A new approach to the synthesis of lamotrigine and other 3,5-diamino-1,2,4-triazine derivatives

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A new in principle method for the synthesis of 6-aryl(hetaryl)-3,5-diamino-1,2,4-triazines by decomposition of pre-synthesized tetrazolo[1,5-*b*][1,2,4]triazines was developed. The advantages of this method over traditional methods were demonstrated using the synthesis of a modern antiepileptic preparation lamotrigine, as an example.

Key words: destruction, 3,5-diamino-1,2,4-triazines, condensation.

The remarkable diversity of the purposes of modern organic synthesis requires new nontrivial approaches and methods for the preparation of heterocyclic compounds, because traditional cyclization routes do not always provide the best results. Therefore, synthetic chemists have to consider once again known transformations that have previously been regarded only as peculiar properties or side processes. Examples of such reactions include diverse degradations of fused azoloazines with a bridging nitrogen atom. Our observations and published data show that degradation processes are rather frequently encountered in these compounds and represent an integral part of their reactivities.[1—8] It should be noted that the destruction route can be controlled to give products of cleavage of both the azole ring and the azine fragment. This strategy resulted in the synthesis of diverse pyrimidine[1,2,3—6] and 1,2,4-triazine[1,2,7,8] derivatives. All these data indicate that cleavage of fused nitrogen heterocycles of this type can appear as a general and efficient synthetic tool.

Nevertheless, no publications in which the destruction of a nitrogen-containing heterocycle has been used deliberately to prepare compounds with useful properties are available. This is not surprising, as this type of reaction has not yet been properly appreciated by organic chemists and the attitude towards this method is rather negative. Indeed, the destruction takes place in some syntheses of practically valuable compounds: drugs, natural products, anomalous nucleosides[9—11] and, therefore, ring opening is treated as an undesirable side process.

This communication demonstrates the expediency of using degradation in the synthesis by presenting examples, convincing from our stanpoint, of synthesis of physiologically active substances, derivatives of 3,5-diamino-6-aryl-1,2,4-triazines,[12,13] having a marked antimalarial action and the antiepileptic drug lamotrigine, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, widely used in clinical practice.[14]

Two key methods for the synthesis of 3,5-diamino-6-aryl-1,2,4-triazines have been reported; these can be exemplified in the preparation of lamotrigine (**1a**). One method is underlain by condensation of arylacetyl cyanide **2** with aminoguanidine[15] (Scheme 1). It is noteworthy that this method, simple as it may seem, has substantial drawbacks. The condensation of compound **2** with aminoguanidine proceeds in a yield not higher than 16%. The synthesis of aroyl cyanide **2** from chloride **3** presents a serious problem itself. The yield of compound **2** can markedly drop due to the side self-condensation, resulting in the formation of α-aroyloxy(α-arylmalono)dinitrile $Ar—C(CN)_2—OCO—Ar$.[16] The overall yield of lamotrigine (**1a**) according to Scheme 1 does not exceed 13%.

The other method used to prepare compound **1a** is based on the replacement of oxo- and thioxo fragments in compound **4**, which is in turn obtained by condensation of thiosemicarbazide with 2,3-dichlorophenylglyoxal **5** [17](Scheme 2). The overall yield of compound **1a** according to Scheme 2 does not exceed 18%.

The presented data indicate that the methods used to prepare lamotrigine can hardly be called perfect.

In this communication, we propose a new method for the synthesis of 6-aryl- and 6-hetaryl-3,5-diamino-1,2,4-triazines based on the strategy of preliminary synthesis of fused heterocycles and subsequent destruction of one

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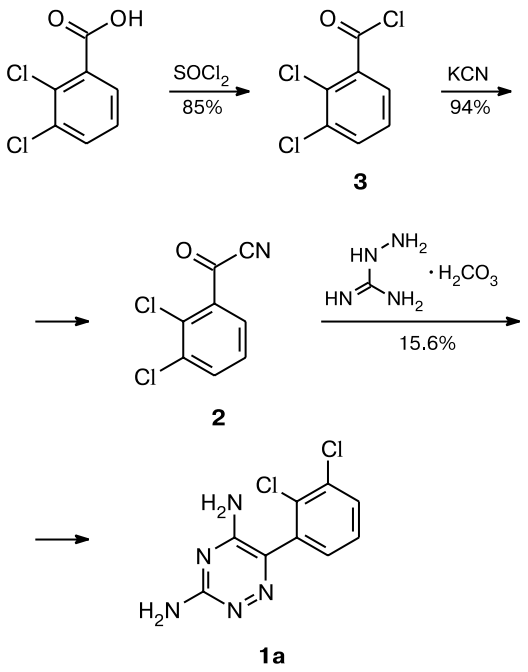
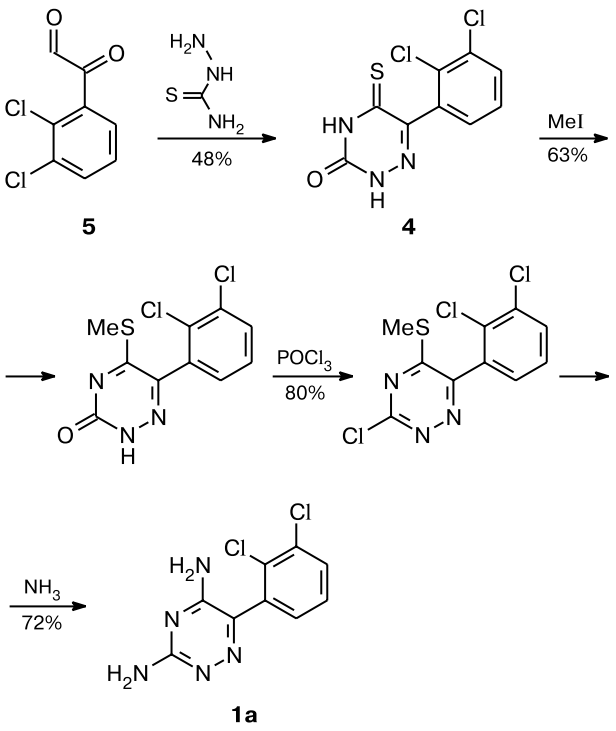
Scheme 1



Scheme 2



cyclic fragment. This method can probably be called "reconstructive," because the structure created initially subsequently undergoes a partial destruction.

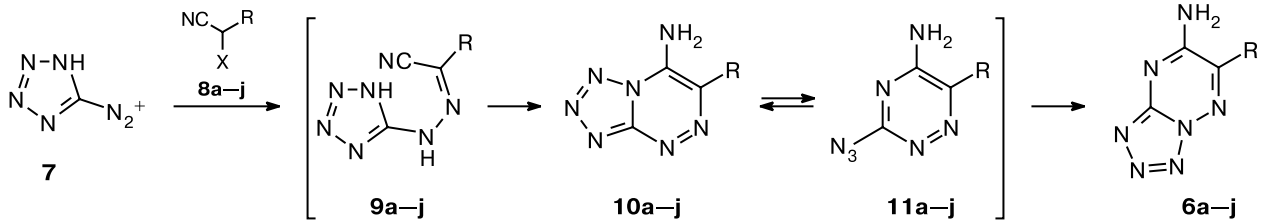
Results and Discussion

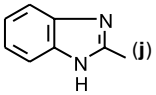
We found that cleavage of fused 6-aryl- and 6-hetaryl-7-aminotetrazolo[1,5-*b*][1,2,4]triazines (**6a—j**) is an efficient and readily accessible method for the synthesis of a number of 6-substituted 3,5-diamino-1,2,4-triazine derivatives **1a—j**.

Compounds **6a—j** were prepared using coupling with tetrazolyldiazonium salt (**7**) (Scheme 3). As the CH-active component, we used α-formyl-α-arylacetonitriles **8a—h** and hetarylacetonitriles **8i,j** (Scheme 3). The use of formyl derivatives **8a—h** is due to the fact that arylacetonitriles themselves do not enter into azo coupling due to the low CH-acidity.[18] In order to increase the CH-activity of arylacetonitriles, we developed a simple approach based on introducing an easily leaving electron-withdrawing substituent, a formyl group, which is eliminated on the formation of hydrazone **9a—h**.

Formylacetonitriles **8b—h** were obtained directly from readily available benzyl cyanides. Compound **8a**

Scheme 3



6,8—11: R = 2,3-$Cl_2C_6H_3$ (**a**); 2,4-$Cl_2C_6H_3$ (**b**), 2-FC_6H_4 (**c**),  (**d**), 3,4-$F_2C_6H_3$ (**e**), 2,3,4,5-F_4C_6H (**f**), Ph (**g**), 3,5-$(CF_3)_2C_6H_3$ (**h**),  (**i**),  (**j**)

8a—h: X = CHO; **8i,j:** X = H

was synthesized from 2,3-dichlorotoluene *via* bromomethyl 2,3-dichlorobenzene, which was then treated with sodium cyanide and formylated. This gave formyl derivative **8a** in a 69% overall yield based on 2,3-dichlorotoluene.

In the case of compounds **8i,j**, the presence of electron-withdrawing pyridine and benzimidazole heterocycle substituents, respectively, markedly facilitates the reaction with compound **7** and does not require additional activation by a formyl group.

Tetrazolyldiazonium salt **7** was obtained from 5-aminotetrazole, which is a commercial chemical or is prepared from aminoguanidine nitrate.[19]

Salt **7** reacts with CH-active components **8a—j** in the presence of sodium carbonate or acetate. The reaction affords hydrazones **9a—j**, which are converted into tetrazolo[1,5-*b*][1,2,4]triazines **6a—j** on refluxing in acetic acid or DMF.

The mass spectra of compounds **6a—j** exhibit a molecular ion peak (Table 1). The ^{1}H NMR spectra contain resonance signals for the aryl protons at 7.00—8.50 ppm. The amino group protons are responsible most often for a two-proton broadened singlet at 7.40—8.80 ppm. Compounds **6i,j** in which the amino group is manifested as two one-proton broadened singlets are exceptions (Table 2).

The IR spectra of compounds **6a—j** exhibit signals at 3150—3350 cm^{-1} due to the stretching vibrations of the amino group (see Table 1). The lack of stretching signals for the azido group at 2120—2160 cm^{-1} confirms that the tetrazole ring in compounds **6a—j** is annelated to the triazine ring.

X-Ray diffraction analysis of compounds **6g** (R = Ph) revealed the mode of annelation of the tetrazole and triazine rings in **6a—j**, which was classified as [1,5-*b*]-annelation (Fig. 1, Table 3). The geometric parameters of the molecule are close to the usual values for tetrazolo[1,5-*b*][1,2,4]triazines.[20] The azole and azine rings are coplanar; their mean plane forms a dihedral angle of 49.4° with the phenyl group. In the crystal, the molecules form centrosymmetric dimers with intermolecular hydrogen bonds (see Fig. 1, Table 4). The dimers, in turn, are linked by weaker hydrogen bonds.

It should be noted that cyclization of hydrazones **9a—j** can yield only compounds **10a—j** in which the azole and azine rings are annelated according to the [5,1-*c*] pattern. The only possible route from compounds **9a—j** to tetrazolo[1,5-*b*]triazines **6a—j** is that *via* azides **11a—j**. Thus, the synthesis of hetarylamines **6a—j** is a sequence of transformations that involves opening of the tetrazole ring in azoloazines **10a—j**.

The most important problem solved in this study is the destruction of the azole ring in tetrazolo[1,5-*b*]-1,2,4-triazines **6a—j**. It is known that the transformation of the tetrazole ring in 8-methoxytetrazolo[1,5-*c*]pyrimidine into an amino group is accomplished using triphenylphosphine.

Table 1. Melting points, yields, molecular masses (according to mass spectrometry data) and IR-spectral data of compounds **1a—j** and **6a—j**

Compound	M.p. /°C	Yield (%)[a]	$[M]^+$, m/z (I (%))	IR spectrum, ν/cm^{-1}
1a	218[b]	76 (A)	256 (67)	3140, 3180, 3420 (NH)
1b	221—222[b]	70 (A) 65 (B)	256 (70)	3160, 3190, 3350 (NH)
1c	230[b]	78 (A)	205 (64)	3180, 3200, 3380 (NH)
1d	254[b]	63 (A) 60 (B)	193 (73)	3150, 3220, 3380 (NH)
1e	219—220[b]	72 (A)	223 (59)	3200, 3330, 3460 (NH)
1f	198[b]	89 (A)	259 (78)	3170, 3210, 3410 (NH)
1g	201[c]	79 (A) 75 (B)	187 (72)	3180, 3200, 3400 (NH)
1h	198—200[b]	72 (A)	323 (65)	3190,3200, 3400 (NH)
1i	225—227[c]	78 (A)	188 (87)	3120, 3230, 3380 (NH)
1j	256[d]	78 (A)	227 (80)	3180, 3200, 3400 (NH)
6a	240[d]	68	282 (41)	3170, 3290 (NH)
6b	210—212[d]	70	282 (34)	3140, 3290 (NH)
6c	226[d]	70	231 (47)	3130, 3280 (NH)
6d	218[d]	72	219 (41)	3120, 3300 (NH)
6e	190[d]	68	249 (37)	3200, 3350 (NH)
6f	218—220[d]	87	285 (44)	3150, 3270 (NH)
6g	228[e]	74	213 (34)	3180, 3310 (NH)
6h	218[d]	85	349 (33)	3190, 3340 (NH)
6i	252[d]	72	214 (27)	3160, 3250 (NH)
6j	272[d]	80	253 (32)	3150, 3300 (NH)

[a] The method of synthesis is indicated in parentheses.
[b] Recrystallized from isopropyl alcohol
[c] Recrystallized from ethanol.
[d] Recrystallized from DMF.
[e] Recrystallized from acetic acid.

6-Amino-5-methoxypyrimidine was formed in this reaction[21].

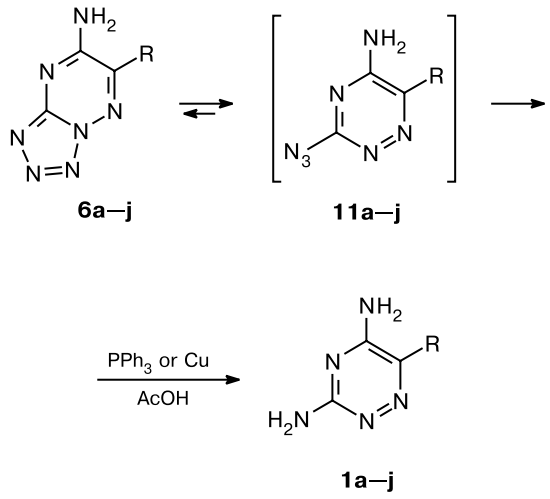
We found that treatment of tetrazolotriazines **6b,d,g** with triphenylphosphine in acetic acid affords diamino-1,2,4-triazines **1b,d,g**. In order to upgrade the standard procedure for degradation of the tetrazole ring in fused

Table 2. ^{1}H NMR data for compounds **1a—j** and **6a—j**

Compound	δ	
	Ar	NH_2 (br.s)
1a	7.33—7.45 (m, 2 H, $C_6H_3Cl_2$); 7.67—7.69 (m, 1 H, $C_6H_3Cl_2$)	6.39, 6.66 (2 H each, NH_2)
1b	7.35—7.45 (m, 2 H, $C_6H_3Cl_2$); 7.53—7.55 (m, 1 H, 2,4-$Cl_2C_6H_3$)	6.18, 6.43 (2 H each, NH_2)
1c	7.16—7.29, 7.39—7.47 (both m, 2 H each, C_6H_4F)	6.18, 6.47 (2 H, NH_2)
1d	7.07—7.11 (m, 1 H, C_4H_3S); 7.38—7.42 (m, 2 H, C_4H_3S)	6.27, 6.75 (2 H each, NH_2)
1e	7.33—7.51 (m, 3 H, $C_6H_3F_2$)	6.23, 6.74 (2 H each, NH_2)
1f	7.23—7.28 (m, 1 H, C_6HF_4)	6.33, 6.72 (2 H each, NH_2)
1g	7.41—7.57 (m, 5 H, Ph)	6.22, 6.55 (2 H each, NH_2)
1h	7.88 (s, 1 H, $C_6H_3(CF_3)_2$); 8.11 (s, 2 H, $C_6H_3(CF_3)_2$)	6.44, 6.90 (2 H, NH_2)
1i	7.24—7.39 (m, 2 H, C_5H_4N+NH); 7.84—7.85 (m, 1 H, C_5H_4N) 8.40—8.53 (m, 2 H, C_5H_4N)	6.54 (2 H, NH_2); 9.20 (1 H, NH)
1j	7.10—7.19 (m, 2 H, C_6H_4); 7.47—7.62 (m, 3 H, C_6H_4+NH)	6.60 (2 H, NH_2); 8.94 (1 H, NH); 12.50 (1 H, NH)
6a	7.57—7.70 (m, 2 H, $C_6H_3Cl_2$); 7.84—7.96 (m, 1 H, $C_6H_3Cl_2$)	8.75 (2 H, NH_2)
6b	7.55—7.70 (m, 3 H, $C_6H_3Cl_2$)	8.72 (2 H, NH_2)
6c	7.31—7.43 (m, 2 H, C_6H_4F); 7.50 (br.s, 2 H, NH_2); 7.60—7.70 (m, 2 H, C_6H_4F)	8.68 (2 H, NH_2)
6d	7.25—7.28 (m, 1 H, C_4H_3S); 7.88—7.90 (m, 2 H, C_4H_3S)	8.20 (2 H, NH_2)
6e	7.51—7.66 (m, 2 H, $C_6H_3F_2$); 7.70—7.74 (m, 1 H, $C_6H_3F_2$)	8.70 (2 H, NH_2)
6f	7.59—7.66 (m, 1 H, C_6HF_4)	7.70, 8.80 (1 H each, NH_2)
6g	7.58—7.60 (m, 3 H, Ph); 7.65—7.74 (m, 2 H, Ph)	7.43 (2 H, NH_2)
6h	8.13 (s, 1 H, $C_6H_3(CF_2)_2$); 8.29 (s, 2 H, $C_6H_3(CF_2)_2$)	8.00 (2 H, NH_2)
6i	7.66—7.71, 8.09—8.16 8.48—8.51, 8.77—8.79 (all m, 1 H each, C_5H_5N); (m, 1 H, C_5H_5N)	9.10 (1 H, NH_2); 10.06 (1 H, NH_2)
6j	7.29—7.38, 7.70—7.81 (both m, 2 H each, C_6H_4); 10.06 (br.s, 1 H, NH)	9.29, 10.00 (1 H each, NH_2)

heterocycles, we developed a new method for the destruction of tetrazolo[1,5-*b*]-1,2,4-triazines in the presence of copper. This method is simpler and less expensive and, in addition, it increases the yields of amino compounds (see Table 1). Thus refluxing of compounds **6a—j** in a weakly acidic medium in the presence of a freshly prepared copper powder gives 3,5-diamino-1,2,4-triazines **1a—j**. Apparently, the destruction of the tetrazole ring in compounds **6a—j** proceeds *via* azides **11a—j** (Scheme 4). The yields of 3,5-diamino-1,2,4-triazines **1a—j** vary from 65 to 90%. The overall yield of compound **1a** was 36% based on dichlorotoluene, which is at least twice as high as the yields in the known syntheses of Lamotrigine (13% from 2,3-dichlorobenzoic acid[15] and 18% from 2,3-dichlorophenylglyoxal[17]).

Scheme 4



1, 6, 11: R = 2,3-$Cl_2C_6H_3$ (**a**), 2,4-$Cl_2C_6H_3$ (**b**), 2-FC_6H_4 (**c**), (**d**), 3,4-$F_2C_6H_3$ (**e**), 2,3,4,5-F_4C_6H (**f**), Ph (**g**), 3,5-$(CF_3)_2C_6H_3$ (**h**), (**i**), (**j**)

The additional two-proton broadened singlet in the ^{1}H NMR spectrum of compounds **1a—j** (see Table 2) attests to the presence of a second amino group resulting from destruction of the tetrazole ring. The same fact is demonstrated by the IR and mass spectra of compounds **1a—j**. The IR spectra were found to exhibit additional signals at 3140—3460 cm^{-1} absent in the spectra of starting tetrazolotriazines **6a—j**. The mass spectra contain molecular ion peaks for diamino-1,2,4-triazines (see Table 1). In addition, all physicochemical characteristics of compound **1a** we prepared are identical to those for a substance of Glaxo Wellcome lamotrigine.

Thus, using the synthesis of the antiepileptic drug Lamotrigine **1a** and other 3,5-diamino-1,2,4-triazine **1b—j** derivatives as examples, we demonstrated that degradation of fused heterocyclic structures can provide an efficient and facile method for the synthesis of heterocycles.

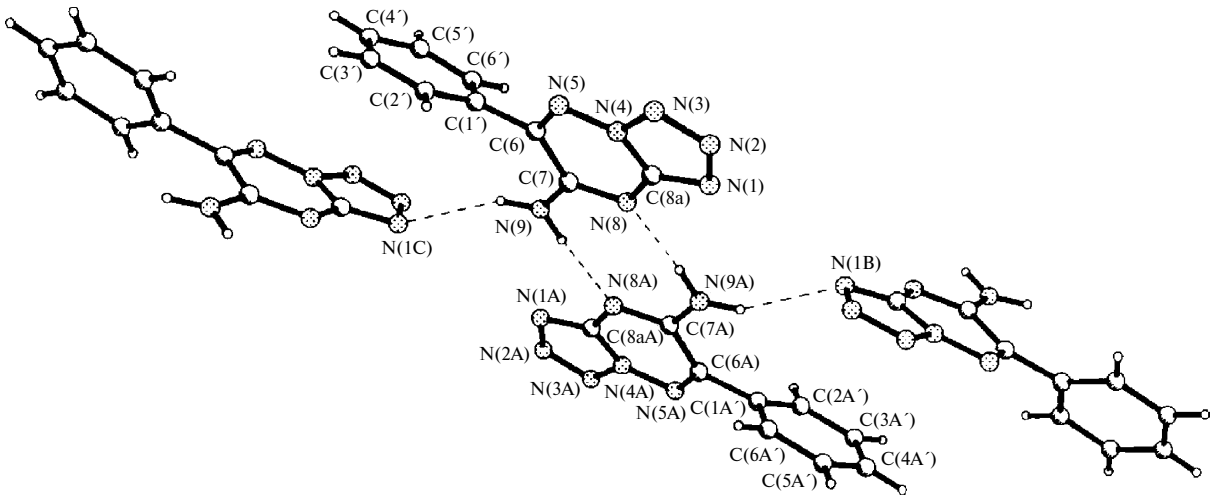


Fig. 1. Structure of molecule **6g**.

Experimental

The IR sperctra of the products were recorded in KBr on a Specord 75 IR spectrometer. ^{1}H NMR spectra (in DMSO-d_6 + CCl_4) were measured on a Bruker WM-250 instrument using Me_4Si as the internal standard. The mass spectra of the compounds were run on a Varian-MAT-311A instrument with direct sample injection into the ion source, the ionizing electron energy was 70 eV, and the temperature in the ionization chamber was 100—300 °C. The melting points were determined on a Boetius hot stage. TLC was performed on Silufol UV-254 plates in ethyl acetate (100%), the plates being visualized by UV irradiation and iodine vapor.

Commercial arylacetonitriles and 2,3-dichlorotoluene (Lancaster) and aminotetrazole (Aldrich) were used.

Aryl(formyl)acetonitriles 8a—h were synthesized by a reported procedure.[22]

2-Cyanomethylpyridine 8i and 2-cyanomethylbenzimidazole 8j were prepared by previously described procedure.[23,24]

Table 3. Selected bond lengths (*d*) and bond angles (ω) in compounds **6g**

Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å
N(1)—N(2)	1.3631(19)	N(4)—C(8a)	1.3531(16)	C(6)—C(7)	1.4765(16)	C′(2)—C′(3)	1.3904(18)
N(1)—C(8a)	1.3315(16)	N(5)—C(6)	1.3015(16)	C(6)—C′(1)	1.4867(16)	C′(3)—C′(4)	1.380(2)
N(2)—N(3)	1.2963(18)	N(8)—C(8a)	1.3379(16)	C′(1)—C′(2)	1.3903(17)	C′(4)—C′(5)	1.381(2)
N(3)—N(4)	1.3563(15)	N(8)—C(7)	1.3356(14)	C′(1)—C′(6)	1.3912(18)	C′(5)—C′(6)	1.389(2)
N(4)—N(5)	1.3540(14)	N(7)—C(2)	1.3212(16)				

Angle	ω/deg	Angle	ω/deg	Angle	ω/deg
N(1)—N(2)—N(3)	112.90(11)	N(1)—C(8a)—N(4)	107.32(12)	C′(2)—C′(1)—C′(9)	119.83(11)
N(2)—N(1)—C(8a)	105.33(11)	N(8)—C(8a)—N(4)	122.14(11)	C′(2)—C′(1)—C(6)	118.90(11)
N(2)—N(3)—N(4)	10.30(11)	N(9)—C(7)—N(8)	119.48(10)	C′(6)—C′(1)—C(6)	121.06(11)
N(5)—N(4)—N(3)	123.63(11)	N(9)—C(7)—C(6)	119.57(10)	C′(1)—C′(2)—C′(3)	120.00(13)
C(8a)—N(4)—N(3)	110.14(11)	N(8)—C(7)—C(6)	120.95(11)	C′(4)—C′(3)—C′(2)	120.04(14)
C(8a)—N(4)—N(5)	125.92(11)	N(5)—C(6)—C(7)	122.31(10)	C′(3)—C′(4)—C′(5)	120.02(13)
C(6)—N(5)—N(4)	113.11(10)	N(5)—C(6)—C′(1)	114.98(10)	C′(4)—C′(5)—C′(6)	120.58(14)
N(1)—C(8a)—N(8)	130.50(12)	C(7)—C(6)—C′(1)	122.69(10)	C′(5)—C′(6)—C′(1)	119.50(13)
C(7)—N(8)—C(8a)	114.98(10)				

Table 4. Hydrogen bonds H...A < *r*(A) + 2.000 Å and D—H...A angles (deg)

D—H	*d*(D—H)	*d*(H...A)	∠D—H...A	*d*(D...A)	A
N(9)—H_a(9)	0.934	2.111	176.16	3.043	N(8) (−*x*, −*y*, −*z* + 1)
N(9)—H_b(9)	0.888	2.290	155.60	3.120	N(1) (*x*, −*y* + 1/2, *z* + 1/2)

Table 5. Elemental analysis data for compounds **1a—j** and **6a—j**

Compound	Found / Calculated (%)			Molecular formula
	C	H	N	
1a	42.32 / 42.21	2.63 / 2.76	27.24 / 27.35	$C_9H_7N_5Cl_2$
1b	42.05 / 42.21	2.80 / 2.76	27.50 / 27.35	$C_9H_7N_5Cl_2$
1c	48.76 / 48.43	4.51 / 4.52	31.51 / 31.38	$C_9H_8N_5F \cdot H_2O$
1d	43.44 / 43.51	3.65 / 3.65	35.97 / 36.24	$C_7H_7N_5S$
1e	45.23 / 44.82	3.75 / 3.76	29.14 / 29.04	$C_9H_7N_5F_2 \cdot H_2O$
1f	42.00 / 41.71	2.13 / 1.94	26.98 / 27.02	$C_9H_5N_5F_4$
1g	57.71 / 57.74	4.83 / 4.85	37.29 / 37.41	$C_9H_9N_5$
1h	40.69 / 40.88	2.07 / 2.18	21.65 / 21.67	$C_{11}H_7N_5F_6$
1i	51.14 / 51.06	4.28 / 4.28	44.97 / 44.66	$C_8H_8N_6$
1j	52.45 / 52.86	3.83 / 3.99	43.23 / 43.15	$C_{10}H_9N_7$
6a	38.45 / 38.32	2.05 / 1.79	34.55 / 34.76	$C_9H_5N_7Cl_2$
6b	38.38 / 38.32	2.12 / 1.79	34.81 / 34.76	$C_9H_5N_7Cl_2$
6c	46.90 / 46.76	2.43 / 2.62	42.73 / 42.41	$C_9H_6N_7F$
6d	38.18 / 38.35	2.16 / 2.30	45.20 / 44.72	$C_7H_5N_7S$
6e	43.34 / 43.38	2.03 / 2.02	39.37 / 39.35	$C_9H_5N_7F_2$
6f	38.06 / 37.91	1.14 / 1.06	34.56 / 34.38	$C_9H_3N_7F_4$
6g	51.01 / 50.70	3.41 / 3.31	45.75 / 45.99	$C_9H_7N_7$
6h	37.95 / 37.84	1.44 / 1.44	28.09 / 28.08	$C_{11}H_5N_7F_6$
6i	44.76 / 44.86	2.87 / 2.82	52.23 / 52.31	$C_8H_6N_8$
6j	47.58 / 47.43	2.72 / 2.79	49.71 / 49.78	$C_{10}H_7N_9$

All other domestically produced solvents and reagents were used without additional purification.

The product yields and the solvents used for crystallization are indicated in Table 1, and the results of elemental analysis are in Table 5.

X-Ray diffraction study of 6g was carried out on a CAD-4 Enraf-Nonius automated diffractometer (λ-Mo-Kα, graphite monochromator, ω-scan mode, $2\theta_{max} = 60°$). The crystals are monoclinic $a = 10.935(2)$, $b = 6.7330(10)$, $c = 13.279(3)$ Å, $\beta = 93.20(3)°$, $Z = 4$, $d_{calc} = 1.451$ g cm^{-3}, $\mu = 0.105$ mm^{-1}, $V = 976.1(3)$ Å^3, space group $P2_1/c$. The structure was solved by the direct method and refined by least-squares calculations using the SHELXS-97[25] and SHELXL-97[26] software in the anisotropic (or isotropic for H atoms) approximation down to $R = 0.0473$ ($wR_2 = 0.1426$) for 1949 reflections with $F^2 > 4\sigma(F^2_o)$, the fitting factor GOOF being 1.001.

2,3-Dichlorophenylacetonitrile. A suspension of 2,3-dichlorotoluene (10 g, 0.062 mol) and bromosuccinimide (10.6 g, 0.059 mol) in 30 mL of CCl_4 was refluxed for 2 h and the precipitate was filtered off. A solution of NaCN (4 g, 0.082 mol) in 20 mL of water and 18-crown-6 (0.2 g) were added to the resulting solution. The reaction mixture was stirred for 48 h, the organic layer was separated, and CCl_4 was evaporated to give 2,3-dichlorophenylacetonitrile as a dark oil, which was used without further purification.

6-Aryl- and 6-hetaryl-7-aminotetrazolo[1,5-*b*][1,2,4]triazines 6a—j. Concentrated HCl (5 mL) was added to a solution of aminotetrazole (2 g, 0.02 mmol) in 100 mL of water. After cooling the reaction mixture to −2 °C, $NaNO_2$ (1.4 g, 0.02 mol) in 20 mL of water was added dropwise with intense stirring and the mixture was kept for 30 min at −2 °C. A mixture of aryl(formyl)acetonitrile (**8a—h**) or hetarylacetonitrile (**8i,j**) (0.02 mol) and sodium acetate (4.9 g) in 5 mL of water and 15 mL of ethanol were added to the resulting diazonium salt and the mixture was stirred for 2 h at room temperature and filtered. The precipitate was dissolved in 7 mL of acetic acid or 10 mL of DMF and the solution was refluxed and cooled. The precipitate was filtered off, crystallized, and dried.

6-Aryl- and 6-hetaryl-3,5-diamino-1,2,4-triazines 4a—j. ***A.*** A mixture 6-aryl- and 6-hetaryl-7-aminotetrazolo[1,5-*b*][1,2,4]triazine **6a—j** (0.02 mol), a copper powder (2.52 g, 0.04 mol) freshly prepared by a known method,[27] and 5 mL of acetic acid was refluxed for 2 h. Aqueous ammonia (25%, 80 mL) was added and the product was filtered off, crystallized, and dried.

B. A mixture of 6-aryl- and 6-hetaryl-7-aminotetrazolo[1,5-*b*][1,2,4]triazine **6b,d,g** (0.02 mol) and triphenylphosphine (5.30 g, 0.02 mol) and 10 mL of acetic acid was refluxed for 2 h. Aqueous ammonia (25%, 80 mL) was added to the reaction mixture and the product was filtered off, washed with diethyl ether, crystallized, and dried.

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