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Inverse Neighboring Group Participation: Explanation of an Unusual S→N Alkyl Migration of Isothiuronium Salts Containing a Lactone Group

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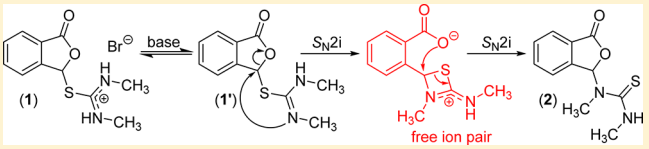
Supporting Information

ABSTRACT: A detailed experimental and DFT study of the *S* to *N* alkyl migration of substituted *S*-(1(3*H*)-isobenzofuranon-3-yl)isothiuronium bromide to *N*,*N*′-dimethyl-*N*-(3-oxo-1,3-dihydro-2-benzofuran-1-yl)thiourea provided evidence for the existence of an unusual double displacement mechanism involving two consecutive back-side S_N2 reactions where a carboxylate anion has a crucial role both as a leaving group as well as an internal nucleophile. The thiazetidine zwitterionic species that is involved in this mechanism as an intermediate was characterized by infrared multiphoton dissociation spectroscopy and was trapped with methyl iodide. It was found that the intermediate has a structure of a free ion pair. The double-displacement mechanism can be considered as a new type of *inverse* lactone neighboring group participation.

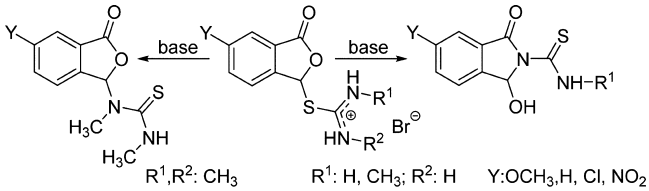


INTRODUCTION

The presence of sulfur atoms in biomolecules is crucial for many biological processes. One of the most important properties of sulfur-containing groups is their nucleophilicity. In particular, the phenomenon of the proximity of sulfur nucleophiles next to nitrogen nucleophiles attracts great attention. It is mainly due to the S→N acyl migration, which is one step of native chemical ligation (NCL) reactions.[1] These reactions enable chemoselective synthesis of large peptides using a concept of the capture/rearrangement of the *N*-terminal cysteine peptides. A similar S→N transfer was also observed during the rearrangement of the glycosyl moiety in glycosylsulfanyloxadiazoles.[2] These reactions are practically important yet very interesting from a mechanistic point of view. Although both reactions can be formally considered as an S→N migration, the proposed reaction mechanisms are completely different.[2,3] The rearrangement of glycosylsulfanyl-oxadiazoles is not fully understood and seems to resemble the extensively discussed mechanism of retaining glycosyltransferases.[4]

In our work, we are constantly dealing with transformation reactions of isothiuronium salts containing either a lactam or a lactone moiety which represent versatile starting materials for synthesis of many important heterocycles including thiazoles, thiazolidines, thiazines, isoindoles, etc.[5,6] Many of these syntheses involve acid−base-catalyzed ring transformations (rearrangements) proceeding under very mild conditions, even at physiological pH.[6] Recently, we have studied an unexpected course of rearrangement of substituted *S*-(1(3*H*)-isobenzofuranon-3-yl)isothiuronium bromides giving either 2*H*-isoindol-2-carbothioamides or *N*,*N*′-dimethyl-*N*-(3-oxo-1,3-dihydro-2-benzofuran-1-yl)thioureas (Scheme 1) depending on substitution at the isothiuronium moiety.[7] The latter reaction represents unusual S→N alkyl migration for which we present a detailed mechanistic study based on a variety of experiments and theoretical calculations including a trapping and spectroscopic characterization of the key reaction intermediate.

Scheme 1. Rearrangement of Substituted *S*-(1(3*H*)-Isobenzofuranon-3-yl)isothiuronium Bromides



RESULTS AND DISCUSSION

The ring transformation of *N*,*N*′-dimethyl *S*-(1(3*H*)-isobenzofuranon-3-yl)isothiuronium bromide (**1**) to *N*,*N*′-dimethyl-*N*-(3-oxo-1,3-dihydro-2-benzofuran-1-yl)thiourea (**2**) can be formally considered as alkyl migration from sulfur to nitrogen.

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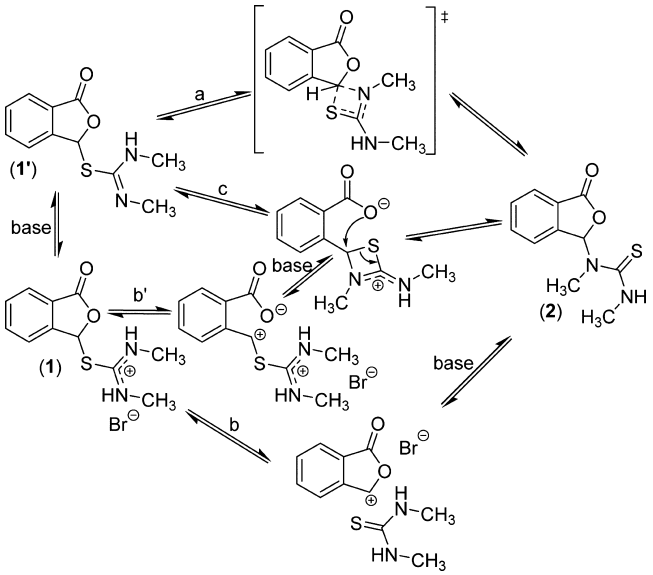
In contrast to the well-known S→N acyl migration[3] in *S*-acylthioureas which takes place via a four-membered ring under mild reaction conditions, a similar S→N alkyl migration has not been observed at all. According to the classical Winstein scheme for nucleophilic substitution reactions, the following four limiting reaction mechanisms (Scheme 2) can be

Scheme 2. Possible Mechanisms of Rearrangement of *S*-(1(3*H*)-Isobenzofuranon-3-yl)isothiuronium Bromide (1)



proposed. First, three possibilities involve intramolecular front-side S_N2 reaction through a four-membered transition state (path *a*) or an intramolecular S_N1 reaction involving rearrangement of the ion pair formed after dissociation of the thiourea moiety (path *b*) or carboxylate (path *b*′). The fourth possibility (path *c*) involves a double-displacement mechanism i.e. two consecutive back-side S_N2 reactions where the carboxylate anion acts as both leaving group as well as internal nucleophile. This reaction pathway involves the formation of a four-membered thiazetidine intermediate.

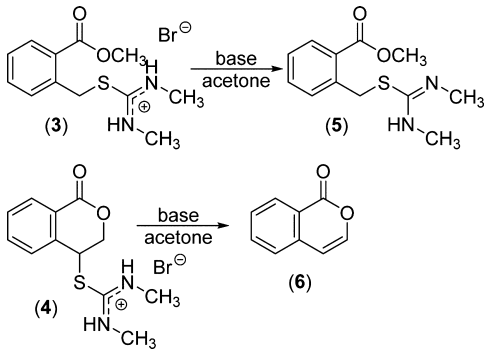
The front-side S_N2 reaction pathway (*a*) belongs to a relatively rarely suggested mechanisms for reactions associated with a retention of the configuration. It was proposed for intramolecular decomposition of alkyl chlorosulfites,[8] for the reaction of cumylarenesulfonates and anilino thioethers with anilines[9] and especially for some glycosyltranferase-catalyzed reactions.[10] On the other hand, an S_N1 reaction proceeding through an intimate ion pair can also explain the retention of configuration.[11] Moreover, most quantum chemical calculations[12] give energy barriers of 170−200 kJ·mol^{-1} higher for front-side attack as compared to the classical back-side S_N2 reaction pathway although the difference steeply decreases for protonated alcohols and amines containing bulky alkyl group.[13] During the transformation following path *b* the oxygen atom can stabilize (by its +M effect) the positive charge at the benzylic carbon of an ion pair. However such stabilization is weak due to cross-conjugation of the lone electron pair on the oxygen atom with the adjacent carbonyl group (as seen from comparison[14] of $\sigma_R(OCH_3)$ = −0.43 and $\sigma_R(OCOCH_3)$ = −0.19). The forth possibility (path *c*) avoids energetically demanding front-side attack as well as cleavage of a relatively poor leaving group (*N*,*N*′-dimethylthiourea). The formation of a four-membered thiazetidine intermediate can be energetically allowed due to the presence of a sulfur atom and hence an easier torsional deformation. In fact four-membered rings containing sulfur atom with bonding angle smaller than 90° have been observed.[15] The double displacement mechanism closely resembles the addition−elimination mechanism occurring during S→N acyl migration[3] in *S*-acylthioureas.

It is well-known that the inversion of absolute configuration is an inherent and consistent characteristic of the bimolecular nucleophilic substitution S_N2. In order to prove or disprove the retention of configuration at carbon C-3 during the rearrangement **1** to **2** we tried to prepare optically pure starting salt **1** using bromide interchange with silver L-tartrate, L-lactate, or camphor sulfonate and crystallization. Unfortunately, we always recovered either the starting racemate of **1** or the product of rearrangement **2**.

Therefore, we have chosen another useful tool which is able to distinguish between the S_N1 and S_N2 reaction mechanisms, i.e., α-secondary kinetic isotope effect (α-SKIE). Typical values[16] of α-SKIE for S_N1 mechanism are around 1.15−1.25 and for S_N2 around unity or even slightly less. In our case, the measured α-SKIE for **1** and its 3-deuterio analogue is 0.95, which shows that there is probably no carbenium ion on the reaction coordinate and the S_N1 mechanism (paths *b* and *b*′) is not involved.

The oxygen atom can, beside its weak stabilizing effect, play another role in the reaction mechanism; it can act as a relatively good leaving group. To get better insight into the reaction mechanism and in order to prove the role of lactone oxygen we studied under same conditions reactions of similar isothiouronium salts **3** and **4** where the double displacement mechanism (analogous to path *c*) is impossible. For both salts, we found that no product of S→N alkyl migration was formed and only free isothiourea **5** or elimination product **6** (1*H*-isochromen-1-one) were isolated (Scheme 3).

Scheme 3. Base-Catalyzed Reaction of *S*-[2-(Methoxycarbonyl)benzyl]-*N*,*N*′-dimethylisothiuronium Bromide (4) and *S*-(1-Oxo-3,4-dihydro-1*H*-isochromen-4-yl)-*N*,*N*′-dimethylisothiuronium Bromide



From both observations, one can conclude that the presence of the oxygen atom adjacent to the benzylic carbon is an essential feature for the S→N alkyl migration which supports the double-displacement mechanism (path *c*).

Important evidence for the suggested double-displacement mechanism in Scheme 2 (path *c*) would be the trapping of the thiazetidine intermediate. Therefore, we added 10-fold excess of methyl iodide into the reaction mixture containing isothiouronium salt **1** along with sodium carbonate in acetone in order to convert the carboxylate anion of the thiazetidine intermediate

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to its methyl ester. The ^{1}H and ^{13}C NMR spectra showed a complicated mixture of products including signals at 3.79 ppm in the ^{1}H and 166.9 ppm in the ^{13}C NMR spectrum whose long-range correlation was confirmed using HMBC NMR technique (see Experimental Section and the Supporting Information). The chemical shifts of these two signals are in a very good agreement with those measured for the analogue compound **3** (3.86 and 167.0 ppm). In addition, the mass spectrum of the reaction mixture contains peak at m/z 250 which corresponds to the *O*-methylated thiazetidine intermediate. Moreover, the increasing concentration of methyl iodide leads to the linear increase of the methyl ester amount (Table 1), which confirms competition between backward intramolecular attack of carboxylate group on the thiazetidine carbon and intermolecular carboxylate attack of the methyl iodide. Unfortunately, all attempts to isolate *O*-methylated thiazetidine intermediate have failed due to its instability.

Table 1. Dependence of the Methyl Ester Content (%) in the Reaction Mixture on the Concentration of Added Methyl Iodide

$c(CH_3I)$ (mol·L^{-1})	methyl ester content (%)	$c(CH_3I)$ (mol·L^{-1})	methyl ester content (%)
0.39	4.2	1.45	14.6
0.76	8.4	2.08	23.7

Further evidence for the existence of the thiazetidine intermediate was obtained in the gas phase using infrared multiphoton dissociation spectroscopy (IRMPD).[17] Compounds **1** and **2** were first analyzed by mass spectrometry and their structures were probed by IRMPD spectrometry, which provides action infrared spectra for the mass selected ions (see the Experimental Section). Prerequisite for the direct observation and investigation of reactive intermediates using mass spectrometry is that the species have to be charged, which is fulfilled for the starting salt **1**.[18] The IRMPD spectrum of the isothiuronium cation **1** in the gas phase agrees well with its theoretical IR spectrum (Figure 1), thereby confirming that the ion is transferred to the gas phase in an identical form as observed in the solid state and in the solution.

Transformation of **1** to the product **2** does not proceed in the form of the salt because of the positively charged isothiuronium moiety, but instead a neutral form (**1′**) has to be generated by addition of a base. Hence, all suggested structures of possible intermediates are neutral; therefore, they can be observed only in their protonated forms. The ions generated from **1** do not readily undergo the rearrangement; therefore, we have also tested a possible reverse transformation from the side of the product **2**.

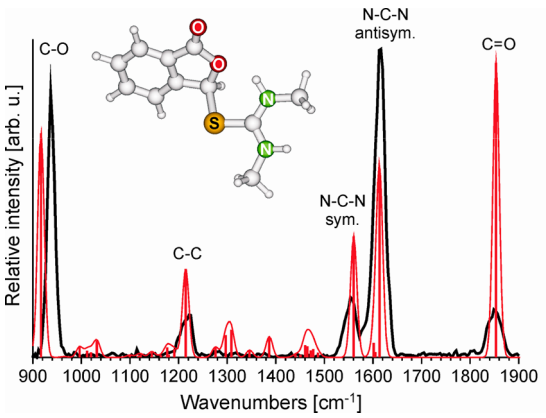

Figure 1. IRMPD spectrum of **1** (black line) and theoretical IR spectrum (red bars, red line represents the theoretical spectrum folded with Gaussian with full width at half-maximum of 16 cm^{-1}).

The electrospray ionization of a methanolic solution of **2** did not lead to the generation of the corresponding ions. However, upon addition of a drop of hydrochloric acid, the protonated ions with the corresponding mass represented the most abundant ions. The IRMPD spectrum of the generated ions (Figure 2) is completely different from that of **2**, which suggests that we have generated different isomeric ions. Comparison of the IRMPD spectrum with the theoretical IR spectrum of the most stable isomer found for protonated **2** (Figure 2a) clearly shows that the protonated ions do not retain this structure. Hence, we have searched for possible structures of intermediates. The IR spectrum of the protonated form of the intermediate suggested in the double-displacement mechanism almost perfectly fits the experimental IRMPD spectrum (Figure 2b). Namely, the intense peaks at about 1670 and 1710 cm^{-1} correspond to the stretching vibration of the exocyclic C−N bond and to the C═O vibration of the free carboxylic group. These two bands were found only for this type of intermediate; IR spectra of all the other structures did not reproduce the experimental results. It is to be noted that a weak band at about 1830 cm^{-1} corresponds to the C═O

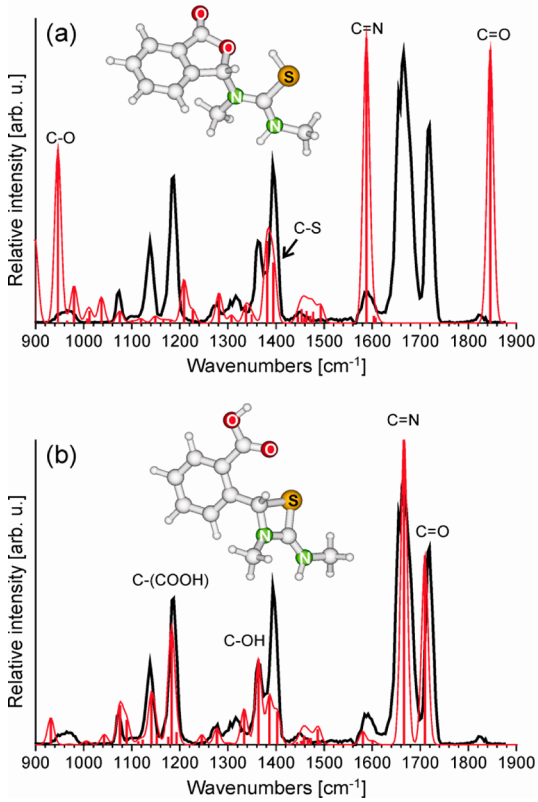

Figure 2. IRMPD spectrum of ions generated from **2** upon addition of HCl (black line) and its comparison with the theoretical IR spectra (red bars, red lines represent the theoretical spectra folded with the Gaussian function with full width at half-maximum of 16 cm^{-1}) of (a) protonated **2** and (b) a possible thiazetidine intermediate (see Scheme 2, path *c*).

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stretching mode of the cyclic lactone (the same band can be also observed in the spectrum of **1** in Figure 1), and hence, we most probably sample a minor population of protonated product **2**.

From the above-mentioned experiments, it can be concluded that the whole lactone group can serve as a relatively good leaving group which is cleaved simultaneously with back-side attack at the benzylic carbon by the isothiourea nitrogen. The intermediate thus formed containing a four-membered thiazetidine ring then undergoes rotation around the C−C single bond which enables the second back-side S_N2 attack at the benzylic carbon atom by the carboxylate anion with sulfur acting as a better leaving group. Such mechanism necessitates substantial rotational freedom of the thiazetidine ring around the C−C single bond as well as rotational freedom of the carboxylate anion. In other words, the zwitterionic thiazetidine intermediate would have the structure of a relatively loose ion pair. The "tightness" of the zwitterionic thiazetidine intermediate was therefore the subject of our further investigation.

In order to evaluate the tightness of the ion pair of thiazetidine intermediate, we prepared[19] the isothiuronium salt **1** labeled at the carbonyl oxygen by the ^{18}O isotope (25% enrichment). If the zwitterionic thiazetidine intermediate formed from this salt would have a relatively rigid structure (tight ion pair) then no scrambling of ^{18}O isotope would occur in the product **2** (i.e., 100% in C═^{18}O) On the other hand, if this intermediate adopts the form of a loose or even free ion pair then statistical scrambling of ^{18}O isotope would be observed (i.e., 50% in C═^{18}O and 50% in C−^{18}O) in product **2**. The last possibility involves synchronous rotation of both thiazetidine and carboxylate groups like two cogwheels which would lead to 100% occurrence of ^{18}O isotope "inside" the lactone ring of product **2** (i.e., 100% in C−^{18}O). The position of ^{18}O isotope in C═^{18}O or C−^{18}O can be easily determined from ^{13}C NMR and IR spectra.

The ^{13}C NMR spectrum of the C═^{18}O enriched isothiuronium salt **1** shows two signals of carbonyl carbon atom (Figure 3) whose ^{18}O-isotope upfield shift is 0.036 ppm,[20] whereas only a single signal is observable for the benzylic carbon atom. Similar information can be gained from the IR spectrum which shows two bands for carbonyl vibrations at 1782 and 1750 cm^{-1} (see the Supporting Information). Completely different results were obtained for the rearranged product **2** where three signals for the carbonyl carbon atom at 168.716 ppm (O═C−O−), 168.704 ppm (O═C−^{18}O−) and 168.681 ppm (^{18}O═C−O−) and two signals for the benzylic carbon atom at 89.957 ppm and 89.928 ppm were observed in the ^{13}C NMR spectrum (Figure 3).

From the same integral intensity of the two latter signals for carbonyl group it can be concluded that the total scrambling has occurred and the structure of thiazetidine intermediate closely resembles that of a free ion pair. This result is also consistent with above-mentioned trapping experiment because only a loose or a free ion pair with a sufficiently long lifetime can effectively attack methyl iodide. The existence of ^{18}O scrambling definitely rules out both pathways *a* and *b* in Scheme 2.

Finally, we also modeled two possible reaction pathways involving the thiazetidine intermediate and the front-side S_N2 attack in the gas phase and in water using Gaussian B3LYP/6-311+G(2d,p) (Figure 4).[21]

While the front-side S_N2 reaction pathway involves a smaller energy barrier in the gas phase, the double displacement

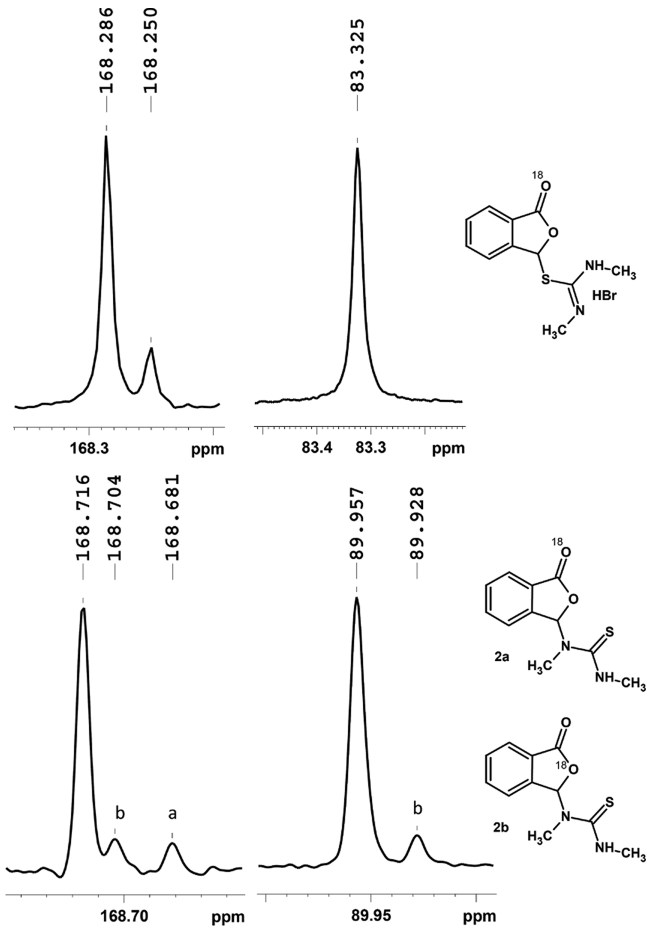

Figure 3. Selected signals in ^{13}C NMR spectra of ^{18}O-enriched compound **1** and **2**.

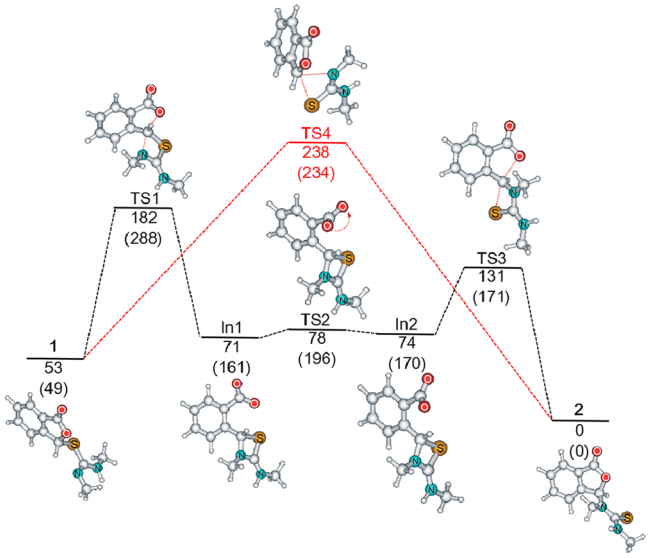

Figure 4. Potential energy surfaces (B3LYP/6-311+G(2d,p) for the transformation of 1 to 2. (a) Double displacement mechanism (black); (b) front-side S_N2 reaction (red). The relative energies are given in kJ·mol^{-1} at 298 K in water and at 0 K in the gas phase (numbers in parentheses).

mechanism involving thiazetidine species is clearly preferred in water. The situation in the gas phase is in good agreement with calculations by Uggerud and co-workers,[13] who showed the

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activation energies for front-side and classical back-side S_N2 reactions in the gas phase approaches. The results in water reveal the first reaction step (i.e., the nucleophilic attack of nitrogen to the benzylic carbon atom accompanied by leaving of the carboxylate group) to be rate limiting with an activation barrier of 129 kJ·mol^{-1}. The second stage of the mechanism involving rotation of the thiazetidine/carboxylate groups has very small activation energy which explains the ^{18}O scrambling in the product **2**. The relatively high activation energies of the forward and backward reaction (57 kJ·mol^{-1} and 111 kJ·mol^{-1}, respectively) indicate sufficient thiazetidine intermediate stability enabling its trapping with methyl iodide.

The rearrangement of **1** to **2** represents a very unusual type of reaction. At first sight it can resemble two well-known phenomena in organic chemistry, i.e., neighboring group participation[22] or degenerate ring transformation reaction.[23] However, the classical neighboring group participation always involves direct interaction of the reaction center with a lone pair of electrons of an atom or with the electrons of a σ- or π-bond contained within the parent molecule but not conjugated with the reaction center to give temporary cyclic intermediate which subsequently decomposes to the noncyclic product. In our case, the reaction sequence proceeds in the reverse direction; i.e., the lactone group behaves as neighboring leaving group first and then as an internal nucleophile in a second step. A ring is temporarily opened and not closed as during classical neighboring group participation. Therefore, we called this process as *inverse* neighboring group participation. To the best of our knowledge, such an inverse neighboring group participation has not yet been published. The reaction also does not fulfill criteria for degenerate ring transformation reaction because such reactions always involve ring-opening and closing caused by the attack of an external nucleophile whose heteroatom is incorporated into the final product but the size of the ring, the kind and number of individual heteroatoms remains unchanged. In our case the internal nucleophile (side chain) undergoes the rearrangement but none of its heteroatoms is incorporated into a heterocyclic ring.

CONCLUSIONS

Treatment of the *N,N′*-dimethylisothiuronium salts derived from 3-bromo-1(3*H*)-isobenzofuranone with bases gives an unexpected product of S→N *S*-(1(3*H*)-isobenzofuranon-3-yl) migration, i.e., *N,N′*-dimethyl-*N*-(3-oxo-1,3-dihydro-2-benzofuran-1-yl)thiourea. A detailed study of this S→N alkyl migration provided an evidence for an unusual double displacement mechanism involving two consecutive back-side S_N2 reactions where a carboxylate anion has a crucial role both as a leaving group as well as an internal nucleophile. The thiazetidine zwitterionic species which is involved in this mechanism as an intermediate was characterized by infrared multiphoton dissociation spectroscopy and was trapped with methyl iodide. It was found that the intermediate has a structure of a free ion pair. The double displacement mechanism can be considered as a new type of *inverse* lactone neighboring group participation which has not yet been reported in the literature.

Our reaction involving carboxylate group assistance can be also considered as model for understanding the nature of preorganizational effects and their relative contributions to the enhanced rates observed in enzymatic reactions[24] because it is well-known that active sites of enzymes very often contain carboxylic groups which acts as a nucleophilic catalysts retaining and inverting glycosyltransferases.[4]

EXPERIMENTAL SECTION

Compounds. Preparation and characterization of *S*-(1(3*H*)-isobenzofuranone-3-yl)isothiuronium bromide (**1**), its 3-deuterio analogue, ^{18}O-labeled analogue, and *N,N′*-dimethyl-*N*-(3-oxo-1,3-dihydro-2-benzofuran-1-yl)thiourea (**2**) was described elsewhere.[7,19]

Starting 4-bromo-3,4-dihydro-1*H*-isochromen-1-one was synthesized from isochromanone[22] according to the procedure described in ref 23: yield 52%; mp 201−203 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14−8.12 (m, 1H), 7.64 (dt, 1H, J = 7.6, 1.6 Hz), 7.54−7.47 (m, 2H), 5.36 (t, 1H, J = 3.2 Hz), 4.75 (dq, 2H, J = 12.4, 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 139.4, 134.4, 130.7, 129.9, 127.3, 123.8, 71.9, 41.0; EI-MS m/z 228 [M + (^{81}Br)], 226 [M + (^{79}Br)], 170, 168, 147 [M$^+$ − Br] (100), 141, 130, 119, 102, 91, 85, 77, 63, 51, 39. Anal. Calcd for $C_9H_7BrO_2$ C, 47.61; H, 3.11; Br, 35.19. Found: C, 47.82; H, 3.17; Br, 35.26.

Methyl 2-(bromomethyl)benzoate[27] was synthesized by radical bromination of the corresponding commercially available methyl 2-methylbenzoate and was used without further purification for synthesis of corresponding isothiuronium salt.

Procedure for the Preparation of Isothiuronium Salts 3 and 4. To a hot solution containing 2.5 mmol of 4-bromo-3,4-dihydro-1*H*-isochromen-1-one or methyl 2-(bromomethyl)benzoate in acetone (10 mL) was added a saturated solution of *N,N′*-dimethylthiourea (2.5 mmol) in acetone (ca. 15 mL). The mixture was refluxed for 5 min and left to stand overnight. Precipitated crystals were collected by filtration.

Transformation of Isothiuronium Salts 3 and 4. Aqueous solution of sodium carbonate (15 mL; c = 1 mol·L^{-1}) was added to the 0.5g of the salt and left to stand for 1 h. After this time, the mixture was extracted by 2 × 20 mL of dichloromethane. Combined extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated.

*S-[2-(Methoxycarbonyl)benzyl]-N,N′-dimethylisothiuronium bromide (**3**):* yield 0.68 g (84%); mp 103−104 °C; ^1H NMR (400 MHz, DMSO) δ 9.58 (bs, 1H), 9.35 (bs, 1H), 7.96 (dd, 1H, J = 7.6, 1.2 Hz), 7.71 (d, 1H, J = 7.2 Hz), 7.66 (dt, 1H, J = 7.6, 1.2 Hz), 7.54 (dt, 1H, J = 7.6, 1.2 Hz), 4.95 (s, 2H), 3.91 (s, 3H), 3.03 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 166.4, 165.7, 135.8, 132.8, 131.5, 130.9, 128.8, 52.4, 34.3, 31.2, 30.9; HRMS calcd for $C_{12}H_{17}N_2O_2S$ 253.1005, found 253.0993. Anal. Calcd for $C_{12}H_{17}BrN_2O_2S$: C, 43.25; H, 5.14; Br, 23.98; N, 8.41; S, 9.62. Found: C, 43.20; H, 4.92; Br, 23.83; N, 8.63; S, 9.37.

*S-(1-Oxo-3,4-dihydro-1H-isochromen-4-yl)-N,N′-dimethylisothiuronium bromide (**4**):* yield 0.47 g (57%); mp 200−202 °C; ^1H NMR (400 MHz, DMSO) δ 9.88 (bs, 1H), 9.44 (bs, 1H), 8.02 (dd, 1H, J = 8.0, 1.2 Hz), 7.80 (dt, 1H, J = 7.6, 1.2 Hz), 7.63−7.71 (m, 2H), 5.65 (s, 1H), 4.95 (dd, 1H, J = 12.8, 2.4 Hz), 4.66 (dd, 1H, J = 12.8, 1.6 Hz), 3.00 (2 × s, 6H); ^{13}C NMR (100 MHz, DMSO) δ 163.1, 162.9, 136.0, 134.7, 130.2, 130.0, 128.2, 124.7, 68.9, 42.5, 31,5, 31.0; HRMS calcd for $C_{12}H_{15}N_2O_2S$ 251.0849, found 251.0841. Anal. Calcd for $C_{12}H_{15}BrN_2O_2S$: C, 43.51; H, 4.56; Br, 24.12; N, 8.46; S, 9.68. Found: C, 43.38; H, 4.67; Br, 24.15; N, 8.26; S, 9.84.

*Methyl 2-[[(dimethylcarbamimidoyl)sulfanyl]methyl]benzoate (**5**):* yield 0.35 g (93%); oil; ^1H NMR (400 MHz, DMSO) δ 7.82 (dd, 1H, J = 12.4, 1.2 Hz), 7.54−7.47 (m, 2H), (dt, 1H, J = 7.6, 1.6 Hz), 4.51 (s, 2H), 3.85 (s, 3H), 2,75 (s, 6H); ^{13}C NMR (100 MHz, DMSO) δ 167.6, 152.8, 139.7, 132.6, 131.7, 130.8, 129.8, 127.9, 52.6, 33.0, 32.6. Anal. Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10; S, 12.71. Found: C, 56.81; H, 6.25; N, 10.92; S, 12.45.

*1H-Isochromen-1-one (**6**).* Compound **6** has the same mp and NMR spectra as reported in ref 28.

Trapping Experiment. To the 25 mL flask were added 0.1 mmol of isothiouronium salt, 200 mg of sodium carbonate, 5 mL of acetone, and 8 mmol (0.5 mL) of methyl iodide. The reaction mixture was refluxed for 4 h, filtered, and evaporated. The resulting oil was analyzed using NMR and MS.

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NMR Experiments. ^{1}H and ^{13}C NMR spectra were recorded on a 400 or 600 MHz Bruker Avance instruments. Chemical shifts δ are referenced to TMS ($\delta = 0$) or solvent residual peaks δ(DMSO-d_6) = 2.50 (^{1}H) and 39.6 ppm (^{13}C), and $\delta(CDCl_3)$ = 7.27 (^{1}H) and 77.0 (^{13}C). $^{1}H-^{13}C$ HMBC NMR experiment was carried out using the manufacturer's settings at 400 MHz with coupling constant 10 Hz.

Mass Spectrometric Experiments. The gas-phase infrared (IR) spectra of mass-selected ions were recorded using an quadrupole ion trap mounted to a free electron laser at CLIO (Centre Laser Infrarouge Orsay, France).[29] The free electron laser (FEL) was operated in the 43.5 MeV electron-energy range, and it provided light in a 900−1900 cm^{-1} range. The relative spectral line width of the FEL is of about 1% and the precision of the measurement of the wavenumbers with a monochromator is about 1 cm^{-1}. Each point in a raw spectrum is an average of 20 measurements. The ions were generated by electrospray ionization from methanolic solution of compounds **1** and **2**. The ions were mass-selected and stored in the ion trap. The fragmentation was induced by 4 to 5 laser macropulses of 8 μs admitted to the ion trap and the dependence of the fragmentation intensities on the wavelength of the IR light gives the infrared multiphoton dissociation (IRMPD) spectra. The reported IRMPD spectra are averages of 2 raw spectra and are not corrected for the power of the free-electron laser, which slightly changes in dependence of the wavenumbers. The positive ions for HRMS spectra were generated by electrospray ionization (ESI) from methanolic solutions and detected in microTOF-Q detector.

Computational details. The calculations were performed using the density functional method B3LYP[30] in conjunction with 6-311+G(2d,p) basis set as implemented in the Gaussian 09 suite.[21] For all optimized structures, frequency analyses at the same level of theory were used in order to assign them as genuine minima on the potential-energy surface. The solvent effect was included using IEFPCM model. The calculated frequencies in the IR spectra were scaled by a factor of 0.98.[31] All geometries, energies, as well as IR spectra can be found in the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

All NMR and IR spectra and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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