JOC The Journal of Organic Chemistry

Article

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

Yian Feng, Minming Zou, Runjiang Song, Xusheng Shao, Zhong Li, and Xuhong Qian

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01307 • Publication Date (Web): 25 Aug 2016

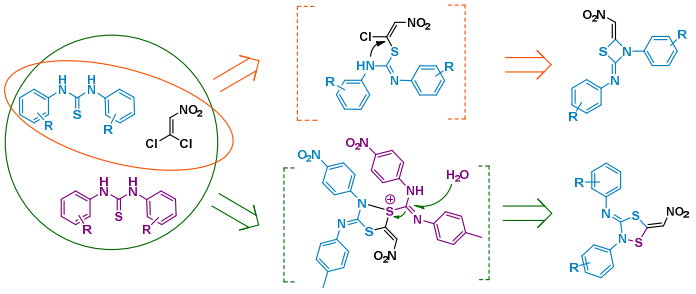
ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

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

Yian Feng[‡a] , Minming Zou[‡a], Runjiang Song[a], Xusheng Shao[a,*], Zhong Li[a,b] and Xuhong Qian[a]

[a] *Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai, 200237, China.*
[b] *Shanghai Collaborative Innovation Center for Biomanufacturing Technology, 130 Meilong Road, Shanghai 200237, China.*



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. Solvent has significant influence on the formation of product type. 1,4,2-dithiazolidines were formed in aprotic solvent chloroform, while in protic solvent ethanol, the 1,3-thiazetidines were the main products.

INTRODUCTION

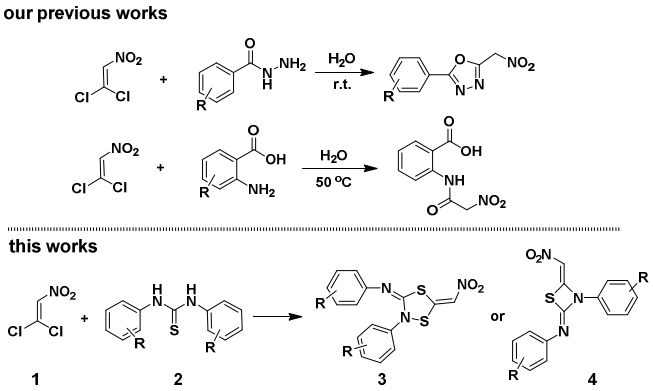
The main N, S-containing heterocycles (NSHs) include thiazoles,[1] isothiazoles,[2] thiadiazoles,[3] dithiazoles,[4] thio-morpholines,[5] 1,4-thiazepines[6] and thiazetidines[7] and their dihydro/tetrahydro-derivatives. The ascendancy and impacts of NSHs are well understood by scientists across various 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 involved 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 reaction of phosphorodithioate, aldehydes and aldimines.[14]

The utilizations regarding with 1,4,2-dithiazolidines were scarcely reported probably due to their limited synthetic choices.[15] The rarely reported synthetic methods of DTAs included cyclization of (methylsulfinyl)methyl carbamimi-dothioate,[14] reaction of 1,3-dithietane with anilines[16] and condensation of thione S-imide with diphenylmethanethione.[17] However, these synthetic methods have some draw-backs of using uncommon intermediates and limited patterns

* Corresponding author. e-mail: shaoxusheng@ecust.edu.cn

of substituents.



Scheme 1. Reactions of DCNE with aryl hydrazides, anthranilic acids and phenylthiourea

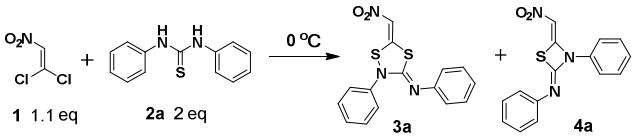
Despite the chemical or pharmaceutical importance of TADs and DTAs, limited efforts have been made for their synthetic methodologies, in particular the synthetic availabilities for DTAs. We discovered herein a straightforward synthesis of TADs and DTAs from thioureas and 1,1-dichloro-2-nitroethene (DCNE) through solvent-dependent product selectivity. TADs were formed in protic solvent ethanol, while in the aprotic solvent chloroform, the 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 massively used in polymers science.[19] The highly-polarized ethylene system makes DCNE has the similar reactivity with that of phosgene, making it can be attacked by nucleophiles such as amines, aryl alcohols and mercaptans.[18] Our recent studies on DCNE chemistry revealed its ability in oxadiazoles construction and nitroacetylation in reacting with aryl hydrazides and anilines, respectively. (Scheme 1)[19] The above observations stimulated us to explore its reaction behaviors towards 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 afterwards assigned with the aid of X-ray crystallography studies of their analogues **3g** and **4e**, confirming the products were five-membered **3a** and four-membered **4a** rings, respectively.

Having identified the interesting heterocyclic scaffolds, we started the reaction-condition optimization to raise the yields and improve the selectivity. Initially, the product dependency on solvents was investigated. A model reaction of DCNE with DPTU **2a** was evaluated in molecular ratio of 1.1:2 at 0 °C (Table 1). Screening of the solvents indicated that the reaction was sensitive to the solvents. Acetonitrile and ethyl acetate provided almost a 1:1 formation of **3a** and **4a** (Table 1, entry 1 and 2). The maximum formation of **3a** was achieved in chloroform with a ratio of 5:1 of **3a**:**4a** (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).

Table 1. Solvent dependency of the formation of DTA **3a** and TAD **4a**



Entry	Solvent	**3a** (yields, %) [a]	**4a** (yields, %) [a]
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 the HPLC analysis. [b] n.r., no reaction.

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 the increase of the yield to 49%, while further lowering the temperature caused the yields decrease. Increase the ratio of DCNE would not have the positive effects to the yields (Table 2, entry 5-8). Acid captures Na_2CO_3 and Cs_2CO_3 had the detrimental effects to the reaction accompanying with the great loss of the formation of **3a** (Table 2, entry 10 and 11).

Since the conversion proceeded with the formation of side products due to the high reactive feature of the reactants, therefore, catalysts that can stabilize the DCNE or thioureas were 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 could catalyze a variety of nitro compounds including nitroalkenes.[21] Thus, diphenylurea (DPU) was evaluated to see 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. For the fact that thiourea derivatives are good receptor for anion recognition in particular fluorine anion, by forming strong host-guest complex,[22] therefore, tetrabutylammonium fluoride (TBAF) was subjected to the reaction. It is interesting to observe a significant yield increase (67%) and a lower reaction rate (Table 2, entry 13), suggesting the 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). The highest yielding of **4a** was achieved using ethanol at -25 °C. Notably, the catalysts DPU or TBAF did not have any beneficial effects to this transformation.

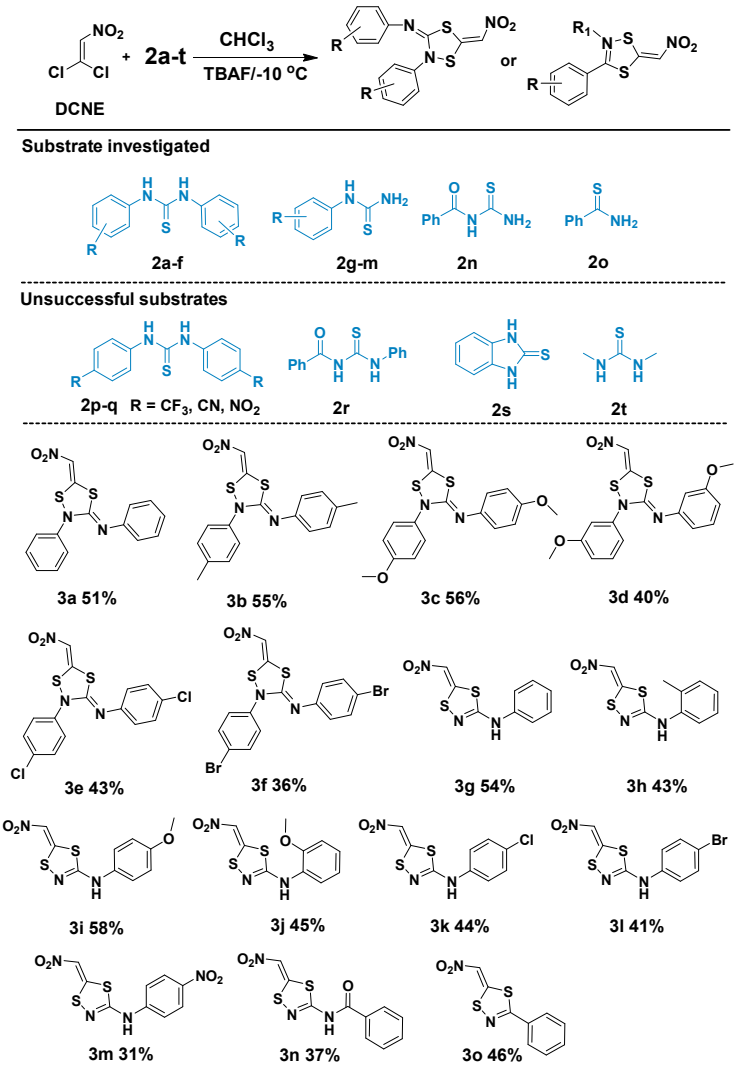
Table 2. Optimization of the formation of DTA **3a**

Entry	T (°C)	2a:1	Additive	Yields (%)
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], 0.2eq	65
13	-10	2:1.1	TBAF[b], 2eq	67
14	-10	2:1.2	DPU, 0.2eq TBAF, 2eq	23

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

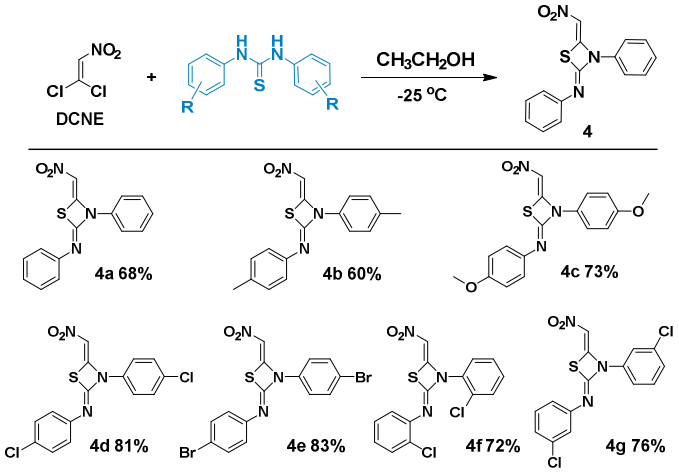
By applying the conditions to favor the DTA **3** formation, the reaction scopes were investigated with varying thioureas (Scheme 2). DPTUs with electron-donating substituents were well tolerated, despite the moderate yields. Using DPTUs with electron-withdrawing groups (cyano, nitro, and trifluoromethyl) 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 endo-cyclic one. The substrate **2m** with strong-withdrawing nitro group generated the DTA **3m** in 31% yield.

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 cyclic thiourea **2s**. Reaction of 1,3-dimethylthioure **2t** gave an intractable mixture without any separable products.



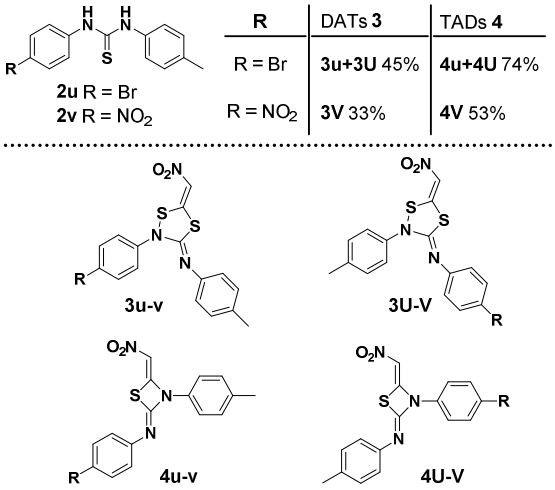
Scheme 2. Substrate investigation on synthesizing DTA **3**

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 substituents of electron density may cause their ring-opening reaction, providing a possible explanation for the specific substrate requirements in TAD formation.



Scheme 3. Substrate investigation on the formation of TAD **4**

When studying asymmetrical DPTUs **2u** and **2v**, 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. In evaluating DPTU **2u** with methyl and bromo substituents at each of phenyl rings, a mixture of **3u** and **3U** or **4u** and **4U** were separated in a total yield of 45% and 74%, respectively. This observation can be rationalized by the slight difference between methyl and bromo in the electronic contributions. For DPTU **2v** with strong 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 2Z,4Z configuration for 4V was assigned according to the steric effect of the adjacent phenyl substituent.

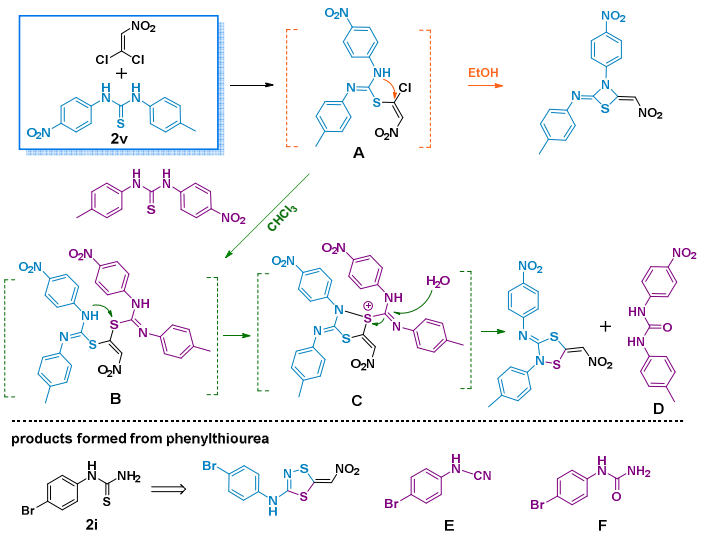


Scheme 4. Selectivity investigation on the asymmetrical diphenylthioureas.

Based on 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 four-membered product. While, 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. Besides the formation of DTA, side product diphenylurea **D** was also separated, which generated by intermediate **C** formed in the reaction. While for the phenylthiourea **2i**, cyanamide **E** and phenylurea **F** were detected as the side products (Scheme 5). The nitro olefin may exist in *trans* or *cis* configuration, however, only one thermal stable isomer were observed and no *trans-cis* isomerization occurred during the store 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 the simplicity and generality, we expect this protocol would have wide application for the preparation of functional molecules.



Scheme 5. Proposed mechanism and side products for the formation of DTA and TAD.

EXPERIMENTAL SECTION

General information

Chromatographic analysis was performed using an ACQUITY UPLC-H Class system, equipped with BEH C18 reversed phase column. The mobile phase was a mixture of MilliQ ultrapure water with 0.01% trifluoroacetic acid (A) and acetonitrile (B). The following elution gradient totally lasted 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 nm 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 added to the flask, drop added the 1,1-dichloroethylene (31.0 g, 0.315 mol) in 3 h, and kept at 20-25 °C. The mixture was continuously stirred for 1 h, then washed with water, and extracted by $CHCl_3$, collected the organic phase, then added it to 235 mL 4% NaOH solution in the ice bath, after simple separation and chloroform washing, the organic phase was concentrated, and dried with anhydrous magnesium sulfate, then obtained 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

Aniline compounds (50 mmol) was dissolved in C_2H_5OH (30 mL), 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), stirred at room temperature. NH_4SCN (62.5 mmol) was dissolved in acetone (10 mL), then added dropwise to the reaction mixture, stirred for 15 min. The precipitate was moved by filtration, then the filtrate was dissolved in ethyl acetate (20 mL). Aniline compounds (50 mmol) was dissolved in ethyl acetate (10 mL), then added dropwise to the reaction mixture at room temperature, 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, stirred at room temperature until the reaction was complete as monitored by TLC. The reaction mixture was adjusted pH to 7 by HCl, stirred under ice-bath. Filtered to afford product (yield: 80-85%).

General procedure for the synthesis of compounds 3

Compounds **2a-m** (3 mmol) and tetrabutyl ammonium fluoride (783 mg, 3 mmol) were stirred in $CHCl_3$ (15 mL) at -10 ^{o}C, 1,1-dichloro-2-nitroethene (255 mg, 1.8 mmol) were added to the stirred solution. The reaction mixture was stirred at -10 ^{o}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,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, 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-d6): 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-d6): 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 Tetrabutyl ammonium fluoride (0.783 g, 3 mmol) were stirred in $CHCl_3$ (15 mL) at -10 ^oC, 1,1-dichloro-2-nitroethene (0.255 g, 1.8 mmol) were added to the stirred solution. The reaction mixture was stirred at -10 ^oC 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 ^oC; ^1H NMR (400 MHz, DMSO-d6): 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; 13C 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 Tetrabutyl ammonium fluoride (0.783 g, 3 mmol) were stirred in $CHCl_3$ (15 mL) at -10 ^oC, 1,1-dichloro-2-nitroethene (0.255 g, 1.8 mmol) were added to the stirred solution. The reaction mixture was stirred at -10 ^oC 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 ^oC; ^1H 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 Tetrabutyl ammonium fluoride (0.783 g, 3 mmol) were stirred in $CHCl_3$ (15 mL) at -10 ^oC, 1,1-dichloro-2-nitroethene (0.255 g, 1.8 mmol) were added to the stirred solution. The reaction mixture was stirred at -10 ^oC 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^oC; 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). 13C 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 in C_2H_5OH (15 mL) at -25 ^oC, 1,1-dichloro-2-nitroethene (0.511 g, 3.6 mmol) were added to the stirred solution. The reaction mixture was stirred at -25 ^oC 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 ^oC; ^1H 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 ^oC; ^1H 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 ^oC; ^1H 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 ^oC; ^1H 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) 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 (100MHz, 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 including optimization of the formation of TAD **4a**, Copies of NMR spectra.

Crystallography

CCDC: 1423225 (**3g**), 1423226 (**4e**) and 1423227 (**4V**) contain the 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.

AUTHOR INFORMATION

Corresponding Authors

* E-mail: shaoxusheng@ecust.edu.cn; Phone: (+86) 21-64253967

‡ These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

This work was financial supported by National Natural Science Foundation of China (21372079, 21472046), Shanghai Pujiang Program (14PJD012).

REFERENCES

1. Mishra, C. B.; Kumari, S.; Tiwari, M., *Eur. J. Med. Chem.* **2015,** *92* (1), 1-34.

2. Clerici, F.; Gelmi, M. L.; Pellegrino, S.; Pocar, D., *Top. Heterocycl. Chem.* **2007,** *9* (Bioactive Heterocycles III), 179-264.

3. Shang, X.; Li, W.; Wei, X.; Zhang, H.; Fu, Z.; Zhang, J.; Xu, X., *Heteroatom Chem.* **2015,** *26* (2), 142-149.

4. Popov, V. V.; Konstantinova, L. S.; Rakitin, O. A., *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2011,** *47* (7), 789-806.

5. Bower, J. F.; Rujirawanich, J.; Gallagher, T., *Org. Biomol. Chem.* **2010,** *8* (7), 1505-1519.

6. Kaishap, P. P.; Shekarrao, K.; Saikia, P.; Gogoi, S.; Boruah, R. C., *Tetrahedron Lett.* **2014,** *55* (11), 1927-1930.

7. Rai, A.; Yadav, L. D. S., *Tetrahedron Lett.* **2011,** *52* (30), 3933-3936.

8. (a) Alvárez-Builla, J.; Barluenga, J., Wiley-VCH Verlag GmbH & Co. KGaA: 2011; pp 1-9; (b) Dua, R.; Shrivastava, S.; Sonwane, S. K.; Srivastava, S. K., *Adv. Biol. Res.* **2011,** *5* (3), 120-144; (c) Saini, M. S.; Kumar, A.; Dwivedi, J.; Singh, R., *Int. J. Pharma Sci. Res.* **2013,** *4* (3), 66-77; (d) Taylor, R. D.; MacCoss, M.; Lawson, A. D., *J. Med. Chem.* **2014,** *57* (14), 5845-5859.

9. (a) Baum, E. W.; Crouse, G. D.; Dent, W. H.; Sparks, T. C.; Creemer, L. C. WO2013116052A1, 2013; (b) Ding, Q.; Jiang, N.; Weikert, R. J. WO2014135472A1, 2014; (c) Segawa, J.; Kitano, M.; Kazuno, K.; Matsuoka, M.; Shirahase, I.; Ozaki, M.; Matsuda, M.; Tomii, Y.; Kise, M., *J. Med. Chem.* **1992,** 35 (25), 4727-4638.

10. (a) Forgber, S.; Cleve, D.; Rudorf, W. D., *J. Sulfur Chem.* **2005,** *26* (6), 499-507; (b) Jin, C.; Liu, C.; Su, W., *Synlett* **2009,** (4), 607-610; (c) Okajima, N.; Okada, Y., *J. Heterocycl. Chem.* **1991,** *28* (1), 177-185.

11. Akhmetova, V. R.; Vagapov, R. A.; Nadyrgulova, G. R.; Tyumkina, T. y. V.; Starikova, Z. A.; Antipin, M. Y.; Kunakova, R. V.; Dzhemilev, U. M., *Tetrahedron* **2007,** *63* (47), 11702-11709.

12. Tsuchiya, T.; Yasumoto, M.; Shibuya, I.; Taguchi, Y.; Yonemoto, K.; Goto, M., *Chem. Lett.* **1990,** (8), 1423-1426.

13. Goerdeler, J.; Ho, C. H., *Chem. Ber.* **1983,** *116* (4), 1297-1308.

14. Yadav, L. D. S.; Rai, V. K., *Tetrahedron* **2007,** *63* (29), 6924-6931.

15. Capps, N. K.; Davies, G. M.; McCabe, R. W.; Young, D. W., *J. Chem. Soc., Perkin Trans. 1* **1999,** (24), 3569-3571.

16. Claus, P. K.; Jaeger, E., *Monatsh. Chem.* **1985,** *116* (10), 1153-1164.

17. Mloston, G.; Celeda, M.; Roesky, H. W.; Parisini, E.; Ahlemann, J. T., *Eur. J. Org. Chem.* **1998,** (3), 459-465.

18. (a) Buevich, V. A.; Nakova, N. Z.; Perekalin, V. V., *Zh. Org. Khim.* **1979,** *15* (7), 1473-1476; (b) Iwata, F.; Harada, K.; Sugise, R. EP115323A2, 1984.

19. (a) Zhu, F.; Tian, X.; Shao, X.; Li, Z., *Tetrahedron Lett.* **2015,** *56* (43), 5945-5949; (b) Zhu, F.; Zou, M.; Shao, X.; Li, Z., *RSC Adv.* **2015,** *5* (76), 61752-61758.

20. (a) Auvil, T. J.; Schafer, A. G.; Mattson, A. E., *Eur. J. Org. Chem.* **2014,** (13), 2633-2646; (b) So, S. S.; Oottikkal, S.; Badjic, J. D.; Hadad, C. M.; Mattson, A. E., *J. Org. Chem.* **2014,** *79* (11), 4832-4842.

21. (a) Etter, M. C., *Acc. Chem. Res.* **1990,** *23* (4), 120-126; (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y., *J. Am. Chem. Soc.* **2005,** *127* (1), 119-125.

22. (a) Boyle, E. M.; Comby, S.; Molloy, J. K.; Gunnlaugsson, T., *J. Org. Chem.* **2013,** *78*, 8312; (b) Lin, S.; Jacobsen, E. N., *Nat. Chem.* **2012,** *4*, 817; (c) Wu, F.-Y.; Li, Z.; Wen, Z.-C.; Zhou, N.; Zhao, Y.-F.; Jiang, Y.-B., *Org. Lett.* **2002,** *4*, 3203.

23. (a) Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K., *Org. Lett.* **2006,** *8*, 5397-5399; (b) Yella, R.; Ghosh, H.; Patel, B. K., *Green Chem.* **2008,** *10*, 1307.