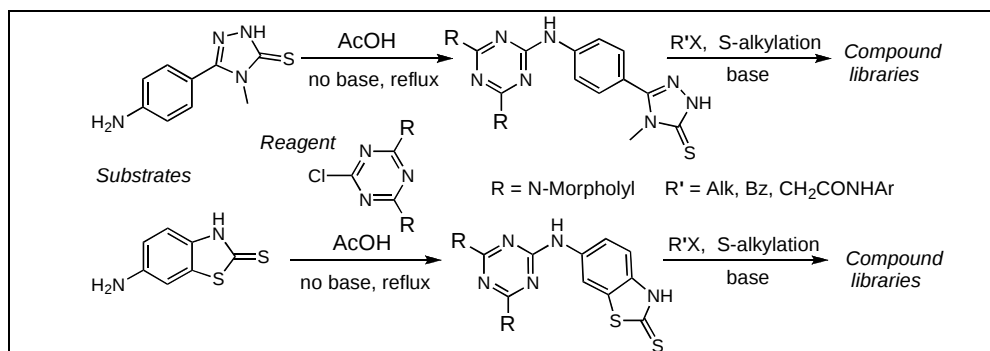


Kirill A. Kolmakov*

Department of Chemistry, University of Toronto, Toronto, ON, M5S 3H6, Canada

E-mail: kkolmakov@chem.utoronto.ca

Received July 10, 2007



In acetic acid medium, 2-chloro-4,6-dimorpholin-4-yl-[1,3,5]triazine undergoes amination by bifunctional heterocyclic compounds containing both amino and thioamide groups. The reactions are high-yielding and selective; the thioamide functions are unaffected under the requisite conditions. The reactions do not proceed in satisfactory yields in other solvents and, thus, require acetic acid. The resulting thioamides, consisting of multiple biologically relevant residues, are easily alkylated at the sulfur (thiol-thione) centers to furnish new thioethers in subsequent steps.

J. Heterocyclic Chem., **45**, 1215 (2008).

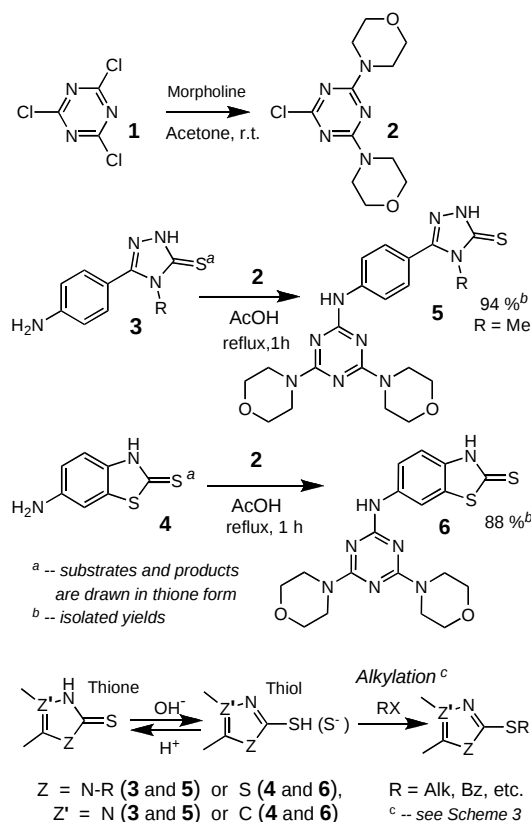
INTRODUCTION

Heterocyclic compounds with two or more functional groups are highly attractive for combinatorial chemistry because the reactive sites can, in principle, be modified in a stepwise fashion, providing access to large compound libraries. To take advantage of multiple reactive sites for combinatorial applications, it is necessary to develop high-yielding synthetic protocols, by which a given functional group can be selectively modified. Here we report the first examples of amination of a chloro-substituted 1,3,5-triazine moiety, using heterocyclic substrates containing both amino and thioamide groups. The latter exhibit thiol-thione tautomerism, and are highly reactive towards electrophiles. When the reactions are conducted in acetic acid, the amino groups are selectively modified, in high yield, while the thioamide (thiol-thione) functions are unaffected.

Sulfur- and nitrogen-containing heterocycles, particularly 1,2,4-triazoles and benzothiazoles, have received considerable attention owing to their biological activities and are common scaffolds in drug discovery [1]. Cyanuric chloride (2,4,6-trichloro[1,3,5]triazine, **1**, Scheme 1) is a useful, inexpensive reagent whose 1,3,5-triazine moiety is also a part of many biologically active and medicinally significant compounds [2]. Cyanuric chloride can undergo stepwise nucleophilic substitution at its three C-Cl sites, [3] making it a versatile reagent for generating functionalized triazine cores. We have sought to incorporate biologically relevant nitrogen- and sulfur-containing

heterocycles (triazoles or thiazoles) in scaffolds that also contain a 1,3,5-triazine group.

Scheme 1



In our approach, amine-substituted triazoles or thiazoles are coupled to a 1,3,5-triazine core by amination reactions at the C-Cl group of the 1,3,5-triazine moiety. Morpholine groups occur in a huge number of biologically potent compounds, often in conjunction with a 1,3,5-triazine core (see [2a,b]). As a triazine-containing reagent, we chose 2-chloro-4,6-dimorpholin-4-yl-[1,3,5]triazine (**2**), which is readily obtained by reaction of **1** with 2 equiv. of morpholine in acetone (Scheme 1) [3b]. The replacement of the chlorine atom in compound **2** by nucleophiles, including aliphatic amines requires harder conditions or microwave irradiation [3c,d,e]. The characteristic feature of all known recipes for the chlorine substitution in compounds **1** and **2** is the use of bases or hydrogen chloride acceptors [3a-e].

Our approach relies on selective modification of the amino group (NH₂) in heterocyclic substrates (**3** and **4**) that also contain thioamide functions as a part of the ring system. It is known that cyanuric chloride (**1**) reacts with some thioamides at the thioamide sulfur. For example, substitution of all three chlorine atoms in **1** is achieved with thiourea as a nucleophile [4].

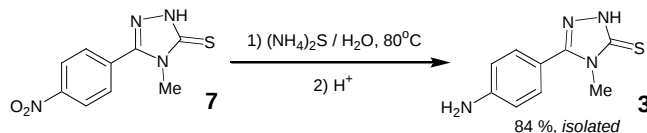
We have devised a method to induce amination at the C-Cl site of **2**, without affecting the thioamide groups of the triazole or benzothiazole reagents. This method has allowed us to generate new heterocyclic molecules that contain multiple residues with potential biological activity (1,2,4-triazole or benzothiazole, 1,3,5-triazine and morpholine groups). Two known bifunctional (amine- and thioamide-containing) heterocyclic compounds were chosen as representative substrates for reaction with **2**: 5-(4-aminophenyl)-4-methyl-2,4-dihydro-[1,2,4]triazole-3-thione (**3**) and 6-amino-3*H*-benzothiazole-2-thione (**4**) (Scheme 1). As a scaffold in combinatorial chemistry, compound **3** is of special interest because it has an additional variable N-R site incorporated in the 1,2,4-triazole ring (R = Me). Heterocyclic compounds that contain thioamide groups (Scheme 1) undergo alkylation in basic media to give thioethers (S-alkylation products) (Scheme 1, bottom). Numerous data [5] indicate that thiolate anions of a general formula $\text{N}=\text{C}(\text{Z})\text{S}^-$ (see Scheme 1), generated from compounds containing fragment $\text{NH}-\text{C}(\text{Z})=\text{S}$ in heterocyclic rings (Z = N,O,S), act as strong nucleophiles. On the other hand, in the solid state and in neutral solutions these compounds exist predominantly in thione (thioamide) form [6,7,8].

RESULTS AND DISCUSSION

6-Amino-benzothiazole-2-thiol (**4**) was prepared from readily accessible benzothiazole-2-thione by nitration, followed by reduction, according to the reported procedure [6]. Our synthesis of compound **3** also involved reduction of a nitro group in the final step (Scheme 2). Its precursor, nitro compound **7**, containing 1,2,4-triazole

core, was obtained *via* previously reported synthetic route that involved the condensation of 4-nitrobenzoic acid hydrazide and methyl isothiocyanate followed by base-assisted cyclization [7].

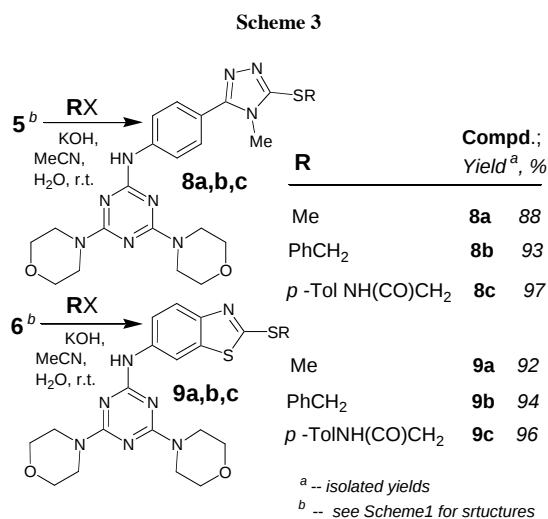
Scheme 2



In our initial attempts to aminate compound **2** with amine-containing heterocycles **3** and **4** (Scheme 1), we screened a variety of high-boiling organic solvents (DMF, 1,4-dioxane, ethanol, acetonitrile, benzene, dichloroethane) and we employed sodium acetate or pyridine as HCl acceptors. Of the solvents examined for this transformation, noticeable conversion to the desired aminated products (**5** or **6**, Scheme 1) was observed only in DMF; for the other solvents we screened, the reaction did not proceed, even upon prolonged reaction times at elevated temperatures. While the desired aminated species were formed in DMF in low yields, selectivity was poor (several products, including S-alkylation products were detected in the product mixture) and the reaction was slow (< 30 % conversion after 1 h at 150 °C). Dimethyl-sulfoxide (DMSO) is unsuitable as a solvent for these reactions because it reacts with the chloride **2**, to form, presumably, hydroxy compound **11** (see Scheme 4 below) [9]. Ultimately, we discovered that the desired amination reactions (amination of **2** with **3** or **4**) readily proceed in glacial acetic acid. Despite being a potentially attractive solvent by virtue of its high polarity/boiling point and its environmental compatibility, acetic acid has limited application in organic synthesis (as compared to that of many other solvents). Particularly, no attempts to perform amination reactions in acetic acid medium have been reported so far. Initial tests showed that the desired modification, indeed, occurs in acetic acid. Moreover, the reaction proceeded even in the absence of CH₃COONa, or other proton acceptors, which simplifies product purification. Upon heating **2** in acetic acid solutions of **3** or **4**, reaction starts immediately, as evidenced visually by the evolution of HCl from the boiling solutions and the formation of precipitates. Amination products **5** or **6** are formed in excellent yields, on a convenient timescale (1 h at 118 °C) (see Scheme 1 and Experimental Section) when the reactions are carried out in acetic acid. Importantly, the thioamide groups in substrates **3** and **4** are not affected under these conditions. Further, product isolation is extremely convenient: the desired products, compounds **5** and **6**, precipitate from acetic acid and can be isolated by simple filtration. The identity of N-substituted products **5** and **6** was verified by spectroscopic

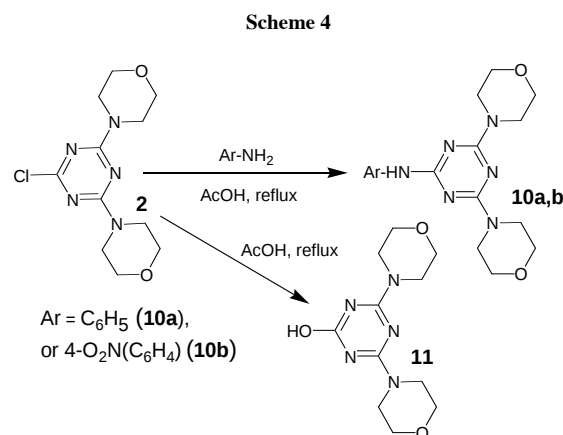
methods (IR, NMR), mass spectrometry and elemental analysis (see Experimental Section).

S-Alkylation products of general structures **8** and **9** were obtained from compounds **5** and **6** respectively (Scheme 3) to demonstrate the possibility of substitution (S-alkylation) at the second reactive site (thioamide group). This reactivity provides a convenient route to derivatives of **5** and **6** with potential biological activity. The S-alkylation of the thioamides (thiol-thiones) **5** and **6** can be performed under mild conditions and the reactions are complete after 2-4 h at ambient temperature. The reactions and isolation protocols are simple and are therefore amenable to automation. Three carbon-based electrophiles of general structure RCH_2X (Scheme 3) were taken as examples: methyl iodide, benzyl chloride and 2-chloro-*N*-*p*-tolylacetamide ($R = 4\text{-Me}(\text{C}_6\text{H}_4)\text{NH}(\text{CO})\text{CH}_2$). Members of the latter class of electrophile (chloroacetic acid amides) are readily accessible from aromatic amines and are widely used in combinatorial chemistry [5,10]. Six new compounds were obtained in a parallel-synthetic fashion with excellent yields (see Scheme 3 and Experimental Section), and were characterized by NMR, IR, mass spectrometry, and elemental analysis.



In addition to the experiments with substrates **3** and **4** in acetic acid medium, it seemed reasonable to explore the reactivity of chloride **2** towards "regular", monofunctional aromatic amines (anilines) in the same solvent. Aniline and less nucleophilic 4-nitroaniline were taken as representative substrates. The reaction between **2** and amines can be considered as the final third stage of nucleophilic substitution in cyanuric chloride (**1**). Replacement of the chlorine atom in **2** gives trisubstituted 1,3,5-triazine compounds of type **10** (see Scheme 4). The final substitution stage, to introduce a third nucleophilic substituent on 1,3,5-triazine core, is difficult to achieve,

especially with aromatic amines. Synthetic routes to trisubstituted 1,3,5-triazine derivatives generally involve long reaction times and elevated temperatures [3a,3e]. The only reported synthesis of compound **10a** was undertaken in 1998 by Shibuya and co-workers [2a], starting from *N*-formanilide and *N,N*-dimorpholino-cyanamide. According to the authors, this approach was chosen to avoid slow, low-yielding substitution reactions at the C-Cl groups of cyanuric chloride. Compound **10b** (Ar = 4-NO₂(C₆H₄), Scheme 4), a potential anti-malarial drug, was synthesized by Agarwal [2b] and co-workers, by amination of cyanuric chloride with 1 equiv of 4-NO₂(C₆H₄)NH₂, followed by amination of the remaining two C-Cl sites with morpholine in refluxing THF. If the two morpholine groups were installed first, it is likely that the third amination step, using less nucleophilic 4-NO₂(C₆H₄)NH₂, would be prohibitively slow in commonly used solvents, such as THF.



However, with acetic acid as the solvent, the introduction of a third amine substituent to **2** is easily achieved: compounds **10a** and **10b** were obtained in 90 % and 58 % yields respectively, by treating **2** with PhNH₂ or 4-NO₂(C₆H₄)NH₂ in refluxing acetic acid (Scheme 4). The lower yield of **10b** is the result of a side reaction in which **2** undergoes solvolysis by acetic acid to furnish **11** (Scheme 4). The hydroxy compound **11** was identified by means of ¹H NMR and mass-spectrometry [11].

The reactions between **2** and more nucleophilic amine substrates (e.g., aniline) are much faster and product loss via solvolysis is minimal. Note that solvolysis of cyanuric chloride **1** (Scheme 1) in boiling acetic acid was observed previously and has been used as a convenient method for the preparation of cyanuric acid [3a]. In dry acetic acid, acetyl chloride is formed as byproduct. In the course of the reaction between **2** and substrates **3** and **4**, the solvolysis occurs to a much lesser extent. Importantly, the side-product **11** is soluble in aqueous acetic acid and does not contaminate target compounds **5** and **6**. Solvolysis of **2** was only observed in the reaction with less nucleophilic 4-NO₂(C₆H₄)NH₂,

because amination is much slower in that case. The results as a whole indicate that acetic acid, as solvent, favors the reaction of chloride **2** with aromatic amines and makes it possible to utilize weak nucleophiles, such as 4-nitroaniline, and substrates **3** and **4** in amination of **2**.

The consideration of donor-acceptor properties of solvents might help to explain why acetic acid is superior to other solvents in the amination of **2**. Among the solvents screened (DMF, 1,4-dioxane, acetonitrile, ethanol, benzene, chlorinated hydrocarbons), acetic acid, in addition to being very polar, possesses the highest acceptor number value (about 53, see ref. [12]) and consequently the lowest nucleophilicity. On the other hand, "nucleophilic" solvents, i.e. DMF or alcohols, must strongly solvate reagent **2** and thus compete with the substrates. As a result, the reaction rate is insufficiently low. Also importantly, under acidic conditions the thione forms of substrates **3** and **4** predominate, which completely suppresses the undesirable substitution at the sulfur (thiol-thione) centers. All these make acetic acid the solvent of choice for the title reaction. In contrast to conventional procedures for the chlorine substitution in 1,3,5-triazine derivatives **1** and **2**, the use of HCl acceptors in the amination of **2** in acetic acid medium becomes unnecessary, which simplifies product isolation. Our method of preparing compound **10a** is superior to the previously reported multi-step synthesis [2a], which involves prolonged heating under elevated pressure.

CONCLUSION

Clean and high-yielding procedures for selective modification of amino groups in two bifunctional heterocyclic substrates (**3** and **4**) have been developed. These amination reactions require acetic acid as solvent, as they do not proceed in other high-boiling organic solvents. The thioamide groups in substrates **3** and **4** are stable towards the conditions used for amination, although they can be easily alkylated in a subsequent step. New compounds **5**, **6**, **8a-c** and **9a-c** contain multiple residues with potential biological activity. We also showed that the 1,3,5-triazine compound **2** undergoes amination by aromatic amines, including weakly nucleophilic 4-nitroaniline, when acetic acid is used as solvent.

EXPERIMENTAL

General. All chemicals were purchased from Aldrich Chemical Company. Progress of the reactions was monitored by HPLC or TLC on silica gel SIL G/UV 254 plates and chloroform/acetone (10:1) as mobile phase. HPLC was performed using 5500 Varian Vista chromatograph equipped with Waters Symmetry C-18 reverse-phase column (4.6/150 mm, 5 μ particle size, methanol/water (80:20 vol.) as mobile phase). Mass-spectra were recorded on Micromass 70S-250 sector mass spectrometer, IR – on Shimadzu FTIR 8700 spectrometer. Elemental analyses were carried out at Guelph

Laboratories, Guelph ON, Canada. NMR spectra were recorded on Varian spectrometer at 300 MHz (^1H) and 75 MHz (^{13}C). Acetic acid (Aldrich, 99.7 %, ACS reagent grade) was freshly distilled and subjected to fractional crystallization for initial experiments. Later, in all the synthetic procedures described below acetic acid was used without purification. All other solvents were purified by conventional methods. All the syntheses described below were performed without protection from air or moisture, unless otherwise noted.

2-Chloro-4,6-dimorpholin-4-yl-[1,3,5]triazine (2) was prepared according to the classical procedure [3b] from cyanuric chloride and morpholine (purity was checked by means of ^1H NMR and TLC).

6-Amino-3H-benzothiazole-2-thione (4) was obtained in high yield and purity (checked by means of NMR and HPLC) according to the known procedure from commercially available 2-mercaptobenzothiazole. The melting point (260–262 °C) and ^1H NMR agreed with reported [6].

5-(4-Aminophenyl)-4-methyl-2,4-dihydro-[1,2,4]triazole-3-thione (3). Nitro compound **7** (4-methyl-5-(4-nitrophenyl)-2,4-dihydro-[1,2,4]triazole-3-thione (Scheme 2)), was prepared according to the previously described procedure, starting from 4-nitrobenzoic acid hydrazide [7]. The reduction of **7** to the corresponding amine **3** was accomplished as follows:

Sodium sulfide nanohydrate ($\text{Na}_2\text{S} \times 9\text{H}_2\text{O}$, 144 g, 0.60 mol) and NH_4Cl (32.5 g, 0.60 mol) were successively dissolved in 500 mL of water. Then compound **7** (40 g, 0.17 mol) was added upon stirring, and the mixture heated to 70 °C. The solid dissolved completely, and an exothermic reaction started to give a raise in temperature up to 95–100 °C. Heating was ceased, and about 50 mL of cold water was poured straight into the solution to prevent it from boiling off. For TLC analysis, a small portion (1 mL) of the solution was acidified with AcOH to pH = 5 – 6 and diluted with 5-fold excess of acetone. The analysis of the probe showed the absence of the starting nitro compound **7**. The rest of the solution was then acidified with 60 mL (~1.0 mol) of AcOH in 200 mL of water (**CAUTION! H_2S !**), the precipitate separated and washed to neutral pH with cold water (~100 mL $\times$ 2). The crude amine **3** was dissolved in 1 L of water containing 40 mL (0.47 mol) of conc. HCl upon heating to 80 °C. The solution was cooled to room temperature and an insoluble material (mostly elementary sulfur) was filtered off. The pure compound (28.7 g, 84 %) was precipitated as pale yellow needles when 83 g (0.60 mol) of $\text{CH}_3\text{COONa} \times 3\text{H}_2\text{O}$ was added to the acidic solution. The melting point (176–178 °C), IR and ^1H NMR spectra of **3** were in a good accordance with that reported by S. Rollas and co-workers, who originally prepared this compound via a different route [8]. IR (KBr): 3360-2800 (br. m), 1610, 1516, 1485, 1448, 1340, 1300, 1148 cm^{-1} . ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 3.51 (s, 3H, N- CH_3), 5.46 (s, 2H, NH_2), 6.72 (d, $J=9\text{Hz}$, 2H $_{\text{Ar}}$), 7.33 (d, $J=9\text{Hz}$, 2H $_{\text{Ar}}$), 13.52 (s, 1H, NH) ppm.

Modification of bifunctional heterocyclic substrates 3 and 4 in acetic acid medium; General procedure. 0.01 mol of the amine substrate (**3** or **4**) was dissolved in 75 mL of glacial acetic acid upon boiling, and chloride **2** (3.58 g, 0.0125 mol) was carefully added in few portions. The solution was refluxed for 1 h (until no trace of starting compounds was detected by means of TLC). Hot solutions with precipitates were quenched with equal volume of water and cooled to room temperature. The precipitates were separated by filtration and washed twice with 30 mL of boiling water. For further purification, the moist

products were dissolved in a mixture of DMF (25 mL) and Et₃N (3.6 mL 0.025 mol) upon heating and stirring. The solutions were diluted with 150 mL of water and filtered to separate a small amount of insoluble material. Compounds **5** and **6** with purity > 98 % (NMR, HPLC) were isolated after the solutions were acidified with 2.5 mL (0.04 mol) of AcOH and boiled for 5 min for better aggregation the precipitates filtered, thoroughly washed with hot water and dried in air.

5-[4-(4,6-Di-morpholin-4-yl-[1,3,5]triazin-2-ylamino)phenyl]-4-methyl-2,4-dihydro-[1,2,4]triazole-3-thione (5) was isolated as a colorless crystalline product; yield 94 %; mp 296–298 °C. Very slightly soluble in most organic solvents, except DMF and DMSO; readily soluble in aqueous KOH. IR (KBr): 3440, 3000–2800 br. m, 1610, 1575, 1508, 1440, 1390, 1410, 1390, 1360, 1255, 1110 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 3.54 (s, 3H, CH₃), 3.64 – 3.76 (m, 16H, Morph), 7.78 (d, 2H_{Ar}), 7.87 (d, *J*=9Hz, 2H_{Ar}), 13.84 (s, 1H, NH) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 31.79 (N-CH₃), 43.46, 66.10 (CH₂, Morph.), 118.59, 119.24, 128.91, 142.70, 151.57, 164.09, 164.74 (7C_{Ar}), 167.30 (C=S) ppm. MS (EI, 70 eV): *m/z* (%) = 455 (100) [M⁺], 423 (60) [M⁺ – S], 407 (30) [M⁺ – SCH₃], 394 (20) [M⁺ – S – NCH₃], 205 (20). HRMS (EI) calc. for [M⁺] C₂₀H₂₅N₉O₂S 455.1852, observed 455.1849. Anal. Calc. C 52.73; H 5.53; N 27.67. Found: C 52.36; H 5.31; N 27.52.

6-(4,6-Di-morpholin-4-yl-[1,3,5]triazin-2-ylamino)-3H-benzothiazole-2-thione (6) was isolated as a colorless crystalline product; yield 88 %, decomp. t ~ 220–230 °C. Very slightly soluble in most organic solvents, except DMF and DMSO; readily soluble in aqueous KOH, triethylamine, and ammonia. IR (KBr): 3440, 3100–2800 br. m, 1600, 1580, 1528, 1514, 1485, 1444, 1400, 1360, 1258, 1330, 1223, 1110, 1030 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 3.62–3.76 (m, 16H, Morph), 7.19 (d, *J*=7Hz, 2H_{Ar}), 7.65 (d, *J*=7Hz, 2H_{Ar}), 7.86 (s, 1H_{Ar}), 12.69 (s, 1H, NH) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 43.46, 66.10 (CH₂, Morph.), 111.97, 112.31, 119.65, 129.74, 135.98, 137.39, 163.98, 164.69 (8 C_{Ar}), 188.32 (C=S) ppm. MS (EI, 70 eV): *m/z* (%) = 431 (50) [M⁺], 399 (100) [M⁺ – S], 265 (30), 181 (20), 166 (25). HRMS (EI) calc. for [M⁺] C₁₈H₂₁N₇O₂S₂ 431.1198, observed 431.1186. Anal. Calc. C 50.10; H 4.90; N 22.27. Found: C 49.78; H 4.71; N 22.04.

S-alkylation of compounds 5 and 6; General procedure for the preparation of compound libraries (compounds 8 and 9). Reactions were set up in a parallel-synthesis fashion using 20 mL capacity vials, and were performed on a 0.30-mmol scale in two groups of three reactions. The solutions of 0.32 mmol of the thiols **5** or **6** and 0.45 mmol of KOH in a mixture MeCN-H₂O (1:1 vol., 5 mL) were added in one portion to 5 mL of MeCN containing 0.30 mmol of the alkylating reagents (methyl iodide, benzyl chloride or 2-chloro-*N-p*-tolylacetamide). The resulting solutions were left for 4 h at 20–25 °C and then diluted with equal volume of water. (Bulky precipitates were formed within 5–15 min after the reagents were combined.) Crystalline solids were collected by filtration, washed with water (10 mL × 2) to neutral pH and dried in air to afford thioethers **8a-a** and **9a-c** in excellent yields and with high purity (> 98 %, according to NMR and HPLC).

(4,6-Di-morpholin-4-yl-[1,3,5]triazin-2-yl)-[4-(4-methyl-5-methylsulfanyl-4H-[1,2,4]triazol-3-yl)-phenyl]-amine (8a). Colorless solid, yield 88 %, mp 149–151 °C, IR (KBr): 3440, 3000–2800 (br. m), 1602, 1570, 1523, 1500, 1481, 1446, 1410, 1361, 1258, 1113 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ = 2.63 (s, 3H, SCH₃), 3.52 (s, 3H, N-CH₃), 3.64 – 3.76 (m, 16H, Morph), 7.32 (m 5H, Ph) 7.52 (d, *J*=9Hz, d, 2H_{Ar}),

7.83 (d, *J*=9Hz, 2H_{Ar}), 9.22 (s, 1H, NH) ppm. ¹³C NMR δ (75 MHz, DMSO-d₆): δ 15.09 (SCH₃), 31.61 (N-CH₃), 43.43, 66.05 (CH₂, Morph.), 119.30, 119.79, 128.63, 129.04, 141.93, 151.29, 164.07, 164.76 (8C_{Ar}) ppm. MS (EI, 70 eV): *m/z* (%) = 469 (100) [M⁺], 454 (20) [M⁺ – CH₃], 422 (30) [M⁺ – CH₂S], 393 (20) [M⁺ – CH₃S – NCH₃], 410 (10), 205 (10). HRMS (EI) calc. for [M⁺] C₂₇H₃₁N₉O₂S 469.2008, observed 469.2011. Anal. Calc. C 53.71; H 5.80; N 26.85. Found: C 53.57; H 5.66; N 26.69.

[4-(5-Benzylsulfanyl-4-methyl-4H-[1,2,4]triazol-3-yl)phenyl]- (4,6-di-morpholin-4-yl-[1,3,5]triazin-2-yl)-amine (8b). Colorless solid, yield 93 %, mp 158–160 °C, IR (KBr): 3440, 3000–2800 (br. m), 1604, 1572, 1523, 1500, 1481, 1446, 1410, 1361, 1258, 1113 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 3.48 (s, 3H, N-CH₃), 3.64 – 3.76 (m, 16H, Morph), 4.36 (s, 2H, SCH₂) 7.32 (m 5H, Ph) 7.52 (d, *J*=9Hz, d, 2H_{Ar}), 7.83 (d, *J*=9Hz, d, 2H_{Ar}), 9.23 (s, 1H, NH) ppm. ¹³C NMR δ (75 MHz, DMSO-d₆): δ = 31.67 (N-CH₃), 37.51 (SCH₂), 43.44, 66.10 (CH₂, Morph.), 119.32, 119.79, 127.61, 128.58, 128.69, 129.04, 137.32, 142.06, 149.73, 155.46, 164.10, 164.76 (12 C_{Ar}) ppm. MS (EI, 70 eV): *m/z* (%) = 545 (100, M⁺), 454 (10, M⁺ – PhCH₂), 422 (40, M⁺ – PhCH₂S), 393 (20, M⁺ – PhCH₂S – NCH₃), 410 (5), 205 (10). HRMS (EI) calc. for [M⁺] C₂₇H₃₁N₉O₂S 545.2321, observed 545.2349. Anal. Calc. C 59.43; H 5.73; N 23.10. Found: C 59.11; H 5.54; N 22.76.

2-{5-[4-(4,6-Di-morpholin-4-yl-[1,3,5]triazin-2-ylamino)-phenyl]-4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-p-tolyl-acetamide (8c). Colorless solid, yield 97 %, mp 174–176 °C, IR (KBr): 3440, 3000–2800 (br. m), 1660 (shoulder, C=O), 1610, 1570, 1520, 1500, 1481, 1446, 1410, 1362, 1258, 1113 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 2.32 (s, 3H, CH₃Ar), 3.48 (s, 3H, N-CH₃), 3.64 – 3.76 (m, 16H, Morph), 4.02 (s, 2H, SCH₂), 7.05 – 7.84 (m, 8H_{Ar}), 9.22 (s, 1H, NH), 10.25 (s, 1H, NH) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 20.51 (CH₃Ar), 31.90 (N-CH₃), 37.77 (SCH₂), 43.47, 66.10 (CH₂, Morph.), 119.25, 119.33, 119.69, 128.69, 129.26, 132.65, 136.31, 142.06, 149.96, 155.51, 164.10, 164.77 (12C_{Ar}), 165.65 (C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 602 (100) [M⁺], 511 (20) [M⁺ – TolNH], 422 (30) [M⁺ – TolNH(CO)CH₂S], 205 (10). HRMS (EI) calc. for [M⁺] C₂₉H₃₄N₁₀O₃S 602.2536, observed 602.2562. Anal. Calc. C 57.79; H 5.69; N 23.24. Found: C 57.44; H 5.54; N 23.08.

(4,6-Di-morpholin-4-yl-[1,3,5]triazin-2-yl)-(2-methylsulfanyl-benzothiazol-6-yl)-amine (9a). Colorless solid, yield 92 %, mp 173–174 °C, IR (KBr): 3430, 3100–2800 (br. m), 1593, 1564, 1527, 1503, 1477, 1443, 1406, 1360, 1258, 1113 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 2.74 (s, 3H, SCH₃), 3.62 – 3.80 (m, 16H), 7.71 – 7.78 (m, 2H_{Ar}), 8.24 (s, 1H_{Ar}), 9.22 (s, 1H, NH). ¹³C NMR (75 MHz, DMSO-d₆): δ 15.57 (SCH₃), 43.41, 66.05 (CH₂, Morph.), 111.30, 119.36, 120.64 (br.), 135.01, 137.25, 147.96, 164.06, 164.74 (9C_{Ar}) ppm. MS (EI, 70 eV): *m/z* (%) = 578 (100) [M⁺], 430 (20) [M⁺ – PhCH₂], 398 [20, M⁺ – PhCH₂S], 181 (15). HRMS (EI) calc. for [M⁺] C₁₉H₂₃N₇O₂S₂ 445.1355, observed 445.1361. Anal. Calc. C 51.22; H 5.20; N 22.01. Found: C 50.96; H 5.08; N 21.93.

(2-Benzylsulfanyl-benzothiazol-6-yl)-(4,6-di-morpholin-4-yl-[1,3,5]triazin-2-yl)-amine (9b). Colorless solid, yield 94 %, mp 178–180 °C, IR (KBr): 3430, 3100–2800 (br. m), 1595, 1564, 1527, 1500, 1477, 1443, 1406, 1360, 1258, 1113 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 3.58–3.76 (m, 16H, Morph.), 4.52 (s, 2H, SCH₂), 7.32 – 7.70 (m, 7H_{Ar}), 8.26 (s, 1H_{Ar}), 9.23 (s, 1H, NH) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 36.84 (SCH₂), 43.43, 66.10 (CH₂, Morph.), 111.32, 119.41, 120.91, 127.63,

128.63, 129.10, 135.29, 136.70, 137.56, 147.70, 162.93, 164.08, 164.74, (13 C_{Ar}) ppm. MS (EI, 70 eV): m/z (%) = 578 (100) [M⁺], 430 (20) [M⁺ – PhCH₂], 398 (20) [M⁺ – PhCH₂S], 181 (15). HRMS (EI) calc. for [M⁺] C₂₃H₂₇N₇O₂S₂ 521.1668, observed 521.1659. Anal. Calc. C 57.56; H 5.22; N 18.80. Found: C 57.48; H 5.14; N 18.68.

2-[6-(4,6-Di-morpholin-4-yl-[1,3,5]triazin-2-ylamino)-benzothiazol-2-ylsulfanyl]-N-p-tolylacetamide (9c). Colorless solid, yield 96 %, mp 181–182 °C, IR (KBr): 3440, 3100–2800 (br. m), 1660 (shoulder, C=O), 1606, 1564, 1502, 1527, 1477, 1442, 1406, 1360, 1258, 1113 cm⁻¹. ¹H NMR (300 MHz, DMSO-d₆): δ 2.32 (s, 3H, CH₃Ar), 3.53 – 3.67 (m, 16H, Morph), 4.31 (s, 2H, SCH₂), 7.11 – 7.71 (m, 6H_{Ar}), 8.26 (s, 1H_{Ar}), 9.22 (s, 1H, NH), 10.25 (s, 1H, HNCO) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 20.54 (CH₃Ar), 37.86 (SCH₂), 43.45, 66.12 (CH₂, Morph.), 111.41, 119.27, 119.43, 120.84, 129.31, 132.70, 135.40, 136.34, 137.57, 147.64, 163.02, 164.09, 164.76 (13 C_{Ar}), 165.14 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 578 (60) [M⁺], 472 (30) [M⁺ – TolNH], 430 (10) [M⁺ – TolNH(CO)CH₂], 398 (100) [M⁺ – TolNH(CO)CH₂S], 181 (10). HRMS (EI) calc. for [M⁺] C₂₇H₃₀N₈O₃S₂ 578.1882, observed 578.1889. Anal. Calc. C 56.04; H 5.23; N 19.36. Found: C 55.78; H 5.03; N 19.14.

2-Chloro-N-p-tolylacetamide was obtained from *p*-toluidine and chloroacetyl chloride [10]. The melting point (161 °C) and ¹H NMR spectrum agreed with reported.

Amination of 2-chloro-4,6-dimorpholin-4-yl-[1,3,5]triazine (2) with aromatic amines in acetic acid medium.

4,6-Di-morpholin-4-yl-[1,3,5]triazin-2-yl)-phenylamine (10a). Chloride **2** (286 mg, 1 mmol) and aniline (102 mg, 1.1 mmol) were refluxed for 45 min in 3 mL of AcOH. The solution was quenched with 20 mL of brine, a colorless precipitate was collected, washed with water and dried to afford 308 mg (90 %) of chromatographically (HPLC, TLC) pure compound with mp 173–174 °C, which is close to that reported in [4] (168–169 °C). ¹H NMR (300 MHz, DMSO-d₆): δ 3.60 – 3.76 (m, 16H, Morph), 6.89 (t, *J* = 7.5 Hz, 2H_{Ar}), 7.20 (t, *J* = 8 Hz, 2H_{Ar}), 7.63 (d, *J* = 7.5 Hz, 1H_{Ar}), 9.02 (s, 1H, NH) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 43.77, 66.52 (CH₂, Morph.), 119.95, 121.77, 128.68, 140.75, 164.42, 165.13 (6C_{Ar}) ppm. MS (EI, 70 eV): m/z (%) = 342 (100) [M⁺], 265 (20) [M⁺ – Ph], 256 (25) [M⁺ – Morph]. HRMS (EI) calc. for [M⁺] C₁₇H₂₂N₆O₂ 342.1804, observed 342.1803.

4,6-Di-morpholin-4-yl-[1,3,5]triazin-2-yl)-4-nitrophenylamine (10b). 4-Nitroaniline (138 mg, 1 mmol) and chloride **2** (357 mg, 1.25 mmol) were refluxed for 1 h in 3 mL of AcOH under argon atmosphere. The solution was quenched with 20 mL of brine; the precipitate was filtered, dissolved in 6 mL of acetone and diluted with a solution of KOH (30 mg, 0.5 mmol) and NaCl (2g) in 20 mL of H₂O. The solid was collected and dried. For further purification it was dissolved in 1.5 mL of pyridine, and boiling benzene (~5 mL) was added. 224 mg (58 %) of the pure compound with m.p. 256–259 °C was isolated upon cooling. ¹H NMR (300 MHz, DMSO-d₆): δ 3.60 – 3.76 (m, 16H, Morph), 7.93 (d, *J* = 9 Hz, 2H_{Ar}), 8.13 (d, *J* = 9 Hz, 2H_{Ar}), 9.75 (s, 1H, NH) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 43.89, 66.54 (CH₂, Morph.), 118.92, 124.97, 140.92, 147.57, 164.37, 165.06 (6C_{Ar}) ppm. MS (EI, 70 eV): m/z (%) = 387 (100) [M⁺], 341(40) [M⁺ – NO₂], 301 (30) [M⁺ – Morph.], 255 (30) [M⁺ – NO₂ – Morph.]. HRMS (EI) calc. for [M⁺] C₁₇H₂₁N₇O₄ 387.1655, observed 387.1649.

Acknowledgement. The author thanks the University of Toronto Chemistry Department (Canada) for fellowship support,

ChemDiv, Inc. for the financial support at the early stage of this work, and is also grateful to D. J. Harrison (University of Toronto) for help in preparing the final manuscript.

REFERENCES AND NOTES

- [1] For various examples of 1,2,4-triazole-3-thiones, 3*H*-benzothiazoles and their biological activities see: [a] Mukerjee, A. K.; Ashare, R. *Chem. Reviews* **1991**, *91*, 1–24. [b] Wang, Z. Y.; Shi, H. X.; Shi, H. J. *J. Heterocycl. Chem.* **2001**, *38*, 355–357. [c] Chaaban, I.; Oji, O. O. *J. Indian Chem. Soc.* **1984**, *61*, 523. [d] Oruc, E. E.; Rollas, S.; Kabasakal, L.; Uysal, M. K. *Drug Metabolism and Drug Interactions* **1999**, *15*, 127–140. [e] Zahradnik, P.; Sidorova, E.; Frydrych, Z.; Sevcik, B.; *Ceskoslovenska farmacie* **1988**, *37*, 440–442. [f] El-Sherief, H. A.; Mahmoud, A. M.; Abdel-Rahman, A. E.; El-Naggar, G. M. *J. Indian Chem. Soc.* **1983**, *60*, 58–60.
- [2] For the syntheses of biologically active compounds containing 1,3,5 - triazine core see: [a] Shibuya, I.; Oishi, A.; Yasumoto, M. *Heterocycles* **1998**, *48*, 1659–1662. [b] Agarwal, A.; Srivastava, K.; Puri, S. K.; Chauhan, Prem M. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 531–533. [c] Borkovec, A. B.; De Milo, A. B. *J. Med. Chem.* **1967**, *10*, 457. [d] Heitmeier, D. E.; Gray, A. P. *J. Med. Chem.* **1964**, *7*, 288. [e] Irikura, T.; Abe, K.; Okamura, K.; Higo, A.; Maeda, A.; Morinaga, F.; Hatae, S. *J. Med. Chem.* **1970**, *13*, 1081. [f] Goodrow, M. H.; Harrison, R. O.; Hammock, B. D. *J. Agric. Food Chem.* **1990**, *38*, 990–996.
- [3] For the nucleophilic substitution in cyanuric chloride and in 2-chloro-4,6-dimorpholin-4-yl-[1,3,5]triazine see: [a] Smolin E. M.; Rapoport, L. *s-Triazines and derivatives* Weissberger A.; Ed. The Chemistry of Heterocyclic Compounds; Interscience, NY-L, 1959, Vol. 13, pp. 53–56. [b] Pearlman, W. M.; Banks, C. K. *J. Am. Chem. Soc.* **1948**, *70*, 3726–3728. [c] Kurteva, V. B.; Afonso, C. A. M. *Green Chemistry* **2004**, *6*, 183–187 [d] Mikhailichenko, S. N.; Chesnyuk, A. A.; Suslov, V. I.; Shkrebet, A. I.; Yukhonenko, M. M.; Zaplishny, V. N. *Izvestiya Vysshikh Uchebnykh Zavedenii, Khimiya i Khimicheskaya Tekhnologiya* **2002**, *45*, 136–141. [e] Freiberg, R.; Bulka, E. *J. Prakt. Chem.* **1985**, *327*, 471–478.
- [4] For the reactions of thioamides with cyanuric chlorides see: Pollak, A.; Stanovnik, B.; Tišler, M. *Can. J. Chem.* **1966**, *44*, 829–832.
- [5] For the alkylation of 3*H*-Benzothiazole-2-thione see: [a] Kumar, R. V.; Kumar, K.; Gopal, K. R. *J. Heterocycl. Chem.* **2005**, *42*, 153–156. [b] Hu, Y.; Chen, Z. C.; Le, Z. G.; Zheng, Q. G. *Syn. Comm.* **2004**, *34*, 2039–2046. [c] Orio O. A.; Gaspio, N. B. *Annali dell' Istituto Superiore di Sanita* **1967**, *3*, 392–394. For the alkylation of 1,2,4-triazole-3-thiones see: [d] Andersen, H. S.; Kampen, G. C.; Christensen, I. T.; Mogensen, J. P.; Larsen, A. R. US Pat. 2003-467362 20030502, **2004**; *Chem. Abstr.* **2004**, *141*, 366233. [e] Klimesova, V.; Zahajaska, L.; Waisser, K.; Kaustova, J.; Mollmann, U. *Farmaco* **2004**, *59*, 279.
- [6] For the preparation and properties of 6-amino-3*H*-benzothiazole-2-thione see: [a] Drozdov, N. S.; Stavrovskaya, V. I. *Zhurnal Obshchei Khimii* **1937**, *7*, 2813–2818. [b] Sidoova, E.; Odlerova, Z.; Spaldonova, R. *Chem. Papers* **1985**, *39*, 543–551.
- [7] Kubota S.; Uda, M. *Chem. Pharm. Bull.* **1975**, *23*, 955–956.
- [8] Rollas, S.; Kalyoncuogly, N.; Sur-Altiner, D.; Yegenogly, Y. *Pharmazie* **1993**, *48*, 308–309.
- [9] For the reaction of sulfoxides with cyanuric chloride see: Olah, G. A.; Fung, B. G.; Gupta, B.; Narang, S. C. *Synthesis* **1980**, 221.
- [10] Matulenko, M. A.; Surber, B.; Fan, L.; Kolasa, T.; Nakane, M.; Terranova, M. A.; Uchic, M. E.; Miller, L. N.; Chang, R.; Donnelly-Roberts, D. L.; Namovic, M. T.; Morel, R. B.; Brioni J. D.; Stewart, A. O. *Bioorg. Med. Chem.* **2004**, *12*, 3471–3483.
- [11] For properties of compd. **11** see: Mikhailichenko, S. N.; Chesnyuk, A. A.; Zavodnik, V. E.; Firgand, S. I.; Konyushkin, L. D.; Zaplishny, V. N. *Chem. Heterocycl. Comp.* **2002**, *38*, 292–299.
- [12] For electronic properties of organic solvents see: [a] Mayer, U.; Gutmann, V.; Gerger, W. *Monatshefte für Chemie*, **1975**, *106*, 1235–1257. [b] Umemura, Y.; Kanno, H.; Takahashi, S. *J. Raman Spectroscopy* **1998**, *27*, 527–531.