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The interaction between 4-oxothiazolidine-2-ylidene thioamides and iodine: a regioselective two-component 4-oxothiazolidine-2-ylidene thioamide to thiazolo[3,2-c]pyrimidine transformation mediated by iodine

ALEKSANDAR RAŠOVIĆ

Institute of Chemistry Technology and Metallurgy, University of Belgrade, Njegoševa 12, 11000 Beograd, Serbia.

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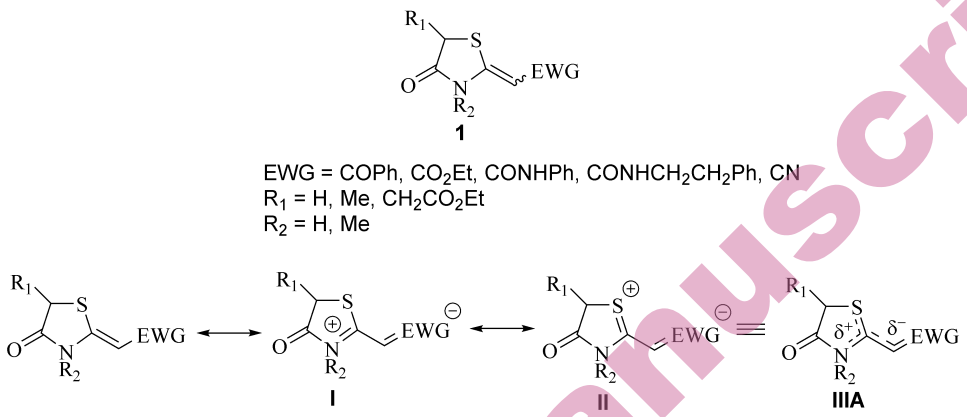
Abstract: This study investigated the interaction between selected 4-oxothiazolidine-2-ylidene thioamides **2a-c** and iodine in acetone. The interaction followed two main reaction pathways: (1) iodine-mediated cyclization resulting in the formation of thiazolopyrimidine **7**, and (2) electrophilic iodine attack on the thioamide sulfur atom, producing a complex mixture of iodine adducts. Due to the equilibrium of *Z*/*E* isomerization being strongly shifted to the *Z*-isomer in polar solvents, only the thioamide (*E*)-**2b** successfully formed thiazolopyrimidine **7**. The other two derivatives, (*Z*)-**2a** and (*Z*)-**2c**, followed the second reaction pathway. The factors influencing the heterocyclization of (*E*)-**2b** and its intermediates were thoroughly examined. This research provides the first description of an iodine-mediated heterocyclization leading to a thiazolopyrimidine scaffold. The literature on iodine-mediated heterocyclization leading to fused pyrimidines is limited, highlighting the significance of this study..

Keywords: 2-alkylidene-4-oxothiazolidine; heterocyclization; thiazolopyrimidine; *push–pull* effect.

INTRODUCTION

As we previously reported, 4-oxothiazolidines **1** having an exocyclic C=C double bond at the C(2)-position (Scheme 1), synthesized in our laboratory, proved to be an excellent heterocyclic scaffold displaying intrinsic reactivity through their versatile transformations that led to diverse heterocycles, such as 3,3aλ^4,4-trithia-1-azapentalenes,[1-4] 1,3-thiazines,[1] and other thiazolidine derivatives.[5] Among them, the reactions involving their nucleophilic sites, i.e., ring nitrogen atom, carbonyl oxygen atom and carbon atoms C(5) and C(2'), having high affinity for electrophiles,[5] have also attracted great attention (Fig. 1; Scheme 2).



Scheme 1. The structure of 2-alkylidene-4-oxothiazolidines.

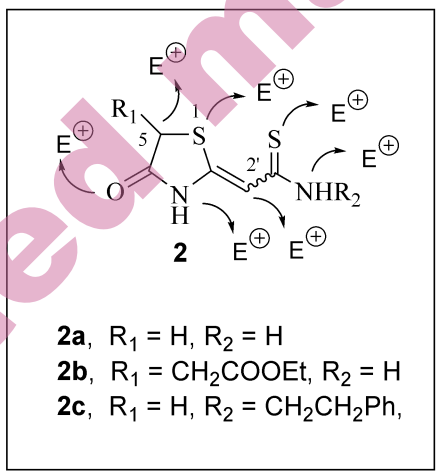


Fig. 1. Nucleophilic sites in 4-oxothiazolidine-2-ylidene thioamides.

The high affinity of **1**, belonging to the biologically important thiazolidines[5,6] and the class of *push–pull* alkenes[7-10] to participate in the versatile hetero-functionalization reactions with electrophiles (Scheme 2), which led to the diverse thiazolidine derivatives, such as vinyl bromides **3**, pyridinium salts **4**, thiazolidine derivative **5**, possessing two exocyclic bonds, and fused bicyclic thiazolidine **6**,[5] has understood in the light of their *push–pull* effect, that is, the π–electron interaction between two electron donors (-NH and -S-) and one electron-withdrawing group (EWG; Scheme 1). As a result, the thiazolidine ring and the exocyclic C=C double bond of **1** are highly polarized, which can best described by the **hybrid structure IIIA** possessing nucleophilic sites, as summarized in Fig. 1. As we reported previously, the 4-oxothiazolidine-2-ylidene thioamides **2** exhibits

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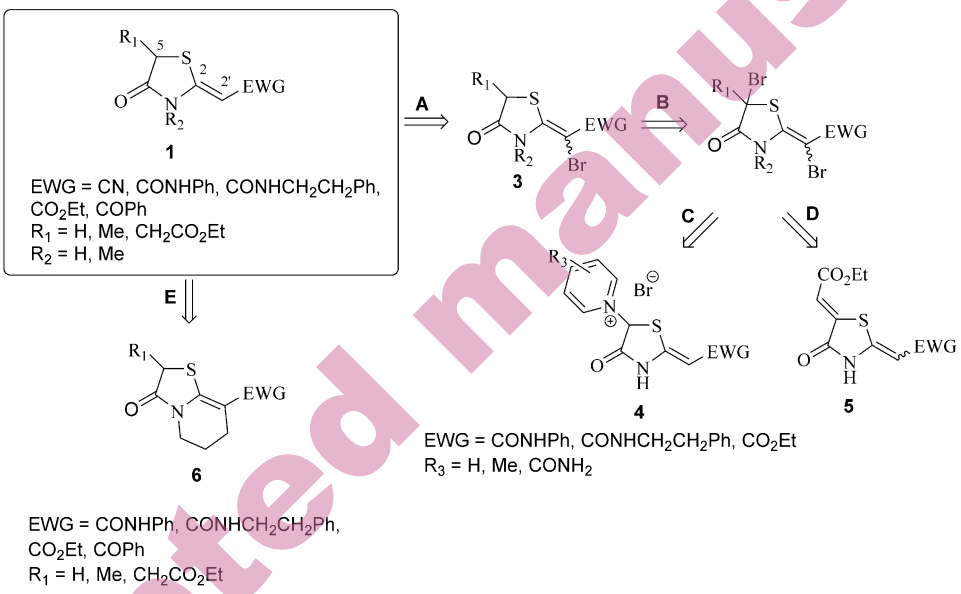
a larger *push–pull* effect than **1**.[10] Thus, compared with **1**, their structures are likely to be more highly polarized hybrid structure **IIIA** (Scheme 1). Furthermore, instead of exocyclic oxygen in thiazolidine analogues **1**, the nucleophilic site in **2** is exocyclic sulfur (Scheme 1; Fig. 1). All these show that the thiazolidines **2** could be at the centre of research interest regarding their reactivity toward potential electrophiles.



Scheme 2. The transformations of 2-alkylidene-4-oxothiazolidines **1** involving their nucleophilic sites.

Other main physicochemical properties of 2-alkylidene-4-oxothiazolidines arising from this so-called "*push–pull* effect" are (i) their low solubility in the versatile solvents (especially in nonpolar ones), (ii) the significant lowering of the rotational barriers around the C(2)C(2') double bond,[10] resulting, as we showed previously, (iii) the facile *Z/E* configurational isomerization.[10-12]

Since the factors above-mentioned, determining structural features of 2-alkylidene-4-oxothiazolidines **1**-**2**, represent the main reason for their high potential reactivity, it was intriguing to continue the examination of their conversions leading to the functionally significant heterocyclic compounds. To choose the suitable electrophile for transformations of 4-oxothiazolidine-2-ylidine thioamides **2**, as the target substrate of this work, iodine seemed to be a good choice. That was supported by the iodine electron deficiency, resulting in its rich chemistry that involves the electrophilic iodination of organic compounds and its employment in the construction of versatile heterocyclic systems. In this sense, the iodine promotes cyclization of the many significant heterocycles, such as

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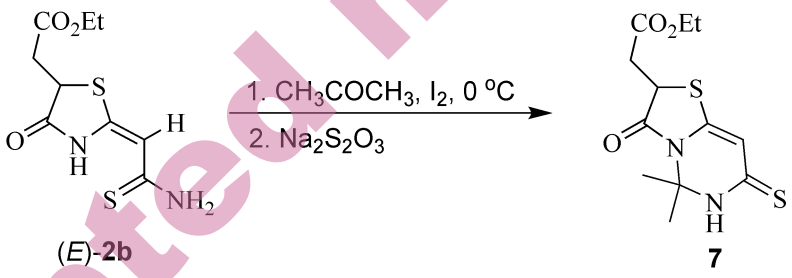
benzofurans, benzoxazoles and benzothiazoles, isoxazoles, pyrroles, thiophenes, indoles, pyrans, pyridines, isoquinolines, pyrimidines, etc.[13]

Therefore, concerning the **2a-b**/I_2 interaction in acetone, only the thioamide (*E*)-**2b** successfully formed a heterocyclic product. Thus, as outlined in Scheme 3, the two-component heterocyclization reaction between (*E*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)ethanthioamide **2b** and acetone mediated by iodine led to the formation of thiazolo[3,2-c]pyrimidine **7**. However, despite its limitations, this transformation significantly contributed to a better understanding of the chemistry of 4-oxothiazolidines. That is especially true for reactions with electrophiles. Besides, it undoubtedly opens up applications for transformations of similar molecular systems. Moreover, this research describes an iodine-mediated heterocyclization leading to a thiazolopyrimidine scaffold as the biologically important class of heterocyclic compounds. Generally, the literature on iodine-mediated heterocyclization leading to fused pyrimidine scaffolds is limited, with just a few reports published thus far.[13-15]



(*E*)-**2b** **7**

Scheme 3. The 2-alkylidene-4-oxothiazolidine to thiazolo[3,2-c]pyrimidine transformation is mediated by iodine.

EXPERIMENTAL

General

Melting points were determined on a Micro-Heiztisch Boetius PHMK apparatus or Büchi apparatus. Analytical thin-layer chromatography (TLC) was carried out by using Merck 60 F254 precoated silica gel plates (0.20 mm thickness), and the spots were visualized by iodine. Column chromatography was carried out on SiO_2 (silica gel 60Å, 12-26, ICN Biomedicals). The NMR spectra were obtained using a Varian Gemini 2000 instrument (^{1}H at 200 MHz, ^{13}C at 50.3 MHz). Chemical shifts are reported in parts per million (ppm) on the δ scale from TMS as an internal standard in the solvents specified. Low-resolution mass spectra were recorded using a Finnigan MAT 8230 BE spectrometer at 70 eV (EI). Isobutane was used as the ionizing gas for the chemical ionization (CI) mass spectra. Elemental analyses were performed at the microanalysis laboratory at the Department of Chemistry, University of Belgrade. HRMS of ethyl 2-(5,5-dimethyl-3-oxo-7-thioxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-c]pyrimidin-2-yl)–acetate **7** was carried out on 6210 TOF LC/MS coupled with HPLC 1200 Series Agilent Technologies.

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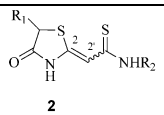
Experimental procedures for synthesising starting compounds and their analytical and spectral data are provided in the Supplementary material to this paper.

Synthesis of ethyl 2-(5,5-dimethyl-3-oxo-7-thioxo-3,5,6,7-tetrahydro-2H-thiazolo[3,2-c]pyrimidin-2-yl)acetate 7

To a stirred suspension of (*E*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)ethanthioamide **2b** (0.10 g, 0.39 mmol) and acetone (10 mL) was added one molar equivalent of iodine (0.10 g, 0.39 mmol) at 0 °C (an ice bath). After 10 min, when was added another molar equivalent of iodine, the initially heterogeneous mixture became homogeneous. The reaction was prolonged at this temperature for an additional 2.5 h when TLC indicated the complete consumption of starting *E*-(**2b**). Afterwards, the reaction mixture was kept in the refrigerator for 48 h, heated to room temperature and evaporated. To the dryness, the dark residue was added CH_2Cl_2 (15 mL) and the obtained solution was extracted twice with 1.2 % $Na_2S_2O_3$ (20 mL). The collected extracts were dried under Na_2SO_4, filtered and evaporated to dryness. The filtered solution was concentrated under reduced pressure, and the resulting solid residue was chromatographed (toluene/ethyl acetate, 10:0 → 6:1, v/v), affording the desired product as a yellow solid in moderate yield (0.059 g, 51 %).

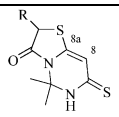
Analytical and spectral data of compound **7** are given in the Supplementary material to this paper.

Table I. Selected ^{13}C and ^{1}H NMR (DMSO-d_6) chemical shifts (ppm) of ethyl thiazolo[3,2-c] pyrimidin-2-yl)acetate **7** and thiazolidine derivatives **2a-c**



2

2a, R_1 = H, R_2 = H
2b, R_1 = CH_2COOEt, R_2 = H
2c, R_1 = H, R_2 = CH_2CH_2Ph



7

R = CH_2COOEt

Ent.	Compd.	Solvent	C=S	C=O_{lactam}	C(2')-*H*	C(2)	C(2')	$\Delta\delta_{C(2)=C(2')}$
1	(*Z*)-**2a**	DMSO-d_6	193.2	174.4	6.16	158.4	100.6	57.8
2	(*E*)-**2b**	DMSO-d_6	191.4	174.4	5.64	154.9	97.2	57.7
3	(*Z*)-**2c**	DMSO-d_6	190.4	174.3	6.21	156.1	101.2	54.9
4			C=S	C=O_{lactam}	C(8)-*H*	C(8)	C(8a)	$\Delta\delta_{C(8)=C(8a)}$
5	**7**	DMSO-d_6	184.5	172.2	5.73	146.8	101.0	45.8

RESULTS AND DISCUSSION

The structural assignment of **7** (Scheme 3; Table I) was made based on spectroscopic data (^{1}H and ^{13}C NMR, HRMS). Careful analysis of its NMR

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spectroscopic data revealed spectral features that correlated it with the structure of ethyl thiazolo[3,2-c]pyrimidin-2-yl)acetate **7**. Further, the compound had the HRMS spectrum consistent with an elemental composition of $C_{12}H_{16}N_2O_3S_2$.

Regarding the comparison between the structural characteristics of thiazolodines **2a-c** and thiazolopyrimidine **7**, their selected experimental ^{1}H NMR and ^{13}C NMR chemical shifts are presented in Table I (entries 1-3 for **2a-c**; entry 5 for **7**). In principle, compounds **2a-c** and **7** showed similar ^{1}H and ^{13}C NMR spectral characteristics for almost all identical structural motifs, including those for thioamide carbon atoms (column 4, DMSO-d_6; δ 190.4-193.2 ppm for **2a-c**; δ 184.5 ppm for **7**), lactam carbon atoms (column 5, DMSO-d_6; δ 174.3-174.4 ppm for **2a-c**; δ 172.2 ppm for **7**) and the olefinic protons (column 6, DMSO-d_6; δ 5.64-6.21 ppm for **2a-c**; δ 5.73 ppm for **7**). These results strongly indicated that thiazolodines **2a-c** and thiazolopyrimidine **7** belong to the structurally closely related compounds.

Furthermore, concerning the ^{13}C NMR spectral data of olefinic carbon atoms of the C=C double bond of these compounds (Table I; C(2)C(2')/**2a-c**; C(8)C(8a)/**7**), they showed the low field position of the signal corresponding to the C(2) and C(8a) atoms at the donor side of **2a-c** and **7**, respectively, (column 7, DMSO-d_6; δ 154.9-158.4 ppm for **2a-c**; δ 146.8 ppm for **7**) and the high field position of the signal assigned to their C(2') and C(8a) atoms at the acceptor side of the C=C double bond, respectively, (column 8, DMSO-d_6; δ 97.2-101.2 ppm for **2a-c**; δ 101.0 ppm for **7**). This difference in the chemical shift values ($\Delta\delta_{C=C}$) of their olefinic carbon atoms is a characteristic feature of their *push–pull* character, i.e., the significant charge polarization occurred within the C=C double bond. Therefore, since, as we proved previously,[10] experimentally determined $\Delta\delta_{C=C}$ values should increase with the increasing *push–pull* character of the double bond for the 2-alkylidene-4-oxothiazolidines possessing a similar EWG, the *push–pull* effect of the **7** is considerably lower than of the **2a-c** (column 9, DMSO-d_6; δ 54.9-57.8 ppm for **2a-c**; δ 45.8 ppm for **7**).

Since in both **7** and **2a-c**, the (Don)2–C=C–EWG fragments are very similar, the resultant significant reduction of the *push–pull* effect upon going from **2a-c** to **7** could be a result of the difference in the electron-donating ability of their donors (NH_{ring}/S_{ring}, **2a-c**; N_{ring}/S_{ring}, **7**; Scheme 4). In this sense, they have a much better electron-donating ability (increased base strength) in **2a-c** compared with **7** due to the better stabilization of **IIIA** than **IIIB** by the strong NH/S intramolecular hydrogen bonding in the *E*-(**IIIA**) and by the strong S_{exo}/S_{endo} intramolecular interaction in the *Z*-(**IIIA**). Finally, due to a weaker *push–pull* effect in **7** compared to **2a-c,** the interaction between **7** and I_2 is significantly lower. That facilitated the (*E*)-**2b** to **7** heterocyclization and the refinement procedure of compound **7**.

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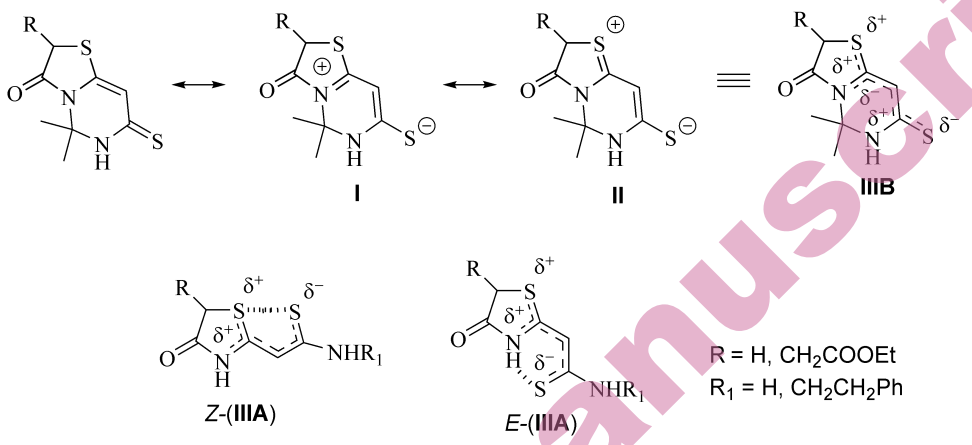
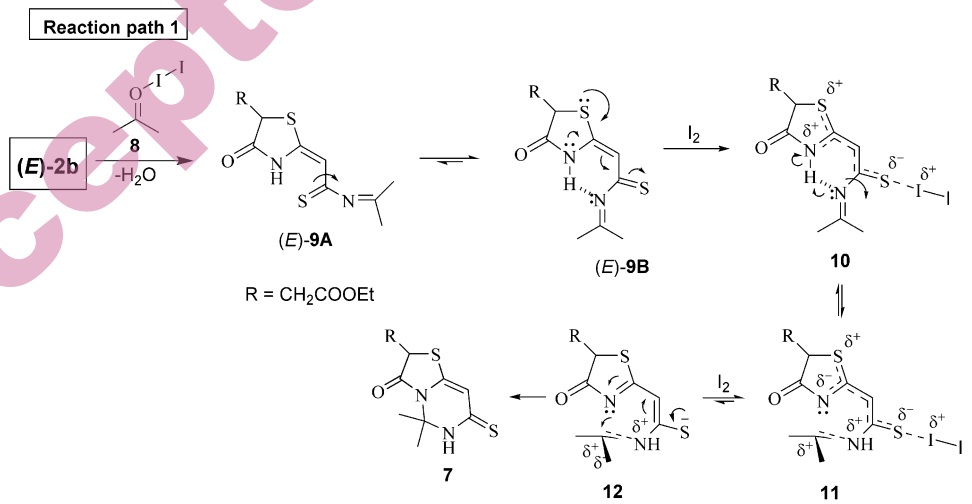


Scheme 4. The structures of thiazolo[3,2-c]pyrimidine **7** and thiazolidines **2a-c**.

During the planning of a synthetic strategy of 4-oxothiazolidine-2-ylidine thioamide **2** transformations with iodine, the two reaction paths were assumed: (i) the iodine-mediated cyclization, affording to the heterocycles such as product **7**, containing a pyrimidine heterocyclic core (reaction path **1**; Schemes 3 and 5) and (ii) the nucleophilic iodine attack on the thioamide sulfur atom, producing the complex mixture of iodine adducts **13**, **14** and **15**, respectively (reaction path **2**; Scheme 6).



Scheme 5. The proposed reaction mechanism of 4-oxothiazolidine (*E*)-**2b** to thiazolo[3,2-c]pyrimidine **7** transformations.

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Generally, the proposed undesired reaction path **2** (Scheme 6), as well as the performed synthetic route **1** in terms of iodine-promoted heterocyclization leading to **7** (Schemes 3 and 5), are based on the ability of the halogens X (typically, X= Cl, Br and I) that, as electron acceptor species, as the RX (Lewis acids), where the R ranges from another halogen atom to the large organic or inorganic residue interact with donor species D (Lewis bases), yielding a subclass of the charge transfer (CT), or electron donor-acceptor (EDA) complex family (adducts).[16-27] In these so-called halogen-bonded (XB) complexes (adducts) RX···D, the donor species can be an anion or a neutral species possessing at least one nucleophilic region, e.g., one or more electron lone pairs containing atoms (e.g., electron donor atoms such as oxygen, nitrogen, sulfur, selenium or π−system). To those, the interaction of iodine with various Lewis bases, expressed via association constants ($\mathbf{K}_{XB}$),[19,21,28,29] showed that the interactions between iodine and thioamides are medium to strong I_2/Lewis base interactions, which corroborates with the proposed reaction mechanisms in Schemes 5 and 6.

Regarding the potential trend in the behaviour of **2** under reaction conditions assumed in Scheme 6, which could lead to the complex mixture of iodine adducts, all possible products have been proposed based on the literature data related to the medium (product **13**) to strong (products **14**/**15b** and more complex ones) thioamide/I_2 interactions.[16-25] The previously published data on the brominating reactions of thiazolidine derivatives 1 (products **3** and **5**; Scheme 2)[5] were patterns of potential ligands in the **14** and **15b**. Therefore, the possible formation of iodine adducts such as **13** and ionic species **14** and **15b**, which consist of iodine(I) cation coordinated with two thioamide ligands, respectively,[17,19-23,25] suggested in Scheme 6, or even more complex structures forming as a result of further oxidation transformations, such as disulfide cations,[16-19,24] could be the best rationalized in the light of the MO theory: the increased the donor-acceptor interaction, the greater the amount of negative charge transferred from the donor to the σ* anti-bonding orbital of I_2, and the greater the I−I bond lengthening,[21] leading to the **13** with reduced I–I bond order or even more complex adducts **14** and **15b** produced by I–I bond heterolytic cleavage.

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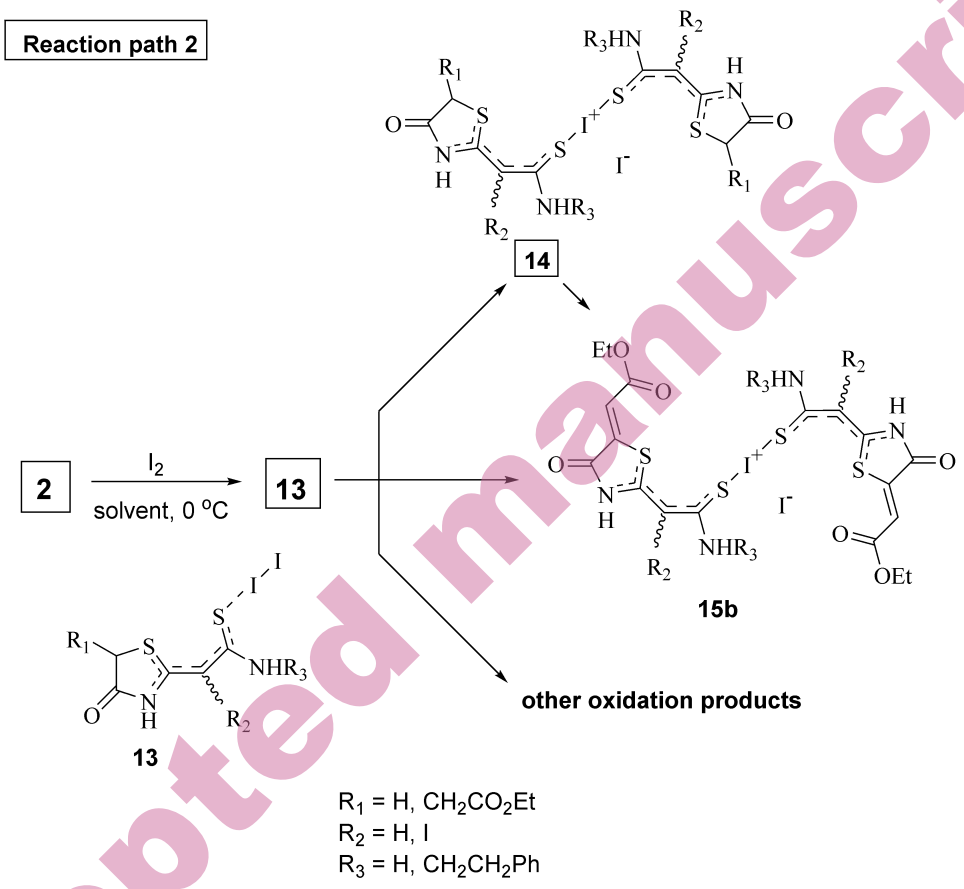

Scheme 6. The assumed **2**/I_2 interactions produce the complex mixture of iodine adducts.

The main factors that determined the possibility of occurrence of the 2-alkylidene-4-oxothiazolidine to thiazolo[3,2-c]pyrimidine transformation are (i) the nature of 4-oxothiazolidine derivatives, i.e., their *push–pull* effect and their strong affinity toward electrophile species, (ii) the iodine chemistry and, closely related with this, the halogen bonding[26,27] as the crucial one that, along with the *push–pull* effect of **2**, pulled in the direction of this transformation, and as a third factor (iii) the reaction conditions. In this sense, the mechanism of 4-oxothiazolidine (*E*)-**2b** to thiazolo[3,2-c]pyrimidine **7** heterocyclization (Scheme 5) can be rationalized by the series of steps involving an initial attack **on the carbonyl carbon of iodine-acetone adduct 8** by the nucleophilic thioamide nitrogen atom of (*E*)-**2b**, which occurs with the loss of H_2O, giving rise to **the like Schiff base 9.** The conformational change (*E*)-**9A** → (*E*)-**9B** produced a hydrogen-bonded six-membered chelate ring in the (*E*)-**9B**, which was transformed in the **10** by the addition of iodine. Then, the proton shifted from the lactam to the imine

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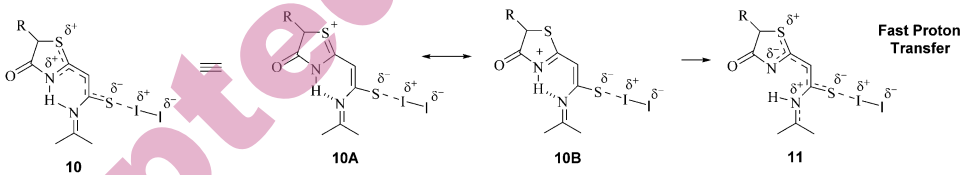
nitrogen atom in the **10** to give **11**. That followed the **11** → **12** transformations, which set the step for the cyclization. Thus, the final attack of the lactam nitrogen on the positively charged carbon atom of iminium ion **12** led to the formation of the pyrimidine ring in product **7**.

Additionally, to my knowledge, the (*E*)-**2b** → **7** reaction mechanism outlined in Scheme 5 represents a new one. Regarding this, a few steps have drawn particular attention, as follows, and described below: (i) (*E*)-**2b** → (*E*)-**9** transformation, (ii) the **10** → **11** rearrangements, and (iii) formation of vinylogous *N*-thioacyliminium ion **12** in the **11** → **12** transformations.

Concerning the (*E*)-**2b** → (*E*)-**9** reaction as the slowest step of the (*E*)-**2b** → **7** transformations, at first look, it seems that this type of transformation producing the Schiff bases like **9** is a widespread one, occurring among the numerous thioamides and carbonyl compounds. However, it is limited to only one report so far.[30]

Furthermore, the **10** → **11** rearrangements could be a crucial step in a complete (*E*)-**2b** → **7** transformations (Schemes 5 and 7). Since the hydrogen bond is an initial stage to proton-transfer reactions, which can proceed in the case of strong ones,[31] then compound **10** is one in which a strong hydrogen bond has established, leading to a very rapid proton transfer and the formation of product **11**.



Scheme 7. Intramolecular proton transfer in the **11**.

This work has postulated that iminium ion **12** could be a key intermediate of the (*E*)-**2b** → **7** transformations (Scheme 5). Generally, the iminium ions, such as Mannich-intermediate **16**, *N*-acyl derivative **17**, carbamate **18**, amide **19**, *N*-tosyl cations **20**, hydrazonium cation **21**, and vinylogous *N*-acyliminium ion **22**, are well known in the literature and they are involved in the construction of many heterocyclic compounds (Scheme 8).[32-34] In this sense, the novel vinylogous *N*-thioacyliminium ion **12**, as well as the iodine adducts of an iminium ion like **10** and **11**, as the key intermediates in (*E*)-**2b** → **7** transformation present additional contributions in the field in terms of better understanding this type transformation (Scheme 5).

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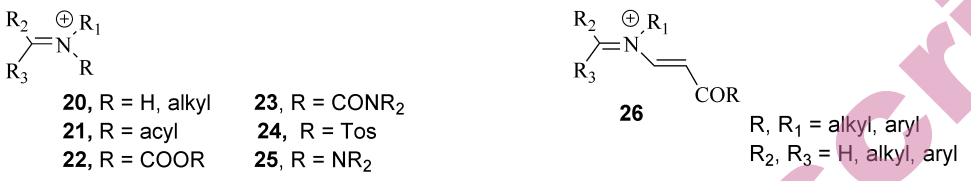

Scheme 8. The iminium ions.

In conclusion, for a series of reaction steps of the (*E*)-**2b** → 7 transformations (Scheme 5), one can conclude that is the strict regularity of the catalytic activity of iodine based on the principle of a switch-on/ turn-off act, i.e., "act purposefully" according to the structural characteristics of the intermediates. In this way, the action of iodine results in the production of a series of intermediates ending with chelate intermediate **10**, where the activity of iodine culminates in the promotion of proton transfer from the thiolactam NH group to imino group to form intermediate **11**.

Finally, as described below, the difference in the interaction of **2a-c** with iodine in the presence of acetone can be explained by their different structural characteristics, closely related to their different behaviour in potential **Z/E** configurational isomerization in a polar solvent.

Our previous works described the basic principle of *Z*/*E* isomerization of thiazolidine derivatives **1** and **2**.[10-12] These results unequivocally proved that due to the *push–pull* effect, the facile *Z*/*E* configurational isomerization of **1**,**2** occurs spontaneously in solution due to the lowering of the rotational barrier around the C=C double bond. The direction of this isomerization dictates the solvent polarity. Thus, forming the stable solvent-solute intermolecular interactions and breaking the intramolecular hydrogen bond in the (*E*)-**1** and (*E*)-**2**, depicted in Scheme 9 as the structure **I**, the polar solvents shift the Z/E equilibrium to the left. On the other hand, in nonpolar solvents, intramolecular hydrogen bonding is favoured, and in such conditions (*E*)-isomers become the dominant species.

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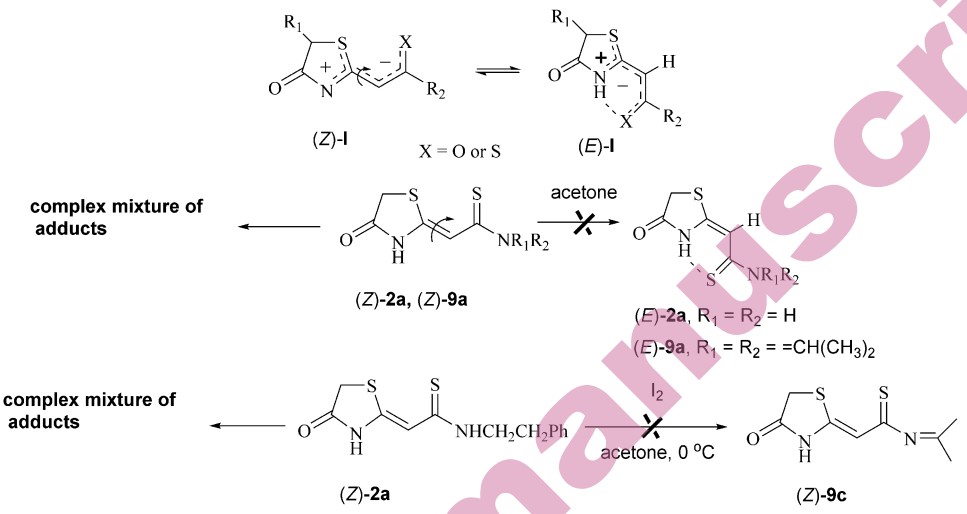

Scheme 9. Configurational isomerization of thiazolidines **1,2** and the interactions of the **2a** and **2c** derivatives with iodine in acetone.

Therefore, when considering the failed potential (*Z*)-**2a** to **7a** transformation via its counterpart (*E*)-**2a** (Scheme 9), the best explanation for this could be, as we previously proved, the trend to complete or complete shift to the left of the *Z/E* configurational isomerization of 2-alkylidene-4-ocoxothiazolidines **1** and **2**, occurring under polar solvent conditions.[10-12] In this sense, as in the case of most thiazolidine derivatives (**Z**)-**1**,[12] there is no evidence that **(Z)-2a to (E)-2a** transformation occurs under polar solvent conditions. Even if it happened to a low extent in acetone, it probably would not lead to a valid amount of **7a** due to competition between (*Z*)-**2a** to **7a** and (*Z*)-**2a** to (*Z*)-**2a**/iodine adducts transformations via (*Z*)-**2b** → (*E*)-**2b** isomerization (Scheme 9). Regarding those, the behaviour of (**E**)-**2b**, under polar solvent conditions**, constitutionally very** similar to **(Z)-2a,** corroborates with the above conclusions and findings.[10] Concerning the **(Z)-2c**/iodine interaction, the **(Z)-2c** → **7c** transformation is impossible due to this compound belonging to secondary thioamides, and the formation of a Schiff base 9c did not occur.

Given the above-described, competitions between (*E*)-**2b** → **7** and (*Z*)-**2b**,(*Z*)-**9** → (*Z*)-**2b**,(*Z*)-**9**/iodine adducts transformations via (*E*)-**2b**,(*E*)-**9** → (*Z*)-**2b**,(*Z*)-**9** isomerizations could be reliable (Scheme 10). Thus, in that case, the regioselective 2-alkylidene-4-oxothiazolidine (*E*)-**2b** to thiazolopyrimidine **7** transformation should be a kinetically controlled reaction. Furthermore, based on the proposed reaction mechanism of the (*E*)-**2b** → **7** transformation (Scheme 5), it is powerfully guided by the electron deficiency of iodine, which strengthens the thiazolidine *push–pull* effect in the series iodine adduct intermediates such as **10** and **11**. The same should be for reaction path **2** (Scheme 6), affording to the complex mixture

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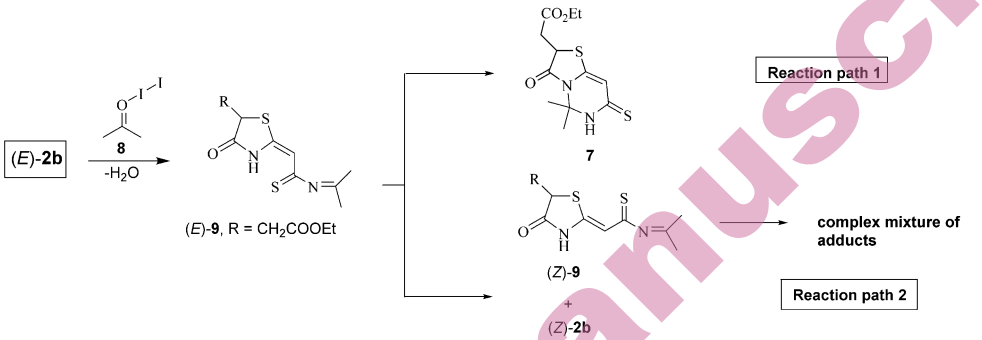
of the iodine adducts, which could take place between the precursor compounds (*Z*)-**2b** and (*Z*)-**9** with iodine, as the reactive species (Scheme 10).



Scheme 10. Competition between reaction paths **1** and **2** in the interaction of thiazolidine (*E*)-**2b** with iodine.

CONCLUSION

In conclusion, the interaction between thioamides **2a-c** and iodine in acetone followed two main reaction pathways: (1) heterocyclization of thiazolidine (*E*)-**2b** to give a thiazolopyrimidine **7** (reaction path **1**) and (2) electrophilic iodine attack on the thioamide sulfur atom of derivatives (*Z*)-**2a** and (*Z*)-**2c**, producing a complex mixture of iodine adducts (reaction path **2**). The difference in the interaction of **2a-c** with iodine in the presence of acetone has been explained by their different structural characteristics, closely related to their different behaviour in potential **Z**/**E** configurational isomerization in a polar solvent, such as acetone. In such conditions, the equilibrium of *Z*/*E* isomerization has strongly shifted to the *Z*-isomer. Furthermore, this research thoroughly studied the (**E**)-**2b** to **7** transformations as the first description of an iodine-mediated heterocyclization leading to a thiazolopyrimidine scaffold.

SUPPLEMENTARY MATERIAL

Additional data are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12725, or from the corresponding author on request.

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ИНТЕРАКЦИЈА ИЗМЕЂУ 4-ОКСОТИАЗОЛИДИН-2-ИЛИДЕН ТИОАМИДА И ЈОДА: РЕГИОСЕЛЕКТИВНА ДВОКОМПОНЕНТНА ТРАНСФОРМАЦИЈА 4-ОКСОТИАЗОЛИДИН-2-ИЛИДЕН ТИОАМИДА У ТИАЗОЛО[3,2-Ц]ПИРИМИДИН ПОСРЕДОВАНА ЈОДОМ

АЛЕКСАНДАР РАШОВИЋ

Центар за хемију ИХТМ, Универзитет у Београду, 11 000 Београд.

Ова студија истраживала је интеракцију између одабраних 4-оксотиазолидин-2-илиден тиоамида **2a**-**c** и јода у ацетону. Интеракција је пратила два главна реакциона пута: (1) циклизација посредована јодом која је резултирала формирањем тиазолопиримидина 7, и (2) електрофилни напад јода на атом сумпора тиоамида, стварајући сложену смешу јодних адуката. Пошто је у поларним растварачима равнотежа *Z*/*E* изомеризације снажно померена према (*Z*)-изомеру, само је тиоамид (*E*)-**2b** успешно формирао тиазолопиримидин 7. Друга два деривата, (*Z*)-**2a** и (*Z*)-**2c**, пратила су други реакциони пут. Фактори који утичу на хетероциклизацију (*E*)-**2b** и на њене интермедијере детаљно су испитани. Ово истраживање даје први опис хетероциклизације посредоване јодом која води до тиазолопиримидинске структуре. Литература о хетероциклизацији посредованој јодом којом се добијају кондензовани пиримидини је ограничена, што наглашава значај ове студије.

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