PAPER

Dimroth-type N/S-interchange of *N*-aminothioglycolurils in the synthesis of 2-hydrazonoimidazo[4,5-*d*]thiazolones†

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An original method for the synthesis of 2-hydrazonoimidazo[4,5-*d*]thiazolone derivatives has been developed based on a one-pot acid-induced sequence of hydrazone formation from 3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazinones and aromatic aldehydes, triazine ring contraction to imidazolidine one, and Dimroth-type N/S-interchange of *N*-aminothioglycolurils formed *in situ* into 2-hydrazonoimidazo[4,5-*d*]thiazolones. 3-Phenylacroleine derivatives are also suitable substrates for the reaction with thioxoperhydroimidazotriazinones.

Introduction

Nitrogen- and sulfur-containing heterocycles are found in many natural products and biologically active molecules.[1] This diversity of compounds includes imidazolidin-2-one and hydrogenated thiazole derivatives. For example, biotin (5-[2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]pentanoic acid) is involved in a wide range of metabolic processes in living organisms as a cofactor for carboxylase enzymes,[2] and leucogen (2-(2-ethoxy-2-oxo-1-phenylethyl)thiazolidine-4-carboxylic acid) is a veterinary vaccine used to protect cats against feline leukemia virus.[3]

Furthermore, 2-hydrazonothiazolidin-4-one derivatives possess antifungal[4] and anti-*Toxoplasma gondii* activities[5] while the biological activity of their imidazolidine fused analogues, *i.e.* 2-hydrazonoimidazo[4,5-*d*]thiazoles, has not been studied. Among the imidazo[4,5-*d*]thiazole derivatives, only 3,4-dihydro-2-phenylimino-2*H*-imidazo[4,5-*d*]thiazole **1** was recently described as anticancer agent against human colorectal carcinoma (HCT-116), human prostate adenocarcinoma (PC-3), and human liver hepatocellular carcinoma (HepG-2) cell lines (Fig. 1).[6] Apparently, this is due to the low availability of these compounds. Few examples of imidazo[4,5-*d*]thiazole derivatives are found in the literature.

Presented at Fig. 1 compound **1** was produced from thiazole-4,5-diamine derivative with D-glucose in acetic acid in the presence of iodine used as the oxidizing agent at room temperature.[6] 3*a*,6*a*-Diphenylimidazo[4,5-*d*]thiazolediones **2** were prepared by the reaction of 1-substituted 5-hydroxy-4,5-diphenyl-1*H*-imidazol-2(5*H*)-ones with potassium thiocyanate in the presence of acetic acid in acetonitrile in the yields of 53–92%; however, only 3*a*,6*a*-diphenylimidazothiazoles are accessible by this method (Fig. 2).[7] 3*a*,6*a*-Bis(trifluoromethyl)imidazo[4,5-*d*]thiazolones **3** and **4** were synthesized by treatment of 4,5-dihydroxy-4,5-bis(trifluoromethyl)imidazolidin-2-one(thione) with NH₄SCN or thiourea, respectively.[8] Imidazo[4,5-*d*]thiazoles **5** devoid of substituents at positions 3*a*,6*a* were prepared in several stages by the cycloaddition of isothiocyanates with *N*-
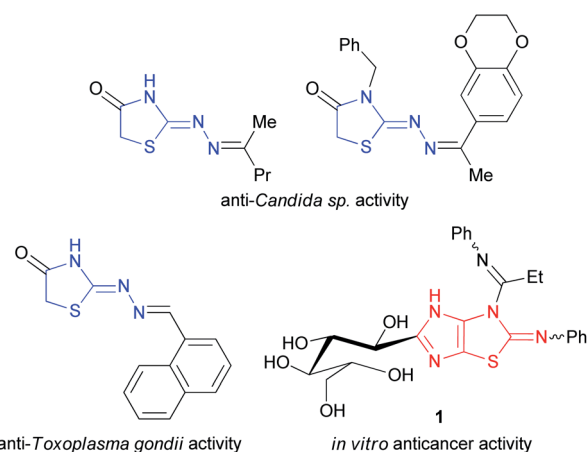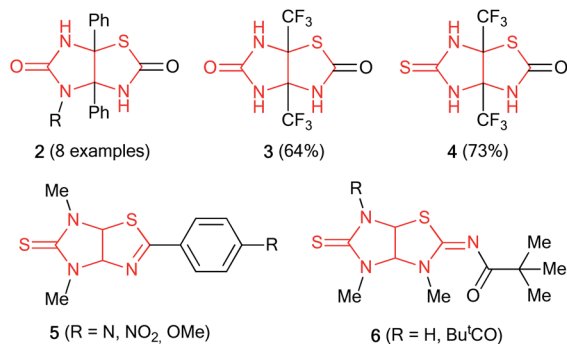
[a]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prosp., 47, Moscow 119991, Russian Federation. E-mail: gaz@ioc.ac.ru*

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Fig. 1 Bioactive 2-hydrazonothiazolidin-4-one and imidazo[4,5-*d*]thiazole derivatives.

anti-*Candida sp.* activity

anti-*Toxoplasma gondii* activity

in vitro anticancer activity

Fig. 2 Some imidazo[4,5-*d*]thiazole derivatives.

benzylsubstituted 4-methyl-5-(2-hydroxyethyl)thiazolium ylides followed by treatment with liquid ammonia and thermal desulfurization.[9] Imidazothiazoles **6** (R = H, Piv) were isolated as by-products when 1,6-dimethylthioglycoluril was acylated with pivaloyl chloride and potassium *tert*-butoxide in the yields of 4 and 16%, respectively.[10] Thus, the development of synthetic approaches to imidazo[4,5-*d*]thiazoles is still relevant as no general method for their synthesis has been designed.

Amidst the imidazo[4,5-*d*]thiazole derivatives, compound **6** (R = H) is resulted from rearrangement of imidazolidinethione ring of thioglycoluril **7**. Authors[10] suppose that deprotonation of compound **7** lead to formation of thioglycoluril anion which can undergo neighboring ring opening followed by the reclosure at sulfur (Scheme 1a). This fact encouraged us to research possibility of thioglycolurils rearrangement.
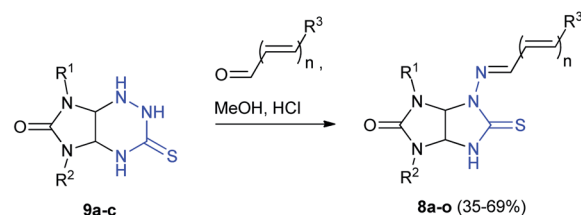
Recently,[11] we have developed an approach to preparation of thioglycolurils **8** based on the tandem hydrazone formation and triazine ring contraction reaction of 3-thioxoperhydroimidazo [4,5-*e*]-1,2,4-triazin-6-ones **9** with aromatic aldehydes or 3-phenylacrylaldehyde derivatives.

Here, we propose an original method for the synthesis of 2-hydrazonoimidazo[4,5-*d*]thiazolone derivatives **10** based on the

one-pot acid-induced sequence of hydrazone formation from thioxoperhydroimidazo[4,5-*e*]triazinones **9** and aromatic aldehydes or 3-phenylacrylaldehyde derivatives, triazine ring contraction to imidazolidine one, and rearrangement, *i.e.* Dimroth-type N/S-interchange, of thioglycolurils **8** formed *in situ* into 2-hydrazonoimidazo[4,5-*d*]thiazolones (Scheme 1b).
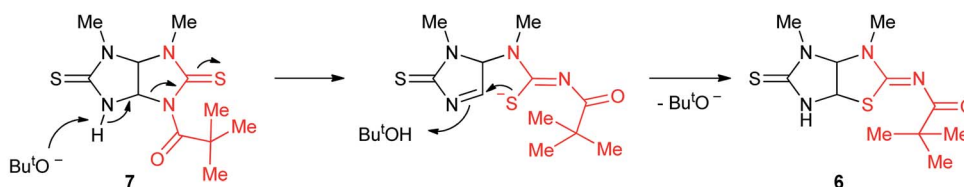
Results and discussion

At first, *N*-aminothioglycoluril derivatives **8a–o** were prepared according to earlier developed procedure starting from 3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazines **9a–c** and aromatic aldehydes or 3-phenylacrylaldehyde derivatives (Scheme 2).[11]
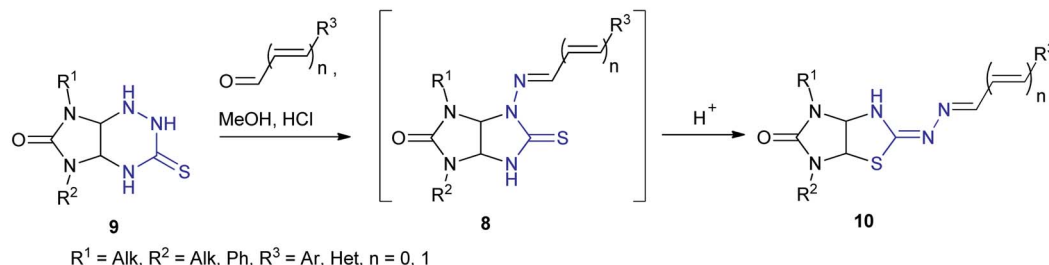

9: R^1 = R^2 = Me (**a**), Et (**b**), R^1 = Me, R^2 = Ph (**c**)

Compound	n	R^1	R^2	R^3	Yield [%]
8a	0	Me	Me	Ph	55[11a]
8b	0	Me	Me	2-FC$_6$H$_4$	49[11b]
8c	0	Me	Me	4-FC$_6$H$_4$	62[11a]
8d	0	Me	Me	4-MeOC$_6$H$_4$	44[11c]
8e	0	Me	Me	2-thienyl	41[11d]
8f	0	Et	Et	Ph	61[11a]
8g	0	Et	Et	2-FC$_6$H$_4$	48[11b]
8h	0	Et	Et	4-FC$_6$H$_4$	65[11b]
8i	0	Et	Et	4-MeOC$_6$H$_4$	69[11c]
8j	0	Et	Et	2-thienyl	54[11d]
8k	0	Me	Ph	Ph	35
8l	1	Me	Me	Ph	44[11e]
8m	1	Me	Me	2-MeOC$_6$H$_4$	43[11e]
8n	1	Et	Et	2-MeOC$_6$H$_4$	63[11e]
8o	1	Me	Ph	2-MeOC$_6$H$_4$	40[11e]

Scheme 2 Synthesis of thioglycolurils **8a–o**.

Scheme 1 Background and general concept of this work.

The yields of thioglycolurils **8a–j, l–o** were close to described values.[11] New compound **8k** was synthesized in 35% yield. Introduction of phenyl substituent at the N(5) atom of starting compound **9c** led to the significant decrease of the reaction product yield compared to the yields of **8a,f**.

To optimize the procedure for the rearrangement of thioglycolurils **8**, compound **8a** was chosen as a model substrate. The solvent, base/acid, reaction time, and temperature were varied. The representative results were summarized in Table 1.

The Dimroth rearrangement was carried out upon treatment with bases, acids, heat, or, rarely, light.[12] Therefore, we started our research by testing sodium methylate and potassium hydroxide (Table 1, entries 1, 2). However, no rearrangement products were obtained under these conditions. The rearrangement of thioglycoluril **8a** was observed in concentrated HCl at room temperature (entry 3). Subsequently, we screened the acid reaction conditions.

Addition of methanol that dissolved starting compound **8a** to hydrochloric acid (in a volume ratio of 1 : 10) provided an increase of the yield of the desired product **10a** to 70% (entry 4). Heating the reaction mixture at 60 °C for the same time (2 h) reduced the yield of the rearrangement product by almost four times (entry 5). Increasing the share of methanol (1 : 1) in the reaction mixture at room temperature enhanced the yield of **10a** to 80% (entry 6). Prolongation of the reaction time to 3 h didn't lead to improvement of the yield of target compound **10a** (entry 7). When the reaction was carried out in an organic acid (acetic and formic acids) compound **10a** was not formed at all (entries
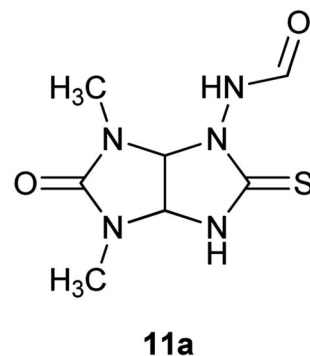

Fig. 3 Structure of N-{4,6-dimethyl-5-oxo-2-thioxohexahydroimidazo[4,5-d]imidazol-1(2H)-yl}formamide (**11a**).

8–11). Starting thioglycoluril **8a** or known N-{4,6-dimethyl-5-oxo-2-thioxohexahydroimidazo[4,5-d]imidazol-1(2H)-yl}formamide (**11a**) were isolated (Fig. 3).[13] Thus, the best result was achieved performing rearrangement in the mixture of equal volumes of methanol and concentrated hydrochloric acid at room temperature for 2 h (method A).

The scope of the Dimroth-type N/S-interchange of 1,3-disubstituted 4-[(arylmethylidene)amino]thioglycolurils **8a–k** was subsequently investigated under the optimized conditions. It was found that apart from model substrate **8a**, 1,3-diethyl- and 3-methyl-1-phenylsubstituted thioglycolurils containing 4-benzylideneamino fragment (**8f,k**), 1,3-dimethyl- and 1,3-diethylsubstituted compounds with electron withdrawing (**8b,c,g,h**) and electron donating substituents in arylmehtylideneamino moieties at position 4 (**8d,i**), as well as with 4-[(thiophene-2-ylmethylidene)amino] fragment (**8e,j**) underwent rearrangement to afford the desired products **10a–k** in 50–86% yields (Scheme 3).

Next, we studied behavior of [(E)-((E)-3-phenylallylidene)amino]thioglycolurils **8l–o** under these conditions. The rearrangement of compounds **8l–o** also proceeded successfully to give imidazothiazoles **10l–o** in the yields of 53–80% (Scheme 4).
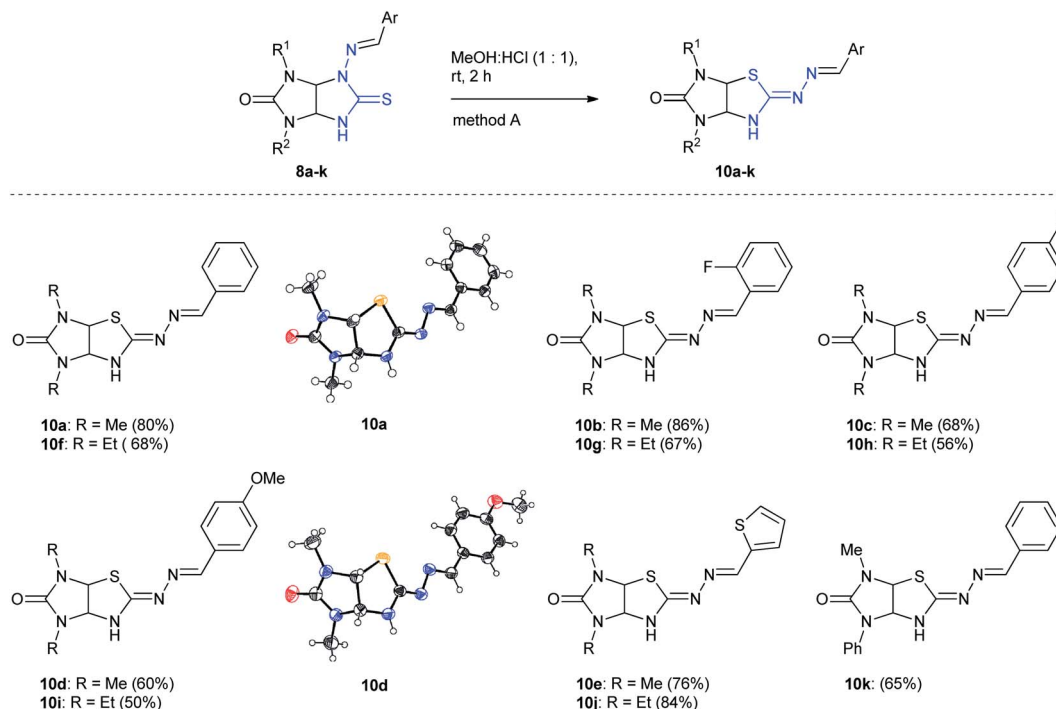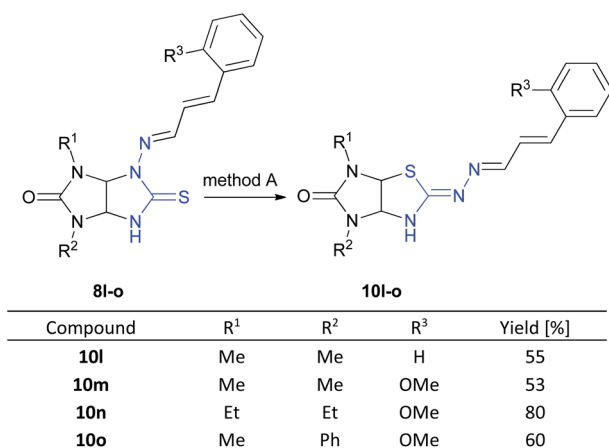
Finally, we tried to carry out these reactions in one-pot version starting from imidazotriazines **9a–c** and aldehydes because both the synthesis of thioglycolurils **8** and their rearrangement into imidazothiazole derivatives **10** proceeded in methanol with hydrochloric acid (Scheme 5, method B). A mixture of imidazotriazine **9**, corresponding aldehyde and methanol in the presence of hydrochloric acid (1 drop, 0.03 mL, 0.33 mmol) was refluxed with stirring for 1.5 h. Then the reaction mixture was cooled to room temperature, diluted with hydrochloric acid (in a volume ratio of 1 : 1), and stirred for 2 h. The yields of imidazothiazoles **10a–o** obtained by one-pot method were higher (36–63%) as compared to yields of 23–45% obtained by two step method (Schemes 2–4) based on starting imidazotriazine **9**.

The structures of new compounds **10a–o** were established by IR, ^{1}H and ^{13}C NMR and HRMS analysis. The IR spectra of imidazothiazoles **10a–o** showed intense absorption bands at 1682–1727 cm^{-1} that are characteristic of carbonyl group. Characteristic of C=N bonds absorption bands were observed at 1599–1636 cm^{-1}. In the ^{1}H NMR spectra of imidazothiazoles

Table 1 Variation of reaction conditions for rearrangement of thioglycoluril **8a** into imidazothiazole derivative **10a**^{a}

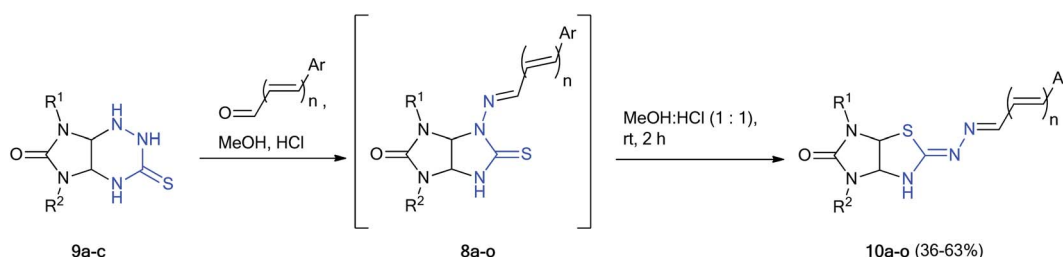| Entry	Solvent (base/acid)	T, °C	Time, h	Yield of **10a**, %^{b}
1	MeOH (NaOMe)	rt	2	0
2	MeOH (KOH)	rt	2	0
3	HCl^c	rt	2	47
4	MeOH : HCl^c (1 : 10)	rt	2	70
5	MeOH : HCl^c (1 : 10)	60	2	18
6	**MeOH : HCl^c (1 : 1)**	**rt**	**2**	**80**
7	MeOH : HCl^c (1 : 1)	rt	3	78
8	AcOH	rt	5	0
9	AcOH	60	2	0
10	AcOH	110	2	0
11	HCOOH	60	2	0^d

^{a} Reaction conditions: stirring the mixture of thioglycoluril **8a** (1.0 mmol) and base (1.0 mmol) in methanol (20 ml) either stirring the suspension of thioglycoluril **8a** (1.0 mmol) in acid (or in the mixture of MeOH with acid) (20 ml) for 2–3 h. ^{b} Isolated yield. ^{c} d = 1.170, C = 34.18%. ^{d} Compound **11a** was formed in the 62% yield.

Scheme 3 Synthesis of imidazothiazoles **10a–k** by method A.

Scheme 4 Synthesis of imidazothiazoles **10l–o** (method A: MeOH : HCl (1 : 1), rt, 2 h).

(Fig. 4). Protons of CH_2-groups of *N*-ethyl fragments are diastereotopic and resonate as four separate complicated signals which partially overlap. The structures of **10a** and **10d** were also confirmed using single-crystal X-ray diffraction analysis. Bond lengths and angles in the structures are within normal ranges that was confirmed by the Mogul geometry check.[14] The configurations of C=N and N=CH double bonds were *Z* and *E*, respectively. The hydrogen atoms at the C(3*a*) and C(6*a*) atoms are in the *cis* arrangement similar to that in thioglycolurils **8**.[11] So, both compounds **10** and thioglycolurils **8** are formed as a racemate. Other diastereomer with the *trans* arrangement of hydrogen atoms or other substituents at the bridged C(3*a*) and C(6*a*) atoms has never been observed.[10,11,15]

A plausible rearrangement mechanism is depicted in Scheme 6. Probably, rearrangement is a result of imidazolidinethione ring opening of compound **8** upon treatment with acid and recyclization of the thiazolidine ring involving other nucleophilic center, sulfur atom. The reaction proceeds towards the product with a bulk substituent localized on an exocyclic heteroatom.

10a–o as compared to the spectra of **8a–o**, there are upfield shifts of the signals of NH-, N=CH-groups, aromatic protons, one of the bridged CH-proton, and one of the NMe-groups

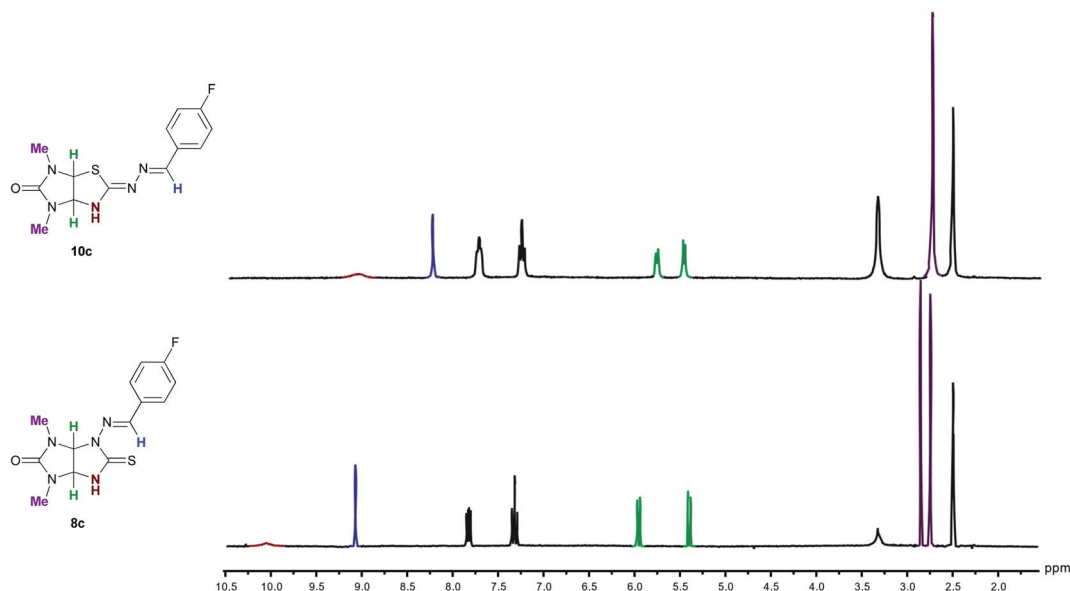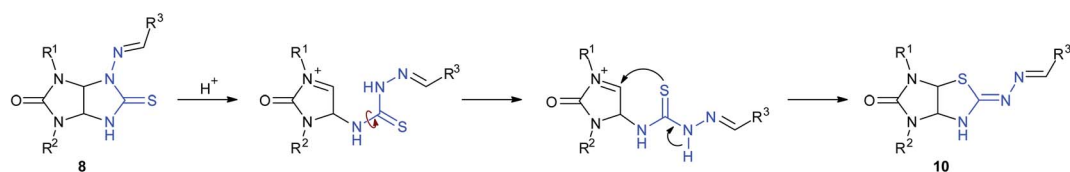**Scheme 5** One-pot synthesis of imidazothiazoles **10a–o** by method B.

Fig. 4 Comparison of the ^{1}H NMR spectra of thioglycoluril **8c** and imidazothiazole **10c** in the region 2.0–10.5 ppm in DMSO-d_6.

Scheme 6 Plausible rearrangement mechanism.

As we shown earlier,[11c] formation of thioglycolurils **8** accompanied by side process: instead of a recyclization step, the elimination of aldehyde thiosemicarbazone can occur. Apparently, the process takes place also during the rearrangement under study that result in decrease of the product yields.

Conclusion

We have developed an original method for the synthesis of earlier unavailable 2-hydrazonoimidazo[4,5-*d*]thiazolone derivatives based on the one-pot acid-induced sequence of hydrazone formation from 3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazinones and aromatic aldehydes or 3-phenylacroleine derivatives, triazine ring contraction to imidazolidine one, and Dimroth-type N/S-interchange of *N*-aminoimidazolidine-2-thione ring into 2-hydrazonothiazolidine fragment. The synthesized structures represent a new class of promising bioactive heterocyclic compounds. Investigations of antiproliferative activity of the prepared products against cancer cell lines are in progress.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

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