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Iodine(III)-Mediated Intramolecular Sulfeno- and Selenofunctionalization of β, γ-unsaturated Tosyl Hydrazones and Oximes

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Jing-miao Yu,[a] Chun Cai*[a]

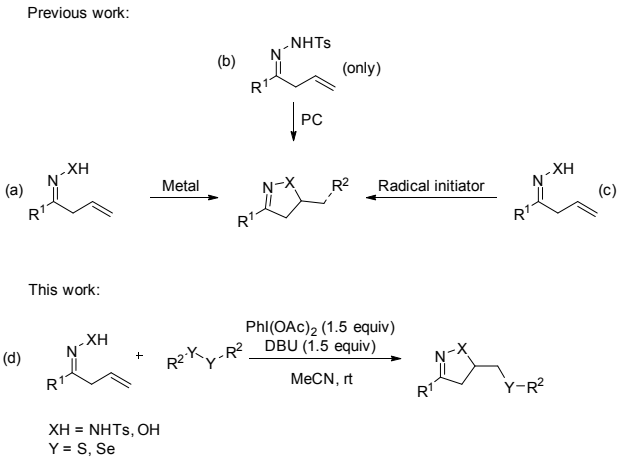
A cascade radical cyclization/sulfenylation or selenylation of β, γ-unsaturated hydrazones and oximes was realized under mild conditions with phenyliodine(III) diacetate (PIDA) as the sole oxidant, leading to the construction of various diversely functionalized heteroatom-containing pyrazoline and isoxazoline derivatives. This metal-free radical process is suggested to encompass a sequential C-N/O and C-S/Se bond fomation.

Introduction

Pyrazolines[1] and isoxazolines[2] represent two classes of privileged heterocycles that widely exist in biologically active natural products and pharmaceuticals such as anti-amoebic, hypotensive, analgesic, anti-cancer, anti-bacterial, anti-depressant and nonsteroidal anti-inflammatory agents. Consequently, a plethora of novel and elegant methodologies for construction of these five-membered heteroatom-containing heterocycles have received extensive attention.

β, γ-unsaturated hydrazones and oximes have recently emerged as versatile synthons in a variety of transition-metal-catalyzed and transition-metal-free reactions, affording pyrazoline and isoxazoline derivatives. Representative transition-metal-catalyzed(e.g., cobalt[3], copper[4], palladium[5], etc.) cyclizations of β,γ-unsaturated hydrazones and oximes are powerful approaches for the synthesis of diversely functionalized pyrazolines and isoxazolines(Scheme **1a**). For instance, in 2014, Wang et al.[4b] reported Cu-catalyzed intramolecular oxytrifluoromethylthiolation of internal alkenes of unsaturated oximes by using $AgSCF_3$ as the SCF_3-souce. Recently, Huang et al.[5c] reported Pd-catalyzed tandem aminomethylation/cyclization/aromatization reaction of β, γ-unsaturated hydrazones with aminals via C–N bond activation. However, the utility and applicability of the above reactions were limited by high cost or toxicity of the transition metals and/or harsh reaction conditions.

Apart from this, a visible-light-induced photocatalytic hydroamination and oxyamination of β,γ-unsaturated hydrazones, pioneered by the work of Xiao and co-workers



Scheme 1. Strategies for cyclization of β, γ-unsaturated hydrazones and oximes

demonstrated in 2014[6], is a considerable elegant approach. Major progresses[6-7] along this line have been mainly achieved focused on the photocatalytic hydrazonyl radical-mediated radical cascade reactions(Scheme **1b**). Although visible light photoredox catalysis played very important role in the direct generation of hydrazonyl radicals from N-H bonds, the β,γ-unsaturated oximes proved to be not suitable for this strategy, presumably by the higher redox potential of oximes relative to that of the photocatalyst. Meanwhile, the development of metal-free reactions initiated by radical initiators (e.g.,TEMPO[8], TBN[9], TBHP[10], hypervalent iodine[11], etc.) is crucial for solving this problem(Scheme **1c**).

Hypervalent iodine reagents are well-known as nonexplosive and readily available oxidizing reagents for mediating organic reactions involving the formation of new carbon–carbon bond and carbon–heteroatom bond[12]. Therefore, hypervalent iodine reagents have been employed to mediate the difunctionalization of unactivated alkenes[13], which provides an alternative platform for this transformation. In 2015, Wang et al.[11a] described the intramolecular oxy-

[a] Chemical Engineering College, Nanjing University of Science and Technology, 200 Xiao Ling Wei Street, Nanjing, Jiangsu, People's Republic of China.
E-mail: c.cai@njust.edu.cn.

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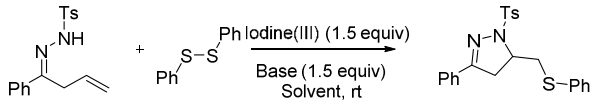
fluorination of alkenyl oximes by employing $PhI(OPiv)_2$ as the mediator and HF-pyridine as the F-source, and Xiao et al.[11b] reported the $PhI(OAc)_2$-promoted radical cyclization of β,γ-unsaturated hydrazones and oximes. However, to our knowledge, there are no reports of iodine(III)-mediated intramolecular sulfeno- and selenofunctionalization of β,γ-unsaturated hydrazones and oximes.

Inspired by these mentioned facts, organosulfur and organoselenium chemistry[14], we envisioned the direct generation of the N-centered radicals from N-H bonds or the O-centered radicals from O-H bonds mediated by hypervalent iodine reagent, followed by radical cyclization/sulfenylation or selenylation cascade reactions. Herein, we report the application of β,γ-unsaturated tosyl hydrazones and oximes in radical cyclization/sulfenylation or selenylation reactions catalyzed by hypervalent iodine reagent. During this reaction, benign PIDA($PhI(OAc)_2$) was used as the oxidant and disulfides/ diselenides were employed as the S/Se-sources(Scheme **1d**).

Results and discussion

The initial investigation was focused on the reaction of β,γ-unsaturated tosyl hydrazone **1a** with disulfide **2a** and various iodine(III) sources in the presence of DBU(2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine) as the base (Table1, entries 1-3). Compare to other iodine(III) sources like PhIO and PIFA,

Table 1. Optimization of the Reaction Conditions [a]



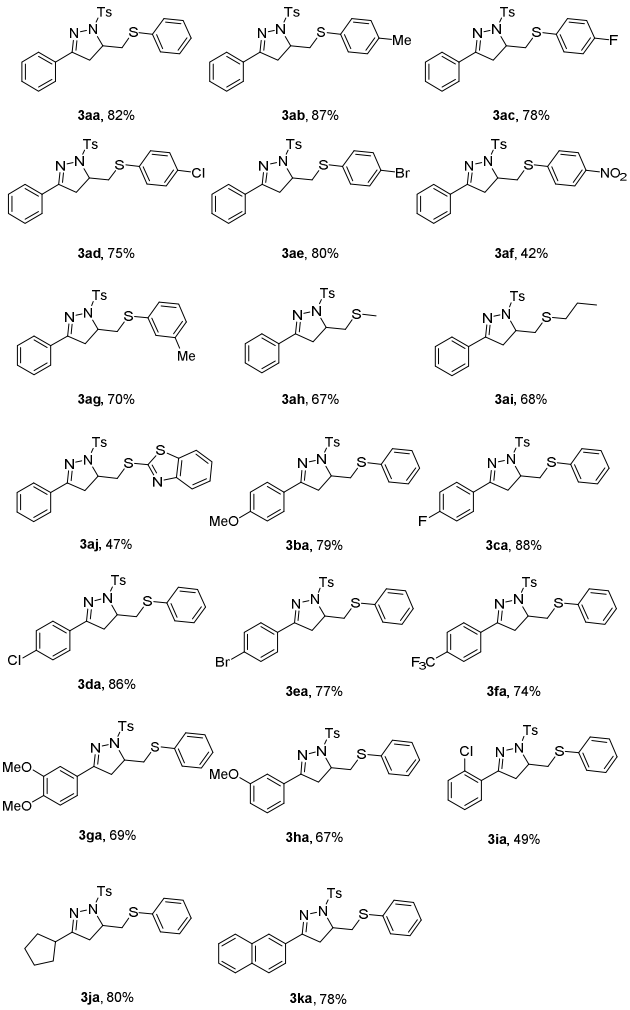
1a 2a 3aa

Entry	iodine(III)	Base	Solvent	Yield 3a[b]
1	PhIO	DBU	THF	45
2	PIDA	DBU	THF	67
3	PIFA	DBU	THF	32
4	PIDA	K_2CO_3	THF	21
5	PIDA	NaOH	THF	25
6	PIDA	TBD	THF	43
7	PIDA	TMG	THF	34
8	PIDA	DBU	MeOH	Trace
9	PIDA	DBU	DMF	11
10	PIDA	DBU	PhMe	52
11	PIDA	DBU	DCM	49
12	**PIDA**	**DBU**	**MeCN**	**82**
13[c]	PIDA	DBU	MeCN	62
14[d]	PIDA	DBU	MeCN	87
15[e]	PIDA	DBU	MeCN	73
16[f]	PIDA	DBU	MeCN	83
17	-	DBU	MeCN	0
18	PIDA	-	MeCN	0

[a] Reaction conditions: β,γ-unsaturated tosyl hydrazone **1a** (0.2 mmol), disulfide **2a** (0.15 mmol), iodine(III) (0.3 mmol), base (0.3 mmol) and solvent (2.0 mL), Ar, at room temperature, stirred for 6h. [b] Isolated yield. [c] 1.2 equiv of PIDA. [d] 2 equiv of PIDA. [e] 1.2 equiv of DBU. [f] 2 equiv of DBU.

Table 2. Iodine(III)-mediated intramolecular sulfenofunctionalization of β, γ-unsaturated tosyl hydrazones with disulfides [a, b]

1 2 3



[a] Reaction conditions: β,γ-unsaturated tosyl hydrazone **1a** (0.2 mmol), disulfides **2** (0.15 mmol), PIDA(1.5 equiv), DBU (1.5 equiv) in MeCN (2 mL) under an Ar atmosphere at room temperature for 6 h. [b] Isolated yield.

PIDA was approved to be the best choice to generate the target product **3aa** in 67% yield (Table 1, entry 2). Encouraged by this result, some other inorganic bases such as K_2CO_3 and NaOH and organic bases such as TBD and TMG were studied, which virtually did not lead to any significant improvement (Table 1, entries 4-7). Further investigation on different solvents revealed that other solvents such as MeOH, DMF, toluene and DCM either gave inferior results or completely hindered the reaction(Table 1, entries 8-11). To our gratification, an improved yield of target product **3aa** was achieved in MeCN (Table 1, entry 12). Varying the equivalents

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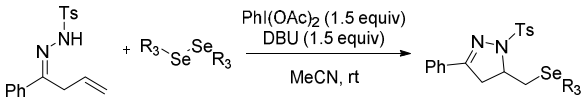
of PIDA and DBU, and both 1.5 equivalents of PIDA and DBU were the best choices for production of the desired product (Table 1, entries 13-16). In addition, control experiments showed that no product was obtained in the absence of oxidant or base (Table 1, entries 17-18).

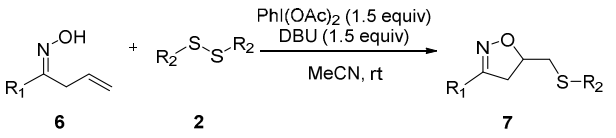
With the optimized reaction condition in hand, we proceeded to explore the scope of the reaction. We first examined the reaction between β,γ-unsaturated tosyl hydrazone **1a** and various disulfides **2**. In general, disulfides with different substituents on the *para*- or *meta*-position of the phenyl ring worked effectively. Substituents on substrates **2** have some effect on the reactions. For example, electron-donating group at the para-positions of the phenyl ring (**1d-1g**) performed well in the reaction with **1a** to furnish the desired product **3ab** in a 87% yield (Table 2, **3ab**), while electron-deficient disulfides (**2c-e**) resulted in slightly lower yields(Table 2, **3ac-e**). However, too strong electron-withdrawing group such as 4-nitro group led to a quite lower yield(42%) (Table 2, **3af**). Substrates bearing methyl at different positions of the phenyl ring could reacted smoothly with **2a** to furnish the products in fairly good yields(Table 2, **3ac** and **3aj**). Aliphatic and heterocyclic disulfides, such as dimethyl disulfide, di-n-propyl disulfide and were also tolerated, and the yields of corresponding products ranged from 47% to 68% (Table 2, **3ah–j**). Next, the substrate generality with respect to the alkenyl tosyl hydrazones **1** was investigated. The reactions proceeded smoothly for β,γ-unsaturated tosyl hydrazones with either electron-withdrawing or electron-donating substituents present on the aromatic ring (**1b–i**) to afford the desired products in moderate to high yields (Table 2, **3ba–ia**). In general, the substituent groups or substitution patterns of the aromatic ring have no obvious effect on this reaction. As for a cyclic aliphatic- or 2-naphthyl-substiuted tosyl hydrazone, the reaction proceeded fairly well under the optimized condition either, giving products **3ja–ka** in moderate yields (Table 2, **3ja–ka**).

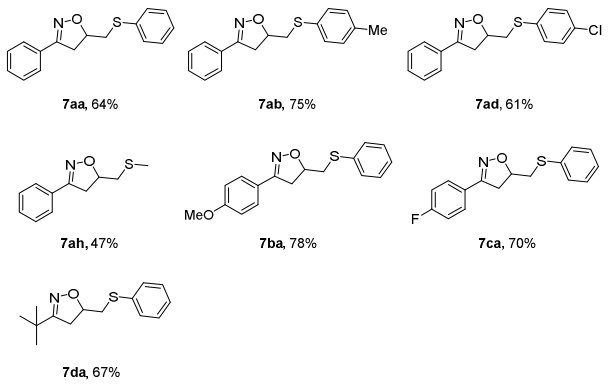


Scheme 2. Selenofunctionalization of β, γ-unsaturated tosyl hydrazone. Reaction conditons: **1a** (0.2 mmol), diselenides **4** (0.15 mmol) PIDA(1.5 equiv), DBU (1.5 equiv) in MeCN (2 mL) under an Ar atmosphere at room temperature for 6 h.

To further explore the influence of heteroatom and expand the scope of structures, we then simply examined the cascade cyclization/addition reaction of β,γ-unsaturated tosyl hydrazone **1a** with diselenides(as an alternative to disulfides)(Scheme **2**). In line with our expectation, diselenides also proved to be suitable for this transformation, and the desired products **5aa-c** were obtained in excellent yields, highlighting the efficiency of this synthetic methodology**.**

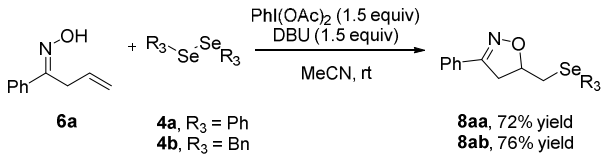
Table 3. Iodine(III)-mediated intramolecular sulfenofunctionalization of β, γ-unsaturated oximes with disulfides [a, b]





[a] Reaction conditions: β,γ-unsaturated oximes **1** (0.2 mmol), disulfides **2** (0.15 mmol), PIDA(1.5 equiv), DBU (1.5 equiv) in MeCN (2 mL) under an Ar atmosphere at room temperature for 6 h. [b] Isolated yield.

We next found that β, γ-unsaturated oximes **6** could be used as substrates (to replace hydrazones **1**) under the same condition, affording suflur-containing isoxazolines as the products in a similar fashion. In all the studied examples, disulfides with electron-donating group or electron-withdrawing one at the phenyl ring could transform to the corresponding isoindolinones **7ab** and **7ad** smoothly in good yields (Table 3, **7ab** and **7ad**). Besides, dimethyl disulfide **2h** was employed and gave product **7ah** in 47% yield (Table 3, **7ah**). Similarly, β,γ-unsaturated oximes with electron-withdrawing or electron-donating substituents on the aromatic ring could convert to the desired products in good yields (Table 3, **7ba** and **7ca**). Alkyl-substiuted oxime **6d** was found to be accommodated, affording the desired product 7la in 67% yield (Table 3, **7da**). Gratifyingly, diselenides also proceeded well to furnish the corresponding selenium-containing isoxazolines (Scheme **3**).



Scheme 3. Selenofunctionalization of β, γ-unsaturated oxime. Reaction conditons: **6a** (0.2 mmol), diselenides **4** (0.15 mmol) PIDA(1.5 equiv), DBU (1.5 equiv) in MeCN (2 mL) under an Ar atmosphere at room temperature for 6 h.

Finally, some control experiments were carried out in order to reveal the reaction pathway of this transformation (Scheme **4**). TEMPO was added as radical scavenger under the standard reaction conditions, which resulted in the formation of **9a** and

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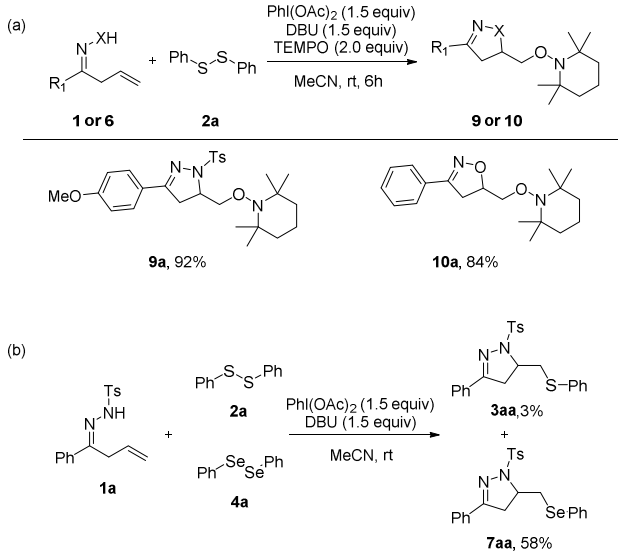
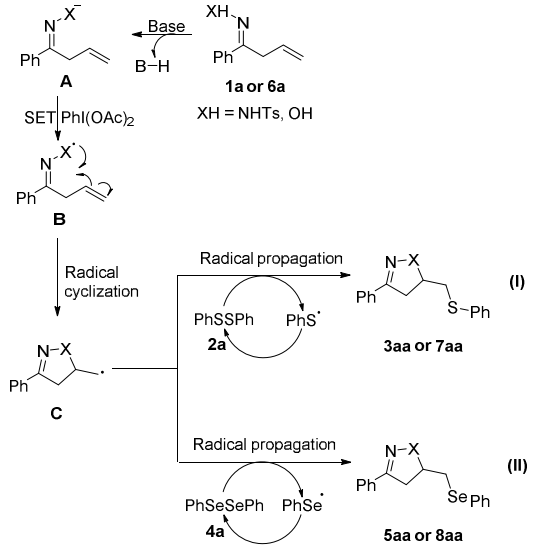
10a in 92% and 84% yield respectively (Scheme **4a**). This finding



Scheme 4. Control experiments. (a) Reaction condition: **1b or 6a** (0.2 mmol), disulfide **2a** (0.15 mmol), PIDA(1.5 equiv), DBU (1.5 equiv), TEMPO (2.0 equiv) in MeCN (2 mL) under an Ar atmosphere at room temperature for 6 h. (b) Reaction condition: **1a** (0.2 mmol), disulfide **2a** (0.15 mmol), diselenide **4a** (0.15 mmol), PIDA(1.5 equiv), DBU (1.5 equiv), in MeCN (2 mL) under an Ar atmosphere at room temperature for 6 h.

suggests that the process does indeed involve C-centered radical intermediate C. One pot reaction of **1a**, **2a** and **4a** was tested for the the reactivity of **2a** and **4a** (Scheme **4b**). The result shows that the ratio of the corresponding product **3aa** and **7aa** is 1:19, indicating that the reactivity of **4a** is superior to **2a**.

On the basis of previous work and experimental observations[8-11], a plausible mechanism was proposed as illustrated in Scheme **5**. At the beginning, deprotonation of the



Scheme 5. Proposed mechanism

β,γ-unsaturated tosyl hydrazone **1a** or oxime **6a** affords the anionic intermediate **A** under basic conditions. Subsequently, a single-electron oxidation of **A** by PIDA gives the N-centered or O-centered radical **B**. The formed hyadrazone or oxime radical **B** would undergo a radical intramolecular cyclization to produce the C-centered radical C. The C-centered radical **C** reacted with diphenyl disulfide **2a** to form the desired product **3aa** or **7aa** via a radical propagation and regenerate the sulfenyl radical which could recombine to diphenyl disulfide **2a**(Scheme **5**, Path **I**). The C-centered radical **C** could also reacted with diphenyl diselenide **4a** to form the desired product **5aa** or **8aa** in a similar way(Scheme **5**, Path **II**).

Conclusions

In conclusion, we have developed a novel and efficient iodine(III)-mediated intramolecular sulfeno- and selenofunctionalization of β, γ-unsaturated hydrazones and oximes using disulfides and diselenides as sulfur and selenium sources. This reaction provides a convenient and straightforward method to prepare a variety of useful heteroatom-containing pyrazoline and isoxazoline derivatives. In addition, this method features a broad substrate scope, wide group tolerance and chemoselectivity.

Experimental

General experimental method

All chemical reagents are obtained from commercial suppliers and used without further purification. All unknown compounds are characterized by ^{1}H NMR, ^{13}C NMR, MS. Analytical thin-layer chromatography are performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm), and the plates are visualized by exposure to ultraviolet light.^{1}H NMR and ^{13}C NMR spectra are recorded on an AVANCE 500 Bruker spectrometer operating at 500 MHz and 125 MHz in $CDCl_3$, respectively, and chemical shifts are reported in ppm. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Mass spectra are taken on a Waters UPLC H-class LC-MS instrument in the electrospray ionization (ESI) mode. Only molecular ions (M + 1) are given for the ESI-MS analysis.

A typical procedure for the synthesis of 3-phenyl-5-((phenylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3aa)

A 10 mL reaction vessel with a magnetic stirring bar was equipped with β,γ-unsaturated hydrazone (**1a**) (0.2 mmol), disulfide (**2a**) (0.15 mmol), PIDA (0.3 mmol), DBU (0.3 mmol) and MeCN (2 mL). The mixture was stirred under Ar atmosphere at r.t. for 6 h. The reaction solution was diluted with ethyl acetate, washed with water, dried over anhydrous Na_2SO_4. After the solvent had been removed under reduced pressure, the residue was purified by flash chromatography using PE-AcOEt (10:1-5:1, v/v) as the eluent to sulfer- containing pyrazoline (**3aa**).

The rest products were prepared by a similar procedure.

3-phenyl-5-((phenylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3aa), white solid. Yield: 69 mg, 82%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.63 (m, 4H), 7.57 – 7.50 (m, 2H), 7.49 – 7.38 (m, 5H), 7.35 – 7.31 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.07 (dd, *J* = 13.7, 3.2 Hz, 1H), 3.97 (tdd, *J* = 10.6, 9.2, 3.2 Hz, 1H), 3.27 (dd, *J* = 17.4,

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10.8 Hz, 1H), 3.12 – 3.06 (m, 2H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.68, 143.35, 133.37, 130.64, 129.71, 128.79, 128.55, 128.25, 127.66, 125.96, 125.72, 60.06, 38.83, 37.62, 20.61. ESI-MS *m/z*: 423 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{23}H_{22}N_2O_2S_2]$ requires $[M+H]^+$ 423.1195, found 423.1194.

3-phenyl-5-((*p*-tolylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ab), white solid. Yield: 76 mg, 87%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.67 (m, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.48 – 7.39 (m, 5H), 7.23 (dd, *J* = 8.2, 3.0 Hz, 4H), 4.01 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.93 (qd, *J* = 10.4, 3.2 Hz, 1H), 3.27 (dd, *J* = 17.4, 10.7 Hz, 1H), 3.11 – 3.02 (m, 2H), 2.43 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125 Hz, $CDCl_3$) δ 156.70, 143.30, 135.92, 130.63, 129.69, 129.51, 128.99, 128.50, 127.65, 125.95, 60.16, 38.76, 38.19, 20.62, 20.13. ESI-MS *m/z*: 437 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{24}H_{24}N_2O_2S_2]$ requires $[M+H]^+$ 437.1352, found 437.1349.

5-(((4-fluorophenyl)thio)methyl)-3-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ac), white solid. Yield: 69 mg, 78%. ^{1}H NMR (500 MHz, CDCl3) δ 7.72 – 7.67 (m, 2H), 7.63 (d, J = 8.3 Hz, 2H), 7.57 – 7.47 (m, 2H), 7.47 – 7.40 (m, 3H), 7.25 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.7 Hz, 1H), 3.98 – 3.87 (m, 2H), 3.28 (dd, J = 17.3, 10.7 Hz, 1H), 3.12 – 3.06 (m, 2H), 2.41 (s, 3H). ^{19}F NMR (470 MHz, CDCl3) δ -114.59. ^{13}C NMR (125 MHz, CDCl3) δ 156.61, 143.43, 131.74, 131.68, 130.59, 129.74, 128.54, 128.28, 127.67, 127.59, 125.94, 115.44, 115.27, 60.01, 38.73, 20.60. ESI-MS m/z: 441 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{23}H_{21}FN_2O_2S_2]$ requires $[M+H]^+$ 441.1101, found 441.1099.

5-(((4-chlorophenyl)thio)methyl)-3-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ad), white solid. Yield: 68 mg, 75%.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.63 (m, 4H), 7.51 – 7.34 (m, 7H), 7.26 (d, *J* = 8.1 Hz, 2H), 3.99 (dd, *J* = 13.7, 3.1 Hz, 1H), 3.92 (qd, *J* = 10.3, 3.1 Hz, 1H), 3.27 (dd, *J* = 17.4, 10.8 Hz, 1H), 3.12 – 3.05 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.62, 143.49, 131.95, 130.60, 130.19, 129.77, 129.61, 128.60, 128.36, 127.68, 127.60, 125.96, 59.84, 38.76, 37.90, 20.63. ESI-MS *m/z*: 457 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{23}H_{21}ClN_2O_2S_2]$ requires $[M+H]^+$ 457.0806, found 457.0808.

5-(((4-bromophenyl)thio)methyl)-3-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ae), white solid. Yield: 80 mg, 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.68 (m, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.49 – 7.37 (m, 5H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.00 (dd, *J* = 13.7, 3.1 Hz, 1H), 3.92 (tdd, *J* = 10.5, 9.3, 3.1 Hz, 1H), 3.28 (dd, *J* = 17.4, 10.8 Hz, 1H), 3.12 – 3.05 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.60, 143.50, 132.62, 131.28, 130.55, 130.34, 129.78, 129.59, 128.62, 127.68, 127.60, 125.95, 119.66, 59.79, 38.76, 37.71, 20.63. ESI-MS *m/z*: 501 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{23}H_{21}BrN_2O_2S_2]$ requires $[M+H]^+$ 501.0301, found 501.0299.

5-(((4-nitrophenyl)thio)methyl)-3-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrazole (3af), white solid. Yield: 39 mg, 42%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 – 8.15 (m, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.64 – 7.56 (m, 3H), 7.51 (d, *J* = 8.9 Hz, 2H), 7.42 – 7.32 (m, 3H), 7.21 (s, 1H), 4.09 – 3.96 (m, 2H), 3.27 – 3.15 (m, 2H), 3.04 (dd, *J* = 17.4, 8.6 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.55, 144.11, 143.75, 130.77, 129.92, 129.39, 128.74, 127.74, 127.55, 125.95, 125.44, 123.48, 123.22, 59.13, 38.78, 36.12, 20.62. ESI-MS *m/z*: 468 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{23}H_{21}N_3O_4S_2]$ requires $[M+H]^+$ 468.1046, found 468.1043.

3-phenyl-5-((*m*-tolylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ag), white solid. Yield: 61 mg, 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.59 (m, 4H), 7.48 – 7.39 (m, 3H), 7.35 – 7.29 (m, 3H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 6.7 Hz, 1H), 4.07 (dd, *J* = 13.7, 3.2 Hz, 1H), 3.98 (tdd, *J* = 10.7, 9.2, 3.2 Hz, 1H), 3.27 (dd, *J* = 17.4, 10.8 Hz, 1H), 3.12 – 3.03 (m, 2H), 2.44 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.65, 143.28, 138.09, 130.74, 129.69, 129.08, 128.51, 128.06, 127.63, 126.47, 125.95, 125.57, 60.03, 38.83, 37.44, 20.59. ESI-MS *m/z*: 437 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{24}H_{24}N_2O_2S_2]$ requires $[M+H]^+$ 437.1352, found 437.1349.

5-((methylthio)methyl)-3-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ah), white solid. Yield: 48 mg, 67%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.74 – 7.69 (m, 2H), 7.49 – 7.40 (m, 3H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.12 (dtd, *J* = 10.6, 9.0, 3.2 Hz, 1H), 3.30 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.26 – 3.16 (m, 2H), 3.01 (dd, *J* = 13.5, 8.9 Hz, 1H), 2.44 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.85, 143.40, 131.10, 129.67, 128.63, 127.64, 125.98, 60.44, 38.46, 38.32, 20.63, 15.24. ESI-MS *m/z*: 361 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{18}H_{20}N_2O_2S_2]$ requires $[M+H]^+$ 361.1039, found 361.1041.

3-phenyl-5-((propylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ai), colorless oil. Yield: 52 mg, 68%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.74 – 7.69 (m, 2H), 7.47 – 7.40 (m, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.08 (dtd, *J* = 10.7, 9.2, 3.3 Hz, 1H), 3.34 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.25 (dd, *J* = 17.3, 10.7 Hz, 1H), 3.16 (dd, *J* = 17.3, 9.1 Hz, 1H), 2.98 (dd, *J* = 13.4, 9.3 Hz, 1H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.44 (s, 3H), 1.74 (dt, *J* = 14.6, 7.3 Hz, 2H), 1.07 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.81, 143.37, 131.11, 129.80, 129.65, 128.61, 127.64, 125.98, 60.73, 38.44, 36.30, 33.75, 22.12, 20.63, 12.43. ESI-MS *m/z*: 389 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{20}H_{24}N_2O_2S_2]$ requires $[M+H]^+$ 389.1352, found 389.1353.

2-(((3-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrazol-5-yl)methyl)thio)benzo[*d*]thiazole (3aj), white solid. Yield: 45 mg, 47%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.94 (m, 1H), 7.94 – 7.89 (m, 2H), 7.87 – 7.79 (m, 1H), 7.71 – 7.66 (m, 2H), 7.51 (ddd, *J* = 8.4, 7.3, 1.2 Hz, 1H), 7.47 – 7.36 (m, 4H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.50 – 4.39 (m, 2H), 3.72 – 3.65 (m, 1H), 3.28 (dd, *J* = 9.9, 2.9 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.47, 156.81, 152.06, 143.48, 134.65, 130.79, 129.72, 129.61, 128.61, 127.84, 127.64, 125.99, 125.23, 123.57, 120.60, 120.17, 60.30, 38.23, 36.65, 20.63. ESI-MS *m/z*: 480 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{24}H_{21}N_3O_2S_3]$ requires $[M+H]^+$ 480.0869, found 480.0867.

3-(4-methoxyphenyl)-5-((phenylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ba), white solid. Yield: 71 mg, 79%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 4H), 7.56 – 7.50 (m, 2H), 7.42 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.95 – 6.90 (m, 2H), 4.06 (dd, *J* = 13.7, 3.2 Hz, 1H), 3.93 (tdd, *J* = 10.6, 9.1, 3.2 Hz, 1H), 3.87 (d, *J* = 0.6 Hz, 3H), 3.23 (dd, *J* = 17.3, 10.7 Hz, 1H), 3.10 – 3.02 (m, 2H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.63, 156.45, 143.22, 133.41, 130.57, 128.70, 128.48, 128.22, 127.67, 127.60, 125.65, 122.31, 113.05, 59.87, 54.42, 38.90, 37.59, 20.59. ESI-MS *m/z*: 453 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{24}H_{24}N_2O_3S_2]$ requires $[M+H]^+$ 453.1301, found 453.1299.

3-(4-fluorophenyl)-5-((phenylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ca), light yellow oil. Yield: 77 mg, 88%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.62 (m, 4H), 7.56 – 7.50 (m, 2H), 7.42 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.35 – 7.31 (m, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.15 – 7.06 (m, 2H), 4.06 (dd, *J* = 13.7, 3.2 Hz, 1H), 3.97 (tdd, *J* = 10.6, 9.3, 3.2 Hz, 1H), 3.25 (dd, *J* = 17.4, 10.8 Hz, 1H), 3.11 – 3.04 (m, 2H), 2.40 (s, 3H). ^{19}F NMR (470 MHz, $CDCl_3$) δ -108.76. ^{13}C NMR (125 MHz,

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$CDCl_3$) δ 164.19, 162.19, 155.62, 143.40, 133.28, 130.60, 128.79, 128.54, 128.24, 128.00, 127.93, 127.63, 125.96, 125.75, 114.92, 114.75, 60.12, 38.85, 37.56, 20.61. ESI-MS *m/z*: 441 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{23}H_{21}FN_2O_2S_2]$ requires $[M+H]^+$ 441.1101, found 441.1099.

3-(4-chlorophenyl)-5-((phenylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3da), yellow oil. Yield: 78 mg, 86%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 16.2, 8.0 Hz, 4H), 7.47 (d, *J* = 7.7 Hz, 2H), 7.39 – 7.31 (m, 4H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 2H), 4.00 (dd, *J* = 13.7, 3.1 Hz, 1H), 3.92 (qd, *J* = 10.4, 3.2 Hz, 1H), 3.19 (dd, *J* = 17.4, 10.8 Hz, 1H), 3.07 – 2.96 (m, 2H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.58, 143.47, 135.80, 133.24, 130.55, 128.80, 128.58, 128.26, 127.96, 127.61, 127.16, 125.77, 60.20, 38.70, 37.54, 20.62. ESI-MS **($C_{23}H_{21}ClN_2O_2S_2$)** *m/z*: 457 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{23}H_{21}ClN_2O_2S_2]$ requires $[M+H]^+$ 457.0806, found 457.0808.

3-(4-bromophenyl)-5-((phenylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ea), yellow oil. Yield: 77 mg, 77%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.52 – 7.44 (m, 6H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 4.01 (dd, *J* = 13.8, 3.2 Hz, 1H), 3.92 (tdd, *J* = 10.7, 9.3, 3.2 Hz, 1H), 3.20 (dd, *J* = 17.4, 10.8 Hz, 1H), 3.08 – 2.96 (m, 2H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.65, 143.48, 133.23, 130.92, 130.55, 128.80, 128.58, 128.26, 127.60, 127.35, 125.77, 124.20, 60.22, 38.65, 37.54, 20.62. ESI-MS *m/z*: 501 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{23}H_{21}BrN_2O_2S_2]$ requires $[M+H]^+$ 501.0301, found 501.0299.

5-((phenylthio)methyl)-1-tosyl-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrazole (3fa), colorless oil. Yield: 73 mg, 75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.66 (dd, *J* = 8.1, 5.7 Hz, 4H), 7.58 – 7.49 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.37 – 7.32 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 4.10 – 3.97 (m, 2H), 3.30 (dd, *J* = 17.5, 10.7 Hz, 1H), 3.15 – 3.06 (m, 2H), 2.40 (s, 3H). ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.92. ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.14, 143.59, 133.18, 130.62, 128.88, 128.64, 128.29, 127.58, 126.16, 125.85, 124.65, 60.40, 38.63, 37.57, 20.62. ESI-MS *m/z*: 491 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{24}H_{21}F_3N_2O_2S_2]$ requires $[M+H]^+$ 491.1069, found 491.1068.

3-(3,4-dimethoxyphenyl)-5-((phenylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ga), white solid. Yield: 67 mg, 69%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 2H), 7.57 – 7.50 (m, 2H), 7.45 – 7.36 (m, 3H), 7.35 – 7.30 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.07 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.05 (dd, *J* = 13.7, 3.2 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 4H), 3.24 (dd, *J* = 17.3, 10.7 Hz, 1H), 3.10 – 3.01 (m, 2H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.61, 150.48, 148.17, 143.28, 133.36, 130.53, 128.71, 128.49, 128.23, 127.65, 125.67, 122.58, 119.86, 109.46, 108.02, 59.91, 55.20, 55.00, 38.86, 37.61, 20.59. ESI-MS *m/z*: 483 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{25}H_{26}N_2O_4S_2]$ requires $[M+H]^+$ 483.1407, found 483.1406.

3-(3-methoxyphenyl)-5-((phenylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ha), white solid. Yield: 61 mg, 67%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.52 – 7.45 (m, 2H), 7.38 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.31 – 7.26 (m, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.16 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.96 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 4.01 (dd, *J* = 13.7, 3.2 Hz, 1H), 3.95 – 3.88 (m, 1H), 3.83 (s, 3H), 3.21 (dd, *J* = 17.4, 10.8 Hz, 1H), 3.06 – 3.00 (m, 2H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.72, 156.69, 143.38, 133.33, 130.97, 130.53, 128.78, 128.66, 128.55, 128.24, 127.61, 125.71, 118.64, 115.88, 110.70, 60.06, 54.50, 38.89, 37.60, 20.61. ESI-MS *m/z*: 453 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{24}H_{24}N_2O_3S_2]$ requires $[M+H]^+$ 453.1301, found 453.1299.

3-(2-chlorophenyl)-5-((phenylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ia), light yellow oil. Yield: 45 mg, 49%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.60 (m, 2H), 7.56 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.40 – 7.32 (m, 3H), 7.32 – 7.21 (m, 5H), 4.07 – 3.87 (m, 2H), 3.35 (dd, *J* = 17.9, 10.4 Hz, 1H), 3.24 (dd, *J* = 17.9, 9.7 Hz, 1H), 3.10 (dd, *J* = 13.7, 10.3 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.83, 143.50, 133.45, 131.88, 130.64, 130.15, 129.61, 129.53, 129.18, 128.95, 128.56, 128.23, 127.75, 125.89, 125.75, 60.72, 41.81, 37.58, 20.64. ESI-MS *m/z*: 457 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{23}H_{21}ClN_2O_2S_2]$ requires $[M+H]^+$ 457.0806, found 457.0808.

3-cyclopentyl-5-((phenylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ja), colorless oil. Yield: 66 mg, 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.56 (m, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.33 – 7.29 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 3.95 (dd, *J* = 13.7, 3.2 Hz, 1H), 3.77 (tdd, *J* = 10.7, 9.0, 3.2 Hz, 1H), 2.98 (dd, *J* = 13.7, 10.6 Hz, 1H), 2.75 (td, *J* = 17.1, 16.4, 9.3 Hz, 2H), 2.64 (dd, *J* = 17.8, 9.1 Hz, 1H), 2.44 (s, 3H), 1.80 (ddd, *J* = 12.3, 8.1, 5.1 Hz, 2H), 1.71 – 1.60 (m, 4H), 1.50 (dtd, *J* = 24.7, 7.5, 4.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.34, 143.14, 133.54, 130.35, 128.42, 128.27, 128.17, 127.77, 125.51, 59.28, 39.71, 39.40, 37.50, 29.33, 24.35, 20.62. ESI-MS *m/z*: 415 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{22}H_{26}N_2O_2S_2]$ requires $[M+H]^+$ 415.1508, found 415.1507.

3-(naphthalen-2-yl)-5-((phenylthio)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (3ka), white solid. Yield: 74 mg, 78%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.91 (d, *J* = 1.6 Hz, 1H), 7.87 (ddd, *J* = 8.1, 4.0, 2.0 Hz, 3H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.60 – 7.53 (m, 4H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.36 – 7.32 (m, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 4.10 (dd, *J* = 13.7, 3.2 Hz, 1H), 4.01 (tdd, *J* = 10.6, 9.2, 3.2 Hz, 1H), 3.41 (dd, *J* = 17.3, 10.8 Hz, 1H), 3.21 (dd, *J* = 17.3, 9.2 Hz, 1H), 3.12 (dd, *J* = 13.7, 10.6 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.71, 143.34, 133.36, 131.84, 130.70, 128.80, 128.53, 128.25, 127.66, 127.49, 127.27, 126.86, 126.52, 125.81, 125.72, 122.53, 60.14, 38.78, 37.66, 20.57. ESI-MS *m/z*: 473 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{27}H_{24}N_2O_2S_2]$ requires $[M+H]^+$ 473.1352, found 473.1353.

3-phenyl-5-((phenylselanyl)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrazole (5aa), yellow oil. Yield: 75 mg, 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (td, *J* = 7.2, 6.6, 1.8 Hz, 4H), 7.59 – 7.54 (m, 2H), 7.42 – 7.33 (m, 6H), 7.18 (d, *J* = 8.1 Hz, 2H), 3.95 – 3.85 (m, 2H), 3.25 (dd, *J* = 17.4, 10.7 Hz, 1H), 3.07 (dd, *J* = 13.0, 11.0 Hz, 1H), 2.98 (dd, *J* = 17.3, 9.6 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.33, 143.25, 132.11, 130.60, 129.66, 128.49, 128.41, 127.64, 126.49, 125.93, 61.09, 39.43, 31.26, 20.61. ESI-MS *m/z*: 471 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{23}H_{22}N_2O_2SSe]$ requires $[M+H]^+$ 471.0640, found 471.0642.

5-((benzylselanyl)methyl)-3-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrazole (5ab), white solid. Yield: 90 mg, 93%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.68 – 7.65 (m, 2H), 7.43 (dddd, *J* = 14.2, 8.4, 5.9, 2.3 Hz, 5H), 7.37 (dd, *J* = 8.5, 6.8 Hz, 2H), 7.33 – 7.28 (m, 3H), 4.11 – 4.05 (m, 1H), 3.97 (s, 2H), 3.31 (dd, *J* = 12.7, 3.3 Hz, 1H), 3.16 – 3.05 (m, 2H), 2.92 (dd, *J* = 17.3, 8.8 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.67, 143.36, 138.46, 131.17, 129.66, 128.61, 128.02, 127.70, 127.62, 125.98, 60.99, 39.18, 28.62, 27.30, 20.65. ESI-MS *m/z*: 485 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{24}H_{24}N_2O_2SSe]$ requires $[M+H]^+$ 485.0796, found 485.0797.

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5-((methylselanyl)methyl)-3-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrazole (5ac), white solid. Yield: 72 mg, 88%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.74 – 7.70 (m, 2H), 7.47 – 7.41 (m, 3H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.15 (dtd, *J* = 10.7, 9.1, 3.1 Hz, 1H), 3.33 – 3.25 (m, 2H), 3.14 – 3.04 (m, 2H), 2.44 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.55, 143.38, 131.11, 129.79, 129.65, 128.62, 127.63, 125.95, 61.06, 39.19, 29.69, 20.63, 4.18. ESI-MS *m/z*: 409 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{18}H_{20}N_2O_2SSe]$ requires $[M+H]^+$ 409.0483, found 409.0481.

3-phenyl-5-((phenylthio)methyl)-4,5-dihydroisoxazole (7aa), light yellow solid. Yield: 34 mg, 64%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 2H), 7.47 – 7.38 (m, 5H), 7.32 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.27 – 7.21 (m, 1H), 4.88 (dddd, *J* = 10.8, 9.1, 6.6, 4.5 Hz, 1H), 3.48 – 3.42 (m, 1H), 3.38 (dd, *J* = 13.6, 4.5 Hz, 1H), 3.28 (dd, *J* = 16.8, 6.6 Hz, 1H), 2.99 (dd, *J* = 13.6, 8.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.30, 133.75, 129.21, 128.40, 128.21, 127.77, 125.90, 125.77, 78.58, 38.59, 36.82. ESI-MS *m/z*: 270 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{16}H_{15}NOS]$ requires $[M+H]^+$ 270.0947, found 270.0945.

3-phenyl-5-((*p*-tolylthio)methyl)-4,5-dihydroisoxazole (7ab), yellow oil. Yield: 42 mg, 75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 2H), 7.41 (dd, *J* = 5.2, 2.1 Hz, 3H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 4.85 (dddd, *J* = 10.8, 9.0, 6.6, 4.6 Hz, 1H), 3.47 – 3.41 (m, 1H), 3.38 – 3.23 (m, 2H), 2.94 (dd, *J* = 13.5, 8.9 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.29, 136.20, 129.99, 129.21, 129.00, 128.46, 127.76, 125.78, 78.69, 38.55, 37.45, 20.10. ESI-MS *m/z*: 284 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{17}H_{17}NOS]$ requires $[M+H]^+$ 284.1104, found 284.1103.

5-(((4-chlorophenyl)thio)methyl)-3-phenyl-4,5-dihydroisoxazole (7ad), white solid. Yield: 37 mg, 61%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 2H), 7.47 – 7.39 (m, 3H), 7.39 – 7.32 (m, 2H), 7.31 – 7.27 (m, 2H), 4.88 (dddd, *J* = 10.2, 8.4, 6.6, 4.7 Hz, 1H), 3.46 (dd, *J* = 16.8, 10.3 Hz, 1H), 3.33 (dd, *J* = 13.7, 4.7 Hz, 1H), 3.27 (dd, *J* = 16.8, 6.6 Hz, 1H), 3.01 (dd, *J* = 13.7, 8.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.29, 132.40, 132.00, 130.52, 129.32, 128.35, 127.81, 125.79, 78.41, 38.62, 37.17. ESI-MS *m/z*: 304 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{16}H_{14}ClNOS]$ requires $[M+H]^+$ 304.0557, found 304.0558.

5-((methylthio)methyl)-3-phenyl-4,5-dihydroisoxazole (7ah), colorless liquid. Yield: 19 mg, 47%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 2H), 7.45 – 7.37 (m, 3H), 5.00 – 4.92 (m, 1H), 3.47 (dd, *J* = 16.7, 10.3 Hz, 1H), 3.29 (dd, *J* = 16.7, 7.0 Hz, 1H), 2.86 (dd, *J* = 13.8, 4.9 Hz, 1H), 2.72 (dd, *J* = 13.7, 7.6 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.44, 131.23, 129.19, 127.76, 125.76, 79.43, 38.63, 37.09, 15.28. ESI-MS *m/z*: 208 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{11}H_{13}NOS]$ requires $[M+H]^+$ 208.0791, found 208.0789.

3-(4-methoxyphenyl)-5-((phenylthio)methyl)-4,5-dihydroisoxazole (7ba), white solid. Yield: 47 mg, 78%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.54 (m, 2H), 7.45 – 7.36 (m, 2H), 7.30 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.25 – 7.19 (m, 1H), 6.97 – 6.87 (m, 2H), 4.83 (dddd, *J* = 10.1, 8.9, 6.5, 4.5 Hz, 1H), 3.83 (s, 3H), 3.47 – 3.32 (m, 2H), 3.23 (dd, *J* = 16.7, 6.5 Hz, 1H), 2.97 (dd, *J* = 13.5, 8.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.18, 154.86, 133.86, 129.12, 128.20, 127.31, 125.84, 120.97, 113.18, 78.29, 54.41, 38.84, 36.79. ESI-MS *m/z*: 300 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{17}H_{17}NO_2S]$ requires $[M+H]^+$ 300.1053, found 300.1052.

3-(4-fluorophenyl)-5-((phenylthio)methyl)-4,5-dihydroisoxazole (7ca), white solid. Yield: 40 mg, 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.56 (m, 2H), 7.48 – 7.36 (m, 2H), 7.31 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.25 – 7.18 (m, 1H), 7.13 – 7.01 (m, 2H), 4.87 (dddd, *J* = 10.8, 9.0, 6.6, 4.5 Hz, 1H), 3.46 – 3.33 (m, 2H), 3.24 (dd, *J* = 16.8, 6.7 Hz, 1H), 2.98 (dd, *J* = 13.6, 8.9 Hz, 1H). ^{19}F NMR (470 MHz, $CDCl_3$) δ -109.72. ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.84, 161.84, 154.32, 133.71, 129.20, 128.22, 127.74, 127.67, 125.93, 124.70, 115.00, 114.83, 78.72, 38.63, 36.80. ESI-MS *m/z*: 288 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{16}H_{14}FNOS]$ requires $[M+H]^+$ 288.0853, found 288.0851.

3-(*tert*-butyl)-5-((phenylthio)methyl)-4,5-dihydroisoxazole (7da), colorless oil. Yield: 33 mg, 67%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dt, *J* = 8.1, 1.4 Hz, 2H), 7.34 (td, *J* = 7.7, 1.6 Hz, 2H), 7.26 (td, *J* = 7.2, 1.4 Hz, 1H), 4.78 – 4.65 (m, 1H), 3.31 (ddd, *J* = 13.5, 4.5, 1.5 Hz, 1H), 3.10 (ddd, *J* = 17.0, 10.1, 1.5 Hz, 1H), 2.96 – 2.87 (m, 2H), 1.23 (d, *J* = 1.6 Hz, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.72, 134.03, 128.99, 128.14, 125.72, 77.60, 37.93, 36.64, 32.05, 27.11. ESI-MS *m/z*: 250 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{14}H_{19}NOS]$ requires $[M+H]^+$ 250.1260, found 250.1258.

3-phenyl-5-((phenylselanyl)methyl)-4,5-dihydroisoxazole (8aa), white solid. Yield: 46 mg, 72%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.62 (m, 2H), 7.57 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.41 (dd, *J* = 5.3, 2.0 Hz, 3H), 7.33 – 7.27 (m, 3H), 4.91 (dddd, *J* = 11.0, 9.3, 6.8, 4.5 Hz, 1H), 3.45 (dd, *J* = 16.8, 10.2 Hz, 1H), 3.32 (dd, *J* = 12.6, 4.6 Hz, 1H), 3.21 (dd, *J* = 16.8, 6.8 Hz, 1H), 3.01 (dd, *J* = 12.6, 9.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.23, 132.30, 129.20, 128.38, 127.76, 126.62, 125.75, 79.43, 39.12, 30.47. ESI-MS *m/z*: 318 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{16}H_{15}NOSe]$ requires $[M+H]^+$ 318.0392, found 318.0391.

5-((benzylselanyl)methyl)-3-phenyl-4,5-dihydroisoxazole (8ab), colorless liquid. Yield: 50 mg, 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.41 (dd, *J* = 5.1, 2.0 Hz, 3H), 7.36 – 7.25 (m, 4H), 7.25 – 7.18 (m, 1H), 4.88 (dtd, *J* = 10.3, 7.4, 4.8 Hz, 1H), 3.92 – 3.88 (m, 2H), 3.39 (dd, *J* = 16.7, 10.3 Hz, 1H), 3.11 (dd, *J* = 16.7, 7.2 Hz, 1H), 2.84 (dd, *J* = 12.9, 4.9 Hz, 1H), 2.73 (dd, *J* = 12.9, 7.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.38, 138.03, 129.12, 128.54, 128.03, 127.72, 127.63, 125.98, 125.74, 79.90, 39.38, 26.90, 26.49. ESI-MS *m/z*: 332 $[M+1]^+$. HRMS (ESI) Calcd for $[C_{17}H_{17}NOSe]$ requires $[M+H]^+$ 332.0548, found 332.0547.

Conflicts of interest

There are no conflicts to declare.

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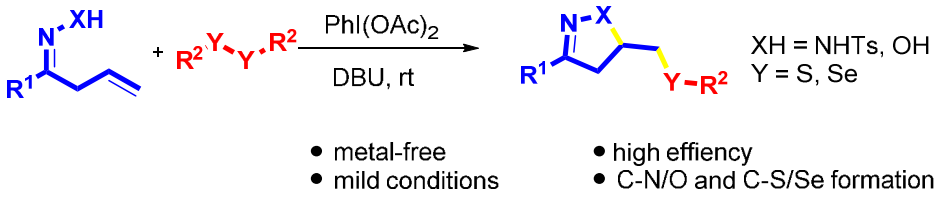
Iodine(III)-Mediated Intramolecular Sulfeno- and Selenofunctionalization of β, γ-unsaturated Hydrazones and Oximes

Jing-miao Yu,[a] Chun Cai*[a]



A cascade radical cyclization/sulfenylation or selenylation of β, γ-unsaturated hydrazones and oximes was realized under mild conditions with phenyliodine(III) diacetate (PIDA) as the sole oxidant, leading to the construction of various diversely functionalized heteroatom-containing pyrazoline and isoxazoline derivatives. This metal-free radical process is suggested to encompass a sequential C-N/O and C-S/Se bond fomation.