Chemistry of Heterocyclic Compounds, Vol. 30, Nos. 11-12, 1994

THE VERSATILE CHEMISTRY OF THIOPHENE. SOME CONTRIBUTIONS BY THE GRONOWITZ' GROUP

Salo Gronowitz

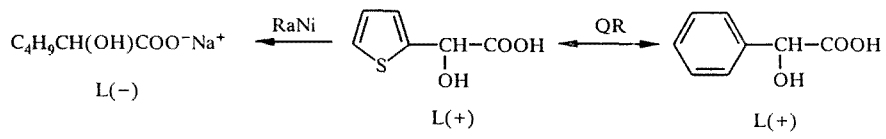
Investigations of the author in thiophene chemistry developed during the last four decades are reviewed. Stereochemical studies, metallation and halogen-metal exchange, spectral studies (mainly those of NMR in thiophene and related series), studies of tautomerism in hydroxythiophenes and atropisomerism in bithienyl derivatives, ring opening of 3-thienyllithium derivatives and thiophene-1,1-dioxides, as well as studies of thieno-fused heteroaromatic boron compounds are considered in detail.

STEREOCHEMICAL STUDIES

This is a personal review of my work in thiophene chemistry. It is now over 40 years since I published my first paper in the field of thiophene chemistry [1]. It was submitted by my teacher, the late Professor Arne Fredga, to Arkiv für Kemi, which was a journal of the Royal Swedish Academy of Sciences, to which, in the tradition of the French Academy of Sciences, only members of the Academy could submit their papers and those of their pupils. This paper was the result of undergraduate research, which one had to undertake for higher grades in chemistry. Fredga was at that time heavily engaged in finding out the uses and limits of the quasi-racemate method for steric correlations of optically active compounds – in other words, to determine relative configurations by melting-point diagrams. Many of his students worked at that time with this problem. The idea behind using thiophene derivatives was to determine the configuration relative to optically active benzene derivatives, as the thiophene ring has similar dimensions as the benzene ring, and then by Raney-nickel desulfurization correlate aromatic compounds with aliphatic ones. Already in this first paper, I used X-ray powder photographs to show the isomorphic nature of 2- and 3-thenylsuccinic acid with benzyl succinic acid. In a later paper together with my first student, Sven Larsson, I determined the relative configuration of 3-thenylsuccinic acid (T) to benzylsuccinic acid (B) (Fig. 1).

The melting point diagrams show that the compounds with opposite rotation give a quasi-racemate, while those having the same mode of rotation give a solid solution [2]. X-Ray powder photographs and solid state IR spectra were used for the quasi-racemate correlations in this case, as the acids were unstable at their melting points. Applying the quasi-racemate method to 2-thienylglycolic acid and mandelic acid followed by Ra-Ni desulfurization gave a definite correlation of mandelic acid to the series of α-hydroxy acids such as lactic acid (Scheme 1) [3].

Scheme 1



Also 3-thienylgycolic acid could be correlated to mandelic acid through the quasi-racemate method [4]. When starting my Ph.D. work, Professor Fredga suggested to me to study the synthesis of 3-substituted thiophenes and compare their reactions and physical properties with the more common 2-substituted derivatives.

Organic Chemistry 1, Chemical Center, Lund University, S-221 00 Lund, Sweden. Published in Khimiya Geterotsiklicheskikh Soedinenii, Nos. 11-12, pp. 1445-1481, November-December, 1994. Original article submitted October 29, 1994.

 0009-3122/94/1112-1252$12.50

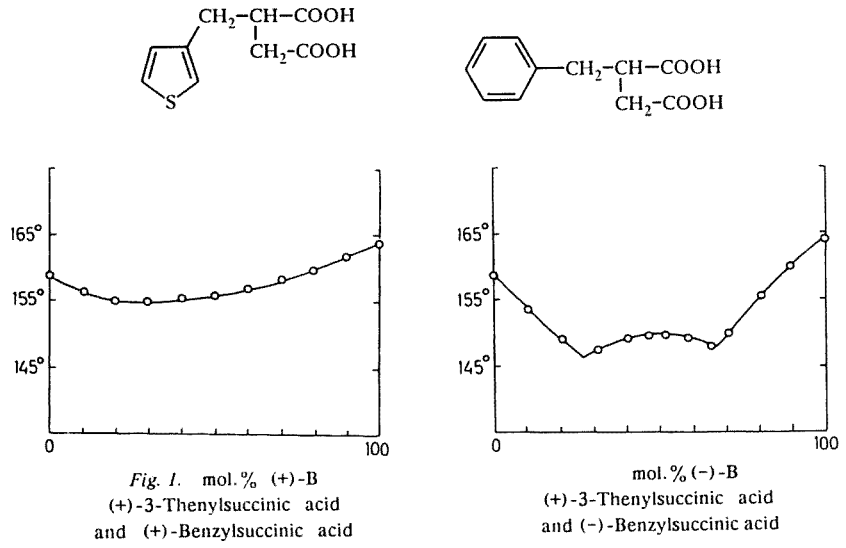


Fig. 1. mol.% (+)-B (+)-3-Thenylsuccinic acid and (+)-Benzylsuccinic acid

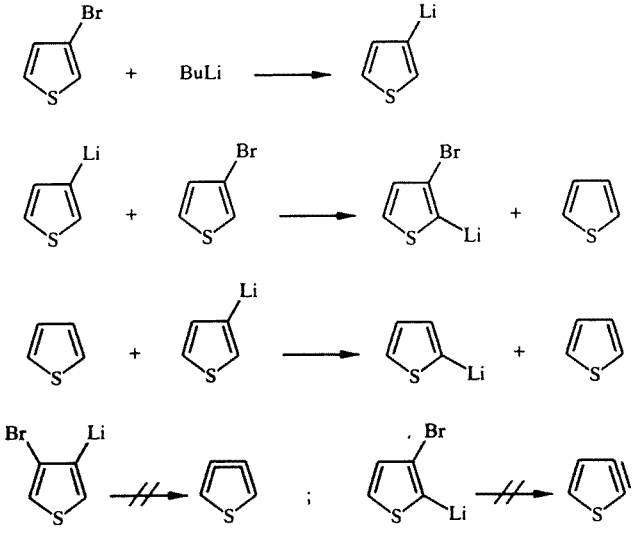
Fig. 1

METALLATION AND HALOGEN-METAL EXCHANGE

At that time the route to 3-substituted thiophenes consisted of radical side-chain bromination of 3-methylthiophene with N-bromosuccinimide introduced by Campaigne [5]. This reaction could be very erratic, and ring substitution could occur, giving large amounts of 2-bromo-3-methylthiophene. In addition, the 3-thenyl bromide was very unstable and very lachrymatory.

3-Bromothiophene had already been prepared by Steinkopf, but it did not give a Grignard reagent, except through the entrainment method, where a co-reagent like ethyl bromide has to be used in large excess. However, I had read the works of Wittig and of Gilman on halogen-metal exchange and started to try this reaction on 3-bromothiophene [6, 7]. At that time there was no commercial butyllithium, and one had to prepare it from metallic lithium and butyl chloride, which was quite a job due to the hardness of lithium metal. I found out that the halogen-metal exchange had to be carried out at —70°C, as at higher temperature the so-called halogen-dance started (Scheme 2).

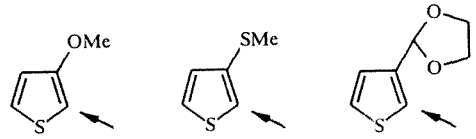
Scheme 2



In this early work, it was also discovered that at —70°C 4-bromo-3-thienyllithium and 3-bromo-2-thienyllithium were stable (Scheme 3). They did not split off lithium bromide as o-bromophenyllithium to give dehydro derivatives [8]. This opened

a route for the synthesis of numerous disubstituted thiophenes as shown for compounds like 3-methylthiothiophenethiol, 2-methyl-3-thiophene aldehyde [9] or 5-fluoro-3-thiophenecarboxylic acid [10], bithienyls [11, 12] and chloro derivatives [13]. Consecutive halogen-metal exchange of dibromothiophenes was also used for the preparation of o-formylthiophenecarboxylic acid. In contrast to phthalaldehydic acid, they do not exhibit ring-chain tautomerism [14]. Often one-pot procedures can be used as in the preparation of o-formylthiophenecarboxylic acids or o-formylthiopheneboronic acids [15], which were key intermediates for the synthesis of heteroaromatic boron compounds (see below). Later on my group studied halogen-metal exchange and halogen-dance in mixed dihalothiophenes such as 2-bromo-3-iodothiophene [16, 17]. In contrast to the extremely unstable 2-bromo-3-thienyllithium, the Grignard reagents, obtained by entrainment of 2-bromo-3-iodo- and 3-bromo-2-chlorothiophene, gave 2-halo-3-thiophene magnesium bromide of use for the synthesis of 2,3-disubstituted thiophenes [18]. The effect of the organolithium reagent and the size of the alkyl group on selectivity in the halogen-metal exchange of 2,5-dibromo-3-alkylthiophene was elucidated [19].

Scheme 3



Heteroatom facilitated metallation

Reacting 3-thienyllithium derivatives with trans-chlorovinyl iodoso dichloride leads to di-(3-thienyl) iodonium chloride, which has inverted reactivity. With nucleophiles nitrothiophenes, thiocyano-, phenylsulfinyl-, and phenoxy derivatives were obtained [20-24].

I became interested in the metallation of thiophene and studied its mechanism by investigating the tritium isotope effect in collaboration with Kjell Halvarson, a coworker of professor Lars Melander, who at that time was at the Nobel Institute of Chemistry in Stockholm [25]. I then took up a study of the directing effect of substituents in the 3-position on metallation, studying for instance 3-methoxythiophene, 3-methylthiothiophene, the acetal from 3-thiophene aldehyde, and 3-cyanothiophene [26-29]. I thus discovered the so-called heteroatom facilitated metallation, which has become such a popular field nowadays. I had at that young age not the cleverness to coin slogans. A systematic study of the influence of the size of the alkyl group and the metallating reagent in the metallation of 3-alkylthiophenes was carried out later [19].

SPECTROSCOPIC STUDIES

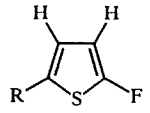
I was from the beginning interested in the study of spectroscopic properties of thiophene derivatives. Already in 1955, when Arne Tiselius had acquired one of the first Perkin Elmer model 21 IR spectrophotometers for the biochemistry department in Uppsala, I studied together with Andreas Rosenberg, who later became professor of biochemistry in the United States, the conjugation in 2- and 3-thiophenecarboxylic acids and aldehydes by looking at the carbonyl stretching frequencies [30]. Later in 1963 together with Professor Alan Katritzky, the IR spectra of 3-substituted thiophenes were analyzed [31]. I also published in 1958 an investigation of the UV spectra of thiophenes [32].

However, I was very fortunate when Professor Kai Siegbahn in 1957 bought one of the first Varian model V-4300 NMR spectrometers for the Physics Department. He put an extremely gifted physicist, Ragnar Hoffman, in charge of the apparatus and in 1958 we started collaboration which lasted until his untimely death in 1970.

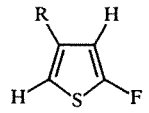
In our first paper, published in 1958, we studied the NMR spectra of 2- and 3-monosubstituted thiophenes, determined the ranges of the characteristic coupling constants, and discussed the effect of the substituents on the chemical shifts [33]. Our collaboration led to more than 25 publications on thiophenes [34-38] and furans [39, 40], on long-range couplings, and on determination of relative signs of coupling constants by special techniques [41-48]. This collaboration was continued with Hoffman's students in Uppsala.

I kept my interest in the NMR spectra of thiophenes. When more advanced spectrometers became available, we prepared substituted fluorothiophenes through the reaction of thienyllithium derivatives and perchloryl fluoride [49]. Fifty-five substituted fluorothiophenes were obtained and their ^{19}F and ^{1}H NMR-spectra studied in detail [50-53].

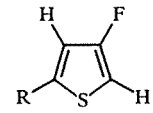
TABLE 1. Regression Equations Relating the ^{19}F Chemical Shifts[a] of Monosubstituted Fluorothiophenes and Fluorobenzenes[b] to the Substituent Constants F and R



I



II



III

Equation	σ^c	c^d	N^e
$\delta_{FI} = -3{,}8 \pm 1{,}1 - (7{,}5 \pm 1{,}8)\ F - (25{,}0 \pm 3{,}1)\ R$	2,2	0,96	12
$\delta_{FII} = -1{,}3 \pm 0{,}5 - (8{,}0 \pm 0{,}9)\ F + (5{,}3 \pm 1{,}6)\ R$	0,9	0,94	10
$\delta_{FIII} = -1{,}6 \pm 0{,}6 - (6{,}4 \pm 1{,}0)\ F + (4{,}9 \pm 1{,}6)\ R$	1,1	0,89	11
$\delta_F^p = 1{,}0 \pm 0{,}8 - (5{,}0 \pm 1{,}2)\ F - (22{,}5 \pm 1{,}5)\ R$	1,5	0,98	16
$\delta_F^m = 0{,}9 \pm 0{,}3 - (4{,}2 \pm 0{,}4)\ F - (0{,}6 \pm 0{,}5)\ R$	0,5	0,95	14

[a]In the regression analyses the shifts are given in ppm relative to that of the unsubstituted compound, and a minus sign of a shift means a downfield shift.

[b]The experimental shifts of the *para* and *meta* substituted fluorobenzenes are taken from [39].

[c]Standard deviation in ppm.

[d]Correlation coefficient.

[e]Number of substituents in the regression analysis.

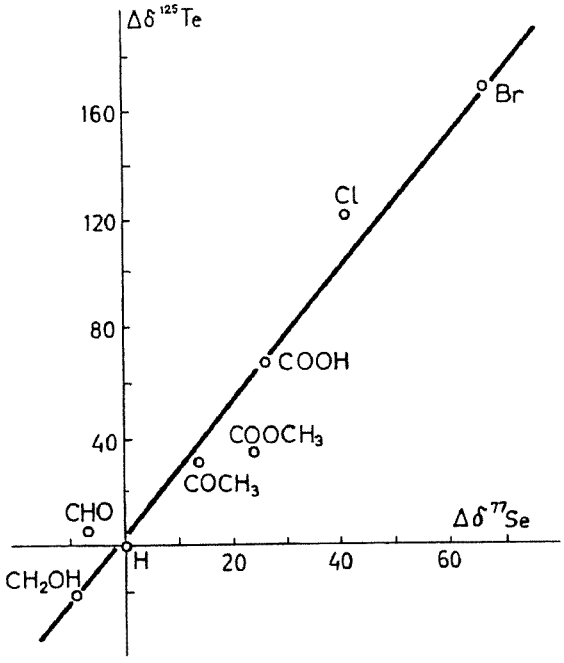


Fig. 2. Plot of substituent-caused ^{125}Te chemical shifts of 2-substituted tellurophenes against the ^{77}Se chemical shifts of the corresponding selenophenes. $\Delta\delta^{125}Te = 2.44 \cdot \Delta\delta^{77}Se + 4.64$ (r = 0.98).

Chemical shifts and spin-spin coupling constants of 5- and 4-substituted 2-fluorothiophenes and of 5-substituted 3-fluorothiophene were correlated with the reactivity constants F and R of Swain and Lupton by means of linear two-parameter equations (Table 1) [53].

Similar correlations with reactivity parameters were also carried out for ^{13}C shifts of monosubstituted thiophenes, furans, and selenophenes [54-57] and very good correlations of the 5-carbon ^1H and ^{13}C chemical shifts in 2-substituted selenophenes versus those of thiophenes were observed [56]. A comparative study was also undertaken of ^1H and ^{13}C spectra

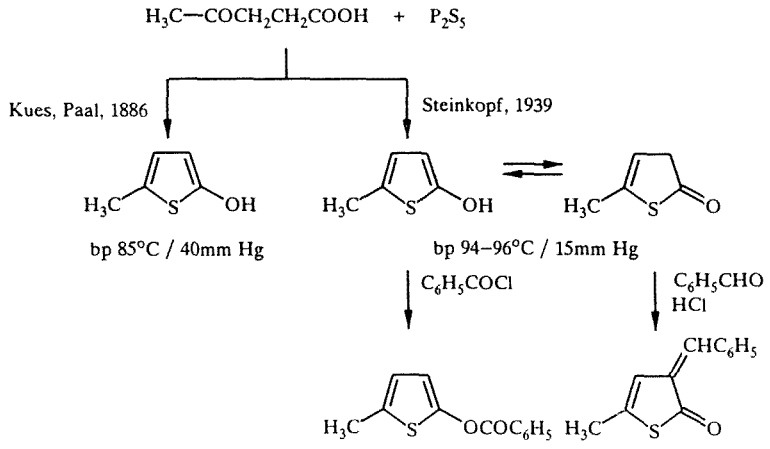
of 2-substituted furans, thiophenes, selenophenes, and tellurophenes, Fringuelli and Taticchi of Perugia providing most of the tellurophenes [58, 59].

^{77}Se parameters have also been determined for a series of 2- and 3-substituted selenophenes [60, 61]. Together with our Italian colleagues also ^{125}Te NMR parameters of 2-substituted tellurophenes were studied [62]. Figure 2 shows the excellent correlation between ^{125}Te and ^{77}Se shifts of 2-substituted selenophenes versus 2-substituted tellurophenes.

TAUTOMERISM IN HYDROXYTHIOPHENES

The early study of the NMR spectra of thiophenes opened a new research interest in my group. In connection with the study of substituent effects on chemical shifts, I wanted to prepare 2-hydroxythiophene, the analogue of phenol. Looking into the literature, I found that Kues and Paal [63] (Scheme 4) already in 1886 had prepared a compound, which they described as 5-methyl-2-hydroxythiophene, from the reaction of levulinic acid with P_2S_5. Their product had a boiling point of 85°C at 40 mm Hg. In 1939 Steinkopf repeated their work and obtained a higher boiling point, 94-98°/15 mm Hg [64]. Steinkopf just dismissed Kues and Paal's result but there was an important difference in their work-ups. Kues and Paal treated the distillate from reaction with P_2S_5 with base, then acidified the alkaline solution, extracted the organic product and then distilled, while Steinkopf directly distilled the product without the base and acid treatment. Steinkopf found that the reaction of the product with benzoyl chloride gave 5-methyl-2-benzoyloxythiophene, while in the reaction with benzaldehyde under acidic conditions the aldol product was formed. Not being aware of the danger of assigning structures of tautomeric systems from reactivity, he claimed that a mixture of 5-methyl-2-hydroxythiophene and of 5-methyl-4-thiolen-2-one had been obtained. The NMR spectra showed clearly that Kues and Paal had obtained the 4-thiolen-2-one form, while Stenkopf's product was the 3-thiolen-2-one form. The hydroxy form could not be detected [65].

Scheme 4



It was thus clear that the 2-hydroxythiophene system was quite different from the phenols, that three tautomeric forms were possible depending on substituents, and that these three forms had one common trident carbanion (Scheme 5). With my first Ph.D. student, Dr. Anna-Britta Hörnfeldt, I started an extensive study of the chemistry of the hydroxythiophene systems [66, 67], which was continued independently by her and her students, Rolf Lantz and Björn Cederlund.

Scheme 5

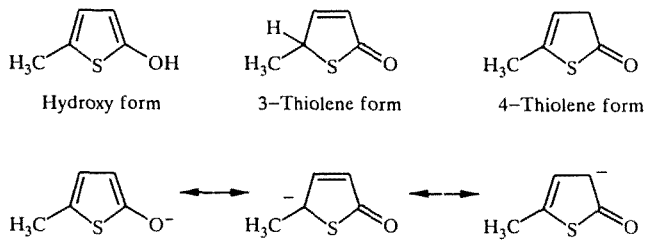
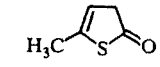
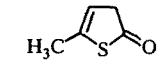
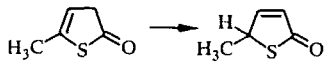
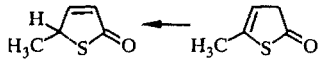


TABLE 2. Rate Constants and Thermodynamic Parameters of Deuterium Exchange and Isomerization Reactions of 5-Methyl-4-thiolen-2-one in Pyridine Solutions at 18°C

Reaction	Base conc, C mole l^{-1}	k 10^3 min^{-1}	ΔH kcal $mole^{-1}$	ΔF kcal $mole^{-1}$	ΔS cal $mole^{-1}$ $degree^{-1}$
Deuterium–exchange 	0,001	23	7,0	21,6	-50,1
Deuterium–exchange 	0,2	18,35	7,0	19,1	-41,4
Isomerization 	0,2	25,3	10,9	21,5	-36,5
Isomerization 	0,2	2,2	12,5	22,9	-35,9

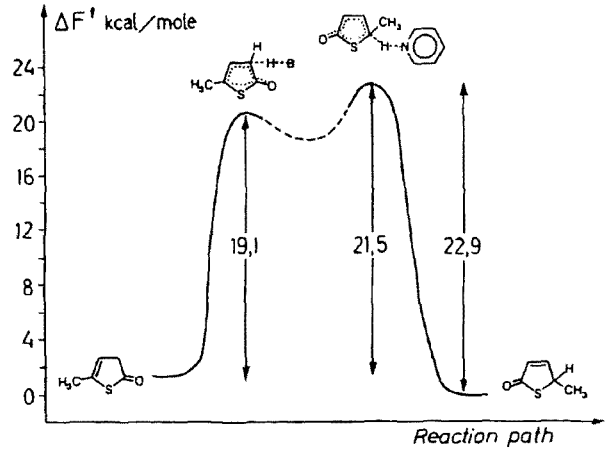


Fig. 3. The two-step tautomerization mechanism of the unsaturated thiolactones.

5-Substituted 2-hydroxythiophene systems were prepared by oxidation of thiopheneboronic acids with hydrogen peroxide, and the boronic acids were prepared from the lithium derivatives through reaction with boric esters. Their tautomeric structure and tautomeric equilibria were determined [66-68]. A detailed study of the base-catalyzed tautomerization of 5-methyl-4-thiolen-2-one and 5-*t*-butyl-4-thiolen-2-one was undertaken using pyridine as base [69], and the rate of rearrangement under the influence of various pyridine bases was measured [70]. The rate of deuterium exchange was measured at low pyridine concentrations [71] (Table 2).

The kinetic investigations supported a two-step mechanism for the tautomerization of the unsaturated thiolactones (Fig. 3).

The rate of the tautomeric rearrangement of the 5-alkylthiolen-2-ones was compared with that of the corresponding butenolides [72]. The tautomeric rearrangements of 5-chloro- and 5-fluorothiolen-2-ones were also studied [73]. Dissociation

TABLE 3. Methylation of 3-Thiolen-2-ones

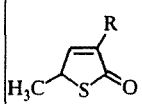
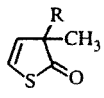
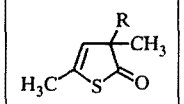
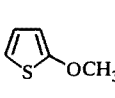
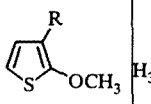
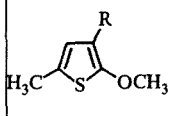
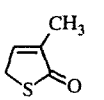
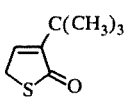
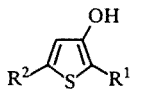
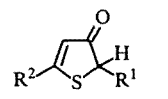
Substrates	Reagents	Yield, %	Products and relative yields						
									
			R = CH_3						
	CH_3I	53	59,0	4,5	8,7	1,3	21,6	3,9	1,0
	$(CH_3)_2SO_4$	87	3,6	—	—	—	94,0	2,4	—
			R = CH_3						
	CH_3I	64	9,0	6,0	55,0	2,0	—	28,0	—
	$(CH_3)_2SO_4$	74	6,0	—	4,0	—	—	90,0	—
			R = $C(CH_3)_3$						
	CH_3I	72	23,0	15,0	12,0	4,0	—	37,0	9,0
	$(CH_3)_2SO_4$	78	15,0	—	—	—	—	85,0	—

TABLE 4. Tautomeric Properties and Tautomeric Equilibria in Carbon Disulfide Solution at 31°C for Some 2,5-Dialkyl-3-hydroxythiophene Systems

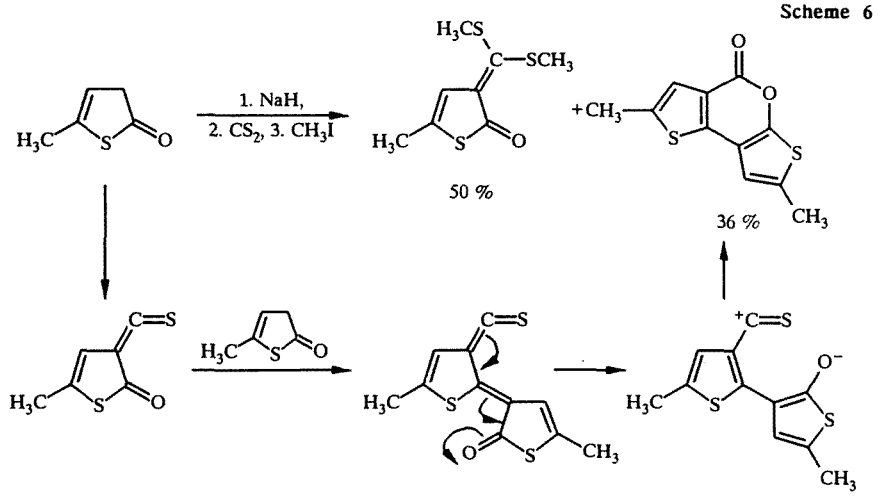
R^1	R^2			K = Keto/Enol
CH_3	CH_3	32	68	2,13
CH_3	C_2H_5	35	65	1,86
CH_3	$CH(CH_3)_2$	39	61	1,56
CH_3	$C(CH_3)_3$	43	57	1,33
C_2H_5	CH_3	29	71	2,45
$C(CH_3)_3$	CH_3	26	74	2,85

constants and UV-spectra of 5-methyl- and 5-*t*-butyl thiolen-2-ones were determined [74]. The structure of dimerization products [75] and oxidative coupling products was elucidated [76].

The methylation of some 2-hydroxythiophene systems were also studied in detail and it was found that hard reagents like dimethyl sulfate gave almost exclusively O-methyl ethers, while the soft methyl iodide gave predominantly C-alkylated products (Table 3) [77-80].

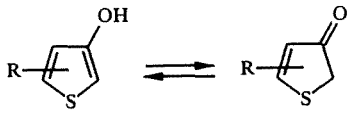
As already mentioned before, the active methylene group in the 3-position of the 4-thiolen-2-one form can be condensed with aldehydes. We found a curious reaction when condensing the anion with carbon disulfide followed by methyl iodide, which besides the expected product gave a dithieno-α-pyrone, the structure of which was proven by X-ray crystallography (Scheme 6) [81].

Scheme 6



For the 3-hydroxythiophene system two forms are possible: a hydroxy form and a keto form (Scheme 7).

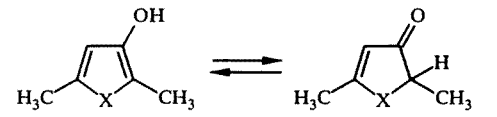
Scheme 7



A number of 5-alkyl-2-methyl- and 2-allyl-5-methyl-3-hydroxythiophene systems were prepared and characterized as acetoxy derivatives; tautomerism is very fast, so that the different forms cannot be isolated. However, the position of the equilibrium could easily be determined by NMR (Table 4) [82].

The equilibrium position in 2,5-dimethyl-3-hydroxythiophene was compared with that of the furan and selenophene analogues. It is obvious that the position of the equilibrium reflects the higher aromaticity of thiophene over that of furan and selenophene (Scheme 8).

Scheme 8



K=Keto/Enol

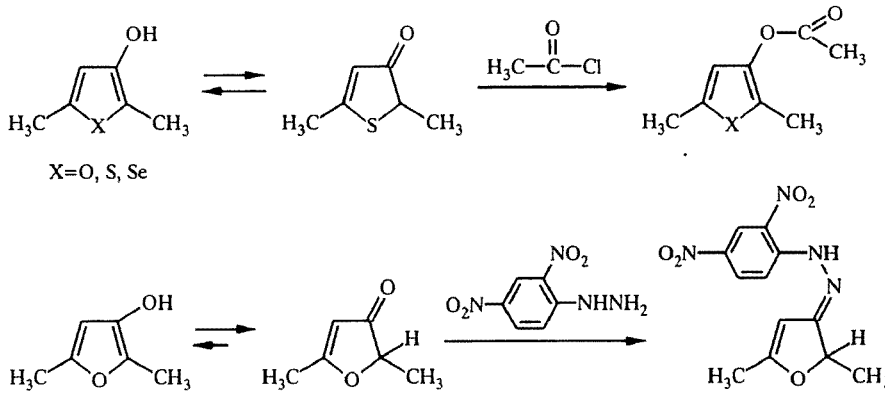
X=O	4%	96%	K=23,9
X=S	23%	77%	K=3,4
X=Se	6%	94%	K=16,9

in cyclohexane at 26°C

The differences in aromaticity of these five-membered heterocycles are also reflected in the alkylation of the ambident ions (Table 5).

Again the hard electrophile dimethyl sulfate gave predominantly O-methylation while methyl iodide gave C-methylation. The 3-hydroxythiophene systems react both in the hydroxy form in acetylation and in the keto form with 2,4-dinitrophenylhydrazine giving the hydrazone (Scheme 9) [83].

Scheme 9



X=O, S, Se

Ionization potentials have been used for tautomeric analysis of 2-hydroxy [84] and 3-hydroxy derivatives of thiophenes, selenophenes, and furans [85], as well as of the corresponding thiols [86].

We have recently renewed our studies on hydroxythiophenes and investigated the preparation and tautomeric properties of the pyridyl-substituted hydroxythiophenes [87, 88].

ATROPISOMERISM

Still in Uppsala, I became interested in atropisomeric bithienyls [89] in order to study their rate of racemization and their ORD and CD spectra and to determine their configuration relative to optically active biphenyls.

Among the first to be prepared were the thiophene analogues of the classical o,o'-dinitrodiphenic acid (Scheme 10) [90, 91].

Scheme 10

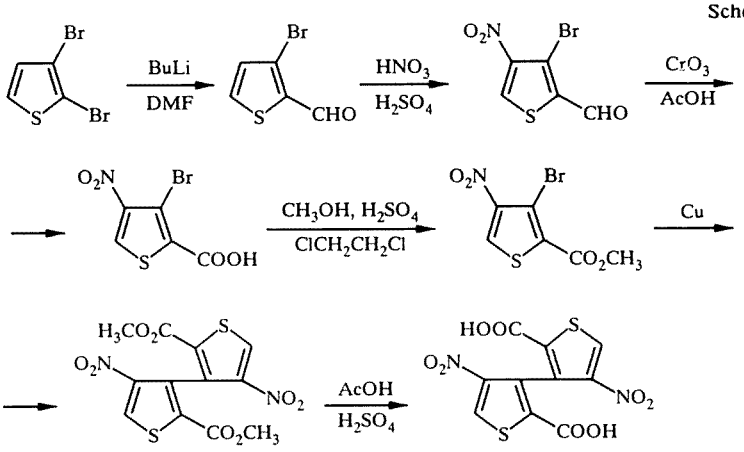
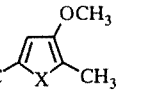
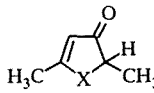
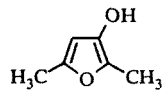
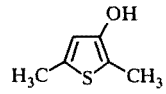
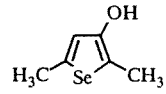


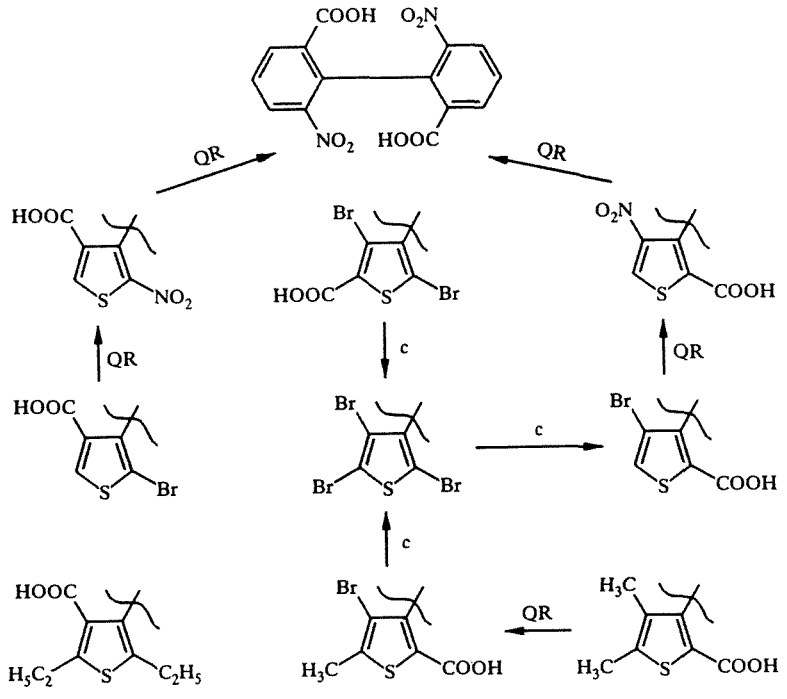
TABLE 5. Methylation of 3-Hydroxy-2,5-dimethyl-substituted Furan, Thiophene, and Selenophene

Substrates	Reagent	Yield,%	Products and relative yields	
				
	CH_3I	45	2	98
	$(CH_3)_2SO_4$	80	54	46
	CH_3I	66	35	65
	$(CH_3)_2SO_4$	96	90	10
	CH_3I	53	15	85
	$(CH_3)_2SO_4$	53	93	7

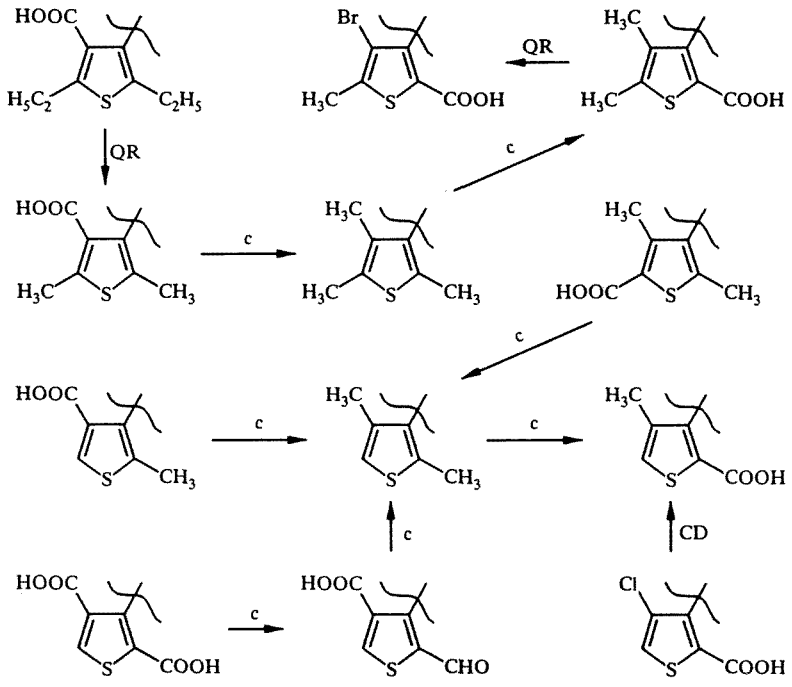
The approach most often used was the coupling of thienyllithium derivatives with cupric chloride followed by functionalization shown for the synthesis of 2,2'-dinitro-4,4'-dicarboxy-3,3'-bithienyl [90, 92]. In order to obtain the 4,4'-dinitro-2,2'-dicarboxy-3,3'-bithienyl, Ullman coupling was used [91, 93]. Melting point curves were used for correlations and an extension of the quasi-racemate method was applied. Quite early I also used CD curves for correlations [93]. Some racemization studies were carried out with 4,4'-dicarboxy-2,2',5',5'-tetramethyl-3,3'-bithienyl [94] and also the corresponding tetraethyl-3,3'-bithienyl [95] could be racemized at 90°C in 0.1 N sodium hydroxide, while the analogous 3,3'6,6'-tetramethyldiphenic acid [96] could not be racemized due to greater steric hindrance in the benzene series.

The research in this field was continued in Lund by my second Ph.D. student Rolf Hakansson, who is now university lecturer at Kalmar College. Together with graduate students Erik Wiklund, Anders Almqvist, and Arne Svensson, a large number of atropisomeric bithienyls were synthesized and resolved into optical antipodes and their relative configuration determined by chemical methods, the quasi-racemate method, and ORD-CD. Schemes 11 and 12 show, some but not all, compounds which were synthesized and correlated. Compounds with suitably sized substituents were also racemized. For a detailed review see [97].

Scheme 11



Scheme 12



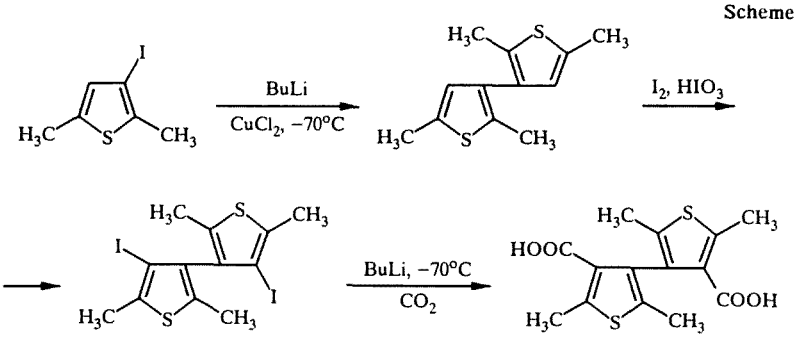
DIRECTING EFFECTS OF ARYL AND HETARYL RINGS ON SUBSTITUTION OF THIOPHENE

While in Oslo, I took up a new field, namely syntheses, electrophilic substitution, and metallation of aryl- and hetarylthiophenes. Systems studied were phenylthiophenes [98-102], 2- and 3-(4-pyrimidyl)thiophene [103], 2-(2-thienyl)pyrimidine and 2-(3'-thienyl)pyrimidine [104], 5-(2-thienyl)pyrimidine and 5-(3'-thienyl)pyrimidine [105], 1-(2'-thienyl)pyrazole and 1-(3'-thienyl)pyrazole [106], and 4-(2-thienyl)pyrazole and 4-(2'-thienyl)pyrazole [107]. The synthesis of this mixed biheterocycle was rather tedious. The development of the Pd(0)-catalyzed carbon–carbon bond formation through the Suzuki [108, 109] and Stille couplings has changed the situation dramatically, as was demonstrated by the synthesis of all six isomeric thienylpyridines [110] and a number of substituted thienylpyrimidines [111-113].

RING OPENING OF 3-THIENYLLITHIUM DERIVATIVES

The work on optically active bithienyl led accidentally to another discovery, which proved very useful. In 1970 Torbjörn Frejd, as an undergraduate student, was assigned the task of preparing and resolving 4,4'-dicarboxy-2,2'-5,5'-tetramethyl-3,3'-biselenienyl. I thought that this should be easily prepared in the same way as the corresponding bithienyl, which is one of the most easily accessible bithienyls, through coupling of the lithium derivative with cupric chloride followed by iodination, halogen-metal exchange, and reaction with carbon dioxide [94] (Scheme 13).

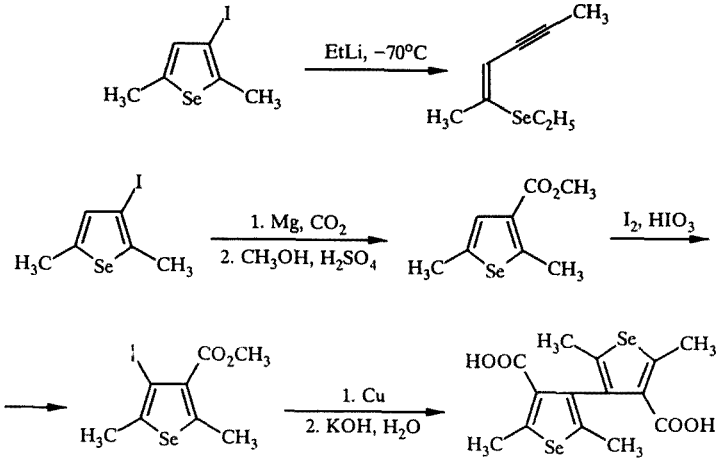
Scheme 13



When Frejd repeated the first step with 2,5-dimethyl-3-iodoselenophene, no biselenienyl was obtained. After many attempts, Frejd finally found the answer. Ring opening had occurred, leading to the ethylselenovinylacetylene [114-116].

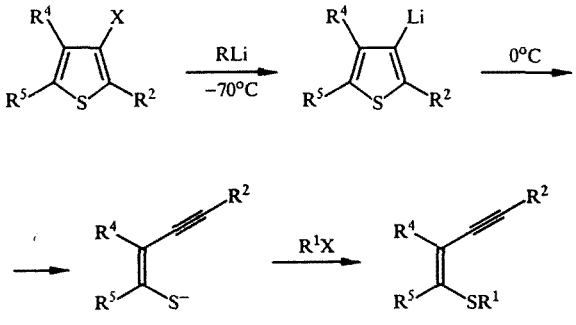
This then led to extensive study of the use of ring opening of 3-thienyllithium derivatives for the synthesis of unsaturated aliphatic compounds. However, Frejd did not like to give up a project. He found that 2,5-dimethyl-3-selenienyllithium was stable for a short time at —110°C and reacted with carbon dioxide to give 2,5-dimethyl-3-selenophenecarboxylic acid in 50% yield. He also found that the Grignard reagent could be prepared from 2,5-dimethyl-3-iodoselenophene and was stable and could be used for the preparation of the carboxylic acid, which was esterified, iodinated, and then through Ullman coupling and hydrolysis transformed to the desired acid, which was resolved into its antipodes. Their stereochemistry was related to the thiophene analogue and the rate of racemization studied (Scheme 13a) [117].

Scheme 13a



However, his main interest which led to his Ph.D. thesis in 1975 was the ring-opening reaction. It was of course time to check if similar ring openings occur with 3-thienyllithium derivatives, and Frejd found that indeed such reactions occurred smoothly at 0°C to room temperature. It was found that the reaction was very general, any kind of substituent in the 4- and 5-position was tolerated, except of course those which react with organolithium derivatives (Scheme 14).

Scheme 14

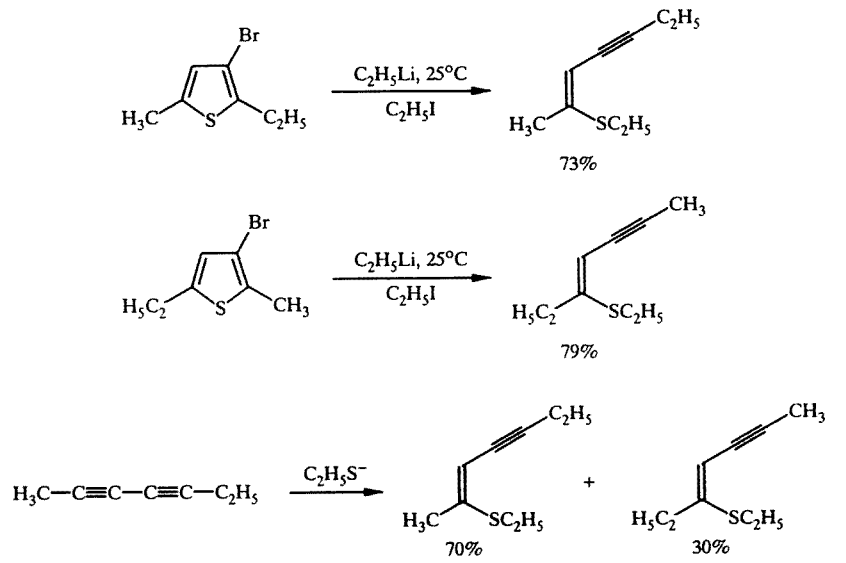


X=Br, I; R^2, R^4, R^5=Alkyl, Arylheterocycles, Vinyl; R^4, R^5=OCH_3, SCH_3 etc.

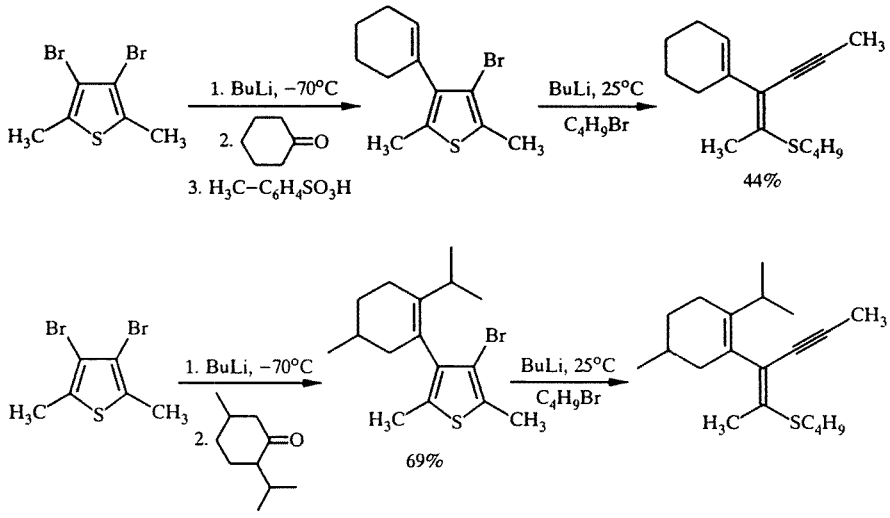
In the 2-position the types of substituents which could be present were somewhat more limited, as groups which can coordinate organolithium derivatives either intra- or intermolecularly, such as methoxy- and dimethylaminomethyl groups, stabilized the 3-thienyllithium derivative, so it did not ring-open. The opening to the thioenyne is stereospecific and in almost all cases the indicated isomer is obtained after reaction with the electrophile, mostly an alkyl halide. If the halogen-metal exchange is carried out with phenyllithium, any kind of alkyl halide can be used. If alkyllithium derivatives are used in the halogen-metal exchange, the alkyl halide formed is doing the alkylation. The ring opening works best when the 2- and 5-positions are substituted. If α-hydrogens are present, ring opening is slow and transposition of the lithium to the most acidic position may compete [118-121]. The products obtained after alkylation of the ring opening of 2,5-dialkyl-3-thienyllithium derivatives can also be obtained through the addition of thiolates to a diacetylene. This reaction, however, in contrast to the

route via ring opening, is not regiospecific, although the same stereochemistry is obtained (Scheme 15). Of course 2,4,5-trisubstituted derivatives give products (Scheme 16) which cannot be prepared from diacetylenes or easily in any other way [118]. Another example is the synthesis of an acetylenic mixed ketenethioacetal through the ring opening of 2-methyl-5-methylthiothiophene (Scheme 17) [122].

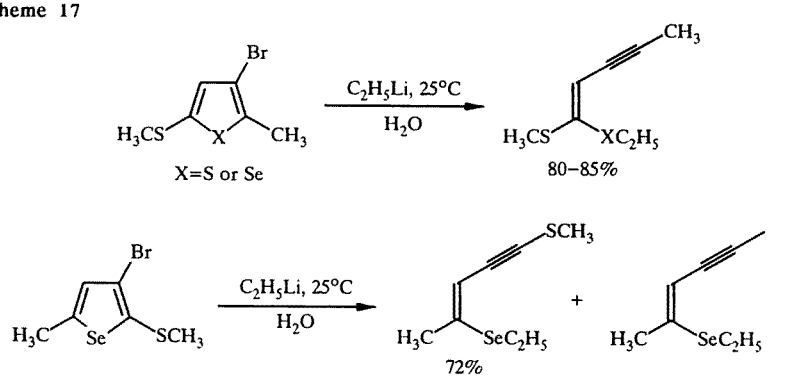
Scheme 15

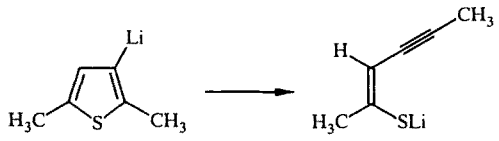


Scheme 16



Scheme 17





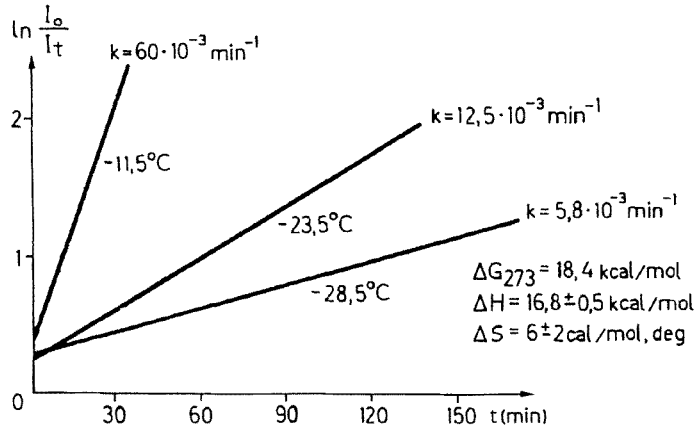
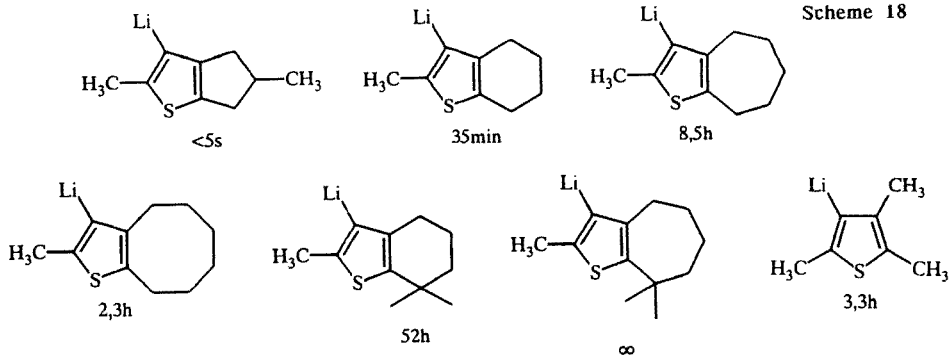


Fig. 4. First order kinetics of ring opening of 2,5-dimethyl-3-thienyl lithium.

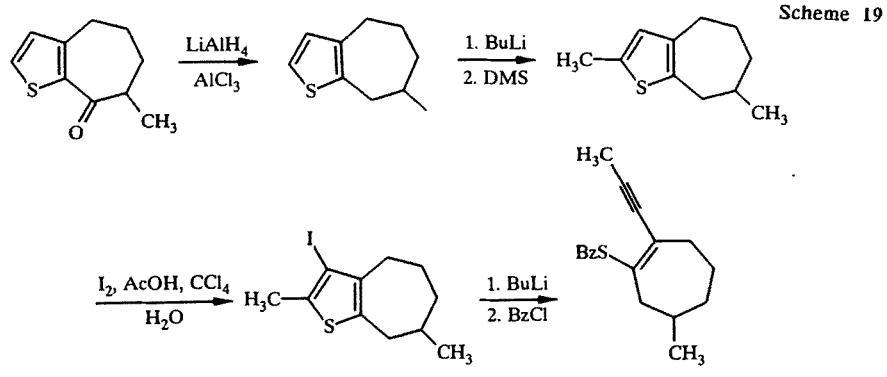
The ring opening could be followed by NMR in the temperature range between —30°C and —10°C, and the thermodynamic parameters determined (Fig. 4) [123]. The ring-opening rates are sensitive to substituents and to strain factors, as can be seen in Scheme 18 for cycloalkane [b]annelated 3-thienyllithium derivatives. The five-membered ring opens much faster than the six-membered, while the seven- and eight-membered compounds open quite slowly. With the gem-dimethyl group in the α-benzylic position the seven-ring-annelated compound appears to be completely stable [124].

The ring opening of cyclo [b]annelated compounds is also quite useful for the preparation of, for instance, cycloheptene derivatives. The cycloheptanone derivative is prepared from the corresponding acid by electrophilic ring closure, reduction to the methylene compound with $LiAlH_4/AlCl_3$, iodination, and treatment with phenyllithium and benzyl chloride. This leads to a product where the positions of the triple and double bond as well as the methyl and benzylthio group are exactly defined, which would be very difficult to achieve without the use of the thiophene ring as a template (Scheme 19) [125].

Scheme 18



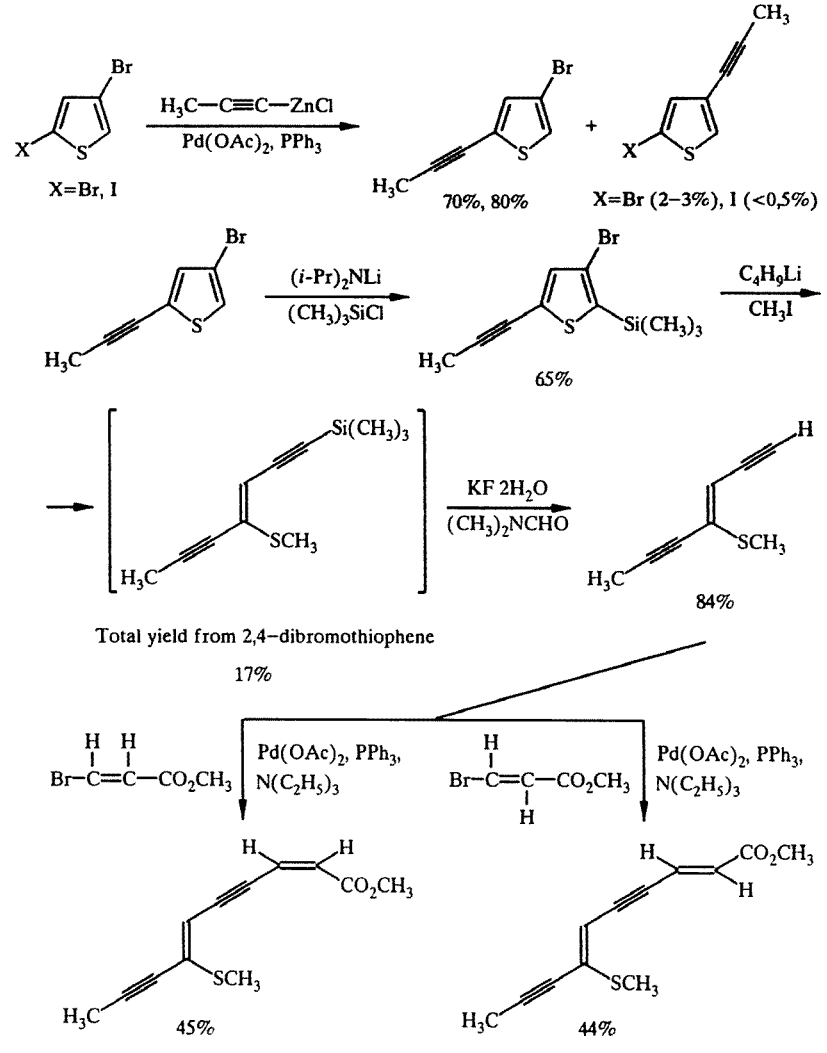
Scheme 19

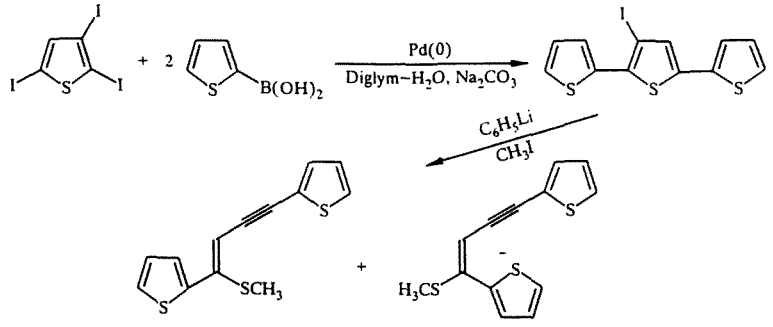


The reaction of 2-chloro-5-methoxythiophene with butyllithium at room temperature gave, after reaction with dimethyl sulfate, 1-methylthio-4-(5-chloro-2-methoxy-3-thienyl)butadiyne, the formation of which has been elucidated [126]. Ring-opening of 2,5-dimethoxy-3-thienyllithium has also been observed [127].

The ring-opening could also be used for the synthesis of a number of naturally occurring methylthiovinylacetylenes isolated mainly by the late Professor Bohlmann from *Compositae*. Besides the ring opening, various Pd(0)-catalyzed coupling steps were essential. Thus, starting from 2,4-dibromo- or 4-bromo-2-iodothiophene followed by coupling with methyl-acetylenezinc chloride gave the 2-(methylacetylenyl)-4-bromothiophene, which was silylated in the 5-position to hinder transmetallation and increase the rate of ring opening. Halogen-metal exchange with butyllithium followed by methyl iodide gave the trimethylsilyl protected methylthiovinylacetylene, which without purification was desilylated. Heck coupling with the *cis*- and *trans*-3-bromoacrylic esters then gave the desired natural products in 17% total yield (Scheme 20) [128]. Introduction of a trimethylsilyl group in the 2-position of 3-halothiophenes and selenophenes is essential for avoiding rearrangements and increases the rate of ring opening [129]. Another product from *Anthemis* was prepared starting from 4-bromo-2-methylthiophene, which was iodinated in the 5-position and then through Pd(0)-catalyzed coupling with trimethyl-silyl-acetylenezinc chloride the trimethylsilylacetylene group was introduced. Now everything was set up for the ring opening, and after desilylation a very good yield of the methylthiovinyldiacetylene was obtained. Unfortunately the Heck coupling with *cis*-3-bromacrylic ester proceeded with low yield, probably due to the instability of the product [130]. Finally, by using our modification of the Pd (0)-catalyzed Suzuki cross coupling [108, 109] we prepared the iodinated terthienyl, which upon treatment with phenyllithium and methyl iodide gave the natural products from *Arctotidea* (Scheme 20) [131].

Scheme 20

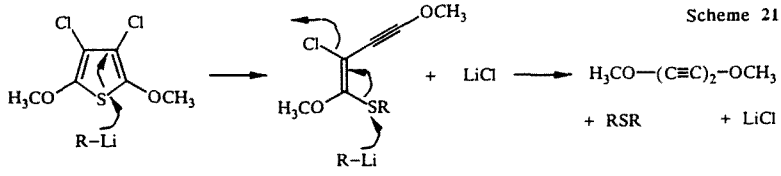




45% overall

The mechanism of the ring openings I have hitherto discussed, which Frejd called RO-1, is the most common and looks like a retro-Michael reaction. We have also found a few examples of the RO-II type reaction, which in principle leads to the same product. From the reaction of 3,4-dichloro-2,5-dimethoxythiophene with butyllithium and phenyllithium, dibutyl sulfide and diphenyl sulfide were isolated in 35% and 27%, respectively. Dimethyldiacetylene should also have been formed but this compound is probably so unstable that it could not be detected (Scheme 21) [132]. In the selenophene series several other examples of the RO-II reaction have been found [133, 134]. Lateral metallation followed by ring opening was observed in the reaction of 2,5-dimethylthiophene with alkyllithium-TMEDA complex [135]. It is therefore clear that the use of thiophene as template, utilizing its aromatic character to introduce almost any substituent in any desired position through electrophilic substitution or metallation and halogen-metal exchange, followed by ring opening gives a very good approach for the synthesis of highly unsaturated aliphatic compounds. For previous reviews see [136, 137].

Scheme 21

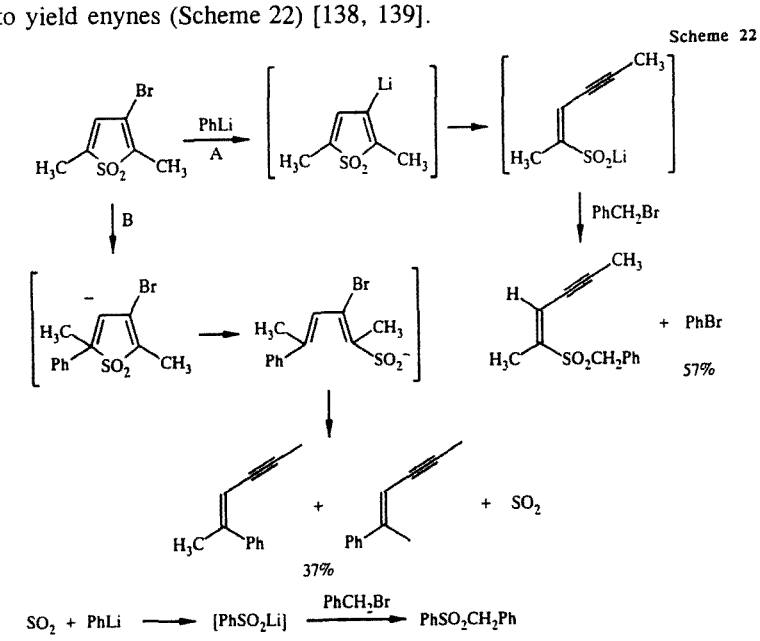


R=Bu, 35%; R=Ph, 27%

RING OPENING AND OTHER REACTIONS OF THIOPHENE-1,1-DIOXIDES

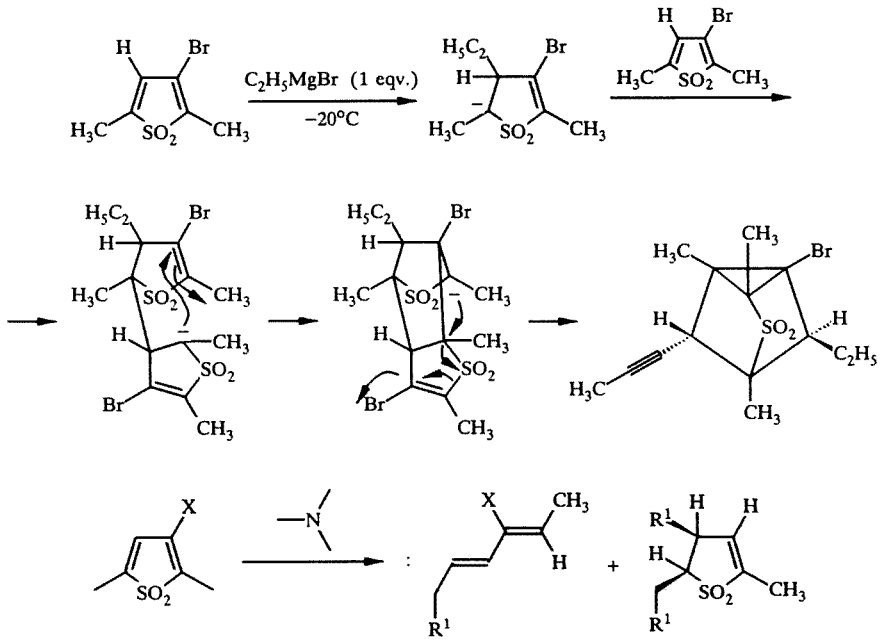
The ring-opening reactions of 3-halothiophenes via lithium derivatives were then expanded to the corresponding thiophene-1,1-dioxides. It was found that 2,5-dialkyl-3-bromothiophene reacted with alkyllithium derivatives in two competing ways: a) via halogen-metal exchange and ring opening to lithium enynesulfinate and b) via organolithium attack on the 5-carbon followed by ring opening to yield enynes (Scheme 22) [138, 139].

Scheme 22



The reaction of 2,5-dimethyl-3-bromothiophene-1,1-dioxide with ethylmagnesium bromide led, on the other hand, through a series of Michael additions to a heterotricycloheptane derivative (Scheme 23) [140].

Scheme 23



Reaction with secondary amines led to a stereoselective synthesis of diaminoalkyl-substituted halobutadienes via amine-induced ring opening through attack on the exomethylene tautomer of 2,5-dimethyl-3-bromothiophene-1,1-dioxide (Table 6) [141, 142].

Also the reaction of such thiophene-1,1-dioxides with thiolates and alkoxides was studied [143]. The reaction with alkyl or aryl copper reagents gave trialkyl- or aryl-substituted thiophene-1,1-dioxides [144]. A new synthesis of pentasubstituted benzenes was achieved by tandem dimerization ring opening of 3-halo-2,5-dialkylthiophene-1,1-dioxides (Scheme 24) [145]. Through the use of silylated thiophene-1,1-dioxides, this type of reaction could be used for the synthesis of 1,2,3-trisubstituted benzenes [146]. With some derivatives thiophene-1,1-dioxides could be dimerized giving benzo[b]thiophene-1,1-dioxides as products [147]. A review of our work on thiophene-1,1-dioxides has recently been published [148].

Scheme 24

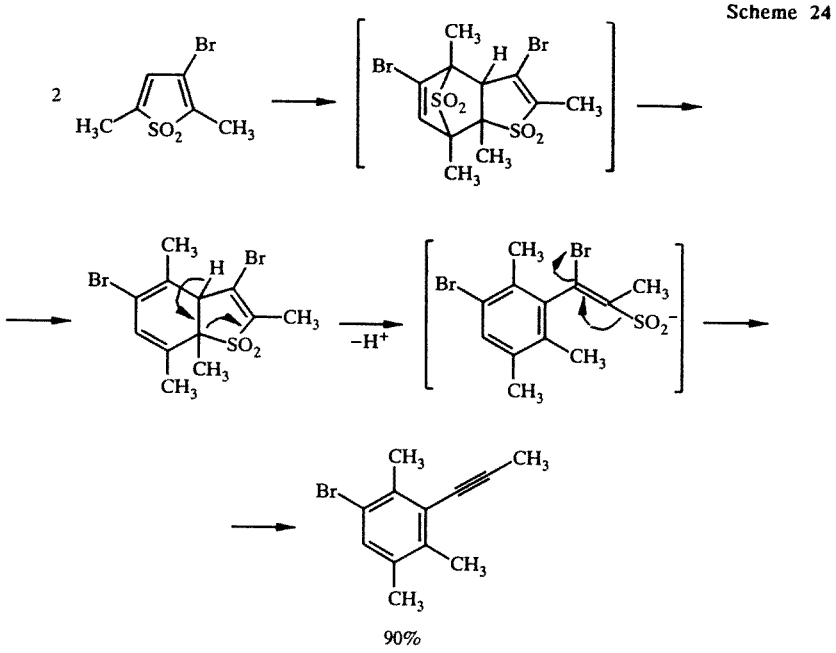


TABLE 6. Reactions of 2,5-Dimethyl-1,1-dioxide and Its 3-Halosubstituted Derivatives with Cyclic Secondary Amines

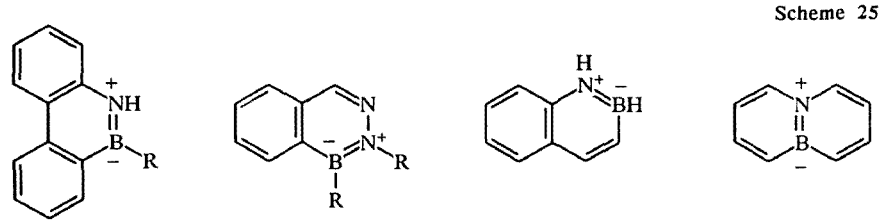
Entry	Time, h	X	R^1	Yield:	
1	3	Cl	pyperidino	58	<5
2	24	Cl	pyrrolidino	48	10
3	72	Cl	morfolino	42	10
4	3	Br	pyperidino	52	13
5	24	Br	pyrrolidino	39	14
6	72	Br	morfolino	31	10
7	72	H	pyperidino	92*	<5

*Glc yields.

HETEROAROMATIC BORON COMPOUNDS

In Oslo in 1964, I read Dewar's earlier work on heteroaromatic boron compounds, in which an isoelectronic B-N group substitutes for a C=C group in an aromatic system [149]. Some examples are given in Scheme 25.

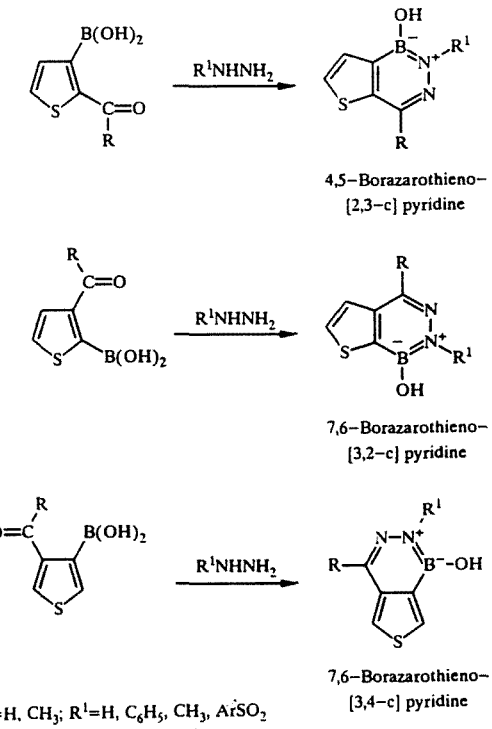
Scheme 25



Dewar 1958 Dewar 1964 Dewar 1958 Dewar 1968

I found borazaroisoquinoline especially interesting [150], as I realized that the corresponding thiophene annelated systems should be very easily available from o-formylthiopheneboronic acids [151], which were later available in one-pot procedures from the o-dibromothiophenes [15]. Also the corresponding o-acetylboronic acids were later prepared in the same way [152]. Upon reaction with hydrazines these acids then gave through hydrazone formation and elimination the stable heteroaromatic systems (Scheme 26) [151-153].

Scheme 26



4,5-Borazarothieno-[2,3-c] pyridine

7,6-Borazarothieno-[3,2-c] pyridine

7,6-Borazarothieno-[3,4-c] pyridine

R=H, CH_3; R^1=H, C_6H_5, CH_3, $ArSO_2$

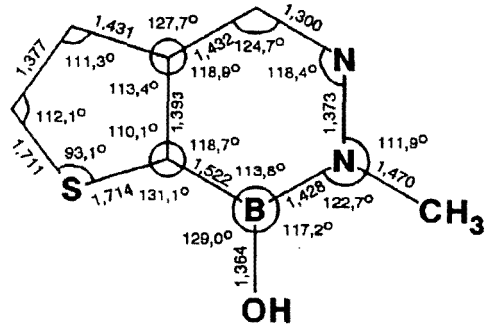


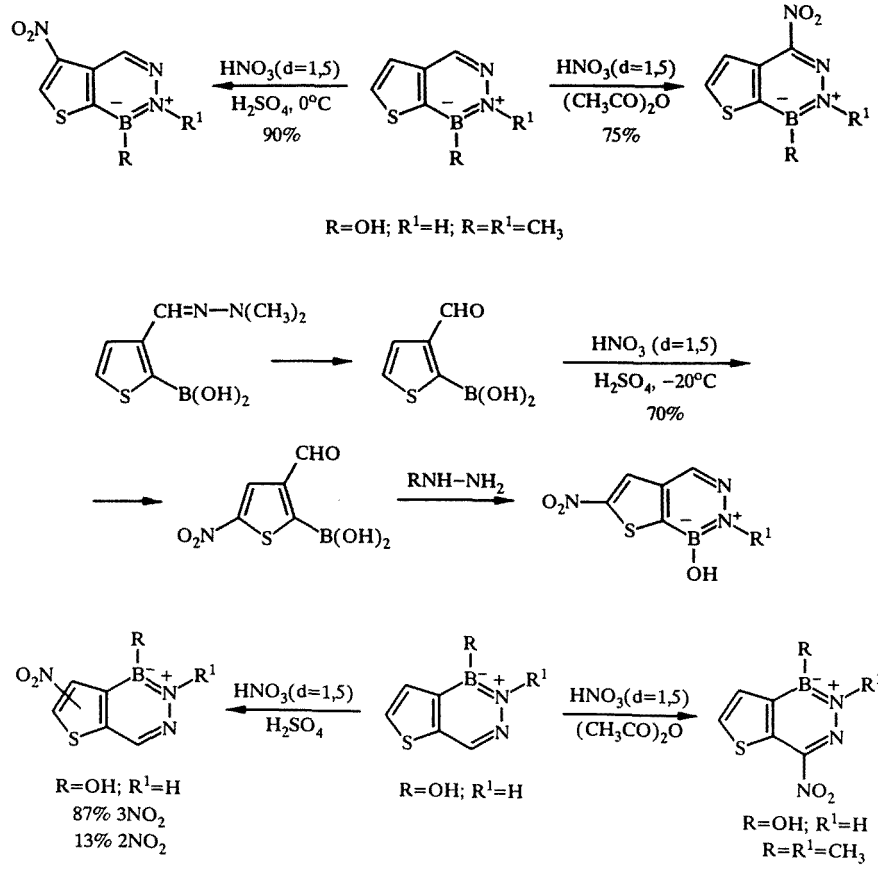
Fig. 5. Bond angles and valence angles in 6-methyl-7-hydroxy-7,6-borazarothieno[3,2-c]pyridine molecule.

Using the nomenclature suggested by Dewar, the ring systems should be called 4,5-borazarothieno[2,3-c]pyridine, 7,6-borazarothieno[3,2-c]pyridine, and 7,6-borazarothieno[3,4-c]pyridine. However, the correct name for the first system is 1,2-dihydrothieno[2,1-d][1.2.3]diazaborine, which is much more clumsy and does not indicate the aromatic nature (Scheme 26). The study of such compounds became especially interesting when we found that a great number of the arylsulfonyl derivatives prepared through reaction with sulfonylhydrazines had activity against Gram-negative bacteria [154-156].

In particular, the two b-fused systems were found to be quite stable towards acid and alkaline ring cleavage. An X-ray crystallographic investigation by Professor Aurivillius also confirmed the aromaticity of the borazaropyridine ring part (Fig. 5) [157].

Detailed studies of aromatic substitution of the thieno-fused borazaropyridines were undertaken, especially nitration [158, 159]. Thus, under very strong acidic conditions 7,6-borazarothieno[3,2-c]pyridine was nitrated exclusively in the 3-position, while with acetyl nitrate, reaction occurred exclusively in the 4-position (Scheme 27) [160].

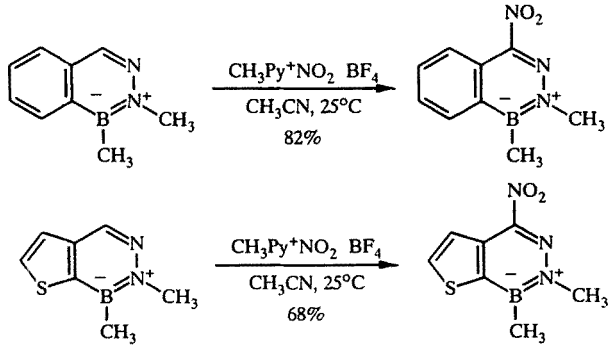
Scheme 27



Another possibility to demonstrate that the cyclodehydration led to aromatic systems was to study open models. However, the dimethylhydrazone decomposed, so the 3-formyl-2-thiopheneboronic acid was used as a model and, in contrast to the cyclic system, it was nitrated in the 2-position. In the nitration of the 4,5-borazarothienopyridines peri effects from the substituent on the boron led to formation of 15-25% of the 2-isomer due to deactivation of the 3-position (Scheme 27). This was even more pronounced in the nitration of 4-methyl-7,6-borazarothienopyridines when the 3- and 2-isomers were formed in about equal amounts [160].

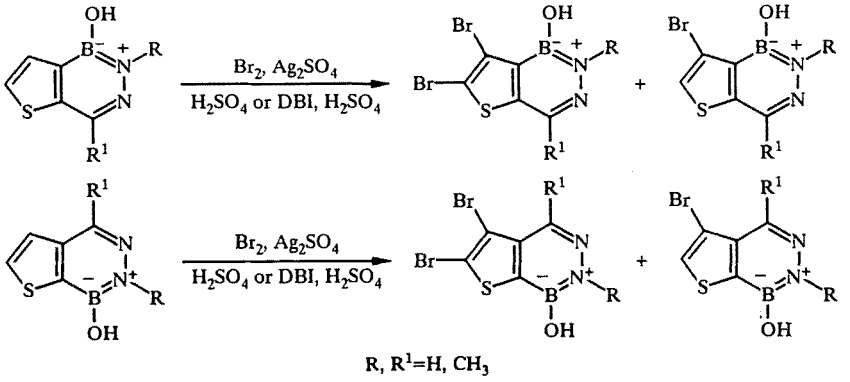
The best reagent for nitration in the borazaropyridine ring was 1-nitropicolinium fluoborate. The great advantage was that it did not oxidize B-alkyl group to B-hydroxyl groups (Scheme 28) [161].

Scheme 28



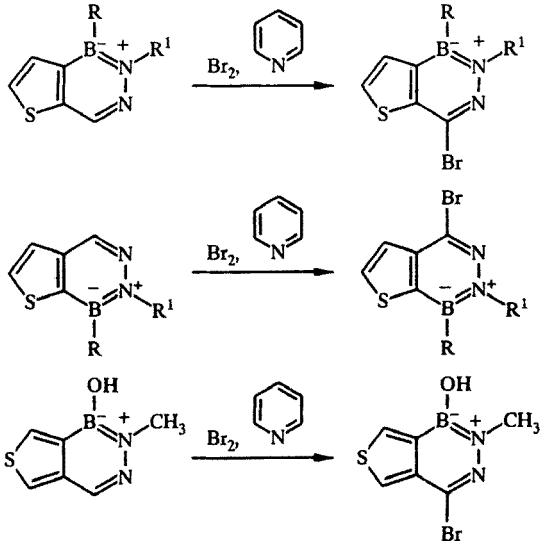
Bromination with bromine and silver sulfate in sulfuric acid or with N,N-dibromoisocyanuric acid in fuming sulfuric acid occurred in the thiophene ring and gave mixtures of 3-mono- and 2,3-dibromo-substituted derivatives with one equivalent of bromine. With two equivalents high yields of the dibromo derivative were obtained (Scheme 29). Under neutral conditions, on the other hand, using bromine in pyridine-carbon tetrachloride, bromination occurred in high yields in the borazaropyridine ring (Scheme 30).

Scheme 29



R, R^1=H, CH_3

Scheme 30



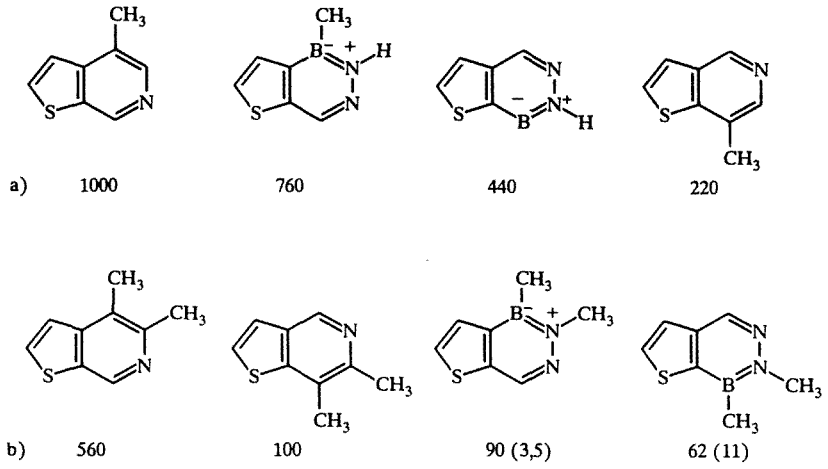
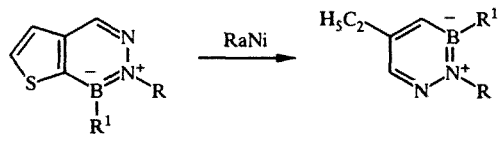


Fig. 6. Pseudo-first order constants ($min^{-1} \times 10^4$) in 95.2% D_2SO_4: a) at 75.0°C, b) at 45.0°C for exchange in the 3-position; in parentheses) exchange of the 2-position.

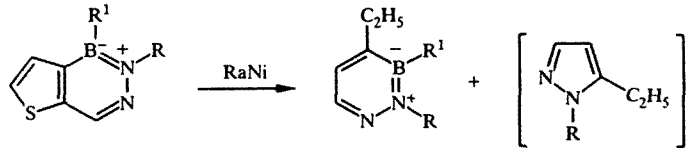
Parallel with our study of the borazaropyridines, the isoelectronic thieno[c]pyridines were prepared [162-164] and their NMR spectra [165] and substitution reactions [166] elucidated. A quantitative study of the rate of electrophilic hydrogen exchange of the borazaro systems and the similarly substituted thiophene analogues of isoquinoline was then undertaken using NMR (Fig. 6). All react in the thiophenic β-position, and the similarities are striking. The parent compounds are more reactive by a factor of two [167].

There was of course again a special plan behind working with thiophene-fused system, which I became familiar with when I started my first research with Arne Fredga, namely to use Raney-nickel desulfurization in order to prepare the monocyclic 3,2-borazaropyridines. This was indeed achieved by a commercial Raney-nickel catalyst LS-35 from, at that time, Liljeholmens stearinfabrik, which had a high desulfurizing effect combined with low hydrogenating properties. We used methanol or ethanol as solvents and used preferentially the B-CH_3 derivatives. The yields were at best around 40-50% (Scheme 31) [168, 169].

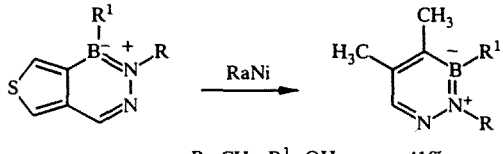
Scheme 31



$R=CH_3$, $R^1=OH$ (43%); R=H, $R^1=OH$ (27%);$R=CH_3$, $R^1=CH_3$ (49%)



$R=CH_3$, $R^1=OH$ (49%); R=H, $R^1=OH$ (34%);$R=CH_3$, $R^1=CH_3$ (44%)



$R=CH_3$; $R^1=OH$ 41%

There was no doubt about the aromatic nature of the 3,2-borazaropyridines. Due to the difficulty in preparing dimethylethylpyridines, we used trimethylpyridines for comparison. The smell of the compounds was the same. The UV spectra were almost identical (Fig. 7).

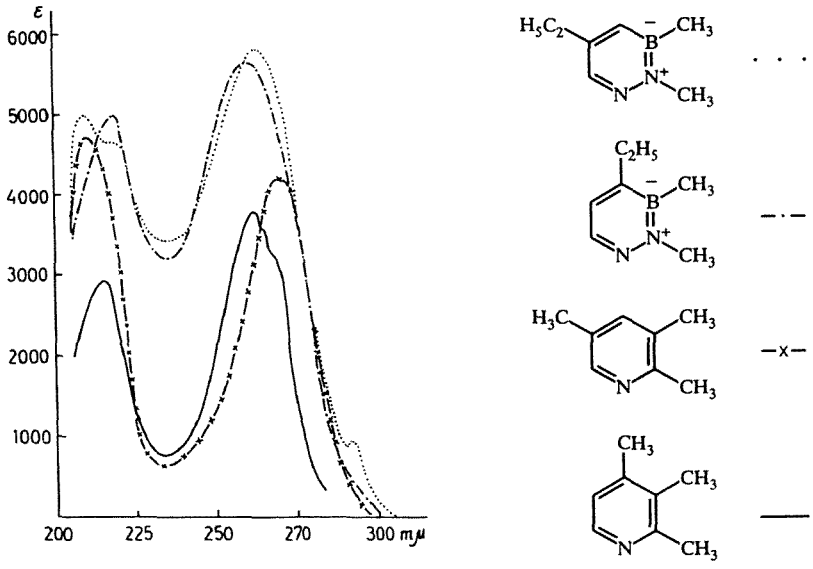


Fig. 7. UV spectra of some 3,2-borazaropyridines and pyridines.

The dipole moments of the borazaropyridines were lower than those of the corresponding pyridines (Scheme 32).

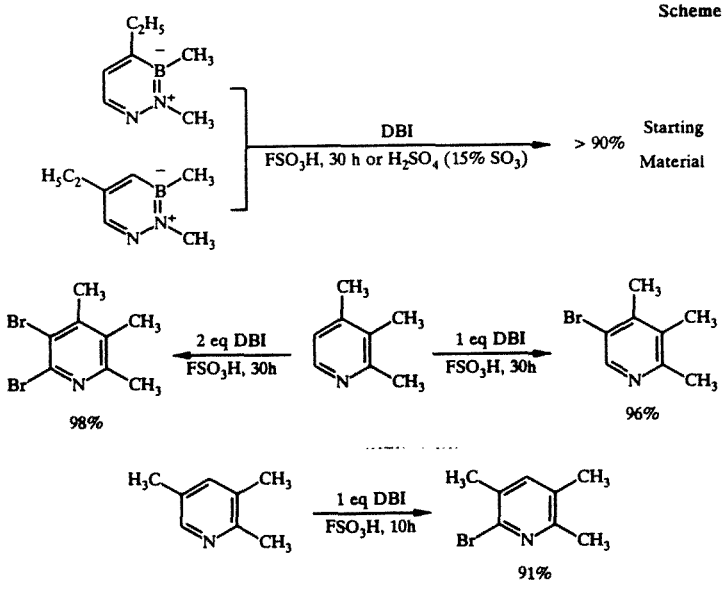
Scheme 32

μ=1,3 D	μ=1,2 D	μ=2,5 D	μ=2,3 D
bp=177–180°C	bp=177–178°C	bp=187°C	bp=184°C
Mw=136,0	Mw=136,0	Mw=121,2	Mw=121,2

This is most probably due to the fact that the B-N-π-moment which is opposed to the pyridinic moment is larger than the B-N-σ-moment, which is in the same direction as the pyridinic dipole moment. As a consequence of the lower polarities the borazaropyridines have lower boiling points than the pyridines although the molecular weight is higher. We have also determined the pKa values in 50% ethanol-water. The borazaropyridines are four powers of ten less basic than the analogue pyridines [169].

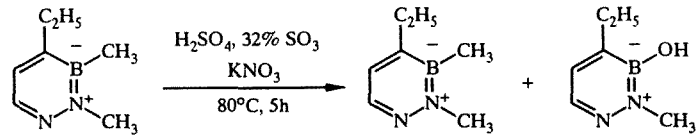
With strong electrophilic reagents which smoothly brominate the pyridines, the borazaropyridines do not react (Scheme 33)[170]. The same is true for nitration with potassium nitrate in oleum; only oxidation of the B-CH_3 group occurs (Scheme 34).

Scheme 33

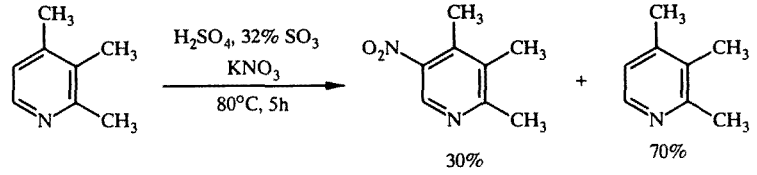


Scheme 34

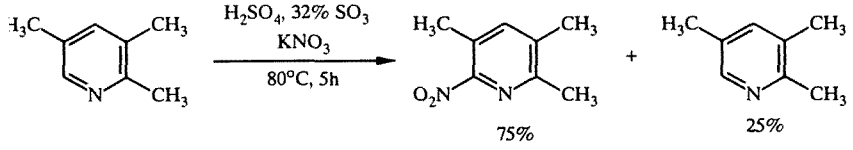
Aromatic substitution, Nitration



< 90% Starting material recovered



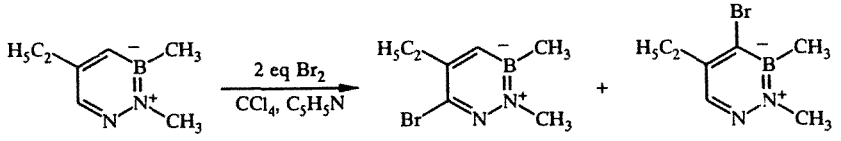
30% 70%



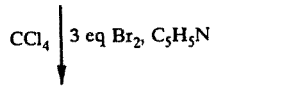
75% 25%

On the other hand, bromination with bromine in pyridine occurred easily but was not very selective, and mixtures of mono- and dibromopyridines were obtained with the 5-ethyl derivative (Scheme 35) [171]. Iodination is more selective and with iodine chloride in pyridine-acetonitrile only iodination in the 4-position was achieved (Scheme 36) [171]. With the 5-ethyl derivative both bromination and nitration occurred in the 6-position. Nitration with N-nitropicolinium fluoroborate in acetonitrile at room temperature (Scheme 37) gave with the 5-ethyl derivative a mixture of 6- and 4-nitro, while the 4-ethyl derivative of course only gave the 6-nitro isomer. I should stress once more that the pyridines do not react under these conditions [161]. Halogen-lithium exchange could be carried out with the halogenated derivatives, and the lithium derivatives used for further functionalization of the 3,2-borazaropyridines [172]. Some heteroaromatic borohydrides were also prepared. They showed no reducing or hydroborating properties [173].

Scheme 35

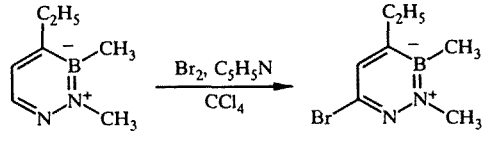


15% 15%



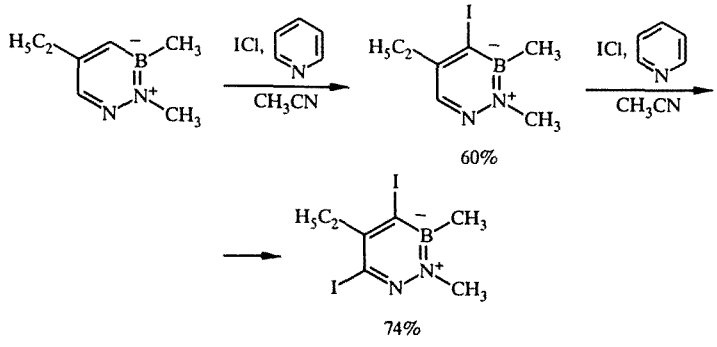
Starting Material

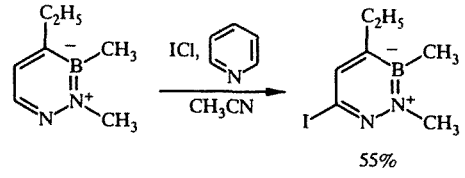
46% 78%



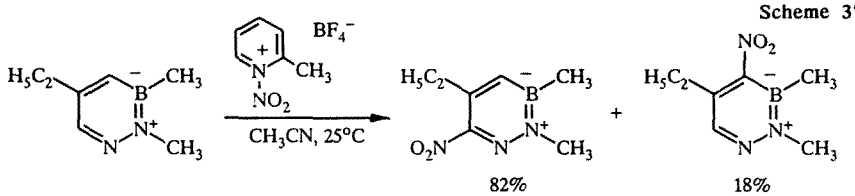
71%

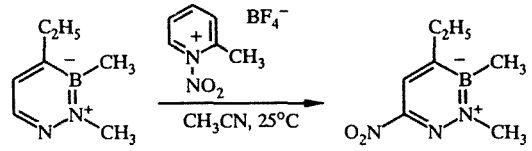
Scheme 36





Scheme 37

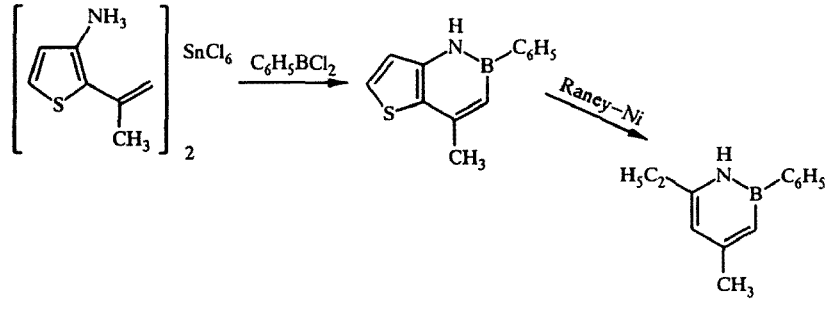


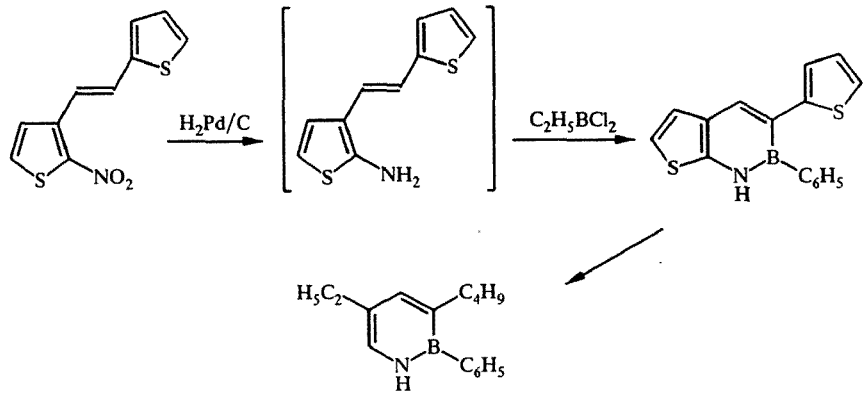


Various brominated borazarothienopyridines have been prepared from the corresponding brominated o-formylthiopheneboronic acids. They could, via bromolithium exchange and nucleophilic substitution, be transformed to chloro and cyano derivatives [174]. The nitro derivatives could be reduced to amino derivatives and functionalized [156].

We also have prepared other heteroaromatic boron compounds. Thus the dithienoborepin, isoelectronic with the dithienotropylium ion, has been prepared from the *cis*-1,2-(3-bromo-2-thienyl)ethene through halogen-metal exchange and reaction with diethylaminoboron dichloride [175, 176]. A number of other thiophene condensed heteroaromatic boron compounds such as 4,5-borazarobenzo[1,2-b;4,3-b']dithiophene [177], 5,4-borazarobenzo[b]thiophene [178], and 6,7-borazarobenzo[b]thiophenes [179] were also prepared and the preparation of monocyclic systems attempted by Raney-nickel desulfurization. Thus 6-phenyl-5-(2-thienyl)-6,7-borazarobenzo[b]thiophene was prepared through reaction of the unstable 1-(2-amino-3-thienyl)-2-(2-thienyl)ethene with phenylboron dichloride. Raney-nickel desulfurization gave 5-ethyl-2-phenyl-2,1-borazarene along with lower homologues [179]. From the hexachlorostannate salt of 3-amino-2-isopropenylthiophene, 7-methyl-5-phenyl-5,4-borazarobenzo[b]thiophene was obtained which upon desulfurization gave 6-ethyl-4-methyl-2-phenyl-2,1-borazaren together with lower homologues (Scheme 38) [178].

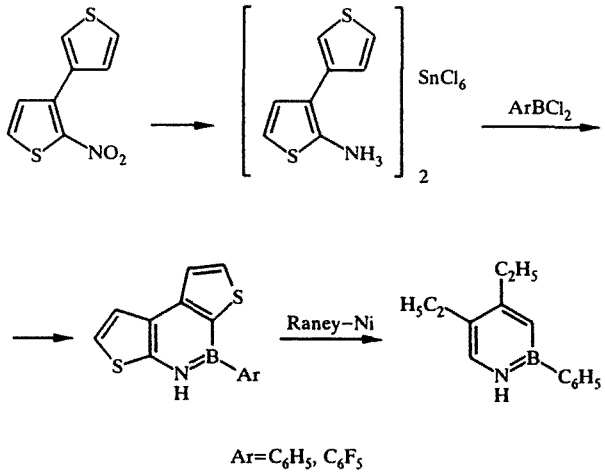
Scheme 38





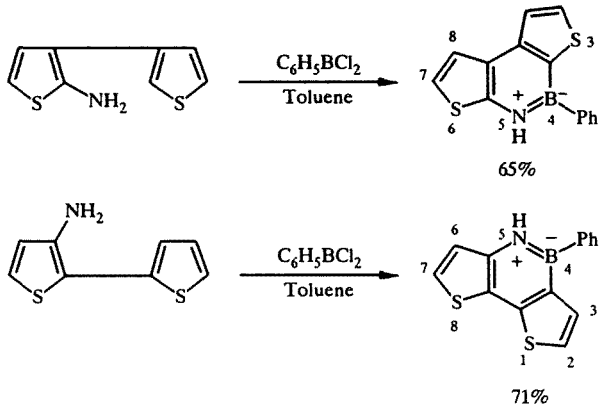
Starting from 2-nitro-3,3-bithienyl reduction to the amino derivative and reaction with arylboron dichloride gave analogues of borazarobenzodithiophenes, which upon Raney-nickel desulfurization gave 2,1-borazarene (Scheme 39) [177]. The whole class of these compounds with different annelation patterns became available when I, together with Professor Paolo Zanirato from the University of Bologna, developed a new synthetic route. Starting from various o-bromobithienyls, which at that time were prepared through coupling of thienyl copper derivatives, halogen-lithium exchange at —70°C, followed by tosyl azide, gave the azido derivatives. These were reduced with hydrogen sulfide to the amino derivatives, which were quite stable [180]. The reaction of the aminobithienyls with phenylboron dichloride then gave the dithienoborazarobenzenes (Scheme 40) [181]. I have summarized our work on heteroaromatic boron compounds in a review [182].

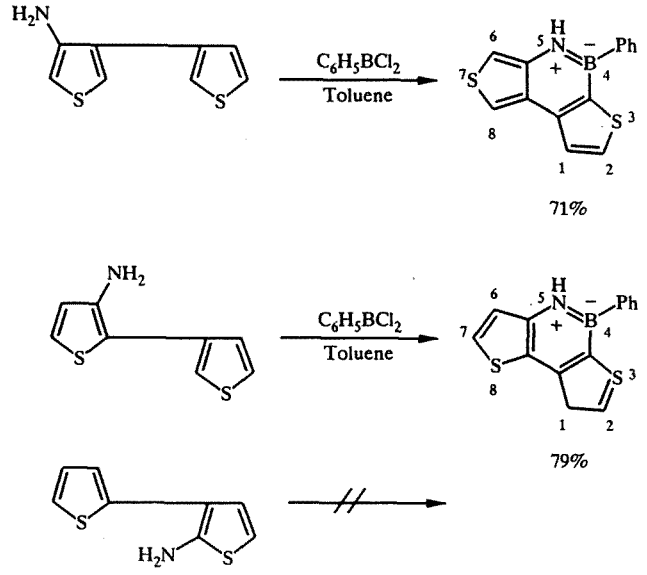
Scheme 39



Ar=C_6H_5, C_6F_5

Scheme 40





Since the beginning of the 1960's, I have been interested in studying the effect of the mode of annelation of various aromatic heterocyclic rings on the b-side and c-side of thiophene and the consequences this has on reactivity and spectroscopic properties. I will summarize this work in a rather condensed form by just mentioning the systems. An early study was concerned with the synthesis, tautomerism, and metallation of thiophene analogues of indene [183, 184]. Thieno[2,3-b]thiophene has been prepared [185] and its ^{13}C NMR spectra [186] as well as the photoelectron spectra [187] of thieno[2,3-b]- and thieno[3,2-c]thiophene, have been studied. NMR spectra [188] of selenolo[2,3-c]thiophene as well as its metallation and Vilsmeier formylation [189] have been studied. Konar has in his thesis carried out extensive work on selonoloselenophenes [190-195]. Substitution reactions, cycloadditions, NMR spectra, and ^{77}Se spectra were analyzed. It was proven that selonolo[3,2-b]selenophene was the selenophene formed as by-product in the synthesis of selenophene [196] from selenium with acetylene [197]. A very convenient method for the synthesis of furo-, thieno-, and selenolo[3,2-b]pyridines has been developed by applying the Friedländer reaction to 3-amino-2-formyl derivatives [198]. Furo-, thieno-, and selenolo[3,2-b]pyrroles were synthesized from 3-azido-2-vinyl derivatives [199]. Thermal decomposition of 3-azido-2-formyl derivatives was used for the preparation of furo-, thieno-, and selenolo[3,2-c]isoxazoles, and their electrophilic substitution reactions were elucidated [200]. The reaction of 3-azido-2-formylthiophene and -selenophene with hydrazine hydrate or by diazotization and subsequent reduction of 3-amino-2-formylthiophene and -selenophene was used for the preparation of thieno- and selenolo[3,2-c]pyrazoles. A study of their reactions was undertaken [201].

With regard to tricyclic compounds, we started with an investigation of the syntheses, acidity, and cycloaddition reaction of thiophene analogues of fluorene [202-206]. We then prepared heterocyclic fused tropylium ions, such as 9H-dithieno[2,2-b;4,5-b']tropylium perchlorate, 4H-dithieno[1,2-b;5,4-b']tropylium perchlorate, 9H-dithieno[2,1-b;4,5-c']-tropylium fluoroborate, and 9H-dithieno[1,2-c';4,5-c']tropylium fluoroborate [207-209], as well as some differently annelated dithienotropylium ions such as 4H-dithieno[2,1-b;3,4-b']tropylium fluoroborate and 7H-dithieno[1,2-b;4,3-b']tropylium fluoroborate [210, 211]. Also furothienotropylium ions and benzothienotropylium ions were prepared [212, 213]. The stabilities, electrophilic deuterations [214], as well as UV spectra [215] of some of the annelated tropylium ions were studied.

A detailed investigation of benzodithiophenes, the thiophene analogues of phenanthrene, has been undertaken. They were prepared from the six *cis*-1,2-di(*ortho*-bromothienyl)ethenes through halogen-lithium exchange followed by reaction with cupric chloride [216]. Electrophilic substitution reactions and cycloadditions [217], as well as electronic spectra, were elucidated [218].

Through the use of Pd(0)-catalyzed coupling reactions, tricyclic heterocyclic systems, previously unknown, became very easily available, and during the last ten years extensive work on the reactivity and spectral properties have been carried out in order to understand the influence of the mode of annelation. Thus convenient methods for the preparation of phenanthridine and some benzo- and thieno-c-fused quinolines [219], of phenanthridine-N-oxide and some thieno-fused analogues [220] and of isomeric dithiophene analogues of phenanthridine-N-oxides [221] have been found. All nine isomeric dithienopyridines with angular annelation pattern were thus prepared [222-224]. Detailed NMR studies, also leading to the determination of all $^{13}C—^{13}C$ coupling constants of thieno[c]quinolines and -isoquinolines [225] and of the nine dithieno-

pyridines [226] were carried out. Recently the He I photoelectron spectra of these nine isomers were studied and the structure for two of them determined by X-ray crystallography [227]. Nitration of the six thieno-fused analogues of phenanthridine-N-oxide [228] and their bromination [229] and NMR spectra [230] have been studied. Experimental and theoretical studies of the orientation in nitration of five of the isomeric dithienopyridine and of some of their N-oxides were carried out [231-236]. Bromination [237, 238] of some dithieno[b,d]pyridines has been studied as well as halogen-lithium exchange [239]. Experimental and theoretical studies of the orientation in lithiation of dithieno[2,3-b;3',2'-d]pyridine agreed with the experimental results [240].

Through the Pd(0)-catalyzed reaction between o-formylthiopheneboronic acids or o-formyltrialkylstannylthiophenes and o-amino-bromopyridine derivatives all twelve thieno[c]naphthyridines have been prepared [241, 242]. All twelve thieno[b]naphthyridines have similarly been prepared in a one-pot reaction from o-formyltrimethylstannyl derivatives and t-butyl-N-(o-halothienyl)carbamates [243]. The effect of cocatalysts such as silver oxide [244] and especially cupric oxide [245] on yields and rates was elucidated. Thieno[c]fused 1,5-naphthyridine-9-oxides and 5-oxides have been prepared [246], and bromination of both the N-oxides and parent compounds has been studied [247, 248]. The work on these tricyclic compounds has recently been reviewed in detail [249].

REFERENCES

1. Gronowitz S., Arkiv Kemi, 1953, Vol. 6, P. 283.
2. Gronowitz S., Larsson S., Arkiv Kemi, 1955, Vol. 8, P. 567.
3. Gronowitz S., Arkiv Kemi, 1958, Vol. 13, P. 87.
4. Gronowitz S., Arkiv Kemi, 1958, Vol. 13, P. 231.
5. Campaigne E., LeSuer W. E. M., J. Amer. Chem. Soc., 1948, Vol. 70, P. 1555.
6. Gronowitz S., Arkiv Kemi, 1954, Vol. 7, P. 267.
7. Gronowitz S., Arkiv Kemi, 1954, Vol. 7, P. 361.
8. Moses P., Gronowitz S., Arkiv Kemi, 1961, Vol. 18, P. 119.
9. Gronowitz S., Moses P., Hörnfeldt A.-B., Hakansson R., Arkiv Kemi, 1961, Vol. 17, P. 165.
10. Gronowitz S., Rosen U., Chem. Scr., 1971, Vol. 1, P. 33.
11. Gronowitz S., Karlsson H.-O., Arkiv Kemi, 1961, Vol. 17, P. 89.
12. Gronowitz S., Acta Chem. Scand., 1961, Vol. 15, P. 1393.
13. Gronowitz S., Hörnfeldt A.-B., Petterson K., Synth. Commun., 1973, Vol. 3, P. 213.
14. Gronowitz S., Beizais A., Mathiasson B., Arkiv Kemi, 1963, Vol. 21, P. 265.
15. Michael U., Gronowitz S., Acta Chem. Scand., 1968, Vol. 22, P. 1353.
16. Gronowitz S., Holm B., Acta Chem. Scand., 1969, Vol. 23, P. 2207.
17. Gronowitz S., Holm B., Acta Chem. Scand., 1976, Vol. B 30, P. 505.
18. Gronowitz S., Petterson K., J. Heterocycl. Chem., 1976, Vol. 13, P. 1099.
19. Gronowitz S., Gederlund B., Hörnfeldt A.-B., Chem. Scr., 1964, Vol. 5, P. 217.
20. Gronowitz S., Holm B., Chem. Scr., 1972, Vol. 2, P. 245.
21. Gronowitz S., Holm B., Chem. Scr., 1974, Vol. 6, P. 133.
22. Gronowitz S., Holm B., Synth. Commun., 1974, Vol. 4, P. 63.
23. Gronowitz S., Holm B., Tetrahedron, 1977, Vol. 33, P. 537.
24. Gronowitz S., Holm B., J. Heterocycl. Chem., 1977, Vol. 14, P. 281.
25. Gronowitz S., Halvarson K., Arkiv Kemi, 1955, Vol. 8, P. 343.
26. Gronowitz S., Arkiv Kemi, 1958, Vol. 12, P. 239.
27. Gronowitz S., Arkiv Kemi, 1958, Vol. 13, P. 269.
28. Gronowitz S., Gestblom B., Mathiasson B., Arkiv Kemi, 1963, Vol. 20, P. 407.
29. Gronowitz S., Eriksson B., Arkiv Kemi, 1963, Vol. 21, P. 335.
30. Gronowitz S., Rosenberg A., Arkiv Kemi, 1955, Vol. 8, P. 23.
31. Gronowitz S., Katritzky A. R., Reavill R. E., J. Chem. Soc., 1963, P. 3881.
32. Gronowitz S., Arkiv Kemi, 1958, Vol. 13, P. 239.
33. Gronowitz S., Hoffman R. A., Arkiv Kemi, 1958, Vol. 13, P. 279.

34. Gronowitz S., Hoffman R. A., Arkiv Kemi, 1959, Vol. 15, P. 45.
35. Hoffman R. A., Gronowitz S., Arkiv Kemi, 1960, Vol. 16, P. 501.
36. Hoffman R. A., Gronowitz S., Arkiv Kemi, 1960, Vol. 16, P. 515.
37. Gronowitz S., Hoffman R. A., Arkiv Kemi, 1960, Vol. 16, P. 539.
38. Hoffman R. A., Gronowitz S., Arkiv Kemi, 1960, Vol. 16, P. 563.
39. Gronowitz S., Sörlin G., Gestblom B., Hoffman R. A., Arkiv Kemi, 1962, Vol. 19, P. 483.
40. Rodmar S., Forsen S., Gestblom B., Gronowitz S., Hoffman R. A., Acta Chem. Scand., 1965, Vol. 19, P. 485.
41. Hoffman R. A., Gronowitz S., J. Amer. Chem. Soc., 1961, Vol. 83, P. 3910.
42. Gronowitz S., Gestblom B., Hoffman R. A., Acta Chem. Scand., 1961, Vol. 15, P. 1201.
43. Hoffman R. A., Gestblom B., Gronowitz S., Forsen S., J. Molecular Spectr., 1963, Vol. 11, P. 454.
44. Forsen S., Gestblom B., Gronowitz S., Hoffman R. A., Acta Chem. Scand., 1964, Vol. 18, P. 313.
45. Gestblom B., Gronowitz S., Hoffman R. A., Mathiasson B., Rodmar S., Arkiv Kemi, 1965, Vol. 23, P. 483.
46. Gestblom B., Gronowitz S., Hoffman R. A., Rodmar S., Arkiv Kemi, 1965, Vol. 23, P. 501.
47. Mathiasson B., Gronowitz S., Hoffman R. A., Mathiasson B., Arkiv Kemi, 1965, Vol. 23, P. 517.
48. Rodmar S., Rodmar B., Khan A. A., Gronowitz S., Pavulans V., Acta Chem. Scand., 1966, Vol. 20, P. 2515.
49. Gronowitz S., Rosen U., Chem. Scr., 1971, Vol. 1, P. 33.
50. Gronowitz S., Rodmar S., Moraga L., Rosen U., Acta Chem. Scand., 1971, Vol. 25, P. 3309.
51. Rodmar S., Rodmar B., Sharma M. K., Gronowitz S., Christiansen H., Rosen U., Acta Chem. Scand., 1968, Vol. 22, P. 907.
52. Christiansen H., Gronowitz S., Rodmar B., Rodmar S., Rosen U., Sharma M. K., Arkiv Kemi, 1969, Vol. 30, P. 561.
53. Rodmar S., Gronowitz S., Rosen U., Acta Chem. Scand., 1971, Vol. 25, P. 3841.
54. Gronowitz S., Johnson I., Rodmar S., Acta Chem. Scand., 1972, Vol. 26, P. 1726.
55. Gronowitz S., Johnson I., Hörnfeldt A.-B., Chem. Scr., 1975, Vol. 7, P. 76.
56. Gronowitz S., Johnson I., Hörnfeldt A.-B., Chem. Scr., 1975, Vol. 7, P. 111.
57. Gronowitz S., Johnson I., Hörnfeldt A.-B., Chem. Scr., 1975, Vol. 7, P. 211.
58. Fringuelli F., Gronowitz S., Hörnfeldt A.-B., Johnson I., Taticchi A., Acta Chem. Scand., 1974, Vol. 28, P. 175.
59. Fringuelli F., Gronowitz S., Hörnfeldt A.-B., Johnson I., Taticchi A., Acta Chem. Scand., 1976, Vol. B 30, P. 605.
60. Gronowitz S., Johnson I., Hörnfeldt A.-B., Chem. Scr., 1973, Vol. 3, P. 94.
61. Gronowitz S., Johnson I., Hörnfeldt A.-B., Chem. Scr., 1975, Vol. 8, P. 8.
62. Frakenberg T., Fringuelli F., Gronowitz S., Hörnfeldt A.-B., Johnson I., Taticchi A., Chem. Scr., 1976, Vol. 10, P. 139.
63. Kues W., Paal C., Chem. Ber, 1886, Bd 19, S. 555.
64. Steinkopf W., Thormann F., Ann., 1939, Bd 540, S. 1.
65. Gronowitz S., Hoffman R. A., Arkiv Kemi, 1960, Vol. 15, P. 499.
66. Gronowitz S., Hörnfeldt A.-B., Acta Chem. Scand., 1962, Vol. 16, P. 789.
67. Gronowitz S., Hörnfeldt A.-B., Arkiv Kemi, 1963, Vol. 21, P. 239.
68. Hörnfeldt A.-B., Arkiv Kemi, 1964, Vol. 22, P. 211.
69. Hörnfeldt A.-B., Acta Chem. Scand., 1967, Vol. 21, P. 673.
70. Hörnfeldt A.-B., Arkiv Kemi, 1968, Vol. 29, P. 461.
71. Hörnfeldt A.-B., Arkiv Kemi, 1968, Vol. 29, P. 455.
72. Hörnfeldt A.-B., Arkiv Kemi, 1968, Vol. 29, P. 229.
73. Hörnfeldt A.-B., Arkiv Kemi, 1968, Vol. 29, P. 427.
74. Hörnfeldt A.-B., Arkiv Kemi, 1968, Vol. 29, P. 247.
75. Hörnfeldt A.-B., Arkiv Kemi, 1968, Vol. 28, P. 363.
76. Hörnfeldt A.-B., Acta Chem. Scand., 1967, Vol. 21, P. 1953.
77. Cederlund B., Hörnfeldt A.-B., Acta Chem. Scand., 1971, Vol. 25, P. 3546.
78. Cederlund B., Hörnfeldt A.-B., Acta Chem. Scand., 1971, Vol. 25, P. 3324.
79. Cederlund B., Jesperson A., Hörnfeldt A.-B., Acta Chem. Scand., 1971, Vol. 25, P. 3656.
80. Cederlund B., Hörnfeldt A.-B., Chem. Scr., 1973, Vol. 8, P. 140.
81. Gronowitz S., Cynkier I., Hörnfeldt A.-B., Chem. Scr., 1983, Vol. 22, P. 129.

82. Lantz R., Hörnfeldt A.-B., Chem. Scr., 1972, Vol. 2, P. 9.
83. Lantz R., Hörnfeldt A.-B., Chem. Scr., 1976, Vol. 10, P. 126.
84. Thorstad O., Undheim K., Cederlund B., Hörnfeldt A.-B., Acta Chem. Scand., 1975, Vol. B 29, P. 647.
85. Thorstad O., Undheim K., Lantz R., Hörnfeldt A.-B., Acta Chem. Scand., 1975, Vol. B 29, P. 652.
86. Cederlund B., Lantz R., Hörnfeldt A.-B., Thorstad O., Undheim K., Acta Chem. Scand., 1977, Vol. B 31, P. 198.
87. Gronowitz S., Zhang Y., Hörnfeldt A.-B., Acta Chem. Scand., 1992, Vol. 46, P. 654.
88. Zhang Y., Hörnfeldt A.-B., Gronowitz S., J. Heterocycl. Chem., 1993, Vol. 30, P. 1293.
89. Gronowitz S., Frostling H., Tetrah. Lett., 1961, P. 604.
90. Gronowitz S., Gustafson P., Arkiv Kemi, 1963, Vol. 20, P. 289.
91. Gronowitz S., Dahlgren K., Arkiv Kemi, 1963, Vol. 21, P. 201.
92. Gronowitz S., Hagen S., Arkiv Kemi, 1967, Vol. 27, P. 153.
93. Gronowitz S., Arkiv Kemi, 1965, Vol. 23, P. 307.
94. Gronowitz S., Beselin R., Arkiv Kemi, 1963, Vol. 21, P. 349.
95. Gronowitz S., Skramstad J., Arkiv Kemi, 1967, Vol. 28, P. 115.
96. Gronowitz S., Hansen G., Arkiv Kemi, 1967, Vol. 27, P. 145.
97. Hakansson R., in: Thiophene and Its Derivatives, S. Gronowitz (ed.), Vol. 44, Part 5, P. 755.
98. Gronowitz S., Gjos N., Acta Chem. Scand., 1967, Vol. 21, P. 2823.
99. Gronowitz S., Gjos N., Acta Chem. Scand., 1967, Vol. 21, P. 2893.
100. Gronowitz S., Gjos N., Arkiv Kemi, 1968, Vol. 30, P. 225.
101. Gronowitz S., Gjos N., Acta Chem. Scand., 1970, Vol. 24, P. 99.
102. Gjos N., Gronowitz S., Acta Chem. Scand., 1972, Vol. 26, P. 1851.
103. Gronowitz S., Boler J., Arkiv Kemi, 1968, Vol. 28, P. 587.
104. Gronowitz S., Liljefors S., Acta Chem. Scand., 1977, Vol. B 31, P. 771.
105. Gronowitz S., Liljefors S., Chem. Scr., 1978-1979, Vol. 13, P. 39.
106. Gronowitz S., Liljefors S., Chem. Scr., 1978-1979, Vol. 13, P. 157.
107. Gronowitz S., Liljefors S., Chem. Scr., 1980, Vol. 15, P. 102.
108. Gronowitz S., Lawitz K., Chem. Scr., 1983, Vol. 22, P. 265.
109. Gronowitz S., Bodosic V., Lawitz K., Chem. Scr., 1984, Vol. 32, P. 120.
110. Gronowitz S., Lawitz K., Chem. Scr., 1984, Vol. 24, P. 5.
111. Gronowitz S., Peters D., Hörnfeldt A.-B., J. Heterocycl. Chem., 1990, Vol. 27, P. 2165.
112. Peters D., Hörnfeldt A.-B., Gronowitz S., Heterocycles, 1990, Vol. 30, P. 645.
113. Peters D., Hörnfeldt A.-B., Gronowitz S., J. Heterocycl. Chem., 1991, Vol. 28, P. 1613.
114. Gronowitz S., Frejd T., Acta Chem. Scand., 1969, Vol. 23, P. 2540.
115. Gronowitz S., Frejd T., Acta Chem. Scand., 1970, Vol. 24, P. 2656.
116. Gronowitz S., Frejd T., Int. J. Sulfur Chem., 1972, Vol. A 2, P. 165.
117. Gronowitz S., Frejd T., Acta Chem. Scand., 1972, Vol. 26, P. 2279.
118. Gronowitz S., Frejd T., Acta Chem. Scand., 1976, Vol. B 30, P. 287.
119. Gronowitz S., Frejd T., Acta Chem. Scand., 1976, Vol. B 30, P. 313.
120. Gronowitz S., Frejd T., Acta Chem. Scand., 1976, Vol. B 30, P. 439.
121. Gronowitz S., Frejd T., Acta Chem. Scand., 1976, Vol. B 30, P. 485.
122. Gronowitz S., Frejd T., Acta Chem. Scand., 1973, Vol. 27, P. 2242.
123. Frejd T., J. Heterocycl. Chem., 1977, Vol. 14, P. 1085.
124. Frejd T., Karlsson J. O., Acta Chem. Scand., 1983, Vol. B 37, P. 895.
125. Frejd T., Karlsson J. O., Gronowitz S., J. Org. Chem., 1981, Vol. 46, P. 3132.
126. Gronowitz S., Hallberg A., Frejd T., Chem. Scr., 1980, Vol. 15, P. 1.
127. Hallberg A., Frejd T., Gronowitz S., J. Chem. Soc. Perkin Trans. I, 1980, P. 1390.
128. Karlsson J. O., Gronowitz S., Frejd T., J. Org. Chem., 1982, Vol. 47, P. 374.
129. Gronowitz S., Frejd T., Karlsson O., Lawitz K., Pedaja P., Pettersson K., Chem. Scr., 1981, Vol. 18, P. 192.
130. Karlsson J. O., Svensson A., Gronowitz S., J. Org. Chem., 1984, Vol. 49, P. 2018.
131. Gronowitz S., Svensson A., Israel J. Chem., 1986, Vol. 27, P. 25.
132. Hallberg A., Frejd T., Gronowitz S., Chem. Scr., 1978-1979, Vol. 13, P. 186.

133. Gronowitz S., Hallberg A., Frejd T., Tetrahedron, 1979, Vol. 35, P. 2607.
134. Frejd T., Chem. Scr., 1976, Vol. 10, P. 133.
135. Gronowitz S., Frejd T., Acta Chem. Scand., 1975, Vol. B 29, P. 818.
136. Gronowitz S., Frejd T., Khim. Geterotsikl. Soedinenii, 1978, No. 00, S. 435.
137. Frejd T., The Chemistry of Heterocyclic Compounds, Volume 44: Thiophene and Its Derivatives, Part 5, P. 257, Salo Gronowitz (ed.), 1992.
138. Karlsson J. O., Gronowitz S., Hallberg A., Acta Chem. Scand., 1982, Vol. B 36, P. 341.
139. Karlsson J. O., Gronowitz S., Hallberg A., Chem. Scr., 1982, Vol. 20, P. 37.
140. Gronowitz S., Nikitidis G., Hallberg A., Stalhandske C., Acta Chem. Scand., 1991, Vol. 45, P. 636.
141. Gronowitz S., Nikitidis G., Hallberg A., Stalhandske C., Acta Chem. Scand., 1991, Vol. B 41, P. 297.
142. Gronowitz S., Hallberg A., Nikitidis G., Tetrahedron, 1987, Vol. 43, P. 493.
143. Gronowitz S., Nikitidis G., Hallberg A., Chem. Scr., 1988, Vol. 28, P. 289.
144. Gronowitz S., Bugarcic Z., Hörnfeldt A.-B., J. Heterocycl. Chem., 1992, Vol. 29, P. 1077.
145. Gronowitz S., Nikitidis G., Hallberg A., Servin R., J. Org. Chem., 1988, Vol. 53, P. 3351.
146. Gronowitz S., Nikitidis G., Hallberg A., Stalhandske C., Acta Chem. Scand., 1991, Vol. 45, P. 636.
147. Gronowitz S., Nikitidis G., Hallberg A., Acta Chem. Scand., 1991, Vol. 45, P. 632.
148. Gronowitz S., Phosphorus, Sulfur and Silicon, 1993, Vol. 74, P. 113.
149. Dewar M. J. S., Steinberg H., McCloskey A. L. (eds.), Progress in Boron Chemistry, Pergamon Press, 1964, Vol. 1, P. 235.
150. Dewar M. J. S., Dougherty R. C., J. Amer. Chem. Soc., 1964, Vol. 86, P. 433.
151. Gronowitz S., Bugge A., Acta Chem. Scand., 1965, Vol. 19, P. 1271.
152. Gronowitz S., Roos C., Acta Chem. Scand., 1975, Vol. 29, P. 990.
153. Gronowitz S., Namtvedt J., Acta Chem. Scand., 1967, Vol. 21, P. 2151.
154. Gronowitz S., Dahlgren T., Namtvedt J., Roos C., Sjögren B., Forsgren U., Acta Pharm. Suecica, 1971, Vol. 8, P. 377.
155. Gronowitz S., Dahlgren T., Namtvedt J., Roos C., Rosen G., Sjöberg B., Forsgren U., Acta Pharm. Suecica, 1971, Vol. 8, P. 623.
156. Gronowitz S., Glennow C., Acta Pharm. Suecica, 1978, Vol. 15, P. 287.
157. Aurivillius B., Löfving I., Acta Chem. Scand., 1974, Vol. B 28, P. 989.
158. Gronowitz S., Namtvedt J., Tetrah. Lett, 1966, P. 2967.
159. Gronowitz S., Namtvedt J., Acta Chem. Scand., 1966, Vol. 20, P. 1448.
160. Namtvedt J., Acta Chem. Scand., 1968, Vol. 22, P. 1611.
161. Gronowitz S., Maltesson A., Acta Chem. Scand., 1975, Vol. B 29, P. 457.
162. Gronowitz S., Sandberg E., Arkiv Kemi, 1970, Vol. 32, P. 217.
163. Sandberg E., Chem. Scr., 1972, Vol. 2, P. 241.
164. Sandberg E., Chem. Scr., 1975, Vol. 7, P. 223.
165. Gronowitz S., Sandberg E., Arkiv Kemi, 1970, Vol. 32, P. 269.
166. Gronowitz S., Sandberg E., Arkiv Kemi, 1970, Vol. 32, P. 249.
167. Gronowitz S., Roos C., Sandberg E., Clementi S., J. Heterocycl. Chem., 1977, Vol. 14, P. 893.
168. Namtvedt J., Gronowitz S., Acta Chem. Scand., 1968, Vol. 22, P. 1373.
169. Gronowitz S., Maltesson A., Acta Chem. Scand., 1971, Vol. 25, P. 2435.
170. Gronowitz S., Maltesson A., Chem. Scr., 1972, Vol. 2, P. 79.
171. Gronowitz S., Maltesson A., Acta Chem. Scand., 1975, Vol. B 29, P. 461.
172. Gronowitz S., Maltesson A., Acta Chem. Scand., 1975, Vol. B 29, P. 1036.
173. Gronowitz S., Maltesson A., Acta Chem. Scand., 1977, Vol. 31, P. 765.
174. Gronowitz S., Glennow C., Chem. Scr., 1977, Vol. 11, P. 76.
175. Gronowitz S., Gassne P., Yom-Tov B., Acta Chem. Scand., 1969, Vol. 23, P. 2927.
176. Gronowitz S., Jeffries A. T., Chem. Scr., 1973, Vol. 4, P. 183.
177. Gronowitz S., Ander I., Chem. Scr., 1980, Vol. 15, P. 23.
178. Gronowitz S., Ander I., Chem. Scr., 1980, Vol. 15, P. 135.
179. Gronowitz S., Ander I., Chem. Scr., 1980, Vol. 15, P. 145.

180. Gronowitz S., Spagnolo P., Zanirato P., J. Org. Chem., 1982, Vol. 47, P. 3177.
181. Gronowitz S., Ander I., Zanirato P., Chem. Scr., 1983, Vol. 22, P. 55.
182. Gronowitz S., J. Heterocycl. Chem., 1975, Vol. 125, P. 17.
183. Gronowitz S., Meth-Cohn O., Acta Chem. Scand., 1966, Vol. 20, P. 1577.
184. Gronowitz S., Meth-Cohn O., Acta Chem. Scand., 1966, Vol. 20, P. 1733.
185. Gronowitz S., Persson B., Acta Chem. Scand., 1967, Vol. 21, P. 812.
186. Gronowitz S., Johnson I., Bugge A., Acta Chem. Scand., 1976, Vol. B 30, P. 417.
187. Gleiter R., Kobayashi M., Spanget-Larsen J., Gronowitz S., Konar A., Farnier M., J. Org. Chem., 1977, Vol. 42, P. 2230.
188. Gronowitz S., Konar A., Abroni I. A., Litvinov V. P., Izv. Akad. Nauk SSSR. Ser. Khim., 1981, P. 1285.
189. Gronowitz S., Konar A., Litvinov V. P., Izv. Akad. Nauk SSSR. Ser. Khim., 1981, P. 1363.
190. Gronowitz S., Konar A., Chem. Commun., 1977, P. 163.
191. Gronowitz S., Konar A., Hörnfeldt A.-B., Chem. Scr., 1982, Vol. 19, P. 5.
192. Gronowitz S., Konar A., Litvinov V. P., Chem. Scr., 1980, Vol. 15, P. 206.
193. Gronowitz S., Konar A., Tetrahedron, 1980, Vol. 36, P. 3317.
194. Gronowitz S., Konar A., Chem. Scr., 1984, Vol. 23, P. 5.
195. Gronowitz S., Johannsen I., Eggert H., Hörnfeldt A.-B., Chem. Scr., 1987, Vol. 27, P. 359.
196. Gronowitz S., Frejd T., Moberg-Ogard A., Trege L., J. Heterocycl. Chem., 1976, Vol. 13, P. 1319
197. Gronowitz S., Frejd T., Hörnfeldt A.-B., Chem. Scr., 1974, Vol. 5, P. 236.
198. Gronowitz S., Westerlund C., Hörnfeldt A.-B., Acta Chem. Scand., 1975, Vol. 29, P. 233.
199. Gronowitz S., Westerlund C., Hörnfeldt A.-B., Acta Chem. Scand., 1976, Vol. B 30, P. 391.
200. Gronowitz S., Westerlund C., Hörnfeldt A.-B., Chem. Scr., 1976, Vol. 10, P. 165.
201. Gronowitz S., Westerlund C., Hörnfeldt A.-B., Chem. Scr., 1977, Vol. 12, P. 1.
202. Gronowitz S., Skramstad J. E., Eriksson B., Arkiv Kemi, 1967, Vol. 28, P. 99.
203. Gronowitz S., Wiersema A., Acta Chem. Scand., 1969, Vol. 23, P. 2923.
204. Gronowitz S., Wiersema A., Acta Chem. Scand., 1970, Vol. 24, P. 2593.
205. Gronowitz S., Wiersema A., Acta Chem. Scand., 1970, Vol. 24, P. 2653.
206. Gronowitz S., Wiersema A., Acta Chem. Scand., 1971, Vol. 25, P. 1195.
207. Gronowitz S., Yom-Tov B., Chem. Scr., 1973, Vol. 3, P. 37.
208. Gronowitz S., Yom-Tov B., Chem. Scr., 1973, Vol. 3, P. 165.
209. Yom-Tov B., Gronowitz S., J. Heterocycl. Chem., 1978, Vol. 15, P. 285.
210. Gronowitz S., Pedaja P., Tetrahedron, 1978, Vol. 34, P. 587.
211. Pedaja P., Gronowitz S., Chem. Scr., 1982, Vol. 20, P. 53.
212. Gronowitz S., Michael U., Chem. Scr., 1973, Vol. 4, P. 126.
213. Pedaja P., Gronowitz S., Chem. Scr., 1983, Vol. 22, P. 53.
214. Gronowitz S., Yom-Tov B., Michael U., Acta Chem. Scand., 1973, Vol. 27, P. 2257.
215. Liljefors T., Michael U., Yom-Tov B., Gronowitz S., Acta Chem. Scand., 1973, Vol. 27, P. 2485.
216. Gronowitz S., Dahlgren T., Chem. Scr., 1977, Vol. 12, P. 57.
217. Gronowitz S., Dahlgren T., Chem. Scr., 1977, Vol. 12, P. 97.
218. Dahlgren T., Glans J., Gronowitz S., Davidson A., Norden B., Pedersen P. B., Thulstrup E. W., Chem. Phys, 1979, Vol. 40, P. 397.
219. Gronowitz S., Hörnfeldt A.-B., Yang Y., Chem. Scr., 1986, Vol. 26, P. 311.
220. Gronowitz S., Hörnfeldt A.-B., Yang Y.-H., Chem. Scr., 1986, Vol. 26, P. 383.
221. Gronowitz S., Hörnfeldt A.-B., Yang Y., Croatica Chim. Acta, 1986, Vol. 59, P. 313.
222. Gronowitz S., Yang Y., Hörnfeldt A.-B., Chem. Scr., 1988, Vol. 28, P. 275.
223. Gronowitz S., Yang Y., Hörnfeldt A.-B., Chem. Scr., 1988, Vol. 28, P. 281.
224. Yang Y., Hörnfeldt A.-B., Gronowitz S., Synthesis, 1989, P. 130.
225. Gronowitz S., Servin R., Yang Y., Magn. Reson. Chem., 1989, Vol. 27, P. 1099.
226. Gronowitz S., Hörnfeldt A.-B., Yang Y., Edlund U., Eliasson B., Johnels D., Magn. Reson. Chem., 1990, Vol. 28, P. 33.
227. Brett W. A., Rademacher P., Boese R., Gronowitz S., Yang Y., J. Chem. Soc. Perkin II, 1994, P. 2051.

228. Gronowitz S., Timari G., Chem. Scr., 1989, Vol. 29, P. 305.
229. Gronowitz S., Timari G., Chem. Scr., 1989, Vol. 29, P. 309.
230. Gronowitz S., Timari G., J. Heterocycl. Chem., 1990, Vol. 27, P. 1127.
231. Szabo K. J., Hörnfeldt A.-B., Gronowitz S., J. Org. Chem., 1991, Vol. 56, P. 1590.
232. Gronowitz S., Szabo K. J., Oluwadiya J. O., J. Heterocycl. Chem., 1991, Vol. 28, P. 351.
233. Szabo K. J., Hörnfeldt A.-B., Gronowitz S., J. Mol. Structure, 1992, Vol. 258, P. 67.
234. Szabo K. J., Hörnfeldt A.-B., Gronowitz S., J. Chem. Soc. Perkin Trans. II, 1992, P. 1875.
235. Szabo K. J., Gronowitz S., J. Heterocycl. Chem., 1993, Vol. 30, P. 561.
236. Gronowitz S., Szabo K. J., Olugbade T. A., J. Heterocycl. Chem., 1992, Vol. 29, P. 1635.
237. Gronowitz S., Hörnfeldt A.-B., Temciuc E., J. Heterocycl. Chem., 1993, Vol. 30, P. 533.
238. Szabo K. J., Gronowitz S., Hassan M. A., J. Heterocycl. Chem., 1993, Vol. 30, P. 543.
239. Gronowitz S., Temciuc E., Hörnfeldt A.-B., J. Heterocycl. Chem., 1994, Vol. 31, P. 167.
240. Gronowitz S., Szabo K. J., Hassan M. A., J. Org. Chem., 1992, Vol. 57, P. 4552.
241. Gronowitz S., Malm J., Hörnfeldt A.-B., Collect. Czech Chem. Commun., 1991, Vol. 56, P. 2340.
242. Malm J., Rehn B., Hörnfeldt A.-B., Gronowitz S., J. Heterocycl. Chem., 1994, Vol. 31, P. 11.
243. Björk P., Hörnfeldt A.-B., Gronowitz S., J. Heterocycl. Chem., 1994, Vol. 31, P. 1135.
244. Malm J., Björk P., Gronowitz S., Hörnfeldt A.-B., Tetrahedron Lett., 1992, Vol. 33, P. 2199.
245. Gronowitz S., Björk P., Malm J., Hörnfeldt A.-B., J. Organomet. Chem., 1993, Vol. 460, P. 127.
246. Malm J., Hörnfeldt A.-B., Gronowitz S., Heterocycles, 1993, Vol. 35, P. 245.
247. Malm J., Hörnfeldt A.-B., Gronowitz S., J. Heterocycl. Chem., 1994, Vol. 31, P. 521.
248. Malm J., Hörnfeldt A.-B., Gronowitz S., Heterocycles, 1994, Vol. 37, P. 331.
249. Gronowitz S., J. Heterocycl. Chem., 1994, Vol. 31, P. 641.