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Formation of 1,4,2-Dithiazolidines or 1,3-Thiazetidines from 1,1-Dichloro-2-nitroethene and Phenylthiourea Derivatives

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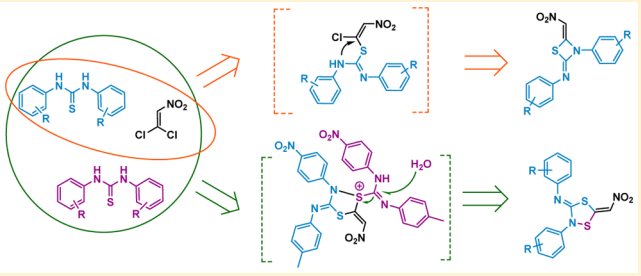
Supporting Information

ABSTRACT: A method for preparation of 1,4,2-dithiazolidine or 1,3-thiazetidine heterocycles was developed by reactions of phenylthioureas with 1,1-dichloro-2-nitroethene. The solvent has a significant influence on the type of product formation. 1,4,2-Dithiazolidines were formed in the aprotic solvent chloroform, while in the protic solvent ethanol, 1,3-thiazetidines were the main products.



INTRODUCTION

The main N,S-containing heterocycles (NSHs) include thiazoles,[1] isothiazoles,[2] thiadiazoles,[3] dithiazoles,[4] thiomorpholines,[5] 1,4-thiazepines,[6] and thiazetidines[7] and their dihydro/tetrahydro derivatives. The ascendancy and effects of NSHs are well understood by scientists across various areas due to their broad applications.[8] Thus, discovering novel synthetic methods or unexploited NSHs is important for fundamental science studies and practical applications.

The NSHs addressed in this article are 1,3-thiazetidines (TADs) and 1,4,2-dithiazolidines (DTAs). The four-membered 1,3-thiazetidines find uses as important intermediates and pesticidal, antibacterial, or antiviral compounds.[9] Their preparations involve cyclization of thiourea derivatives with dihaloalkanes or triphosgene,[10] cyclothiomethylation of anilines by formaldehyde and hydrogen sulfide,[11] high-pressure reactions of carbon disulfide, dialkylcyanamides, and benzylideneaniline,[12] addition of isothiocyanates with imines,[13] and three-component reactions of phosphorodithioate, aldehydes, and aldimines.[14]

The procedures regarding 1,4,2-dithiazolidines have been scarcely reported probably due to the limited synthetic choices.[15] The rarely reported synthetic methods of DTAs include cyclization of (methylsulfinyl)methyl carbamimidothioate,[14] reaction of 1,3-dithietane with anilines,[16] and condensation of thione *S*-imide with diphenylmethanethione.[17] However, these synthetic methods have some drawbacks of using uncommon intermediates and limited patterns of substituents.

Despite the chemical or pharmaceutical importance of TADs and DTAs, limited efforts have been made toward their synthetic methodologies, in particular the synthetic availabilities of DTAs. We detail herein a straightforward synthesis of TADs and DTAs from thioureas and 1,1-dichloro-2-nitroethene (DCNE) through solvent-dependent product selectivity. TADs were formed in the protic solvent ethanol, while in the aprotic solvent chloroform, DTAs were the main products.

RESULTS AND DISCUSSION

DCNE can be readily prepared by the chloronitration/dehydrochlorination sequence of the easily available 1,1-dicloroethylene, which is extensively used in polymer science.[19] The highly polarized ethylene system gives DCNE a reactivity similar to that of phosgene, meaning that it can be attacked by nucleophiles such as amines, aryl alcohols, and mercaptans.[18] Our recent studies on DCNE chemistry revealed its ability in oxadiazole construction and nitroacetylation in reactions with aryl hydrazides and anilines, respectively (Scheme 1).[19] The above observations stimulated us to explore its reaction behaviors toward thioureas. To probe the feasibility, diphenylthiourea (DPTU, **2a**) was treated with DCNE at 0 °C in acetonitrile, affording two new products through direct purification using flash chromatography. However, NMR and HRMS analysis could not unequivocally confirm the structure. The exact chemical structures of the two products were assigned afterward with the aid of X-ray crystallography studies of their analogues **3g** and **4e**, confirming that the products had five-membered (**3a**) and four-membered rings (**4a**), respectively.

Having identified the interesting heterocyclic scaffolds, we started optimization of the reaction conditions to raise the

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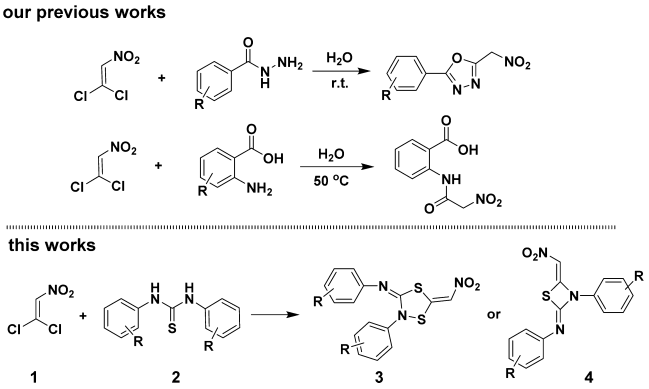
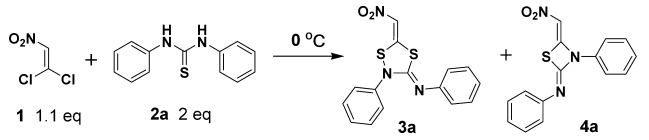
Scheme 1. Reactions of DCNE with Aryl Hydrazides, Anthranilic Acids, and Phenylthiourea



yields and improve the selectivity. Initially, the product dependence on the solvent was investigated. A model reaction of DCNE with DPTU (**2a**) was evaluated at a molecular ratio of 1.1:2 at 0 °C (Table 1). Screening of the solvents indicated

Table 1. Solvent Dependence of the Formation of DTA 3a and TAD 4a



		yield (%)[a]	
entry	solvent	3a	4a
1	CH_3CN	25	23
2	EtOAc	10	10
3	CH_2Cl_2	23	8
4	$C_2H_4Cl_2$	26	8
5	$CHCl_3$	35	7
6	acetone	8	31
7	C_2H_5OH	2	66
8	DMF	0	10
9	THF	trace	trace
10	toluene	trace	trace
11	H_2O	n.r.[b]	n.r.

[a]The yields were determined by HPLC analysis. [b]n.r. denotes no reaction.

that the reaction was sensitive to the solvent. Acetonitrile and ethyl acetate provided almost a 1:1 formation of **3a** and **4a** (Table 1, entries 1 and 2). The maximum formation of **3a** was achieved in chloroform with a **3a**:**4a** ratio of 5:1 (Table 1, entry 5). In contrast, the reaction progressed well in ethanol with excellent selectivity for TAD **4a** (66:2) and good yields (Table 1, entry 7).

With the elucidation of the solvent effects on the reaction, the formation of DTA **3a** was then screened in chloroform. Reducing the reaction temperature to −10 °C (Table 2, entry 2) led to an increase in the yield to 49%, while further lowering the temperature caused a decrease in yield. An increase in the ratio of DCNE did not have positive effects on the yields (Table 2, entries 5−8). The acid capture agents Na_2CO_3 and Cs_2CO_3 had detrimental effects on the reaction accompanied by a great loss in the formation of **3a** (Table 2, entries 10 and 11).

Table 2. Optimization of the Formation of DTA 3a

entry	T (°C)	2a:1	additive	yield (%)
1	0	2:1.1		35
2	−10	2:1.1		49
3	−15	2:1.1		40
4	−20	2:1.1		35
5	−10	2:1.5		46
6	−10	2:1.7		49
7	−10	1:1		41
8	−10	1:2		40
9	−10	3:1.2		49
10	−10	2:1.1	Na_2CO_3	<5
11	−10	2:1.1	Cs_2CO_3	<5
12	−10	2:1.1	DPU[a] (0.2 equiv)	65
13	−10	2:1.1	TBAF[b] (2 equiv)	67
14	−10	2:1.2	DPU (0.2 equiv), TBAF (2 equiv)	23

[a]DPU denotes diphenylurea. [b]TBAF denotes tetrabutylammonium fluoride.

Since the conversion proceeded with the formation of side products due to the highly reactive nature of the reactants, catalysts that could stabilize the DCNE or thioureas were therefore investigated. Ureas are usually used as organic catalysts operating through formation of hydrogen-bonding interactions with the substrates.[20] Etter et al. observed that a urea and a nitro compound can form urea−nitro group recognition which can catalyze a variety of nitro compounds, including nitroalkenes.[21] Thus, diphenylurea (DPU) was evaluated to find its influence on the reaction. To our delight, the reaction proceeded with more efficiency with a 16% yield increase, reaching up to 65% (Table 2, entry 12). In this observation, the diminished activity of DCNE by hydrogen bonding with urea would favor the formation of **3a**. With the above success, we then turned our attention to stabilize the thiourea. Due to the fact that thiourea derivatives are good receptors for anion recognition, in particular fluorine anions, by forming strong host−guest complexes,[22] we therefore subjected tetrabutylammonium fluoride (TBAF) to the reaction. It is interesting to observe a significant yield increase (67%) and a lower reaction rate (Table 2, entry 13), suggesting attenuated reactivity of the thiourea by H bonding with TBAF. However, coapplication of the DPU and TBAF led to a dramatic decrease in the yields (Table 2, entry 14).

A similar optimization process was then performed for the generation of TAD **4a** using DCNE and DPTU (**2a**) in a ratio of 1.1:1 (Table S1 in the Supporting Information). The highest yield of **4a** was achieved using ethanol at −25 °C. Notably, the catalysts DPU and TBAF did not have any beneficial effects on this transformation.

On application of the conditions favoring the formation of DTA **3**, the reaction scopes were investigated with varying thioureas (Scheme 2). DPTUs with electron-donating substituents were well tolerated, despite the moderate yields. Using DPTUs with electron-withdrawing groups (cyano, nitro, and trifluoromethyl) met with no success, with the recovery of the staring materials, probably due to the low nucleophilicity of the thiourea. A selection of phenylthioureas were also accommodated in this process. In these observations the exocyclic double bond isomerized to an endocyclic bond. The substrate **2m** with a strongly withdrawing nitro group generated the DTA **3m** in 31% yield.

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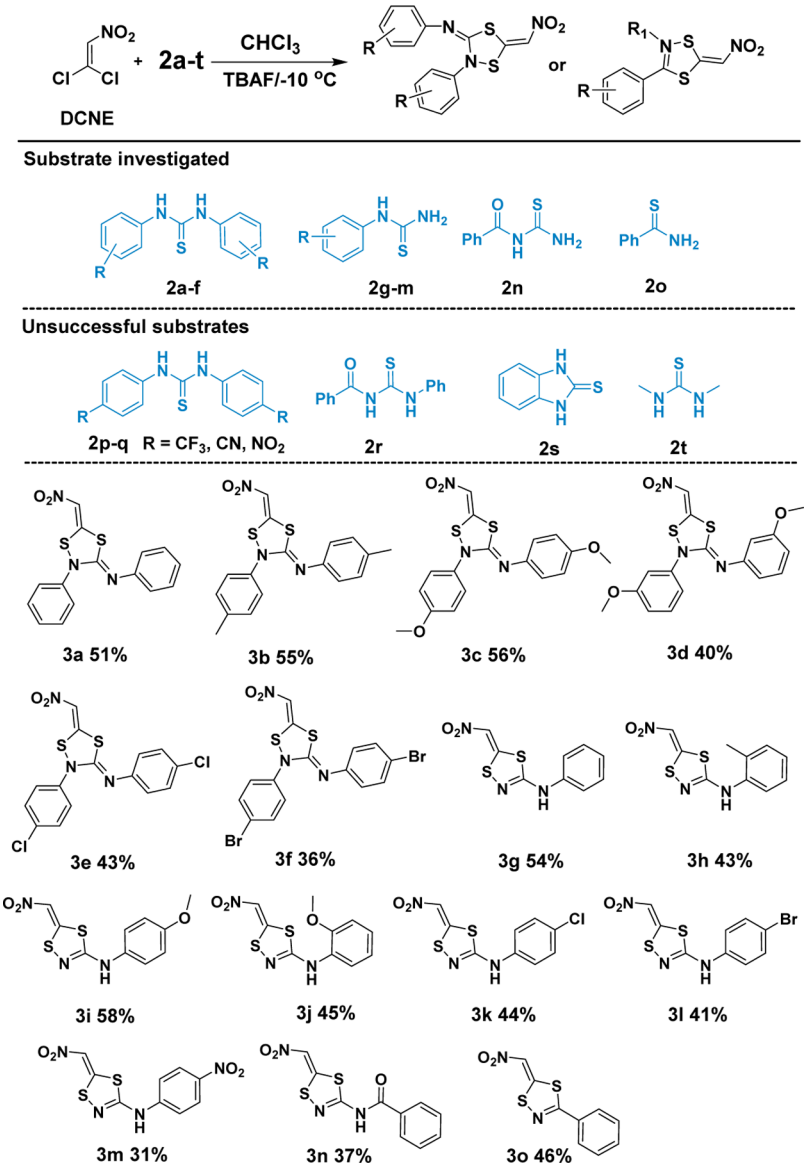
Scheme 2. Substrate Investigation on the Synthesis of DTA 3



N-Carbamothioylbenzamide (**2n**) and benzothioamide (**2o**) were also competent substrates, affording **3n** and **3o** in 37% and 46% yields, respectively. No reactions occurred on *N*-(phenylcarbamothioyl)benzamide (**2r**) or the cyclic thiourea **2s**. Reaction of 1,3-dimethylthiourea (**2t**) gave an intractable mixture without any separable products.

A strong substrate specificity on the formation of TADs **4** was observed (Scheme 3). The substrates applicable to this conversion are limited to DPTUs, and no corresponding TADs were detected on other thioureas. Four-membered rings are less stable because of ring strain. Slight changes in the electron density of substituents may cause their ring-opening reaction, providing a possible explanation for the specific substrate requirements in TAD formation.

When asymmetrical DPTUs **2u** and **2v** were studied, the issue of regioselectivity arose from the possibility of forming two different regioisomers (Scheme 4).[23] Regioselectivity tends to be steered by the intrinsic electronic effects of the substrate, in particular the substituent influences. On evaluation of DPTU **2u** with methyl and bromo substituents at each of the phenyl rings, **3u**/**3U** and **4u**/**4U** mixtures were separated in total yields of 45% and 74%, respectively. This observation can be rationalized by the slight difference between methyl and bromo groups in the electronic contributions. For DPTU **2v** with a strongly electron withdrawing nitro group at one end, the C−N bond formation was preferred for the less-electron-rich nitrogen, resulting in the isolation of pure major isomer **4V** (53%), whose structure was established by X-ray diffraction analysis. By applying the optimal conditions favoring the DTA formation, **2v** provided **3V** as the sole product. Although the desired single-crystal structure for X-ray diffraction was not obtained, its structure can be deduced according to the regioselectivity in the formation of **4V**. The 2*Z*,4*Z* configuration for **4V** was assigned according to the steric effect of the adjacent phenyl substituent.

On the basis of the clues afforded by the above experimental observations, a plausible reaction pathway was proposed (Scheme 5), exemplified by substrate **2v**. Electrophilic attack of DCNE to DPTU (**2v**) afforded intermediate **A**. Intramolecular cyclization of **A** occurred in ethanol, generating the

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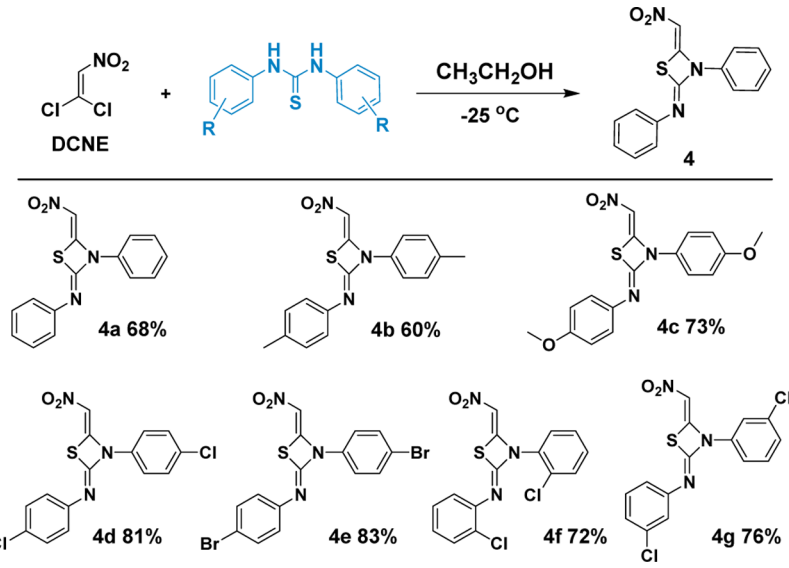
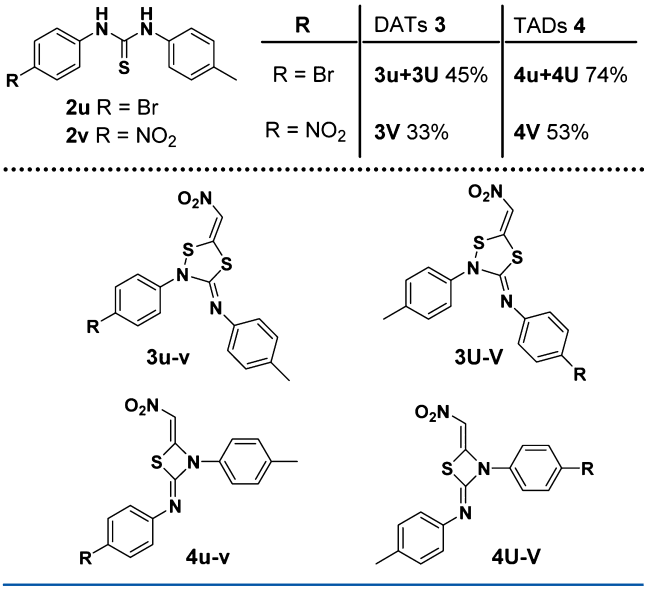
Scheme 3. Substrate Investigation on the Formation of TAD 4



Scheme 4. Selectivity Investigation on the Asymmetrical Diphenylthioureas



four-membered product. However, intermolecular attack of **A** by another molecule of **2v** gave intermediate **B**, which further underwent cyclization, delivering the five-membered compound. The regioselectivity for the asymmetrical DPTU can be explained by the fact that the C═N double bond in transition state **A** was prone to form with the electron-rich nitrogen. In addition to the formation of DTA, the diphenylurea side product **D** was also separated, which was generated by intermediate **C** formed in the reaction. However, for the phenylthiourea **2i**, cyanamide **E** and phenylurea **F** were detected as the side products (Scheme 5). The nitro olefin may exist in a trans or cis configuration; however, only one thermally stable isomer was observed and no trans−cis isomerization occurred during the storage or analysis of the compounds.

CONCLUSIONS

We have disclosed a novel synthetic methodology for access of 1,4,2-dithiazolidines or 1,3-thiazetidines from 1,1-dichloro-2-nitroethene and phenylthioureas. The products can be obtained independently with a high selectivity under the control of solvent. Given its simplicity and generality, we expect this protocol would have wide applications to the preparation of functional molecules.

EXPERIMENTAL SECTION

General Information. Chromatographic analysis was performed using an ACQUITY UPLC-H Class system, equipped with a BEH C18 reversed phase column. The mobile phase was a mixture of Milli-Q ultrapure water with 0.01% trifluoroacetic acid (A) and acetonitrile (B). The following elution gradient lasted a total of 15 min: initial mobile-phase composition, 90/10 (v/v) phase A/B; 0−8 min, linear change from 10 to 100% B; 8−10 min 100% B; 10−11 min, 90/10 (v/v) phase A/B. The detectors of products **3** and **4** were set at 426 and 365 nm, respectively.

Synthesis of 1,1-Dichloro-2-nitroethene. Hydrochloric acid (41.7 g, 0.411 mol, 36%) and nitric acid (39.8 g, 0.411 mol, 65%) were placed in a flask, 1,1-dichloroethylene (31.0 g, 0.315 mol) was added dropwise over 3 h, and the mixture was kept at 20−25 °C. The mixture was continuously stirred for 1 h, washed with water, and extracted by $CHCl_3$, the organic phase was collected, and then 235 mL of 4% NaOH solution was added to it in the ice bath; after simple separation and chloroform washing, the organic phase was concentrated and dried with anhydrous magnesium sulfate, to give the pure product.

Isolated yield: 66% (29.5 g, 0.208 mol), yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 136.4 ppm. HRMS (ESI): m/z calcd for $C_2H^{35}Cl_2NO_2$ $(M + H)^+$, 140.9384; found, 140.9382; calcd for $C_2H^{35}Cl^{37}ClNO_2$ $(M + H)^+$, 142.9355; found, 142.9356.

General Procedure for the Synthesis of 1,3-Diphenylthiourea Derivatives 2a−f. The aniline compound (50 mmol) was dissolved in C_2H_5OH (30 mL), and CS_2 (75 mL) was added to the stirred solution. The reaction mixture was stirred under reflux until the reaction was complete as monitored by TLC. The precipitate was collected by filtration and recrystallized by hot ethanol to give the pure product (yield: 60−80%).

General Procedure for the Synthesis of 1-Phenylthiourea Derivatives 2g−m. Benzoyl chloride (50 mmol) was dissolved in acetone (20 mL), and the solution was stirred at room temperature.

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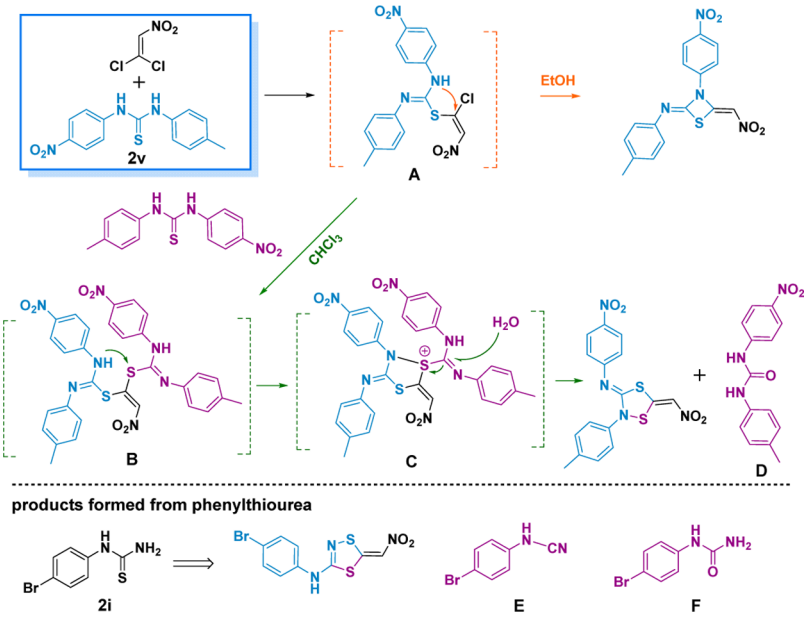
Scheme 5. Proposed Mechanism and Side Products for the Formation of DTA and TAD



NH_4SCN (62.5 mmol) was dissolved in acetone (10 mL) and then added dropwise to the reaction mixture, which was then stirred for 15 min. The precipitate was removed by filtration, and then the filtrate was dissolved in ethyl acetate (20 mL). The aniline compound (50 mmol) was dissolved in ethyl acetate (10 mL) and then added dropwise to the reaction mixture at room temperature, which was stirred until the reaction was complete as monitored by TLC. The white precipitate was collected by filtration and dissolved in C_2H_5OH (30 mL). NaOH solution (100 mmol) was added dropwise to the reaction mixture, which was then stirred at room temperature until the reaction was complete as monitored by TLC. The reaction mixture was adjusted pH to 7 with HCl, stirred in an ice bath, and filtered to afford the product (yield: 80−85%).

General Procedure for the Synthesis of Compounds 3. Compounds **2a−m** (3 mmol) and tetrabutylammonium fluoride (783 mg, 3 mmol) were stirred in $CHCl_3$ (15 mL) at −10 °C, and then 1,1-dichloro-2-nitroethene (255 mg, 1.8 mmol) was added to the stirred solution. The reaction mixture was stirred at −10 °C until the reaction was complete as monitored by TLC. After it was cooled to room temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was further purified by column chromatography (petroleum ether and ethyl acetate (6/1 v/v)).

*(3Z,5Z)-5-(Nitromethylene)-N,2-diphenyl-1,4,2-dithiazolidin-3-imine (**3a**).* Isolated yield: 51% (252 mg, 0.77 mmol). Yellow solid; mp 124.9−126.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.2, 150.7, 149.8, 136.3, 129. 8, 129.8, 128.5, 127.5, 124.6, 121.0, 121.0 ppm. HRMS (ESI): m/z calcd for $C_{15}H_{12}N_3O_2S_2$ $(M + H)^+$, 330.0371; found, 330.0370.

*(3Z,5Z)-5-(Nitromethylene)-N,2-di-p-tolyl-1,4,2-dithiazolidin-3-imine (**3b**).* Isolated yield: 55% (295 mg, 0.83 mmol). Yellow solid; mp 124.3−125.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.84 (d, J = 8.2 Hz, 2H), 2.36 (s, 3H), 2.28 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 149.8, 148.4, 138.2, 133.6, 133.6, 130.2, 130.2, 127.4, 120.8, 120.8, 20.7, 20.4 ppm. HRMS (ESI): m/z calcd for $C_{17}H_{16}N_3O_2S_2$ $(M + H)^+$, 358.0684; found, 358.0685.

*(3Z,5Z)-N,2-Bis(4-methoxyphenyl)-5-(nitromethylene)-1,4,2-dithiazolidin-3-imine (**3c**).* Isolated yield: 56% (327 mg, 0.84 mmol). Yellow solid; mp 130.2−131.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.10 (d, J = 7.2 Hz, 2H), 6.98−6.80 (m, 4H), 3.82 (s, 3H), 3.74 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-$d6$): δ 160.5, 159.2, 156.2, 149.4, 144.2, 129.4, 128.4, 122.0, 120.8, 115.0, 114.9, 55.5, 55.2 ppm. HRMS (EI): m/z calcd for $C_{17}H_{15}N_3O_4S_2$ $[M]^+$, 389.0504; found, 389.0505.

*(3Z,5Z)-N,2-Bis(3-methoxyphenyl)-5-(nitromethylene)-1,4,2-dithiazolidin-3-imine (**3d**).* Isolated yield: 40% (234 mg, 0.60 mmol). Yellow solid; mp 132.2−133.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (s, 1H), 7.47 (t, 1H), 7.34−7.20 (m, 3H), 7.04 (d, 1H), 6.72 (d, J = 6.0 Hz, 1H), 6.61−6.50 (m, 2H), 3.81 (s, 3H), 3.74 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 160.4, 160.1, 152.0, 145.0, 137.2, 130.6, 130.6, 120.9, 119.4, 114.2, 113.3, 112.9, 110.4, 106.5, 55.5, 55.1 ppm. HRMS (ESI): m/z calcd for $C_{17}H_{16}N_3O_4S_2$ $[M + H]^+$, 390.0583; found, 390.0582.

*(3Z,5Z)-N,2-Bis(4-chlorophenyl)-5-(nitromethylene)-1,4,2-dithiazolidin-3-imine (**3e**).* Isolated yield: 43% (257 mg, 0.65 mmol). Yellow solid; mp 134.8−135.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 (s, 1H), 7.73 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.0, 150.6, 149.4, 135.0, 132.9, 129.7, 129.7, 129.3, 128.7, 122.9, 121.2 ppm. HRMS (ESI): m/z calcd for $C_{15}H_{10}N_3O_2S_2{}^{35}Cl_2$ $(M + H)^+$, 397.9592; found, 397.9690; calcd for $C_{15}H_{10}N_3O_2S_2{}^{35}Cl^{37}Cl$ $(M + H)^+$, 399.9562; found, 399.9554.

*(3Z,5Z)-N,2-Bis(4-bromophenyl)-5-(nitromethylene)-1,4,2-dithiazolidin-3-imine (**3f**).* Isolated yield: 36% (263 mg, 0.54 mmol). Yellow solid; mp 151.7−153.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.69−7.55 (m, 4H), 7.11 (d, J = 8.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.2, 144.4, 142.8, 133.2, 132.7, 132.5, 125.6, 123.6, 120.8, 118.8, 116.2 ppm. HRMS (EI): m/z calcd for $C_{15}H_9N_3O_2S_2{}^{79}Br_2$ $[M]^+$, 484.8503, found 484.8496; calcd for $C_{15}H_9N_3O_2S_2{}^{79}Br^{81}Br$ $[M]^+$, 486.8483; found, 486.8490.

*(Z)-5-(Nitromethylene)-N-phenyl-1,4,2-dithiazol-3-amine (**3g**).* Isolated yield: 54% (205 mg, 0.81 mmol). Yellow solid; mp 201.9−203.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, 1H), 8.35 (s, 1H), 7.65 (d, 2H), 7.43 (t, J = 16.5, 8.8 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.2, 155.7, 139.3, 129.1, 123.4, 118.1, 117.4 ppm. HRMS (EI): m/z calcd for $C_9H_7N_3O_2S_2$ $[M]^+$, 252.9980; found, 252.9982.

*(Z)-5-(Nitromethylene)-N-(o-tolyl)-1,4,2-dithiazol-3-amine (**3h**).* Isolated yield: 43% (173 mg, 0.65 mmol). Yellow solid; mp 133.4−134.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.12 (s, 1H), 8.27 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 11.0, 6.2 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.15 (t, J = 7.3 Hz, 1H), 2.25 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.2, 158.7, 137.5, 131.3, 130.8, 126.6,

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125.8, 123.7, 117.2, 17.8 ppm. HRMS (EI): m/z calcd for $C_{10}H_9N_3O_2S_2$ $[M]^+$, 267.0136; found, 267.0137.

*(Z)-N-(4-Methoxyphenyl)-5-(nitromethylene)-1,4,2-dithiazol-3-amine (**3i**).* Isolated yield: 58% (246 mg, 0.87 mmol). Yellow solid; mp 214.9−216.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.72 (s, 1H), 8.28 (s, 1H), 7.49 (d, 2H), 6.95 (d, 2H), 3.74 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.6, 156.4, 155.5, 132.6, 120.2, 117.2, 114.3, 55.2 ppm. HRMS (ESI): m/z calcd for $C_{10}H_{10}N_3O_3S_2$ $(M + H)^+$, 284.0164; found, 284.0164.

*(Z)-N-(2-Methoxyphenyl)-5-(nitromethylene)-1,4,2-dithiazol-3-amine (**3j**).* Isolated yield: 45% (191 mg, 0.68 mmol). Yellow solid; mp 177.1−179.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.27 (s, 1H), 8.29 (s, 1H), 8.04 (d, J = 7.6 Hz, 1H), 7.11 (d, J = 6.9 Hz, 2H), 6.98 (t, J = 6.5 Hz, 1H), 3.84 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 172.3, 157.1, 149.4, 129.2, 128.1, 124.8, 120.5, 117.0, 111.4, 55.8 ppm. HRMS (EI): m/z calcd for $C_{10}H_9N_3O_3S_2$ $[M]^+$, 283.0085; found, 283.0086.

*(Z)-N-(4-Chlorophenyl)-5-(nitromethylene)-1,4,2-dithiazol-3-amine (**3k**).* Isolated yield: 44% (190 mg, 0.66 mmol). Yellow solid; mp 245.6−246.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.96 (s, 1H), 8.30 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.9, 155.5, 138.3, 129.0, 126.8, 119.6, 117.5 ppm. HRMS (ESI): m/z calcd for $C_9H_7N_3O_2S_2{}^{35}Cl$ $[M + H]^+$, 287.9668; found, 287.9665; calcd for $C_9H_7N_3O_2S_2{}^{37}Cl$ $[M + H]^+$, 289.9639; found, 289.9634.

*(Z)-N-(4-Bromophenyl)-5-(nitromethylene)-1,4,2-dithiazol-3-amine (**3l**).* Isolated yield: 41% (205 mg, 0.62 mmol). Yellow solid; mp 162.6−163.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.94 (s, 1H), 8.30 (s, 1H), 7.54 (s, 4H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.9, 1554, 138.7, 131.9, 119.9, 117.5, 114.8 ppm. HRMS (ESI): m/z calcd for $C_9H_7N_3O_2S_2{}^{79}Br$ $[M + H]^+$, 331.9163; found, 331.9166; calcd for $C_9H_7N_3O_2S_2{}^{81}Br$ $[M + H]^+$, 333.9143; found, 333.9153.

*(Z)-5-(Nitromethylene)-N-(4-nitrophenyl)-1,4,2-dithiazol-3-amine (**3m**).* Isolated yield: 31% (139 mg, 0.47 mmol). Yellow solid; mp 223.7−225.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.52 (s, 1H), 8.34 (s, 1H), 8.27 (d, J = 9.2 Hz, 2H), 7.80 (d, J = 9.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 154.9, 145.1, 141.9, 125.4, 118.0, 117.6 ppm. HRMS (EI): m/z calcd for $C_9H_6N_4O_4S_2$ $[M]^+$, 297.9830; found, 297.9832.

Synthesis of Compound 3n. 1-Benzoyl-2-thiourea (0.541 g, 3 mmol) and tetrabutylammonium fluoride (0.783 g, 3 mmol) were stirred in $CHCl_3$ (15 mL) at −10 °C, and then 1,1-dichloro-2-nitroethene (0.255 g, 1.8 mmol) was added to the stirred solution. The reaction mixture was stirred at −10 °C until the reaction was complete as monitored by TLC. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was further purified by column chromatography (petroleum ether and ethyl acetate (6/1 v/v)).

*(Z)-N-(5-(Nitromethylene)-1,4,2-dithiazol-3-yl)benzamide (**3n**).* Isolated yield: 37% (156 mg, 0.56 mmol). Yellow solid; mp 245.8−246.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.22 (s, 1H), 8.41 (s, 1H), 8.08 (d, J = 7.7 Hz, 2H), 7.70 (t, J = 7.2 Hz, 1H), 7.58 (t, J = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.0, 165.9, 155.2, 133.5, 130.5, 128.7, 128.6, 117.8 ppm. HRMS (EI): m/z calcd for $C_{10}H_7N_3O_3S_2$ [M]+, 280.9929; found, 280.9934.

Synthesis of Compound 3o. Thiobenzamide (0.412 g, 3 mmol) and tetrabutylammonium fluoride (0.783 g, 3 mmol) were stirred in $CHCl_3$ (15 mL) at −10 °C, and then 1,1-dichloro-2-nitroethene (0.255 g, 1.8 mmol) was added to the stirred solution. The reaction mixture was stirred at −10 °C until the reaction was complete as monitored by TLC. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was further purified by column chromatography (petroleum ether and ethyl acetate (6/1 v/v)).

*(Z)-5-(Nitromethylene)-3-phenyl-1,4,2-dithiazole (**3o**).* Isolated yield: 46% (165 mg, 0.69 mmol). Yellow solid; mp 188.4−190.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.48 (s, 1H), 7.92 (d, J = 7.3 Hz, 2H), 7.66 (t, 1H), 7.59 (t, J = 16.6, 9.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.9, 165.2, 132.7, 130.5, 129.7, 127.9, 119.1 ppm. HRMS (EI): m/z calcd for $C_9H_6N_2O_2S_2$ $[M]^+$, 237.9871; found, 237.9873.

Synthesis of Compound 3V. 1-(4-Nitrophenyl)-3-(4-tolyl)-thiourea (0.862 g, 3 mmol) and tetrabutylammonium fluoride (0.783 g, 3 mmol) were stirred in $CHCl_3$ (15 mL) at −10 °C, and then 1,1-dichloro-2-nitroethene (0.255 g, 1.8 mmol) was added to the stirred solution. The reaction mixture was stirred at −10 °C until the reaction was complete as monitored by TLC. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was further purified by column chromatography (petroleum ether and ethyl acetate (6/1 v/v)).

*(3Z,5Z)-5-(Nitromethylene)-N-(4-nitrophenyl)-2-(p-tolyl)-1,4,2-dithiazolidin-3-imine (**3V**).* Isolated yield: 33% (193 mg, 0.50 mmol). Yellow solid; mp 142.9−143.4 °C. 1H NMR (400 MHz, DMSO-d_6): δ 8.35 (s, 1H), 8.24 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 7.7 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 159.6, 156.3, 150.9, 143.6, 138.8, 133.0, 130.3, 127.5, 125.6, 122.1, 121.2, 20.7. HRMS (EI): m/z calcd for $C_{16}H_{12}N_4O_4S_2$ $[M]^+$, 388.0300; found, 388.0299.

General Procedure for the Synthesis of Products 4. Diphenylthiourea derivatives (3 mmol) were added to C_2H_5OH (15 mL) at −25 °C, and then 1,1-dichloro-2-nitroethene (0.511 g, 3.6 mmol) was added to the stirred solution. The reaction mixture was stirred at −25 °C until the reaction was complete as monitored by TLC. After being cooled to room temperature, the solvent was removed by vacuum and the solid was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was further purified by column chromatography.

*(2Z,4Z)-4-(Nitromethylene)-N,3-diphenyl-1,3-thiazetidin-2-imine (**4a**).* Isolated yield: 68% (607 mg, 2.04 mmol). Yellow solid; mp 121.9−123.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14 (s, 1H), 7.69 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.9 Hz, 2H), 7.48−7.41 (m, 3H), 7.28 (t, J = 7.4 Hz, 1H), 7.16 (d, J = 7.5 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.9, 143.8, 143.6, 134.1, 129.9, 129.6, 128.1, 126.3, 123.5, 121.4, 115.7 ppm. HRMS (EI): m/z calcd for $C_{15}H_{11}N_3O_2S$ $[M]^+$, 297.0572; found, 297.0574.

*(2Z,4Z)-4-(Nitromethylene)-N,3-di-p-tolyl-1,3-thiazetidin-2-imine (**4b**).* Isolated yield: 60% (586 mg, 1.8 mmol). Yellow solid; mp 128.7−130.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (s, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.04 (d, J = 8.1 Hz, 2H), 2.36 (s, 3H), 2.31 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.3, 143.2, 141.0, 137.9, 135.7, 131.7, 130.3, 123.0, 123.6, 121.3, 115.3, 20.7, 20.5 ppm. HRMS (EI): m/z calcd for $C_{17}H_{15}N_3O_2S$ $[M]^+$, 325.0885; found, 325.0884.

*(2Z,4Z)-N,3-Bis(4-methoxyphenyl)-4-(nitromethylene)-1,3-thiazetidin-2-imine (**4c**).* Isolated yield: 73% (783 mg, 2.19 mmol). Yellow solid; mp 151.1−151.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (s, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.09 (dd, J = 8.3, 4.9 Hz, 4H), 7.00 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 3.77 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.9, 157.7, 156.1, 142.6, 136.3, 126.9, 125.9, 122.7, 115.1, 114.8, 114.7, 55.5, 55.3 ppm. HRMS (EI): m/z calcd for $C_{17}H_{15}N_3O_4S$ $[M]^+$, 357.0783; found, 357.0782.

*(2Z,4Z)-N,3-Bis(4-chlorophenyl)-4-(nitromethylene)-1,3-thiazetidin-2-imine (**4d**).* Isolated yield: 81% (890 mg, 2.43 mmol). Yellow solid; mp 166.7−169.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (s, 1H), 7.71 (d, J = 9.6 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.9 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.3, 144.5, 142.4, 132.8, 132.4, 130.6, 129.8, 129.6, 125.5, 123.3, 116.2 ppm. HRMS (EI): m/z calcd for $C_{15}H_9N_3O_2S^{35}Cl_2$ $[M]^+$, 364.9793; found, 364.9785; calcd for $C_{15}H_9N_3O_2S^{35}Cl^{37}Cl$ $[M]^+$, 366.9763; found, 366.9760.

*(2Z,4Z)-N,3-Bis(4-bromophenyl)-4-(nitromethylene)-1,3-thiazetidin-2-imine (**4e**).* Isolated yield: 83% (1133 mg, 2.49 mmol). Yellow solid; mp 183.5−184.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (s, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.64 (t, 4H), 7.11 (d, J = 8.6 Hz, 2H)

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ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.2, 144.4, 142.8, 133.2, 132.7, 132.5, 125.6, 123.6, 120.8, 118.8, 116.2 ppm. HRMS (EI): m/z calcd for $C_{15}H_9N_3O_2S^{79}Br_2$ $[M]^+$, 452.8782; found, 452.8779; calcd for $C_{15}H_9N_3O_2S^{79}Br^{81}Br[M]^+$, 454.8762; found, 454.8770.

*(2Z,4Z)-N,3-Bis(2-chlorophenyl)-4-(nitromethylene)-1,3-thiazetidin-2-imine (**4f**).* Isolated yield: 72% (791 mg, 2.16 mmol). Yellow solid; mp 128.3−130.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (s, 1H), 7.86 (d, J = 7.3 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.68−7.53 (m, 3H), 7.41 (t, J = 7.6 Hz, 1H), 7.32−7.21 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ 155.1, 145.4, 140.8, 132.3, 131.3, 130.7, 130.6, 130.4, 130.1, 128.6, 128.5, 127.4, 126.7, 121.4, 116.6 ppm. HRMS (EI): m/z calcd for $C_{15}H_9N_3O_2SCl_2$ $[M]^+$, 364.9793; found, 364.9790; calcd for $C_{15}H_9N_3O_2S^{35}Cl^{37}Cl$ $[M]^+$, 366.9763; found, 366.9745.

*(2Z,4Z)-N,3-Bis(3-chlorophenyl)-4-(nitromethylene)-1,3-thiazetidin-2-imine (**4g**).* Isolated yield: 76% (835 mg, 2.28 mmol). Yellow solid; mp 116.2−118.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 (s, 1H), 7.81 (t, J = 1.8 Hz, 1H), 7.65 (d, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.54−7.43 (m, 2H), 7.34 (dd, 1H), 7.24 (t, J = 1.9 Hz, 1H), 7.13 (dd, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.9, 145.1, 145.1, 135.0, 134.1, 133.8, 131.5, 131.2, 128.2, 126.1, 123.5, 122.3, 121.6, 119.9, 116.6 ppm. HRMS (EI): m/z calcd for $C_{15}H_9N_3O_2SCl_2$ $[M]^+$, 364.9793; found, 364.9791; calcd for $C_{15}H_9N_3O_2S^{35}Cl^{37}Cl$ $[M]^+$, 366.9763; found, 366.9768.

*(2Z,4Z)-4-(Nitromethylene)-3-(4-nitrophenyl)-N-(p-tolyl)-1,3-thiazetidin-2-imine (**4V**).* Isolated yield: 53% (567 mg, 1.59 mmol). Yellow solid; mp 132.9−134.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 8.36 (d, J = 8.9 Hz, 2H), 7.99 (d, J = 8.9 Hz, 2H), 7.27 (d, J = 7.9 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.0, 145.1, 142.9, 140.7, 139.4, 136.0, 130.4, 125.0, 123.4, 121.3, 117.0, 20.5. HRMS (EI): m/z calcd for $C_{16}H_{12}N_4O_4S$ $[M]^+$, 356.0579; found, 356.0580.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01307. CCDC files 1423225 (**3g**), 1423226 (**4e**), and 1423227 (**4V**) also contain supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Optimization of the formation of TAD **4a** and NMR spectra (PDF)
Crystallographic data for **3g** (CIF)
Crystallographic data for **4e** (CIF)
Crystallographic data for **4V** (CIF)

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Notes

The authors declare no competing financial interest.

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