# C—H-Functionalization of 1,2,4-triazines: oxidation and elimination pathways of aromatization of $\sigma^H$-adducts*

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An approach to the synthesis of 1,2,4-triazine thienyl and furyl derivatives through the reaction of aromatic nucleophilic substitution of hydrogen was suggested. Oxidation and *cine*-elimination pathways of aromatization of the intermediate $\sigma^H$-adducts were considered.

**Key words:** 1,2,4-triazines, aromatic nucleophilic substitution of hydrogen, thiophenes, furans.

1,2,4-Triazines are one of the most important class of nitrogen-containing heterocycles widely used in medicine, agrichemistry and as ligands for a number of metals.[1—5] Triazine derivatives are also known to be used as dyes.[6]

Triazine derivatives are of huge value in therapy of malaria, epilepsy, cancer, and a number of other diseases.[7—12] Besides, triazines are convenient synthetic blocks for the preparation of a wide range of heterocyclic compounds, in particular, pyridine derivatives, by the Diels—Alder reaction.[12—14] This shows that 1,2,4-triazine derivatives are of very much interest.

Synthesis of 1,2,4-triazine functional derivatives is based on two principally different approaches. In the first case, functional substituents are introduced into the heterocycle in the step of formation of cyclic system by condensation reaction.[1,15] Second approach consists in functionalization of heterocyclic system through the transformation of substituents in the triazine ring,[1,15] including application of cross-coupling reactions.[16—18]

The problem of nucleophilic substitution of hydrogen in 1,2,4-triazines was considered in a number of papers and monographs.[19—25] For example, a number of C-nucleophiles were reported to be successfully introduced in the 1,2,4-triazine ring,[22,23] in particular, alkylphenols[24] and crown-ethers.[25] Thus, the dissolution of 1,2,4-triazines in trifluoroacetic or acetic acid results to the formation of protic NH-triazinium salts, which at room temperature easily react with 2,6-dimethylphenol and resorcinol.[23] This reaction leads to a reverse formation of C(6)-adducts stable only in strongly acidic solutions ($^1$H NMR spectroscopic data). Attempted isolation of these adducts in the free state failed, but acylation appeared to be one of the successful pathways for their stabilization.[23] Another route for modification of 1,2,4-trizine adducts is their oxidation. In a number of cases the adducts can be oxidized by atmospheric oxygen, other cases require oxidants such as DDQ, lead tetraacetate, or potassium hexacyanoferrate.

The purpose of the present work is studies of the reaction of 3-substituted 1,2,4-triazines with furans and thiophenes. We have chosen readily available 3-methylthio-1,2,4-triazine (**1**) and 3-amino-1,2,4-triazine (**2**) as the starting compounds.

The reaction of triazines **1** and **2** with a number of thiophenes in the presence of the oxidation mixture $K_3(Fe(CN)_6)$—KOH gave good yields of the products of substitution of the hydrogen atom at atom C(5) of the triazine ring (Scheme 1).

It was found that the product of the addition of thiophene to the triazine ring is formed in the first step of the reaction. The composition of the reaction mixtures was analyzed by GLC-MS (Table 1). In a number of cases, $\sigma^H$-adducts turned out to be so stable that they were isolated in the free form. Stability of $\sigma^H$-adducts depends on the character of substituent in the thiophene ring. The larger is the donor effect of such a substituent (for example, phenyl), the more stable is the addition product and, therefore, the higher is the yield of the adduct. Conversely, in the case of thienyl-2-carbaldehyde we isolated neither the corresponding adduct nor the product of nucleophilic aromatic substitution of hydrogen.

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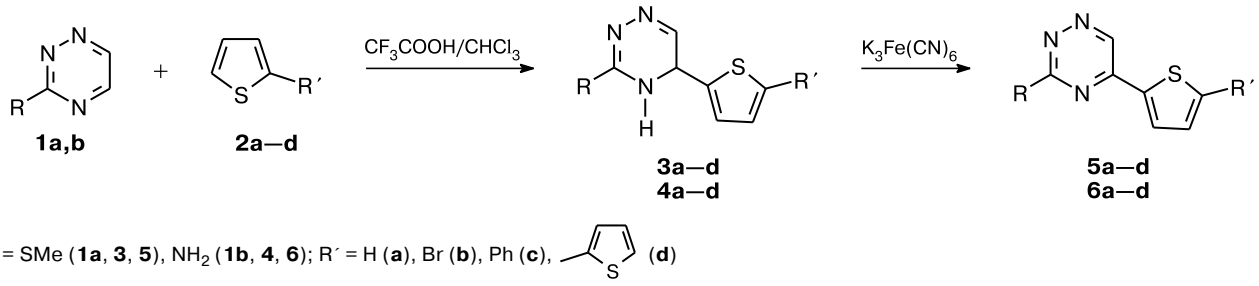
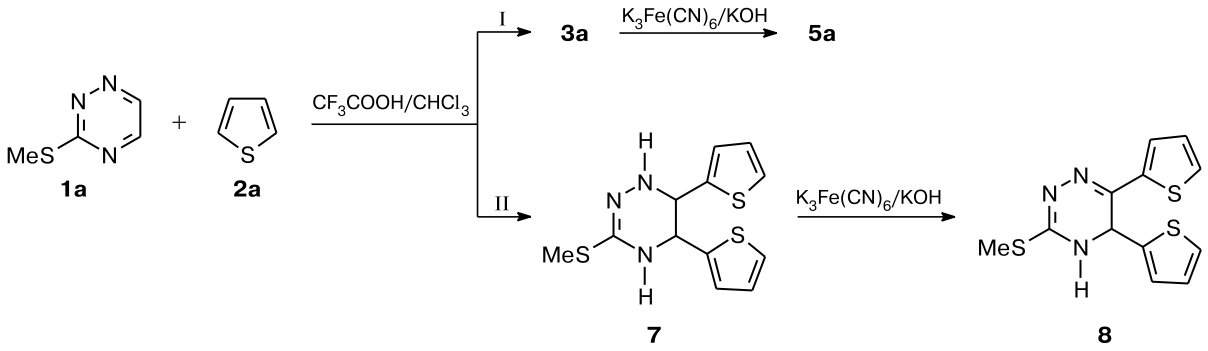
**Scheme 1**




R = SMe (**1a**, **3**, **5**), $NH_2$ (**1b**, **4**, **6**); R′ = H (**a**), Br (**b**), Ph (**c**),  (**d**)

**Scheme 2**




The second step consists in the aromatization of the adducts. In this case, the oxidant can be applied to both the reaction mixture (without isolation of the intermediate compound) and to the individual dihydrotriazine (if it is stable). The structures of synthesized compounds were confirmed by a combination of spectroscopic methods, as well as by X-ray diffraction studies using product **5d** as an example (Fig. 1).

The reaction of triazine **1** with a 10-fold excess of thiophene (Scheme 2, pathway II) gives adduct **7**, however, the GLC-MS data show that the same reaction with 1.5—2-fold excess of thiophene leads to the formation of only monoadduct **3a** (Scheme 2, pathway I).

**Table 1.** Composition of the reaction mixtures in the reaction of 3-methylthio-1,2,4-triazine with thiophene and furan

| Ratio triazine/nucleophile | Composition of mixture (%) |
|---|---|
| **1a** : **2a**, 1 : 10 | **3a** (3), **7** (80) |
| **1a** : **2a***, 1 : 10 | **8** (8), **7** (65) |
| **1a** : **2a**, 1 : 2 | **3a** (73), **5a** (17) |
| **1a** : **9***, 1 : 2 | **10** (40), **11** (58) |
| **1a** : **9***, 1 : 10 | **11** (100) |
| **12** : **2a***, 1 : 2 | **6a** (84), **13** (13) |

* $K_3(Fe(CN)_6)$/KOH.

Compounds **3a** and **7** have different resistance to oxidants. Compound **7** appears to be comparatively stable to such oxidants as atmospheric oxygen, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and $K_3[Fe(CN)_6]$.

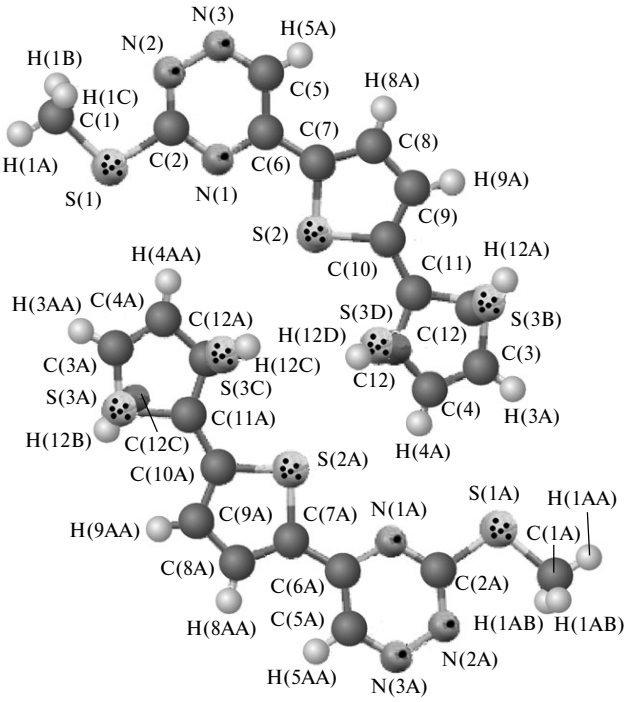
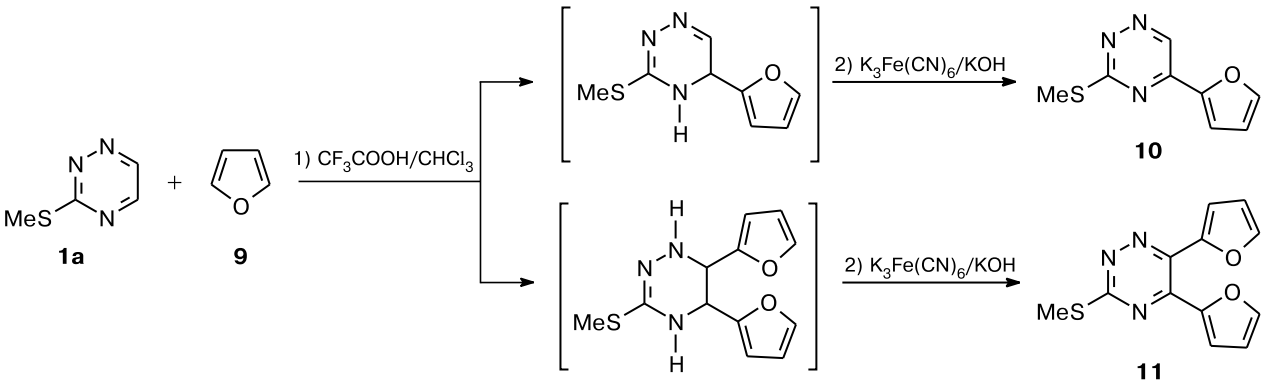



**Fig. 1.** Geometry of compound **5d** in crystal.

**Scheme 3**




For example, analysis of the reaction mixture of **7** and $K_3(Fe(CN)_6$—KOH showed the presence of only 8% of partially oxidized product **8**. At the same time, compound **3a** quite readily undergoes aromatization to 5-thienyl-substituted triazine **5a**.

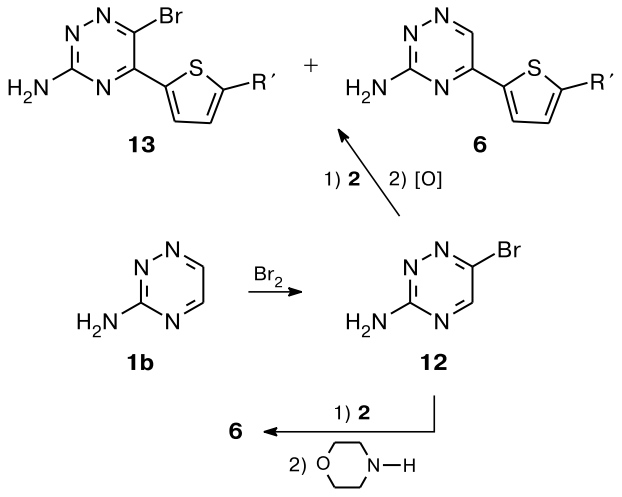
Similarly, the reaction of 3-methylthiotriazine **1a** with a 10-fold excess of furan (**9**) in the presence of an oxidant leads to the formation of only disubstitution product **11**, but the intermediate monoadduct were not even detected in the reaction mixture. In turn, in the reaction with a twofold excess of furan under oxidation conditions, a mixture of compounds **10** and **11** is formed, in which case compound **10** was isolated and characterized (Scheme 3).

Attempted introduction of halogen atom at position C(6) of the 1,2,4-triazine ring in order to increase synthetic potential of obtained thiophene and furan derivatives of 3-methylthiotriazine failed. However, bromination of 3-amino-1,2,4-triazine proceeds rather smoothly, giving rise to 3-amino-6-bromotriazine in good yield.

3-Amino-6-bromo-1,2,4-triazine (**12**) was found to react with thiophenes under acid-catalyzed conditions with subsequent oxidation by $K_3[Fe(CN)_6]$—KOH to the *cine*-substitution products **6** (Scheme 4). GLC-MS analysis of the reaction mixture in the case of the reaction of compound **12** with thiophene in the step of addition of the latter to 3-amino-6-bromo-1,2,4-triazine (**12**) showed the absence of the molecular peak corresponding to the expected $\sigma^H$-adduct. Analysis of the same reaction mixture after completion of the reaction showed that formation of compound **6a** (84%) is the main reaction result, whereas the product of oxidative substitution of hydrogen **13** was formed only in 13% yield. These data allowed us to suggest that in the case of 6-bromo-1,2,4-triazine, aromatization follows mainly elimination *cine*-mechanism with the loss of the halogen atom. In fact, the reaction can be carried out without oxidant, but with addition of a base (morpholine) to the reaction mixture, which results in the formation of the only product **6a**.

In conclusion, in the work we showed a possibility of a direct C—H-functionalization of 1,2,4-triazine derivatives with thiophene and furan derivatives. New mono- and dithienyl or furyl derivatives of 3-substituted 1,2,4-triazines were obtained.

**Scheme 4**




## Experimental

Solvents and reactants were dried and purified according to the procedures taken from the literature.[26]

$^1$H NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 MHz), using $SiMe_4$ as an internal standard. Elemental analysis was performed on a Perkin Elmer PE-2400 automated analyzer. Melting points were determined on combined Boetius heating stages and were not corrected. Flash-chromatography was performed using Lancaster 0.040—0.063 mm silica gel (230—400 mesh).

Reaction progress and purity of products were monitored by TLC on Sorbfil plates, visualizing under UV light or in $I_2$ vapors.

X-ray diffraction study was carried out on a Xcalibur-3 X-ray diffractometer with a CCD-detector according to the standard procedure: ($\lambda$Mo-K$\alpha$), graphite monochromator, $\omega$-scan technique. The structures of all the compounds were solved by direct method using the SHELXS-97 program and refined using the SHELXL-97 program in anisotropic (isotropic for hydrogen

atoms) approximation. No correction for absorption was made. The results of X-ray diffraction study of compound **5d** were deposited with the Cambridge Structural Database (CCDC 993541). These materials are available free of charge and can be requested at: wwwwww.ccdc.cam.ac.uk/data_request/cif.ccdc.cam.ac.uk/data_request/cif.

**3-Methylsulfanyl-1,2,4-triazine (1a).** Triazine **1a** was obtained according to the known procedure[27] as a yellow powder. The yield was 92%, m.p. 31—33 °C. Found (%): C, 38.07; H, 3.80; N, 33.00. $C_4H_5N_3S$. Calculated (%): C, 37.80; H, 3.94; N, 33.07. $^1$H NMR (DMSO-$d_6$), δ: 8.65 (d, 1 H, triazine, $J$ = 2.3 Hz); 8.32 (d, 1 H, triazine, $J$ =2.3 Hz); 2.27 (s, 3 H, S—$CH_3$).

**3-Amino-1,2,4-triazine (1b).** Triazine **1b** was obtained according to the known procedure[28] as a yellow powder. The yield was 90%, m.p. 174—176 °C. Found (%): C, 37.80; H, 4.00; N, 58.50. $C_3H_4N_4$. Calculated (%): C, 37.50; H, 4.20; N, 58.31. $^1$H NMR (DMSO-$d_6$), δ: 8.55 (d, 1 H, triazine, $J$ = 2.28 Hz); 8.21 (d, 1 H, triazine, $J$ = 2.28 Hz); 7.19 (br.s, 2 H, $NH_2$).

**3-Amino-6-bromo-1,2,4-triazine (12).** Triazine **12** was obtained according to the known procedure[29] as a yellow powder. The yield was 58%, m.p. >300 °C. Found (%): C, 19.93; H, 1.70; N, 31.83. $C_3H_3N_4Br$. Calculated (%): C, 20.59; H, 1.73; N, 32.02. $^1$H NMR (DMSO-$d_6$), δ: 8.40 (s, 1 H, triazine); 7.47 (br.s, 2 H, $NH_2$).

**Synthesis of $\sigma^H$-adducts of 5-hetaryl-3-*R*-1,2,4-triazines (general procedure).** The starting triazine (1 mmol) was dissolved in a mixture of trifluoroacetic acid and chloroform (dichloromethane) (2 mL, 1 : 1), then thiophene or furan (1.1 mmol) was added.

The mixture obtained was refluxed for 1.5 h (method *A*) or stirred for 24 h at room temperature (method *B*).

Then, the reaction mixture was concentrated, an oily residue was neutralized with saturated aqueous sodium bicarbonate. A precipitate formed was filtered off. The products were additionally purified by recrystallization from proper solvents.

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The mixture obtained was refluxed for 1.5 h (method *A*) or stirred for 24 h at room temperature (method *B*).

Then, the reaction mixture was neutralized with saturated aqueous sodium bicarbonate. A mixture of KOH (3 mmol) and $K_3(Fe(CN)_6$ (3 mmol) in water (5 mL) was added to the two-phase system, which was stirred for 5 h. The organic phase was separated, the aqueous phase was additionally washed with chloroform (3×5 mL). The combined organic phase was washed with water, dried with $Na_2SO_4$, and concentrated. An oily residue was separated on silica gel (eluent $CHCl_3$—EtOH (8 : 2)). The products were additionally purified by recrystallization from proper solvents.

**Synthesis of 5,6-dihetaryl-3-*R*-1,2,4-triazines and their tetrahydro adducts (general procedure).** The starting triazine (1 mmol) was dissolved in a mixture of trifluoroacetic acid and chloroform (dichloromethane) (2 mL, 1 : 1), followed by addition of thiophene or furan (10 mmol). The reaction mixture was stirred for 24 h at room temperature and concentrated, an oily residue was neutralized with saturated aqueous sodium bicarbonate. A precipitate formed was filtered off. The products were additionally purified by recrystallization from proper solvents. A compound obtained was dissolved in chloroform, followed by addition of KOH (6 mmol) and $K_3(Fe(CN)_6$ (6 mmol) in water (10 mL). The reaction mixture was stirred for 5 h. Then, the organic phase was separated, the aqueous phase was additionally washed with chloroform (3×5 mL). The combined organic phase was washed with water, dried with $Na_2SO_4$, and concentrated. An oily residue was separated on silica gel (eluent $CHCl_3$—EtOH (8 : 2)). The products were additionally purified by recrystallization from proper solvents.

Compounds **3**, **5**, and **6** were obtained by both methods *A* and *B*.

**3-Methylsulfanyl-5-(thiophen-2-yl)-4,5-dihydro-1,2,4-triazine (3a).** The product was obtained by methods *A* and *B*. A colorless powder. The yield was 58% (*A*), m.p. 143—144 °C. Found (%): C, 45.60; H, 4.45; N, 20.04. Calculated (%): C, 45.47; H, 4.29; N, 19.89. $C_8H_9N_3S_2$. $^1$H NMR (DMSO-$d_6$), δ: 10.83 (br.s, 1 H, NH); 7.40—7.43 (m, 1 H, C(6)H); 7.24—7.26 (m, 1 H, thiophene); 6.86—7.04 (m, 2 H, thiophene); 5.03. (s, 1 H, C(5)H); 2.36 (s, 3 H, S—$CH_3$).

**3-Methylsulfanyl-(5-thiophen-2-yl)-1,2,4-triazine (5a).** The product was obtained by methods *A* and *B* and isolated by recrystallization from ethanol as a light yellow powder. The yield was 65% (*A*), m.p. 98—100 °C. Found (%): C, 45.74; H, 3.12; N, 20.03. $C_8H_7N_3S_2$. Calculated (%): C, 45.91; H, 3.37; N, 20.08. $^1$H NMR (DMSO-$d_6$), δ: 9.71 (s, 1 H, C(6)H); 8.33 (dd, 1 H, thiophene, $J_1$ = 1.04 Hz, $J_2$ = 3.84 Hz); 8.06 (dd, 1 H, thiophene, $J_1$ = 1.04 Hz, $J_2$ = 4.92 Hz); 7.35 (dd, 1 H, thiophene, $J_1$ = 3.84 Hz, $J_2$ = 4.92 Hz); 2.69 (s, 3 H, S—$CH_3$).

**3-Amino-5-(thiophen-2-yl)-1,2,4-triazine (6a).** The product was obtained by methods *A* and *B* and isolated by recrystallization from ethanol as a light yellow powder. The yield was 70% (*A*), m.p. 120—121 °C. Found (%): C, 47.34; H, 3.12; N, 31.15. $C_7H_6N_4S$. Calculated (%): C, 47.18; H, 3.39; N, 31.44. $^1$H NMR (DMSO-$d_6$), δ: 9.61 (s, 1 H, C(6)H); 8.53 (dd, 1 H, thiophene, $J_1$ = 1.00 Hz, $J_2$ = 3.80 Hz); 8.16 (dd, 1 H, thiophene, $J_1$ = 1.00 Hz, $J_2$ = 4.85 Hz); 7.45 (br.s, 2 H, $NH_2$), 7.27 (dd, 1 H, thiophene, $J_1$ = 3.80 Hz, $J_2$ = 4.85 Hz).

**5-(5-Bromothiophen-2-yl)-3-methylsulfanyl-1,2,4-triazine (5b).** The product was obtained by methods *A* and *B* and isolated by recrystallization from ethanol as yellow crystals. The yield was 78% (*A*), m.p. 144—146 °C. Found (%): C, 33.45; H, 2.30; N, 14.25. $C_8H_6N_3S_2Br$. Calculated (%): C, 33.34; H, 2.10; N, 14.58. $^1$H NMR ($CDCl_3$), δ: 9.12 (s, 1 H, C(6)H); 7.64 (d, 1 H, thiophene, $J$ = 4.0 Hz); 7.19 (d, 1 H, thiophene, $J$ = 4.0 Hz); 2.67 (s, 3 H, S—$CH_3$).

**3-Amino-5-(5-bromothiophen-2-yl)-1,2,4-triazine (6b).** The product was obtained by methods *A* and *B* and isolated by recrystallization from acetonitrile as a colorless powder. The yield was 88% (*A*), m.p. >300 °C. Found (%): C, 32.58; H, 2.10; N, 24.49. $C_7H_5N_4SBr$. Calculated (%): C, 32.70; H, 1.96; N, 21.79. $^1$H NMR (DMSO-$d_6$), δ: 9.16 (s, 1 H, triazine); 8.01 (d, 1 H, thiophene $J$ = = 4.0 Hz); 7.43 (d, 1 H, thiophene $J$ = 4.0 Hz); 7.28 (br.s, 2 H, $NH_2$).

**3-Methylsulfanyl-5-(5-phenylthiophen-2-yl)-1,2,4-triazine (5c).** The product was obtained by methods *A* and *B* and isolated by recrystallization from ethanol as a yellow powder. The yield was 69% (*A*), m.p. 138—139 °C. Found (%): C, 88.30; H, 4.02; N, 14.57. $C_{14}H_{11}N_3S_2$. Calculated (%): C, 58.92; H, 3.89; N, 14.72. $^1$H NMR ($CDCl_3$), δ: 9.18 (s, 1 H, C(6)H); 7.87—7.88 (m, 1 H, phenyl); 7.68—7.70 (m, 2 H, thiophene); 7.32—7.48 (m, 4 H, phenyl); 2.70 (s, 3 H, S—$CH_3$).

**3-Amino-5-(5-phenylthiophen-2-yl)-1,2,4-triazine (6c).** The product was obtained by method *A* and isolated by recrystallization from ethanol as a yellow powder. The yield was 65%, m.p. 163—164 °C. Found (%): C, 61.55; H, 4.34; N, 22.04. $C_{13}H_{10}N_4S$. Calculated (%): C, 61.40; H, 3.96; N, 22.03. $^1$H NMR ($CDCl_3$), δ: 9.58 (s, 1 H, C(6)H); 7.67—7.68 (m, 1 H, phenyl); 7.58—7.60 (m, 2 H, thiophene); 7.32 (br.s, 2 H, $NH_2$), 7.22—7.38 (m, 4 H, phenyl).

**5-(2,2′-Bithiophen-5-yl)-3-methylsulfanyl-1,2,4-triazine (5d).** The product was obtained by method *A* and isolated by

recrystallization from ethanol as a brown powder. The yield was 78%, m.p. 122—124 °C. Found (%): C, 49.60; H, 3.09; N, 14.52. $C_{12}H_9N_3S_3$. Calculated (%): C, 49.46; H, 3.11; N, 14.42. $^1$H NMR ($CDCl_3$), δ: 9.15 (s, 1 H, C(6)H); 7.80—7.81 (m, 1 H, thiophene); 7.34—7.35 (m, 2 H, thiophene); 7.26—7.27 (m, 2 H, thiophene); 2.67 (s, 3 H, S—$CH_3$).

**3-Amino-5-(2,2´-bithiophen-5-yl)-1,2,4-triazine (6d).** The product was obtained by method *A* and isolated by recrystallization from acetonitrile as a brown powder. The yield was 67%, m.p. 225—226 °C. Found (%): C, 50.60; H, 3.09; N, 21.47. $C_{11}H_8N_4S_2$. Calculated (%): C, 50.75; H, 3.10; N, 21.52. $^1$H NMR ($CDCl_3$), δ: 9.55 (s, 1 H, C(6)H); 7.68—7.71 (m, 1 H, thiophene); 7.38—7.39 (m, 2 H, thiophene); 7.36—7.29 (m, 2 H, thiophene); 7.25 (br.s, 2 H, $NH_2$).

**3-Methylsulfanyl-5,6-bis(thiophen-2-yl)-1,4,5,6-tetrahydro-1,2,4-triazine (7).** The product was obtained by method *B* and isolated by recrystallization from ethanol as a colorless powder. The yield was 80%, m.p. >250 °C. Found (%): C, 48.71; H, 4.41; N, 13.98. $C_{12}H_{13}N_3S_3$. Calculated (%): C, 48.78; H, 4.44; N, 14.22. $^1$H NMR (DMSO-$d_6$), δ: 7.40—7.41 (m, 2 H, thiophene); 7.16 (br.s, 1 H, NH); 6.87—6.89 (m, 2 H, thiophene); 6.77—6.78 (m, 2 H, thiophene), 6.31 (br.s, 1 H, NH); 4.67—4.69 (m, 1 H, C(5)H); 4.12—4.13 (m, 1 H, C(6)H); 2.27 (s, 3 H, S—$CH_3$).

**3-Methylsulfanyl-5-(furan-2-yl)-1,2,4-triazine (10).** The product was obtained by method *B* and isolated by recrystallization from acetonitrile as a yellow powder. The yield was 30%, m.p. 154—155 °C. Found (%): C, 49.34; H, 3.60; N, 21.58. $C_8H_7N_3OS$. Calculated (%): C, 49.73; H, 3.65; N, 21.75. $^1$H NMR (DMSO-$d_6$), δ: 9.85 (s, 1 H, triazine); 8.42—8.44 (m, 1 H, furan); 8.15—8.16 (m, 1 H, furan); 7.37—7.39 (m, 1 H, furan); 2.63 (s, 3 H, S—$CH_3$).

**3-Methylsulfanyl-5,6-bis(furan-2-yl)-1,2,4-triazine (11).** The product was obtained by method *B* and isolated by recrystallization from ethanol as a yellow powder. The yield was 53%, m.p. 170—171 °C. Found (%): C, 55.34; H, 3.25; N, 16.18. $C_{12}H_9N_3O_2S$. Calculated (%): C, 55.59; H, 3.50; N, 16.21. $^1$H NMR (DMSO-$d_6$), δ: 8.06 (dd, 1 H, furan, $J_1$ = 0.68 Hz, $J_2$ = 1.68 Hz); 7.96 (dd, 1 H, furan, $J_1$ = 0.76 Hz, $J_2$ = 1.76 Hz); 7.05 (dd, 1 H, furan, $J_1$ = 0.76 Hz, $J_2$ = 3.4 Hz); 6.89 (dd, 1 H, furan, $J_1$ = 0.68 Hz, $J_2$ = 3.64 Hz); 6.75—6.78 (m, 2 H, furan); 2.69 (s, 3 H, S—$CH_3$).

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