SYNTHESIS OF THE NEW SERIES OF NOVEL HETEROCYCLIC SKELETON ISOXAZOLO [4,5-e] 1,2,4-TRIAZINES AND NEW SERIES OF THE PYRAZOLO [4,3-e] 1,2,4-TRIAZINES.

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Summary. Nitrosation and coupling reactions on the active methylene group of the 3-substituted-5-(substituted benzyl)-6-oxo-1,6-dihydro-1,2,4-triazines gave oximes and arylhydrazones of the 3-substituted-5-(substituted benzoyl)-6-oxo-1,6-dihydro-1,2,4-triazines. These compounds were cyclized to the 3,5-disubstituted isoxazolo [4,5-e] 1,2,4-triazines and 3-methyl-5,7-diaryl pyrazolo [4,3-e] 1,2,4-triazines.

Keywords. Pyrazolo [4,3-e] 1,2,4-triazines, isoxazolo [4,5-e] 1,2,4-triazines

Introduction

In this work we investigated the possibility of nitrosation reaction on the active methylene group of the compounds **1**[1,2]. This reaction leads to the oximes **3** that we have also prepared in other way using reaction of the previously described dichloroderivates **2a**, **2b**[3] with hydroxylamine in water-ethanolic solution. In both cases the reaction proceeds smoothly.

The compounds **3** are useful precursors for cyclization reaction to the 3,5-disubstituted isoxazolo [4,5-e] 1,2,4-triazines. This condensed bicyclic system has not been described till the present time.

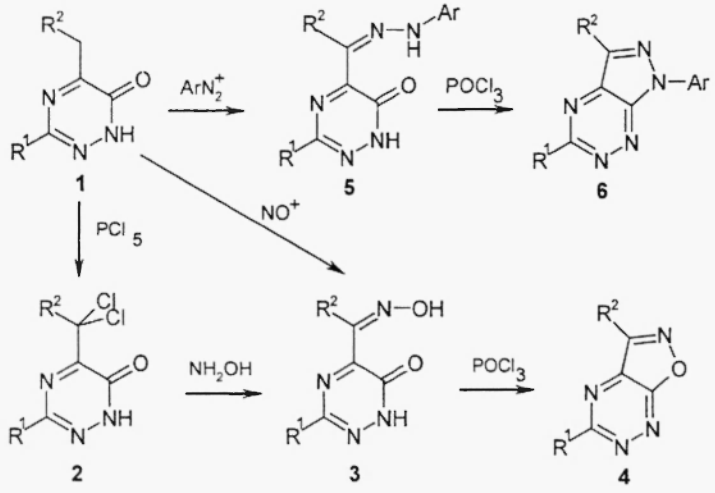
The arylhydrazones **5** are obtained in good yield and purity in the coupling reaction with aryldiazonium salts on the active methylene group of the compounds **1c**, **1d**. Similarly to the compounds **3** they are easily cyclized to the 3-methyl-5,7-diaryl pyrazolo [4,3-e] 1,2,4-triazines.

There has already been published the serie of these 3-phenyl-5,7-diaryl pyrazolo [4,3-e] 1,2,4-triazines[4]. We now report analogous synthesis of the new serie of the 3-methyl-5,7-diaryl pyrazolo [4,3-e] 1,2,4-triazines.

Results and discussion.

The constitution of all newly synthetised compounds was determined with elemental analyses, infrared spectra and ^{1}H-NMR spectra of selected compounds. Table 1 summarizes chemical and physical data of newly synthetised compounds. Table 2 gives ^{1}H-NMR data of selected compounds and Table 3 IR frequencies of **3a-6c**. The absence of carbonyl group signal for compounds **4** and **6** proves the cyclization. We have unsuccesfully tried a few cyclization media for the cyclization: polyphosphoric acid, acetic anhydride, acetic acid and various mixtures of acetic acid and ethanol. However phosphorus oxychloride closes new ring during short reflux and compounds **4** or **6** are formed. The cyclization reaction performed in the polyphosphoric acid leads to impure products.

Scheme 1.



1	R^1	R^2	2	R^1	R^2	3,4	R^1	R^2	5,6	R^1	R^2	Ar
a	C_6H_5	C_6H_5	a	C_6H_5	C_6H_5	a	C_6H_5	C_6H_5	a	CH_3	C_6H_5	C_6H_5
b	C_6H_5	4-Cl-C_6H_4	b	C_6H_5	4-Cl-C_6H_4	b	C_6H_5	4-Cl-C_6H_4	b	CH_3	C_6H_5	4-NO_2-C_6H_4
c	CH_3	C_6H_5				c	CH_3	4-Cl-C_6H_4	c	CH_3	C_6H_5	4-Cl-C_6H_4
d	CH_3	4-Cl-C_6H_4							d	CH_3	C_6H_5	2-MeO- C_6H_4
									e	CH_3	4-Cl-C_6H_4	C_6H_5
									f	CH_3	4-Cl-C_6H_4	4-NO_2-C_6H_4
									g	CH_3	4-Cl-C_6H_4	4-Cl-C_6H_4

Table 1. Physical and chemical data of **3a-6c.**

Compound	Formula	M. w.	M.P.(°C) (solvent)	Yield (%)	Elemental Analysis Calcd.(Found)		
					%C	%H	%N
3a	$C_{16}H_{12}N_4O_2$	293.18	217-220 E*	96**A** 28**B**	65.8(66.0)	4.1(4.0)	19.2(19.0)
3b	$C_{16}H_{11}N_4O_2$	327.55	232-234 E	90**A** 33**B**	58.8(58.7)	3.4(3.6)	17.2(17.0)
3c	$C_{11}H_{12}N_4O_2Cl$	265.32	194-195 E	92**A**	49.9(50.1)	3.4(3.5)	21.2(21.1)
4a	$C_{16}H_{10}N_4O$	274.29	163-165 E	88	70.1(69.7)	3.7(3.9)	20.4(20.6)
4b	$C_{16}H_9N_4OCl_2$	308.74	211-213 E	85	62.3(62.0)	2.9(2.7)	18.2(18.0)
4c	$C_{11}H_9N_4OCl$	246.66	127-128 E	78	53.6(53.8)	2.9(2.8)	22.7(22.6)
5a	$C_{17}H_{15}N_5O$	305.36	125-126 E	63	66.9(66.7)	5.0(4.8)	22.9(22.8)
5b	$C_{17}H_{14}N_6O_3$	350.36	143-145 E-B*	75	58.3(58.4)	4.0(3.8)	24.0(23.8)
5c	$C_{17}H_{14}N_5OCl$	339.80	175-177 T*	86	60.1(60.0)	4.1(3.9)	20.6(20.5)
5d	$C_{18}H_{17}N_5O_2$	335.38	181-182 E	89	64.5(64.4)	5.1(5.1)	20.9(20.6)
5e	$C_{17}H_{14}N_5OCl$	339.80	217-219 E	59	60.1(60.2)	4.2(4.4)	20.6(20.5)
5f	$C_{17}H_{13}N_6O_3Cl$	384.80	238-240 E-B	66	53.1(53.3)	3.4(3.2)	21.6(21.7)
5g	$C_{17}H_{13}N_5OCl_2$	374.24	151-153 E	84	54.6(54.6)	3.8(3.7)	18.7 (18.9)
6a	$C_{17}H_{13}N_5$	287.34	141-143 E	96	71.1(71.3)	4.6(4.5)	24.4(24.1)
6b	$C_{17}H_{12}N_6O_2$	332.34	214-216 E	92	61.4 (61.3)	3.6(3.5)	21.1(21.0)
6c	$C_{17}H_{12}N_5Cl$	321.78	184-185 E	95	63.5(63.3)	3.8(3.5)	21.8(21.1)
6d	$C_{18}H_{15}N_5O$	317.36	173-175 E	94	68.1(68.1)	3.8(3.9)	21.8(22.0)
6e	$C_{17}H_{12}N_5Cl$	321.78	121-123 E	97	63.5(63.6)	3.8(3.6)	21.8(21.8)
6f	$C_{17}H_{11}N_6O_2Cl$	366.78	194-195 E	92	57.3 (57.5)	3.1(3.0)	19.7(19.5)
6g	$C_{17}H_{11}N_5Cl_2$	356.22	247-248 E	93	55.7(55.4)	3.0(3.2)	22.9(22.8)

*: E= ethanol, E-B= ethanol-benzene (1:1), T= toluene.

Table 2. ^{1}H-NMR data of selected compounds (δ in ppm).

Compound	^{1}H-NMR spectrum
4c	3.13(s, 3H, CH_3); 7.60(m, 1H, ArH); 7.68(m, 2H, ArH); 7.80(d, 2H, J = 8.98, ArH); 8.49(d, 2H, J = 8.97 , ArH); 8.55(d, 2H, J = 7.11, ArH)
4d	3.12(s, 3H, CH_3); 3.81(s, 3H, OCH_3);7.26(t, 1H, J = 7.65, ArH); 7.43(d, 1H, J = 7.56, ArH); 7.57(t, 1H, J = 7.44, ArH); 7.71(m, 4H, ArH); 8.49(d, 2H, J = 7.09, ArH)
4e	3.10(s, 3H, CH_3); 7.49(t, 1H, J = 7.42, ArH); 7.70(m, 4H, ArH); 8.37(dd, 2H, J1 = 7.82, J2 = 6.67, ArH); 8.49(d, 2H, J = 8.69, ArH)
4g	3.13(s, 3H, CH_3); 7.75(d, 2H, J = 8.70, ArH); 7.79(d, 2H, J = 9.02, ArH); 8.46(d, 2H, J = 9.01, ArH); 8.54(d, 2H, J =8.70, ArH)
5a	7.50(m, 3H, ArH); 7.62(m, 1H, ArH); 7.98(m, 1H, ArH); 12.53(s, 1H, NH); 13.75(Brs, 1H, OH)
5b	7.50(m, 3H, ArH); 7.55(d, 2H, J = 8.66 , ArH); 7.67(d, 2H, J = 8.61 , ArH); 7.97(m, 2H, ArH); 12.71(s, 1H, NH); 13.70(Brs, 1H, OH)
6a	7.76(m, 6H, ArH); 8.54(dd, 2H, J1 = 5.94, J2 = 2.24); 8.64(dd, 2H, J1 = 6.0, J2 = 2.39, ArH)
6b	7.72(t, 3H, J = 3.30, ArH); 7.87(d, 2H, J = 8.69, ArH); 8.55(d, 2H, J = 8.66, ArH); 8.64(m, 2H, ArH)
6c	3.12(s, 3H, CH_3); 7.83(d, 2H, J = 8.62 , ArH); 8.43(d, 2H, J = 8.63, ArH)

Table 3. IR frequencies of **3a-6c**.

Compound	IR spectrum
3a	3127, 2938, 2813, 1672, 1601, 1538, 1496, 1387, 1236, 1199, 903, 745, 689
3b	3024, 2845, 1679, 1596, 1516, 1439, 1385, 1252, 1193, 900, 743, 701
3c	3203, 3067, 2873, 1660, 1562, 1495, 1443, 1239, 1138, 1090, 834, 700
3d	2922, 1686, 1596, 1489, 1323, 1258, 1111, 1000, 852
3e	3023, 2927, 1668, 1525, 1493, 1381, 1239, 1203, 903, 832
3f	3063, 2887, 1649, 1591, 1490, 1426, 1246, 1145, 1089, 998, 833, 706, 605
3g	1686, 1558, 1485, 1323, 1258, 1111, 852
4a	1595, 1499, 1459, 1433, 1272, 1132, 759, 686
4b	1602, 1509, 1436, 1294, 1250, 1141, 1026, 758, 694
4c	1595, 1497, 1438, 1270, 1134, 1089, 978, 831
4d	1596, 1519, 1437, 1352, 1272, 1114, 852, 687
4e	1598, 1499, 1427, 1267, 1130, 1083, 975, 835, 750, 682
4f	1578, 1499, 1435, 1407, 1271, 1131, 1088, 976, 845, 691
4g	1594, 1499, 1412, 1340, 1080, 851
5a	3297, 3029, 2890, 1660, 1552, 1446, 1241, 1027, 847, 694
5b	3314, 3064, 2932, 1657, 1549, 1491, 1359, 1087, 1011, 817, 607
5c	3128, 1669, 1562, 1489, 1329, 120, 1088, 103, 914, 821
6a	1598, 1470, 1424, 1365, 1095, 1055, 993, 865, 724
6b	1453, 1369, 1331, 1056, 857, 709, 692
6c	1473, 1425, 1354, 1094, 867, 841

Experimental

Melting points were determined on a Boetius block and are uncorrected. The IR spectra were recorded with an AT1 Unicam Genesis FTIR using KBr pellets. Elemental analyses were determined with an EA 1108 Elemental Analyser (Fisons Instrument). ^{1}H-NMR spectra were recorded on a Bruker AMX 300 NMR spectrometer.

Synthesis of arylhydrazones of the 3-substituted-5-(substituted benzoyl)-6-oxo-1,6-dihydro-1,2,4-triazines 5 – General procedure:

Preparation of the aryldiazonium salt:

To a cooled and mixed solution of the substituted aniline (3.00 mmol) in a mixture of water (4.5mL) and concentrated hydrochloric acid (0.5 mL) is slowly added a cooled solution

of sodium nitrite (3.10 mmol) in water (5 mL). During the additon is the temperature maintained between 0-5 °C. The mixture is then stirred for 20 minutes on the ice-bath and immediately used.

A solution of aryldiazonium salt is then slowly added to a stirred solution of 3-substituted-5-arylmethylene-6-oxo-1,6-dihydro-1,2,4-triazine (3.0 mmol) in pyridine (25 mL) keeping temperature between 0-3°C. The mixture is kept for 24 hours at 0°C and than dilluted with water (15 mL). Precipitate is filtered off, washed with water and recrystallized from (see Table 1).

Synthesis of oximes of the 3-substituted-5-(substituted benzoyl)-6-oxo-1,6-dihydro-1,2,4-triazines 3 – General procedure **A**:

Preparation of the nitrosylsulphuric acid:

A concentrated sulphuric acid (5.0 mL) is cooled on an ice-bath to 5°C and sodium nitrite (6.00 mmol, 0,414g) is added with stirring in a few portions so that the temperature is maintained between 5-10°C. After adding the last portion is the mixture stirred for 30 minut and then heated with stirring to 70°C for 1 minute and cooled to room temperature.

A solution of 1 (3.0 mmol) in concentrated sulphuric acid (5.0 mL) is cooled to 0°C and 5.0 ml of 0.5M nitrosylsulphuric acid is slowly added. The mixture was stirred for 1 hour and kept at 0°C overnight. The solution was poured over crushed ice (100 g) and the solid formed was filtered off and washed with saturated aqueous solution of sodium carbonate and with water and finally recrystalized from (see Table 1).

Synthesis of oximes of the 3-substituted-5-(substituted benzoyl)-6-oxo-1,6-dihydro-1,2,4-triazines 3 – General procedure **B**:

A solution of **2** (3.0 mmol) in the mixture of water (70 mL) and ethanol (100 mL) is refluxed with hydroxylamine hydrochloride (6.0 mmol) for 10 hours. It is evaporated to 50 mL volume and after 24 hours is the precipitate filtered off and washed with water-ethanol (1:1). It is twice recrystallized from ethanol.

Synthesis of 4 and 6 – General procedure:

1.0 mmol of compound **4** or **5** is refluxed in mixture of phosphorus oxychloride (5.0mL) and N,N-dimethylaniline (0.5 mL) on boiling water bath for 2 hours. Than is the solvent vacuum evaporeted and after cooling, dioxane (5 mL) is added. The solution is poured over crushed ice (50 g). Solid precipitate is filtered off and washed with water and finally recrystallized from (see Table 1).

Acknowledgement

This research was supported by the grant of the Ministry of Education, Youth and Sports No.: MSM 153100013.

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Received on July 5, 2002