A Simple One Pot Synthesis of Condensed 1,2,4-Triazines by Using the Tandem A_N–S_N^{ipso} and S_N^H–S_N^{ipso} Reactions

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A new synthetic approach to condensed 1,2,4-triazines based on using the tandem A_N–S_N^{ipso} and S_N^H–S_N^{ipso} reactions has been developed. 5-Methoxy-3-penyl-1,2,4-triazine and its N_1-methyl quaternary salt were found to react with C,N-, C,O- and *N*,*N*'-bifunctional nucleophiles (*m*-phenylenediamine, resorcinol, semicarbazide and ureas) into triazacarbazoles, benzofuro[2,3-*e*][1,2,4]-triazines, and 6-azapurine derivatives. In all cases nucleophiles attack first the unsubstituted C-6 carbon of the triazine ring, while the final stage is replacement of the methoxy group affording cyclization products.

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Introduction.

A very common approach for functionalization of π-deficient heteroaromatic compounds is based on nucleophilic displacements of the so-called good leaving groups, such as halides, nitro, dialkylamino, sulfones, *etc*. These reactions are usually abbreviated as the S_N^{ipso} type of substitution [1]. A feature of the S_N^{ipso} reactions is that the replacement of good leaving groups is often accompanied by fast and reversible formation of σ^H-adducts, thus making nucleophilic substitution of hydrogen (S_N^H) a concurrent reaction, which can be realized under appropriate conditions [2-4]. Many examples of S_N^H-substitutions as well as the formation of relatively stable σ^H-adducts as the prevailing direction for the reactions of six-membered azaaromatic compounds with nucleophiles have been documented in the literature [2-4].

In previous papers we described new possibilities to modify the structure of 1,2,4-triazines by using the S_N^H-reactions and other related processes based on nucleophilic mono- or diaddition reactions at unsubstituted carbons of the triazine ring [5-11]. In the course of these studies we have established that the 1,2,4-triazine ring is prone to undergo diaddition reactions with bifunctional nucleophiles at C-5 and C-6 leading to the formation of condensed triazines [6,8,10,11].

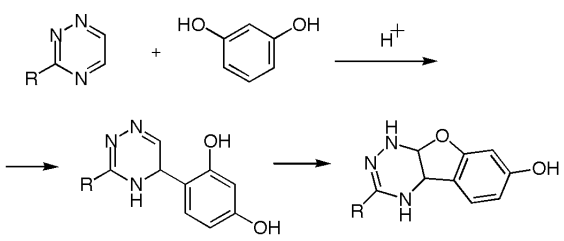


Figure 1

We though it would be worth studying how 1,2,4-triazines bearing a good leaving group in one of these positions would behave in the reactions with bifunctional reagents, since combination of the S_N^H and the S_N^{ipso} methodologies might expand preparative possibilities of these cyclizations. Therefore, an easily accessible 5-methoxy-3-phenyl-1,2,4-triazine (**1**) [12] was chosen as an appropriate substrate for these studies.

Results and Discussion.

The reactivity of 5-methoxy-1,2,4-triazine (**1**) towards nucleophiles is somewhat lower than that of the parent compound due to the presence of the electron-donating methoxy group, therefore it is understandable that the reactions of **1** with *m*-phenylenediamine, resorcinol, and urea derivatives require charge activation of the triazine ring. Some nucleophiles have been found to react with *N*-protonated 1,2,4-triazines [10], however acidic conditions are not always acceptable, since protonation of nucleophilic species may also take place. This can be avoided by using other types of charged triazines, in particular quaternary *N*-alkyl-1,2,4-triazinium salts [2,5,6,10,13]. Three isomeric *N*-alkyl-1,2,4-triazinium salts can plausibly be derived from *N*-alkylation of 1,2,4-triazines [6]. Previous studies have shown that the N_1-alkyl quaternary salts are formed predominantly, when 1,2,4-triazines react with trialkyloxonium tetrafluoroborates [6,13,14]. Indeed, we have found that methylation of 5-methoxy-3-phenyl-1,2,4-triazine

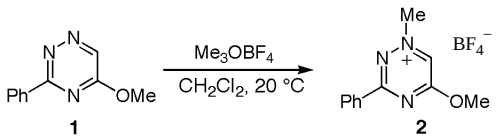


Figure 2

with trimethyloxonium tetrafluoroborate is also the site-selective process yielding the N_1-methyl salt **2** (Figure 2).

The structural evidence for the triazinium salt **2** has been obtained by the X-ray crystallography analysis (see supplementary materials). 1-Methyl-5-methoxy-1,2,4-triazinium tetrafluoroborate (**2**) proved to be rather active, and by reacting with *m*-phenylenediamine in methanol at 20 °C it caused the tandem A_N-S_N^{ipso} reaction transforming **2** into triazacarbazole **4** in 68% yield (Scheme 3).

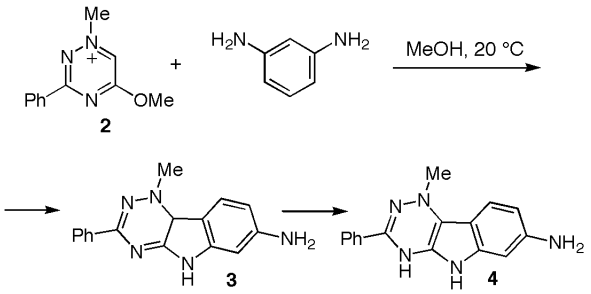
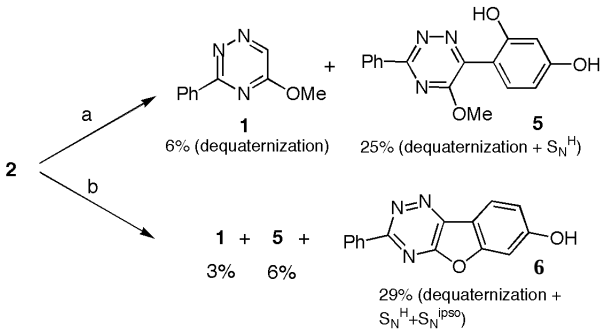


Figure 3

The reaction of **2** with resorcinol is somewhat different. It takes place in methanol only on reflux and is accompanied by dequaternization, yielding the starting 5-methoxy-1,2,4-triazine **1** in addition to 6-substituted 1,2,4-triazine **5** as the S_N^H-product (Scheme 4).



Reagents and conditions: (a) resorcinol, methanol, reflux; (b) resorcinol, DMF, 20 °C

Figure 4

When the same reaction was carried out in DMF, benzofurotriazine **6** was obtained, in addition to **1** and **5**, due to the following cascade of reactions: dequaternization, S_N^H and S_N^{ipso} substitutions. Dequaternization is likely to go first, followed by the attack at C-6, and, finally, displacement of the methoxy group affords the cyclization product **6**. It is substantiated by the experiment in which non-quaternized 5-methoxy-1,2,4-triazine **1** and resorcinol were allowed to react in DMF in the presence of air and boron trifluoride to give **6** in 26% yield.

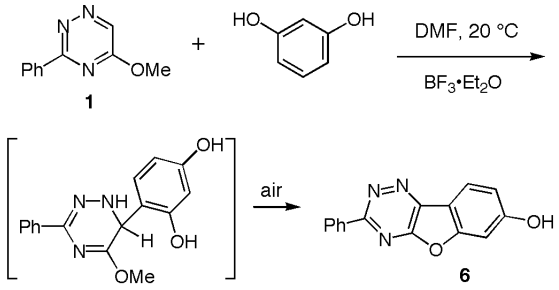


Figure 5

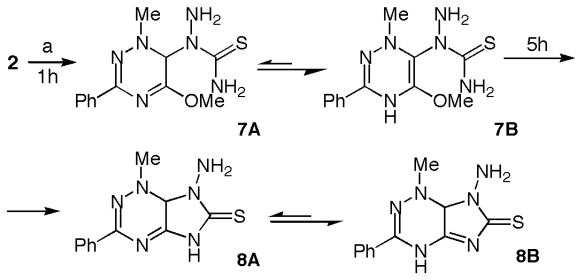
Due to steric reasons a nucleophilic attack at the unsubstituted 6-position of the triazine ring seems to be preferential, although displacement of the 5-methoxy group might also be the first step, since this would correspond to the classical theory of nucleophilic substitution reactions and the data of from quantum-chemistry calculations (Table 1).

Table 1

Electron Densities on C-atoms of Triazines **1** and **2** (ab initio, STO-3G basis set)

Compound	Partial charge on C-atom		
	C3	C5	C6
1	0.190	0.239	-0.002
2	0.233	0.280	0.104

Interaction of the triazinium salt 2 with N,N-binucleophiles proceeds in a similar manner. The reaction of 2 with thiosemicarbazide appears to be a combination of the A_N and S_N^{ipso} processes leading to imidazo[4,5-e][1,2,4]-triazin-6-thione **8**.

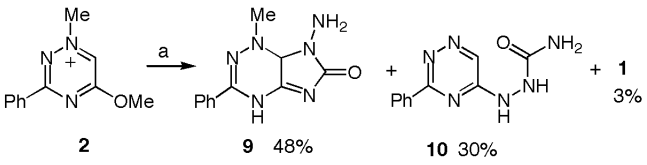


Reagents and conditions: (a) Thiosemicarbazide, MeOH, NEt_3, 20 °C.

Figure 6

Intermediate **7**, which can be isolated in 1 hour after the beginning of the reaction, indicates that nucleophilic attack at unsubstituted 6-position of the triazine ring proceeds faster, while the final stage of the reaction is displacement of the 5-methoxy group, yielding cyclization product. A "conventional" S_N^{ipso} process is also possible. Indeed, the

reaction of **2** with semicarbazide affords some quantities of the *ipso*-substitution product **10** in addition to condensed triazine **9** (Scheme 7).



Reagents and conditions: (a) Semicarbazide · HCl, MeOH, NEt_3, 20 °C, 1 hour.

Figure 7

Other reaction conditions are necessary for cyclizations of 5-methoxy-1,2,4-triazine with ureas (urea, thiourea and their mono- and dialkyl derivatives). In all these cases triazine **1** can be activated by acyl anhydrides. The reactions involve a number of successive steps, and depending on the reaction conditions, the nature of reagents and acylating agents, they afford either open-chain adducts or cyclizations products. Nucleophilic attack takes place first at unsubstituted 6-position, similar to the reactions described above. Thus, the reaction of **1** with urea in acetic anhydride at 20 °C affords the adduct **11a**.

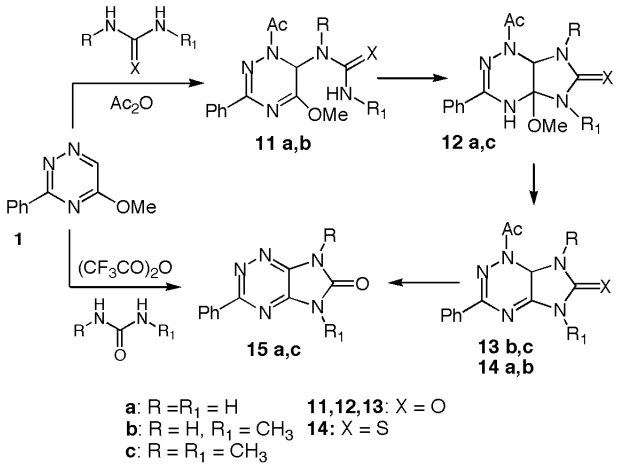


Figure 8

Thiourea and *N*-metylthiourea proved also to be rather active towards **1** and, through the addition at C-6 and the displacement of the 5-methoxy group, which proceeds easily at room temperature, they afford 6-azapurine derivatives **14 a,b**.

The feature of the reaction of **1** with *N*,*N*'-dimethyl urea performed at 20 °C is that it is not stopped at the stage of mono-adduct formation but results in the cycloadduct **12c** isolated in crystalline form. A similar compound **12a** has been obtained by heating the mixture of **1** and urea in acetic anhydride at 90 °C. It is worth noting that these examples are rare cases of the reactions in which intermediates of the S_N^{ipso} substitutions might be isolated. Heating solutions of **12c** in $CHCl_3$ or CH_3CN for a long period of time causes elimination of methanol, thus giving dihydrotriazine **13c** in 85% yield. Reaction time can be reduced by the use of acetic anhydride and/or a higher temperature. Thus, heating a mixture of equivalent amounts of 1,2,4-triazine **1** and *N*,*N*'-dimethylurea or *N*-methylurea in acetic anhydride at 70 °C gave dihydrotriazines **13b,c** in high yields, however attempts to isolate any intermediates failed. Increasing the temperature up to 110 °C facilitated aromatization of dihydrotriazines **13** into 6-azapurinones **15,** as the S_N^H- S_N^{ipso} products. Trifluoroacetic anhydride proved to be a stronger activator for the reaction of 1,2,4-triazine with ureas, and aromatization of the *N*-acylated adducts was found to proceed much easier. Indeed, when 5-methoxy-1,2,4-triazine **1** reacted with ureas at 20 °C in the presence of trifluoroacetic anhydride, aromatic azapurines **15a,c** were isolated in 46-80% yields. The aromatization of **13** and **14** into **15** by elimimination of acetaldehyde is similar to the aromatization of Reissert compounds.

Structural elucidation of the obtained compounds were made using ^{1}H- and ^{13}C-NMR spectroscopy (see Experimental Section), including NOESY and ^{1}H-^{13}C-COSY experiments. The ^{1}H-NMR spectrum of triazacarbazole **4** indicated a typical AMX pattern for the 1,2,4-trisubstituted benzene ring. These data exclude the formation of isomeric compound **16**.

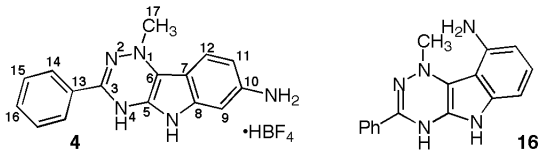


Figure 9

The absence of the C_6-H proton resonance signal suggests that indolotriazine **4** exists exclusively in the enamine form. Chemical shifts of C_7, C_9 and C_{12} (Fig. 9) were determined by the ^{1}H-^{13}C-COSY experiment. The quaternary C_6 and C_3 carbons of the triazine ring were identified with the aid of long-range ^{1}H-^{13}C couplings with protons of the N-CH_3 and *ortho*-hydrogens of 3-Ph in the ^{1}H-^{13}C-COSY spectrum. Regio-orientation for the fused indole fragment was established on the basis of long-range ^{1}H-^{13}C couplings between C_6 carbon and H-C_{12}.

The evidence for the structure of **5** is provided by its ^{1}H NMR spectrum in which two low-field broadened singlets of the hydroxy groups, two multiplets of the 3-phenyl substituent (5H), characteristic multiplets of the 1,2,4-substituted benzene ring (3H), and the singlet of the methoxy group (3H)

were observed. In the mass-spectrum of **5** the molecular ion M^+ = 295 was observed. The character of substitution in the resorcinol fragment of **6** was established in a similar way as for indolotriazine **4**.

Imidazotriazines **8** and **9** can exist in several tautomeric forms and are shown in Figure 10.

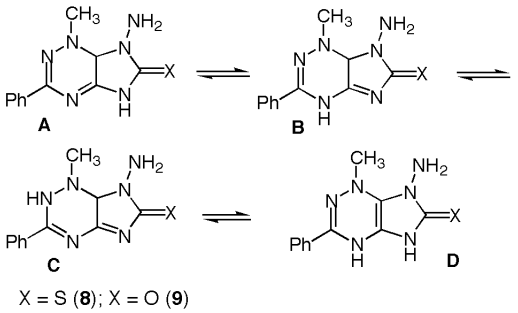


Figure 10

The cross-peak of the *ortho*-hydrogen (C_{13}-H, Figure 11) of 3-Ph and the broad NH signal at δ = 8.7 ppm in the ^{1}H-^{1}H NOESY spectrum of **9** indicate that NH occupies either the position 4 or 2 of the triazine ring, while the *ab-initio* quantum-chemical calculations with the STO-3G basis set are in favor of the tautomer C structure (ΔE = 88.2 kcal/mol).

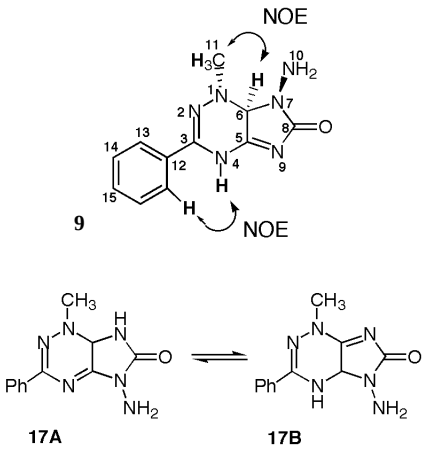


Figure 11

The data obtained from NOESY spectra enabled us to establish orientation of the imidazole moiety in compounds **8** and **19**. In the alternative structure **17** tautomeric equilibrium can only be realized by means the structure **17B** having N_4-H and C_5-H hydrogen atoms, while no tautomeric structures bearing N_4-H and C_6-H are possible. The second cross-peak of C_6-H and N_1-CH_3 in the ^{1}H-^{1}H NOESY spectrum of **9** allows one to estimate roughly the relative stereoistry of these groups (Figure 11). Comparison of the ^{1}H and ^{13}C-NMR spectra of azapurinones **8** and **9** has shown that no annelation of the thiazole ring in the reaction of triazine **2** with thiosemicarbazide occurred. In the ^{13}C-NMR spectrum of **8**, the resonance signal corresponding to C=S at δ = 175 ppm is observed. The ^{1}H NMR spectrum of the C_6-adduct **7** indicated the presence of two methyl groups. The enamine form **7B** was found to be dominating over the azomethine form **7A**, since no indication for the C_6-H resonance signal was observed in the spectrum.

The spectral data for compounds **11**-**15** are in full agreement with the proposed structures. The ^{1}H NMR spectra indicated the presence of acyl groups as singlets at δ = 2.30 – 2.89 ppm, signals of C_6-H as doublets at δ = 6.4 ppm for compound **11** or singlets at δ = 4.7- 6.12 ppm for compounds **12**-**13**. Since thiourea addition products (**14**) can hardly be dissolved in organic solvents, their NMR spectra were measured in trifluoracetic acid. In TFA these compounds probably exist as a mixture of tautomers **B** or **C**. This conclusion is based on the data of the ^{1}H-NMR spectra which show the absence of the C_6-H resonance signal.

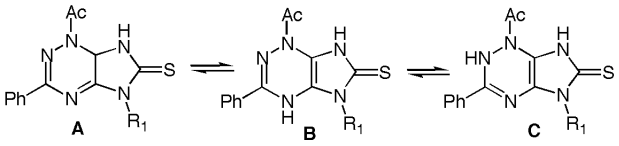


Figure 12

The regio-orientation of the methylurea moiety was not in question, due to observation of a signal corresponding to NH-CH_3 as the quartet in the ^{1}H NMR spectrum of **11b**.

Chemical shifts of the sp^3 ring carbons were found to be in the range of 54–65 ppm. In the ^{13}C NMR spectrum of **12c** the resonance signal of C_5 at 95.9 ppm was observed in addition to a peak at 64.1 ppm (C_6). These data provide unequivocal evidence for the σ-adduct formation.

EXPERIMENTAL

5-Methoxy-3-phenyl-1,2,4-triazine was obtained according to the described procedure [8]. Other reagents were obtained from commercial suppliers and used without further purification. Column chromatography was performed on silica gel by using CH_2Cl_2-CH_3OH as eluent. All melting points were uncorrected and were taken on a Boetius melting point apparatus. Elemental analysis data were obtained with Carlo Erba 1108 CHNO Analyser. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Brucker AC300 and ARX300 spectrometers with TMS as internal standard.

1-Methyl-5-methoxy-3-phenyl-1,2,4-triazinium Tetrafluoroborate (**2**).

Trimethyloxonium tetrafluoroborate (140 mg, 1.29 mmol) was added to solution of 5-methoxy-3-phenyl-1,2,4-triazine (**1**) (240 mg, 1.29 mmol) in dry CH_2Cl_2 (2 ml) and the reaction mixture

was stirred for 2 hours at 20 °C. The precipitate was isolated by filtation and washed with CH_2Cl_2 to yield 260 mg (70%) of compound **2**, mp 148-149 °C (dec). ^{1}H NMR (DMSO-d_6): δ 4.38 (s, 3H, OCH_3), 4.52 (s, 3H, NCH_3), 7.75-7.79 (m, 2H), 7.76-7.72 (m, 1H), 8.38-8.42 (m, 2H), 9.49 (s, 1H, C6-H); ^{13}C NMR (DMSO-d_6): δ 52.3 (N1-CH_3), 58.1 (5-OCH_3), 131.5, 128.9, 130.0, 135.0, 165.8 ($C3_{triazine}$), 168.5 ($C5_{triazine}$), 139.2 ($C6_{triazine}$).

Anal. Calcd for $C_{11}H_{12}N_3O•BF_4$: C, 45.71; H, 4.18; N, 14.54. Found: C, 45.78; H, 4.30; N, 14.59.

7-Amino-1-methyl-3-phenyl-4,5-dihydro-1*H*[1,2,4]triazino-[5,6-*b*]indole (**4** x HBF_4).

A suspension of **2** (150 mg, 0.50 mmol) and *m*-phenylenediamine (55.2 mg, 0.51 mmol) in methanol (4 ml) was stirred for 2 hours at 20 °C. After evaporation of solvent *in vacuo*, the residue was separated by column chromatography to give 5-methoxy-3-phenyl-1,2,4-triazine (**1**) (4.5 mg, 2%) and compound **4** (127 mg, 68%) as red crystals, mp 234-236 °C. ^{1}H NMR (DMSO-d_6): δ 4.56 (s, 3H, NCH_3), 5.73 (bs, 2H, NH), 7.46 (bs, 2H, NH), 6.68 (d, *J* = 1.7 Hz, 1H), 6.77 (dd, *J* = 1.7 Hz, 9.0 Hz, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.75-7.57 (m, 3H), 8.26-8.31 (m, 2H); ^{13}C NMR (DMSO-d_6, See Figure 9): δ 47.6 (C17), 95.7 (C9), 100.5 (C7), 113.5 (C11), 127.6 (C14), 129.1 (C12), 129.3 (C15), 131.6 (C16), 134.2 (C13), 151.7 (C10), 155.91 (C3), 157.12 (C5), 158.2 (C6), 158.2 (C8).

Anal. Calcd for $C_{16}H_{15}N_5•HBF_4$: C, 52.63; H, 4.42; N, 19.18. Found: C, 52.14; H, 4.37; N, 18.98.

6-(2,4-Dihydroxyphenyl)-5-methoxy-3-phenyl-1,2,4-triazine (**5**).

A mixture of **2** (200 mg, 0.68 mmol), resorcinol (74.8 mg, 0.68 mmol) and dry methanol (5 ml) was refluxed for 24 hours. The reaction mixture was subjected to column chromatography on silica gel to give compound **1** (8 mg, 6%) and compound **5** (50 mg, 25%), mp 238-239 °C. ^{1}H NMR (DMSO-d_6): δ 3.97 (s, 3H), 6.41 (dd, *J* = 2.2 Hz, 8.5 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.48-7.56 (m, 3H), 8.21 (dd, *J*= 7.8 Hz, 1.6 Hz, 2H), 10.01 (bs, 1H), 10.41 (bs, 1H).

Anal. Calcd for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.10; H,4.50; N,14.30.

6-(2,4-Dihydroxyphenyl)-5-methoxy-3-phenyl-1,2,4-triazine (**5**) and 7-Hydroxy-3-phenylbenzo[4,5-*e*]furo[2,3-*e*][1,2,4]triazine (**6**).

A solution of **2** (150 mg, 0.50 mmol) and resorcinol (74.8 mg, 0.50 mmol) in DMF (1.5 ml) was stirred for 3 days. Solvent was evaporated *in vacuo* and the residue was separated by column chromatography to give compounds **1** (3 mg, 3 %), **5** (44 mg, 29%, mp 238-239 °C) and **6** as a complex 1:1 with DMF (10 mg, 6%, mp 208-209 °C).

7-Hydroxy-3-phenyl-benzo[4,5-*e*]furo[2,3-*e*][1,2,4]triazine (**6**).

Boron trifluoride etherate (61 mg, 0.43 mmol) was added to a solution of **1** (80 mg, 0.43 mmol) and resorcinol (47 mg, 0.43 mmol) in DMF (2 ml). The reaction mixture was stirred for 3 days at 20 °C with bubbling of air through the solution. Solvent was evaporated *in vacuo* and the residue was purified by column chromatography to give compound **6** as a complex with the DMF, mp 208 °C (decomp.) (38 mg, 26%). ^{1}H NMR (DMSO-d_6): δ 2.69 (s, 3H, DMF), 2.89 (s, 3H, DMF), 6.18 (d, *J* = 8.7 Hz, 1H), 6.33 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, *J* = 2.4 Hz, 8.7 Hz, 1H), 7.57–7.68 (m, 3H), 7.96 (s, 1H, DMF), 8.09-8.14 (m, 2H), 9.97 (b.s, 1H).

Anal. Calcd for $C_{15}H_9N_3O_2•C_3H_7NO$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.45; H, 4.73; N, 16.38.

6-(1-Aminothioureido)-5-methoxy-1-methyl-3-phenyl-1,4-dihydro-1,2,4-triazine (**7** x HBF_4).

Triethylamine (0.014 ml, 0.1 mmol) was added to a mixture of **2** (150 mg, 0.51 mmol), thiosemicarbazide (55.6 mg, 0.61 mmol) and methanol (1.5 ml), and the reaction mixture was stirred for 24 hours at 20 °C followed by reflux for 1 hour. Solvent was removed *in vacuo*. The residue was separated by column chromatography to give compound **1** (10 mg, 11%), compound **7** as yellow solid with mp 228 °C (dec) (41 mg, 21%) and compound **8** (9 mg, 5%). **7:** ^{1}H NMR (DMSO-d_6): δ 3.54 (s, 3H), 4.13 (s, 3H), 7.38-7.48 (m, 3H), 7.94-7.98 (m, 2H), 8.09 (bs, ~1H), 9.02 (bs, ~1H) (two NH protons are exchanged with the signal of water); ^{13}C NMR (DMSO-d_6): δ 41.5, 55.1, 125.2, 128.47, 129.2, 130.3, 133.7, 141.9, 158.3, 174.9.

7-Amino-1-methyl-3-phenyl-4,6,7,7a-tetrahydro-1*H*-imidazo[4,5-*e*][1,2,4]-triazin-6-thione (**8**•H[BF_4]).

A mixture of **2** (200 mg, 0.68 mmol), thiosemicarbazide (74.4 mg, 0.82 mmol) and methanol (2 ml) was stirred at 20 °C for 24 hours. Then the reaction mixture was refluxed for 5 hours. Solvent was removed *in vacuo* and the residue was purified by column chromatography to give compound **8** as red crystals, mp 191-193 °C (40 mg, 14%). ^{1}H NMR (DMSO-d_6): δ 3.90 (d, *J* = 0.9 Hz, 3H), 7.37 (bs, 2H) , 7.50-7.53 (m, 3H), 8.12-8.16 (m, 2H), 8.23 (d, *J* = 0.9 Hz, 1H, C6-H), 9.55 (bs, 1H); ^{1}H NMR (Acetone-d_6): δ 4.04 (d, *J* = 0.9 Hz, 3H), 7.19 (bs, 2H), 7.40-7.70 (m, 3H), 8.09 (d, *J* = 0.9 Hz, 1H, C6-H), 8.21-8.24 (m, 2H), 9.67 (bs, 1H); ^{13}C NMR (DMSO-d_6): δ 49.1(N1-CH_3), 127.2, 128.4, 131.4, 134.3, 139.1 ($C6_{triazine}$) 145.1 ($C5_{triazine}$), 163.5 ($C3_{triazine}$), 175.1 (C=S).

Anal. Calcd for $C_{11}H_{12}N_6S•HBF_4$: C, 37.95; H, 3.76; N, 24.14. Found: C, 37.82; H, 3.68; N, 24.25.

7-Amino-1-methyl-3-phenyl-4,6,7,7a-tetrahydro-1*H*-imidazo[4,5-*e*][1,2,4]triazin-6-one tetrafluoroborate (**9** x HBF_4) and 5-Semicarbazido-3-phenyl-1,2,4-triazine (**10**).

Triethylamine (62 mg, 0.61 mmol) was added to a suspension of **2** (150 mg, 0.51 mmol) and semicarbazide hydrochloride (88.3 mg, 0.61 mmol) in methanol (2 ml), and the mixture was stirred for 24 hours at 20 °C and at which time it was refluxed for 2 hours. After that the reaction mixture was separated by column chromatography to give triazine **10** as yellow solid with mp 154-156 °C (36 mg, 30%): ^{1}H NMR (DMSO-d_6): δ 6.13 (b.s), 6.22 (b.s), 7.47-7.63 (m, 3H), 8.10-8.13 (m, 2H), 8.13 (b.s), 8.33 (b.s), 8.80 (s, 1H, C6-H).

Anal. Calcd for $C_{10}H_{10}N_6O$: C, 52.17; H, 4.38; N, 36.50. Found: C, 52.20; H, 4.35; N, 36.41.

Compound **9** was obtained as dark red crystals, mp 210-214 °C (80 mg, 48%); ^{1}H NMR (DMSO-d_6): δ 3.82 (d, *J* = 0.6 Hz, 3H), 6.18 (b.s, 2H), 7.42-7.54 (m, 3H), 8.10 (d, *J* = 0.6 Hz, 1H, C6-H), 8.11-8.19 (m, 2H), 8.7 b.s (1H, NH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 49.1, 127.7, 128.5, 131.5, 135.2, 139.8 ($C6_{triazine}$), 144.0 (C=O), 156.4 ($C5_{triazine}$), 164.2 ($C3_{triazine}$).

Anal. Calcd for $C_{11}H_{12}N_6O•H[BF_4]$: C, 39.79; H, 3.95; N, 25.31. Found: C, 39.58; H, 3.84; N, 25.25.

1-Acetyl-5-methoxy-3-phenyl-6-ureido-1,6-dihydro-1,2,4-triazine (**11a**).

A mixture of **1** (50 mg, 0.27 mmol) and urea (16 mg, 0.27 mmol) in acetic anhydride (1.5 ml) was stirred for 48 hours at 20 °C. The

precipitate was isolated by filtration and washed with hot methanol to yield 51 mg (65%) of **11a**, mp 210-212 °C. ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3H), 3.99 (s, 3H), 5.60 (b.s, 2H), 6.39 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.44-7.55 (m, 3H), 7.80-7.83 (m, 2H).

Anal. Calcd for $C_{13}H_{15}N_5O_3$: C, 53.97; H, 5.23; N, 24.21. Found: C, 53.58; H, 5.27; N, 24.25.

1-Acetyl-5-methoxy-3-phenyl-6-(3-methylureido)-1,6-dihydro-1,2,4-triazine (**11b**).

A mixture of **1** (120 mg, 0.65 mmol) and methylurea (48 mg, 0.68 mmol) in acetic anhydride (2 ml) was stirred for 48 hours at 20 °C. The precipitate was isolated by filtration and washed with hot methanol to yield 114 mg (58%) of **11b**, mp 210-212 °C. ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 3H), 2.54 (d, 3H), 3.49 (s, 3H), 5.72 (q, *J* = 4.4Hz, 1H), 6.38 (d, *J* = 8.2Hz, 1H), 7.25 (d, *J* = 8.2Hz, 1H); 7.47-7.52 (m, 3H), 8.04-8.15 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 20.9, 26.1, 50.5, 54.4, 126.3, 128.3, 129.8, 134.4, 145.4, 156.3, 165.6, 171.2.

Anal. Calcd for $C_{14}H_{17}N_5O_3$: C, 55.44; H, 5.65; N, 23.04. Found: C, 55.28; H, 5.80; N, 23.17.

1-Acetyl-4a-methoxy-3-phenyl-4,4a,5,6,7,7a-hexahydro-1*H*-imidazo[4,5-*e*]-1,2,4-triazin-6-one (**12a**).

A solution of **1** (80 mg, 0.43 mmol) and urea (25.8 mg, 0.43 mmol) in acetic anhydride (1.5 ml) was stirred for 2 hours at 90 °C. After evaporation of solvent *in vacuo* the residue was washed with ether to yield **12a** (20 mg, 17%), mp 184-185 °C; ^{1}H NMR (DMSO-d_6): δ 2.38 (s, 3H), 4.12 (s, 3H), 6.10 (d, *J* = 6.5 Hz, 1H) 7.21 (d, *J* = 6.5 Hz, 1H), 7.45-7.48 (m, 3H), 7.69 (bs, 2H), 8.09-8.12 (m, 2H).

Anal. Calcd for $C_{13}H_{15}N_5O_3$: C, 53.97; H, 5.23; N, 24.21. Found: C, 53.62; H, 5.26; N, 24.02.

1-Acetyl-5,7-dimethyl-4a-methoxy-3-phenyl-4,4a,5,6,7,7a-hexahydro-1*H*-imidazo-[4,5-*e*]-1,2,4-triazin-6-one (**12c**).

A solution of **1** (50 mg, 0.27 mmol) and *N*,*N*'-dimethylurea (24 mg, 0.27 mmol) in acetic anhydride (1 ml) was stirred for 48 hours at 20 °C. After evaporation of solvent *in vacuo*, the oily residue was dissolved in diethyl ether (1 ml). The precipitated colorless crystals were isolated by filtration to yield **3** (55 mg, 64%), mp 110-112 °C (dec). ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 3H), 2.59 (s, 3H), 2.78 (s, 3H), 3.27 (s, 3H), 6.12 (s, 1H), 7.44-7.55 (m, 3H), 7.80-7.83 (m, 2H), 8.69 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 21.2 (CO-CH_3), 23.8 and 27.9 (N-CH_3), 50.4 (5-OCH_3), 64.1 ($C6_{triazine}$), 95.9 ($C5_{triazine}$), 126.9, 128.4, 130.6, 131.8, 147.8 ($C3_{triazine}$), 155.8 and 170.9 (C=O).

Anal. Calcd for $C_{15}H_{19}N_5O_3$: C, 56.77; H, 6.03; N, 22.07. Found: C, 56.62; H, 5.99; N, 22.13.

1-Acetyl-7-methyl-3-phenyl-5,6,7,7a-tetrahydro-1*H*-imidazo[4,5-*e*]-1,2,4-triazin-6-one (**13b**).

A solution of **11b** (70 mg, 0.23 mmol) in acetonitrile (1.5 ml) was refluxed for 20 hours. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography to yield compound **13b** (14 mg, 22%), mp 186-188 °C. ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H), 3.28 (s, 3H), 5.12 (s, 1H) 6.81 (b.s, 1H), 7.41-7.47 (m, 3H), 8.09-8.15 (m, 2H).

Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.38; H, 4.80; N, 25.78.

1-Acetyl-5,7-dimethyl-3-phenyl-5,6,7,7a-tetrahydro-1*H*-imidazo[4,5-*e*]-1,2,4-triazin-6-one (**13c**).

Method 1.

A solution of **12c** (100 mg, 0.31 mmol) in $CHCl_3$ (2 ml) was refluxed for 48 hours. After evaporation of solvent *in vacuo* the residue was dissolved in CH_2Cl_2 and chromatography on silica gel gave 77 mg (87%) of **13c**, mp 141-143 °C. ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H), 3.27 (s, 3H), 3.32 (s, 3H), 4.71 (s, 1H), 7.40-7.44 (m, 3H), 8.07-8.14 (m, 2H); ^{13}C NMR ($CDCl_3$): 27.1, 29.9, 35.4, 62.5, 126.7, 128.4, 130.3, 133.9, 148.8, 156.3, 157.9, 179.4.

Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 59.05; H, 5.26; N, 24.41.

Method 2.

A mixture of **1** (200 mg, 1.08 mmol), *N*,*N*'-dimethylurea (95 mg, 1.08 mmol) and acetic anhydride (3 ml) was stirred for 1.5 hours at 85-90 °C. Solvent was removed *in vacuo* and the colourless crystals were washed with ether to yield 140 mg (45%) of compound **13c**, mp 144-146 °C.

1-Acetyl-3-phenyl-5,6,7,7a-tetrahydro-1*H*-imidazo[4,5-*e*]-1,2,4-triazin-6-thione (**14a**).

A mixture of **1** (80 mg, 0.27 mmol), thiourea (20.5 mg, 0.27 mmol) and acetic anhydride (1 ml) was stirred for 3 hours at 100 °C. The residue was isolated by filtration and washed with hot acetone to yield compound **14a**, mp 174-176 °C (14 mg, 22%). ^{1}H NMR (CF_3COOD): δ 2.66 (s, 3H), 7.75-7.84 (m, 3H), 8.35-8.45 (m, 2H) (three NH protons are exchanged with CF_3COOD).

Anal. Calcd for $C_{12}H_{11}N_5OS$,: C, 52.73; H, 4.06; N, 25.63. Found, C, 53.01; H, 4.50; N, 25.17.

1-Acetyl-7-methyl-3-phenyl-5,6,7,7a-tetrahydro-1*H*-imidazo-[4,5-*e*]-1,2,4-triazin-6-thione (**14b**).

A mixture of **1** (80 mg, 0.27 mmol), *N*-methylthiourea (24.3 mg, 0.27 mmol) and acetic anhydride (1 ml) was stirred for 48 hours at 20 °C. The residue was isolated by filtration and washed with hot acetone to yield imidazotriazine **14b** (56 mg, 72%), mp 250-252 °C. ^{1}H NMR (CF_3COOD): δ 2.79 (s, 3H), 4.15 (s, 3H), 7.75-7.94 (m, 3H), 8.32-8.38 (m, 2H) (two NH protons are exchanged with CF_3COOD); ^{13}C NMR (CF_3COOD): δ 24.4, 39.1, 129.1, 131.0, 132.6, 138.5, 158.7, 162.9, 178.8, 180.5.

Anal. Calcd for $C_{13}H_{13}N_5OS$: C, 54.34; H, 4.56; N, 24.37. Found: C, 54.52; H, 4.48; N, 24.43.

3-Phenyl-6,7-dihydro-5*H*-imidazo[4,5-*e*]-1,2,4-triazin-6-one (**15a**).

To a solution of **1** (80 mg, 0.43 mmol) in dry dichloromethane (1 ml) was added trifluoracetic anhydride (0.2 ml). The reaction mixture was stirred for 15 minutes at 20 °C, urea (26 mg, 0.45 mmol) was added, and the mixture was stirred for additional 48 hours. The reaction mixture was then concentrated at reduced pressure. The oily residue was washed with diethyl ether. The precipitate was isolated by filtration and washed with diethyl ether to yield 73 mg (80%) of compound **15a,** mp 120-125 °C. ^{1}H NMR (DMSO-d_6): δ 7.33 (bs, 2H), 7.56-7.65 (m, 3H), 8.00-8.12 (m, 2H).

Anal. Calcd for $C_{10}H_7N_5O$: C, 56.33; H, 3.31; N, 32.85. Found: C, 56.09; H, 3.34; N, 32.71.

5,7-Dimethyl-3-phenyl-6,7-dihydro-5*H*-imidazo[4,5-*e*]-1,2,4-triazin-6-one (**15c**).

Method 1.

A solution of **1** (50 mg, 0.27 mmol) and *N*,*N*'-dimethylurea (24 mg, 0.27 mmol) in acetic anhydride (1.5 ml) was heated at 110 °C

for 6 hours with stirring. The solvent was evaporated *in vacuo*, the colourless precipitate was filtered off and washed with diethyl ether to give 31 mg (48%) of compound **15c**: m.p. 198-200 °C. ^{1}H NMR ($CDCl_3$): δ 3.47 (s, 3H), 3.53 (s, 3H), 7.40-7.46 (m, 3H), 8.34-8.40 (m, 2H).

Anal. Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.50; H, 4.42; N, 28.88.

Method 2.

To a solution of **1** (50 mg, 0.27 mmol) in dry CH_2Cl_2 was added trifluoracetic anhydride (0.2 ml), and the mixture was stirred for 15 minutes at 20 °C. *N*,*N*'-Dimethylurea (24 mg, 0.27 mmol) was added, and the reaction solution was stirred for additional 48 hours. The reaction mixture was concentrated under reduced pressure. The oily residue was washed with diethyl ether. The precipitate was isolated by filtration and recrystallized from methanol to give 30 mg (46%) of compound **15c** (mp 199-200 °C).

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