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# Halo-heterocyclization of *trans*-5-phenyl-3-cinnamylsulfanyl[1,2,4]triazine into [1,3]thiazino[3,2-*b*][1,2,4]triazin-9-ium systems

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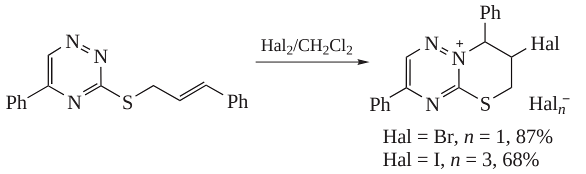
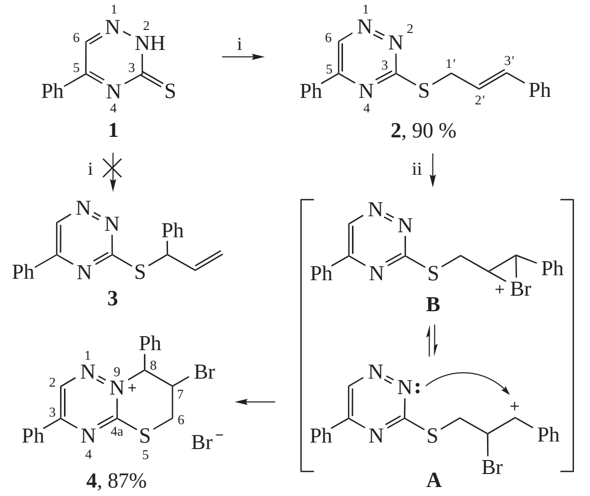
**Treatment of *trans*-5-phenyl-3-cinnamylsulfanyl[1,2,4]triazine with bromine or iodine in dichloromethane leads to halo-annulation onto the thiazine moiety with formation of (7*r*,8*t*)-7-halo-3,8-diphenyl-7,8-dihydro-6*H*-[1,3]thiazino[3,2-*b*][1,2,4]-triazin-9-ium salts. The product structure was confirmed by X-ray study.**



3,5,6-Trisubstituted [1,2,4]triazines have aroused interest as potential pharmacological preparations.[1,2] They can inhibit thrombocyte aggregation in blood, exhibit aniviral,[3] antitumor[4] and antimicrobic[5] activities, can help against HIV and leukemia.[6] 5-Substituted 2,3-dihydro[1,2,4]triazine-3-thiones work on the spinal cord centers, they are strong in spasmolytic, antihistamine,[7] and neuroprotective[8] action. The triazine cycle is the key component in the composition of various herbicides and insecticides.[9,10] 5,6-Disubstituted [1,2,4]triazine-3-thiones can be used as reagents for spectrophotometric determination of copper and palladium.[11–13] Derivatives of [1,2,4]triazine are widely employed in organic synthesis,[14–19] for example, in the Diels–Alder reaction with the aim of obtaining new fused pyridine systems.

In the present study, triazinethione **1** was used as the starting material to prepare novel fused triazinium systems (Scheme 1). Its alkylation with *trans*-cinnamyl chloride in acetone in the presence of trimethylamine afforded previously unknown *trans*-5-phenyl-3-cinnamylsulfanyl[1,2,4]triazine **2**. This reaction, apparently, proceeds according to the $S_N2$ mechanism since the possible $S_N1$ substitution product **3** was not detected. The initial triazinethione **1** was obtained by cyclization of phenylglyoxal thiosemicarbazone under the action of NaOH or $K_2CO_3$ solutions.



**Scheme 1** *Reagents and conditions*: i, (*E*)-PhCH=CHCH$_2$Cl, Et$_3$N, acetone, ~20 °C, 24 h; ii, Br$_2$, CH$_2$Cl$_2$, 0–5 °C, 24 h.

In the $^1$H NMR spectrum of compound **2**, the signal of the SCH$_2$ protons is 0.28 ppm shifted downfield compared to 3-allylsulfanyl-5-phenyl[1,2,4]triazine.[20] The difference for the –CH= signal is 0.60 ppm, obviously, due to the influence of the phenyl group at the multiple bond. The value of the spin–spin coupling constant ($^3J$ 15.7 Hz) in the –CH=CHPh fragment testifies that compound **2** has *trans*-configuration.

The literature sources contain conflicting data on thiazole annulation in the course of halocyclization of 3-alkenyl(alkynyl)-sulfanyl[1,2,4]triazines under the action of halogens,[20–23] stating participation of either N$^4$ or N$^2$ atoms. As an extension of the earlier study[24] on the synthesis of [1,3]thiazino[1,2,4]triazine systems, we have herein investigated the reaction of cinnamyl sulfide **2** with bromine for the first time. It has been established that unlike 3-allylsulfanyl-5-phenyl[1,2,4]triazine,[20] this reaction proceeds as annulation of the 6-membered thiazine cycle and formation of (7*r*,8*t*)-7-bromo-3,8-diphenyl-7,8-dihydro-6*H*-[1,3]-thiazino[3,2-*b*][1,2,4]triazin-9-ium bromide **4** (see Scheme 1). Evidently, it is caused by the heterocyclization of the phenyl-stabilized carbocation **A**. If the reaction occurred through bromonium ion **B**, the annulation into 5-membered thiazole cycle would be probable due to steric constraints.

The structure of salt **4** was supported by the X-ray analysis data (Figure 1).† In one unit cell of bromide **4** there are eight triazinium cations and eight bromide anions. The atoms of the triazinium heterocycle, S(1), C(1) and C(3) are essentially located on the same plane. The C(2) atom of thiazine cycle, Br(2) and Br$^-$ anion deviate from the plane by 0.739, 2.583 and 0.228 Å, respectively. Intermolecular short contacts are evidenced between

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† *Crystal data for* **4**: C$_{18}$H$_{15}$N$_3$SBr$_2$ ($M$ = 465.20), monoclinic, space group $C2/c$. At 293 K: $a$ = 25.220(2), $b$ = 11.062(1) and $c$ =18.552(1) Å, $\beta$ = 134.79(2)°, $V$ = 3673(5) Å$^3$, $Z$ = 8, $d_{calc}$ = 1.683 g cm$^{-3}$, $\mu$(MoKα) = = 4.532 mm$^{-1}$, $F$(000) = 1840; 16655 reflections ($R_{int}$ = 0.033) were used for refinement and led to $R_1$ = 0.0437. Data were collected on a Bruker D8 QUEST diffractometer (MoKα radiation, $\lambda$ = 0.71073 Å, graphite monochromator). Data collection, their editing, and refinement of the unit cell parameters, as well as the accounting for absorption, were conducted using programs SMART and SAINT-Plus.[25] All calculations for structure determination and refinement were carried out by the program SHELXL/PC[26] and OLEX2.[27] The structures were determined by the direct method and refined by the least-squares method in the anisotropic approximation for non-hydrogen atoms.

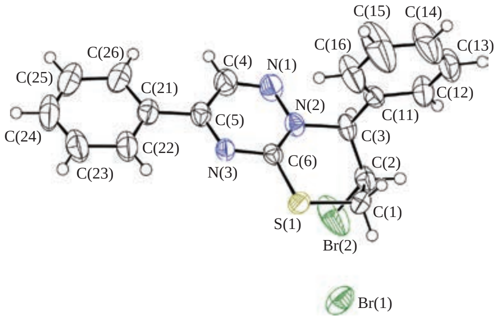
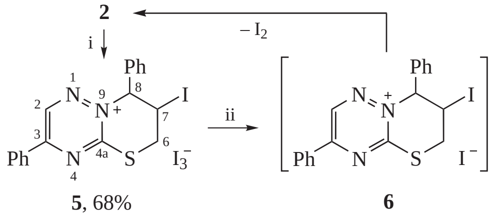


**Figure 1** Molecular structure of compound **4**.

the Br⁻ anion and S(1), C(1) and H(1a) atoms. The distances Br(1)···S(1), Br(1)···C(1) and Br(1)···H(1a) are 3.260, 3.494 and 2.962 Å, respectively, which is less than the sum of the Van der Waals radii of these atoms.[28] The molecules of the compound form layers on the basis of intermolecular support contacts between the H(3) atom of one molecule and the H(1a) atom of another molecule (2.213 Å).

The reaction of cinnamyl sulfide **2** with iodine in dichloromethane at room temperature proceeds in the same manner as with bromine, with annulation of the thiazine cycle to afford 7-iodo-3,8-diphenyl-7,8-dihydro-6*H*-[1,3]thiazino[3,2-*b*][1,2,4]-triazin-9-ium triiodide **5** (Scheme 2).



**Scheme 2** *Reagents and conditions*: i, $I_2$, $CH_2Cl_2$, 0–5 °C, 24 h; ii, NaI, acetone, ~20 °C, 20 min.

It is known that triiodides of organic cations react with sodium iodide in acetone to form the relative monoiodides, precipitating from the reaction solution.[20,21] Unexpectedly, when sodium iodide was reacted with triiodide **5** in acetone, monoiodide **6** was not obtained while the parent cinnamyl sulfide **2** was isolated from the reaction mixture. Most probably, monoiodide **6** is not stable when formed, so it would decompose into olefin sulfide **2** and iodide (see Scheme 2).

Notably, in heterocyclization products **4** and **5**, in contrast to the starting cinnamyl sulfide **2**, the diastereotopic $SCH_2$ protons resonate as two upfield signals in the $^1$H NMR spectra. Also, their H-6 signal is shifted downfield compared to reactant **2** by 0.7 and 0.62 ppm, respectively, which is due to formation of triazinium cation.

In conclusion, reaction of *trans*-5-phenyl-3-cinnamylsulfanyl-[1,2,4]triazine with halogens proceeds with annulation of the thiazine cycle to afford previously unknown halogen-containing [1,3]thiazino[3,2-*b*][1,2,4]triazinium system. Triiodide **5**, unlike the described triiodides of triazinium systems, undergoes decyclization under the action of sodium iodide in acetone.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.019.

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CCDC 1824791 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.