Reactions of 3-allyl-4-oxothieno[2,3-*d*]pyrimidin-2-yl disulfides with iodine

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Reactions of 3-allyl-4-oxothieno[2,3-*d*]pyrimidin-2-yl disulfides with iodine afforded 2-iodomethyl-2,3-dihydrothieno[2,3-*d*][1,3]thiazolo[3,2-*a*]pyrimidin-5-ones. A probable mechanism of this transformation was theoretically justified.

Key words: thienothiazolopyrimidines, electrophilic intramolecular cyclization.

Earlier,[1,2] it has been found that bromination of 3-allyl-2-mercapto-4-oxothieno[2,3-*d*]pyrimidines gives 2-bromomethyl-2,3-dihydrothieno[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-one hydrobromides. Halogenation of sodium salts of the above thiols yields disulfides **1**, subsequent bromination of which results in addition of the bromine to the double bond of the allyl fragment.[1]

In connection with this, it was interesting to study reactions of disulfides **1** with iodine, which is often used as an efficient cyclization agent in electrophilic intramolecular cyclization.

Theoretically, reactions of compounds **1** with iodine can follow two pathways involving either the allyl or disulfide fragments. In the former case, electrophilic iodine should attack, according to the Markownikoff rule, the terminal C atom of the allyl fragment, finally yielding compounds **2**. In the latter case, possible products are sulfenyl iodides **3**, which should undergo cyclization into thiazinothienopyrimidine derivatives **4**.

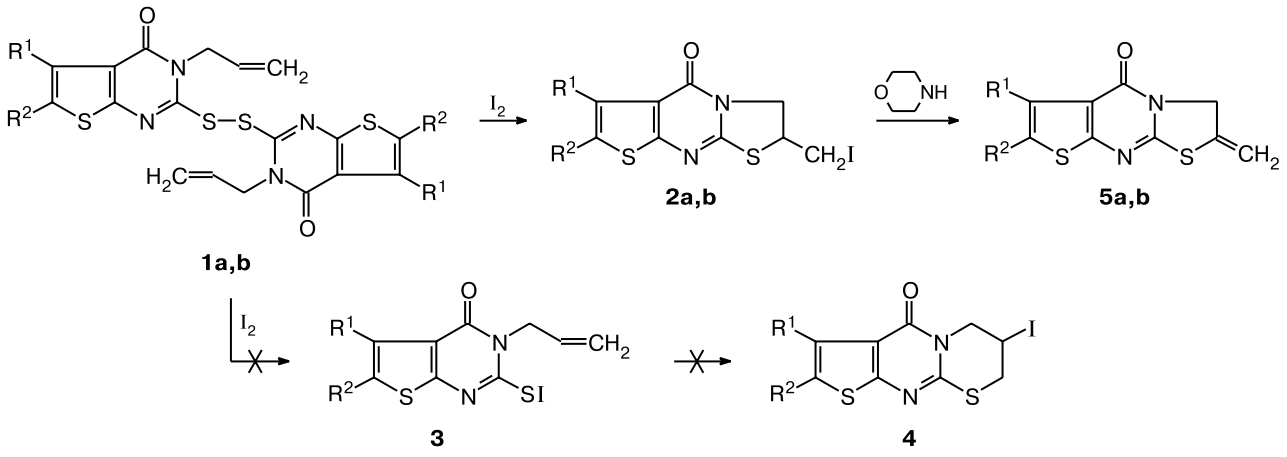
Results and Discussion

Reactions of 3-allyl-4-oxothieno[2,3-*d*]pyrimidin-2-yl disulfides with iodine. In the present work, we found that the reactions of disulfides **1** with iodine in the molar 1 : 1 ratio give only thienothiazolinopyrimidines **2** in nearly quantitative yields. To prove their structures, the latter were converted, *via* elimination of hydrogen iodide, into known[2] compounds **5** (Scheme 1).

The ^{1}H NMR spectra of compounds **5** show characteristic signals for the protons of the thiazoline ring at δ 5.04—5.06 (t, CH_2 of the ring, J = 2.4—2.7 Hz) and 5.45—5.46 and 5.58—5.59 (both q, exocyclic CH_2=, J = 1.8 Hz), which unambiguously indicate the regiochemistry of the reaction of disulfides **1** with iodine.

Thus, we proved experimentally that the reactions of compounds **1a,b** with iodine give only products **2a,b** and do not follow the alternative pathway.

Scheme 1



R^1R^2 = $(CH_2)_4$ (**a**), R^1 = R^2 = Me (**b**)

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Quantum-chemical calculations. The unusual stoichiometry of the reaction studied (two allyl groups in compounds **1a,b** react with only one iodine molecule and the reaction easily gives Markownikoff adducts in virtually quantitative yields) motivated us to perform semiempirical PM3 [3] calculations of probable steps of this reaction to explain such an experimental result and propose the most justified step-by-step reaction scheme. Because reactions of halogens with unsaturated compounds in solutions follow the electrophilic mechanism, we considered the cation I^+ as a possible electrophilic species in the reaction of disulfide **1b** with iodine.

We calculated different sequences of transformations of the reagents (interactions of I^+ with the allyl and disulfide groups, subsequent dissociation of the S—S bond, *etc.*). The data given below correspond to the reaction mechanism with the lowest activation energies for each step. This mechanism suggesting an initial interaction of I^+ with one of the allyl groups agrees with experimental data on the reaction stoichiometry; its first steps are shown in Scheme 2.

Note that the torsion angle X—S—S—X in ground-state disulfides is nearly right;[4] as a rule, rotation about the S—S bond is relatively easy (rotational barrier is only 21—33 kJ mol^{-1}).[5]

It can be seen from Scheme 2 that the initial interaction of disulfide **1b** with the iodine cation involves the C=C bond of one of the allyl groups. Data that characterize the energies of formation of the reagents, intermediates, and probable products in the reaction of disulfide **1b** with I^+–(I^-) are given in Table 1.

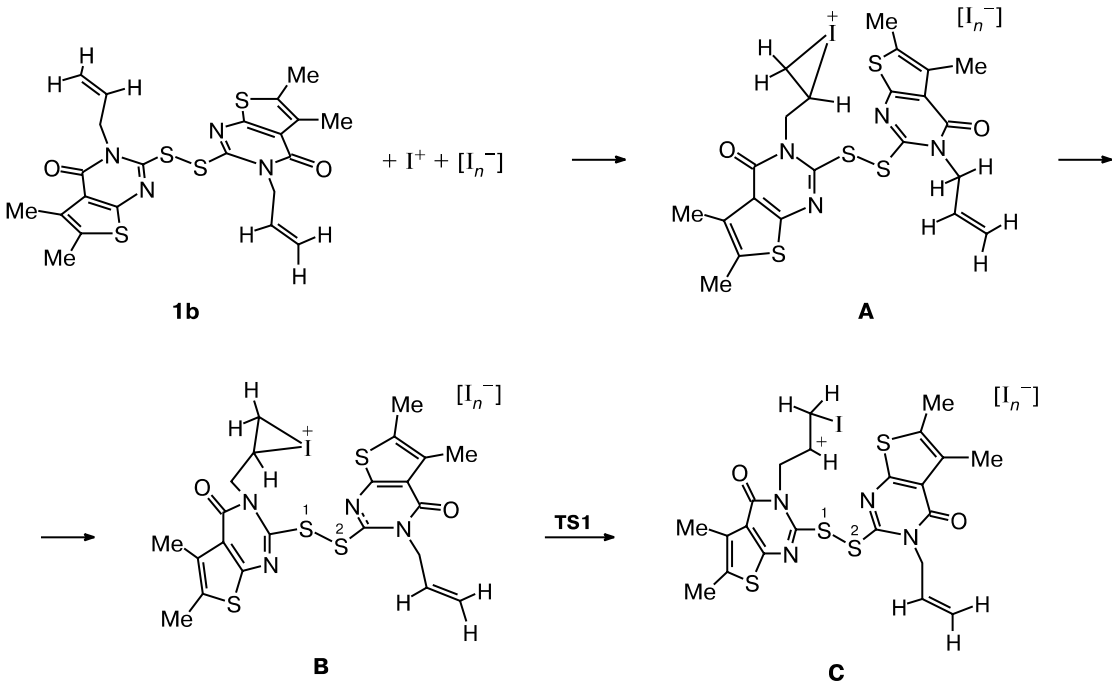
Table 1. Energies of formation (kJ mol^{-1}) of the reagents, transition states, intermediates, and products in the reaction of disulfide **1b** with iodine

Compound	ΔH_f	Compound	$\Delta H_{обр}$
1b	104.5	**A**	1144.9
2 **2b**	214.5	**B**	1119.7
I^+	1187.1	**C**	1118.0
I^-	−270.4	**D**	1007.8
TS1	1147.7	**E**	999.2
TS2	1127.3	**F**	982.1
TS3	1004.8	**G**	947.1
TS4	984.1	**H**	209.9
TS5	238.5		

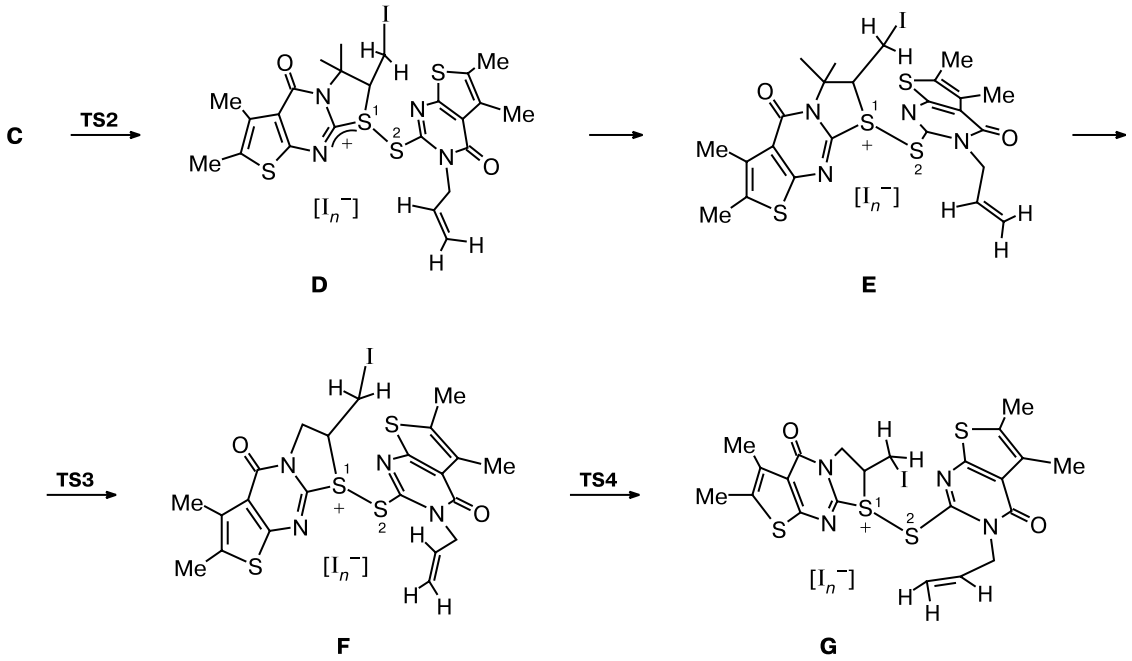
Initially, the cation I^+ can add to disulfide **1b** from its "exterior". Because both the allyl fragments and the disulfide group are conformationally very mobile, these conformers readily transform into thermodynamically more favorable ones, which can subsequently undergo chemical transformations.*

* Since the conformational transformations by themselves are of limited interest, their detailed discussion is not expedient here and they will be mentioned only when being substantial for understanding of the nature of chemical transformations.

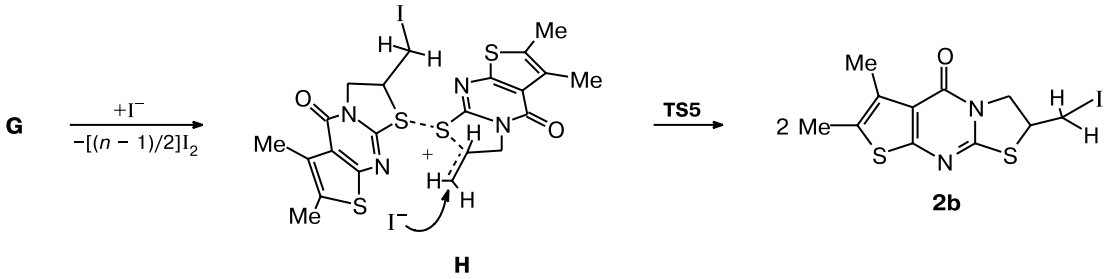
Scheme 2



Scheme 3



Scheme 4



The initially formed cyclic iodonium cation **A** transforms virtually without activation (*via* inward rotation of the iodoallyl fragment) into carbocation **B**, which undergoes ring opening through a transition state (**TS1**) to give "acyclic" cation **C** (see Scheme 2). A rotation of the $C_3H_5I^+$ group in cation **C** toward the disulfide bond gives rise, through **TS2**, to sulfonium cation **D**, *i.e.*, the positive charge is transferred to the S(1) atom of the disulfide group, with accompanying closure of a five-membered heterocycle (Scheme 3).

Sulfonium cation **D** transforms, *via* a rotation of its "noncyclized" moiety about the S—S bond through 26°, into cation **E** nearly without activation, in which the retained (second) allyl fragment rotates to form, through **TS3**, thermodynamically more favorable conformation **F**.

Subsequent transformations of cation **F** are due to a rotation of the intact allyl group, which makes it approach the positively charged reactive site, the S(1) and S(2) atoms. The activation energy of this rotation through **TS4** is only 2.5 kJ mol^{-1}; apparently, conformer **G** is substantially stabilized (by 34.7 kJ mol^{-1}) by an interaction between the cationic and allyl fragments. In conformation **G**, favorable prerequisites exist for cyclization involving the second allyl group.

However, according to our data, such a cyclization does not occur until a nucleophile (iodide anion) forms a "tight" ion pair with conformer **G** (Scheme 4)*.

An initial transformation of the neutral ion pair (I^-—G^+) gives rise to intermediate **H**. In its "cationic" part, the positive charge is delocalized over both the S atoms and the allyl fragment. The reaction is completed when intermediate **H** transforms, through transition state **TS5**, into compound **2b** with an activation energy of

* The counterion I^- (I_n^-) is produced by dissociation of I_2 even during the formation of cyclic iodonium cation **A** (see Scheme 2).

~29 kJ mol^{-1} (two molecules of the final product are formed).

After the iodine cation has added to the double bond of either allyl group, all subsequent transformations up to final product **2b** require low activation energies and the energies of formation of all intermediates and products monotonically decrease (*i.e.*, all these processes are thermodynamically favorable).

Thus, we found that initial intermediate **A** undergoes a sequence of conformational transformations, heterocyclization involving the first reactive site, a "transfer of the electrophilic reactive site to the S atoms of the disulfide fragment, and stabilization of the cation *via* new conformational transformations. According to our data, the new cation can undergo, by itself, no subsequent transformations. However, after (or simultaneously with) attachment of the "second" part of the attacking reagent, namely, the counterion I^-, cyclization involves the second allyl group, producing two molecules of the final product. It is because the transformations following the addition of I^+ to the double C=C bond proceed relatively easily and are thermodynamically favorable that the second allyl group of the reagent does not interact with I^+ (after the first cyclization and/or cleavage of the S—S bond, detachment of the proton and/or neutralization of the positive charge). Instead, it interacts with the "starting" anion I^-, thus ensuring the observed stoichiometry of the reaction (1 : 1). This agrees with the experimentally determined stoichiometry of the reaction shown in Scheme 1.

Experimental

The IR spectra of compounds **1a,b**, **2a,b**, and **5a,b** were recorded on a UR-20 instrument (KBr pellets). ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (300 MHz) in $CDCl_3$ (**1a,b**) and DMSO-d_6 (**2a,b**, **5a,b**) with Me_4Si as the internal standard.

3-Allyl-5-R^1-6-R^2-4-oxothieno[2,3-*d*]pyrimidin-2-yl disulfides 1a,b were prepared according to a known procedure.[1]

3-Allyl-4-oxo-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-2-yl disulfide (1a). The yield was 99%, m.p. 210—213 °C (dioxane) (*cf.* Ref. 1: 198—199 °C). Found (%): C, 56.17; H, 4.73; N, 10.08; S, 23.11. $C_{26}H_{26}N_4O_2S_4$. Calculated (%): C, 56.29; H, 4.72; N, 10.10; S, 23.12. IR, ν(C=O): 1700 cm^{-1}. ^{1}H NMR, δ: 1.78—1.87 (m, 4 H, 2 CH_2); 2.72, 2.97 (both m, 4 H, 2 CH_2); 5.00 (d, 2 H, CH_2, J = 5.4 Hz); 5.26—5.38 (m, 2 H, =CH_2); 5.98—6.11 (m, 1 H, =CH).

3-Allyl-5,6-dimethyl-4-oxothieno[2,3-*d*]pyrimidin-2-yl disulfide (1b). The yield was 99%, m.p. 185—187 °C (ethanol) (*cf.* Ref. 1: 179—181 °C). Found (%): C, 52.48; H, 4.33; N, 11.18; S, 25.46. $C_{22}H_{22}N_4O_2S_4$. Calculated (%): C, 52.56; H, 4.41; N, 11.15; S, 25.51. IR, ν(C=O): 1700 cm^{-1}. ^{1}H NMR, δ: 2.34, 2.43 (both s, 6 H, 2 CH_3); 5.00 (d, 2 H, CH_2, J = 5.4 Hz); 5.27—5.38 (m, 2 H, =CH_2); 5.98—6.11 (m, 1 H, =CH).

2-Iodomethyl-6-R^1-7-R^2-2,3-dihydrothieno[2,3-*d*][1,3]thiazolo[3,2-*a*]pyrimidin-5-ones (2a,b) (general procedure). Iodine (0.254 g, 1 mmol) in chloroform or acetic acid (20 mL) was added to cooled and stirred disulfide **1a,b** (1 mmol) in the same solvent (20 mL). The reaction mixture was stirred for 12—14 h. The chloroform was removed under reduced pressure. The residue was triturated with ether, filtered off, and washed with hexane. With acetic acid as a solvent, the reaction mixture was concentrated under reduced pressure to ~1/3 of the original volume and the crystallized product was filtered off and washed with hexane.

2-Iodomethyl-2,3,6,7,8,9-hexahydrobenzo[*b*]thieno[2,3-*d*][1,3]thiazolo[3,2-*a*]pyrimidin-5-one (2a). The yield was 0.71 g (88%) in chloroform and 0.75 g (93%) in acetic acid, m.p. 151—153 °C (ethanol). Found (%): C, 38.57; H, 3.23; I, 31.37; N, 6.88; S, 15.81. $C_{13}H_{13}IN_2OS_2$. Calculated (%): C, 38.62; H, 3.24; I, 31.39; N, 6.93; S, 15.86. IR, ν(C=O): 1680 cm^{-1}. ^{1}H NMR, δ: 1.77 (m, 4 H, 2 CH_2); 2.70, 2.82 (both m, 4 H, 2 CH_2); 3.70 (d, 2 H, CH_2, J = 6.0 Hz); 4.31—4.44 (m, 3 H, CH + CH_2).

2-Iodomethyl-6,7-dimethyl-2,3-dihydrothieno[2,3-*d*][1,3]thiazolo[3,2-*a*]pyrimidin-5-one (2b). The yield was 0.63 g (83%) in chloroform and 0.69 g (91%) in acetic acid, m.p. 163—165 °C (ethanol). Found (%): C, 34.87; H, 2.91; I, 33.51; N, 7.38; S, 16.87. $C_{11}H_{11}IN_2OS_2$. Calculated (%): C, 34.93; H, 2.93; I, 33.55; N, 7.41; S, 16.95. IR, ν(C=O): 1680 cm^{-1}. ^{1}H NMR, δ: 2.32, 2.35 (both s, 6 H, 2 CH_3); 3.70 (d, 2 H, CH_2, J = 6.0 Hz); 4.30—4.42 (m, 3 H, CH + CH_2).

2-Methylene-6-R^1-7-R^2-2,3-dihydrothieno[2,3-*d*][1,3]thiazolo[3,2-*a*]pyrimidin-5-ones (5a,b) were obtained from compounds **2** according to a known procedure.[2]

2-Methylene-2,3,6,7,8,9-hexahydrobenzo[*b*]thieno[2,3-*d*][1,3]thiazolo[3,2-*a*]pyrimidin-5-one (5a). The yield was 86%, m.p. 184—186 °C (ethanol) (*cf.* Ref. 2: 189—190 °C). Found (%): C, 56.38; H, 4.31; N, 10.07; S, 23.16. $C_{13}H_{12}N_2OS_2$. Calculated (%): C, 56.49; H, 4.38; N, 10.14; S, 23.20. IR, ν(C=O): 1690 cm^{-1}. ^{1}H NMR, δ: 1.78 (m, 4 H, 2 CH_2); 2.69, 2.81 (both m, 4 H, 2 CH_2); 5.04 (t, 2 H, CH_2, J = 2.7 Hz); 5.45, 5.58 (both q, 1 H each, CH, J = 1.8 Hz).

6,7-Dimethyl-2-methylene-2,3-dihydrothieno[2,3-*d*][1,3]thiazolo[3,2-*a*]pyrimidin-5-one (5b). The yield was 93%, m.p. 198—200 °C (ethanol) (*cf.* Ref. 2: 200—203 °C). Found (%): C, 52.71; H, 3.99; N, 11.06; S, 25.53. $C_{11}H_{10}N_2OS_2$. Calculated (%): C, 52.78; H, 4.03; N, 11.19; S, 25.62. IR, ν(C=O): 1690 cm^{-1}. ^{1}H NMR, δ: 2.33, 2.35 (both s, 6 H, 2 CH_3); 5.06 (t, 2 H, CH_2, J = 2.4 Hz); 5.46, 5.59 (both q, 1 H each, CH, J = 1.8 Hz).

References

1. I. V. Smolanka, A. A. Dobosh, and S. M. Khripak, *Khim. Geterotsikl. Soedin.*, 1973, 1289 [*Chem. Heterocycl. Compd.*, 1973 (Engl. Transl.)].
2. F. Sauter, W. Deinhammer, and K. Danksagmuller, *Monatsh. Chem.*, 1974, **105**, 863.
3. J. J. P. Stewart, *J. Comput.-Aided Mol. Des.*, 1990, **4**, 1.
4. R. A. Naumov and O. N. Kataeva, *Molekulyarnoe stroenie organicheskikh soedinenii kisloroda i sery v gazovoi faze* [*Molecular Structures of Organic Compounds of Oxygen and Sulfur in the Gas Phase*], Nauka, Moscow, 1990, 192 pp. (in Russian).
5. A. Rauk, *J. Am. Chem. Soc.*, 1984, **106**, 6517.

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