NaOH, H_2O.

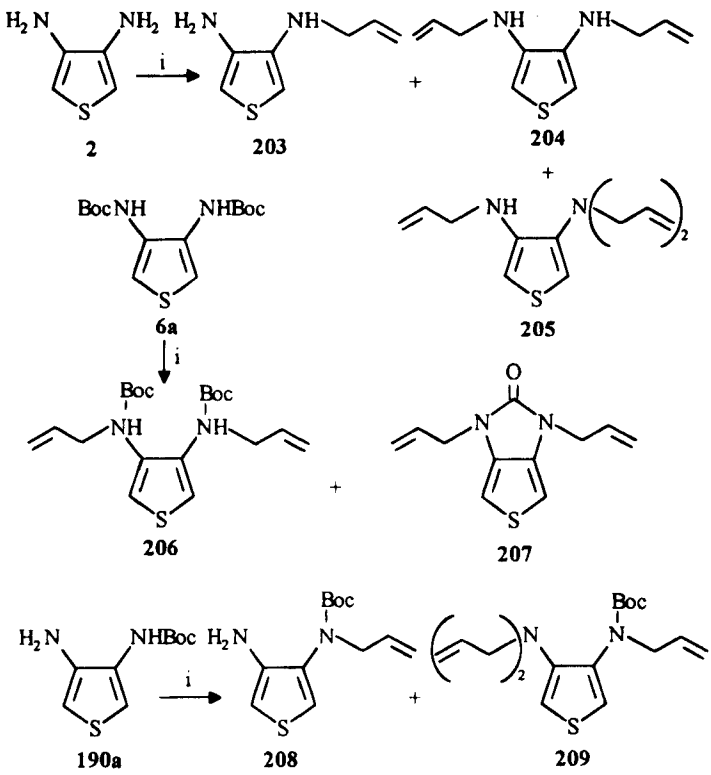
SCHEME 52

4.5. *Stability, Basicity and Reactivity*

3,4-Diaminothiophene **2** is a stable colorless crystalline compound (mp 96 °C) and can be stored in the refrigerator when protected from light and moisture. It is soluble in chloroform, dichloromethane, alcohols and tetrahydrofuran, but only slighly soluble in ether. The *N*-alkyl derivatives **192**, **195**, **196**, **200**, **202**, and **203** are stable oils purifiable by silica gel chromatography.

The pK_{a1} values of 3,4-diaminothiophene **2**, 3,4-bis(methylamino)thiophene **192a** and 3,4-bis(dimethylamino)thiophene **195** have been determined in a water-DMSO mixture (50:50).[79] They are bases comparable to *o*-phenylenediamine (pK_{a1} =4.17) (pK_{a1}; **(2)**: 3.96; pK_{a1} **(192a)**: 3.46; pK_{a1} **(195)**: 3.69).[30,79]

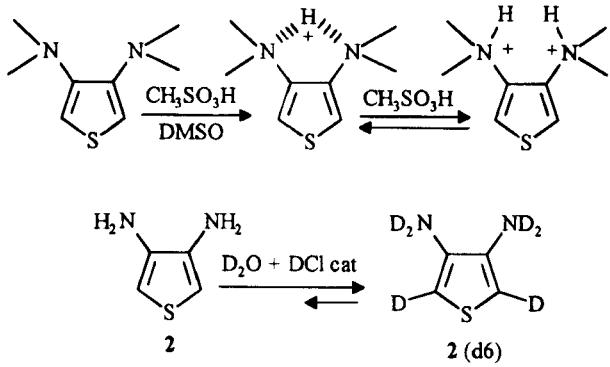
The ^1H NMR chemical shifts of the thiophene protons are indicative of symmetrically protonated forms (Scheme 54). Treatment of diamine **2** with D_2O and a catalytic amount of acid leads to an instantaneous H→D exchange of the two α-protons confirming the pronounced double enaminic character of the structure.



SCHEME 53

The chemical shifts of the thiophenic protons in DMSO, 5.83 for diamine **2**,[79] 5.77 for **192a**,[30] and 6.42 for **195**[30] indicate a significant decrease of the electronic density on the α-carbon atoms upon complete substitution of the two amino groups. This observation suggests a weaker enaminic behaviour for tertiary diamines such as **195** as already observed for 3-(dimethylamino)-thiophene **11a** (see Section 3.8).

The C-nucleophilicity of the diamines **2, 192a**, and **195** was also studied through their reactions with DNBF like with the monoamines **1**, **9a**, and **11a** (see Section 2.6, Scheme 16).[30,79] No-adducts are formed while they can be characterized with aniline and *o*-phenylenediamine. Only mono- and double C-adducts were observed in DMSO by ^{1}H NMR and by stop-flow spectrometry in a mixture water/DMSO or in methanol. The rate con-



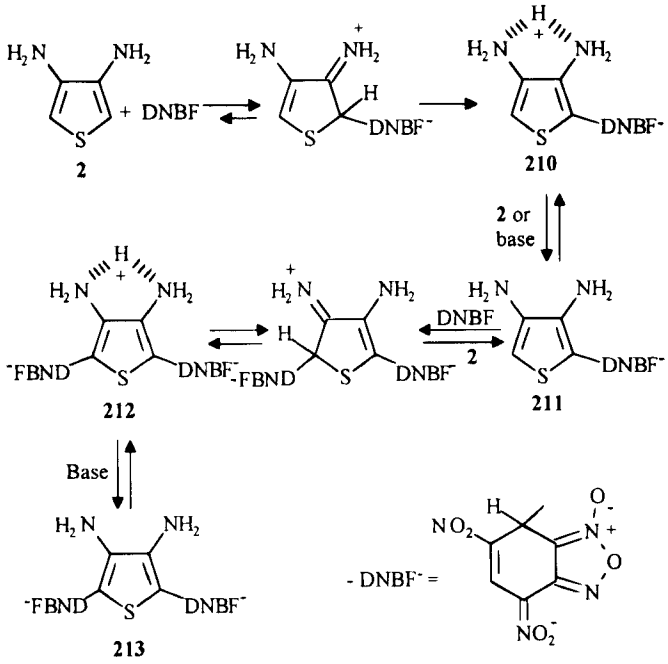
SCHEME 54

stant k_1 of diamine **2** was estimated to $9 \cdot 10^5$ $1 \cdot mol^{-1} \cdot s^{-1}$. This value is one of the more important ones observed in C-complexation with DNBF.[30] Diamine **2** is much more reactive than 3-aminothiophene **1**. An equilibrium appears between the diadduct **212** and the monoadduct **210** which can be isolated when the reaction is carried out at low temperature like those formed from the diamines **192a** and **195**. From the ^1H NMR spectra it is apparent that the three diadducts appear as mixtures of diastereoisomers as a consequence of one asymmetric center on each DNBF moiety. With a large excess of diamine **2**, the anionic adduct **211** has been observed[30,79] (Scheme 55).

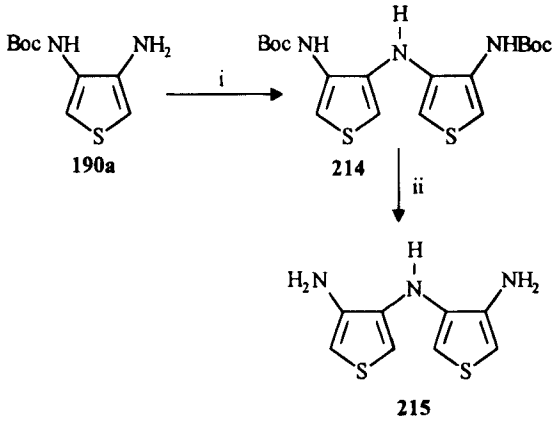
Acid-catalyzed transamination occurs also with monoprotected 3,4-diaminothiophenes such as the monocarbamate **190a** as already seen with monoamines (see Section 2.6, Scheme 13). Upon heating in the presence of acetic acid **190a** forms the dithienylamine derivative **214**. The two carbamate functions can be hydrolyzed to produce the triamine **215**[76] (Scheme 56).

5. CYCLIZATIONS BETWEEN THE AMINO GROUPS OF 3,4-THIOPHENEDIAMINES

In this chapter we will see reactions involving only the two amino groups of diamine **2** leading to thieno-fused diazaheterocycles. This subject has been partially reviewed some years ago.[2]



SCHEME 55

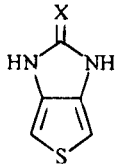


i) AcOH, C_6H_6, Δ. ii) HBr, AcOH.

SCHEME 56

5.1. *Thieno[3,4-d]imidazoles*

The formation of thieno[3,4-*d*]imidazolones such as **216** (X = O) is important in the perspective of biotin synthesis (see Section 6.7). Generally, the imidazolone ring is formed upon treatment of a diamine with phosgen. Thieno[3,4-*d*]imidazolone **216** (X = O) has been prepared by this method.[71] Diamine **2** reacts also with carbon disulfide under basic conditions to give thieno[3,4-*d*]imidazolethione **216** (X = S).[80]



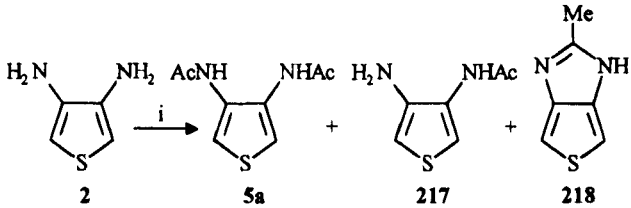
216 (X = O, S)

FIGURE 10

We have already seen in the preceding chapter that thieno[3,4-*d*]imidazolone derivatives are formed in reactions involving mono- and dicarbamates derived from diamine **2** (compounds **186**, **197**, **207**). We will see later that thieno[3,4-*d*]imidazoles are obtained as by-products in the Vilsmeier formylation of the diacetamides **6a** and **6c** (see Section 6.4).

Acetic anhydride treatment of diamine **2** in THF gave a mixture of diacetamide **5a**, monoacetamide **217** and the methylthienoimidazole **218** as the major product (60 %)[47] (Scheme 57).

Several patents have described the synthesis and pharmacological properties of thieno[3,4-*d*]imidazoles, i.e. **219**[82] as ulcer inhibitors and **220** as



i) Ac_2O (1 eq.), THF, RT.

SCHEME 57

angiotensin II antagonists,[82,83] antihypertensives,[84] and for heart disease treatment.[85] Compounds of structure **221** proposed as angiotensin II antagonists have been prepared from the corresponding 3,4-diamino-5-methyl-2-thiophenecarboxylic acid.[86] The formation of the imidazole ring in compounds **220** was achieved by reaction of diamine **2** with imidates[88,84] or trimethyl orthocarboxylates.[85]

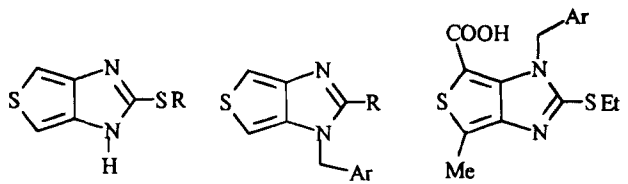


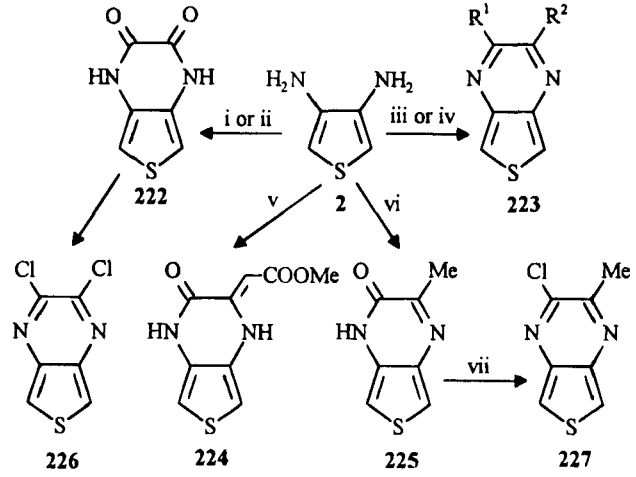
FIGURE 11

5.2. *Thieno[3,4-b]pyrazines*

Tetrahydrothienopyrazinedione **222** was first synthesized from the hexachlorostannate **180**.[71] We have prepared this pyrazinedione from the diamine **2** and oxalic acid or ethyl oxalate.[80] Condensation of **2** with α-oxo aldehydes or α-diketones gave the thieno[3,4-*b*]pyrazines **223**.[80] The thienopyrazinone ester **224** resulted from cyclization with dimethyl acetylenedicarboxylate[80] and the methylthienopyrazinone **225** from reaction with ethyl pyruvate. Phosphorus oxychloride treatment of **222** and **225** leads to the chloropyrazines **226**[73] and **227**,[28] respectively (Scheme 58).

Some other pyrazines of the general formula **223** have been synthetized from the diamine **2**.[87,89] 2,3-Dimethylthienopyrazine **223** ($R^1 = R^2 = Me$), prepared from the hexachlorostannate salt **180** and diacetyl was oxidized with *m*-chloroperbenzoic acid giving a mixture of the 1-oxide and 1,4-dioxide **228** and **229**.[44]

Thienopyrazines **230** having two functional groups on the thiophene nucleus have been prepared from the corresponding diamines **178** (see Section 4.1).[69] Poly(2,3-dihexylthieno[3,4-*b*]pyrazine) **231**, a soluble semiconductive polymer, dark blue in the neutral state and light yellow when doped, was prepared by oxidative polymerization of pyrazine **223**[90] (Scheme 59). Poly[5,7-di(2-thienylthieno[3,4-*b*]pyridazines)] **232** have also been prepared from thienopyrazine monomers synthetized by reaction of α-diketones with the diamine **182** (R = H).[75]



i) $(COOH)_2$, HCl, H_2O, Δ. ii) $(COOEt)_2$, EtOH, Δ. iii) R^1COCHO, NaOH, H_2O, Δ. iv) R^1COCOR^2, EtOH, Δ. v) MeOOCC≡COOMe, $CHCl_3$, Δ. vi) $CH_3COCOOEt$, ether. vii) $POCl_3$, pyridine.

SCHEME 58

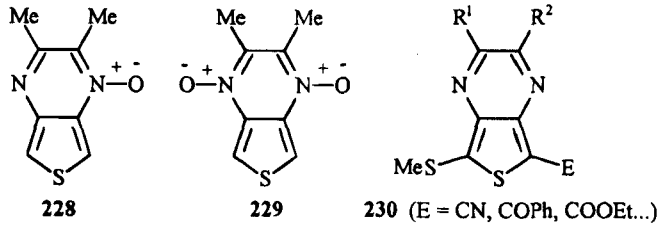
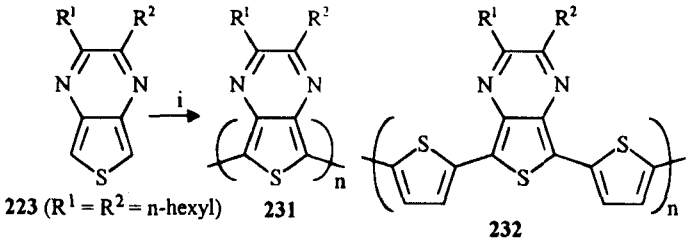


FIGURE 12

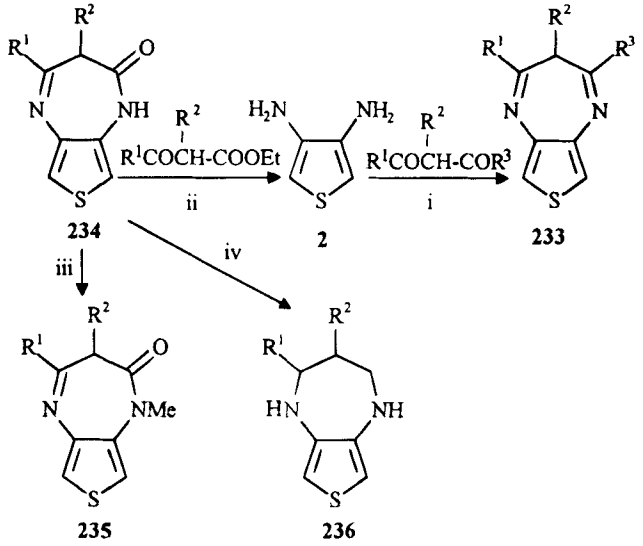


i) $FeCl_3$, $CHCl_3$, air, Δ.

SCHEME 59

5.3. *Thieno[3,4-b][1,4]diazepines*

3*H*-Thieno[3,4-*b*][1,4]diazepines **233**, rather unstable compounds, have been obtained in fair yields and characterized by ^{1}H NMR spectroscopy. In a first step their hydrochloride salt were isolated after reaction of diamine **2** with β-diketones under acidic conditions[80] (Scheme 60). Thienodiazepinones **234** resulted from the corresponding condensation with β-oxo esters. Methylation of the lactam nitrogen atom was easily achieved giving the diazepinones **235**. Concomitant reduction of the carbonyl and imine double bonds gives access to the tetrahydrothienodiazepines **236**[91] (Scheme 60).



i) EtOH, AcOH, Δ; HCl, H_2O, ether. ii) Xylene, Δ or xylene, KOH, EtOH, Δ. iii) MeI, K_2CO_3, DMF, Δ. iv) $LiAlH_4$, ether, Δ.

SCHEME 60

The synthesis of the thienodiazepinones **237–240** has been previously achieved by condensation of the diamino nitrile **178** with ethyl acetoacetate, diethyl acetonedicarboxylate, diketene, or ethyl benzoylacetate, respectively.[92]

5.4. *Thieno[3,4-c][1,2,5]thiadiazoles*

The non-classical thieno[3,4-*c*][1,2,5]thiadiazoles **242a** have been obtained by reaction of *N*-sulfinylbenzenamine with the diamine **2** under basic con-

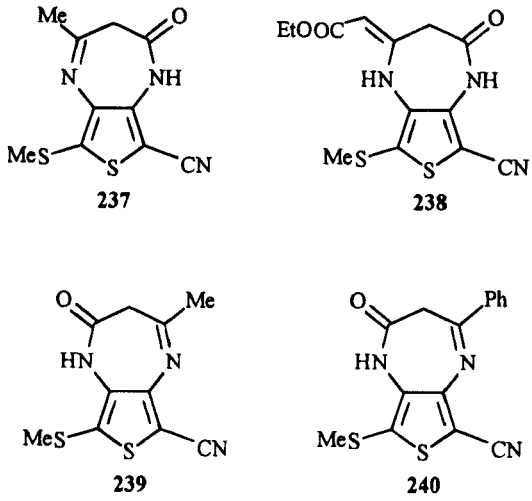
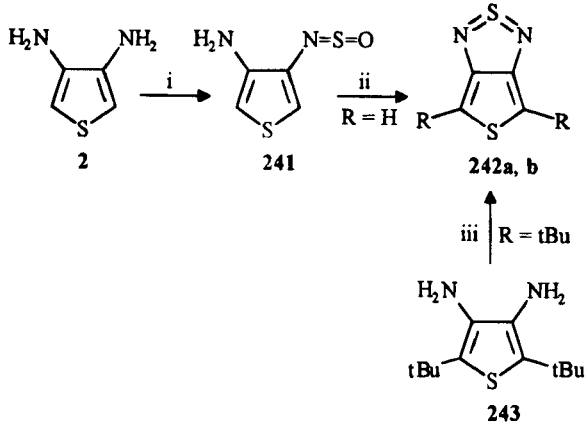


FIGURE 13

ditions after isolation of the intermediate **241** (Scheme 61). The thienothiadiazole **242b** was also obtained from 3,4-diamino-2,5-di(*t*-butyl)thiophene **243**.[93]

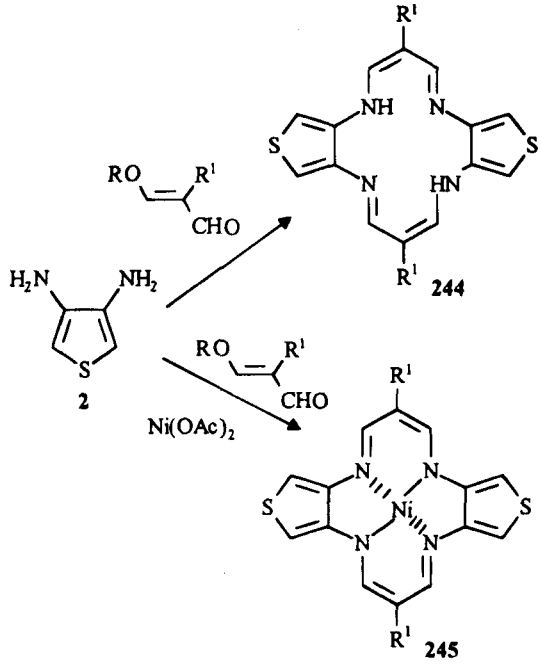


i) PhN=S=O, Et_3N. ii) Me_3SiCl, pyridine, Δ. iii) PhN=S=O, pyridine, Δ.

SCHEME 61

5.5. *Dithienotetraaza-14-annulenes*

Tetraaza-14-annulenes **244** symmetrically fused with two thiophene nuclei and their corresponding Ni(II) chelates **245** have been prepared by cyclization of diamine **2** and β-alkoxy enals in stoichimetric amounts[94] (Scheme 62).



SCHEME 62

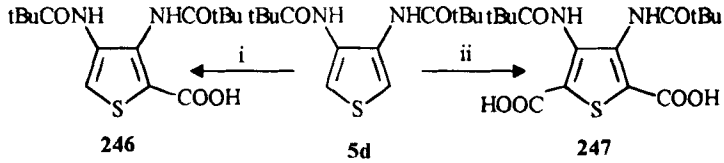
6. REACTIONS ON THE NUCLEUS OF 3,4-THIOPHENEDIAMINES

As for 3-aminothiophenes and their derivatives, the more important results concern electrophilic substitutions achieved in the 2- and 5-positions of the ring. In the first paragraph, results concerning the metallation of the dipivalamide **5d** are presented.

6.1. *C-Lithiation of Dipivalamide 5d*

Ortho-directed BuLi metallation cannot be achieved with the dicarbamates **6** without formation of thienoimidazolones as already seen for *N*-alkylation

reactions (see Section 4.2). The first *N*-lithiation leads to a nucleophilic attack of the second alkoxycarbonyl group. We have, however, observed that dipivalamide **5d** can be deprotonated with butyllithium. The di- and tetralithio derivatives react with carbon dioxide. Mono- and dicarboxylic acids **246** and **247** can be prepared depending upon the amount of butyllithium[72] (Scheme 63).



i) BuLi (3 eq.), THF, 15 °C; CO_2; H_3O^+. ii) BuLi (6 eq.), ether, 15 °C; CO_2; H_3O^+.

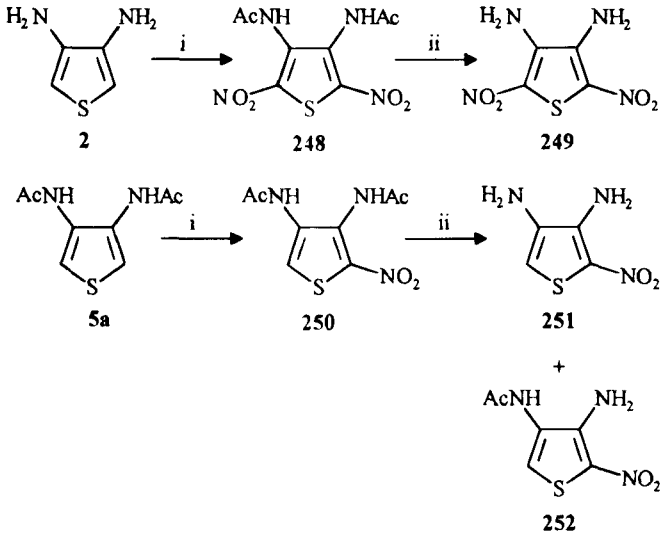
SCHEME 63

6.2. *Nitration*

Nitration of the diamine **2** in acetic acid in the presence of acetic anhydride gives the dinitrodiacetamide **248** in fair yield. Sulfuric acid treatment of **248**, as previously used for the hydrolysis of the nitro acetamide **65** (see Section 3.3), gives access to 3,4-diamino-2,5-dinitrothiophene **249**.[72] Mononitration succeeded with the diacetamide **5a** as the substrate. Acidic hydrolysis of **250**, however, leads to a mixture of the diaminonitrothiophene **251** and the aminonitroacetamide **252**. Curiously, the 4-acetamido group is more resistant to hydrolysis[72] (Scheme 64).

6.3. *Thiocyanation*

Double Kaufmann thiocyanation of diamine **2** affords the dithiocyanate **253** in very good yield.[80] According to the amounts of reagents, the monothiocyanate **254** and the dithiocyanate **255** were obtained in the reaction with the diacetamide **5a**[80] (Scheme 65). Sodium sulfide reduction of the dithiocyanate **253** gives the sodium bissulfide **256** which can be alkylated leading, for example, to 3,4-diamino-2,5-di(methylthio)thiophene **257**. Treatment of this salt **256** with bromoacetic acid leads to double cyclization to the dioxothiazinoth-



i) HNO_3, AcOH, Ac_2O, RT. ii) Conc. H_2SO_4, Δ.

SCHEME 64

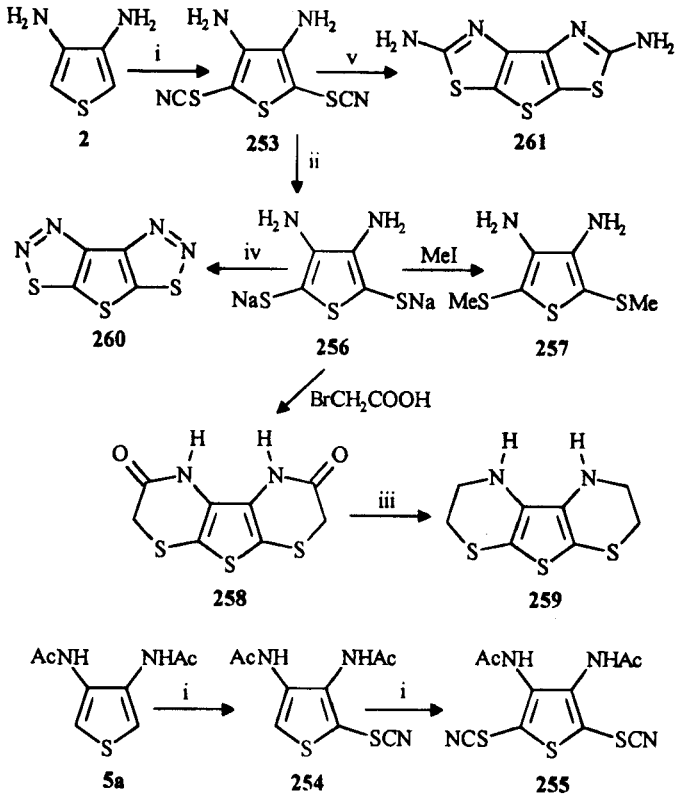
ienothiazine **258** which in turn can be reduced to the thiazinothienothiazine **259**.[80] Diazotation of **256** leads to the thiazolothienothiazole **260**.[80] The diamino dithiocyanate **253** undergoes thermal isomerization under acidic conditions leading to the diaminothiazolothienothiazole **261**[80] (Scheme 65).

6.4. *Acetylation and Formylation*

Friedel-Crafts acylation has only been studied in the case of diacetamide **5a.** Upon heating with acetyl chloride in the presence of aluminum chloride, the methyl ketone **262** was isolated and hydrolyzed according to the conditions described above (see Sections 3.6 and 6.2). As observed in the hydrolysis of the nitrodiacetamide **250**, the monoamine **263** was the main product isolated[47] (Scheme 66).

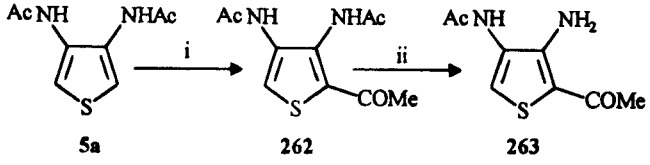
Vilsmeier formylation of the amides **5c**, **5d**, and **5e** and of the carbamate **6b** has been investigated.[47,72] The corresponding monoaldehydes **264c–e** and **265b** have been prepared in good yields.

The preparation of the monoaldehyde **266** from the diacetamide **5a** was complicated by the competing formation of the thieno[3,4-*c*]imidazoles **267**



i) NH_4SCN (4 eq.), Br_2, MeOH, 0 °C. ii) Na_2S, H_2O. iii) $LiAlH_4$, ether. iv) $NaNO_2$, H_2SO_4, H_2O, 0 °C. v) HCl, H_2O, Δ; NH_4OH.

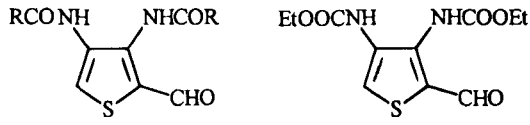
SCHEME 65



i) AcCl, $AlCl_3$, Δ. ii) Conc. H_2SO_4, Δ.

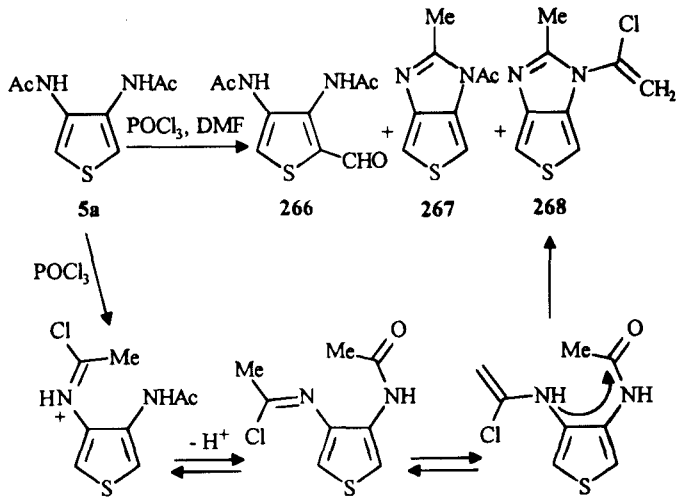
SCHEME 66

and **268**. Excess of phosphorus oxychloride explains the cyclization to an imidazole as presented in Scheme 67.[72] The reaction was not further studied, but we have observed that a complex mixture is obtained on heating with excess of DMF and $POCl_3$. Chlorothienopyridinecarbaldehydes, chloro- and formylpyridothienopyridines have been detected by ^1H NMR spectroscopy.[47]



264 (R = Et, Ph, tBu) **265b**

FIGURE 14

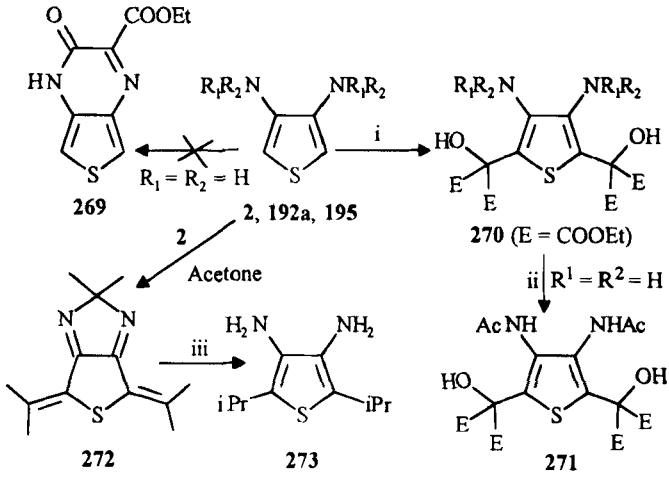


SCHEME 67

6.5. *Reductive C-Alkylation of 3,4-Diaminothiophenes and Derivatives*

Two typical features can illustrate the very strong double enaminic character of diamine **2**, *N,N'*-dimethyldiamine **192a** and *N,N,N'N'*-tetramethyldiamine **195**. With the purpose to prepare the pyrazinone ester **269** from diamine **2** and diethyl oxomalonate, as described for *o*-phenylenediamine,

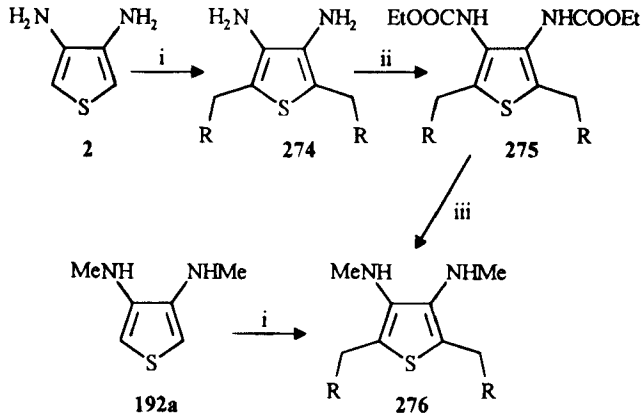
we were surprised to isolate the tetraester **270** ($R^1 = R^2 = H$) in quantitative yield. The compounds **270** were derivatized to the diacetamides **271**. This double electrophilic reaction occurs even at low temperature[28] (Scheme 68). The second unexpected result was the isolation of 2,5-bis(isopropylidene)thieno[3,4-*c*]imidazole **272** by simple dissolution of diamine **2** in acetone. This compound was hydrogenated to 3,4-diamino-2,5-diisopropyltiophene **273**[73] (Scheme 68).



i) $(EtOOC)_2CO$, ether. ii) Ac_2O. iii) H_2, Pd/C.

SCHEME 68

We have therefore studied the reductive *C*-alkylation reactions of these diamines using aldehydes and selenophenol with acid catalysis as for 3-aminothiophenes and derivatives (see Section 3.8). The result is that the second *C*-alkylation occurs faster than the first one. 2,5-Dialkyl-3,4-diaminothiophenes **274** have been synthesized in fair yields from the diamine **2**.[28] The double condensation has occurred more slowly with acetone and the diamine **273** was isolated in poor yield.[28] Some 2,5-disubstituted 3,4-diaminothiophenes **274** have been converted to the dicarbamates **275** and then reduced leading to the bis(methylamino)thiophenes **276**. These diamines have also been synthesized by double alkylation of 3,4-bis(methylamino)thiophene **192a**[76] (Scheme 69).

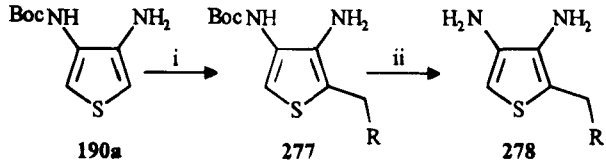


i) RCHO, CH_2Cl_2, PhSeH (5 eq.), *p*-TSA, RT. ii) ClCOOEt, NaOEt. iii) $LiAlH_4$, ether.

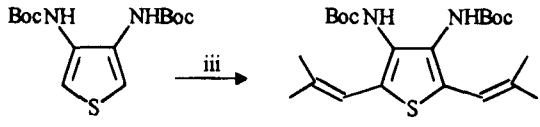
SCHEME 69

Considering that monoalkylation of 3,4-diaminothiophene derivatives is an important reaction in the context of biotin synthesis (see Section 6.7), we subjected the monocarbamate **190a** to the procedure described above. As expected, the α-carbon near the amino group is more reactive toward protonated aldehydes. No dialkylated products were found and *t*-butyl (5-alkyl-4-amino-3-thienyl)carbamates **277** were isolated in fair yields[76] and the corresponding diamines **278** were obtained after hydrolysis (Scheme 70). We have also observed that, as for 3-aminothiophene derivatives (see Section 3.8, Scheme 37), the use of α-branched aldehydes leads to *C*-vinylation. With the dicarbamate **6a** as substrate, the divinylthiophene **279** is obtained in fair yield[76] (Scheme 70).

With one-half equivalent of aldehyde and without selenophenol, the reaction follows the same route as for 3-aminothiophene derivatives (see Section 3.8, Scheme 34). The corresponding bis(diaminothienyl)-methane derivatives **280**, however, could not be isolated. The two-step alkylation is immediately followed by a dehydrogenation-transamination process (see Section 3.8, Scheme 35) leading to the dithienopyridines **281**. The two functional groups of **281** can then be hydrolyzed allowing isolation of the 8-alkyl-3,5-diaminodithieno[3,2-*b*:2′,3′-*e*]pyridines **282**[76] (Scheme 71).



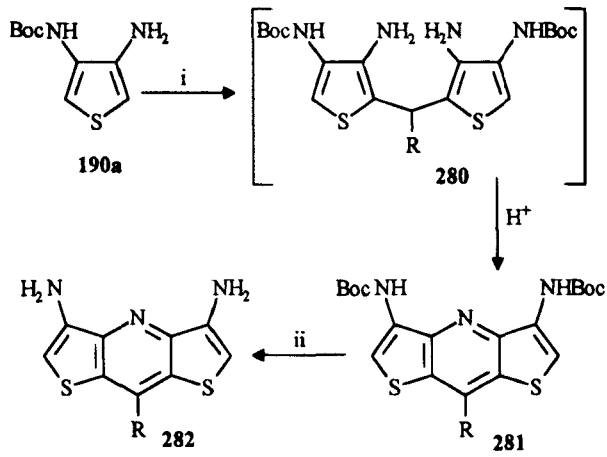
190a 277 278



6a 279

i) RCHO, CH_2Cl_2, *p*-TSA, PhSeH, RT. ii) HBr, AcOH; 4 N NaOH, ether. iii) Isobutanal, conc. HCl, THF, RT.

SCHEME 70



190a 280 282 281

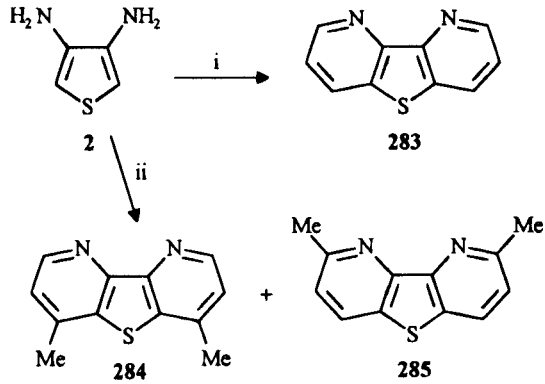
i) RCHO (0.5 eq.), CH_2Cl_2, *p*-TSA, RT. ii) HBr, AcOH; NaOH, H_2O, ether.

SCHEME 71

6.6. *Synthesis of Pyrido[2′,3′:4,5]thieno[3,2-b]pyridines and 3-Aminothieno[3,2-b]pyridines*

The diamine **2** has been subjected to the Skraup reaction.[80] Double cyclisation occurs, but the pyridothienopyridine **283** is only isolated in poor yield.

The experimental conditions were probably not well adapted to the substrate (Scheme 72). Using the procedure previously described for the synthesis of the methylthieno[3,2-*b*]pyridines **116** and **149** (see Section 3.9., Scheme 38), methyl vinyl ketone and diamine **2** form a mixture of dimethyl derivatives **284** and **285** (ratio 62:38) in modest yield[80] (Scheme 72).

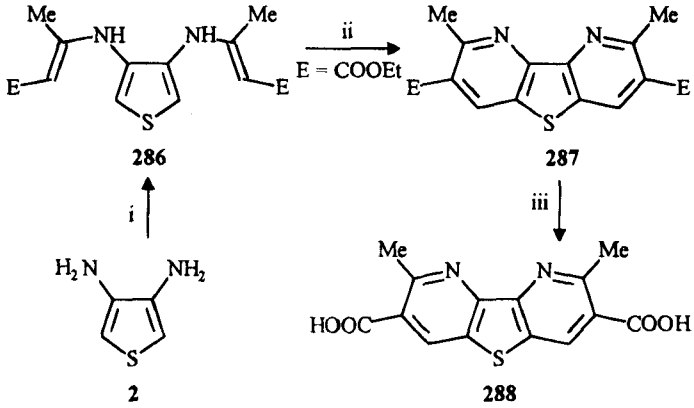


i) Glycerol, As_2O_5, H_2SO_4, Δ. ii) CH_2=CHCOMe, $FeCl_3$, $ZnCl_2$, EtOH, Δ.

SCHEME 72

Double *N*-vinylation was observed in the reaction of ethyl acetoacetate and the diamine **2** under neutral conditions. The double enamino ester **286** was isolated. Subjected to treatment with Vilsmeier reagent, this intermediate allows the formation of the two pyridine rings. Diester **287** was hydrolyzed to the diacid **288**[47] (Scheme 73).

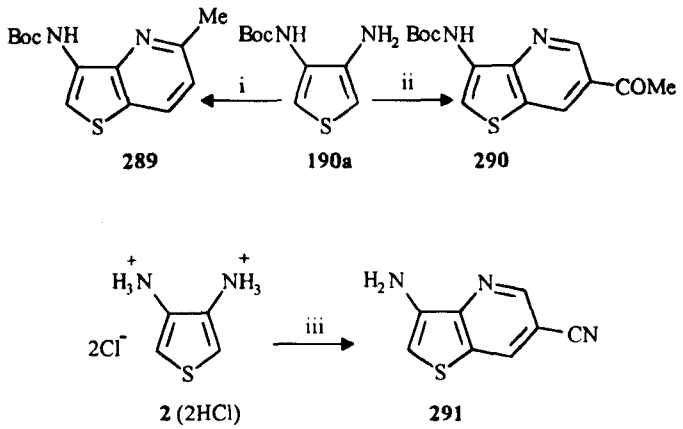
With the goal to synthesise pyridothienopyridines diversely substituted on the pyridine rings we have applied this α-vinylation reaction to the monocarbamate **190a**. 3-Oxobutanal freshly prepared in solution from its acetal was used (see Section 3.9, Scheme 41). This particular experimental procedure was dictated by secondary reactions due to the presence of the carbamate function. The same conclusions can be made as for the formation of the 5-methyl- and the 6-acetylthieno[3,2,-*b*]pyridines **116** and **151**. Here, the corresponding 3-aminothieno[3,2-*b*]pyridine derivatives **289** and **290** were isolated, however in modest yields[76] (Scheme 74). The dihydrochloride of diamine **2** and 3,3-dimethoxy-2-formylpropionitrile sodium salt,



i) CH_3COCH_2COOEt, RT. ii) $POCl_3$, DMF, $CHCl_3$, Δ. iii) NaOH, H_2O, EtOH.

SCHEME 73

under acidic conditions suffers monocyclization to 3-aminothieno[3,2-*b*]pyridine-6-carbonitrile **291**[95] (Scheme 74).

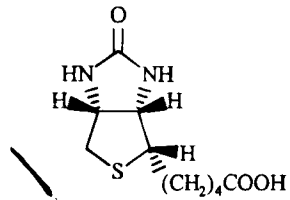


i) CH_3COCH_2CHO (1 eq.), CH_2Cl_2, *p*TSA. ii) CH_3COCH_2CHO (2 eq.) CH_2Cl_2, *p*TSA. iii) $(MeO)_2CH\text{-}C(CN)=CHO^-Na^+$, conc. HCl, MeOH, Δ.

SCHEME 74

6.7. *Synthesis of Biotin*

d-Biotin **292**, a member of the B vitamin complex, is a very important growth-promoting factor which plays an essential role in nutrition. Several total syntheses of biotin in racemic form have been developed over the last fifty years and resolution into *d*-biotin is well-known.[96] The proposed methods require many steps and the overall yields are very low. Some of them use the thiophene route. Hydrogenation of the heteroaromatic ring into thiophane is compatible with the *all-cis* configuration of biotin. This stereochemistry corresponds to the thermodynamically least stable isomer of a thiophane derivative with three contigous asymmetric centers.



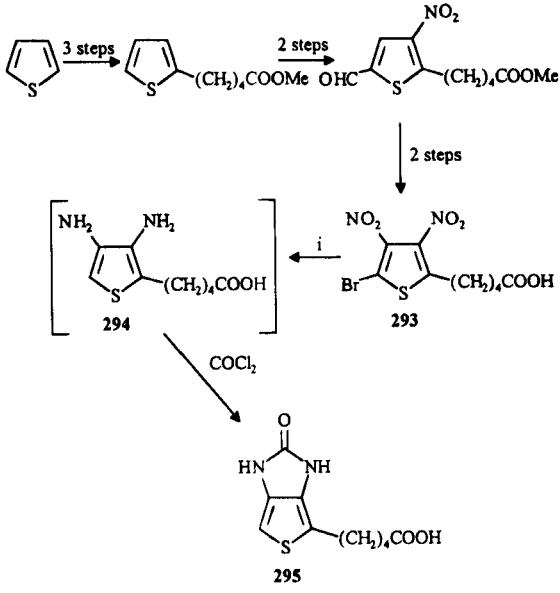
292

FIGURE 15

These considerations have stimulated several investigations of 3,4-diaminothiophenes bearing various substituents or functional groups on the nucleus. Since the first work in this area[70,71,97] in which 3,4-diaminothiophene **2** was used as intermediate without isolation, some others studies have appeared.

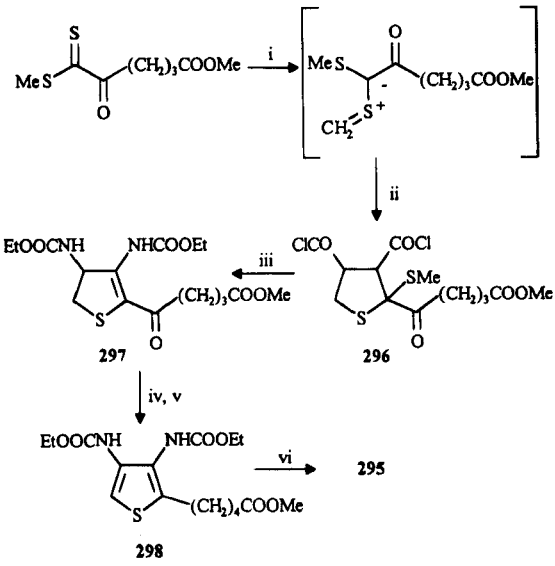
One of the proposals is the reduction of the bromodinitrothiophene **293**, prepared in seven steps from thiophene, to the diamine **294** (not isolated) which is subjected to reaction with phosgene giving the thienoimidazolone **295**[98] (Scheme 75). Hydrogenation of the aromatic ring was previously achieved[71] and dl-biotin synthetized from compound **295**.

The thienoimidazolone **295** can also be prepared by another route. The thiophene ring is formed by cycloaddition between a thiocarbonyl ylide and fumaroyl chloride leading to the intermediate **296**. The corresponding di(carbonyl azide) is subjected to Curtius rearrangement. The isolated dihydrothiophenedicarbamate **297** undergoes reduction and aromatization leading to the thiophenedicarbamate **298**. Treatment of **298** with a base gave imidazolone **295**[99] (Scheme 76).



i) Sn, HCl; NaOH, H_2O.

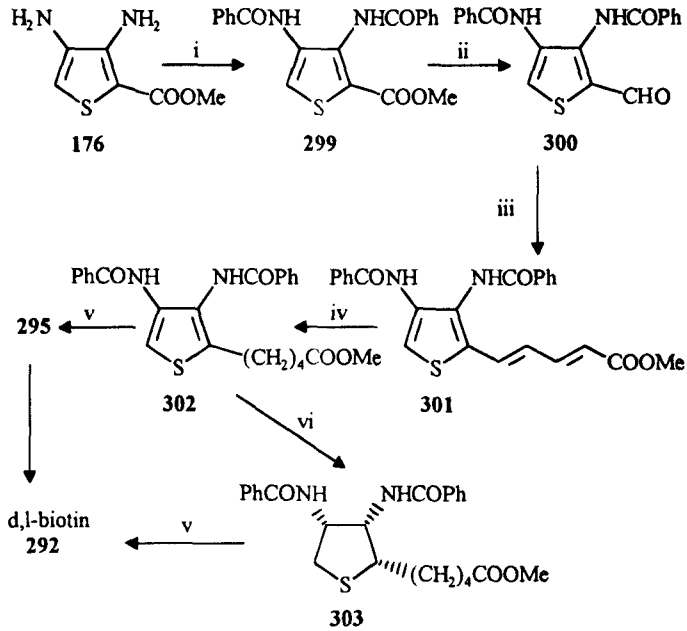
SCHEME 75



i) CH_2N_2, hexane, CH_2Cl_2, - 90 °C. ii) fumaroyl chloride, - 60 °C. iii) HN_3, pyridine; EtOH, Δ. iv) conc. H_2SO_4, P_2O_5, CH_2Cl_2; pyridine. v) $NaBH_4$, THF; MsCl, pyridine. vi) KOH, MeOH, Δ.

SCHEME 76

The third route to the thienoimidazolone **295** starts from the diamino ester **176** whose dibenzamide **299** is reduced to aldehyde **300**. A Wittig reaction with **300** gives the dienic ester **301** which in turn is hydrogenated to the dibenzamide ester **302**. Aqueous barium hydroxide treatment, followed by phosgene addition, completes the sequence leading to imidazolone **295**, finally reduced to biotin. Hydrogenation of the thiophene **302** can be achieved before imidazolone ring formation and the dibenzamide **303** is a possible intermediate in this biotin synthesis[68] (Scheme 77).

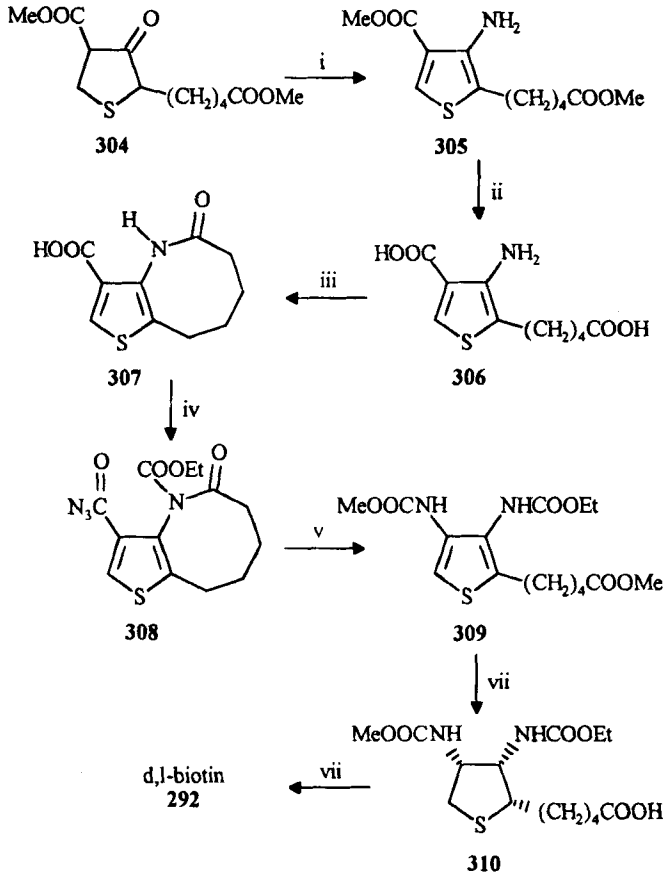


i) PhCOCl, pyridine, $CHCl_3$. ii) $LiAlH_4$, THF; PCC, CH_2Cl_2. iii) Ph_3P=CH-CH=CH-COOMe, toluene. iv) H_2, Pd/C, MeOH. v) $Ba(OH)_2$, H_2O; Cl_2CO. vi) H_2 (90 bar), Pd/C, AcOH, Δ.

SCHEME 77

The dicarbamate **309**, analogous to **298**, has been prepared according to Scheme 78.[100] The oxime derived from ketone **304** was rearranged to the amino diester **305** and the latter hydrolyzed to the diacid **306**. Upon heat-

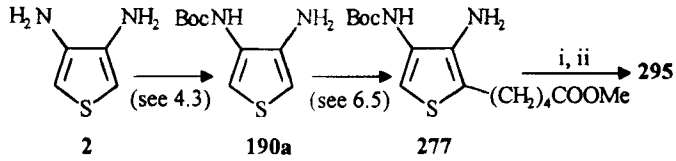
ing this diacid forms the lactam **307** which is then treated with ethyl chloroformate and sodium azide. The imido acyl azide **308** undergoes Curtius rearrangement giving the mixed dicarbamate **309**. Catalytic hydrogenation was achieved, first leading to thiophane **310**. Cyclization was achieved by phosgene treatment and *d,l*-biotin was isolated in 37% yield (9 steps) from **304**.



i) NH_2OH, HCl, pyridine; HCl, ether. ii) NaOH, MeOH; HCl, H_2O. iii) Xylene, Δ. iv) ClCOOEt, acetone, H_2O, Et_3N; NaN_3. v) MeOH, Δ. vi) NaOH, H_2O, MeOH; HCl, H_2O; H_2, Pd/C, H 50 °C (1800 psi). vii) BaOH, H_2O, Δ.

SCHEME 78

Our results relative to the alkylation of the monocarbamate **190a** (see Section 6.5, Scheme 70) led us to propose an alternative and simple route to the thienoimidazolone **295** and thus to biotin (Scheme 79). α-Monoalkylation of the monocarbamate **190a** was carried out with methyl 5-oxopentanoate as previously described (see Section 6.5). Transformation of **277** (R = $(CH_2)_4COOMe$) to the corresponding dicarbamate and base treatment led to isolation of the thienoimidazole **295**. Formally, biotin can be synthetized in five steps from diamine **2**.[76]



i) $(Boc)_2O$, CH_2Cl_2. ii) KOH, MeOH, Δ.

SCHEME 79

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