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HETEROCYCLIZATION OF DERIVATIVES OF 4-OXOALKANOIC ACIDS TO 1,5-DISUBSTITUTED PYRROLIN-2-ONES

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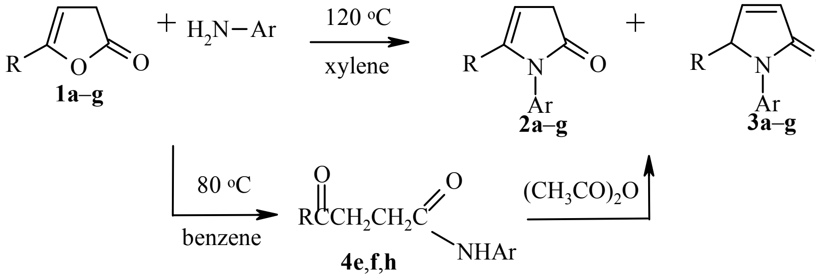
Conditions were developed for the synthesis and production of 1-aryl-5-alkyl(aryl)-3H- and 1-aryl-5-alkyl(aryl)-5H-pyrrolin-2-ones from the amides and esters of 4-oxoalkanoic acids. It was established that the yield and ratio of the 3H and 5H isomers depend on the substrate employed in the reaction.

Keywords: 4-oxoalkanamides, 1-aryl-5-alkyl(aryl)-3H-pyrrolin-2-ones, 1-aryl-5-alkyl(aryl)-5H-pyrrolin-2-ones, 4-oxoalkanoic esters.

Unsaturated five-membered nitrogen-containing 2-oxo heterocycles occupy an important place in organic chemistry in connection with their discovery in the form of fragments of natural compounds and also the production of substances with various types of biological activity from them [1]. The production of 1,5-disubstituted pyrrolin-2-ones in the reactions of N-substituted succinimides with the Grignard reagent and of *L*-angelicolactone with primary amines has been described [2, 3].

The present paper gives the results of the synthesis of 5-alkyl(aryl)-3H- and 5-alkyl(aryl)-5H-pyrrolin-2-ones from the amides and esters of 4-alkanoic acids and also the internal esters of these acids — 3H-furan-2-ones — by their reaction with amines of the aromatic series under various conditions.

5-Alkyl(aryl)-3H-furan-2-ones (**1a-g**) react with primary aromatic amines (aniline, *p*-toluidine, *p*-bromoaniline) in xylene solution at 120°C with the reagents in a ratio of 1:3 and form mixtures of 1-aryl-5-alkyl(aryl)-3H-pyrrolin-2-ones (**2a-g**) and 1-aryl-5-alkyl(aryl)-5H-pyrrolin-2-ones (**3a-f**). The products were isolated mainly in the form of the 3H isomers of 1,5-disubstituted pyrrolin-2-ones **2a-g** (yields 70-75%). The amounts of compounds **3a-f** in the reaction mixtures were insignificant.



1-4 a R = CH_3, Ar = C_6H_5; **b** R = C_4H_9, Ar = C_6H_5; **c** R = *i*-C_4H_9, Ar = C_6H_5;
d R = C_5H_{11}, Ar = C_6H_5; **e** R = C_6H_{13}, Ar = C_6H_5; **f** R = C_7H_{15}, Ar = C_6H_5;
g R = C_6H_5, Ar = $C_6H_4CH_3$-*p*; **h** R = C_7H_{15}, Ar = C_6H_4Br-*p*

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It should be noted that 1-(4-methylphenyl)-5-phenylpyrrolin-2-one (**2g**) only exists in the form of the 3H isomer both in the solid state and in solution in deuterochloroform, and the 5H form could not be isolated.

Compounds **2a-g** and **3a-f** are formed through a stage involving opening of the furan ring as a result of ammonolysis of the initial compounds **1a-g** by the aromatic amines. The obtained 4-oxoalkanamides **4** undergo successive cyclization to the tautomeric 2-aryl-5-alkyl(aryl)-5-hydroxy-2-oxopyrrolidines with further dehydration and partial isomerization of the 3H form **2a-f** to the more stable 5H isomers **3a-f**. Isomerization of compounds (**2a-f** to compounds **3a-f** also takes place during storage in air under room conditions.

The intermediates **4e-g** were obtained intentionally under milder conditions as a result of boiling the furanones **1** with amines in benzene with reduction of the process time by half. Their physical constants are given in Table 1.

The IR spectra of compounds **4e-g** contain the absorption bands of the amide carbonyl at 1589-1540 cm^{-1}, the carbonyl group at 1690-1660 cm^{-1}, and the NH group at 3330-3230 cm^{-1}.

Comparison of the IR spectra of compounds **2a-g** and **3a-f** shows that the largest difference in them is observed in the region of the vibrations of the lactam carbonyl. For compounds **2a-g** the absorption band of the C=O group is observed in the region of 1690-1665 cm^{-1}, whereas this band in the isomers **3a-f** is observed in the region of 1705-1700 cm^{-1}.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % Calculated, %			bp, °C/mm Hg	n_D^{20}	Yield, %
		C	H	S			
2a	$C_{11}H_{11}NO$	76.58 76.36	6.30 6.41	8.01 8.10	155-158/4	1.5280	63
2b	$C_{14}H_{17}NO$	78.15 78.20	7.65 7.97	6.45 6.52	157-160/4	1.5340	68
2c	$C_{14}H_{17}NO$	78.02 78.20	7.71 7.97	6.40 6.52	165-168/4	1.5328	72
2d	$C_{15}H_{19}NO$	78.51 78.67	8.15 8.36	6.02 6.12	170-172/4	1.5360	72
2e	$C_{16}H_{21}NO$	79.18 79.08	8.80 8.71	5.60 5.76	168-170/4	1.5368	70
2f	$C_{17}H_{23}NO$	76.40 76.47	8.52 8.68	5.30 5.63	172-175/4	1.5380	75
2g*	$C_{17}H_{15}NO$	79.98 82.00	5.72 5.07	5.61 5.63	179-181	—	82
3a	$C_{11}H_{11}NO$	76.21 76.36	6.35 6.41	8.15 8.10	165-167/4	1.5484	35
3b	$C_{14}H_{17}NO$	78.25 78.20	7.80 7.97	6.50 6.52	165-168/4	1.5523	20
3c	$C_{14}H_{17}NO$	78.01 78.20	7.57 7.97	6.42 6.52	170-173/4	1.5490	17
3d	$C_{15}H_{19}NO$	78.15 78.67	8.10 8.36	5.98 6.12	175-178/4	1.5510	15
3e	$C_{16}H_{21}NO$	78.95 79.08	8.60 8.71	5.15 5.76	176-178/4	1.5560	15
3f	$C_{17}H_{23}NO$	76.12 76.47	8.60 8.68	5.05 5.25	178-180/4	1.5580	10
4e*	$C_{16}H_{23}NO_2$	73.51 73.62	8.60 8.88	5.07 5.37	98-100	—	87
4f*	$C_{17}H_{25}NO_2$	74.32 74.24	9.35 9.16	5.00 5.09	99-102	—	85
4h*	$C_{17}H_{24}BrNO_2$	56.81 57.68	6.70 6.83	4.12 3.96	55-56	—	76

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*mp, °C

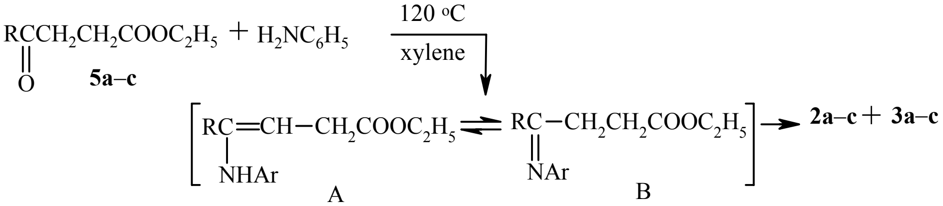
TABLE 2. The ^{1}H NMR Spectra of 1-Phenyl-5R-3H-pyrrolin-2-ones **2** and 1-Phenyl-5R-5H-pyrrolin-2-ones **3**

Compound	Chemical shifts, δ, ppm, *J* (Hz)				
	R	Ph	3-H (2H, dd)	4-H (1H, dd)	5-H (1H, m)
2a	1.60 (3H, s)	7.15-7.46	3.00	5.20 J_{34} = 3.30, 3.38	—
2b	0.81-1.92 (9H, m)	7.45-8.00	3.10	5.19 J_{34} = 3.44, 3.54	—
2c	0.80-1.94 (9H, m)	7.30-7.90	3.02	5.25 J_{34} = 3.42, 3.55	—
3a	1.60 (3H, d)	7.25-7.46	6.07	7.14 J_{45} = 5.74, J_{34} = 6.54	3.95
3b	0.81-1.92 (9H, m)	7.40-8.00	6.10	7.16 J_{45} = 5.70, J_{34} = 6.62	3.87
3c	0.80-1.94 (9H, m)	7.30-7.80	6.18	7.17 J_{45} = 5.71, J_{34} = 6.60	3.90

In the ^{1}H NMR spectrum (deuterochloroform) of pyrrolin-2-ones **2a-c** there is a signal for the vinyl proton in the region of 5.19-5.25 ppm (d), and there are also signals for the protons at position 3 of the ring in the region of 2.70-3.10 ppm, the form of which confirms the structure of the 3H form (Table 2).

In the spectra of compounds **3a-c** there are signals of the vinyl protons 3-H and 4-H in the region of 6.07-6.18 and 7.14-7.17 ppm respectively and also a multiplet for the 5-H proton in the region of 2.27-2.35 ppm (Table 2).

The reaction of the ethyl 4-oxoalkanoates **5a-c** with aromatic amines on boiling in xylene leads to the formation of the desired 1-aryl-5-alkyl(aryl)-3H-pyrrolin-2-ones **2a-c** with yields of 63-75% and also the isomeric 1-aryl-5-alkyl-5H-pyrrolin-2-ones **3a-c** with yields of 10-35%.



If the reaction is carried out under mild conditions in solution in ethyl alcohol, the yields of compounds **2a-c** and **3a-c** in each case are no more than 18% in total, since the reaction takes place through the formation of the intermediate enamines **A** and **B**, the cyclization of which is hindered as a result of the decrease in the basicity of the nitrogen atom. The evidence for the formation of the intermediates **A** and **B** is based on the data from the ^{1}H NMR spectra recorded for the reaction mixture. Thus, for the tautomer **A** the signals for the protons of the group at $CH_2C=O$ are observed in the region of 2.77 ppm (d) and those of the vinyl proton are in the region of 6.15 ppm (t). At 8.2 ppm there is a broad signal for the NH group. In the spectra there are also signals in the region of 2.12 (m) and 3.63 (m) ppm, corresponding to the protons of the $CH_2CH_2C=O$ group belonging to form **B**. The signals for the protons of the phenyl substituent are in the region of 7.01-7.10 ppm, and those for the alkyl are in the region of 0.80-1.84 ppm.

The presence of the signal of the vinyl proton and the retention of the signals for the protons of the ester group in the region of 4.95 (q, 2H) and 2.56 (t, 3H) ppm with spin–spin coupling constant 4.52 Hz make it possible to conclude that the reaction takes place through a stage involving the formation of the intermediates **A** and **B**.

The physicochemical and spectral characteristics of compounds **2a-g** and **3a-f**, obtained from the 3H-furanones **1a-g**, the amides **4e**,**f**,**h**, and the esters **5a-c** agree fully (Tables 1 and 2).

Thus, it is more expedient to base the synthesis of 1,5-disubstituted 3H-pyrrolin-2-ones on the cyclic esters of 4-oxoalkanoic acids – 3H-furan-2-ones.

EXPERIMENTAL

The IR spectra were recorded on an IKS-29 instrument. The ^{1}H NMR spectra were obtained on a Varian FT-80A instrument at 80 MHz with deuterochloroform as solvent. The chemical shifts are given on the δ scale with TMS as internal standard. The yields and characteristics of the obtained compounds are given in Tables 1 and 2. The ethyl 4-oxoalkanoates **5** were obtained by the familiar method [4], and the 5-alkyl-3H-furan-2-ones were obtained by the method in [5].

1-Aryl-5-alkyl(aryl)-3H-pyrrolin-2-ones (2a-g). A mixture of the compound **1a-g** (0.025 mol) and the aminating agent (0.1 mol) in absolute xylene was boiled for 3 h. The solvent was distilled, and the residue was submitted to fractional distillation under vacuum.

1-Aryl-5-alkyl-3H-pyrrolin-2-ones (2a-c) and 1-Aryl-5-alkyl-5H-pyrrolin-2-ones (3a-c) Based on Ethyl 4-Oxoalkanoates (5a-c). A mixture of the compound **5a-c** (0.2 mol), aniline (0.3 mol), and absolute *o*-xylene (80 ml) was boiled under a reflux condenser for 3 h. The product was isolated by vacuum distillation.

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