Reactions of Unsaturated Carbanions with Isothiocyanates: A New Avenue to Fundamental Heterocycles

Boris A. Trofimov

Irkutsk Institute of Chemistry, Russian Academy of Sciences, Siberian Branch*,
Favorsky Street, 1, 664033, Irkutsk, Russia

J. Heterocyclic Chem., **36**, 1469 (1999).

Introduction.

A number of syntheses of fundamental heterocycles are known to be based on diverse rearrangements of heterodiene or -triene systems. These are, for instance, the Fischer-Piloty reaction leading to indoles and pyrroles *via* prototropic and [3,3] sigmatropic shifts in diaza-1,3-dienes (azines) (Scheme 1) [1,2] and the Brandsma reactions, comprising the [3,3] sigmatropic shift in propargyl vinyl sulfides (thiaenynes), electrocyclization in corresponding intermediary dienic thiones, accompanying by prototropic shifts to afford 2*H*-thiopyrans and thiophenes (Scheme 1) [3-5].

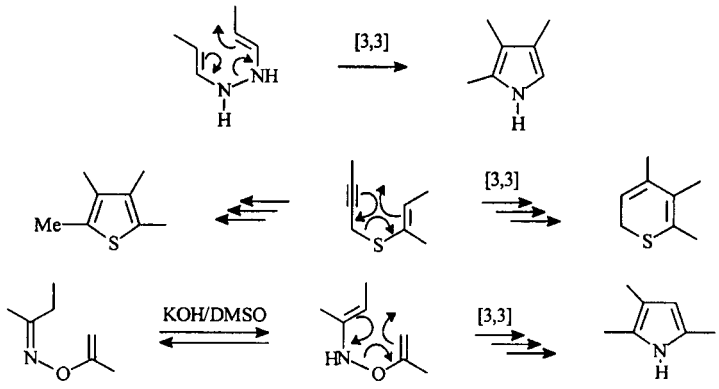
The same is observed in the pyrrole synthesis from ketoximes and acetylenes (the Trofimov reaction) in the presence of super bases such as potassium hydroxide/dimethylsulfoxide, where the intermediary *O*-vinyl oximes (oxazadienes) undergo the [3,3] sigmatropic shift, after the preliminary [1,3] prototropic shift (Scheme 1) [6,7].

The unsaturated carbanions produced from acetylenic and dienic precursors under the action of super bases attack aggressively these heterocumulenes, usually at very low temperature, to give a great diversity of heteroanionic intermediates capable of ring-closing in a number of modes engaging both heteroatoms in a variety of addition and electrocyclization reactions, sigmatropic and prototropic shifts (Scheme 2).

Some examples as evidence that the concept could be a fruitful one have been reported. These are the elegant syntheses of (alkylthio)thiophenes, thienothiophenes and thienodithiines by addition of unsaturated carbanions from acetylenic precursors to carbon disulfide developed by L. Brandsma (Scheme 3) [8,9].

As the objects for exploring the concept we have selected, on the one hand, acetylenic, allenic and 1,3-dienic compounds, readily convertible to the corresponding carbanions, and, on the other hand, available isothiocyanates.

Scheme 1



Heterocyclic chemistry is very rich in examples of this kind. Keeping this in mind we conceive the following general concept: "Heterodienes or -trienes and their anionic species easily generated from available acetylenic and dienic compounds, on the one hand, and heterocumulenes, on the other hand, are to be generalized convenient building blocks to design fundamental heterocycles with diverse combination of rare substituents such as alkoxy, alkylthio and amino groups".

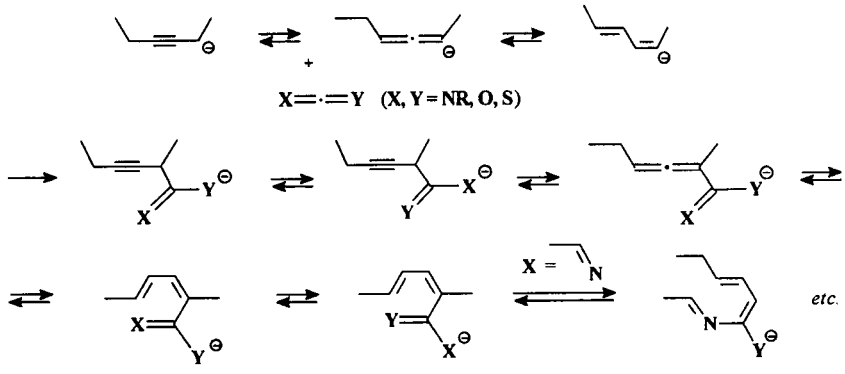
As the simplest accessible heterocumulenes, carbon disulfide, isocyanates, isothiocyanates, diimides and the like can be engaged.

This lecture is a concise survey of the newly discovered reactions and syntheses (by the joint Dutch-Russian team under Professor Brandsma) leading to a number of fundamental heterocycles bearing alkoxy, hydroxy, alkylthio and amino substituents.

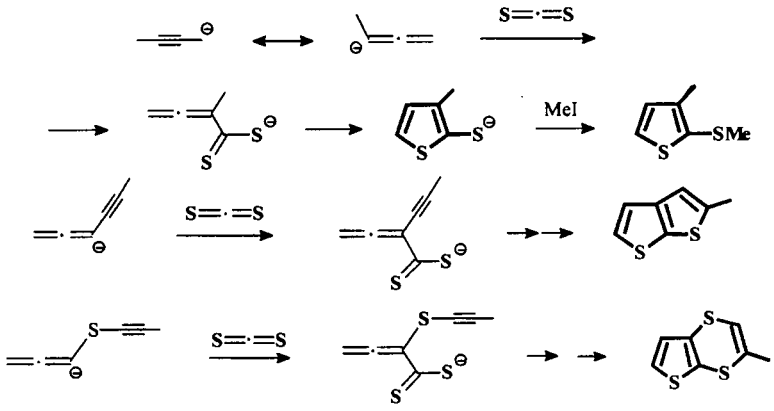
The following topics are to be discussed:

- Pyrroles (alkoxy, hydroxy, alkylthio)
- Cyclobuta[*b*]pyrroles
- Thiophenes (amino, alkylthio)
- Thiazoles and imidazoles (amino, alkylthio)
- Dihydropyridines (alkoxy, alkylthio)
- Pyridines (alkylthio, thione)
- Quinolines (alkylthio)

Scheme 2



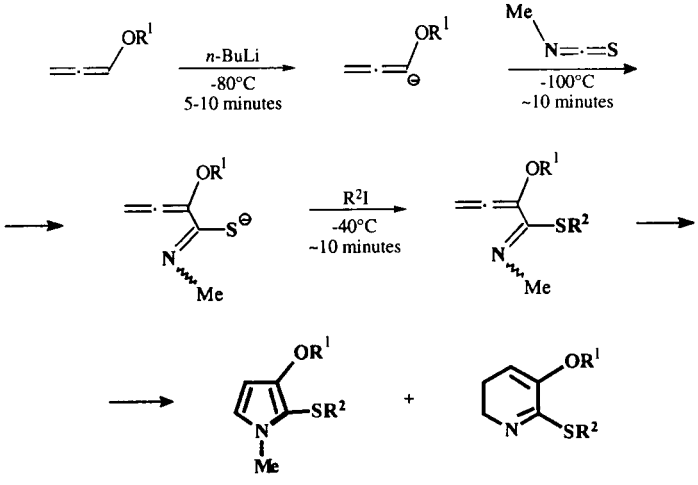
Scheme 3



1. Isomeric Pyrroles and Dihydropyridines.

When carbanions derived from allenic ethers available through propargylic ethers are allowed to contact with alkyl isothiocyanates at -100° as shortly as 10 minutes and the adducts are alkylated, mixtures of 1-alkyl-2-(alkylthio)-3-(alkoxy)pyrroles and isomeric 2,3-dihydropyridines are formed in a yield of around 80%, the ratio in case of all methyl substituents being 7:3 in favor of the pyrrole. The isomers are easily separated by a diluted strong acid extraction owing to a much higher basicity of dihydropyridines as compared with the corresponding pyrroles (Scheme 4) [10,11].

Scheme 4



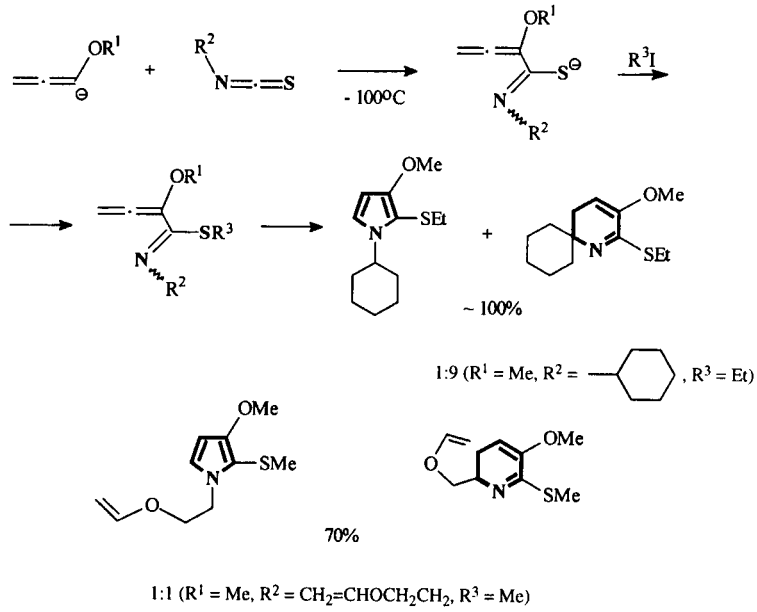
A great body of chemical and microbiological data on the known 3-alkoxypyrrole natural products, in particular, of the prodigiosin series, give hope for these new 3-alkoxypyrroles to be also a potent biologically active family.

The pyrrole/dihydropyridine ratio is strongly dependent of the isothiocyanate structure and for cyclohexyl isothiocyanate it becomes 1:9, this time favoring the dihydropyridine, with other substituents being methyl and ethyl and the total yield almost quantitative. In the case of vinyloxyethyl isothiocyanate we come up with a 1:1 mixture isolated in a 70% yield, other substituents being methyls. The latter example demonstrates the applicability of the reaction to functional isothiocyanates (Scheme 5). No wonder, that the pyrrole/dihydropyridine ratio is dependent of the allenic carbanion structure either [12,13].

There are the combinations of the substituents which allow the dihydropyridines to be synthesized as the only products. For example, when the allene substituents are methyl or methylthio (such anions are readily generated from the corresponding available acetylenes) and the isothiocyanate substituents are ethyl, functionalized ethyl or isopropyl, the corresponding 6-(alkylthio)-2,3-dihydropyridines are formed selectively in 57-80% yields (Scheme 6) [11,14,15].

A branching alkyl substituent like *tert*-butyl in allene does not infringe the selectivity of the dihydropyridine assembly. The *tert*-butylallene carbanion adds instantly to methyl isothiocyanate at -100° and, after methylation of the intermediate at -50°, we arrive at the azatriene which can be isolated practically in a quantitative yield. This

Scheme 5



2. Selective Synthesis of Dihydropyridines.

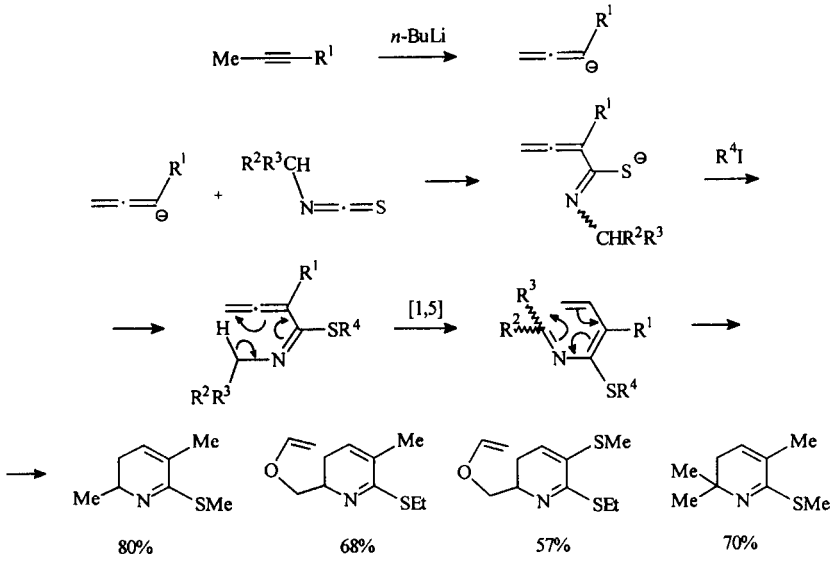
It is evident, that the pyrroles are formed from the allenic intermediate protected against the sulfur anionic attack by the early alkylation, while for the dihydropyridine formation the [1,5] hydrogen shift to give the 1,3,5-azatriene is required. The latter then undergoes the electrocyclization, provided it possesses a favorable configuration, both relative to carbon-carbon and carbon-nitrogen double bonds. Therefore, those radicals, both in the allenic anion and in the isothiocyanate, which secure these requirements, are beneficial for the dihydropyridine formation and otherwise (Scheme 6) [11,14,15].

compound is wonderfully stable and stands heating up to 200°, beyond which the exothermic process, including [1,5] hydrogen shift and electrocyclization, takes place to afford selectively 3-*t*-butyl-6-(methylthio)-2,3-dihydropyridine in 85% yield. Upon heating at 220° for 30 minutes it expectedly eliminates hydrogen to give the corresponding pyridine in 75% yield (Scheme 7) [16,17].

3. Cyclobuta[*b*]pyrroles.

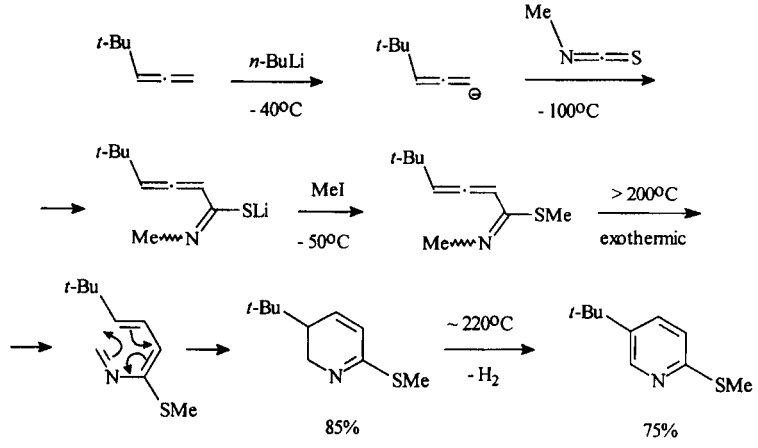
Up to what extent the substituent branching, both in allene and isothiocyanate, does not prevent the dihydropyridine or pyrrole assembly? It turned out that the tetrasubstituted azatriene, quantitatively assembled from

Scheme 6



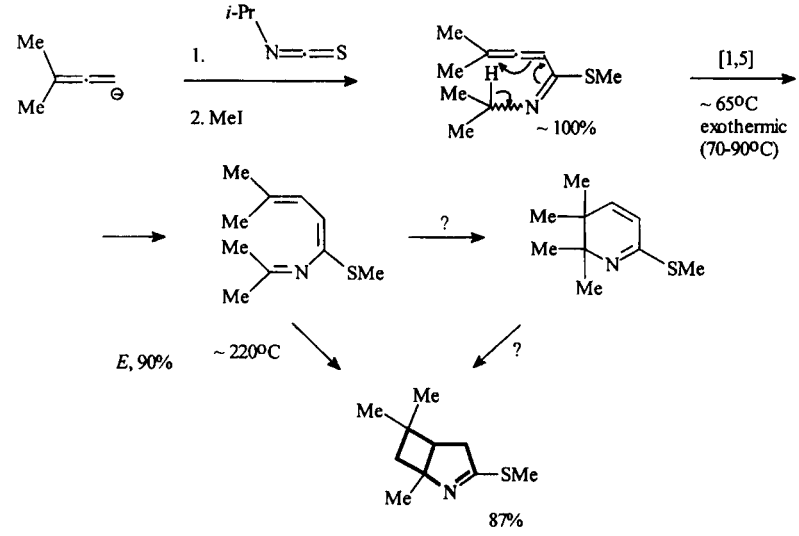
R^1 = Me, SMe; R^2 = Me, CH_2=$CHOCH_2$; R^3 = H, Me; R_4 = Me, Et

Scheme 7



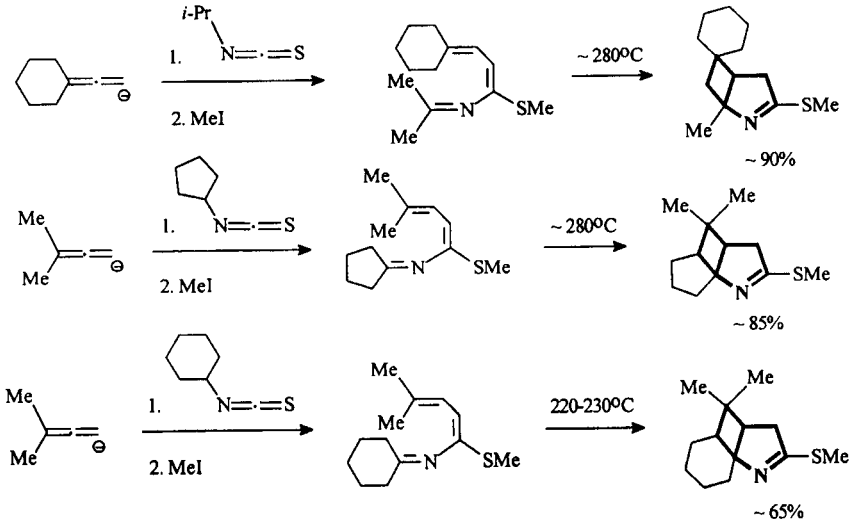
1,1-dimethylallene and isopropyl isothiocyanate, failed to cyclize to the dihydropyridine. Instead, at 65° it exothermically rearranges in a [1,5] hydrogen shift fashion to furnish stereoselectively the all-conjugated azatriene of a single configuration, presumably, *E*, isolated in 90% yield. Again, the compound is amazingly stable remaining unchanged up to 220°, thereafter undergoing a rapid, completely unexpected, peculiar cyclization to a cyclobuta[*b*]pyrrole derivative isolated in 87% yield (Scheme 8) [18,19].

Scheme 8



The reaction proved to be of general character. What one needs to assemble these peculiar fused pyrrole derivatives and other ones with even more extended bridging or spirocyclic systems, presumably even more strained, in a yield of 65-90%, are a 1,1-substituted allene and a secondary alkyl isothiocyanate. These include vinylidenecyclohexane, cyclopentyl and cyclohexyl isothiocyanates. In all these cases we have isolated as final precursors (in high yields) the same all-conjugated azatrienes, some of them being stable up to 280°, thereafter converting to the cyclobuta[*b*]pyrrole derivatives with the corresponding spirocyclic or fused moiety, in 65-90% yield (Scheme 9) [20,21].

Scheme 9



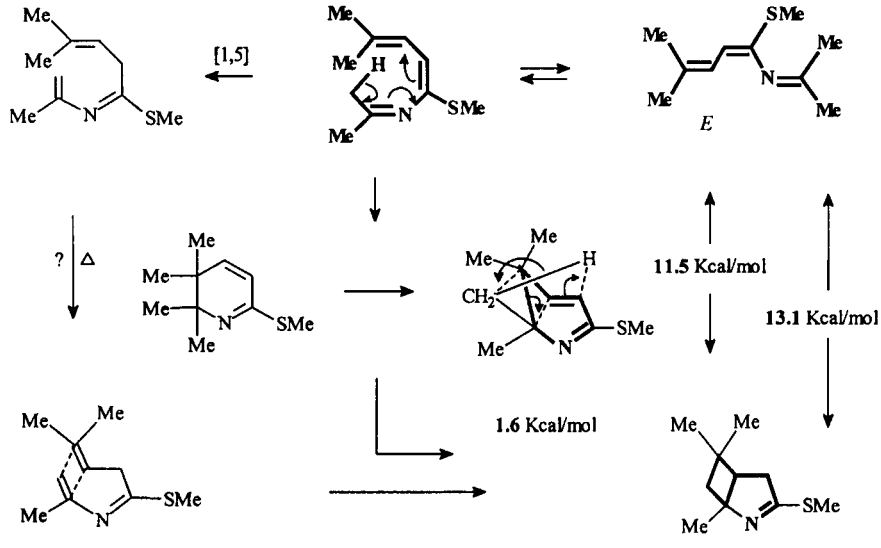
To rationalize this quite an irrational cyclization we performed non-empirical quantum chemical calculations in two different basis sets for the starting azatriene, corresponding cyclobuta[*b*]pyrrole and two suspect intermediates (the expected dihydropyridine and non-conjugated azatriene admittedly able to close the cyclobuta[*b*]pyrrole in a kind of [2+2] process, though forbidden symmetrically). The cyclobuta[*b*]pyrrole proved to be the lowest in energy, thus confirming that its formation is thermodynamically justified. The energy gain for conversion of the all-conjugated azatriene of *E*-configuration to the cyclobuta[*b*]pyrrole is 13.1 Kcal/mol and that to the dihydropyridine is 11.5 Kcal/mol. Therefore, the latter can be an intermediate lying higher than cyclobuta[*b*]pyrrole by 1.6-1.8 Kcal/mol. The conversion may be assumed to proceed as a combination of synchronous [1,5]-like hydrogen and two [1,3]-like sigmatropic shifts. The non-conjugated azatriene as having a higher energy ($\Delta\Delta H$ = 9.2 against 7.5 for the azatriene and 2.7 Kcal/mol for the dihydropyridine relative to cyclobuta[*b*]pyrrole, AM1 calculation) is a less probable intermediate (Scheme 10) [22].

A side reaction in the synthesis of cyclobuta[*b*]pyrrole from 1,1-dimethylallene and cyclohexyl isothiocyanate affording the 1,2-dihydropyridine-2-thione (*ca* 20% yield) results from the concerted migration of the double bonds in the intermediate with retaining their conjugation, thus again confirming the deconjugation to be unfavorable process for such compounds. The thiamide function is created due to a quite unusual elimination of methane from the dihydropyridine intermediate (Scheme 11) [23].

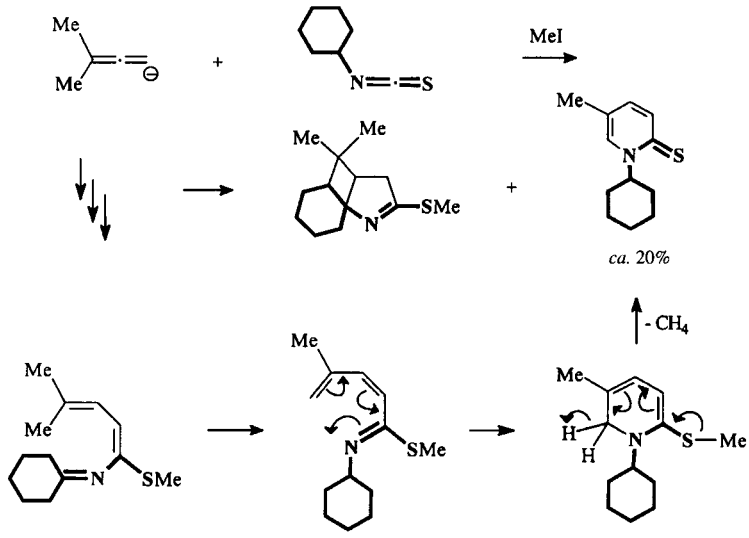
4. Selective Synthesis of Pyrroles.

The selective one-pot synthesis of 2-(alkylthio)pyrroles from the same reactants proved to be possible in the presence of copper(I) salts. When to the alkylated allene-isothiocyanate adduct a few percents of copper(I) bromide or copper(I) iodide is added at 0°, a mild exothermic reaction is observed to result in 2-(alkylthio)pyrroles as the only products in 65-80% yields. The convincing variety of substituents including various alkyls, alkoxy groups and aryls both in the allene or isothiocyanate components for which this is valid, shows a wide scope and promising future of this new pyrrole synthesis (Scheme 12) [24].

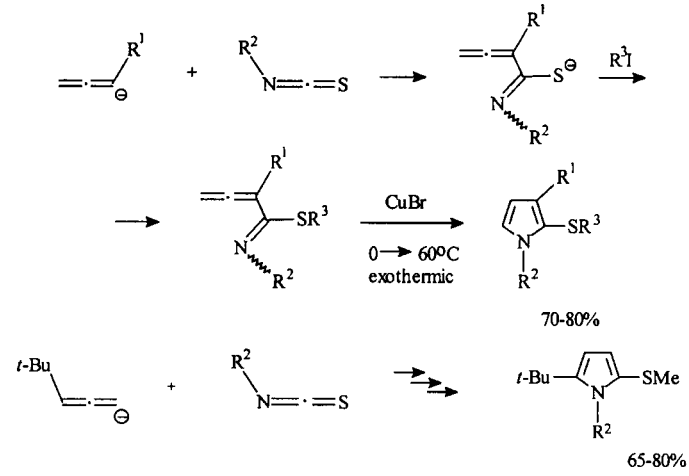
Scheme 10



Scheme 11



Scheme 12

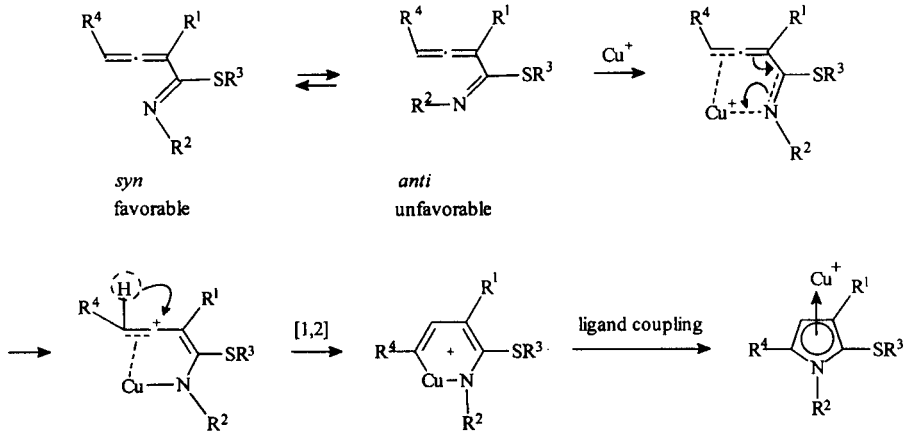


R^1 = Me, OMe, OBu-*t*; R^2 = Me, Et, *i*-Pr, *c*-C_5H_9, *c*-C_6H_{11}, CH_2=CHO$(CH_2)_2$, Ar; R^3 = Me.

What is the role of copper cation in the regioselective cyclization of the 2-(organylthio)-1,3,4-azatrienes? Obviously, it fixes a favorable *syn*-configuration of the triene due to complexing both with the nitrogen and the allenic sites. This prevents the [1,5] hydrogen shift necessary for the dihydropyridine ring-closure.

Instead, the copper cation, due to its flexible coordination ability, appears to induce the double bond shifts towards itself, thus precluding the isomerization towards the nitrogen substituent leading to the dihydropyridines. Simultaneously, this develops a positive charge at the allenic moiety and consequently the [1,2] hydride shift to form a cationic 1,3-azadienic copper complex finally delivering the pyrrole *via* ligand coupling (Scheme 13).

Scheme 13



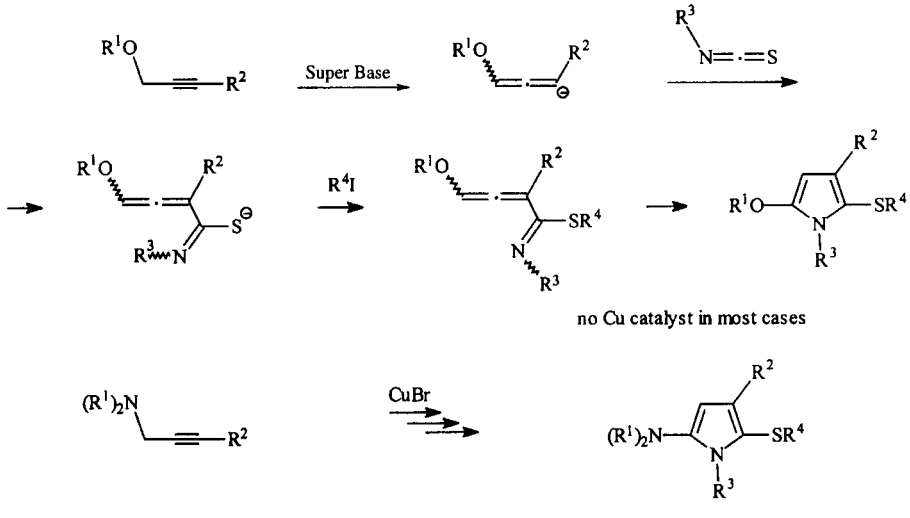
The scope of this reaction has even been much more extended by involving into the synthesis substituted propargyl ethers, which, thanks to their other mode of deprotonation, allow the pyrroles, having simultaneously alkoxy and alkylthio groups at the 2- and 5-positions, to be readily prepared. In this case, even no copper catalyst is required.

Likewise, substituted propargyl amines with organyl isothiocyanates in the same low-temperature one-pot procedure (but this time with copper(I) bromide as a catalyst) give exotic pyrroles having amino and alkylthio groups at the positions 2 and 5, the yields in most cases being above 70% (Scheme 14) [25].

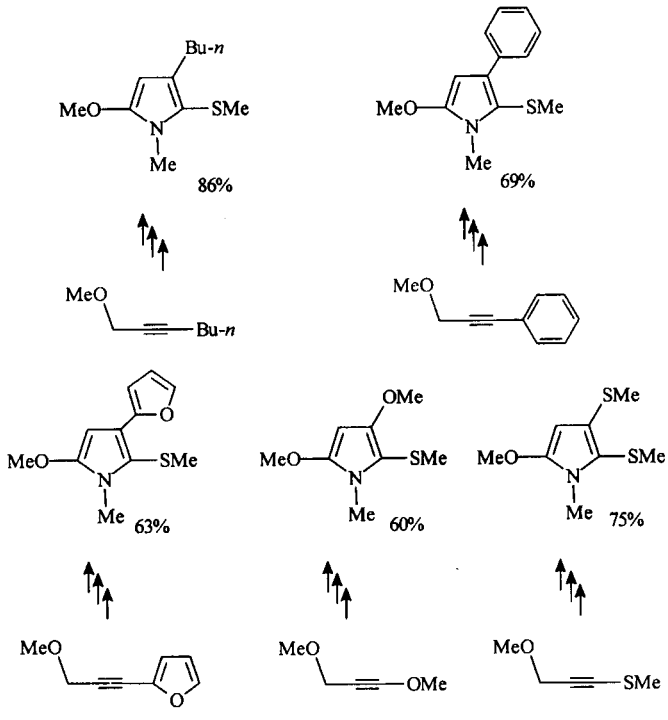
In Schemes 15 and 16, some typical representatives of tetra-substituted 2-alkoxy-5-(alkylthio)pyrroles synthesized from substituted methyl propargyl ethers and methyl isothiocyanate are shown. It is seen, that the reaction works excellently with a great diversity of substituents in the propargyl ether including alkyl, aryls, hetaryls, alkoxy and alkylthio groups. All these pyrroles can hardly be synthesized by earlier existing methods (Scheme 15) [25].

The same is true for the 2- or 4-amino-5-(alkylthio)pyrroles, which are readily assembled from these same three building blocks: an acetylenic compound (this time a propargylamine), an isothiocyanate and an alkylating agent in a fast one-pot low-temperature cascade of

Scheme 14



Scheme 15



highly-selective reactions: deprotonation of the acetylene, the carbanion addition to the isothiocyanate, alkylation of the thiolate and the pyrrole ring-closure. Among the propargyl amines successfully utilized for the pyrrole synthesis there are those with alkyl, aryl, alkoxy and amino substituents.

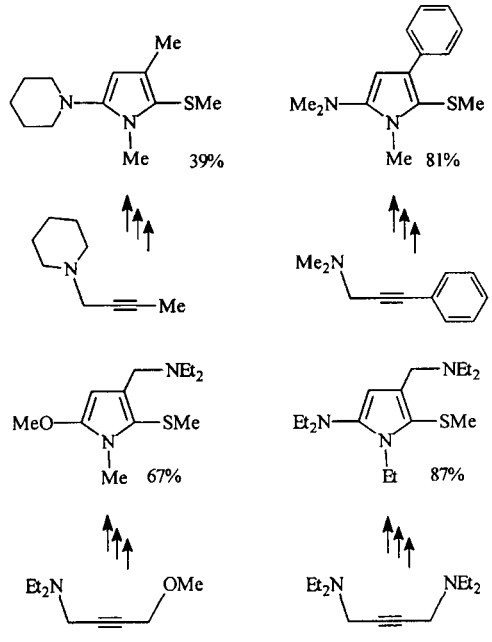
There is seen plenty of space and possibilities for combinatorial chemistry with rich libraries of rarely functionalized pyrroles (Scheme 16) [25].

5. 3-Hydroxypyrroles.

3-Hydroxypyrroles are highly electron-rich aromatic heterocycles, therefore more often than not compensating by tautomerism to 1*H*-pyrrol-3(2*H*)-ones. In fact, there are just a few examples, when a 3-hydroxypyrrole predominates in a tautomeric mixture.

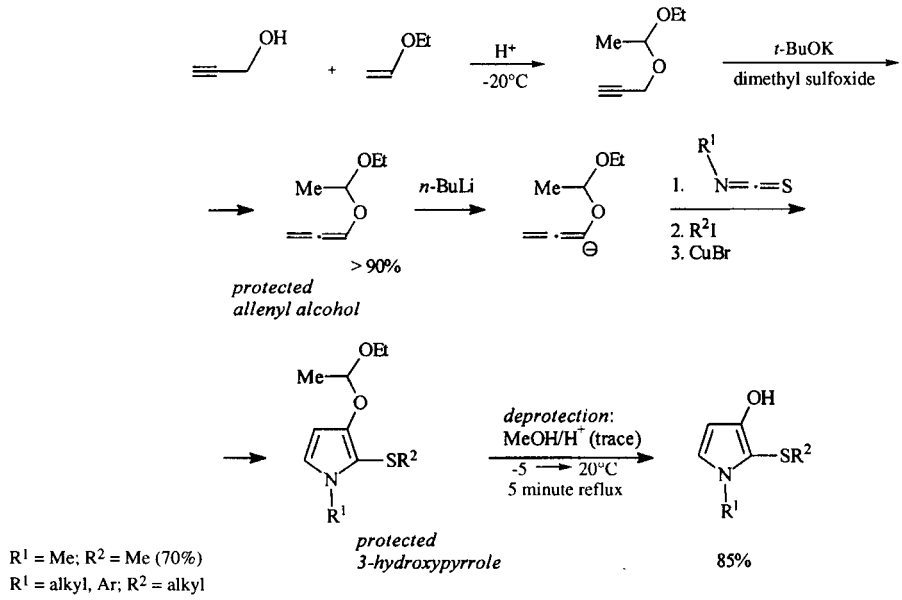
The isothiocyanate-based pyrrole synthesis allowed a new family of 3-hydroxypyrroles to be readily assembled *via* the protected allenyl alcohol. The latter easily comes in a yield of higher than 90% from the electrophilic addition of propargyl alcohol to a vinyl ether followed by the smooth prototropic rearrangement. The allenyl acetal is then subjected to the same pyrrole-assembling sequence: deprotonation, addition to an isothiocyanate, alkylation and ring-closing in the presence of copper(I) bromide to furnish the acetal-protected 3-hydroxypyrrole in a yield of 70%, for the two substituents (R^1 and R^2) being methyl. Deprotonation occurs very smoothly in methanol with just

Scheme 16



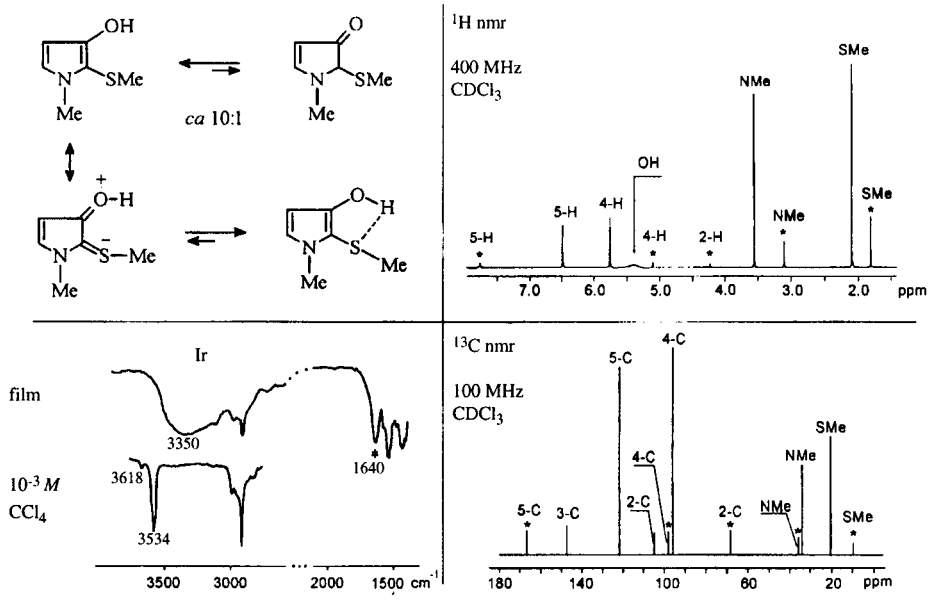
a trace of acid hydrocloric at -5 till 20° ended up by a 5 minute reflux to release 3-hydroxypyrroles in 85% yield for the all-methyl derivative (Scheme 17) [26].

Scheme 17



Unlike most of 3-hydroxypyrroles reported in the literature as highly unstable compounds readily converting to 3-pyrrolones and mostly existing in this form, the 1-alkyl-2-(alkylthio)-3-hydroxypyrroles we synthesized turned out to be quite stable compounds having a good shelf life which can be handled without special precautions. Their ir spectra run, as a film, consist of the expected very intense broad hydroxyl absorption band at 3350 cm^{-1} and a rather strong absorption at 1640 cm^{-1} apparently belonging to the pyrrolone tautomer along with the hydroxyl deformations. At high dilution in tetrachloromethane such as 10^{-3} mol/l, in the spectrum just one major hydroxyl band remains (at 3534 cm^{-1}) indicating an unexpectedly strong intra-molecular hydrogen bonding between the hydroxyl and alkylthio group to exist in these molecules. This may be caused by a partial electron density transfer from oxygen to the sulfur lower vacant orbitals through the pyrrole ring as depicted by one of the resonance structures (Scheme 18). The free hydroxyl appears as a weak band at 3618 cm^{-1}. The ^1H and ^{13}C nmr spectra of 3-hydroxypyrroles consist completely with their structure containing just low intensity signals of the pyrrolone tautomer corresponding to about 10% concentration of the latter (Scheme 18) [27].

Scheme 18



*Pyrrol-3-one tautomer

6. Quinolines.

The structure of aryl isothiocyanate does not allow the double bond migrating over the nitrogen atom, hence no azatriene appropriate for the above dihydropyridine ring-closure can be formed. In the absence of the copper catalyst, except for a few special cases, the pyrrole formation is hindered either. The hindrance even further increases when the carbanion is generated from a multi-substituted allene. Therefore, what should we expect in this case is the involvement of the benzene ring into electrocyclization to assemble the quinoline derivatives.

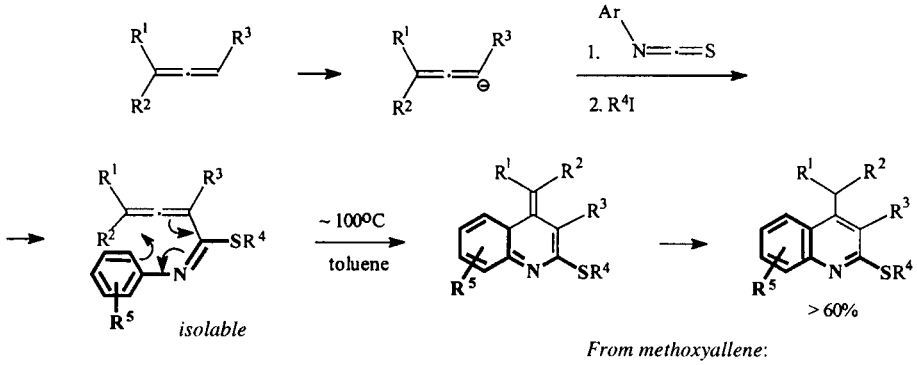
This is what really occurs. The initial adducts after alkylation afford the arylazatrienes, which happen to be remarkably stable and can be isolated in high yields. Upon reflux in toluene, they are readily transformed *via* the intermediate methylenedihydroquinoline into substituted quinolines in a yield of above 60%. This novel versatile synthesis allows a great diversity of substituents to be easily introduced in the quinoline structure. Among such substituents are various alkyl, alkoxy, alkylthio and amino groups, as well as fluorine, chlorine, bromine atoms (what is quite astonishing in the presence of super bases) and trifluoromethyl, the latter are being introduced from the aryl isothiocyanate counterpart.

Only in the case of less substituted methoxyallene and phenyl isothiocyanate a 1:1 mixture of the corresponding quinoline and the pyrrole has been obtained. However, their separation is easy: the quinoline as more basic is plainly extracted with diluted acid hydrochloric (Scheme 19) [18,28-30].

Further functionalization of the quinolines can be accomplished in the very assembling process on the stage of the azatriene formation: the initial adduct of allenic carbanion and isothiocyanate is treated, prior to alkylation, by one more equivalent of butyllithium to give the dianion, which upon double alkylation, undergoes the thermal electrocyclization to an additionally substituted quinoline derivative in an average yield of 85%.

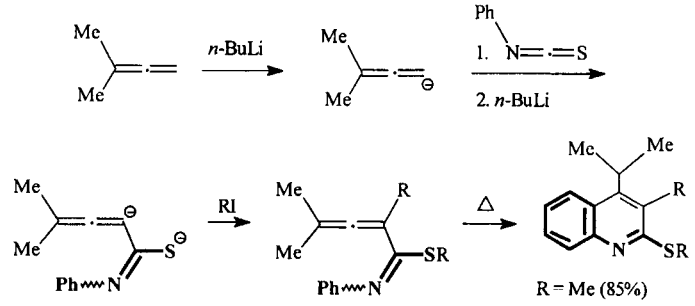
Owing to the different nature of the anionic centers in the azatriene dianion, their discrimination by different electrophiles is conceivable. Indeed, when the dianion from 1,1-dimethylallene and phenyl isothiocyanate was treated first with trimethylchlorosilane and then with methyl iodide, the two substituents have been expectedly introduced into the forming quinoline system, although the isolated (in 25% yield) product proved to be not the target 2-(methylthio)-3-trimethylsilyl-4-isopropylquinoline, but its non-aromatic dihydro isomer, though other than the intermediate resulted right from the electrocyclization. It is amazing but fact, that the [1,3] hydrogen shift towards silicon, along with the corresponding migration of the double bonds, happens to be more thermodynamically preferred, than that towards the methylene group followed by aromatization. Probably, it is due to a steric strain imposed by the trimethylsilyl group, which releases when this group becomes out of plane (Scheme 20) [31].

Scheme 19

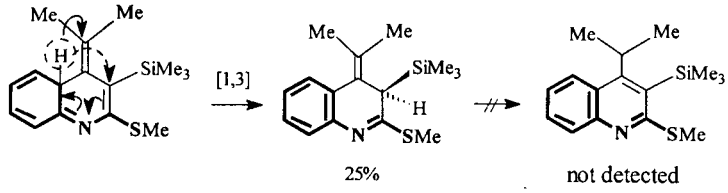


R^1 = H, Me, *t*-Bu; R^2 = H, Me;
R^1-R^2 = $(CH_2)_5$;
R^3 = H, OMe, SMe; R^4 = Me;
R^5 = H, Me, OMe, NMe_2,
F, Cl, Br, CF_3

Scheme 20



Discrimination between the two anionic sites (1. Me_3SiCl, 2. MeI)



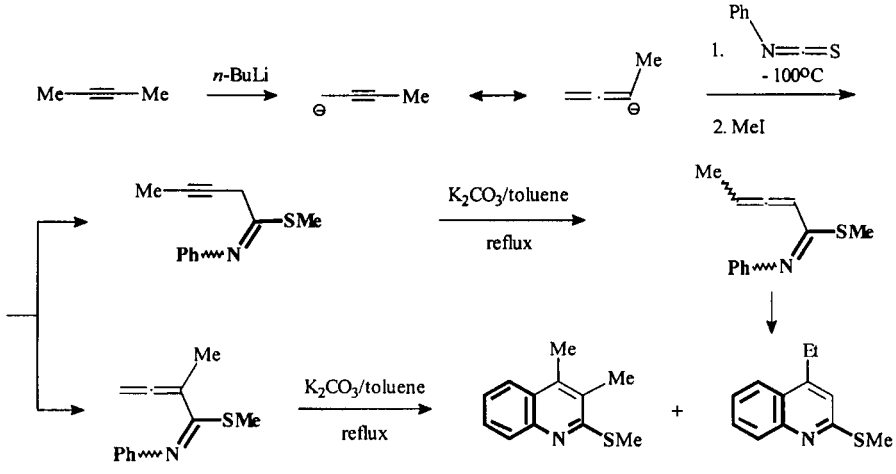
Ambident anions generated from 2-alkynes, upon their lithiation, can also be used in the aryl isothiocyanate-based quinoline synthesis thus even more extending the preparative value of the method. For example, 2-butyne with phenyl isothiocyanate, after a typical low-temperature, fast, one-pot reaction sequence, gives a 1:4 mixture of isomeric 3,4-dimethyl- and 4-ethyl-2-(methylthio)quinolines in 70% yield. This indicates that initial major intermediate is the acetylenic one, which needs to be rearranged to the allene prior to the quinoline ring-closure. This is why a trace amount of potassium carbonate on the electrocyclization stage proved to be beneficial (Scheme 21) [32].

7. Aminothiophenes.

So far we considered cyclizations of allenic or acetylenic carbanion-isothiocyanates adducts, wherein the sulfur-centered anion was deactivated by alkylation to let the nitrogen atom only participate in assembling nitrogen heterocycles. It is, however, quite obvious, that the sulfur site, when non-alkylated, should attack the allenic moiety to close the dihydrothiophene ring. Therefore, we may switch from the pyrrole to the thiophene ring-closure just by postponing the alkylation to the later stage.

Indeed, the azatrienic thiolates, generated as above from allenes or acetylenes and isothiocyanates, when

Scheme 21

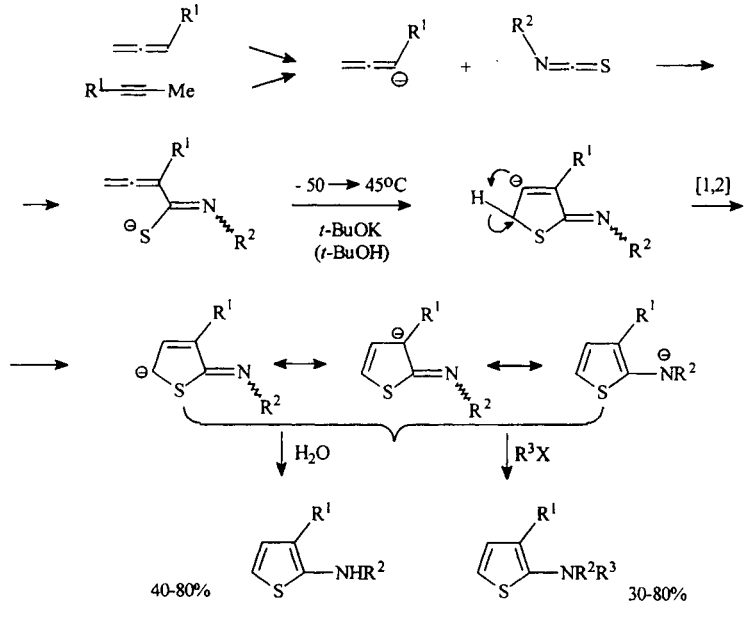


allowed to warm up to 45° in the presence of potassium *tert*-butoxide and (optionally) *tert*-butyl alcohol and then quenched with water or alkylated, give 2-aminothiophenes with secondary or tertiary amino groups in a yield ranging from 30 to 80%. Apparently, the initial dihydrothiophene anion undergoes the [1,2] hydrogen shift to aromatize as the aminothiophene anion with the anionic site localized at the amino group. This new one-pot synthesis of inaccessible aminothiophenes proved to cover allenes and acetylenes with alkyl, alkoxy and alkylthio substituents and alkyl and aryl isothiocyanates, the latter having alkyl, fluorine, chlorine, trifluoromethyl substituents in their benzene ring (Scheme 22) [33-35].

oxythiophenes were found to exist in two tautomeric forms: amino and imino, the latter having *anti*-configuration only (regardless of the substituents). Semi-empirical quantum chemical calculations confirm the *anti*-isomer to be by 1.5 Kcal/mol more stable than *syn*-isomer. This is also supported by ^{13}C nmr spectra simulation giving calculated value for C-2 of *anti*-isomer almost the same as observed and much lower for the *syn*-isomer (Scheme 24).

The tautomer ratio turned out to be very strongly solvent-dependent: in tetrachloromethane it equals 1:1, whereas in the 1:1 mixture of tetrachloromethane/chloroform it becomes 1:7 in favor of the imino-form and in neat chloroform we have almost pure imino-form (1:15),

Scheme 22



R^1 = Me, Et, OMe, SMe; R^2 = Me, Ar (Me, F, Cl, CF_3); R^3 = Me; X = I

The means, which help switching from the pyrrole to the thiophene ring-closure, are the following (Scheme 23):

- no low-temperature alkylation - to keep the thiolate anion free until its addition to the unsaturated moiety;
- a potassium strong base additive - to loosen the ion pair by detaching the Li cation;
- a proton donor additive - for the same above reason;
- a bulky substituent in the isothiocyanate molecule - for steric assistance to a favorable disposition of the thiolate and allenic moieties.

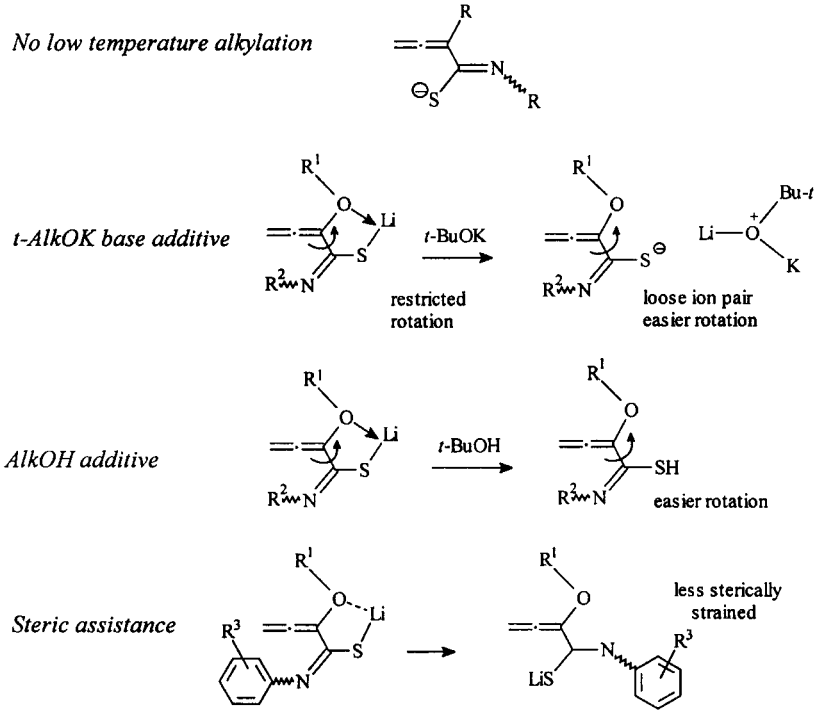
Unknown before our work, 2-amino-3-alkoxy[3-(alkylthio)]thiophenes represent a fresh and exciting object for chemical, physico-chemical and biochemical studies.

In particular, 2-(alkylamino)- and 2-(arylamino)-3-alk-

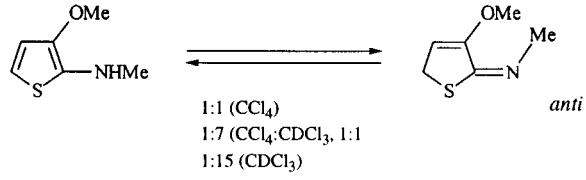
apparently due to its better stabilization as more basic by complexing with chloroform. As expected, the tautomer ratio depends on the substituent structure. Unlike the above example, 2-(phenylamino)-3-methoxythiophene in chloroform exists preferably as amino-form (1.4:1) and in acetone-d_6 it is practically pure the aminothiophene (33:1), apparently, due to the chemical amine-carbonyl interaction.

For 2-amino-3-(methylthio)thiophene no imino-tautomer was detected in its ^1H and ^{13}C nmr spectra. This is likely to result from a weaker conjugation of sulfur with the double bond as compared with oxygen and the coplanarity distortion because of a larger volume and a lesser valence angle in the methylthio group (Scheme 24) [36].

Scheme 23

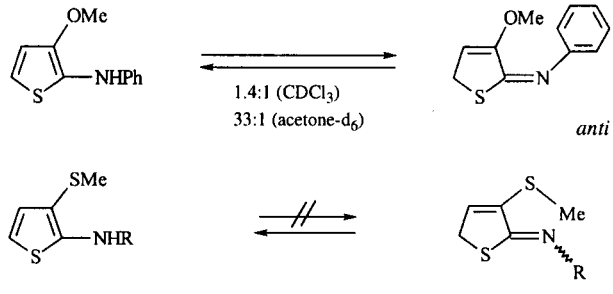


Scheme 24



AM1: $\Delta\Delta H$ (*syn*/*anti*) = 1.5 Kcal/mole

^{13}C nmr Simulation (C-2, ppm): Found 163.6; Calcd. 160.7 ± 7.8 (*anti*), 150 ± 4.3 (*syn*)



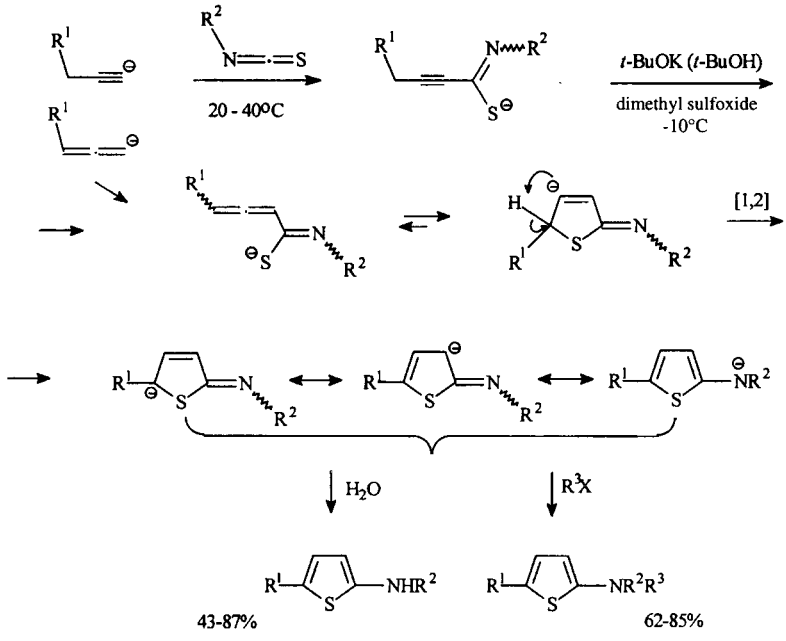
no tautomerism detected (^1H, ^{13}C nmr)

R = Me, Ph

Of special interest is the one-pot synthesis of 2-aminothiophenes starting from available 1-alkynes. Their anions add smoothly to isothiocyanates at 20-40° to yield acetylenic iminothiolates which (in the presence of potassium *tert*-butoxide/dimethyl sulfoxide) prototropically spread their triple bond up to the familiar azatriene system (also accessible from some 1-substituted allenes), which undergoes the transformations already considered above to afford 2-(organylamino)- or 2-[di(organyl)amino]-5-substituted thiophenes in a yield of 43-87% or 62-85%, respectively, depending on whether we quench the reaction mixture with water or alkylate it. The 5-substituents include alkyl, alkoxy and dialkylamino groups (Scheme 25) [34,37].

1,1-Disubstituted allenes, when subjected to the same reaction sequence, give the intermediates unable to be aromatized due to the presence of two substituents in position 5. Therefore, after neutralization with a proton donor, it gives 2-imino-2,5-dihydrothiophenes in a yield up to quantitative, meaning that we have an excellent one-pot synthesis of another family of heretofore unknown thiophene derivatives (Scheme 26) [38].

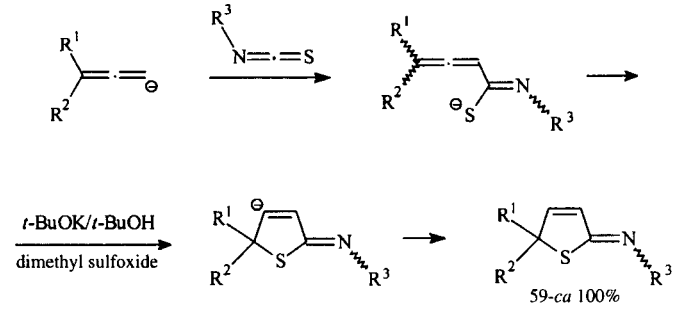
Scheme 25



For 1-Alkynes: R^1 = H, Me, OMe, NMe_2; R^2 = Me, Et, *i*-Pr, Ph; R^3 = Me; X = I

For t-Alkylallenes: R^1 = *t*-Bu; R^2 = Me, Ph

Scheme 26



R^1 = Me; R^2 = Me; R^1-R^2 = $(CH_2)_5$; R^3 = Me, Et, *i*-Pr, Ph

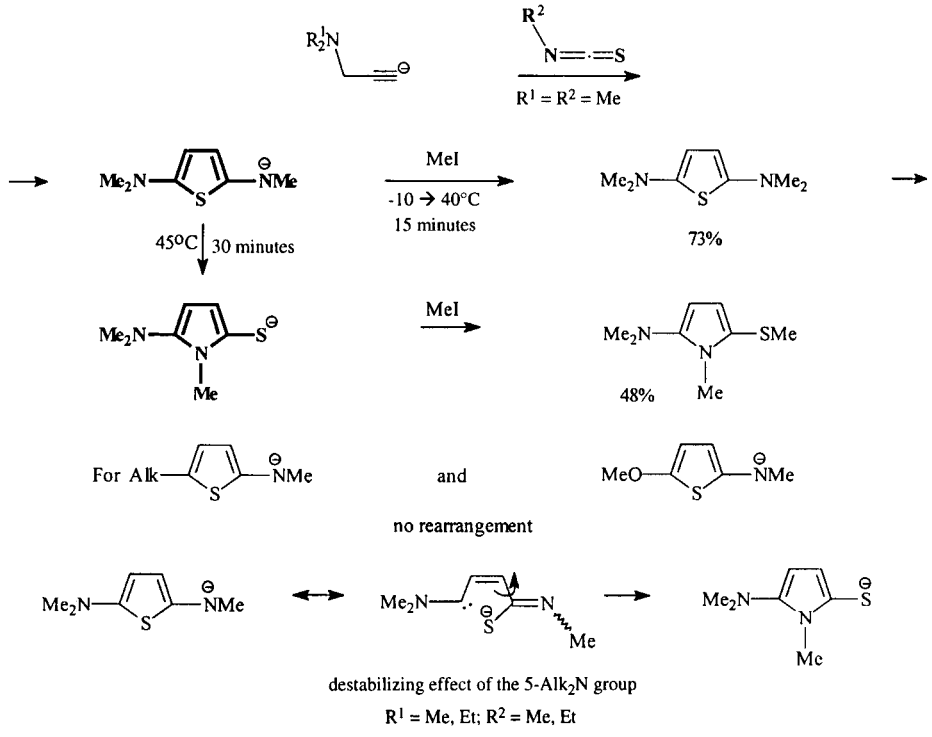
Propargyldialkylamines with alkyl isothiocyanates under the same conditions give 2,5-bis(dialkylamino)thiophenes in a yield above 73%, thus once more demonstrating the general character of the method. If, however, prior to alkylation, the intermediate 2,5-di(amino)thiophene anion is allowed to be warmed up to 45° for 30 minutes it rearranges to 2-aminopyrrole-5-thiolate, alkylation of which affords 2-dialkylamino-5-(alkylthio)pyrrole in a yield about 50%. Neither 5-alkyl- nor 5-alkoxy-2-alkylaminothiophene anions undergo such a kind of recyclization to pyrroles under the same conditions. Obviously, 5-dialkylamino group causes an additional destabilizing effect onto the anion due to the ready transmittance of the charge to position 5: disruption of the C-5-S bond in a ultimate resonance structure with the corresponding rotation resulting in a more stable sulfur-centered anion (Scheme 27) [37].

8. 1,2-Dihydropyridines and 5,6-Dihydro-2*H*-thiopyrans.

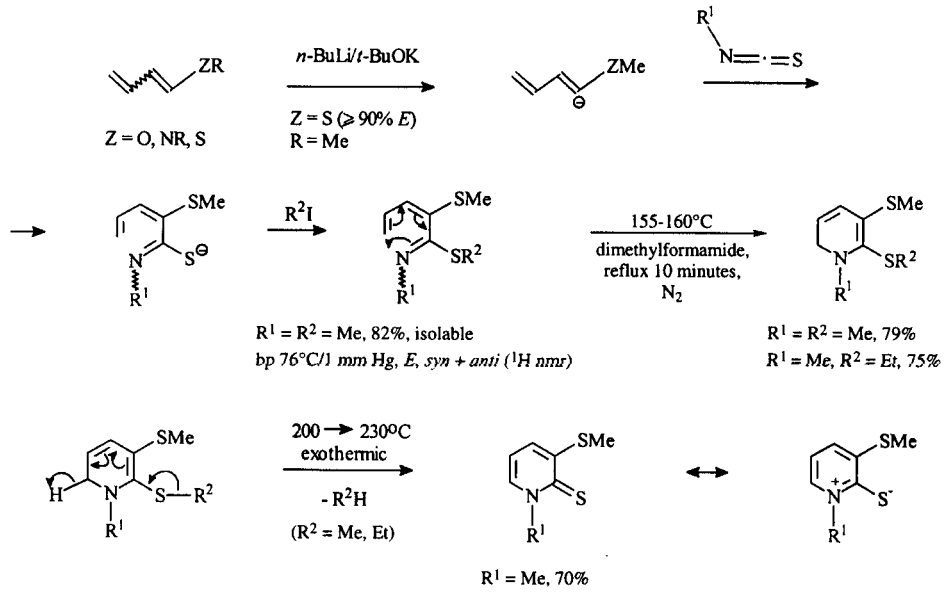
This general approach to design heterocycles is not limited, of course, by starting acetylenic and allenic compounds. Available 1-hetero-1,3-butadienes provide another large stock of four-membered building blocks for azatriene thiolates. Indeed, the carbanion of *E*-1-methylthio-1,3-butadiene, generated in the super base pair butyllithium/potassium *tert*-butoxide, adds to alkyl isothiocyanates, as usually smoothly, to give after alkylation the expected azatrienes ready for the electrocyclization (Scheme 28). This does happen, when they are refluxed in *N*,*N*-dimethylformamide for 10 minutes under nitrogen to result in 1-alkyl-5,6-di(alkylthio)-1,2-dihydropyridines in 75-79% yield. The azatrienes remain unchanged up to 150° and can be isolated in a yield of around 80%. The ^{1}H nmr spectra show that, like the starting diene, they have an *E*-configuration relative to the C(3)-C(4) bond what explains the smooth electrocyclization. Inconvenient for the ring-closure *syn*-isomer (relative to the N=C bond), discernable by ^{1}H nmr along with the *anti*-isomer, seems to isomerize to the *anti*-isomer upon heating. When the dihydropyridines thus prepared are heated up to 200-230°, an exothermic reaction starts to end up with pyridine-2(1*H*)-thiones in a yield around 70%.

Again we encounter here the very unusual elimination of hydrocarbons from the alkylthio substituent and dihydropyridine ring already once mentioned while discussing the side formation of these very pyridinethiones during the cyclobuta[*b*]pyrrole synthesis. The driving force of this elimination is likely the tendency to reach a more conjugated state (Scheme 28) [39,40].

Scheme 27

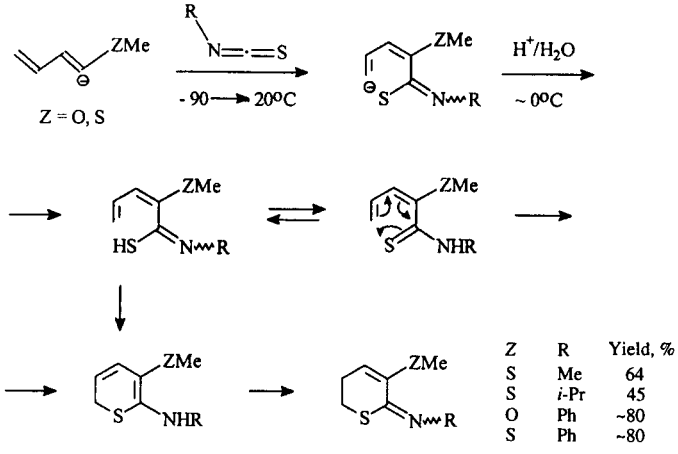


Scheme 28



Like the pyrrole-to-thiophene switching, here a similar switch-over from nitrogen to sulfur is also feasible. What we need for this is to keep the sulfur anionic center non-alkylated until it added to the dienic moiety. Indeed, the azatrienic thiolates generated from deprotonated 1-hetero-1,3-dienes and isothiocyanates, when poured in icy acidified water, convert to the corresponding thiols, which either *via* intramolecular addition or *via* electrocyclization of the thioamide tautomer further transform into 5,6-dihydro-2*H*-thiopyran imines in a yield of 45-80%, depending on heteroatom of starting dienes and substituent of isothiocyanates (Scheme 29) [41,42].

Scheme 29

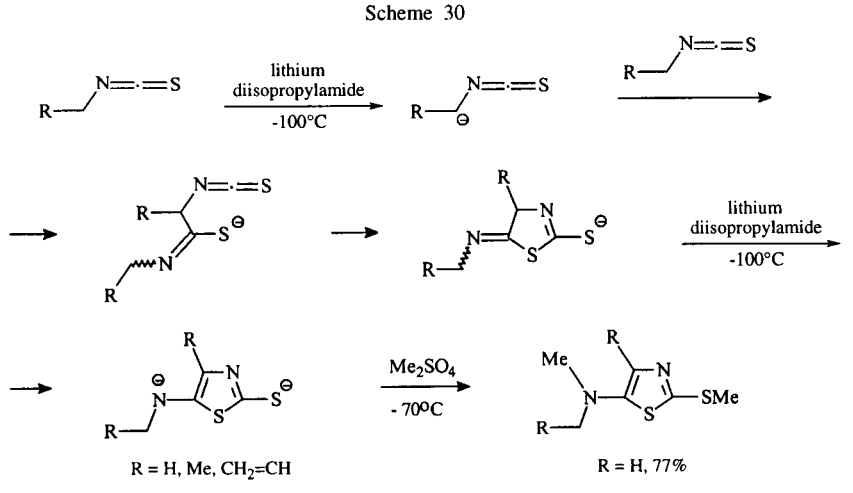


9. Thiazoles and Imidazoles.

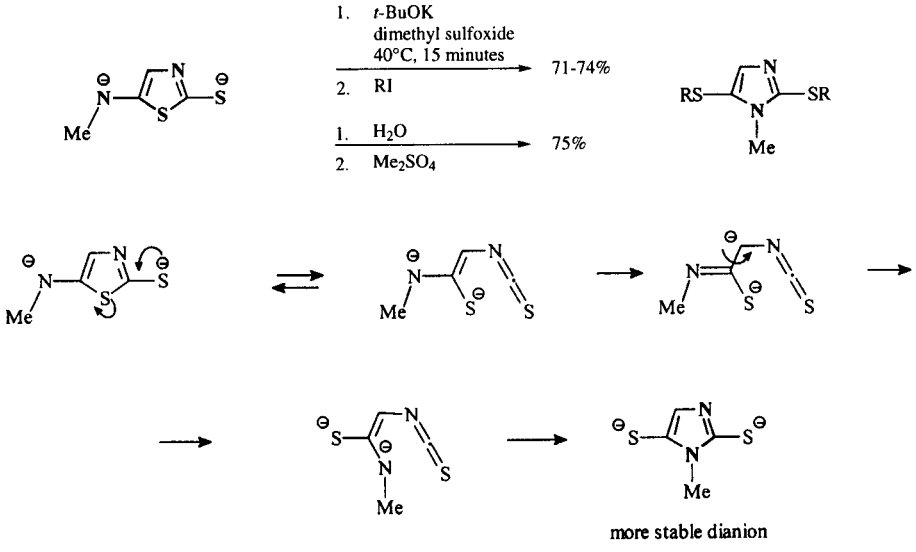
Deprotonated alkyl isothiocyanates are actually unsaturated anions themselves and as such can add to their own molecules, thus undergoing dimerization, trimerization and, as ultimate case, polymerization. Following and further developing Hoppe's work in this area, we have found that alkyl isothiocyanates under the action of excess lithium diisopropylamide at -100° are readily deprotonated at the position next to the nitrogen and the anion formed adds to the second molecule of isothiocyanate to give the diazathiatriene-thiolate which expectedly closes up to the imino thiazoline-thiolate. Meanwhile, the excess lithium diisopropylamide keeps deprotonating to end up with the aminothiazole thiol dianion, which, after alkylation, affords 2-alkylthio-5-aminothiazoles, the yield in the methyl isothiocyanate case being 77%. Thus, a new highly synthetically potent reaction for the old class of compounds has been discovered (Scheme 30) [43-46].

Now, having known, that aminothiophene anions are prone to recyclization to pyrrole thiolates, we wondered, whether a similar recyclization (nitrogen *in*-sulfur *out* of the cycle) is also feasible for the above aminothiazolethiol dianion. To accomplish this, we used, as earlier, the potassium *tert*-butoxide/dimethyl sulfoxide super base to tie up the lithium counter ion, to loosen the ion pairs and therefore to additionally activate the both anionic centers. For the same reason, prior to alkylation, the reaction temperature was increased up to 40°. The result was as expected: after alkylation we came up with the 2,5-di(alkylthio)-imidazoles in yields above 70% (Scheme 31) [44,47-49].

Scheme 30



Scheme 31



Another route to the same imidazoles with the same good preparative yields proved to be the aqueous treatment of the thiazole dianion followed by alkylation. Apparently, what we have here is the ring-opening of the thiazole dianion to release the isothiocyanate function, rotation in the open dianion and the imidazole ring-closure at the expense of nitrogen-centered anionic site. Therefore, we run into one more new synthetically attractive reaction of the same old class of compounds known for more than a century.

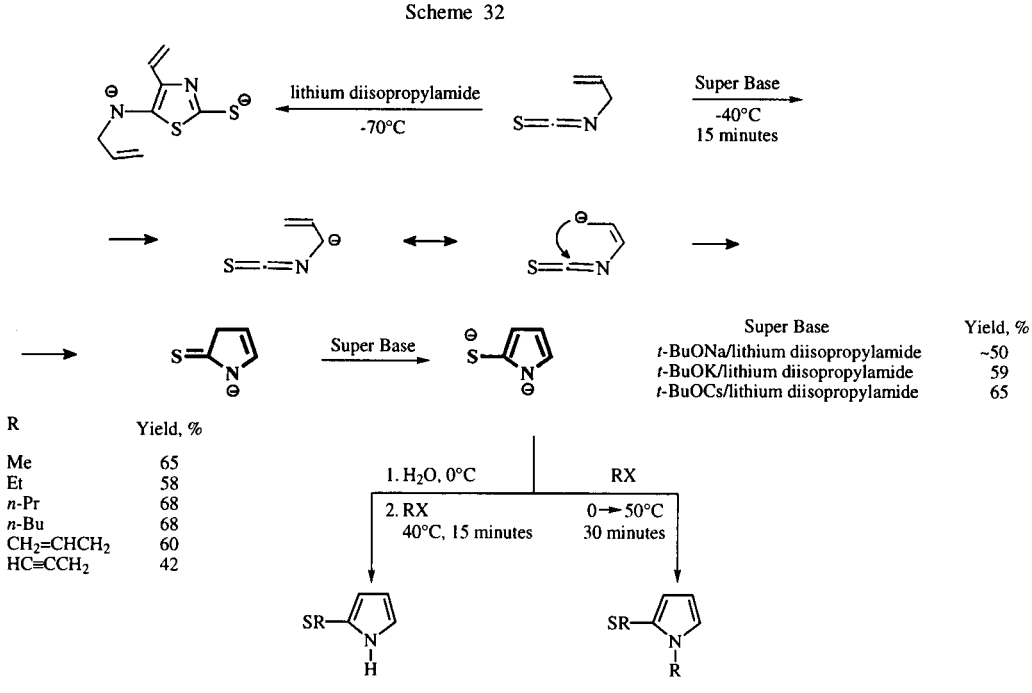
10. 2-(Alkylthio)pyrroles from Allyl Isothiocyanate.

The anion generated from allyl isothiocyanate proved to be capable of self-biting thus undergoing a "scorpio"-like reaction, that first leads to the pyrroline-2-thione anion and further on, under the action of excess super base, to the pyrrole-2-thiolate dianion (Scheme 32). Because of the different basicity of these two anionic centers, they are quenched by electrophiles selectively, so allowing 1*H*-2-(organylthio)pyrroles to be synthesized by the sequential treatment first with water at 0° and then - with an alkylating agent at 40° for 40 minutes. The non-optimized yield ranges from 42 to 68% depending on the nature of alkylating agent. When alkylated hereupon within 0-50° during 30 minutes, it gives *N*-substituted 2-(organylthio)pyrroles in the same 50-65% yield. The "scorpio" reaction takes place specifically with a particular complex super base such as alkali metal tertiary alkoxide-lithium diisopropylamide at 40° for 15 minutes, the yield of the pyrroles expectedly increasing from Na to Cs. In the same order, activity of the allyl isothiocyanate carbanion is assumed to increase due to the ion pair separation. With lithium diisopropylamide alone at -70°, the above dimerization to the aminothiazole-thiolate dianion occurs (Scheme 32) [37,50,51].

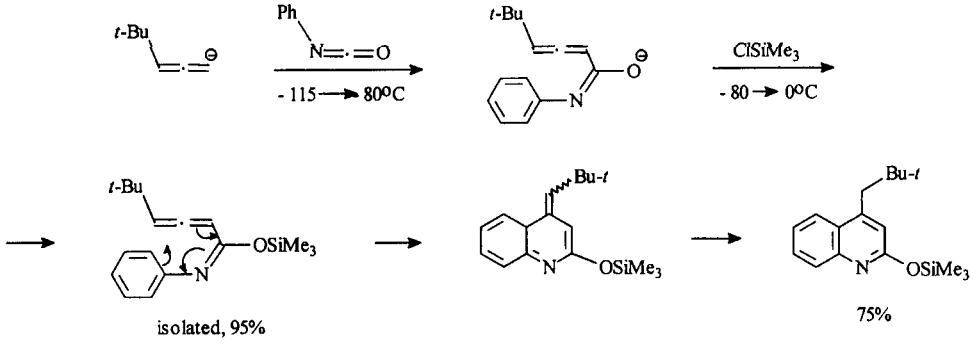
Conclusion.

In conclusion, it makes sense to come back to the starting general concept as a reminder, that isothiocyanates are but one member of the heterocumulene family and that other members are available to be reacted with acetylenic, allenic and 1,3-dienic carbanions to design new heterocyclic systems with rare substituents and new reactions and methods leading thereto. As just one example of the unlimited potential of the concept, the reaction of the allenyl carbanion with phenyl isocyanate can be noted. It follows the same patterns through the azatrienic alkoxide anion, which upon quenching with trimethylchlorosilane gives the isolatable (in 95% yield) silyl derivative which can be electrocyclized to the quinoline derivative (Scheme 33) [52].

Scheme 32



Scheme 33

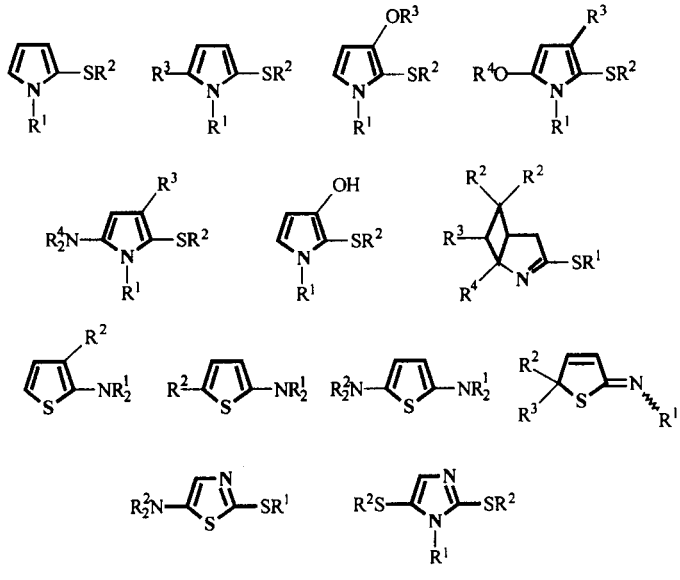


In summary, a number of new reactions and methods for assembling fundamental heterocycles with rare substituents from unsaturated carbanions and isothiocyanates have been discovered and developed. Among the five-membered heterocycles synthesized are pyrroles with alkylthio, alkoxy and amino substituents and their combinations, most of which are unknown, as well as such exotic representatives as 3-hydroxy-2-(alkylthio)pyrroles and cyclobuta[*b*]pyrrole derivatives, diverse aminothiophenes, amino(alkylthio)thiazoles and bis(alkylthio)imidazoles (Scheme 34).

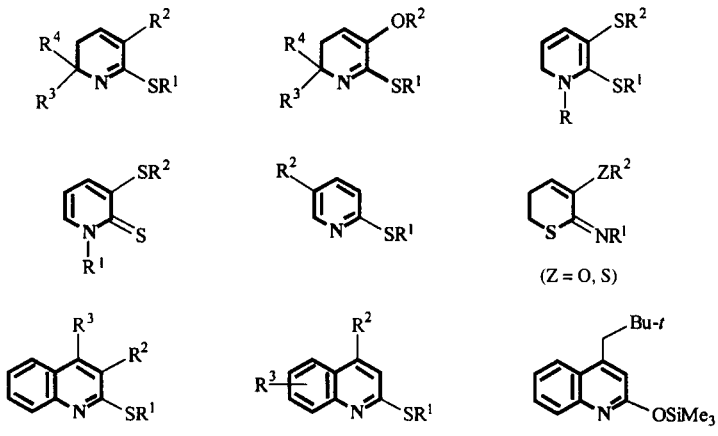
Six-membered heterocycles obtained from the same general concept include (alkylthio)dihydropyridines, various alkoxy(alkylthio)dihydropyridines, pyridinethiones, dihydro-2*H*-iminothiopyrans and quinolines with uncommon substituents (Scheme 35).

This listing seems to be convincing enough to believe that the general concept we have reported is far from being exhausted.

Scheme 34



Scheme 35



Acknowledgments.

This lecture would never see the light without the highly skillful and dedicated work of D. Sc. Nina A. Nedolya, Dr. Olga A. Tarasova, D. Sc. Anastasiya G. Mal'kina, Hermann D. Verkruijsse, Dr. Robertus L. P. de Jong, Dr. Sc. Vladimir Yu. Vvedensky, Dr. Robbert-Jan de Lang under permanent supervision, conceptual and methodological guidance of Professor Lambert Brandsma, to whom the author addresses his most hearty thanks and admiration.

REFERENCES AND NOTES

[*] Most of the results presented here have been obtained by D. Sc. Nina A. Nedolya (Irkutsk Institute of Chemistry) at the laboratory of Professor Lambert Brandsma (Utrecht University, The Netherlands).

[†] Fax: (3952)39-60-46; E-mail: bat@irioch.irk.ru

[1] S. Fischer, *Ber.*, **16**, 2241 (1883).

[2] O. Piloty, *Ber.*, **43**, 489 (1910).

[3] L. Brandsma and P. J. W. Schuijl, *Rec. Trav. Chim.*, **88**, 30 (1969).

[4] L. Brandsma, *Int. J. Sulfur Chem. B.* **6**, 85 (1971).

[5] R. A. van der Welle and L. Brandsma, *Rec. Trav. Chim.*, **92**, 667 (1973).

[6] B. A. Trofimov and A. I. Mikhaleva, *Khim. Geterotsikl. Soed. (Russ.)*, 1299 (1980).

[7] B. A. Trofimov, *Adv. Heterocyclic Chem.*, **51**, 177 (1990).

[8] R. L. P. de Jong and L. Brandsma, *J. Organomet. Chem.*, **312**, 277 (1986).

[9] R. L. P. de Jong and L. Brandsma, *Synth. Commun.*, **21**, 145 (1991).

[10] N. A. Nedolya, L. Brandsma and B. A. Trofimov, *Zh. Obshch. Khim. (Russ.)*, **66**, 2042 (1996).

[11] N. A. Nedolya, R.-J. de Lang, L. Brandsma and B. A. Trofimov, *Zh. Org. Khim. (Russ.)*, **33**, 87 (1997).

[12] N. A. Nedolya, L. Brandsma and B. A. Trofimov, *Khim. Geterotsikl. Soed. (Russ.)*, 917 (1996).

[13] N. A. Nedolya, L. Brandsma, V. P. Zinov'eva and B. A. Trofimov, *Zh. Org. Khim. (Russ.)*, **33**, 91 (1997).

[14] N. A. Nedolya, L. Brandsma and B. A. Trofimov, *Dokl. Akad. Nauk (Russ.)*, **350**, 68 (1996).

[15] N. A. Nedolya, L. Brandsma and B. A. Trofimov, *Izv. Akad. Nauk, Ser. Khim. (Russ.)*, 2813 (1996); *Russ. Chem. Bull.*, **45**, 2670 (1996).

[16] N. A. Nedolya, L. Brandsma, R.-J. de Lang and B. A. Trofimov, *Zh. Org. Khim. (Russ)*, **33**, 637 (1997).

[17] N. A. Nedolya, L. Brandsma, V. P. Zinov'eva and B. A. Trofimov, *Zh. Org. Khim. (Russ.)*, **34**, 1559 (1998).

[18] L. Brandsma, N. A. Nedolya, H. D. Verkruijsse, N. L. Owen, Du Li and B. A. Trofimov, *Tetrahedron Letters*, **38**, 6905 (1997).

[19] L. Brandsma, N. A. Nedolya, A. C. H. T. M. van der Kerk, W. Heerma, E. T. H. G. Lutz, R.-J. de Lang, A. V. Afonin and B. A. Trofimov, *Izv. Akad. Nauk, Ser. Khim. (Russ.)*, 865 (1997).

[20] N. A. Nedolya, L. Brandsma, A. C. H. T. M. van der Kerk, W. Heerma, E. T. H. G. Lutz, R.-J. de Lang, A. V. Afonin and B. A. Trofimov, *Zh. Org. Khim. (Russ.)*, **33**, 1435 (1997).

[21] L. Brandsma, N. A. Nedolya, W. Heerma, A. C. H. T. M. van der Kerk, E. T. H. G. Lutz, R.-J. de Lang, A. V. Afonin and B. A. Trofimov, *Khim. Geterotsikl. Soed. (Russ.)*, 572 (1997).

[22] B. A. Trofimov, N. A. Nedolya, L. Brandsma, Yu. L. Frolov, E. Yu. Larionova, D.-S. D. Toryashinova and N. M. Vitkovskaya, *Sulfur Letters*, (1999) in press.

[23] N. A. Nedolya, L. Brandsma and B. A. Trofimov, *to be published.*

[24] N. A. Nedolya, L. Brandsma, O. A. Tarasova, H. D. Verkruijsse and B. A. Trofimov, *Tetrahedron Letters*, **39**, 2409 (1998).

[25] L. Brandsma, N. A. Nedolya and B. A. Trofimov, *Eur. J. Org. Chem.*, (1999) in press.

[26] L. Brandsma, N. A. Nedolya and B. A. Trofimov, *to be published.*

[27] L. Brandsma, N. A. Nedolya and B. A. Trofimov, *to be published.*

[28] L. Brandsma, N. A. Nedolya, R.-J. de Lang and B. A. Trofimov, *Izv. Akad. Nauk, Ser. Khim. (Russ.)*, 3024 (1996); *Russ. Chem. Bull. (Engl.)*, **45**, 2873 (1996).

[29] L. Brandsma, N. A. Nedolya, R.-J. de Lang and B. A. Trofimov, *Khim. Geterotsikl. Soed. (Russ.)*, 571 (1997).

[30] N. A. Nedolya, L. Brandsma, R.-J. de Lang and B. A. Trofimov, *Zh. Org. Khim. (Russ.)*, **33**, 1437 (1997).

[31] N. A. Nedolya, L. Brandsma and B. A. Trofimov, *to be published.*

[32] F. Taherirastgar, N. A. Nedolya, L. Brandsma, R.-J. de Lang and B. A. Trofimov, *Dokl. Akad. Nauk (Russ.)*, **353**, 64 (1997).

[33] L. Brandsma, N. A. Nedolya, O. A. Tarasova, L. B. Klyba, L. M. Sinegovskaya and B. A. Trofimov, *Dokl. Akad. Nauk (Russ.)*, **357**, 350 (1997).

[34] O. A. Tarasova, V. Yu. Vvedensky, N. A. Nedolya, B. A. Trofimov, L. Brandsma and H. D. Verkruijsse, *Eur. J. Org. Chem.*, 253 (1998).

[35] L. Brandsma, O. A. Tarasova, V. Yu. Vvedensky, R. L. P. de Yong, H. D. Verkruijsse, L. B. Klyba, N. A. Nedolya and B. A. Trofimov, *Zh. Org. Khim.* (*Russ.*), (1999) in press.

[36] L. Brandsma, V. Yu. Vvedensky, N. A. Nedolya, O. A. Tarasova and B. A. Trofimov, *Tetrahedron Letters*, **39**, 2433 (1998).

[37] O. A. Tarasova, N. A. Nedolya, V. Yu. Vvedensky, L. Brandsma and B. A. Trofimov, *Tetrahedron Letters*, **38**, 7241 (1997).

[38] N. A. Nedolya, L. Brandsma and B. A. Trofimov, *to be published.*

[39] N. A. Nedolya, L. Brandsma, H. D. Verkruijsse, A. C. H. T. M. van der Kerk and B. A. Trofimov, *Dokl. Akad. Nauk* (*Russ.*), **360**, 356 (1998).

[40] N. A. Nedolya, L. Brandsma, A. C. H. T. M. van der Kerk, V. Yu. Vvedensky and B. A. Trofimov, *Tetrahedron Letters*, **39**, 1995 (1998).

[41] N. A. Nedolya, L. Brandsma, H. D. Verkruijsse, A. C. H. T. M. van der Kerk and B. A. Trofimov, *Tetrahedron Letters*, **39**, 2631 (1998).

[42] N. A. Nedolya, L. Brandsma, H. D. Verkruijsse and B. A. Trofimov, *Khim. Geterotsikl. Soed.* (*Russ.*), 626 (1998).

[43] N. A. Nedolya, L. Brandsma, A. C. H. T. M. van der Kerk, A. V. Afonin, R.-J. de Lang and B. A. Trofimov, *Zh. Obshch. Khim.* (*Russ.*), **67**, 701 (1997).

[44] N. A. Nedolya, L. Brandsma and B. A. Trofimov, *Tetrahedron Letters*, **38**, 6279 (1997).

[45] L. Brandsma, N. A. Nedolya and B. A. Trofimov, *Izv. Akad. Nauk, Ser. Khim.* (*Russ.*), 541 (1998); *Russ. Chem. Bull.* (*Engl.*), **47**, 523 (1998).

[46] N. A. Nedolya, L. Brandsma, A. C. H. T. M. van der Kerk, A. V. Afonin, R.-J. de Lang and B. A. Trofimov, *Zh. Org Khim.* (*Russ.*), **34**, 722 (1998).

[47] L. Brandsma, N. A. Nedolya, H. D. Verkruijsse and B. A. Trofimov, *Khim. Geterotsikl. Soed.* (*Russ.*), 1275 (1997).

[48] N. A. Nedolya, L. Brandsma and B. A. Trofimov, *Izv. Akad. Nauk, Ser. Khim.* (*Russ.*), 186 (1998); *Russ. Chem. Bull.* (*Engl.*), **47**, 187 (1998).

[49] N. A. Nedolya, L. Brandsma and B. A. Trofimov, *Dokl. Akad. Nauk* (*Russ.*), **358**, 72 (1998).

[50] N. A. Nedolya, L. Brandsma, H. D. Verkruijsse and B. A. Trofimov, *Dokl. Akad. Nauk* (*Russ.*), **358**, 196 (1998).

[51] N. A. Nedolya, L. Brandsma, H. D. Verkruijsse and B. A. Trofimov, *Zh. Org. Khim.* (*Russ.*), **34**, 950 (1998).

[52] N. A. Nedolya, L. Brandsma and B. A. Trofimov, *Mendeleev Commun.*, 92 (1997).