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CYCLOCONDENSATION OF 3-AMINO-1,2,4-TRIAZOLES WITH ESTERS OF SUBSTITUTED CINNAMIC ACIDS AND AROMATIC UNSATURATED KETONES

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We have studied the reactions of 3-amino, 3,5-diamino-, and 3-amino-5-trifluoromethyl-1,2,4-triazole with esters of substituted cinnamic acids and aromatic unsaturated ketones; we have established the directionality of formation of the tetrahydrooxopyrimidine ring. We have carried out hydrolysis and hydrazinolysis of 7-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-a]pyrimidin-5-one. We have conducted an X-ray diffraction study of isopropylidene hydrazide of 3-(5-amino-1,2,4-triazol-1-yl)-3-phenylpropionic acid.

Keywords: 3-amino-1,2,4-triazoles, arylidenemethyl ketones, 7-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidin-5-one, esters of cinnamic acids, X-ray diffraction analysis.

Cyclocondensation of heterocyclic amines with dielectrophilic carbonyl compounds is a convenient method for the formation of azolopyrimidine systems [1, 2]. In this work, we have studied the reaction of 3-amino- (**1**), 3,5-diamino- (**2**), and 3-amino-5-trifluoromethyl-1,2,4-triazole (**3**) with esters of substituted cinnamic acids **4a-g**, α-chlorocinnamic acid (**5**) and its methyl ester (**6**). To determine the structure of the products obtained (**7-10**), as the reference systems we synthesized dihydroazolopyrimidines **12a-c** and **13a-c** from amines **2** and **3** and unsaturated ketones **11a-c**. In all cases, the reaction was carried out by boiling equimolar amounts of reagents in dimethylformamide (2-5 h). Comparison of the time required for the process, determined using TLC for the different amines, allows us to arrange the latter in order of increase in activity in the following series: **3** < **1** < **2**.

In reaction of amine **1** with α-chlorocinnamic acid **5** or its methyl ester **6**, cleavage of HCl and formation of compound **10** occurred. Under these conditions, aminoazoles **1-3** do not react with cinnamic acid.

Partially hydrogenated azolopyrimidines when treated with acids can undergo degradation to the starting aminoazole and unsaturated carbonyl compound [3], but compounds **7, 13c** remained unchanged when their alcoholic solutions were boiled with an equimolar amount of HCl. Heating or room-temperature holding of dihydroazolopyrimidine **13c** in alcoholic or aqueous alcoholic solutions of NaOH in air led to formation of the heteroaromatic derivative **14**. Compound **7** under analogous conditions is easily hydrolyzed with formation of amine **1** and the salt of cinnamic acid, but its hydrazinolysis leads to compound **15**, which under the reaction conditions undergoes further degradation.

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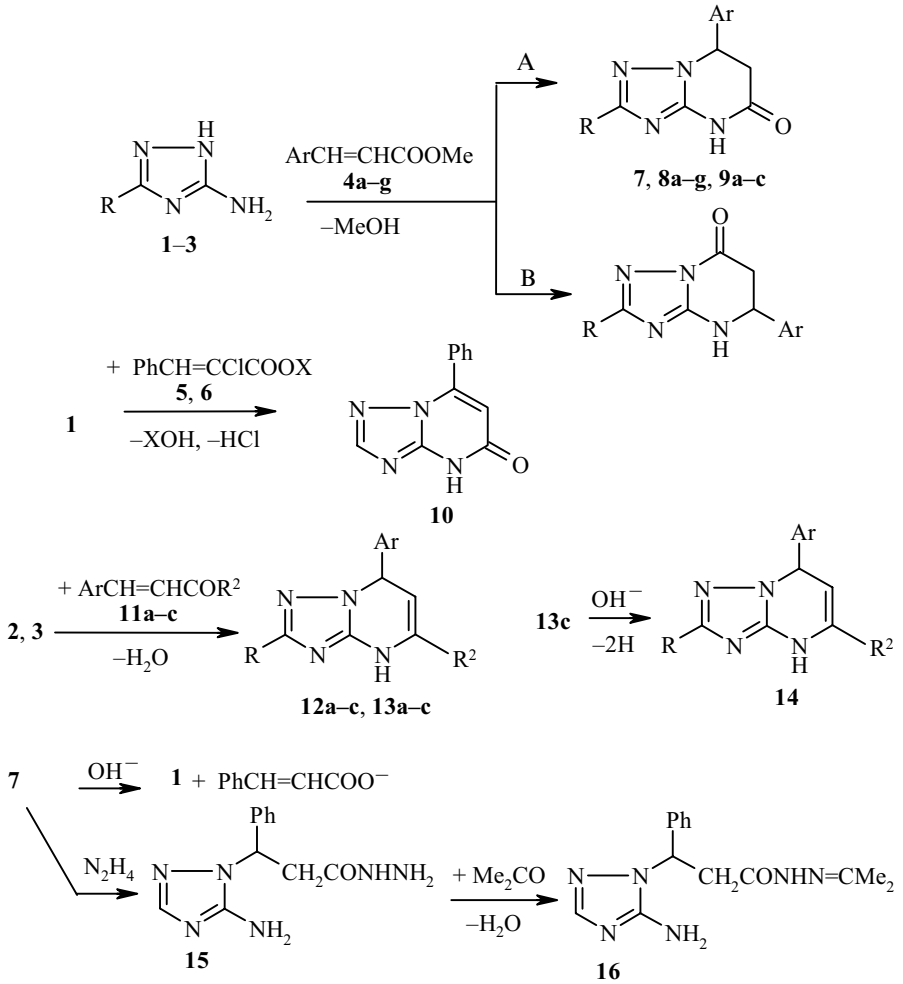

1, 7 R = H; **2, 8, 12** R = NH_2; **3, 9, 13** R = CF_3. **4, 7–9 a** Ar = Ph, **b–f** Ar = $C_6H_4R^1$, **b** R^1 = Me-4, **c** R^1 = OMe-4, **d** R^1 = F-4, **e** R^1 = Cl-4, **f** R^1 = NO_2-3, **g** Ar = $C_6H_3(OMe)_2$-2,4; **5** X = H, **6** X = Me; **11–13 a** Ar = Ph, R^2 = Me, **b** Ar = C_6H_4OMe-4, R^2 = Me, **c** Ar = R^2 = Ph

The structure of the compounds obtained is confirmed by the elemental analysis results, IR and ^{1}H NMR spectra (Tables 1 and 2). Compounds **7, 12c** were described earlier in [4, 5]. The structure of compound **15** is also supported by X-ray diffraction analysis of hydrazone **16** obtained from it.

In the IR spectra of triazolopyrimidinones **7-10**, there are intense bands in the 1684-1720 and 1520-1596 regions, and also a broad band in the 3450-3100 cm^{-1} region, characteristic of cyclic amides; in the spectra of dihydroazolopyrimidines **12, 13**, there is a $\nu_{C=C}$ band in the region of 1672-1695 cm^{-1} (Table 1) which is rather typical for such systems.

According to the results of previous investigations of reactions of aminoazoles with esters of unsaturated acids in the aliphatic series [1], in the condensation we have studied we might expect formation of both 5- and 7-oxo derivatives of tetrahydrotriazolopyrimidines from cinnamic acid derivatives, i.e, occurrence of the reaction via route A and B. An unambiguous answer to the question concerning the directionality of the reaction comes from comparison of the ^{1}H NMR spectra of compounds **8, 9** and **12,13**. In these spectra, we see signals from aromatic protons, protons of the NH group and the substituents R^1, R^2, and also protons in positions 6 and 7 of the pyrimidine ring, characterizing ABX- (**8,9**) or AX- (**10**) systems (in the spectra of compounds **10, 14**, the 6-H proton appears as a singlet). The downfield shift (by 2.2-3.0 ppm, Table 2) of the signal from the imine proton in the spectra of compounds **8,9** compared with the spectra of compounds **12,13** is a consequence of its amide

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found N, % / Calculated N, %	mp, °C*	IR spectrum (KBr), ν, cm^{-1}	Reaction time, h	Yield, %
8a	$C_{11}H_{11}N_5O$	29.8 / 30.6	252-254	1700, 1580	2.0	63
8b	$C_{12}H_{13}N_5O$	28.2 / 28.8	235-237	1700, 1596	2.0	50
8c	$C_{12}H_{13}N_5O_2$	26.5 / 27.0	220-222	1700, 1590	1.5	67
8d	$C_{13}H_{15}N_5O_3$	23.9 / 24.2	219-221	1700, 1596	1.5	47
8e	$C_{11}H_{10}N_5FO$	27.5 / 28.3	259-261	1704, 1584	1.0	69
8f	$C_{11}H_{10}N_5ClO$	26.1 / 26.6	258-260	1704, 1588	1.0	57
8g	$C_{11}H_{10}N_6O_3$	29.9 / 30.7	255-257	1708, 1560	1.5	45
9a	$C_{12}H_9N_4F_3O$	19.2 / 19.9	212-213	1720, 1544	3.5	48
9b	$C_{13}H_{11}N_4F_3O$	18.3 / 18.9	207-209	1720, 1544	4.0	42
9c	$C_{12}H_8N_4F_4O$	18.1 / 18.8	216-217	1720, 1544	4.5	54
10	$C_{11}H_8N_4O$	25.9 / 26.4	233-235	1700, 1636	2.0	62
12a	$C_{12}H_{13}N_5$	30.7 / 30.8	305-307	1683	0.2	80
12b	$C_{13}H_{15}N_5O$	27.0 / 27.2	292-294	1661	0.2	50
13a	$C_{13}H_{11}N_4F_3$	20.3 / 20.0	171-173	3222, 1690	1.0	60
13b	$C_{14}H_{13}N_4F_3O$	18.0 / 18.1	180-182	3225, 1695	1.0	55
13c	$C_{18}H_{13}N_4F_3$	16.2 / 16.4	188-189	3250, 1672	1.0	51
14	$C_{18}H_{11}N_4F_3$	16.6 / 16.5	147-149	—		76
15	$C_{11}H_{14}N_6O$	33.9 / 34.2	162-164	1672, 1664, 1568		77
16	$C_{14}H_{18}N_6O$	29.8 / 29.4	205-206	1684, 1652, 1524		85

* Compounds **8a-g, 9a-c, 10** were crystallized from 2:1 *i*-PrOH–DMF mixture; **12a,b, 13a-c**, from 1:1 PhH–DMF mixture; **14**, from EtOH; **15**, from CCl_4.

character, which allows us to reject the alternative 7-oxo structures for these compounds and consequently to reject also cyclocondensation route B. Realization of route A for the reaction is also indirectly supported by the structure established by X-ray diffraction for hydrazone **16**, a derivative of tetrahydrotriazolopyrimidinone **7**.

According to X-ray diffraction data (Fig. 1, Table 3), in the molecule of **16**, the aminotriazole moiety is located in the same plane as the $H_{(4)}$ hydrogen atom (torsional angle $C_{(5)}$–$N_{(3)}$–$C_{(4)}$–$H_{(4)}$ 4(1)°), and the amino group is on the same side as the $H_{(4)}$ atom, despite the shortened intramolecular contacts $C_{(4)}\cdots H_{(6NB)}$ 2.77 Å, $H_{(4)}\cdots N_{(6)}$ 2.62 Å, $H_{(4)}\cdots H_{(6NB)}$ 2.16 Å (the sum of the van der Waals radii is 2.87 Å [6]). The $N_{(6)}$ nitrogen atom, as in the case of 3-amino-2H-1,2,4-triazole [7], has a trigonal–pyramidal configuration (the sum of the bond angles is 351.1(3)°). The phenyl ring $C_{(7)}\cdots C_{(12)}$ is rotated by 53.3(2)° relative to the $C_{(4)}$–$H_{(4)}$, and lies practically in the same plane as the $C_{(3)}$ atom (torsional angle $C_{(3)}$–$C_{(4)}$–$C_{(7)}$–$C_{(12)}$ 7.4(4)°), despite the shortened contacts $C_{(3)}\cdots H_{(12)}$ 2.64 Å, $H_{(3B)}\cdots C_{(12)}$ 2.84 Å.

The carbonyl group is rotated by 33.2(3)° relative to the $C_{(3)}$–$C_{(4)}$ bond (torsional angle $O_{(1)}$–$C_{(2)}$–$C_{(3)}$–$C_{(4)}$). The O=C–NH–N=C moiety has an *s-cis-s-trans* configuration relative to the bonds $C_{(2)}$–$N_{(2)}$ and $N_{(1)}$–$N_{(2)}$ (torsional angles $O_{(1)}$–$C_{(2)}$–$N_{(2)}$–$N_{(1)}$ 7.6(3)°, $C_{(1)}$–$N_{(1)}$–$N_{(2)}$–$C_{(2)}$ 165.0(2)°). The conjugated system $C_{(1)}$–$N_{(1)}$–$N_{(2)}$–$C_{(2)}$–$O_{(1)}$ is

TABLE 2. ^{1}H NMR Spectral Characteristics of Compounds **8-10, 12-16***, δ (ppm) and Spin–spin Coupling Constant (*J*), Hz

Com-pound	NH (1H, br. s)	NH_2 (2H, s)	H_{Ar}, m	Protons of heterocyclic moiety	CH_3 (3H, s)
8c	11.4	5.27	6.8-7.2 (4H)	5.30 (1H, t, 7-H_X); 3.26 (1H, dd, 6-H_B); 2.77 (1H, dd, 6-H_A) J_{AX} = 5.0, J_{BX} = 7.0, J_{AB} = -16.3	3.72 (OCH_3)
8e	12.0	5.43	7.3-7.5 (4H)	5.55 (1H, dd, 7-H_X); 3.50 (1H, dd, 6-H_B); 3.01 (1H, dd, 6-H_A) J_{AX} =7.5, J_{BX} = 7.5, J_{AB} = -16.0	
8f	11.4	5.33	7.1-7.4 (4H)	5.40 (1H, t, 7-H_X); 3.33 (1H, m, 6-H_B); 2.84 (1H, dd, 6-H_A) J_{AX} = 7.5, J_{BX} = 7.5, J_{AB} = -17.5	
9a	12.0	—	7.1-7.4 (5H)	5.82 (1H, t, 7-H_X); 3.39 (1H, dd, 6-H_B); 3.06 (1H, dd, 6-H_A) J_{AX} = 7.0, J_{BX} =7.0, J_{AB} = -17.0	
9b	12.0	—	7.1-7.3 (4H)	5.76 (1H, t, 7-H_X); 3.00 (1H, dd, 6-H_B); 3.39 (1H, dd, 6-H_A) J_{AX} = 7.0, J_{BX} = 7.0, J_{AB} = -16.8	2.30
9c	11.9	—	7.1-7.5 (4H)	5.96 (1H, t, 7-H_X); 3.65 (1H, dd, 6-H_B); 3.40 (1H, dd, 6-H_A) J_{AX} = 6.6, J_{BX} = 6.6, J_{AB} = -16.2	
10	13.0		7.7-8.1 (5H)	8.26 (1H, s, 2-H); 6.47 (1H, s, 6-H)	
12a	9.2	4.99	7.1-7.4 (5H)	5.66 (1H, br. s, 7-H); 4.46 (1H, br. s, 6-H)	1.82
12c	9.3	5.03	6.8-7.4 (4H)	5.61 (1H, br. s, 7-H); 4,48 (1H, br. s, 6-H)	1.84; 3.84 (OCH_3)
13a	9.2	—	7.0-7.4 (5H)	5.97 (1H, br. s, 7-H); 4.62 (1H, br. s, 6-H)	1.97
13b	9.0	—	6.8-7.3 (4H)	5.95 (1H, br. s, 7-H); 4.62 (1H, br. s, 6-H)	2.00; 3.79 (OCH_3)
13c	7.8	—	7.3-7.5 (10H)	6.14 (1H, d, 7-H); 5.15 (1H, d, 6-H), J = 3.6	
14	—	—	7.2-8.3 (10H)	7.78 (1H, s, 6-H)	
15	9.1	6.25 (2H, 3-NH_2) 4.15 (2H, $NHNH_2$)	7.2-7.4 (5H)	*[2]5.78 (1H, t, CH_X); 3.07 (1H, dd, H_B in CH_2); 2.85 (1H, dd, H_A in CH_2); J_{AX} = 8.0; J_{BX} = 10.0; J_{AB} = -18.0	
16	11.5	7.46	8.5-8.6 (5H)	*[2]7.06 (1H, dd, CH_X); 4.95 (1H, dd, H_B in CH_2); 4.25 (1H, dd, H_A in CH_2), J_{AX} = 7.0; J_{BX} = 7.0; J_{AB} = -15.0	3.02 3.06

* The spectra of the compounds were recorded in the following solvents: **9c**, in Py-d_5; **8c,e,f, 9a,b, 12a,b, 13a-c–16**, in DMSO-d_6; **10**, in DMF-d_7.

*[2] For compounds **15** and **16**, we indicate signals from protons of the –$CHCH_2CO$ moiety.

nonplanar. The bond angle $C_{(13)}$–$C_{(1)}$–$N_{(1)}$ 125.5(2)° is increased compared with the angle $C_{(14)}$–$C_{(1)}$–$N_{(1)}$ 117.0(2)°. This is probably due to the intramolecular shortened contacts $H_{(2N)}\cdots C_{(13)}$ 2.47 Å, $H_{(2N)}\cdots H_{(13C)}$ 2.16 Å (2.32 Å), $N_{(2)}$–$H_{(13C)}$ 2.57 Å (2.66 Å), $H_{(2N)}\cdots H_{(3A)}$ 2.28 Å.

The molecules in the crystal form three-dimensional networks as a result of the hydrogen bonds $H_{(2N)}\cdots N_{(4')}$ (-1 - *x*, 1 - *y*, -*z*) (H···N 2.29 Å, N–H···N 162°), $H_{(6NA)}\cdots N_{(5')}$ (-*x*, 2-*y*, 1-*z*) (H···N 2.28 Å, NH···H 162°).

TABLE 3. Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters ($Å^2 \times 10^3$) of Non-hydrogen Atoms in the Molecule of Compound **16**

Atom	*x*	*y*	*z*	U_{eq}
$O_{(1)}$	948(3)	7079(2)	1979(2)	29(1)
$N_{(1)}$	45(3)	7881(3)	-315(2)	28(1)
$C_{(1)}$	-241(4)	7941(3)	-1497(3)	26(1)
$N_{(2)}$	-1188(3)	6479(2)	-166(2)	24(1)
$C_{(2)}$	-663(4)	6222(3)	1031(3)	21(1)
$N_{(3)}$	-2641(3)	6313(2)	2795(2)	19(1)
$C_{(3)}$	-2203(4)	4767(3)	1136(2)	20(1)
$N_{(4)}$	-4538(3)	6156(2)	2082(2)	23(1)
$C_{(4)}$	-2122(4)	5034(3)	2527(2)	19(1)
$N_{(5)}$	-2618(3)	8480(2)	3688(2)	23(1)
$C_{(5)}$	-1536(4)	7702(3)	3745(2)	21(1)
$N_{(6)}$	352(3)	8170(3)	4635(2)	34(1)
$C_{(6)}$	-4405(4)	7487(3)	2673(3)	24(1)
$C_{(7)}$	-3369(4)	3615(3)	2849(2)	21(1)
$C_{(8)}$	-3149(4)	3770(3)	4147(3)	28(1)
$C_{(9)}$	-4241(4)	2530(3)	4507(3)	35(1)
$C_{(10)}$	-5579(4)	1102(3)	3574(3)	35(1)
$C_{(11)}$	-5826(4)	913(3)	2281(3)	35(1)
$C_{(12)}$	-4717(4)	2166(3)	1917(3)	28(1)
$C_{(13)}$	-679(5)	6609(3)	-2723(3)	35(1)
$C_{(14)}$	983(5)	9470(3)	-1661(3)	42(1)

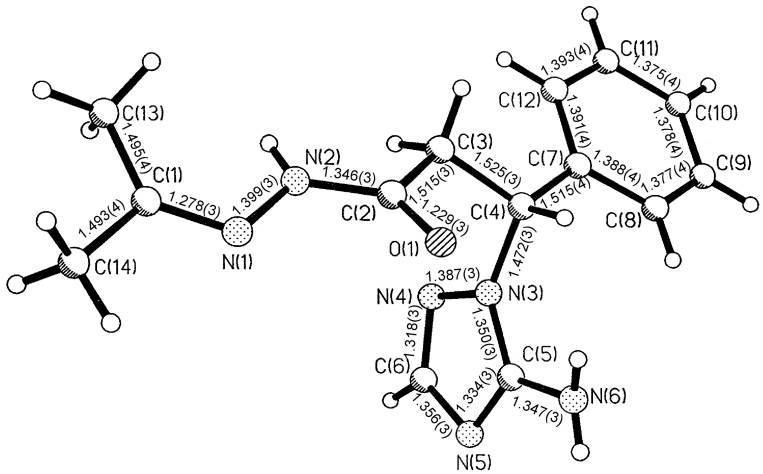

Fig. 1. Structure of the compound **16** molecule and the bond lengths (Å).

EXPERIMENTAL

X-ray Diffraction Study of Compound 16. The crystals of isopropylidene hydrazide of 3-(5-amino-1,2,4-triazol-1-yl)-3-phenylpropionic acid **16** are triclinic. At 20°C, a = 7.965(2), b = 9.629(3), c = 11.205(3) Å; α = 67.44(5)°, β = 109.82(2)°, γ = 112.64(2)°; V = 715.2(3) $Å^3$; d_{calc} = 1.330 g/cm^3; Z = 2; space group $P1$. The cell parameters and the intensities of 2736 independent reflections were measured on a Siemens P3/PC automatic four-circle diffractometer (αMoK_α, graphite monochromator, $\theta/2\theta$ scanning, $2\theta_{max}$ = 50°).

The structure was solved by the direct method using the software package SHELXTL PLUS [8]. The positions of the hydrogen atoms were calculated geometrically and refined using the rider model with fixed U_{iso}. Full-matrix least-squares refinement with respect to F^2 in the anisotropic approximation for the non-hydrogen atoms using 2535 reflections was carried out to $wR_2 = 0.119$ ($R_1 = 0.053$ using 1539 reflections with $F > 4\sigma(F)$, $S = 0.89$). The coordinates of the atoms are given in Table 3.

The IR spectra were measured on a Specord M-82 in KBr disks. The ^{1}H NMR spectra were recorded on a Bruker 300 spectrometer in DMSO-d_6 (compounds **7-10, 12, 13c, 15, 16**) and a Bruker AM-400 spectrometer (compounds **13a,b, 14**), internal standard TMS. The course of the reactions and the purity of the compounds formed were monitored by TLC on Silufol UV-254 plates in the 1:1 $CHCl_3$–MeOH system.

2-Amino-5-oxo-7-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimid-5-one (8). Solution of cinnamic acid ester **4a** (0.32 g, 2 mmol) and diaminotriazole **2** (0.2 g, 2 mmol) in DMF (2 ml) was boiled for 2 h, cooled, and mixed with 2-propanol (10 ml). Compound **8a** (0.29 g) was filtered off.

Compound **7** with mp 215°C was obtained similarly from ester **4a** and aminotriazole **1**. Lit. mp, 215-217°C [4]. Compounds **8b-g** were synthesized from esters **4b-g** and aminotriazole **2**; compounds **9a-c** were synthesized from esters **4a,b,e** and amino(trifluoromethyl)triazole; and compound **10** was synthesized from chlorocinnamic acid **5** or its ester **6** and aminotriazole **1**.

2-Amino-5-methyl-7-phenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (12a). Solution of diaminotriazole **2** (0.5 g, 5 mmol) and benzalacetone **11a** (0.8 g, 5.5 mmol) in DMF (1 ml) was boiled for 10 min, cooled, and mixed with acetone (30 ml). Compound **12a** (0.9 g) was filtered off.

Compounds **12b,c** were obtained similarly from diamine **2** and ketones **11b,c**; products **13a-c** were obtained from amino(trifluoromethyl)triazole **3** and ketones **11a-c**. Compound **12c** has mp 306-307°C. Lit. mp 305-307°C [5].

5,7-Diphenyl-2-trifluoromethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (14). Compound **13c** (0.34 g, 1 mmol) was boiled for 20 min in 3% methanol solution of KOH (10 ml), cooled, and neutralized with 1:1 HCl solution. The precipitate of product **14** formed was separated by filtration. Yield 0.26 g.

Hydrolysis of 5-Oxo-7-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (7). Compound **7** (0.2 g, 1 mmol) was boiled for 20 min in 3% alcoholic KOH solution (5 ml), cooled, acidified with 1:1 HCl solution to pH ~1, and extracted with benzene. Cinnamic acid (0.135 g, 91%) was isolated from the extract; mp 133°C. Lit. mp 133-134°C [9]. The aqueous layer was neutralized with $NaHCO_3$ and evaporated on a water bath. 3-Amino-1,2,4-triazole **1** (0.05 g) was isolated from the dry residue upon recrystallization from 1:1 chloroform–ether mixture; mp 159°C. Lit. mp 159°C [9].

Hydrazide of 3-(5-Amino-1,2,4-triazol-1-yl)-3-phenylpropionic acid (15). Solution of compound **7** (0.4 g, 2 mmol) in 2-propanol (13 ml) containing 20% hydrazine hydrate (3 ml) was boiled for 20 min, cooled, neutralized with dilute HCl solution, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and filtered. The solvent was driven off and the residue was crystallized from CCl_4. Product **15** (0.38 g) was obtained.

Isopropylidene Hydrazide of 3-(5-Amino-1,2,4-triazol-1-yl)-3-phenylpropionic Acid (16). Acetone (3 ml) was added to solution of compound **15** (0.25 g, 1 mmol) in methanol (10 ml). The reaction mixture was stirred at room temperature for 30 min. The precipitate formed was separated by filtration. Product **16** (0.23 g) was obtained.

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