PYRROLES FROM KETOXIMES AND ACETYLENE. 41.* SOME REACTIONS OF 1-VINYL-2-(2-FURYL)- AND -(2-THIENYL)PYRROLES

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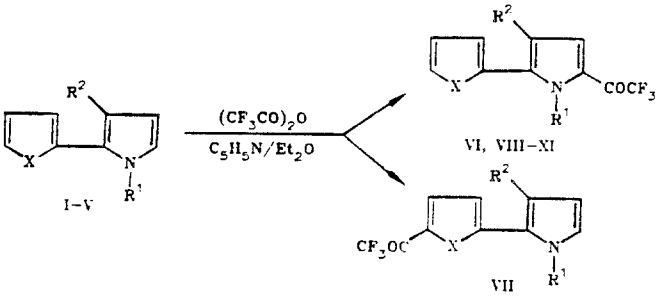
We have studied the reaction of 1-vinyl-2-(2-furyl)- and -(2-thienyl)pyrroles with trifluoroacetic anhydride, with hydrogen in the presence of catalysts (Raney nickel, palladium black, palladous chloride), with propargyl alcohol in electrophilic conditions [catalysis by perfluorobutyric acid in the system azoisobutyrodinitrile (AIBN)—CCl_4), and with alkane thiols with AIBN initiation. The products are novel substituted hetarylpyrroles.

The development and successful use of the Trofimov and related reactions [1, 2] applied to furan and thiophene oximes has led to the synthesis of a series of 1-vinyl-2-(2-furyl)- and -(2-thienyl)pyrroles [2, 3]. These compounds are interesting in terms of the comparative reactivity of both heterocycles and the effect of the heterocycle on the course of reactions of 1-vinylpyrroles [2] via the electronic interaction of heteroatoms and vinyl group.

Our study of the trifluoroacetylation of 1-vinyl-(2-furyl)- and -(2-thienyl)pyrroles [4] has been extended to novel compounds in the series with 3-alkyl substituents.

Trifluoroacetylation of 1-vinyl-2-(2-thienyl)-3-alkylpyrroles II and III gave only the α-substitution products VIII and IX, respectively. In contrast to 1-vinyl-2-(2-furyl)-pyrrole [4], attack of the furylpyrrole I by the trifluoroacetyl cation is directed principally toward the pyrrole ring. The structurally isomeric trifluoroacetyl pyrroles VI and VII are formed in approximately 35 and 27% yields, respectively. As in [4], and in contrast to [5], the products of simultaneous bis(trifluoroacetylation) on both heterocycles was not observed. Exchange of the vinyl group on the nitrogen atom for ethyl (pyrrole IV) does not change the usual direction of trifluoroacetylation [2]. This is also retained in the presence of a rather bulky group (triethylsilylethyl), although it is known [6] that the route of electrophilic attack on the pyrrole can be changed by such substituents.



I, VI, VII X=O, II—V, VIII—XI X=S; I—III, VI—IX R^1=CH=CH_2, IV, X R^1=C_2H_5, V, XI R^1=$CH_2CH_2Si(C_2H_5)_3$; I, II, VI—VIII R^2=CH_3, III, IX R^2=C_2H_5, IV, V, X, XI R^2=H

The physicochemical constants for the trifluoroacetylpyrroles VI, VIII-XI, and pyrrole VII are given in Table 1 and their structures were confirmed by IR spectral data (Table 1) and PMR and ^{13}C NMR spectral data (Tables 2 and 3).

We have carried out, for the first time, the hydrogenation of 1-vinyl-2-(2-furyl)- and -(2-thienyl)pyrroles with catalysts like Raney nickel, palladium charcoal, and palladous chloride, and found that hydrogenation of the vinyl group of XII occurs over Raney nickel (80°C, 60 atm) as readily and selectively as for 1-vinyl-2-alkyl(aryl)pyrroles [2] in a yield for the pyrrole XV of 94% (see scheme on page 274).

*See [1] for Communication 40.

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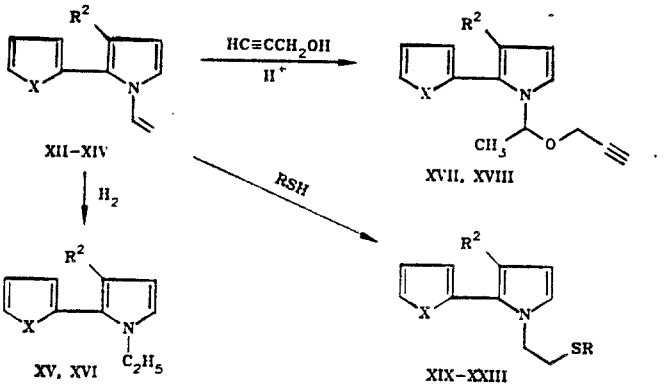
TABLE 1. Physicochemical Constants and IR Spectra of the Pyrroles

Compound	bp, °C (hPa)	d_4^{20}	n_D^{20}	IR spectra, cm^{-1}	Yield, %
VI	40...41*			1642 ($NCH=CH_2$); 1680 (C=O)	35
VII	148 (3,99...5,32)			1632 ($NCH=CH_2$); 1662, 1672 (C=O)	27
VIII	132...135 (3,99)	1,2709	1,5840	1620 ($NCH=CH_2$); 1660 (C=O)	76
IX	120...122 (5,32)	1,2664	1,5826	1630 ($NCH=CH_2$); 1660 (C=O)	53
X	130...132 (6,65)	1,0790	1,5899	1676 (C=O); 2940, 2990 (C_2H_5)	54
XI	32...33*			1662 (C=O); 2880, 2915, 2955 (C_2H_5)	75
XV	85...86 (3,99)	1,0416	1,5670	2835, 2880 (C_2H_5)	94 (A), 74 (B)
XVI	98...99 (3,99)	1,1118	1,6056	2870, 2975 (C_2H_5)	46
XVII	112 (3,99...5,32)	1,0831	1,5446	2100 (C≡C); 3270 (≡CH); 1035, 1090 (C—O—C)	52
XVIII	139...141 (6,65)	1,1357	1,5870	2100 (C≡C); 3270 (≡CH); 1035; 1085 (C—O—C)	71
XIX	125...130 (2,66...3,99)	1,0976	1,5313	2868...2970 (C_2H_5)	84
XX	155...156 (1,33)	1,1185	1,6111	2870...2970 (C_2H_5)	78
XXI	186...188 (1,33)	1,0556	1,5752	2868...2970 (C_3H_7)	95
XXII	167...169 (1,33)	1,0876	1,5950	2868...2970 (C_3H_7)	80
XXIII	175...179 (1,33)	1,0614	1,5892	2870...2970 (C_4H_9)	88

*Melting point given.



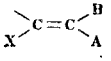
XII, XV X=O, R^2=H; XIII, XVI X=S, R^2=H; XVII X=O, R^2=H; XVIII X=S, R^2=H; XIX X=O, R=C_2H_5, R^2=H; XX X=S, R=C_2H_5, R^2=H; XIV, XXI X=S, R=C_2H_5, R^2=C_3H_7; XXII X=S, R=R^2=C_3H_7; XXIII X=S, R=C_2H_5, R^2=C_4H_9

The hydrogen pressure affects the rate of hydrogenation of the vinyl group over Raney nickel. Lowering it to 10-12 atm with the other parameters unchanged leads to a sharp decrease in reaction velocity and decrease in yield of ethyl pyrrole XV to 65%. Using palladous chloride (15% based on the weight of vinylpyrrole, 80°C, 40 atm) for the hydrogenation raises the yield of ethyl pyrrole to 75%. The pyrrole and furan rings are not affected, hydrogenolysis of these heterocycles not being observed. In agreement with [7, 8], the thiophene ring must complicate the hydrogenation of pyrrole XIII due to poisoning of the Raney nickel catalyst. In fact, reducton of vinylpyrrole XIII occurs with difficulty using Raney nickel (50°C, 48 atm). After vacuum distillation, the reaction product contains only 15% of the desired XVI together with 85% of the starting material. Further hydrogenation of this mixture (80°C) gives a final ratio of target product to starting pyrrole of 1:1.5 (PMR data). Use of a threefold amount of catalyst when compared with the above (50% of the vinylpyrrole weight) raised the yield of XVI to 46% but this is also accompanied

TABLE 2. PMR Spectra of Pyrroles

Compound	Chemical shift, ppm							$^1H-^1H$* spin–spin coupling, J, Hz								
	4-H	5-H	3-H	4'-H	5'-H	H-R^1	H-R^2	AB**	AX**	BX**	34	35	45	3'4'	3'5'	4'5'	4(4')F
VI	7,01	—	6,44	6,43	7,46	5,08***; 4,79; 7,30	2,14	0,7	8,6	15,5				3,5	0,8	1,8	2,2
VII	6,06	6,99	6,44	7,48	—	4,83; 5,15; 7,38	2,24	1,2	8,6	15,4			3,2	4,6			1,2
VIII	7,07	—	7,21	7,05	7,41	5,06; 4,78; 7,28	2,09	0,8	8,6	15,2				3,3	1,5	4,6	
IX	7,06	—	7,22	7,08	7,42	5,04; 4,83; 7,28	2,49; 1,16	0,8	8,5	15,6				3,3	1,2	4,9	
X	7,13	—	7,13	7,13	7,41	4,46; 1,41	6,33				4,5				1,7	4,8	
XV	6,13	6,48	6,20	6,24	7,23	3,96; 1,26	5,95				3,1	1,6	2,6	3,5	0,8	1,6	
XVI	5,99	6,59	6,94	6,94	7,16	3,95; 1,26	6,11				3,4	1,8	2,6		1,4	4,3	
XVII	6,30	6,93	6,23	6,38	7,41	5,83; 1,63; 3,72; 2,38	6,23							3,0	1,0	2,0	
XVIII	6,12	6,85	6,99	6,95	7,20	5,69; 1,58; 3,75; 2,07	6,12								1,8	4,5	
XIX	6,20	6,54	6,20	6,30	7,20	4,10; 2,57; 2,24; 1,03	5,96				3,1	1,6	2,6	3,4	0,8	1,6	
XX	6,01	6,62	6,98	6,96	7,17	4,16; 2,60; 2,27; 1,12	6,16				3,4	1,8	2,8		1,4	4,3	

*10% solution in $CDCl_3$, 25°C.

**Vinyl protons given in the order A, B, X 

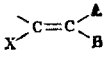
***Vinyl group protons given in the order A, B, X 

TABLE 3. ^{13}C NMR Spectra of Pyrroles*

Compound	Chemical shifts, δ, ppm (in $CDCl_3$)*										
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(2')}$	$C_{(3')}$	$C_{(4')}$	$C_{(5')}$	C—R¹	C—R²	C—R⁵(R⁵')
VI	132,5	122,8	124,8	125,1	144,7	113,1	112,5	143,3	132,4; 111,3	11,9	168,2; 117,0
VII	119,5	126,3	113,5	121,9	145,6	110,2	125,8	155,2	132,5; 102,0	12,9	167,4; 116,0
VIII	135,8	123,2	124,4	125,2	130,8	128,0	129,9	127,1	131,8; 113,5	11,6	169,3; 117,1
XV	124,2	108,2	109,6	122,1	148,4	105,9	111,0	141,3	43,0; 97,8		
XVI	126,8	108,2	110,6	121,9	135,4	125,5	127,2	124,8	42,2; 16,7		

*10% solution of pyrroles in $CDCl_3$, 25°C.

TABLE 4. Effect of Reaction Conditions on Yields of Pyrroles XVII, and XVIII*

XII (XIII): PA, mole	X	PFBA, % relative to XII (XIII)	t_r, min	T_r, °C	Pyrrole yield, %
1 : 2,0**	O	3,0	5,0	96	48,0
1 : 1,5	O	2,0	1,30	96	55,0
1 : 2,0	S	2,6	2,30	96	60,6
1 : 1,5	S	1,6	2,30	96	71,0
1 : 1,0	S	1,0	3,0	96	52,0
1 : 1,5	S	1,0	4,0	100	31,0

*PA) propargyl alcohol; PFBA) perfluorobutyric acid; t_p) reaction time; T_p) reaction temperature.
**In dioxane.

by low-boiling hydrogenolysis products. Using $PdCl_2$ at room temperature, the yield of XVI was only 7%, and increasing the temperature to 80°C (40 atm) only increased the yield slightly to 13.5%. The hydrogenation did not occur in the presence of palladium black (80°C, 40 atm).

IR, PMR, and ^{13}C NMR spectral data confirm the structure of the ethylpyrroles XV and XVI (see Tables 1-3).

Of considerable interest in the reaction of 1-vinyl-2-(2-furyl)- and -2(thienyl)pyrroles (XII, XIII) with alcohols (in particular propargyl alcohol), which leads to compounds with useful practical properties [9, 10]. The reaction is carried out at 96°C without solvent. If carried out at or above 100°C, or for a longer time, much tarring occurs. As in the synthesis of 1-(1-propargyloxyethyl)-2-phenylpyrrole, the best catalyst is perfluorobutyric acid. With the AIBN-CCl_4 catalytic system as used in the introduction of alkoxyethyl on nitrogen [2], the optimum yield of pyrrole XVIII is 71%. The yield of the α-adduct is also affected by the catalyst concentration and the molar ratio of vinylpyrrole to propargyl alcohol (PA) (Table 4).

Thiylation has been successfully used for purification of 2-(2-thienyl)pyrroles from their 1-vinyl derivatives [1, 3] and provides a convenient method for synthesis of 1-(2-alkylthioethyl)-2-(2-thienyl)- and -(2-furyl)pyrroles, whch are compounds of potential biological interest.

As with 1-vinyl-2-alkyl(aryl)pyrroles [2], addition of alkanethiols to 1-vinyl-2-(2-furyl)- and -(2-thienyl)pyrroles takes place readily and with a high degree of selectivity when carried out with AIBN at 70-80°C for 20-25 h. This is obvious from the NMR spectra of the reaction products in which signals for the protons of the RSCH—CH_3 group in α-adducts are absent. The yield of β-adducts XIX-XXIII are 78-95% (Table 1) and their structures are confirmed by PMR (Table 2) and IR spectra (Table 1).

EXPERIMENTAL

IR spectra were recorded on UR-20 or Specord IR-75 spectrometers for thin films (liquids) or as KBr tablets (crystalline solids). PMR and ^{13}C NMR spectra were obtained on Bruker WP-200, and Tesla BS-487 and BS-567 spectrometers using HMDS or TMS as internal standard.

Elemental organic analysis for C, H, F, N, and S for VI-IX and XV-XXIII agreed with those calculated.

1-Vinyl-2-(2-furyl)-3-methyl-5-trifluoroacetylpyrrole (VI, $C_{13}H_{10}F_3NO_2$) and 1-Vinyl-2-(5-trifluoroacetyl-2-furyl)-3-methylpyrrole (VII, $C_{13}H_{10}F_3NO_2$). Trifluoroacetic anhydride (5.8 g, 28 mmole) in ether (10 ml) was added over 2 h at room temperature tovinylpyrrole I (3.8 g, 22 mmole) in ether (40 ml) with pyridine (1.9 g). The product was stirred for a further 3 h and poured into a 50% solution of sodium bicarbonate. The organic layer was separated, combined with the ether extracts, washed with water, and dried with potassium carbonate. After removal of ether the residue was chromatographed on thin-layer, unbounded Al_2O_3* (hexane—ether eluent, 4:3) to give pyrroles VI (2 g) and VII (1.6 g).

1-Vinyl-2-(2-thienyl)-3-methyl-5-trifluoroacetylpyrrole (VIII, $C_{13}H_{10}F_3NOS$). Vinylpyrrole II (1.9 g, 10 mmole), trifluoroacetic anhydride (2.9 g, 14 mmole), and dry ether (50 ml) were held at room temperature for 5 h. After workup as above, chromatography on Al_2O_3 (thin, unbonded layer, hexane—chloroform—ethanol eluent, 20:10:1) gave pyrrole VIII (2.2 g).

The **trifluoroacetylpyrroles IX-XI** were obtained similarly (Table 1).

1-Ethyl-2-(2-furyl)pyrrole (XV, $C_{10}H_{11}NO$). A. A mixture of vinylpyrrole XII (2 g, ≃13 mmole), Raney nickel (0.4 g), and ethanol (50 ml) was heated at 80°C in an autoclave under 60 atm hydrogen pressure. The liquid was filtered from catalyst, the solvent removed by distillation, and the residue fractionally distilled in vacuo to give pyrrole XV (1.9 g).

B. Vinylpyrrole XII (2 g, ≃13 mmole), $PdCl_2$ (0.3 g), $CaCO_3$ (0.6 g), and ethanol (50 ml) were heated at 80°C for 5 h under hydrogen (40 atm). Workup as described above gave XV (1.5 g).

1-Ethyl-2-(2-thienyl)pyrrole (XVI, $C_{10}H_{11}NS$). In a 1-liter autoclave and a hydrogen pressure of 48 atm, vinylpyrrole XIII (3 g, 17 mmole), Raney nickel (0.6 g), and ethanol (50 ml) were heated for 5 h at 50°C. After standard treatment and vacuum distillation, the mixture was treated with catalyst (0.6 g) and ethanol (50 ml) and again heated in an autoclave saturated with hydrogen (80°C, 5 h). The treatment was repeated adding a fresh portion of catalyst (0.6 g) and again heating with hydrogen under the same conditions to give pyrrole XVI (1.4 g).

1-(1-Propargyloxyethyl)-2-(2-furyl)pyrrole (XVII, $C_{13}H_{13}NO_2$). A mixture of vinylpyrrole XII (3.5 g, 22 mmole), propargyl alcohol (1.7 g, 30 mmole), and dioxane (10 ml) was acidified with perfluorobutyric acid (0.1 g), and heated to 96°C for 5 h. The product was cooled to room temperature, treated with NaOH solution (50%), and extracted with ether. The ether extracts were washed with water, dried with potassium carbonate, the ether removed, and the residue distilled in vacuo. The product was chromatographed on Al_2O_3 (hexane—ether, 4:1) to give pyrrole XVII (2.3 g).

1-(1-Propargyloxyethyl)-2-(2-thienyl)pyrrole (XVIII, $C_{13}H_{13}NOS$). Vinylpyrrole XIII (7 g, 40 mmole), propargyl alcohol (3.3 g, 60 mmole), and perfluorobutyric acid (0.11 g) were heated at 96°C for 2.5 h and worked up as described for XVII. Vacuum distillation gave pyrrole XVIII (6.5 g).

1-(2-Ethylthioethyl)-2-(2-furyl)pyrrole (XIX, $C_{12}H_{15}NOS$). A mixture of vinylpyrrole XII (2.4 g, 15 mmole), ethanethiol (1 g, 16 mmole), and AIBN (0.015 g) was heated in a sealed ampul at 80°C for 25 h. Fractional distillation in vacuo gave pyrrole XIX (2.8 g).

1-(2-n-Propylthioethyl)-2-(2-thienyl)-3-n-propylpyrrole (XXII, $C_{16}H_{23}NS_2$). The method for pyrrole XIX above was used with vinylpyrrole XIV (3.3 g, 15 mmole) and propanethiol (1.2 g, 16 mmole) in the presence of AIBN (0.015 g) to give pyrrole XXII (3.6 g).

Pyrroles XX, XXI, and XXIII were obtained similarly.

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*Here and below, we have used aluminum oxide prepared as follows: washing with 10% KOH solution (1.5 liter for 1 kg Al_2O_3), then water to pH 9, drying for 3 days in air, then 2 h at 120°C.

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LACTAM AND ACID AMIDE ACETALS. 64.* ACYLATION OF ENAMINO KETONES OF THE INDOLIN-3-ONE AND 2-PYRROLIN-4-ONE SERIES AND SYNTHESIS OF 2-INDOLYL- AND 5-PYRROLYLACRYLIC ACID DERIVATIVES

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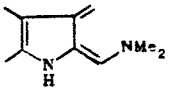
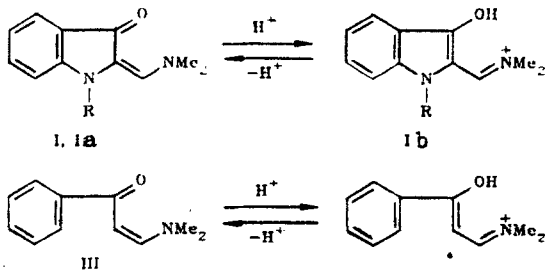
The reaction of 2-(N,N-dimethylaminomethylene)indolin-3-one and 2-methyl-3-ethoxycarbonyl-5-(N,N-dimethyl aminomethylene)-2-pyrrolin-4-one with acyl halides was used to synthesize immonium salts, the aqueous hydrolysis of which leads to 2-formyl-3-hydroxyindole and 4-hydroxy-5 formylpyrrole derivatives. α-Cyano-β-(2-indolyl)- and α-cyano-β-(5-pyrrolyl)acrylic acid derivatives were synthesized by reaction of immonium salts of the pyrrole series, 4 acyloxy-5-formylpyrrole and 2-formyl-3-acyloxyindole derivatives, with compounds that contain an active methylene group.

It is known that, depending on the presence and location of substituents, the acylation of enamino ketones may take place at the oxygen atoms, the β-carbon atom, and the NH group (for primary and secondary enamino ketones) [2; p. 197]. Thus far, however, the question of the acylation of enamino ketones that have a monosubstituted amino group in the β position has not been examined in the literature. Recently, on the basis of reactions of N-acetylindoxyl and 2-methyl-3-ethoxycarbonyl-2-pyrrolin-4-one with DMF diethylacetal, we synthesized tertiary enamino ketones I and II containing, in the β position of the enamine, a secondary amino group conjugated with a benzene ring (I) or making up part of the β-aminodicarbonyl system (II). From an examination of the unusual structural fragment A, which is peculiar to I and II,



A

it follows that the most likely site of attack by electrophilic reagents such as acyl halides are the carbonyl oxygen atom and the secondary amino group; O-acylation is preferable, since an aromatic indole or pyrrole system should be realized



I, Ia — Ib

III

I R=H, ΔpK_a=4,5; Ia R=$COCH_3$, ΔpK_a=6,15; Ib R=H, $COCH_3$; III ΔpK_a=8,12

*See [1] for Communication 63.

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