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Bipyrroles, furyl- and thienylpyrroles

S E Korostova (deceased), A I Mikhaleva, B A Trofimov

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Abstract. Data on the methods of preparation of bipyrroles and furyl-, thienyl- and selenienylpyrroles are summarised and described systematically. The reactivity and the prospects of application of these compounds are discussed. Particular attention is paid to a new convenient one-step method for the synthesis of hetaryl-substituted pyrroles starting from alkyl hetaryl ketoximes and acetylene. The bibliography includes 191 references.

I. Introduction

Derivatives of five-membered aromatic heterocycles (pyrrole, furan, thiophene and selenophene) are, as a rule, endowed with high biological activity and other useful properties and find ever-increasing uses in medicine, agriculture and technology.[1–11]

Of five-membered aromatic heterocycles, pyrrole possesses the highest reactivity and most diverse chemical properties. It is not accidental that it is pyrrole that Nature has 'chosen' for constructing the 'vital pigments' chlorophylls and hemoglobin, as well as other vitally important supramolecular structures (various porphyrins, chlorins, prodigiosins, vitamin B_{12}, *etc*.). For this reason, amongst all five-membered aromatic heterocycles the molecules containing the pyrrole nucleus attract the greatest attention of researchers and are studied in most detail.

The chemistry of bipyrroles as well as of pyrroles with furan, thiophene and selenophene substituents is a very recent field in the chemistry of heterocyclic compounds. Until recently, no sufficiently efficient and general methods of their preparation existed; therefore, these compounds remained attractive but hard to access and little studied subjects. The development of this field began in the 1970s, when new methods for pyrrole synthesis appeared or the existing procedures were modified to allow for linking five-membered aromatic heterocycles to the pyrrole ring. A very simple and versatile method based on the reaction of ketoximes with acetylene (the Trofimov reaction) has been developed, which allows the synthesis not only of hetarylpyrroles non-substituted at the nitrogen atom but also their 1-vinyl derivatives from accessible alkyl hetaryl ketoximes. This also stimulated studies of reactivity, structure, biological activity and of other useful properties of hetarylpyrroles.

Some aspects of the chemistry of pyrroles with furyl, thienyl and selenienyl substituents have been presented in monographs,[4,12] reviews,[5,6,13–21] the US physical and technical encyclopedia (chapter 'Acetylene'),[22] and Ph.D. and D.Sc. theses.[23–27] Nevertheless, generalising papers that summarise the progress in the chemistry of hetaryl-substituted pyrroles are missing. We have attempted to fill this gap by generalising and systematising the currently available literature on the methods of synthesis, reactivity, biological and other properties of pyrroles linked to five-membered aromatic heterocycles.

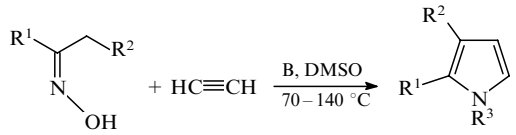
II. Methods of synthesis

Conventional methods for the synthesis of pyrroles — the Knorr, Hantzch, Piloty, Yuriev (except for the Paal–Knorr synthesis) reactions — have not found wide use for the preparation of pyrroles bound to other five-membered heterocycles. This goal can be reached most efficiently using the method based on the reaction of alkyl hetaryl ketoximes with acetylene (the Trofimov reaction), which is carried out in one step using accessible initial compounds.

New methods have been developed for the preparation of hetarylpyrroles based on activated acetylenes, *e.g*., by condensation of hetarylacetylenes with trimethylsilyl cyanide, as well as those with the use of isocyanides, other cyano compounds, azides, *etc*.

1. Synthesis from ketoximes and acetylene (the Trofimov reaction)

In the early 1970s, heterocyclisation of ketoximes with acetylene in a superbasic system (strong base–polar aprotic solvent) was discovered, which yielded in one step 1*H*- and 1-vinylpyrroles (the Trofimov reaction).[4,5,14–20,23,24,26]



R^1 = Alk, Ar, Het; R^2 = H, Alk, Ar; $R^1–R^2$ = $(CH_2)_n$; n = 3–5; B = MOH, MOR, MON=⟨; M is alkali metal; R^3 = H, CH=CH_2.

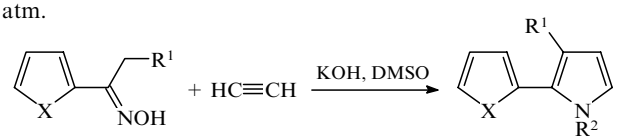
Later it was established that this reaction is of a general character and embraces virtually all ketoximes that have at least

S E Korostova, A I Mikhaleva, B A Trofimov Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, ul. Favorskogo 1, 664033 Irkutsk, Russian Federation. Fax (7-395) 239 60 46. Tel. (7-395) 246 64 09 (A I Mikhaleva), (7-395) 246 14 11. E-mail: but@acet.irkutsk.su (B A Trofimov)

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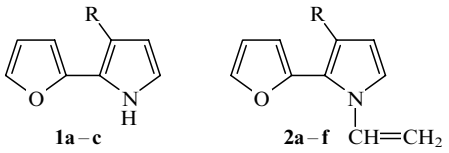
one CH_3 or CH_2 group in the α-position relative to the oxime function and contain no groups unstable in the presence of strong bases. This finding has led to successful syntheses of pyrroles and 1-vinylpyrroles with alkyl, alkenyl, cyclopropyl, aryl and hetaryl substituents in the ring; condensed pyrrole systems of the type of cycloheptano[*b*]pyrrole, dihydrobenzo[*g*]indole and 5-azaindoles including stable free radicals with the NO$^{\bullet}$ group at position 5, *etc*.[13–24, 26, 28–33]

Synthesis of hetarylpyrroles with furyl and thienyl substituents by this method was first described by Trofimov *et al*.[34–36] 2-(2-Furyl)-3-methyl-1-vinyl- and 3-ethyl-2-(2-furyl)-1-vinylpyrroles were synthesised from the corresponding ketoximes and acetylene in yields up to 85%.[35] An analogous approach was used to prepare 2-(2-thienyl)- and 2-(2-thienyl)-1-vinylpyrroles in 60% and 50% yields, respectively.[36] The reactions were carried out in an autoclave under an initial pressure of acetylene from 6 to 16 atm.



R^1 = H, Me, Et; R^2 = H, CH=CH_2; X = O, S.

Subsequently, this method has successfully been used for the preparation of 3-alkyl-2-(2-furyl)pyrroles **1a–c** and their 1-vinyl derivatives **2a–f**.[37]



Compound	R	Yield (%)	Compound	R	Yield (%)
1a	H	36	**2c**	Et	85
1b	Me	23	**2d**	Pr^n	77
1c	Et	39	**2e**	Pr^i	81
2a	H	80	**2f**	Bu^n	76
2b	Me	92			

Under conditions close to those established[4] earlier for aliphatic ketoximes [100 °C, ketoxime : KOH = 5 : 3 (w/w), excess of acetylene, pressure 10–16 atm.], the reaction of 2-furyl methyl ketoxime with acetylene produces a mixture consisting of 1*H*- (**1a**) and 1-vinyl-2-(2-furyl)pyrroles (**2a**) in the ratio of *ca* 1 : 4 and an overall yield of 71% (16% and 55%, respectively).[37]

Under analogous conditions 2-(2-furyl)-3-methyl-1-vinylpyrrole (**2b**, 57% yield) and the corresponding pyrrole **1b** (8% yield) are formed from ethyl 2-furyl ketoxime. At a higher temperature (130 °C) and an equimolar ketoxime : KOH ratio this reaction proceeds selectively with the formation of vinylpyrrole alone (**2b**, 92% yield).

The yield of furylpyrroles **1a** and **2a** upon the reaction of 2-furyl methyl ketoxime and acetylene depends on the reaction temperature (Table 1). At temperatures below 100 °C, the rate of ketoxime cyclisation into pyrrole **1a** and vinylation of the latter to vinylpyrrole **2a** is too low (the ketoxime conversion does not exceed 40%). At 130–150 °C, one observes resinification that decreases the yield of 1-vinylpyrrole **2a**. In addition, at a high temperature the process of deoximation of the initial oxime to 2-acetylfuran becomes noticeable. The optimal conditions for the synthesis of 3-alkyl-2-(2-furyl)-1-vinylpyrroles are as follows: 110–130 °C, 3 h, excess of acetylene (initial pressure 10–14 atm) and equimolar ratio ketoxime : KOH).

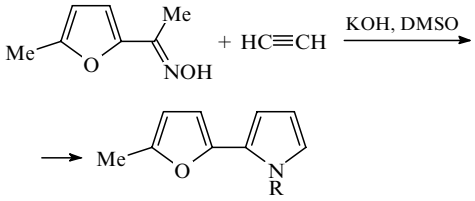
It should be pointed out that lithium hydroxide, which catalyses selectively the stage of heterocyclisation in an analogous reaction with methyl phenyl and benzyl phenyl ketoximes,[38, 39] is not selective in this case: even at 100 °C a mixture of 1*H*- (**1a**) and 1-vinylpyrroles (**2a**) is formed in the ratio 15 : 1, while the total yield of pyrroles is lower than with KOH (~ 50% instead of 72%, GLC).

Table 1. Dependence of the yield of 2-(2-furyl)- (**1a**) and 2-(2-furyl)-1-vinylpyrroles (**2a**) on the reaction temperature (molar ratio ketoxime : KOH = 1 : 1, C_2H_2 pressure 10–14 atm, 3 h).[37]

Temperature /°C	Yield of mixed products (%)	Composition of mixture (%)[a]			Ketoxime conversion (%)
		ketoxime	compound **1a**	compound **2a**	
70	85	60	26	14	40
90	82	20	24	56	80
110	70	traces	39	71	~100
120	65	"	15	85	~100
130	46	undetected	traces	~100	~100
150	21	"	"	~100	~100

[a] According to ^{1}H NMR data.

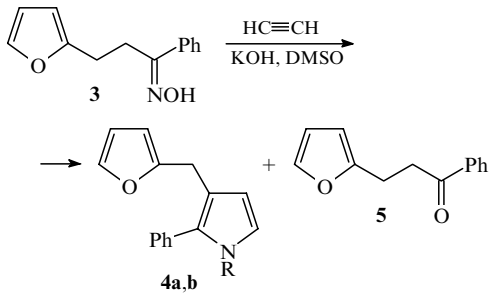
The corresponding pyrrole is also readily formed from methyl (5-methyl-2-furyl) ketoxime and acetylene.[40]



R = H (53%), CH=CH_2 (62%).

Under atmospheric pressure (100 °C, 5 h, equimolar ratio ketoxime : KOH) the yield of 2-(5-methyl-2-furyl)pyrrole is 53% and the conversion of ketoxime is 80%. Under these conditions 2-(5-methyl-2-furyl)-1-vinylpyrrole is formed in a rather low yield (15%). Under acetylene pressure of 12 atm (90 °C, 3 h, molar ratio ketoxime : KOH = 1 : 2), the same reaction produces vinylpyrrole in 62% yield, though being accompanied by resinification. According to GLC data, no more than ~ 3% of the corresponding 1*H*-pyrrole remains unconsumed under these conditions.[40]

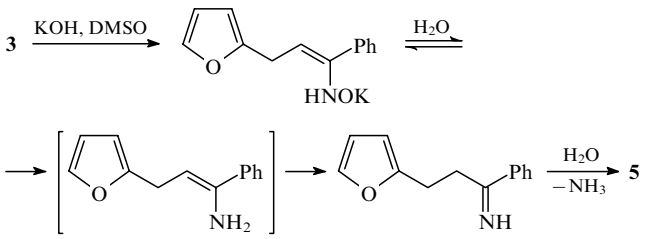
It is known that even at 50–60 °C and atmospheric pressure alkyl phenyl ketoximes react readily with acetylene to form the corresponding pyrroles in yields up to 83%.[41] The reaction of ethyl 2-furyl ketoxime with acetylene under a pressure of 10 atm and 100 °C produces 2-(2-furyl)-3-methyl- and 2-(2-furyl)-3-methyl-1-vinyl-pyrroles in yields of 8% and 57%, respectively.[37] Quite unexpectedly, in the condensation of the oxime **3** with acetylene (10 atm, 100 °C) the conversion of oxime **3** was no more than 65%, while the yield of pyrrole **4a** was as low as 30%. The reaction is accompanied by considerable resinification.



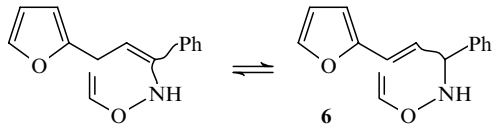
R = H (**a**), CH=CH_2 (**b**).

A decrease in the reaction temperature to 75–80 °C did not lead to higher yield of compound **4a**, because even at this

temperature ketoxime **3** seems to undergo deoximation to the ketone **5**.



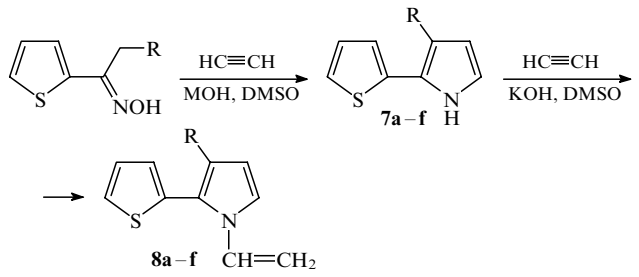
Vinylpyrrole **4b** was detected in the reaction mixture only by GLC.[40] Low yield of pyrroles **4a**,**b** was explained by the decrease in the reactivity of ketoxime **3** due to the presence of bulky phenyl and furyl groups preventing the approach of oximate anion to the triple bond. An intermediate formed from ketoxime **3** isomerises easily into a substituted vinylfuran **6**, which cannot undergo the [3,3]-sigmatropic shift and, consequently, the pyrrole formation.



These two side reactions seem to account for resinification and formation of by-products, which prevent isolation of pure pyrroles **4a**,**b**. Additional difficulties appear to be associated with oligomerisation of acetylene, which occurs in the NH_3 (amine) – KOH – DMSO systems.[42]

Condensation of alkyl 2-thienyl ketoximes with acetylene catalysed by superbases (MOH – DMSO) produced 1*H*- (**7a** – **f**) (50% – 60%) and 3-alkyl-2-(2-thienyl)-1-vinylpyrroles (**8a** – **f**) (in 60% – 70% yields).[43,44] The reaction proceeds smoothly at 100 – 130 °C and may be carried out under both elevated (10 – 16 atm) and atmospheric pressures of acetylene.

The effect of reaction conditions (temperature, acetylene concentration, addition of water, the nature of cation in the alkali metal hydroxide) on the ratio of pyrroles to their vinyl derivatives formed in the same synthesis was studied in the example of methyl 2-thienyl ketoxime.

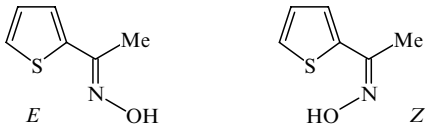


R = H (**a**), Me (**b**), Et (**c**), Pr^n (**d**), Bu^n (**e**), n-C_6H_{13} (**f**); M = Li, K.

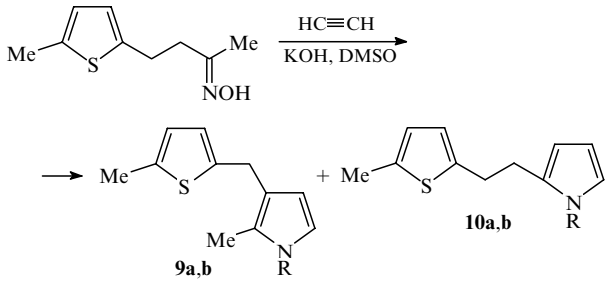
Synthesis of 2-(2-thienyl)-1-vinylpyrrole (**8a**) is best carried out in an autoclave, at 120 °C for 3 h under elevated acetylene pressure, 17 mass. % – 30 mass. % of KOH with respect to the ketoxime.[26,37] The increase in the reaction time to 5 h and more as well as in the temperature to 140 – 150 °C lead to more pronounced resinification and a lower product yield. 2-(2-Thienyl)pyrrole (**7a**) free of its vinyl derivative is produced in > 60% yield with the use of a superbasic pair LiOH – DMSO (100 °C, 3 h, 10 – 16 atm) which, as in the case of condensation of methyl phenyl ketoxime with acetylene,[38,39] catalyses the stage of pyrrole ring formation and is virtually inactive in the stage of vinylation. The amount of lithium hydroxide added is ~ 18 mass. % with respect to the ketoxime. The same pyrrole was obtained in 47% yield under atmospheric pressure (130 – 140 °C, 7 h, 30% LiOH). The addition of water to DMSO (10% – 15%) and the use of KOH (equimolar ratio of KOH to the oxime) inhibit the vinylation process and make possible the preparation of 2-thienylpyrrole (**7a**) in 53% yield. Heating of propyl 2-thienyl ketoxime with acetylene (100 – 120 °C, 0.8 mol KOH, 11% H_2O, 7 h) leads to the formation of 3-ethyl-2-(2-thienyl)pyrrole (**7c**) also in 53% yield.

The length of the carbon chain of the alkyl radical in the original alkyl 2-thienyl ketoxime does not exert any noticeable effect on the composition and yield of the final products.

The starting ketoximes are a mixture of *E*- and *Z*-isomers. It was established that only the *anti*-isomer participates in the reaction with acetylene, while the *syn*-isomer is recovered unaltered after the reaction. It could be supposed that the oximes with a large content of *anti*-isomer would give thienylpyrroles in higher yields. This is not the case because of easy *syn* – *anti*-isomerisation. This was demonstrated for methyl thienyl ketoximes, where pure *syn*- and *anti*-isomers isolated by preparative TLC were used in the reaction with acetylene.[26]

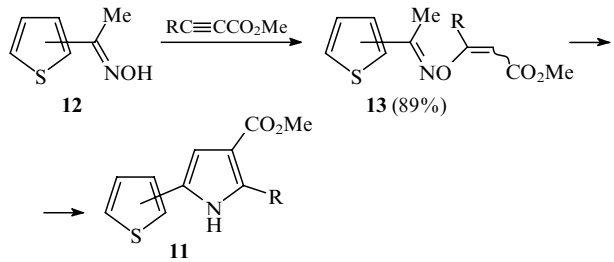


Like in the case of alkyl methyl[45] and alkyl benzyl ketoximes,[46] the reaction of (*E*)-methyl 2-(5-methyl-2-thienyl)ethyl ketoxime with acetylene involves the methylene group in the *anti*-position relative to the hydroxy group.[40] At 95 °C and atmospheric pressure, the ratio of structurally isomeric pyrroles **9a** and **10a** is 33 : 1 [yields 46% and 1.4%, respectively (GLC)], whereas vinylpyrrole **10b** was detected in the reaction products only in trace amounts. Despite a rather high total yield of pyrroles **9** and **10** (61%), their isolation from the reaction mixture proved to be problematic due to the presence of a number of unidentified by-products. More drastic conditions (120 °C) favour the increased proportion of the reaction products formed with the participation of the methyl group and also the vinylation of pyrroles **9a** and **10a**; the ratios of pyrroles **9a** : **10a** and **9b** : **10b** become equal to 24 : 1 and 5 : 1, respectively.[40]



R = H (**a**), CH = CH_2 (**b**).

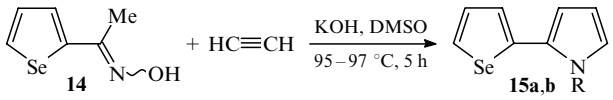
2-(2-Thienyl)- and 2-(3-thienyl)pyrroles **11** were synthesised recently using a modification of the Trofimov reaction consisting in the addition of methyl 2-thienyl and methyl 3-thienyl ketoximes **12** to methyl propiolate and dimethyl acetylenedicarboxylate.[47]



R = H, CO_2Me.

The reaction is conducted in two stages: intermediate *O*-vinyloximes **13** are transformed into thienylpyrroles **11** on boiling in xylene.

Selenienylpyrroles have remained virtually unstudied until now since no efficient methods for their synthesis had been developed. Mikhaleva *et al.*[48] have shown the possibility of preparing the corresponding pyrroles from methyl 2-selenienyl ketoxime (**14**) by its reaction with acetylene at 95–97 °C: 2-(2-selenienyl)pyrrole (**15a**) and -2-(2-selenienyl)-1-vinylpyrrole (**15b**) were produced in yields of 10% and 2%, respectively.



R = H (**a**), CH=CH$_2$ (**b**).

Ketoxime **14** was used in this reaction as a mixture of *E*- and *Z*-isomers (1 : 1). Under these conditions, the *Z*-isomer reacted predominantly (or exclusively), which correlates with the results of the analogous reaction with methyl 2-thienyl ketoxime[43] and 2-benzoimidazolyl methyl ketoxime.[49]

The low yield of pyrrole **15a** is explained by its instability in the KOH–DMSO system.[48] Further temperature increase to 110–120 °C results only in a lower yield and resinification. Apparently, the C–Se bond is less stable and more sensitive to the attack by a strong base compared with the C–O and C–S bonds (as mentioned above, under the same conditions the total yield of furyl and thienyl analogues reaches 80%–90%).

a. 1,2-Dichloroethane as an acetylene equivalent

The reaction of alkyl hetaryl ketoximes **16** with 1,2-dichloroethane (DCE), which is a synthetic equivalent of acetylene under the conditions of the Trofimov reaction, is a version of the synthesis of furyl- and thienylpyrroles.[50]

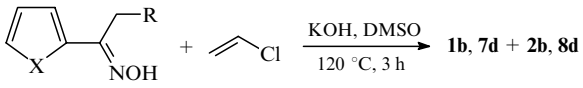
The ratio of the reaction products [hetarylpyrroles **1** and **7**, 1-vinylhetarylpyrroles **2** and **8**, intermediate *O*-2-chloroethyl (**17**) and *O*-vinyl (**18**) hetaryl ketoximes] and by-products, *viz*. 1,2-bis(hetarylalkylideneiminoxy)ethanes (**19**), depends on many factors: reaction temperature and time, the nature of the hydroxide cation, its concentration and the presence of water in the catalytic system (Scheme 1).

An advantage of this version consists in the substitution of acetylene by a more accessible, safe and handling-convenient DCE. The synthesis can be performed in a trivial apparatus under atmospheric pressure and in the temperature range 100–135 °C.[50] The highest yields of furyl- and thienylpyrroles were attained at 120 °C (6–9 h, molar ratio ketoxime : NaOH : DCE = 1 : 2 : 7). When KOH was used as a base, better results were obtained upon addition of 5%–10% of water (120 °C, 7 h, molar ratio ketoxime : KOH : DCE = 1 : 2 : 10); however, in this version the yields of 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles did not exceed 25%. In the presence of lithium hydroxide, the yields of pyrroles were lower (18%). In an NaOH–DMSO + 10% H_2O system, the reaction stops at the stage of intermediates **18**, *viz*., *O*-methyl 2-thienyl *O*-vinylketoximes (R = H, yield 43%) or 2-furyl methyl *O*-vinylketoximes (R = H, yield 6%).[50]

The detection of *O*-vinylketoximes **18** and methyl 2-thienyl *O*-(2-chloroethyl)ketoximes **17** (X = S, R = H, yield 24%) among the main reaction products has made it possible to suggest[50] that in the case of DCE, two alternative pathways of the formation of pyrroles and 1-vinylpyrroles are realised. According to the first pathway,[4] in a strongly basic medium DCE serves as the source of acetylene, and the reaction proceeds as usual (see Section II.1). The second pathway consists in the nucleophilic substitution of one chlorine atom in DCE by the oximate anion with the formation of *O*-(2-chloroethyl)ketoximes **17** with subsequent elimination of HCl to afford *O*-vinylketoximes (**18**). Intermediates **18** undergo cyclisation into the corresponding pyrroles, which react with DCE to form, apparently, 1-(2-chloroethyl)pyrroles **20**. These are further transformed into *N*-vinylpyrroles upon elimination of HCl.[50] The possibility of formation of 1-(2-chloroethyl)pyrroles **20** under these conditions is in accord with the data reported in Ref. 51.

b. Vinyl chloride as an acetylene equivalent

A simple and industrially acceptable method of synthesis of furyl- and thienylpyrroles is based on the reaction of the corresponding ketoximes with vinyl chloride in a KOH–DMSO suspension.[26] The condensation is carried out at 120 °C with a sixfold excess of KOH relative to the ketoxime. This results in the formation of a mixture of pyrroles and their 1-vinyl derivatives. In this modification of the Trofimov reaction, vinyl chloride serves as the acetylene equivalent.

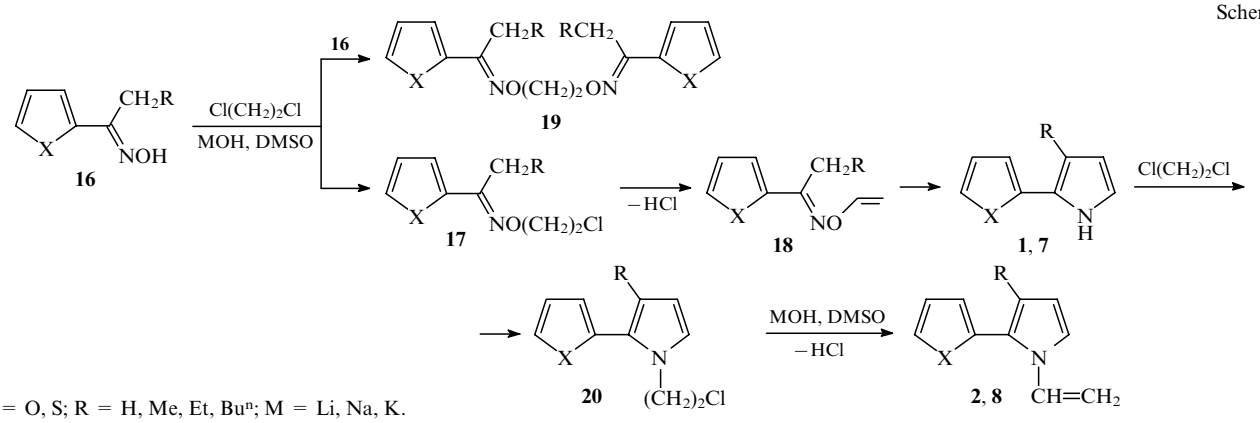


Compound	X	R	Yield (%)
1b	O	Me	40
2b	O	Me	36
7d	S	Pr^n	46
8d	S	Pr^n	26

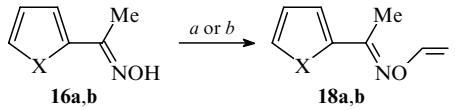
c. Intermediates and the reaction mechanism

Systematic studies on the synthesis of pyrroles from hetaryl ketoximes and acetylene in the superbasic KOH–DMSO medium have allowed not only identification of the reaction intermediates, such as *O*-vinylketoximes or 3*H*-pyrroles, but also the development of methods for their preparation.[43, 50, 52–55] For instance, 2-furyl methyl (**18a**) and methyl 2-thienyl (**18b**) *O*-vinylketoximes were obtained in yields of 38% and 32%, respectively, by the reaction of 2-furyl methyl (**16a**) and methyl 2-thienyl ketoximes (**16b**) with acetylene in the KOH–DMSO system (initial pressure 12 atm, 3 h, 50–60 °C).[52–54]

Scheme 1



X = O, S; R = H, Me, Et, Bu^n; M = Li, Na, K.



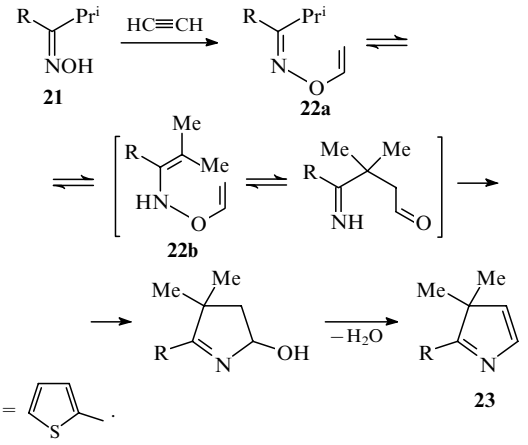
16a,b **18a,b**

X = O (**a**), S (**b**); (*a*) HC≡CH, MOH, DMSO, H_2O; (*b*)$Cl(CH_2)_2Cl$, MOH, DMSO, H_2O; M = K, Li.

Upon addition of 4% of water to the KOH – DMSO system, the yield of *O*-vinylketoxime **18b** increased to 44%.[54] Under similar conditions, the yield of the corresponding furyl derivative **18a** did not exceed 13%.[54] Under atmospheric pressure of acetylene, the synthesis of *O*-vinylketoximes is less efficient. 1,2-Dichloroethane is also suitable for the preparation of ketoximes **18a**,**b**. The optimal conditions for the synthesis of compound **18b** are the use of LiOH – DMSO system and addition of 10% of water (100 C, 4 h, yield 43%).[50] In the NaOH – DMSO system containing 10% of water, *O*-vinylketoxime **18b** is not formed, whereas the yield of *O*-vinylketoxime **18a** is as low as 6%.[50]

Ketoximes **18a**,**b** are transformed upon thermolysis into the corresponding pyrroles as do alkyl aryl *O*-vinylketoximes,[56] methyl (1-methyl-2-pyrrolyl) *O*-vinylketoxime [57] or *O*-vinylketoximes formed upon heating of *O*-(2-iodoethyl)ketoximes with Bu^tOK in Bu^tOH.[58] Thus, heating of 2-furyl methyl and methyl 2-thienyl *O*-vinylketoximes (100 °C) in the KOH – DMSO system led to 2-(2-furyl)- and 2-(2-thienyl)pyrroles in yields of 60% and 50%, respectively.[56] 2-(2-Thienyl)- and 2-(3-thienyl)-4-methoxycarbonyl- and -4,5-di(methoxycarbonyl)pyrroles **13** were obtained by heating of the corresponding *O*-vinylketoximes **12** in xylene [47] (see Section II.1).

The reaction of isopropyl 2-thienyl ketoxime (**21**) with acetylene afforded 3,3-dimethyl-2-(2-thienyl)-3*H*-pyrrole (**23**), the yield of which depended on the reaction conditions and in the best case (addition of Al_2O_3 to the catalytic system) reached 43% with respect to the consumed ketoxime.[55]



21 **22a** **22b** **23**

R =

The formation of the pyrrole **23** from the oxime **21** indicates that the reaction pathway includes the stage of prototropic isomerisation of *O*-vinylketoxime **22a** into *O*,*N*-divinylhydroxyamine **22b**.

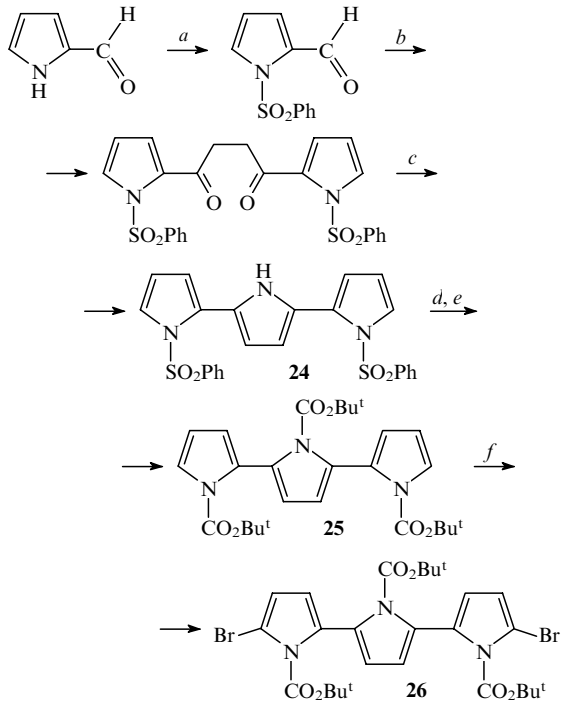
This scheme of the formation of pyrroles from oximes is also supported by the identification [59,60] of other reaction intermediates (hydroxypyrrolines) and their transformation into the corresponding pyrroles upon condensation of alkyl aryl ketoximes with acetylene.[41] The fact that pyrroles cannot be synthesised from *O*-alkyl ketoximes under the conditions of the Trofimov reaction,[24] as well as the predominant formation of β-phenylpyrroles in the case of phenylacetylene [61] support the proposed reaction scheme.

2. The Paal – Knorr synthesis

The Paal – Knorr synthesis is widely used for the preparation of pyrrolyl-, furyl- and thienylpyrroles. As a rule, it is carried out under mild conditions and provides for high yields of the target products in the final stage. However, the preparation of the initial 1,4-diketones and/or amines with furyl and thienyl substituents remains a challenge: their synthesis includes several stages which do not always give high yields, which restricts substantially the applicability of this method.

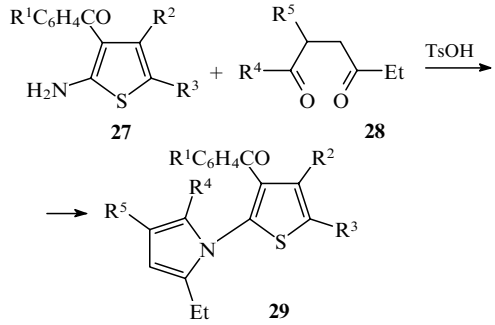
N,*N*′,*N*″-Tris(*tert*-butoxycarbonyl)-5,5″-dibromo-2,2′ : 5′,2″-terpyrrole (**26**) was obtained from 2-formylpyrrole [62] in several steps (Scheme 2). In the intermediate disulfone **24**, two sulfonyl groups were substituted by *tert*-butoxycarbonyl protective groups. Simultaneously, the third pyrrole ring was *N*-protected; the totally protected terpyrrole **25** was then selectively brominated with *N*-bromosuccinimide (NBS) to pyrrole **26**.

Scheme 2



(*a*) NaH, $PhSO_2Cl$, DMF, 20 °C; (*b*) SO_2, EtOH, Δ; (*c*) $AcONH_4$, Ac_2O, $EtCO_2H$, 140 °C; (*d*) NaOH, MeOH, 20 °C; (*e*) $(Bu^tO_2C)_2$, Bu^tOK, THF, Δ; (*f*) NBS, THF, −70 °C.

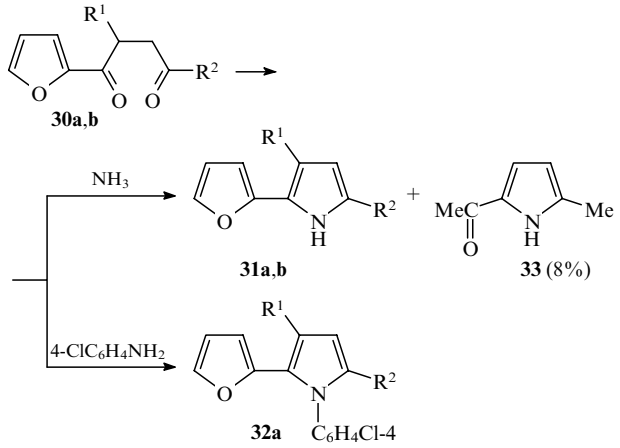
In a Japanese patent [63] it was proposed to prepare 1-(2-thienyl)pyrroles **29** (yields up to 80%) by the reaction of 2-aminothiophenes **27** with 1,4-diketones **28** on boiling for 20 min in benzene in the presence of *p*-toluenesulfonic acid.



27 **28** **29**

R^1	R^2	R^3	R^4	R^5
2-Cl	Me	Me	Me	Me
2-Cl	Me	Me	Me	H
H	H	Me	Me	H
H	H	Et	Me	H
H	Me	Me	Me	Me

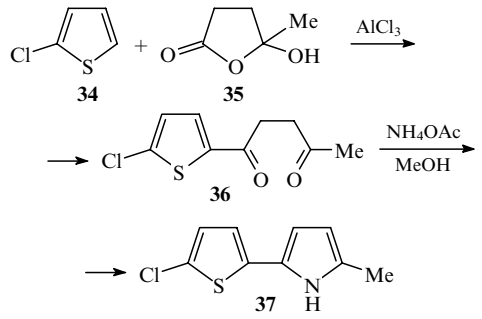
Furylpyrroles (**31a**,**b** and **32a**) were prepared from 1-(2-furyl)pentane-1,4-dione (**30a**) or 1-(2-furyl)-2,4-diphenylbutane-1,4-dione (**30b**) and ammonia (NH_4Cl, 180 °C, 20 h, yields of 40% and 50%, respectively) or 4-chlorophenylamine (AcOH, EtOH, 7 h, yield 85%) under atmospheric or elevated pressure.[64]



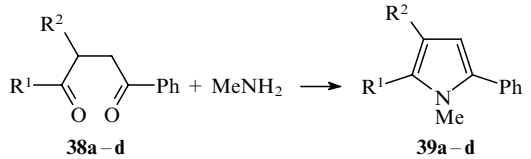
R^1 = H, R^2 = Me (**a**); R^1 = R^2 = Ph (**b**).

If ammonia is replaced by ammonium carbonate and the reaction is carried out in ethanol in the presence of acetic acid, a twofold increase in the yield of pyrrole **31a** is achieved.[64] It should be noted that the reaction of diketone **30a** with ammonia is accompanied by the formation of pyrrole **33** (yield 8%), while 2,4,5-tri(2-furyl)imidazole and 2,3,5,6-tetra(2-furyl)pyrazine (5% yield of each) are formed from diketone **30b**.[64]

1-(5-Chloro-2-thienyl)pentane-1,4-dione (**36**) obtained from 5-chlorothiophene (**34**) and 5-methyl-5-hydroxytetrahydrofuran-2-one (**35**) reacts with ammonium acetate in methanol at 25 °C for 3 h to give 2-(5-chloro-2-thienyl)-5-methylpyrrole **37** in 65% yield.[65]

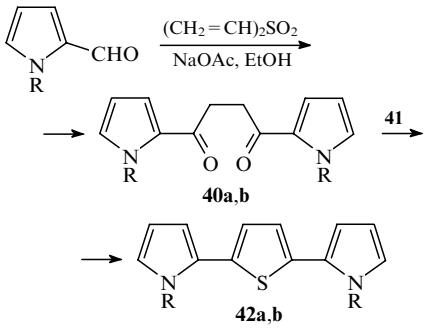


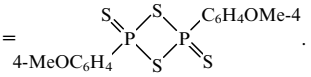
Pyrroles **39a**–**d** containing two thienyl substituents in the ring were obtained in high yields from the corresponding diketones **38a**–**d** and methylamine in boiling propanol containing methylamine hydrochloride.[66, 67]



Compound **39**	R^1	R^2	Yield (%)
a	2-thienyl	2-thienyl	85
b	3-thienyl	2-thienyl	97
c	2-thienyl	3-thienyl	90
d	3-thienyl	3-thienyl	99

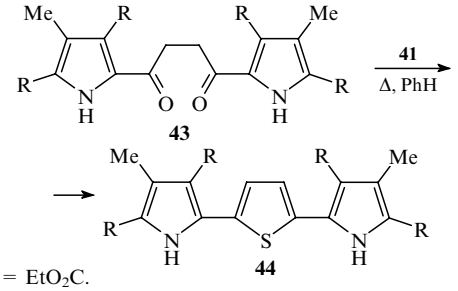
Synthesis of 2,5-bis(2-pyrrolyl)thiophenes **42** (yield 65%) was brought about[62, 68] by cyclisation of symmetrical 1,4-diketones **40a**,**b** with Lawesson's reagent (**41**) upon boiling in toluene.



R = $MeSO_2$ (**a**), $PhSO_2$ (**b**); **41** = 

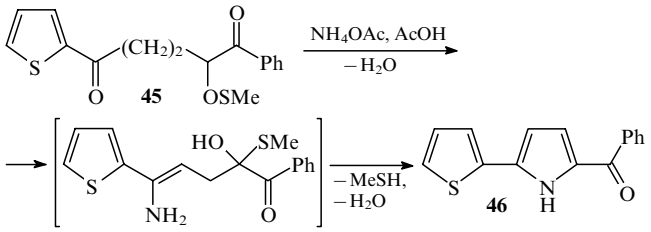
Diketones **40a**,**b** are obtained from pyrrole-2-carboxaldehydes in ethanol in the presence of NaOAc, divinyl sulfone and a thiazolium salt as the catalyst (yields 70% and 74%, respectively).

2,5-Bis[3,5-di(ethoxycarbonyl)-4-methyl-2-pyrrolyl]thiophene (**44**) was prepared in 76% yield from diketone **43** [synthesised by the reaction of 3,5-bis(ethoxycarbonyl)-4-methyl-2-formylpyrrole with divinyl sulfone in dioxane at 80 °C in the presence of triethylamine] and Lawesson's reagent **41**.[68]

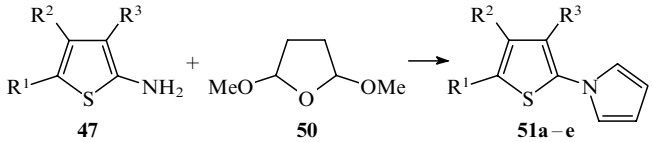


R = EtO_2C.

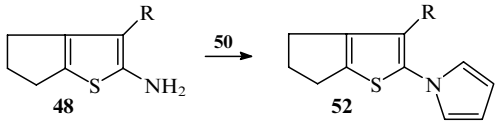
The reaction of 2-methylsulfinyl-1-phenyl-5-(2-thienyl)pentane-1,5-dione (**45**) with ammonium acetate in acetic acid (Δ, 10 min) leading to 2-(2-thienyl)pyrrole (**46**) with a yield of 19% may be regarded as a variant of the Paal–Knorr synthesis.[69]



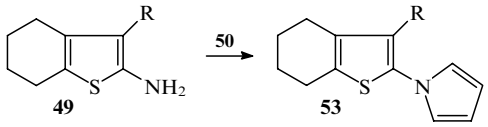
An elegant and efficient synthesis of 1-(2-thienyl)pyrroles **51**–**53** is based on the condensation of 2-aminothiophenes **47**, 2-amino-4,5-dihydrocyclopenta[*b*]thiophene **48** or 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophenes **49** with 2,5-dimethoxytetrahydrofuran (**50**) in acetic acid.[70, 71]



Compound **51**	R^1	R^2	R^3	Yield (%)
a	Me	Me	H	86
b	Me	Et	CO_2H	96
c	Me	Me	CO_2H	97
d	H	H	CO_2Et	72
e	Me	Me	CO_2Et	70

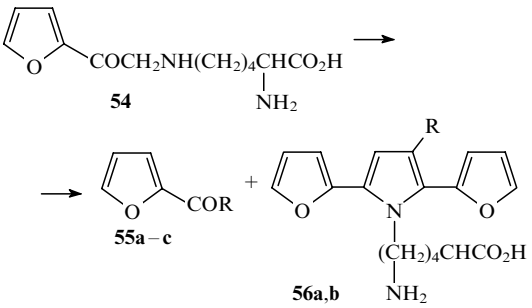


R = CO_2H (96%), CO_2Et (71%).



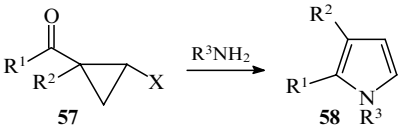
R = H (70%), CO_2H (97%), CN (86%), CO_2Et (59.5%).

The oxidation products of aminoacylfuran **54** are supposed to contain, along with the major compounds **55a–c**, insignificant amounts of furylpyrroles **56a,b**.[72]



R = OH (**a**), $NH(CH_2)_4CH(NH_2)CO_2H$ (**b**), $CONH(CH_2)_4CH(NH_2)CO_2H$ (**c**).

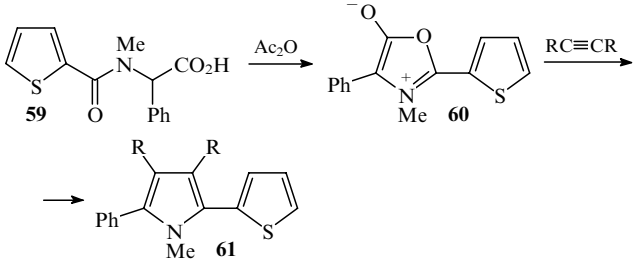
The reaction of cyclopropyl ketones **57** with amines leads to the formation of hetarylpyrroles **58** in high yields.[73,74] The presence of an electron-acceptor substituent X (OMe, OEt, Cl) in the cyclopropane ring facilitates its isomerisation leading to the formation of a carbonyl group equivalent.



R^1 = 2-furyl, 2-thienyl; R^2 = H; R^3 = H, Alk, Ar; X = OMe, OEt, Cl.

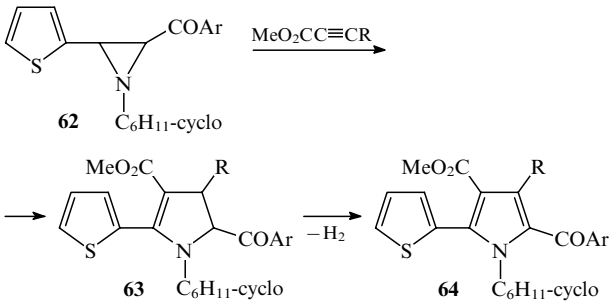
3. Syntheses involving activated acetylenes

Oxazolium oxide **60** formed from *N*-methyl-*N*-thenoylamino acid **59** and acetic anhydride is transformed into 2-(2-thienyl)pyrrole **61** upon boiling in benzene with dimethyl acetylenedicarboxylate (yield 89%).[75]



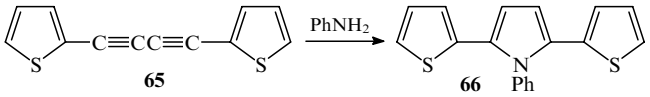
R = CO_2Me.

A general method for the synthesis of thienylpyrroles **64** has been developed, which is based on 1,3-dipolar cycloaddition of 2-(2-thienyl)aziridines **62** to activated acetylenes.[76,77] The reaction proceeds on heating of the reagents in benzene with the formation of intermediate thienylpyrrolines **63**, which are readily dehydrogenated under the action of tetrachloro-1,4-benzoquinone to give pyrroles **64**, as a rule, in moderate yields.

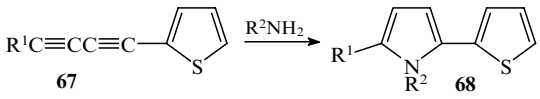


R	Ar	Yield of **64** (%)	R	Ar	Yield of **64** (%)
H	Ph	32	H	2-naphthyl	36
H	4-MeC_6H_4	26	CO_2Me	4-MeC_6H_4	53
H	4-$MeOC_6H_4$	39	CO_2Me	4-$MeOC_6H_4$	65
H	3-$NO_2C_6H_4$	25	CO_2Me	3-$NO_2C_6H_4$	32

Heating of 1,4-di(2-thienyl)butadiyne (**65**) with aniline at 140–160 °C in the presence of cuprous chloride leads to the formation of 2,5-di(2-thienyl)-1-phenylpyrrole (**66**) in 68% yield.[78]

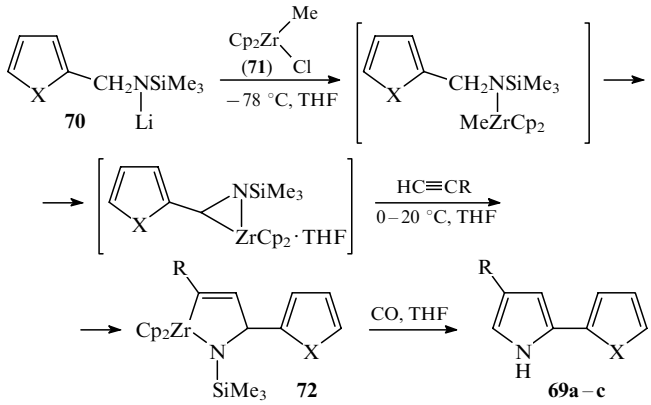


This reaction has a general character. Asymmetrically substituted butadiynes **67** react with amines, which allows preparation of various 2-(2-thienyl)pyrroles **68**.[78] Ethanol, dioxane and DMF are used as solvents.



R^1 = H, Me, Et, Ph; R^2 = H, Me, Et, Bu^n, Ph.

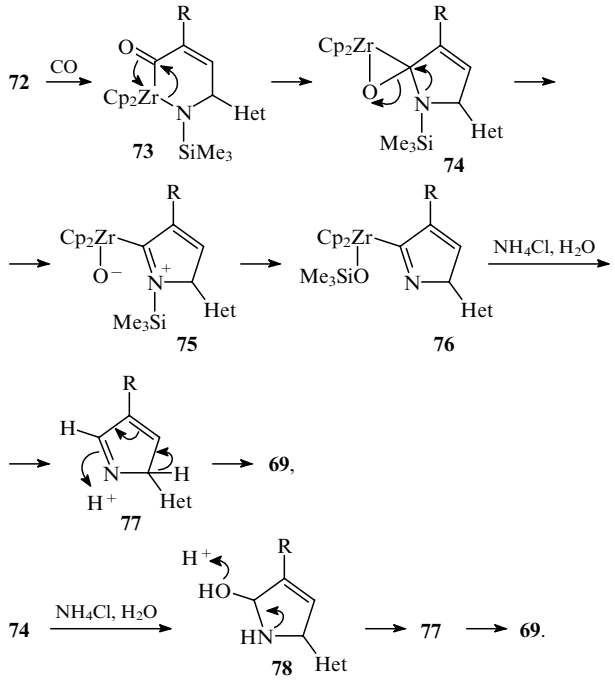
A new method has been developed for the synthesis of 2-(2-pyrrolyl)-, 2-(2-furyl)- and 2-(2-thienyl)pyrroles **69a–c** from the corresponding amines **70**, acetylenes **71** and carbon monoxide with the use of zirconium cyclopentadienyl complexes.[79]



X = N, R = Pr^n (**69a**, 68%); X = O, R = Ph (**69b**, 49%); X = S, R = Pr^n (**69c**, 41%).

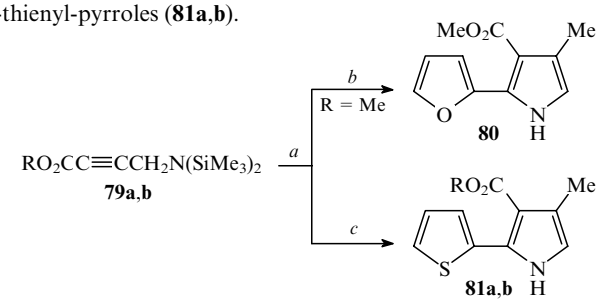
The reaction with CO leading to hetarylpyrroles may be realised both with and without isolation of metallocycles **72**. This reaction can be carried out in the presence of NH_4Cl, under CO pressure of ~ 100 atm, at ~ 20 °C, for 24 h (method A) or in the absence of NH_4Cl, at 80 °C, CO pressure of ~ 6 atm and for 36 h (method B). The former method is more efficient, though the role of NH_4Cl is still unclear.

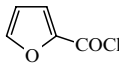
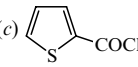
The following mechanism of this reaction has been proposed:[79]



Insertion of CO into the C–Zr bond gives metallocycle **73**. Migration of the nitrogen atom from zirconium to the acyl carbon (formally, reductive elimination) leads to the zirconium complex **74**. The intermediate **74** can undergo ring opening with the formation of a zwitter-ion **75**, which after migration of the trimethylsilyl group from nitrogen to zirconium gives compound **76**. Its hydrolysis yields intermediate **77**, which undergoes prototropic rearrangement into pyrrole **69**. An alternative pathway is possible: hydrolysis of the complex **74** to the alcohol **78**, which is dehydrated to give the intermediate **77** with subsequent formation of pyrrole **69**.[79]

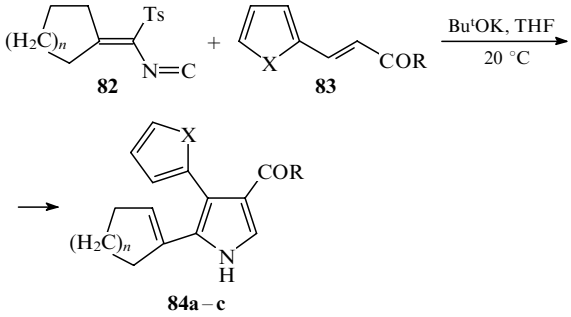
Synthesis of pyrroles[80] through carbocupration of *N,N*-bis(trimethylsilyl) derivatives of alkyl 4-aminobut-2-ynoates with subsequent treatment with acyl chlorides has opened a route to new polyheterocyclic compounds, including furyl- and thienylpyrroles and tetrapyrrole macrocycles. Thus, the reaction of lithium methyl(hexynyl)cuprate with methyl (**79a**) or ethyl 4-aminobut-2-ynoates (**79b**) with subsequent treatment with 2-furoyl or 2-thienoyl chlorides leads to 2-furyl- (**80**) and 2-thienyl-pyrroles (**81a**,**b**).



R = Me (**81a**, 30%), Et (**81b**, 58%); (*a*) ($Bu^nC{\equiv}C$)MeCuLi, Et_2O, −40 °C; (*b*) ; (*c*) .

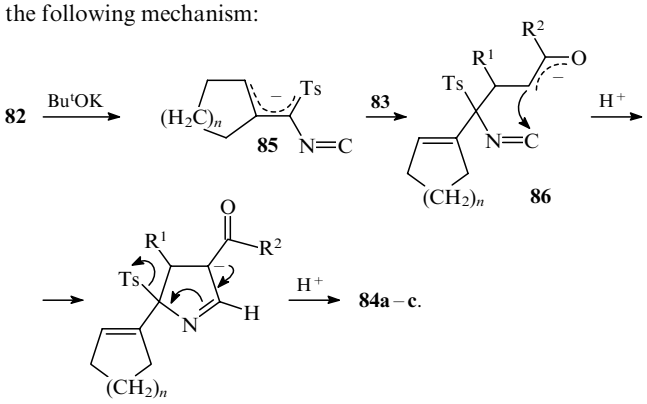
4. Synthesis involving isocyanides

Isocyanides are rather common components in the synthesis of hetarylpyrroles.[81–87] 3-(2-Furyl)- (**84a**,**b**) and 3-(2-thienyl)pyrroles **84c** were synthesised by addition of 1-tosylalk-1-enyl isocyanides **82** to chalcone analogues **83** in the presence of Bu^tOK.[81] The initial isocyanides **82** can be easily obtained by the reaction of tosylmethyl isocyanide with carbonyl compounds.



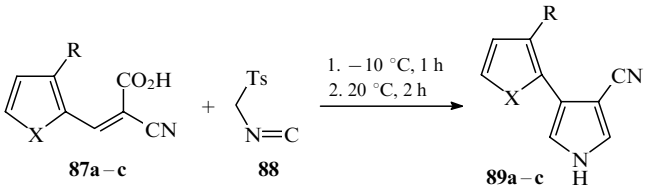
Compound **84**	X	*n*	R	Yield (%)
a	O	1	2-furyl	93
b	O	3	Ph	89
c	S	2	2-thienyl	85

It is presumed[81] that the formation of pyrroles **84** occurs by the following mechanism:



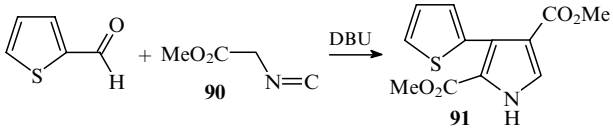
The Michael addition of the allylic anion **85**, formed under the action of a base, to the vinyl ketone **83** and subsequent cyclisation of the enolate anion **86** and elimination of the tosylate anion yield the final reaction product.

Pyrroles **89a**–**c** were obtained from 2-cyano-3-(2-furyl)- and -(2-thienyl)acrylic acids **87a**–**c** and tosylmethyl isocyanide (**88**) in a superbasic system KOH–dimethoxyethane.[82]

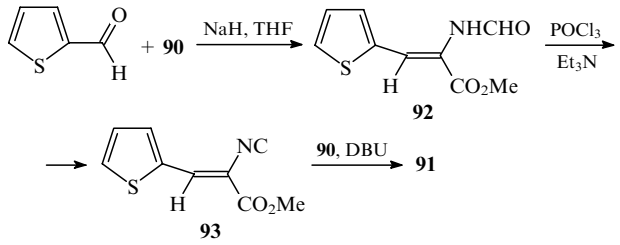


Compounds **87**, **89**	X	R	Yield of **89** (%)
a	O	H	92
b	S	H	97
c	S	Me	89

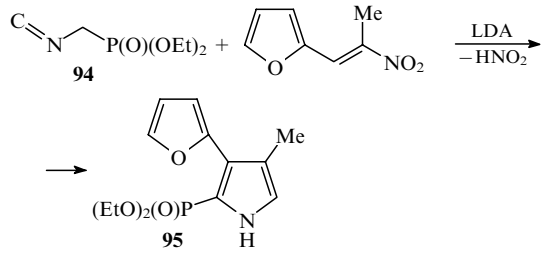
The addition of methyl isocyanoacetate (**90**) to thiophene-2-carbaldehyde in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF at 40–50 °C (15 h) leads to 3-(2-thienyl)-pyrrole (**91**) in 70% yield.[85,87]



Sakai *et al.*[85] have obtained pyrrole **91** by a different scheme including intermediates **92** and **93**.

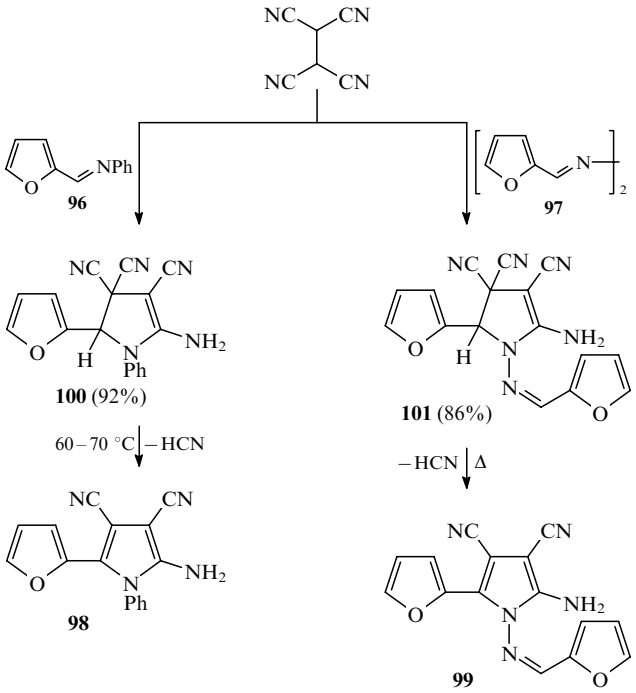


Phosphorylated 3-(2-furyl)pyrrole **95** was synthesised in 54% yield by the reaction of isocyanide **94** with 2-(2-nitroprop-1-enyl)furan in the presence of lithium diisopropylamide (LDA) (THF, −78 °C, 3 h; ~ 20 °C, 72 h; reflux, 2 h) with subsequent treatment with ammonium chloride.[86]



5. Syntheses from cyanides

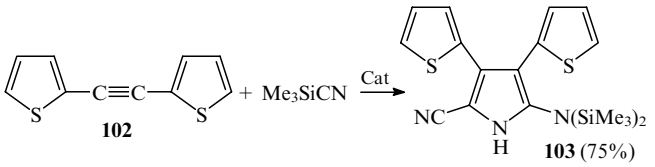
A simple and efficient method for the synthesis of 2-(2-furyl)pyrroles **98**, **99** is based on the reaction of tetracyanoethane with azomethine **96** or azine **97**.[88–92]



Pyrrole **98** is synthesised either by heating (90–100 °C) of tetracyanoethane and azomethine **96** in aqueous dioxane (yield 60%–65%)[88] or with the intermediate isolation of pyrroline **100**, which is transformed into pyrrole **98** in 98% yield upon heating for 5–25 min at 60–70 °C in DMF.[89]

Similarly, upon gentle heating in an aqueous-ethanolic or ethanolic medium pyrroline **101** loses one molecule of hydrocyanic acid and is transformed into pyrrole **99**.[91]

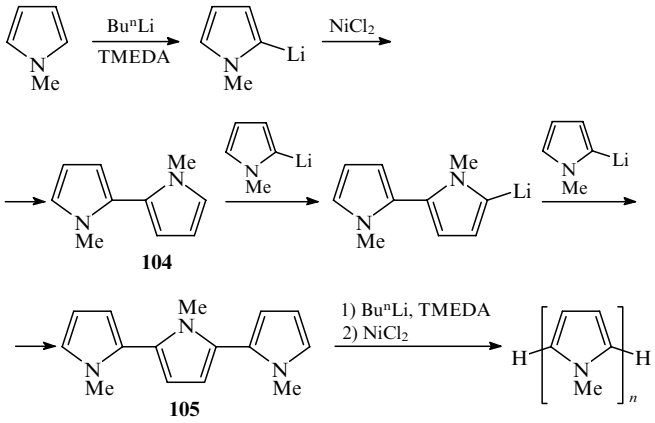
Condensation of bis(2-thienyl)acetylene **102** with an excess of trimethylsilyl cyanide catalysed by palladium or nickel chloride in pyridine yields 3,4-bis(2-thienyl)pyrrole (**103**).[93]



The reaction involves such a profound rearrangement of trimethylsilyl cyanide that it is hardly possible to propose any reasonable mechanism of this reaction.

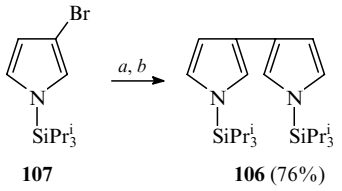
6. Organometallic synthesis

Kaufmann and Lexy[94] have synthesised bipyrrole **104** by α-lithiation of *N*-methylpyrrole with subsequent oxidative coupling of the intermediate obtained. Bipyrrole **105** was used for the preparation of terpyrrole and then oligopyrrole.



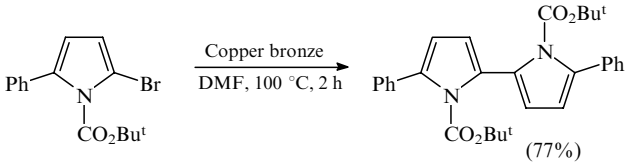
TMEDA is tetramethylethylenediamine; $n = 6$.

3,3-Bipyrrole **106** was obtained[95] by a Wurtz-type reaction from 3-bromo-1-(triisopropylsilyl)pyrrole (**107**) upon treatment of the latter with *tert*-butyllithium in the presence of CuI.

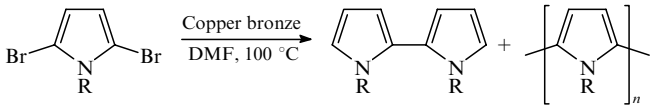


(*a*) Bu^tLi, CuI, n-C_5H_{12}–THF, −78 °C, 10 min; (*b*) 20 °C, 2 h.

Groenendaal *et al.*[96] have described dimerisation of 5-bromo-1-*tert*-butoxycarbonyl-2-phenylpyrrole according to Ullmann.



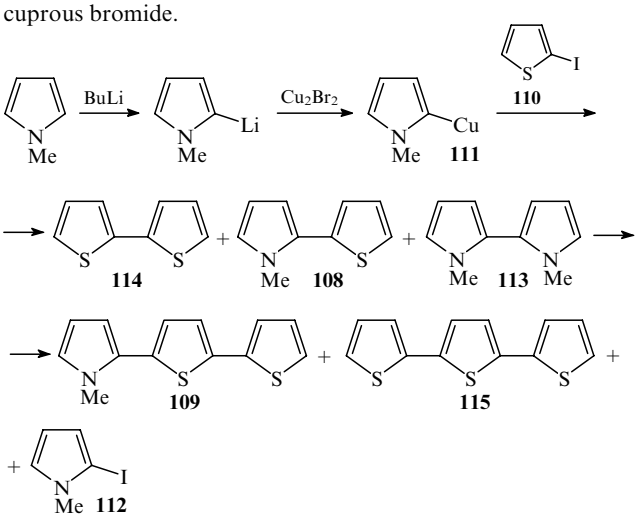
Under the same conditions,[96] 2,5-dibromo-1-*tert*-butoxycarbonylpyrrole afforded a dimer and other oligomers containing up to 24 pyrrole rings, which were isolated as individual products by preparative HPLC.



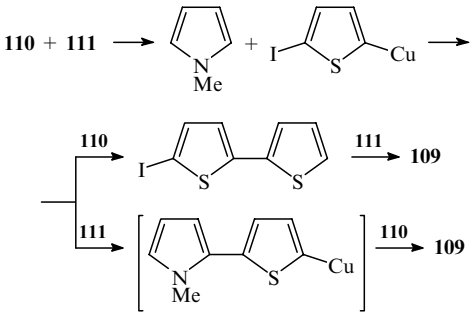
R = CO_2Bu^t; $n = 3–24$.

Gjøs and Gronowitz[97] have developed a method for the synthesis of thienylpyrroles **108** and **109** by reaction of 2-iodo-

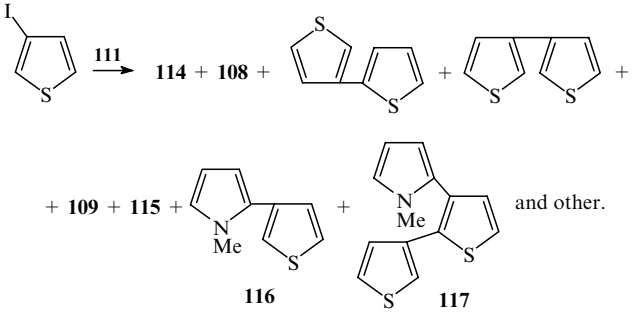
thiophene **110** with 1-methyl-2-pyrrolylcopper (**111**) prepared by metallation of 1-methylpyrrole with butyllithium in a mixture of ether and tetramethylethylenediamine followed by treatment with cuprous bromide.



The course of the reaction and the ratio of the products formed are substantially influenced by its duration: when the reaction was conducted for 1 h, a mixture was obtained that contained, along with thienylpyrrole **108**, the initial iodothiophene (**110**), iodopyrrole **112**, bipyrrole **113** and bithiophene **114**; when the mixture was allowed to react for 4 h, a decrease in the concentration of bithiophene **114** and an increase in the content of thienylpyrrole **108** and bipyrrole **113** were observed. Trace amounts of 1-methyl-2-[5-(2,2′-bithienyl)]pyrrole **109** and terthiophene **115** were also formed. According to GLC data, the ratio of products **108**:**109**:**113**:**114**:**115** was 53:14:24:7:< 1. The major product, *viz*., thienylpyrrole **108**, was isolated in 40% yield, while the yield of compound **109** was 15%.[97] The formation of the latter product is explained by the following scheme:

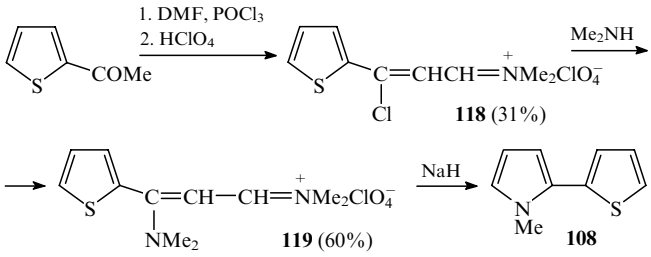


The reaction of the copper intermediate **111** with 3-iodothiophene leads to a more complex mixture of products.[97]



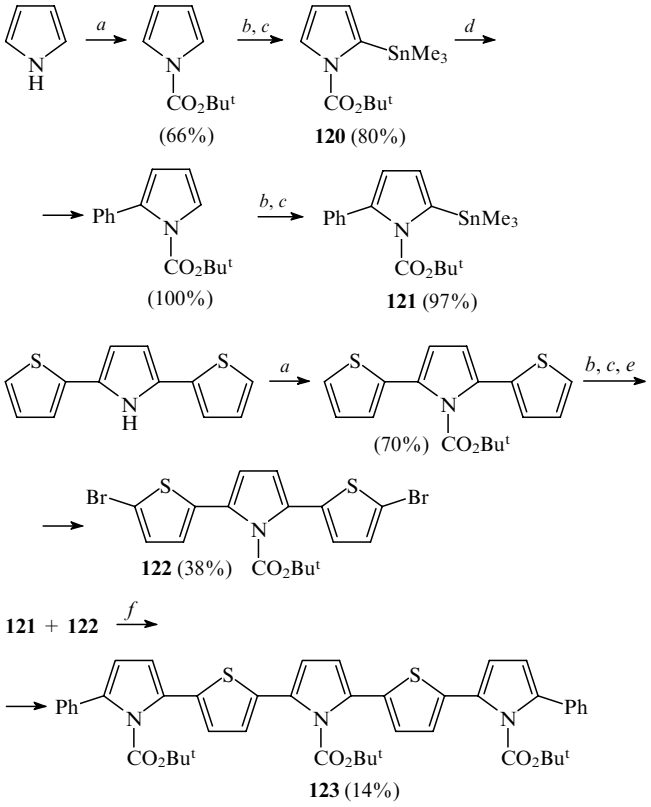
According to GLC data, bicyclic and tricyclic compounds constitute 7% and 30% of this mixture, respectively. Column chromatography with subsequent distillation and recrystallisation gave 1-methyl-2-(3-thienyl)pyrrole (**116**) (yield 72%), thienylpyrrole **108** (yield 6%) and tricyclic compound **117** (yield 9%).

Thienylpyrrole **108** was obtained by the same authors[97] in three steps:



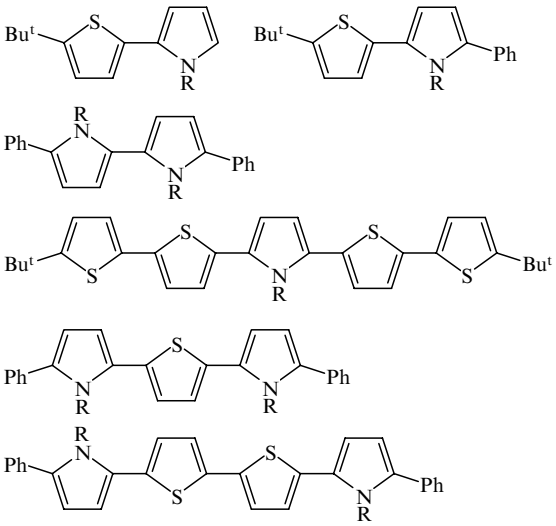
The reaction of 2-acetylthiophene with dimethylformamide and phosphorus oxychloride followed by treatment of the reaction mixture with $HClO_4$ yields perchlorate **118**. The reaction of salt **118** with dimethylamine gives perchlorate **119**; its heterocyclisation leads to thienylpyrrole **108**, although in a low yield.[97]

The use of the Stille reaction allowed one to synthesise oligoheterocyclic compounds containing pyrrole and thiophene units, *e.g*., *N*-*tert*-butoxycarbonyl-di-2-(5-*tert*-butoxycarbonyl-5-phenyl-2-pyrrolyl)thienyl]pyrrole (**123**).[98] Organotin derivative **120** is prepared by stannylation of a substituted pyrrole. Cross-coupling of compound **120** with bromobenzene according to Stille in the presence of palladium[tetrakis(triphenylphosphine)] followed by stannylation of the reaction product yields compound **121**. Pyrrole **122** is obtained by distannylation of *tert*-butyl 2,5-bis(2-thienyl)pyrrole-*N*-carboxylate with subsequent bromination of the reaction product with *N*-bromosuccinimide. Cross-coupling of compounds **121** and **122** according to the Stille method leads to the oligoheterocycle **123**.



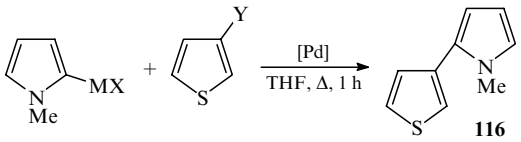
(*a*) $(Bu^tO_2C)_2$, Bu^tOK, THF, Δ; (*b*) tetramethylpiperidine, Bu^nLi, THF, −70 °C; (*c*) Me_3SnCl, THF, $Pd(PPh_3)_4$, −70 °C; (*d*) PhBr, $Pd(PPh_3)_4$, PhMe, H_2O, Na_2CO_3; (*e*) NBS, THF; (*f*) $Pd(PPh_3)_4$, PhMe, Na_2CO_3, H_2O, Δ.

Cross-coupling according to Stille was also used to prepare the following compounds:[98]



R = Bu^tO_2C.

Cross-coupling of *N*-methylpyrrolylmagnesium(zinc) halides with 3-halogenothiophenes in the presence of a palladium catalyst leads to 1-methyl-2-(3-thienyl)pyrrole (**116**) in high yield.[99, 100]

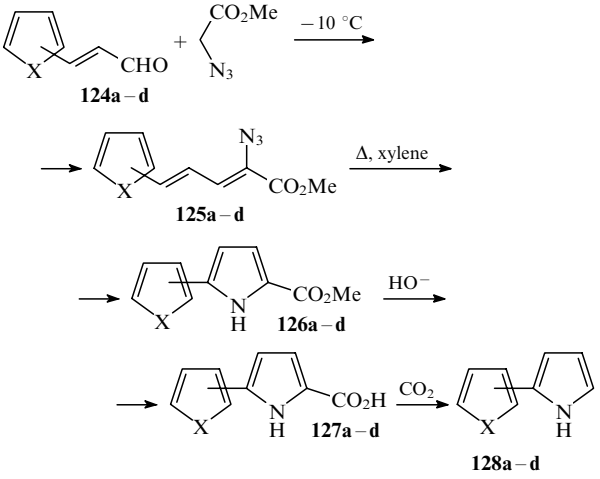


M = Mg, Zn; X = Cl, Br, I; Y = Cl, Br;

[Pd] = $PdCl_2$, $Ph_2P(CH_2)_4PPh_2$ (2.5 mol %).

7. Synthesis from azides

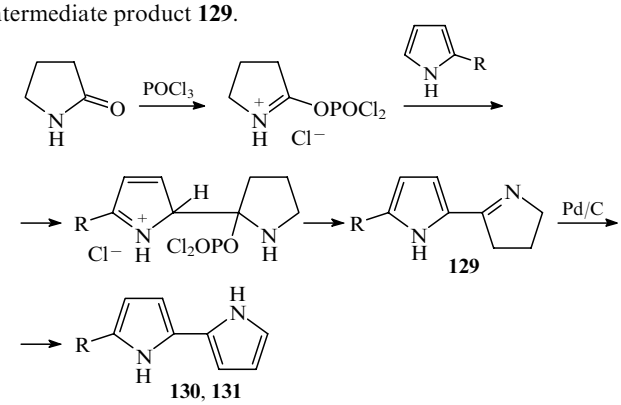
Thermolysis of azidobutadienes **125a–d** containing a hetaryl substituent yields the corresponding 2-hetarylpyrroles **126a–d**. The starting compounds for the preparation of azides **125a–d** were β-2(3)furyl- and β-2(3)-thienylacroleins **124a–d** and methyl azidoacetate. Alkaline hydrolysis of compounds **126a–d** and subsequent decarboxylation of acids **127a–d** in quinoline (with barium-promoted copper chromite as a catalyst) lead to the corresponding 2-(2-furyl)- and 2-(2-thienyl)pyrroles (**128a**,**b**) or 2-(3-furyl)- and 2-(3-thienyl)pyrroles **128c**,**d**.[101]



Compound	Substituent position	X	Yield (%)		
			126	**127**	**128**
a	2	O	90	79	68
b	2	S	90	75	46
c	3	O	92	79	43
d	3	S	87	89	57

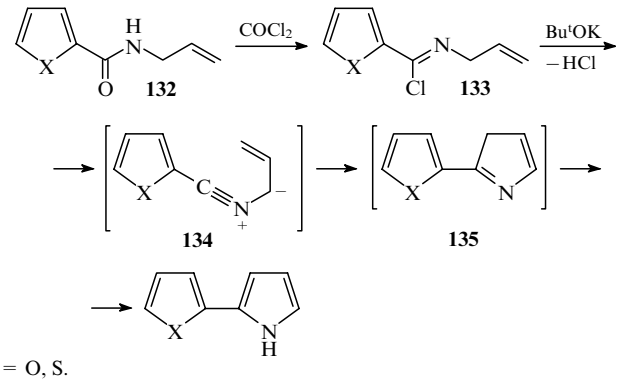
8. Synthesis from unsaturated aminocarbonyl compounds

Rapoport *et al.*[102-106] have synthesised 2,2-bipyrrole (**130**) and 2,2′:5′,2″-terpyrrole (**131**) by the reaction of 2-pyrrolidone with phosphorus oxychloride and subsequent dehydrogenation of the intermediate product **129**.



R = H (**130**), 2-pyrrolyl (**131**).

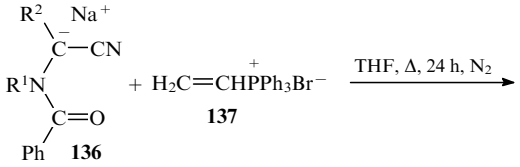
2-(2-Furyl)- and 2-(2-thienyl)pyrroles have been synthesised in 86% yields by the reaction of *N*-allyl carboxamides **132** with phosgene followed by the elimination of HCl from the chloroimines **133**.[107]

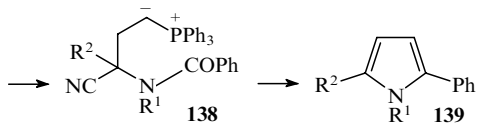


X = O, S.

The construction of the pyrrole ring is presumed [107] to result from the intramolecular 1,5-dipolar cyclisation of the intermediate nitrile ylides **134** to 3*H*-pyrroles **135**, which are further isomerised to 1*H*-pyrroles.

1-(2-Thienyl)pyrroles **139** were obtained in good yields in the reaction of sodium derivatives of cyanoamides **136** with vinyltriphenylphosphonium bromide (**137**) followed by the intramolecular cyclisation of the intermediate **138** under the action of a base with elimination of HCN and Ph_3PO.[108]

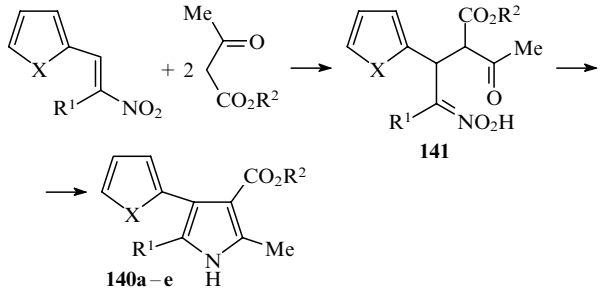




R^1 = 2-thienyl: R^2 = Ph, 4-ClC_6H_4.

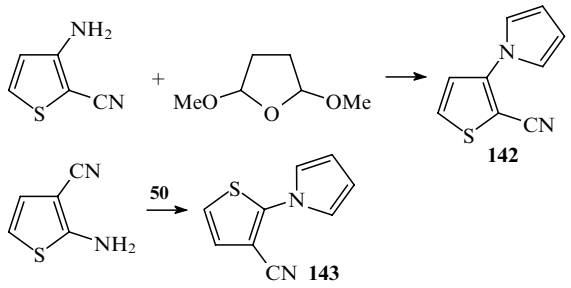
9. Miscellaneous methods

Boberg *et al.*[109] have proposed to obtain 3-(2-furyl)- (**140a**) and 3-(2-thienyl)pyrroles (**140b–e**) from nitronic acids **141** formed upon reaction of nitrovinylfurans or -thiophenes with alkyl acetoacetates. Heterocyclisation of compound **141** takes place at 60 °C in the presence of reducing agents, such as a mixture of sodium sulfide with ammonium chloride, aqueous ammonia with ammonium sulfide or Zn in HCl. This method does not have any preparative value because of low yields of pyrroles.

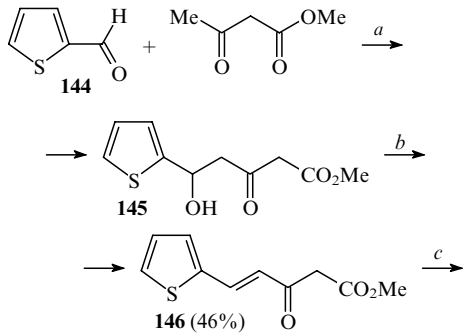


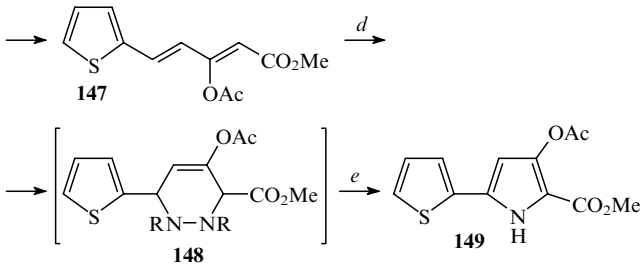
Compound **140**	X	R^1	R^2	Yield (%)
a	O	Et	Et	1
b	S	Me	Et	17
c	S	Et	Et	14
d	S	Me	Bu^t	10
e	S	Ph	Et	8

Synthesis of 1-(2-cyano-3-thienyl)pyrrole (**142**) and 1-(3-cyano-2-thienyl)pyrrole (**143**) by the reaction of 2,5-dimethoxytetrahydrofuran (**50**) with 3-amino-2-cyano- and 2-amino-3-cyanothiophenes, respectively, has been described.[110–113]



Kresze *et al.*[114] have carried out a multistep synthesis of 4-acetoxy-5-(methoxycarbonyl)-2-(2-thienyl)pyrrole (**149**) in which the key compound is a tetrahydropyridazine derivative **148**.

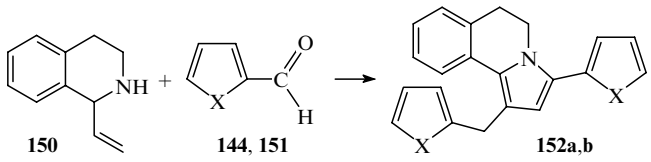




(*a*) NaH, THF, Bu^nLi, 0 °C, 3 h; (*b*) 1. *p*-TsCl, Py, 20 °C, 12 h; 2. 80 °C, 0.5 h; (*c*) MeCOCl, Py, 0 °C, 5 h; (*d*) RN=NR (R = Cl_3CCH_2OCO), Δ, PhH; (*e*) Zn, AcOH, MeOH, 55 °C, 3 h.

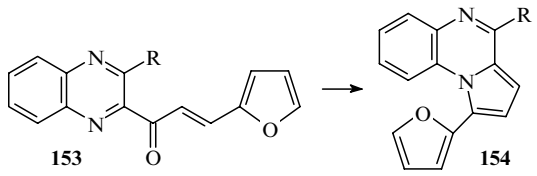
Condensation of 2-formylthiophene **144** with ethyl acetoacetate leads to hydroxy ketone **145** (yield of a crude product 93%) dehydration of which yields *E*-olefin **146**.[114] Its *O*-acetylation affords a mixture of *E*- and *Z*-isomers of diene **147** from which the *Z*-isomer was isolated by crystallisation from ether (yield 31%). The Diels–Alder reaction of the *Z*-diene with trichloroethyl azo-*N,N′*-dicarboxylate results in a tetrahydropyridazine derivative **148** as an intermediate; its treatment with Zn powder in acetic acid yields thienylpyrrole **149**.[114]

1-Vinyltetrahydroisoquinoline (**150**) (obtained from 3,4-dihydroisoquinoline and vinylmagnesium bromide) reacts with 2-formylfuran (**151**) or 2-formylthiophene (**144**) to form polycyclic systems (**152a,b**) with 2-furyl or 2-thienyl substituents.[115]



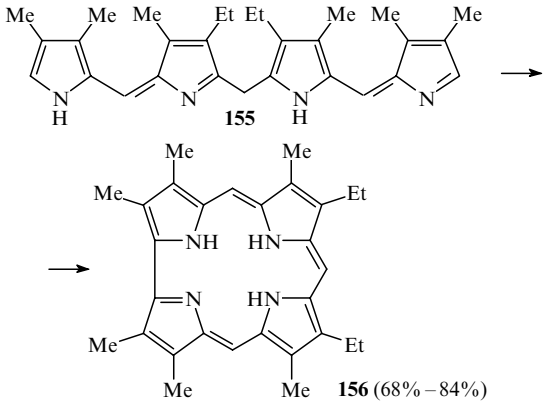
X = O (**a**, 40%), S (**b**, 53%).

Pyrrolo[1,2-*a*]quinoxalines **154** containing a 2-(2-furyl)-pyrrole fragment have been synthesised by the cyclisation of 2-(2-furfurylideneacetyl)quinoxalines **153** under the action of HCl or $HClO_4$.[116]



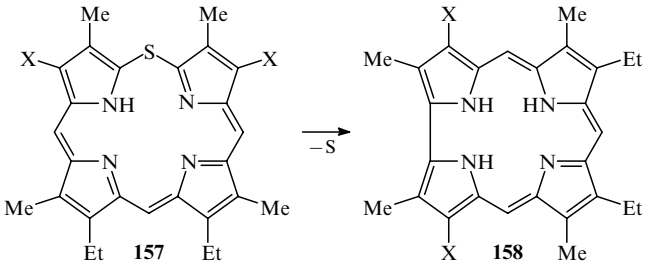
R = H, Me.

Corrole **156** is prepared by the oxidative cyclisation of a linear tetrapyrrole **155** in an alkaline medium.[117]



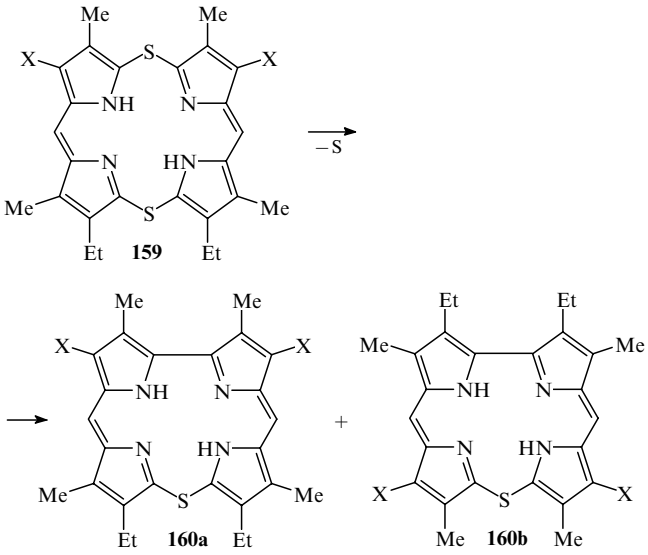
As expected, boiling of *meso*-thiaphlorin **157** in *o*-dichlorobenzene resulted in elimination of sulfur with the formation of

corrole **158** in 35%–40% yield.[118] In the presence of triphenylphosphine, the yield of corrole **158** reaches 60%.



X = CO_2Et.

In the case of *meso*-dithia macrocycle **159**, the extrusion of sulfur occurs less readily (213 °C, 10 h, triphenylphosphine) and leads to two isomers of *meso*-thiacorrole **160a**,**b** in a total yield of 42% (ratio 1 : 1).[118]



X = CO_2Et.

III. Reactivity

Until recently, chemical properties of pyrroles bound to five-membered aromatic heterocycles have been very little studied because of the absence of reliable general methods for their synthesis. There were only fragmentary data on some reactions that included mostly interactions of their functional substituents (with the exception of formylation of the pyrrole fragment). The development of methods for the synthesis of hetaryl-substituted pyrroles in the last two decades has led to a considerable expansion of the array of preparatively accessible representatives of this group of compounds and to the appearance of real conditions for systematic studies of their reactivity and other properties.

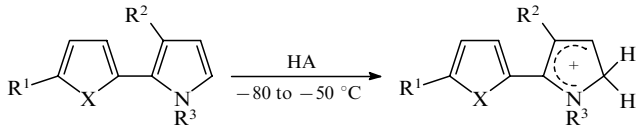
1. Electrophilic substitution

a. Protonation

It is known [1–3, 119–125] that the most characteristic reaction of the pyrrole ring is electrophilic substitution, which is also typical of substituted furans and thiophenes.[121–125] The simplest reaction of this type is reversible protonation (degenerate electrophilic substitution of hydrogen).

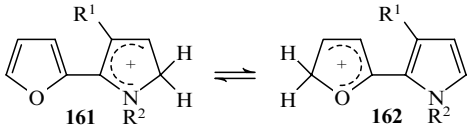
Over the last decade, the ^1H NMR method was used for the systematic studies of protonation of the series of 2-(2-furyl)- and 2-(2-thienyl)pyrroles and their 1-vinyl derivatives.

Numerous studies [21, 25, 27, 126–133] have shown that at −80 to −50 °C all pyrroles, regardless of the nature of the second heterocycle and the acid (except for the 'magic' acid $HSO_3F–SbF_5$), are protonated at the C(5) atom of the pyrrole ring; in the case of vinyl derivatives (R^3 = CH=CH_2), the double bond is retained.



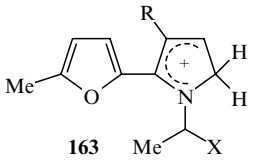
X = O, S; R^1 = H, Me; R^2 = H, Me, Pr^i; R^3 = H, CH=CH_2, Et; A = Cl^-, Br^-, CF_3COO^-, FSO_3^-.

The reaction of furylpyrroles with hydrogen halides (HCl, HBr) at −30 °C yields a mixture of pyrrolium **161** and furanium **162** cations.[21, 25, 128] An analogous mixture is also formed on gradual elevation of temperature from −80 to −30 °C.[21, 25, 128]



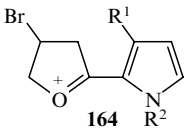
Protonation of vinyl derivatives (−30 °C) is accompanied by the addition of HX to the 1-vinyl group.[21, 25, 27, 126–131]

On warming from −80 to −30 °C, the cation in which both α-positions in the furan ring are occupied adds HX only to the double bond with the formation of the pyrrolium ion **163**.[21, 25, 27, 128]



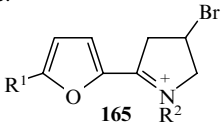
R = H, Me; X = Cl, Br.

As the temperature is increased to 0 °C, the reaction of furylpyrroles with HBr leads to 4-bromo-4,5-dihydro-2-(2-pyrrolyl)furanium bromides **164** as the result of addition of HBr to the protonated furan ring.[21, 25, 27, 128]



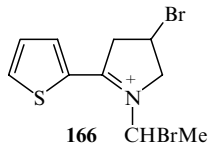
R^1 = H: R^2 = H, CHBrMe, Et; R^1 = Me: R^2 = H, CHBrMe.

At 20 °C, dihydrofuranium cations **164** are completely transformed into 4-bromo-4,5-dihydro-2-(2-furyl)pyrrolium bromide **165** with the rearomatisation of the furan moiety of the molecule.[21, 25, 27, 128]



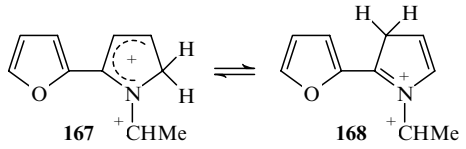
R^1 = H, Me; R^2 = CHBrMe.

In contrast to the furan ring, the thiophene ring is not involved in the reaction with HBr. In this case, the formation of only 4-bromo-4,5-dihydro-2-(2-thienyl)pyrrolium bromide (**166**) is observed.[21, 25, 130, 131]



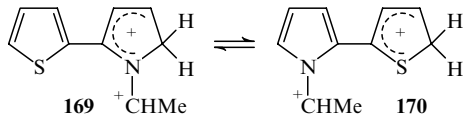
166

Unlike ordinary acids, the superacidic system HSO_3F-SbF_5 reacts with 2-(2-furyl)-1-vinylpyrrole at $-70\,^{\circ}C$ to give an equilibrium mixture of dications: 1-(1-ethanio)-2-(2-furyl)-5*H*-pyrrolium (**167**) and 1-(1-ethanio)-2-(2-furyl)-3*H*-pyrrolium (**168**) in the ratio 3 : 1.[21, 25]



167 **168**

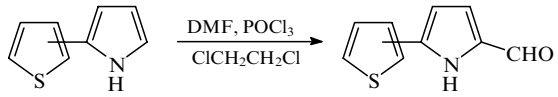
In the reaction with the superacidic system $HSO_3F-SbF_5-SO_2$, 2-(2-thienyl)-1-vinylpyrrole forms two cations: 1-(1-ethanio)-2-(2-thienyl)-5*H*-pyrrolium (**169**) and 2-[1-(1-ethanio)-2-pyrrolyl)-5*H*-thiophenium (**170**) in the ratio 2 : 1. Heating of the reaction mixture up to 10 °C changes the ratio **169** : **170** to 1 : 2.[21, 25, 130, 131]



169 **170**

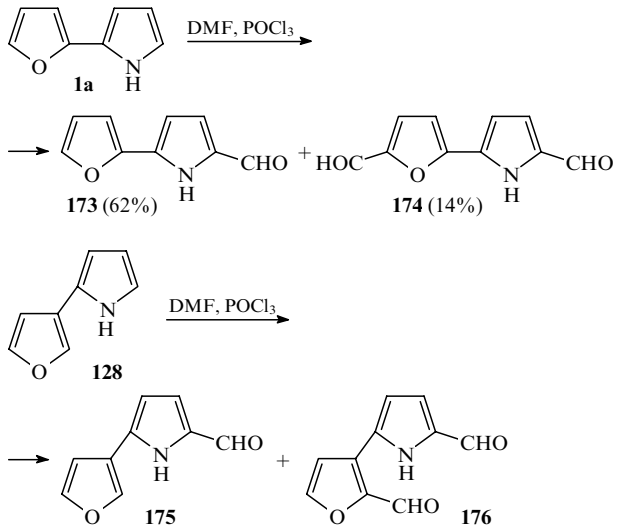
b. Formylation

Formylation of 2-(2-furyl)-, 2-(2-thienyl)-, 2-(3-furyl)- and 2-(3-thienyl)pyrroles and their α-methoxycarbonyl derivatives under conditions of the Vilsmeier reaction has been studied.[101, 134] Thienylpyrroles are formylated only at the α-position of the pyrrole ring with the formation of 2-thienyl- (**171**) (yield 75%) and 3-thienyl-2-formylpyrrole (**172**).



171, **172**

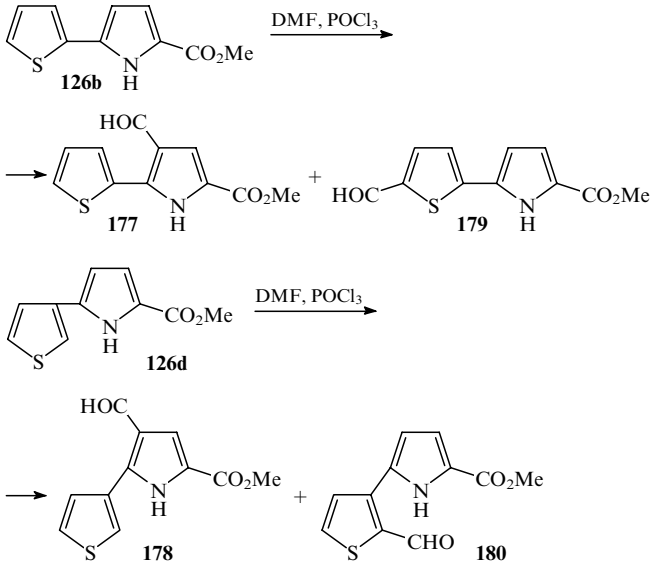
Formylation of furylpyrroles results in a mixture of mono- (**173**, **175**) and diformyl derivatives (**174**, **176**), the former being predominant.[101, 134]



1a **173** (62%) **174** (14%) **128** **175** **176**

In 2-(3-furyl)pyrrole (**128**), both α-positions of the furan ring are free. However, the formyl group enters the position 2 of the furan ring, which is in accord with the standard orientation rule.

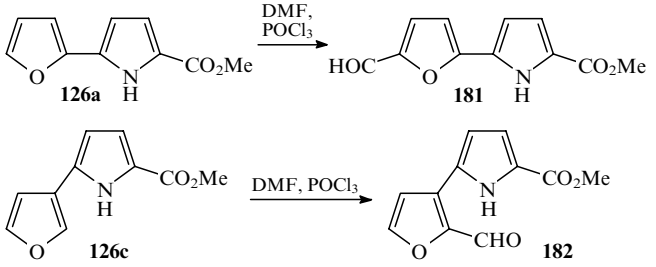
5-Methoxycarbonyl-2-(2-thienyl)- (**126b**) and -2-(3-thienyl)pyrrole (**126d**) give a mixture of 3-formyl-substituted pyrroles (**177**, **178**) and 2-(5-formyl-2-thienyl)- (**179**) and 2-(2-formyl-3-thienyl)-derivatives **180**, respectively.[134]



126b **177** **179** **126d** **178** **180**

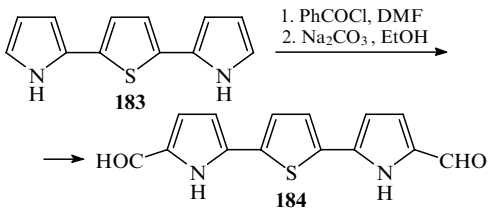
Because of the orienting effect of the α-methoxycarbonyl group, formylation in pyrroles **126b**,**d** occurs mostly in the β-position of the pyrrole ring (95%); the formylation product in the α-position of the thiophene ring is formed in the yield not exceeding 5%.

Unlike its thienyl analogues, 2-(2-furyl)- (**126a**) and 2-(3-furyl)-5-methoxycarbonypyrrole (**126c**) form in this case virtually only the products of formylation at positions 5 and 2 of the furan ring, *viz*., pyrroles **181**, **182**.[134]



126a **181** **126c** **182**

Heating of 2,5-di(2-pyrrolyl)thiophene **183** with benzoyl chloride in DMF leads to the formation of 2,2-di(5-formyl-2-pyrrolyl)thiophene **184** in 47% yield.[62]

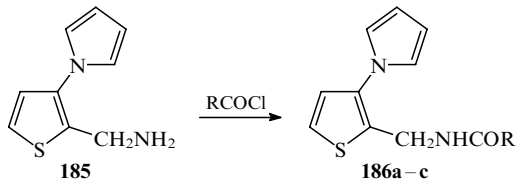


183 **184**

c. Acylation

Acylation of bipyrroles, furyl- and thienylpyrroles devoid of functional substituents with carboxylic acid anhydrides and halides has not been studied, except for trifluoroacetylation.

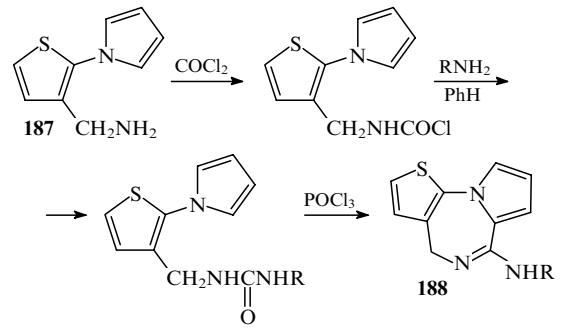
Acylation of 1-(2-aminomethyl-3-thienyl)pyrrole **185** occurs exclusively at the amino group with the formation of 1-(2-aroylamidomethyl-3-thienyl)pyrroles **186a**–**c**.[111]



185 186a–c

R = Ph (**a**, 82%), 4-ClC_6H_4 (**b**, 89%), 4-$NO_2C_6H_4$ (**c**, 74%).

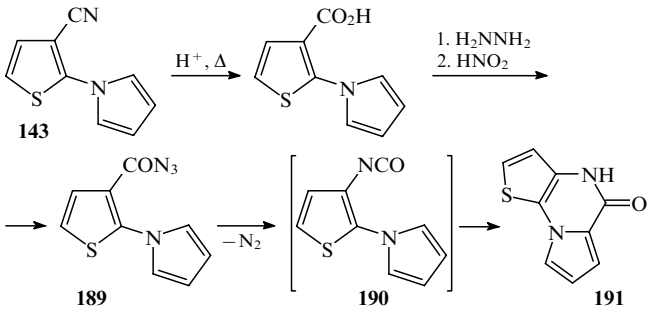
Starting from an isomeric aminomethylthienylpyrrole **187**, thienylpyrrolodiazepines **188** were obtained.[111,113]



187 188

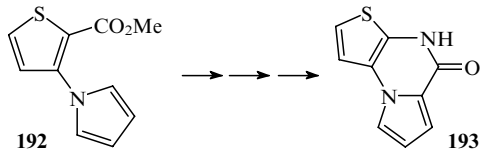
R = H, Me, Et, Ph, MeC_6H_4, 2-thienyl, NHPh.

Tricyclic compound **191** was obtained from 1-(3-cyano-2-thienyl)pyrrole (**143**) by a series of consecutive reactions, including the rearrangement of the azide **189** into an intermediate **190**.[112]



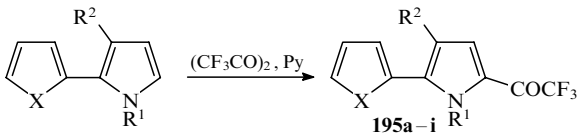
143 189 190 191

Similarly, isomeric tricyclic compound **193** was synthesised from thienylpyrrole **192**.[112]



192 193

Trifluoroacetyl derivatives of various pyrrole systems have been attracting attention of researchers since the 1960–1970s.[135–145] Trifluoroacetylation was often used on many occasions for comparing reactivities of various pyrrole, furan and thiophene derivatives in electrophilic substitution reactions.[121,124,135–137] The relative trifluoroacetylation rates of pyrrole, furan and thiophene with trifluoroacetic anhydride are 5.3×10^4, 1.4×10^2 and 1, respectively.[121,124] This ratio of rates illustrates the well known fact that pyrrole, owing to the higher, compared to other five-membered aromatic heterocycles, ability of its nitrogen atom to delocalise the positive charge in cationic σ-complexes, is appreciably more reactive than furan and the more so thiophene in reactions of electrophilic substitution.[122] It was thus believed[146] that 2-(2-furyl)- (**1a**) and 2-(2-thienyl)pyrroles (**7a**), as well as their 1-vinyl (**2a**,**b**, **8a**–**c**), 1-ethyl (**194a**) and 1-triethylsilylmethyl derivatives (**194b**), would be acylated with trifluoroacetic anhydride only at position 5 of the pyrrole ring.

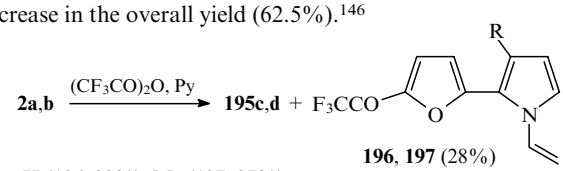


195a–i

Initial compound	X	R^1	R^2	Reaction product	Yield of **195** (%)
1a	O	H	H	**195a**	41
7a	S	H	H	**195b**	75
2a	O	$CH_2=CH$	H	**195c**	18
2b	O	$CH_2=CH$	Me	**195d**	34
8a	S	$CH_2=CH$	H	**195e**	78
8b	S	$CH_2=CH$	Me	**195f**	76
8c	S	$CH_2=CH$	Et	**195g**	63
194a	S	Et	H	**195h**	54
194b	S	CH_2SiEt_3	H	**195i**	75

It was shown[146,147] that it is compounds **195** that are formed upon trifluoroacetylation of furyl- and thienylpyrroles. In the case of 2-(2-furyl)pyrrole **1a**, the reaction mixture contains, in addition to the initial pyrrole and the final 2-(2-furyl)-5-trifluoroacetylpyrrole **195a**, an admixture of a third compound, presumably the product of trifluoroacetylation in the α-position of the furan ring or the β-position of the pyrrole ring. The latter is possible for activated pyrroles.[122] In contrast to 2-phenylpyrrole,[145] under comparable conditions the trifluoroacetylation of 2-(2-furyl)- (**1a**) and 2-(2-thienyl)pyrroles (**7a**) is not complete: the degree of conversion is 50%–60%, and the yields of the corresponding 5-trifluoroacetylpyrroles **195a**,**b** are 40%–50% with respect to the initial pyrrole. The use of a twofold excess of anhydride relative to pyrrole and the increase in the reaction temperature to 50 °C do not change its direction, though the yield of compound **195b** increases to 75%.

2-(2-Thienyl)-1-vinylpyrrole **8a** is acylated with both the equimolar amount and the twofold excess of trifluoroacetic anhydride to give virtually only one compound **195e**, whereas the major route of trifluoroacetylation of 2-(2-furyl)-1-vinylpyrrole **2a** is the attack at the α-position of the furan ring with the formation of compound **196**. With the twofold excess of anhydride, the content of isomer **195c** increases to 40% along with the increase in the overall yield (62.5%).[146]



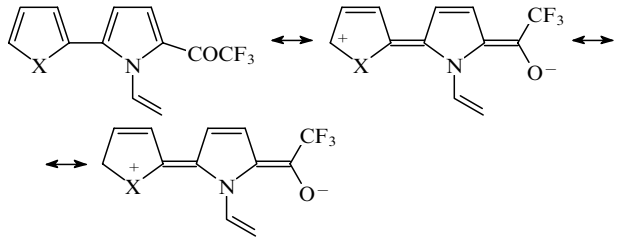
2a,**b** → **195c**,**d** + **196**, **197** (28%)

R = H (**196**, 28%); Me (**197**, 27%).

Substitution of α-hydrogen in the pyrrole ring by the trifluoroacetyl group is facilitated with the increase in its basicity, as is the case with 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles with alkyl substituents at position 3. In contrast to compound **2a**, the attack of 2-(2-furyl)-3-methyl-1-vinylpyrrole (**2b**) by the trifluoroacetyl cation is directed mostly not at the furan but at the pyrrole ring. Structurally isomeric trifluoroacetylpyrroles **195d** and **197** are formed in 34% and 27% yields, respectively.[148] 3-Alkyl-2-(2-thienyl)-1-vinylpyrroles **8b**,**c** form only α-trifluoroacetylpyrroles **195f**,**g**. Substitution of the vinyl group by the ethyl group at the nitrogen atom (compound **194a**) does not change the direction of trifluoroacetylation. It also occurs in the pyrrole ring of compound **194b** in which there is a rather bulky triethylsilylmethyl substituent.[148]

In order to interpret the results obtained, Trofimov *et al.*[146] considered the following factors; (*a*) an appreciably larger nucleophilicity of the furan ring compared to that of thiophene; (*b*) a decrease in the electron density in the pyrrole ring due to competitive conjugation of the vinyl group with the unshared electron pair on nitrogen and also owing to its negative inductive effect; (*c*) possible steric hindrance due to the vinyl group for the

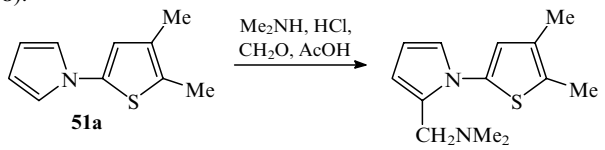
attack at the α-position of the pyrrole ring. The reactivity of the thiophene ring is so low compared to the furan ring, and the more so, the pyrrole ring, that the factors (*a*) and (*b*) seem to be insufficiently strong for changing the direction of trifluoroacetylation of 2-(2-thienyl)-1-vinylpyrrole. The absence of double acetylation products points to a very strong influence of the electron-acceptor trifluoroacetyl substituent that is transferred to the thiophene ring. The mechanism of such a transfer cannot be reduced solely to the inductive effect but should include formation of a common conjugation system.[146]



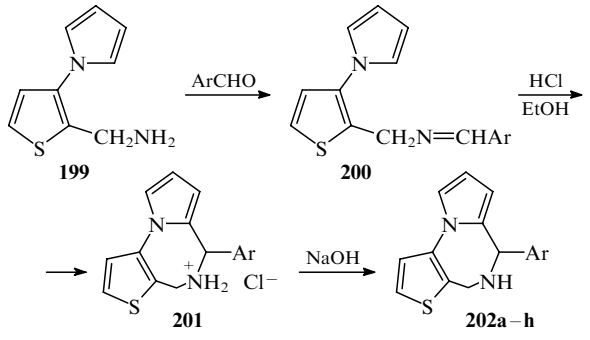
It is known that trifluoroacetylation of 1-vinylamides,[149] ethyl iminoacetoacetate[150] and 9-alkenylcarbazoles[151] can result in electrophilic substitution of hydrogen in the 1-vinyl group. This reaction route was not observed for 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles.

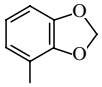
d. Aminomethylation

The reaction 1-(4,5-dimethyl-2-thienyl)pyrrole (**51a**) with the aminomethylation system $Me_2NH-HCl-CH_2O$ in acetic acid results in a 2-dimethylaminomethyl derivative of this pyrrole (**198**).[109]



4-Aryl-5,6-dihydro-4*H*-pyrrolo[1,2-*a*]thieno[2,3-*f*]-1,4-diazepines **202a–h** were synthesised by the reaction of 1-(2-benzylideneaminomethyl-3-thienyl)pyrroles **200**, obtained from 1-(2-aminomethyl-3-thienyl)pyrrole (**199**) and the corresponding aromatic aldehydes, with hydrogen chloride in dry ethanol (Δ, 45 min) with subsequent treatment of the hydrochlorides formed (**201**) with dilute NaOH.[110]

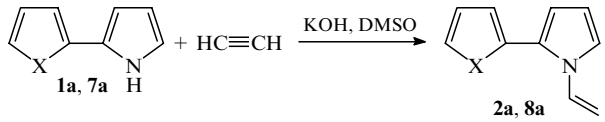


Compound **202**	Ar	Yield (%)
a	Ph	48
b	2-ClC_6H_4	62
c	3-ClC_6H_4	56
d	4-ClC_6H_4	53
e	3-$MeOC_6H_4$	65
f	4-MeC_6H_4	63
g	3,4-$(MeO)_2C_6H_3$	52
h		62

2. Nucleophilic addition to the triple bond

Vinylation of NH-heterocycles with acetylene is usually carried out under a pressure of 20–40 atm at 160–200 °C. This process has limited laboratory uses because of its explosion hazard and the need for special equipment, though several such technologies have been realised on the industrial scale.[22]

The use of superbasic catalytic systems of the KOH–DMSO type allows vinylation of alkyl- and arylpyrroles at 100–200 °C and atmospheric pressure.[152] Under these conditions, 2-(2-furyl)- (**1a**) and 2-(2-thienyl)pyrroles (**7a**) are successfully vinylated.[153] The results of vinylation of compounds **1a**, **7a** and 2-phenylpyrrole are presented in Table 2.



X = O (**1a**, **2a**), S (**7a**, **8a**).

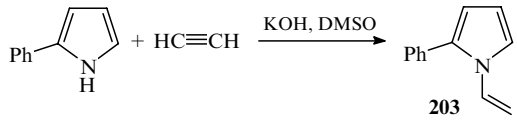


Table 2. Effect of vinylation conditions on the yield of 2-(2-furyl)- (**2a**), 2-(2-thienyl)- (**8a**) and 2-phenyl-1-vinyl-pyrroles (**203**).[153]

Temperature /°C	Time /h	Yield of the vinylation product [a, b]		
		2a	**8a**	**203**
110	4	(2 : 98)	(15 : 85)	–
110	4.5	98	(3 : 97)	(12 : 78)
110	5	–	98.5	(5 : 95)
110	5.5	–	–	(2 : 98)
110	6	–	–	(~0.1 : 99.9)
120	3	86	(5 : 95)	(7 : 93)
120	4	–	(~0.1 : 99.9)	87

[a] The yield was calculated after distillation. [b] The ratio of the initial compound to the reaction product (according to GLC) is indicated in parentheses.

Acetylene was passed through the reaction mixture under atmospheric pressure. Vinylation was carried out at a fivefold molar excess of KOH. Virtually quantitative yields (96%–98.5%) of 1-vinylpyrroles were attained at 110 °C within 4.5–6 h (see Table 2). With increase in the temperature to 120 °C the duration of vinylation is reduced, although the yield of 1-vinylpyrroles drops by 9%–16% because of side processes.

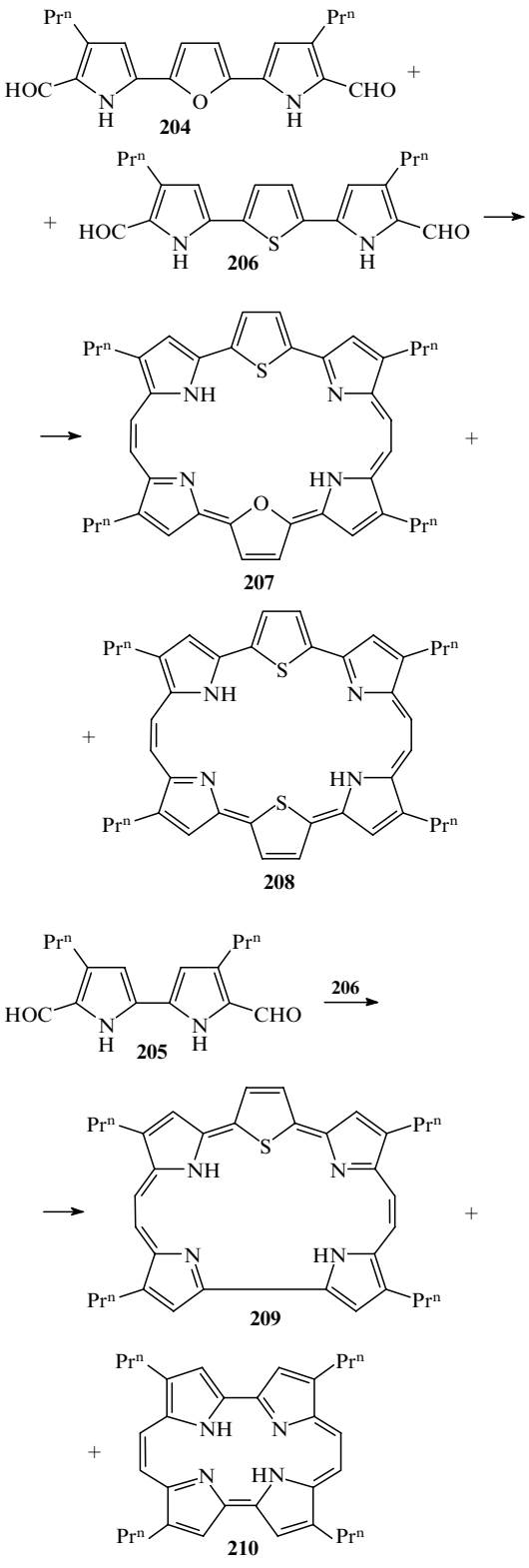
When vinylation was conducted in an autoclave (initial acetylene pressure 10–14 atm, maximal pressure 20–30 atm, DMSO, threefold molar excess of KOH, 120 °C), the yield of vinylpyrroles did not exceed 80% due to resinification. Thus, vinylation of aryl- and hetarylpyrroles under atmospheric pressure is not only safe but also more efficient.

The vinylation rate of pyrroles increases in the sequence 2-phenylpyrrole < 2-(2-thienyl)pyrrole < 2-(2-furyl)pyrrole (see Table 2). Their NH acidity increases in the same order. (Jackson[3] did not give the value of 2-(2-furyl)pyrrole acidity, but it can be estimated from the cited dependence of pK_a on induction constants of substituents in the pyrrole ring). The observed order of reactivity of pyrroles fully confirms the previously established general regularity[153–157] that the rate of base-catalysed addition of structurally similar azoles to acetylene, including 2-furyl- and 2-thienylpyrroles, increases with their acidity. However, it was reported[153] that the yield of 1-vinyl derivatives of tetrahydro-γ-carbolines increases with the introduction into their molecule of a methyl group, which decreases the NH-acidity. Thus, the infor-

mation available at that time did not give any clear idea about the influence of NH-acidity (nucleophilicity) of azoles on the rate of their addition to acetylene.

In order to assess the influence of substituents on the vinylation rate of pyrroles, the kinetic curves of vinylation of the series of NH-pyrroles for which precise values of pK_a of relative acidity are known have been compared quantitatively [156] with the correlation equations relating these parameters to the substituent constants.[4, 157, 158] Vinylation was carried out in a KOH – DMSO system at 100 °C under atmospheric pressure. The course of the process was monitored using GLC. It was found [156] that the vinylation rates of 2-benzyl-3-phenyl-, 3-hexyl-2-phenyl-, 2,3-diphenyl-, 2-(4-ethylphenyl)- and 2-(4-methoxyphenyl)pyrroles increase with the decrease in their acidity (increase in pK_a values [159]). However, 2-(2-furyl)- and 2-(2-thienyl)pyrroles are vinylated more readily than expected from consideration only of the values of their acidity, *i.e.*, possessing a stronger acidity than that of 2-phenylpyrroles, they have higher vinylation rates. The observed deviation may be explained by the fact that the nucleophilicity of anions is determined not only by their basicity (pK_a values of conjugated acids) but also by their polarisability and ionisation potential. Therefore, furyl- and thienylpyrroles, which are more easily polarised and possess lower ionisation potentials (owing to the heteroatoms conjugated with the pyrrole moiety of the molecule), should form anions of increased nucleophilicity with concomitantly decreased basicity. Despite the fact that the acidity of pyrroles increases and the basicity of the corresponding anions decreases in the order: 2-phenylpyrrole < 2-(2-thienyl)pyrrole < 2-(2-furyl)pyrrole, the reaction rate increases in the same order since the ionisation potentials [160, 161] decrease in the following order (eV): 2-phenylpyrrole (7.61) > 2-(2-thienyl)pyrrole (7.41) > 2-(2-furyl)pyrrole (7.29). Thus, the 2-(2-furyl)- and 2-(2-thienyl)pyrrole anions, while being less basic than the 2-phenylpyrrole anion, are superior to it in their nucleophilicity.

Yet another peculiarity of the vinylation reaction of pyrroles has been revealed:[156] all kinetic curves are clearly S-shaped, which is characteristic of autocatalytic reactions. In principle, autocatalysis should be characteristic of vinylation reactions in aprotic and especially superbasic media. Indeed, with the consumption of protogenic substrate (the NH group of pyrrole in this case) one observes an increase in both nucleophilicity of the remaining anions (due to lower solvation) and the degree of ionisation of the remaining substrate molecules (owing to increased medium basicity). At the same time, the chemical activity of acetylene molecules is enhanced owing to complexation with partially dehydrated molecules of the base serving as the catalyst (KOH). The presence of a one-electron route of nucleophilic addition to the triple bond can also contribute to the manifestation of this effect.[156] This reaction can occur by a chain mechanism and be inhibited by admixtures that quench radical and non-radical intermediates. Such a mechanism is highly probable for superbasic systems in which highly reactive, dehydrated anions are especially prone to electron transfer. This is also consistent with the reported [156] approximate correlation between the reaction rate and the ionisation potentials of the initial pyrroles. The presumed existence of a one-electron route in the vinylation reaction of pyrroles has been confirmed in later studies.[162 – 164]

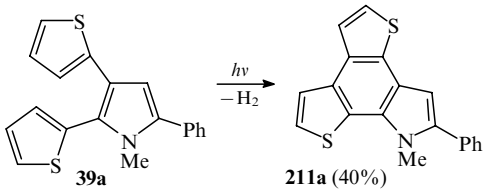


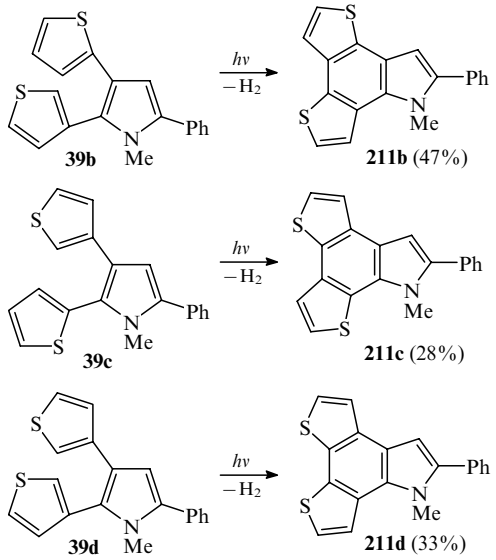
3. Cyclisation

Cyclisation of pyrroles linked to aromatic five-membered heterocycles leads to difficultly accessible polycyclic systems.

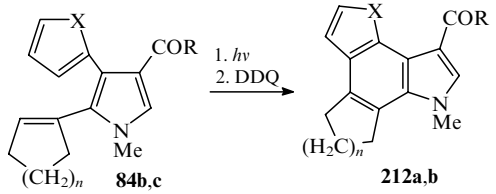
Porphyrin-like macrocycles **207** – **210** have been obtained by the reaction of 2,5-bis(5-formyl-4-n-propyl-2-pyrrolyl)furan **204** or dipyrroledicarbaldehyde **205** with 2,5-bis(5-formyl-4-n-propyl-2-pyrrolyl)thiophene **206**.[165]

Oxidative photocyclisation of isomeric 2,3-dithienyl-5-phenylpyrroles **39a** – **d** resulted in a series of isomeric dithienoindoles **211a** – **d** in 28% – 47% yields.[66]



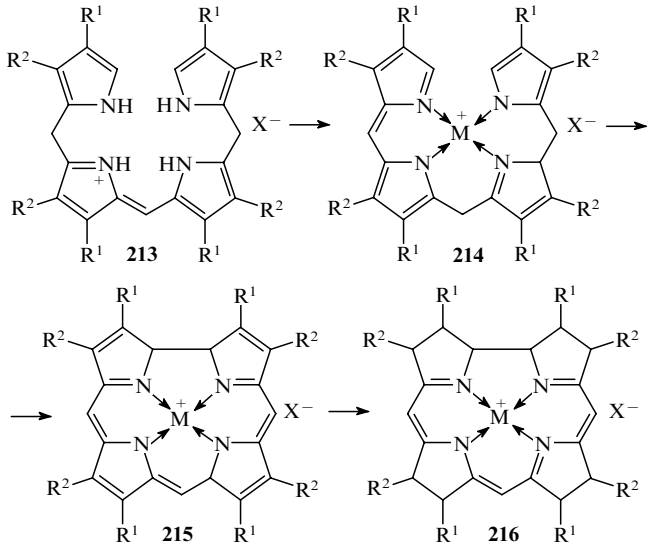


Photochemical electrocyclisation of 3-(2-furyl)- and 3-(2-thienyl)pyrroles **84b**,**c** with subsequent dehydrogenation with 2,3-dichloro-5,6-dicyanoquinone (DDQ) leads to indole derivatives **212a**,**b**.[81] Irradiation was carried out with a high-pressure mercury lamp at room temperature for 12 h in cyclohexane.



Compound **212**	X	*n*	R	Yield of **212** (%)
a	O	3	Ph	73
b	S	2	2-thienyl	78

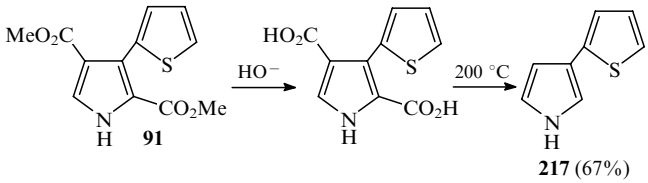
Linear tetrapyrrole intermediates (**213**) form complexes (**214**) with transition metal salts (M = Ni, Co; X = Cl, Br, ClO_4) upon heating in *o*-dichlorobenzene (100 °C, 14 h). These complexes are oxidised by atmospheric oxygen to corrole-like macrocycles **215** containing the bipyrrole fragment. Subsequent reduction of the latter under drastic conditions (100 °C, 100 atm) leads to corrins. Their structural element forms the basis of numerous vitally important compounds, including vitamin B_{12}.[166,167]



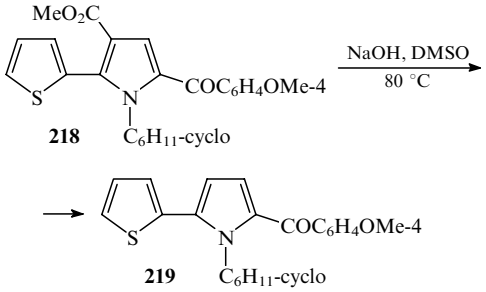
R^1, R^2 = Me, Et; M = Ni, Co; X = Cl, Br, ClO_4.

4. Hydrolysis, decarboxylation, oxidation and other reactions of substituents

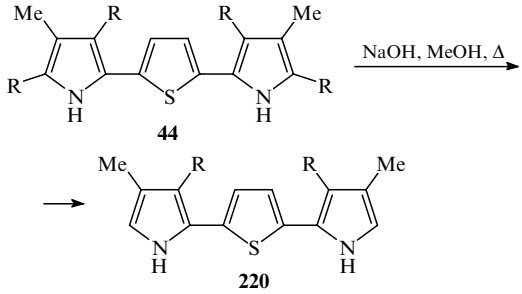
Hetaryl-substituted pyrroles often contain alkoxycarbonyl groups. These can be eliminated by hydrolysis and decarboxylation (200 °C) (see Section II.7, synthesis of compounds **1a**, **7a**, **128**, **129**).[101] 3-(2-Thienyl)pyrrole (**217**) was obtained in this way from the diester **91**.[85]



Alkaline hydrolysis of the ester **218** leading to thienylpyrrole **219** has been described.[76]

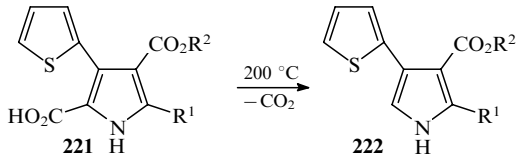


When di(pyrrolyl)thiophene **44** with four ethoxycarbonyl groups in the α- and β-positions of the pyrrole rings was boiled in methanolic NaOH, only the α-positions were selectively liberated with the formation of di(pyrrolyl)thiophene **220**.[68]



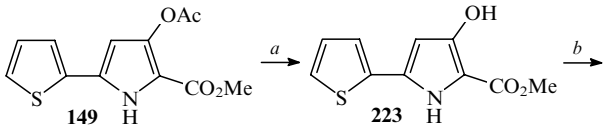
R = CO_2Et.

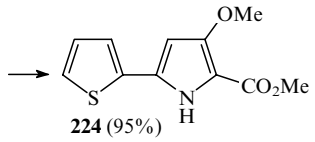
Esters of 4-(2-thienyl)pyrrole-3-carboxylic acids **222** were synthesised by decarboxylation of 3-(2-thienyl)-2,4-pyrroledicarboxylic acid derivatives **221**.[168]



R^1 = H, Alk; R^2 = Alk.

Solvolysis of thienylpyrrole **149** results in its deacetylation and formation of 4-hydroxy-5-methoxycarbonyl-2-(2-thienyl)pyrrole (**223**).[114] Its methylation with dimethyl sulfate gives pyrrole **224**.[114]

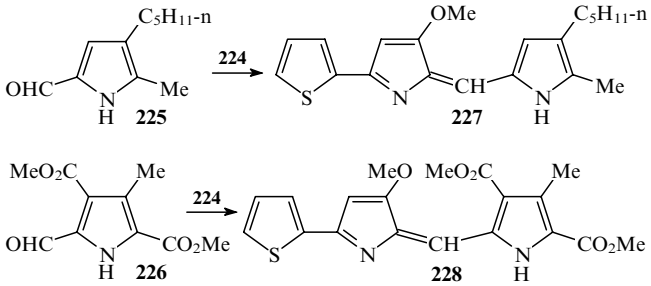




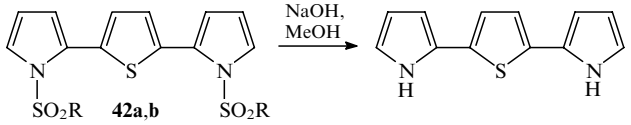
224 (95%)

(*a*) 5N NaOMe, MeOH, 3 h; (*b*) Me_2SO_4, NaH, THF.

Pyrrole-2-carbaldehydes **225**, **226** form prodigiosin analogues **227**, **228** upon reaction with the pyrrole **224** (yields up to 95%).[114]

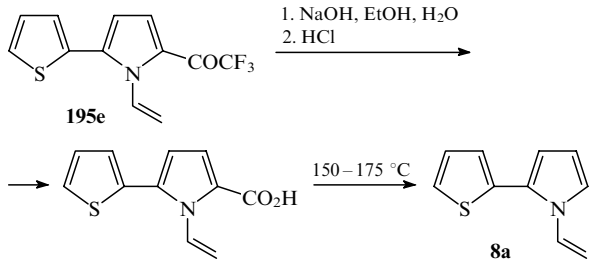


The *N*-sulfonyl protective groups in dipyrrolylthiophenes **42a**,**b** are removed by boiling with methanolic NaOH.[68]

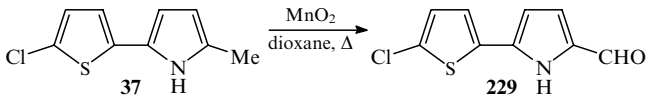


R = Me (**a**), Ph (**b**).

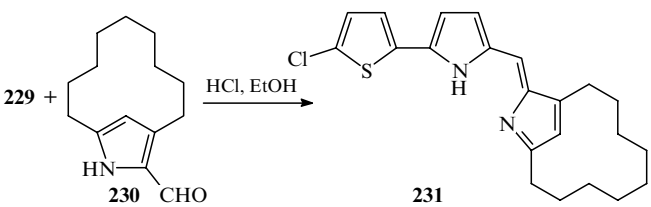
Treatment of 2-(2-thienyl)-5-trifluoroacetyl-1-vinylpyrrole **195e** with boiling ethanolic NaOH gave 2-(2-thienyl)pyrrole-carboxylic acid (yield 88%), which is decarboxylated to vinylpyrrole **8a** upon heating (150–175 °C).[169]



α-Formyl derivative of 2-(5-chloro-2-thienyl)pyrrole **229** was synthesised in 45% yield by the oxidation of pyrrole **37** with MnO_2 in dioxane.[65]



The aldehyde **229** reacts with 2,4-pyrrolophane **230** in ethanol in the presence of concentrated HCl (8 °C, 15 min; 0 °C, 24 h) to give pyrrolophane **231**.[65]



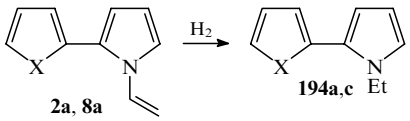
5. Reactions of the *N*-vinyl group

Systematic studies of the reactivity of 2-(2-furyl)- and 2-(thienyl)-1-vinylpyrroles became possible after the development of a convenient and efficient method for their synthesis.[4] Before that, there were virtually no data on the *N*-vinylpyrroles linked to five-membered aromatic heterocycles. Studies of reactions involving the *N*-vinyl groups of furyl- and thienylpyrroles open wide possibilities for the synthesis of new hetaryl-substituted pyrroles.

a. Hydrogenation

Hydrogenation of substituted pyrroles is a rather well-studied reaction,[1,2] which allows one to synthesise pyrrolines and pyrrolidines in high yields. Platinum, ruthenium and nickel catalysts are most often used for catalytic hydrogenation of pyrroles.[1,2,170] Depending on the nature of the substituent and its position in the ring, it is possible to bring about selective hydrogenation of either the pyrrole ring or the side chain.[1,2] Electron-acceptor substituents in the α- and β-positions of the ring impede its reduction, whereas substituents at the nitrogen atom facilitate this process.[1,2]

Hydrogenation of 2-(2-furyl)-1-vinyl- and 2-(2-thienyl)-1-vinylpyrroles in the presence of catalysts such as Raney nickel, platinum black, palladium chloride was first studied by Korostova *et al.*[148] It was shown that hydrogenation on Raney nickel (80 °C, 60 atm) results in the reduction of the vinyl group in 2-(2-furyl)-1-vinylpyrrole (**2a**) to the ethyl group which occurs as easily and selectively as in 2-alkyl(aryl)-1-vinylpyrroles,[171] giving 1-ethyl-2-(2-furyl)pyrrole **194c** in 94% yield.[148]

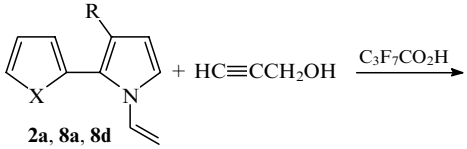


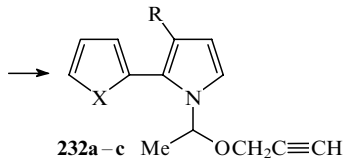
X = O (**2a**, **194c**); S (**8a**, **194a**).

In the hydrogenation over Raney nickel, a decrease in the hydrogen pressure to 10–12 atm (all other conditions remaining the same) leads to a sharp deceleration of the reaction and a decrease in the yield of ethylpyrrole **194c** to 65%. In the hydrogenation over palladium chloride (15 mass. % with respect to vinylpyrrole, 80 °C, 40 atm) the yield of ethylpyrrole **194c** amounts to 75%. In contrast with the data reported by Lunn,[172] who succeeded in reducing pyrrole to pyrrolidine in the presence of a nickel–aluminium alloy, the pyrrole and furan rings of compound **2a** remain intact under the described conditions.[148] The presence of the thiophene ring complicates hydrogenation of 2-(2-thienyl)-1-vinylpyrrole (**8a**) over nickel catalyst (50 °C, 48 atm) due to poisoning of the catalyst. Only the use of a very large amount of the catalyst (50 mass. % with respect to vinylpyrrole) has allowed preparation of ethylpyrrole **194a** in 46% yield; in this case, hydrogenolysis resulted in the formation of low-boiling products. When $PdCl_2$ was used at room temperature, the yield of ethylpyrrole **194a** was as low as 7%. In the presence of palladium black (80 °C, 40 atm), 2-(2-thienyl)-1-vinylpyrrole is not hydrogenated.

b. Addition of alcohols

Electrophilic addition of alcohols to 2-(2-furyl)- and -2-(2-thienyl)-1-vinylpyrroles was studied in the example of reaction with propargyl alcohol in the presence of perfluorobutyric acid (PFBA).[148,173,174] This reaction is conducted at 96 °C. Higher temperature and longer reaction time enhance resinification. The yield of adducts **232a**–**c** depends on the catalyst's concentration and the ratio of reagents: the optimum conditions are 1.5-fold excess of propargyl alcohol and 1.5%–2% of PFBA relative to the substrate.



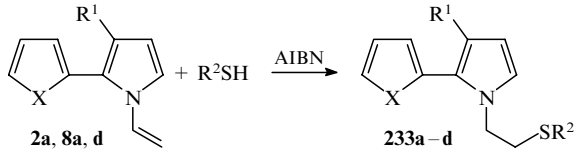


232a–c

R = H: X = O (**232a**, 55%), S (**232b**, 71%); R = Me, X = S (**232c**, 56%).

c. Addition of thiols

Free-radical thiylation of 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles initiated by azobis(isobutyronitrile) (AIBN) gives *anti*-Markovnikoff formation of solely β-adducts **233**.[148]



2a, 8a, d **233a–d**

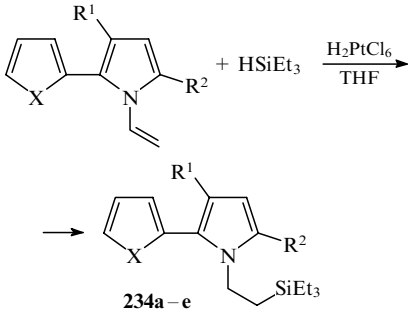
Substrate	X	R^1	R^2	Product	Yield (%)
2a	O	H	Et	**233a**	84
8a	S	H	Et	**233b**	78
8d	S	Pr^n	Et	**233c**	95
8d	S	Pr^n	Pr^n	**233d**	80

At 70–80 °C, the reaction is completed within 18–25 h (the yield of adducts **233a–d** is 80%–95%). Under comparable conditions without initiator, the yield drops to 15%–20%.[148] This reaction has been successfully used for purification of 2-(2-thienyl)pyrroles from their 1-vinyl derivatives.[43]

d. Hydrosilylation

Kopylova *et al.*[175] performed hydrosilylation of 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles in the presence of different catalysts; they also used various hydrosilylation agents.

The highest yields of silyl derivatives were reached upon hydrosilylation with triethylsilane at an equimolar ratio of reagents in the presence of 0.05 M solution of $H_2PtCl_6 \cdot 6H_2O$ in THF (140 °C, 5 h). The reaction proceeded regiospecifically with the formation of β-adducts **234a–e**. (The yields were calculated relative to the consumed vinylpyrrole. [175])



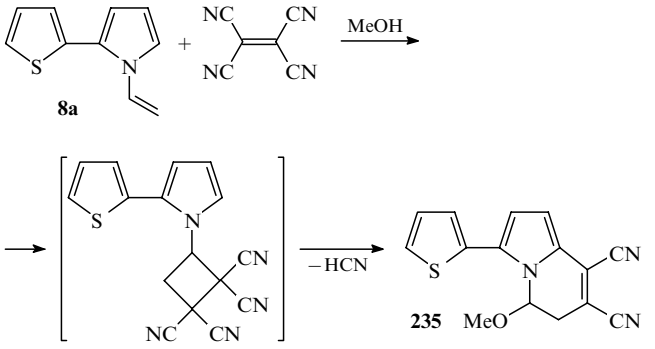
234a–e

Compound **234**	X	R^1	R^2	Yield (%)
a	O	H	H	40
b	S	H	H	70
c	S	Me	H	65
d	S	Et	H	44
e	S	H	$COCF_3$	10

The Wilkinson complex $[(Ph_3P)_3RhCl]$ also catalyses this reaction. Longer reaction time and the use of polar solvents (THF, dioxane) favour an increase in yields of the adducts. No positive results have been reported for the reactions involving trichloro-, triethoxy- and alkylchlorosilanes. Only upon reaction of methyldichlorosilane with 2-(2-thienyl)-1-vinylpyrrole, the formation of the corresponding adduct in ~7% yield was observed. In the absence of catalysts, the reaction does not take place under UV-initiation. The yield of adducts depends not only on the nature of the silane but also on the substituents in the pyrrole ring. Thus the yield of the pyrrole **234b** was 70%; upon introduction of an electron-acceptor substituent ($R^2 = COCF_3$) into the pyrrole ring, the yield of the corresponding pyrrole **234e** drops to 10%.[175]

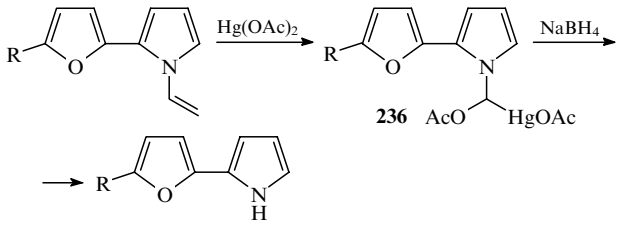
e. Cyclisation

7,8-Dicyano-5-methoxy-3-(2-thienyl)-5,6-dihydroindolizine (**235**) was synthesised from 2-(2-thienyl)-1-vinylpyrrole (**8a**), tetracyanoethylene and methanol.[176]



f. 2-(2-Furyl)-1-vinylpyrroles as protected pyrroles

Protection of the NH group of the pyrrole fragment is often the key stage in the synthesis of complex pyrrole derivatives. In this case, not only the acidity of the NH group is temporarily blocked, but the reactivity of different positions of the pyrrole ring is substantially changed due to steric and electronic effects of the protective groups. The role of protective group is played by, *e.g.*, trialkylsilyl, tosyl, pyridylethyl, phenylsulfonyl or *N*-β-alkylthioethyl groups. The *N*-vinyl group may also be rather successfully used for the protection of the NH group.[51, 95, 177–180] In this case, deprotection can be effected by acid hydrolysis in the presence of hydroxylamine hydrochloride [181] or by mercuration with mercuric acetate followed by treatment with sodium borohydride.[51] 2-(2-Furyl)- and 2-(5-methyl-2-furyl)-1-vinylpyrroles have thus been transformed into the corresponding 1*H*-pyrroles in 93% and 83% yields, respectively (relative to the consumed vinylpyrrole).[182]



R = H, Me.

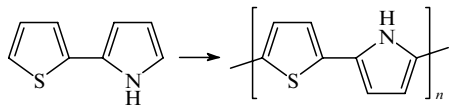
Mercuration is carried out at room temperature until disappearance of the initial 1-vinylpyrrole with subsequent *in situ* reduction of the intermediate mercuric acetate **236** with sodium borohydride.

Despite complete disappearance of the starting vinylpyrrole in the mercuration stage, it appears again in small amount after the reduction with sodium borohydride. It is presumed that the intermediate **236** is preceded by a complex of vinylpyrrole with the mercury cation, the reduction of which leads to regeneration of 1-vinylpyrrole.[182]

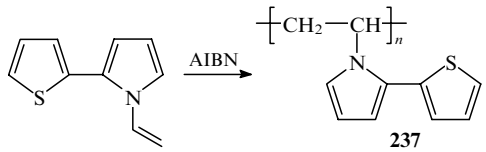
g. Polymerisation

Polymerisation of furyl- and thienylpyrroles and their vinyl derivatives has been little studied so far. Electrochemical polymer-

isation of 2-(2-thienyl)pyrrole yielded poly(thienylpyrrole), apparently with alternating thienyl and pyrrole rings.[183]



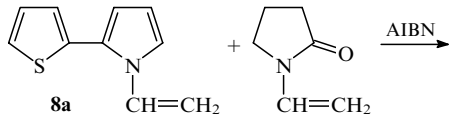
Under the conditions of radical initiation, *i.e.*, under the action of azobis(isobutyronitrile), 2-(2-thienyl)-1-vinylpyrrole forms homopolymers **237** with a molecular mass of 3700 Da.[184]



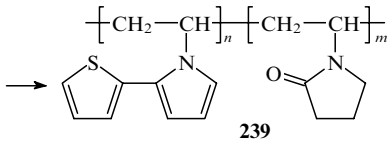
237

The formation of polymers with involvement of only the *N*-vinyl group was proved by spectral data (IR, ^{1}H NMR) and turbidimetric titration data in different solvent–precipitant systems. It was suggested [184] that poly(1-vinylpyrroles) **237** form complexes upon contact with atmospheric oxygen; this suggestion is supported by intense EPR signals in polymers following their prolonged exposure in air.

Free-radical copolymerisation of 2-(2-thienyl)-1-vinylpyrrole **8a** with vinylpyrrolidone **238** yielded a copolymer **239** enriched in the vinylpyrrolidone units.[185, 186] The molecular mass and the yield of the copolymer depend directly on the concentration of vinylpyrrolidone.



8a **238**



239

IV. Prospects for the use

The chemistry of pyrroles linked to five-membered aromatic heterocycles is still in its infancy. Nonetheless, the currently available data on their properties allow one to consider them and their derivatives as promising compounds for medicine, agriculture and some industrial fields.

This concerns primarily the 1-vinyl derivatives of furyl- and thienylpyrroles. Reactions of electrophilic substitution in the pyrrole ring and addition reactions to the vinyl group occur highly selectively making it possible to use these compounds as building blocks for the synthesis of various derivatives.

The potentialities of furyl- and thienylpyrroles are still far from being fully disclosed. Poly(furylpyrroles) and poly(thienylpyrroles) with regularly alternating rings can differ appreciably in their electrophysical properties [184] from polypyrroles — organic metals, which are already applied in novel technologies.[187–190] Indolizines with thienyl substituents have been recommended as efficient photosensitisers.[176]

The antiviral activity of a series of 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles has been investigated. 2-(2-Thienyl)-1-vinylpyrrole was found to be moderately active against the herpes virus, whereas 3-ethyl-2-(2-thienyl)-1-vinylpyrrole proved to be active against the pox virus.[26] It should be pointed out that furylvinyl- and thienylvinylpyrroles are as a rule moderately or weakly toxic compounds [23, 24, 26] (Table 3).

Table 3. Toxicity of 1-vinyl-2-(2-hetaryl)pyrroles, some of their precursors and derivatives.

Compound	LD_{50}/mg kg^{-1} (see [a])
3-Ethyl-2-(2-furyl)-1-vinylpyrrole	760
2-(2-Furyl)-3-isopropyl-1-vinylpyrrole	1300
3-Butyl-2-(2-furyl)-1-vinylpyrrole	270
2-(2-Thienyl)pyrrole	260
2-(2-Thienyl)-1-vinylpyrrole	630
3-Methyl-2-(2-thienyl)-1-vinylpyrrole	30
3-Ethyl-2-(2-thienyl)-1-vinylpyrrole	830
3-Propyl-2-(2-thienyl)-1-vinylpyrrole	1370
3-Butyl-2-(2-thienyl)-1-vinylpyrrole	620
3-Hexyl-2-(2-thienyl)-1-vinylpyrrole	1500
2-(2-Thienyl)-5-trifluoroacetylpyrrole	3900
2-(2-Thienyl)-5-trifluoroacetyl-1-vinylpyrrole	1870
2-(2-Thienyl)-1-vinyl-5-pyrrolecarboxylic acid	270

[a] Approximate values.

The activity of a series of 2-(2-furyl)- and 2-(2-thienyl)pyrroles towards 11 strains of different bacterial and fungal species has been assayed. 2-(2-Thienyl)-1-vinylpyrrole proved to be the most active against staphyllococci and candidas as well as against the anthracoid bacilli.[26]

Investigation into the repellent and insecticidal activity of furylvinyl- and thienylvinylpyrroles has revealed that 2-(2-furyl)-1-vinylpyrrole is a highly active and selective repellent for forest pests (black coniferous longhorn beetle) and is non-toxic for warm-blooded animals and the ichthiofauna of rivers; 3-ethyl-2-(2-thienyl)-1-vinylpyrrole was also found to manifest weak repellent activity.[4, 24, 26] The same vinylpyrroles proved to be moderately toxic for the larvae of the coniferous longhorn beetle.[4, 26]

The assay of insecticidal activity of a series of 2-(2-furyl)- and 2-(2-thienyl)pyrroles has revealed moderate activity of 3-propyl-2-(2-thienyl)-1-vinylpyrrole against sugar-beet root aphid and high activity of 2-(2-thienyl)-, 3-ethyl- and 3-propyl-1-vinylpyrroles against larvae of the domestic fly.[26] 3-Propyl-2-(2-thienyl)-1-vinylpyrrole possesses high herbicidal activity, while 2-(2-thienyl)-1-vinylpyrrole and its copolymer with *N*-vinylpyrrolidone exhibit the growth-regulating activity.[26, 186, 191]

A number of 4-cyano-3-furyl- and 3-thienylpyrroles were recommended as starting compounds for the synthesis of medicinal substances and pesticides,[82] while esters of 4-(2-thienyl)-3-pyrrolecarboxylic acids seem to be appropriate drugs for the therapy of cardiac insufficiency.[168]

V. Conclusion

The data discussed in this review demonstrate appreciable progress in the field of the synthesis of pyrroles linked to other heterocycles, *viz*., bipyrroles, furyl-, thienyl- and selenienylpyrroles and their derivatives.

Broad synthetic potential of hetarylpyrroles and especially of their *N*-vinyl derivatives in various reactions, such as electrophilic substitution, nucleophilic addition to the triple bond, cyclisation, hydrogenation, thiylation, hydrosilylation, polymerisation, as well as useful properties inherent in certain compounds of this series open up broad prospects for their use in fine organic synthesis, medicine, agriculture and some technological fields.

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References

1. A Gossauer *Die Chemie der Pyrrole* (Berlin: Springer, 1974)
2. R A Jones, G P Bean *The Chemistry of Pyrroles* (New York: Academic Press, 1977)
3. A H Jackson, in *Comprehensive Organic Chemistry* Vol. 4 (Eds D Barton, W D Ollis) (New York: Pergamon Press, 1979)
4. B A Trofimov, A I Mikhaleva *N-Vinylpirroly* (*N*-Vinilpyrroles) (Novosibirsk: Nauka, 1984)
5. B A Trofimov *Usp. Khim.* **58** 1703 (1989) [*Russ. Chem. Rev.* **58** 967 (1989)]
6. B A Trofimov, A I Mikhaleva, L V Morozova *Usp. Khim.* **54** 1034 (1985) [*Russ. Chem. Rev.* **54** 609 (1985)]
7. E Ya Lukevits (Ed.) *Uspekhi Khimii Furana* (The Progress in the Chemistry of Pyrrole) (Riga: Zinatne, 1978)
8. P Bauerle, T Fischer, B Bidlingmeier, A Stabel, J P Rabe *Angew. Chem.* **107** 335 (1995)
9. L I Belen'kii (Ed.) *Khimiya Organicheskikh Soedinenii Sery* (The Chemistry of Organic Compounds of Sulfur) (Moscow: Khimiya, 1988)
10. P I Buchin, A E Lipkin *Proizvodnye Tiofena i Bitiofena kak Perspektivnye Antiseptiki Novoi Gruppy* (Thiophene and Bithiophene Derivatives as Perspective Antiseptics of New Group) (Saratov: Saratov State University, 1974)
11. V P Litvinov, V D Dyachenko *Usp. Khim.* **66** 1025 (1997) [*Russ. Chem. Rev.* **66** 923 (1997)]
12. B A Trofimov, N I Golovanova, N I Shergina, A I Mikhaleva, S E Korostova, A N Vasil'ev *Spektry Pogloshcheniya Proizvodnykh Pirrola i 1-Vinilpirrola v Infrakrasnoi, Ul'trafioletovoi i Vidimoi Oblastyakh. Atlas Spektrov Aromaticheskikh i Geterotsiklicheskikh Soedinenii* (Absorption Spectra of Pyrrole and 1-Vinylpyrrole Derivatives in Infrared, Ultraviolet and Visible Regions. Atlas of Spectra of Aromatic and Heterocyclic Compounds) No. 21 (Ed. V A Koptyug) (Novosibirsk: Novosibirsk Institute of Organic Chemistry, Siberian Branch of Academy of Sciences of the USSR, 1981)
13. B A Trofimov, L N Sobenina, A I Mikhaleva *Organicheskaya Khimiya, T. 7 (Itogi Nauki i Tekhniki)* [Organic Chemistry, Vol. 7 (Advances in Science and Engineering Series)] (Moscow: Izd. VINITI, 1987)
14. B A Trofimov, A I Mikhaleva *Khim. Geterotsikl. Soedin.* 1299 (1980) [a]
15. L N Sobenina, A I Mikhaleva, B A Trofimov *Usp. Khim.* **58** 275 (1989) [*Russ. Chem. Rev.* **58** 163 (1989)]
16. B A Trofimov *Adv. Heterocycl. Chem.* **51** 177 (1990)
17. G P Bean, in *The Chemistry of Heterocyclic Compounds* Vol. 48 (Ed. R A Jones) (New York: Wiley, 1990) Part 1, p. 105
18. B A Trofimov, in *The Chemistry of Heterocyclic Compounds* Vol. 48 (Ed. R A Jones) (New York: Wiley, 1992) Part 2, p. 131
19. B A Trofimov, A I Mikhaleva *Heterocycles* **37** 1193 (1994)
20. B A Trofimov *Phosphorus Sulfur Silicon Relat. Elem.* **95**–**96** 145 (1994)
21. M V Sigalov, B A Trofimov *Zh. Org. Khim.* **31** 801 (1995) [b]
22. R J Tedeschi, in *Encyclopedia of Physical Science and Technology* Vol. 1 (New York: Academic Press, 1992) p. 27
23. A I Mikhaleva, Doctoral Thesis in Chemical Sciences, Irkutsk Institute of Organic Chemistry, Siberian Branch of Russian Academy of Sciences, Irkutsk, 1984
24. S E Korostova, Doctoral Thesis in Chemical Sciences, Irkutsk Institute of Organic Chemistry, Siberian Branch of Russian Academy of Sciences, Irkutsk, 1993
25. M V Sigalov, Doctoral Thesis in Chemical Sciences, Irkutsk Institute of Organic Chemistry, Siberian Branch of Russian Academy of Sciences, Irkutsk, 1994
26. R N Nesterenko, Candidate Thesis in Chemical Sciences, Irkutsk Institute of Organic Chemistry, Siberian Branch of Russian Academy of Sciences, Irkutsk, 1985
27. E Yu Shmidt, Candidate Thesis in Chemical Sciences, Irkutsk Institute of Organic Chemistry, Siberian Branch of Russian Academy of Sciences, Irkutsk, 1988
28. M A Yurovskaya, V V Druzhinina, M A Tyurekhodzhaeva, Yu G Bundel' *Khim. Geterotsikl. Soedin.* 69 (1984) [a]
29. M A Yurovskaya, A Z Afanas'ev, Yu G Bundel' *Khim. Geterotsikl. Soedin.* 1077 (1984) [a]
30. T N Borisova, A V Varlamov, N D Sergeeva, A T Soldatenkov, O V Astakhov, N S Prostakov *Khim. Geterotsikl. Soedin.* 973 (1987) [a]
31. A V Varlamov, T N Borisova, A E Aliev, I A Stazharova, A A Sinitsyna, E A Sakhnova *Khim. Geterotsikl. Soedin.* 681 (1993) [a]
32. A V Varlamov, T N Borisova, L G Voskresenskii *Khim. Geterotsikl. Soedin.* 136 (1995) [a]
33. S E Korostova, A I Mikhaleva, E E Sirotkina *Izv. Akad. Nauk SSSR, Ser. Khim.* 1448 (1989) [c]
34. B A Trofimov, A I Mikhaleva, S E Korostova, L N Balabanova, in *The Vth International Congress on Heterocyclic Chemistry (Abstracts of Reports), Ljubljana, 1975* A 1, p. 63
35. B A Trofimov, A I Mikhaleva, R I Polovnikova, R N Nesterenko, F G Trofimova *Zh. Org. Khim.* **14** 2628 (1978) [b]
36. B A Trofimov, A I Mikhaleva, R N Nesterenko, A N Vasil'ev, A S Nakhmanovich, M G Voronkov *Khim. Geterotsikl. Soedin.* 1136 (1977) [a]
37. B A Trofimov, A I Mikhaleva, R I Polovnikova, S E Korostova, R N Nesterenko, N I Golovanova, V K Voronov *Khim. Geterotsikl. Soedin.* 1058 (1981) [a]
38. B A Trofimov, S E Korostova, L N Balabanova, A I Mikhaleva *Zh. Org. Khim.* **14** 1733 (1978) [b]
39. USSR P. 601 282; *Byull. Izobret.* (13) 79 (1978)
40. S E Korostova, S G Shevchenko, B A Trofimov *Zh. Org. Khim.* **30** 905 (1994) [b]
41. S E Korostova, A I Mikhaleva, L N Sobenina, S G Shevchenko, V V Shcherbakov *Khim. Geterotsikl. Soedin.* 1501 (1985) [a]
42. B A Trofimov, A I Mikhaleva, S E Korostova, T I Vakul'skaya, I S Poguda, M G Voronkov *Zh. Prikl. Khim.* **41** 117 (1978) [d]
43. S E Korostova, A I Mikhaleva, R N Nesterenko, N V Maznaya, V K Voronov, N M Borodina *Zh. Org. Khim.* **21** 406 (1985) [b]
44. B A Trofimov, A I Mikhaleva, in *Sintez i Reaktsionnaya Sposobnost' Organicheskikh Soedinenii Sery (Tez. Dokl. XVII Vsesoyuz. Konf.), Tbilisi, 1989* [Synthesis and Reactivity of Organic Compounds of Sulfur (Abstracts of Reports of the XVIIth All-Union Conference), Tbilisi, 1989] p. 24
45. B A Trofimov, A I Mikhaleva, A N Vasil'ev, M V Sigalov *Khim. Geterotsikl. Soedin.* 54 (1978) [a]
46. B A Trofimov, C E Korostova, L N Sobenina, A I Mikhaleva, V M Bzhezovskii, M V Sigalov, A A Atavin *Khim. Geterotsikl. Soedin.* 193 (1982) [a]
47. G A Pinna, M A Pirisi, G Paglietti *J. Chem. Res. (S)* 210 (1993)
48. A I Mikhaleva, R N Nesterenko, A M Vasil'tsov, G A Kalabin, E N Deryagina, N A Korchevin, N I Golovanova *Khim. Geterotsikl. Soedin.* 708 (1992) [a]
49. B A Trofimov, A I Mikhaleva, A N Vasil'ev, V A Lopyrev, I A Titova, V M Bzhezovskii, M V Sigalov *Khim. Geterotsikl. Soedin.* 1422 (1981) [a]
50. C E Korostova, R N Nesterenko, A I Mikhaleva, R I Polovnikova, N I Golovanova *Khim. Geterotsikl. Soedin.* 901 (1989) [a]
51. S Gonzalez, R Greenhouse, R Tallabs, J M Muchowski *Can. J. Chem.* **61** 1697 (1983)
52. USSR P. 1 095 593; *Byull. Izobret.* (6) 196 (1994)
53. O A Tarasova, S E Korostova, A I Mikhaleva, B A Trofimov, in *Reaktiv 94 (Tez. Dokl. VII Soveshchaniya po Khimicheskim Reaktivam), Ufa, 1994* [Agent 94 (Abstracts of Reports of the VIIth Meeting on Chemical Agents), Ufa, 1994] p. 53
54. O A Tarasova, S E Korostova, A I Mikhaleva, L N Sobenina, R N Nesterenko, S G Shevchenko, B A Trofimov *Zh. Org. Khim.* **30** 810 (1994) [b]
55. S E Korostova, S G Shevchenko, M V Sigalov *Khim. Geterotsikl. Soedin.* 1371 (1991) [a]
56. B A Trofimov, S E Korostova, A I Mikhaleva, L N Sobenina, A N Vasil'ev, R N Nesterenko *Khim. Geterotsikl. Soedin.* 273 (1983) [a]
57. S E Korostova, S G Shevchenko, M V Sigalov *Khim. Geterotsikl. Soedin.* 187 (1991) [a]
58. D Dhanak, C B Reese, S Romana, G Zappia *J. Chem. Soc., Chem. Commun.* 903 (1986)
59. S E Korostova, A I Mikhaleva, L N Sobenina, in *Tez. Dokl. Vsesoyuz. Simpoziuma po Organicheskomu Sintezu, Moskva, 1984* (Abstracts of Reports of the All-Union Symposium on Organic Synthesis, Moscow, 1984) p. 110

60. B A Trofimov, S E Korostova, A I Mikhaleva, L N Sobenina, V V Shcherbakov, M V Sigalov *Khim. Geterotsikl. Soedin*. 276 (1983) [a]
61. S E Korostova, A I Mikhaleva, B A Trofimov, S G Shevchenko, M V Sigalov *Khim. Geterotsikl. Soedin*. 485 (1992) [a]
62. B A Merril, E Le Goff *J. Org Chem*. **55** 2904 (1990)
63. Jpn. P. 77 100 496; *Chem. Abstr*. **88** 50 934 (1978)
64. Ning Fugiang, Hua Wenting *Beitszin Dasyue Syuebao* **28** 185 (1992); *Ref. Zh. Khim*. 19 Zh 189 (1992)
65. H Berner, G Schulz, H Reinshagen *Monatsh. Chem*. **108** 285 (1977)
66. D M Perrine, J Kagan, D-B Huang, K Zeng, B-K Teo *J. Org. Chem*. **52** 2213 (1987)
67. H Stetter, J Krasselt *J. Heterocycl. Chem*. **14** 573 (1977)
68. B A Merril, E Le Goff, in *The 197th American Chemical Society National Meeting (Abstracts of Reports), Dallas, TX, 1989* p. 732
69. P Messinger, C Kunick *Synthesis* 213 (1986)
70. USSR P. 251 581; *Byull. Izobret*. (28) 20 (1969)
71. V I Shvedov, I A Kharizomenova, A N Grinev *Khim.-Farm. Zh*. **3** (12) 12 (1969) [e]
72. F Ledl, F Schleicher *Angew. Chem*. **102** 597 (1990)
73. Yu N Romashin, Al' Mokhana Nadim, in *Tez. Dokl. II Konf. Molodykh Uchenykh-Khimikov, Donetsk, 1990* (Abstracts of Reports of the Second Conference of Young Chemist Scientists, Donetsk, 1990) p. 167
74. V L Sorokin, Yu N Romashin, Al' Mokhana Nadim, Azzuz Alib, O G Kullinkovich, in *Khimiya Azotsoderzhashchikh Geterotsiklicheskikh Soedinenii (Tez. Dokl. V Vsesoyuz. Konf.),Chernogolovka, 1991* [The Chemistry of Nitrogen-Containing Heterocyclic Compounds (Abstracts of Reports of the Fifth All-Union Conference), Chernogolovka, 1991] Part 1, p. 267
75. R Huisgen, H Gotthardt, H O Bayer, F Schaefer *Chem. Ber*. **103** 2611 (1970)
76. J W Lown, K Matsumoto *Can. J. Chem*. **48** 2215 (1970)
77. J W Lown, K Matsumoto *Can. J. Chem*. **48** 3399 (1970)
78. K E Schulte, J Reisch, H Walker *Chem. Ber*. **98** 98 (1965)
79. C L Buchwald, M W Wannamaker, B T Watson *J. Am. Chem. Soc*. **111** 776 (1989)
80. F H Carre, R J P Corrin, G Bolin, J J E Morean, C Vernhet *Organometallics* **12** 2478 (1993)
81. J Moskal, A M van Leusen *J. Org. Chem*. **51** 4131 (1986)
82. Jpn. P. 61 200 984; *Ref. Zh. Khim*. 23 O 82P (1987)
83. Jpn. P. 76 128 963; *Chem. Abstr*. **87** 5797 (1977)
84. Jpn. P. 5 885 861; *Chem. Abstr*. **99** 12 229 (1983)
85. K Sakai, M Suzuki, K Numami, N Yoneda, Y Onoda, Y Iwasawa *Chem. Pharm. Bull*. **28** 2384 (1980)
86. C Yuan, W Huang *Synthesis* 473 (1993)
87. K Matsumoto, M Suzuki, Y Ozaki, M Miyoshi *Agrich. Biol. Chem*. **40** 2271 (1976)
88. O E Nasakin, V V Alekseev, V Yu Promonenkov *Khim. Geterotsikl. Soedin*. 402 (1981) [a]
89. O E Nasakin, V V Alekseev, P B Terent'ev, A Kh Bulai, M Yu Zablotskaya *Khim. Geterotsikl. Soedin*. 1062 (1983) [a]
90. O E Nasakin, V V Alekseev, A Kh Bulai, P B Terent'ev, in *Khimiya Geterotsiklicheskikh Soedinenii (Tez. Dokl. III Konf.) Rostov-na-Donu, 1983* [The Chemistry of Heterocyclic Compounds (Abstracts of Reports of the Third Conference), Rostov on Don, 1983] p. 44
91. O E Nasakin, V V Alekseev, P B Terent'ev, A Kh Bulai, M Yu Zablotskaya *Khim. Geterotsikl. Soedin*. 1067 (1983) [a]
92. USSR P. 979 339; *Byull. Izobret*. (45) 99 (1982)
93. N Chatorri, T Hanafusa *Tetrahedron Lett*. **27** 4201 (1986)
94. T Kaufmann, H Lexy *Chem. Ber*. **114** 3674 (1981)
95. B L Bray, P H Mathies, R Naef, D R Solas, T T Tidwell, D R Artis, J M Muchowski *J. Org. Chem*. **55** 6317 (1990)
96. L Groenendaal, H W I Peerlings, J L J van Dongen, E E Havinga, J A J M Vekemans, E W Meijer *Am. Chem. Soc., Div. Polym. Chem., Polym. Prepr*. **35** 194 (1994)
97. N Gjøs, S Gronowitz *Acta Chim. Scand*. **25** 2596 (1971)
98. L Groenendaal, H W I Peerlings, E E Havinga, J A J M Vekemans, E W Meijer *Synth. Met*. **69** 467 (1995)
99. A Minato, K Tamao, T Hayashi, K Suzuki, M Kumada *Tetrahedron Lett*. **22** 5319 (1981)
100. Jpn. P. 5 896 063; *Chem. Abstr*. **99** 139 759 (1983)
101. J-P Boukou-Poba, M Farnier, R Guilard *Tetrahedron Lett*. 1717 (1979)
102. H Rapoport, N Castagnoli *J. Am. Chem. Soc*. **84** 2178 (1962)
103. H Rapoport, K G Holden *J. Am. Chem. Soc*. **84** 635 (1962)
104. H Rapoport, N Castagnoli, K G Holden *J. Org. Chem*. **29** 883 (1964)
105. H Rapoport, J Bordner *J. Org. Chem*. **29** 2727 (1964)
106. J Bordner, H Rapoport *J. Org. Chem*. **30** 3824 (1965)
107. N Engel, W Steglich *Angew. Chem*. **90** 719 (1978)
108. J V Cooney, W E McEwen *J. Org. Chem*. **46** 2570 (1981)
109. F Boberg, K H Garburg, K J Gorlich, E Piepereit, M Ruhr *Liebigs Ann. Chem*. 239 (1985)
110. S Vega, M S Gil *J. Heterocycl. Chem*. **28** 945 (1991)
111. S Rault, M Cugnon de Sevricourt, M Robba *C. R. Hebd. Seances Acad. Sci., Ser. C* **284** 533 (1977)
112. S Rault, M Cugnon de Sevricourt, M Robba *Heterocycles* **14** 651 (1980)
113. S Rault, M Cugnon de Sevricourt, H El Khashef, M Robba *C. R. Hebd. Seances Acad. Sci., Ser. C* **290** 169 (1980)
114. G Kresze, M Morper, A Bijev *Tetrahedron Lett*. 2259 (1977)
115. R Grigg, H Q N Gunaratne *Tetrahedron* **46** 1599 (1990)
116. Matoba Katsutude, Itoh Kenicci, Kondo Kakuya, Yamozaki Takao, Nagata Masanori *Chem. Pharm. Bull*. **29** 2442 (1981)
117. D Dolphin, A W Johnson, J Leng, P van den Brock *J. Chem. Soc., C* 880 (1966)
118. M J Broadhurst, R Grigg, A W Johnson *J. Chem. Soc., Perkin Trans. 1* 1124 (1972)
119. E Baltazzi, L I Krimen *Chem. Rev*. **63** 511 (1963)
120. J M Patterson *Synthesis* 281 (1976)
121. Dzh Marino *Khim. Geterotsikl. Soedin*. 579 (1973) [a]
122. L I Belen'kii *Khim. Geterotsikl. Soedin*. 1587 (1980) [a]
123. I A Abronin, G M Zhidomirov *Khim. Geterotsikl. Soedin*. 3 (1977) [a]
124. J A Joule, G F Smith *Heterocyclic Chemistry* (London: Van Nostrand Reinhold, 1972)
125. V I Ivanskii *Khimiya Geterotsiklicheskikh Soedinenii* (The Chemistry of Heterocyclic Compounds) (Moscow: Vysshaya Shkola, 1978)
126. M V Sigalov, E Yu Shmidt, B A Trofimov, in *Tez. Dokl. IV Vsesoyuz. Konf. po Khimii Azotsoderzhashchikh Soedinenii, Novosibirsk, 1987* (Abstracts of Reports of the Fourth All-Union Conference on the Chemistry of Nitrogen-Containing Compounds, Novosibirsk, 1987) p. 70
127. M V Sigalov, E Yu Shmidt, B A Trofimov *Izv. Akad. Nauk SSSR, Ser. Khim*. 2136 (1987) [c]
128. M V Sigalov, E Yu Shmidt, A B Trofimov, B A Trofimov *Khim. Geterotsikl. Soedin*. 1343 (1989) [a]
129. M V Sigalov, E Yu Schmidt, A B Trofimov, B A Trofimov *J. Org. Chem*. **57** 3934 (1992)
130. M V Sigalov, A B Trofimov, E Yu Schmidt, B A Trofimov *J. Phys. Org. Chem*. **6** 471 (1993)
131. M V Sigalov, A B Trofimov, E Yu Shmidt, B A Trofimov *Khim. Geterotsikl. Soedin*. 825 (1993) [a]
132. M V Sigalov, E Yu Shmidt, A I Mikhaleva, S E Korostova, I M Lazarev, B A Trofimov *Khim. Geterotsikl. Soedin*. 48 (1993) [a]
133. M V Sigalov, E Yu Schmidt, B A Trofimov, in *The 10th IUPAC Conference on Physical Organic Chemistry (Abstracts of Reports), Haifa, 1990* p. 247
134. J-P Boukou-Poba, M Farnier, R Guilard *Can. J. Chem*. **59** 2962 (1981)
135. S Clementi, G Marino *Tetrahedron* **25** 4599 (1969)
136. S Clementi, G Marino *J. Chem. Soc., Perkin Trans 2* 71 (1972)
137. A N Kost, V A Budylin *Zh. Vses. Khim. O-va im. D I Mendeleeva* **22** 315 (1977) [f]
138. K Imuro, T Hanafusa *Bull. Chem. Soc. Jpn*. **49** 1363 (1976)
139. A N Kost, V A Budylin, N N Romanova, A I Matveeva *Khim. Geterotsikl. Soedin*. 1233 (1981) [a]
140. D J Chadwick, G D Meakins, C A Rhodes *J. Chem. Res. (S)* 42 (1980)
141. D J Chadwick, S T Hodgson *J. Chem. Soc., Perkin Trans 1* 93 (1983)
142. M W Majchrzak, G Simchen *Tetrahedron* **42** 1299 (1986)
143. N K Genkina, V N Eraksina, N N Suvorov *Zh. Org. Khim*. **16** 2154 (1980) [b]

144. B A Trofimov, A I Mikhaleva, S E Korostova, L N Sobenina, A N Vasil'ev, L V Balashenko *Zh. Org. Khim.* **15** 2042 (1979) [b]
145. S E Korostova, A I Mikhaleva, L N Sobenina, S G Shevchenko, I M Karataeva, B A Trofimov *Khim. Geterotsikl. Soedin.* 48 (1980) [a]
146. B A Trofimov, S E Korostova, A I Mikhaleva, R N Nesterenko, M V Sigalov, V K Voronov, R I Polovnikova *Zh. Org. Khim.* **18** 894 (1982) [b]
147. S E Korostova, A I Mikhaleva, R N Nesterenko, R I Polovnikova, V K Voronov, B A Trofimov, in *Tez. Dokl. IV Vsesoyuz. Konf. po Khimii Ftororganicheskikh Soedinenii, Tashkent, 1982* (Abstracts of Reports of Fourth All-Union Conference on the Chemistry of Organofluorine Compounds, Tashkent,1982) p. 218
148. S E Korostova, R N Nesterenko, A I Mikhaleva, S G Shevchenko, G A Kalabin, R I Polovnikova *Khim. Geterotsikl. Soedin.* 337 (1991) [a]
149. M Hojo, R Masudo, Ho Shioda, S Matsuno *Chem. Lett.* 499 (1976)
150. S I Yakimovich, L A Kayukova *Zh. Org. Khim.* **14** 2496 (1978) [b]
151. N V Moskalev, V D Filimonov, E E Sirotkina *Khim. Geterotsikl. Soedin.* 1066 (1988) [a]
152. A I Mikhaleva, B A Trofimov, S E Korostova, A N Vasil'ev, L N Balabanova *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim.* (4) 105 (1979)
153. B A Trofimov, R N Nesterenko, A I Mikhaleva, A B Shapiro, I A Aliev, I V Yakovleva, G A Kalabin *Khim. Geterotsikl. Soedin.* 481 (1986) [a]
154. G G Skvortsova, E S Domnina, N P Glazkova, L P Makhno, in *Trudy III Vsesoyuz. Konf. po Khimii Atsetilena* (Proceedings of the Third All-Union Conference on the Chemistry of Acetylene) (Moscow: Nauka, 1972) p. 115
155. B V Trzhtsinskaya, N D Abramova, L F Teterina, L V Andriyankova, A V Afonin *Izv. Akad. Nauk SSSR, Ser. Khim.* 416 (1989) [c]
156. B A Trofimov, S E Korostova, S G Shevchenko, E A Polubentsev, A I Mikhaleva *Zh. Org. Khim.* **26** 1110 (1990) [b]
157. G I Koldobskii, V A Ostrovskii *Khim. Geterotsikl. Soedin.* 579 (1988) [a]
158. E S Petrov *Usp. Khim.* **52** 1974 (1983) [*Russ. Chem. Rev.* **52** 1144 (1983)]
159. B A Trofimov, A I Shatenshtein, E S Petrov, M I Terekhova, N I Golovanova, A I Mikhaleva, S E Korostova, A N Vasil'ev *Khim. Geterotsikl. Soedin.* 632 (1980) [a]
160. A F Ermikov, V K Turchaninov, K B Petrushenko, A I Vokin, S E Korostova, L A Ostroukhova, Yu L Frolov *Zh. Obshch. Khim.* **58** 450 (1988) [g]
161. V K Turchaninov, A F Ermikov, S E Korostova, V A Shagun *Zh. Obshch. Khim.* **59** 791 (1988) [g]
162. B A Trofimov, A B Shapiro, R N Nesterenko, A I Mikhaleva, G A Kalabin, N I Golovanova, I V Yakovleva, S E Korostova *Khim. Geterotsikl. Soedin.* 350 (1988) [a]
163. B A Trofimov, T I Vakul'skaya, S E Korostova, S G Shevchenko, A I Mikhaleva *Izv. Akad. Nauk SSSR, Ser. Khim.* 142 (1990) [c]
164. T I Vakul'skaya, B A Trofimov, A I Mikhaleva, S E Korostova, S G Shevchenko, L N Sobenina *Khim. Geterotsikl. Soedin.* 1056 (1992) [a]
165. D C Miller, M R Johnson, J A Ibers *J. Org. Chem.*, **59** 2877 (1994)
166. A H Jackson, K M Smith, in *The Total Synthesis of Natural Products* Vol 1 (Ed. J ApSimon) (New York: Wiley-Interscience, 1973) p. 144
167. R Grigg, A W Johnson *J. Chem. Soc.* 3315 (1964)
168. US P. 4 560 700; *Chem. Abstr.* **105** 114 896 (1986)
169. L N Sobenina, M P Sergeeva, A I Mikhaleva, M V Sigalov, S E Korostova, N I Golovanova, V N Salaurov, E V Bakhareva, N A Vasil'eva *Khim. Geterotsikl. Soedin.* 612 (1990) [a]
170. H-P Keiser, J M Muchowski *J. Org. Chem.* **49** 4203 (1984)
171. B A Trofimov, S E Korostova, A I Mikhaleva, L N Balabanova, A N Vasil'ev *Khim. Geterotsikl. Soedin.* 215 (1977) [a]
172. G Lunn *J. Org. Chem.* **52** 1043 (1984)
173. B A Trofimov, S E Korostova, A I Mikhaleva, in *Tez. Dokl. Konf. po Khimii i Tekhnologii Atsetalei i Ikh Geteroanalogov, Ufa, 1981* (Abstracts of Reports of the Conference on the Chemistry and Technology of Acetals and Their Heteroanalogs, Ufa, 1981) p. 60
174. S E Korostova, A I Mikhaleva, S G Shevchenko, V V Shcherbakov, R N Nesterenko, M V Sigalov, B A Trofimov *Zh. Org. Khim.* **22** 2489 (1986) [b]
175. L I Kopylova, S E Korostova, L N Sobenina, R N Nesterenko, M V Sigalov, A I Mikhaleva, B A Trofimov, M G Voronkov *Zh. Obshch. Khim.* **51** 1778 (1981) [g]
176. USSR P. 1 199 757; *Byull. Izobret.* (47) 111 (1985)
177. K-P Stefan, W Schuhmann, H Parlar, F Kocte *Chem. Ber.* **122** 169 (1989)
178. N A Bumagin, A F Sokolova, I P Beletskaya, G Vol'ts *Zh. Org. Khim.* **29** 162 (1993) [b]
179. G Simchen, M W Majchrzak *Tetrahedron Lett.* **26** 5035 (1985)
180. J M Muchowski, D R Solos *Tetrahedron Lett.* **24** 3455 (1983)
181. B A Trofimov, S E Korostova, A I Mikhaleva, L N Sobenina, A N Vasil'ev *Khim. Geterotsikl. Soedin.* 1631(1982) [a]
182. B A Trofimov, S E Korostova, S G Shevchenko, A I Mikhaleva, N L Matel' *Zh. Org. Khim.* **32** 897 (1996) [b]
183. S Nalton *Synth. Met.* **18** 237 (1987)
184. L V Morozova, A I Mikhaleva, S E Korostova, I L Filimonova, in *Elektronika Organicheskikh Materialov* (Electronics of Organic Materials) (Moscow: Nauka, 1985) p. 305
185. L V Morozova, A I Mikhaleva, M V Markova, in *Vodorastvorimye Polimery i Ikh Primenenie (Tez. Dokl. IV Vsesoyuz. Konf.), Irkutsk, 1991* [Water-Soluble Polymers and Their Applications (Abstracts of Reports of the Fourth All-Union Conference), Irkutsk, 1991] p. 79
186. L V Morozova, A I Mikhaleva, M V Markova, B A Trofimov, in *Biologicheski Aktivnye Polimery i Polimernye Reagenty dlya Rastenievodstva (Tez. Dokl. Vsesoyuz. Soveshch.), Nal'chik, 1988* [Bioactive Polymers and Polymer Agents for Plant Growing (Abstracts of Reports of the All-Union Meeting), Nal'chik, 1988] p. 33
187. T Skotheim, I Lundstrom, J Prejra *J. Electrochem. Soc.* **128** 1625 (1981)
188. S Komaba, K Fujihana, T Osaka *J. Electrochem. Soc.* **145** 1126 (1998)
189. R A Simon, A J Ricco, M S Wrighton *J Am. Chem. Soc.* **104** 2032 (1982)
190. R Noufi, A J Frank, A J Nozik *J. Am. Chem. Soc.* **103** 1849 (1981)
191. L V Morozova, A I Mikhaleva, M V Markova, O Yu Molchanov, T V Putan, in *Khimiya i Primenenie Pestitsidov* (The Chemistry and Application of Pesticides) (Moscow: All-Union Research Institute of Chemical Facilities of Plant Defence, 1990) p. 7

[a] — *Chem. Heterocycl. Compd. (Engl. Transl.)*
[b] — *Russ. J. Org. Chem. (Engl. Transl.)*
[c] — *Russ. Chem. Bull. (Engl. Transl.)*
[d] — *Russ. J. Appl. Chem. (Engl. Transl.)*
[e] — *Pharm. Chem. J. (Engl. Transl.)*
[f] — *Mendeleev Chem. J. (Engl. Transl.)*
[g] — *Russ. J. Gen. Chem. (Engl. Transl.)*