Organic &
Biomolecular Chemistry

PAPER

View Article Online
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Cite this: *Org. Biomol. Chem.*, 2025, **23**, 7157

Multi-purpose thiocyanate protic ionic liquids in chemodivergent transformations of imidazolidin-2-(thi)one-based diols†

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Received 30th April 2025,
Accepted 1st July 2025

DOI: 10.1039/d5ob00709g

rsc.li/obc

Multi-purpose thiocyanate-containing protic ionic liquids were utilised in concert as a solvent, a Brønsted acidic catalyst, and a nucleophile source for the conversion of 4,5-dihydroxy-4,5-diarylimidazolidine-2-(thi)ones into imidazo[4,5-*d*]oxazolethiones and imidazo[4,5-*d*]thiazolones. A key advantage of this process is chemoselectivity switching by tuning the electron-donating nature of aryl substituents while carefully controlling the reaction temperature. In the case of unactivated arenes, oxazolethione was forced to rearrange into thiazolone in the new highly acidic protic ionic liquid, 1-methylpyrazolium triflate. The operationally simple experimental set-up is complemented by an eco-friendly aqueous work-up/filtration procedure providing pure crystalline products.

Introduction

The study of ionic liquids (ILs), defined as compounds that exist entirely in ionic form and possess melting points typically[1] under 100 °C, has significantly increased in recent decades.[2] The unique physicochemical properties of ILs enable their utilisation as versatile solvents in a wide range of applications, including various synthetic processes,[3] separations and extractions,[4] valorisation of biomass,[5] polymer materials,[6] energy-related[7] and electrochemical studies,[8] biomedical applications[9] and others. Given that the majority of ILs' applications necessitate highly inert ions, they typically feature quaternary ammonium or phosphonium cations paired with stable unreactive anions such as sulfate, sulfonates, phosphates, nitrate, carboxylates, *etc.*

An important subgroup of ILs that have found wide application both in laboratory and industrial practice are protic ionic liquids (PILs).[10] These salts, generated through the transfer of a proton from an acid to an organic base, contain some portion of non-ionised acidic and basic species, the amount of which is determined by the position of equilibrium for the proton transfer. This amount is the difference in acidity(ΔpK_a) between an acid and a protonated base that make up the PIL.[11] The value of this difference, which allows the quantity of uncharged species to be considered insignificant, depends on the problems solved in a specific study. The pK_a values of the components amalgamated in PILs regulate not only the stability but also the acidity of such salts. Adhering to the above considerations, a combination of a strong acid and a moderately basic amine (or phosphine) should exhibit acidic properties. Therefore, unlike aprotic ionic liquids, PILs can serve concurrently as both a reaction medium and a Brønsted acidic catalyst, boosting their usefulness in the organic synthesis field.[10]

We recently extended the utility of protic ionic liquids in organic synthesis by adding a new role for them, namely, to perform as a reagent. Relying on the concepts discussed above, thiocyanate ion-containing PILs act as a trifunctional reaction system—solvent, acid catalyst, and nucleophilic reagent—imitating (iso)thiocyanic acid, which is unstable in

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† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data and copies of ^{1}H, ^{13}C and ^{19}F (where applicable) NMR spectra for all products, 2D NMR spectra for selected compounds, single-crystal X-ray data, results of quantum-chemical calculations. CCDC 2444500–2444503. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5ob00709g

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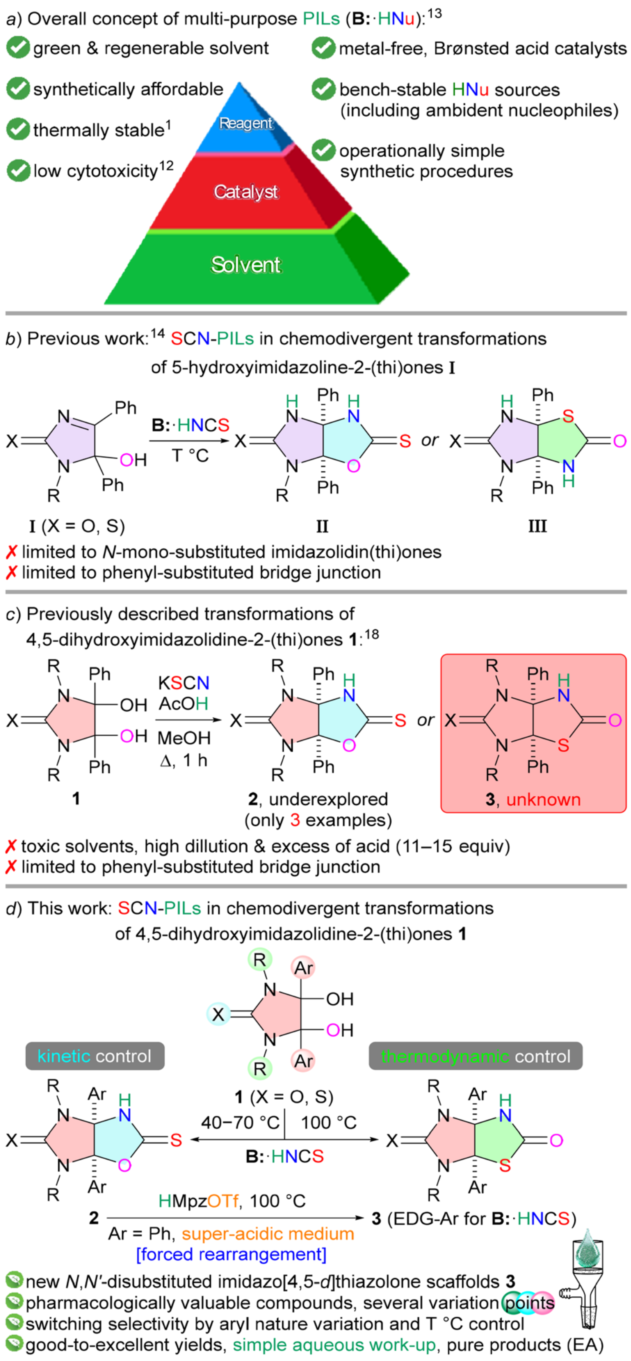
pure form. These PILs, possessing a number of virtues,[1,12] were used for the synthesis of diverse *N*,*S*-comprising heterocyclic scaffolds in telescopic or chemodivergent mode (Scheme 1a).[13]

The broad applicability of the designed approach was then validated by choosing a novel substrate type, 5-hydroxyimidazoline-2-(thi)ones **I** (Scheme 1b),[14] due to the recognised bioactivity of compounds containing the imidazolidin-2-(thi)one moiety (Fig. 1).[15] Furthermore, hybrid molecules with dual modes of action have garnered significant attention in recent years.[16] The reaction of **I** with isothiocyanic acid PIL surrogate produces pharmacologically relevant§ oxazolidine-2-thione **II** or thiazolidin-2-one **III** derivatives[17] in a chemodivergent manner (Scheme 1b).[14] These results stimulated us to investigate the conversion of the related 4,5-dihydroxy-4,5-diarylimidazolidine-2-(thi)ones **1** under treatment with thiocyanate-based PILs, keeping in mind that the corresponding *N*,*N'*-disubstituted imidazo[4,5-*d*]oxazolethiones **2** are scarcely studied, with the synthesis of only three compounds of this type reported to date (Scheme 1c).[18] Moreover, *N*,*N'*-disubstituted imidazo[4,5-*d*]thiazolones **3** are unknown completely, in striking contrast to the facile **I** to **III** reaction of *N*-monosubstituted substrates (Scheme 1b).[14,17b]



Scheme 1 Concept of multi-purpose PILs and their application in the chemodivergent synthesis of imidazo[4,5-*d*]oxazolethiones and imidazo[4,5-*d*]thiazolones.

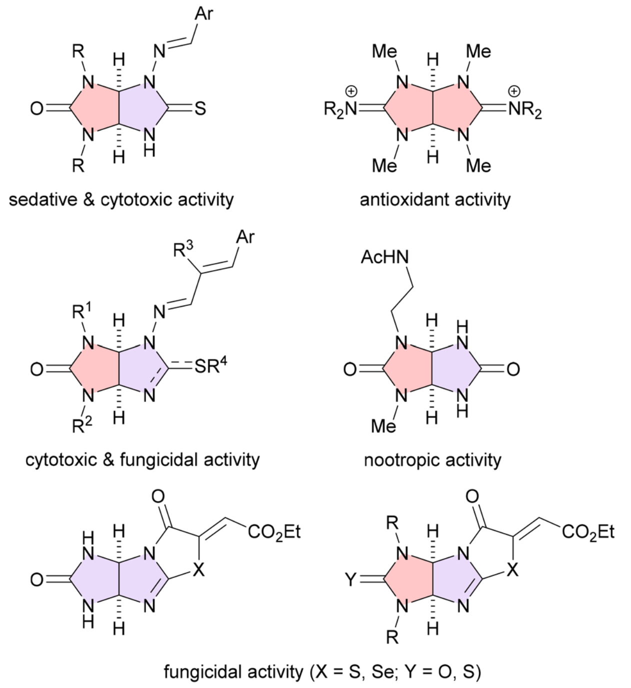


Fig. 1 Examples of bioactive compounds containing *N*,*N'*-disubstituted imidazolidin-2-(thi)one (filled in pink), *NH*-imidazolidin-2-(thi)one or their derivatives (filled in purple).

In the present study, we reveal that the thermal treatment of **1** in thiocyanate-containing PIL media yields either products of kinetic control **2** or thermodynamic control **3**, reliant on the electron-donating ability of aryl substituents under precise control of the reaction temperature (Scheme 1d). Also, we demonstrate the forced **2** → **3** rearrangement using the newly synthesized 1-methylpyrazolium triflate (HMpzOTf), which is presumably the most acidic protic ionic liquid currently known.

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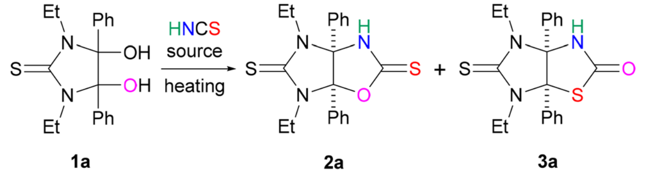
§ For bioactivity of oxazolidine-2-thione and thiazolidin-2-one scaffolds, see the corresponding references in ref. 14

Results and discussion

We started this work by searching for optimal conditions for the transformation of **1a** in thiocyanate-PIL media.[14] First, we applied 1-methylimidazolium thiocyanate (HMimNCS) under previously described reaction conditions (Table 1, entry 1), which demonstrated high efficiency in the ring-openings of donor–accepor (DA) cyclopropanes and oxiranes.[13a,c] The TLC control of the reaction progress after heating at 70 °C for 1 h displayed only the presence of a single spot, with the retention factor corresponding to that of the starting material. Thus, we increased the temperature to 100 °C and heated the reaction for 15.5 hours. The TLC still showed the same spot but also the presence of some other products. Surprisingly, ^{1}H NMR spectrum of the crude mixture revealed the absence of **1a**. Instead, a combination of signals attributed to product **2a** and a previously unknown compound **3a** in *ca.* 0.6 : 1 ratio was detected. Apparently, we conflated **1a** with **2a**, because of their identical retention indices, rendering it impossible to monitor the progress of the reaction towards products **2** using TLC. The results obtained above required us to adhere to the precise control of the reaction temperature in order to achieve the exclusive chemodivergence between products **2** and **3**.

Heating **1a** at 70 °C for 1 h (Table 1, entry 2), followed by the aqueous filtration work-up, provided pure imidazo[4,5-*d*]oxazoledithione **2a** in a high yield of 84%, which exceeds the 80% yield obtained under conventional conditions (Table 1, entry 10).[18] Decreasing the reaction temperature to 50 °C resulted in incomplete conversion of the starting material (Table 1, entry 3), indicating the lower reactivity of dihydroxyimidazolidines **1** in comparison to hydroxyimidazolines **I**. Therefore, we found that heating **1a** at 70 °C for 1 h is the optimal condition for the synthesis of **2a**.

Table 1 Optimisation of reaction conditions for the transformation of **1a** into **2a** and **3a** [a]



Entry	HNCS source	*T*, °C	Time, h	Yield[b] 1a	2a	3a
1[c]	HMimNCS	70 → 100	1 + 15.5	—	31	51
2	**HMimNCS**	**70**	**1**	—	**84**[d]	—
3	HMimNCS	50	1	36	60	—
4	HMimNCS	100	5	—	75	13
5	HMimNCS	120	5	—	—	46[e]
6	HMimNCS	120	10	—	—	57[e]
7	HMimNCS	120	15	—	—	52[e]
8	$Et_3N{\cdot}HNCS$	70	1	71[e]	—	—
9	$Et_3N{\cdot}HNCS$	100	4.5	—	40	—
10[f]	KSCN/AcOH, MeOH	65	1	—	80[d]	—

[a] 1 M solution of **1a** in PIL; the reaction mixture was subjected to the aqueous work-up, causing the precipitation of products; yields for filtered and dried precipitates are provided. [b] NMR yield, %. [c] The reaction mixture was subjected to an extraction/evaporation procedure. [d] Isolated yield of pure product, %. [e] Contains admixtures. [f] Literature conventional conditions: the reaction mixture was concentrated, the precipitate was filtered and recrystallised from methanol.[18]

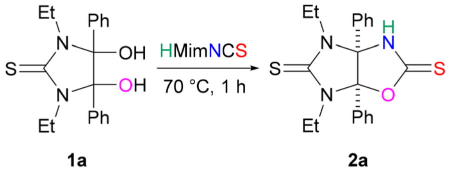
Then, we attempted to obtain **3a** selectively. However, increasing the reaction temperature to 100 or 120 °C and extending the reaction time (Table 1, entries 4–7) resulted in the formation of the target product **3a** in moderate yield and was accompanied by the decomposition of the starting material, leading to inseparable impurities.

We previously demonstrated that replacing HMimNCS with triethylammonium thiocyanate ($Et_3N{\cdot}HNCS$) can affect the yields and product outcome.[13a,c,14] Therefore, we attempted to use $Et_3N{\cdot}HNCS$ in the transformation of **1a**. Heating at 70 °C for 1 h (Table 1, entry 8) afforded only contaminated starting material. In turn, performing the reaction at 100 °C for 4.5 h (Table 1, entry 9) provided only **2a** in a moderate yield. Thus, replacement of the HNCS source did not help us to obtain **3a** in a pure form and high yield. At this stage, we were unable to find optimal reaction conditions for the synthesis of imidazo[4,5-*d*]thiazolone **3a**.

Calculations using the density functional theory at PBE0-D3/Def2-TZVPP level revealed that **3a** was 7.9 kcal mol^{-1} more stable than **2a**.† These results, in combination with optimisation of reaction conditions, suggest that **2a** is a product of kinetic control, while **3a** is a product of thermodynamic control.

We also investigated how the concentration of the starting **1a** in the reaction mixture could affect the outcome of kinetic control product **2a** (Table 2). We found that reducing the amount of PIL equivalents to *ca.* 3 did not result in a loss of yield (Table 2, entries 2 and 3). Further reducing the excess of HMimNCS to *ca.* 2 equiv. led to incomplete conversion of **1a** (Table 2, entry 4). However, variation of substituents in the starting material affects its solubilisation in SCN-PIL, influencing the reaction rate. Therefore, for further experiments, we

Table 2 Variation of PIL excess for the transformation of **1a** into **2a**



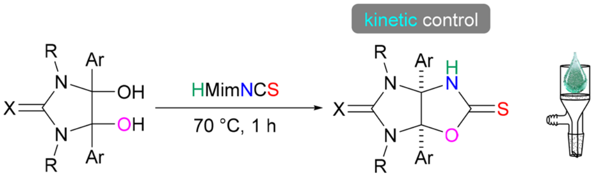
Entry	1a conc., M	PIL equiv.	Yield of 2a [a]
1	1	8.5	84
2	**2**	**4.3**	**87**
3	2.67	3.2	86
4	4	2.1	45[b]

[a] Isolated yield of pure product, %; the reaction mixture was subjected to aqueous work-up, causing the precipitation of products; yields for filtered and dried precipitates are provided. [b] NMR yield, %; incomplete conversion (59%).

used 1 M concentration as the optimal for **1** to **2** transformation.

The key benefit of the designed approach is the straightforward isolation of the resulting products **2**. Their low solubility in water as opposed to the high solubility in water of the second reactant, PIL, makes it possible to precipitate products **2** directly from distilled water in pure form.† This enables their synthesis in an environmentally friendly manner, without the need for organic solvents or column chromatography.

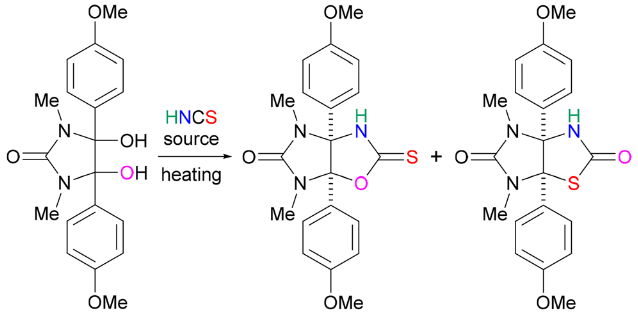
To expand the applicability of the developed procedure, we investigated transformations of a series of 4,5-dihydroxy-4,5-diarylimidazolidine-2-(thi)ones **1** with different substituents both at the nitrogen atoms and in the aromatic ring into imidazo[4,5-*d*]oxazolethiones **2** (Scheme 2). Substrates **1b–i** under heating in HMimNCS at 70 °C typically for 1 h produced the corresponding compounds **2** in high yields (up to 97% for **2g**). Generally, yields of compounds **2** tended to increase with the growth of the side chain, probably due to decreased solubilisation of the products in both SCN-PIL and water upon the work-up step, enhancing their precipitation from aqueous PIL systems. As expected,[14] a gram-scale experiment with **1b** provided **2b** in a higher yield (95% *vs.* 85% at 100 mg scale) due to a reduction in product losses during the aqueous filtration work-up.



1a, X = S, R = Et, Ar = Ph	**2a**, 84%
1b, X = S, R = Me, Ar = Ph	**2b**, 85% (95% gram-scale)
1c, X = O, R = Me, Ar = Ph	**2c**, 86% (2.5 h) [X-ray]
1d, X = O, R = Et, Ar = Ph	**2d**, 87%
1e, X = O, R = *n*-Pr, Ar = Ph	**2e**, 95%
1f, X = O, R = Me, Ar = 4-MeC$_6$H$_4$	**2f**, 90%
1g, X = O, R = Et, Ar = 4-MeC$_6$H$_4$	**2g**, 97%
1h, X = O, R = Me, Ar = 4-FC$_6$H$_4$	**2h**, 83% (4 h)
1i, X = O, R = Et, Ar = 4-FC$_6$H$_4$	**2i**, 86%
1j, X = O, R = Me, Ar = 4-MeOC$_6$H$_4$	**2j**, 88% (40 °C, 2 h; 45 °C, 12 h *kin*:*t/d* = 93:7)
1k, X = O, R = Et, Ar = 4-MeOC$_6$H$_4$	**2k**, 85% (50 °C, 8 h)
1l, X = O, R = *n*-Pr, Ar = 4-MeOC$_6$H$_4$	**2l**, 88%

Scheme 2 Synthesis of oxazolethiones **2** under heating in HMimNCS.

Table 3 Optimisation of reaction conditions for the transformation of donor-arene equipped **1j** into **2j** and **3j**[a]



1j **2j** **3j**

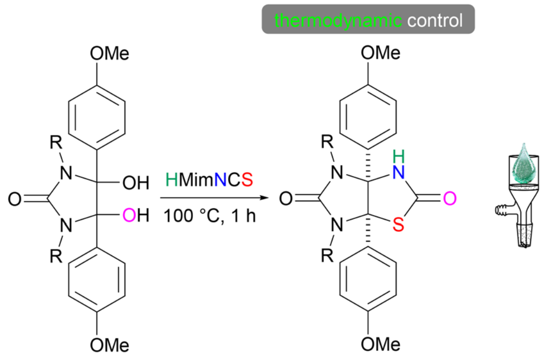
Entry	HNCS source	*T*, °C	Time, h	Yield[b] 1j	2j	3j
1	HMimNCS	70	1	3	72	14
2	HMimNCS	50	1	43	39	—
3	HMimNCS	50	2.5	18	66	3
4	HMimNCS	50	8	2	77	12
5	**HMimNCS**	**40 → 45**	**2 + 12**	—	**81.5**	**6.5**
6	HMimNCS	100	1	—	—	76[c]
7	**Et$_3$N·HNCS**	**100**	**6**	—	—	**83**[c]

[a] 1 M solution of **1j** in PIL; the reaction mixture was subjected to the aqueous work-up; yields for filtered and dried precipitates are provided. [b] NMR yield, %. [c] Isolated yield of pure product, %.

However, after heating of **1j** in HMimNCS at 70 °C for 1 h, we observed a mixture of **2j** and **3j**, with **2j** being predominant, and traces of the starting material (Table 3, entry 1). Therefore, we carried out a new optimisation of the reaction conditions for the conversion of donor-arene equipped dihydroxyimidazolidinone **1j**. We decreased the reaction temperature (Table 3, entries 2–5), but in all cases, the thermodynamic product started to form before the full consumption of the starting material occurred. The best quality of **2j** was achieved by heating **1j** in HMimNCS at 40 → 45 °C for 14 h total (Table 3, entry 5). The oil bath temperature was raised to 45 °C after 2 h due to increasing viscosity of the reaction mixture at 40 °C. Product **2j** contained admixtures of thermodynamic compound **3j** (~7%) and trace amounts of a minor isomer of the starting material **1j**. In contrast, in the case of the same donor-arene equipped **1j**, we obtained thiazoledione **3j** in pure form and good yield by a simple increase of the reaction temperature to 100 °C (Table 3, entry 6). When the reaction was performed in Et$_3$N·HNCS under similar conditions (Table 3, entry 7), **3j** was obtained in better yield (83% *vs.* 76%). With other donor-arene equipped substrates **1k** and **1l** under heating in HMimNCS, **2k** and **2l** were isolated in pure form; the thermodynamic product **3** admixture was not detected in these cases (Scheme 2). Thus, we have significantly expanded the scope of *N*,*N'*-disubstituted imidazo[4,5-*d*]oxazolethiones **2** compared to the seminal publication[18] by varying the nature of *N*-alkyl and arene substituents.[19]

Donor-arene equipped imidazolidine-2-ones **1k** and **1l** had decreased solubilities in Et$_3$N·HNCS, and thus were treated with HMimNCS at elevated temperature (100 °C), which analogously to **1j** provided imidazo[4,5-*d*]thiazolediones **3k** and **3l** (Scheme 3).

After failing to synthesise thiazolones **3** equipped with weak-donor arenes directly from imidazolidine-2-(thi)ones **1**, we attempted to perform the forced rearrangement of **2a** into **3a** (Table 4). The optimal results were achieved in novel 1-methylpyrazolium triflate (HMpzOTf) medium—to the best of our knowledge, the most acidic PIL to date—under heating at 100 °C (Table 4, entry 1). This provided pure **3a** smoothly after simple aqueous work-up in 75% yield. The gram-scale

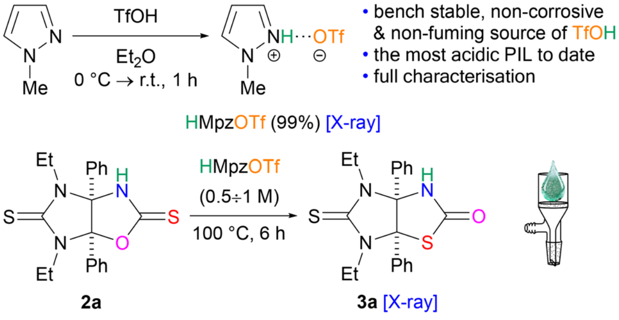


1j, R = Me
1k, R = Et
1l, R = *n*-Pr

3j, 76% (83%, Et_3N·HNCS, 6 h) [X-ray]
3k, 87%
3l, 85% (8 h)

Scheme 3 Synthesis of donor-arene equipped thiazolones **3** under heating in SCN-PILs at 100 °C.

Table 4 Selected optimisations of reaction conditions for the rearrangement of **2a** into **3a**



HMpzOTf (99%) [X-ray]

2a

3a [X-ray]

Entry	Deviations from above	*T*, °C	Time, h	Yield[a] 2a	3a
1[c]	**None**	**100**	**6**	**—**	**75 (97)**[b]
2	HMimNCS (1 M), extraction	100	6	72	—
3[c]	MeOH–HCl (12 M) = 1 : 1, 0.05 M	100	2.5	—	10[b]
4[c]	AcCl (20 equiv.) in MeOH, 5 M	70	5.5	—	28[b]
5[c]	AcCl (20 equiv.) in MeOH, 5 M, evaporation, then aq. crystallisation	70	3	—	79[d]
6	AcCl (20 equiv.) in MeOH, 5 M, evaporation	70	1	13	63[d]
7[c]	HMimCl (10 equiv.)	80 → 100	1 + 4	60	—
8	Et_3N·TfOH (1 M), extraction	120	5	10	34

[a] NMR yield, %. [b] Isolated yield of pure product, %; the value in parentheses corresponds to gram-scale isolated yield of the pure product. [c] The reaction mixture was subjected to the aqueous work-up, causing the precipitation of products; yields for filtered and dried precipitates are provided. [d] Reaction mixture contains inseparable unknown admixtures (*ca.* 20%).

experiment with **2a** gave **3a** in a much higher yield (97% *vs.* 75% at 100 mg scale) due to the reduced product losses during the aqueous filtration. The rearrangement in HMimNCS at 100 °C was unsuccessful, the reaction mixture containing only the starting material and decomposition products (Table 4, entry 2 *vs.* Table 1, entries 1–6). Therefore, we concluded that protic solvents like water (formed during **1a** to **2a** transformation, Table 1, entries 4–7) or alcohols were required in relatively low-acidic conditions to execute the Dimroth-type rearrangement of **2** → **3**. Unfortunately, the MeOH–HCl systems,[20] both aqueous (Table 4, entry 3) and nonaqueous (Table 4, entries 4–6), with various work-up methods, afforded the target product **3a** in low yields or as a mixture with inseparable impurities.

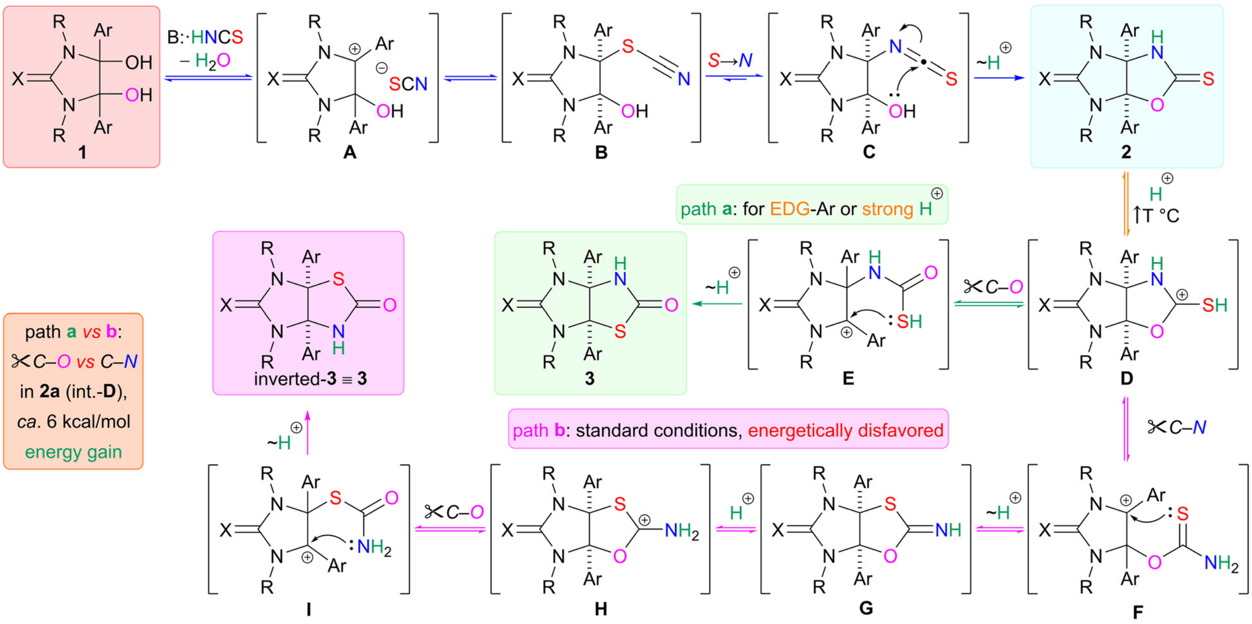
Substituting a hydrochloric acid source with 1-methylimidazolium chloride, HMimCl, did not result in a **2** to **3** rearrangement even at elevated temperatures (Table 4, entry 7). These outcomes can be attributed to insufficient acidity of the HCl-based media, and the arising side processes in the presence of water (Table 4, entry 3) or nucleophilic chloride anion (Table 4, entries 3–7) compared to the 1-methylpyrazolium triflate optimal conditions (Table 4, entry 1).

We then tried another protic ionic liquid, Et_3N·TfOH, which was previously used as a dual-purpose reagent for the ring-opening of DA cyclopropanes with azide ion.[13*b*] Heating of **2a** in Et_3N·TfOH at 120 °C for 5 h (Table 4, entry 8) afforded the mixture of **3a** and the starting material with noticeable weight loss. Thus, deviations from the optimal conditions led to inferior results.

The structures of compounds **2c**, **3a**, **3j**, and HMpzOTf were determined by analyses of their 1D and 2D NMR spectra and were unambiguously confirmed by single-crystal X-ray data (Fig. S1–S4†).

The possible mechanisms for the transformation of 4,5-dihydroxy-4,5-diarylimidazolidine-2-(thi)ones **1** into compounds **2** and **2** to **3** isomerisation are given in Scheme 4. Overall, the **1** to **2** transformation resembles the analogous **I** → **II**.[14] The formation of the kinetically favoured product **2** is proposed to proceed through protonation of either of the diol **1** hydroxy groups and concomitant water elimination, generating carbocation **A**. This undergoes subsequent nucleophilic attack by the thiocyanate sulfur atom, producing thiocyanate **B**, which then rearranges to isothiocyanate **C**.[14] Final assembly of oxazolethiones **2** is achieved *via* intramolecular attack of the remaining hydroxyl on the isothiocyanate moiety.

Since the direct **1** to **3** transformation was not envisioned by us as feasible compared to the **I** → **III** process,[14] only **2** to **3** isomerisation remained probable. Owing to the symmetrical encirclement of thiazolone moiety by substituents in **3**, two rearrangement pathways are possible, granted the aryl-substituents are equipped with electron-donating groups (see Scheme 3), or a strongly acidic medium is employed (see Table 4) to achieve the complete conversion of the starting material and high yields of pure **3** under relatively mild conditions as opposed to Table 1, entries 1, 4–7. According to DFT calculations, C–O bond fission in **2a** (X = S, R = Et, Ar = Ph) is 5.7 kcal mol^{-1} more favourable than C–N bond breaking, ruling out the analogous to **II** → **III**[14,20] path **b**, which is based on two consecutive Dimroth-type rearrangements of thiocarbamate group involving **D** and **F** to **I** intermediates and leading to inverted-**3**. Thus, a straightforward pathway **a** is expected to take place in our case, furnishing thiazolones **3**.



Scheme 4 The possible mechanism for compound **2** formation and **2** to **3** isomerisation.

Conclusions

To summarise, we have developed the chemodivergent method of synthesis of *N*,*N*′-disubstituted imidazo[4,5-*d*] scaffolds—the underexplored oxazolethiones **2** and previously unknown thiazolones **3**—from 4,5-dihydroxy-4,5-diarylimidazolidine-2-(thi)ones **1**, in protic ionic liquids media. PIL served in concert as a source of the nucleophile, reaction medium, and Brønsted acid, initiating the process as a catalyst. The direction of the reaction was controlled by tuning the substituents' electron-donating nature in the starting material while adjusting the reaction temperature. Thus, the library of bioactive scaffolds **2** and **3** was considerably broadened by virtue of several variation points, including chalcogen, *N*-alkyl and arene substituents, which is of potential interest for medicinal chemists. Simple work-up of the reaction mixture with distilled water yielded pure products, enabling synthesis in an environmentally friendly manner. Comparing the designed methodology to the conventional conditions, our procedure avoids the use of toxic solvents like methanol and acetic acid, bypassing high-dilution and recrystallisation procedures, while maintaining high product outcomes at substantially lower loadings and revamping the product scope. The efficiency of the developed procedure is upgraded upon scaling, owing to reduced yield losses during the aqueous filtration work-up. The convenient "just add water" isolation technique could prove valuable for PIL-driven syntheses of *N*,*S*-heterocycles, especially for large-scale laboratory or industrial applications. Finally, we demonstrated the possibility of the forced **2a** → **3a** rearrangement independent of the nature of aryl substituents, introducing the most acidic, as far as we are aware, protic ionic liquid: 1-methylpyrazolium triflate. We hope that the discovery of HMpzOTf will stimulate further studies on the implication of this bench-stable, non-corrosive and non-fuming surrogate of triflic acid in the organic synthesis field.

Author contributions

Valery P. Ermolaev: Investigation. Nina K. Ratmanova: Formal analysis, investigation, methodology, project administration, resources, writing – original draft, writing – review and editing. Vladimir V. Baranov: Investigation, resources, writing – review and editing. Irina I. Levina: Investigation. Victor N. Khrustalev: Investigation. Olga A. Ivanova: Formal analysis, writing – review and editing. Angelina N. Kravchenko: Formal analysis, writing – review and editing. Igor V. Trushkov: Formal analysis, writing – review and editing. Ivan A. Andreev: Conceptualisation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, writing – original draft, writing – review and editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for **2c**, **3a**, **3j** and HMpzOTf have been deposited at the joint CCDC's and FIZ Karlsruhe's service under CCDC 2444500–2444503.†

Acknowledgements

This work was supported by the RUDN University Scientific Projects Grant System, project no. 021411-0-000.

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