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AMINOLYSIS OF 5-PHENYL-2-TETRAZOLYLACETIC ACID ETHYL ESTER

S. M. Putis, V. Yu. Zubarev, V. S. Poplavskii, and V. A. Ostrovskii

It was shown using 5-phenyl-2-tetrazolylacetic acid ethyl ester as an example that aminolysis is a competitive method of synthesizing primary amides. The efficiency of aminolysis by primary amines is linked to the basicity of the initial amine. Highly basic amines display more high reactivity independent of the spatial structure of the substituent. Reaction of the investigated ester with secondary amines occurs ambiguously.

Keywords: 5-phenyl-2-tetrazolylacetamides, 5-phenyl-2-tetrazolylacetic acid ethyl ester, aminolysis.

The tetrazolylacetic acids are extremely attractive subjects in the chemistry of heterocyclic compounds. They are considered as block reagents containing a tetrazole ring for the directed synthesis of biologically active substances [1]. Methods of synthesizing tetrazolylacetic acids have been developed in fair detail [2,3]. The acid–base properties of the isomeric tetrazolylacetic acids have been studied [4,5] and the electronic influence of a tetrazole substituent on the acidity of the carboxyl group has been assessed quantitatively.

The amides of tetrazolylacetic acids are distinct and of significant interest as reagents for the directed synthesis of biologically active compounds. For example, β-lactam antibiotics of the cephalosporin series are used widely (cefazolin and its analogs) and are derivatives of tetrazolylacetic acid amides.

There are practically no known methods for the convenient and universal synthesis of tetrazolylacetic acid amides. Usually the reaction of difficultly accessible tetrazolylacetic acid halides with the appropriate amine is used for this purpose [6]. We have suggested that aminolysis of tetrazolylacetic acid esters can be used for this purpose. The reactions of 5-phenyltetrazolylacetic acid ethyl ester with primary and secondary amines have been considered in the present work to check this hypothesis. Amines used for aminolysis were primary amines of the simplest structure, ammonia, methylamine, and ethylamine, bifunctional primary amines, hydrazine and ethylenediamine, and primary amines containing cyclic and frame substituents, cyclohexylamine and 1-adamantylamine. Secondary amines involved in the aminolysis of 5-phenyl-2-tetrazolylacetic acid ethyl ester were dimethylamine and diethylamine. The process of aminolysis was carried out in a medium of methanol with a 1.5 to 10 fold molar excess in relation to tetrazolylacetic acid ester. An excess of ester **1** was taken to provide efficient aminolysis with ethylenediamine.

St. Petersburg State Technological Institute (Technical University), Saint Petersburg 198013, Russia; e-mail: ostrovskii@mail.convey.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 759-762, June, 2001. Original article submitted November 16, 2000.

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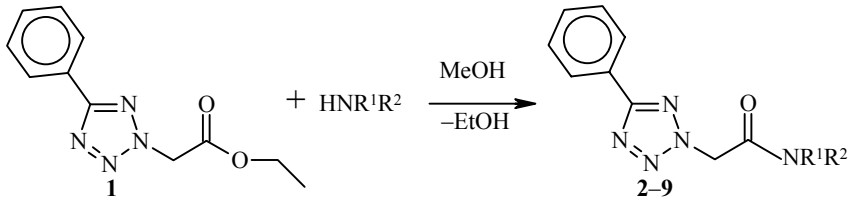
TABLE 1. ^{1}H and ^{13}C NMR Spectra of the Amides **2-9** Synthesized

Compound	Chemical shifts of the ^{1}H NMR signals, δ, ppm				Chemical shifts of the ^{13}C NMR signals, δ, ppm				
	$C_6\underline{H}_5$	$N_{(2)}–C\underline{H}_2$	N<u>H</u>	other signals	C=O	CN_4	C_6H_5	$N_{(2)}–CH_2$	other signals
2	7.55-7.85	5.50	8.10	—	166.9	165.0	131.4; 130.1; 127.8; 127.2	55.5	—
3	7.55-8.08	5.45	9.65	4.80 (2H, s, $N\underline{H}_2$)	165.1	164.8	131.5; 130.1; 127.7; 127.2	54.6	—
4	7.50-8.03	5.48	8.45	2.68 (3H, s, $C\underline{H}_3$)	165.4	165.0	131.4; 130.1; 127.7; 127.2	55.6	26.6 ($\underline{C}H_3$)
5	7.50-8.05	5.90	—	2.87 (3H, s, $C\underline{H}_3$); 3.10 (3H, s, $C\underline{H}_3$)	165.3	164.8	131.4; 130.2; 127.8; 127.1	54.9	36.8 ($\underline{C}H_3$); 36.1 ($\underline{C}H_3$)
6	7.55-8.05	5.50	8.50	1.05 (3H, t, $C\underline{H}_3$); 3.15 (2H, q, $C\underline{H}_2$)	165.4	164.6	131.5; 130.2; 127.7; 127.2	55.7	34.7 ($\underline{C}H_2$); 15.3 ($\underline{C}H_3$)
7	7.55-8.05	5.50	8.40	1.25 (5H, s, $C\underline{H}_2$); 1.70 (5H, s, $C\underline{H}_2$); 2.47 (1H, s, C<u>H</u>)	164.9	163.8	131.4; 130.1; 127.7; 127.2	55.7	48.9 (4-$\underline{C}H_2$); 33.1 (3-$\underline{C}H_2$); 26.0 (2-$\underline{C}H_2$); 25.2 (<u>C</u>H)
8	7.55-7.95	5.05	8.10	1.55 (6H, s, $C\underline{H}_2$); 1.70 (6H, s, $C\underline{H}_2$); 2.05 (3H, s, C<u>H</u>)	167.0	164.1	131.0; 130.0; 128.4; 127.0	57.8	51.3 ($\underline{C}_{quat}$); 36.0 (<u>C</u>H in Ad*); 29.2 ($\underline{C}H_2$ in Ad)
9	7.50-8.05	5.50	8.63	3.25 (4H, s, CON–$C\underline{H}_2$)	165.3	165.0	131.5; 130.1; 127.7; 127.2	55.6	39.2 (CON–$\underline{C}H_2$)

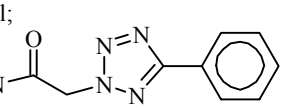
* Ad = 1-adamantyl.



2 $R^1 = R^2 = H$; **3** $R^1 = H$, $R^2 = NH_2$; **4** $R^1 = H$, $R^2 = Me$;

5 $R^1 = R^2 = Me$; **6** $R^1 = H$, $R^2 = Et$; **7** $R^1 = H$, $R^2 = cyclo\text{-}C_6H_{11}$;

8 $R^1 = H$, R^2 = 1-adamantyl;

9 $R^1 = H$, $R^2 = CH_2CH_2HN$ 

All the primary amines investigated form the corresponding amide in good yield in the reaction. It is interesting that the presence of a bulky substituent in the initial primary amine did not in practice inhibit the aminolysis process. In the case of ethylenediamine, in spite of the significant difference in basicity of the amino groups, aminolysis leads to the preparation of the disubstitution product.

A completely different picture was observed on aminolysis with certain secondary amines. The appropriate secondary amide was formed by reaction of ester **1** with dimethylamine. Replacement of dimethylamine by diethylamine leads to the formation of 5-phenyl-2-tetrazolylacetic acid methyl ester and products of its further conversion.

It may be assumed that the aminolysis conditions proposed by us can be used for the synthesis of primary amides of tetrazoleacetic acid of various structure. Other methods may turn out to be preferable for secondary amides.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of the compounds synthesized were recorded on a Bruker DPX 300 instrument in DMSO-d_6 (300 MHz for ^1H and 75 MHz for ^{13}C), internal standard was TMS. The IR spectra were obtained on a Perkin–Elmer Spectrum 1000 instrument in KBr disks. Melting points were determined on a type PTP instrument with a heating rate of 1°/min in the melting range. A check on the progress of reactions was effected by TLC on Merck Kieselgel $60F_{254}$ plates with visualization of spots in UV light. The initial substrate **1** was obtained by the procedure of [7].

General Procedure for Obtaining Amides 2-9. A methanolic or aqueous solution of amine was added to a solution of substrate **1** (4.31 mmol) in methanol (40 ml) at 0-2°C. Amide numbers (molar ratio amine : ester **1**) are **2** (10), **3** (10), **4** (10), **5** (9), **6** (9.5), **7** (10), **8** (2), and **9** (0.3). At the end of the reaction (check by TLC) the reaction solution was processed by procedure A or B. A. The precipitated solid was filtered off and washed with distilled water (3 × 20 ml). B. The solvent was evaporated in vacuum, and the residue was recrystallized from aqueous ethanol.

5-Phenyl-2-tetrazolylacetic Acid Amide (2). Amide **2** (0.5 g, 57%) of mp 185-186°C was obtained by crystallization from 30% aqueous alcohol (A), R_f 0.17 ($CHCl_3$–MeOH, 95 : 5). IR spectrum, ν, cm^{-1}: 1405, 1270, 1172, 1100 (tetrazole), 1448, 730 (C_6H_5), 1670 (C=O), 3314 (N–H), 2950, 1425 (CH_2), 1373, 1072, 1047 (C–N). Found, %: C 52.93; H 4.66; N 34.64. $C_9H_9N_5O$. Calculated, %: C 53.20; H 4.46; N 34.47.

5-Phenyl-2-tetrazolylacetic Acid Hydrazide (3). Hydrazide **3** (0.91 g, 93%) of mp 207-208°C was obtained by crystallization from 10% aqueous ethanol (A), R_f 0.15 ($CHCl_3$–MeOH, 95 : 5). IR spectrum, ν, cm^{-1}: 1411, 1285, 1177, 1100 (tetrazole), 1448, 730 (C_6H_5), 1661 (C=O), 3314, 1551, 1529 (N–H), 2966, 2880 (CH_2), 1379, 1072 1023, (C–N). Found, %: C 49.12; H 4.78; N 38.73. $C_9H_{10}N_6O$. Calculated, %: C 49.54; H 4.62; N 38.51.

5-Phenyl-2-tetrazolylacetic Acid N-Methylamide (4). Amide **4** (0.36 g, 37%) of mp 163-164°C was obtained by crystallization from 20% aqueous ethanol (A), R_f 0.35 ($CHCl_3$–MeOH, 95 : 5). IR spectrum, ν, cm^{-1}: 1404,1278, 1163, 1101 (tetrazole), 1449, 731 (C_6H_5), 1660 (C=O), 3303, 1578, 1528 (N–H), 2964, 2888 (CH_2), 1388, 1073, 1025 (C–N). Found, %: C 55.65; H 5.57; N 32.26. $C_{10}H_{11}N_5O$. Calculated, %: C 55.29; H 5.10; N 32.24.

5-Phenyl-2-tetrazolylacetic Acid N,N-Dimethylamide (5). Amide **5** (0.65 g, 65%) of mp 133-134°C was obtained by crystallization from 10% aqueous ethanol (B), R_f 0.36 ($CHCl_3$–MeOH, 95 : 5). IR spectrum, ν, cm^{-1}: 1401, 1283, 1180, 1130 (tetrazole), 1451, 735 (C_6H_5), 1662 (C=O), 2969, 2933 (CH_2), 1378, 1071, 1029 (C–N). Found, %: C 56.95; H 5.97; N 30.06. $C_{11}H_{13}N_5O$. Calculated, %: C 57.13; H 5.67; N 30.28.

5-Phenyl-2-tetrazolylacetic Acid N-Ethylamide (6). Amide **6** (0.86 g, 86%) of mp 151-152°C was obtained by crystallization from 25% aqueous ethanol (A), R_f 0.45 ($CHCl_3$–MeOH, 95 : 5). IR spectrum, ν, cm^{-1}: 1406, 1277, 1173, 1102 (tetrazole), 1447, 729 (C_6H_5), 1660 (C=O), 3287, 1560, 1527 (N–H), 2954, 2882 (CH_2), 1381, 1070, 1022 (C–N). Found, %: C 57.69; H 6.01; N 30.67. $C_{11}H_{13}N_5O$. Calculated, %: C 57.13; H 5.67; N 30.28.

5-Phenyl-2-tetrazolylacetic Acid N-Cyclohexylamide (7). Amide **7** (0.71 g, 58%) of mp 173-174°C was obtained by crystallization from 50% aqueous ethanol (B), R_f 0.62 ($CHCl_3$–MeOH, 95 : 5). IR spectrum, ν, cm^{-1}: 1421, 1279, 1171, 1091 (tetrazole), 1447, 728 (C_6H_5), 1654 (C=O), 3291, 1556, 1528 (N–H), 2938, 2851 (CH_2), 1371, 1072, 1024 (C–N). Found, %: C 63.64; H 6.72; N 24.97. $C_{15}H_{19}N_5O$. Calculated, %: C 63.14; H 6.71; N 24.54.

5-Phenyl-2-tetrazolylacetic Acid N-1-Adamantylamide (8). Amide **8** (0.91 g, 54%) of mp 263-264°C was obtained by crystallization from 20% aqueous ethanol (B), R_f 0.15 ($CHCl_3$–MeOH, 9 : 1). IR spectrum, ν, cm^{-1}: 1418, 1279, 1177, 1110 (tetrazole), 1452, 730 (C_6H_5), 1632 (C=O), 1562, 1529 (N–H), 3006, 2935, 2912, 2853 (CH_2 and CH), 1073, 1026 (C–N). Found, %: C 66.98; H 6.83; N 20.23. $C_{19}H_{23}N_50$. Calculated, %: C 67.63; H 6.87; N 20.76.

N,N'-Bis(5-phenyl-2-tetrazolylmethylcarbonyl)-1,2-diaminoethane (9). Amide **9** (0.83 g, 44%) of mp 255-256°C was obtained by crystallization from 40% aqueous ethanol (A), R_f 0.55 ($CHCl_3$–MeOH, 9 : 1). IR spectrum, ν, cm^{-1}: 1415, 1284, 1194, 1104 (tetrazole), 1449, 728 (C_6H_5), 1664 (C=O), 3296, 1576, 1528 (N–H), 2953, 2875 (CH_2), 1364, 1072, 1027 (C–N). Found, %: C 55.77; H 4.44; N 32.61. $C_{20}H_{20}N_{10}O_2$. Calculated, %: C 55.55; H 4.66; N 32.39.

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