The formation of 1,2,4-triazolylimidazolidine-2,4-diones in reactions of 3-aryl-1,2,4-triazin-5(2*H*)-ones with alkylureas

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Recyclization of the addition products of alkylureas to 3-aryl-1,2,4-triazin-5(2*H*)-ones affording 1,2,4-triazole derivatives was found to occur in Ac_2O.

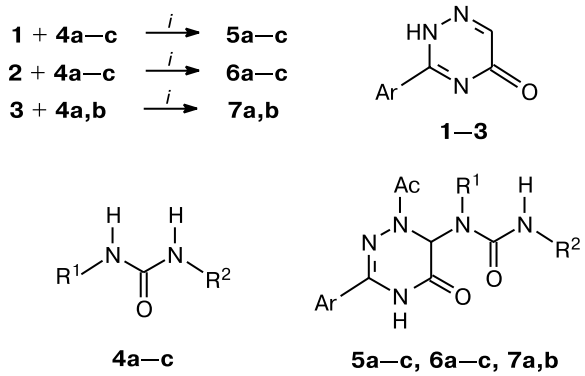
Key words: 1,2,4-triazin-5(2*H*)-ones, ureas, 6-ureido-1,2,4-triazines, 1,2,4-triazolylimidazolidine-2,4-diones, 1,2,4-triazoles, nucleophilic addition to azines.

Transformations at the unsubstituted carbon atom in azaaromatic compounds in reactions with nucleophilic reagents (A_N and S_N^H reactions, *tele*- and *cine*-substitutions) are promising for the modification of the structures of heterocyclic compounds.[1] Reactions of bifunctional nucleophiles with azines often result in 1,2-cyclization[2,3] due to tandem processes A_N-A_N, A_N-S_N^{ipso}, S_N^H-S_N^H, and S_N^H-S_N^{ipso}. The atom bearing a good leaving function (halogen, alkoxy group, *etc*.) along with the unsubstituted carbon atom is an additional electrophilic center. The use of the carbonyl group for annelating a new ring to the azine ring is less common and is represented by several examples in the quinoxalinone and cinnolinone series.[4] In the present work, we studied a possibility of involvement of the carbonyl group of 1,2,4-triazin-5(2*H*)-ones in the tandem transformations. Urea derivatives previously employed in the syntheses of 6-azapurines according to an S_N^H-S_N^{ipso} scheme from 5-methoxy-1,2,4-triazine[5,6] were used as dinucleophiles.

Mixtures of organic acids and anhydrides are the most favorable medium for the reactions of 1,2,4-triazin-5(2*H*)-ones with nucleophiles.[7,8] These conditions enable sufficient activation of the substrate for the nucleophilic attack and stabilization of the reaction products. The reactions of triazinones **1—3** with ureas **4a—c** in a mixture of Ac_2O with CF_3COOH afford nucleophilic addition products to the unsubstituted C atom of the triazine ring **5—7** (Scheme 1).

In the case of *N*,*N*′-dimethylurea (**4c**), adducts **5—7** could not be isolated in the pure state, because their further transformations occur even at room temperature. The presence of compounds **5c** and **6c** can be detected in the ^{1}H NMR spectra of reaction mixtures by the appearance of the C(6)—H signals at δ 5—6, this region being characteristic of the addition products. The reactions of triazinones **1—3** with methyl- (**4a**) or propylureas (**4b**) afford more stable adducts, which were isolated in the analytically pure state and characterized. Based on the ^{1}H NMR spectroscopic data, we established that the addition of nonsymmetrical ureas **4a,b** occurred regioselectively, as should be expected, involving the unsubstituted amino group.

Scheme 1



i. Ac_2O, CF_3COOH.
Ar = Ph (**1**, **5**), 4-Tol (**2**, **6**), 2-Py (**3**, **7**);
R^1 = H, R^2 = Me (**a**); R^1 = H, R^2 = Pr^n (**b**); R^1 = R^2 = Me (**c**)

It is noteworthy that the presence of a strong acid, as well as in other similar cases,[7,8] is prerequisite for the addition of urea. If the reaction is carried out in a mixture of Ac_2O and AcOH, only trace amounts of products **5—7** are detected after 5 h. The dependence of the transformation rate on the acid strength is related, most probably, to the fact that it is the protonated 2-acyl-1,2,4-triazinone formed *in situ* that is the reacting species. This is confirmed by the result of the reaction of 2-acyl-substituted derivative **8** with urea **4a**. Probably, this reaction includes the formation of unstable adduct **9** containing the acyl group in position 2 of the triazine ring followed by the acylotropic rearrangement to more stable 1-acyl derivative **5a** (Scheme 2).

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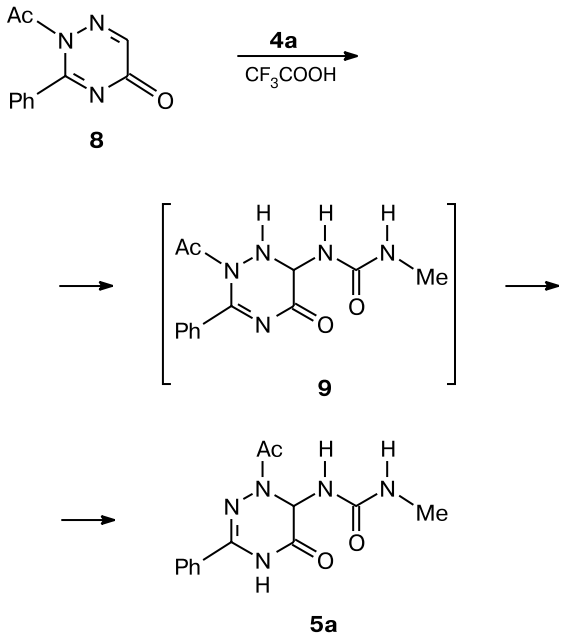
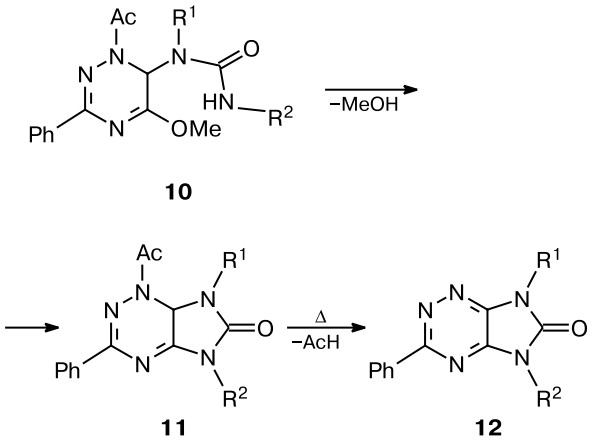
Scheme 2



Annelation of the imidazole ring could be expected for compounds **5—7** on heating, as it has previously been observed, *e.g.*, for the addition products of ureas to 5-methoxy-1,2,4-triazine (Scheme 3).[5,6] In this case, the transformations of adducts **10** included the intramolecular substitution of the methoxy group to form *N*-acetyl derivative **11** followed by elimination of acetaldehyde to give azapurinone **12**.

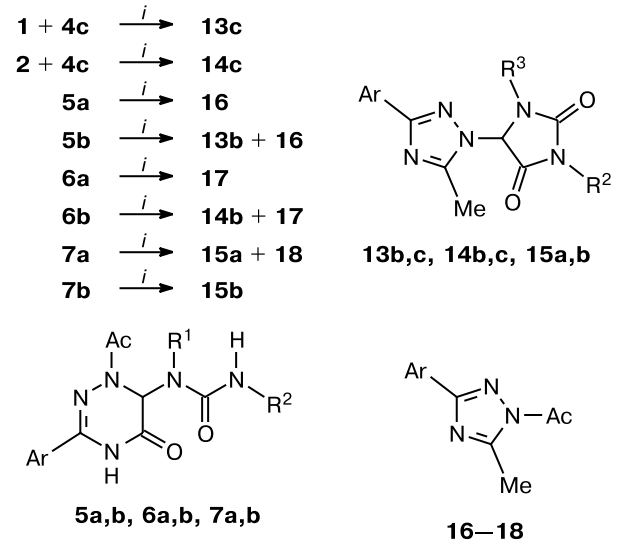
Scheme 3



R^1, R^2 = H, Me

Heating of compounds **5—7** or a mixture of compound **1** (**2**) with urea **4c** in Ac_2O at 70—110 °C produces derivatives of 5-triazolylimidazolidine-2,4-dione **13—15** and 3-aryl-1,2,4-triazole **16—18** (Scheme 4). No cyclization of compounds **5—7** to azapurinone of the type **11** occurs.

Scheme 4



i. Ac_2O, 70 °C → 110 °C.

Starting compounds	Ar	R^1	R^2	R^3	Products (yield (%))	
					13—15	**16—18**
5a	Ph	H	Me	—	—	**16** (40)
5b	Ph	H	Pr^n	Ac	**13b** (20)	**16** (13)
6a	4-Tol	H	Me	—	—	**17** (52)
6b	4-Tol	H	Pr^n	Ac	**14b** (7)	**17** (22)
7a	2-Py	H	Me	Ac	**15a** (20)	**18** (12)
7b	2-Py	H	Pr^n	Ac	**15b** (26)	—
1, 4c	Ph	Me	Me	Me	**13c** (46)	—
2, 4c	4-Tol	Me	Me	Me	**14c** (44)	—

It was established that 3-aryl-1,2,4-triazoles **16—18** represent the decomposition products of compounds **13—15**: 1,2,4-triazole **16** identical to that synthesized by a different method[9] was obtained in 61% yield by refluxing individual 5-triazolylimidazolidine-2,4-dione **13c** in Ac_2O (Scheme 5).

Scheme 5

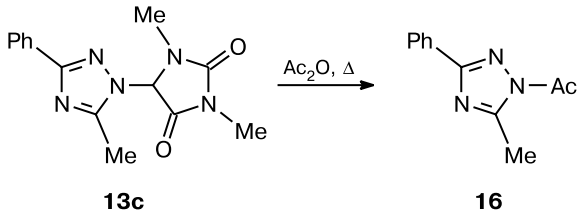


Table 1. Reaction conditions and characteristics of compounds **13—15** and **16—18**

Starting compound	Reaction conditions		Products	Yield (%)	M.p. /°C	MS, m/z (I_{rel} (%))
	T/°C	τ/h				
5a	70	10	**16**	40	83—85*	201 (25); 172 (4); 159 (100); 130 (4); 118 (41); 104 (7);
	90	10				91 (5.5); 63 (3.5); 56(29)
5b	70	12	**13b**	20	125—126	341 (27.2); 299 (3); 159 (100); 118 (13); 104 (8);
	90	10				77 (4); 56 (14)
	110	10	**16**	13	**	**
6a	70	12	**17**	52	103—104	215 (25); 173 (100); 132 (28); 118 (8); 91 (5); 77 (4);
	90	10				65 (2); 56 (18.5)
	110	1				
6b	70	10	**14b**	7	188—190	355 (28); 313 (3); 173 (100); 132 (26); 118(10);
	90	10				91 (8); 56 (17)
	110	10	**17**	22	***	***
7a	70	9	**15a**	20	88—89	314 (84); 272 (35); 160 (100); 132 (51); 119 (5); 105 (30);
	90	15				91 (11); 78 (31.5); 64 (10); 56 (11)
			18	12	105	202 (23); 160 (100); 132 (49); 119 (6); 105 (23); 91 (12);
						78 (29); 64 (7); 56 (11)
7b	70	15	**15b**	26	78—80	342 (29); 300 (9); 160 (100); 132 (43); 119 (6); 105 (26);
	90	10				91 (9); 78 (16); 64 (7); 56 (17)
	110	10				

* The m.p. of triazole **16** coincides with the published data.[9]

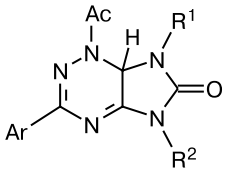
** The m.p. and mass spectrum are identical to the corresponding characteristics for compound **16** obtained from compound **5a**.

***The m.p. and mass spectrum are identical to the corresponding characteristics for compound **17** obtained from compound **6a**.

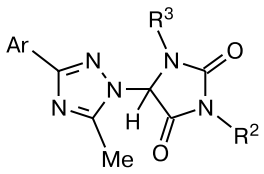
The ratio of the transformation products of ureidotriazines **5—7** depends on both the substituents in the triazine ring (Ar) and the substituents in the ureido fragment (R^1 and R^2) (Scheme 1, Table 1). The presence of either the pyridyl substituent in the triazole ring or two methyl groups (R^2 and R^3) in the imidazolidine fragment favor stabilization of 5-triazolylimidazolidine-2,4-diones **13—15**. For example, for $R^2 = R^3 = CH_3$, after complete conversion of the substrate, 1,2,4-triazoles **16** and **17** are not yet formed: their formation requires prolonged (up to 15 h) refluxing in Ac_2O.

The structures of the resulting compounds were proved on the basis of NMR and mass spectroscopic data. The most characteristic resonance signal in the ^{1}H NMR spectra of ureidotriazines **5a,b—7a,b** is the signal of C(6)H at δ 5.7—6.0 in the form of a doublet with a spin-spin coupling constant of 6.4—7.2 Hz. The spin-spin coupling of the C(6)H protons of the triazine ring and NH group of the ureido substituent in compounds **5—7** indicates that the addition to 1,2,4-triazin-5(2*H*)-ones involves the unsubstituted amino group of urea (Table 2).

The ^{1}H NMR spectra of 5-triazolylimidazolidine-2,4-diones **13—15** exhibit resonance signals of the aromatic substituent and three-proton singlets of the methyl and acetyl groups, the proton at C_{sp3}, and the R^2 substituent (Table 3). A similar set of signals is characteristic of 6-azapurines[5,6] **11** (isomers of compounds **13—15**), which can also be formed in the reaction. The NMR spectra of compounds **11** and **13—15** differ only in the values of chemical shifts of the resonance signals. In particular, the signals of protons at the sp^3-C atom of the heterocyclic system of compounds **13—15** exhibit the downfield shift of 1.0—1.5 ppm compared to the corresponding signals of the isomeric azapurines **11** (R^1 = Me, Ac; R^2 = Me, Pr^n).



11 (R^1 = Me, Ac; R^2 = Me, Pr^n)



13a—c—15a—c

The proof of structures of compounds **13—15** was based on the interpretation of their mass spectra (Scheme 6). In the case of compound **11**, the molecular ion loses one (for R^1 = Me) or two (for R^1 = Ac) acetyl groups upon fragmentation.[6] The mass spectra of synthesized compounds **13**, **14b**, and **15a,b** contain the peak of the $[M - 42]^+$ fragment corresponding to the loss of only one acetyl group. The $[M - 42]^+$ peak was not detected in

Table 2. Data of the ^{1}H NMR spectra of ureidotriazines **5—7** (400 MHz, DMSO-d_6)

Compound	δ (*J*/Hz)				
	C(6)—H	Ar	Ac (s, 3 H)	$NH_{triazole}$ (br.s, 1 H)	6-R
5a	5.80 (d, 1 H, *J* = 7.1)	7.87—7.89 (m, 2 H); 7.41—7.49 (m, 3 H)	2.31	11.28	7.17 (d, 1 H, *J* = 7.1); 5.79 (q, 1 H, *J* = 4.6); 2.54 (d, 3 H, *J* = 4.6)
5b	5.81 (d, 1 H, *J* = 7.2)	7.87—7.89 (m, 2 H); 7.41—7.49 (m, 3 H);	2.31	11.28	7.06 (d, 1 H, *J* = 7.2); 5.9 (t, 1 H, *J* = 5.6); 2.87—2.92 (m, 2 H); 1.32—1.39 (m, 2 H); 0.83 (t, 3 H, *J* = 7.6)
6a	5.93 (d, 1 H, *J* = 7.2);	7.78 (d, 2 H, *J* = 8.4); 7.29 (d, 2 H, *J* = 8.4); 2.29 (s, 3 H)	2.36	11.3	7.24 (d, 1 H, *J* = 7.2); 5.82 (q, 1 H, *J* = 3.7); 2.48 (d, 3 H, *J* = 3.7)
6b	5.93—5.97 (m, 2 H)*	7.78 (d, 2 H, *J* = 8.4); 7.29 (d, 2 H, *J* = 8.4); 2.28 (s, 3 H);	2.36	11.31	7.12 (d, 1 H, *J* = 7.2); 5.93—5.97 (m, 2 H); 2.85—2.89 (m, 2 H); 1.29—1.34 (m, 2 H); 0.78 (t, 3 H, *J* = 7.4)
7a	5.76 (d, 1 H, *J* = 6.8)	8.65 (dd, 1 H, *J* = 1.7; 4.8); 8.12 (d, 1 H, *J* = 8.1); 7.94 (ddd, 1 H, *J* = 1.7; 8.1; 7.8); 7.52 (ddd, 1 H, *J* = 0.9; 4.8; 7.8)	2.35	10.28	7.26 (d, 1 H, *J* = 6.8); 5.84 (q, 1 H, *J* = 4.5); 2.51 (d, 3 H, *J* = 4.5)
7b	5.74 (d, 1 H, *J* = 6.4);	8.64 (d, 1 H, *J* = 4.6); 8.12 (d, 1 H, *J* = 8); 7.93 (ddd, 1 H, *J* = 1.3; 7.7; 8.0); 7.51 (ddd, 1 H, *J* = 0.9; 4.6; 7.7)	2.35	10.28	7.15 (d, 1 H, *J* = 6.4); 5.95 (t, 1 H, *J* = 5.6); 2.84—2.89 (m, 2 H); 1.32—1.38 (m, 2 H); 0.82 (t, 3 H, *J* = 7.5)

* The C(6)—H signal is overlapped with the NH signal of the ureido substituent.

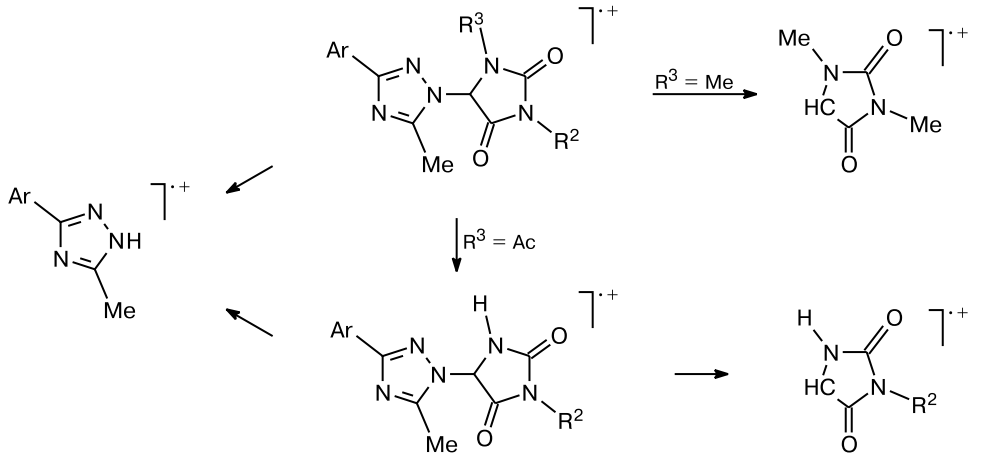
the mass spectra of compounds **13c** and **14c**, which makes it possible to make choice in favor of the structure of 5-triazolylimidazolidine-2,4-dione.

The fragmentation of the molecular ion of compounds **13c** and **14c** and the $[M - 42]^+$ ion of compounds **13b**, **14b**, and **15a,b** (see Scheme 6) is accompanied by the

Table 3. Data of the ^{1}H NMR spectra of compounds **13—15** (400 MHz, DMSO-d_6)

Compound	δ (*J*/Hz)		
	CH (s, 1 H)	Ar	R^2; R^3; Me
13b	6.66	8.00—7.90 (m, 2 H); 7.38—7.47 (m, 3 H)	3.46—3.68 (m, 2 H); 2.68, 2.49 (both s, 3 H each); 1.56—1.92 (m, 2 H); 0.96—1.2 (m, 3 H)
14b	6.67	7.79, 7.17 (both d, 2 H each, *J* = 8.0); 2.47 (s, 3 H)	3.54—3.63 (m, 2 H); 2.71, 2.56 (both s, 3 H each); 1.72—1.77 (m, 2 H); 1.03 (t, 3 H, *J* = 7.4)
15a	6.72	8.59 (dd, 1 H, *J* = 1.8; 4.8); 8.01 (dd, 1 H, *J* = 1.1; 8.1); 7.82 (ddd, 1 H, *J* = 1.8; 8.1; 7.7); 7.35 (ddd, 1 H, *J* = 1.1; 4.8; 7.7)	3.14, 2.7, 2.5 (all s, 3 H each)
15b	6.75	8.59 (dd, 1 H, *J* = 0.8; 4.8); 7.97 (d, 1 H, *J* = 8.0); 7.81 (ddd, 1 H, *J* = 0.8; 8.0; 7.7); 7.35 (ddd, 1 H, *J* = 1.1; 4.8; 7.7)	3.56—3.61 (m, 2 H); 2.7, 2.5 (both s, 3 H each); 1.7—1.75 (m, 2 H); 1.01 (t, 3 H, *J* = 7.4)
13c	6.38	7.95—7.97 (m, 2 H); 7.37—7.42 (m, 3 H)	3.04, 2.8, 2.59 (all s, 3 H each)
14c	6.42	7.81, 7.17 (both d, 2 H each, *J* = 8.2); 2.32 (s, 3 H)	3.00, 2.77, 2.57 (all s, 3 H each)

Scheme 6



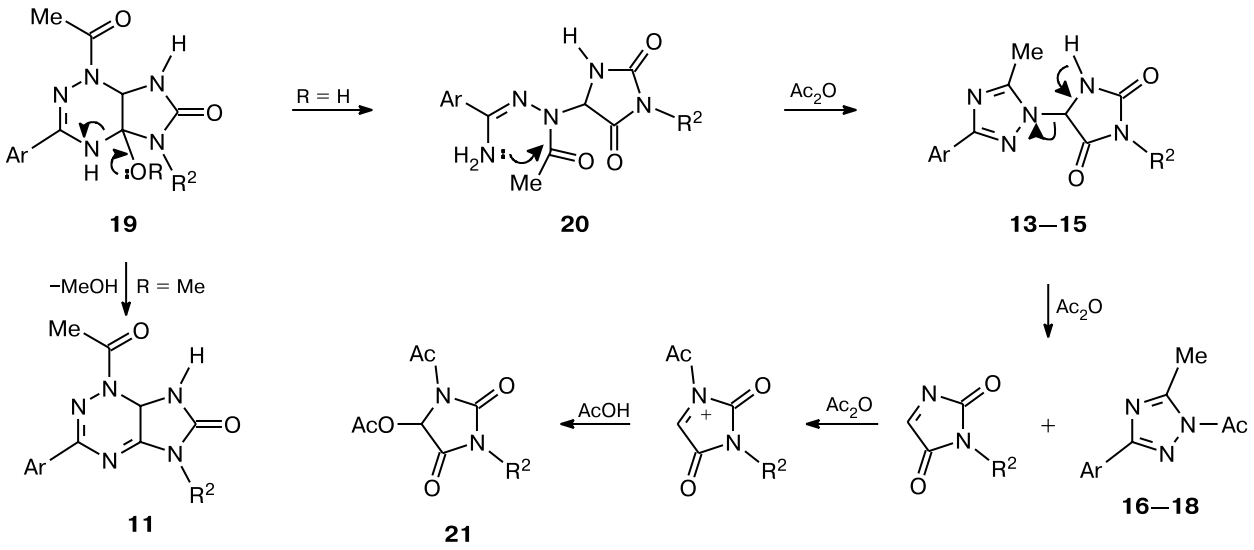
elimination of the imidazole ring and formation of 3-aryl-1,2,4-triazole ions, whose peak in all spectra, except for that of **13c**, are characterized by the maximum intensity. The fragmentation of this ion occurs according to the scheme characteristic of triazoles.

Considering the recyclization mechanism and reasons for the different behavior of 5-methoxy- and 5-oxo derivatives of 1,2,4-triazines, one may conclude that the primary annelation of the imidazole ring occurs in both cases (Scheme 7). In the case of 5-methoxy-1,2,4-triazines, σ^{ipso}-adduct **19** (R = Me) is stabilized by elimination of methanol, whereas for the 5-oxo derivatives (R = H) the triazine ring is cleaved followed by the intramolecular cyclization of intermediate **20** involving the acyl group. Under more drastic conditions, compounds **13—15** undergo destruction to form 1,2,4-triazoles **16—18** and imidazolinediones **21**.

The formation of imidazolinedione **21** ($R^2 = Pr^n$) was detected upon heating of ureidotriazine **7b** in Ac_2O. The mass spectrum of compound **21** contains the peak of the molecular ion *m/z* 242. The ^1H NMR spectrum exhibits resonance signals of the propyl substituent: of the methylene groups as multiplets at δ 3.38—3.48 and 1.58—1.64 and of the methyl group as a triplet at δ 0.92 (J = 7.4 Hz), three-proton singlets at δ 2.43 and 2.09, and a singlet of the proton at δ 6.53.

Thus, we can state that, unlike 5-methoxy-1,2,4-triazine, 5-oxo derivatives react with ureas with annelation of the imidazole ring and subsequent recyclization of the triazine system with ring contraction.

Scheme 7



Experimental

The course of reactions and purity of the synthesized products were monitored by TLC on plates with a fixed layer of ARMSORB KSGK-UF using dichloromethane—methanol (30 : 1) as the eluent and detection in the UV light. Lancaster silica gel (230—400 mesh) was used for preparative column chromatography. ^{1}H NMR spectra were obtained on a Bruker DRX 400 instrument (400 MHz) using Me_4Si as the internal standard. Mass spectra were recorded on a Varian MAT 311-A instrument with the FD/EI combined source (direct inlet of a sample in the ion source, energy of ionizing electrons 70 eV). Elemental analysis was carried out on a Carlo Erba 1108 analyzer. Melting points were determined on a Boetius stage and were not corrected.

The starting triazinones **1—3** have been synthesized by a previously described method.[10]

1-Acetyl-6-alkylureido-3-aryl-1,4,5,6-tetrahydro-1,2,4-triazin-5-ones (5—7a,b) (general procedure). A mixture of 3-aryl-1,2,4-triazin-5(2*H*)-one[10] (0.6 mmol), urea (0.6 mmol), Ac_2O (2 mL), and CF_3COOH (0.06 mL) was stirred at ~20 °C. The precipitate that formed was filtered off, washed with diethyl ether, and dried in air. The duration of the reaction, yields, m.p., and elemental analysis data of compounds **5a,b—7a,b** are presented in Table 4.

1-Acetyl-6-(3-methylureido)-3-phenyl-1,4,5,6-tetrahydro-1,2,4-triazin-5-one (5a). A solution of 1-acetyl-3-phenyl-1,2,4-triazin-5(2*H*)-one (**8**)[10] (50 mg, 0.23 mmol) and *N*-methylurea (**4a**) (17 mg, 0.23 mmol) in CF_3COOH (2 mL) was kept at ~20 °C for 4 days. The solvent was removed *in vacuo*, and the residue was triturated with diethyl ether and recrystallized from methanol. The yield was 36 mg (54%). The product was identical to the sample of **5a** obtained as described above.

5-(3-Aryl-5-methyl-1,2,4-triazol-1-yl)-1,3-dimethylimidazolidine-2,4-diones (13c, 14c). A mixture of 3-aryl-1,2,4-triazin-5(2*H*)-one (**1** or **2**) (0.6 mmol) and *N*,*N*′-dimethylurea (**4c**) (0.6 mmol, 53 mg) was heated to 70 °C in Ac_2O (3 mL) and stirred at this temperature for 6 h. Then the mixture was heated for 2.5 h at 90 °C and for 4 h at 110 °C. The solvent was evaporated, and the resulting yellow oil was chromatographed on a column with silica gel (CH_2Cl_2—MeOH (30 : 1) as the eluent) and recrystallized from methanol.

Compound 13c. The yield was 46%, m.p. 183—184 °C. Found (%): C, 57.10; H, 4.97; N, 23.63. $C_{14}H_{15}N_5O_2$. Calculated (%): C, 58.94; H, 5.30; N, 24.55. MS, *m*/*z* (I_{rel}(%)): 285 (31), 159 (9), 127 (100), 118 (9), 104 (12), 91 (6), 77 (13), 56 (14).

Compound 14c. The yield was 44%, m.p. 180—182 °C. Found (%): C, 59.76; H, 6.10; N, 23.15. $C_{15}H_{17}N_5O_2$. Calculated (%): C, 60.19; H, 5.72; N, 23.40.

1-Acetyl-3-alkyl-5-(3-aryl-5-methyl-1,2,4-triazol-1-yl)imidazolidine-2,4-diones (13b, 14b, 15a,b) and 1-acetyl-3-aryl-5-methyl-1,2,4-triazoles (16—18) (general procedure). Ureidotriazines **5a,b—7a,b** were heated in Ac_2O with gradual increase in the temperature from 70 to 110 °C (temperatures and duration of heating are indicated in Table 1). The solvent was removed *in vacuo*, and the resulting oil was chromatographed on a column with silica gel (CH_2Cl_2—MeOH (30 : 1) as the eluent). 1,2,4-Triazoles **16—18** were eluted first, and then compounds **13—15** were eluted (see Table 1). In the case of **7b**, 5-acetoxy-1-acetyl-3-propylimidazoline-2,4-dione **21** was also isolated (5%).

Table 4. Reaction conditions and characteristics of compounds **5a,b—7a,b**

Compound	τ/h	Yield (%)	M.p. /°C	Found / Calculated (%)		
				C	H	N
5a	4	67	196—198	53.79	5.12	24.15
				53.98	5.22	24.21
5b	2	79	224—226	56.57	6.11	22.02
				56.77	6.03	22.07
6a	3	76	220—223	55.32	5.54	22.97
				55.44	5.65	23.09
6b	3	76	202—204	57.87	6.21	21.02
				57.99	6.39	21.13
7a	2.5	45	222—225	49.27	4.62	28.16
				49.65	4.86	28.95
7b	2	41	236—237	52.84	5.83	26.41
				52.83	5.70	26.40

1-Acetyl-5-methyl-3-phenyl-1,2,4-triazole (16). A solution of 1,3-dimethyl-5-(5-methyl-3-phenyl-1,2,4-triazol-1-yl)imidazolidine-2,4-dione (**13c**) (28 mg, 0.1 mmol) in Ac_2O (1 mL) was refluxed for 15 h, the solvent was removed *in vacuo*, and the residue was recrystallized from methanol. The yield was 12 mg (61%). The product was identical to triazole **16** synthesized by another method.

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