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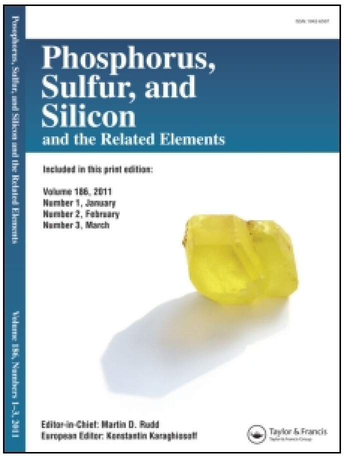

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Sulfur-Containing Pyrroles

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SULFUR-CONTAINING PYRROLES

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1 Favorsky Street, 664033 Irkutsk, Russia

Abstract The ketoxime-acetylene-based pyrrole synthesis provides two general versatile approaches to sulfur-containing pyrroles: (i) *via* sulfur-containing ketones, particularly such as acylated aryl sulfides or thiophenes and (ii) *via* thiylation reactions (including those *via* metallation) of N-vinylpyrroles or dithiocarbonization of pyrroles available from the reaction of ketoximes with acetylene or its synthetic equivalents. Syntheses of alkylthiopyrroles, alkylthioarylpyrroles, 2-(2-thienyl)pyrroles (and their N-vinyl derivatives), N-(alkylthio or arylthio)ethylpyrroles, pyrrole-1- and pyrrole-2-dithiocarboxylates (by the reaction of pyrroles with carbon disulfide) and their derivatives such as functionalized 2-(1-alkylthiovinyl)pyrroles, 1-alkylthio-3-imino-3H-pyrrolizines, 1-alkylthio-3H-pyrrolizin-3-ones, are discussed.

Key Words ketoxime, acetylene, pyrrole, N-vinylpyrrole, thiylation, alkylthiopyrroles, 2-(2-thienyl)pyrroles, pyrrole-2-dithiocarboxylates, (alkylthio)iminopyrrolizines, (alkylthio)pyrrolizinones

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1. INTRODUCTION

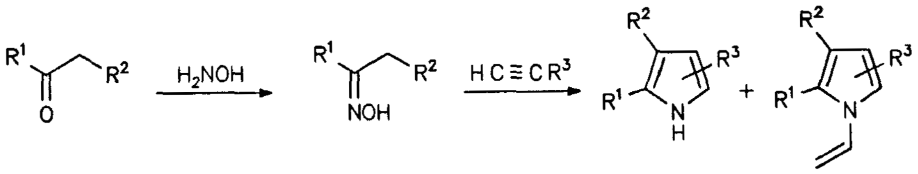
The importance of the pyrrole structural unit in the creativeness of the Living Nature, organic synthesis and drug design is well known to become even a truism. However, up till now in the whole chemistry of pyrrole, sulfur plays just an occasional and amazingly modest role in spite of being one of key elements of organic synthesis. Yet, the pyrrole-sulfur love story contains glorious pages associated with the synthesis of corroles and vitamin B_{12} and such names as Woodward, Hoffman[1] and other outstanding chesmists[2].

As a representative examples of the synthetic approaches to the sulfur containing pyrroles the reaction between the copper derivative of 1-methylpyrrole and iodo thiophenes to afford thienyl and di(thienyl)pyrroles can be cited[3].

After discovery of a general versatile method for the preparation of pyrroles from ketoximes and acetylenes (Scheme 1) or their synthetic equivalents (actually, the two-step transformation of ketones into pyrroles and their N-vinyl derivatives[4-7]) new opportunities for the synthesis of sulfur containing pyrroles appeared.

By this reaction the following two general ways of the sulfur-containing pyrrole design are feasible:

i) to make use of the ketones or acetylenes with substituents (R^1, R^2 or R^3) containing sulfur

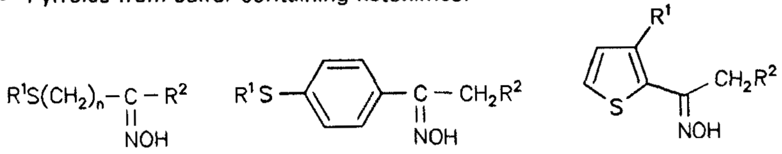


SCHEME 1

ii) introduction of a sulfur entity into the pyrroles (obtained by the above reaction) using their unsaturated or functional substituents or special substituent effect.

Correspondingly, in this paper the following topics are covered:

- Pyrroles from sulfur-containing ketoximes:



n = 1, 2

- Addition of thiols to 1-vinyl- and 1-allenylpyrroles
- Dithiocarbonization of pyrroles with CS_2 and further transformations

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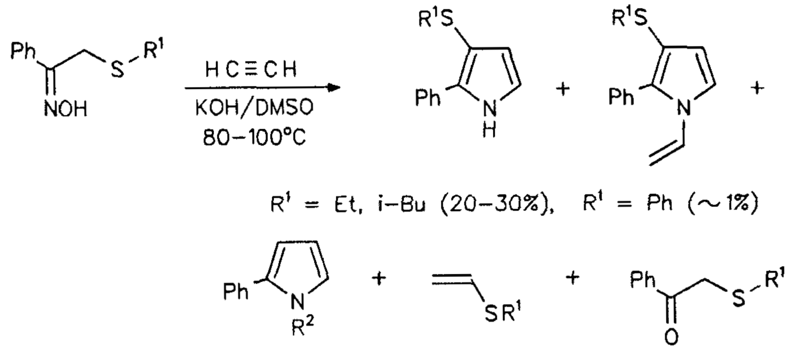
2. PYRROLES FROM SULFUR-CONTAINING KETOXIMES

2.1. Ketoximes with Sulfur at *α*- and ß-positions

In attempt to develop an approach to the synthesis of scarcely known sulfur-substituted pyrroles we have examined the reaction of the phenacyl sulfides oximes (readily synthesized from chloroacetophenone) with acetylene (Scheme 2) under conditions normally employed for the pyrrole synthesis (KOH/DMSO, 80-100°C)[4-7].



SCHEME 2 R^2 = H; CH=CH_2 R^1 = Ph (8%) R^1 = Ph (12%)

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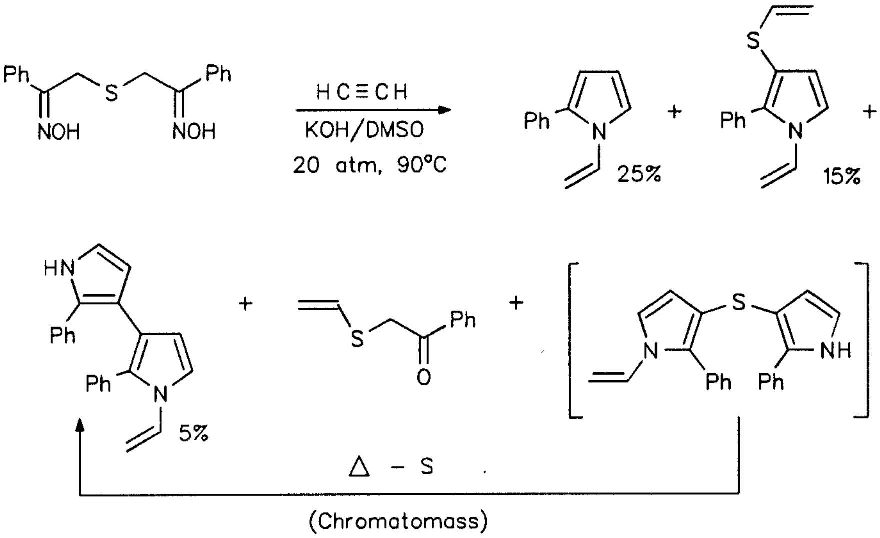
These oximes were found to undergo reductive cleavage of the C-S bond to form pyrroles free of sulfur along with the expected 3-alkylthio- or 3-phenylthiopyrroles, the yields of which being from poor (R = Ph, ~ 1%) to modest (R = Et, 27%). Such a type of decomposition is known to be common to *α*-heterosubstituted ketones and their derivatives[8]. Other products of this reaction, except for resinous ones, are vinyl sulfides and phenacyl sulfides, the latter resulting from deoximation of the starting ketoximes.

Di(phenacyl)sulfide dioxime with acetylene (~ 20 atm, 90-94 °C, 5-fold molar excess of KOH) gave a product mixture where 2-phenyl-1-vinylpyrrole, 2-phenyl-3-vinylthio-1-vinylpyrrole and 2,2'-diphenyl-1-vinyl-3,3'-dipyrrolyl were discernible by IR, ^{1}H NMR and chromatomass-spectrometry with the estimated yields being 25, 15 and 5% (on the dioxime consumed), respectively (Scheme 3).

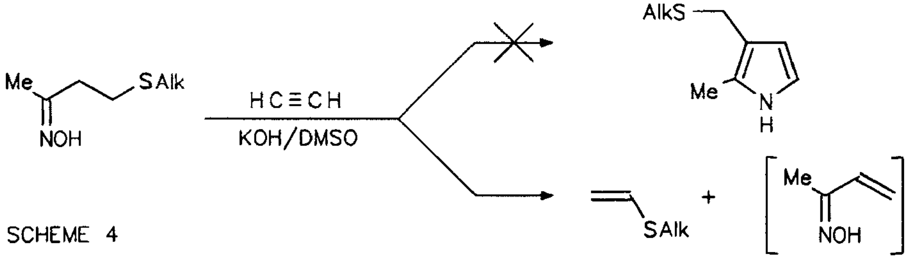


SCHEME 3

The dipyrrolyl formation seems to result from the expected dipyrrolyl sulfide by the extrusion of sulfur upon the chromatomass analysis of the product mixture (similar to the corrole formation from thiaphlorin).[1,2]

Thus, the ketoximes with the sulfide moiety at the *α*-position to the oxime function react with acetylene in the presence of KOH/DMSO system to give, at best, just modest yields of the expected sulfur-substituted pyrroles, mostly undergoing cleavage of the C-S bond and deoximation.

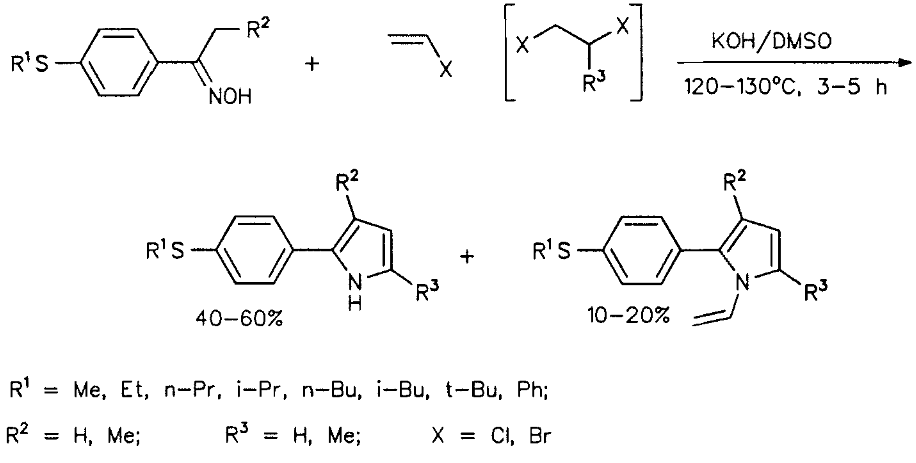
The same happened to be true for ketoximes with the sulfide moiety at the β-position to the oxime function (Scheme 4). In this case no pyrroles at all (neither the expected sulfur-containing nor free of sulfur ones) have been detected in the reaction mixture thus indicating the anticipated ß-elimination to occur much faster than pyrrolization.



SCHEME 4

2.2. Alkylthiophenylpyrroles

A number of rather simple arylpyrrolic antibiotics are known to be isolated from natural sources[9-12]. In this connection sulfur-containing arylpyrroles are also of pharmacological interest. However, no facile route to their preparation was available before the discovery of the pyrrole synthesis from ketoximes and acetylene or its synthons. Recently, acetylene-free versions of this reaction have been successfully employed for the synthesis of 2-(4-alkylthiophenyl)pyrroles and their N-vinyl derivatives from alkyl-4-alkylthiophenyl ketoximes, vinyl halides[13-15] or 1,2-dihaloalkanes[15] being used as synthetic equivalents of acetylene (Scheme 5).



SCHEME 5

As an eliminating and catalytic system the superbasic suspension KOH/DMSO was employed with 3-10-fold excess relative to the ketoxime, the same excess of an acetylenic synthon (vinyl halide or 1,2-dihaloalkanes) is required to reach preparatory yields of the target pyrroles, which normally span 40-60% for NH-pyrroles and 5-20% for their N-vinyl

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derivatives.

Dihaloalkanes as acetylenic synthons in this pyrrole synthesis perform even better than vinyl halides, being in the same time more convenient to handle. When 1,2-dibromopropane was used, the corresponding 5-methylpyrroles were formed.

In UV spectra of the pyrroles synthesized the long wave absorption band belonged to a π-π^* transition is bathochromically shifted by 16-19 nm relative to the same band of 2-phenylpyrrole[16] and its intensity is increased by 1,5 times. These effects show the sulfur atom to be switched in the common conjugation, apparently as an electron-accepting site. The electron-releasing 5-methyl substituent further strengthens the push-pull character of the whole system which is expressed by a more pronounced bathochromic shift of the longer wave absorption band. On the contrary, the 3-methyl substituent distorts the coplanarity of the benzene and pyrrole rings[17] that leads to a 1,5 times drop in the intensity of the band in question.

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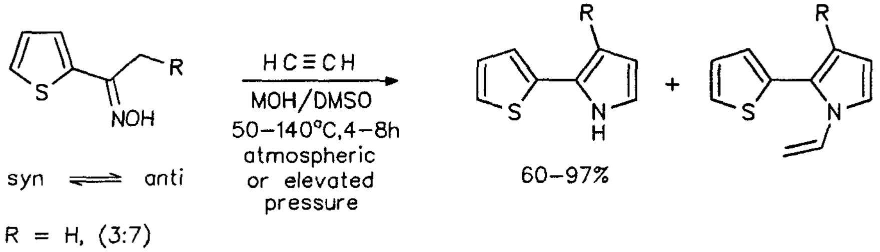
2.3. 2-(2-Thienyl)pyrroles

The ketoxime-based design of pyrrolic structures has allowed a broad series of earlier practically unknown 2-(2-thienyl)pyrroles and their N-vinyl derivatives to become as accessible as starting 2-acetylthiophenes (Scheme 6)[4-7,18-20]. The heterocyclization of alkyl thienyl ketoximes with acetylene proceeds smoothly in superbasic catalytic systems MOH/DMSO at 50-140°C (preferably, 100-130°C). The experimental procedure is simple: acetylene is passed through the heated stirred solution of a ketoxime and MOH in DMSO at atmospheric pressure for 4-8 h. To accelerate the process one may run it in an autoclave under acetylenic pressure (initial pressure of 10-15 atm at ambient temperature reaches its high of 20-25 atm at the reaction temperature and then rapidly drops upon consumption of acetylene). The yield ranges from 60% to a quantitative one.

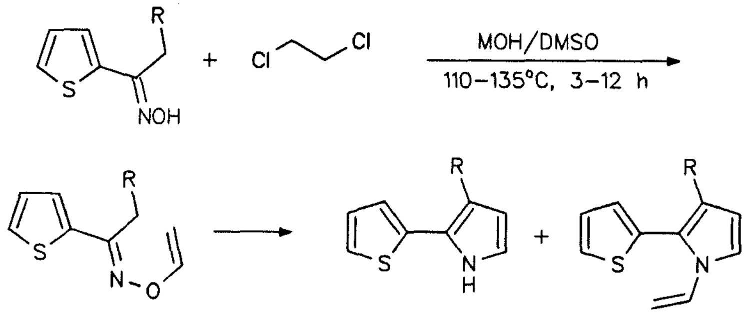


R = H, Me, Et, n–Pr, i–Pr, n–Bu, n–C_6H_{13}; M = Li, Na, K

SCHEME 6

The starting alkyl thienyl ketoximes consists of *syn* and *anti* isomers in different proportions and, since in some other cases, *e.g.*, for oxime of 1-methyl-2-acetylbenzimidazole[21], only the *anti* isomer was found to participate in the pyrrole formation leaving the *syn* isomer intact, one might assume that the oximes with a higher content of *anti* isomer would give better yields of the thienyl pyrroles. In fact, this does not occur[20,21] due to an easy *syn* → *anti* transition as it was observed for methyl thienyl ketoxime, the pure *syn* and *anti* isomer of which were separated (PTLC) and each subjected to the reaction with acetylene.[20]

2-(2-Thienyl)pyrroles and their N-vinyl derivatives can also be obtained by reacting alkyl thienyl ketoximes with 1,2-dichloroethanes in the same systems MOH/DMSO (Scheme 7).[22] The yields of NH-pyrroles are within the 34-54% range and those of N-vinyl derivatives span 15-25%.



20–30% (M = Li)

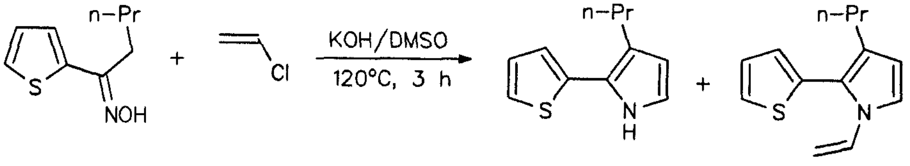
M = Li, Na, K

R	yield, %
H	54
Me	38
Et	34
n–Bu	42

15–25%

SCHEME 7

Replacement of free acetylene by vinyl chloride in the reaction with alkyl 2-thienyl ketoximes appeared to be a rather efficient procedure as well (Scheme 8)[20]. Varying the reagent ratio and the reaction conditions one may obtain 3-alkyl-2-(2-thienyl)-pyrroles and their N-vinyl derivatives in a total yields up to 72%.



SCHEME 8

46%

26%

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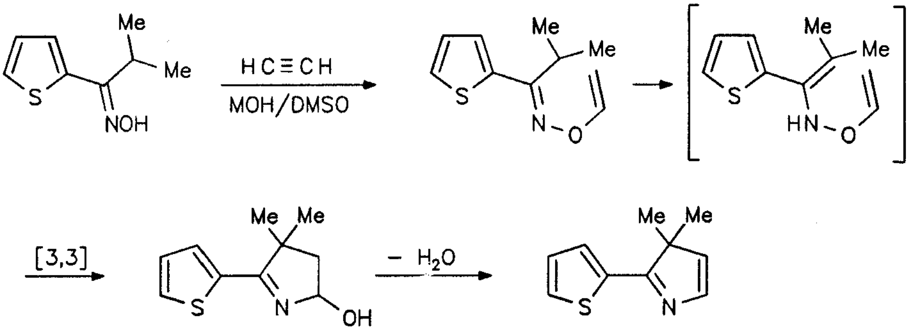
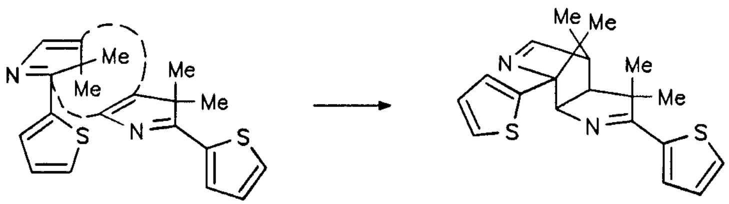
2-(2-Thienyl)-3H-pyrroles were proven[23] to be intermediates in the synthesis of 2-(2-thienyl)pyrroles from ketoximes and acetylene (Scheme 9). In the case of the secondary alkyl adjacent to the oxime function, the 3H-pyrroles can be isolated, thus promising a convenient route to the heretofore inaccessible and highly reactive nonaromatic pyrrole isomers, *e.g.*, 2-(2-thienyl)-3H-pyrrole being isolated in 43% yield (based on the reacted ketoxime)[24]. At a lower temperature, the reaction can be stopped at the intermediate stages: *e.g.*, at 40-60°C, O-vinyl alkyl 2-thienyl ketoximes are formed in a yield up to 70%,[20] which at a higher temperature rearrange into 5-hydroxy-2-(2-thienyl)pyrrolines, in the case of *i*-propyl 2-thienyl ketoxime, the latter eliminating a molecule of water to give the 3H-pyrrole.



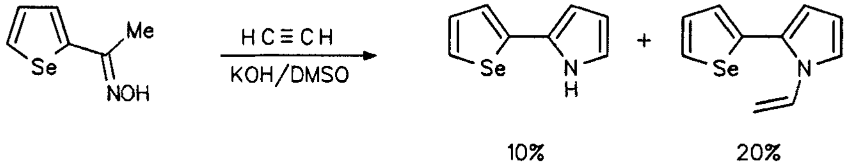
SCHEME 9

When stored in a sealed ampulla, 2-(2-thienyl)-3H-pyrrole dimerizes regio- and stereoselectively in a Diels-Alder fashion (Scheme 10)[25] to afford the representative of a new bridgehead system 3,3,10,10-tetramethyl-4,7-di(2-thienyl)-5,8-diazotricyclo[4.3.1.0^{2,6}]-deca-4,8-diene in *c.a.* 20% yield. Thus, this condensation provides a simple approach to earlier unknown partially reduced di(2-thienyl)pyrrolopyridines.



SCHEME 10

The pyrrolization of methyl 2-selenienyl ketoxime (Scheme 11)[26] under the conditions near to optimal for alkyl 2-thienyl ketoxime leads to the expected 2-selenienyl-1H- and -1-vinylpyrroles in 10 and 20% yields only, whereas a total yield of corresponding 2-(2-furyl)- and 2-(2-thienyl)pyrroles under such conditions tops 80-90%.[4-7,27]



Start: syn : anti ~1:1
Recover: syn : anti ~4:1

SCHEME 11

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The starting ketoxime was a ~ 1:1 mixture of *syn* and *anti* isomers and at 95-97°C the latter preferably reacted to enrich the recovered sample with the *syn* isomer up to 80%, being in accordance with other data[4-7,21] on the reaction stereochemistry. But this does not fully explain, if any, the poor yields of selenienyl pyrroles, which apparently is a result of the instability of the selenophene nucleus under the reaction conditions.

The ^{1}H NMR spectrum (Table I) of the 2-(2-selenienyl)-1-vinylpyrrole shows an unusual down-field shift (0.2-0.5 ppm) of pyrrolic and vinylic protons as compared with those of 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles[7,20,28] which implies an unexpectedly strong π-electron displacement towards the selenophene nucleus. In the UV spectra of 2-(2-furyl)-, 2-(2-thienyl)- and 2-(2-selenienyl)pyrroles, the bathochromic shift of the longer wave in the same order, in consistence with the polarizability of the molecules, is observed (Table I).[26]

2-(2-Thienyl)-1-vinylpyrroles, now accessible, provide versatile routes to 1-substituted 2-(2-thienyl)pyrroles by diverse addition reactions (electrophilic, free-radical and metallocomplex-catalayzed ones) to the N-vinyl group.

They add alcohols, including acetylenic ones, in the presence of perfluorobutyric acid, to afford corresponding 1-(1-alkoxy)- or (1-alkynoxy)ethylpyrroles (electrophilic mechanism) in a yield up to 70%[7,20,27,29,30] whereas thiols, in the presence of radical initiators like azobisisobutyronitrile (ABN), react with N-vinyl-2-(2-thienyl)pyrroles to form anti-Markovnikov adducts in almost quantitative yield (free-radical mechanism).[7,20,27] Hexachloroplatinic acid or rhodium complex $(Ph_3P)_3RhCl$ catalyze the anti-Markovnikov addition of hydrosilanes to the N-vinyl group to give the expected ß-adducts in good yields (up to 70%).[7,20,27,31] The cycloaddition reaction with tetracyanoethylene results in 2-thienyl-5,6-dihydro-5-methoxy-7,8-dicyanoindolizines in near quantitative yield.[7,20,27,32]

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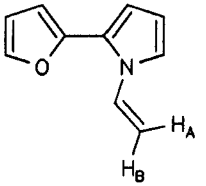
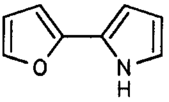
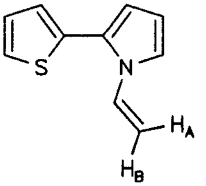
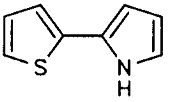
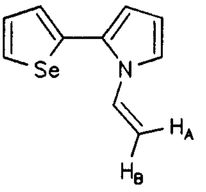
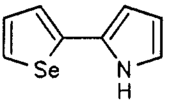
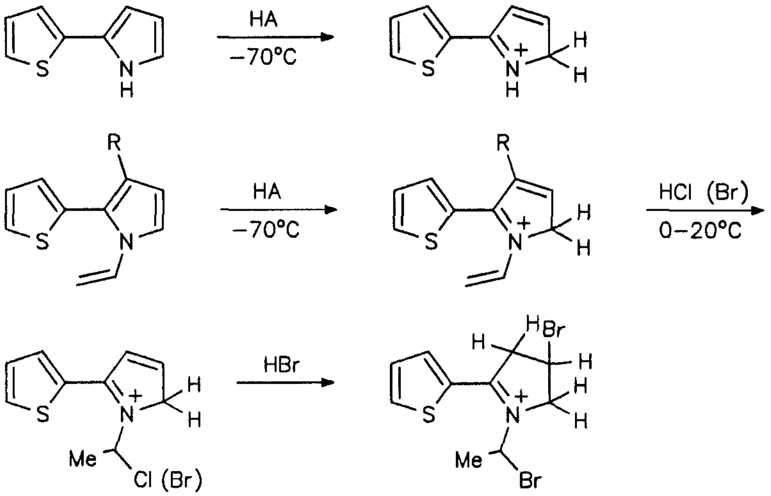
TABLE I Indicators of intramolecular interaction in 2-(2-furyl)-, 2-(2-thienyl)- and 2-(2-selenienyl)pyrroles

Pyrrole	^{1}H NMR δ, ppm (ref^{20})	Pyrrole	UV λ, nm
	5,08 (A) 4,67 (B)		279 (ref^{28}) 287 (ref^{26})
	4,95 (A) 4,65 (B)		305 (ref^{26})
	5,33 (A) 4,80 (B)		317 (ref^{26})

Electrophilic substitution reactions of 2-(2-thienyl)pyrroles extend yet more their synthetic potential. Interestingly, 2-(2-thienyl)-1-vinylpyrrole, on trifluoroacetylation gives a better preparative result than does its non-vinylated precursor (71 and 53%, respectively).[7,20,27,33] It is also noteworthy, that the N-vinyl group remains intact, although vinyl ethers, sulfides, enamines and N-vinylamides under the same conditions are readily trifluoroacylated at the ß-position of the vinyl group.[34] The absence of the secondary acylation products is compatible with the strong deactivating effects of the trifluoroacetyl substituent, which is transmitted to the α-position of the thiophene ring.

2-(2-Thienyl)pyrrole and its 3-alkyl-1-vinyl derivatives are protonated by HSO_3F, CF_3COOH, HCl and HBr at the pyrrole C-5 atom (Scheme 12)[35], at -70°C the only reaction products observed (^{1}H NMR) being the 2-(2-thienyl)pyrrolium ions, independent of the nature of the acid (except for the super acid system).

In contrast to the 2-(2-furyl)pyrroles[36], increasing the sample temperature to 20°C does not result in formation of isomeric cations by alternative protonation of the other heterocyclic ring, although in the case of HCl and HBr their additions to the vinyl group occur. The reaction of 2-(2-thienyl)-1-vinylpyrrole with an excess HBr at 0°C leads to the addition of a second HBr molecule to the protonated pyrrole ring to yield the 1-(1-bromoethyl)-2-(2-thienyl)-4-bromo-4,5-dihydropyrrolium ion. Unlike 2-(2-furyl)pyrroles[36], no addition to the thienyl ring has been observed.



R = H, Me, i−Pr

HA = HSO_3F, CF_3COOH, HCl, HBr

SCHEME 12

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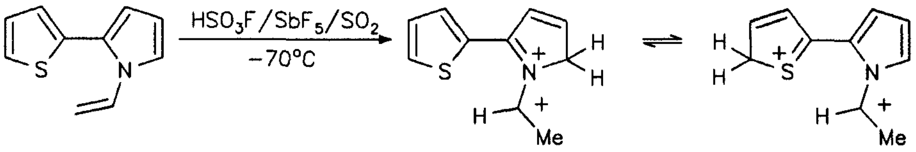
The interaction of 2-(2-thienyl)-1-vinylpyrrole with the super acid system HSO_3F-SbF_5-SO_2 differs sharply from those with the other acids (Scheme 13). The ^1H NMR spectrum of the reaction mixture at -70°C shows reliably the presence of pyrrolium and thiophenium dications in a 2:1 ratio.[35]



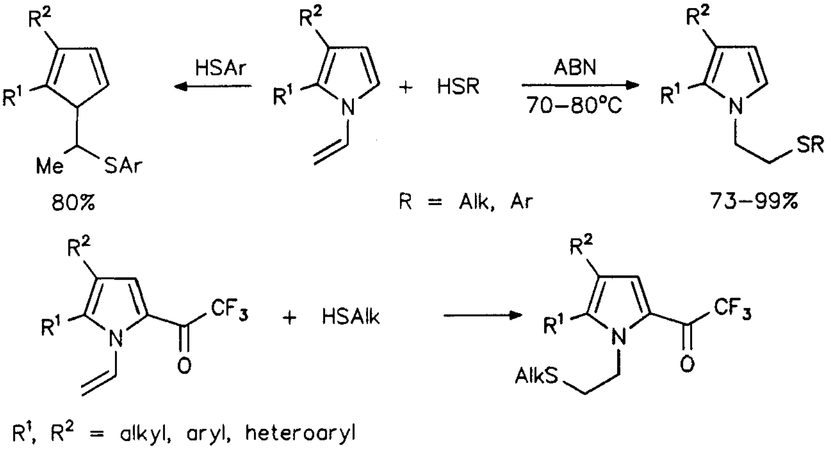
SCHEME 13

The heats of formation (ΔH), charges and HOMO partial electron density for 2-(2-thienyl)pyrrole and its protonated forms have been calculated by the MNDO method.[35] The calculated ΔH values of thienylpyrrolium and pyrrolylthiophenium ions are in agreement with the experimentally observed ratio.[35]

3. REACTIONS OF PYRROLES WITH SULFUR COMPOUNDS

3.1. Thiylation of 1-Vinyl- and 1-Allenylpyrroles

A convenient synthetic route to 1-(2-alkylthioethyl)pyrroles by the addition of alkanethiols to 1-vinylpyrroles, has been developed (Scheme 14).[7,27,37,38] When heated to 70-80°C, 1-vinylpyrroles react with alkanethiols in the presence or absence of a radical initiator to produce only ß-adducts, with ABN their preparative yields being 73-99%.



SCHEME 14

The free-radical thiylation of the 5-trifluoroacetyl-1-vinylpyrroles occurs without complication to form only the ß-adducts.[7,39]

Under free-radical initiation, arenethiols also selectively add to 1-vinylpyrroles to form 1-(2-arylthioethyl)pyrroles.[40] However, the initiator-free version of the addition gives mainly (up to 80%) the 1-(1-arylthioethyl)pyrroles with *c.a.* 20% of the ß-adducts (Scheme 14). Thus, unlike alkanethiols, which add to 1-vinylpyrroles exclusively by the radical mechanism to form the ß-adducts, arenethiols, because of their increased acidity, tend to electrophilic addition leading to the α-adducts.

Methyl 2-(pyrrolyl-1)ethylthioacetates have been synthesized in 53-71% yields by free-radical addition of methyl mercaptoacetate to 1-vinylpyrroles (Scheme 15).[41] With ammonia and hydrazine hydrate the esters give the corresponding amides and hydrazides.

Thiylation of 1-allenyl-4,5,6,7-tetrahydroindole, expectedly, follows different

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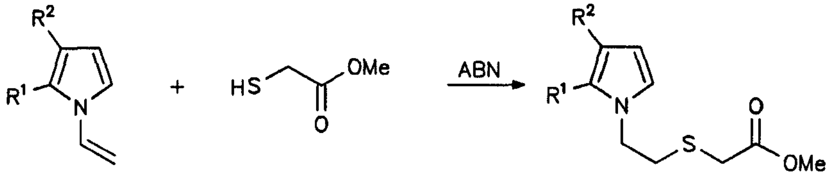
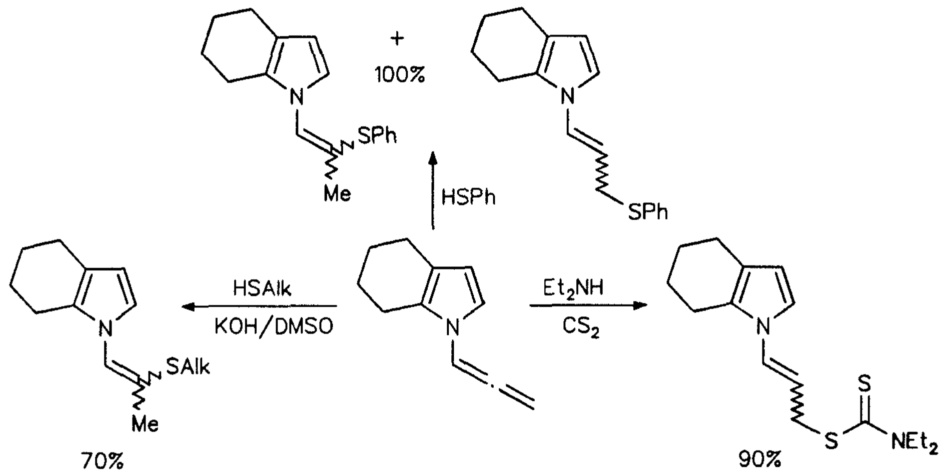


R^1 = Me, Ph; R^2 = H, n–Pr, n–Bu; R^1–R^2 = $(CH_2)_4$

SCHEME 15

directions, depending on the reaction conditions and the reagent (Scheme 16).[42]

Under nucleophilic conditions, alkanethiolate anions add to the internal carbon of the allenyl group to form 1-[2-(alkylthio)propen-1-yl]-4,5,6,7-tetrahydroindole, whereas the non-catalyzed reaction of benzenethiol with the same pyrrole produces both ß- and γ-adducts and with N,N-diethyldithiocarbamic acid, only the γ-adduct being formed.



SCHEME 16

3.2. Dithiocarbonization of Pyrroles

Potassium pyrrolides were reported to react with carbon disulfide in toluene[43] or dry THF[44] to afford the potassium pyrrole-1-dithiocarboxylates which, with organyl halides, form readily the corresponding esters.[43-47] Sodium pyrrole-1-dithiocarboxylate was, reportedly[47,48], prepared by reacting NaH with pyrrole and CS_2 in DMSO. Methyl pyrrole-2-dithiocarboxylate was prepared (47% yield) from the Grignard reagent of pyrrole and CS_2.[49]

Recently, we have found that substituted pyrroles in the KOH/DMSO suspension react readily with carbon disulfide at room temperature to form either selectively salts of pyrrole-2-dithiocarboxylic acids (which, after treatment with alkyl iodides, give the corresponding

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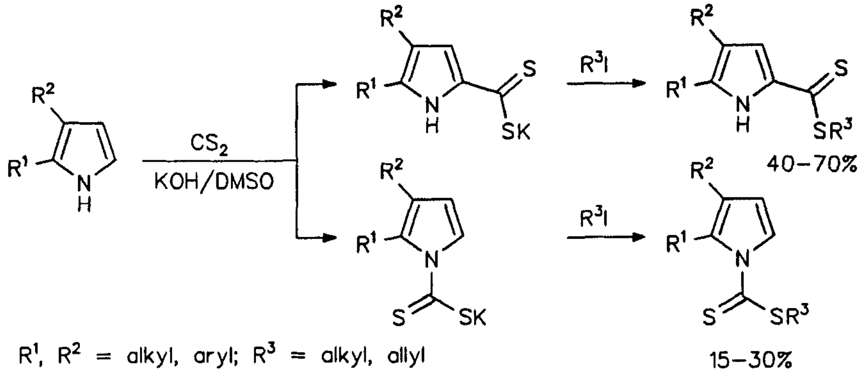
esters, in 40-70% yield) or both the pyrrole-1- and pyrrole-2-dithiocarboxylates (Scheme 17).[51-54]



SCHEME 17

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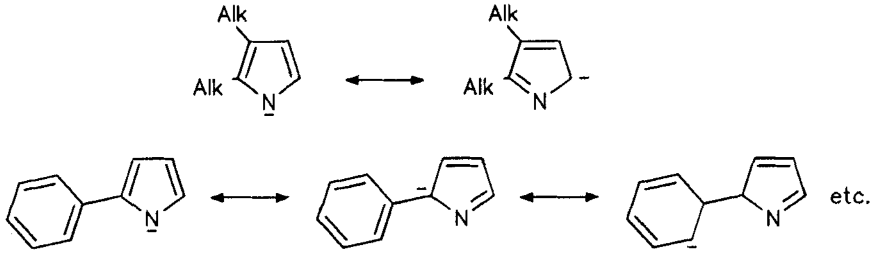
To gain better understanding of the CS_2 insertion into the pyrrole moiety and of the factors governing its selectivity and hence its synthetic applicability, we have examined the substituent effect on the ratio of the pyrrole-2- and pyrrole-1-dithiocarboxylates. The results suggest the difference in the C,N-reactivity of the ambident pyrrole anions to be dependent on the R^1 and R^2 substituent structure (Scheme 18). Evidently, electron-releasing alkyl substituents should concentrate the negative charge at the pyrrole nucleus and displace the electron density towards the C-2 atom, thus facilitating the formation of the C-adducts, whereas electron-withdrawing aryl substituents redistribute the charge and, admittedly, the HOMO locations, from the pyrrole nucleus towards the substituent.



SCHEME 18

Since in this case, the anionic center in the pyrrole ring position adjacent to the aryl substituent is sterically least accessible, the carbon disulfide molecule may be attacked by the nitrogen atom too and, therefore, the probability of the formation of pyrrole-1-dithiocarboxylates increases.

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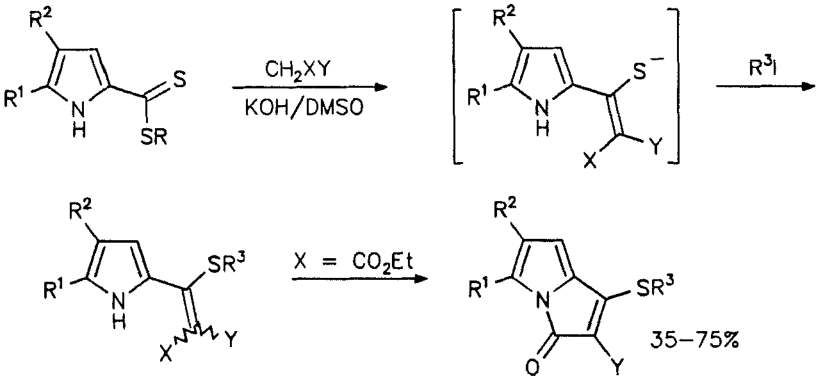
A plausible rearrangement of pyrrole-1-dithiocarboxylate into pyrrole-2-dithiocarboxylates[55] was ruled out by experiments.

Alkanethiols formed by hydrolysis of the pyrrole-1-dithiocarboxylate is oxidized by DMSO[56] to disulfides.

We have found[54,57] the condensation of the pyrrole-2-dithiocarboxylates with diverse CH-acids in the presence of the KOH/DMSO suspension followed by alkylation of the thiolates to be a facile general route to the corresponding 2-[1-(alkylthio)vinyl]pyrroles functionalized at the vinyl moiety (Scheme 19).



R^1 = Et, n–Pr, n–Bu; R^2 = n–Pr, n–Bu; R^2 = H, Et, n–Pr;
R^1–R^2 = $(CH_2)_4$; R^3 = Et, n–Bu, allyl;
X, Y = CN, COMe, CO_2Et, $CONH_2$, $CONHNH_2$

SCHEME 19

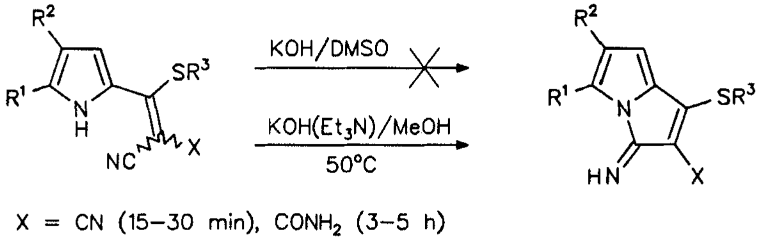
When a CH-acid contains though one carboxylate function, the annelation of the vinylpyrroles to the corresponding pyrrolizin-3-ones accompanies the condensation and its extent depends on configuration of the ethylenic moiety and the reaction conditions.

2-(1-Alkylthio-2,2-dicyanovinyl)pyrroles and 2-(1-alkylthio-2-cyano-2-carbamoylvinyl)-pyrroles are amazingly stable in the presence of the KOH/DMSO system and practically do not undergo intramolecular annelating to the 3-iminopyrrolizines during their synthesis, the latter being presenting in the reaction mixture in an amount of 1-2% (Scheme 20).

In methanol with 0.2% KOH at 50°C, the cyclization is completed almost instantly, but the pyrrolizines are contaminated with the corresponding 1-methoxy- and 1-hydroxy-pyrrolizines, the products of alkylthio group substitution for methoxy and hydroxy groups.

Pure pyrrolizines are prepared by heating (50°C) the vinylpyrroles with small amounts (0.1-0.3%) of Et_3N in methanol. Under these conditions, the 2-(1-alkylthio-2,2-dicyanovinyl)-

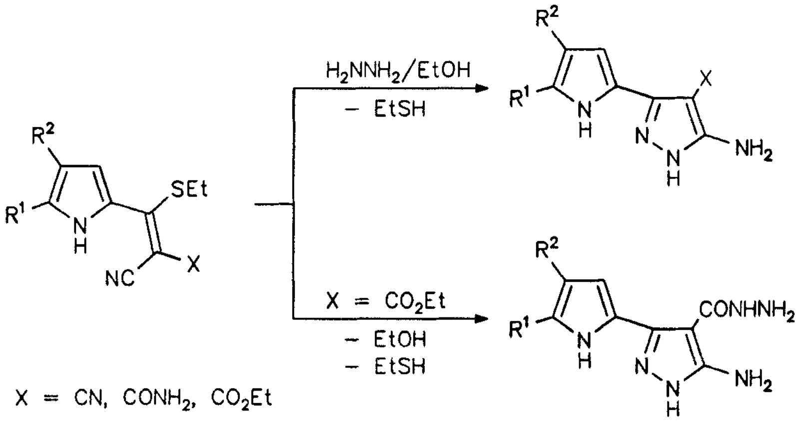
pyrroles cyclize within 15-30 min, whereas the 2-cyano-2-carbamoyl derivatives transform into the 2-carbamoyl pyrrolizines only after 3-5 h heating. Unlike 2-vinylpyrroles with CN and $CONH_2$ functions at the double bond, the corresponding vinylpyrroles with carboxylate groups undergo ring-closure much easier, often during their synthesis[58], when such CH-acids as acetoacetates, malonates or cyanoacetates are allowed to condense with pyrrole-2-dithiocarboxylates in the KOH/DMSO system (Scheme 19). The yields of pyrrolizin-3-ones are 35-75%, the lower values being associated with the expected instability of the esters in the KOH/DMSO system and with geometry requirements.



SCHEME 20

For instance, with cyanoacetic esters independent of the reaction time (0.5-3.5 h), the same product ratio is obtained implying that only the isomer with *syn*-arrangement of the CO_2Et group relative to the pyrrolic NH is annelated to the corresponding pyrrolizin-3-ones.

The functionalized 2-(1-alkylthiovinyl)pyrroles are promising intermediates for a number of other annelations. For example, being heated with hydrazine hydrate in ethanol for 5-10 min they quantitatively yield 5-(5-aminopyrazolyl-3)pyrroles (Scheme 21), the carboxylate function X = CO_2Et transforming smoothly into a hydrazido group.



SCHEME 21

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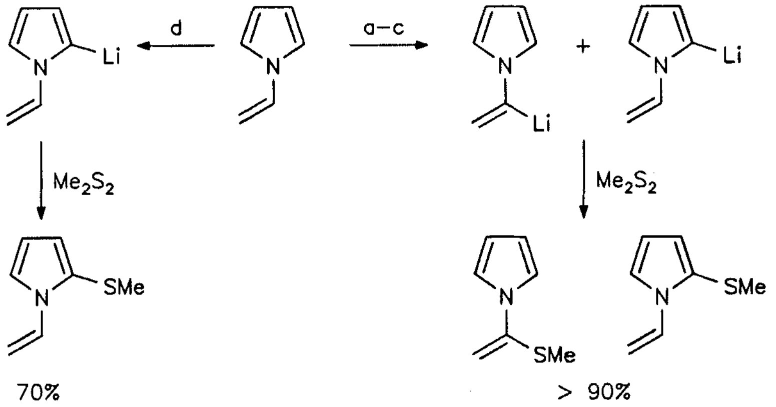
3.3. α-Ring- and α-Vinyl Thiylation of 1-Vinylpyrroles

In the search for methods giving access to derivatives of pyrrole, several authors have studied the metalation of N-substituted pyrroles.[59,60]

The metalation of 1-vinylpyrrole with n-butyllithium in THF/hexane or tetramethylethane diamine (TMEDA)/hexane mixtures proceeds surprisingly fast (at room temperature it is complete within 15 min) to form both α-ring- and α-vinyl lithium derivatives (Scheme 22)[61], which, after treatment with dimethyl disulfide at 30 to 60°C, give the corresponding α-ring- and α-vinyl methylthiopyrroles in almost equal amounts and in excellent yield.



a) BuLi/THF/hexane; b) BuLi/TMEDA/hexane;
c) BuLi/t–BuOK/THF/hexane;
d) BuLi/t–BuOK/THF/hexane/NH(i–Pr)$_2$

SCHEME 22

The product ratio and yield remain the same when a stronger super base BuLi/t-BuOK in the THF/hexane (-80°C) is employed.

The unusually fast ring-metalation of 1-vinylpyrrole (1-methylpyrrole is lithiated much less smoothly under similar conditions[59,60]) may be attributed to both the electron-withdrawing nature of the vinyl group, and to its some coordinating properties towards the lithium cation.

The selevtive ring-metalation and hence thiylation has been achieved by combination of the latter super base system with 5-10 mol % of HN(i-Pr)$_2$ as a very mild proton-transfer agent. We believe that in the presence of this amine, the kinetically-controlled metalation of 1-vinylpyrrole becomes a thermodynamically-controlled one by the proton donation and removal sequence.[61] Under these conditions, 2-methylthio-1-vinylpyrrole has been isolated in 70% yield as the only product.

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Thus, the selective α-ring-metalation of 1-vinylpyrroles followed by thiylation with diorganyl disulfides is proving to be a preparatory attractive entry to a yet more new family of sulfur-containing pyrroles, synthetic intermediates of high potential.

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