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Unusual cyclization of *N*-imidazolyl quinone imines with the formation of thiadiazole ring and its subsequent recyclization

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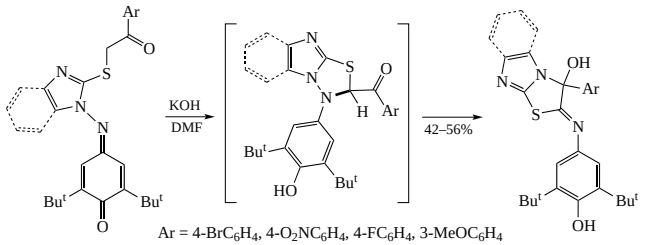
2,6-Di-*tert*-butyl-4-{[2-(2-aryl-2-oxoethylthio)-1*H*-imidazol-1-yl]imino}cyclohexa-2,5-dien-1-ones under the action of bases give products of the 2,3-dihydroimidazo[2,1-*b*]thiazol-3-ol series by subsequent recyclization reaction of the intermediate imidazo[2,1-*b*][1,3,4]thiadiazoles. The structure of imidazo[2,1-*b*]thiazol-3-ol is supported by the X-ray diffraction. The features of the cyclization processes of quinone imine derivatives were stimulated by DFT calculations using the wB97XD/6-311++G method.**



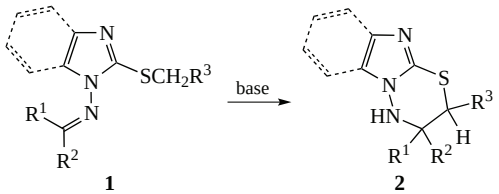
Keywords: *N*-hetaryl quinone imines, recyclization, imidazo[2,1-*b*][1,3,4]thiadiazoles, imidazo[2,1-*b*]thiazoles, DFT calculations.

Derivatives of [1,3,4]thiadiazole and [1,3]thiazole as well as their fused bicyclic analogues find application in medicinal chemistry. Imidazo[2,1-*b*][1,3,4]thiadiazoles and imidazo[2,1-*b*]thiazoles possess anticancer,[1] diuretic,[2] anti-tuberculosis,[3] anti-inflammatory,[4] antifungal[5] and antimicrobial[6] activities. The known methods for their synthesis are based mainly on the reaction of α-halo ketones with 2-amino[1,3,4]thiadiazoles or 2-amino[1,3]thiazoles.[7–10] Previously,[11] the formation of six-membered thiadiazine cycle in the course of base-catalyzed intramolecular cyclization of *S*-alkyl-substituted azole *N*-hetaryl azomethines involving vicinal amino and thiol groups was described. We also reported an intramolecular cyclization of *S*-phenacyl and -benzyl derivatives of *N*-imidazolylimines **1** giving rise to 3,4-dihydro-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazines **2** through the C–C bond formation at thiadiazine ring closing (Scheme 1).[12]

In the present study, we report that in the case of quinone imines **4** the cyclization towards the anticipated spirocyclic imidazo[2,1-*b*][1,3,4]thiadiazines does not occur, and the unexpected formation of the imidazothiazoles of type **5** is observed (Scheme 2).

The starting quinone imines **3** (see Scheme 2) were obtained by the condensation of 1-amino-1*H*-imidazole-2-thiol hydrochlorides or 1-amino-1*H*-benzo[*d*]imidazole-2-thiols with 3,5-di-*tert*-butyl-*p*-quinone. Their subsequent alkylation with phenacyl halides gave *S*-phenacyl derivatives **4**. The structures of compounds **3**, **4** were confirmed by ^{1}H and ^{13}C NMR, and HRMS spectra, while that of **3a** (as well as **5b**, see below) was ultimately established by X-ray study (Figure 1).† In the solid state, molecule **3a** exists in a thione tautomeric form [see Figure 1(*a*)].

Under the action of bases compounds **4** would transform into imidazothiazoles **5**. The proposed mechanism is outlined in Scheme 3. The anionic form **4′** of *S*-phenacyl derivatives formed



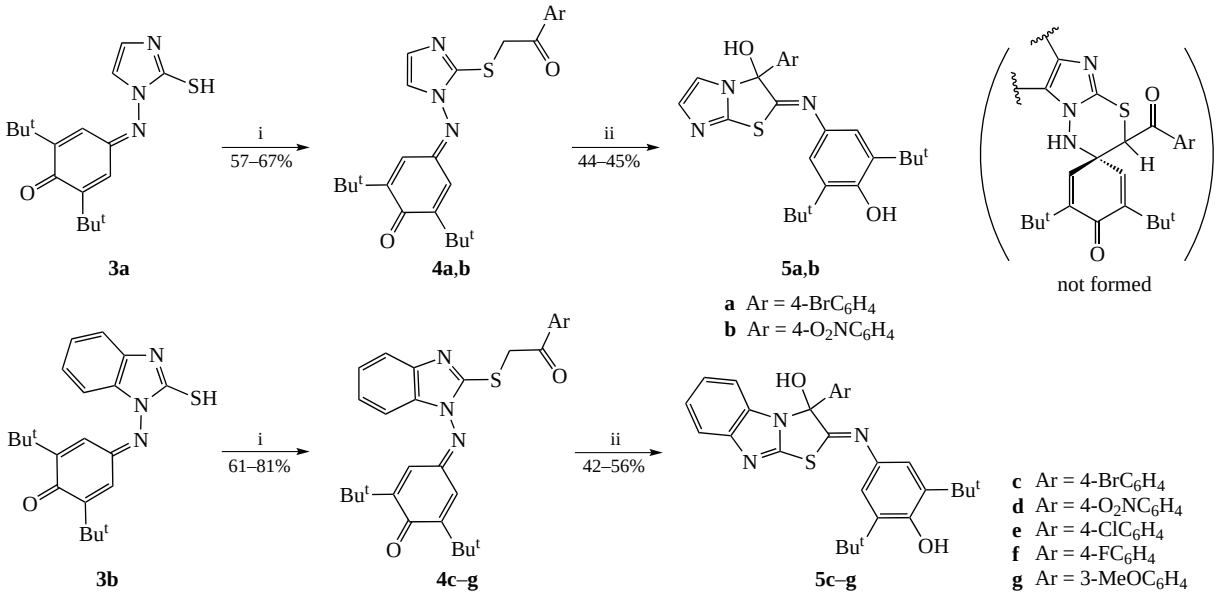
Scheme 1

† *Crystal data for* **3a**. Crystals of $C_{17}H_{23}N_3OS$ (M = 317.44 g mol^{-1}) are monoclinic, space group $P2_1/c$ (no. 14), a = 16.0957(4), b = 10.7722(2) and c = 11.3986(2) Å, β = 104.602(2)°, V = 1912.52(7) Å^3, Z = 4, T = 293(2) K, μ(CuKα) = 1.534 mm^{-1}, d_{calc} = 1.102 g cm^{-3}. 7572 reflections were measured and 7572 independent reflections (R_{sigma} = 0.0141) were used in a further refinement. The final R_1 was 0.0472 [$I > 2\sigma(I)$] and wR_2 was 0.1513 (all data).

Crystal data for **5b**. Crystals of $C_{25}H_{28}N_4O_4S$ (M = 480.57 g mol^{-1}) are monoclinic, space group $P2_1/c$ (no. 14), a = 11.71400(10), b = 9.61590(10) and c = 21.90520(10) Å, β = 90.3090(10)°, V = 2467.38(4) Å^3, Z = 4, T = 293(2) K, μ(CuKα) = 1.482 mm^{-1}, d_{calc} = 1.294 g cm^{-3}. 50172 reflections were measured and 5170 independent reflections (R_{int} = 0.0261, R_{sigma} = 0.0139) were used in a further refinement. The final R_1 was 0.0380 [$I > 2\sigma(I)$] and wR_2 was 0.1070 (all data).

X-ray structural studies were performed on an Agilent SuperNova diffractometer using microfocus X-ray source with copper anode [CuKα (λ = 1.54184)] and Atlas S2 CCD detector at 293 K. Using Olex2,[13] the structures of **3a** and **5b** were solved with ShelXT[14] program using Intrinsic Phasing and refined with the ShelXL[15] using Least Squares minimisation.

CCDC 2109334 and 2109338 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.



3a **4a**,**b** **5a**,**b**

3b **4c–g** **5c–g**

Scheme 2 *Reagents and conditions*: i, $HalCH_2C(O)Ar$, NaOH, MeOH, 40–50 °C, 15 min; ii, KOH, DMF, 50–60 °C, 30 min.

by the action of a base on an activated methylene group is cyclized to imidazothiadiazole **6**. The thiadiazole recyclization reaction starts with the reconstitution of the phenol cycle to quinone imine accompanied by further stabilization of the negative charge in the imidazole ring by the thiadiazole N–N bond cleavage to form an imidazolyl anion intermediate **7**. Then, the imidazolyl *N*-anion interacts with the carbonyl carbon atom forming the thiazole ring followed by its deprotonation, which entails the transformation of the quinone fragment into a phenolic one. A similar recyclization, however of protonated 3-hydroxy-3,9-dihydro-2*H*-benz[4,5]imidazo[2,1-*b*]thiazoles to 3,3,4-trihydroxy-3,4-dihydro-2*H*-benz[4,5]imidazo[2,1-*b*][1,3]thiazinium salts, *via* the formation of β-(*S*-imidazolyl)-containing α-keto aldehydes was reported.[16]

The structural evidence for imidazothiazoles **5** has been obtained from ^1H, ^{13}C, and two-dimensional NMR and HRMS spectra (see Online Supplementary Materials). The structure of compound **5b** was confirmed by single crystal X-ray diffraction [see Figure 1(*b*)]. Note that the racemic mixture of compound **5b** crystallizes to form a centrosymmetric packing arrangement in space group $P2_1/c$.

We succeeded in stopping the reaction at the stage of formation of imidazothiadiazole **6e** by carrying out the cyclization of compound **4e** at reduced temperature. The characteristic signals in the ^1H NMR spectra of thiazoles **5** and thiadiazole **6e** are eighteen-proton singlet of the two *tert*-butyl-

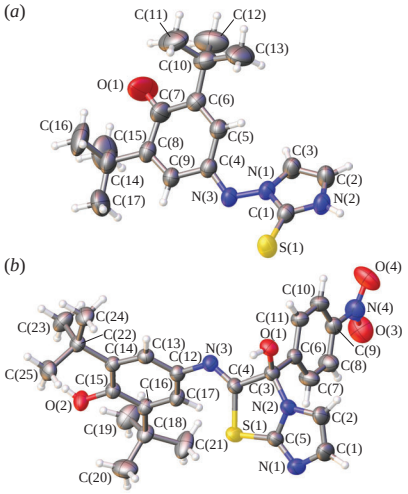
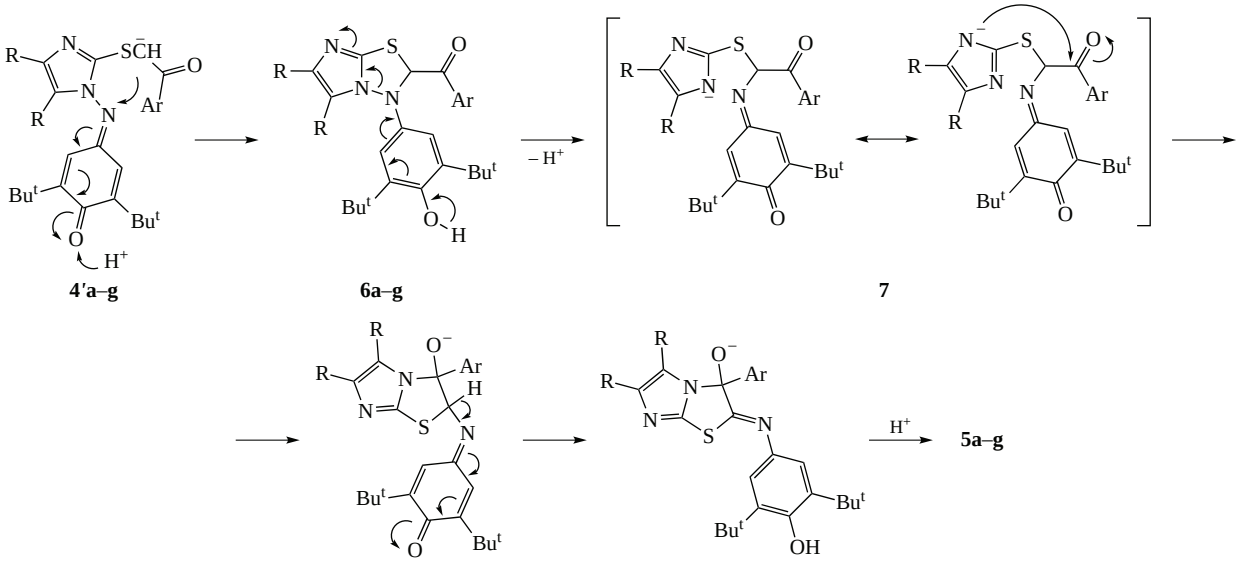


Figure 1 Molecular structure of (*a*) compound **3a** and (*b*) compound **5b** according to XRD data.



4′a–g **6a–g** **7** **5a–g**

Scheme 3

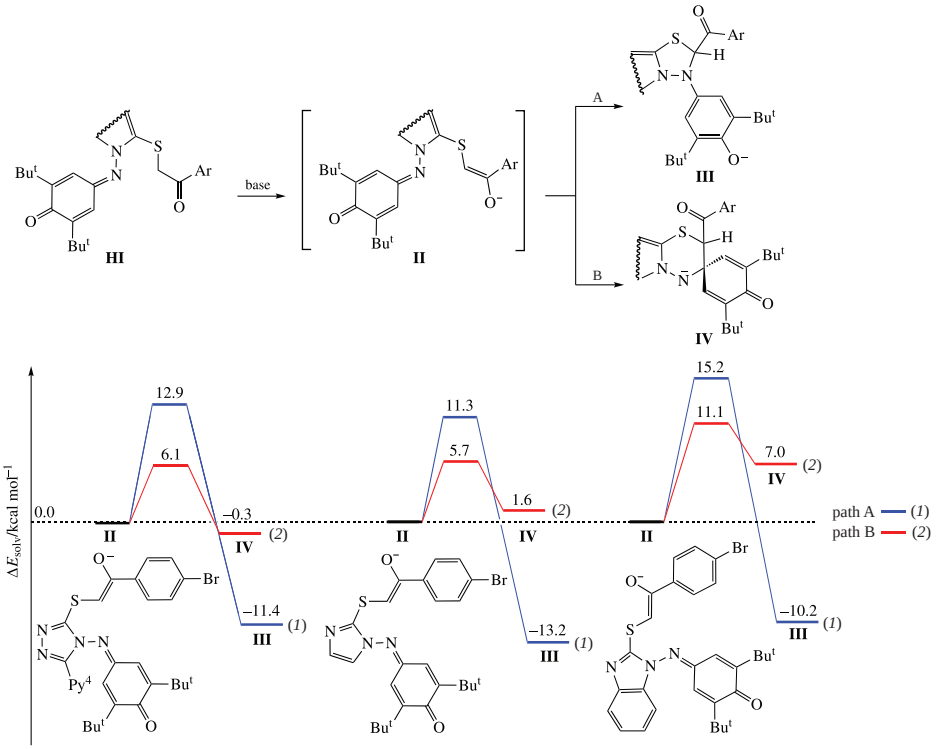


Figure 2 The energy diagrams for cyclization of the anionic form **II** [blue line (*1*) – thiadiazole; red line (*2*) – thiadiazine]. ΔE_{solv} is the relative energy in solvent (EtOH).

groups at 1.4 ppm and two-proton singlet of phenolic ring protons H-2′ and H-6′ at 6.8 ppm. However, in compound **6e**, the H-2 signal of the thiadiazole ring appears at 5.5 ppm, and the phenolic hydroxyl proton signal at 6.0 ppm, while in compounds **5** it migrates to the 7.2–7.3 ppm region, and a proton of thiazole-linked hydroxyl appears at the 8.6–8.9 ppm.

To explain the preferability for an unusual cyclization of quinone imines **4** with the closure of the five-membered ring by the attack of the carbanion on the azomethine nitrogen, rather than with the formation of a six-membered ring as in the case of other imines, we performed quantum chemical calculations. Since previously[17] we observed the similar cyclization with the formation of a dihydrothiadiazole ring for the case of *S*-phenacyl derivatives of 1,2,4-triazolylquinone imines (six examples), we decided to compare the energy profiles of the cyclization reactions of *S*-phenacyl substituted *N*-triazolyl-, *N*-imidazolyl-, and *N*-benzimidazolyl quinoimines. Preliminary calculations (Figure 2) have shown that the hydrogen atom in methylene group of phenacyl substituent has increased acidity and is capable of being easily removed under basic conditions, generating the anionic form of reagent **II** (see Online Supplementary Materials). Therefore, further calculations of the cyclization mechanism were performed for anion **II**.

First of all, it should be noted that the cyclization reactions proceeding both along the pathway **A** and along the pathway **B** are characterized by rather low kinetic barriers (see Figure 2). In all cases and for all directions of cyclization, the activation barriers do not exceed 16.0 kcal mol^{-1}. Even though path **B** is kinetically more preferable for all derivatives, the resulting products **IV** are thermodynamically less stable by 1.6 to 7.0 kcal mol^{-1} than their precursors. Only in the case of pyridyltriazole derivative, the product is stabilized by an insignificant 0.3 kcal mol^{-1}. Analysis of the calculated thermodynamic parameters shows that path **A** is more favorable, since the formation of [1,3,4]thiadiazole ring is accompanied by a decrease in total energy of **II** by 10.2–13.2 kcal mol^{-1}.

To rationalize the obtained picture of regioselectivity of cyclization processes, we performed an NBO analysis. The results obtained show that in the case of phenacyl derivative of quinone imine, the negative charge formed after proton cleavage is localized at the carbonyl oxygen atom of phenacyl substituent, which is depicted by structural formula **II** in Figure 2. During the formation of [1,3,4]thiadiazole ring (pathway A), negative charge is localized at the oxygen atom of quinone fragment, as a result of which the aromaticity of quinone ring is restored and the carbonyl oxygen is reduced into the oxo-form. In the process of closing of the [1,3,4] thiadiazine cycle (pathway B), the negative charge is localized at the imine nitrogen atom of the cycle, while the quinoid structure is retained.

To conclude, the cyclization of quinone imine derivatives of imidazoles was carried out, proceeding through the closure into a thiadiazole ring and its subsequent rearrangement into imidazothiazole. The quantum-chemical modeling of the cyclization reaction mechanism of phenacyl derivatives of quinone imines at the wB97XD/6-311++G** level of theory revealed that even though the formation of thiadiazine ring (path B) is kinetically more preferable than that of the thiadiazole one, the thermodynamic stability of products in this case is insufficient. At the same time, the closure of the thiadiazole ring is kinetically less preferable (path A), but the reaction products formed in this case are much more stable, which is observed in the experiment.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.05.032.

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