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PAPER

Nickel-catalyzed direct C-H bond sulfenylation of acylhydrazines

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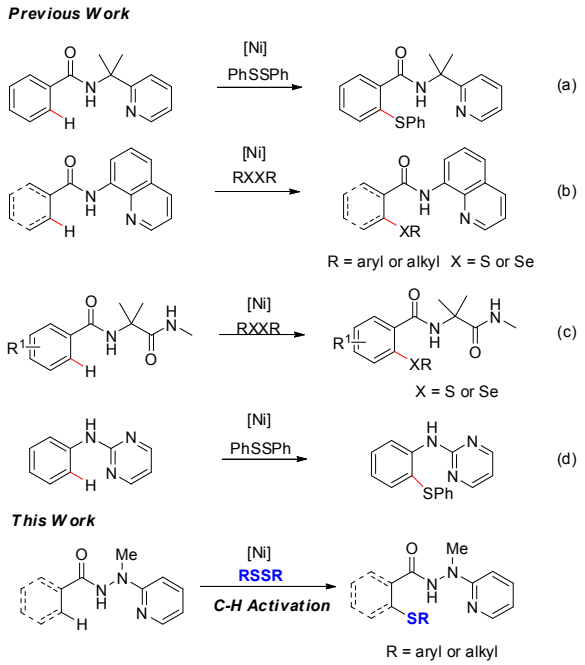
A Ni-catalyzed direct C-H bond sulfenylation of acylhydrazines was developed. The reaction used *N*-(pyridinyl)hydrazine as the bidentate-directing group, which can be smoothly removed through reductive N-N cleavage. This system can bear various important functional groups, providing an efficient route for the preparation of diverse diaryl sulfides.

Introduction

Organosulfur compounds are widely present in pharmaceuticals, agrochemicals and functional materials.[1] These compounds are also useful synthetic intermediates in organic chemistry. Among the best-selling drugs in United States in 2012, organosulfur compounds account for approximately 20%.[2] Thus, the formation of C–S bond is eliciting extensive attention from the industry and academic communities.

The conventional methods for synthesis of aryl sulfides is the transition metal-catalyzed/mediated sulfenylation of arylhalides or its equivalent with thiols and its derivatives.[1c,3] However, these traditional coupling reactions usually need prefunctinalized substrates such as aryl halides, which might restricted the applications of these reactions.[3,4] In view of sustainable chemistry, the most atom-economic method is the direct thiolation of arenes through C-H activation/C-S bond formation.[5] In this regard, most C-H functionalization reactions were well studied and focused on the C-C and C-heteroatom bond forming reactions.[6] Nevertheless, in order to realize direct C-H thiolation, it is necessary to overcome the possible sulfide poisoning of transition metal catalyst.[7]

Recently, Yu,[8] Qing,[9] Cheng,[10] and Daugulis[11] have reported elegant work on Cu-catalyzed direct sulfenylation of unactivated arenes assisted by directing groups. However, these routes are largely restricted to the use of stoichiometric or substoichiometric Cu catalysts. Later, the direct C-S bond-forming reaction catalyzed by Rh[12] or Pd[13] has also been developed, but the use of expensive second-row transition metal catalysts restricted the application of the reaction. Then, our group[14] and Gui's group[15] developed direct sulfenylation of C(sp^2)-H bond with copper catalyst and direct methylthiolation with cobalt catalyst, respectively. More recently, Ni-catalyzed C-H functionalization has attracted tremendous attentions[16] owing to its abundant availability, low cost and relatively low toxicity. Shi[17a] and Lu's[17b] groups have independently realized Ni-catalyzed direct sulfenylation of unactived arene C-H bonds with 2-(pyridine-2-yl)isopropylamine (PIP) directing group (Scheme 1a). Shi and other groups[18] also reported Ni-catalyzed direct thiolation of unactived C(sp^2)-H and C(sp^3)-H bonds with disulfides directed by aminoquinoline group (Scheme 1b). In



Scheme 1 Direct C-H sulfenylation with different directing groups

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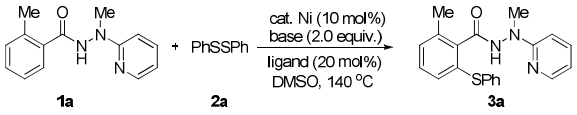
2016, Liu *et al.* described the Ni-catalyzed C–H thiolation of *N*-benzoyl α-amino acid derivatives (Scheme 1c),[19] while Ackermann's group used a monodentate pyrimidyl group to assist the direct C(sp^2)-H thiolation (Scheme 1d).[20]

Recently, we have reported the homo- and cross-coupling reactions of *N*'-tosyl arylhydrazines and *N*'-acyl arylhydrazines[21] to construct important skeletons with antiviral, antitumor, anti-malarial, or bactericidal biological activities.[22] In continuation of our interest in arylhydrazines and C-H bond functionalization, and inspired by Zhai's cobalt-catalyzed C(sp^2)–H bond alkenylation/annulation cascade[23] with *N*-(pyridinyl)hydrazine as bidentate directing group, we envisioned that this kind of directing group might also be used to promote the nickel-catalyzed C-H sulfenylation. Moreover, the *N*-(pyridinyl)hydrazine group can be easily removed via reductive N-N cleavage, which is quite different from the removal of other directing groups like 8-aminoquinoline and PIP through C-N hydrolysis of amide. Herein, we wish to report a Ni-catalyzed direct C-H bond sulfenylation of arylhydrazines.

Results and discussion

Table 1 Optimization of reaction conditions[a]

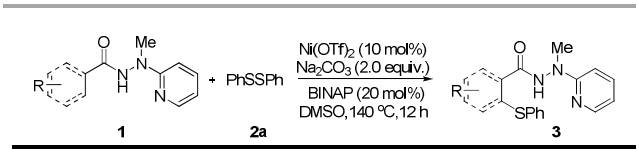


1a 2a 3a

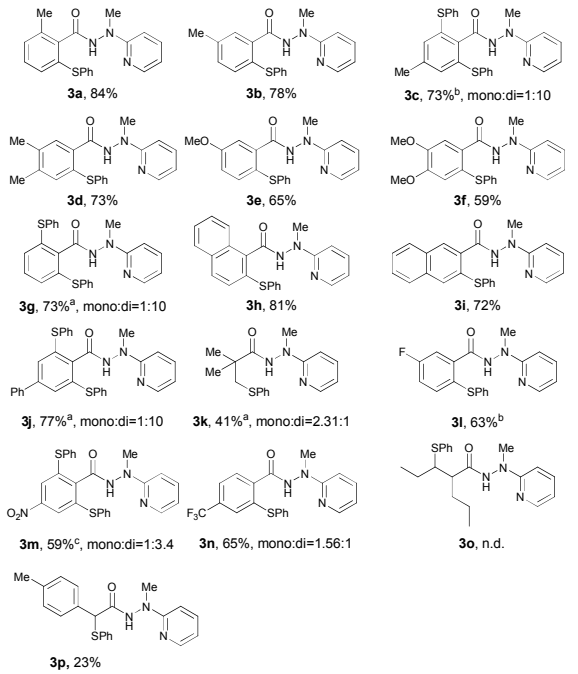
Entry	[Ni]	Base	T (°C)	Ligand	Yield (%)[b]
1	$NiCl_2$	Na_2CO_3	140	-	67
2	$Ni(OTf)_2$	Na_2CO_3	140	-	77(70[c])
3	$NiCl_2(PPh_3)_2$	Na_2CO_3	140	-	69
4	$Ni(OAc)_2{\cdot}4H_2O$	Na_2CO_3	140	-	71
5	$NiCl_2{\cdot}6H_2O$	Na_2CO_3	140	-	35
6	-	Na_2CO_3	140	-	-
7	$Ni(OTf)_2$	Na_2CO_3	140	PPh_3	76
8	$Ni(OTf)_2$	Na_2CO_3	140	DPPP	71
9	$Ni(OTf)_2$	Na_2CO_3	140	BINAP	87(79[c])
10	$Ni(OTf)_2$	KO^tBu	140	BINAP	75
11	$Ni(OTf)_2$	K_2CO_3	140	BINAP	21
12	$Ni(OTf)_2$	NaTFA	140	BINAP	70
13	$Ni(OTf)_2$	DBU	140	BINAP	<10
14	$Ni(OTf)_2$	Cs_2CO_3	140	BINAP	32
15	$Ni(OTf)_2$	$NaHCO_3$	140	BINAP	56
16	$Ni(OTf)_2$	Ag_2CO_3	140	BINAP	<10
17	$Ni(OTf)_2$	LiOAc	140	BINAP	47
18[d]	$Ni(OTf)_2$	Na_2CO_3	140	BINAP	43
19[e]	$Ni(OTf)_2$	Na_2CO_3	140	BINAP	59
19[f]	$Ni(OTf)_2$	Na_2CO_3	110	BINAP	60
20[f]	$Ni(OTf)_2$	Na_2CO_3	120	BINAP	65
21[f]	$Ni(OTf)_2$	Na_2CO_3	130	BINAP	73

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), [Ni] (10 mol%), base (2.0 equiv.), ligand (20 mol%), DMSO (1 mL), 12 h; [b] Yields are based on **1a**, determined by ^{1}H NMR analysis of the crude product; [c] Isolated yields are given in the parentheses; [d] DMF (1 mL); [e] DME (1 mL); [f] 24 h.

We first investigated the reaction between diphenyl disulfide (**2a**) and *N*'-methyl-*N*'-(pyridin-2-yl)benzohydrazide (**1a**), the latter can be easily prepared from 2-(1-methylhydrazinyl)pyridine and carboxylic acid compounds. Fortunately, we found that the reaction of **1a** with **2a** (1.2 equiv.) in the presence of $NiCl_2$ (10 mol%) and Na_2CO_3 (2.0 equiv.) in DMSO at 140 °C gave 67% yield of the desired product **3a** after 12 h (Table 1, entry 1). Through the extensive screening of Ni catalyst, we found that $Ni(OTf)_2$ was proven to be the most effective catalyst, and the product yield increased to 77% (entries 2-5). Importantly, no desired product was obtained in the absence of Ni catalyst, suggesting that the latter played a significant role in this reaction (entry 6). Then the effect of phosphine ligand was investigated. The addition of BINAP was proven to increase the isolated yield to 87% (entry 9). On the contrary, the addition of PPh_3 or DPPP slightly decreased the yields (entries 7-9). Then we examined the effect of base, and results indicated that Na_2CO_3 was optimal (entries 10-17). A solvent



1 2a 3



Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), $Ni(OTf)_2$ (10 mol%), BINAP (20 mol%), Na_2CO_3 (0.4 mmol), DMSO (1 mL), 140 °C, 12 h. [a] **2a** (0.4 mmol, 2.0 equiv.); [b] 100 °C, 24 h; [c] **2a** (0.4 mmol), 100 °C, 24 h.

Scheme 2 Scope of benzamides

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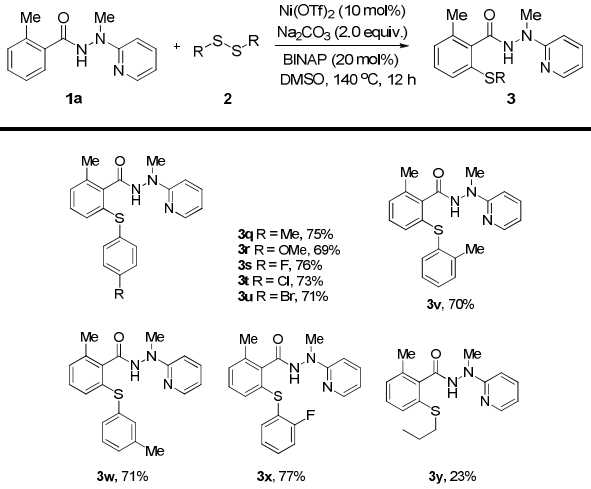
screening revealed that DMSO was superior to other solvent as DMF and DME (entries 18-19). We also tried to decrease the temperature while sacrificing reaction time. However, the starting material couldn't be converted completely and gave the desired product with lower yield even after 24 h (entries 19-21).

After identifying the optimal reaction conditions, we next investigated the substrate scope. A wide range of acylhydrazines were examined (Scheme 2). In general, the acylhydrazine substrates can bear various substituents on the phenyl ring and give the desired products in moderate to good yields. A higher yield can be obtained with the electron-donating substituent on the phenyl ring of acylhydrazine (**3a**-**3f**). When using the *meta*-substituted acylhydrazine, thiolation occurred at less sterically hindered position and gave the monothiolated product (**3b**, **3d**-**3f** and **3l**). By contrast, the acylhydrazines bearing *para*-substituents or simple benzamide derivative gave the mono-thiolated and di-thiolated products simultaneously (**3c**, **3g**, **3j** and **3m-n**). Moreover, naphthyl substrates **1h** and **1i** also worked efficiently with exclusive monothiolated products. We assumed that this regioselectivity might be related with the steric hindrance. Substrates **1l** and 1**m** with fluoro or nitro groups proceeded smoothly to provide the corresponding thiolated products with moderate yields (**3l**, **3m**). We noticed that halogen and nitro groups might be easily broken in DMSO under high temperature or in the presence of transition metal,[24,25] so we performed the reactions of **1l** and **1m** under lower temperature (100 °C). However, the reactions of bromo- and chloro-substituted substrates were poor even under lower temperature, probably for the C-F bond was stronger than the C-Br and C-Cl bonds. The unactived C(sp^3)-H bond of *tert*- butylcarboxamide substrate **1k** also reacted with **2a** successfully and offered the mono- and di-thiolated products, albeit with a lower yield. This sulfenylations of other C(sp^3)-H are a bit complicated, for example, substrate **1o** with methylene C-H led to poor result and no desired product was observed, while substrate **1p** afforded unexpected α-thiolation product **3p** in 23% yield. In-depth experiments are still needed to elucidate the possible mechanism.

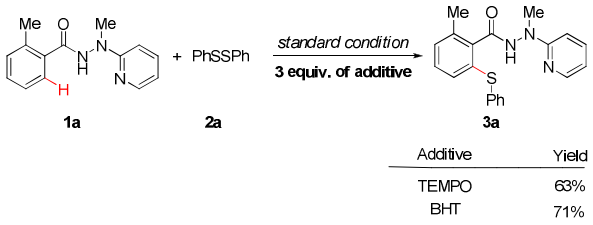
Next, we evaluated the substrate scope of various disulfides (Scheme 3). To our delight, the diaryl disulfides with either an electron-donating or electron-withdrawing substituents at the *ortho*-, *meta*- or *para*-positions were found to be well compatible under the standard reaction conditions (**3q**-**3x**). A wide range of functional groups such as methoxy, methyl, and halogen in the diaryl disulfides, are well tolerated. Furthermore, the dialkyl disulfide also successful gave the desired product **3y**, albeit with a low yield of 23%. We attributed this to the lower nucleophilic abilities of dialkyl disulfides than diaryl disulfides.



Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol, 1.2 equiv.), $Ni(OTf)_2$ (10 mol%), BINAP (20 mol%), Na_2CO_3 (0.4 mmol, 2.0 equiv.), DMSO (1 mL), 140 °C, 12 h.

Scheme 3 Scope of disulfides

To gain mechanistic insight into this reaction, we carried out the radical scavenger experiments. The addition of radical scavengers, such as TMEPO and BHT, wasn't found to inhibit the thiolated reaction obviously. This result suggested that the radical might not be involved in this reaction (Scheme 4). Furthermore, the H/D exchange reaction suggested that the C-H activation step is reversible (Scheme 5).



Scheme 4 Radical scavenger

Scheme 5 H/D exchange reaction

Interestingly, when substrate **1a** was reacted with 4-methylbenzenethiol **4** under the standard reaction, the desired product **3q** can also be obtained in 51% yield. The phenomenon that the thiols can be oxidized to disulfides by DMSO has been previously reported,[26] which was consistent with our control experiment shown in Scheme 6. We also

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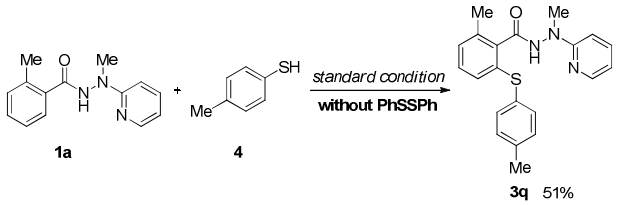
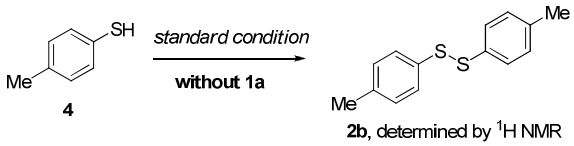
detected dimethyl sulfide, a byproduct of DMSO (Figure S1 in SI) to support the DMSO oxidant.

1) Ni-catalyzed thiolation with **4**

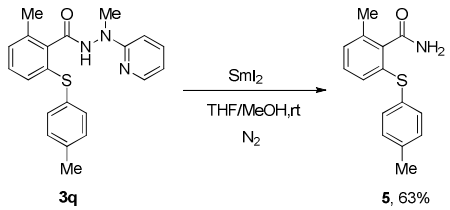


2) Oxidation of thiol **4** to disulfide

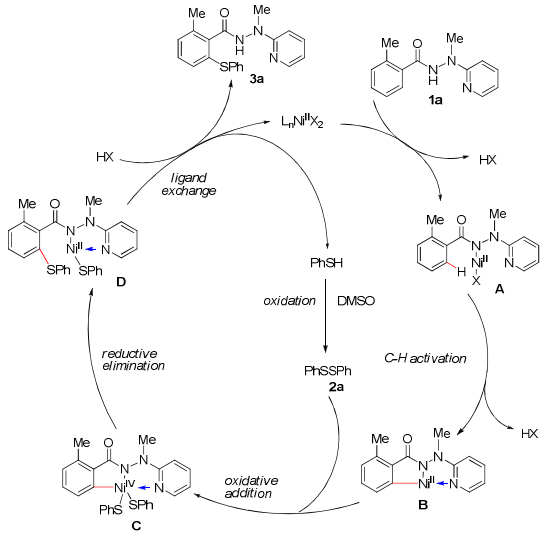


Scheme 6 Thiolation with **4** and the oxidation of thiol **4**

We also conducted a derivatization experiment of the thiolated product **3q** (Scheme 7). The hydrazine structure can be broken to provide the thiolated amide by using the proper reductant as samarium(II) iodide.[27]



Scheme 7 Transformation of hydrazine to amide



Scheme 8 Plausible reaction mechanism

Based on the above mechanistic studies and previous reports,[12-17] a plausible mechanism has been proposed in Scheme 8. Coordination of amide **1a** to a Ni^{II} followed by C-H activative process generates the Ni^{II} complex **B**. Oxidative addition of disulfide **2a** to **B** followed by reductive elimination process provided complex **D**. Subsequent ligand exchange released the desired thiolation product **3a** and benzenethiol with the regeneration of Ni^{II} catalyst. As mentioned above, benzenethiol can be oxidized to disulfide by DMSO and can participate in the reaction again.

Conclusions

In conclusion, we have developed an efficient Ni-catalyzed thiolation of acylhydrazines with disulfide. In this reaction, we used inexpensive Ni catalyst and commercially available substrates. The thiolated products can be hydrolyzed to afford amides which have potential applications in natural products and medicinal chemistry. This catalytic system can tolerate various important functional groups, providing an efficient protocol for the thiolation of unactived $C(sp^2)$-H bond.

Experimental section

General information

All starting materials, which were purchased from commercial sources, were used without further purification. Solvents for column chromatography were technical standard. Chromatography was performed with silica gel 200-400 mesh. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on Burker Avance 400 MHz and 500 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) downfield from the internal standard Me_4Si (TMS). Chemical shifts in ^{13}C NMR spectra are reported relative to the central line of the chloroform signal (δ = 77.0 ppm). Peaks were labeled as singlet (s), doublet (d), triplet (t), quarter (t), and multiplet (m). High resolution mass spectra were obtained with a Shimadzu LCMS-IT-TOF mass spectrometer. Analytical TLC was performed on commercial Merck plates coated with silica gel GF254 (0.2 mm thick). Acylhydrazines **1a-1p** were synthesized according to literatures.[23] Compounds **1a-1c** and **1h** were known compounds.[23]

***N*',3,4-*tri*Methyl-*N*'-(pyridin-2-yl)benzohydrazide 1d**

White solid; yield 83%. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.68 (s, 1H), 8.17 (d, *J* = 4.1 Hz, 1H), 7.63 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.47-7.39 (m, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 6.77-6.59 (m, 2H), 3.38 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.8, 159.4, 147.5, 141.4, 137.6, 137.1, 129.9 (d, *J* = 11.8 Hz), 128.6, 124.7, 114.5, 107.2, 38.7, 19.8 (d, *J* = 17.3 Hz). HRMS (ESI-TOF) calcd. for $C_{15}H_{18}N_3O$ $[M+H]^+$: 256.1444, found: 256.1446.

3-Methoxy-*N*'-methyl-*N*'-(pyridin-2-yl)benzohydrazide 1e

White solid; yield 883%. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.85 (s, 1H), 8.18 (d, *J* = 4.6 Hz, 1H), 7.51-7.44 (m, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.30 (dd, *J* = 16.2, 8.5 Hz, 1H), 7.10-6.99 (m, 1H), 6.71 (dd, *J* = 13.0, 7.6 Hz, 2H), 3.81 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.5, 159.9, 159.3, 147.6, 137.7, 133.9, 129.7, 119.1, 118.5, 114.7, 112.5, 107.2, 55.4, 38.8. HRMS (ESI-TOF) calcd. for $C_{14}H_{16}N_3O_2$ $[M+H]^+$: 258.1237, found: 258.1236.

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3,4-*di*Methoxy-*N*'-methyl-*N*'-(pyridin-2-yl)benzohydrazide 1f

White solid; yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (s, 1H), 8.21 (d, *J* = 4.0 Hz, 1H), 7.58-7.48 (m, 1H), 7.48-7.36 (m, 2H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.80-6.68 (m, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.2, 159.4, 152.2, 149.0, 147.4, 137.8, 125.0, 120.1, 114.6, 110.7, 110.3, 107.2, 56.0, 39.0. HRMS (ESI-TOF) calcd. for $C_{15}H_{18}N_3O_3$ $[M+H]^+$: 288.1343, found: 288.1339.

***N*'-Methyl-*N*'-(pyridin-2-yl)benzohydrazide 1g**

White solid; yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (d, *J* = 36.1 Hz, 1H), 8.20 (d, *J* = 4.0 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.68-7.39 (m, 4H), 6.92-6.56 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.7, 159.3, 147.6, 137.7, 132.6, 132.1, 128.7, 127.3, 114.6, 107.2, 38.8. HRMS (ESI-TOF) calcd. for $C_{13}H_{14}N_3O$ $[M+H]^+$: 228.1131, found: 228.1129.

***N*'-Methyl-*N*'-(pyridin-2-yl)-2-naphthohydrazide 1i**

White solid; yield 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.01 (s, 1H), 8.36 (s, 1H), 8.21 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.91-7.77 (m, 4H), 7.60-7.45 (m, 3H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 6.6, 5.4 Hz, 1H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.7, 159.3, 147.6, 137.7, 135.0, 132.5, 129.7, 129.0, 128.6, 128.0, 127.9, 127.7, 126.8, 123.6, 114.8, 107.2, 39.0. HRMS (ESI-TOF) calcd. for $C_{17}H_{16}N_3O$ $[M+H]^+$: 278.1288, found: 278.1287.

***N*'-Methyl-*N*'-(pyridin-2-yl)biphenyl-4-carbohydrazide 1j**

White solid; yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.11 (s, 1H), 8.20 (d, *J* = 3.8 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.59 (dd, *J* = 7.5, 5.7 Hz, 4H), 7.47 (dt, *J* = 12.7, 4.6 Hz, 3H), 7.39 (t, *J* = 7.2 Hz, 1H), 6.81-6.64 (m, 2H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.4, 159.4, 147.6, 144.9, 139.9, 137.7, 131.1, 129.0, 128.1, 127.9, 127.2 (d, *J* = 7.4 Hz), 114.7, 107.2, 38.9. HRMS (ESI-TOF) calcd. for $C_{19}H_{18}N_3O$ $[M+H]^+$: 304.1420, found: 304.1422.

***N*'-Methyl-*N*'-(pyridin-2-yl)pivalohydrazide 1k**

White solid; yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.98 (s, 1H), 7.43 (ddd, *J* = 8.9, 7.3, 1.9 Hz, 1H), 6.65 (dd, *J* = 6.8, 5.3 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 3.27 (s, 3H), 1.24 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.3, 159.5, 147.6, 137.5, 114.3, 106.8, 38.5, 38.2, 27.3. HRMS (ESI-TOF) calcd. for $C_{11}H_{18}N_3O$ $[M+H]^+$: 208.1131, found: 208.1129.

3-Fluoro-*N*'-methyl-*N*'-(pyridin-2-yl)benzohydrazide 1l

White solid; yield 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.82 (d, *J* = 26.6 Hz, 1H), 8.05-7.92 (m, 1H), 7.49-7.24 (m, 3H), 7.15-6.97 (m, 2H), 6.53 (ddd, *J* = 20.0, 10.4, 5.6 Hz, 2H), 3.14 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.7 (d, *J* = 2.0 Hz), 163.8, 161.3, 159.1, 147.3, 137.8, 134.5 (d, *J* = 6.9 Hz), 130.2 (d, *J* = 7.8 Hz), 122.9 (d, *J* = 2.7 Hz), 119.1, 118.9, 114.9, 114.6, 107.2, 38.5 (d, *J* = 5.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -111.51 (d, *J* = 2.3 Hz). HRMS (ESI-TOF) calcd. for $C_{13}H_{13}FN_3O$ $[M+H]^+$: 246.1037, found: 246.1037.

***N*'-Methyl-4-nitro-*N*'-(pyridin-2-yl)benzohydrazide 1m**

White solid; yield 71%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.10 (s, 1H), 8.45-8.28 (m, 2H), 8.18 (dd, *J* = 6.9, 1.9 Hz, 3H), 7.55 (ddd, *J* = 8.8, 7.2, 1.9 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.76-6.67 (m, 1H), 3.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 164.6, 159.8, 149.9, 147.9, 138.8, 138.0, 129.5, 124.1, 114.5, 107.3, 38.1. HRMS (ESI-TOF) calcd. for $C_{13}H_{13}N_4O_3$ $[M+H]^+$: 278.0982, found: 278.0981.

***N'*-Methyl-*N'*-(pyridin-2-yl)-4-(trifluoromethyl)benzohydrazide 1n**

White solid; yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.55 (s, 1H), 8.19 (d, *J* = 4.8 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.68-7.46 (m, 3H), 6.90-6.59 (m, 2H), 3.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.3, 158.9, 147.4, 138.1, 127.8, 125.7, 125.7, 125.6, 125.6, 115.1, 107.3, 39.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.12 (s). HRMS (ESI-TOF) calcd. for $C_{14}H_{12}N_3OF_3$ $[M+H]^+$: 296.1005, found: 296.1004.

***N'*-Methyl-*N'*-(pyridin-2-yl)-2-(*p*-tolyl)acetohydrazide 1p**

White solid; yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, *J* = 4.0 Hz, 1H), 7.44-7.38 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.08 (t, *J* = 6.8 Hz, 1H), 6.65 (dd, *J* = 6.8, 5.2 Hz, 1H), 6.52 (d, *J* = 8.5 Hz, 1H), 3.58 (s, 2H), 3.26 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.1, 159.1, 150.1, 147.7, 137.6, 129.9, 129.3, 129.2, 114.6, 106.9, 41.8, 38.6, 21.1. HRMS (ESI-TOF) calcd. for $C_{15}H_{18}N_3O$ $[M+H]^+$: 256.1436, found: 256.1444.

General procedure for the thiolation

An oven-dried pressure tube was charged with benzamide **1** (0.2 mmol), disulfide **2** (0.24 mmol), $Ni(OTf)_2$ (7.14 mg, 0.02 mmol), Na_2CO_3 (42 mg, 0.4 mmol), BINAP (24.88 mg, 0.04 mmol), and DMSO (2 mL). The tube was then sealed and stirred vigorously at 140 ^{o}C for 12 h. After cooling to room temperature, the reaction mixture was diluted with water, extracted with CH_2Cl_2 (3×10 mL). The combined phase was then washed with brine and dried over anhydrous sodium sulfate. After concentration, the resulting residue was purified by preparative TLC using CH_2Cl_2/EtOAc as the eluent to afford product **3**.

***N*',2-*di*Methyl-6-(phenylthio)-*N*'-(pyridin-2-yl)benzohydrazide 3a**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.75 (s, 1H), 7.52 (ddd, *J* = 8.8, 7.2, 1.9 Hz, 1H), 7.29-7.26 (m, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 3H), 7.08 (dd, *J* = 13.1, 8.2 Hz, 2H), 6.73 (dd, *J* = 6.8, 5.3 Hz, 1H), 3.50 (s, 3H), 2.50 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.6, 159.3, 147.6, 137.6 (d, *J* = 8.2 Hz), 137.0, 136.6, 133.8, 131.5 (d, *J* = 9.9 Hz), 130.2 (d, *J* = 14.5 Hz), 129.8, 129.3, 114.8, 107.7, 77.4, 77.0, 76.7, 38.3, 21.1, 19.5. HRMS (ESI-TOF) calcd. for $C_{20}H_{20}N_3OS$ $[M+H]^+$: 350.1322, found: 350.1317.

***N*',5-*di*Methyl-2-(phenylthio)-*N*'-(pyridin-2-yl)benzohydrazide 3b**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (s, 1H), 8.18 (d, *J* = 4.1 Hz, 1H), 7.67 (s, 1H), 7.45-7.38 (m, 1H), 7.34-7.22 (m, 7H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.68 (dd, *J* = 6.6, 5.4 Hz, 1H), 3.33 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.8, 159.3, 147.6, 138.8, 137.6, 136.0 (d, *J* = 13.5 Hz), 134.7, 132.5, 130.8, 129.5, 128.6, 127.0, 114.6, 107.4, 38.2, 21.0. HRMS (ESI-TOF) calcd. for $C_{20}H_{20}N_3OS$ $[M+H]^+$: 350.1322, found: 350.1317.

***N*',4-*di*Methyl-2-(phenylthio)-*N*'-(pyridin-2-yl)benzohydrazide 3c**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64 (s, 1H), 8.16-8.03 (m, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.39-7.31 (m, 1H), 7.26-7.16 (m, 5H), 7.11 (d, *J* = 9.1 Hz, 2H), 6.65 (d, *J* = 8.5 Hz, 1H), 6.61 (dd, *J* = 6.6, 5.4 Hz, 1H), 3.26 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.7, 159.2, 147.5, 142.2, 137.6, 135.2, 134.3, 132.7 (d, *J* = 16.2 Hz), 130.2 (d, *J* = 6.8 Hz), 129.5, 128.8, 127.3, 114.6, 107.4, 38.3, 21.3. HRMS (ESI-TOF) calcd. for $C_{20}H_{20}N_3OS$ $[M+H]^+$: 350.1322, found: 350.1317.

***N*',4-*di*Methyl-2,6-bis(phenylthio)-*N*'-(pyridin-2-yl) benzohydrazide 3c'**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 4.2 Hz, 1H), 7.77-7.51 (m, 1H), 7.38-7.16 (m, 11H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.92 (s, 2H), 6.63-6.52 (m, 1H), 3.37 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.3, 159.4, 147.3, 141.3, 137.6, 136.3, 135.0, 134.6, 132.5, 131.1,

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129.5, 127.6, 114.7, 108.3, 37.8, 21.2. HRMS (ESI-TOF) calcd. for $C_{26}H_{24}N_3OS_2$ $[M+H]^+$: 458.1355, found: 458.1364.

_N'_,4,5-_tri_Methyl-2-(phenylthio)-_N'_-(pyridin-2-yl)benzohydrazide 3d

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (s, 1H), 8.16 (d, _J_ = 4.4 Hz, 1H), 7.72 (s, 1H), 7.42-7.34 (m, 1H), 7.34-7.25 (m, 3H), 7.21 (d, _J_ = 6.6 Hz, 2H), 6.66 (dd, _J_ = 10.3, 4.8 Hz, 2H), 3.28 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.5, 159.3, 147.6, 141.2, 138.0, 137.5, 136.6, 136.3, 133.8, 132.0, 129.5, 128.6, 127.6, 126.7, 114.5, 107.3, 77.3, 77.0, 76.7, 38.1, 19.6, 19.3. HRMS (ESI-TOF) calcd. for $C_{21}H_{22}N_3OS$ $[M+H]^+$: 364.1478, found: 364.1478.

5-Methoxy-_N'_-methyl-2-(phenylthio)-_N'_-(pyridin-2-yl) benzohydrazide 3e

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 7.71 (d, _J_ = 4.0 Hz, 1H), 7.58 (d, _J_ = 8.2 Hz, 1H), 7.52 (d, _J_ = 2.3 Hz, 1H), 7.32-7.28 (m, 2H), 7.24 (s, 2H), 7.18 (d, _J_ = 5.8 Hz, 2H), 7.04 (dd, _J_ = 18.7, 8.2 Hz, 2H), 6.63 (d, _J_ = 0.5 Hz, 1H), 3.82 (s, 3H), 3.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.8, 160.9, 159.4, 147.3, 139.0, 137.4, 130.9, 129.4, 128.9 (d, _J_ = 18.6 Hz), 128.5, 127.3, 126.6, 126.0, 123.0, 114.7, 113.6, 108.3, 56.4, 37.6. HRMS (ESI-TOF) calcd. for $C_{20}H_{20}N_3OS$ $[M+H]^+$: 366.1322, found: 366.1317.

4,5-_di_Methoxy-_N'_-methyl-2-(phenylthio)-_N'_-(pyridin-2-yl) benzohydrazide 3f

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.39 (s, 1H), 8.23-8.10 (m, 1H), 7.65 (s, 1H), 7.37-7.26 (m, 3H), 7.20 (t, _J_ = 7.4 Hz, 1H), 7.18-7.10 (m, 2H), 7.04 (s, 1H), 6.65 (dd, _J_ = 6.8, 5.3 Hz, 1H), 6.58 (d, _J_ = 8.5 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 3H), 3.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.8, 159.4, 151.4, 149.9, 147.6, 137.5, 136.7, 129.6 (d, _J_ = 8.3 Hz), 127.3, 126.6, 121.1, 119.0, 114.5, 114.2, 107.2, 56.3, 38.0. HRMS (ESI-TOF) calcd. for $C_{21}H_{22}N_3O_3S$ $[M+H]^+$: 396.1376, found: 396.1382.

_N'_-Methyl-2-(phenylthio)-_N'_-(pyridin-2-yl)benzohydrazide 3g

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (s, 1H), 8.18 (d, _J_ = 3.8 Hz, 1H), 7.78 (d, _J_ = 6.7 Hz, 1H), 7.44 (t, _J_ = 7.5 Hz, 1H), 7.30 (dd, _J_ = 26.5, 6.3 Hz, 8H), 6.79 (d, _J_ = 8.4 Hz, 1H), 6.72-6.61 (m, 1H), 3.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.9, 159.2, 147.5, 137.7, 134.9, 134.6, 134.2, 132.8, 131.5, 131.2, 129.6, 127.7, 127.5, 114.7, 107.4, 38.4. HRMS (ESI-TOF) calcd. for $C_{19}H_{18}N_3OS$ $[M+H]^+$: 336.1165, found: 336.1165.

_N'_-Methyl-2,6-bis(phenylthio)-_N'_-(pyridin-2-yl)benzohydrazide 3g'

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (dd, _J_ = 4.8, 0.9 Hz, 1H), 7.58 (s, 1H), 7.43 (ddd, _J_ = 14.8, 8.3, 1.3 Hz, 5H), 7.38-7.30 (m, 5H), 7.24-7.19 (m, 2H), 7.18-7.05 (m, 2H), 6.69 (dd, _J_ = 6.6, 5.4 Hz, 1H), 3.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.1, 159.4, 147.4, 137.9, 137.5, 135.5, 134.5, 131.7, 131.0, 130.7, 129.6, 127.9, 114.8, 108.3, 77.4, 77.1, 76.7, 37.9. HRMS (ESI-TOF) calcd. for $C_{25}H_{22}N_3OS_2$ $[M+H]^+$: 444.1499, found: 444.1496.

_N'_-Methyl-2-(phenylthio)-_N'_-(pyridin-2-yl)-1-naphthohydrazide 3h

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (dd, _J_ = 4.8, 0.9 Hz, 1H), 8.12 (d, _J_ = 8.3 Hz, 1H), 7.97 (s, 1H), 7.80 (dd, _J_ = 15.1, 8.3 Hz, 2H), 7.63-7.56 (m, 1H), 7.55-7.46 (m, 2H), 7.36 (dd, _J_ = 9.4, 2.3 Hz, 2H), 7.33-7.22 (m, 4H), 7.03 (d, _J_ = 8.5 Hz, 1H), 6.72 (dd, _J_ = 6.8, 5.2 Hz, 1H), 3.53 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.2, 159.2, 147.6, 137.7, 135.5, 134.9, 132.4, 131.1, 130.8, 130.7, 130.6, 129.4, 129.4, 128.2, 127.9, 127.4, 127.0, 125.1, 114.9, 107.6, 38.5. HRMS (ESI-TOF) calcd. for $C_{23}H_{20}N_3OS$ $[M+H]^+$: 386.1322, found: 386.1324.

_N'_-Methyl-3-(phenylthio)-_N'_-(pyridin-2-yl)-2-naphthohydrazide 3i

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (s, 1H), 8.40 (s, 1H), 8.19 (d, _J_ = 4.1 Hz, 1H), 7.96-7.86 (m, 2H), 7.80-7.71 (m, 1H), 7.61-7.52 (m, 2H), 7.43 (dd, _J_ = 11.3, 4.3 Hz, 1H), 7.37-7.25 (m, 5H), 6.79-6.65 (m, 2H), 3.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.6, 159.3, 147.6, 137.7, 135.4, 134.5, 133.9, 132.7, 132.0, 131.1, 129.8, 129.7, 128.6, 128.4, 127.5, 127.4, 114.7, 107.4, 38.2. HRMS (ESI-TOF) calcd. for $C_{23}H_{20}N_3OS$ $[M+H]^+$: 386.1322, found: 386.1321.

_N'_-Methyl-3-(phenylthio)-_N'_-(pyridin-2-yl)biphenyl-4-carbohydrazide 3j

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (s, 1H), 8.13 (d, _J_ = 4.2 Hz, 1H), 7.86 (d, _J_ = 7.9 Hz, 1H), 7.56-7.47 (m, 2H), 7.45-7.24 (m, 10H), 7.19 (s, 1H), 6.70 (d, _J_ = 8.5 Hz, 1H), 6.67-6.59 (m, 1H), 3.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.5, 158.2, 146.6, 143.5, 138.1, 136.6, 133.6, 133.0, 132.6, 130.9, 129.6 (d, _J_ = 5.2 Hz), 128.7, 128.0, 127.3, 126.7, 126.1, 125.4, 113.7, 106.4, 37.4. HRMS (ESI-TOF) calcd. for $C_{25}H_{22}N_3OS$ $[M+H]^+$: 412.1478, found: 412.1484.

_N'_-Methyl-3,5-bis(phenylthio)-_N'_-(pyridin-2-yl)biphenyl-4-carbohydrazide 3j'

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (dd, _J_ = 4.9, 1.0 Hz, 1H), 7.71 (s, 1H), 7.46-7.42 (m, 4H), 7.38-7.26 (m, 13H), 7.25-7.20 (m, 2H), 6.67 (dd, _J_ = 6.7, 5.4 Hz, 1H), 3.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.0, 159.4, 147.4, 143.8, 138.8, 137.6, 137.0, 135.7, 134.6, 131.4, 130.0, 129.6, 129.0, 128.4, 127.9, 127.0, 114.8, 108.3, 37.9. HRMS (ESI-TOF) calcd. for $C_{31}H_{26}N_3OS_2$ $[M+H]^+$: 520.1512, found: 520.1514.

_N'_,2,2-_tri_Methyl-3-(phenylthio)-_N'_-(pyridin-2-yl)propanehydrazide 3k

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, _J_ = 3.9 Hz, 1H), 7.98 (s, 1H), 7.40-7.29 (m, 3H), 7.19 (t, _J_ = 7.5 Hz, 2H), 7.11 (d, _J_ = 7.3 Hz, 1H), 6.67 (d, _J_ = 8.5 Hz, 1H), 6.59 (dd, _J_ = 6.7, 5.2 Hz, 1H), 3.21 (s, 3H), 3.16 (s, 2H), 1.30 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.8, 159.3, 147.6, 137.5, 136.8, 129.7, 129.0, 126.4, 114.5, 107.2, 45.1, 43.4, 38.5, 29.7, 25.0. HRMS (ESI-TOF) calcd. for $C_{17}H_{22}N_3OS$ $[M+H]^+$: 314.1333, found: 314.1328.

_N'_,2-_di_Methyl-3-(phenylthio)-2-((phenylthio)methyl)-_N'_-(pyridin-2-yl)propanehydrazide 3k'

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21-8.15 (m, 1H), 8.10 (s, 1H), 7.44 (ddd, _J_ = 8.8, 7.2, 1.9 Hz, 1H), 7.39 (dt, _J_ = 3.0, 1.9 Hz, 4H), 7.27 (dt, _J_ = 6.1, 1.6 Hz, 5H), 7.22-7.17 (m, 2H), 6.88 (d, _J_ = 8.5 Hz, 1H), 6.72-6.65 (m, 1H), 3.45 (d, _J_ = 12.8 Hz, 2H), 3.30 (d, _J_ = 2.3 Hz, 3H), 3.26 (s, 2H), 1.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.9, 158.2, 146.5, 136.6, 135.2, 128.9, 128.1, 125.6, 113.6, 106.6, 47.4, 42.4, 37.5, 20.1. HRMS (ESI-TOF) calcd. for $C_{23}H_{26}N_3OS_2$ $[M+H]^+$: 424.1512, found: 424.1517.

5-Fluoro-_N'_-methyl-2-(phenylthio)-_N'_-(pyridin-2-yl) benzohydrazide 3l

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (s, 1H), 8.20 (d, _J_ = 3.4 Hz, 1H), 7.67 (d, _J_ = 7.5 Hz, 1H), 7.54 (dd, _J_ = 7.5, 5.0 Hz, 1H), 7.46 (t, _J_ = 7.8 Hz, 1H), 7.32-7.17 (m, 6H), 6.80 (d, _J_ = 8.4 Hz, 1H), 6.76-6.65 (m, 1H), 3.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 165.9 (d, _J_ = 2.9 Hz), 164.2, 162.2, 159.0, 147.7, 141.0, 137.7, 135.4, 131.6 (d, _J_ = 8.7 Hz), 129.4, 128.0, 126.7, 125.4 (d, _J_ = 3.6 Hz), 118.7, 118.6, 114.9, 107.4, 38.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -102.43 (s). HRMS (ESI-TOF) calcd. for $C_{19}H_{17}FN_3OS$ $[M+H]^+$: 354.1098, found: 354.1069.

_N'_-Methyl-4-nitro-2-(phenylthio)-_N'_-(pyridin-2-yl) benzohydrazide

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3m

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.46 (s, 1H), 8.22 (s, 1H), 8.05 (d, *J* = 7.0 Hz, 1H), 7.91-7.75 (m, 2H), 7.49 (dd, *J* = 52.5, 27.5 Hz, 6H), 6.99-6.67 (m, 2H), 3.47 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 165.6, 158.8, 149.4, 147.7, 140.5, 138.1, 137.9, 134.0, 131.0, 130.3, 129.7 (d, *J* = 7.8 Hz), 124.1, 120.6, 115.4, 107.5, 39.1. HRMS (ESI-TOF) calcd. for $C_{19}H_{17}N_4O_3S$ $[M+H]^+$: 381.1016, found: 381.1014.

***N*'-Methyl-4-nitro-2,6-bis(phenylthio)-*N*'-(pyridin-2-yl) benzohydrazide 3m'**

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.15 (s, 1H), 7.94 (t, *J* = 53.5 Hz, 1H), 7.56-7.36 (m, 10H), 7.37-7.11 (m, 4H), 6.69 (s, 1H), 3.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.5, 159.1, 149.0, 147.5, 140.2, 138.8, 137.7, 133.9, 133.0, 131.1, 130.2, 129.9, 129.7, 121.6, 115.3, 108.1, 38.4. HRMS (ESI-TOF) calcd. for $C_{25}H_{21}N_4O_3S_2$ $[M+H]^+$: 489.1050, found: 489.1056.

***N'*-Methyl-2-(phenylthio)-*N'*-(pyridin-2-yl)-4-(trifluoromethyl) benzohydrazide 3n**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (s, 1H), 8.20 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 12.2, 5.2 Hz, 2H), 7.46-7.31 (m, 6H), 6.90-6.61 (m, 2H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.0, 158.9, 147.7, 137.9, 137.5, 132.7, 132.3, 130.0, 129.7, 128.9, 127.6, 127.6, 127.6, 123.5, 123.4, 123.4, 123.3, 115.2, 107.4, 38.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.26 (s). HRMS (ESI-TOF) calcd. for $C_{20}H_{16}N_3OF_3S$ $[M+H]^+$: 404.1039, found: 404.1037.

***N'*-Methyl-2,6-bis(phenylthio)-*N'*-(pyridin-2-yl)-4-(trifluoromethyl) benzohydrazide 3n'**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, *J* = 4.8 Hz, 1H), 7.54-7.47 (m, 5H), 7.45-7.37 (m, 6H), 7.28 (s, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 7.18 (s, 2H), 6.74 (dd, *J* = 6.7, 5.4 Hz, 1H), 3.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.1, 159.1, 147.4, 138.3, 137.8, 132.9, 132.3, 130.0, 129.0, 125.2, 115.1, 108.2, 38.2. HRMS (ESI-TOF) calcd. for $C_{26}H_{20}N_3OF_3S_2$ $[M+H]^+$: 512.1073, found: 512.1072.

***N'*-Methyl-2-(phenylthio)-*N'*-(pyridin-2-yl)-2-(*p*-tolyl)acetohydrazide 3p**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (s, 1H), 8.12 (d, *J* = 5.7 Hz, 1H), 7.47 (d, *J* = 7.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.37-7.27 (m, 4H), 7.20 (d, *J* = 7.9 Hz, 2H), 6.64 (dd, *J* = 6.8, 5.2 Hz, 1H), 6.20 (d, *J* = 8.5 Hz, 1H), 5.08 (s, 1H), 3.18 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.1, 159.0, 147.5, 138.5, 137.5, 134.1, 132.2, 130.5, 129.8, 129.4, 128.1, 127.6, 114.7, 107.0, 55.6, 38.2, 21.2. HRMS (ESI-TOF) calcd. for $C_{21}H_{21}N_3OS$ $[M-H]^-$: 364.1478, found: 364.1473.

***N*',2-*di*Methyl-*N*'-(pyridin-2-yl)-6-(*p*-tolylthio)benzohydrazide 3q**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.75 (s, 1H), 7.52 (ddd, *J* = 8.8, 7.2, 1.9 Hz, 1H), 7.29-7.26 (m, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 3H), 7.08 (dd, *J* = 13.1, 8.2 Hz, 2H), 6.73 (dd, *J* = 6.8, 5.3 Hz, 1H), 3.50 (s, 3H), 2.50 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.6, 159.3, 147.6, 137.6 (d, *J* = 8.2 Hz), 137.0, 136.6, 133.8, 131.5 (d, *J* = 9.9 Hz), 130.2 (d, *J* = 14.5 Hz), 129.8, 129.3, 114.8, 107.7, 77.4, 77.0, 76.7, 38.3, 21.1, 19.5. HRMS (ESI-TOF) calcd. for $C_{21}H_{20}N_3OS$ $[M-H]^-$: 362.1301, found: 362.1396.

2-((4-Methoxyphenyl)thio)-*N*',6-dimethyl-*N*'-(pyridin-2-yl) benzohydrazide 3r

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (d, *J* = 4.1 Hz, 1H), 8.01 (s, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.05 (dd, *J* = 11.0, 8.3 Hz, 2H), 6.88 (dd, *J* = 15.2, 8.3 Hz, 3H), 6.74-6.65 (m, 1H), 3.78 (s, 3H), 3.49 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.8, 159.9, 159.4, 147.5, 137.6, 136.6, 135.7, 135.2, 134.9, 130.0, 128.5, 127.9, 124.3, 115.2, 114.8, 107.8, 55.4, 38.3, 19.4. HRMS (ESI-TOF) calcd. for $C_{21}H_{20}N_3O_2S$ $[M-H]^-$: 378.1282, found: 378.1276.

2-((4-Fluorophenyl)thio)-*N*',6-dimethyl-*N*'-(pyridin-2-yl) benzohydrazide 3s

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20-8.09 (m, 1H), 7.96 (s, 1H), 7.48 (ddd, *J* = 8.9, 7.2, 1.9 Hz, 1H), 7.35 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.22-7.17 (m, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 7.02-6.93 (m, 3H), 6.72-6.61 (m, 1H), 3.45 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.5, 163.7, 161.2, 159.3, 147.5, 137.6, 137.0, 136.8, 133.7, 133.6, 133.5, 130.7, 130.3, 130.2, 129.8, 129.6, 116.7, 116.4, 114.9, 107.7, 77.4, 77.1, 76.7, 38.3, 19.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -113.72 (s). HRMS (ESI-TOF) calcd. for $C_{20}H_{17}FN_3OS$ $[M-H]^-$: 366.1082, found: 366.1074.

2-((4-Chlorophenyl)thio)-*N*',6-dimethyl-*N*'-(pyridin-2-yl) benzohydrazide 3t

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.82 (s, 1H), 7.49 (ddd, *J* = 8.7, 7.3, 1.9 Hz, 1H), 7.29-7.21 (m, 5H), 7.21-7.15 (m, 2H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 6.8, 5.3 Hz, 1H), 3.44 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.4, 159.2, 147.6, 137.7 (d, *J* = 17.3 Hz), 137.2, 134.6, 133.2, 131.9, 131.5, 131.2, 130.3 (d, *J* = 5.5 Hz), 129.5, 115.0, 107.7, 38.4, 19.5. HRMS (ESI-TOF) calcd. for $C_{20}H_{17}ClN_3OS$ $[M-H]^-$: 382.0786, found: 382.0780.

2-((4-Bromophenyl)thio)-*N*',6-dimethyl-*N*'-(pyridin-2-yl) benzohydrazide 3u

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (d, *J* = 4.1 Hz, 1H), 7.90 (s, 1H), 7.54-7.44 (m, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.21-7.11 (m, 4H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 6.8, 5.2 Hz, 1H), 3.43 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.4, 159.2, 147.5, 138.0, 137.6, 137.3, 135.5, 132.4, 131.5 (d, *J* = 13.3 Hz), 130.4 (d, *J* = 6.0 Hz), 121.0, 115.0, 107.7, 77.4, 77.0, 76.7, 38.4, 19.5. HRMS (ESI-TOF) calcd. for $C_{20}H_{18}BrN_3OSNa$ $[M+Na]^+$: 450.0246, found: 450.0232.

***N*',2-*di*Methyl-*N*'-(pyridin-2-yl)-6-(*o*-tolylthio)benzohydrazide 3v**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, *J* = 4.0 Hz, 1H), 7.83 (s, 1H), 7.48-7.39 (m, 1H), 7.25-7.11 (m, 6H), 6.95 (dd, *J* = 14.6, 8.1 Hz, 2H), 6.68 (dd, *J* = 6.7, 5.2 Hz, 1H), 3.42 (s, 3H), 2.47 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.6, 159.3, 147.5, 138.9, 137.6, 137.1, 136.6, 134.2, 132.7, 131.4, 130.7, 130.2, 129.3 (d, *J* = 2.3 Hz), 127.7, 127.0, 114.8, 107.7, 38.1, 20.5, 19.5. HRMS (ESI-TOF) calcd. for $C_{21}H_{20}N_3OS$ $[M-H]^-$: 362.1333, found: 362.1326.

***N*',2-*di*Methyl-*N*'-(pyridin-2-yl)-6-(*m*-tolylthio)benzohydrazide 3w**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.76 (s, 1H), 7.47 (ddd, *J* = 8.8, 7.3, 1.8 Hz, 1H), 7.23 (dd, *J* = 13.8, 6.2 Hz, 1H), 7.19-7.11 (m, 4H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.02 (dd, *J* = 14.7, 7.9 Hz, 2H), 6.69 (dd, *J* = 6.6, 5.2 Hz, 1H), 3.44 (s, 3H), 2.47 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.6, 159.3, 147.5, 139.3, 137.6, 137.1 (d, *J* = 15.4 Hz), 135.4, 132.8, 131.1, 130.7, 130.2, 129.7, 129.3, 128.1, 127.6, 114.8, 107.7, 38.2, 21.3, 19.5. HRMS (ESI-TOF) calcd. for $C_{21}H_{20}N_3OS$ $[M-H]^-$: 362.1333, found: 362.1328.

2-((2-Fluorophenyl)thio)-*N*',6-dimethyl-*N*'-(pyridin-2-yl) benzohydrazide 3x

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.93 (s, 1H), 7.47 (ddd, *J* = 8.8, 7.2, 1.9 Hz, 1H), 7.27-7.18 (m, 3H), 7.13 (dd, *J*

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= 16.2, 7.5 Hz, 2H), 7.09-6.99 (m, 3H), 6.72-6.64 (m, 1H), 3.44 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.5, 162.1, 159.7, 159.3, 147.5, 137.6, 137.5, 137.2, 133.0, 131.2, 130.6, 130.2, 130.1, 129.5, 129.5, 125.0, 125.0, 123.0, 122.8, 116.1, 115.9, 114.8, 107.7, 38.1, 19.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -109.21 (s). HRMS (ESI-TOF) calcd. for $C_{20}H_{19}FN_3OS$ $[M+H]^+$: 368.1227, found: 368.1222.

***N*',2-*di*Methyl-6-(propylthio)-*N*'-(pyridin-2-yl)benzohydrazide 3y**

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.12 (s, 1H), 7.65 (s, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 9.8 Hz, 2H), 7.05 (dd, *J* = 18.4, 7.3 Hz, 2H), 6.65 (s, 1H), 3.44 (s, 3H), 2.83 (d, *J* = 6.2 Hz, 2H), 2.36 (s, 3H), 1.68-1.52 (m, 2H), 0.93 (dd, *J* = 6.5, 5.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 167.0, 158.4, 146.5, 136.5, 136.2, 135.6, 132.8, 128.7, 127.8 (d, *J* = 15.6 Hz), 113.8, 106.8, 37.1, 36.6, 21.6, 18.4, 12.4. HRMS (ESI-TOF) calcd. for $C_{17}H_{22}N_3OS$ $[M+H]^+$: 316.1478, found: 316.1475.

General procedures for the radical trapping

An oven-dried pressure tube was charged with benzamide **1a** (48.2 mg, 0.2 mmol), disulfide **2a** (52.32 mg, 0.24 mmol), $Ni(OTf)_2$ (7.14 mg, 0.02 mmol), Na_2CO_3 (42 mg, 0.4 mmol), BINAP (24.88 mg, 0.04 mmol), TEMPO (93.6 mg, 0.6 mmol) and DMSO (1.0 mL). The tube was then sealed and stirred vigorously at 140 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with water, extracted with CH_2Cl_2 (3×10 mL). The combined phase was then washed with brine and dried over anhydrous sodium sulfate. After concentration, the resulting residue was purified by preparative TLC using CH_2Cl_2/EtOAc as the eluent to afford product **3a** (43.9 mg, 63%).

An oven-dried pressure tube was charged with benzamide **1a** (48.2 mg, 0.2 mmol), disulfide **2a** (52.32 mg, 0.24 mmol), $Ni(OTf)_2$ (7.14 mg, 0.02 mmol), Na_2CO_3 (42 mg, 0.4 mmol), BINAP (24.88 mg, 0.04 mmol), BHT (132.0 mg, 0.6 mmol) and DMSO (1.0 mL). The tube was then sealed and stirred vigorously at 140 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with water, extracted with CH_2Cl_2 (3×10 mL). The combined phase was then washed with brine and dried over anhydrous sodium sulfate. After concentration, the resulting residue was purified by preparative TLC using CH_2Cl_2/EtOAc as the eluent to afford product **3a** (49.6 mg, 71%).

Ni-catalyzed thiolation with 4

To a Schlenk tube was added benzamide **1a** (48.2 mg, 0.2 mmol), 4-methylbenzenethiol **4** (52.32 mg, 0.24 mmol), $Ni(OTf)_2$ (7.14 mg, 0.01 mmol), Na_2CO_3 (42 mg, 0.4 mmol), BINAP (24.88 mg, 0.04 mmol) and DMSO (1.0 mL). The mixture was stirred at 140 °C for 12 h. The mixture was then cooled to room temperature, diluted with water, extracted with CH_2Cl_2 (3×10 mL). The combined phase was then washed with brine and dried over anhydrous sodium sulfate. After concentration, the resulting residue was purified by preparative TLC using CH_2Cl_2/EtOAc as the eluent to afford product **3q** (37.0 mg, 51%).

Oxidation of thiol 4 to form disulfide

To a Schlenk tube was added 4-methylbenzenethiol **4** (0.2 mmol), $Ni(OTf)_2$ (7.14 mg, 0.02 mmol), Na_2CO_3 (42 mg, 0.4 mmol), BINAP (24.88 mg, 0.04 mmol) and DMSO (1.0 mL). The mixture was stirred at 140 °C for 8 h. Then the mixture was cooled to room temperature, diluted with water, extracted with CH_2Cl_2 (3×10 mL). The combined phase was then washed with brine and dried over anhydrous sodium sulfate. After concentration, the resulting residue was purified by preparative TLC using petroleum ether as the eluent to afford product **2b**, which was confirmed by ^{1}H NMR spectrum.

Hydrolysis of hydrazine to amide

To a solution of **3q** (72 mg, 0.2 mmol) in THF/MeOH (20 mL, 4:1 V/V) under N_2 was added SmI_2 (5 mL, 0.1 M in THF) dropwise. Upon addition, the blue color of the SmI_2 solution was decolorized. After complete addition, the reaction was allowed to stir for 30 min. The reaction was then concentrated on a Rotovap, and the resulting residue was purified by preparative TLC using CH_2Cl_2/EtOAc as the eluent to afford product **5**. White solid, yield 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (s, 1H), 7.13 (dt, *J* = 17.8, 8.4 Hz, 4H), 7.05 (d, *J* = 7.7 Hz, 1H), 5.95 (s, 1H), 5.67 (s, 1H), 2.40 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.5, 137.2, 136.6, 134.6, 131.9, 130.7, 130.5, 129.1, 128.5, 128.3, 128.0, 20.1, 18.4.

Conflicts of interest

There are no conflicts of interest to declare.

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