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Thiocyanation of Pyrazoles Using KSCN/$K_2S_2O_8$ Combination

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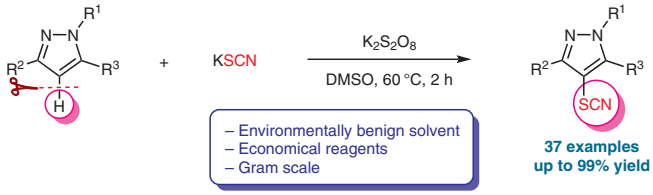

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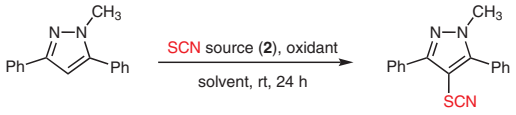
Abstract A convenient and practical thiocyanation of pyrazoles is reported employing a combination of KSCN and $K_2S_2O_8$ in dimethyl sulfoxide (DMSO). The salient features of the present reaction include environmentally benign reagents and solvents, and simple operation. The reaction shows wide functional group tolerance and gives moderate to excellent yields.

Key words thiocyanation, pyrazoles, potassium thiocyanate, potassium persulfate, heterocycle

Sulfur-containing organic molecules are important structural motifs in organic synthesis, organic materials, agrochemicals, nanotechnology and pharmaceutically important compounds in which the unique properties stem from the enhanced physical and chemical features of the sulfur atom.[1] Therefore, there are continuing efforts in the development of convenient methods for the introduction of sulfur moieties into organic molecules and materials as well as pharmaceuticals. Among various sulfur-containing substances, thiocyanate derivatives, particularly aryl- and heteroaryl thiocyanates, are an important class of compounds exhibiting pharmacological potential[2] and serving as versatile synthetic precursors for the synthesis of various organosulfur derivatives such as thiols,[3] thioethers,[4] thiocarbamates,[5] thioesters,[6] disulfides,[7] sulfonic acids,[6] sulfonyl chlorides,[8] and sulfonyl cyanides.[9] A number of synthetic routes are available for the synthesis of aryl- and heteroaryl thiocyanates including coupling of diazonium salts with metal thiocyanates under Sandmeyer type conditions,[10] cyanation of organosulfur and organometallic compounds,[11] metal-catalyzed coupling reaction of arylboronic acids with trimethylsilylisothiocyanate (TMSNCS) or aryl halides with thiocyanate salts[12] and the direct thiocyanation of C–H bonds with thiocyanates.[13] Pyrazoles and their derivatives have attracted increasing interest in the fields of medicine and pharmacology because of their interesting biological properties including antifungal,[14] antibacterial,[15] anticancer,[16] anti-inflammatory,[17] antiviral,[18] antioxidant,[19] cytotoxic,[20] antihypertensive,[21] antitubercular,[22] analgesic,[23] antipyretic,[24] anticonvulsant,[25] and A3 adenosine receptor antagonistic activities.[26] Additionally, pyrazole derivatives are also important in agricultural chemistry.[27] Although thiocyanation of arenes and heterocyclic compounds such as indoles, pyrroles, carbazoles, 8-aminoquinolines and imidazopyridines has been reported,[28] the thiocyanation of pyrazoles has been little explored.[29] Most recently, and during the preparation of this manuscript, Bhat and co-workers reported thiocyanation of phenols, anilines and indoles using $K_2S_2O_8$/NH_4SCN in CH_2Cl_2.[28r] This prompts us to report our study on a direct regioselective C4-thiocyanation of pyrazoles with commercially available and inexpensive potassium thiocyanate (KSCN) in the presence of $K_2S_2O_8$ under environmentally friendly conditions and with short reaction times.

We began our study by employing 1-methyl-3,5-diphenyl-1*H*-pyrazole (**1a**) as a model substrate to screen for optimum reaction conditions. Various reaction parameters including solvent, thiocyanate source, oxidizing agent, reagent stoichiometry, temperature and reaction time were screened and the results are summarized in Table 1. First, various solvents were evaluated using 1-methyl-3,5-diphenyl-1*H*-pyrazole (**1a**; 0.5 mmol), KSCN (**2a**; 2 equiv) and $K_2S_2O_8$ (1.5 equiv) at room temperature for 24 h (entries 1–11). It was found that only trace amounts of **3a** were observed when H_2O, 1,4-dioxane, tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF) and CH_2Cl_2 were employed as the solvents (entries 1–5). Better results were observed when the reactions were performed in EtOH, CH_3OH, EtOAc,

Table 1 Optimization of the Reaction Conditions[a]



1a **3a**

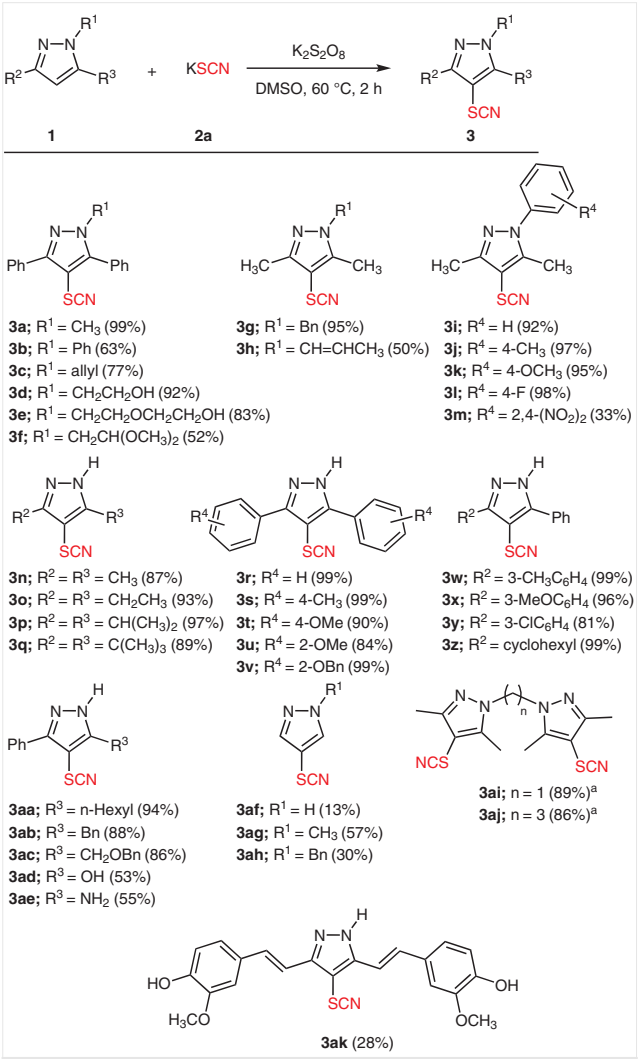
Entry	SCN source (**2**)	Oxidant	Solvent	**1a** (%)	**3a** (%)[b]
1	KSCN (**2a**)	$K_2S_2O_8$	H_2O	98	trace
2	KSCN (**2a**)	$K_2S_2O_8$	1,4-dioxane	93	trace
3	KSCN (**2a**)	$K_2S_2O_8$	THF	98	trace
4	KSCN (**2a**)	$K_2S_2O_8$	DMF	91	1
5	KSCN (**2a**)	$K_2S_2O_8$	CH_2Cl_2	85	2
6	KSCN (**2a**)	$K_2S_2O_8$	EtOH	66	34
7	KSCN (**2a**)	$K_2S_2O_8$	CH_3OH	15	75
8	KSCN (**2a**)	$K_2S_2O_8$	EtOAc	80	17
9	KSCN (**2a**)	$K_2S_2O_8$	CH_3CN	47	47
10	KSCN (**2a**)	$K_2S_2O_8$	DCE	54	35
11	KSCN (**2a**)	$K_2S_2O_8$	DMSO	1	96
12	NaSCN (**2b**)	$K_2S_2O_8$	DMSO	7	91
13	NH_4SCN (**2c**)	$K_2S_2O_8$	DMSO	12	86
14	KSCN (**2a**)	OXONE®	DMSO	31	66
15	KSCN (**2a**)	$Na_2S_2O_8$	DMSO	2	95
16	KSCN (**2a**)	DIB	DMSO	85	14
17	KSCN (**2a**)	IBX	DMSO	90	8
18	KSCN (**2a**)	TBHP	DMSO	96	trace
19	KSCN (**2a**)	CAN	DMSO	53	43
20	KSCN (**2a**)	–	DMSO	98	–
21[c]	**KSCN (2a)**	**$K_2S_2O_8$**	**DMSO**	**0**	**99**
22[d]	KSCN (**2a**)	$K_2S_2O_8$	DMSO	5	95
23[e]	KSCN (**2a**)	$K_2S_2O_8$	DMSO	19	79

[a] Reaction conditions: **1a** (0.5 mmol), **2** (2.0 equiv) and oxidant (1.5 equiv) in solvent (3 mL), open air at room temperature for 24 h.
[b] Isolated yield after column chromatography.
[c] Reaction conditions: **1a** (0.5 mmol), **2** (1.5 equiv) and oxidant (1.5 equiv) in DMSO (3 mL), open air at 60 °C for 2 h.
[d] Reaction conditions: entry 21 and in the presence of TsOH (1 equiv).
[e] Reaction conditions: entry 21 and in the presence of K_2CO_3 (1 equiv).

CH_3CN, 1,2-dichloroethane (DCE) and DMSO (entries 6–11), and DMSO provided the highest yield of the desired product **3a** of 96% (entry 11). Under the optimized conditions (entry 11), the source of thiocyanate was next examined and KSCN gave the optimal results (entries 11–13). Among oxidizing agents screened including $K_2S_2O_8$, OXONE®, $Na_2S_2O_8$, (diacetoxyiodo)benzene (DIB), 2-iodoxybenzoic acid (IBX), *tert*-butyl hydroperoxide (TBHP) and cerium(IV) ammonium nitrate (CAN), $K_2S_2O_8$ was optimum (entries 11, 14–19). Finally, no desired product **3a** was observed when the oxidizing agent was excluded from the reaction (entry 20). After the optimal solvent, thiocyanate source and oxidizing agent were identified, we further optimized the reagent stoichiometry, temperature and reaction time. We were pleased to observe that **3a** was obtained in excellent yield (99% yield) when the reaction was performed in DMSO at 60 °C for 2 h, employing KSCN (1.5 equiv) and $K_2S_2O_8$ (1.5 equiv) (entry 21). Notably, the yield slightly dropped when *p*-toluenesulfonic acid (TsOH, 1 equiv) was added as an additive (entry 22). In contrast, the presence of K_2CO_3 (1 equiv) significantly lowered the yield of **3a** (entry 23). Finally, no improvement was observed when the stoichiometry of KSCN or $K_2S_2O_8$ was increased. After extensive experimentations, the optimum reaction conditions were chosen as: **1** (0.5 mmol; 1.0 equiv), KSCN (1.5 equiv) and $K_2S_2O_8$ (1.5 equiv) in DMSO at 60 °C for 2 h (entry 21).

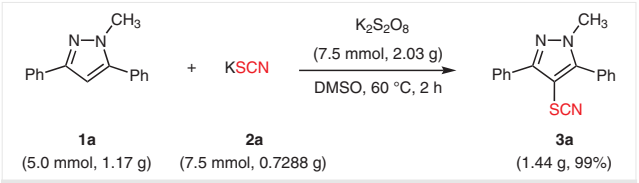
With optimized reaction conditions established (Table 1, entry 21), the substrate scope and limitations of the reaction were evaluated; the results are summarized in Scheme 1. A variety of *N*-substituted-3,5-diphenyl- and *N*-substituted-3,5-dimethylpyrazoles was first examined. The reactions of *N*-substituted-3,5-diphenylpyrazoles including *N*-methyl-, *N*-phenyl-, *N*-allyl-, *N*-alkyl- and *N*-(2,2-dimethoxyethyl)-3,5-diphenylpyrazoles proceeded smoothly to yield the corresponding thiocyanated products **3a–f** in moderate to excellent yields (52–99%). *N*-Benzyl-3,5-dimethylpyrazole (**1g**) also worked well to provide the corresponding product **3g** in 95% yield. On the other hand, the reaction of *N*-(1-propenyl)-3,5-dimethylpyrazole (**1h**) proceeded with lower efficiency, yielding **3h** in 50% yield. *N*-Aryl-3,5-dimethylpyrazoles bearing electronically different substituents on the phenyl ring were also investigated. *N*-Aryl-3,5-dimethylpyrazoles bearing electron-donating groups (4-CH_3 and 4-OCH_3) afforded **3i–k** in high yields (92–97%). The reaction of *N*-(4-fluorophenyl)-3,5-dimethylpyrazole (**1l**) provided **3l** in 98% yield. A low yield was observed when *N*-(2,4-dinitrophenyl)-3,5-dimethylpyrazole (**1m**) was employed as a substrate. Next, the reactions of 1*H*-pyrazoles, including symmetrical 3,5-dialkyl-1*H*-pyrazoles **1n–q**, symmetrical 3,5-diaryl-1*H*-pyrazoles **1r–v** and unsymmetrical 3,5-disubstituted-1*H*-pyrazoles **1w–ac**, were also evaluated. Gratifyingly, it was found that the corresponding thiocyanated products **3n–ac** were isolated in good to excellent yields (81–99%). Notably, the *N*-unprotected-1*H*-pyrazoles are potentially useful for further synthetic manipulation. 3-Phenyl-1*H*-pyrazol-5-ol (**1ad**) and 3-phenyl-1*H*-pyrazol-5-amine (**1ae**) gave moderate yields of **3ad** (53% yield) and **3ae** (55% yield). Pyrazole, *N*-methylpyrazole and *N*-benzylpyrazole (**1af–ah**) smoothly underwent the reaction to yield C4-thiocynated products (**3af–ah**) in low to moderate yields (13–57%). These results implied that the present thiocyanation reaction took place regioselectively at C4 of the pyrazole core. Moreover, the reactions of bis(3,5-dimethylpyrazol-1-yl)methane (**1ai**) and 1,3-bis(3,5-dimethylpyrazol-1-yl)propane (**1aj**) proceeded readily under standard reaction conditions (with the use of KSCN and $K_2S_2O_8$, 3.0 equiv each) to yield the corresponding

products in high yields (89% and 86%, respectively). Finally, the reaction of curcumin-derived pyrazole (**1ak**) provided the thiocyanated product **3ak** in 28% yield.

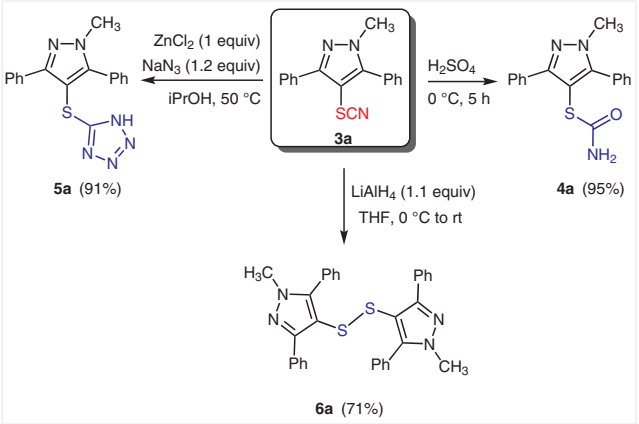


Scheme 1 Substrate scope of C4 thiocyanation of pyrazoles. Reaction conditions: **1** (0.5 mmol), KSCN (1.5 equiv) and $K_2S_2O_8$ (1.5 equiv) in DMSO (3 mL), open air, 60 °C, 2 h. Isolated yield after column chromatography given in parentheses. [a] KSCN (3.0 equiv) and $K_2S_2O_8$ (3.0 equiv) were used.

To demonstrate the utility of the present reaction further, a scale-up reaction was carried out. Under standard reaction conditions, **1a** (1.17 g, 5 mmol) was efficiently converted into **3a** in 99% yield (Scheme 2). Additionally, further synthetic manipulations of **3a** were also demonstrated (Scheme 3).[3b,28p,30] The thiocyanate group of **3a** can be transformed into thiocarbamate **4a** in 95% yield. Cycloaddition reaction of **3a** with NaN_3 mediated by $ZnCl_2$ provided thiotetrazole **5a** in 91% yield. Finally, upon treatment of **3a** with $LiAlH_4$, the disulfide **6a** was obtained in 71% yield.



Scheme 2 Gram-scale synthesis of thiocyanated pyrazole **3a**



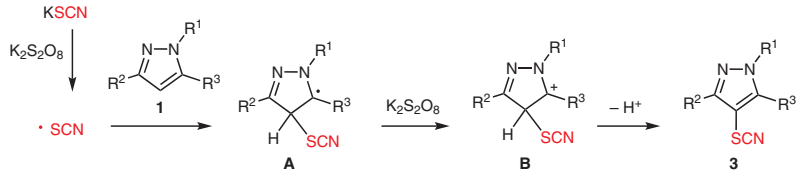
Scheme 3 Synthetic applications of thiocyanated pyrazole **3a**

To understand the reaction mechanism better, control experiments were carried out (Scheme 4). The yields of **3a** dropped significantly when the reactions of **1a** were carried out in the presence of either 2,6-di-*tert*-butyl-4-methylphenol (BHT) or hydroquinone. In the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), the reaction was totally closed down. Finally, styrene, commonly used as a radical trapping compound, was found to react competitively with reactive species formed in the reaction. Compound **1a** was recovered in 58% yield and **3a** was obtained as an inseparable mixture contaminated with unidentified materials. The observed experimental results imply that the reaction process is likely to involve a radical pathway.

radical inhibitor (2 equiv)	yield (%)
BHT	84
hydroquinone	56
TEMPO	no reaction
styrene	contaminated **3a** and **1a** (58%)

Scheme 4 Control experiments

On the basis of the control experiments and the previous related reports,[28f,28m] a possible reaction pathway can be proposed (Scheme 5). First, a thiocyanate radical is



Scheme 5 Possible reaction mechanism

generated by the oxidation of KSCN with $K_2S_2O_8$. This thiocyanate radical then reacts with pyrazole **1** to give a radical intermediate **A**, which could be oxidized to carbocationic intermediate **B** by $K_2S_2O_8$. Finally, deprotonation of intermediate **B** takes place to provide the desired product **3**.

In conclusion, we have demonstrated a facile method for thiocyanation of pyrazole derivatives. The reaction was found to be general and pyrazole derivatives bearing a wide variety of substituents are well tolerated. The use of commercially available and inexpensive reagents and the possibility of reaction scale-up make this protocol attractive for future development. Initial efforts to prove the reaction mechanism suggest that the reaction proceeds via radical intermediates.

All isolated compounds were characterized on the basis of ^{1}H NMR, ^{13}C NMR, IR spectroscopic spectra, and HRMS data. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Ascend™ spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts are reported in ppm using tetramethylsilane or the residual non-deuterated solvent peak as an internal standard. Infrared spectra were recorded with a Bruker ALPHA FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded with a Bruker micro TOF spectrometer in ESI mode. Melting points were recorded with a Sanyo Gallenkamp apparatus. Reactions were monitored by thin-layer chromatography and visualized by UV and $KMnO_4$ solution. Solvents and some pyrazoles (**1af** and **1ag**) were obtained from commercial sources and used without further purification. Other pyrazoles were synthesized according to reported procedures (see the Supporting Information). Purification of the reaction products was carried out by column chromatography on silica gel (0.063–0.200 mm). After column chromatography, analytically pure solids were obtained by crystallization from CH_2Cl_2–hexanes.

C4 Thiocyanation of Pyrazoles; General Procedure

A 10 mL round-bottom flask was charged with pyrazole **1** (0.5 mmol), KSCN (72.9 mg, 0.75 mmol), $K_2S_2O_8$ (202.7 mg, 0.75 mmol) and DMSO (3 mL). The resulting solution was stirred under air (open flask) at 60 °C for 2 h. After completion of the reaction, the mixture was cooled to r.t. and was diluted with H_2O (10 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel to provide the desired product **3**.

1-Methyl-3,5-diphenyl-4-thiocyanato-1*H*-pyrazole (3a)

Prepared from 1-methyl-3,5-diphenyl-1*H*-pyrazole (**1a**, 117.1 mg). Purification by column chromatography (20% EtOAc/hexanes) afforded **3a** (99%, 144.4 mg) as a white solid.

Mp 137.0–138.0 °C; R_f = 0.57 (30% EtOAc/hexanes).

IR (neat): 2154 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.8 Hz, 2 H), 7.62–7.57 (m, 3 H), 7.55–7.44 (m, 5 H), 3.87 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1 (C), 149.2 (C), 131.2 (C), 130.0 (CH), 129.8 (2×CH), 129.0 (2×CH), 128.8 (CH), 128.6 (2×CH), 128.2 (2×CH), 127.5 (C), 111.9 (C), 94.3 (C), 38.2 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}N_3S$: 292.0908; found: 292.0918.

1,3,5-Triphenyl-4-thiocyanato-1*H*-pyrazole (3b)

Prepared from 1,3,5-triphenyl-1*H*-pyrazole (**1b**, 148.2 mg). Purification by column chromatography (10% EtOAc/hexanes) afforded **3b** (63%, 111.6 mg) as a pale-yellow solid.

Mp 130.5–132.0 °C; R_f = 0.64 (30% EtOAc/hexanes).

IR (neat): 2161 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.2 Hz, 2 H), 7.55 (t, *J* = 7.6 Hz, 2 H), 7.51–7.43 (m, 4 H), 7.40–7.37 (m, 2 H), 7.34–7.30 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3 (C), 148.6 (C), 139.2 (C), 131.0 (C), 130.2 (2×CH), 129.9 (CH), 129.2 (CH), 129.1 (2×CH), 128.9 (2×CH), 128.7 (2×CH), 128.5 (2×CH), 128.3 (CH), 127.8 (C), 125.0 (2×CH), 111.8 (C), 96.7 (C).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{15}N_3NaS$: 376.0884; found: 376.0888.

1-Allyl-3,5-diphenyl-4-thiocyanato-1*H*-pyrazole (3c)

Prepared from 1-allyl-3,5-diphenyl-1*H*-pyrazole (**1c**, 130.2 mg). Purification by column chromatography (10% EtOAc/hexanes) afforded **3c** (77%, 122.2 mg) as a white solid.

Mp 110.5–112.0 °C; R_f = 0.61 (30% EtOAc/hexanes).

IR (neat): 2153 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.3 Hz, 2 H), 7.61–7.44 (m, 8 H), 6.06–5.96 (m, 1 H), 5.25 (dd, *J* = 10.3, 1.0 Hz, 1 H), 5.08 (dd, *J* = 17.1, 1.0 Hz, 1 H), 4.73 (t, *J* = 1.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2 (C), 149.2 (C), 132.3 (CH), 131.1 (C), 130.0 (CH), 129.7 (2×CH), 128.9 (2×CH), 128.7 (CH), 128.5 (2×CH), 128.2 (2×CH), 127.3 (C), 118.3 (CH_2), 111.8 (C), 94.4 (C), 53.0 (CH_2).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}N_3S$: 318.1065; found: 318.1076.

2-(3,5-Diphenyl-4-thiocyanato-1*H*-pyrazol-1-yl)ethanol (3d)

Prepared from 2-(3,5-diphenyl-1*H*-pyrazol-1-yl)ethanol (**1d**, 132.2 mg). Purification by column chromatography (40% EtOAc/hexanes) afforded **3d** (92%, 148.2 mg) as a white solid.

Mp 130.0–132.0 °C; R_f = 0.40 (40% EtOAc/hexanes).

IR (neat): 3498 (O–H), 2158 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.4 Hz, 2 H), 7.60–7.54 (m, 3 H), 7.53–7.44 (m, 5 H), 4.15 (t, *J* = 5.2 Hz, 2 H), 3.98 (t, *J* = 5.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3 (C), 149.9 (C), 130.8 (C), 130.04 (CH), 129.95 (2×CH), 128.9 (3×CH), 128.5 (2×CH), 128.1 (2×CH), 127.0 (C), 111.8 (C), 94.5 (C), 61.0 (CH_2), 51.9 (CH_2).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{15}N_3NaOS$: 344.0834; found: 344.0835.

2-(2-(3,5-Diphenyl-4-thiocyanato-1*H*-pyrazol-1-yl)ethoxy)ethanol (3e)

Prepared from 2-(2-(3,5-diphenyl-1*H*-pyrazol-1-yl)ethoxy)ethanol (**1e**, 154.2 mg). Purification by column chromatography (60% EtOAc/hexanes) afforded **3e** (83%, 150.8 mg) as a pale-yellow solid.

Mp 63.0–64.5 °C; R_f = 0.43 (60% EtOAc/hexanes).

IR (neat): 3400 (O–H), 2155 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.0 Hz, 2 H), 7.61–7.43 (m, 8 H), 4.27 (t, *J* = 5.3 Hz, 2 H), 3.88 (t, *J* = 5.3 Hz, 2 H), 3.62 (t, *J* = 4.8 Hz, 2 H), 3.47 (t, *J* = 4.8 Hz, 2 H), 2.53 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4 (C), 150.1 (C), 131.0 (C), 130.0 (3×CH), 128.94 (2×CH), 128.89 (CH), 128.6 (2×CH), 128.2 (2×CH), 127.4 (C), 111.9 (C), 94.6 (C), 72.2 (CH_2), 69.0 (CH_2), 61.4 (CH_2), 50.1 (CH_2).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{19}N_3NaO_2S$: 388.1096; found: 388.1104.

1-(2,2-Dimethoxyethyl)-3,5-diphenyl-4-thiocyanato-1*H*-pyrazole (3f)

Prepared from 1-(2,2-dimethoxyethyl)-3,5-diphenyl-1*H*-pyrazole (**1f**, 154.2 mg). Purification by column chromatography (20% EtOAc/hexanes) afforded **3f** (52%, 94.5 mg) as a white solid.

Mp 75.0–76.5 °C; R_f = 0.57 (20% EtOAc/hexanes).

IR (neat): 2152 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.61–7.44 (m, 8 H), 4.91 (t, *J* = 5.6 Hz, 1 H), 4.18 (d, *J* = 5.6 Hz, 2 H), 3.32 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5 (C), 150.4 (C), 131.2 (C), 130.3 (2×CH), 130.0 (CH), 129.1 (3×CH), 128.6 (2×CH), 128.3 (2×CH), 127.3 (C), 112.0 (C), 103.1 (CH), 94.6 (C), 55.1 (2×CH_3), 51.9 (CH_2).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{19}N_3NaO_2S$: 388.1096; found: 388.1094.

1-Benzyl-3,5-dimethyl-4-thiocyanato-1*H*-pyrazole (3g)

Prepared from 1-benzyl-3,5-dimethyl-1*H*-pyrazole (**1g**, 93.1 mg). Purification by column chromatography (100% CH_2Cl_2) afforded **3g** (95%, 115.0 mg) as a white solid.

Mp 82.5–83.5 °C; R_f = 0.50 (100% CH_2Cl_2).

IR (neat): 2155 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 3 H), 7.10 (d, *J* = 6.6 Hz, 2 H), 5.22 (s, 2 H), 2.36 (s, 3 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.8 (C), 143.8 (C), 135.4 (C), 128.7 (2×CH), 127.8 (CH), 126.7 (2×CH), 110.9 (C), 94.9 (C), 53.7 (CH_2), 11.8 (CH_3), 10.0 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{13}N_3NaS$: 266.0728; found: 266.0729.

3,5-Dimethyl-1-(prop-1-en-1-yl)-4-thiocyanato-1*H*-pyrazole (3h)

Prepared from 3,5-dimethyl-1-(prop-1-en-1-yl)-1*H*-pyrazole (**1h**, 68.1 mg). Purification by column chromatography (30% EtOAc/hexanes) afforded **3h** (50%, 47.9 mg) as a yellow solid.

Mp 56.0–58.0 °C; R_f = 0.48 (20% EtOAc/hexanes).

IR (neat): 2151 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.66 (dd, *J* = 13.7, 1.7 Hz, 1 H), 6.27 (dq, *J* = 13.7, 6.9 Hz, 1 H), 2.39 (s, 3 H), 2.35 (s, 3 H), 1.83 (dd, *J* = 6.9, 1.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8 (C), 142.6 (C), 124.0 (CH), 117.3 (CH), 110.8 (C), 95.5 (C), 15.0 (CH_3), 11.9 (CH_3), 10.1 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_9H_{12}N_3S$: 194.0752; found: 194.0752.

3,5-Dimethyl-1-phenyl-4-thiocyanato-1*H*-pyrazole (3i)

Prepared from 3,5-dimethyl-1-phenyl-1*H*-pyrazole (**1i**, 86.1 mg). Purification by column chromatography (100% CH_2Cl_2) afforded **3i** (92%, 106.0 mg) as white crystals.

Mp 89.0–90.0 °C; R_f = 0.62 (100% CH_2Cl_2).

IR (neat): 2151 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.39 (m, 5 H), 2.43 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0 (C), 144.3 (C), 139.1 (C), 129.4 (2×CH), 128.6 (CH), 125.0 (2×CH), 110.8 (C), 96.6 (C), 12.0 (CH_3), 11.5 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}N_3S$: 230.0752; found: 230.0766.

3,5-Dimethyl-4-thiocyanato-1-(*p*-tolyl)-1*H*-pyrazole (3j)

Prepared from 3,5-dimethyl-1-(*p*-tolyl)-1*H*-pyrazole (**1j**, 93.1 mg). Purification by column chromatography (10% EtOAc/hexanes) afforded **3j** (97%, 118.5 mg) as colorless crystals.

Mp 85.5–88.0 °C; R_f = 0.66 (30% EtOAc/hexanes).

IR (neat): 2151 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.18 (s, 4 H), 2.32 (s, 3 H), 2.31 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.5 (C), 144.0 (C), 138.4 (C), 136.3 (C), 129.6 (2×CH), 124.5 (2×CH), 110.7 (C), 95.9 (C), 20.9 (CH_3), 11.8 (CH_3), 11.2 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}N_3S$: 244.0908; found: 244.0908.

1-(4-Methoxyphenyl)-3,5-dimethyl-4-thiocyanato-1*H*-pyrazole (3k)

Prepared from 1-(4-methoxyphenyl)-3,5-dimethyl-1*H*-pyrazole (**1k**, 101.1 mg). Purification by column chromatography (20% EtOAc/hexanes) afforded **3k** (95%, 123.5 mg) as colorless needles.

Mp 89.0–91.0 °C; R_f = 0.34 (20% EtOAc/hexanes).

IR (neat): 2149 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.9 Hz, 2 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 3.74 (s, 3 H), 2.32 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4 (C), 151.3 (C), 144.2 (C), 131.8 (C), 126.2 (2×CH), 114.2 (2×CH), 110.7 (C), 95.6 (C), 55.3 (CH_3), 11.7 (CH_3), 11.1 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}N_3OS$: 260.0858; found: 260.0860.

1-(4-Fluorophenyl)-3,5-dimethyl-4-thiocyanato-1*H*-pyrazole (3l)

Prepared from 1-(4-fluorophenyl)-3,5-dimethyl-1*H*-pyrazole (**1l**, 95.1 mg). Purification by column chromatography (30% EtOAc/hexanes) afforded **3l** (98%, 120.9 mg) as a pale-yellow solid.

Mp 77.0–79.0 °C; R_f = 0.37 (20% EtOAc/hexanes).

IR (neat): 2156 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 2 H), 7.18–7.12 (m, 2 H), 2.378 (s, 3 H), 2.375 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1 (d, *J* = 247.7 Hz, C), 151.8 (C), 144.2 (C), 135.0 (C), 126.8 (d, *J* = 8.8 Hz, 2×CH), 116.1 (d, *J* = 23.0 Hz, 2×CH), 110.5 (d, *J* = 6.7 Hz, C), 96.6 (C), 11.8 (CH_3), 11.2 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –112.03.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}FN_3S$: 248.0658; found: 248.0658.

1-(2,4-Dinitrophenyl)-3,5-dimethyl-4-thiocyanato-1*H*-pyrazole (3m)

Prepared from 1-(2,4-dinitrophenyl)-3,5-dimethyl-1*H*-pyrazole (**1m**, 131.1 mg). Purification by column chromatography (10% EtOAc/hexanes) afforded **3m** (33%, 51.5 mg) as a pale-yellow solid.

Mp 79.0–81.5 °C; R_f = 0.41 (30% EtOAc/hexanes).

IR (neat): 2160 (C≡N), 1535 and 1349 (N–O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (d, *J* = 2.5 Hz, 1 H), 8.63 (dd, *J* = 8.7, 2.5 Hz, 1 H), 7.77 (d, *J* = 8.7 Hz, 1 H), 2.41 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3 (C), 147.4 (C), 146.0 (C), 145.7 (C), 136.8 (C), 130.1 (CH), 127.9 (CH), 121.2 (CH), 109.9 (C), 99.4 (C), 12.0 (CH_3), 10.9 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_9N_5NaO_4S$: 342.0273; found: 342.0268.

3,5-Dimethyl-4-thiocyanato-1*H*-pyrazole (3n)

Prepared from 3,5-dimethyl-1*H*-pyrazole (**1n**, 48.1 mg). Purification by column chromatography (20% EtOAc/CH_2Cl_2) afforded **3n** (87%, 66.3 mg) as a white solid

Mp 57.0–59.0 °C; R_f = 0.43 (30% EtOAc/CH_2Cl_2).

IR (neat): 3272 (N–H), 2163 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (br s, 1 H), 2.40 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5 (2×C), 110.8 (C), 94.9 (C), 11.0 (2×CH_3).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_6H_7N_3NaS$: 176.0258; found: 176.0251.

3,5-Diethyl-4-thiocyanato-1*H*-pyrazole (3o)

Prepared from 3,5-diethyl-1*H*-pyrazole (**1o**, 62.1 mg). Purification by column chromatography (20% EtOAc/CH_2Cl_2) afforded **3o** (93%, 84.0 mg) as a colorless oil.

R_f = 0.43 (30% EtOAc/CH_2Cl_2).

IR (neat): 3174 (N–H), 2156 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.82 (br s, 1 H), 2.75 (q, *J* = 7.6 Hz, 4 H), 1.26 (t, *J* = 7.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7 (2×C), 111.3 (C), 92.8 (C), 19.0 (2×CH_2), 12.8 (CH_3), 12.6 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_8H_{12}N_3S$: 182.0752; found: 182.0761.

3,5-Diisopropyl-4-thiocyanato-1*H*-pyrazole (3p)

Prepared from 3,5-diisopropyl-1*H*-pyrazole (**1p**, 76.1 mg). Purification by column chromatography (5% EtOAc/CH_2Cl_2) afforded **3p** (97%, 101.0 mg) as a colorless oil.

R_f = 0.47 (30% EtOAc/CH_2Cl_2).

IR (neat): 3178 (N–H), 2156 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (br s, 1 H), 3.27 (sept, *J* = 7.0 Hz, 2 H), 1.34 (d, *J* = 7.0 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6 (2×C), 111.6 (C), 91.2 (C), 26.0 (2×CH), 21.6 (4×CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{16}N_3S$: 210.1065; found: 210.1073.

3,5-Di-*tert*-butyl-4-thiocyanato-1*H*-pyrazole (3q)

Prepared from 3,5-di-*tert*-butyl-1*H*-pyrazole (**1q**, 90.1 mg). Purification by column chromatography (5% EtOAc/CH_2Cl_2) afforded **3q** (89%, 105.4 mg) as a colorless solid.

Mp 155.5–157.5 °C; R_f = 0.61 (30% EtOAc/CH_2Cl_2).

IR (neat): 3259 (N–H), 2150 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.11 (br s, 1 H), 1.51 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3 (2×C), 112.7 (C), 90.6 (C), 33.0 (2×C), 29.3 (6×CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{20}N_3S$: 238.1378; found: 238.1385.

3,5-Diphenyl-4-thiocyanato-1*H*-pyrazole (3r)

Prepared from 3,5-diphenyl-1*H*-pyrazole (**1r**, 110.1 mg). Purification by column chromatography (10% EtOAc/CH_2Cl_2) afforded **3r** (99%, 137.5 mg) as a white solid.

Mp 171.5–174.5 °C; R_f = 0.39 (30% EtOAc/CH_2Cl_2).

IR (neat): 3185 (N–H), 2157 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.04 (br s, 1 H), 7.64 (dd, *J* = 7.6, 1.6 Hz, 4 H), 7.48–7.40 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1 (2×C), 129.7 (2×CH), 128.9 (4×CH), 128.7 (2×C), 128.3 (4×CH), 111.7 (C), 93.4 (C).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}N_3S$: 278.0752; found: 278.0757.

4-Thiocyanato-3,5-di-*p*-tolyl-1*H*-pyrazole (3s)

Prepared from 3,5-di-*p*-tolyl-1*H*-pyrazole (**1s**, 124.2 mg). Purification by column chromatography (10% EtOAc/CH_2Cl_2) afforded **3s** (99%, 150.5 mg) as a white solid.

Mp 186.5–188.5 °C; R_f = 0.58 (30% EtOAc/CH_2Cl_2).

IR (neat): 3185 (N–H), 2157 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (br s, 1 H), 7.56 (d, *J* = 8.1 Hz, 4 H), 7.23 (d, *J* = 7.9 Hz, 4 H), 2.41 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1 (2×C), 139.7 (2×C), 129.6 (4×CH), 128.1 (4×CH), 125.8 (2×C), 111.9 (C), 92.8 (C), 21.4 (2×CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}N_3S$: 306.1065; found: 306.1060.

3,5-Bis(4-methoxyphenyl)-4-thiocyanato-1*H*-pyrazole (3t)

Prepared from 3,5-bis(4-methoxyphenyl)-1*H*-pyrazole (**1t**, 140.2 mg). Purification by column chromatography (10% EtOAc/CH_2Cl_2) afforded **3t** (90%, 152.6 mg) as a white solid.

Mp 188.0–189.0 °C; R_f = 0.43 (60% EtOAc/CH_2Cl_2).

IR (neat): 3187 (N–H), 2155 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.7 Hz, 4 H), 6.89 (d, *J* = 8.7 Hz, 4 H), 3.84 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5 (2×C), 151.8 (2×C), 129.6 (4×CH), 121.1 (2×C), 114.3 (4×CH), 112.1 (C), 92.2 (C), 55.3 (2×CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}N_3O_2S$: 338.0963; found: 338.0962.

3,5-Bis(2-methoxyphenyl)-4-thiocyanato-1*H*-pyrazole (3u)

Prepared from 3,5-bis(2-methoxyphenyl)-1*H*-pyrazole (**1u**, 140.2 mg). Purification by column chromatography (10% EtOAc/CH_2Cl_2) afforded **3u** (84%, 142.5 mg) as a pale-yellow solid.

Mp 132.5–134.0 °C; R_f = 0.43 (60% EtOAc/CH_2Cl_2).

IR (neat): 3154 (N–H), 2154 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.59 (br s, 1 H), 7.73 (dd, *J* = 7.6, 1.6 Hz, 2 H), 7.44 (td, *J* = 7.6, 1.6 Hz, 2 H), 7.09 (td, *J* = 7.6, 0.7 Hz, 2 H), 7.02 (d, *J* = 8.3 Hz, 2 H), 3.83 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9 (2×C), 148.1 (2×C), 130.9 (2×CH), 130.7 (2×CH), 120.8 (2×CH), 118.0 (2×C), 111.9 (C), 111.1 (2×CH), 95.7 (C), 55.4 (2×CH_3).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{15}N_3NaO_2S$: 360.0783; found: 360.0782.

3,5-Bis(2-(benzyloxy)phenyl)-4-thiocyanato-1*H*-pyrazole (3v)

Prepared from 3,5-bis(2-(benzyloxy)phenyl)-1*H*-pyrazole (**1v**, 216.3 mg). Purification by column chromatography (5% EtOAc/CH_2Cl_2) afforded **3v** (99%, 242.2 mg) as a pale-yellow solid.

Mp 104.5–106.5 °C; R_f = 0.39 (30% EtOAc/CH_2Cl_2).

IR (neat): 3187 (N–H), 2153 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.00 (br s, 1 H), 7.73 (d, *J* = 7.5 Hz, 2 H), 7.44–7.29 (m, 12 H), 7.13–7.06 (m, 4 H), 5.11 (s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8 (2×C), 147.6 (2×C), 136.2 (2×C), 130.7 (2×CH), 130.6 (2×CH), 128.3 (4×CH), 127.7 (2×CH), 126.8 (4×CH), 121.1 (2×CH), 118.4 (2×C), 113.0 (2×CH), 111.7 (C), 96.0 (C), 70.4 (2×CH).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{24}N_3O_2S$: 490.1589; found: 490.1597.

5-Phenyl-4-thiocyanato-3-(*m*-tolyl)-1*H*-pyrazole (3w)

Prepared from 5-phenyl-3-(*m*-tolyl)-1*H*-pyrazole (**1w**, 117.2 mg). Purification by column chromatography (5% EtOAc/CH_2Cl_2) afforded **3w** (99%, 144.2 mg) as a white solid.

Mp 167.0–169.0 °C; R_f = 0.51 (5% EtOAc/CH_2Cl_2).

IR (neat): 3206 (N–H), 2153 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.29 (br s, 1 H), 7.56 (d, *J* = 8.3 Hz, 2 H), 7.42–7.32 (m, 5 H), 7.26–7.19 (m, 2 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1 (C), 151.9 (C), 138.6 (C), 130.4 (CH), 129.5 (CH), 128.8 (2×CH), 128.73 (CH), 128.69 (CH), 128.3 (2×C), 128.1 (2×CH), 125.3 (CH), 111.8 (C), 93.0 (C), 21.3 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}N_3S$: 292.0908; found: 292.0904.

3-(3-Methoxyphenyl)-5-phenyl-4-thiocyanato-1*H*-pyrazole (3x)

Prepared from 3-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazole (**1x**, 125.2 mg). Purification by column chromatography (40% EtOAc/hexanes) afforded **3x** (96%, 148.0 mg) as a pale-yellow solid.

Mp 92.5–94.0 °C; R_f = 0.55 (40% EtOAc/hexanes).

IR (neat): 2155 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.14 (br s, 1 H), 7.54 (d, *J* = 7.0 Hz, 2 H), 7.41–7.31 (m, 3 H), 7.23 (t, *J* = 8.1 Hz, 1 H), 7.13 (d, *J* = 6.7 Hz, 2 H), 6.92 (dd, *J* = 8.5, 1.6 Hz, 1 H), 3.69 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (C), 151.9 (2×C), 129.9 (CH), 129.7 (C), 129.6 (CH), 128.8 (2×CH), 128.4 (C), 128.1 (2×CH), 120.3 (CH), 115.6 (CH), 113.2 (CH), 111.8 (C), 93.1 (C), 55.1 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{13}N_3NaOS$: 330.0677; found: 330.0675.

3-(3-Chlorophenyl)-5-phenyl-4-thiocyanato-1*H*-pyrazole (3y)

Prepared from 3-(3-chlorophenyl)-5-phenyl-1*H*-pyrazole (**1y**, 127.4 mg). Purification by column chromatography (40% EtOAc/hexanes) afforded **3y** (81%, 126.0 mg) as a white solid.

Mp 139.0–141.0 °C; R_f = 0.64 (40% EtOAc/hexanes).

IR (neat): 2155 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.81 (br s, 1 H), 7.57–7.54 (m, 3 H), 7.51–7.43 (m, 2 H), 7.42–7.36 (m, 3 H), 7.30 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.7 (C), 151.1 (C), 134.7 (C), 130.7 (C), 130.05 (CH), 129.98 (CH), 129.6 (CH), 129.0 (2×CH), 128.1 (CH), 128.0 (2×CH), 127.5 (C), 126.3 (CH), 111.3 (C), 93.6 (C).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{10}ClN_3NaS$: 334.0182; found: 334.0182.

3-Cyclohexyl-5-phenyl-4-thiocyanato-1*H*-pyrazole (3z)

Prepared from 3-cyclohexyl-5-phenyl-1*H*-pyrazole (**1z**, 113.2 mg). Purification by column chromatography (40% EtOAc/hexanes) afforded **3z** (99%, 139.6 mg) as a pale-yellow solid.

Mp 87.0–89.0 °C; R_f = 0.66 (40% EtOAc/hexanes).

IR (neat): 3158 (N–H), 2155 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.63 (br s, 1 H), 7.65 (dd, *J* = 7.6, 2.0 Hz, 2 H), 7.44–7.38 (m, 3 H), 2.96–2.90 (m, 1 H), 1.90 (d, *J* = 10.7 Hz, 2 H), 1.79–1.71 (m, 3 H), 1.48–1.28 (m, 4 H), 1.18–1.10 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8 (C), 152.0 (C), 129.6 (C), 129.2 (CH), 128.6 (2×CH), 128.1 (2×CH), 111.6 (C), 92.2 (C), 35.6 (CH), 31.7 (2×CH_2), 26.1 (2×CH_2), 25.5 (CH_2).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{18}N_3NaS$: 306.1041; found: 306.1053.

5-Hexyl-3-phenyl-4-thiocyanato-1*H*-pyrazole (3aa)

Prepared from 5-hexyl-3-phenyl-1*H*-pyrazole (**1aa**, 114.2 mg). Purification by column chromatography (5% EtOAc/CH_2Cl_2) afforded **3aa** (94%, 134.2 mg) as a colorless oil.

R_f = 0.68 (5% EtOAc/CH_2Cl_2).

IR (neat): 3165 (N–H), 2156 (C≡N) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.70 (br s, 1 H), 7.69–7.67 (m, 2 H), 7.45–7.44 (m, 3 H), 2.62 (t, *J* = 7.7 Hz, 2 H), 1.58–1.53 (m, 2 H), 1.30–1.21 (m, 6 H), 0.88 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8 (C), 151.9 (C), 129.6 (C), 129.3 (CH), 128.7 (2×CH), 128.0 (2×CH), 111.3 (C), 93.3 (C), 31.2 (CH_2), 28.8 (CH_2), 28.4 (CH_2), 25.2 (CH_2), 22.3 (CH_2), 13.9 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{19}N_3NaS$: 308.1197; found: 308.1199.

5-Benzyl-3-phenyl-4-thiocyanato-1*H*-pyrazole (3ab)

Prepared from 5-benzyl-3-phenyl-1*H*-pyrazole (**1ab**, 117.2 mg). Purification by column chromatography (40% EtOAc/hexanes) afforded **3ab** (88%, 127.8 mg) as a yellow solid.

Mp 121.5–122.5 °C; R_f = 0.56 (40% EtOAc/hexanes).

IR (neat): 3211 (N–H), 2154 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.90 (br s, 1 H), 7.56 (dd, *J* = 7.4, 1.3 Hz, 2 H), 7.41–7.33 (m, 3 H), 7.21–7.13 (m, 3 H), 7.08 (d, *J* = 7.8 Hz, 2 H), 3.95 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3 (C), 150.7 (C), 136.3 (C), 129.5 (CH), 128.8 (2×CH), 128.7 (C), 128.6 (2×CH), 128.5 (2×CH), 127.9 (2×CH), 126.9 (CH), 110.9 (C), 93.7 (C), 31.6 (CH_2).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$calcd for $C_{17}H_{13}N_3NaS$: 314.0728; found: 314.0732.

5-((Benzyloxy)methyl)-3-phenyl-4-thiocyanato-1*H*-pyrazole (3ac)

Prepared from 5-((benzyloxy)methyl)-3-phenyl-1*H*-pyrazole (**1ac**, 132.2 mg). Purification by column chromatography (40% EtOAc/hexanes) afforded **3ac** (86%, 137.6 mg) as a pale-yellow solid.

Mp 146.5–150.0 °C; R_f = 0.52 (40% EtOAc/hexanes).

IR (neat): 3156 (N–H), 2155 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.72 (br s, 1 H), 7.68–7.65 (m, 2 H), 7.47–7.43 (m, 3 H), 7.34–7.30 (m, 5 H), 4.66 (s, 2 H), 4.58 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2 (C), 149.9 (C), 136.8 (C), 133.2 (C), 129.5 (CH), 128.8 (2×CH), 128.3 (2×CH), 127.9 (CH), 127.86 (2×CH), 127.82 (2×CH), 110.9 (C), 93.8 (C), 73.0 (CH_2), 62.5 (CH_2).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{15}N_3NaOS$: 344.0834; found: 344.0831.

3-Phenyl-4-thiocyanato-1*H*-pyrazol-5-ol (3ad)

Prepared from 3-phenyl-1*H*-pyrazol-5-ol (**1ad**, 80.1 mg). Purification by column chromatography (10% MeOH/CH_2Cl_2) afforded **3ad** (53%, 57.2 mg) as a green solid.

Mp 170.0 °C (decomp.); R_f = 0.46 (20% MeOH/CH_2Cl_2).

IR (neat): 3290 (O–H), 2157 (C≡N) cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.65–7.64 (m, 2 H), 7.42 (t, *J* = 7.3 Hz, 2 H), 7.36 (d, *J* = 7.4 Hz, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 161.8 (C), 145.7 (C), 130.3 (C), 128.5 (2×CH), 128.4 (C), 128.1 (2×CH), 125.0 (CH), 86.9 (C).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_7N_3NaOS$: 240.0208; found: 240.0214.

3-Phenyl-4-thiocyanato-1*H*-pyrazol-5-amine (3ae)

Prepared from 3-phenyl-1*H*-pyrazol-5-amine (**1ae**, 79.6 mg). Purification by column chromatography (5.0% EtOAc/hexanes) afforded **3ae** (55%, 59.0 mg) as a pale-yellow solid.

Mp 94.5–96.0 °C; R_f = 0.52 (100% EtOAc).

IR (neat): 3275 (N–H), 2152 (C≡N) cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.65–7.63 (m, 2 H), 7.40–7.37 (m, 2 H), 7.32–7.29 (m, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 153.8 (C), 146.4 (C), 131.0 (C), 128.4 (2×CH), 127.8 (2×CH), 126.8 (C), 125.2 (CH), 88.8 (C).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9N_4S$: 217.0548; found: 217.0548.

4-Thiocyanato-1*H*-pyrazole (3af)

Prepared from pyrazole (**1af**, 34.0 mg). Purification by column chromatography (30% EtOAc/hexanes) afforded **3af** (13%, 7.9 mg) as a white solid.

Mp 165.5–167.0 °C; R_f = 0.47 (50% EtOAc/hexanes).

IR (neat): 3211 (N–H), 2154 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (s, 2 H), 6.52 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5 (2×CH), 111.2 (C), 98.1 (C).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_4H_3N_3NaS$: 147.9945; found: 147.9935.

1-Methyl-4-thiocyanato-1*H*-pyrazole (3ag)

Prepared from 1-methyl-1*H*-pyrazole (**1ag**, 41.0 mg). Product **3ag** (57%, 42.6 mg) was afforded as a colorless liquid.

IR (neat): 2156 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (s, 1 H), 7.68 (s, 1 H), 3.94 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2 (CH), 134.9 (CH), 111.2 (C), 97.0 (C), 39.5 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_5H_5N_3NaS$: 162.0102; found: 162.0107.

1-Benzyl-4-thiocyanato-1*H*-pyrazole (3ah)

Prepared from 1-benzyl-1*H*-pyrazole (**1ah**, 79.1 mg). Purification by column chromatography (5% acetone/hexanes) afforded **3ah** (30%, 29.6 mg) as a colorless oil.

R_f = 0.40 (30% acetone/hexane).

IR (neat): 2156 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1 H), 7.64 (s, 1 H), 7.41–7.36 (m, 3 H), 7.27–7.24 (m, 2 H), 5.30 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4 (CH), 134.7 (C), 134.1 (CH), 129.1 (2×CH), 128.7 (CH), 128.1 (2×CH), 111.2 (C), 97.6 (C), 56.9 (CH_2).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_9N_3NaS$: 238.0415; found: 248.0414.

Bis(3,5-dimethyl-4-thiocyanato-1*H*-pyrazol-1-yl)methane (3ai)

Prepared from bis(3,5-dimethyl-1*H*-pyrazol-1-yl)methane (**1ai**, 102.1 mg). Purification by column chromatography (40% EtOAc/hexanes) afforded **3ai** (89%, 141.1 mg) as colorless crystals.

Mp 87.5–89.5 °C; R_f = 0.53 (40% EtOAc/hexanes).

IR (neat): 2154 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.05 (s, 2 H), 2.59 (s, 6 H), 2.28 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9 (2×C), 145.5 (2×C), 110.3 (2×C), 96.6 (2×C), 60.9 (CH_2), 11.8 (2×CH_3), 10.2 (2×CH_3).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}N_6NaS_2$: 341.0619; found: 341.0624.

1,3-Bis(3,5-dimethyl-4-thiocyanato-1*H*-pyrazol-1-yl)propane (3aj)

Prepared from 1,3-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)propane (**1aj**, 116.2 mg). Purification by column chromatography (40% EtOAc/hexanes) afforded **3aj** (86%, 148.3 mg) as a white solid.

Mp 71.0–73.0 °C; R_f = 0.50 (100% EtOAc).

IR (neat): 2157 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 (t, *J* = 6.7 Hz, 4 H), 2.31 (quin, *J* = 6.7 Hz, 2 H), 2.254 (s, 6 H), 2.249 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.8 (2×C), 143.6 (2×C), 110.7 (2×C), 94.3 (2×C), 46.1 (2×CH_2), 28.6 (CH_2), 11.6 (2×CH_3), 9.7 (2×CH_3).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{18}N_6NaS_2$: 369.0932; found: 369.0933.

4,4′-(1*E*,1′*E*-(4-Thiocyanato-1*H*-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (3ak)

Prepared from 4,4′-((1*E*,1′*E*)-(1*H*-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (**1ak**, 182.2 mg). Purification by column chromatography (4% MeOH/CH_2Cl_2) afforded **3ak** (28%, 51.6 mg) as a yellow solid.

Mp 197.0–198.0 °C; R_f = 0.30 (10% MeOH/CH_2Cl_2).

IR (neat): 3239 (O–H), 2158 (C≡N) cm^{-1}.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.87 (s, 1 H), 7.38 (d, *J* = 16.6 Hz, 2 H), 7.19 (d, *J* = 1.7 Hz, 2 H), 7.02 (s, 1 H), 6.70–6.97 (m, 3 H), 6.75 (d, *J* = 8.2 Hz, 2 H), 3.80 (s, 6 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 147.9 (2×C), 147.8 (2×C), 133.3 (2×C), 128.5 (C), 121.1 (2×CH), 114.9 (4×CH), 112.0 (C), 110.8 (C), 109.5 (4×CH), 92.5 (C), 55.4 (2×CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}N_3O_4S$: 422.1175; found: 422.1165.

Synthesis of *S*-(1-Methyl-3,5-diphenyl-1*H*-pyrazol-4-yl)carbamothioate (4a)[5a]

A solution of 1-methyl-3,5-diphenyl-4-thiocyanato-1*H*-pyrazole (**3a**, 145.7 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was added to concentrated sulfuric acid (0.8 mL). The resulting solution was stirred at 0 °C for 5 h. The reaction mixture was allowed to warm to r.t. and diluted with H_2O (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator.

Product **4a** (95%, 146.7 mg) was obtained as a pale-yellow solid.

Mp 178.0–179.0 °C; R_f = 0.39 (30% EtOAc/hexanes).

IR (neat): 3454 (N–H), 1656 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.81 (d, *J* = 7.2 Hz, 2 H), 7.67 (br s, 1 H), 7.53–7.48 (m, 5 H), 7.47–7.43 (m, 2 H), 7.40–7.38 (m, 1 H), 3.81 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.7 (C), 152.2 (C), 148.6 (C), 132.8 (C), 129.9 (2×CH), 129.3 (CH), 128.8 (C), 128.6 (2×CH), 128.3 (2×CH), 128.0 (CH), 127.7 (2×CH), 101.1 (C), 38.0 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{15}N_3NaOS$: 332.0834; found: 332.0842.

Synthesis of 5-((1-Methyl-3,5-diphenyl-1*H*-pyrazol-4-yl)thio)-1*H*-tetrazole (5a)[30]

NaN_3 (39.0 mg, 0.6 mmol) and $ZnCl_2$ (68.2 mg, 0.5 mmol) were added to a solution of 1-methyl-3,5-diphenyl-4-thiocyanato-1*H*-pyrazole (**3a**, 145.7 mg, 0.5 mmol) in *i*-PrOH (2 mL) at 50 °C. The resulting solution was stirred at 50 °C for 24 h, then the solvent was evaporated. Then, 5% NaOH (25 mL) was added and the mixture was stirred at r.t. for 20 min until the original precipitate had dissolved and a suspension of $Zn(OH)_2$ was observed. The precipitate was filtered and washed with 5% NaOH (10 mL). The pH of filtrate was adjusted to pH 1.0 with concentrated HCl, which caused the product to form. The product was filtered, washed with 9% HCl (2 × 10 mL) and dried.

Product **5a** (91%, 152.0 mg) was obtained as a white solid.

Mp 178.1–180.9 °C; R_f = 0.33 (100% EtOAc).

IR (neat): 1476 (C–N) cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.76–7.74 (m, 2 H), 7.48–7.36 (m, 8 H), 3.87 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 157.8 (C), 154.2 (C), 151.1 (C), 133.0 (C), 131.1 (CH), 131.0 (2×CH), 130.0 (2×CH), 129.8 (CH), 129.5 (2×CH), 129.3 (C), 129.2 (2×CH), 99.1 (C), 38.5 (CH_3).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{14}N_6NaS$: 357.0898; found: 357.0905.

Synthesis of 1,2-Bis(1-methyl-3,5-diphenyl-1*H*-pyrazol-4-yl)disulfane (6a)[3b]

A solution of 1-methyl-3,5-diphenyl-4-thiocyanato-1*H*-pyrazole (**3a**, 145.7 mg, 0.5 mmol) in anhydrous THF (2 mL) was added to a suspension of $LiAlH_4$ (20.9 mg, 0.55 mmol) in anhydrous THF (4 mL) at 0 °C. The resulting mixture was stirred at r.t. overnight. After that time, water and 1.0 M HCl were added and the mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator.

Purification by column chromatography (30–70% EtOAc/hexanes) afforded **6a** (71%, 94.2 mg) as a pale-yellow solid.

Mp 223.5–224.0 °C; R_f = 0.57 (60% EtOAc/hexanes).

IR (neat): 1461 (C–N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (dd, *J* = 7.9, 2.1 Hz, 2 H), 7.42–7.41 (m, 3 H), 7.36–7.34 (m, 3 H), 7.10 (dd, *J* = 7.5, 2.0 Hz, 2 H), 3.64 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.7 (2×C), 148.7 (2×C), 132.1 (2×C), 130.1 (4×CH), 128.9 (2×CH), 128.15 (2×C), 128.13 (6×CH), 128.0 (4×CH), 127.9 (2×CH), 107.5 (2×C), 37.6 (2×CH_3).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2S$: 553.1497; found: 553.1579.

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References

(1) (a) Solladie, G. *Synthesis of Sulfides, Sulfoxides and Sulfones*, In *Comprehensiue Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 133. (b) Ogura, K. *Sulfur Stabilization*, In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 505. (c) Zhang, D.; Xu, W.; Jia, C.; Li, H.; Zhu, D. *ARKIVOC* **2003**, 165. (d) Gingras, M.; Chabre, Y. M.; Roy, M.; Roy, R. *Chem. Soc. Rev.* **2013**, *42*, 4823. (e) Garoufis, A.; Hadjikakou, S. K.; Hadjiliadis, N. *Coord. Chem. Rev.* **2009**, *253*, 1384. (f) Ali, V.; Nozaki, T. *Clin. Microbiol. Rev.* **2007**, *20*, 164. (g) Faucher, A.-M.; White, P. W.; Brochu, C.; Grand-Maître, C.; Rancourt, J.; Fazal, G. *J. Med. Chem.* **2004**, *47*, 18. (h) Dutta, S.; Abe, H.; Aoyagi, S.; Kibayashi, C.; Gates, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 15004. (i) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832. (j) Murphy, A. R.; Fréchet, J. M. J. *Chem. Rev.* **2007**, *107*, 1066.

(2) (a) Owens, R. G. In *Fungicides: An Advanced Treatise*; Torgeson, D. C., Ed.; Academic Press: New York, **1967**, Chapter 5, p 14. (b) Houmam, A.; Hamed, E. M.; Still, I. W. J. *J. Am. Chem. Soc.* **2003**, *125*, 7258. (c) MacKinnon, D. L.; Farrell, A. P. *Environ. Toxicol. Chem.* **1992**, *11*, 1541. (d) Pham, A. T.; Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J. *Tetrahedron Lett.* **1991**, *32*, 4843. (e) Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K. *Tetrahedron Lett.* **1997**, *38*, 363. (f) Pina, I. C.; Gautschi, J. T.; Wang, G.-Y.-S.; Sanders, M. L.; Schmitz, F. J.; France, D.; Cornell-Kennon, S.; Sambucetti, L. C.; Remiszewski, S. W.; Perez, L. B.; Bair, K. W.; Crews, P. *J. Org. Chem.* **2003**, *68*, 3866. (g) Yasman; Edrada, R. A.; Wray, V.; Proksch, P. *J. Nat. Prod.* **2003**, *66*, 1512. (h) Elhalem, E.; Bailey, B. N.; Docampo, R.; Ujváry, I.; Szajnman, S. H.; Rodriguez, J. B. *J. Med. Chem.* **2002**, *45*, 3984. (i) Promkatkaew, M.; Gleeson, D.; Hannongbua, S.; Gleeson, M. P. *Chem. Res. Toxicol.* **2014**, *27*, 51.

(3) (a) Coates, R. M.; Ho, A. W. W. *J. Am. Chem. Soc.* **1969**, *91*, 7544. (b) Wei, Z.-L.; Kozikowski, A. P. *J. Org. Chem.* **2003**, *68*, 9116. (c) Brock, N. L.; Nikolay, A.; Dickschat, J. S. *Chem. Commun.* **2014**, 5487.

(4) (a) Verkruijsse, H. D.; Brandsma, L. *Synthesis* **1991**, 818. (b) Still, I. W. J.; Toste, F. D. *J. Org. Chem.* **1996**, *61*, 7677. (c) Ke, F.; Qu, Y.; Jiang, Z.; Li, Z.; Wu, D.; Zhou, X. *Org. Lett.* **2011**, *13*, 454.

(5) (a) Riemschneider, R.; Wojahn, F.; Orlick, G. *J. Am. Chem. Soc.* **1951**, *73*, 5905. (b) Riemschneider, R. *J. Am. Chem. Soc.* **1956**, *78*, 844. (c) Guo, L.-N.; Gu, Y.-R.; Yang, H.; Hu, J. *Org. Biomol. Chem.* **2016**, *14*, 3098.

(6) (a) Bunyagidj, C.; Piotrowska, H.; Aldridge, M. H. *J. Org. Chem.* **1981**, *46*, 3335. (b) Toste, F. D.; LaRonde, F.; Still, I. W. J. *Tetrahedron Lett.* **1995**, *36*, 2949.

(7) (a) Prabhu, K. R.; Ramesha, A. R.; Chandrasekaran, S. *J. Org. Chem.* **1995**, *60*, 7142. (b) Sengupta, D.; Basu, B. *Tetrahedron Lett.* **2013**, *54*, 2277.

(8) Johnson, T. B.; Douglass, I. B. *J. Am. Chem. Soc.* **1939**, *61*, 2548.

(9) Blanco, J. M.; Caamano, O.; Fernández, F.; Gómez, G.; López, C. *Tetrahedron: Asymmetry* **1992**, *3*, 749.

(10) Some examples of Sandmeyer type reactions to prepare thiocyanates: (a) Guy, R. G.; Lau, R.; Rahman, A. U.; Swinbourne, F. J. *Spectrochim. Acta, Part A* **1997**, *53*, 361. (b) Butt, N.; Guy, R. G.; Winbourne, F. J. *Spectrochim. Acta, Part A* **1995**, *51*, 1715. (c) Bangher, A.; Guy, R. G.; Pichot, Y.; Sillence, J. M.; Steel, C. J.; Swinbourne, F. J.; Tamiatti, K. *Spectrochim. Acta, Part A* **1995**, *51*, 1703. (d) Whiteker, G. T.; Lippard, S. J. *Tetrahedron Lett.* **1991**, *32*, 5019. (e) Yokoyama, M.; Ohteki, H.; Kurauchi, M.; Hoshi, K.; Yanagisawa, E.; Suzuki, A.; Imamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2635. (f) Barbero, M.; Degani, I.; Diulgheroff, N.; Dughera, S.; Fochi, R. *Synthesis* **2001**, 585.

(11) (a) Fujiki, K.; Yoshida, E. *Synth. Commun.* **1999**, *29*, 3289. (b) Takagi, K.; Takachi, H.; Sasaki, K. *J. Org. Chem.* **1995**, *60*, 6552. (c) Teng, F.; Yu, J.-T.; Yang, H.; Jiang, Y.; Cheng, J. *Chem. Commun.* **2014**, 12139.

(12) (a) Suzuki, H.; Abe, H. *Synth. Commun.* **1996**, *18*, 3413. (b) Sun, N.; Che, L.; Mo, W.; Hu, B.; Shen, Z.; Hu, X. *Org. Biomol. Chem.* **2015**, *13*, 691.

(13) For selected examples, see: (a) Nair, V.; Nair, L. G. *Tetrahedron Lett.* **1998**, *39*, 4585. (b) Yang, H.; Duan, X.-H.; Zhao, J.-F.; Guo, L.-N. *Org. Lett.* **2015**, *17*, 1998. (c) Yang, X.; She, Y.; Chong, Y.; Zhai, H.; Zhu, H.; Chen, B.; Huang, G.; Yan, R. *Adv. Synth. Catal.* **2016**, *358*, 3130. (d) Terent'ev, A. O.; Yu Sharipov, M.; Glinuskin, A. P.; Krylov, I. B.; Gaidarenko, D. V.; Nikishin, G. I. *Mendeleev Commun.* **2016**, *26*, 226. (e) Zhang, X.-Z.; Ge, D.-L.; Chen, S.-Y.; Yu, X.-Q. *RSC Adv.* **2016**, *6*, 66320. (f) Jiang, G.; Zhu, C.; Li, J.; Wu, W.; Jiang, H. *Adv. Synth. Catal.* **2017**, *359*, 1208.

(14) (a) Ashish, K. T.; Anil, M. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2006**, *45*, 489. (b) Mert, S.; Kasımoğulları, R.; İça, T.; Çolak, F.; Altun, A.; Ok, S. *Eur. J. Med. Chem.* **2014**, *78*, 86.

(15) (a) Sangapure, S. S.; Bodke, Y.; Raga, B. *Indian J. Heterocycl. Chem.* **2001**, *11*, 31. (b) Lupsor, S.; Aonofriesei, F.; Iovu, M. *Med. Chem. Res.* **2012**, *21*, 3035. (c) Kumar, R.; Arora, J.; Ruhil, S.; Phougat, N.; Chhillar, A. K.; Prasad, A. K. *Adv. Chem.* **2014**, 329681.

(16) Nimavat, K. S.; Popat, K. H. *Indian J. Heterocycl. Chem.* **2007**, *16*, 333.

(17) (a) Udupi, R. H.; Bhat, A. R.; Krishna, K. *Indian J. Heterocycl. Chem.* **1998**, *8*, 143. (b) Abd-El, Gawad. N. M.; Georgey, H. H.; Ibrahim, N. A.; Amin, N. H.; Abdelsalam, R. M. *Arch. Pharmacal. Res.* **2012**, *35*, 807.

(18) Ouyang, G.; Cai, X.-J.; Chen, Z.; Song, B.-A.; Bhadury, P. S.; Yang, S.; Jin, L.-H.; Xue, W.; Hu, D.-Y.; Zeng, S. *J. Agric. Food Chem.* **2008**, *56*, 10160.

(19) Rangaswamy, J.; Kumar, H. V.; Harini, S. T.; Naik, N. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4773.

(20) Hassan, G. S.; Kadry, H. H.; Abou-Seri, S. M.; Ali, M. M.; El-Din, Mahmoud. A. E. *Bioorg. Med. Chem.* **2011**, *19*, 6808.

(21) Turan-Zitouni, G.; Chevallet, P.; Kiliç, F. S.; Erol, K. *Eur. J. Med. Chem.* **2000**, *35*, 635.

(22) Chetan, B. P.; Mulwar, V. V. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2000**, *44*, 232.

(23) Palaska, E.; Aytemir, M.; Uzbay, İ. T.; Erol, D. *Eur. J. Med. Chem.* **2001**, *36*, 539.

(24) Souza, F. R.; Souza, V. T.; Ratzlaff, V.; Borges, L. P.; Oliveira, M. R.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P.; Mello, C. F. *Eur. J. Pharmacol.* **2002**, *451*, 141.

(25) Ashok, K.; Archana; Sharma, S. *Indian J. Heterocycl. Chem.* **2001**, *9*, 197.

(26) Baraldi, P. G.; Caciari, B.; Romagnoli, R.; Spalluto, G.; Moro, S.; Klotz, K.-N.; Leung, E.; Varani, K.; Gessi, S.; Merighi, S.; Borea, P. A. *J. Med. Chem.* **2000**, *43*, 4768.

(27) (a) Sauter, H.; Steglich, W.; Anke, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 1328. (b) Shiga, Y.; Okada, I.; Ikeda, Y.; Takizawa, E.; Fukuchi, T. *J. Pestic. Sci.* **2003**, *28*, 313. (c) Ohno, R.; Watanabe, A.; Matsukawa, T.; Ueda, T.; Sakurai, H.; Hori, M.; Hirai, K. *J. Pestic. Sci.* **2004**, *29*, 15.

(28) For selected examples, see: (a) Chakrabarty, M.; Sarkar, S. *Tetrahedron Lett.* **2003**, *44*, 8131. (b) Yadav, J. S.; Reddy, B. V. S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* **2004**, *45*, 2951. (c) Wu, G.; Liu, Q.; Shen, Y.; Wu, W.; Wu, L. *Tetrahedron Lett.* **2005**, *46*, 5831. (d) Yadav, J. S.; Reddy, B. V. S.; Krishna, A. D.; Reddy, Ch. S.; Narsaiah, A. V. *Synthesis* **2005**, 961. (e) Yadav, J. S.; Reddy, B. V. S.; Krishna, B. B. M. *Synthesis* **2008**, 3779. (f) Pan, X.-Q.; Lei, M.-Y.; Zou, J.-P.; Zhang, W. *Tetrahedron Lett.* **2009**, *50*, 347. (g) Iranpoor, N.; Firouzabadi, H.; Khalili, D.; Shahin, R. *Tetrahedron Lett.* **2010**, *51*, 3508. (h) Nikoofar, K. *Chem. Sci. Trans.* **2013**, *2*, 691. (i) Fotouhi, L.; Nikoofar, K. *Tetrahedron Lett.* **2013**, *54*, 2903. (j) Fan, W.; Yang, Q.; Xu, F.; Li, P. *J. Org. Chem.* **2014**, *79*, 10588. (k) Zhu, D.; Chang, D.; Shi, L. *Chem. Commun.* **2015**, 7180. (l) Mitra, S.; Ghosh, M.; Mishra, S.; Hajra, A. *J. Org. Chem.* **2015**, *80*, 8275. (m) Yang, D.; Yan, K.; Wei, W.; Li, G.; Lu, S.; Zhao, C.; Tian, L.; Wang, H. *J. Org. Chem.* **2015**, *80*, 11073. (n) Zhang, H.; Wei, Q.; Wei, S.; Qu, J.; Wang, B. *Eur. J. Org. Chem.* **2016**, 3373. (o) Khalili, D. *New J. Chem.* **2016**, *40*, 2547. (p) Venkanna, P.; Rajanna, K. C.; Kumar, M. S.; Venkateswarlu, M.; Ali, M. M. *Synlett* **2016**, *27*, 237. (q) Chen, J.; Wang, T.; Wang, T.; Lin, A.; Yao, H.; Xu, J. *Org. Chem. Front.* **2017**, *4*, 130. (r) Mete, T. B.; Khopade, T. M.; Bhat, R. G. *Tetrahedron Lett.* **2017**, *58*, 415.

(29) (a) Finar, I. L.; Godfrey, K. E. *J. Chem. Soc.* **1954**, 2293. (b) Kinugawa, J.; Ochiai, M. *Chem. Pharm. Bull.* **1964**, *12*, 23. (c) Thiruvikraman, S. V.; Seshadri, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 785. (d) Kokorekin, V. A.; Sigacheva, V. L.; Petrosyan, V. A. *Tetrahedron Lett.* **2014**, *55*, 4306.

(30) Vorona, S.; Artamonova, T.; Zevatskii, Y.; Myznikov, L. *Synthesis* **2014**, *46*, 781.