SYNTHESIS AND PROTOTROPIC ISOMERIZATION OF 1-NITROPHENYL-2-ACYLPYRROLES

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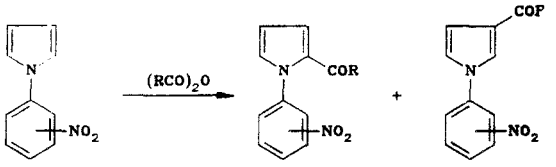
Acylation of 1-nitrophenylpyrroles by acid anhydrides leads to 2-acylpyrroles or their mixtures with 3-acylpyrroles, the formation of the latter being explained by acid isomerization of the 2-isomers.

Use of acylhalides in the synthesis of 2-acylpyrroles in most cases gives poor results [1, 2]; the optimal yields being attained using acid anhydrides with a catalytic amount of orthophosphoric acid [2], and also benzoyl chloride in the presence of triethylamine [3].

We studied the action of 1-(m-nitrophenyl)- and 1-(p-nitrophenyl)pyrroles. Compounds containing acceptor substituents on the nitrogen atom are usually acylated under Friedel–Crafts conditions, however, we showed that a single method, heating the arylpyrrole with an excess of acid anhydride with catalysts by phosphoric acid, is suitable in our case. This usually forms a mixture of 2- and 3-acylpyrroles with prevalence of the 2-isomer and total yield of 80-90% (Table 1).



The isomeric 2- and 3-acylpyrroles do not have different carbonyl group absorptions in the IR spectra, but they have differences in the C–C and C–N stretching regions: The 2-isomers have strong absorption bands at 1470-1445, 1420-1410, and 910-860 cm^{-1}, while the 3-isomers absorb at 1550-1540 and 1280-1260 cm^{-1}. Besides this, for the 3-isomers weak bands at 930 and 825-800 cm^{-1} are characteristic. A signal for the 2-H proton is always present at weak field (7.7-7.8 ppm) in the PMR spectra of the 3-isomers, and is absent for the 2-isomers (Table 2). As a rule, the 3-isomers are higher melting and have lower chromatographic mobility on silica gel.

Electrophilic substitution in the pyrrole ring, including acylation, in general occurs at position 2 [1, 4]. The migration of acyl groups in 2-acylindoles with formation of the 3-substituted indoles [5, 6] is known, and also rearrangement of 2-aroylpyrroles [7]. Recently we showed [8] that 1-(p- and m-nitrophenyl)-2-formylpyrroles are completely isomerized to the 3-isomers upon heating with acids. These data confirm the possible occurrence of rearrangement under acylation reaction conditions. We heated 2-acylpyrroles in PPA or trifluoroacetic acid for additional confirmation of the possibility of such rearrangement in a series of pyrrole ketones and obtained the 3-isomers with quantative yield (Table 1).

It was shown earlier [6] that prototropic isomerization of 2-acylindoles occurs due to initial protonation of the carbonyl oxygen and subsequent electrophilic attack by the acyl cation at the 3 position with hydride shift. Using the example of 2-formyl-1-(p-nitrophenyl)pyrrole we showed that in trifluoroacetic acid the protonation also occurs at

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TABLE 1. Data for Acylpyrroles

NO_2 position	R	Empirical formula	Reaction conditions*		mp, °C	IR spectrum, cm^{-1}		UV spectrum, λ_{max}, nm (log ε)	Yield, %	
			time, h	temperature, °C		C=O	NO_2		2-isomer	3-isomer
2-Isomers										
p	CH_3	$C_{12}H_{10}N_2O_3$	2	30	119...120	1670	1530, 1350	204 (4,22), 217 (4,08), 280 (4,23)	82	—
m	CH_3	$C_{12}H_{10}N_2O_3$	2	30	104...105	1670	1535, 1355	208 (4,09), 264 (4,22)	73	—
p	C_2H_5	$C_{13}H_{12}N_2O_3$	2	30	89...90	1655	1510, 1330	218 (4,28), 276 (4,53)	49	4
m	C_2H_5	$C_{13}H_{12}N_2O_3$	2	30	88...90	1660	1535, 1330	214 (4,04), 262 (4,22)	46	4
p	CF_3	$C_{12}H_7F_3N_2O_3$	10	30	116...117	1675	1520, 1345	212 (4,28), 278 (4,38)	90	—
m	CF_3	$C_{12}H_7F_3N_2O_3$	10	30	90...91	1670	1535, 1350	214 (4,09), 271 (4,07)	93	—
p	C_6H_5	$C_{17}H_{12}N_2O_3$	1	50	124...126	1635	1525, 1345	204 (4,45), 217 (4,23), 294 (4,32)	26	45
m	C_6H_5	$C_{17}H_{12}N_2O_3$	1	50	Oil	1630	1520, 1340	204 (4,45), 217 (4,38), 251 (4,36), 300 (4,24)	27	49
3-Isomers										
p	H	$C_{11}H_8N_2O_3$	4		143...144	1672	1515, 1345	213 (4,19), 261 (4,09), 313 (4,30)		55
m	H	$C_{11}H_8N_2O_3$	4		155...156	1675	1520, 1360	230 (4,17), 268 (4,35)		58
p	CH_3	$C_{12}H_{10}N_2O_3$	1(1)		206...207	1670	1530, 1340	204 (4,42), 213 (4,31), 261 (4,18), 317 (4,29)		93**
m	CH_3	$C_{12}H_{10}N_2O_3$	1		127...128	1665	1530, 1365	267 (4,25)		87
p	C_2H_5	$C_{13}H_{12}N_2O_3$	(1)		212...213	1655	1525, 1335	210 (4,43), 259 (4,29), 316 (4,55)		88
m	C_2H_5	$C_{13}H_{12}N_2O_3$	(1)		120...122	1660	1535, 1345	242 (4,44), 265 (4,59)		90
p	C_6H_5	$C_{17}H_{12}N_2O_3$	1		190...192	1645	1525, 1340	204 (4,28), 315 (4,15)		92
m	C_6H_5	$C_{17}H_{12}N_2O_3$	***		203...205	1640	1545, 1360	205 (4,44), 244 (4,36), 276 (4,37)		49

*For the 3-isomers, the reaction time by method A is given, that for method B in parentheses.
**Yield by method B, 90%.
*** Obtained by acylation of the corresponding pyrrole.

TABLE 2. PMR Spectra of Acylindoles, ppm (in $CDCl_3$)

NO_2 position	R	Isomer	2(3)-H	4-H	5-H	R protons
p	H	2	7,20	6,49	7,13	9,62
		2*	7,25	6,25	7,07	8,95
		3	7,78	6,89	7,20	9,90
m	H	2	7,22	6,49	7,13	9,61
		3	7,75	6,88	7,18	9,91
p	CH_3	2	7,15	6,37	6,96	2,46
		3	7,73	6,84	7,14	2,49
m	CH_3	2	7,14	6,36	6,96	2,45
		3	7,72	6,82	7,12	2,49
p	C_2H_5	2	7,14	6,35	6,96	1,14 2,84
m	C_2H_5	2	7,12	6,35	6,95	1,15 2,84
		3	7,96	6,82	7,13	1,21 2,82
p	CF_3	2	7,44	6,52	7,19	—
m	CF_3	2	7,43	6,53	7,18	—
p	C_6H_5	2	6,93	6,48	—	7,64 8,30
		3	7,68	6,93	7,19	7,58 8,35
m	C_6H_5	2	6,96	6,37	7,13	7,5...8,5
		3	7,91	6,84	7,73	7,5...8,5

*Spectrum in CF_3COOH.

the oxygen atom of the aldehyde group, which is evident both in the practically constant position of the pyrrole proton signals in the PMR spectrum while the general form of the spectrum changes and in the shift of the aldehyde proton signal to strong field (8.95 vs. 9.62 ppm), analogous to what occurs in indoles [6].

Thus, it can be assumed that the prototropic isomerization mechanism of 2-acylpyrroles corresponds to that proposed for 2-acylindoles. A similar reaction scheme explains the dependence of the isomerization on the character of the acyl moiety which shows up first in the sources of acylation: 2-trifluoroacetylpyrroles do not undergo rearrangement under various conditions, since protonation at the carbonyl oxygen atom is hindered here, and only the 2-isomer is obtained upon acylation. On the other hand, isomerization of 1-(m-nitrophenyl)-2-acetylpyrrole occurs readily even at room temperature: After 3 days signals of 3-acetylpyrrole appear in its PMR spectrum in trifluoroacetic acid, after a month the conversion reaches 45-50%, and after 3 months, it is complete. Nevertheless, we were able to separate the pure 2-isomer upon acetylation under mild conditions (15 min, 60-70°C), while heating at 80-90°C for 1 h leads to isomerization. The benzoyl group not only gives a relatively stable cation upon protonation, but also a more stable intermediate state, so that upon benzoylation we observed practically simultaneous formation of 2- and 3-benzoylpyrroles, and the final reaction mixture contains predominantly the 3-isomer.

EXPERIMENTAL

UV spectra were recorded on a Specord instrument, IR spectra on SP-1000 (Pye Unicam) and UR-20 instruments, and PMR spectra on a FX-90Q (Jeol) instrument. The reaction and purity of products obtained were monitored by TLC on Silufol UV-254 plates using benzene and purification was done on columns with Merck-60 silica gel with benzene eluent. Elemental analyses for C and H corresponded to those calculated.

Starting (p- and m-nitrophenyl)-2-formylpyrrole and p- and m-nitrophenylpyrroles were obtained by the method of [9]. Constants and yields of the synthesized acylpyrroles are given in Table 1 and 2.

1-(p- and m-Nitrophenyl)-2-acetylpyrroles. To a mixture of 5 mmole 1-(p- or m-nitrophenyl)pyrrole and 15 ml acetic anhydride with constant stirring were added 4-5 drops of orthophosphoric acid. Stirring was continued at room temperature for 2 h, then it was heated at 60-70°C for 15 min. It was cooled, diluted with cold water, and basicified with 10% NaOH until neutral. The precipitate was filtered, washed a few times with water, dried, and recrystallized from alcohol.

1-(p- and m-Nitrophenyl)propionylpyrroles. The reaction was done by the previous method. After cooling the polycrystalline mass obtained, it was dissolved in chloroform, washed with water until neutral, and dried with $CaCl_2$. The solvent was removed, and a mixture of the 2- and 3-isomers (see Table 1) was obtained, which was separated chromatographically on a column.

1-(p- and m-Nitrophenyl)benzoylpyrroles. A mixture of 8 g (35 mmole) benzoic anhydride and 0.5 g (2.6 mmole) nitrophenylpyrrole was carefully heated to 50°C until melted and 4-5 drops of orthophosphoric acid were added to the transparent solution which was held at 50°C for 1 h. Then 30 ml water were added and it was heated at 50°C for 30 min. It was cooled, basicified with 20% NaOH to pH 10 and again heated at 50°C for 30 min. Ten ml water were added, it was cooled, and the aqueous layer decanted. The remaining polycrystalline mass was dissolved in chloroform, washed with water until neutral, and dried with $CaCl_2$. The solvent was evaporated and the residue was chromatographed on a column.

1-(p- and m-Nitrophenyl)-2-trifluoroacetylpyrroles. A mixture of 0.5 g (2.6 mmole) nitrophenylpyrrole and 10 ml trifluoroacetic anhydride were mixed at room temperature for 10 h and cold water was slowly added. The precipitate was filtered, washed a few times with water, dried, and recrystallized from alcohol.

Prototropic Isomerization of 2-Acylpyrroles into the 3-Isomers. A. A mixture of 1 g (4.6 mmole) 1-(p-nitrophenyl)-2-formylpyrrole and polyphosphoric acid, obtained from 10 g P_2O_5 and 5 ml 85% orthophosphoric acid, was heated at 100°C for 4 h, after which it was poured into cold water. The precipitate which formed was thoroughly ground with water, filtered, and boiled a few times with alcohol. The extract obtained was evaporated and the residue was separated on a column.

B. A mixture of 0.2 g (0.8 mmole) 1-(m-nitrophenyl)-2-acetylpyrrole and 10 ml trifluoroacetic acid was heated at 100°C for 1 h, cooled, and poured into cold water. The precipitate which formed was thoroughly ground with water and filtered.

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