S_N^H-Reactions of triazolo[4,3-*b*]- and tetrazolo[1,5-*b*]-1,2,4-triazines with methylene-active carbonyl compounds

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Unsubstituted triazolo[4,3-*b*]- and tetrazolo[1,5-*b*]-1,2,4-triazines react with carbanions generated from dimedone and barbituric acid to give adducts of a C-nucleophile with the heterocyclic system through the C=N double bond. The adducts can be oxidized under mild conditions into products of nucleophilic hydrogen substitution. Analogous adducts with carbanions produced in the reactions of ethyl cyanoacetate and ethyl malonate with Bu^{t}OK proved to be unstable; in this case, the title azolotriazines immediately yield products of nucleophilic hydrogen substitution in position 7. Tautomerism of the S_N^H products obtained is discussed.

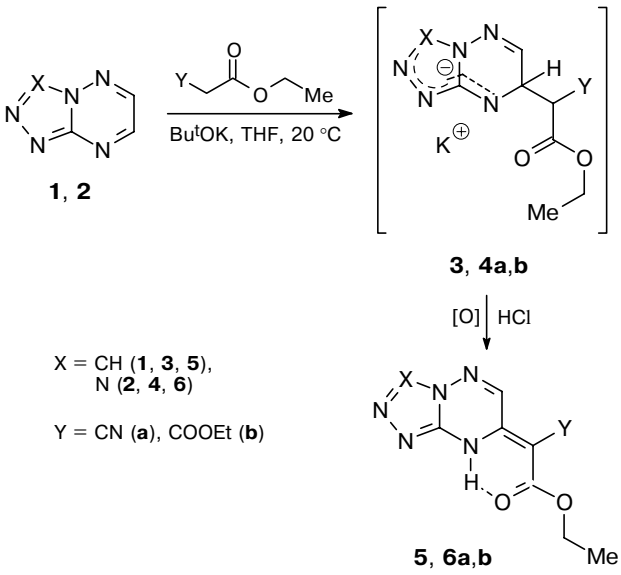
Key words: 1,2,4-triazines, triazolo[4,3-*b*]-1,2,4-triazine, tetrazolo[1,5-*b*]-1,2,4-triazine, ethyl malonate, ethyl cyanoacetate, dimedone, barbituric acid, nucleophilic addition, nucleophilic substitution of hydrogen, σ^H-adducts.

Azolo-1,2,4-triazines are mainly functionalized by replacing easily leaving groups (Hal, OR, SR, *etc.*).[1] Oxidative nucleophilic substitution of hydrogen is known to occur in the reaction of imidazotriazine with phenyllithium.[2] In other cases, C-nucleophiles attack the unsubstituted carbon atom of the triazine ring to yield their stable adducts through the C=N bond.[3,4]

Azoloannelated 1,2,4-triazines react with C-nucleophiles either when their triazine ring is additionally activated (by *N*-protonation and *N*-alkylation or by introduction of electron-withdrawing substituents[3—6]) or when highly reactive organometallic compounds are used as nucleophiles.[2,7]

In the present work, we studied the reactions of unsubstituted triazolo[4,3-*b*]-1,2,4-triazine (**1**) and tetrazolo[1,5-*b*]-1,2,4-triazine (**2**) with methylene-active carbonyl compounds (ethyl malonate, ethyl cyanoacetate, dimedone, and barbituric acid) and proposed a new method of modifying azoloannelated 1,2,4-triazines *via* S_N^H-substitution.[8] The nucleophilic substitution of hydrogen readily proceeds when compounds **1** and **2** react with ethyl malonate and ethyl cyanoacetate at room temperature in the presence of an equimolar amount of Bu^{t}OK. We believe that the reaction starts with the formation of σ^H-adducts **3** and **4**, which then are oxidized by oxygen contained in the solvent and in the air to the corresponding S_N^H-products **5** and **6** (Scheme 1). Apparently, the oxidation precedes acidification, since a potassium salt of compound **5b** was isolated until the reaction mixture was neutralized. It is worth noting that the most difficult stage in the S_N^H-reactions of azoloannelated 1,2,4-triazines with π-abundant nucleophiles, namely, the oxidation of σ^H-adducts, is very easy to occur[4] even at room temperature so that compounds **3** and **4** were not detected either by TLC or by UV spectroscopy. Nor were adducts **3** and **4** detected when the reactions were carried out in an inert atmosphere in an NMR spectrometer, because of limited solubilities of the reagents and the products.

Scheme 1



In our opinion, such an easy oxidation of compounds **3** and **4** is favored by their specific conformation in which the bond to be oxidized is retained in the ring plane due to hydrogen bonding between the H atom of

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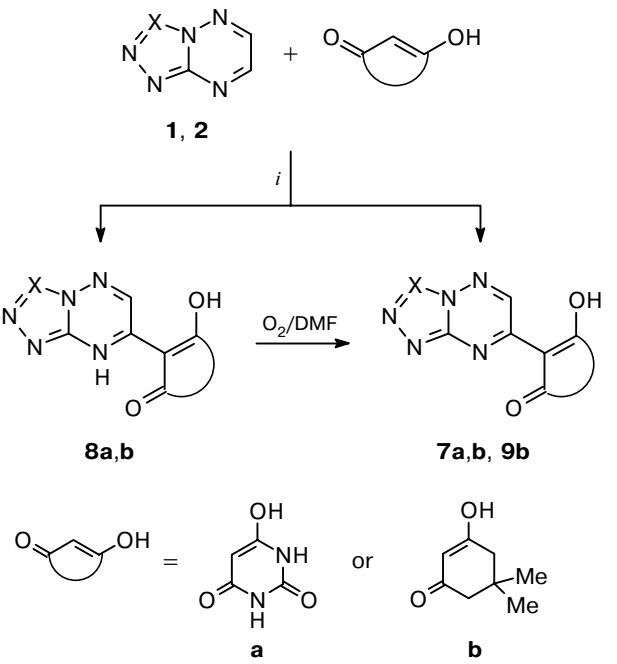
the N(8)—H fragment in the triazine ring and the carbonyl O atom. This is not the case with adducts of CH-reactive compounds with 3-substituted 1,2,4-triazines, for which the H—N(2) isomer is thermodynamically more stable. Because of this, adducts of nonannelated 3-substituted 1,2,4-triazines with carbanions generated *in situ* from ethyl malonate and ethyl cyanoacetate are stable and can be oxidized only under more drastic conditions.[9] It should be noted that a weaker base (*e.g.*, triethylamine) can also be involved in this reaction, but the reaction time should be extended, and the yields of the products decrease to 30%.

Azoloannelated 1,2,4-triazines behave differently in the reactions with cyclic diketones (dimedone and barbituric acid), but the reaction outcome is independent of the base nature (Bu^tOK, LiH, or Et_3N). The reactions of triazolo[4,3-*b*]-1,2,4-triazine (**1**), like those with malonic acid derivatives, do not stop at the stage of adduct formation, but lead to S_N^H-products **7a**,**b**. In contrast, tetrazolo[1,5-*b*]-1,2,4-triazine (**2**) reacts with dimedone and barbituric acid to give stable adducts **8a**,**b** involving the C=N bond of the heterocycle. Note that the reaction of tetrazolotetrazine **2** with barbituric acid in the presence of Et_3N without acidification allows adduct **8a** to be isolated as a triethylammonium salt. S_N^H-substitution product **9b** was obtained only by refluxing compound **7b** in DMF in a flow of oxygen. One could assume that adducts **8a**,**b** are in the azide form and behave like nonannelated 3-substituted 1,2,4-triazines. However, the IR spectra of compounds **8a**,**b** obtained in chloroform, methanol, and methanol with an equimolar amount of Bu^tOK show no absorption band at 2100—2200 cm^{-1} characteristic of the azido group.

Scheme 2



Reagents and conditions. *i.* 1) Bu^tOK, O_2, THF, 20 °C, 2) HCl; or 1) LiH, THF, 20 °C, 2) HCl; or 1) NEt_3, EtOH, 78 °C, 2) HCl.

^{1}H NMR study revealed prototropic and ring-chain tautomerism for compounds **5** and **6** (Table 1).[10]

7-Substituted triazolo[4,3-*b*]-1,2,4-triazines **5a**,**b** can exist in several tautomeric forms (Scheme 3), with domi-

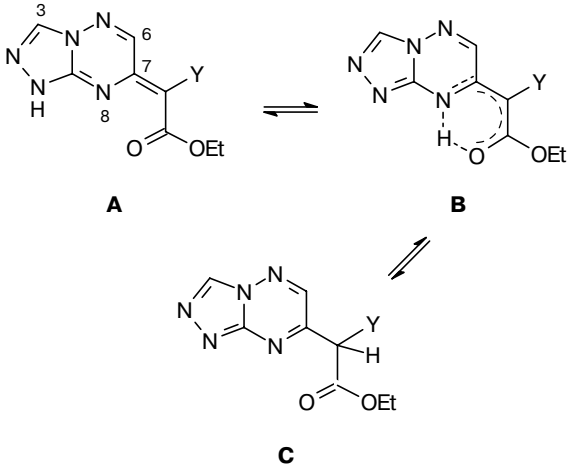
Table 1. Chemical shifts (δ) in the ^{1}H NMR spectra of compounds **5** and **6***

Compound	Solvent	C(3)H	C(6)H	7-R
5a	Acetone-d_6	9.61 (s, 1 H)	8.95 (s, 1 H)	4.21 (q, 2 H, J = 7.10 Hz); 1.28 (t, 3 H, J = 7.10 Hz)
	DMSO-d_6	9.52 (s, 1 H)	9.14 (s, 1 H)	4.28 (q, 2 H, J = 7.10 Hz); 1.29 (t, 3 H, J = 7.10 Hz)
5b (K-salt)	DMSO-d_6	9.38 (s, 0.02 H, A); 9.01 (s, 0.98 H, B)	8.73 (0.02 H, A); 8.45 (0.98 H, B)	4.19, 4.23 (both q, 1 H); 1.23, 1.21 (both t, 3 H)
6a	Acetone-d_6	—	9.61 (s, 0.33 H, B); 9.12 (s, 0.02 H, A); 8.63 (s, 0.65 H, D)	4.14, 4.22, 4.38 (all q, 2 H), 1.32 (m, 3 H)
	$CDCl_3$	—	9.21 (s, 0.06 H, B); 8.47 (s, 0.94 H, D)	4.28 (q, 0.18 H, B); 4.43 (q, 1.88 H, D); 1.35 (t, 0.24 H, B); 1.42 (t, 2.82 H, D)
	DMSO-d_6	—	9.50 (s, 0.73 H, B); 9.09 (s, 0.17 H, A); 8.47 (s, 0.1 H, D)	4.10 (m, 2 H); 1.22 (m, 3 H)
6b	Acetone-d_6	—	9.21 (s, 0.52 H, C); 8.59 (s, 0.48 H, B)	5.45 (s, 0.52 H, C); 4.34 (m, 4 H); 1.29 (m, 3 H)
	$CDCl_3$	—	9.02 (s, 0.25 H, C); 8.43 (s, 0.75 H, B)	5.15 (s, 0.25 H, C); 4.36 (m, 4 H); 1.36, 1.53 (both t, 6 H)
	DMSO-d_6	—	9.17 (s, 0.3 H, C); 8.70 (s, 0.7 H, B)	5.56 (s, 0.3 H, C); 4.26 (m, 4 H); 1.28 (m, 6 H)

* Atomic numbering matches that in Scheme 3; integrated signal intensities and signal assignment to different tautomers are given in parentheses (Schemes 3 and 4).

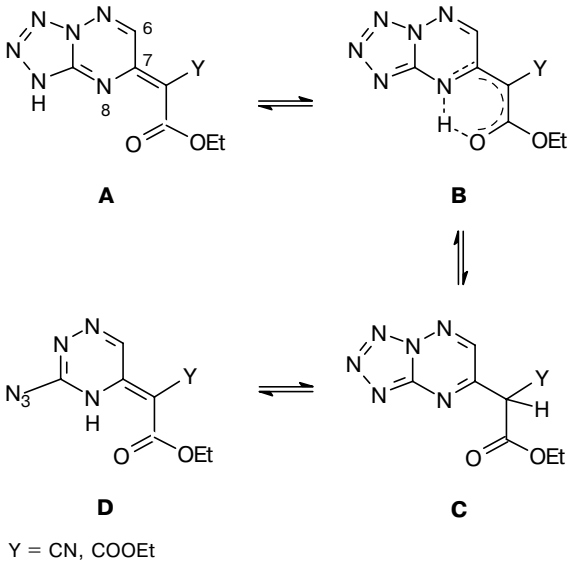
nation of structure **B** (90—98%). Form **C** was excluded since the ^{1}H NMR spectrum contains no singlet at δ 5.0—5.6 characteristic of the methine proton. Doubling of proton signals for the C(6)—H and C(3)—H fragments in the ethyl groups indicates the tautomeric equilibrium **A** ⇌ **B**. We could not determine an actual tautomeric form in superimposed structure **B** because the spectrum shows no signal for a proton involved in keto-enol tautomerism.

Scheme 3



Prototropic and azide-tetrazole tautomerism is characteristic of 7-substituted tetrazolotriazines **6a**,**b** (Scheme 4).

Scheme 4



The ^{1}H NMR spectrum of compound **6b** in $CDCl_3$ contains resonance signals for tautomers **B** and **C**, namely, two signals at δ 9.02 (0.25 H) and δ 8.43 (0.75 H) for the C(6)—H protons of the triazine ring, a signal at δ 5.15 (0.25 H) for the methine proton in tautomer **C**, and doubled signals for the ethyl protons. To prove that signals at δ 8.40—9.40 for the protons in compound **6b** belong to different tautomers of the same compound, a temperature dependence of the spectral pattern was studied. When compound **6b** was heated in DMSO-d_6, signals for the C(6)—H protons came closer to each other and broadened, and a proton signal at δ 5.15 became broader, which indicates an increased rate of tautomer exchange. The coalescence threshold was not reached because compound **6b** decomposes on heating.

The ^{1}H NMR spectrum of compound **6a** in $CDCl_3$ contains two signals for the C(6)—H protons and no characteristic singlet at δ 5.15—5.60 for the methine proton in tautomer **C**, which suggests the existence of an equilibrium azide form **D**. A decreased integrated intensity of the signal for the C(6)—H proton of the azide form in more polar solvents correlates well with the published data[11] and indirectly confirms the existence of the azide structure. Thus, according to the ^{1}H NMR data in $CDCl_3$, the content of the azide form in compound **6a** is 94%, while in DMSO-d_6 the tetrazole form is dominant (see Table 1).

The results obtained agree with IR data (Table 3). The IR spectra ($CHCl_3$) of compound **6a** show both absorption bands corresponding to the stretching vibrations of the tetrazole ring and a band of the azido group.[11] In the spectrum recorded in Vaseline oil, the intensity of the latter is negligible. This suggests that compound **6a** in the solid state is tetrazolo[1,5-*b*]-1,2,4-triazine.

The IR spectrum of the product contains an absorption band characteristic of the CN stretching vibrations, which is additional evidence in favor of its structure.

The CO stretching vibrations of the substituent appear at 1660—1680 cm^{-1}.

The formation of tautomer **B** is confirmed by the presence of a broadened band at 3350—3480 cm^{-1} in the IR spectrum of compound **6a** (a hydrogen bond of the type C=N...H—O— absorbs in this range). A low intensity of the absorption band can also be due to

Table 2. Characteristic absorption bands in the IR spectra of compound **6a**

Fragment	ν/cm^{-1}	
	Vaseline oil	$CDCl_3$ (d = 0.6)
Tetrazole fragment	1290 m, 1080 m, 950 m	1290 s, 1090 m, 990 m
N_3	—	2140
CN	2210	2205
C=O	1675	1665
NH_{triaz}	3080	2965
O...H...N=C	3410	3390

Table 3. Chemical shifts (δ) in the ^{1}H NMR spectra of compounds **7—9**

Compound	Solvent	C(3)H	N(8)H	C(6)H	C(7)H	7-R
7a	DMSO-d_6	9.69 (s, 1 H)		9.22 (s, 1 H)		11.09 (br.s, OH)
7b	DMSO-d_6	9.52 (s, 1 H)		9.41 (s, 1 H)		2.08 (s, 4 H, CH_2); 1.11 (s, 6 H, CH_3)
8a · Et_3N	DMSO-d_6	—	7.91 (br.s, 1 H)	6.87 (br.s, 1 H)	5.29 (br.s, 1 H)	—
	DMSO-d_6—CD_3OD	—	—	6.86 (br.s, 1 H)	5.29 (br.s, 1 H)	—
8b	DMSO-d_6	—	7.93 (dd, 1 H, J = 1.77, 1.32 Hz);	7.11 (dd, 1 H, J = 2.94, 1.77 Hz)	5.46 (dd, 1 H, J = 2.94, 1.32 Hz)	2.26 (s, 4 H, CH_2); 1.01 (s, 6 H, Me); 11.71 (br.s, OH)
	DMSO-d_6—CD_3COOD	—	—	7.09 (d, 1 H, J = 2.94 Hz)	5.48 (d, 1 H, J = 2.94 Hz)	2.26 (s, 4 H, CH_2); 0.99 (s, 6 H, Me)
9b	DMSO-d_6	—	—	9.56 (s, 1 H)	—	2.31 (s, 4 H, CH_2); 1.06 (s, 6 H, CH_3)

strong intramolecular hydrogen bonding that stabilizes a six-membered ring system.[12]

The ^{1}H NMR data (Table 2) indicate that compounds **8a** and **8b** are adducts, which is evidenced by a signal at 5.29—5.48 for the proton at the sp^3-hybridized C(7) atom. The absence of a signal for the proton at the β-atom of the cyclic diketone suggests that the cyclic dicarbonyl residue exists in the enol form. Compound **8b** exists exclusively as the N(8)—H tautomer, as is obvious from the spin-spin coupling constants between the C(6)—H and N(8)—H protons (J = 1.9 Hz) and between the C(7)—H and N(8)—H protons (J = 1.1 Hz) in its ^{1}H NMR spectrum. A low vicinal coupling constant between the C(7)—H and N(8)—H protons can be explained by a specific conformation in which the H(8)—N(8)—C(7)—H(7) torsion angle corresponds to the minimum of the Carplus dependence of the coupling constant on the torsion angle.[13]

The ^{1}H NMR spectra of compounds **7b** and **9b** show signals for only one tautomer displayed in Scheme 2. Hypothetically, these compounds could exist in form **B** (like compounds **5** and **6**), but their spectra, in contrast to those of **5** and **6** contain a distinct signal for the CH proton at δ 11.9—12.00, which is close to a signal for the hydroxyl proton in unsubstituted dimedone (δ 11.2—11.5).

Thus, the aforesaid reactions are not only a convenient method for structural modification of unsubstituted 1,2,4-triazines, but also a rare example of easy oxidation of σ^H-adducts during the S_NH-process.

Experimental

^{1}H NMR spectra were recorded on Bruker DRX 400 (400 MHz) and Tesla BS 587A (80 MHz) instruments with Me_4Si as the internal standard. Mass spectra were recorded on a Varian MAT 311-A instrument with a combined FD/EI source (direct inlet into the ion source, ionizing voltage 70 eV). IR spectra were recorded on a Specord IR-75 instrument. Elemental analysis was carried out on a Carlo Erba 1108 analyzer. The course of the reaction was monitored and the purity of products was checked by TLC on plates with a fixed ARMSORB KSGK-UF layer in dichloromethane—methanol (10 : 1); spots were detected in UV light. Flash chromatography was performed on Woelm DC silica gel. Melting points were determined on combined Boetius stages and are given noncorrected. The starting triazolo[4,3-*b*]- and tetrazolo[1,5-*b*]-1,2,4-triazines were obtained according to the known procedures.[14,15]

Ethyl 2-(7,8-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4-triazin-7-ylidene)cyanoacetate (5a). 1,2,4-Triazolo[4,3-*b*]-1,2,4-triazine (**1**) (50 mg, 0.41 mmol) was added with stirring to a solution of a salt prepared from potassium *tert*-butoxide (47 mg, 0.41 mmol) and ethyl cyanoacetate (0.044 mL, 0.41 mmol). The reaction mixture was stirred at ~20 °C for 8 h, and then the solvent was removed. The residue was dissolved in water and neutralized with 0.1 *M* HCl. The bright yellow precipitate that formed was filtered off, recrystallized from methanol, and dried in air. The yield of **5a** was 60 mg (63%), m.p. >340. Found (%): C, 46.67; H, 3.40; N, 36.44. $C_9H_8N_6O_2$. Calculated (%): C, 46.55; H, 3.47; N, 36.19.

Diethyl 2-(7,8-dihydro-1,2,4-triazolo[4,3-*b*]-1,2,4-triazin-7-ylidene)malonate (5b). Potassium *tert*-butoxide (47 mg, 0.41 mmol) was added to a stirred solution of ethyl malonate (0.062 mL, 0.41 mmol) in 3 mL of THF. 1,2,4-Triazolo[4,3-*b*]-1,2,4-triazine (**1**) (50 mg, 0.41 mmol) was added to the resulting suspension, and the reaction mixture was stirred at ~20 °C for 6 h. An analytically pure potassium salt of compound **5b** that formed as a yellow precipitate was filtered off. The yield of **5b** was 57 mg (50%), m.p. >340. Found (%): C, 41.50; H, 3.72; N, 21.87. $C_{11}H_{12}K\,N_5O_4$. Calculated (%): C, 41.63; H, 3.81; N, 22.07.

Ethyl 2-(7,8-dihydrotetrazolo[4,3-*b*]-1,2,4-triazin-7-ylidene)cyanoacetate (6a). Potassium *tert*-butoxide (188 mg, 1.64 mmol) was added to a stirred solution of ethyl cyanoacetate (0.174 mL, 1.64 mmol) in 3 mL of THF. Tetrazolo[1,5-*b*]-1,2,4-triazine (200 mg, 1.64 mmol) was added to the resulting suspension. The reaction mixture was stirred at ~20 °C for 2 h, and then the solvent was removed. The residue was dissolved in water and acidified to pH 3. The bright yellow precipitate that formed was filtered off and recrystallized with charcoal from methanol. The yield of **6a** was 230 mg (60%), m.p. 140—142 °C. Found (%): C, 41.15; H, 3.05; N, 42.43. $C_8H_7N_7O_2$. Calculated (%): C, 41.20; H, 3.03; N, 42.05. MS, m/z (I_{rel} (%)): 233 [M^+] (47), 207 (11), 188 (12), 177 (31), 161

(13), 149 (84), 135 (13), 120 (100), 104 (48), 92 (80), 77 (34), 69 (32), 52 (52).

Diethyl 2-(7,8-dihydrotetrazolo[1,5-*b*]-1,2,4-triazin-7-ylidene)malonate (6b). Ethyl malonate (0.062 mL) was added to a suspension of potassium *tert*-butoxide (47 mg, 0.41 mmol) in THF, and the resulting mixture was stirred at ~20 °C for 15 min. Then tetrazolo[1,5-*b*]-1,2,4-triazine (**2**) (50 mg, 0.41 mol) was added with stirring. After the reaction was completed, the solution was concentrated, and the residue was dissolved in water and neutralized with dilute HCl. The pale yellow precipitate that formed was filtered off, recrystallized with activated carbon from methanol, and dried in air. The yield of **6b** (71 mg, 62%), m.p. 104—106 °C. Found (%): C, 42.46; H, 4.26; N, 30.38. $C_{10}H_{12}N_6O_4$. Calculated (%): C, 42.85; H, 4.32; N, 30.00.

5-(1,2,4-Triazolo[4,3-*b*]-1,2,4-triazin-7-yl)tetrahydropyrimidine-2,4-dione (7a). Triethylamine (0.1 mL) was added dropwise to a stirred solution of 1,2,4-triazolo[4,3-*b*]-1,2,4-triazine (50 mg, 0.41 mmol) and barbituric acid (52.5 mg, 0.41 mmol) in acetonitrile. The reaction mixture was stirred at ~20 °C for 24 h, and then the solvent was removed. The residue was dissolved in water and neutralized. The red precipitate that formed was filtered off, recrystallized from methanol, and dried in air. The yield of **7a** was 41 mg (40%), m.p. 164 °C (decomp.). Found (%): C, 38.47; H, 2.08; N, 39.72. $C_8H_5N_7O_3$. Calculated (%): C, 38.87; H, 2.04; N, 39.66.

3-Hydroxy-5,5-dimethyl-2-(1,2,4-triazolo[4,3-*b*]-1,2,4-triazin-7-yl)cyclohexen-1-one (7b). Powdered lithium hydride (4 mg, 0.41 mmol) was added with stirring to a solution of dimedone (58 mg, 0.41 mmol) in 4 mL of THF. 1,2,4-Triazolo[4,3-*b*]-1,2,4-triazine (50 mg, 0.41 mmol) was added to the resulting suspension. The reaction mixture was stirred at ~20 °C for 3 h, and the solvent was removed. The residue was dissolved in water and neutralized with dilute HCl. The colorless precipitate that formed was filtered off. The yield of **7b** was 32 mg (30%), m.p. 139—140 °C. Found (%): C, 55.80; H, 4.89; N, 27.30. $C_{12}H_{13}N_5O_2$. Calculated (%): C, 55.59; H, 5.05; N, 27.01. MS, m/z (I_{rel}(%)): 259 [M^+] (90), 241 (18), 185 (65), 175 (100), 162 (22), 135 (24), 83 (89), 55 (40).

5-(7,8-Dihydrotetrazolo[1,5-*b*]-1,2,4-triazin-7-yl)-6-hydroxy-1,2,3,4-tetrahydropyrimidine-2,4-dione (8a). Tetrazolo[1,5-*b*]-1,2,4-triazine (**2**) (50 mg, 0.41 mmol) was added to a solution of barbituric acid (53 g, 0.41 mmol) and triethylamine (0.069 mL, 0.5 mmol) in 3 mL of ethanol. The reaction mixture was refluxed for 2 h. The yellow precipitate of a triethylammonium salt of compound **8a** was filtered off and recrystallized from methanol. The yield of **8a** · Et_3N was 35 mg (25%), m.p. 159 °C (decomp.). Found (%): C, 44.30; H, 5.64; N, 35.67. $C_{13}H_{21}N_9O_3$. Calculated (%): C, 44.43; H, 6.03; N, 35.88.

2-(7,8-Dihydrotetrazolo[1,5-*b*]-1,2,4-triazin-7-yl)-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (8b). Dimedone (57 mg, 0.42 mmol) was added to a suspension of lithium hydride (3.5 mg, 0.41 mmol) in 2 mL of THF, and the reaction mixture was stirred at ~20 °C until hydrogen evolution ceased. Tetrazolo[1,5-*b*]-1,2,4-triazine (50 mg, 0.41 mmol) was added to the resulting gel, and the reaction mixture was stirred for 7 h and neutralized. The yellow precipitate that formed was filtered off and recrystallized from methanol. The yield of **8b** was 100 mg (87%), m.p. 212 °C (decomp.). Found (%): C, 50.48; H, 5.46; N, 32.17. $C_{11}H_{14}N_6O_2$. Calculated (%): C, 50.37; H, 5.38; N, 32.05.

3-Hydroxy-5,5-dimethyl-2-(tetrazolo[1,5-*b*]-1,2,4-triazin-7-yl)cyclohexen-1-one (9b). A solution of compound **8b** (30 g, 0.11 mmol) in 5 mL of DMF was refluxed with oxygen bubbling for 20 h. The solvent was removed *in vacuo*, and the residue was dissolved in 3 mL of a CH_2Cl_2—MeOH mixture (20 : 1). The product was isolated by flash chromatography. The yield of **9b** was 20 mg (70%), yellow crystals, m.p. 187—189 °C. Found (%): C, 51.02; H, 4.87; N, 32.05. $C_{11}H_{12}N_6O_2$. Calculated (%): C, 50.77; H, 4.65; N, 32.29.

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