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Transition Metal-Free One-Pot Synthesis of Fused 1,4-Thiazepin-5(4*H*)-ones and Theoretical Study of the S−N Type Smiles Rearrangement Process

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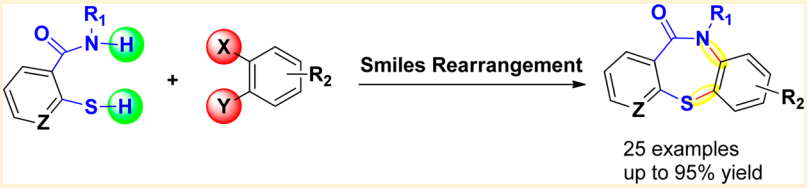
Supporting Information



ABSTRACT: A series of 1,4-thiazepin-5(4*H*)-one derivatives were synthesized via a transition metal-free one-pot Smiles rearrangement process at room temperature. Regioselective seven-membered heterocycles were constructed in good to excellent yields. To gain an in-depth understanding of the S−N type Smiles rearrangement mechanism, a theoretical study was also performed by quantum chemistry calculations.

INTRODUCTION

1,4-Thiazepin-5(4*H*)-one derivatives have attracted a great deal of interest because of their outstanding biological and medicinal properties. Compounds containing thiazepine functionalities have been broadly used to cure all kinds of diseases. For example, clentiazem is an important calcium channel blocker, used in the treatment of angina pectoris and hypertension.[1] Clotiapine acts as an antipsychotic for the treatment of bipolar disorder, depressive disorder, and schizophrenia.[2] Ethyl 4-(11-propyldibenzo[*b*,*f*][1,4]thiazepine-2-carboxamido)piperidine-1-carboxylate (**1**) was reported as a potential inverse agonist.[3] *N*-Hydroxy-6-(11-oxodibenzo[*b*,*f*][1,4] thiazepin-10(11*H*)-yl)-hexanamide (**2**) and its analogues exhibit high antitumor activities (Scheme 1).[4] Fused thiazepine scaffolds also have antimicrobial,[5] anti-inflammatory,[6] antihypertensive,[7] and analgesic activities.[8]

As a result, various methods have been explored for the synthesis of 1,4-thiazepin-5(4*H*)-one scaffolds, including the Friedel−Crafts reaction beginning with 4-chlorobenzenethiol and 2-chloronicotinic acid,[9] the heating of 4,6-dichloropyrimidin-5-amine with benzenethiols,[10] and the copper-catalyzed Ullmann arylations using 2-mercaptobenzoic acid and 1-bromo-4-methoxy-2-nitrobenzene.[11] Ottesen also reported the synthesis of 1,4-thiazepin-5(4*H*)-one derivatives by coupling 4-chloro-1-fluoro-2-nitrobenzene with 2-mercaptobenzoate,[12] and the product was obtained after four steps in low yields. Panda and co-workers assembled these compounds via copper ferrite ($CuFe_2O_4$)-catalyzed cyclizations.[13] However, these methods either need vigorous reaction conditions or involve multiple steps.

A one-step synthetic route would be a very useful improvement. We have been focusing on the development of a direct synthesis of heterocyclic systems using tandem reactions.[14] Herein, we report an efficient and convergent one-pot synthetic strategy approach to 1,4-thiazepin-5(4*H*)-one derivatives under mild conditions. Thiazepine scaffolds were obtained through the reaction of N-substituted 2-mercaptonicotinamides and substituted benzenes at room temperature.

Computational chemistry has been regarded as a valuable tool for elucidating the mechanism of various chemical processes. To improve our understanding of the molecular mechanism of observed Smiles rearrangement products, quantum chemical calculations have been conducted in the framework of density functional theory[15] (DFT) that is one of the most popular tools in electronic structure theory.

RESULTS AND DISCUSSION

Synthesis. To determine the optimized conditions, the 2-mercapto-*N*-(*p*-tolyl)nicotinamide **3c** and 1,2-difluoro-4-nitrobenzene **4a** were chosen as models. As shown in Table 1, the reaction base, solvent, and time were investigated. The reaction proceeded with different bases in DMSO at room temperature, and Cs_2CO_3 provided the highest yields (Table 1, entries 1−6). In strongly basic systems such as NaOH or *t*-KOBu, no desired

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Scheme 1. Structures of Some Biologically Important Thiazepines

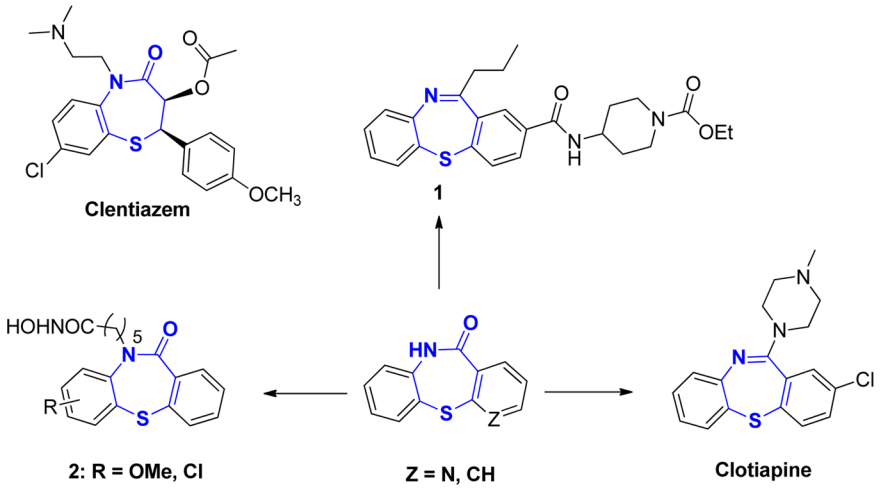
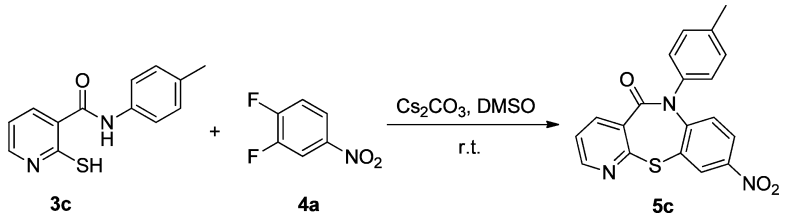


Table 1. Optimization of Conditions[a]



entry	base	solvent	time (h)	yield (%)[b]
1	KOH	DMSO	8	nd
2	NaOH	DMSO	8	nd
3	*t*-BuOK	DMSO	8	nd
4	Et_3N	DMSO	8	nd
5	K_2CO_3	DMSO	8	76
6	Cs_2CO_3	DMSO	6	90
7	Cs_2CO_3	CH_3CN	10	40

[a]Reaction conditions: 2-mercapto-*N*-(*p*-tolyl)nicotinamide **3c** (1.0 equiv), 1,2-difluoro-4-nitrobenzene **4a** (1.0 equiv), base (3.0 equiv). [b]Isolated yields.

product **5c** was obtained (Table 1, entries 1−3). When we used organic base Et_3N in the reaction, no desired compound **5c** was detected either. To construct **5c**, Cs_2CO_3 performed much better than K_2CO_3 with a yield of 90% (Table 1, entries 5 and 6). The investigation on the solvent proved that the yields of the product in DMSO were higher than in CH_3CN with the same base system (Table 1, entries 6 and 7). Finally, we chose Cs_2CO_3 in DMSO as the most efficient system to accomplish the synthesis of the 1,4-thiazepin-5(4*H*)-one derivatives **3** (Table 1, entry 6).

To explore the range of this methodology, various amines were studied (Table 2) under the selected reaction condition (Scheme 2). Structures of products **5a−h** are shown in Figure 1. As shown in Table 2, both aliphatic and aromatic amides led to formation of tricyclic products in high yields. The reactions of 1,2-dihalo-4-nitrobenzene **4** with *N*-aromatic-substituted 2-mercaptonicotinamides (Table 2, entries 5−16) gave yields higher than those of aliphatic 2-mercaptonicotinamides (Table 2, entries 1−4). However, *N*-aromatic-substituted amides with electron-donating groups (Table 2, entries 5 and 6) afforded yields better than the yields of those with electron-withdrawing groups (Table 2, entries 7 and 8).

Additionally, the steric hindrance affected the reaction slightly. *N*-Aromatic-substituted 2-mercapto-*N*-(3,4,5-trimethoxyphenyl)nicotinamide and *N*-(3,5-dimethylphenyl)-2-mercaptonicotinamide (Table 2, entries 13−16) gave high yields of **5** in the reactions. Furthermore, reactions of 2-mercaptonicotinamides with 1,2-difluoro-4-nitrobenzene gave the corresponding products in yields higher than the yields of those with 1,2-dichloro-4-nitrobenzene.

As shown in Table 3, a variety of substituted benzenes **4** were used to expand the applicability of this methodology. A substituted benzene-bearing methyl gave a low yield of 40% in the reaction (Table 3, entry 3), whereas benzenes with electron-withdrawing groups produced higher yields (Table 3, entries 1 and 2). The structures of products **5i−k** are shown in Figure 2.

On the basis of our previous work on Smiles rearrangement chemistry, a plausible reaction mechanism is presented in Scheme 3. Compounds **3** and **4** underwent nucleophilic substitution, providing compound **8**. Then carboxamide anion **9** was formed. Subsequently, intermediate **9** could proceed via two pathways (a and b). Pathway b led to **10** by direct intramolecular cyclization. In contrast, pathway a formed intermediate **11** via Smiles rearrangement followed by an

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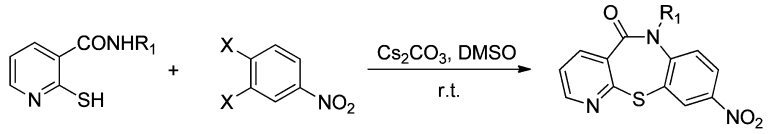
Table 2. Synthesis of 9-Nitrobenzo[*b*]pyrido[3,2-*f*][1,4]thiazepin-5(6*H*)-ones[a]

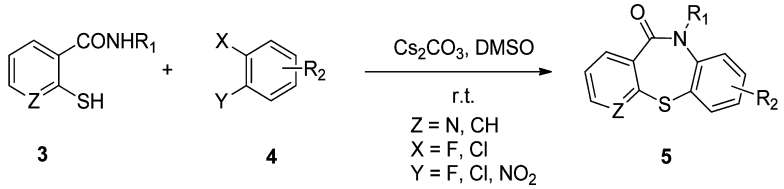


3 4 5

entry	R^1	X	time (h)	product	yield (%)[b]
1	Pr[c]	F	5	**5a**	78
2	Pr[c]	Cl	6	**5a**	65
3	Bu[c]	F	5	**5b**	80
4	Bu[c]	Cl	6	**5b**	78
5	4-MeC_6H_4	F	6	**5c**	90
6	4-MeC_6H_4	Cl	6	**5c**	73
7	4-FC_6H_4	F	6	**5d**	88
8	4-FC_6H_4	Cl	6	**5d**	75
9	4-ClC_6H_4	F	6	**5e**	95
10	4-ClC_6H_4	Cl	6	**5e**	78
11	4-BrC_6H_4	F	6	**5f**	91
12	4-BrC_6H_4	Cl	6	**5f**	76
13	3,5-dimethylphenyl	F	6	**5g**	95
14	3,5-dimethylphenyl	Cl	6	**5g**	80
15	3,4,5-$(MeO)_3C_6H_2$	F	6	**5h**	90
16	3,4,5-$(MeO)_3C_6H_2$	Cl	6	**5h**	76

[a]Reaction conditions: 2-mercaptonicotinamides **3** (1.0 equiv), 1,2-dihalo-4-nitrobenzene **4** (1.0 equiv), Cs_2CO_3 (3.0 equiv). [b]Isolated yields. [c]Pr and Bu stand for propyl and butyl, respectively.

Scheme 2. Synthesis of 1,4-Thiazepin-5(4*H*)-one Derivatives



3 4 5

intramolecular nucleophilic substitution with a loss of a fluorine atom, leading to the corresponding product **5**. To demonstrate this mechanism, the molecular structure of product **5e** was determined by X-ray crystallographic analysis (Figure 3).

In addition, to extend the substrate scope, 2-mercaptobenzamides **6** were treated with different substituted aromatic compounds **4**, and the results are shown in Table 4. A variety of *N*-aryl-substituted 1,4-thiazepin-5(4*H*)-ones **7** were obtained in good to excellent yields.

Theoretical Results. Scheme 3 schematically shows the Smiles rearrangement pathway (pathway a) and the direct nucleophilic substitution pathway (pathway b). Table 5 gathers optimized geometries of minimal and transition states along two pathways, and Figure 4 gives calculated relative free energy profiles. R denotes the most stable geometry of the anionic reactant.

However, to perform subsequent transformation via the *ipso*-Smiles rearrangement (pathway a) or the direct nucleophilic substitution (pathway b), R must be converted to its conformational isomer, R′, which lies above R by 7.9 kcal/mol. Intrinsic reaction coordinate (IRC)[5,6] calculations indicate that R′ is the common starting point along with two pathways, in which the negatively charged N3 atom is ready to attack C1 or C2.

TS1 corresponds to the transition state in which N3 is nucleophilically attacking the positively charged C1. The forward product from TS1 is IM1, a metastable intermediate located on the potential energy surface, where the C−N bond has formed and the C1−S bond has broken. The free energy barrier from R to IM1 is calculated to be 14.2 kcal/mol.

Once formed, IM1 would be immediately brought to a stable intermediate IM2, which lies below R by 13.7 kcal/mol. Subsequently, IM2 is converted into the precursor of Smiles rearrangement product, P_a, via TS2 with a free energy barrier of 36.1 kcal/mol. In TS2, the C2−S bond is forming and the C−F bond is breaking. From Figure 4, it is clear that the Smiles rearrangement pathway (pathway a) consists of two elementary steps, and the second step is the rate-determining step.

Alternatively, if the reaction proceeds via the direct nucleophilic substitution pathway (pathway b), the transition state involved is TS3, which lies above R by 22.6 kcal/mol. Compared to TS1 involved in pathway a, TS3 is energetically less favorable by 8.4 kcal/mol. Therefore, from an energetic point of view, R prefers to evolve along pathway a, resulting in P_a, rather than along pathway b to form P_b. The calculated results are in good agreement with the experimental observation that the *ipso*-Smiles rearrangement product is substantially predominant over the ortho position nucleophilic substitution product.

CONCLUSION

In conclusion, a variety of benzo[*b*]pyrido[3,2-*f*][1,4]thiazepin-5(6*H*)-one and dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-one deriv-

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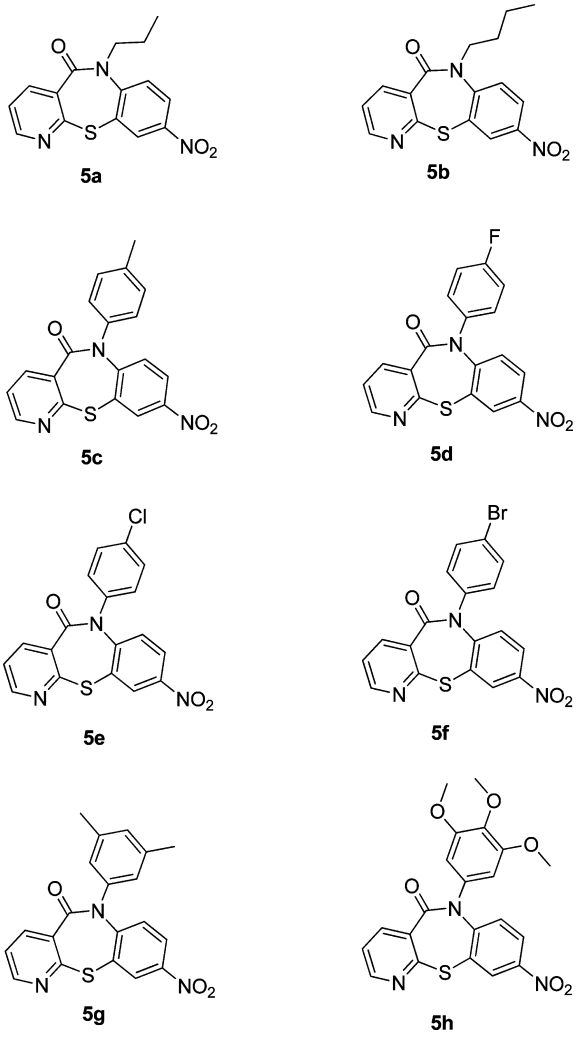


Figure 1. Structures of desired compounds **5a–h**.

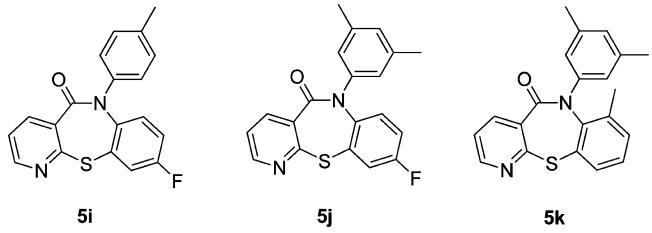


Figure 2. Structures of desired compounds **5i–k**.

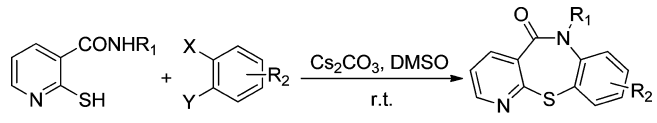
atives were synthesized in good to excellent yields via Smiles rearrangement. The tricyclic systems were constructed by an efficient one-pot transition metal-free process at room temperature. Furthermore, to gain a better understanding of the reaction mechanism, a theoretical study was performed by quantum chemistry calculations. The results show that the Smiles rearrangement pathway has a barrier that is lower by 14.2 kcal/mol^{-1}; thus, it is energetically more favorable than the direct intramolecular nucleophilic substitution pathway. This green and clean synthetic methodology has potential applications in the synthesis of biologically and medicinally relevant compounds.

EXPERIMENTAL SECTION

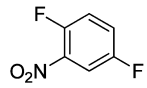
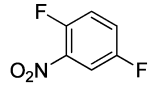
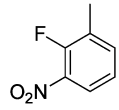
General Procedure. ^{1}H and ^{13}CNMR spectra were recorded with a 300 spectrometer or a 400 spectrometer in $CDCl_3$. HRMS spectra were recorded on a Q-TOF spectrograph. Compounds **3a–h** were prepared according to the literature. Other reagents (Adamas) were commercially available and were used without further purification. All reactions were monitored by thin-layer chromatography (TLC).

Computational Methods. All calculations were conducted using the B3LYP functional[16,17] combined with the 6-311+(d,p) basis set, as implemented in Gaussian 03.[18] Vibrational analyses at the same level of theory were also conducted to confirm all stationary points as minima (zero imaginary frequencies) or first-order saddle points (one imaginary frequency) and to provide free energies at 298.15 K. Solvent effects have also been taken into account by calculating the single-point energies of the geometries obtained in the gas phase by using the simple self-consistent reaction field (SCRF) method[19] based on the polarizable continuum (PCM)[20] model. Dimethyl sulfoxide (DMSO)

Table 3. Synthesis of Benzo[*b*]pyrido[3,2-*f*][1,4]thiazepin-5(6*H*)-one Derivatives[a]



3 4 5

Entry	R^1	4	Time (h)	Product 5	Yield (%)[b]
1	4-MeC_6H_4		6	**5i**	83
2	3,5-Dimethyl phenyl		6	**5j**	93
3	3,5-Dimethyl phenyl		8	**5k**	40

[a]Reaction conditions: 2-mercaptonicotinamides **3** (1.0 equiv), substituted benzenes **4** (1.0 equiv), Cs_2CO_3 (3.0 equiv). [b]Isolated yields.

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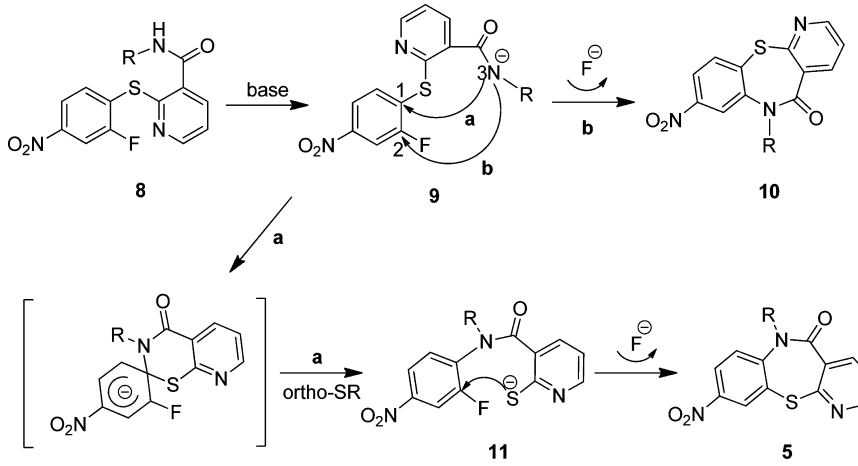
Scheme 3. *ipso*-Smiles Rearrangement (pathway a) versus the Direct Nucleophilic Substitution at the Ortho Position (pathway b)



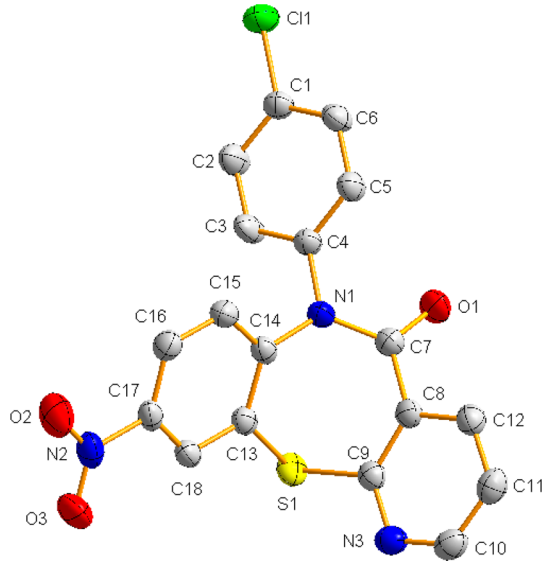


Figure 3. X-ray structure of compound **5e**.

was employed as a solvent, corresponding to the experimental conditions.

General Experimental Procedure for 9-Nitro-6-propylbenzo[*b*]pyrido[3,2-*f*][1,4]thiazepin-5(6*H*)-one (5a). To a solution of DMSO (15 mL) were added 2-mercapto-*N*-propylnicotinamide **3a** (0.20 g, 1.0 mmol), 1,2-difluoro-4-nitrobenzene **4a** (0.08 g, 0.5 mmol), and Cs_2CO_3 (0.98 g, 3.0 mmol), and the mixture was stirred for 1 h at room temperature; then another 1,2-difluoro-4-nitrobenzene **4a** (0.08 g, 0.5 mmol) was added and the mixture stirred at rt for 4 h. Brine (40 mL) was poured into the solution, and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were combined and dried with anhydrous Na_2SO_4. The product was purified by flash chromatography on silica gel (5:1 hexane/EtOAc). Compound **5a** was obtained as a white solid (0.24 g, 0.78 mmol): mp 153−155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.61 (d, J = 2.7 Hz, 1H), 8.50 (dd, J = 4.8, 1.8 Hz, 1H), 8.22 (dd, J = 9.0, 2.7 Hz, 1H), 8.02 (dd, J = 7.8, 1.8 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.34 (dd, J = 7.5, 4.8 Hz, 1H), 4.65−4.75 (m, 1H), 3.60−3.69 (m, 1H), 1.59−1.78 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 157.4, 151.3, 148.3, 144.9, 140.1, 135.1, 133.8, 129.5, 126.1, 124.9, 124.0, 53.0, 21.5, 11.4; HRMS calcd for $C_{15}H_{13}N_3O_3S$ [(M + H)$^+$] 316.0750, found 316.0747.

General Experimental Procedure for 7-Nitro-10-(*p*-tolyl)dibenzo[*b*,*f*][1,4]thiazepin-11(10*H*)-one (7a). This compound was prepared in the same way as described for **5a** by using 2-mercapto-*N*-(*p*-tolyl)benzamide (0.24 g, 1.0 mmol), 1,2-difluoro-4-nitrobenzene **4a** (0.16 g, 1.0 mmol), and Cs_2CO_3 (0.98 g, 3.0 mmol) in DMSO (15 mL) at room temperature. The product was purified by flash chromatography on silica gel (5:1 hexane/EtOAc) to afford **7a** (0.34 g, 0.9 mmol) as a white solid: mp 62−64 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.53 (d, J = 2.6 Hz, 1H), 7.97 (dd, J = 9, 2.6 Hz, 1H), 7.79−7.81 (m, 1H), 7.51−7.54 (m, 1H), 7.39−7.42 (m, 2H), 7.24−7.29 (m, 4H), 7.13 (d, J = 9.0 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 150.2, 144.2, 140.2, 138.3, 138.1, 137.1, 135.7, 131.8, 131.7, 131.3, 130.4, 129.4, 128.4, 128.1, 124.2, 21.2; FT-HRMS (ESI) calcd for $C_{20}H_{14}N_2O_3S$ [(M + H)$^+$] 363.0798, found 363.0803.

X-ray Crystal Structure Analysis of Compound 5e.[21] Single crystals of **5e** suitable for X-ray crystal analysis were obtained by recrystallization from a hexane/CH_2Cl_2 mixed solvent. Intensity data were collected at 293 K on an X-ray diffractometer with Mo Kα radiation (λ = 0.71073 Å) and a graphite monochromator. A total of 9276 reflections were measured at a maximal 2θ angle of 50.0°, of which 3792 were independent reflections (R_{int} = 0.0500). The structure was determined by direct methods (SHELXS-97)[22] and refined by the full-matrix least-squares method on F^2 (SHELEXL-97).[22] The crystal data are as follows: $C_{18}H_{10}ClN_3O_3S$, F_W = 383.01, crystal size of 0.12 mm × 0.10 mm × 0.10 mm, monoclinic, $P121/c1$, a = 8.784(3) Å, b = 16.217(5) Å, c = 14.313(4) Å, V = 1700.5(9) Å^3, Z = 4. The refinement converged to R_1 = 0.0467, wR_2 = 0.1352 [$I > 2\sigma(I)$], and GOF = 1.111.

6-Butyl-9-nitrobenzo[*b*]pyrido[3,2-*f*][1,4]thiazepin-5(6*H*)-one (5b): 264 mg (80% yield); pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.60 (d, J = 1.8 Hz, 1H), 8.49 (dd, J = 4.8, 1.2 Hz, 1H), 8.22 (dd, J = 8.7, 2.1 Hz, 1H), 8.01 (dd, J = 7.8, 1.2 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.33 (d, J = 7.8, 5.1 Hz, 1H), 4.69−4.79 (m, 1H), 3.62−3.71 (m, 1H), 1.58−1.69 (m, 2H), 1.32−1.1.44 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.4, 157.4, 151.3, 148.3, 144.9, 140.1, 135.1, 133.8, 129.4, 126.1, 124.9, 124.0, 51.0, 30.2, 20.1, 13.7; FT-HRMS (ESI) calcd for $C_{16}H_{15}N_3O_3S$ [(M + H)$^+$] 330.0907, found 330.0933.

9-Nitro-6-(*p*-tolyl)benzo[*b*]pyrido[3,2-*f*][1,4]thiazepin-5(6*H*)-one (5c): 326 mg (90% yield); white solid; mp 185−187 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 (d, J = 2.7 Hz, 1H), 8.55 (dd, J = 4.8, 1.8 Hz, 1H), 8.12 (dd, J = 7.8, 1.8 Hz, 1H), 8.02 (dd, J = 9.0, 2.7 Hz, 1H), 7.39 (dd, J = 7.8, 4.8 Hz, 1H), 7.24−7.32 (m, 5H), 7.19 (d, J = 9.0 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 157.0, 151.7, 149.1, 144.6, 140.2, 139.5, 138.7, 134.1, 133.2, 130.4, 129.4, 128.1, 124.5, 124.1, 21.2; FT-HRMS (ESI) calcd for $C_{19}H_{13}N_3O_3S$ [(M + H)$^+$] 364.0750, found 364.0766.

6-(4-Fluorophenyl)-9-nitrobenzo[*b*]pyrido[3,2-*f*][1,4]-thiazepin-5(6*H*)-one (5d): 322 mg (88% yield); white solid; mp 148−150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.65 (d, J = 2.4 Hz, 1H),

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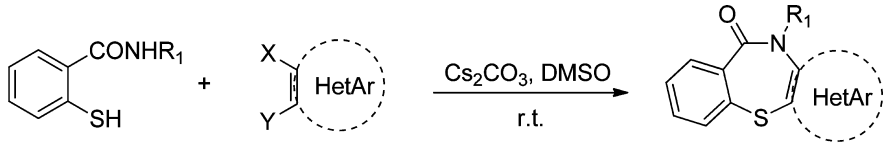
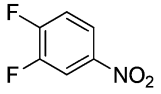
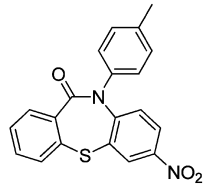
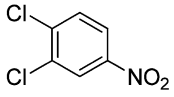
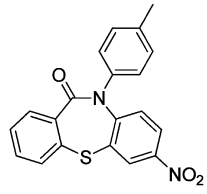
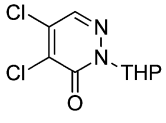
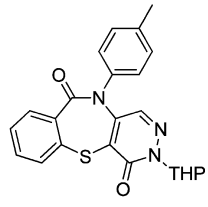
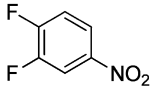
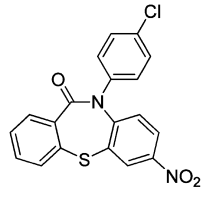
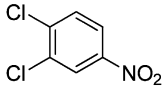
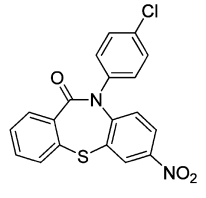
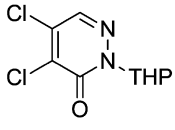
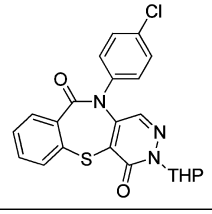
Table 4. Synthesis of 1,4-Thiazepin-5(4*H*)-one Derivatives[a]



6 4 7

Entry	6	R^1	4	Structure of 4	Time (h)	Product 7	Structure of 7	Yield (%)[b]
1	**6a**	4-MeC_6H_4	**4a**		5	**7a**		93
2	**6a**	4-MeC_6H_4	**4b**		6	**7a**		85
3	**6a**	4-MeC_6H_4	**4e**		5	**7b**		95
4	**6b**	4-ClC_6H_4	**4a**		5	**7c**		85
5	**6b**	4-ClC_6H_4	**4b**		6	**7c**		73
6	**6b**	4-ClC_6H_4	**4e**		5	**7d**		89

[a]Reaction conditions: 2-mercaptonicotinamides **3** (1.0 equiv), substituted benzenes **4** (1.0 equiv), Cs_2CO_3 (3.0 equiv). [b]Isolated yields.

8.56 (d, J = 3.3 Hz, 1H), 8.13 (d, J = 1.2 Hz, 1H), 8.05 (dd, J = 9.0, 2.7 Hz, 1H), 7.36–7.42 (m, 3H), 7.15–7.22 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 162.0 ($^1J_{C,F}$ = 248 Hz), 157.0, 151.9, 148.8, 144.8, 140.3, 137.9 ($^4J_{C,F}$ = 3 Hz), 133.5 ($^2J_{C,F}$ = 19 Hz), 130.2 ($^3J_{C,F}$ = 9 Hz), 129.5, 128.0, 124.7, 124.2, 117.0, 116.6; FT-HRMS (ESI) calcd for $C_{18}H_{10}FN_3O_3S$ [$(M + H)^+$] 368.0500, found 368.0516.

6-(4-Chlorophenyl)-9-nitrobenzo[*b*]pyrido[3,2-*f*][1,4]-thiazepin-5(6*H*)-one (5e): 363 mg (95% yield); white solid; mp 195–196 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.65 (d, J = 2.7 Hz, 1H), 8.56 (dd, J = 4.8, 1.8 Hz, 1H), 8.11 (dd, J = 7.8, 1.8 Hz, 1H), 8.05 (dd, J = 9, 2.7 Hz, 1H), 7.45–7.50 (m, 2H), 7.39 (dd, J = 7.8, 4.8 Hz, 1H), 7.31–7.36 (m, 2H), 7.16 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.3, 157.0, 151.9, 148.6, 144.9, 140.4, 140.3, 134.4, 133.7,

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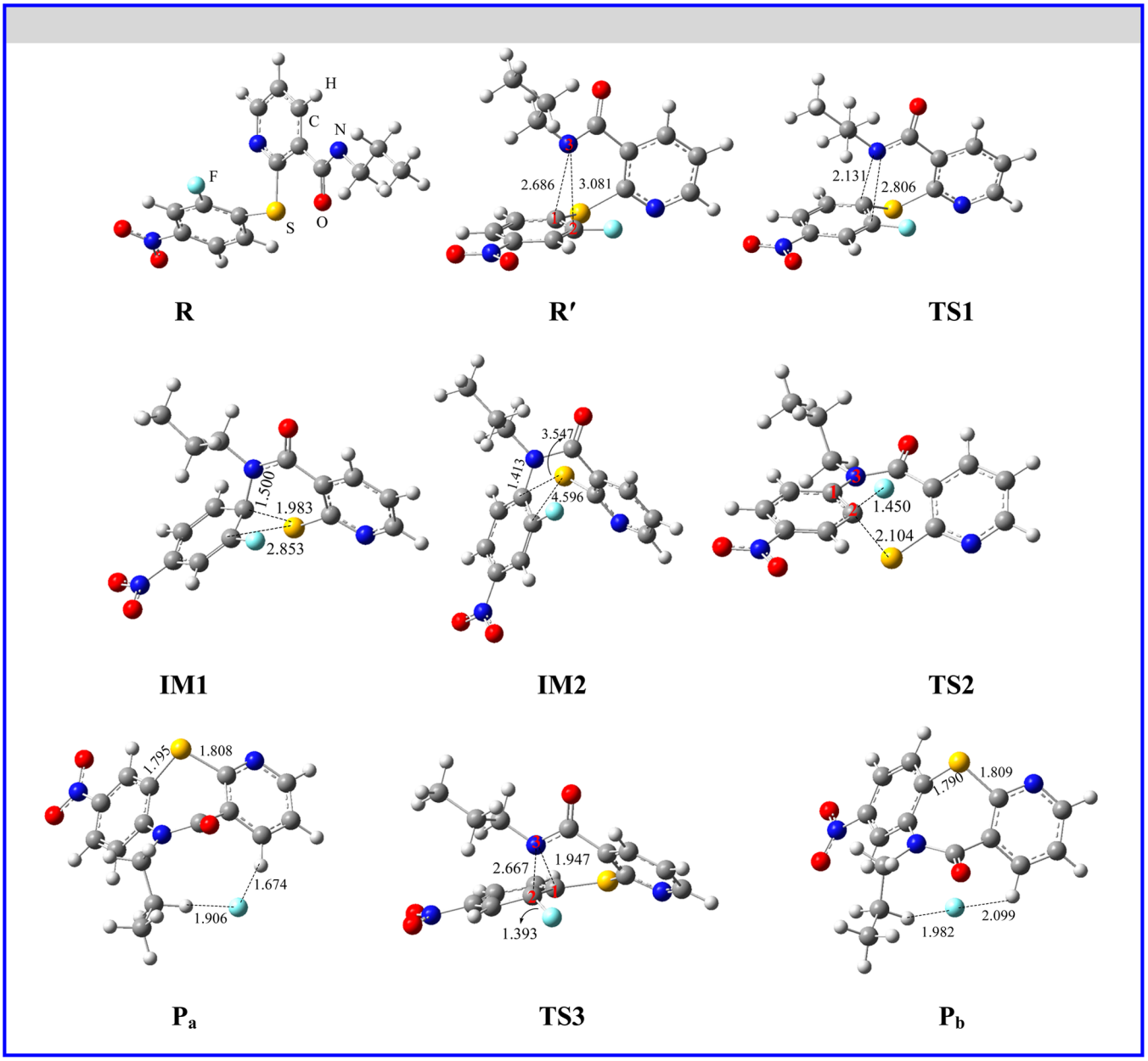
Table 5. Optimized Structures for Transition States, Intermediates, and Products Involved along Pathways a and b Shown in Scheme 3[a]



[a]Distances are in angstroms.

133.6, 130.0, 129.7, 129.5, 128.1, 124.7, 124.2; FT-HRMS (ESI) calcd for $C_{18}H_{10}ClN_3O_3S$ [(M + H)$^+$] 384.0204, found 384.0214.

6-(4-Bromophenyl)-9-nitrobenzo[*b*]pyrido[3,2-*f*][1,4]-thiazepin-5(6*H*)-one (5f): 388 mg (91% yield); white solid; mp 216−218 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.65 (d, J = 2.7 Hz, 1H), 8.56 (dd, J = 4.8, 1.8 Hz, 1H), 8.11 (dd, J = 7.8, 1.8 Hz, 1H), 8.05 (dd, J = 9.0, 2.7 Hz, 1H), 7.60−7.65 (m, 2H), 7.39 (dd, J = 7.8, 4.8 Hz, 1H), 7.25−7.29 (m, 2H), 7.15 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.2, 157.0, 151.9, 148.5, 144.9, 141.0, 140.3, 133.7, 133.0, 130.0, 129.5, 128.1, 124.7, 124.2, 122.5; FT-HRMS (ESI) calcd for $C_{18}H_{10}BrN_3O_3S$ [(M + H)$^+$] 427.9699, found 427.9673.

6-(3,5-Dimethylphenyl)-9-nitrobenzo[*b*]pyrido[3,2-*f*][1,4]-thiazepin-5(6*H*)-one (5g): 358 mg (95% yield); white solid; mp none; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.64 (d, J = 2.4 Hz, 1H), 8.55 (d, J = 1.4 Hz, 1H), 8.10 (d, J = 7.7 Hz, 1H), 8.02 (dd, J = 9.0, 2,4 Hz, 1H), 7.38 (dd, J = 7.7, 2.9 Hz, 1H), 7.22 (d, J = 9.0 Hz, 1H), 7.04 (s, 1H), 6.99 (s, 2H), 2.36 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 157.0, 151.6, 149.0, 144.6, 141.9, 140.1, 139.7, 134.2, 133.1, 130.4, 129.4, 128.0, 126.0, 124.5, 124.1, 21.2; FT-HRMS (ESI) calcd for $C_{20}H_{15}N_3O_3S$ [(M + H)$^+$] 378.0907, found 378.0919.

9-Nitro-6-(3,4,5-trimethoxyphenyl)benzo[*b*]pyrido[3,2-*f*]-[1,4]thiazepin-5(6*H*)-one (5h): 395 mg (90% yield); white solid; mp 228−230 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.65 (d, J = 2.7 Hz, 1H), 8.56 (dd, J = 4.8, 1.8 Hz, 1H), 8.12 (dd, J = 7.8, 1.8 Hz, 1H), 8.07 (dd, J = 9.0, 2.7 Hz, 1H), 7.39 (dd, J = 7.8, 4.8 Hz, 1H), 7.30 (d, J = 9.0 Hz, 1H), 6.58 (s, 2H), 3.89 (s, 3H), 3.87 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 156.9, 154.0, 151.8, 148.8, 144.7, 140.2, 138.3, 137.4, 134.0, 132.9, 129.5, 127.7, 124.7, 124.2, 106.0, 60.9, 56.4; FT-HRMS (ESI) calcd for $C_{21}H_{17}N_3O_6S$ [(M + H)$^+$] 440.0872, found 440.0853.

9-Fluoro-6-(*p*-tolyl)benzo[*b*]pyrido[3,2-*f*][1,4]thiazepin-5(6*H*)-one (5i): 278 mg (83% yield); white solid; mp 152−153 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51 (dd, J = 4.8, 1.8 Hz, 1H), 8.12 (dd, J = 7.8, 1.8 Hz, 1H), 7.46 (dd, J = 7.8, 3 Hz, 1H), 7.35 (dd, J = 7.8, 4.8 Hz, 1H), 7.26 (s, 5H), 7.06 (dd, J = 9.0, 5.1 Hz, 1H), 6.87−

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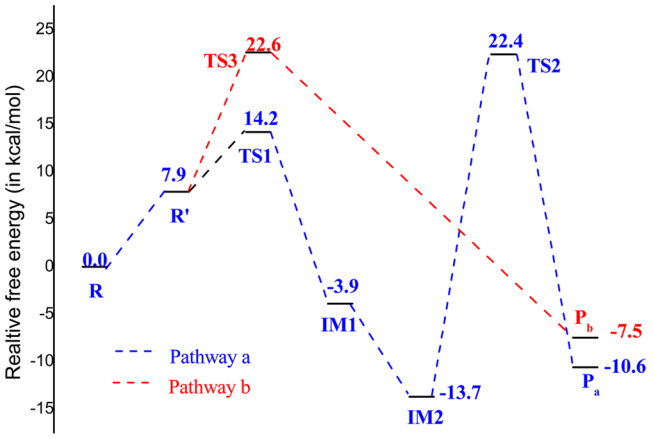

Figure 4. Calculated relative free energy profiles along the *ipso*-Smiles rearrangement pathway (pathway a) and the direct nucleophilic substitution pathway (pathway b).

6.94 (m, 1H), 2.39 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.3, 166.7, 162.8 ($^1J_{C,F}$ = 232 Hz), 158.1, 157.8, 156.1, 150.9, 140.1 ($^3J_{C,F}$ = 9 Hz), 140.0, 137.8, 134.5, 130.1, 129.1 ($^3J_{C,F}$ = 8 Hz), 127.8, 123.8, 120.4 ($^2J_{C,F}$ = 22 Hz), 117.1 ($^2J_{C,F}$ = 22 Hz), 21.2; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −114.23; FT-HRMS (ESI) calcd for $C_{19}H_{13}FN_2OS$ [(M + H)$^+$] 337.0766, found 337.0790.

6-(3,5-Dimethylphenyl)-9-fluorobenzo[*b*]pyrido[3,2-*f*][1,4]-thiazepin-5(6*H*)-one (5j): 315 mg (93% yield); white solid; mp 148−150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (dd, J = 4.8, 1.5 Hz, 1H), 8.12 (d, J = 4.8 Hz, 1H), 7.46 (dd, J = 7.8, 2.7 Hz, 1H), 7.36 (dd, J = 7.8, 4.8 Hz, 1H), 7.10 (dd, J = 9.0, 5.1 Hz, 1H), 7.00 (s, 3H), 6.88−6.95 (m, 1H), 2.35 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.6, 157.0,156.8, 149.8, 141.5, 139.2, 138.9 ($^4J_{C,F}$ = 4 Hz), 138.3, 133.6, 133.1 ($^3J_{C,F}$ = 9 Hz), 128.7, 128.1 ($^3J_{C,F}$ = 9 Hz), 124.7, 122.9, 119.5 ($^2J_{C,F}$ = 23 Hz), 116.1 ($^2J_{C,F}$ = 22 Hz), 20.3; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −114.36; FT-HRMS (ESI) calcd for $C_{20}H_{15}FN_2OS$ [(M + H)$^+$] 351.0962, found 351.0972.

6-(3,5-Dimethylphenyl)-7-methylbenzo[*b*]pyrido[3,2-*f*][1,4]-thiazepin-5(6*H*)-one (5k): 138 mg (40% yield); white solid; mp 190−192 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.43 (dd, J = 4.8, 1.8 Hz, 1H), 8.06 (dd, J = 7.5, 1.8 Hz, 1H), 7.68 (dd, J = 7.2, 2.4 Hz, 1H), 7.30 (dd, J = 7.8, 4.8 Hz, 1H), 7.08−7.15 (m, 2H), 6.98 (s, 2H), 6.86 (s, 1H), 2.30 (s, 6H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 150.0, 141.4, 140.8, 139.5, 137.9, 137.3, 136.8, 135.1, 132.9, 132.1, 128.2, 127.4, 124.7, 123.6, 21.4, 20.0; FT-HRMS (ESI) calcd for $C_{21}H_{18}N_2OS$ [(M + H)$^+$] 347.1213, found 347.1224.

9-(Tetrahydro-2*H*-pyran-2-yl)-6-(*p*-tolyl)pyridazino[4,5-*b*]-pyrido[3,2-*f*][1,4]thiazepine-5,10(6*H*,9*H*)-dione (7b): 398 mg (95% yield); white crystal; mp 98−100 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (m, 1H), 7.52−7.57 (m, 1H), 7.39−7.46 (m, 2H), 7.35 (s, 1H), 7.22−7.31 (m, 4H), 5.99 (dd, J = 10.5, 1.8 Hz, 1H), 4.07 (d, J = 11.4 Hz, 1H), 3.68−3.76 (m, 1H), 2.40 (s, 3H), 1.92−2.09 (m, 2H), 1.51−1.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 145.3, 139.2, 138.1, 137.0, 136.9, 134.4, 132.4, 132.0, 131.9, 130.5, 129.3, 128.3, 83.6, 68.8, 28.6, 24.8, 22.7, 21.2; FT-HRMS (ESI) calcd for $C_{23}H_{21}N_3O_3S$ [(M + H)$^+$] 420.1376, found 420.1382.

10-(4-Chlorophenyl)-7-nitrodibenzo[*b*,*f*][1,4]thiazepin-11-(10*H*)-one (7c): 324 mg (85% yield); white solid; mp 98−100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, J = 2.6 Hz, 1H), 8.00 (dd, J = 8.9, 2.6 Hz, 1H), 7.78−7.81 (m, 1H), 7.53−7.55 (m, 1H), 7.40−7.46 (m, 4H), 7.33 (d, J = 8.7 Hz, 1H), 7.10 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.1, 149.7, 144.5, 141.1, 137.6, 137.1, 136.2, 134.1, 131.9, 131.8, 131.4, 130.0, 129.9, 129.5, 128.6, 128.1, 124.4; FT-HRMS (ESI) calcd for $C_{19}H_{11}ClN_2O_3S$ [(M + H)$^+$] 383.0252, found 383.0253.

11-(4-Chlorophenyl)-3-(tetrahydro-2*H*-pyran-2-yl)benzo[*f*]-pyridazino[4,5-*b*][1,4]thiazepine-4,10(3*H*,11*H*)-dione (7d): 390 mg (89% yield); white crystal; mp 138−140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, J = 4.9 Hz, 1H), 7.55 (d, J = 3.7 Hz, 1H), 7.43−7.52 (m, 4H), 5.98 (d, J = 10.2 Hz, 1H), 4.07 (d, J = 11.4 Hz, 1H), 7.31 (d, J = 4.0 Hz, 3H) 1.98−2.05 (m, 2H), 1.52−1.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.5, 158.4, 144.9, 138.1, 137.7, 137.0, 135.0, 134.2, 132.6, 132.3, 132.1, 130.1, 130.0, 129.4. 83.8, 68.9, 28.7, 24.8, 22.7; FT-HRMS (ESI) calcd for $C_{22}H_{18}ClN_3O_3S$ [(M + H)$^+$] 440.0830, found 440.0864.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all compounds, X-ray data of **5e** in CIF format, and Cartesian coordinates and absolute energies for all structures involved in theoretical calculations. 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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(21) For the crystal data of **5e**, see the Supporting Information. CCDC 994893 (**5e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crysallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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