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PYRROLES FROM KETOXIMES AND ACETYLENE.

38.* NEW REPRESENTATIVES OF TRIFLUOROACETYLPYRROLES. SYNTHESIS AND TRANSFORMATIONS

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A series of previously unknown trifluoroacetyl derivatives of pyrroles were obtained with high yields by the reaction of pyrroles, including N-vinyl-substituted pyrroles, with trifluoroacetic anhydride in the presence of pyridine at room temperature. The solvent and the substituents at the α and β positions of the pyrrole ring do not affect the direction of electrophilic substitution.

It is known [2-12] that the trifluoroacetylation of compounds of the pyrrole series leads to α -or β -substitution products, depending on the structure and on the reaction conditions. While continuing an investigation into this reaction in the series of substituted pyrroles we attempted to determine the effects of substituents in the pyrrole ring and the effect of the medium on the direction of attack by the trifluoroacetyl cation and on the yield of the final products.

*For Communication 37, see [1].

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The effect of solvents was investigated mainly for the case of the reaction of trifluoroacetic anhydride with 2-phenylpyrrole. It was found that, in dry benzene, dioxane, dichloroethane, chloroform, and carbon tetrachloride the attack by the $COCF_3$ cation is directed exclusively toward the α position of the pyrrole ring. [In all cases the PMR spectrum of the trifluoroacetylpyrrole (I) contained signals for the 3- and 4-H protons.] The possible attack by the electrophile at the NH group [7] was not observed. The physicochemical characteristics of the only reaction product (2-phenyl-5-trifluoroacetylpyrrole) coincided with the previously obtained data [2]. The investigated solvents did not affect the yield of the trifluoroacetylpyrrole (I). Thus, the yields of the pyrrole (I) in ether, benzene, dioxane, dichloroethane, chloroform, and carbon tetrachloride amounted to 87, 83, 90, 84, 83, and 85%, respectively. As a result we chose ether as working solvent in the synthesis of the trifluoroacetylpyrroles (II-IX, XI-XV, XVII, XVIII) as being the most readily obtainable and most convenient solvent for the extraction of the trifluoroacetylpyrroles from the reaction mixture.

The yields of the trifluoroacetylpyrroles (III-VIII) unsubstituted at the nitrogen atom do not depend on the structure of the aryl substituent at position 2 of the pyrrole ring and are, as a rule, not less than 80% (Table 1). The trifluoroacetylation of the N-vinyl-2phenylpyrroles (X-XIV) with alkyl substituents (C_2H_5 , C_3H_7 , C_5H_{11} , C_9H_{19}) at position 3 of the pyrrole ring is also regiospecific (only at the α position) and takes place as readily as for the pyrroles (I-VIII) unsubstituted at the nitrogen atom.

The regioselectivity of the reaction is not lost in the reaction of N-vinyl-2-phenylpyrrole with trifluoroacetic anhydride in DMFA, but its rate is reduced appreciably. In this version the production of a satisfactory yield (58%) of the trifluoroacetylpyrrole (IX) requires a twofold excess of the anhydride and an increase of the reaction time to 7 h instead of the usual 4-5 h.

The reactivity of the synthesized N-vinyltrifluoroacetylpyrroles was investigated for the cases of hydrogenation, thiylation, electrophilic addition of alcohols, and oximation. The catalytic hydrogenation of N-vinyl-2-aryl-5-trifluoroacetylpyrroles (IX, XV-XVII) takes place readily and almost quantitatively and gives N-ethyl-2-aryl-5-(1-hydroxy-2,2,2-trifluoroethyl)pyrroles (XXIII-XXVI).



XXIII $R^1 = C_6H_5$; XXIV $R^1 = 4 - CH_3C_6H_4$; XXV $R^1 = 4 - C_2H_5C_6H_4$; XXVI $R^1 = 4 - CH_3OC_6H_4$

2-Phenyl-5-trifluoroacetylpyrrole is reduced under the same conditions with the formation of 2-phenyl-5-(1-hydroxy-2,2,2-trifluoroethyl)pyrrole (XXVII)* with a yield of 97%. In contrast to the data in [9], where the synthesis of pyrrolidine compounds during the hy-



^{*}The preparation procedures (without experimental details), constants, and data on the antimicrobial activity of the pyrroles (XXIII, XXIV, XXVII) are given in [12].

Com- pound †	R ‡	bp, °C (pres- sure, mm Hg) [mp, °C]	Yield, %	Com- pound †	R‡	bp,°C (pres- sure,mm Hg) [mp,°C]	Yield, %
I III IV VV VI VII VIII IX XI	$\begin{array}{c} C_{6}H_{5} \\ C_{6}H_{5} \\ 4 - CH_{3}C_{6}H_{4} \\ 4 - C_{2}H_{5}C_{6}H_{4} \\ 4 - CH_{3}OC_{6}H_{4} \\ 4 - CH_{3}OC_{6}H_{4} \\ 4 - BrC_{6}H_{4} \\ 4 - BrC_{6}H_{4} \\ C_{10}H_{7} \\ (naphthy1) \\ C_{6}H_{5} \\ C_{6}H_{5} \\ C_{6}H_{5} \\ \end{array}$	$\begin{array}{c} 156 \ldots 158 \\ 114 \ldots 115 \\ 197 \ldots 199 \\ 169 \ldots 169,5 \\ 195 \ldots 196 \\ 189 \ldots 191 \\ 193 \ldots 194 \\ 184 \ldots 186 \\ 145 \ldots 146 \\ (3 \ldots 4) \\ 136 (1) \\ 56 \ldots 57 \end{array}$	87 84 93 92 84 82 83 80 85 93 86	XII XIII XIV XVI XVII XVIII XIX XXI XXI	$\begin{array}{c} C_6H_5\\ C_6H_5\\ +C_1H_5C_6H_4\\ +C_2H_5C_6H_4\\ +C_2H_5C_6H_4\\ +CH_3OC_6H_4\\ +CIC_6H_4\\ C_6H_5\\ +CH_3OC_6H_4\\ C_6H_5\\ +C_2H_5C_6H_4\\ \end{array}$	$\begin{array}{c} 45 \dots 47 \\ 183 & (9) \\ 188 & (2) \\ 62 \dots 63 \\ 138 \dots 140 & (1) \\ 59 \dots 60 \\ 84 \dots 86 \\ 169 \dots 172 \\ (2 \dots 3) \\ [59 \dots 60] \\ 188 \dots 192 & (1) \\ 170 \dots 172 & (1) \\ 168 \dots 170 & (1) \end{array}$	83 87 90 92 81 80 87 83 92 82

TABLE 1. 5-Trifluoroacetylpyrroles*

*Compounds (X, XVI) were synthesized in carbon tetrachloride [11].

¹¹¹ ⁺ IX d_4^{20} 1.2582, n_D^{20} 1.5885; XIII d_4^{20} 1.0807, n_D^{20} 1.5055; XIV n_D^{20} 1.5080; XIX n_D^{20} 1.5700; XX d_4^{20} 1.2511; XXI d_4^{20} 1.2075, n_D^{20} 1.5680; XXII d_4^{20} 1.1934, n_D^{20} 1.5710. [‡]I, III-IX, XV-XVIII, XX-XXII $R^2 = H$; II, XI $R^2 = C_2H_5$; X, XIX $R^2 = CH_3$; XII $R^2 = C_3H_7$; XIII $R^2 = C_5H_{11}$; XIV $R^2 = C_9H_{19}$; I-VIII $R^3 = H$; IX-XVIII $R^3 = CH_2=CH$; XIX, XX, XXII $R^3 = (CH_2)_2SC_2H_5$; XXI $R^3 = (CH_2)_2SC_3H_7$.

TABLE	2.	PMR	Spectra	of	the	Trifluoroacetylpyrroles*
			opeerra	OT.	CIIC	1111140104cccy1py1101c3

, p	δ, ppm							
Com	3-H	4-H	R ¹	R ²	R ³			
I VV VII VIII XIII XIII XV XVIII XXVIII XXII	6,63 6,56 6,70 6,78 7,07 6,38 6,41 6,23	7,25 7,20 7,20 7,25 7,25 7,30 7,20 7,30 7,20 7,30	$7.4 \dots 7.8 7.2 \dots 7.6 7.5 \dots 7.9 7.2 \dots 7.8 7.56 \dots 7.97 7.3 \dots 7.5 7.3 \dots 7.5 7.20 7.35 7.40$	2,34 (α); 1,45 (β); 0,83 (γ) 2,35 (α); 1,24 (β , γ , δ); 0,82 (ϵ)	10,6 12,6 12,8 7,30 (α); 4,94 (β -cis); 4,56 (β -trans) 1,30 (α); 4,87 (β -cis); 4,46 (β -trans) 7,38 (α); 5,13 (β -cis); 4,76 (β -trans) 7,38 (α); 5,15 (β -cis); 4,74 (β -trans) 4,42 (α); 2,57 (β); 2,23 (SCH ₂); 1,40 (CH ₂); 0,86 (CH ₃)			

*The spectra of compounds (I, XII, XVIII) were recorded in deuterochloroform, those of (IV, V, VII, VIII, XV) were recorded in DMSO-D₆, and those of (XIII, XXI) were recorded in carbon tetrachloride.

drogenation of substituted pyrroles in the presence of Raney nickel was reported, the pyrrole ring is not reduced either fully or partly under the investigated conditions. Only the vinyl and carbonyl groups are reduced.

In spite of the presence of the strong electron-withdrawing COCF_3 group in the molecule of these N-vinylpyrroles, the reaction of alkanethils with N-vinyl-5-trifluoroacetylpyrroles, initiated by azoisobutyronitrile at 70-80°C, takes place in the usual way [2] with the formation of only the β -adducts, i.e., 1-(2-alkylthioethyl)-2-aryl-5-trifluoroacetylpyrroles (XIX-XXII) with yields of up to 92%. The possible products from addition at the carbonyl group were not detected. In order to obtain alkoxyethylpyrroles with the general formula (XXVIII), containing the $COCF_3$ group in the pyrrole ring, we attempted the addition of primary aliphatic alcohols (R = CH_3 , C_2H_5 , C_4H_9) to the N-vinyl-2-phenyl-5-trifluoroacetylpyrrole (IX) under electrophilic conditions [2].



However, it was found that the presence of the strongly electron-withdrawing group $(COCF_3)$, which reduces the nucleophilic activity of the double bond, prevents such a reaction. It was also impossible to realize path 2 under the investigated conditions.



Like the acetylpyrroles [13], the trifluoroacetyl derivatives of pyrroles, such as trifluoroacetylpyrrole (I), are oximated by hydroxylamine hydrochloride.

The IR and PMR spectra confirm the structures of the synthesized compounds (Table 2). In the IR spectra of the pyrroles (I-VIII) and alkylthioethylpyrroles (XIX-XXII) the carbonyl group is represented by absorption at 1660 and 1670-1690 cm⁻¹, respectively. The pyrroles (I-VIII) are characterized by a strong absorption band in the regions of 3320 and 3330 ($\nu_{\rm NH}$), and the vinylpyrroles (X-XVII) give bands at 1635 and 1640 ($\nu_{\rm C=C}$ of the N-vinyl group) as a shoulder on a very strong band at 1660-1680 cm⁻¹ ($\nu_{\rm C=O}$). In the IR spectra of compounds (XXIII-XXVI) the $\nu_{\rm OH}$ band appears at 3400 cm⁻¹, while the absorption of the carbonyl (1680) and vinyl (1640 cm⁻¹) groups is absent. IR spectrum of oxime (XXIX) (potassium bromide): 1500, 1600 ($\nu_{\rm C=C}$ of pyrrole ring), 3450 ($\nu_{\rm OH}$), 935 ($\nu_{\rm N=O}$), 1640 cm⁻¹ ($\nu_{\rm C=N}$).

EXPERIMENTAL

The initial pyrroles and N-vinylpyrroles were obtained from the ketoximes and acetylene by the Trofimov reaction [2], and the alkylthioethylpyrroles were obtained by the method in [14]. The IR spectra were recorded on a UR-20 instrument for microlayers [the pyrroles (IX, X, XIII, XIV, XX-XXII)] or for tablets with potassium bromide [compounds I-VIII, XI, XII, XV, XVII, XVIII, XXVI, XXIX)]. The PMR spectra were obtained on a Tesla BS-487C spectrometer at 80 MHz with HMDS as internal standard. The elemental analyses of compounds (I-XXII, XXV, XXIX) for C, H, F, and N agreed with calculated data.

<u>Typical Procedure for the Production of α -Trifluoracetylpyrroles (I-IX, XI-XV, XVII, XVIII)</u>. To a solution of 30 mmoles of pyrrole and 40 mmoles of pyridine in 40 ml of ether at 20°C we added dropwise over 2.0-2.5 h 40 mmoles of trifluoroacetic anhydride in 10 ml of ether. The mixture was stirred at the same temperature for a further 2-3 h and added to cold water. The organic layer was separated, and the aqueous layer was extracted with ether. The organic layer and the extracts were washed (3-5 times) with cold water and dried with magnesium sulfate. The ether was removed, and the residue was distilled under vacuum or (in the case of the crystalline substance) recrystallized from ethanol or hexane. The yields and constants of the trifluoroacetylpyrroles are given in Table 1.

The trifluoroacetylation was conducted similarly in other solvents.

<u>1-Ethyl-2-(4-ethylphenyl)-5-(1-hydroxy-2,2,2-trifluoroethyl)pyrrole (XXV, $C_{16}H_{18}F_{3}NO$).</u> The reaction mixture from 4.4 g (15 mmoles) of N-vinyl-2-(4-ethylphenyl)-5-trifluoroacetylpyrrole in 50 ml of ethanol and hydrogen (initial pressure 40 atm) in the presence of 1 g of Raney nickel was heated at 50°C for 5 h in a 1-liter rotating autoclave. The catalyst was separated from the liquid, the solvent was distilled, and 4.2 g (94%) of the pyrrole (XXV) was obtained; mp 56-57°C. <u>2-Phenyl-5-trifluoroacetylpyrrole Oxime (XXIX, $C_{12}H_9F_3N_2O$).</u> To a mixture of 3.1 g (12 mmoles) of 2-phenyl-5-trifluoroacetylpyrrole, 1.55 g (22 mmoles) of hydroxylamine hydrochloride, 10 ml of ethanol, and 2 ml of water we added 5 ml of benzene. Over 0.5 h with vigorous stirring we added 1.84 g (46 mmoles) of sodium hydroxide. The mixture was then heated at 60-70°C for 2 h. After cooling it was poured into water (~100 ml) which had been acidified with hydrochloric acid. The oxime (XXIX) was extracted with ether, and the extracts were washed with water and dried with potassium carbonate. After removal of the ether we obtained 2 g (60%) of the oxime (XXIX); mp 250°C (decomp.).

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