JOC The Journal of Organic Chemistry

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Thermal Ring Contraction Reactions of 9-Aryl-5*H*,7*H*-[1,2,5]thiadiazolo[3,4-*h*][2,3,4]benzothiadiazepine 6,6-Dioxides. Experimental and Computational Studies for Understanding the Course of the Transformations

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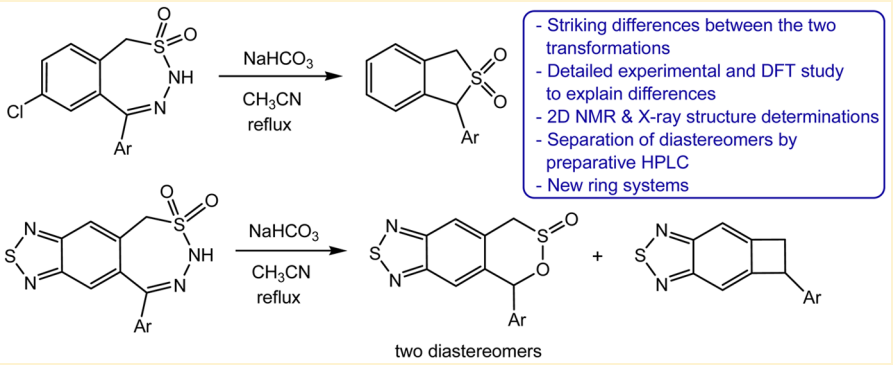
Supporting Information



ABSTRACT: When refluxing with sodium hydrogen carbonate in acetonitrile, 7-chloro-5-(4-fluorophenyl)-1,3-dihydro-2,3,4-benzothiadiazepine 2,2-dioxide afforded, after loss of dinitrogen and subsequent ring contraction, the corresponding sulfone in 83% yield. Similar treatment of the related thiadiazolo-fused tricycles, i.e. 9-aryl-5*H*,7*H*-[1,2,5]thiadiazolo[3,4-*h*][2,3,4]-benzothiadiazepine 6,6-dioxides, resulted in a substantially different product mixture: formation of sultines and benzocyclobutenes was observed, while only small amounts of the sulfones were formed, if any. Density functional theory calculations support the mechanism proposed for the transformations involving a zwitterionic intermediate formed by the tautomerization of the thiadiazepine ring followed by dinitrogen extrusion. When starting from 7-chloro-substituted 2,3,4-benzothiadiazepine 2,2-dioxide, the formation of sulfone via *o*-quinodimethane is the preferred pathway from the zwitterion. However, in the case of thiadiazolobenzothiadiazepine 6,6-dioxides it has been found that the ring closure of the zwitterion leading to the formation of sultines was kinetically preferred over the loss of sulfur dioxide leading to *o*-quinodimethane, which is the key intermediate to benzocyclobutene-type products. The calculations explain the differences observed between the product distributions of the chloro-substituted and the thiadiazolo-fused derivatives.

INTRODUCTION

In a recent publication we disclosed that 7-chloro-5-(4-fluorophenyl)-1,3-dihydro-2,3,4-benzothiadiazepine 2,2-dioxide (**1**), when refluxing with sodium hydrogen carbonate in acetonitrile, afforded 6-chloro-1-(4-fluorophenyl)-1,3-dihydro-2-benzothiophene 2,2-dioxide ("sulfone", **2**) in 83% yield (Scheme 1).[1] A similar ring contraction was observed by King et al. in the case of the only 2,3,4-benzothiadiazepine 2,2-dioxide described earlier, the parent compound **3** itself, when heated at 175−180 °C for 5 min in melt to give 1,3-dihydro-2-benzothiophene 2,2-dioxide (**4**, Scheme 1).[2]

Formation of 3*H*-2,1-benzoxathiole 1-oxide ("sultine", **5**) was observed in the thermolysis of 2*H*-1,2,3-benzothiadiazine 1,1-dioxide (**6**) at 500 °C.[3] It was suggested[2−4] that ring opening of the azosulfone-type tautomer **7** of the starting compound **6** led to diazonium sulfinate **8** which, after loss of dinitrogen and subsequent ring closure, provided sultine **5** (Scheme 2). Supposing a similar transformation of benzothiadiazepine 2,2-dioxide **1**, the formation of sultine **9**

Received: October 10, 2016
Published: January 17, 2017

DOI: 10.1021/acs.joc.6b02463
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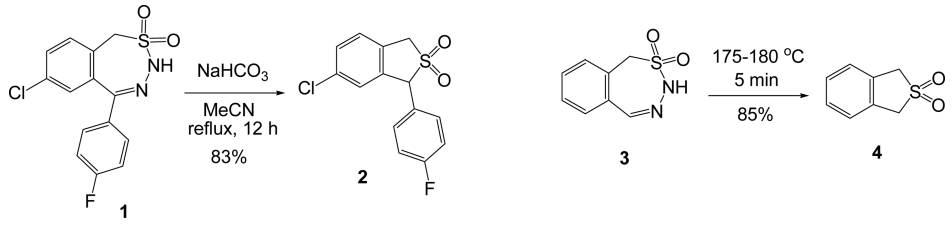
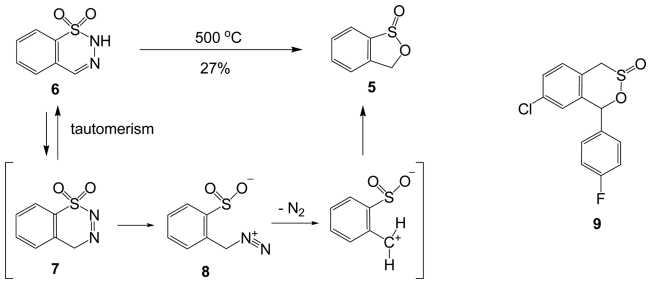
Scheme 1. Thermal Ring Contraction of 1,3-Dihydro-2,3,4-benzothiadiazepine 2,2-Dioxides 1 and 3



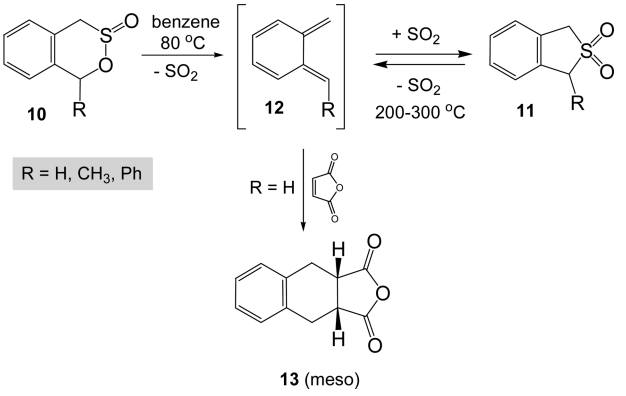
(Scheme 2) would be expected instead of sulfone **2** actually obtained.

Scheme 2. Thermolysis of 2*H*-1,2,3-Benzothiadiazine 1,1-Dioxide (6)



However, Durst et al. demonstrated that 1,4-dihydrobenzo-2,3-oxathiin-3-oxides (**10**), i.e. sultines related to compound **9**, isomerized in boiling benzene (80 °C) to sulfones **11** (Scheme 3). The thermal rearrangement proceeds via 5,6-

Scheme 3. Thermal Rearrangement of Sultine 10 via *o*-Quinodimethane 12



dimethylidenecyclohexa-1,3-diene ("*o*-quinodimethane") **12** formed in a retro-Diels–Alder reaction. The intermediacy of *o*-quinodimethane **12** (R = H) was confirmed by trapping with maleic anhydride to give compound **13**.[5] Sultines (e.g., **10**) were used also by other research groups for the generation of *o*-quinodimethanes under mild conditions, which later could be transformed to fused heterocyclic ring systems by trapping with various dienophyles.[6,7] The synthesis of sultines using the green reagent rongalit (sodium hydroxymethanesulfinate dihydrate) and their application for the generation of *o*-quinodimethanes has been reviewed by Kotha et al.[8a] Recently, compound **10** and its analogues have been used as SO_2 donors under physiological conditions, in order to study the biological role of SO_2.[8b] It is interesting to mention that the cheletropic extrusion of SO_2 from sulfones **11** to regenerate *o*-quinodimethanes **12** requires a much higher temperature (200–300 °C).[5,9,10]

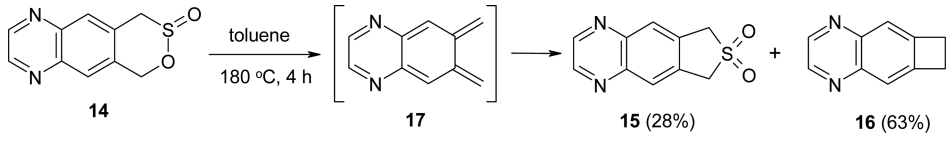
Upon heating sultine **14** at 180 °C in toluene in a sealed tube for 4 h, Chung et al. obtained, in addition to a minor amount of sulfone **15**, 6,7-dihydrocyclobuta[*g*]quinoxaline (**16**, type "benzocyclobutene") as the main product (Scheme 4). The latter product obviously originates from the primarily formed *o*-quinodimethane **17**, the presence of which was also demonstrated by trapping with several dienophiles.[7a] To the best of our knowledge, this is the only example in the literature for the formation of benzocyclobutene-type compounds during the thermolysis of sultines. The same authors also described the synthesis of an isomer of compound **16** exhibiting a cyclobutane ring condensed with the hetero ring of quinoxaline (1,2-dihydrocyclobuta[*b*]-quinoxaline).[7b]

Based on the analogies mentioned above, the transformation of 2,3,4-benzothiadiazepine 2,2-dioxide **1** to sulfone **2**, when refluxing with sodium hydrogen carbonate in acetonitrile, can be explained as follows: tautomerization of compound **1** to **18** followed by ring opening and loss of dinitrogen affords zwitterionic intermediate **19**, which provides sultines **9** (mixture of diastereomers) by cyclization (Scheme 5, route A). Sultines **9** isomerize to sulfone **2** via *o*-quinodimethane **20**. It should be noted that direct formation of **20** and **2** from zwitterion **19** (Scheme 5, routes B and C) cannot be excluded.

RESULTS AND DISCUSSION

The purpose of the present work was to carry out further studies on the chemical behavior of 2,3,4-benzothiadiazepine 2,2-dioxides when heated under various conditions. First we intended to support the reaction mechanism outlined in Scheme 5 by trapping *o*-quinodimethane intermediate **20** in a Diels–Alder reaction. Therefore, 7-chloro-5-(4-fluorophenyl)-1,3-dihydro-2,3,4-benzothiadiazepine 2,2-dioxide (**1**) was

Scheme 4. Thermal Rearrangement of Sultine 14



DOI: 10.1021/acs.joc.6b02463
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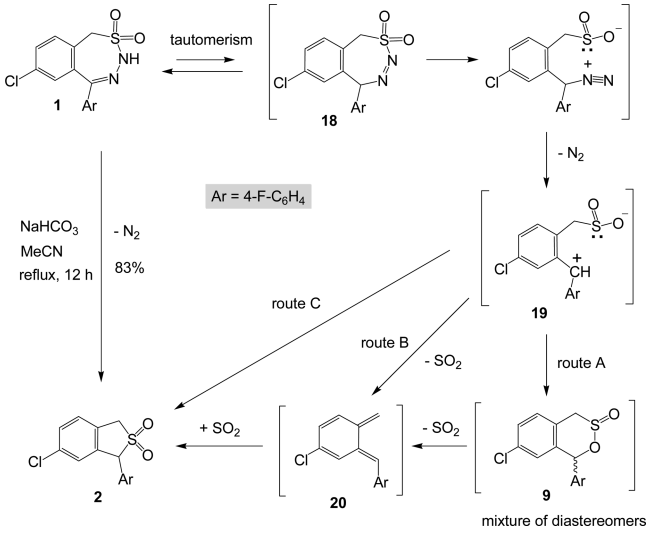
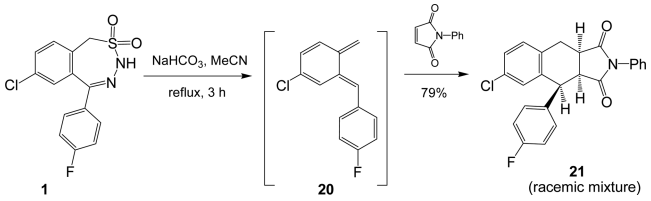
Scheme 5. Supposed Mechanisms for the Thermal Ring Contraction of 2,3,4-Benzothiadiazepine 2,2-Dioxide 1



refluxed for 3 h in acetonitrile in the presence of sodium hydrogen carbonate (10 equiv) and a large excess of *N*-phenylmaleimide (5 equiv). The expected tetrahydrobenzo[*f*]isoindoledione derivative **21** was obtained in good yield (79%, Scheme 6) thus proving the generation of *o*-quinodimethane **20** from compound **1**. The structure of adduct **21** has been characterized also by single crystal X-ray diffraction (Figure 1).

Scheme 6. Trapping of *o*-Quinodimethane Intermediate 20 with *N*-Phenylmaleimide



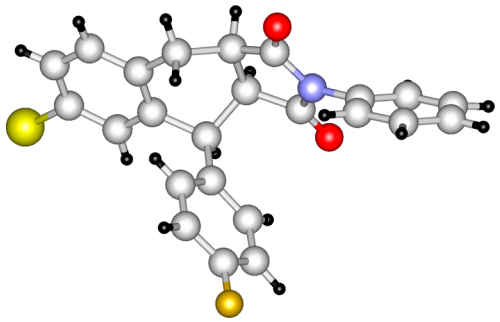
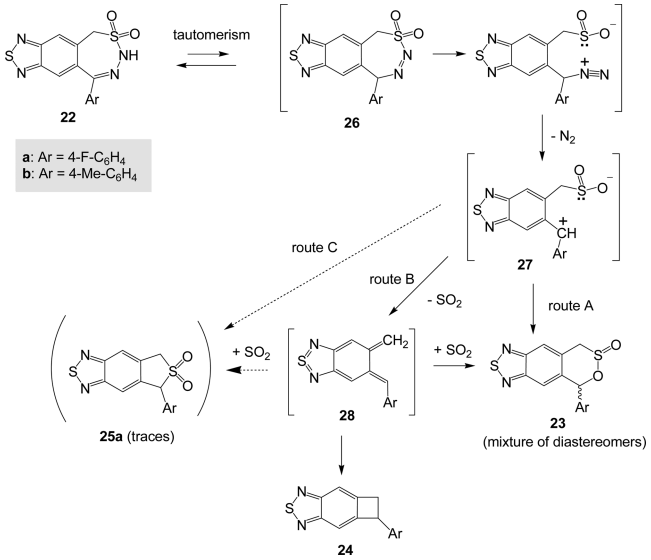


Figure 1. Molecular diagram of **21** (racemic mixture).

In continuation of our studies on the chemical behavior of 2,3,4-benzothiadiazepine 2,2-dioxides, we treated thiadiazolo-fused derivatives **22a**[1,11] and **22b**[11] under reflux for 1.5−2 h in acetonitrile in the presence of sodium hydrogen carbonate (Scheme 7). Substantial amounts of sultines **23** (diastereomeric mixtures) and benzocyclobutenes **24** were formed in both cases (for the yields, see Table 1, entries 1 and 3). When starting from 4-fluorophenyl derivative **22a**, a small amount of

Scheme 7. Supposed Mechanisms for the Thermal Ring Contraction of Thiadiazolobenzothiadiazepines 22



sulfone **25a** was also isolated (entry 1). The diastereomers of **23a** (**23aa**, **23ab**) were separated by preparative HPLC and characterized by single crystal X-ray diffraction (Figure 2). The structure of sulfone **25a** was also determined by X-ray diffraction (see Supporting Information). The stability of sultine diastereomeric mixture **23a** under these conditions was also justified in a separate experiment by refluxing it in acetonitrile (81 °C) in the presence of sodium hydrogen carbonate for 13 h, where no reaction occurred.

Our results obtained in the ring contraction reaction of thiadiazolobenzothiadiazepines **22** are fundamentally different from that found with compound **1**, suggesting a reaction pathway different from that outlined in Scheme 5. Ring opening of tautomer **26** followed by loss of dinitrogen leads to zwitterionic intermediate **27** (Scheme 7), which may be transformed directly to sultines **23** (route A) or to *o*-quinodimethanes **28** (route B). The latter is the intermediate leading to benzocyclobutenes **24**. The formation of sultines **23** may also occur from **28** by hetero Diels−Alder cycloaddition. The negligible formation of sulfones **25** indicates that, contrary to our observation in the case of benzothiadiazepine **1**, neither *o*-quinodimethanes **28** nor zwitterions **27** function as intermediates of the corresponding sulfones **25**.

The presumed tautomerization of compounds **22**, as the introductory step, is supported by the role of sodium hydrogen carbonate in the transformation (Scheme 7). Compound **22a** does not change at all, when refluxing for 30 h in the absence of sodium hydrogen carbonate (Table 1, entry 2). Although the transformation of *p*-tolyl derivative **22b** could be carried out also in the absence of a base providing practically the same product distribution (Table 1, entry 4), it required a much longer reaction time (10 h) than with sodium hydrogen carbonate.

It is worthwhile to mention that, to our knowledge, the ring system of 5,6-dihydrocyclobuta[*f*][2,1,3]benzothiadiazoles **24** is unprecedented in the literature, while for the skeleton of 5*H*,8*H*-[1,2]oxathiino[4,5-*f*][2,1,3]benzothiadiazoles **23**, only one representative, namely compound **29** (Figure 3) has been described.[12]

DOI: 10.1021/acs.joc.6b02463
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Table 1. Conditions and Products of the Thermal Ring Contraction Reactions of Thiadiazolobenzothiadiazepines 22

entry	22–28	Ar	reaction conditions	yield of isolated product 23 (%)	yield of isolated product 24 (%)	yield of isolated product 25 (%)
1	a	4-F-C_6H_4	MeCN, $NaHCO_3$, reflux, 2 h	59	19	2.5
2	a	4-F-C_6H_4	MeCN, reflux, 30 h[a]	starting material 22a recovered		
3	b	4-Me-C_6H_4	MeCN, $NaHCO_3$, reflux, 1.5 h	52	24	0
4	b	4-Me-C_6H_4	MeCN, reflux, 10 h[a]	54	24	0

[a]In the absence of $NaHCO_3$.

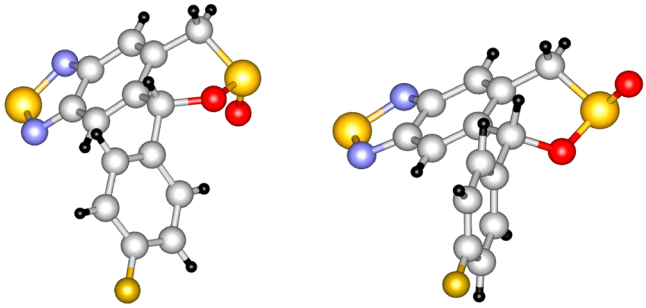
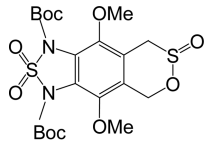


Figure 2. Molecular diagrams of diastereomers **23aa** (left) and **23ab** (right).

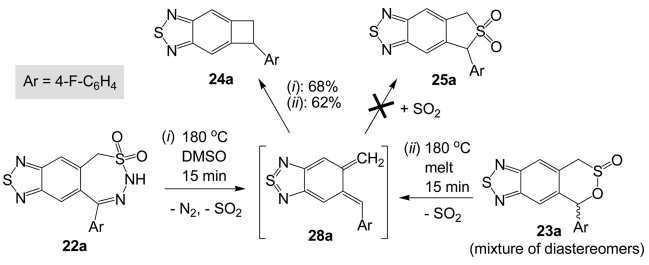


29

Figure 3. The only analogue of compounds **23** appearing in the literature.

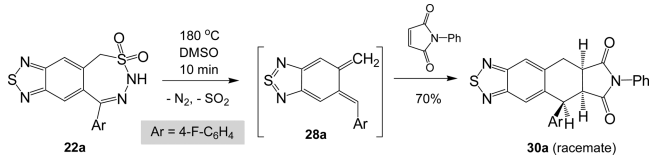
When heating (i) benzothiadiazepine **22a** in DMSO in a stoppered flask at 180 °C for 15 min, or (ii) sultine diastereomeric mixture **23a** at 180 °C for 15 min in melt in a closed vial, the formation of a single product, benzocyclobutene **24a**, was observed (68% and 62%, respectively), demonstrating that under these harsh conditions the cheletropic addition of SO_2 to *o*-quinodimethane **28a** (to give sulfone **25a**) did not compete with the cyclization to benzocyclobutene **24a** (Scheme 8). Consequently, contrary to the analogous literature reactions mentioned above,[5,7a] sultines **23a** do not isomerize to sulfone **25a**.

Scheme 8. Reactions Performed in a Closed System Leading to Benzocyclobutene 24a



o-Quinodimethane intermediate **28a** was trapped with *N*-phenylmaleimide (5 equiv) by heating benzothiadiazepine **22a** in DMSO at 180 °C for 10 min (Scheme 9). The structure of Diels–Alder adduct **30a** has been proven by single crystal X-ray diffraction (Figure 4). It should be noted that, by using various dienophiles, *o*-quinodimethane intermediate **28a** renders the synthesis of several new ring systems possible.

Scheme 9. Trapping of *o*-Quinodimethane Intermediate 28a with *N*-Phenylmaleimide



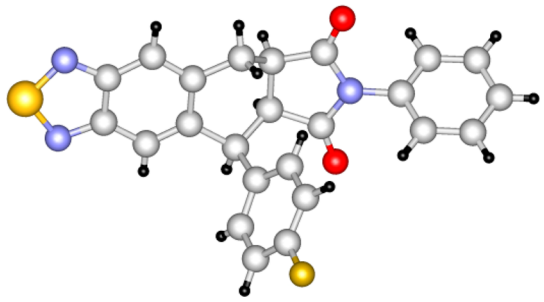


Figure 4. Molecular diagram of **30a** (racemic mixture, one of the conformers).

To shed some light on the reaction mechanism and to provide an explanation for the different outcome of reactions starting from chlorobenzothiadiazepines **1** and from thiadiazolobenzothiadiazepines **22**, density functional theory (DFT) calculations have been carried out. The proposed mechanism to account for the formation of sulfone **2** is depicted in Figure 5. The initial step, i.e. the proton-mediated tautomerization of compound **1** leading to **18**, is endergonic by 12.1 kcal/mol. The formation of **18** is followed by a very fast (2.5 kcal/mol) and very exergonic (−44.6 kcal/mol) dinitrogen extrusion, resulting in the zwitterionic intermediate **19**. Despite the high relative stability of **19** in comparison to **18**, it is anticipated to have a very short lifetime, as the dissociation of SO_2 (route B, see also Scheme 5) and intramolecular ring closure (route C) can proceed with practically no free energy barrier, affording *o*-quinodimethane **20** and sulfone **2** with a reaction free energy of −20.1 and −5.6 kcal/mol, respectively. The intramolecular ring closure of zwitterionic intermediate **19** to sultine **9** (route A) associated with an activation free energy of 4.9 kcal/mol cannot compete with routes B and C.

In route B (Figure 5) the diene **20** is a bifurcation point which can theoretically lead to the substituted benzocyclobutene **31** via an intramolecular ring closure. This step is exergonic by −10.9 kcal/mol with a free energy barrier of 21.8 kcal/mol. The second viable reaction channel is the hetero Diels–Alder cycloaddition between **20** and SO_2 resulting in sultine **9**, which is exergonic as well by −8.7 kcal/mol with a free energy barrier of 8.0 kcal/mol. The third

DOI: 10.1021/acs.joc.6b02463
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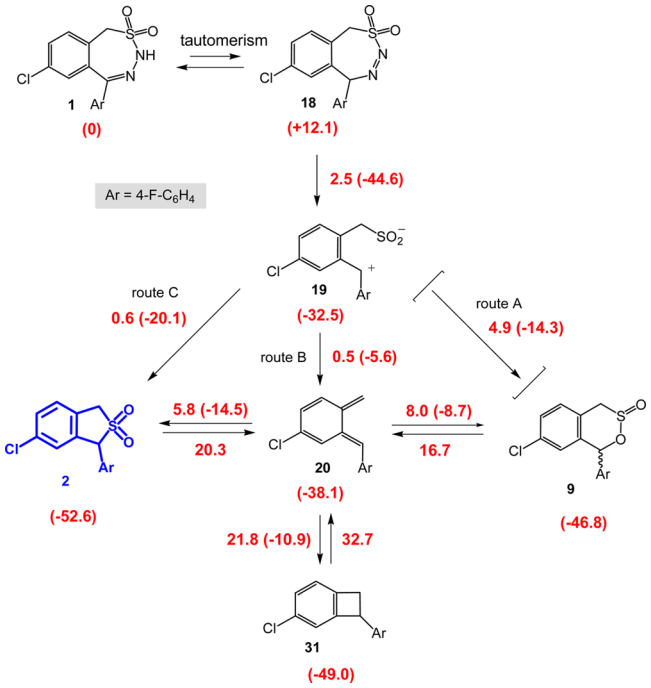

Figure 5. DFT calculations for the transformation of the benzothiadiazepine **1** to sultone **2**, sultine **9** and benzocyclobutene **31** with activation free energies and reaction free energies (in parentheses) for each individual step. Relative free energies for each species are given in parentheses below the structural formulas. All free energies are in kcal/mol. Isolated product **2** is shown in blue color.

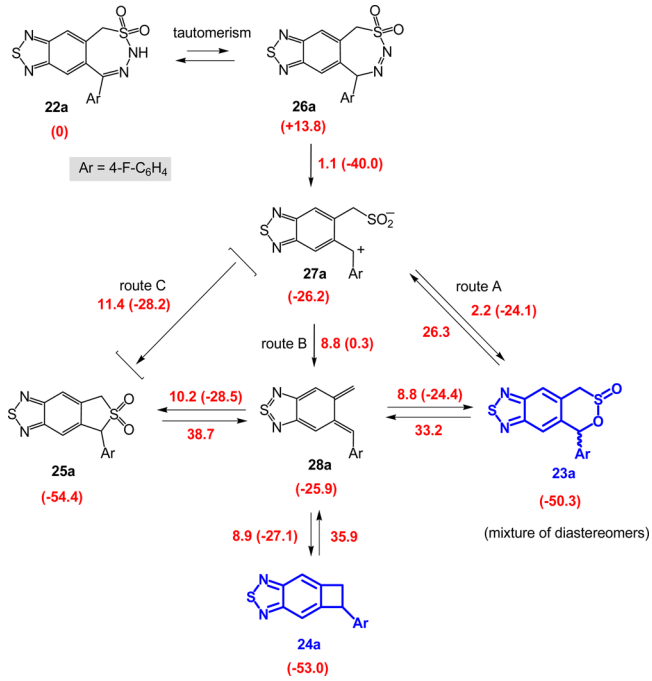

Figure 6. DFT calculations for the transformation of the benzothiadiazepine **22a** to sultone **25a**, sultine **23a**, and benzocyclobutene **24a** with activation free energies and reaction free energies (in parentheses) for each individual step. Relative free energies for each species are given in parentheses below the structural formulas. All free energies are in kcal/mol. Isolated products **23a** and **24a** are shown in blue color.

possible step starting from **20** is the cheletropic addition of SO_2 affording sultone **2**. The rate associated with this process is expected to be much higher than that leading to benzocyclobutene, and even exceeds that of the hetero Diels–Alder reaction, as the activation free energy is merely 5.8 kcal/mol. The cheletropic addition is exergonic as well by −14.5 kcal/mol, meaning that sultone **2** is the global minimum on the potential energy surface of the reaction starting from benzothiadiazepine **1**. After all, according to DFT calculations, it can be stated that sultone **2** is the preferred product both kinetically and thermodynamically, in accord with the experimental results. It can be formed via two possible reaction channels (routes B and C). Nevertheless, in the presence of a dienophile the *o*-quinodimethane pathway (route B) dominates, as demonstrated by the high-yielding formation of the Diels–Alder adduct **21** (Scheme 6). It should be noted that we found no direct route for the interconversion between sultine **9** and sultone **2**. Sordo and co-workers also reported that this type of rearrangement took place with a very high barrier.[13]

The initial step for the interconversion of thiadiazolobenzothiadiazepine **22a** is very similar to that of chloro analogue **1**, starting with the endergonic tautomerization (13.8 kcal/mol) to compound **26a** followed by the formation of the zwitterionic intermediate **27a** via dinitrogen extrusion (Figure 6). The latter process is very exergonic (−40 kcal/mol), proceeding with an activation free energy of 1.1 kcal/mol. In contrast to the zwitterionic chloro-substituted intermediate **19**, the analogous **27a** exhibits different reactivity. The direct transformation of **27a** to sultone **25a** via ring closure (route C, Figure 6) proceeds with a free energy barrier of 11.4 kcal/mol, which makes route C the least preferred pathway among the three alternatives. It is important to mention that resonance structures **19** and **27a** do not represent an adequate description of the electron distribution of the zwitterion. There is a significant delocalization of the negative and especially of the positive charge. The different reactivity of **27a** toward sultone formation in comparison to that of **19** might be interpreted with the natural population analysis (NPA) charges of the carbon atoms substituted with two aryl groups, which is +0.042 in **27a** and −0.022 in **19**. The negative carbon partial charge for the latter may result in a more pronounced attractive force to the positively charged sulfur atom of the SO_2^- moiety (+1.433 and +1.491, respectively).

The intramolecular ring closure of **27a** to sultine **23a** (route A, Figure 6) takes place with a lower activation free energy (2.2 kcal/mol) than that for the formation of chloro analogue **9**. This step is also clearly irreversible with a reaction free energy of −24.1 kcal/mol. The elimination of sulfur dioxide, that is the reaction **27a** → **28a** + SO_2 (route B, Figure 6), is an equilibrium process with a free energy change of 0.3 kcal/mol. Because of this fact and the higher activation free energy associated with this process (8.8 kcal/mol), it can be stated that route A is more preferred both kinetically and thermodynamically than route B and C, unlike in the reaction starting from chloro congener **1**.

However, the significant formation of benzocyclobutene **24a** indicates that route B is also to be taken into account. The three possible reactions starting from diene **28a** show remarkably different relative rates as opposed to those from chloro-substituted diene **20**. All three processes are exergonic and the barriers are quite low in all cases. Cheletropic

DOI: 10.1021/acs.joc.6b02463
J. Org. Chem. 2017, 82, 1895−1903

addition of sulfur dioxide to **28a** is the slowest among the three reactions, in accordance with the negligible formation of sulfone **25a**. The hetero Diels–Alder reaction toward sultine **23a** takes place with a barrier of 8.8 kcal/mol, whereas the ring closure step resulting in benzocyclobutene **24a** proceeds with almost the same activation free energy, namely 8.9 kcal/mol. Thus, the relative rates of these steps are anticipated to be very similar, indicating the formation of comparable amounts of products **23a** and **24a** via diene **28a**. The reason, however, why sultine **23a** is the major product of the reaction is that route A, starting from intermediate **27a**, is the kinetically preferred pathway. It is interesting to mention that the interconversion of sultine **23a** to sulfone **25a**, via either zwitterion **27a** or *o*-quinodimethane **28a**, is hindered by high energy barriers (26.3 and 33.2 kcal/mol).

Comparing the two models subjected to DFT calculation, it is interesting to mention that dienes **20** and **28a** exhibit quite similar reactivities toward hetero Diels–Alder cycloaddition, as reflected by the similar activation free energies (8.0 vs 8.8 kcal/mol). The reactivity toward the cheletropic addition, however, shows a notable difference (5.8 vs 10.2 kcal/mol) which may be attributed to the higher negative partial charge of the substituted methylidene group in **20** than in **28** (−0.141 as opposed to −0.110), thus enabling a stronger attractive interaction toward the positively charged sulfur atom of the SO_2 molecule.

The key intermediates and transition states accounting for the outcome of the interconversion of **27a**, thus for the eventual product distribution, are depicted in Figure 7 including all three possible pathways. The intramolecular ring closure pathway (route A, Scheme 7, Figure 6) involves a transition state (**TS27a–23a**) where the C–S bond is somewhat rotated to get one of the oxygen atoms of the SO_2^- moiety closer to the sp^2 carbon. It is interesting to note that the C–S bond distance in **TS27a–23a** does not change at all compared to that in **27a**, while the distance of the forming C–O bond of the sultine ring is 3.480 Å; thus, **TS27a–23a** can be considered as an early transition state. The C–S distance in **23a** is 1.852 Å which is exactly the same distance as reported by Vogel et al. for the sultine formed in the hetero Diels–Alder reaction of buta-1,3-diene with SO_2.[14]

The transition state **TS27a–28a** is associated with the key step in route B, namely the dissociation of SO_2 from the zwitterionic intermediate **27a**. The C–S bond distance is increased to 2.681 Å in **TS27a–28a** as opposed to 2.076 Å in **27a**. The structure of the remaining diene scaffold is fairly reminiscent of the structure in **27a**; thus, **TS27a–28a** seems to be a late transition state, albeit with a somewhat stronger C–S bond in comparison to the transition state leading to diene **20** (in which the C–S distance is 2.726 Å). This might serve as an explanation why route B is faster than route A for the transformation of **19** while it is not the case for that of **27a**.

It should be noted that, according to the kinetic measurements of Vogel et al.,[14] both the cheletropic addition and the hetero Diels–Alder reaction of SO_2 with 1,2-dimethylidenecyclohexane show a second-order rate with respect to SO_2. In our case, however, the only sources for SO_2 are the zwitterionic intermediates; thus, SO_2 should be present only in a very low concentration and therefore all additional reaction channels involving more than one SO_2 are of negligible relevance.

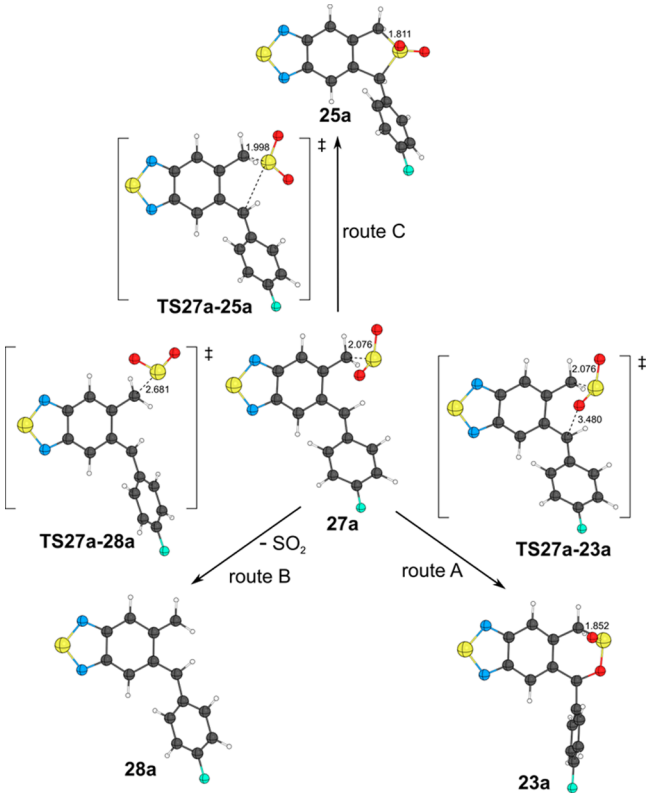

Figure 7. Key intermediates and transition states of the transformation of zwitterionic intermediate **27a** following routes A–C.

CONCLUSION

7-Chloro-5-(4-fluorophenyl)-1,3-dihydro-2,3,4-benzothiadiazepine 2,2-dioxide **1**, when refluxing with sodium hydrogen carbonate in acetonitrile, afforded sulfone **2** in 83% yield. The intermediacy of *o*-quinodimethane intermediate **20** in the course of this transformation has been demonstrated by trapping it with *N*-phenylmaleimide in a Diels–Alder reaction. Similar treatment of a related tricycle, thiadiazolo-2,3,4-benzothiadiazepine 2,2-dioxides **22**, produced a substantially different result: the formation of sultines **23** and thiadiazolobenzocyclobutenes **24** (a new ring system) was found, and only a small amount of sulfone **25a** was isolated. It was shown that *o*-quinodimethane **28a** generated from sultine **23a** did not transform into sulfone **25a**. DFT calculations support the mechanism proposed for the transformations and explain the differences observed in the product distribution. In the case of 7-chloro-substituted 2,3,4-benzothiadiazepine 2,2-dioxide **1** the formation of sulfone **2** is preferred both kinetically and thermodynamically via two possible reaction channels: by ring closure of zwitterionic intermediate **19** and by the intermediacy of *o*-quinodimethane **20**. However, DFT calculations for the transformation of thiadiazolo-2,3,4-benzothiadiazepine 2,2-dioxide **22a** revealed that zwitterion **27a** afforded mainly sultines **23a** in preference to *o*-quinodimethane **28a**, which latter cyclized to thiadiazolobenzocyclobutene **24a**. The formation of sulfone **25a** via cyclization of zwitterion **27a** and/or by cheletropic addition of SO_2 to *o*-quinodimethane **28a** proved to be kinetically unfavorable.

DOI: 10.1021/acs.joc.6b02463
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EXPERIMENTAL SECTION

All melting points were determined on a capillary melting point apparatus and are uncorrected. IR spectra were obtained on a FT-IR spectrometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded at 303 K on various instruments: a 200 MHz (200 and 50 MHz for ^{1}H and ^{13}C NMR spectra, respectively), a 400 MHz (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively), and a 500 MHz spectrometer (500 and 125 MHz for ^{1}H and ^{13}C NMR spectra, respectively). DMSO-d_6 or $CDCl_3$ was used as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. Single-crystal X-ray measurements were carried out on an image plate diffractometer with Cu−K_α radiation. The structures have been deposited at the Cambridge Crystallographic Data Centre under the deposition numbers CCDC 1508587 (**21**), CCDC 1508588 (**23aa**), CCDC 1508586 (**23ab**), CCDC 1508687 (**25a**), and CCDC 1508585 (**30a**). Elemental analyses were performed with microtube elemental analyzers, and the chlorine (and in certain cases the sulfur) contents were determined by titration. EI mass spectra were obtained at 70 eV with a GC-MS instrument. ESI mass spectra were recorded on a quadrupole mass spectrometer−UPLC combination. Separation of product mixtures by flash chromatography was carried out using 40−60 μm silica gel columns. For preparative TLC separations, 20 × 20 cm glass plates coated with silica gel (thickness of adsorbent layer 1.5 mm) were used. The preparative HPLC separation was carried out using an instrument equipped with a UV detector. The reactions were followed by analytical thin layer chromatography on silica gel 60 F_{254}. All reagents were purchased from commercial sources. Analytical samples of new compounds were obtained by recrystallization from the solvents given below in parentheses. All evaporations to dryness were carried out at reduced pressure (ca. 2 kPa). $MgSO_4$ was used as the drying agent.

(3a*RS*,4*RS*,9a*SR*)-6-Chloro-4-(4-fluorophenyl)-2-phenyl-3a,4,9,9a-tetrahydro-1*H*-benzo[*f*]isoindole-1,3(2*H*)-dione (21). A mixture of compound **1**[1] (1.00 g, 3.08 mmol), *N*-phenylmaleimide (2.67 g, 15.4 mmol), sodium hydrogen carbonate (2.50 g, 29.7 mmol), and acetonitrile (50 mL) was refluxed until the starting benzothiadiazepine 2,2-dioxide was consumed (TLC, eluent: DCM). The reaction mixture was allowed to cool to room temperature, sodium hydrogen carbonate was filtered off, and the filtrate was dried and evaporated to dryness. Flash chromatography of the residue (eluent: hexane−EtOAc 7:3) afforded **21** (0.99 g, 79%) as a colorless solid, mp 147−148 °C (EtOH). IR (KBr, cm^{-1}): 1708, 1509, 1380, 1187, 821. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38−7.33 (m, 2H), 7.35−7.30 (m, 1H), 7.28−7.26 (m, 2H), 7.22 (dd, J = 5.3, 8.6 Hz, 2H), 7.17−7.15 (m, 1H), 6.98 (t, J = 8.7 Hz, 2H), 6.79−6.76 (m, 2H), 4.59 (d, J = 6.0 Hz, 1H), 3.60 (dd, J = 6.0, 9.5 Hz, 1H), 3.56−3.50 (m, 1H), 3.37 (dd, J = 6.3, 16.5 Hz, 1H), 3.24 (dd, J = 9.5, 16.5 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.9, 176.1, 162.2 (d, J = 247.6 Hz), 139.5, 133.2, 132.3 (d, J = 3.4 Hz), 131.4, 131.3 (d, J = 7.8 Hz), 130.0, 129.1, 128.7, 128.1, 127.9, 126.3, 115.5 (d, J = 21.5 Hz), 45.7, 45.6, 39.7, 27.5 ppm. MS (EI): m/z (%) = 405 (98) M$^+$, 407 (33) M$^+$, 257 (58), 221 (55), 197 (100), 196 (98). Elemental analysis for $C_{24}H_{17}ClFNO_2$ (405.86): calculated C 71.03, H 4.22, Cl 8.74, N 3.45%; found C 70.87, H 4.34, Cl 8.68, N 3.31%.

Thermal Reactions of 9-(4-Fluorophenyl)-5*H*,7*H*-[1,2,5]thiadiazolo[3,4-*h*][2,3,4]benzothiadiazepine 6,6-Dioxide (22a) under Basic Conditions To Afford 5-(4-Fluorophenyl)-5*H*,8*H*-[1,2]oxathiino[4,5-*f*][2,1,3]benzothiadiazole 7-Oxide (23a) Diastereomers (23aa, 23ab), 5-(4-Fluorophenyl)-5,6-dihydrocyclobuta[*f*][2,1,3]benzothiadiazole (24a), and 5-(4-Fluorophenyl)-5*H*,7*H*-thieno[3,4-*f*][2,1,3]benzothiadiazole 6,6-Dioxide (25a). *Step 1.* A mixture of compound **22a**[1,11] (1.00 g, 2.87 mmol), sodium hydrogen carbonate (1.5 g, 17.8 mmol), and acetonitrile (50 mL) was refluxed until, according to TLC (eluent: DCM−EtOAc 20:1), the starting material **22a** was consumed (2 h). The reaction mixture was allowed to cool to room temperature and evaporated to dryness. The residue was dissolved in DCM (30 mL), washed with water (2 × 10 mL), dried, and evaporated to dryness. The residue was triturated with hot EtOH (20 mL) and after cooling with ice, the precipitate was filtered off to give colorless crystals of **23a** as a diastereomeric mixture [0.54 g, 59%, dr (**23aa**:**23ab**) = 59:41 (HPLC, 220 nm)]. Elemental analysis for $C_{14}H_9FN_2O_2S_2$ (320.37): calculated C 52.49, H 2.83, N 8.74, S 20.02%; found C 52.37, H 2.86, N 8.90, S 20.00%. The diastereomers were separated by preparative HPLC using the following procedure. The diastereomeric mixture (300 mg) was dissolved in acetonitrile (90 mL) at ambient temperature. Addition of water (135 mL) induced slow precipitation overnight. The precipitate was collected and washed (MeCN/water =40/60, 1 mL) to afford diastereomer 1 (142 mg) in 97% HPLC purity (220 nm). The mother liquor enriched in diastereomer 2 was chromatographed on a preparative HPLC column (250 × 50 mm, guard column 15 × 30 mm, particle size 10 μm) using isocratic MeCN/water = 40/60 as eluent at a flow rate of 64 mL/min. The UV detection wavelength was set to 220 nm. Diastereomer 1 eluted first (32.5−39.0 min), completely separating from diastereomer 2 (51.0−62.0 min). The fractions were extracted twice with one tenth of their volumes using dichloromethane, unusually forming an upper organic layer in the first extraction step. The combined organic phases were evaporated to dryness in vacuo on a 40 °C bath. 40 mg of diastereomer 1 and 120 mg of diastereomer 2 were obtained in >99% HPLC purity (220 nm).

*Major Diastereomer (diastereomer 2, 5RS,7RS, **23aa**).* Colorless solid, mp 180−181 °C. IR (KBr, cm^{-1}): 1508, 1224, 1106, 747. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (s, 1H), 7.46 (dd, J = 5.3, 8.6 Hz, 2H), 7.30 (s, 1H), 7.21 (t, J = 8.6 Hz, 2H), 6.02 (s, 1H), 4.38 (d, J = 14.0 Hz, 1H), 4.18 (dd, J = 1.1, 14.0 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.3 (d, J = 249.3 Hz), 154.3, 154.2, 138.1, 132.7 (d, J = 3.7 Hz), 130.9 (d, J = 8.7 Hz), 127.2, 124.0, 120.2, 116.1 (d, J = 22.0 Hz), 80.6, 56.1. MS (LC): m/z = 319 [M − H]$^-$, 301, 271.

*Minor Diastereomer (diastereomer 1, 5RS,7SR, **23ab**).* Colorless solid, mp 170−171 °C. IR (KBr, cm^{-1}): 1509, 1220, 1102, 801. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.46 (dd, J = 5.3, 8.7 Hz, 2H), 7.38 (s, 1H), 7.19 (t, J = 8.5 Hz, 2H), 6.50 (s, 1H), 4.90 (d, J = 15.5 Hz, 1H), 3.91 (dd, J = 1.7, 15.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.2 (d, J = 248.7 Hz), 154.1, 153.7, 140.5 (d, J = 1.0 Hz), 131.5 (d, J = 3.5 Hz), 130.1 (d, J = 8.7 Hz), 130.1, 121.6, 119.5, 116.0 (d, J = 21.9 Hz), 74.2, 59.5. MS (LC): m/z = 319 [M − H]$^-$, 301, 271.

Step 2. The mother liquor of **23a** was evaporated, and the residue was worked up by preparative TLC (DCM−EtOAc 20:1) to yield **24a** (0.14 g, 19%) and **25a** (0.023 g, 2.5%).

*5-(4-Fluorophenyl)-5,6-dihydrocyclobuta[f][2,1,3]benzothiadiazole (**24a**).* Colorless solid, mp 87−88 °C (EtOH). IR (KBr, cm^{-1}): 1508, 1226, 857, 822. ^{1}H NMR (DMSO-d_6, 500 MHz): 7.89 (t, J = 1.5 Hz, 1H), 7.84 (q, J = 1.3 Hz, 1H), 7.41 (dd, J = 5.5, 8.8 Hz, 2H), 7.18 (t, J = 8.9 Hz, 2H), 4.93 (t, J = 5.6 Hz, 1H), 3.88 (ddd, J = 1.3, 7.2, 15.8 Hz, 1H), 3.26 (ddd, J = 1.6, 4.3, 15.9 Hz, 1H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): 161.2 (d, J = 242.7 Hz), 155.3, 155.0, 152.1, 147.7, 137.8 (d, J = 2.9 Hz), 129.0 (d, J = 7.8 Hz), 115.5 (d, J = 21.0 Hz), 115.3, 114.9, 44.5, 37.7 ppm. MS (LC): m/z = 257 MH$^+$, 242, 237, 230, 224, 198. Elemental analysis for $C_{14}H_9FN_2S$ (256.30): calculated C 65.61, H 3.54, N 10.93, S 12.51%; found C 65.23, H 3.54, N 10.87, S 12.55%.

*5-(4-Fluorophenyl)-5H,7H-thieno[3,4-f][2,1,3]benzothiadiazole 6,6-Dioxide (**25a**).* Colorless solid, mp 203−204 °C (Et_2O). IR (KBr, cm^{-1}): 1508, 1306, 1152, 1130. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.10 (s, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.38 (dd, J = 5.1, 8.7 Hz, 2H), 7.18 (t, J = 8.5 Hz, 2H), 5.59 (d, J = 1.8 Hz, 1H), 4.66−4.62 (m, 1H), 4.62−4.57 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) 163.7 (d, J = 250.7 Hz), 154.1, 154.1, 138.3, 132.7, 132.6 (d, J = 8.4 Hz), 124.5 (d, J = 3.0 Hz), 119.9, 119.1, 116.4 (d, J = 21.7 Hz), 70.2, 54.3. MS (LC): m/z = 319 [M − H]$^-$, 271, 255, 243. Elemental analysis for $C_{14}H_9FN_2O_2S_2$ (320.36): calculated C 52.49, H 2.83, N 8.74, S 20.02%; found C 52.49, H 2.86, N 8.56, S 20.46%.

Thermal Reaction of Compound 22a without Base To Afford 24a. A solution of **22a** (100 mg, 0.287 mmol) in DMSO (0.2 mL) was heated in a stoppered vial at 180 °C for 15 min. The

DOI: 10.1021/acs.joc.6b02463
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solution was allowed to cool and poured into water (5 mL). The product, compound **24a** (50 mg, 68%), was isolated by extraction with EtOAc (2 × 3 mL) and purified by preparative TLC (eluent: DCM).

Thermal Reaction of Compound 23a without Base To Afford 24a. Compound **23a** (100 mg, 0.312 mmol) was heated at 180 °C for 15 min in melt in a closed vial. The resulting viscous brown resin was worked up by preparative TLC (eluent: DCM) to afford benzocyclobutene **24a** (50 mg, 62%).

Thermal Reactions of 9-(4-Methylphenyl)-5*H*,7*H*-[1,2,5]-thiadiazolo[3,4-*h*][2,3,4]benzothiadiazepine 6,6-Dioxide (22b) under Basic Conditions To Afford 5-(4-Methylphenyl)-5*H*,8*H*-[1,2]oxathiino[4,5-*f*][2,1,3]benzothiadiazole 7-Oxide (23b) and 5-(4-Methylphenyl)-5,6-dihydrocyclobuta[*f*][2,1,3]benzothiadiazole (24b). A mixture of compound **22b**[11] (1.00 g, 2.90 mmol), sodium hydrogen carbonate (2.50 g, 29.7 mmol), and acetonitrile (100 mL) was refluxed until, according to TLC (DCM–EtOAc 20:1), the starting **22b** was consumed (1.5 h). The reaction mixture was allowed to cool to room temperature and evaporated to dryness. The residue was dissolved in DCM (50 mL), and the solution was washed with water (2 × 20 mL), dried, and evaporated to dryness. The residue was worked up by flash chromatography (eluent: DCM–EtOAc 20:0 → 20:1) to yield **23b** (0.48 g, 52%, after trituration with diethyl ether) and **24b** (0.18 g, 24%). Diastereomers of **23b** (ratio 2:3) could not be separated by flash chromatography under these conditions.

*5-(4-Methylphenyl)-5H,8H-[1,2]oxathiino[4,5-f][2,1,3]benzothiadiazole 7-Oxide (**23b**).* Colorless solid, mp 155–162 °C (dec.). IR (KBr, cm^{-1}): 1512, 1104, 873, 797. ^1H NMR ($CDCl_3$, 500 MHz): δ diastereomer 1 (minor): 8.04 (d, J = 0.7 Hz, 1H), 7.35–7.33 (m, 2H), 7.33 (s, 1H), 7.32–7.28 (m, 2H), 5.98 (d, J = 1.6 Hz, 1H), 4.35 (d, J = 13.9 Hz, 1H), 4.16 (dd, J = 1.5, 13.9 Hz, 1H), 2.44 (s, 3H); diastereomer 2 (major): 7.97–7.95 (m, 1H), 7.43 (d, J = 0.5 Hz, 1H), 7.36–7.34 (m, 2H), 7.30–7.28 (m, 2H), 6.46 (d, J = 0.7 Hz, 1H), 4.84 (d, J = 15.3 Hz, 1H), 3.88 (dd, J = 1.6, 15.3 Hz, 1H), 2.44 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ diastereomer 1: 154.3, 154.3, 139.4, 138.5, 133.7, 129.7, 128.8, 127.5, 123.7, 120.3, 81.4, 56.0, 21.3; diastereomer 2: 154.1, 153.9, 140.8, 139.5, 132.7, 130.2, 129.6, 128.1, 121.5, 119.7, 75.0, 59.4, 21.3 ppm. MS (LC): m/z = 317 MH^+, 253, 225 (both diastereomers). Elemental analysis for $C_{15}H_{12}N_2O_2S_2$ (316.40): calculated C 56.94, H 3.82, N 8.85, S 20.27%; found C 56.87, H 3.86, N 8.97, S 20.11%.

*5-(4-Methylphenyl)-5,6-dihydrocyclobuta[f][2,1,3]benzothiadiazole (**24b**).* Colorless solid, mp 71–72 °C (EtOH). IR (KBr, cm^{-1}): 1510, 1252, 859, 812, 545. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.70–7.68 (m, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 4.82–4.79 (m, 1H), 3.87–3.82 (m, 1H), 3.29–3.23 (m, 1H), 2.34 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.7, 155.4, 152.1, 147.7, 138.5, 136.6, 129.4, 126.8, 115.2, 114.8, 45.6, 38.2, 21.0 ppm. MS (EI): m/z (%) = 252 (20) M^+, 237 (100). Elemental analysis for $C_{15}H_{12}N_2S$ (252.34): calculated C 71.40, H 4.79, N 11.10, S 12.71%; found C 71.40, H 4.85, N 11.22, S 12.53%.

Thermal Reaction of Compound 22b without Base To Afford 23b and 24b. A solution of compound **22b** (0.200 g, 0.58 mmol) in acetonitrile (20 mL) was refluxed for 10 h. The solvent was evaporated, and the residue was worked up by preparative TLC (eluent: DCM–EtOAc 20:1) to yield **23b** (0.099 g, 54%) and **24b** (0.035 g, 24%).

(5*RS*,5a*RS*,8a*SR*)-5-(4-Fluorophenyl)-7-phenyl-8a,9-dihydro-5*H*-isoindolo[5,6-*f*][2,1,3]benzothiadiazole-6,8(5a*H*,7*H*)-dione (30a). A mixture of compound **22a** (0.70 g, 2.00 mmol), *N*-phenylmaleimide (1.73 g, 10.0 mmol), and DMSO (2 mL) was heated at 180 °C for 10 min until **22a** was consumed (TLC, eluent: DCM–EtOAc 20:1). The reaction mixture was allowed to cool to room temperature. Water (60 mL) and EtOAc (30 mL) were added, the mixture was stirred for 5 min, and then the layers were separated. The organic layer was washed with brine (10 mL), dried, and evaporated. Flash chromatography of the residue (DCM–EtOAc 20:1) afforded **30a** (0.61 g, 70%) as a colorless solid, mp 193–194 °C (MeOH). IR (KBr, cm^{-1}): 1711, 1599, 1511, 1384, 1228. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.97 (s, 1H), 7.78 (s, 1H), 7.46 (dd, J = 5.3, 8.7 Hz, 2H), 7.37–7.31 (m, 2H), 7.34–7.30 (m, 1H), 7.06 (t, J = 8.7 Hz, 2H), 4.80 (d, J = 5.3 Hz, 1H), 3.77 (dd, J = 5.4, 9.5 Hz, 1H), 3.67–3.62 (m, 1H), 3.60–3.54 (m, 1H), 3.49–3.43 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.3, 175.9, 162.3 (d, J = 247.6 Hz), 154.3, 154.2, 140.7, 137.4, 132.1 (d, J = 3.4 Hz), 131.8 (d, J = 8.3 Hz), 131.3, 129.1, 128.8, 126.2, 120.2, 119.7, 115.6, 46.1, 45.3, 40.2, 29.7 ppm. MS (LC): m/z = 428 $[M - H]^-$, 410, 400, 386, 335, 309, 281. Elemental analysis for $C_{24}H_{16}FN_3O_2S$ (429.48): calculated C 67.12, H 3.76, N 9.78, S 7.47%; found C 66.84, H 3.77, N 9.80, S 7.52%.

Computational Details. All minima and transition states were optimized employing the M06-L[15] functional developed by Truhlar and Zhao along with the 6-311+G(d,p) basis set[16] using the Gaussian 09 suite of programs.[17] The M06-L functional was found to be accurate for main group thermochemistry, and it is especially accurate for systems with noncovalent interactions.[18] Local minima were identified by the absence of the negative eigenvalues in the vibrational frequency analyses, whereas the Hessian matrix of transition states has only one negative eigenvalue. Intrinsic reaction coordinate (IRC) analyses[19] were carried out at the same level as the geometry optimizations to make sure that the corresponding local minima and transition states are smoothly connected to each other. To estimate the effect of the solvent, all the optimizations were performed employing the SMD solvation model introduced by Truhlar and co-workers[20] with the dielectric constant of ε = 35.688 for acetonitrile. Natural Population Analysis (NPA)[21] has been performed on some key species, employing the GENNBO 5.0 program.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02463.

CIF structure files (atomic coordinates, bond lengths, bond angles, torsion angles) of compounds **21**, **23aa**, **23ab**, **25a** and **30a** (ZIP)

X-ray structure reports (including molecular diagrams) of compounds **21**, **23aa**, **23ab**, **25a** and **30a** (ZIP)

^1H and ^{13}C NMR spectra of compounds **21**, **23aa**, **23ab**, **23b**, **24a**, **24b**, **25a**, and **30a** (PDF)

Computed atomic coordinates and internal energies for all species (PDF)

Special NMR (NOE, NOESY, COSY, HSQC, HMQC, HMBC) spectral data of compounds **21**, **23aa**, **23ab**, **23b**, **24a**, **24b**, and **30a** (PDF)

Thermal ellipsoid plots of compounds **21**, **23aa**, **23ab**, **23b**, **24a**, **24b**, **25a**, **30a** with 50% probability, conditions of the single-crystal X-ray measurements and summarizing table of crystal parameters and refinement metrics (PDF)

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Notes

The authors declare no competing financial interest.

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DOI: 10.1021/acs.joc.6b02463
J. Org. Chem. 2017, 82, 1895−1903