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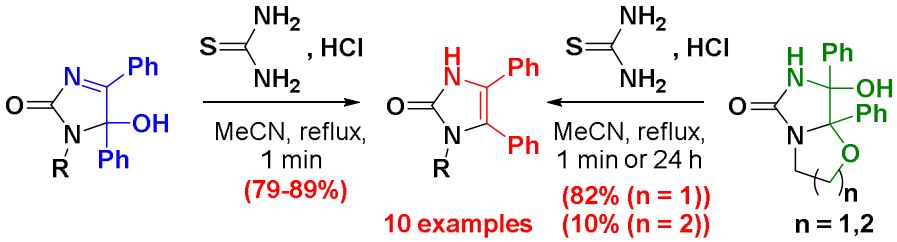


Unexpected reductive transformation of 1-substituted 5-hydroxy-4,5-diphenyl-1*H*-imidazol-2(5*H*)-ones and their cyclic analogs by the reaction with thiourea and hydrochloric acid.

Vladimir V. Baranov[a,b,*], Maria M. Antonova[a], Valentina A. Karnoukhova[c], and Angelina N. Kravchenko[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., Moscow, 119991, Russian Federation, Fax: +7 499 135 5328, Phone: +7 499 137 2944 e-mail: ase1313@mail.ru*

[b] *Peoples' Friendship University of Russia (RUDN University), 6 Miklukho-Maklaya St., Moscow, 117198 Russian Federation*

[c] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilova St., Moscow, 119991, Russian Federation*

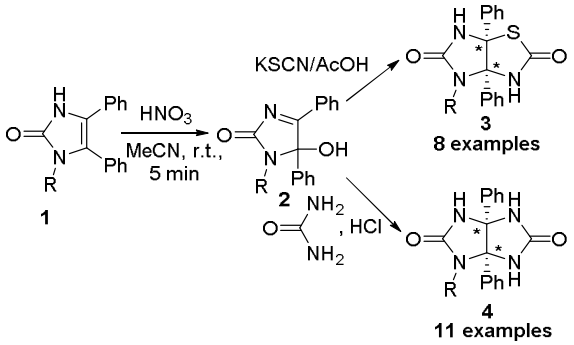
Abstract

An unexpected reductive transformation of 1-substituted 5-hydroxy-4,5-diphenyl-1*H*-imidazol-2(5*H*)-ones (imidazolones) and their cyclic analogs to give 1-substituted 4,5-diphenyl-1*H*-imidazol-2(5*H*)-ones (imidazolinones) upon reaction with thiourea and hydrochloric acid was discovered.

Keywords: *Imidazolinones, Imidazolones, Thiourea, Reductive transformation, Heterocycles*

1-Substituted 1*H*-imidazol-2(3*H*)-ones (imidazolinones) **1** are biologically active compounds possessing antioxidant,[1,2] cytotoxic,[3] antifungal,[4] anticonvulsant,[2] antiinflammatory, antitumor, cardiotonic,[5] or receptor agonist[5,6] properties. Various methods for the synthesis of imidazolinones **1** have been described in the literature.[7] Previously, these compounds were used for the formation of 1-substituted 5-hydroxy-4,5-diphenyl-1*H*-imidazol-2(5*H*)-ones (imdazolones) **2** in nitric acid, and a wide range of imidazothiazoles **3** and glycolurils **4** were

prepared from compounds **2** upon reaction with KSCN and AcOH or urea and HCl, respectively (Scheme 1).[8]

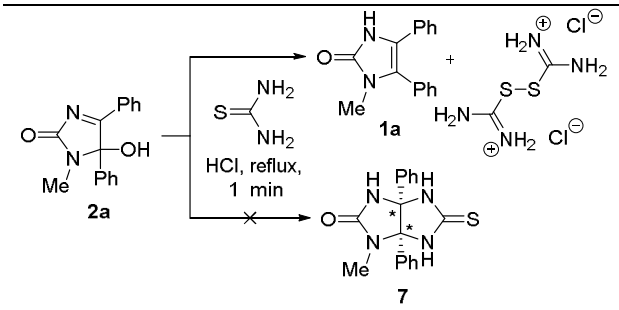


Scheme 1. Preparation of imidazothiazoles **3** and glycolurils **4** from imidazolinones **1**.

Herein, the reaction of imidazolones **2a-h** and their cyclic analogs (7-hydroxy-7,7*a*-diphenyltetrahydroimidazo[5,1-*b*]oxazol-5(6*H*)-one (imidazooxazolone) **5** and 8-hydroxy-8,8*a*-diphenyltetrahydro-2*H*-imidazo[5,1-*b*][1,3]oxazin-6(7*H*)-one (imidazooxazinone) **6** with thiourea and hydrochloric acid was studied.

We began our investigation by studying the model reaction of imidazolone **2a** with thiourea (Table 1). However, the expected thioglycoluril **7** was not formed; imidazolinone **1a** and the hydrochloric salt of formamidine disulfide were obtained in 33% yield (Entry 1). The failure of thioglycoluril **7** formation could be explained by the rapid reaction of thiourea as an *S*-nucleophile (see below). The reaction conditions were next optimized using MeCN or MeOH as solvents and different amounts of thiourea (1, 2 or 3 eq.) and hydrochloric acid (0.5, 1 or 2 mL/1.5 mmol of **2a**) (Table 1). Optimal conditions for the synthesis of imidazolinone **1a** (85%) were heating a solution of imidazolone **2a**, thiourea (2 eq.) and HCl (1 mL, 35%/1.5 mol of **2a**) in MeCN at reflux for 1 min. (Table 1, entry 2).

Table 1. Screening conditions for the reaction of imidazolone **2a** with thiourea and hydrochloric acid.

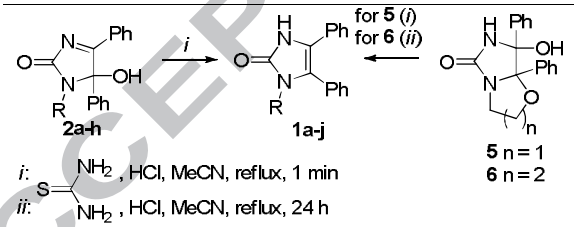


Entry	Solvent	HCl 35% (mL)	Thiourea (eq.)	Yield **1a** (%)
1	MeCN	1	1	33
2	**MeCN**	**1**	**2**	**85**
3	MeCN	0.5	2	48
4	MeCN	2	2	83
5	MeCN	1	3	84
6	MeOH	1	2	-

Reagents and conditions: **2a** (1.5 mmol), thiourea, solvent (15 mL), 60 °C, then 35% HCl dropwise, reflux, 1 min.

The reaction was extended to the synthesis of a series of imidazolinones **1a-i**, which were obtained in 79-89% yield (Table 2, entries 1-9). In contrast, imidazolinone **1j** was obtained in only 10% yield even after heating at reflux for 24 h (Entry 10). The low yield of imidazolinone **1j** could be explained by the difficulty of the six-membered ring-opening process in imidazooxazinone **6**.[9]

Table 2. Synthesis of imidazolinones **1a-j**.



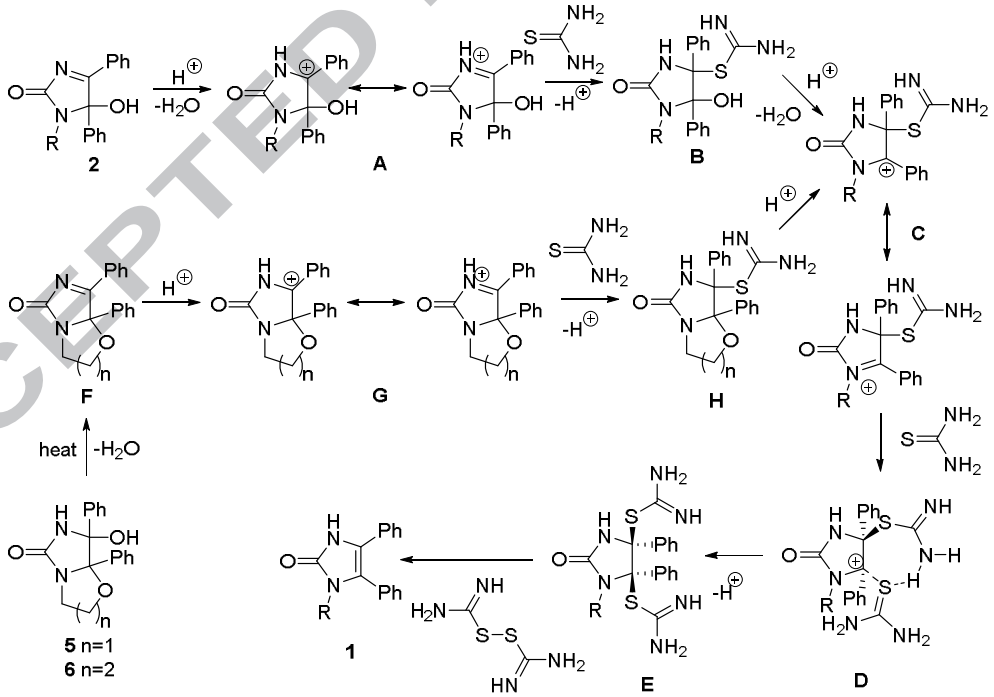
Entry	Reagent	R	Product	Yield **1** (%)
1	**2a**	Me	**1a**	85[a]
2	**2b**	Et	**1b**	79[a]
3	**2c**	Pr	**1c**	84[a]
4	**2d**	Bu	**1d**	80[a]
5	**2e**	Bn	**1e**	89[a]
6	**2f**	$(CH_2)_2OAc$	**1f**	87[a]
7	**2g**	$(CH_2)_3OAc$	**1g**	80[a]
8	**2h**	$(CH_2)_4OAc$	**1h**	84[a]

9	**5**	$(CH_2)_2OH$	**1i**	82 [a]
10	**6**	$(CH_2)_3OH$	**1j**	10 [b]

[a]Reagents and conditions: **2a-h, 5** (1.5 mmol), thiourea (3 mmol), MeCN (15 mL), 60 °C, then 35% HCl (1mL) dropwise, reflux, 1 min.

[b] **6** (1.5 mmol), thiourea (3 mmol), MeCN (15 mL), 35% HCl (1mL), reflux, 24 h.

Plausible mechanisms for the formation of imidazolinones **1** are shown in Scheme 2. Initially, formation of cation **A** (for compounds **2a-h**), followed by nucleophilic attack of thiourea as an *S*-nucleophile gives intermediate **B**. Protonation of intermediate **B** on the –OH group leads to the elimination of water with the formation of cation **C**. Cation **C** and a second molecule of thiourea are assembled with NH_2…S=C H-bonds to give intermediate **D**, which is converted to intermediate **E** with *cis*-orientation of the thiourea moieties. Formamidine disulfide is then eliminated from intermediate **E** and imidazolinones **1** are formed. Under heating, bicyclic compounds **5**, **6** eliminate H_2O to form intermediate **F**.[10] The mechanisms for the formation of imidazolinones **1** from imidazolones **2** or intermediates **F** should be similar, however protonation of intermediate **H** with opening of the *O*-containing ring is required for the formation of cation **C**.



Scheme 2. Plausible mechanisms for the formation of imidazolinones **1** from imidazolones **2** and cyclic analogs **5**,**6**.

Compounds **1a-i** have been described in the literature,[8,9b,10-13] but compounds **1b-d** were not sufficiently characterized. The structures of compounds **1b-d**,**j** were confirmed by ^{1}H, ^{13}C NMR spectroscopy, HRMS and single-crystal X-Ray diffraction (Fig. 1).[14]

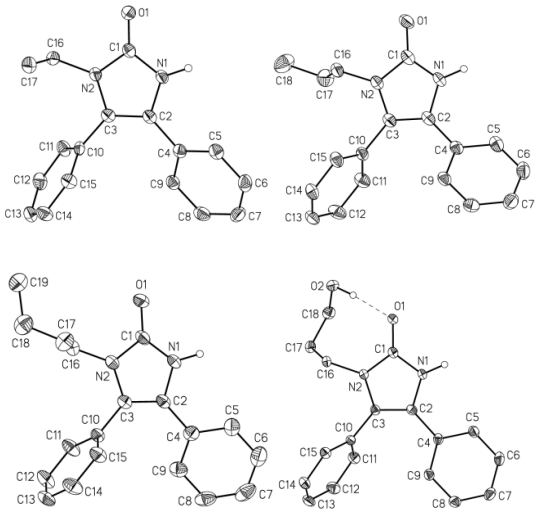


Figure 1. X-ray crystal structures of compounds **1b**, **1c**, **1d**, **1j**. Hydrogen atoms connected to carbon atoms are omitted for clarity.

In conclusion, the unexpected formal red-ox transformation of imidazolones **2a-h** and their cyclic analogs (imidazooxazole **5** and imidazooxazine **6**) to give imidazolinones **1a-j** upon reaction with thiourea and hydrochloric acid was discovered.

Acknowledgment

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Supplementary data

Supplementary data (^{1}H, ^{13}C NMR spectral data for compounds **1b-d**,**j**) associated with this article can be found in the online version, at

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(14) Crystallographic data for **1b-d** and **1j** have been deposited at the Cambridge Crystallographic Data Centre (CCDC) with the reference numbers 1532152-1532155. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

(15) 1-Substituted 4,5-diphenyl-1*H*-imidazol-2(3*H*)-ones 1a-i; General Procedure

A mixture of the corresponding 1-substituted 4,5-diphenyl-1*H*-imidazol-2(3*H*)-one **2a-i** (1.5 mmol), thiourea (0.228 g, 3 mmol) and MeCN (15 mL) was heated to 60 °C, then HCl (1 mL) was added dropwise. The reaction mixture was then heated at reflux for 1 minute. The white precipitate containing the hydrochloric salt of formamidine disulfide was filtered off. Compound **1a-i** precipitated from the filtrate after 24 h and was filtered off then washed with MeCN.

1-(3-hydroxypropyl)-4,5-diphenyl-1*H*-imidazol-2(3*H*)-one 1j.

A mixture of 8-hydroxy-8,8*a*-diphenyltetrahydro-2*H*-imidazo[5,1-*b*][1,3]oxazin-6(7*H*)-one **6** (0.465 g, 1.5 mmol), thiourea (0.228 g, 3.0 mmol), HCl (1 mL) and MeCN (15 mL) was heated at reflux for 24 h. The white precipitate was filtered off. Compound **1j** precipitated from the filtrate after 24 h and was filtered off then washed with MeCN. Colorless crystals; yield: 0.044 g (10%); mp 237 – 240 °C (MeCN). ^{1}H NMR (300 MHz, $DMSOd_6$): δ = 1.42–1.57 (m, 2H, CH_2), 3.22–3.32 (m, 2H, CH_2), 3.44–3.54 (m, 1H, CH_2), 7.09–7.24 (m, 5H, Ph), 7.34–7.44 (m, 2H, Ph), 7.45–7.58 (m, 3H, Ph), 10.80 (m, 1H, NH). ^{13}C NMR (75 MHz, $DMSOd_6$): δ = 32.23, 37.85, 58.10 (CH_2) 117.22, 120.51, 125.32, 126.42, 128.33, 128.90, 129.08, 129.72, 130.74 (Ph-C=C-Ph), 153.19 (C=O). HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{18}H_{18}N_2O_2$+H: 295.1442; found: 295.1438.

Highlights

- Unexpected reduction of imidazolones and analogs into imidazolinones was discovered
- 10 examples of imidazolinones were synthesized
- Plausible mechanisms for the formation of imidazolinones were proposed
- The structures were confirmed by ^{1}H, ^{13}C NMR spectroscopy, HRMS and X-Ray