The Versatile Chemistry of Thiophenes: The Effects of *b*-side contra *c*-side Annelation on Reactivity

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The synthesis of the nine dithienopyridines and twenty-four thienonaphthyridines with angular annelation is described. They are all conveniently obtained by Pd(0)-catalysed couplings between heterocyclic *o*-formylboronic acids or *o*-formylstannyl derivatives with heterocyclic *o*-amino-halo derivatives. The effect of the use of silver oxide and cupric oxide as co-reagent is discussed.

Differences in electrophilic substitution, metalation and cycloaddition of *b*- and *c*-fused isomers is treated. Theoretical calculations at the RHF/3-21G* level are in agreement with the orientation and reactivity in the nitration of dithieno[3,4-*b*:3',4'-*d*] pyridine and dithieno[2,3-*b*:3',2'-*d*] pyridine observed experimentally. The preparation of *N*-oxides of the above-mentioned ring-systems and their reactivity will also be discussed.

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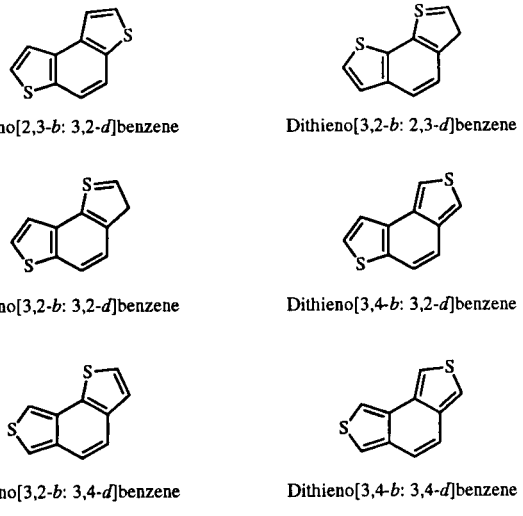
Introduction.

Much of the reactivity of fused planar heterocycles is not well understood. Thus, while thiophene undergoes electrophilic substitution predominantly in the 2-position, benzo[*b*]thiophene reacts in the 3-position and thieno[2,3-*b*]thiophene again in the 2-position. In the tricyclic naphtho[2,1-*b*]thiophene, substitution occurs in the 2-position.

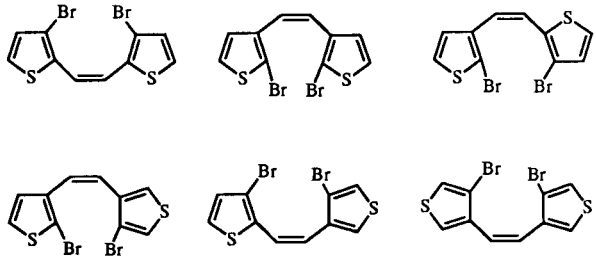
It has been known for a long time that the mode of annelation of other aromatic rings onto the *b*-side and *c*-side of thiophene leads to systems with sometimes very different physical and chemical properties. Thus, while benzo[*b*]thiophene is a stable aromatic system [1], benzo[*c*]thiophene is very unstable and easily undergoes cycloaddition reactions [2,3]. The driving force for this is the creation of a complete benzenoid system. During recent years many of my graduate students worked on the syntheses, reactions and physical properties of tricyclic systems with angular annelation, which may be considered as heterocyclic analogues of phenanthrene.

Together with Torsten Dahlgren, I studied the six isomeric dithienobenzenes (Scheme 1). There are three isomers in which the thiophene rings are [*b*,*b*]-fused, two in which these rings are [*b*,*c*]-fused, and one which is [*c*,*c*]-fused. They could all be prepared in good yields by the same synthetic approach. The *cis* di-(*o*-bromothienyl)-ethenes, which could be prepared by Wittig reactions (Scheme 2), were ring-closed through halogen-metal exchange, followed by reaction with cupric chloride (Scheme 3) [4]. The [*b*,*c*]-fused systems were quite unstable and dimerized upon attempted isolation. In the presence of dimethyl acetylenedicarboxylate, cycloaddition followed by elimination of sulfur occurred leading to naphtho[2,1-*b*]- and naphtho[1,2-*b*]thiophene (Scheme 4) [4]. Nitration of dithieno[2,3-*b*;3,2-*b*']benzene with fuming nitric acid in acetic acid yields the 4-nitro-, 2-nitro- and 1-nitro isomers in 59%, 35% and 6% yield, respectively, while dithieno[3,2-*b*; 2,3-*d*] benzene under the same conditions gives only the 2-nitro derivative in 90% yield (Scheme 5) [5]. The first-mentioned compound,

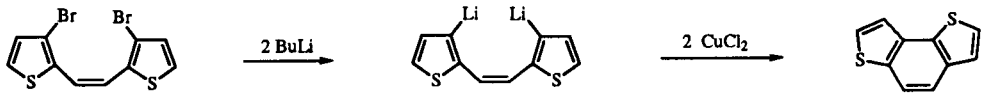
Scheme 1



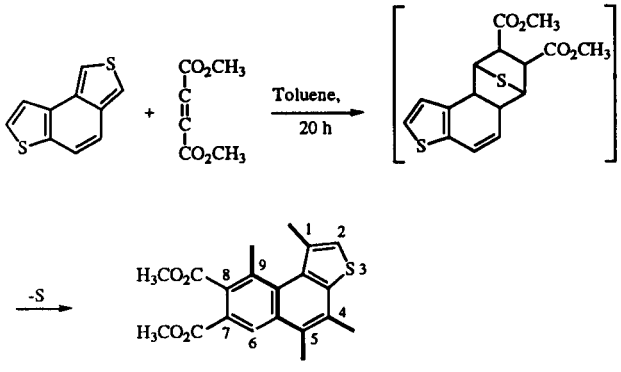
Scheme 2



Scheme 3



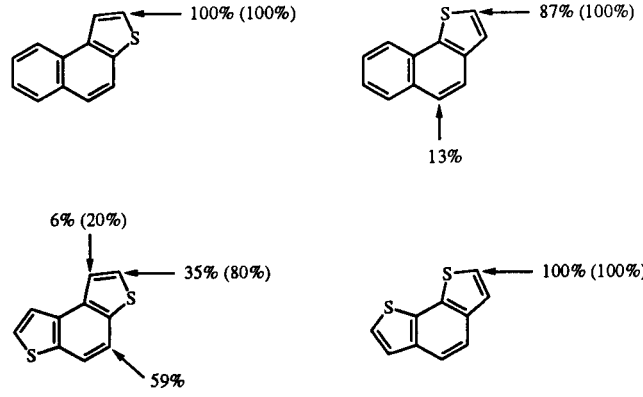
Scheme 4



upon monobromination with bromine in chloroform, gave the 2-bromo and 1-bromo derivative in a ratio of 5:1. Further bromination led to di- and tri-substituted compounds, but the tetrasubstituted derivative could not be obtained. The bromination of the other [*b,b*]-fused systems selectively gave the 2-bromo derivative and the tetrabrominated product could be obtained in this case [5]. Attempts at bromination of the [*c,c*]-fused isomers only led to unstable products, which were not characterized. Naphtho[2,1-*b*]thiophene, on the other hand, was found by Scrowston and co-workers to be exclusively nitrated, as well as formylated and acetylated, in the 2-position, while bromination gave a mixture of the 2- and the 2,5-dibromo-derivatives. Nitration of the naphtho[1,2-*b*]thiophene gave 87% of the 2-isomer and 13% of the 5-isomer [6,7]. LCAO-MO-calculations on the naphthothiophenes predicted, contrary to the experimental results, that electrophilic substitution should occur in the β-positions [7,8]. I therefore concluded at that time that "it is obvious that sophisticated MO-calculations are necessary to attain an understanding of the substitution pattern of these dithienobenzenes" [5]. To make such calculations became possible in the 1980's due to the availability of supercomputers like the Cray XMP-48, which allowed *ab initio* calculations to be carried out. At the same time we had developed efficient Pd(0)-catalysed coupling reactions for the syntheses of new tricyclic heterocyclic systems. Furthermore, the developments in separation techniques (hplc) made it possible to separate different isomeric substitution products and finally modern nmr techniques such as HETCOR and INADEQUATE made it possible to determine the structures of the substitution products. I therefore decided in 1985 that the syntheses of all nine dithienopyridines and the twenty-four thienonaphthyridines with angular annelation patterns was feasible, making possible an experimental and theoretical study of electrophilic, substitution and other reactions.

Scheme 5

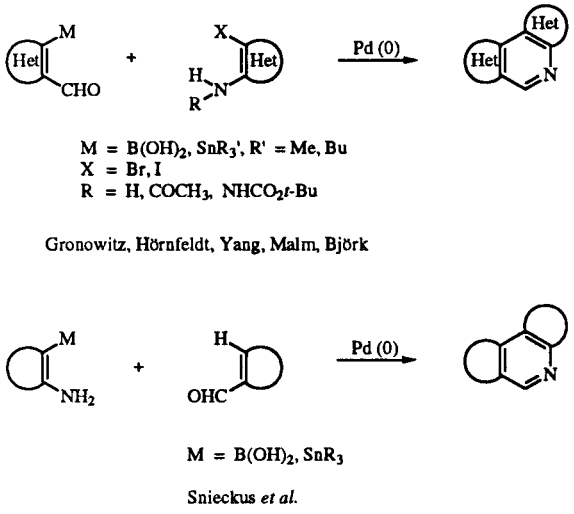
Nitration and (Bromination)



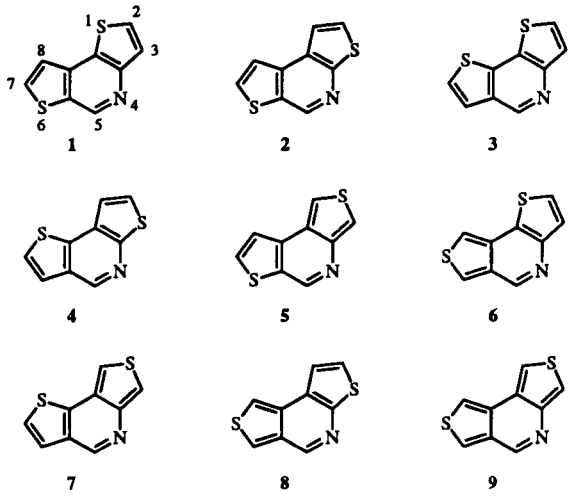
Syntheses.

The route to all these compounds was opened through our development of the Suzuki reaction between aromatic boronic acids and aromatic halides [9]. When the coupling was carried out in water-dimethoxyethane in the presence of sodium hydrogen carbonate, we were successful in suppressing the deboronation of heterocyclic boronic acids such as 2-thiopheneboronic acid [10]. We then applied the coupling reaction to the *o*-formylthiophene boronic acids, which we had previously prepared in connection with our work on heteroaromatic boron compounds, and which are very easily available in one-pot reactions [11], using *t*-butyl-*N*-(*o*-halothienyl)carbamates as the other component in the Pd(0)-catalyzed reaction. The latter compound was prepared from the easily available *o*-halothiophenecarboxylic acids by the Yamada modification of the Curtius reaction [12]. Later we found that the Stille coupling, which is carried out under neutral

Scheme 6



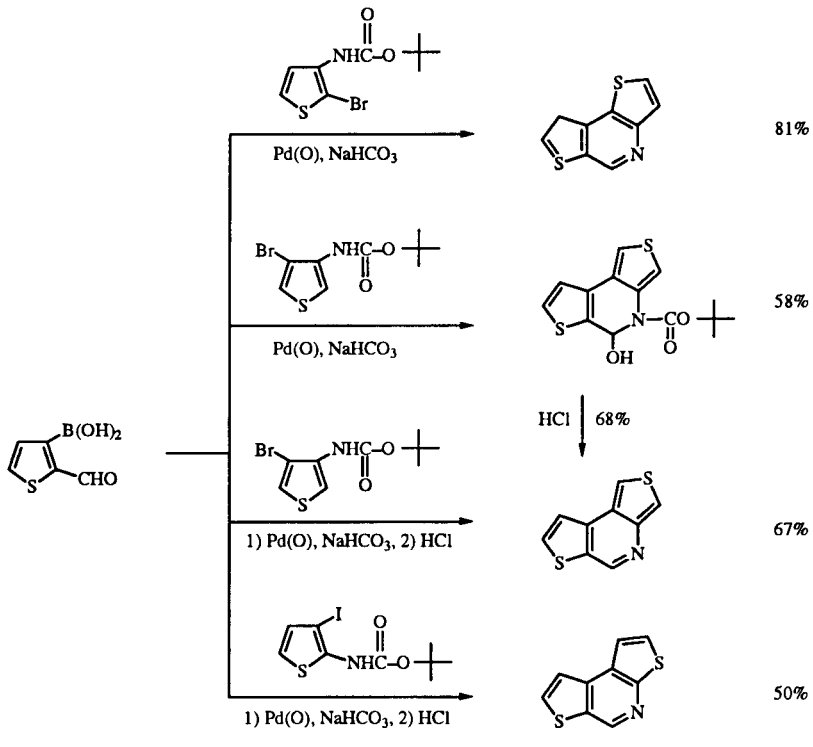
Scheme 7



conditions, using *o*-formyltrialkylstannyl derivatives, could be successfully applied in cases when the Suzuki method failed or gave low yields (Scheme 6). Victor Snieckus started about the same time to couple *o*-amino-benzeneboronic acids or *o*-amino-trialkylstannyl derivatives, prepared via heteroatom-facilitated metalation, with *o*-bromobenzaldehydes for the preparation of substituted phenanthridines and phenanthridones [13]. We have also used our methodology for the synthesis of phenanthridine and thieno[*c*]quinolines and thieno[*c*]isoquinolines [14,15].

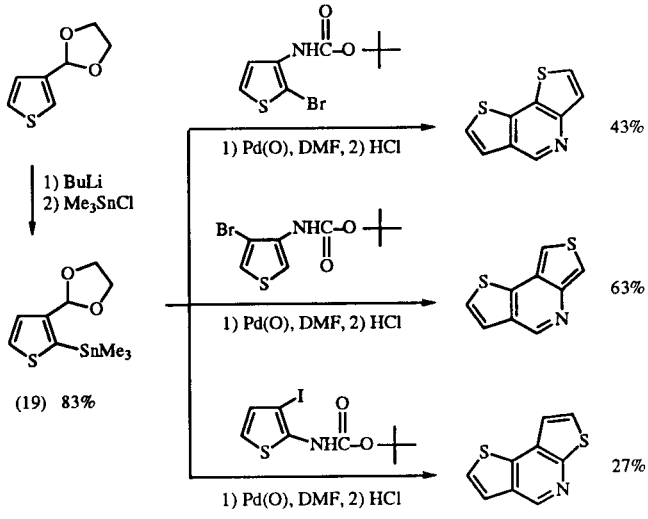
Of the nine isomeric dithieno[*b*,*d*]pyridines, four are *b*,*b*-fused, four are *b*,*c*-fused and one is *c*,*c*-fused (Scheme 7). As we will see, all of them could be prepared and were stable compounds. 2-Formyl-3-thiopheneboronic acid gave compounds **1** and **5** with *t*-butyl-*N*-(2-bromo-3-thienyl)carbamate and *t*-butyl-*N*-(4-bromo-3-thienyl)carbamate. The coupling with *t*-butyl-*N*-(3-bromo-2-thienyl)-

Scheme 8

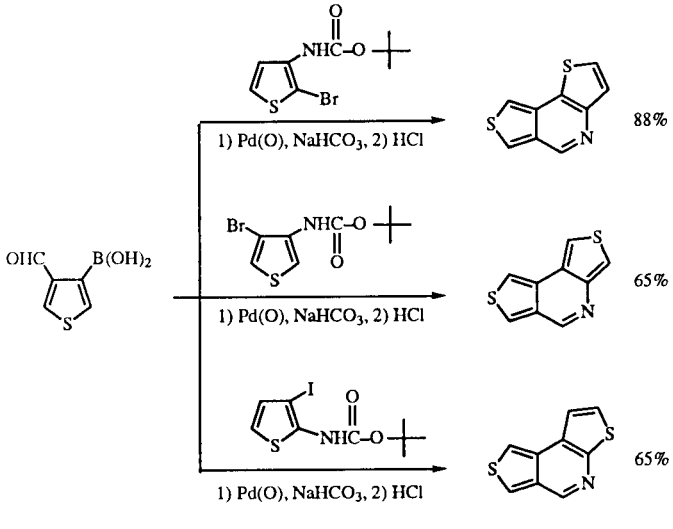


carbamate, however, proceeded so slowly that only trace amounts of the corresponding product was obtained. Changing to the more reactive 3-iodo derivative gave a 50% yield. It can be noticed that in the preparation of the [*b,c*]-fused system **5**, spontaneous aromatization through elimination of carbon dioxide and *t*-butyl alcohol did not occur, and compound **16** could be isolated. Aromatization was achieved by refluxing with 2 *N* hydrochloric acid [16] (Scheme 8). Using 4-formyl-3-thiopheneboronic acid in the coupling with the carbamates gave compounds **6, 9** and **8** in good yields after refluxing with 2 *N* hydrochloric acid [16] (Scheme 9). However, with 3-formyl-2-thiopheneboronic acid, deboronation was faster than coupling and only low yields were obtained at best. We therefore turned to the Stille coupling. Metalation of the ethylene acetal of 3-thiophenaldehyde followed by reaction with tributylstannyl chloride gave 3-(2-tributylstannyl-3-thienyl)-1,3-dioxolane. However, all attempts to couple this compound were unsuccessful, probably due to steric hindrance. It was, however, possible to hydrolyse the acetal with 1 *N* hydrochloric acid without breaking the carbon-tin bond. The coupling of 2-tributylstannyl-3-thiophenaldehydes with the carbamates was successful, and compound **3, 7** and **4** were obtained in 59%, 75% and 42% yield, respectively [17]. It was even more convenient to use the acetal of 2-trimethylstannyl-3-thiophenaldehyde directly, which indeed coupled, and upon treatment with hydrochloric acid hydrolyzed and ring-closed (Scheme 10) [18].

Scheme 10



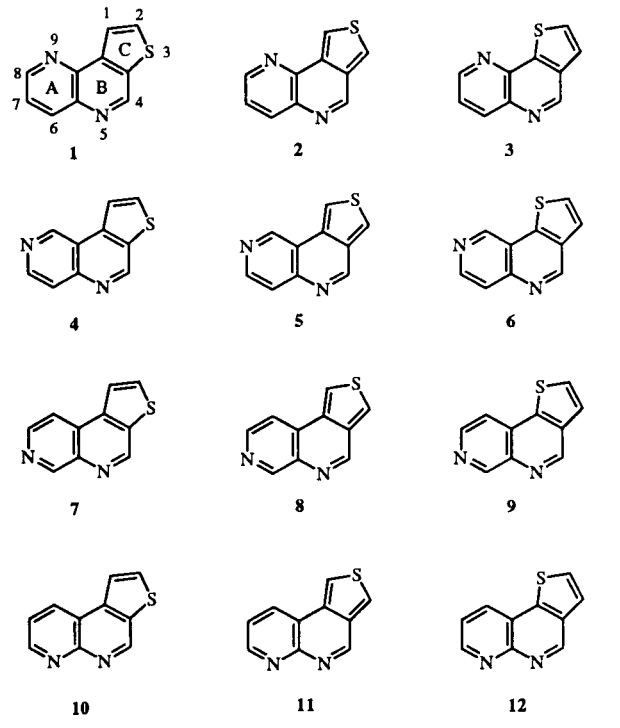
Scheme 9



The ^{1}H and ^{13}C nmr spectra of all nine dithieno[*b,d*]-pyridines were studied in detail. All $^{1}J(^{13}C\text{-}^{13}C)$ coupling constants were determined using the INADEQUATE technique, and all ^{1}H and ^{13}C chemical shifts and coupling constants were also measured. A multivariate principal components data analysis of $^{1}J(^{13}C\text{-}^{13}C)$ was also carried out [19]. Together with Professor Rademacher in Essen, the He(I) photoelectron spectra of all nine isomers were reported and discussed. The ionization potentials were assigned to molecular orbitals using the results of MNDO, AM1 and PM3 calculations. The crystal and mol-

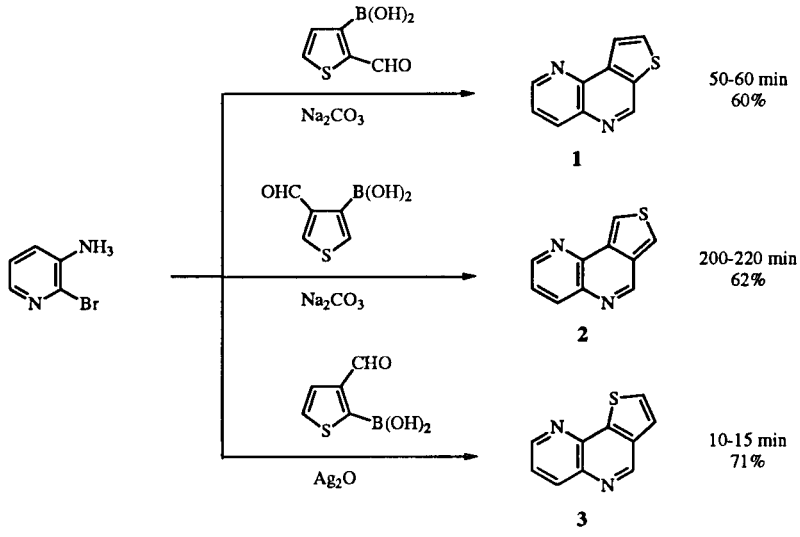
Scheme 11

Thieno[*c*]naphthyridines



Scheme 12

Thieno[*c*]-1,5-naphthyridines

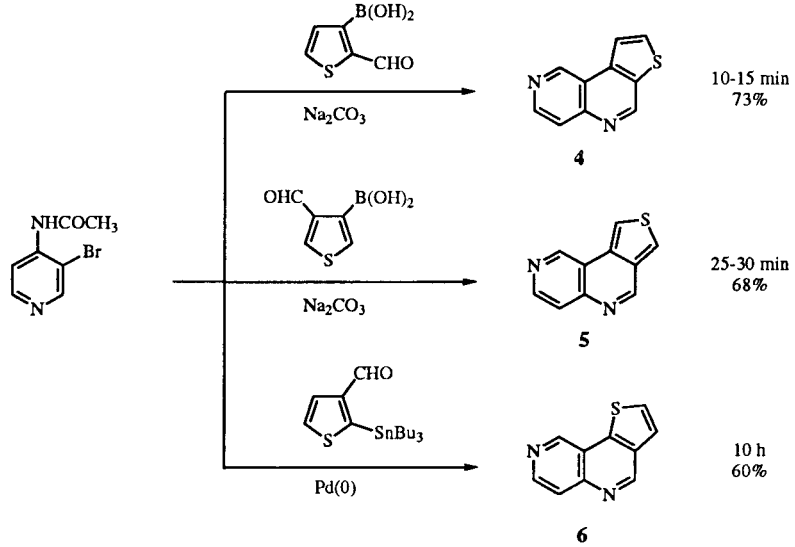


ecular structures of **4** and **5** were determined by X-ray diffraction [20].

The same methodology was used in the synthesis of the twenty-four thieno-fused naphthyridines. Twelve of them, which have the nitrogen of the middle ring bound to pyridine are all *c*-fused (Scheme 11), and should in principle be available from 2- and 4-formylthiopheneboronic acid and 2-(tributylstannyl)-3-thiophenaldehyde and the four *o*-haloaminopyridine derivatives. Acceptable yields were obtained in the couplings of the two *o*-formylthiopheneboronic acids with 3-amino-2-bromopyridine and 4-acetamido-3-bromopyridine, while 4-amino-3-bromopyridine gave much lower yields. The coupling of 2-(tributylstannyl)-3-thiophenaldehyde with 3-acetamido-2-bromopyridine was quite slow, and a reaction time of 8 hours in *N,N*-dimethylformamide at 100° had to be used. We then tried different additives and found that if silver oxide was added as a co-reactant the reaction was over in 2-3 minutes and the same yield of 69% of the product was obtained. On the other hand, in the reaction with 4-acetamido-3-bromopyridine, the addition of silver oxide had a detrimental effect on the yield and gave no rate increase in the coupling (Schemes 12 and 13) [21]. We therefore undertook an investigation on the effect of the

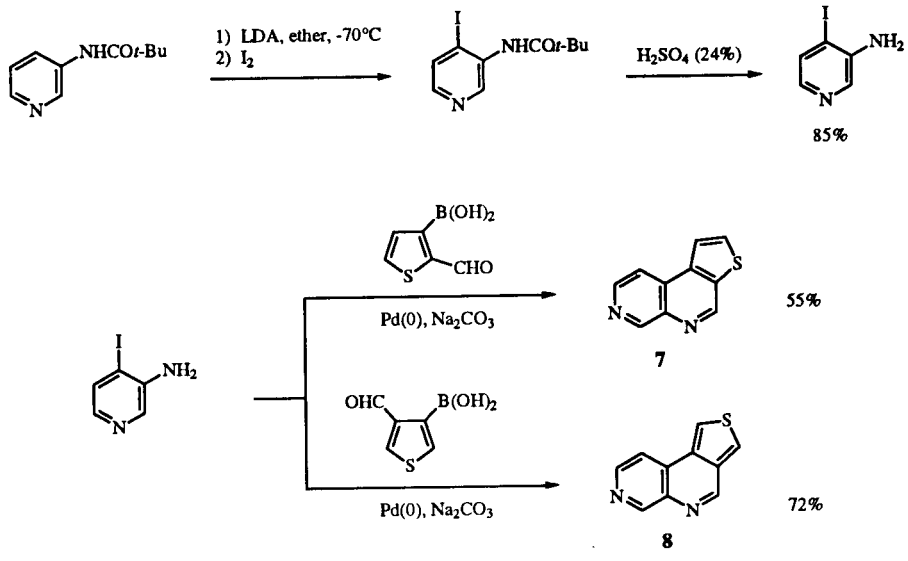
Scheme 13

Thieno[*c*]-1,6-naphthyridines



Scheme 14

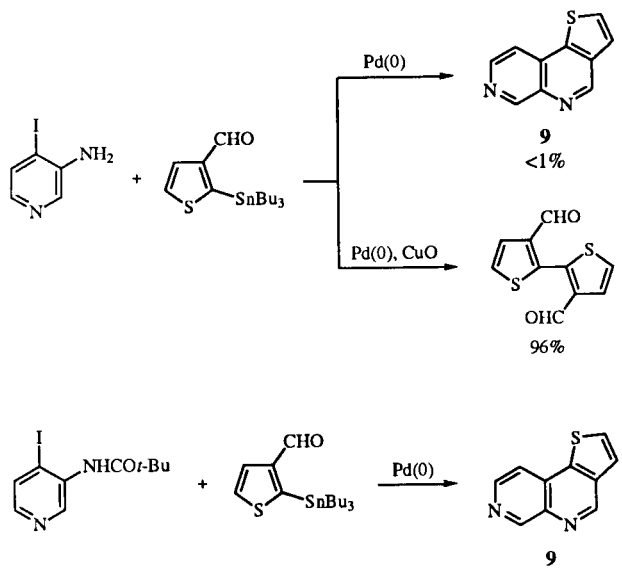
Thieno[*c*]-1,7-naphthyridines



addition of silver oxide on the Stille reaction and found that it greatly promoted the coupling of hetaryl trialkylstannanes with a great variety of heterocyclic halides [22]. Later we found that the addition of cupric oxide had an even better effect on the rate and the yields of the Stille coupling [23].

Coupling of 3-amino-4-iodopyridine, prepared by lithiation of 2,2-dimethyl-*N*-(3-pyridyl)propanamide with lithium diisopropylamide, followed by reaction with iodine [24] and acid hydrolysis of the 4-iodo amide with acid, gave good yields of thieno[*c*]-1,7-naphthyridine in the coupling with 2- and 4-formylthiopheneboronic acid, while the reaction with 2-tributyl-3-thiophenaldehyde failed (Scheme 14). The addition of cupric oxide had no effect and led to the formation of 2,2'-diformyl-3,3'-bithienyl in almost quantitative yield. However, by using the amide the yield could be increased to 44% (Scheme 15) [25]. The coupling of 2-amino- or 2-acetamido-3-bromopyridine with 2- and 4-formyl-3-thiopheneboronic acid gave moderate yields of thieno[*c*]naphthyridines. 2-Tributylstannyl-3-thiophenaldehyde gave a reasonable yield with 2-acetamido-3-bromopyridine which could be increased to 61% by the addition of cupric oxide (Scheme 16) [25].

Scheme 15

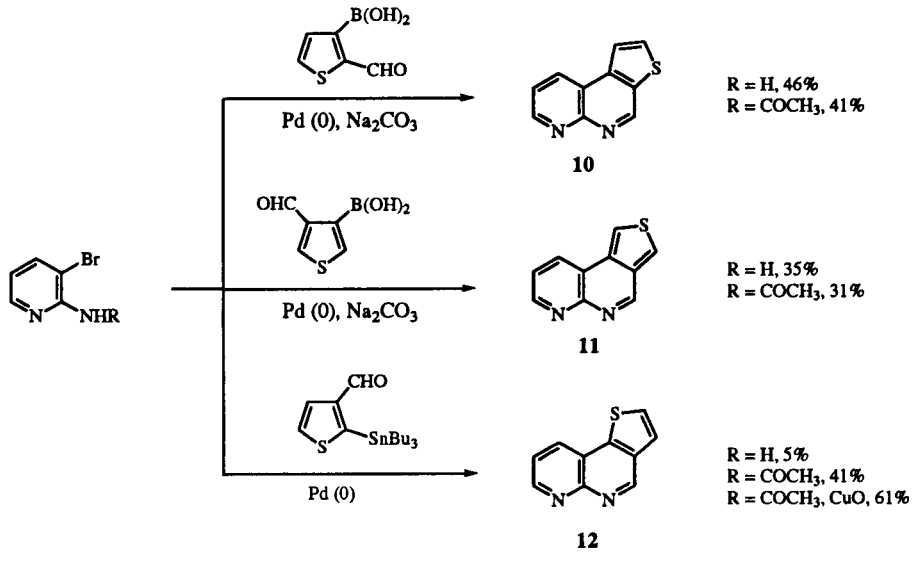


The other twelve isomeric thienonaphthyridines have the nitrogen of the middle ring bound to the thiophene ring (Scheme 17). In order to compare them with the corresponding [*c*]-fused compounds, the thieno[*h*]-1,6-naphthyridines are called thieno[*b*]-2,5-naphthyridines and the thieno[*f*]-1,7-naphthyridines are called thieno[*b*]-2,8-naphthyridines.

These compounds can in principle be prepared by coupling of the three *t*-butyl-*N*-(*o*-halothienyl)carbamates with the four isomeric *o*-trialkylstannylpyridine aldehydes or their acetals or with *o*-formylpyridineboronic acids. Alternatively, the *o*-trialkylstannylaminothiophene derivatives or *o*-aminothiopheneboronic acid can be coupled with the four isomeric *o*-halopyridinaldehydes (Scheme 18). We chose the first-mentioned approach to the synthesis of the thieno[*b*]naphthyridines, and in all cases pyridine-tin derivatives were used. Three of the four isomeric *o*-formyl(trialkylstannyl)pyridines were prepared by a convenient technique, recently introduced by Comins and Killpack [26] (Scheme 19), who *o*-metalated pyridin-

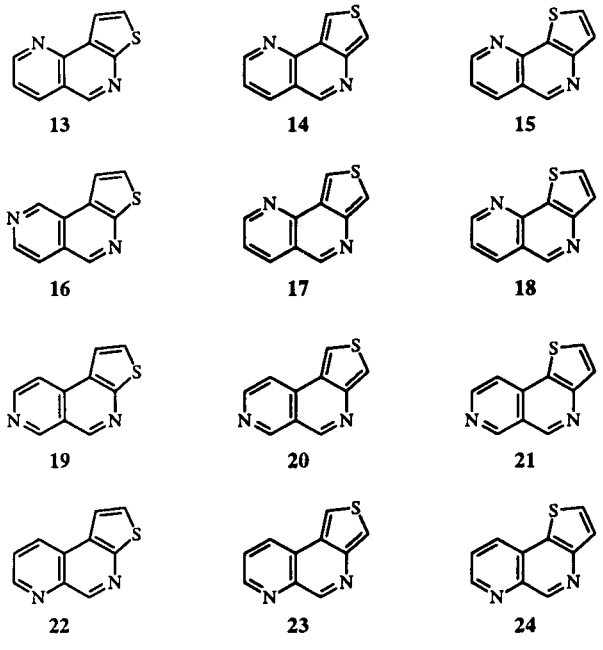
Scheme 16

Thieno[*c*]-1,8-naphthyridine s

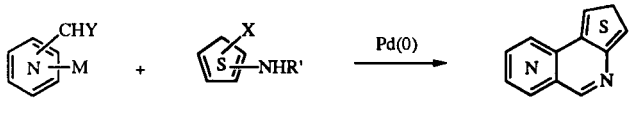


Scheme 17

Thieno[*b*]naphthyridines



Scheme 18

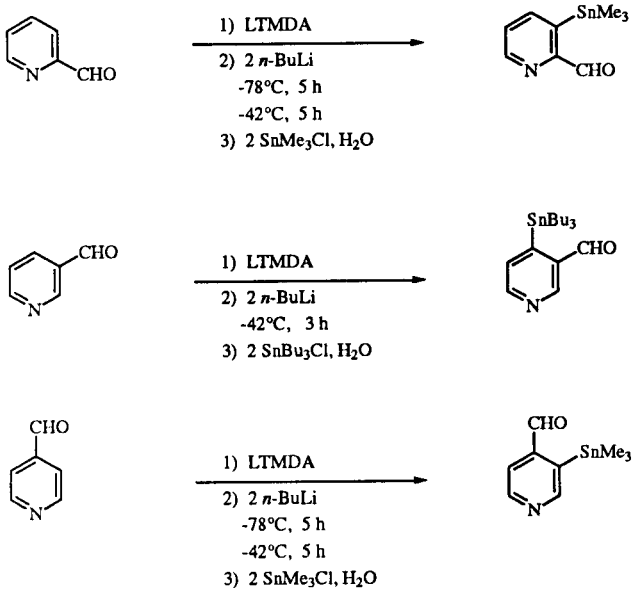


M = $B(OH)_2$, SnR_3, R = Me, Bu; X = Br, I;

Y = O, OCH_2CH_2O; R' = CO_2t-Bu

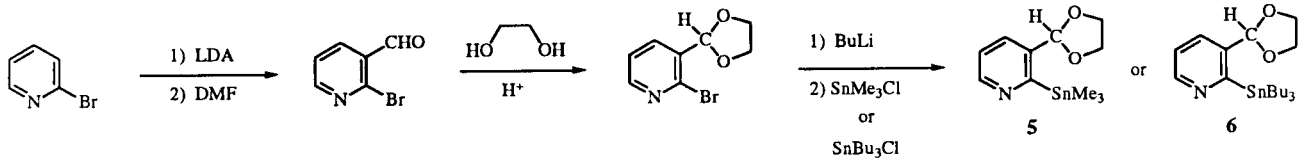
aldehydes with butyllithium after protection of the carbonyl function through reaction with *N*-lithio-*N,N,N'* -trimethylethylenediamine. Using this technique, 2-pyridinaldehyde gave 3-trimethylstannyl-2-pyridinaldehyde in 63% yield, after reaction with trimethylstannyl chloride. The lithiation of the protected 3-pyridinaldehyde occurred selectively in the 4-position and the derivative thus obtained gave after reaction with tributylstannyl chloride 4-(tributylstannyl)-3-pyridinaldehyde in 32% after reaction with trimethylstannyl chloride. When our work was in progress, Kelly and Kim [27] reported the synthesis of 4-(trimethylstannyl)-3-pyridinaldehyde in 66% yield by the same approach. From 4-pyridinaldehyde, as expected 3-(trimethylstannyl)-4-pyridinaldehyde was obtained in 42% yield (Scheme 19). In order to obtain 2-(trialkylstannyl)-3-pyridinaldehyde, the necessary starting material for the three thieno[*b*]-2,5-naphthyridines, another route obviously had to be used. Starting from 2-bromopyridine, 2-bromo-3-pyridinaldehyde was prepared by metalation with lithium diisopropyl amide followed by reaction with *N,N*-dimethylformamide [28]. The aldehyde was then protected by acetal formation with ethylene glycol. Halogen-metal exchange at -78° followed by reaction with trimethylstannyl chloride or tributylstannyl chloride yielded the 2-(2-trialkylstannyl-3-pyridyl)-1,3-dioxolanes (Scheme 20). In contrast to the corresponding acetals in the thiophene series [17] and in the furan series [29], where the acetals are hydrolyzed to the aldehydes without breaking the carbon-tin bond, this could not be achieved with **5** and **6** using a variety of acetal hydrolysing reagents. We therefore used the acetals directly in the Pd(0) catalyzed cou-

Scheme 19



aldehyde, which then spontaneously would ring-close to the tricyclic system. We found, however, that the rate of the coupling and the yields were quite unsatisfactory. After experimenting with several co-reagents, we found that in the reaction of **5** with *t*-butyl-*N*-(3-bromo-2-thienyl)carbamate, cupric oxide gave the fastest reaction [22,23] and the best yield of **13** using Pd(0) as catalyst (Scheme 21). We also tried some other Pd(0)-catalysts, which in this case did not increase the yields. Recently, another group has confirmed our findings of the beneficial effect of cupric oxide on the yields and rates of the Stille reaction [30]. The reaction of 3-(trimethylstannyl)-4-pyridinaldehyde (Scheme 22) with the three carbamates leads to the thieno[*b*]-2,6-naphthyridines. The yields were, especially in the synthesis of **16**, quite unsatisfactory, in spite of trying other types of Pd-catalysts. We found that the best conditions were to use dichloro (diphenylphosphinebutane)palladium, [$PdCl_2$(dppb)] as catalyst and cupric oxide as co-reagent. As in the synthesis of the dithieno[*b,d*]pyridines in which the thiophene ring is annelated with its *c*-side, the reaction stops at the dihydro

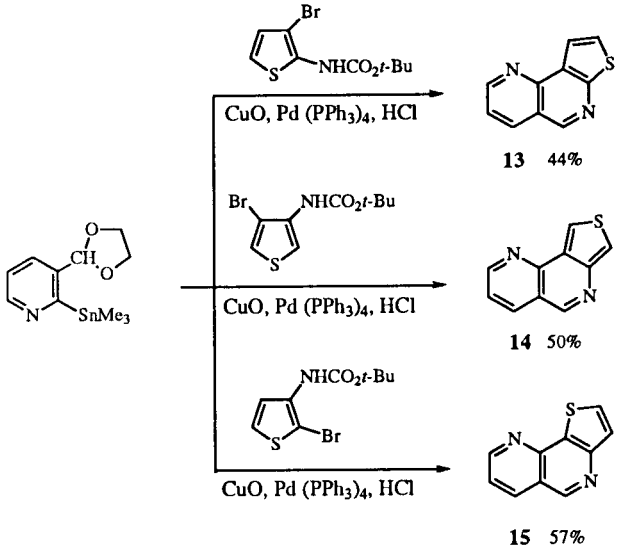
Scheme 20



pling with the three *t*-butyl-*N*-(*o*-halothienyl)carbamates, expecting that treatment of the unsymmetrical coupled product with hydrochloric acid would produce the free

Scheme 21

Thieno[*b*]-2, 5-naphthyridines



derivative, which then was aromatized by refluxing with 2 *N* hydrochloric acid. The yields were also quite unsatisfactory in the preparation of two of the thieno [*b*]-2,8-naphthyridines (Scheme 23), while the yields were better in the syntheses of the thieno[*b*]-2,7-derivatives (Scheme 24).

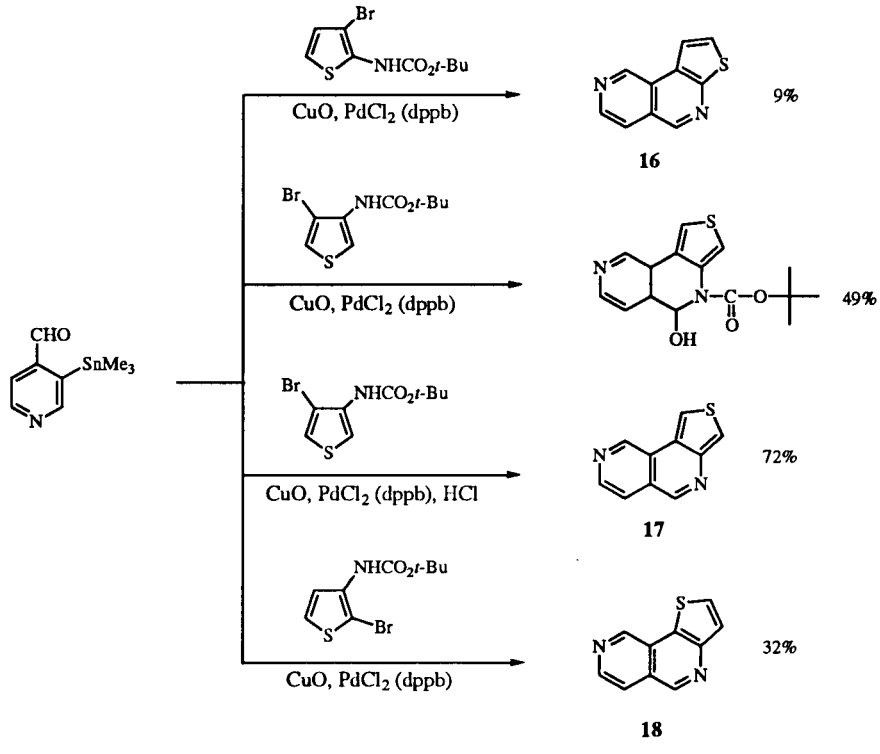
We are trying to optimize the reactions and it is possible that the other approach, switching the positions of the halogen and the tin substituents, might give better yields. The amounts prepared were, however, enough for an extensive study of the nmr parameters and for a study on their photoelectron spectra, which is in progress in collaboration with Professor Rademacher.

Our approach to tricyclic heterocycles is a very general one and can be applied to many other heterocyclic systems. We have prepared furo-annelated compounds [31] and are at present working on the syntheses of pyrrolo- and imidazolo-fused systems.

We have also prepared another type of angular tricyclic heterocyclic systems in collaboration with Hungarian researchers, namely the pyridino[2,1-α]phthalazinium system and their three thiophene fused analogues, the pyrido[1,2-*b*]thieno[*d*]pyridazinium perchlorates (Scheme

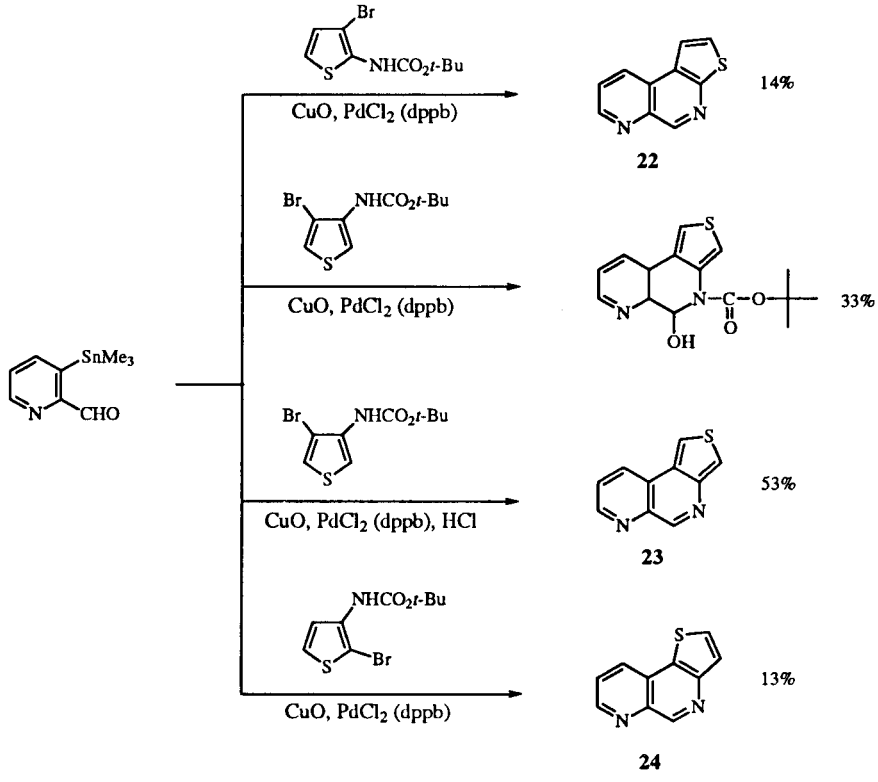
Scheme 22

Thieno[*b*]-2,6-naphthyridines



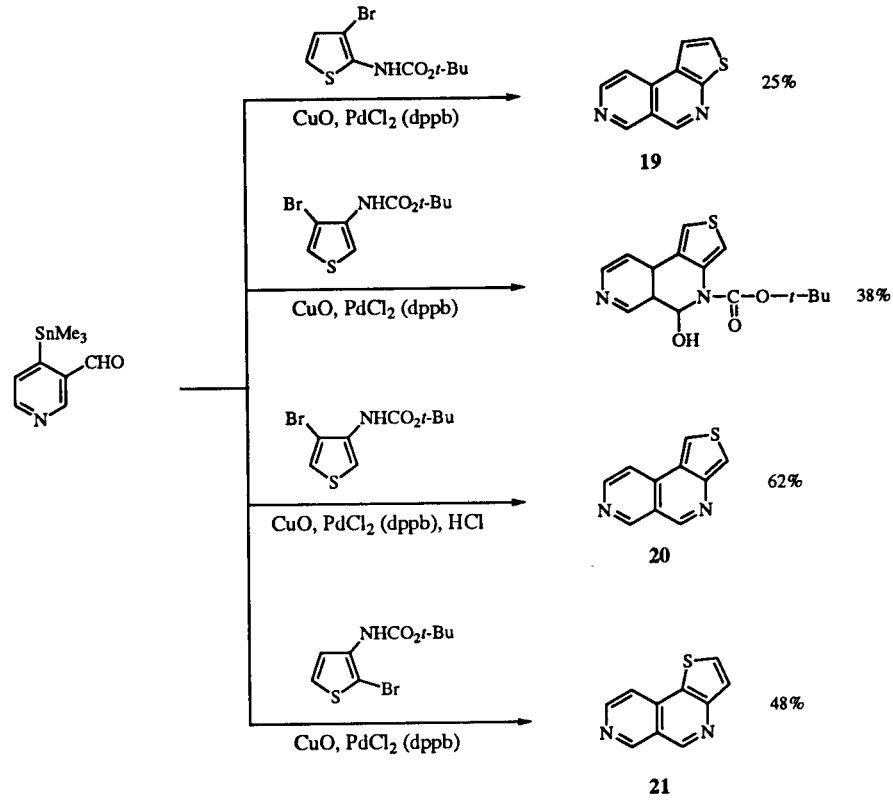
Scheme 23

Thieno[*b*]-2,8-naphthyridines

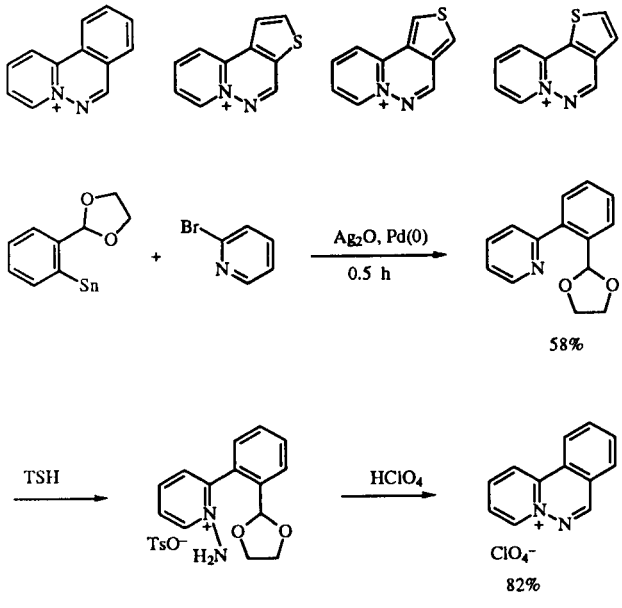


Scheme 24

Thieno[*b*]-2,7-naphthyridines



Scheme 25



25). Coupling of the acetal of o-(trimethylstannyl)-benzaldehyde in the presence of silver oxide, which is essential, gave the phenyl pyridine in 58% yield, which upon amination with *O*-tosylhydroxylamine and treatment with perchloric acid gave deacetalization and ring-closure to the desired system. In order to prepare the thiophene analogues, 2- and 4-formyl-3-thiopheneboronic acids and (2-trimethylstannyl)-3-thiophenaldehyde were coupled with 2-bromopyridine. Silver oxide was necessary as co-reagent in the Stille reaction. Treatment with *O*-tosylhydroxylamine and perchloric acid then gave the desired systems (Scheme 26) [32].

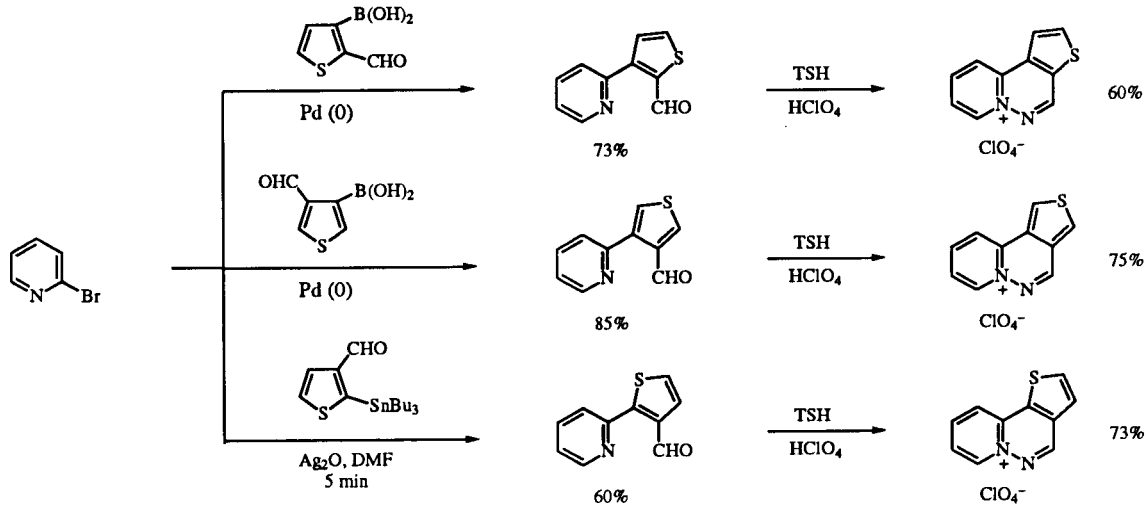
Reactions.

a. Nitration.

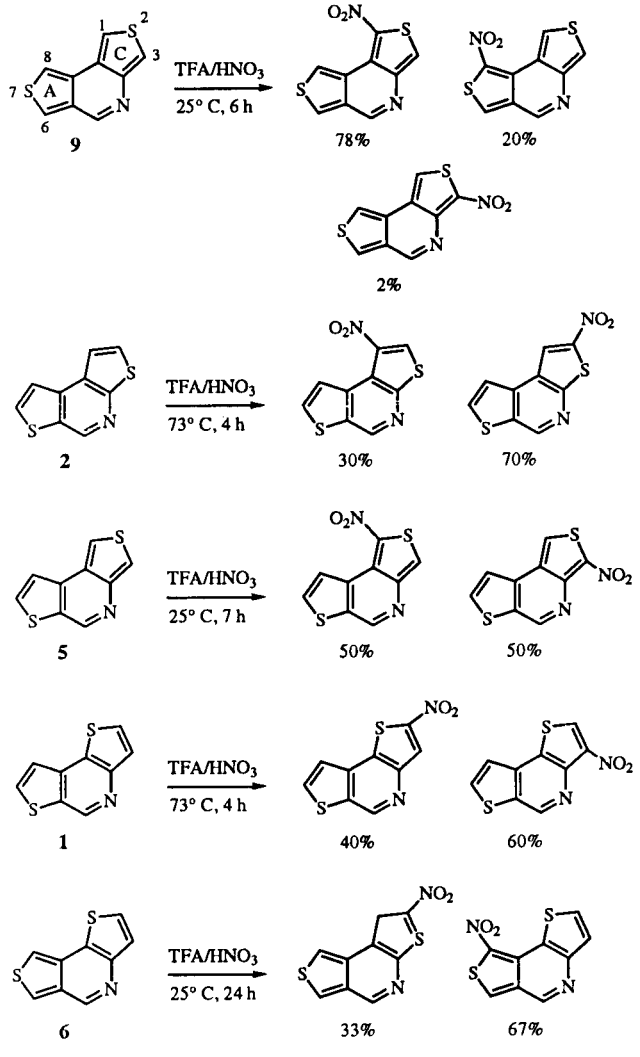
We have most extensively studied electrophilic nitration of the dithieno[*b*,*d*]pyridines. Of the nine systems five have been studied experimentally, the [*c*,*c*]-fused system, two [*b*,*b*]-fused systems and two [*b*,*c*]-fused systems. Nitration was carried with nitric acid in trifluoroacetic acid. In these acidic media it is the protonated forms of the thienopyridines that react, since the basicities are comparable with that of quinoline. Urea was added to the nitration mixture in order to avoid nitration *via* nitrosation. The reactions are assumed to take place through classical ionic electrophilic substitution (S_E2). The electron transfer (ET) mechanism was excluded due to the high oxidation potential of **9** and the high calculated ionization potentials of the conjugate acids of **9** and **2**. The

Scheme 26

Pyrido[1,2-*b*]thieno[*d*]pyridazinium perchlorates



Scheme 27

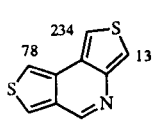


[*c*,*c*]-fused system and the [*b*,*c*]-fused systems react smoothly already at room temperature, while the [*b*,*b*]-fused systems have to be heated to 75°. Compound **9** gives 78% of the 1-isomer in the thiophene ring bound to nitrogen 20% of the 8-isomer and 2% of the 3-isomer (Scheme 27). The isomers were separated by chromatography and advanced nmr-spectroscopic techniques were used for the structure determinations [33]. Dinitration proceeds smoothly and leads to the 1,8-dinitro isomer, in which both groups are in the bay-area. In the [*b*,*b*]-fused system **2** the reactivity is much lower but we can notice that again the thiophene ring bound to nitrogen is the most reactive and a mixture of 30% of the 1-isomer and 70% of the 2-isomer is obtained [34]. The same is true for the other more unsymmetrical [*b*,*b*]-fused system **1**: in the nitration a mixture of 40% of the 2-nitro and 60% of the 3-nitro isomer is obtained [35]. The [*b*,*c*]-fused system **5** is nitrated in the *c*-fused ring, but no selectivity is observed and the 1- and 3-nitro isomers are obtained in equal amounts. Isomer **6** is quite interesting. The question is if activation of the *c*-annelated ring or of the nitrogen-bound *b*-annelated ring will determine the outcome of the nitration. As can be seen from the experimental results the first-mentioned factor is more important, and the 2- and 8-isomers are formed in a ratio of 2:1 [35].

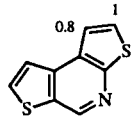
We also carried out competitive nitration of **9** and **2**. All seven products were determined by hplc and uv-spectroscopy. The relative rates are given in Scheme 28. It is remarkable that the annelation effects are responsible for the 200-fold faster nitration of **9** compared to **2**.

It is of course clear that the isomer distributions obtained in the nitration of these tricycles cannot be explained by counting numbers of resonance structures of the various Wheland intermediates or similar techniques.

Scheme 28



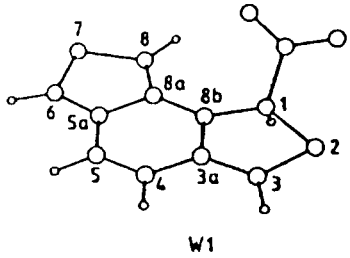
9



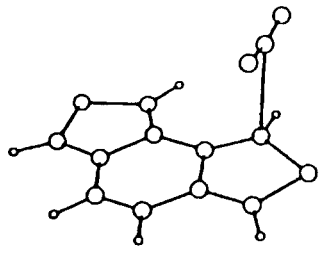
2

Fortunately, at that time a national Cray XMP 416 supercomputer came to Linköping, and in the beginning free time was available from the National Science Research Council. Dr. Szabo, who had experience in calculations, used the Gaussian 86 and 90 and CADPAC computer programs. In most cases, single-determinant restricted Hartree-Fock calculations were carried out using the split valence 3-21(G*) basis set. The d-orbitals on the sulfur atom were included. Stationary points including the transition states were optimized by using Schlegel's gradient technique.

Scheme 29



W1



T1

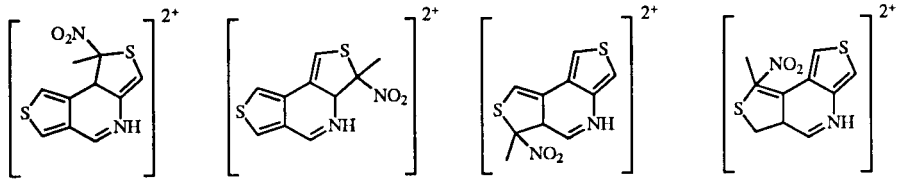
The most interesting results of the calculations are that the Wheland intermediates (Scheme 29) fail to predict the experimental product distribution. As can be seen, the Wheland intermediates predict that the 8-position and the 3-position are the most reactive, followed by the 1-position. Calculation of the transition states towards the Wheland intermediates predicted the correct order (Scheme 30) [33].

For the *b,b*-fused system, calculations of the Wheland intermediates also failed to predict the experimental results, which showed the formation of about equal amounts of the 1- and 2-nitro isomer (Scheme 31). It predicted that the 2-position should be most reactive followed by the 8-, 3- and 7-positions. Again calculations of the transition states predicted the right order. The computational results suggest a joint transition state (Scheme 32) for positions 1 and 2 nitrations, which explains the similar reactivity of these positions. For both ring systems the transition states show greater similarity to the parent structure than the Wheland intermediate. The calculated TS-energies were also in good agreement with the experimentally measured relative nitration rates (Scheme 32). The energy difference between the transition state for nitration of position 1 in **9** and for the joint transition state for nitration of positions 1 and 2 of **2** is 10 kJ/mole, which corresponds to a rate factor of around 200 [36].

b. Bromination.

We have also studied the bromination of three of the dithienopyridines. It could be carried out under mild aprotic conditions with molecular bromine in chloroform in the presence of a buffer. As in nitration **9** and **5** reacted faster than **2** (Scheme 33). Reaction of **9** with one equivalent of bromine gave a mixture of the 1,3-dibromo derivative and starting material, while **2** gave a mixture of 1-bromo-, 2-bromo- and 1,2-dibromo derivatives together with starting material. The monobromo derivatives could not be separated from each other [37]. On reaction with equimolar amounts bromine **5** also gave a mixture of the 1-bromo-, 3-bromo- and 1,3-dibromo derivatives together with starting material. In this case the two monobromo derivatives could be obtained pure by chromatography [38]. From the preparative point of view, dibromination was most useful, giving the three dibromo derivatives

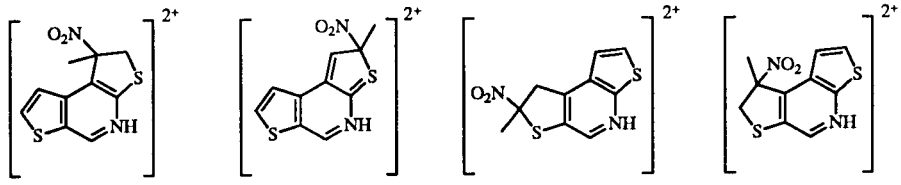
Scheme 30



Wheland intermediate				
Total energy (a.u.)	-1390.072748	-1390.076237	-1390.057799	-1390.076279
Relative energy* (kJ/mol)	59.6	50.4	98.8	50.3
Transition state				
Total energy (a.u.)	-1390.012260	-1390.009476	-1389.999561	-1390.009987
Relative energy* (kJ/mol)	218.4	225.7	251.7	224.3

* Relative to the separated reactants (T.E.: --1390.095442 a.u.)

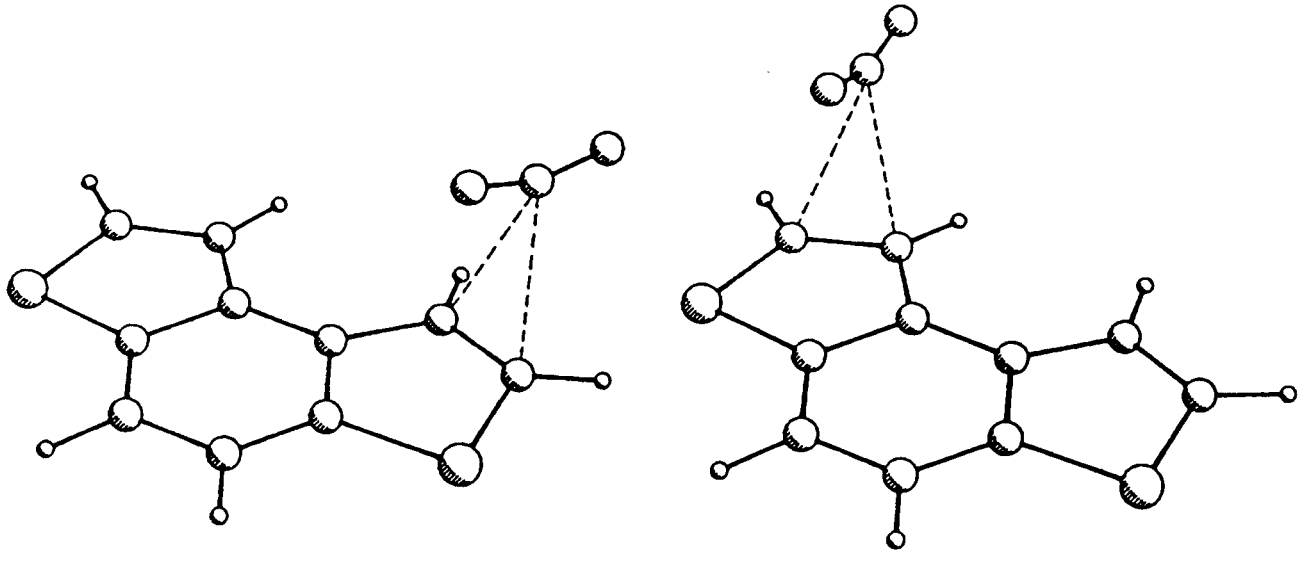
Scheme 31



Wheland intermediate				
Total energy (a.u.)	-1390.062019	-1390.072576	-1390.030711	-1390.067594
Relative energy* (kJ/mol)	143.6	115.9	225.8	129.0
Transition state				
Total energy (a.u.)	-1390.029756	-1390.029756	-1390.024570	-1390.024570
Relative energy* (kJ/mol)	228.3	228.3	241.9	241.9

* Relative to the separated reactants (T.E.: --1390.095442 a.u.)

Scheme 32



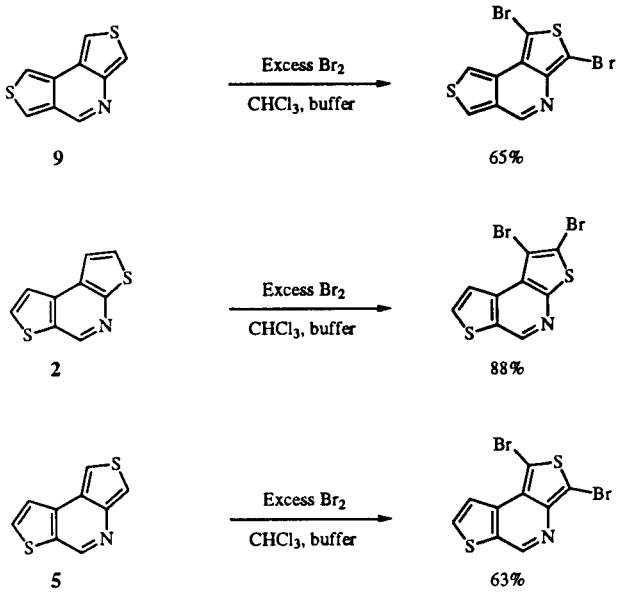
shown in Scheme 33 in good yield.

Lithiation.

Lithium diisopropylamide (LDA) in ether or tetrahydrofuran was used at -70° as the reagent in lithiation reactions. However, lithiation of **9** failed under these reaction conditions and at higher temperatures. On the other hand, **2** reacted smoothly and with *N,N*- dimethylformamide, dimethyl disulfide and bromine to give the 7-formyl, 7-thiomethyl and 7-bromo derivatives of **2** in 50-60% yield. The obvious A ring preference is very fortunate from a synthetic point of view because, as mentioned above, nitration and bromination gave C ring preference (Scheme 34) [39]. In order to explain the A ring preference, the energies of the various anions of **2** were calculated (Scheme 35). Since von Schleyer and coworkers have shown that the relative energies of carbanions and their lithium salts are closely parallel to each other, it is assumed that the stability of the carbanions can be correlated with the relative reactivities of the different positions [40,41]. The theoretical calculations are in good agreement with the experimental results see Scheme 35. Metalation with excess LDA led partly to 2,7-dilithiation but the yield of the 2,7-dimethylthio derivative, from reaction with dimethyl disulfide, was only 15% [39].

Lithiation of **5** with LDA at -70° could be carried out and occurred in the 3-position. The yield of the 3-formyl derivative when one equivalent of LDA was used with a reaction time of six hours was 43%, and 34% of the starting material was recovered. The use of 2.5 equivalents of LDA and DMF led to 50% of the 3-formyl derivative and 29% of the 2,7-diformyl derivative (Scheme 36) [38]. Thus, metalation of **5** occurs selectively in the 3-position, while nitration gave equal amounts of 1- and 3-substitution.

Scheme 33

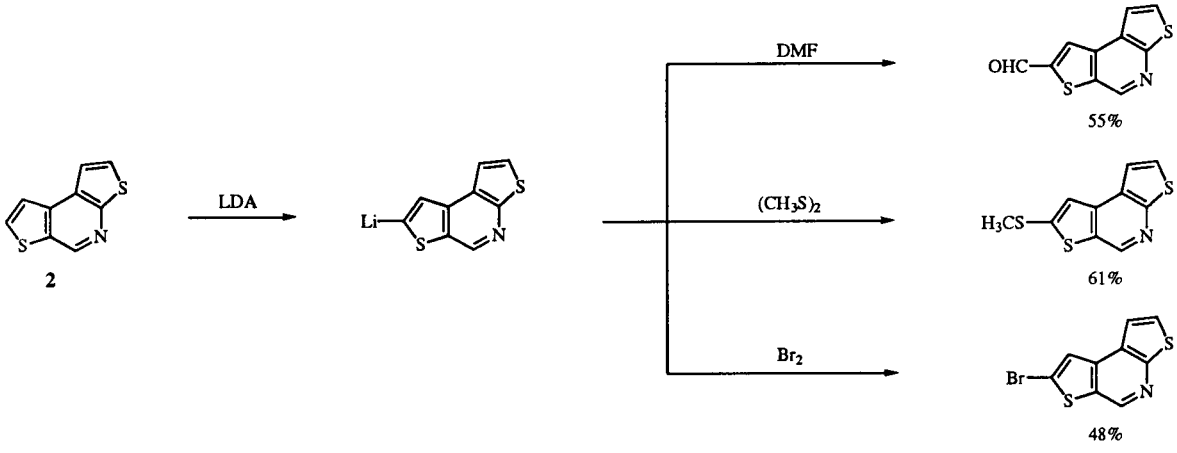


Halogen-metal Exchange.

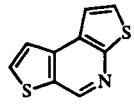
As mentioned previously, dibromo derivatives of the dithienopyridines are easily available by direct bromination. We were therefore interested in finding out if these compounds undergo halogen-lithium exchange, which would make it possible to prepare a number of substituted derivatives. We therefore undertook a study of the reactions of 1,3-dibromodithieno[3,4-*b*;3,2'-*d*] pyridine. Butyllithium was used in several different solvents, such as anhydrous ether, ether (TMEDA) and in tetrahydrofuran at -70°. The yields of 1,3-disubstituted derivatives were somewhat higher in tetrahydrofuran than in ether (TMEDA) and in addition by-products consisting of 3-monosubstituted compounds were formed in smaller amounts. The dilithiated product was reacted with various electrophiles (Scheme 37). In the reaction with *N,N*-dimethylformamide, diethyl carbonate and tetramethyl thiuram disulfide, 4-6% of the 3,7-disubstituted derivatives was also observed, probably due to transmetalation [42].

Scheme 34

Litiation of Dithieno[2,3-*b*:3,2-*d*]pyridine (2)



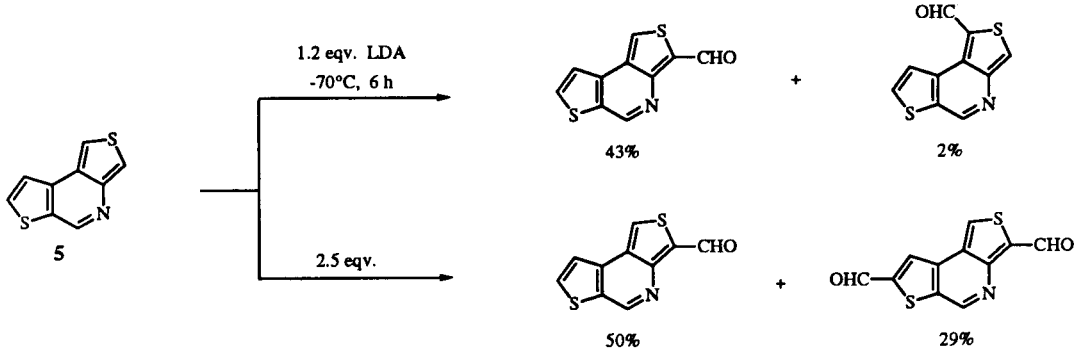
Scheme 35

Energies calculated for anions of  (2)

		A 1	A 2	A 5	A 7	A 8
3-21G(*)// 3-21G(*)						
	E_{tot}	-1186.627713	-1186.642102	-1186.620117	-1186.651009	-1186.633472
	E_{rel}	61.2	23.4	81.1	0.0	46.0
3-21+G(*)// 3-21G(*)						
	E_{tot}	-1186.697525	-1186.708029	–	-1186.718099	-1186.703211
	E_{rel}	54.0	26.4	–	0.0	39.1

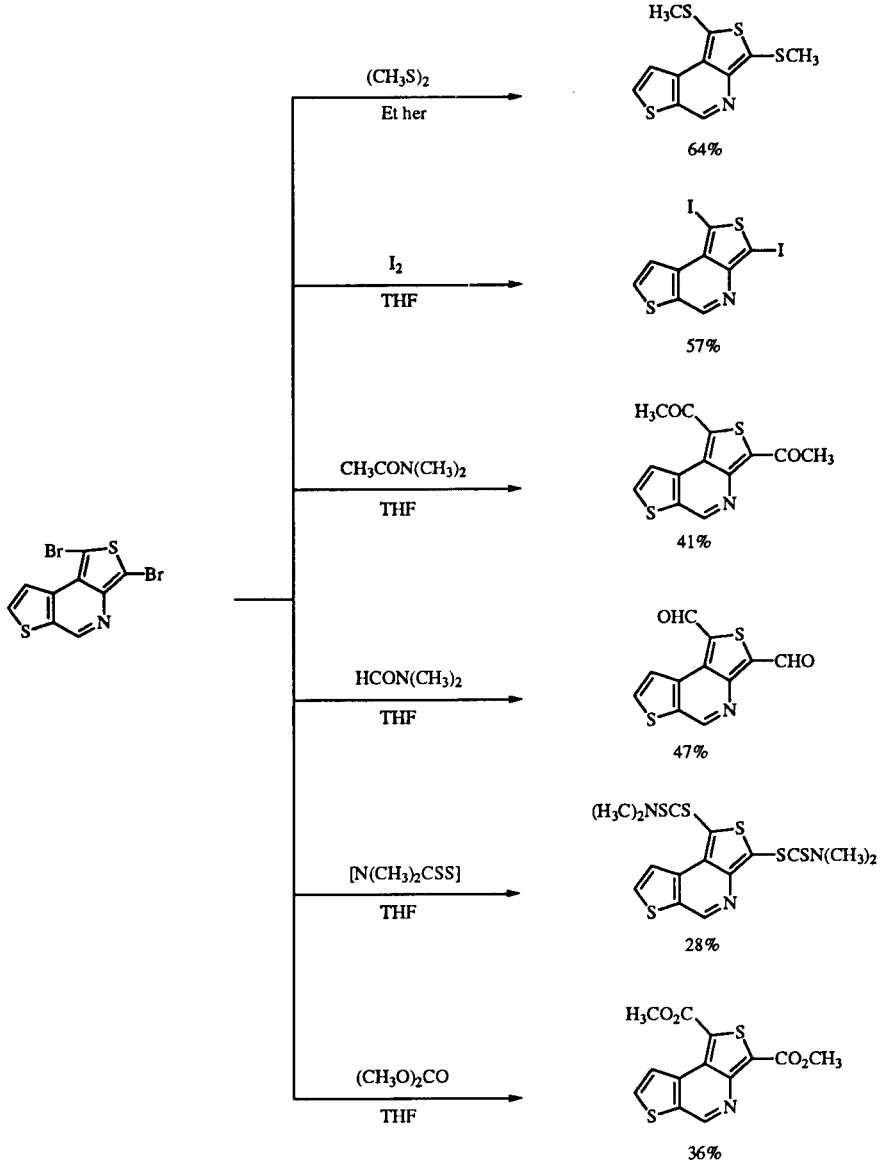
Scheme 36

Lithiation of Dithieno[3,4-*b*:3,2-*d*]pyridine (**5**)

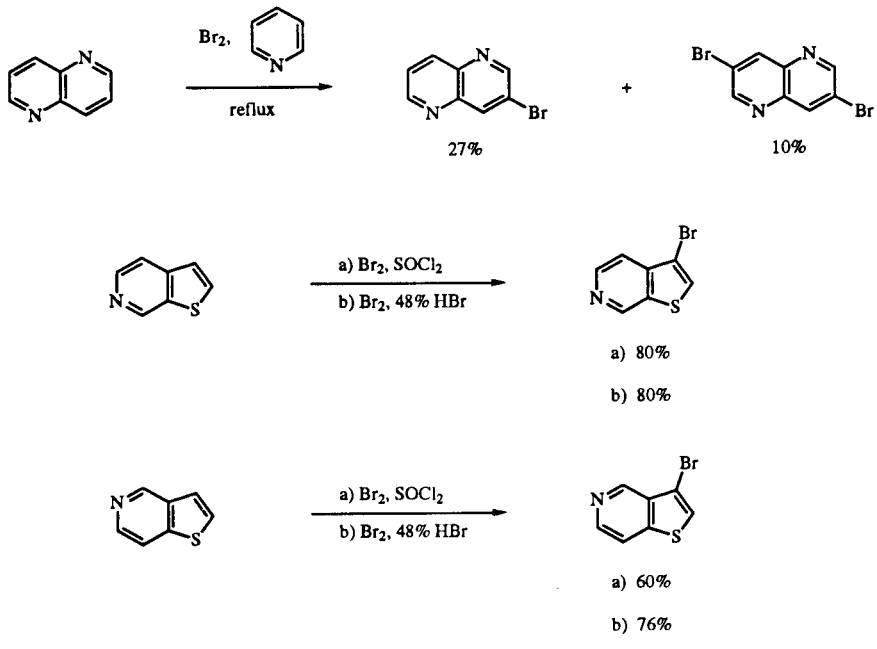


Scheme 37

Halogen-metal exchange of 1,3-dibromodithieno[3,4-*b*:3',2'-*d*]pyridine with 2.2 equivalents of butyllithium at -70°C



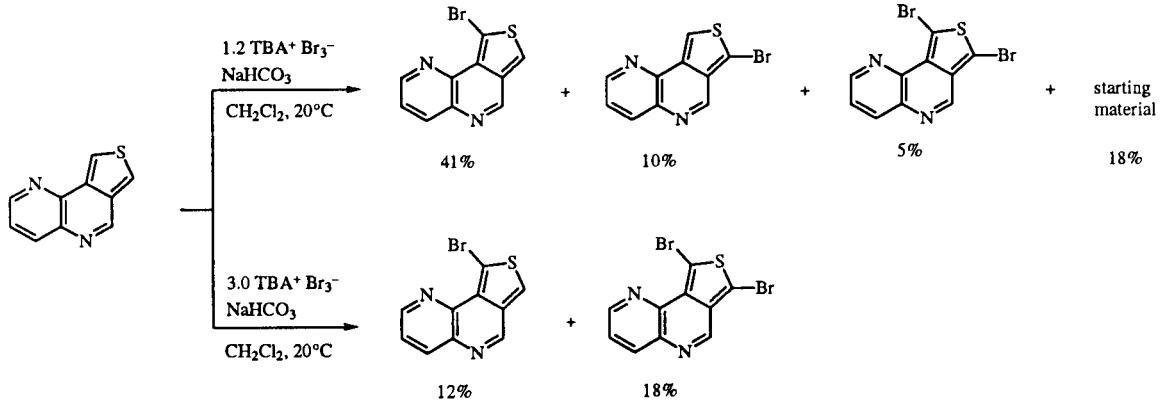
Scheme 38



Bromination of Thieno[*c*]-fused 1,5-Naphthyridines.

We have recently started to study substitution reactions of the thienonaphthyridines. These ring systems consist of a π-deficient ring-moiety, the 1,5-naphthyridine system and a π-excessive moiety, the thiophene ring. Electrophilic substitution of thieno[*c*]fused naphthyridines is therefore expected to be a challenge. In order to find suitable conditions for bromination, we looked for the procedures used for the bromination of 1,5-naphthyridines and of thieno[3,2-*c*]naphthyridine. Paudler and Kress [43] used the reaction with bromine in refluxing pyridine to brominate 1,5-naphthyridine in the 3- and 3,7-positions, but the yields were low (Scheme 38). This bromination method gave low yields with thieno[3,2-*c*]- and thieno[2,3-*c*]pyridines, and mixtures of 3-bromo and 2,3-dibromo derivatives were obtained. The best methods were bromination with molecular bromine in 48% hydrobromic acid, and bromine in thionyl chloride which gave the 3-bromo derivative in high yields and almost no disubstitution. More aggressive bromination methods, like bromine in concentrated sulfuric acid in the presence of silver sulfate and dibromoisocyanuric acid (DBI) in concentrated sulfuric acid, gave appreciable amounts of the dibromo derivative as a by-product [44]. The expectedly most reactive thieno[3,4-*c*]-1,5-naphthyridine gave only 8% of the 1-bromo derivative with DBI in concentrated sulfuric acid, and 45% of the starting material was recovered. Bromination in chloroform in the presence of buffer, as used for the bromination of the dithienopyridines, gave also very low yields and a mixture of 7% of the 1-bromo-

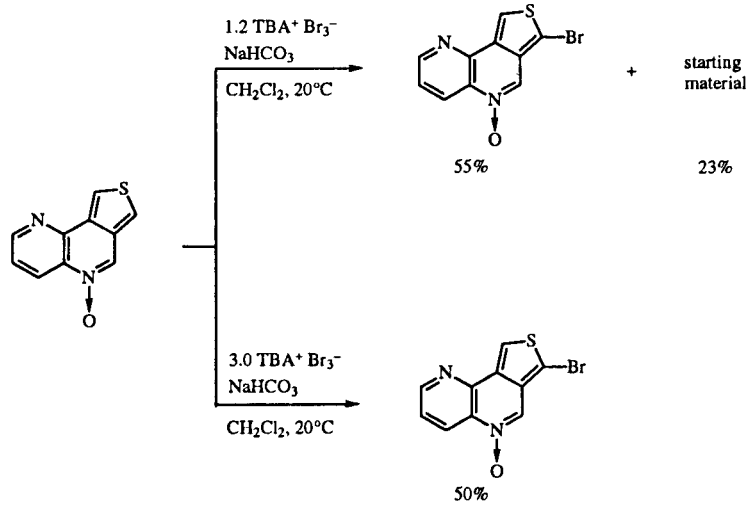
Scheme 39



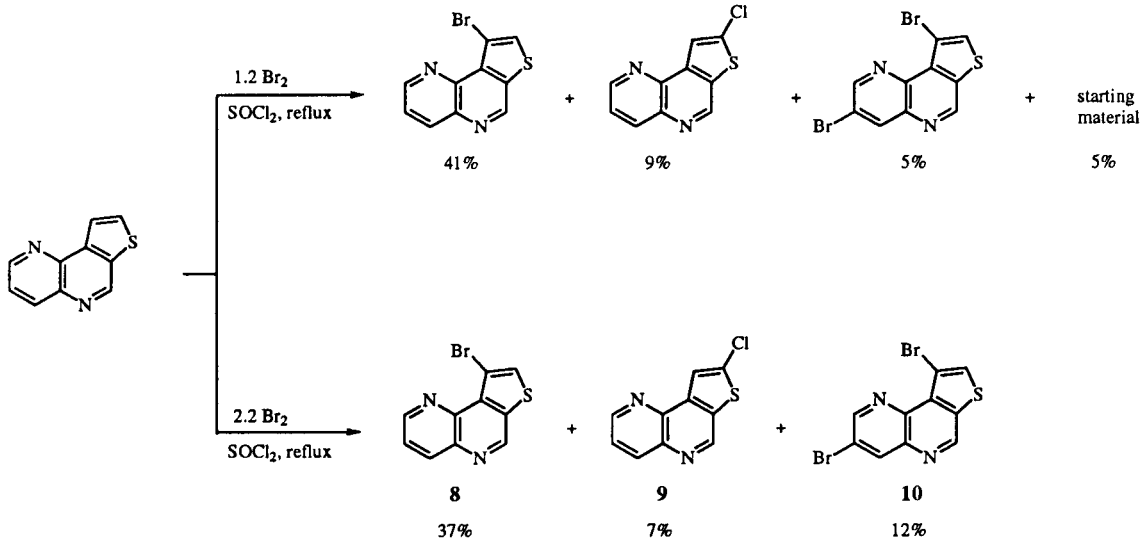
and 8% of the 3-bromo derivative was obtained. However, by using tetrabutylammonium perbromide in dichloromethane in the presence of a large excess of sodium hydrogen carbonate, the 1-bromo, 3-bromo and 1,3-dibromo derivatives were obtained in 41%, 10% and 5% yield, respectively (Scheme 39). Upon attempted dibromination with three equivalents of the brominating agent, low yields of products were obtained, probably due to decomposition. It is interesting to note that the more reactive *N*-oxide (Scheme 40) gave selective substitution in the 3-position and excess of brominating agent led to no dibromination, which is in contrast to the easy dibromination of thieno[3,4-*c*]quinoline *N*-oxide [45].

Thieno[2,3-*c*]-1,5-naphthyridine did not react with tetrabutylammonium perbromide. The use of bromine in concentrated sulfuric acid in the presence of silver sulfate was also unsuccessful, even upon heating the reaction mixture. However, by using bromine in thionyl chloride, a mixture of compounds was obtained in which the 1-bromo derivative was the major product (Scheme 41) [46]. It is interesting to note that the second bromine enters the 7-position of the naphthyridine ring, which is the most reactive position of 1,5-naphthyridine, and not the 2-position, which is the case in continued bromination of 3-bromothieno[3,2-*c*]pyridine. The results of the bromination of thieno[3,2-*c*]-1,5-naphthyridine with bromine in thionyl chloride were disappointing (Scheme 42). Mainly chlorinated products were obtained and the reactions gave low overall yields, despite of the fact that this method gave good results in the bromination of

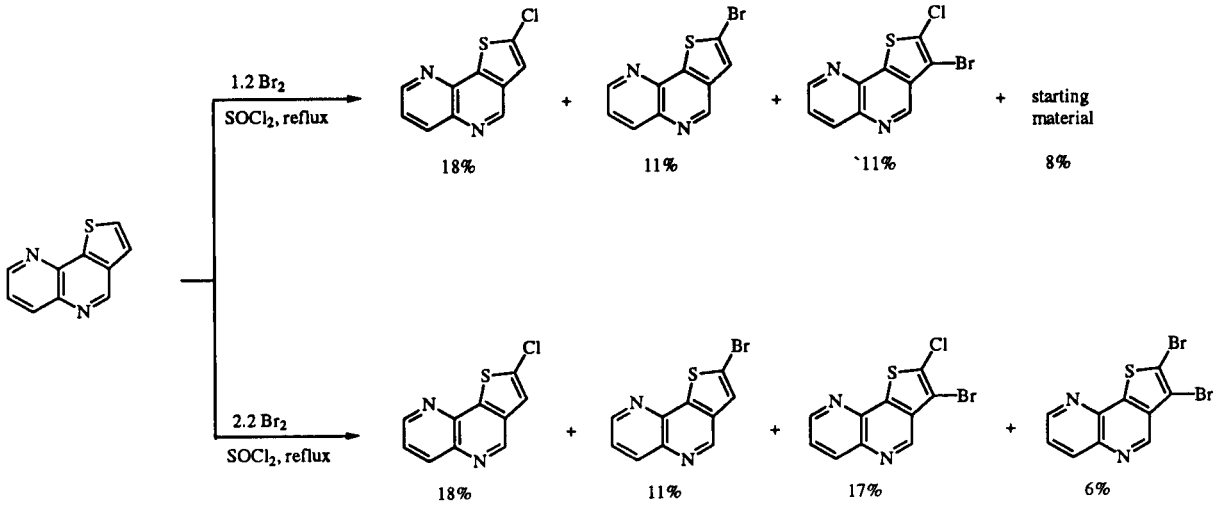
Scheme 40



Scheme 41



Scheme 42

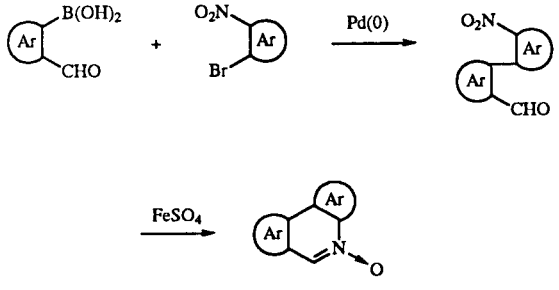


thieno[3,2-*c*]pyridine. We are continuing our study of the bromination of the thieno[*c*]naphthyridines, as these bromo derivatives are essential intermediates for the preparation of compounds of pharmaceutical interest.

N-Oxides.

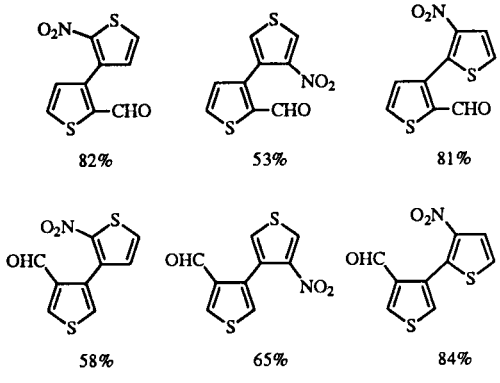
N-Oxides of the dithienopyridines and the thienonaphthyridines can of course be prepared by oxidation with *meta*-chloroperbenzoic acid. It is also an interesting question how the mode of annelation affects the oxidation of the non-equivalent pyridinic nitrogens. *N*-Oxidation should also increase reactivity in electrophilic substitution.

Scheme 43



Historically, the *N*-oxides of the thienopyridines were obtained in our first approach to these ring systems [47]. We planned to couple *o*-formylthiopheneboronic acids with *o*-halonitrothiophenes to give the unsymmetrically substituted bithienyls (Scheme 43) and then hoped to reduce the nitro group to the amino function with ferrous sulfate in ammonia, whereupon ring-closure to the parent compounds was expected to occur. Instead, the intermediate hydroxylamine was trapped by the formyl group to give the *N*-oxides. The yields of the bithienyls (Scheme 44) were quite good. It should, however, be noted that only six of the nine isomers could be obtained in this way (Scheme 45) since the 3-formyl-2-thiopheneboronic acid deboronated during the coupling attempts. The other isomers could be prepared through Stille-coupling or by oxidation of the parent compound. The above-mentioned approach was used for the direct preparation of phenanthridine *N*-oxide, thienoquinoline *N*-oxides and thienoisoquinoline *N*-oxides [48,49].

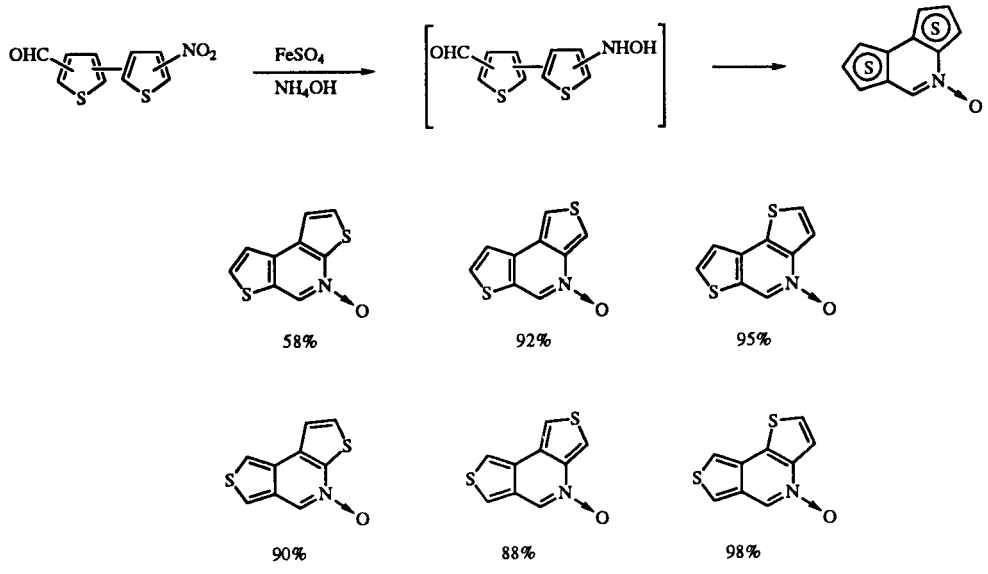
Scheme 44



Nitration of Dithienopyridine *N*-Oxides.

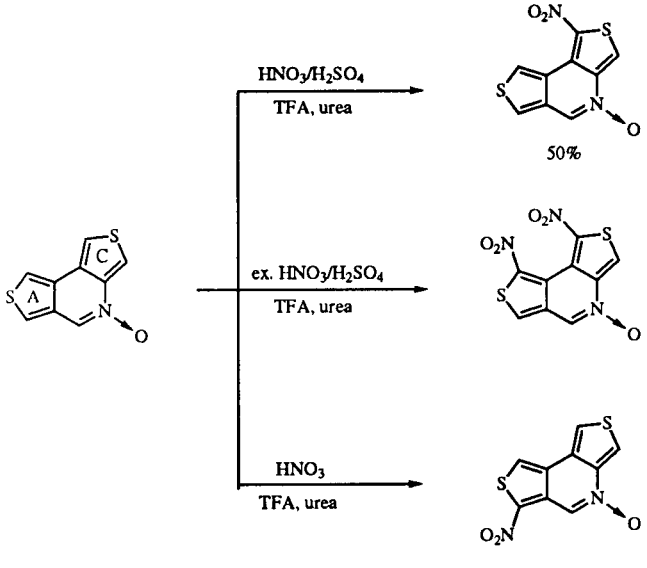
In contrast to the dithienopyridines themselves, the substitution pattern of their *N*-oxides depends strongly on the acidity of the reaction medium. Similar observations were previously made in the nitration of quinoline and isoquinoline *N*-oxide. It was shown that under strongly acidic conditions the conjugated acid was nitrated, while under mild conditions the free base is nitrated. In the nitration of the *N*-oxide of the *c,c*-fused isomer in nitric acid-sulfuric acid, the 1- and 8-nitro isomers are formed

Scheme 45

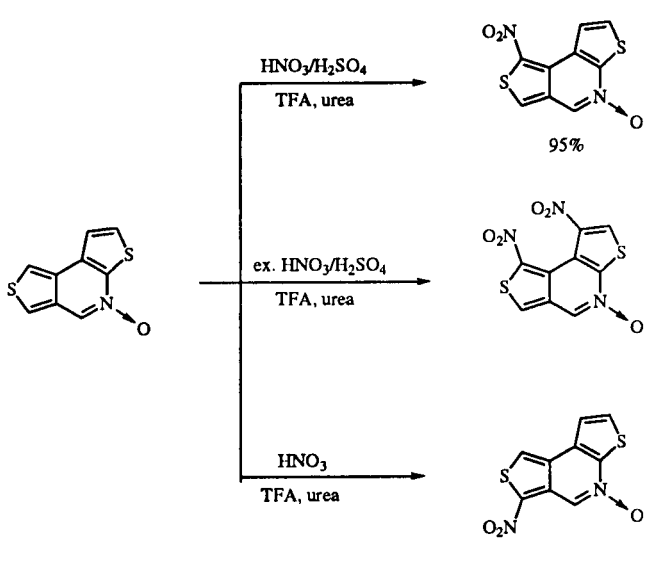


in about equal amounts, in contrast to the nitration of the parent compound, and with excess nitric acid the sterically crowded 1,8-dinitro isomer was obtained (Scheme 46). In the absence of sulfuric acid only the 6-nitro isomer was obtained [50]. This nitration had to be carried out at -15°, since at room temperature decomposition occurred. The *N*-oxide of the *b,c*-fused system gave nitration under strongly acidic conditions reaction only in the *c*-fused ring

Scheme 46

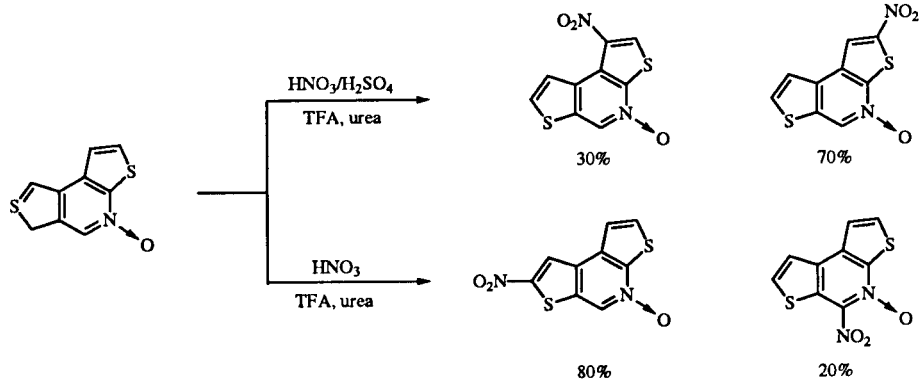


Scheme 47

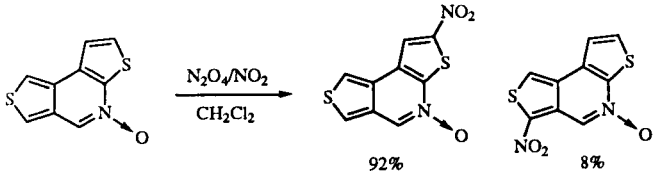


part yielding 95% of the 8-isomer and 5% of the 6-nitro isomer (Scheme 47). With excess nitric isomer only the 1,8-nitro isomer was obtained. Under less acidic conditions, only the 6-nitro isomer was formed. Finally, the [*b,b*]-fused system (Scheme 48) gave the 1- and 2-nitro isomers in 30 and 70% yield, respectively, under strongly acidic conditions while under mildly acidic conditions completely different isomers, the 6-nitro and 5-nitro isomers were obtained in 80% and 20% yield, respectively. In general, under strongly acidic conditions the *N*-oxides give approximately the same isomer distributions of the parent compounds, while under mildly acidic conditions quite different isomer distributions are observed. We also attempted nitration under aprotic conditions, and nitration of the [*b,c*]-fused *N*-oxide was carried out successfully with N_2O_4/NO_2 in methylene chloride (Scheme 49). The reaction with this reagent is considered to involve nitrosonium ion catalysis in some way [51]. With this reagent,

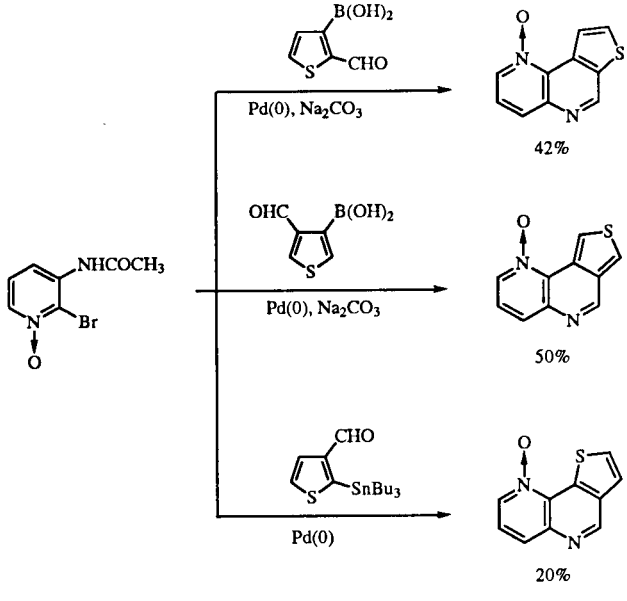
Scheme 48



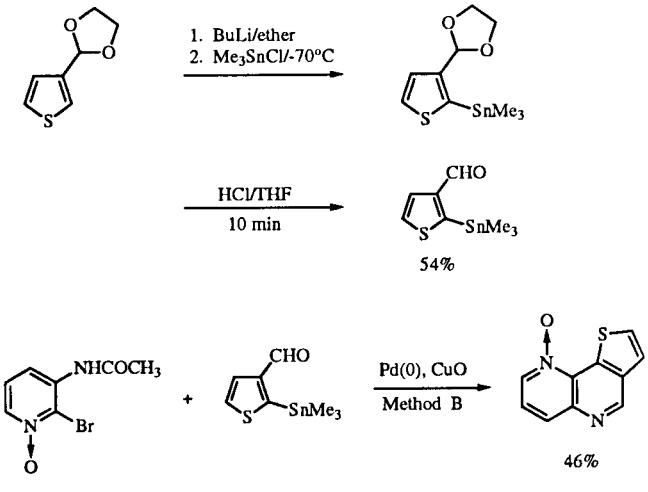
Scheme 49



Scheme 50



Scheme 51

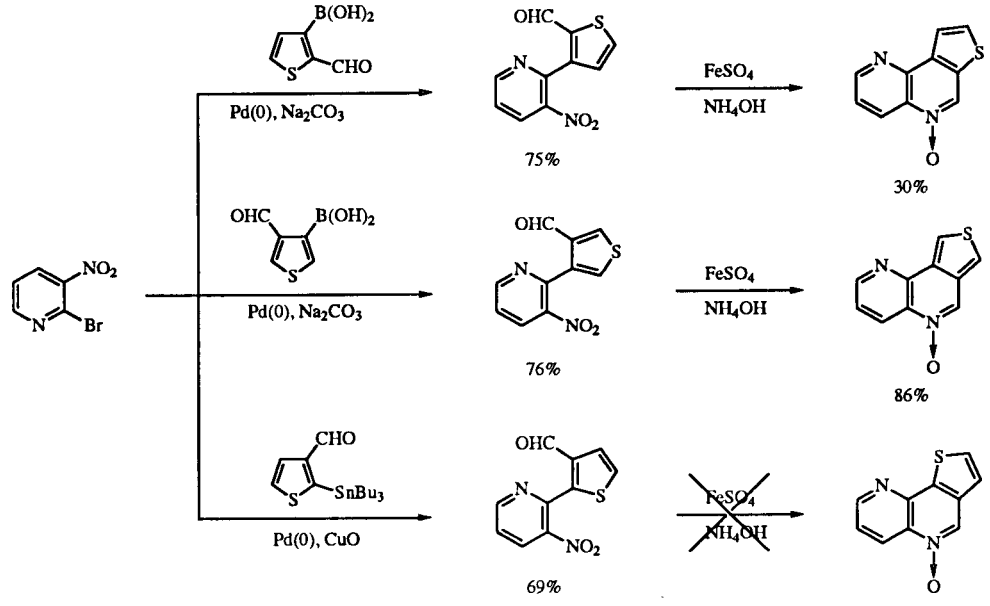


the 2-nitro and 6-nitro isomers were obtained in the proportions 92 to 8. This indicates that nitration under mildly acidic conditions, which gives a quite different isomer distribution can hardly be nitrous acid catalyzed. Nitration of the [*c,c*]-fused *N*-oxide under aprotic conditions resulted in a complex mixture mainly due to decomposition of the starting material, while attempted nitration of the [*b,b*]-fused *N*-oxide only led to recovery of the starting material. Nitration of the [*c,c*]- and [*b,b*]-fused *N*-oxides with nitronium fluoroborate in sulfolane gave the same isomer distributions as nitration under mildly acidic conditions, providing additional evidence for a nitronium ion mediated process. In order to investigate if a radical process is involved in the nitration of the [*c,c*]-fused *N*-oxide under mildly acidic conditions due to its low oxidation potential (E^0 = 1.2V), we measured ^{15}N-CIDNP effects. The reaction at 0° resulted in a small but reproducible enhanced absorption due to the ^{15}N signal of the 6-nitro derivative. The observed nuclear polarization indicates that radicals are involved in the nitration. The low oxidation potential makes it probable that radical pair formation during nitration might be a result of homolytic fission of the Wheland intermediate. *Ab initio* RHF/3-21G(*) and ROHF/3-21G(*) calculations on the nitration of the *c,c*-fused *N*-oxide under mildly and strongly acidic conditions have been carried out, and were in good agreement with the experimental results [52].

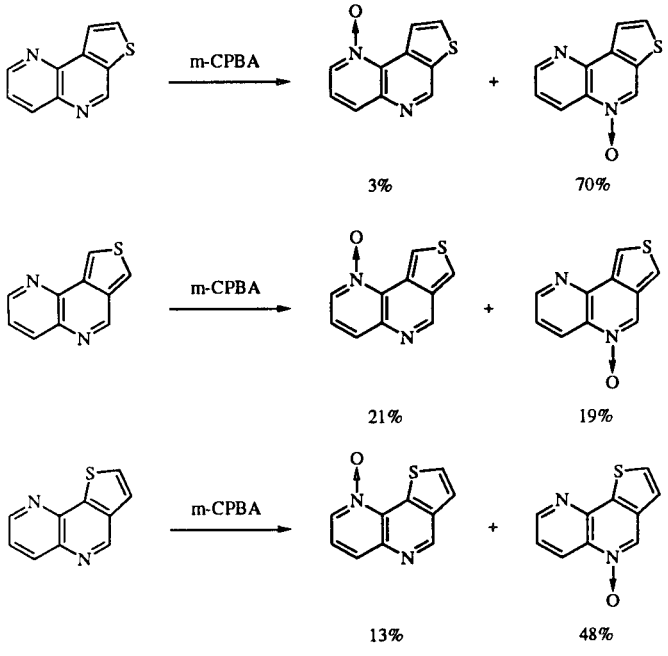
Thieno[*c*]fused 1,5-Naphthyridine 9-Oxides and 5-Oxides.

Three different methods have been developed for the

Scheme 52



Scheme 53



synthesis of these compounds. Suzuki coupling between 3-acetylamino-2-bromopyridine *N*-oxide and 2- and 4-formylthiopheneboronic acid and Stille coupling with 2-(tributylstannyl)-3-thiophenaldehyde gave the 9-*N*-oxides (Scheme 50). The yield of 4-thieno[3,2-*c*]-1,5-naphthyridine 9-oxide could be increased by using the sterically less demanding trimethylstannyl derivative and cupric oxide as a co-catalyst, which gave a yield of 46% (Scheme 51). Two of the 5-oxides were prepared by Suzuki coupling between 2-bromo-3-nitropyridine and 2- and 4-formylboronic acid to yield the unsymmetrically substituted thienylpyridines, followed by reductive ring closure with ferrous sulfate in ammonia (Scheme 52). Although the Stille coupling to the thienopyridine worked well the reductive ring-closure failed.

Finally, we studied the direct oxidation of the naphthyridines to the mono *N*-oxides. The mode of annelation had a great effect on the reactivity of the pyridinic nitrogens (Scheme 53). Thus, thieno[2,3-*c*]-1,5-naphthyridine was almost exclusively oxidized at the 5-nitrogen providing convenient access to the *N*-oxide. The oxidation of thieno[3,2-*c*]-1,5-naphthyridine gave a mixture of 13% of the 9-oxide and 48% of the 5-oxide, which could be separated by hplc. On the other hand, no selectivity was observed in the oxidation of thieno[3,4-*c*]-1,5-naphthyridine, which gave the 9- and 5-*N*-oxides in about equal amounts and in low total yield [53].

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characterization of the products, as well as *ab initio* calculations in his Ph. D. thesis. Mr. Johan Malm is completing his Ph. D. thesis on the thieno[*c*]naphthyridines and Mr. Patrik Björk on the thieno[*b*]naphthyridines.

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