S_NH reactions of 1,2,4-triazine *N*-oxides, pyrazine *N*-oxides, and pterin *N*-oxides with arenethiols*

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1,2,4-Triazine 4-oxides were found to enter into the reactions of nucleophilic substitution of hydrogen with S-nucleophiles (arenethiols) in the presence of acylating agents and trifluoroacetic acid. The reactions proceeded with loss of the *N*-oxide function to form 5-arylthio-1,2,4-triazines. 2-Amino-3-ethoxycarbonylpyrazine 1-oxides and 2-amino-4-oxopterin 8-oxides react with arenethiol analogously.

Key words: nucleophilic substitution of hydrogen, 1,2,4-triazine 4-oxide, pyrazine 1-oxide, pterin 8-oxide, thiophenol.

Aromatic nucleophilic substitution of hydrogen (S_NH) is successfully used for the direct introduction of nucleophilic fragments into electrophilic arenes, non-benzoid aromatic systems, and hetarenes.[1] Due to high π-deficiency of the heterocyclic system, 1,2,4-triazine 4-oxides are readily involved into S_NH reactions with different C-, O-, and N-nucleophiles.[2] Thus aromatic (phenols and anilines) and heteroaromatic (pyrroles and indoles) C-nucleophiles, some cyclic β-diketones (indanedione, dimedone, and 1,3-dimethylbarbituric acid), and water react with 1,2,4-triazine 4-oxides under conditions of acid catalysis to form σ^H-adducts whose aromatization follows several directions. Thus oxidative aromatization affords substituted 1,2,4-triazine 4-oxides,[3] whereas elimination of hydrogen together with the oxygen-containing fragment in the absence of an oxidizing agent (autoaromatization) gives rise to substituted 1,2,4-triazines.[4] The reactions of 1,2,4-triazine 4-oxides with anionic nucleophiles (cyanide anions,[5] stabilized carbanions,[6] and cyanamide in the presence of a base[7]) follow exclusively the deoxygenative S_NH pathway. Ammonia and aliphatic amines also readily react with 1,2,4-triazine 4-oxides. Although the resulting σ^H-adducts are unstable, their oxidation affords the corresponding amino-1,2,4-triazine 4-oxides.[8] 2-Amino-3-ethoxycarbonylpyrazine 1-oxides[9] are involved into the S_NH reactions with indoles and pyrroles in the presence of acyl chlorides with loss of the *N*-oxide function.

Data on the reactions of 1,2,4-triazine *N*-oxides with S-nucleophiles are lacking in the literature. A few examples of the formation of alkylthiopyridines[10] and pyrazines[11,12] in the reactions of the corresponding *N*-oxides with alkanethiols in the presence of acid chlorides and acid anhydrides were reported.

As part of continuing studies in this field, we used the S_NH reaction for the introduction of thioaryl groups into 1,2,4-triazines, pyrazines, and pterins. It appeared that the reactions of 1,2,4-triazine 4-oxides **1** with arenethiol in the presence of trifluoroacetic acid followed by treatment of the reaction mixture with benzoyl chloride afforded 5-phenylthio-1,2,4-triazines **2** in 70—90% yields. Evidently, the reactions proceeded according to the mechanism established[7] for these conditions. In the first stage, thiophenol added as an S-nucleophile to 1,2,4-triazine 4-oxide activated with trifluoroacetic acid. Subsequent acylation of σ^H-adduct **A** at the oxygen atom of the *N*-oxide fragment and autoaromatization of intermediate **B** with elimination of the hydrogen atom together with the fragment of benzoic acid gave rise to product **2** (Scheme 1). The necessity of using the acylating agent (the reaction did not proceed in the absence of benzoyl chloride) stems from the difficulty of aromatization of adduct **A** *via* elimination of water.

The reactions with 1,2,4-triazine 4-oxides **1** and substituted arenethiols (4-chloro-, 4-hydroxy-, and 3-methoxythiophenols) proceed similarly to form the corresponding 5-arylthio-1,2,4-triazines (**3—5**) in 60—90% yields. In all cases, arenethiols react exclusively as S-nucleophiles. These reactions differ significantly from those of 1,2,4-triazine 4-oxides with phenols and resorcinol, the latter reacting only as C-nucleophiles. Therefore, from the viewpoint of the HSAB theory, the softest nucleophilic centers of nucleophiles (the S atom in arenethiols or the C atom in phenols), *i.e.*, the atoms on which the maximum orbital density of

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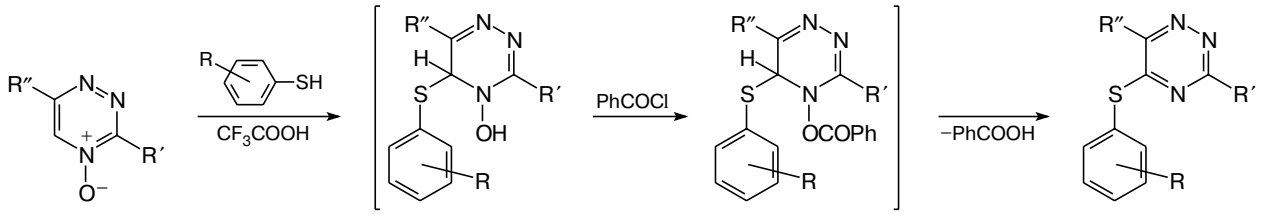
Scheme 1



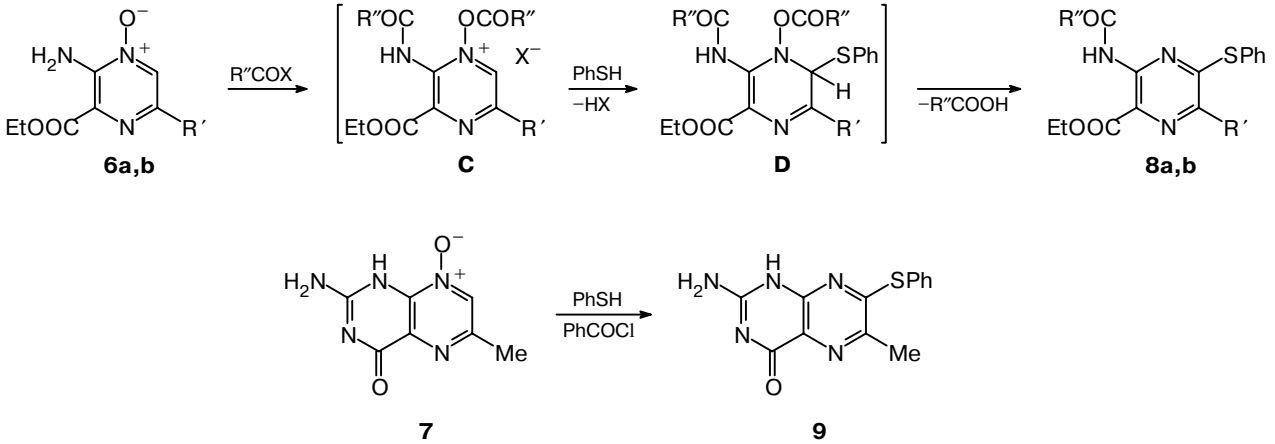
R = H (**2**), 4-Cl (**3**), 4-OH (**4**), 3-OMe (**5**)

	a	**b**	**c**	**d**
R′	Ph	4-$NO_2C_6H_4$	Ph	Ph
R″	Ph	Ph	4-BrC_6H_4	4-MeC_6H_4

the highest occupied molecular orbital (HOMO) is localized, are involved in the reactions with 1,2,4-triazine 4-oxides. It should be noted that our studies of the regioselectivity of the nucleophilic attack in the series of 6-aryl-1,2,4-triazine 4-oxides[13] revealed that under conditions of kinetic control, the nucleophile attacks the C atom at position 5 of the heterocycle. *Ab initio* quantum-chemical calculations with the 6-31G** basis set demonstrated that it is this atom on which the maximum orbital density of the lowest unoccupied molecular orbital (LUMO) is localized. All the above is indicative of the orbital control over the nucleophilic attack in the reactions of 1,2,4-triazine 4-oxides.

Based on the fact that 1,2,4-triazine 4-oxides readily react with arenethiols, other azine *N*-oxides would be expected to react under analogous conditions. We investigated 2-amino-3-ethoxycarbonylpyrazine 1-oxides (**6**) and 2-amino-6-methylpteridin-4(1*H*)-one 8-oxides (**7**) because functionalization of these heterocycles allows one to obtain compounds, in particular, analogs of folic acid, which are of interest from the standpoint of their possible biological activity. Pyrazine 1-oxides **6** were found to enter into the reactions of deoxygenative nucleophilic substitution of hydrogen with thiophenols, although they are less active than 1,2,4-triazine 4-oxides **1**. Arenethiol reacted with pyrazine 1-oxides **6** only in the presence of an excess of an acylating agent (acetic anhydride or benzoyl chloride) upon prolonged heating to form 2-acylamino-3-ethoxycarbonyl-6-phenylthiopyrazines (**8**) in 15—20% yields (Scheme 2). Apparently, the target products were obtained in low yields due to the low reactivity of the aminopyrazine *N*-oxides used. Thus the absence of one N atom in the ring and the presence of the donating amino group lead to a substantial decrease in the electrophilicity of the heterocycle compared to that of 1,2,4-triazine 4-oxides. As in the case of compounds **1**, the application of acid catalysis in the reactions of pyrazine 1-oxides **6** was unsuc-

Scheme 2



R′ = Ph, R″ = Ph, X = Cl (**a**); R′ = 4-MeC_6H_4, R″ = Me, X = AcO (**b**)

cessful. Evidently, this can be attributed to both the low activity of the protonated pyrazinium cations and the low stability of intermediate σ^H-adducts in contrast to σ^H-adducts of type **A** of the 1,2,4-triazine series, which can be sometimes isolated from the reaction mixture in the pure form.[2] Apparently, the mechanisms of the reactions of 1,2,4-triazine 4-oxides **1** and pyrazine 1-oxides **6** are somewhat different. It is believed that the first stage of the reactions of heterocycles **6**, like that of pyridine *N*-oxides,[1] involves acylation of the substrate at the oxygen atom of the *N*-oxide group. The resulting 1-benzoyloxypyrazinium salt **C** is sufficiently active to add arenethiol, and σ^H-adduct **D** that formed readily undergoes aromatization with elimination of benzoic acid (see Scheme 2).

The reaction of arenethiol with oxide **7** in the presence of benzoyl chloride proceeded more smoothly to give 2-amino-6-methyl-7-(phenylthio)pteridin-4(1*H*)-one (**9**) in 80% yield (see Scheme 2). Apparently, the reactions of pterin 8-oxide **7** and pyrazine 1-oxides proceed according to the same mechanism, but the reactivity of the former compound is higher.

The structures of the compounds synthesized correspond to the data from ^{1}H NMR spectroscopy, mass spectrometry, and elemental analysis.

To summarize, we developed a one-step procedure for the introduction of the S-nucleophilic fragments into 1,2,4-triazines, pyrazines, and pterins, which extends the synthetic potential of this series of compounds, including their use in the search for new biologically active compounds.

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 mass spectra were measured on a Varian MAT-311A instrument using electron ionization. 1,2,4-Triazine 4-oxides **1** were synthesized according to a procedure reported previously.[14]

Synthesis of 5-arylthio-1,2,4-triazines 2—5 (general procedure). The corresponding 1,2,4-triazine 4-oxides **1** (1 mmol) and thiophenol (1.05 mmol) were dissolved in a mixture of Me_2CO (50 mL) or DMF (5 mL) and trifluoroacetic acid (1 mL). The reaction mixture was refluxed for 5 min. Then benzoyl chloride (0.14 mL, 1.2 mmol) was added and the mixture was refluxed for 10 min. The solvent was evaporated *in vacuo* and the residue was recrystallized from ethanol.

3,6-Diphenyl-5-phenylthio-1,2,4-triazine (2a). The yield was 81%, m.p. 127 °C. Found: C, 73.99; H, 4.57; N, 12.19. $C_{21}H_{15}N_3S$. Calculated (%): C, 73.87; H, 4.43; N, 12.31. ^{1}H NMR, δ: 7.35—7.65 (m, 11 H); 7.90 and 8.10 (both m, 2 H each). MS, *m/z* (I_{rel} (%)): 341 $[M]^+$ (10).

3-(4-Nitrophenyl)-6-phenyl-5-phenylthio-1,2,4-triazine (2b). The yield was 85%, m.p. 213 °C. Found (%): C, 65.12; H, 3.48; N, 14.64. $C_{21}H_{14}N_4O_2S$. Calculated (%): C, 65.27; H, 3.65; N, 14.50. ^{1}H NMR, δ: 7.50—7.70 (m, 8 H); 7.90 (m, 2 H); 8.26 (s, 4 H, 4-$NO_2C_6H_4$).

3-Phenyl-5-phenylthio-6-(4-tolyl)-1,2,4-triazine (2d). The yield was 71%, m.p. 160 °C. Found (%): C, 74.41; H, 4.73; N, 11.68. $C_{22}H_{17}N_3S$. Calculated (%): C, 74.34; H, 4.82; N, 11.82. ^{1}H NMR, δ: 2.48 (s, 3 H, Me); 7.30—7.50 (m, 5 H); 7.50—7.70 (m, 5 H); 7.80 (d, 2 H); 8.10 (m, 2 H). MS, *m/z* (I_{rel} (%)): 355 $[M]^+$ (10).

5-(4-Chlorophenylthio)-3,6-diphenyl-1,2,4-triazine (3a). The yield was 68%, m.p. 164 °C. Found (%): C, 67.01; H, 3.47; N, 11.14. $C_{21}H_{14}ClN_3S$. Calculated (%): C, 67.10; H, 3.75; N, 11.18. ^{1}H NMR, δ: 7.40—7.50 (m, 3 H); 7.50—7.70 (m, 7 H); 7.90 (m, 2 H); 8.10 (d, 2 H).

5-(4-Hydroxyphenylthio)-3,6-diphenyl-1,2,4-triazine (4a). The yield was 65%, m.p. 246 °C. Found C, 70.81; H, 3.95; N, 11.79. $C_{21}H_{15}N_3OS$. Calculated (%): C, 70.57; H, 4.23; N, 11.76. ^{1}H NMR, δ: 6.90 and 7.30 (both d, 2 H each); 7.40—7.50 (m, 3 H); 7.50—7.70 (m, 3 H); 7.90 (m, 2 H); 8.10 (m, 2 H); 9.80 (s, 1 H, OH).

5-(3-Methoxyphenylthio)-3,6-diphenyl-1,2,4-triazine (5a). The yield was 87%, m.p. 123 °C. Found (%): C, 71.08; H, 4.69; N, 11.24. $C_{22}H_{17}N_3OS$. Calculated (%): C, 71.14; H, 4.61; N, 11.31. ^{1}H NMR, δ: 3.81 (s, 3 H, OMe); 7.10—7.20 (m, 3 H); 7.40—7.50 (m, 4 H); 7.60 (m, 3 H); 7.90 and 8.10 (both m, 2 H each).

6-(4-Bromophenyl)-5-(3-methoxyphenylthio)-3-phenyl-1,2,4-triazine (5c). The yield was 92%, m.p. 142 °C. Found (%): C, 58.61; H, 3.50; N, 9.42. $C_{22}H_{16}BrN_3OS$. Calculated (%): C, 58.67; H, 3.58; N, 9.33. ^{1}H NMR, δ: 3.81 (s, 3 H, OMe); 7.10—7.20 (m, 3 H); 7.40—7.50 (m, 4 H); 7.75—7.85 (m, 4 H, 4-BrC_6H_4); 8.10 (m, 2 H). MS, *m/z* (I_{rel} (%)): 451 (14) and 449 $[M]^+$ (15).

2-Benzoylamino-3-ethoxycarbonyl-5-phenyl-6-phenylthiopyrazine (8a) was prepared on heating oxide **6a** in DMF in the presence of 3-fold excess of PhCOCl at 100 °C for 1 h. The yield was 15%, m.p. 185 °C. Found (%): C, 68.29; H, 4.38; N, 9.32. $C_{26}H_{21}N_3O_3S$. Calculated (%): C, 68.55; H, 4.65; N, 9.22. ^{1}H NMR, δ: 1.23 (t, 3 H, $CH_2C\underline{H}_3$); 4.25 (q, 2 H, $C\underline{H}_2Me$); 7.30—7.60 (m, 11 H); 7.70 and 7.90 (both m, 2 H each); 11.04 (s, 1 H, NH).

2-Acetylamino-3-ethoxycarbonyl-6-phenylthio-5-(4-tolyl)pyrazine (8b) was prepared on heating oxide **6b** in DMF in the presence of 3-fold excess of Ac_2O at 100 °C for 1 h. The yield was 20%, m.p. 147 °C. Found (%): C, 64.61; H, 5.34; N, 10.58. $C_{22}H_{21}N_3O_3S$. Calculated (%): C, 64.85; H, 5.19; N, 10.31. ^{1}H NMR, δ: 1.35 (t, 3 H, $CH_2C\underline{H}_3$); 1.75 (s, 3 H, MeCO); 2.43 (s, 3 H, Me); 4.30 (q, 2 H, $C\underline{H}_2Me$); 7.20—7.60 (m, 7 H); 7.80 (m, 2 H); 10.04 (s, 1 H, NH).

2-Amino-6-methyl-4-oxo-7-(phenylthio)pterin (9) was prepared analogously to triazines **2—5**. The yield was 80%, m.p. >300 °C. Found (%): C, 54.50; H, 3.67; N, 24.21. $C_{13}H_{11}N_5OS$. Calculated (%): C, 54.72; H, 3.89; N, 24.54. ^{1}H NMR, δ: 2.54 (s, 3 H, Me); 6.70 (br.s, 2 H, NH_2); 7.40—7.60 (m, 5 H); 11.20 (br.s, 1 H, NH).

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