FORMATION OF N-α-DIAZOACETYLUREAS BY THE REACTION OF DERIVATIVES OF 5-HYDROXY-1,2,3-TRIAZOLE-4-CARBOXAMIDE WITH PHENYLISOCYANATE AND PHENYL ISOTHIOCYANATE

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The reaction of derivatives of 5-hydroxy-1,2,3-triazole-4-carboxamide with phenyl isocyanate and phenyl isothiocyanate proceeds at the 4-carboxamide fragment of the first, leading to the formation of derivatives of N-phenyl-N'-(2-diazo-2-carbamoylacetyl)urea and -thiourea correspondingly.

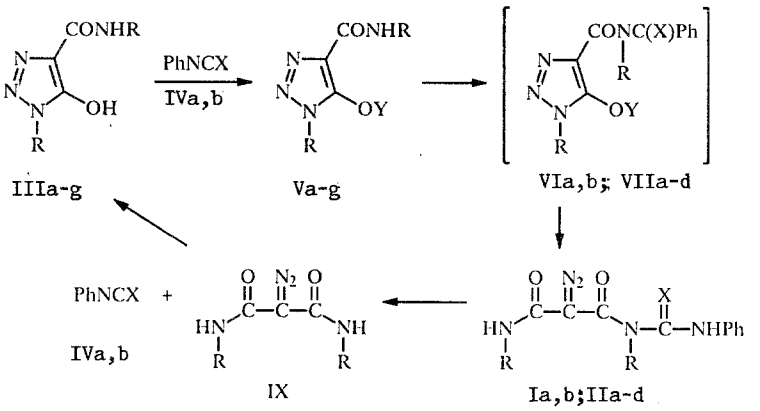
The thermal decomposition of N-acylureas is one of the convenient methods for the synthesis of aryl isocyanates [1]. Moreover, these compounds present independent interest as biologically active compounds [2].

The recyclization of 1,2,3-triazole derivatives containing the ureide fragment may be a possible method for the synthesis of acylureas since it is known that the conversion of substituted 1,2,3-triazoles into derivatives of α-diazoacetamide only proceeds completely when strong electron-acceptor substituents are introduced at position 1 of the heterocycle [3]. Regrettably, there is no information in the literature on the influence of substituents at other positions on the stability of the 1,2,3-triazole ring to recyclization.

With the purpose of establishing the principal possibility of the synthesis of the α-diazoacetylureas (I) and (II), we investigated the reaction of the 4-N-R-derivatives of 5-hydroxy-1,2,3-triazole-4-carboxamine (IIIa-g) with phenyl isocyanate (IVa) and phenyl isothiocyanate (IVb).

The choice of the substance for investigation – compound (III) – was determined by the fact that it contains some nucleophilic centers capable of reacting with isocyanates and isothiocyanates.

We found unexpectedly that the reaction of the triazoles (III) with the compounds (IVa, b) is accomplished at the amide grouping. Such a course for the process is favored by the fact that neither diazomalonic diamide nor 5-hydroxy-1,2,3-triazole-4-carbonitrile nor 1-methyl-5-hydroxy-4-carbonitrile enter into the given reaction under analogous conditions.



I—III, VI, VII, IX a R = H, b R = Ph; II, III, VII, IX c R = 3-NO_2-C_6H_4, d R = 4-Me-C_6H_4; V a R = 3-NO_2-C_6H_4, b R = 4-Me-C_6H_4; III e, V c R = Me; III f, V d R = Bz; III g, V e R = cyclo-C_6H_{11}; IIa–d IVa, VI a,b X = O; IVb, VIIa–d, IIa –d X = S; Va – e, VIb Y = N^+HEt_3; VIa, VIIa–d Y = H

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Table 1. Conditions of Synthesis, Yield, and Melting Temperature of the Compounds (Ia-c), (IIa-d), and (Va-c)

Reacting triazole	Solvent	Reaction time, h	Compound synthesized	Empirical formula	mp, °C	Yield, %
IIIa	Benzene	14,5	Ia	$C_{10}H_9N_5O_3$	226	75
IIIb	"	14,5	Ib	$C_{22}H_{17}N_5O_3$	40	99
IIIc	"	14,5	Ic		—	—
			Va	$C_{21}H_{25}N_7O_6$	20*	99
IIId	"	14,5	Vb	$C_{23}H_{31}N_5O_2$	20*	81
IIIe	"	14,5	Vc	$C_{11}H_{23}N_5O_2$	20*	82
IIIa	DMF	115,5	IIa	$C_{10}H_9N_5O_2S$	115	7
IIIb	"	115,5	IIb	$C_{23}H_{17}N_5O_2S$	150	19
IIIc	"	115,5	IIc	$C_{22}H_{15}N_7O_6S$	224	17
IIId	"	115,5	IId	$C_{24}H_{21}N_5O_2S$	198	7

*Resin at room temperature.

Table 2. Data of the Electronic and IR Spectra of the Compounds (Ia, b), (IIa-d), and (Va-c)

Compound	λ_{max}, nm (log ε)	IR spectrum, cm^{-1}
Ia	263,6(4,20)	3358, 3370, 3180 (NH), 2120 (CN_2), 1710 (CO), 1640 (CO)
Ib	250,4(4,39), 295,3(4,03)	3410, 3260 (NH), 3050 (CH), 2115 (CN_2), 1715 (CO), 1705 (CO)
IIa	268,7(4,15)	3380, 3320, 3160 (NH), 2115 (CN_2), 1670 (CO)
IIb	243,6(4,46), 293,3(4,33)	3400 (NH), 3270 (NH), 3050 (CH),2100 (CN_2), 1660 (CO)
IIc	210(4,38), 244,5(4,37), 265,0(4,33)	3380 (NH), 3235 (NH), 2115 (CN_2), 1665 (CO)
IId	238,9(4,51), 296,7(4,61)	3290 (NH), 3200 (NH), 3030 (CH), 2945, 2910, 2860 (CH_3), 2100 (CN_2)
Va	240,0(4,11), 315,5(4,04)	3275 (NH), 2950, 2020 (CH_3), 1680 (CO)
Vb	250,9(4,31), 295,3(4,09)	3405 (NH), 1695 (CO), 3030 (CH)
Vc	245,4(4,31), 298,7(4,08)	3310 (NH), 2950 (CH_3), 2920 (CH_3), 1660 (CO)

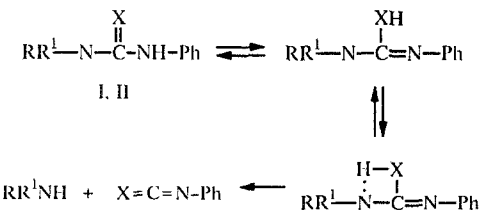
Therefore, the reaction of the triazoles (IIIa-d) with the compounds (IVa, b) leads to the intermediates (VIa, b) and (VIIa-d), which undergo recyclization to the compounds (Ia, b) and (IIa-d). The urea fragment thereby lowers the stability of the heterocycle so much that even the triazolate (VIb) is converted to the N-α-diazoacetylurea (Ib).

Phenyl isocyanate (IVa) reacts readily with the triazoles (IIIa, b) with the formation, for example, of the urea (Ia), likewise in the absence of bases (Table 1). The oil (IVb) only reacts with the triazoles (IIIa-d) in a polar solvent (DMF), whereas the reaction does not proceed in benzene. However, the rate of the process is also lower by far in DMF than in the case of the utilization of compound (IVa), which requires an increase in the time of the synthesis.

Since the triazoles (IIIe-g) do not enter into the given reaction, it can be concluded that the R substituents in the triazoles (III) should have the steric constants E_s close to the value of $E_s = +1.24$ intrinsic for the R substituents in the triazoles (IIIa, b) [4]. This sharply limits the possibilities of the synthesis.

The results obtained indicate that the introduction of substituents into the aromatic ring leads to a significant change in the yield of the ureas (I) and (II), confirming the scheme of the dissociation of the ureas [5] found taking the example of N-alkyl derivatives of ureas and consisting of the following microstages of the process:

The electron-donor substituents at the aryl ring probably lower the stability of the C–N bond on account of the increase in the electron density at the nitrogen atom connected to two substituents and the strengthening of the hydrogen bond in (VIII), leading to a decrease in the energy barrier of the decarbamoylation and dethiocarbamoylation reactions. As a consequence, the concentration of the ureas (I) and (II) decreases and the content of the initial triazoles (III), formed from the corresponding α



R = R^1NHCON_2CO-; R^1 = -C_6H_4-R^2, R^2 = H, 3-NO_2, 4-Me; I, IVa, VIII X = O; II, IVb, VIII X = S

-diazomalonic diamides (IX) – a product of the thermolysis of the compounds (I) and (II), increases. Under the reaction conditions, the compounds (IX) are readily converted to the compounds (III) since the diazomalonic diamides (IX) undergo cyclization to the triazoles (III) in the presence of bases or in a polar solvent [6].

Electron-acceptor substituents retard the rate of reaction with the substances (IVa, b) due to the decrease in the electron density at the nitrogen atom of the 4-carboxamide fragment in the triazoles (III); this is the limiting step of the process.

The spectral characteristics of the compounds (I), (II), and (V) are presented in Tables 2 and 3.

Therefore, a new convenient method for the synthesis of derivatives of the N-(2-diazo-2-carbomoylacetylureas (I) and (II) was developed as a result of the investigations carried out; its perspectives and limits of utilization were also determined.

EXPERIMENTAL

The IR spectra were recorded on the UR-20 and Specord IR-75 spectrophotometers using KBr tablets. The ^1H NMR spectra were obtained on the Perkin–Elmer R-12B (60 MHz) instrument. The ^{13}C NMR spectra were obtained on the Bruker WP-80 (80 MHz) instrument using DMSO-D_6 and TMS as the standard. The UV spectra were taken on the Specord M-40 instrument in ethanol. The course of the reaction and the discreteness of the compounds obtained were monitored using TLC on plates of Silufol UV-254 in the 1:1 system of acetone–hexane.

The characteristics of the compounds synthesized are presented in Tables 1-3.

The data of the elemental analysis of the compounds (Ia, b) and (IIIa-g) for C, H, and N, and of the compounds (IIa-d) for C, H, N, and S correspond with the calculated data.

The initial triazoles (IIIa-g) were obtained by the methods of [7] and [8].

N-(2-Diazo-2-carbomoylacetyl)urea (Ia). The triazole (IIIa) (0.331 g; 2.6 mmole) is suspended in 50 ml of benzene prior to the addition of 0.3 ml (2.76 mmole) of phenyl isocyanate; the mixture is heated to boiling and maintained for 14.5 h. The mixture is cooled to 20°C. The precipitated residue is filtered off and washed with acetone (20 ml) and ethyl ether (40 ml). The yield of 0.478 g (75%) of the urea (Ia) is obtained. The mass spectrum contains the peak of the molecular ion [M^+ 247]. The ^{13}C NMR spectrum is as follows: 164.0 ppm (CO), 163.3 ppm (CO), 149.5 ppm (CO, NH – CO – NH), 137.4 ppm $C_{(1)}$, 129.0 ppm $C_{(3)}$, 119.7 ppm $C_{(2)}$, 123.7 ppm $C_{(4)}$, and 66.0 ppm (CN_2).

The compounds (Va-e) are formed under analogous conditions with the utilization of the 11-fold molar excess of the triethylamine.

N,N′-Diphenyl-N-[2-diazo-2-(N-phenylcarbomoyl)acetyl]urea (Ib). The triazole (IIIb) (0.28 g; 1 mmole) is suspended in 25 ml of benzene prior to the addition of 1.5 ml (10.7 mmole) of triethylamine, and the mixture is heated to the boiling temperature on a metal bath. Phenyl isocyanate (0.2 ml; 1.84 mmole) is added to the reaction mass from a dropping funnel, and the mixture is maintained for 14.5 h at the boiling temperature of the reaction mass. The benzene is distilled in vacuo. Benzene (50 ml) is added and the azeotrope of benzene and phenyl isocyanate is again distilled in vacuo. The residue is crystallized from benzene. The yield of 0.395 g (99%) of compound (Ib) is obtained.

N-Phenyl-N′-(3-nitrophenyl)-N′-(2-diazo-2-[N-(3-nitrophenyl)-carbamoyl)acetyl]thiourea (IIc). To the solution of 95 mg (0.26 mmole) of the triazole (IIIc) in 20 ml of DMF is added 0.06 ml (0.50 mmole) of the phenyl oil, and the mixture is stirred using a magnetic stirrer at room temperature for 115.5 h. Benzene (40 ml) is added prior to the concentration in vacuo. The residue is suspended in 10 ml of chloroform and filtered off. After the concentration of the filtrate in vacuo, the yield of 22.3 mg (17%) of the compound (IIc) is obtained.

The compounds (IIa, b, d) are obtained analogously.

Table 3. Data of the ^1H NMR Spectra of the Compounds (Ia, b), (IIa-d), and (Va-c)

Compound	Chemical shifts, δ, ppm (SSCC, Hz)
Ia	7,103 (1H,t, J = 6,6 Hz, 4-C_6H_5), 7,343 (2H,t, J = 6,6 Hz, 3-C_6H_5), 7,530 (2H,d, J = 6,6 Hz, 2-C_6H_5), 8,035 (2H, s, NH_2), 10,298 (1H,s, NH), 10,469 (1H,s, NH)
IIa	6,9...7,8 (5H,m, C_6H_5), 8,0 (2H.s, NH_2), 9,77 (1H,s, NH)
IId	2,28 (3H,s, CH_3), 2,38 (3H,s, CH_3), 6,9...8,0 (13H,m, 2-C_6H_4, C_6H_5), 10,16 (1H, s, NH), 10,31 (1H,s, NH)
Va	0,7...1,7 (9H,m, CH_3), 3,0...3,6 (6H,m, CH_2), 6,9...8,0 (8H,m, 2-C_6H_4-NO_2-3)
Vb	1,13 (9H, t, J = 9,6 Hz, CH_3), 3,0 (6H, q, J = 9,6 Hz, CH_2), 2,24 (3H,s, CH_3), 2,30 (3H,s, CH_3), 6,7...7,8 (8H,m, 4-C_6H_4), 9,66 (1H,s, NH)
Vc	1,15 (9H,t, J = 9,0 Hz, CH_3), 3,0 (6H, q, J = 9,0 Hz, CH_2), 2,42 (3H,s, CH_3), 2,75 (3H,d, J = 5,0 Hz, CH_3)

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