Chloromethyl-, dichloromethyl-, and trichloromethyl-1,2,4-triazines and their 4-oxides: method for the synthesis and *tele*-substitution reactions with C-nucleophiles

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A simple procedure was developed for the synthesis of 1,2,4-triazines and their 4-oxides containing the $ClCH_2$, Cl_2CH, or CCl_3 group at position 3 by cyclization of 2-aryl-2-hydrazono-1-oximinoethanes with the corresponding chloroacetonitriles. The reaction pathway depends on the number of halogen atoms in the acetonitrile used. The reactions with trichloroacetonitrile, monochloroacetonitrile, and dichloroacetonitrile afford 3-trichloromethyl-1,2,4-triazines, 3-chloromethyl-1,2,4-triazine 4-oxides, and a mixture of the corresponding dichloromethyltriazines and their 4-oxides, respectively. The reactions of 3-trichloromethyl-1,2,4-triazines with indoles and phenols are accompanied by *tele*-substitution with elimination of halogen from the trichloromethyl group to give 5-indolyl- (or 5-hydroxyphenyl)-3-dichloromethyl-1,2,4-triazines.

Key words: *tele*-substitution of chlorine, 3-trichloromethyl-1,2,4-triazines, 3-chloromethyl-1,2,4-triazine 4-oxides, indoles, phenols.

Aromatic nucleophilic substitution reactions proceeding according to the addition—elimination pattern involve two major steps, *viz.*, the formation of adducts and their aromatization.[1—3] An important characteristic feature of these reactions with aromatic and heteroaromatic substrates, including those containing nucleofuge groups (X = Hal, $CHal_3$, OR, OS, CN, or NO_2), is that σ^H-adducts bearing the hydrogen atom at the sp^3-hybridized carbon atom are formed more rapidly than σ^X-adducts.[3] Since elimination of the hydride anion, as such, is thermodynamically unfavorable (unlike *ipso*-substitution resulting in elimination of groups readily leaving as anions), nucleophilic substitution of hydrogen involves other types of aromatization, *viz.*, oxidative aromatization or autoaromatization of σ^H-adducts.[2] Autoaromatization is achieved due to elimination of hydrogen together with the auxiliary group L. The latter can be involved in σ^H-adducts as either a fragment of a nucleophile (vicarious nucleophilic substitution of hydrogen) or a fragment of the substrate (*cine*- and *tele*-substitutions) and can also be formed upon the addition of a nucleophile (deoxygenative nucleophilic substitution of hydrogen in the series of azine *N*-oxides).[2] The *tele*-substitution reactions can proceed through elimination of the leaving group L from both the aromatic (heteroaromatic)[4] ring and the carbon atom in the α position of the side aliphatic chain. Up to now, the latter process has been observed only in reactions of di- and trichloromethyl derivatives of electrophilic arenes and hetarenes with nucleophiles under basic conditions, for example, in the reactions of dichloromethylpyridazine,[5] trichloromethylpyrimidine,[6] or chloromethyl(phenyl)pyridazine[7] with alkoxide anions as well as in the reaction of trichloromethylnitrobenzene with methyl thioglycolate in the presence of triethylamine.[8]

In the present study, we report the data on *tele*-substitution of the chlorine atom from the side chain in the reactions with mild neutral aromatic and heteroaromatic C-nucleophiles. We carried out this reaction with 3-trichloromethyl-1,2,4-triazines **1** as substrates. It seems reasonable to use 1,2,4-triazines taking into account high reactivity of these heterocycles in nucleophilic substitution of hydrogen with different pathways of aromatization of intermediate σ^H-adducts.[9] We rejected the synthesis of the starting chloromethyl-1,2,4-triazines by direct chlorination of the corresponding methyl derivatives[10] and developed a much more facile method. This method involves cyclization of α-oximinoacetophenone hydrazones **2** by the reactions with chloromethylacetonitriles **3a—c** in methanol in the presence of sodium methoxide followed by acidification with trifluoroacetic acid (Scheme 1). As a result, we prepared the corresponding 3-chloromethyl-1,2,4-triazines **1a—c** and/or 3-chloromethyl-1,2,4-triazine 4-oxides **4a—c**. The reaction pathway is determined by the number of chlorine atoms in the acetonitrile molecule. For example, the reaction with trichloroacetonitrile

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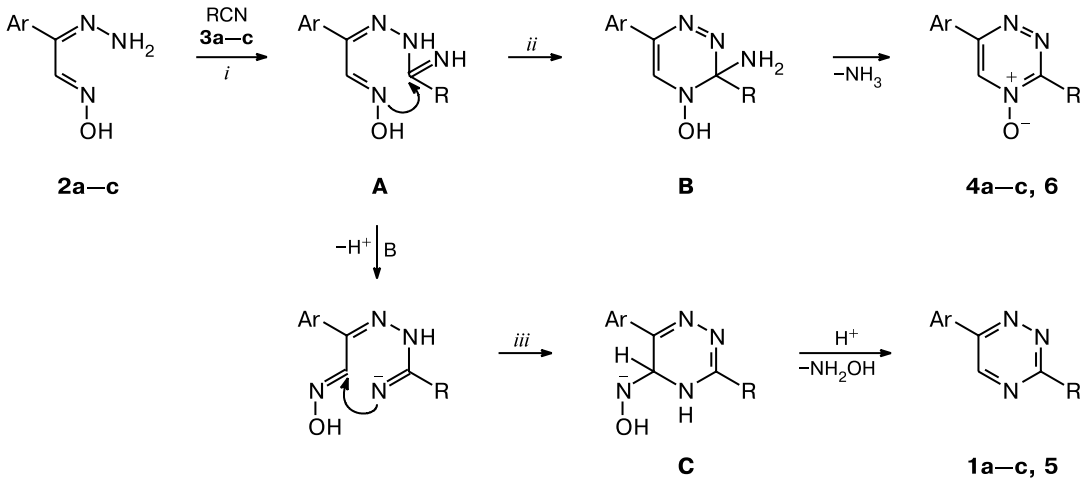
Scheme 1



Reagents and conditions: *i*. 1) MeONa/MeOH; 2) CF_3COOH; *ii*. R = CH_2Cl or $CHCl_2$; *iii*. R = CCl_3 or $CHCl_2$.

Ar = Ph (**a**), 4-Cl-C_6H_4 (**b**), 4-Me-C_6H_4 (**c**); R = CCl_3 (**1**, **3a**), CH_2Cl (**3b**, **4**), $CHCl_2$ (**3c**, **5**, **6**); B is a base

afforded exclusively 3-trichloromethyl-1,2,4-triazines **1a**. On the contrary, the reaction with monochloroacetonitrile produced only 3-chloromethyl-1,2,4-triazine 4-oxides **4b**. Dichloroacetonitrile, as expected, occupies an intermediate place and gave a mixture of 3-dichloromethyl-1,2,4-triazines **5** and their 4-oxides **6** in a nearly 1 : 1 ratio.

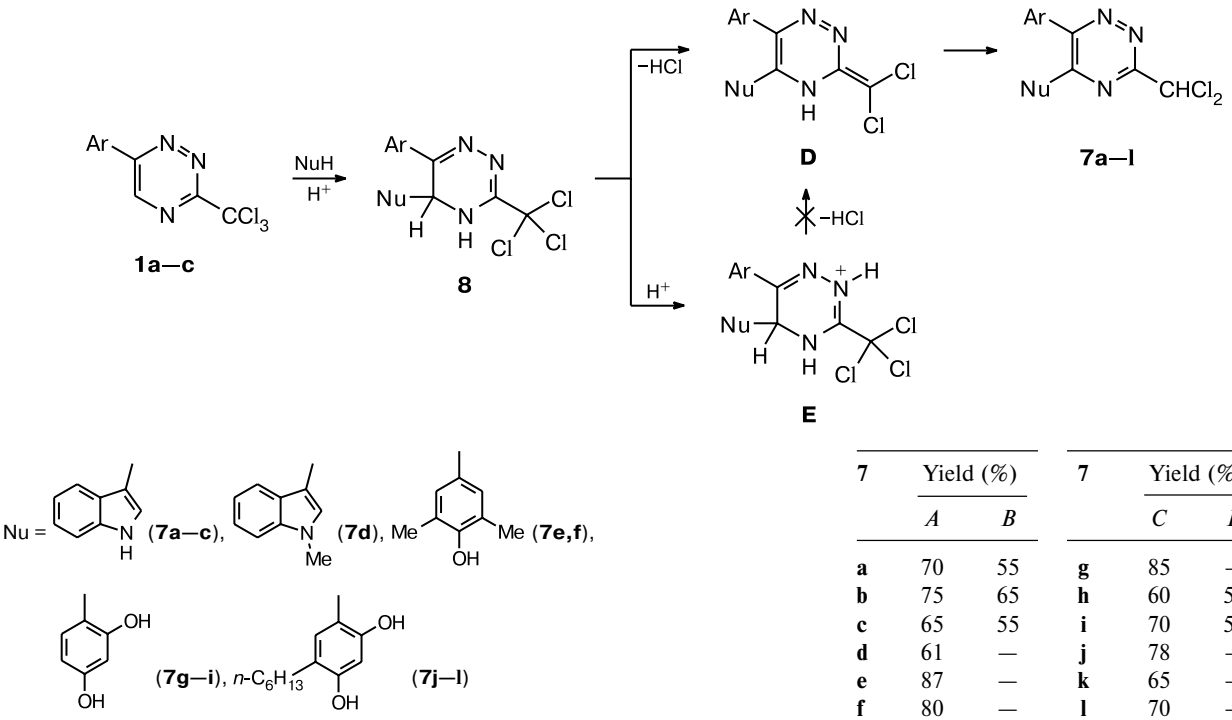
Apparently, the reaction proceeds through intermediate **A**. Further cyclization of the latter can follow two pathways: the attack of the oximine nitrogen atom on the amidine carbon atom followed by elimination of ammonia from intermediate **B** to form 1,2,4-triazine 4-oxides **4** and **6** or, alternatively, the attack of the amino group on the carbon atom of the oximine fragment with elimination of the hydroxylamine molecule from intermediate **C** to give 1,2,4-triazines **1** and **5**. The reaction pathway depends on the electron-withdrawing properties of the substituent R in the starting nitrile. The stronger electron-withdrawing trichloromethyl group directs the reaction toward 1,2,4-triazines **1**, whereas the monochloromethyl groups directs the reaction toward 1,2,4-triazine 4-oxides **4**, and the dichloromethyl group occupies an intermediate place.

The electrophilicity of the heterocycle in 3-trichloromethyl-1,2,4-triazines **1a—c** is additionally enhanced due to the presence of the electron-withdrawing trichloromethyl group. However, it is insufficient for the reaction with aromatic C-nucleophiles to proceed. It is necessary to activate the heterocyclic substrate by protonation giving rise to the more electrophilic azinium cation, which can be involved in the reaction.[11] As a result, 3-trichloromethyl-1,2,4-triazines **1a—c** react with indole or 1-methylindole in the presence of HCl or trifluoroacetic acid to give products of *tele*-substitution, *viz.*, 3-dichloromethyl-5-(indol-3-yl)-1,2,4-triazines **7a—d**, in 60—70% yields (Scheme 2, Table 1), accompanied by elimination of one of the chlorine atoms in the side trichloromethyl group. Aromatic C-nucleophiles (phenols) react with trichloromethyl-1,2,4-triazines analogously to indoles. Refluxing of compounds **1a—c** with 2,6-dimethylphenol, resorcinol, or 4-hexylresorcinol in acetic acid in the presence of trifluoroacetic acid afforded the corresponding 3-dichloromethyl-5-hydroxyphenyl-1,2,4-triazines **7e—l**.

The structures of the compounds synthesized were confirmed by NMR spectroscopy and mass spectrometry. In addition to the signals for the protons of the indole fragment, which is evidence that the reaction proceeds at position 3 of indole, and the signals for the protons of the aromatic substituent, the ^1H NMR spectra of dichloromethyl-1,2,4-triazines **7a—l** show a one-proton singlet for the methine proton of the dichloromethyl group at δ 7.43—7.50. The presence of two chlorine atoms is evidenced by the presence of a triplet of the molecular ion peak in the mass spectra of the products. Besides, the signals for the protons of the indole fragment in the series of 5-indolyl-1,2,4-triazines **7a—d** are characteristic.[12] In this respect, the signal for the proton at position 4′ of the indole fragment is particularly prominent. This signal is substantially shifted downfield compared to the signals of the other protons (δ 8.40—8.60) due to the anisotropic effect of the benzene ring of the substituent at position 6 of the triazine ring.

It is known[9] that under acidic conditions, 1,2,4-triazines and their *N*-oxides rather readily add various nucleophiles, including indoles, to form σ^H-adducts at position 5 of the heterocycle if the latter is devoid of substitu-

Scheme 2



Ar = Ph (**1a**, **7a,d,e,g,j**), 4-ClC_6H_4 (**1b**, **7b,h,k**), 4-MeC_6H_4 (**1c**, **7c,f,i,l**)

7	Yield (%)		7	Yield (%)	
	A	*B*		*C*	*D*
a	70	55	**g**	85	—
b	75	65	**h**	60	51
c	65	55	**i**	70	58
d	61	—	**j**	78	—
e	87	—	**k**	65	—
f	80	—	**l**	70	—

A — THF, CF_3COOH (0.1—0.2 mL); *B* — 1) CF_3COOH—$CHCl_3$, 2) AcOH, 117 °C; *C* — AcOH + + CF_3COOH (0.1—0.2 mL), 117 °C; *D* — 1) CF_3COOH, 2) AcOH, 117 °C.

ents. The formation of such intermediates is reliably detected by NMR spectroscopy or their isolation from reaction mixtures. Apparently, the reaction under consideration also starts with the addition of a nucleophile (indole) at position 5 of 1,2,4-triazine **1** (see Scheme 2). Further aromatization of σ^H-adducts **8** occurs through elimination of hydrogen together with one of the chlorine atoms of the trichloromethyl group. Subsequent prototropic isomerization of intermediate **D** affords aromatic products **7a—l**. We succeeded in finding conditions under which the reaction is terminated in the step of addition of the nucleophile. The presence of an acid at a high concentration does not hinder and even facilitates the addition of the nucleophile to the triazine ring resulting, however, in protonation of intermediates **8** to form the cationic form of the σ-adduct (**E**). Evidently, elimination of HCl from the positively charged molecule **E** seems to be highly improbable. Actually, the use of an excess of trifluoroacetic acid in the reactions of trichloromethyltriazines **1a—c** with indole or resorcinol allowed us to isolate σ^H-adducts **8a—c**. The latter appeared to be insufficiently stable to be purified. Hence, their structures were studied only by ^1H NMR spectroscopy. The spectra show characteristic signals[12] as one-proton singlets at δ 6.2—6.3 corresponding to the protons bound to the sp^3-hybridized carbon atom at position 5 of the triazine ring. σ^H-Adducts **8a—c** undergo aromatization through elimination of HCl already upon heating over a short period in acetic acid to give the corresponding dichloromethylindolyltriazines **7a—c**.

It should be noted that monochloromethyltriazine 4-oxides **4** are not involved in *tele*-substitution reactions under the above-discussed conditions.

To summarize, nucleophilic aromatic substitution of hydrogen (S_NH), where aromatization of intermediate σ^H-adducts occurs through elimination of the hydrogen atom together with an auxiliary group, *viz.*, the halogen atom in the α position of the side chain, can take place in the reactions of neutral nucleophiles with a substrate that is activated by protonation.

Experimental

The NMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz) in DMSO-d_6 with Me_4Si as the internal standard. The electron-ionization mass spectra were obtained

on a Varian MAT-311A instrument. The starting oximinoacetophenone hydrazones were prepared according to a known procedure.[13]

6-Phenyl-3-trichloromethyl-1,2,4-triazine (1a). Trichloroacetonitrile (2.5 mL, 25 mmol) was added with stirring and cooling with cold water to a solution of MeONa, which was prepared from sodium (10 mg) and methanol (10 mL). After 10—20 min, α-oximinoacetophenone hydrazone (**2a**, 3.25 g, 20 mmol) was added. After 20—30 min, the reaction mixture was acidified with trifluoroacetic acid to pH 4 and kept at ~20 °C for 16 h. Crystals of product **1a** were filtered off and recrystallized from ethanol. The yield was 4.3 g (78%), m.p. 145—146 °C. ^{1}H NMR, δ: 7.62 and 8.18 (both m, 3 H, 2 H); 9.65 (s, 1 H, H(5)). MS, *m/z* (I_{rel} (%)): 279 (1), 277 (9), 275 (28), 273 (30) $[M]^+$. Found (%): C, 43.52; H, 2.08; N, 15.07. $C_{10}H_6Cl_3N_3$. Calculated (%): C, 43.75; H, 2.20; N, 15.31.

6-(4-Chlorophenyl)-3-trichloromethyl-1,2,4-triazine (1b) was prepared analogously to **1a** starting from trichloroacetonitrile (2.5 mL, 25 mmol) and 4-chloro-α-oximinoacetophenone hydrazone (**2b**, 3.95 g, 20 mmol). The yield was 4.6 g (75%), m.p. 138—140 °C. ^{1}H NMR, δ: 7.60 and 8.17 (both m, 2 H); 9.64 (s, 1 H, H(5)). Found (%): C, 38.65; H, 1.49; N, 13.34. $C_{10}H_5Cl_4N_3$. Calculated (%): C, 38.87; H, 1.63; N, 13.60.

6-(4-Methylphenyl)-3-trichloromethyl-1,2,4-triazine (1c) was prepared analogously to **1a** starting from trichloroacetonitrile (2.5 mL, 25 mmol) and 4-methyl-α-oximinoacetophenone hydrazone (**2c**, 3.54 g, 20 mmol). The yield was 4.0 g (70%), m.p. 180—181 °C. ^{1}H NMR, δ: 2.46 (s, 3 H); 7.41 and 8.19 (both m, 2 H); 9.57 (s, 1 H, H(5)). MS, *m/z* (I_{rel} (%)): 291 (2), 289 (5), 287 (6) $[M]^+$. Found (%): C, 45.65; H, 2.72; N, 14.34. $C_{11}H_8Cl_3N_3$. Calculated (%): C, 45.79; H, 2.79; N, 14.56.

3-Chloromethyl-6-phenyl-1,2,4-triazine 4-oxide (4a) was prepared analogously to **1a** starting from chloroacetonitrile (1.6 mL, 25 mmol) and α-oximinoacetophenone hydrazone (**2a**, 3.25 g, 20 mmol). The yield was 2.9 g (66%), m.p. 188—189 °C. ^{1}H NMR, δ: 5.01 (s, 2 H, CH_2Cl); 7.58 and 8.20 (both m, 3 H, 2 H); 9.36 (s, 1 H, H(5)). Found (%): C, 54.34; H, 3.63; N, 19.28. $C_{10}H_8ClN_3O$. Calculated (%): C, 54.19; H, 3.64; N, 18.96.

3-Chloromethyl-6-(4-chlorophenyl)-1,2,4-triazine 4-oxide (4b) was prepared analogously to **1a** starting from chloroacetonitrile (1.6 mL, 25 mmol) and 4-chloro-α-oximinoacetophenone hydrazone (**2b**, 3.95 g, 20 mmol). The yield was 4.1 g (80%), m.p. 162—163 °C. ^{1}H NMR, δ: 5.04 (s, 2 H, CH_2Cl); 7.61 and 8.24 (both m, 2 H); 9.36 (s, 1 H, H(5)). Found (%): C, 46.91; H, 2.86; N, 16.71. $C_{10}H_7Cl_2N_3O$. Calculated (%): C, 46.90; H, 2.76; N, 16.41.

3-Chloromethyl-6-(4-methylphenyl)-1,2,4-triazine 4-oxide (4c) was prepared analogously to **1a** starting from chloroacetonitrile (1.6 mL, 25 mmol) and 4-methyl-α-oximinoacetophenone hydrazone (**2c**, 3.54 g, 20 mmol). The yield was 3.4 g (72%), m.p. 130—131 °C. ^{1}H NMR, δ: 2.43 (s, 3 H); 5.00 (s, 2 H, CH_2Cl); 7.38 and 8.12 (both m, 2 H); 9.29 (s, 1 H, H(5)). Found (%): C, 56.25; H, 4.26; N, 18.09. $C_{11}H_{10}ClN_3O$. Calculated (%): C, 56.06; H, 4.28; N, 17.83.

Synthesis of 6-aryl-3-dichloromethyl-1,2,4-triazines and their 4-oxides 5 and 6 (general procedure). Dichloroacetonitrile (0.52 mL, 6.5 mmol) was added to a solution of MeONa, which was prepared from sodium (0.1 g) and methanol (10 mL). After 10 min, the corresponding isonitrosoacetophenone hydrazone (5 mmol) was added. The reaction mixture was kept at room temperature for 20 min and acidified with trifluoroacetic acid to pH 3. The precipitate that formed was filtered off and recrystallized from ethanol to prepare a mixture consisting of triazine and triazine 4-oxide. The products were separated by column chromatography on silica gel using a 5 : 1 $CHCl_3$—hexane mixture as the eluent.

3-Dichloromethyl-6-phenyl-1,2,4-triazine (5a). The yield was 461 mg (1.92 mmol, 38%), m.p. 96—98 °C. ^{1}H NMR, δ: 7.53 (s, 1 H, $CHCl_2$); 7.59 (m, 3 H, Ph); 8.26 (m, 2 H, Ph); 9.54 (s, 1 H, H(5)). MS, *m/z* (I_{rel} (%)): 239 (9) and 241 (6) $[M]^+$. Found (%): C, 50.24; H, 2.83; N, 17.44. $C_{10}H_7Cl_2N_3$. Calculated (%): C, 50.03; H, 2.94; N, 17.50.

3-Dichloromethyl-6-phenyl-1,2,4-triazine 4-oxide (6a). The yield was 328 mg (1.28 mmol, 26%), m.p. 149—151 °C. ^{1}H NMR, δ: 7.58 (m, 4 H, Ph + $CHCl_2$); 8.22 (m, 2 H, Ph); 9.37 (s, 1 H, H(5)). MS, *m/z* (I_{rel} (%)): 255 (20) and 257 (13) $[M]^+$. Found (%): C, 47.68; H, 2.62; N, 16.04. $C_{10}H_7Cl_2N_3O$. Calculated (%): C, 46.90; H, 2.76; N, 16.31.

6-(4-Chlorophenyl)-3-dichloromethyl-1,2,4-triazine (5b). The yield was 494 mg (1.8 mmol, 36%), m.p. 132—133 °C. ^{1}H NMR, δ: 7.53 (s, 1 H, $CHCl_2$); 7.61 and 8.29 (both m, 2 H each, C_6H_4Cl); 9.58 (s, 1 H, H(5)). MS, *m/z* (I_{rel} (%)): 273 (9), 275 (8) and 277 (2) $[M]^+$. Found (%): C, 43.84; H, 2.25; N, 15.16. $C_{10}H_6Cl_3N_3$. Calculated (%): C, 43.75; H, 2.20; N, 15.31.

6-(4-Chlorophenyl)-3-dichloromethyl-1,2,4-triazine 4-oxide (6b). The yield was 290 mg (1 mmol, 20%), m.p. 206—209 °C. ^{1}H NMR, δ: 7.60 (m, 3 H, C_6H_4Cl + $CHCl_2$); 8.23 (m, 2 H, C_6H_4Cl); 9.43 (s, 1 H, H(5)). MS, *m/z* (I_{rel} (%)): 289 (25), 291 (24) and 293 (8) $[M]^+$. Found (%): C, 41.50; H, 1.81; N, 14.12. $C_{10}H_6Cl_3N_3O$. Calculated (%): C, 41.34; H, 2.08; N, 14.46.

3-Dichloromethyl-5-(indol-3-yl)-6-phenyl-1,2,4-triazine (7a). Trichloromethyl-1,2,4-triazine **1a** (550 mg, 2 mmol) and indole (235 mg, 2 mmol) were dissolved in THF (2 mL). Then one—two drops of hydrochloric or trifluoroacetic acid were added and the reaction mixture was kept at ~20 °C for 16 h. The precipitate that formed was filtered off and recrystallized from acetic acid. The yield was 470 mg (70%), m.p. 283 °C. ^{1}H NMR, δ: 6.80 (d, 1 H, H(2′), J = 3.3 Hz); 7.19 and 7.22 (both dd, 1 H, H(5′), H(6′), J = 3.5 Hz, J = 3.5 Hz); 7.40 (m, 1 H, H(7′)); 7.42 (s, 1 H, $CHCl_2$); 7.55—7.70 (m, 5 H, Ph); 8.67 (m, 1 H, H(4′)); 11.77 (br.d, 1 H, NH, J = 3.3 Hz). MS, *m/z* (I_{rel} (%)): 358 (8), 356 (46), 354 (70) $[M]^+$. Found (%): C, 60.64; H, 3.21; N, 15.50. $C_{18}H_{12}Cl_2N_4$. Calculated (%): C, 60.86; H, 3.41; N, 15.77.

6-(4-Chlorophenyl)-3-dichloromethyl-5-(indol-3-yl)-1,2,4-triazine (7b) was prepared analogously to **7a** starting from **1b** (620 mg, 2 mmol) and indole (235 mg, 2 mmol). The yield was 585 mg (75%), m.p. 256—258 °C. ^{1}H NMR, δ: 6.95 (d, 1 H, H(2′), J = 3.3 Hz); 7.19 and 7.23 (both dd, 1 H, H(5′), H(6′), J = 3.5 Hz, J = 3.5 Hz); 7.42 (s, 1 H, $CHCl_2$); 7.44 (m, 1 H, H(7′)); 7.55 and 7.70 (both m, 2 H); 8.63 (m, 1 H, H(4′)); 11.79 (br.d, 1 H, NH, J = 3.3 Hz). MS, *m/z* (I_{rel} (%)): 392 (6), 390 (19), 388 (20) $[M]^+$. Found (%): C, 55.23; H, 2.69; N, 14.09. $C_{18}H_{11}Cl_3N_4$. Calculated (%): C, 55.48; H, 2.85; N, 14.38.

3-Dichloromethyl-5-(indol-3-yl)-6-(4-methylphenyl)-1,2,4-triazine (7c) was prepared analogously to **7a** starting from **1c** (580 mg, 2 mmol) and indole (235 mg, 2 mmol). The yield was 480 mg (65%), m.p. 287—289 °C. ^{1}H NMR, δ: 2.45 (s, 3 H); 6.88 (d, 1 H, H(2′), J = 3.6 Hz); 7.26 and 7.29 (both dd, 1 H, H(5′), H(6′), J = 2.4 Hz, J = 2.4 Hz); 7.44 (m, 2 H); 7.50 (m, 1 H, H(7′)); 7.57 (m, 2 H); 7.71 (s, 1 H, $CHCl_2$); 8.78 (m, 1 H,

H(4′)); 11.89 (br.d, 1 H, NH, J = 3.6 Hz). Found (%): C, 61.64; H, 3.69; N, 14.98. $C_{19}H_{14}Cl_2N_4$. Calculated (%): C, 61.80; H, 3.82; N, 15.17.

3-Dichloromethyl-5-(1-methylindol-3-yl)-6-phenyl-1,2,4-triazine (7d) was prepared analogously to **7a** starting from **1a** (550 mg, 2 mmol) and 1-methylindole (0.26 mL, 2 mmol). The yield was 445 mg (61%), m.p. 239—241 °C. ^{1}H NMR, δ: 3.49 (s, 3 H, NMe); 6.78 (s, 1 H, H(2′)); 7.20—7.33 (m, 2 H, H(5′), H(6′)); 7.43 (s, 1 H, $CHCl_2$); 7.45 (m, 1 H, H(7′)); 7.50—7.70 (m, 5 H, Ph); 8.62 (m, 1 H, H(4′)). MS, m/z (I_{rel} (%)): 372 (5), 370 (30), 368 (46) $[M]^+$. Found (%): C, 61.66; H, 3.74; N, 14.87. $C_{19}H_{14}Cl_2N_4$. Calculated (%): C, 61.80; H, 3.82; N, 15.17.

Synthesis of 3-dichloromethyl-5-hydroxyphenyl-1,2,4-triazines 7e—l (general procedure). Trichloromethyl-1,2,4-triazine (2 mmol) and phenol (2 mmol) were dissolved in acetic acid (5 mL) and then trifluoroacetic acid (1 mL) was added. The reaction mixture was refluxed for 2 h and kept at ~20 °C for 16 h. The precipitate that formed was filtered off and recrystallized from acetic acid.

3-Dichloromethyl-5-(4-hydroxy-3,5-dimethylphenyl)-6-phenyl-1,2,4-triazine (7e). The yield was 87%, m.p. 176—179 °C. ^{1}H NMR, δ: 2.05 (s, 6 H, 2 Me); 7.16 (s, 2 H); 7.51 (m, 5 H); 7.75 (s, 1 H); 9.10 (s, 1 H, OH). Found (%): C, 59.79; H, 4.10; N, 11.52. $C_{18}H_{15}Cl_2N_3O$. Calculated (%): C, 60.01; H, 4.20; N, 11.66.

3-Dichloromethyl-5-(4-hydroxy-3,5-dimethylphenyl)-6-(4-methylphenyl)-1,2,4-triazine (7f). The yield was 80%, m.p. 201—203 °C. ^{1}H NMR, δ: 2.09 (s, 6 H, 2 Me); 2.40 (s, 3 H, Me); 7.17 (s, 2 H); 7.24 (m, 2 H); 7.46 (m, 3 H); 8.92 (s, 1 H, OH). Found (%): C, 60.84; H, 4.54; N, 11.06. $C_{19}H_{17}Cl_2N_3O$. Calculated (%): C, 60.97; H, 4.58; N, 11.23.

3-Dichloromethyl-5-(2,4-dihydroxyphenyl)-6-phenyl-1,2,4-triazine (7g). The yield was 85%, m.p. 218—221 °C. ^{1}H NMR, δ: 6.18 and 6.36 (both m, 1 H each); 7.40 (m, 4 H); 7.50 (s, 1 H, $CHCl_2$); 7.58 (m, 2 H, Ph); 9.81 (s, 1 H, OH). Found (%): C, 54.96; H, 3.18; N, 11.93. $C_{16}H_{11}Cl_2N_3O_2$. Calculated (%): C, 55.19; H, 3.18; N, 12.07.

6-(4-Chlorophenyl)-3-dichloromethyl-5-(2,4-dihydroxyphenyl)-1,2,4-triazine (7h). The yield was 60%, m.p. 215—218 °C. ^{1}H NMR, δ: 6.15 (m, 1 H); 6.38 (m, 2 H); 7.38 (m, 3 H); 7.51 (s, 1 H, $CHCl_2$); 7.59 and 9.72 (both m, 2 H each). Found (%): C, 50.13; H, 2.60; N, 10.95. $C_{16}H_{10}Cl_3N_3O_2$. Calculated (%): C, 50.22; H, 2.63; N, 10.98.

3-Dichloromethyl-5-(2,4-dihydroxyphenyl)-6-(4-methylphenyl)-1,2,4-triazine (7i). The yield was 70%, m.p. 138—139 °C. ^{1}H NMR, δ: 2.35 (s, 3 H, Me); 6.15 and 6.35 (both m, 1 H each); 7.16 (m, 2 H); 7.34 (m, 1 H); 7.47 (m, 3 H); 9.75 (m, 2 H). Found (%): C, 56.06; H, 3.69; N, 11.32. $C_{17}H_{13}Cl_2N_3O_2$. Calculated (%): C, 56.37; H, 3.62; N, 11.60.

3-Dichloromethyl-5-(5-hexyl-2,4-dihydroxyphenyl)-6-phenyl-1,2,4-triazine (7j). The yield was 78%, m.p. 197—198 °C. ^{1}H NMR, δ: 0.86 (m, 3 H, C_6H_{13}); 1.26 (m, 6 H, C_6H_{13}); 1.43 and 2.41 (both m, 2 H each, C_6H_{13}); 6.22 (s, 1 H, H(3′)); 7.18 (s, 1 H, H(6′)); 7.37 (m, 3 H, Ph); 7.55 (m, 1 H, Ph); 7.74 (s, 1 H, $CHCl_2$); 9.74 and 9.85 (both s, 1 H each, OH). Found (%): C, 60.94; H, 5.29; N, 9.59. $C_{22}H_{23}Cl_2N_3O_2$. Calculated (%): C, 61.12; H, 5.36; N, 9.72.

6-(4-Chlorophenyl)-3-dichloromethyl-5-(5-hexyl-2,4-dihydroxyphenyl)-1,2,4-triazine (7k). The yield was 65%, m.p. 210—212 °C. ^{1}H NMR, δ: 0.90 (m, 3 H, C_6H_{13}); 1.30 (m, 6 H, C_6H_{13}); 1.47 and 2.49 (both m, 2 H each, C_6H_{13}); 6.22 (s, 1 H, H(3′)); 7.22 (s, 1 H, H(6′)); 7.39 (m, 2 H, ClC_6H_4); 7.45 (s, 1 H, $CHCl_2$); 7.59 (m, 2 H, ClC_6H_4); 9.65 and 9.67 (both s, 1 H each, OH). Found (%): C, 56.40; H, 4.72; N, 9.00. $C_{22}H_{22}Cl_3N_3O_2$. Calculated (%): C, 56.61; H, 4.75; N, 9.00.

3-Dichloromethyl-5-(5-hexyl-2,4-dihydroxyphenyl)-6-(4-methylphenyl)-1,2,4-triazine (7l). The yield was 70%, m.p. 203—205 °C. ^{1}H NMR, δ: 0.89 and 1.27 (both m, 3 H each, C_6H_{13}); 1.40 (m, 2 H, C_6H_{13}); 2.37 (m, 5 H, C_6H_{13}, Me); 6.23 (s, 1 H, H(3′)); 7.07 (s, 1 H, H(6′)); 7.17 (m, 2 H, MeC_6H_4); 7.44 (s, 1 H, $CHCl_2$); 7.47 (m, 2 H, MeC_6H_4); 9.69 and 9.85 (both s, 1 H each, OH). Found (%): C, 61.68; H, 5.60; N, 9.37. $C_{23}H_{25}Cl_2N_3O_2$. Calculated (%): C, 61.89; H, 5.65; N, 9.41.

Synthesis of 5-substituted 3-trichloromethyl-4,5-dihydro-1,2,4-triazines 8 (general procedure). The corresponding trichloromethyltriazine **1** (1 mmol) and indole or resorcinol (1 mmol) were dissolved in trifluoroacetic acid (3 mL) and kept at ~20 °C for 16 h. The solvent was removed under reduced pressure. The residue was treated with a 5% Na_2CO_3 solution. The precipitate that formed was filtered off. Adducts **8** are unstable, cannot be purified, and were characterized only by ^{1}H NMR spectroscopy.

5-(Indol-3-yl)-6-phenyl-3-trichloromethyl-4,5-dihydro-1,2,4-triazine (8a). The yield was 341 mg (0.87 mmol, 87%). ^{1}H NMR, δ: 6.26 (s, 1 H, H(5)); 7.06 (m, 3 H); 7.32 (m, 4 H); 7.76 (m, 3 H); 10.86 (s, 1 H); 11.52 (br.s, 1 H).

6-(4-Chlorophenyl)-5-(indol-3-yl)-3-trichloromethyl-4,5-dihydro-1,2,4-triazine (8b). The yield was 320 mg (0.75 mmol, 85%). ^{1}H NMR, δ: 6.36 (s, 1 H, H(5)); 7.01 (m, 1 H); 7.08, 7.25, 7.42, and 7.71 (all m, 1 H each); 7.80 (m, 2 H); 11.09 (s, 1 H); 11.16 (br.s, 1 H).

5-(Indol-3-yl)-6-(4-methylphenyl)-3-trichloromethyl-4,5-dihydro-1,2,4-triazine (8c). The yield was 324 mg (0.8 mmol, 90%). ^{1}H NMR, δ: 2.27 (s, 3 H, Me); 6.34 (s, 1 H, H(5)); 7.02 and 7.09 (both m, 1 H each); 7.17 (m, 3 H); 7.35 (m, 1 H); 7.73 (m, 3 H); 11.05 (s, 1 H); 11.85 (br.s, 1 H).

6-(4-Chlorophenyl)-5-(2,4-dihydroxyphenyl)-3-trichloromethyl-4,5-dihydro-1,2,4-triazine (8h). The yield was 294 mg (0.7 mmol, 71%). ^{1}H NMR, δ: 6.13 and 6.15 (both m, 1 H each); 6.35 (s, 1 H, H(5)); 6.80 (m, 1 H); 7.53 and 7.80 (both m, 2 H each); 9.90 (s, 2 H); 11.56 (br.s, 1 H).

5-(2,4-Dihydroxyphenyl)-6-(4-methylphenyl)-3-trichloromethyl-4,5-dihydro-1,2,4-triazine (8i). The yield was 284 mg (0.71 mmol, 71%). ^{1}H NMR, δ: 2.28 (s, 3 H, Me); 6.12 and 6.14 (both m, 1 H each); 6.34 (s, 1 H, H(5)); 6.80 (m, 1 H); 7.18 and 7.64 (both m, 2 H each); 9.84 (s, 2 H); 11.29 (br.s, 1 H).

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References

1. F. Terrier, *Nucleophilic Aromatic Displacement: the Influence of the Nitro Group*, VCH Publishers, Inc., New York, 1991, 460.

2. O. N. Chupakhin, V. N. Charushin, and H. C. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, San Diego, 1994, 246.
3. M. Makosha, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 531 [*Russ. Chem. Bull.*, 1996, **45**, 491 (Engl. Transl.)].
4. H. C. van der Plas, M. Wozniak, and A. van Veldhuizen, *Rec. Trav. Chim.*, 1978, **97**, 130.
5. E. J. J. Grabowski, E. W. Tristram, R. Tull, and P. I. Pollak, *Tetrahedron Lett.*, 1968, 5931.
6. R. S. Dainter, T. Jackson, A. H. H. Omar, H. Suschitzky, B. J. Wakefield, N. Hughes, and A. J. Nelson, *J. Chem. Soc., Perkin Trans. 1*, 1989, 283.
7. G. Heinisch and T. Huber, *Liebigs Ann. Chem.*, 1992, 19.
8. T. Giannopoulos, J. R. Ferguson, B. E. Wakefield, and G. Varvounis, *Tetrahedron*, 2000, **56**, 447.
9. D. N. Kozhevnikov, V. L. Rusinov, and O. N. Chupakhin, *Adv. Heterocycl. Chem.*, 2002, **82**, 261.
10. S. Konno, M. Yokoyama, and H. Yamanaka, *Heterocycles*, 1982, **19**, 1865.
11. V. L. Rusinov, D. N. Kozhevnikov, E. N. Ulomskii, O. N. Chupakhin, G. G. Aleksandrov, and H. Neunhoeffer, *Zh. Org. Khim.*, 1998, **34**, 429 [*Russ. J. Org. Chem.*, 1998, **34**, 400 (Engl. Transl.)].
12. V. L. Rusinov, D. N. Kozhevnikov, I. S. Kovalev, O. N. Chupakhin, and G. G. Aleksandrov, *Zh. Org. Khim.*, 2000, **36**, 1081 [*Russ. J. Org. Chem.*, 2000, **36** (Engl. Transl.)].
13. B. B. Dey, *J. Chem. Soc. London*, 1914, **105**, 1039.

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