Chemistry of Heterocyclic Compounds, Vol. 38, No. 5, 2002

NUCLEOPHILIC ADDITION OF AMINES TO N-ARYL-SUBSTITUTED PYRROLIN-2-ONES

M. A. Sibiryakova, G. F. Muzychenko, S. D. Burlaka, K. S. Pushkareva,
V. G. Glukhovtsev, and Z. I. Tyukhteneva

The nucleophilic addition of n-butyl- and benzylamines to 1-(4-nitrophenyl)-5H-pyrrolin-5-one and 1-(4-sulfamoylphenyl)-5H-pyrrolin-2-one at 50°C in an excess of the amines with the formation of N-substituted amides of 3-alkyl(benzyl)amino-4-(4-R-anilino)butyric acids was investigated. The N-substituted amides of 3-arylamino-4-hydroxybutyric and 4-hydroxy-2-butenoic acids were synthesized from 2(5H)-furanone and aromatic amines (1:3) at 180°C. 4-Alkylamino-1-(4-nitrophenyl)pyrrolid-2-ones were obtained in the reaction of 1-(4-nitrophenyl)-5-pyrrolin-2-one with ammonia or aliphatic, alicyclic, and aromatic amines (1:3, 90°C, in DMF).

Keywords: 4-alkylamino-1-(4-nitrophenyl)pyrrolid-2-ones, 3-amino-4-hydroxybutyramides, 4-hydroxy-2-butenamides, 3,4-diaminobutyramides, amines, 5H-pyrrolin-2-ones, 2(5)-furanone.

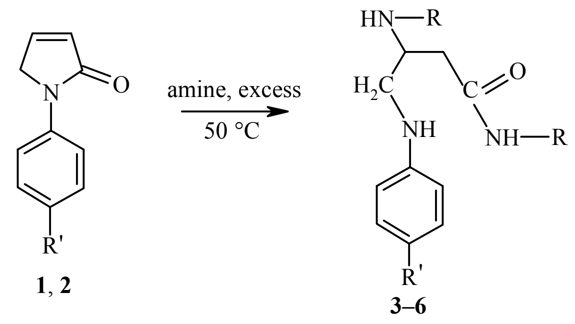
The amides of carboxylic acids and pyrrolidones are of interest as potential physiologically active compounds [1]. The reactions of 2(5H)-furanone, 5-alkyl-2(3H)-furanones, and hydroxyalkylbutanolides with amines, which lead to pyrrolid-2-ones or amides of hydroxy acids depending on the conditions, have been described. By changing the molar ratios of the reagents and the temperature conditions and using the appropriate solvent the authors [2-5] achieved controlled syntheses leading to the targeted products. It was noticed [6, 7] that 2(5H)-furanones with a disubstituted multiple bond react with amines with retention of the lactone ring. Simultaneous opening of the ring with the formation of the amides of unsaturated hydroxy acids was only observed in the presence of ethanol [7].

In view of the more specific characteristics of the N-aryl-substituted pyrrolin-2-ones compared with the 2(5H)- and 2(3H)-furanones and also the absence of published data on their reactivity we investigated the reaction of N-aryl-substituted pyrrolin-2-ones **1** and **2** with aliphatic, alicyclic, and aromatic amines with a view to synthesizing N-substituted amides and pyrrolidones.

The reactivity of compounds **1** and **2** with *n*-butyl- and benzylamines (Scheme 1) was investigated at room temperature in an excess of the amine, which acted as reagent and solvent. The N-substituted amides of 3,4-diaminobutyric acid **3** and **4** were formed after six days, and when the reaction mixture was kept for up to 15 days these compounds were obtained with quantitative yields. To accelerate the reaction the mixture was heated at 70°C for 1 h. Here strong resin formation occurred. The optimum conditions for the reaction were determined as follows: gradual addition of the pyrrolinone to the amine with vigorous agitation at a temperature no higher than 50°C and keeping the reaction mixture until completely crystallized. The purity of the synthesized compounds was confirmed by TLC.

Kuban State Technological University, Krasnodar, Russia; e-mail: organics@kubstu.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 612-618, May, 2002. Original article submitted September 18, 1999. Revision submitted July 12, 2000.

Scheme 1

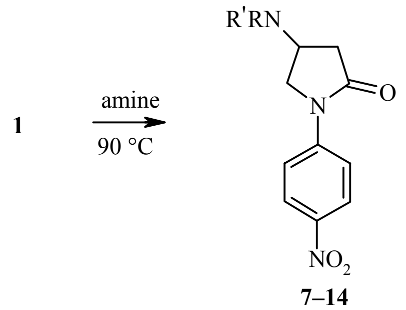


1, 3, 4 R' = NO_2, **2, 5, 6** R' = SO_2NH_2, **3, 5** R = $CH_2C_6H_5$, **4, 6** R = *n*-C_4H_9

The structure of the isolated amides was proved by IR spectroscopy (Table 1). The IR spectra of compounds **3-6** contain characteristic absorption bands for the amide groups: $\nu_{C=O}$ 1645-1530 cm^{-1} and δ_{NH} in the region of 1560-1525 cm^{-1}; the ν_{NH} band at 3315-3300 cm^{-1} indicates opening of the pyrrolidine ring. There are also bands for the stretching vibrations of the benzene ring (1606 and 1501 cm^{-1}), ν_s (1326-1323 cm^{-1}) and ν_{as} (1515-1510 cm^{-1}) of the NO_2 group for compounds **3** and **4**, and ν_s (1170 cm^{-1}) and ν_{as} (1350 cm^{-1}) of the SO_2 group for compounds **5** and **6**. During comparison of the IR spectra of compounds **1** and **2** ($\nu_{C=O}$ 1663, $\nu_{C=C}$ 1645 cm^{-1}) and of the products **3-6** it is seen that the nucleophilic addition of amines to the N-aryl-substituted pyrrolin-2-ones under the selected conditions takes place both at the double bond and at the carbonyl group.

Conditions were found for the addition of aliphatic and aromatic amines to 1-(4-nitrophenyl)-5H-pyrrolin-2-one (**1**) with the formation of 4-alkylamino-1-(4-nitrophenyl)pyrrolid-2-ones without opening the heterocycle (Scheme 2). The highest yields were observed with a threefold excess of the amine at 90°C. The reaction does not occur at room temperature and with heating to 50°C. Increase of the reaction temperature above 90°C leads to resinification of the reaction mixture and to a decrease in the yield of the desired product.

Scheme 2



7–13 R = H; **7** R' = H, **8** R' = Et, **9** R' = *n*-C_4H_9, **10** R' = *t*-C_4H_9, **11** R' = C_6H_{11},
12 R' = CH_2Ph, **13** R' = $(CH_2)_3OH$, **14** R = R' = Et

The purity of compounds **7-14** was confirmed by TLC, and their structure was demonstrated by IR spectroscopy (Table 1). In the spectra the $\nu_{C=O}$ bands (1700-1690 cm^{-1}) are shifted toward higher frequencies compared with the initial pyrrolinone (1663 cm^{-1}). The formation of the desired products is supported by the absence of strong bands for the stretching vibrations of the amide carbonyl group (1650-1620 cm^{-1}) and δ_{NH} in the region of 1570-1520 cm^{-1}. The spectra contain bands for the deformation vibrations of the NH bond at

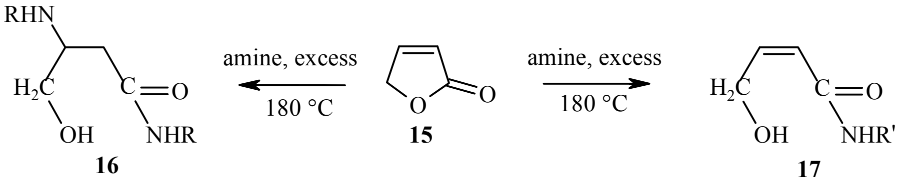
1620 cm^{-1} for compound **7** and weak bands in the region of 1598-1590 cm^{-1} for compounds **8-13**. There are weak broad absorption bands for the stretching vibrations of the combined amino group at 3500-3200 cm^{-1} for compounds **7-13**. In compound **13**, where there is an OH group, the ν_{NH} band is superimposed on the ν_{OH} band, which increases the intensity of the absorption in this range of frequencies. In the spectra there are two absorption bands for the stretching vibrations of the benzene ring at 1610-1605 and 1510-1500 cm^{-1}. The low-intensity absorption band of the benzene ring is superimposed on the ν_{as} band of the NO_2 group and has fairly high intensity. The symmetrical stretching vibrations of the NO_2 group lie in the region of 1328-1321 cm^{-1}.

The UV spectra of compounds **7-9**, **11-14** (Table 1) have identical character, demonstrating the identity of the conjugated system. Evidence for the presence of the conjugated system is provided by the bathochromic shifts of the absorption bands of the NO_2 and C=O groups and also of the benzene ring. In the region of 250-600 nm there are strong maxima at 370 nm with a long-wave shoulder at 423 nm and a less short-wave absorption band at 312 nm. Maxima at 370 and 423 nm belong to the $n\rightarrow\pi^*$ transitions. In all probability the absorption band at 423 nm belongs to the NO_2 group, while the maximum at 370 nm belongs to a charge-transfer band due to the C=O group. An absorption band at 312 nm belongs to the $\pi\rightarrow\pi^*$ transition of the benzene ring.

The proposed assignment of the bands is confirmed by the fact that during acidification of the solutions of these substances there is some decrease in the intensity and a short-wave shift of 5 nm in the absorption bands at 423 and 370 nm, whereas the absorption band at 312 nm remains unchanged.

In order to extend the range of biologically active substances we undertook the synthesis of N-substituted amides of 3-arylamino-4-hydroxybutyric acid from 2(5H)-furanone (**15**) and aromatic amines (Scheme 3).

Scheme 3



16 R = 2,6-$Me_2C_6H_3$, **17** R' = 3-$CF_3C_6H_4$

The reaction was conducted in an excess of the amine in sealed tubes at 180°C. 2,6-Dimethylaniline, *m*-trifluoromethylaniline, *o*-aminophenol, and *o*-methoxyaniline were used as amines.

It was established that 2(5H)-furanone does not react with *o*-aminophenol as a result probably of the reduced basicity of the amine on account of the formation of an intramolecular hydrogen bond. With *o*-methoxyaniline it forms a mixture of products, which could not be separated.

The reaction of 2(5H)-furanone with 2,6-dimethylaniline leads to the formation of the N-(2,6-dimethylphenyl)amide of 4-hydroxy-3-(2,6-dimethylphenylamino)butyric acid (**16**). The structure of **16** was confirmed by the IR spectrum (Table 1), containing two strong amide bands in the region of 1640 ($\nu_{C=O}$) and 1525 (δ_{NH}) cm^{-1}, absorption bands in the region of 3255 cm^{-1} belonging to the stretching vibrations of the NH group, and two bands for the stretching vibrations of the benzene ring at 1495 and 1605 cm^{-1}. The ease with which the reaction with 2,6-dimethylaniline occurs can be explained by its increased basicity on account of the electron-donating effect of the *o*-methyl groups.

The reaction of 2(5H)-furanone with *m*-trifluoromethylaniline only leads to aminolysis of the lactone ring with the formation of the N-(3-trifluoromethylphenyl)amide of 4-hydroxy-2-butenoic acid (**17**). The purity of the product was demonstrated by TLC (Table 2), and the structure was confirmed by spectral methods (Table 1).

TABLE 1. The Spectral Characteristics of Compounds **3-14**, **16**, **17**

Compound	IR spectrum, cm^{-1}						UV spectrum, log ε at λ, nm		
	$\nu_{C=O}$	ν_{NH}	δ_{NH}	ν_{arom}	$\nu_{as\ NO_2}$	$\nu_{s\ NO_2}$	312	370	423
3	1645	3303	1555	1605, 1505	1510	1326			
4	1635	3315	1560	1605, 1505	1515	1323			
5	1645	3300	1525	1590, 1505	*	*			
6	1630	3307	1550	1605, 1505	*	*			
7	1700	3500-3200	1620	1605, 1510	1510	1328	3.98	4.29	4.22
8	1695	3500-3350	1598	1605, 1503	1503	1324	4.14	4.48	4.41
9	1690	3510-3350	1590	1605, 1500	1500	1326	3.94	4.37	3.99
10	1695	3500-3320	1595	1610, 1505	1505	1324			
11	1695	3510-3330	1595	1607, 1503	1503	1322	4.09	4.39	4.19
12	1700	3500-3380	1595	1605, 1505	1505	1325	4.04	4.38	4.08
13	1690	3500-3200	1590	1605, 1505	1505	1326	3.96	4.21	4.20
14	1697			1605, 1505	1520	1321	4.18	4.45	4.17
16	1640	3255	1525	1605, 1495					
17	1693	3400-3100	1543	1603, 1500					

---

* Compounds **5**, **6**: $\nu_{as\ SO_2}$ 1350, $\nu_{s\ SO_2}$ 1170 cm^{-1}.

TABLE 2. The Characteristics of Compounds **3-14**, **16**, **17**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f	Yield, %
		C	H	N			
3	$C_{23}H_{26}N_4O_3$	68.02 67.98	6.42 6.40	13.77 13.79	120	0.48	84
4	$C_{18}H_{30}N_4O_3$	61.74 61.71	8.55 8.57	16.05 16.00	99	0.15	81
5	$C_{24}H_{28}N_4O_3S$	63.66 63.72	6.12 6.19	12.72 12.38	140	0.38	92
6	$C_{18}H_{32}N_4O_3S$	56.21 56.25	8.37 8.33	14.63 14.58	142	0.19	88
7	$C_{10}H_{11}N_3O_3$	54.33 54.29	5.04 4.98	19.11 19.01	329	0.51	38
8	$C_{12}H_{15}N_3O_3$	57.91 57.83	6.11 6.02	16.81 16.87	319	0.31	45
9	$C_{14}H_{19}N_3O_3$	60.71 60.65	6.89 6.86	15.07 15.16	323	0.33	40
10	$C_{14}H_{19}N_3O_3$	60.69 60.65	6.90 6.86	15.09 15.17	326	0.38	28
11	$C_{16}H_{21}N_3O_3$	63.41 63.37	6.21 6.27	13.97 13.86	246	0.36	39
12	$C_{17}H_{17}N_3O_3$	65.31 65.38	5.49 5.45	13.37 13.46	321	0.41	41
13	$C_{13}H_{17}N_3O_4$	56.02 55.91	6.14 6.09	15.01 15.05	262	0.17	40
14	$C_{14}H_{19}N_3O_3$	60.69 60.65	6.89 6.86	15.05 15.16	223	0.79	36
16	$C_{20}H_{26}N_2O_2$	73.53 73.62	7.86 7.97	8.63 8.58	306	0.18	47
17	$C_{11}H_{10}F_3NO_2$	53.81 53.87	4.13 4.08	5.79 5.71	205	0.23	45

A special feature of the IR spectrum of compound **17** is the presence of a $\nu_{C=C}$ band at 1645 cm^{-1}. The band for the stretching vibrations of the amide carbonyl group is in the region of 1693 cm^{-1}. The shift of the frequency of the stretching vibrations of the carbonyl group of the amide fragment can probably be explained by the negative inductive effect of the *m*-trifluoromethylphenyl substituent, the presence of which leads to an increase in the conjugation between the amide nitrogen atom and the benzene ring and destroys its conjugation with the carbonyl group. As a result the $\nu_{C=O}$ band acquires the character of the absorption of a normal α,β-unsaturated carbonyl fragment. Strong δ_{NH} absorption bands are observed at 1543 cm^{-1}, while the ν_{NH} stretching vibrations are superimposed on the ν_{OH} stretching vibrations in the region of 3400-3100 cm^{-1} in the form of a broad strong band. The spectrum also contains bands for the stretching vibrations of the benzene ring (1603 and 1500 cm^{-1}), while strong bands in the region of 1400-1050 cm^{-1} indicate the presence of fluorine atoms in the molecule.

EXPERIMENTAL

The IR spectra were recorded in vaseline oil and methylene chloride on UR-20 and IKS-29 instruments. The UV spectra were obtained in methylene chloride on a Specord M-40 instrument. Thin-layer chromatography was conducted on Silufol 20-H plates (2:1:0.5 acetone–carbon tetrachloride–petroleum ether and 3:10 ethanol–toluene, detection with the vapor of crystalline iodine and 2,4-dinitrophenylhydrazine hydrochloride). The characteristics and yields of the compounds synthesized for the first time are given in Tables 1 and 2.

3-Substituted Amides of 3-Alkyl(benzyl)amino-4-(4-R-anilino)butyric Acids (3-6). The amine (70 mmol) was placed in a three-necked flask with a reflux condenser, a stirrer, and a thermometer. The mixture was heated to 50°C and then compound **1** (0.3 g, 1.47 mmol) was added. The reaction mixture was heated for 30 min with vigorous stirring and thermostating (50±2°C). The mixture was cooled, and the crystals that separated after seven days were washed with diethyl ether and recrystallized from a mixture of acetone and water. The crystals were filtered off and washed with hexane. Yields 81-92%.

4-Amino-1-(4-nitrophenyl)pyrrolid-2-one (7). Compound **1** (0.5 g, 2.5 mmol) and DMF (20 ml) were placed in a flask. Gaseous ammonia, released by heating of a 20% solution of ammonia (60 ml), was passed into the reaction mixture, which had been heated to 90°C, for 2 h with stirring. The reaction mixture was then cooled with stirring. The crystals that separated were filtered off and washed with acetone and diethyl ether. Yield 2.09 g (38%).

4-Alkylamino-1-(4-nitrophenyl)pyrrolid-2-ones (8-14). To a solution of compound **1** (0.5 g, 2.5 mmol) in DMF (20 ml) the amine (7.5 mmol) was added. The reaction mixture was heated with stirring for 2 h, while the temperature was kept at 90±2°C, and was then cooled with stirring. The crystals were filtered off and washed with acetone and with diethyl ether. Yields 28-45%.

N-(2,6-Dimethylphenyl)amide of 4-Hydroxy-3-(2,6-dimethylphenylamino)butyric Acid (16). A mixture of compound **15** (1.68 ml, 20 mmol) and 2,6-dimethylaniline (7.26 ml, 60 mmol) was sealed into a glass tube and heated on an oil bath at 180±2°C for 6 h. The orange-brown liquid that formed was distilled under vacuum, and two fractions were obtained. The first was the initial 2,6-dimethylaniline, and the second was a white crystalline substance. Yield 2.79 g (47%).

N-(3-trifluoromethylphenyl)amide of 4-Hydroxy-2-butenoic Acid (17). A mixture of compound **15** (1.68 ml, 20 mmol) and *m*-trifluoromethylaniline (9.66 ml, 60 mmol) was sealed in a glass tube and heated on an oil bath at 180±2°C for 6 h. The liquid mixture was distilled under vacuum, and a white crystalline substance was obtained. Yield 2.21 g (45%).

REFERENCES

1. L. A. Badovskaya, Z. I. Tyukhteneva, and Yu. V. Naidenov, in: *Chemistry for Medicine and Veterinary Science* [in Russian], Sb. Nauch. Tr. Sarat. Gos. Un-ta, Saratov (1998), p. 7.
2. V. A. Sedavkina and N. A. Morozova, *Khim. Geterotsikl. Soedin.*, 331 (1972).
3. A. A. Ponomarev and V. A. Sedavkina, *Khim. Geterotsikl. Soedin.*, 809 (1969).
4. N. A. Morozova, V. A. Sedavkina, and A. Yu. Egorova, *Khim. Geterotsikl. Soedin.*, 349 (1994).
5. V. A. Sedavkina, N. A. Morozova, and A. Yu. Egorova, in: *Chemistry and Technology of Furan Compounds* [in Russian], Sb. Nauch. Tr. Kuban. Gos. Tekhn. Un-ta, Krasnodar (1995), p. 21.
6. I. K. Kalnin' and E. Yu. Gudrinietse, *Khim. Geterotsikl. Soedin.*, 867 (1972).
7. M. Semonsky, A. Cerny, B. Kakac, and V. Subrt, *Coll. Czech. Chem. Commun.*, **28**, 3278 (1963).