Thiocyanation of Pyrazoles Using KSCN/K₂S₂O₈ Combination

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Abstract
A convenient and practical thiocyanation of pyrazoles is reported employing a combination of KSCN and K₂S₂O₈ 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. 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 and serving as versatile synthetic precursors for the synthesis of various organosulfur derivatives such as thioles, thioesters, thiocarbonates, thioesters, disulfides, sulfonic acids, sulfonyl chlorides, and sulfonyl cyanides. 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, cyanation of organosulfur and organometallic compounds, metal-catalyzed coupling reaction of arylboronic acids with trimethylsilylthiocyanate (TMSNCS) or aryl halides with thiocyanate salts and the direct thiocyanation of C–H bonds with thiocyanates. Pyrazoles and their derivatives have attracted increasing interest in the fields of medicine and pharmacology because of their interesting biological properties including antifungal, antibacterial, antitumor, anti-inflammatory, antiviral, antioxidant, cytotoxic, antihypertensive, antibacterial, antianginal, anti-antihypertensive, anti-inflammatory, antiviral, antioxidant, cytotoxic, antianginal, anti-antihypertensive, and antipotent activities. Additionally, pyrazole derivatives are also important in agricultural chemistry. Although thiocyanation of arenes and heterocyclic compounds such as indoles, pyrroles, carbazoles, 8-aminoquinolines and imidazo[1,2-a]pyridines has been reported, the thiocyanation of pyrazoles has been little explored. Most recently, and during the preparation of this manuscript, Bhat and co-workers reported thiocyanation of phenols, anilines and indoles using K₂S₂O₈/NH₄SCN in CH₂Cl₂. 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 K₂S₂O₈ under environmentally friendly conditions and with short reaction times.

We began our study by employing 1-methyl-3,5-diphenyl-1H-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-1H-pyrazole (1a; 0.5 mmol), KSCN (2a; 2 equiv) and K₂S₂O₈ (1.5 equiv) at room temperature for 24 h (entries 1–5). It was found that only trace amounts of 3a were observed when H₂O, 1,4-dioxane, tetrahydrofuran (THF), N,N-dimethylformamide (DMF) and CH₂Cl₂ were employed as the solvents (entries 1–5). Better results were observed when the reactions were performed in EtOH, CH₃OH, EtOAc,
CH₃CN, 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 K₃S₂O₈, OXONE®, Na₂S₂O₈, (diacetoxyiodo)benzene (DIB), 2-iodoxybenzoic acid (IBX), tert-butyl hydroperoxide (TBHP) and cerium(IV) ammonium nitrate (CAN), K₃S₂O₈ 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 K₃S₂O₈ (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 K₂CO₃ (1 equiv) significantly lowered the yield of 3a (entry 23). Finally, no improvement was observed when the stoichiometry of KSCN or K₃S₂O₈ was increased. After extensive experiments, the optimum reaction conditions were chosen as: 1 (0.5 mmol; 1.0 equiv), KSCN (1.5 equiv) and K₃S₂O₈ (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 α-substituted-3,5-diphenyl- and α-substituted-3,5-dimethylpyrazoles was first examined. The reactions of α-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-CH₃ and 4-OCH₃) afforded 3i–k in high yields (92–97%). The reaction of N-(4-fluorophenyl)-3,5-dimethylpyrazole (11) provided 3i in 98% yield. A low yield was observed when N-(4-dinitrophenyl)-3,5-dimethylpyrazole (1m) was employed as a substrate. Next, the reactions of 1H-pyrazoles, including symmetrical 3,5-dialkyl-1H-pyrazoles 1n–q, symmetrical 3,5-diaryl-1H-pyrazoles 1r–v and unsymmetrical 3,5-disubstituted-1H-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-protected-1H-pyrazoles are potentially useful for further synthetic manipulation. 3-Phenyl-1H-pyrazol-5-ol (1ad) and 3-phenyl-1H-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-thiocyanated 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 K₃S₂O₈, 3.0 equiv each) to yield the corresponding

Table 1: Optimization of the Reaction Conditions

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<th>Entry</th>
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</table>

*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: entry 21 and in the presence of TsOH (1 equiv).
*d Reaction conditions: entry 21 and in the presence of K₂CO₃ (1 equiv).
*e Reaction conditions: entry 21 and in the presence of K₃CO₃ (1 equiv).
products in high yields (89% and 86%, respectively). Finally, the reaction of curcumin-derived pyrazole (1ak) provided the thiocyanated product 3ak in 28% yield.

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). The thiocyanate group of 3a can be transformed into thiocarbamate 4a in 95% yield. Cycloaddition reaction of 3a with NaN₃ mediated by ZnCl₂ provided thiotetrazole 5a in 91% yield. Finally, upon treatment of 3a with LiAlH₄, the disulfide 6a was obtained in 71% yield.

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.

On the basis of the control experiments and the previous related reports, a possible reaction pathway can be proposed (Scheme 5). First, a thiocyanate radical is...
generated by the oxidation of KSCN with K₂S₂O₈. This thiocyanate radical then reacts with pyrazole 1 to give a radical intermediate A, which could be oxidized to carbocationic intermediate B by K₂S₂O₈. 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 ¹H NMR, ¹³C NMR, IR spectroscopic spectra, and HRMS data. ¹H NMR and ¹³C NMR spectra were recorded with a Bruker Ascend™ spectrometer. ¹H NMR and ¹³C 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 KMMo₃ 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 CH₂Cl₂–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), K₂S₂O₈ (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 H₂O (10 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over MgSO₄, 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-1H-pyrazole (3a)
Prepared from 1-methyl-3,5-diphenyl-1H-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; Rₙ = 0.57 (30% EtOAc/hexanes).
IR (neat): 2154 (C≡N) cm⁻¹.
¹H NMR (400 MHz, CDCl₃): 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).
¹³C NMR (100 MHz, CDCl₃): δ = 153.2 (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 (CH₂).

### 1,3,5-Triphenyl-4-thiocyanato-1H-pyrazole (3b)
Prepared from 1,3,5-triphenyl-1H-pyrazole (1b, 148.2 mg). Purification by column chromatography (10% EtOAc/hexanes) afforded 3b (63%, 111.6 mg) as an pale-yellow solid.
Mp 130.5–132.0 °C; Rₙ = 0.64 (30% EtOAc/hexanes).
IR (neat): 2161 (C≡N) cm⁻¹.
¹H NMR (400 MHz, CDCl₃): 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).
¹³C NMR (100 MHz, CDCl₃): 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 (CH), 125.0 (2×CH), 111.8 (C), 96.7 (C).

### 1-Allyl-3,5-diphenyl-4-thiocyanato-1H-pyrazole (3c)
Prepared from 1-allyl-3,5-diphenyl-1H-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; Rₙ = 0.61 (30% EtOAc/hexanes).
IR (neat): 2153 (C≡N) cm⁻¹.
¹H NMR (400 MHz, CDCl₃): 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).
¹³C NMR (100 MHz, CDCl₃): 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 (2×CH), 128.5 (2×CH), 128.2 (2×CH), 127.3 (C), 118.3 (CH₃), 111.8 (C), 94.4 (C), 53.0 (CH₂).

### 2-(3,5-Diphenyl-4-thiocyanato-1H-pyrazol-1-yl)ethanol (3d)
Prepared from 2-(3,5-diphenyl-1H-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; Rₙ = 0.40 (40% EtOAc/hexanes).
IR (neat): 3498 (O–H), 2158 (C≡N) cm⁻¹.

1H NMR (400 MHz, CDCl₃): 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).

13C NMR (100 MHz, CDCl₃): 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 (CH₂), 51.9 (CH₂).


2-[(3,5-Diphenyl-1H-pyrazol-1-yl)ethoxy]ethanol (3f)
Prepared from 2-[(3,5-diphenyl-1H-pyrazol-1-yl)ethoxy]ethanol (1e, 154.2 mg). Purification by column chromatography (60% EtOAc/hexanes) afforded 3f (83%, 150.8 mg) as a yellow solid. Mp 56.0–58.0 °C; Rf = 0.62 (100% CH₂Cl₂).

1H NMR (400 MHz, CDCl₃): δ = 7.84 (d, J = 7.9 Hz, 2 H), 7.71–7.63 (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).

IR (neat): 2151 (C≡N) cm⁻¹.


1-(4-Methoxyphenyl)-3,5-dimethyl-4-thiocyanato-1H-pyrazole (3g)
Prepared from 1-(4-methoxyphenyl)-3,5-dimethyl-1H-pyrazole (1g, 93.1 mg). Purification by column chromatography (100% CH₂Cl₂) afforded 3g (95%, 115.0 mg) as a white solid.

Mp 82.5–83.5 °C; Rf = 0.50 (100% CH₂Cl₂).

IR (neat): 2152 (C≡N) cm⁻¹.

1H NMR (400 MHz, CDCl₃): 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).

13C NMR (100 MHz, CDCl₃): 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×CH₂), 51.9 (CH₂).


1-Benzyl-3,5-dimethyl-4-thiocyanato-1H-pyrazole (3k)
Prepared from 1-benzyl-3,5-dimethyl-1H-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; Rf = 0.66 (30% EtOAc/hexanes).

IR (neat): 2151 (C≡N) cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.51–7.39 (m, 5 H), 2.43 (s, 3 H), 2.42 (s, 3 H).

13C NMR (100 MHz, CDCl₃): δ = 151.5 (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 (CH₃), 11.5 (CH₃).


3.5-Dimethyl-1-(prop-1-en-1-yl)-4-thiocyanato-1H-pyrazole (3j)
Prepared from 3,5-dimethyl-1-(prop-1-en-1-yl)-1H-pyrazole (3i, 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; Rf = 0.66 (30% EtOAc/hexanes).

IR (neat): 2151 (C≡N) cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.18 (s, 4 H), 2.32 (s, 3 H), 2.31 (s, 6 H).

13C NMR (100 MHz, CDCl₃): 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 (CH₃), 11.8 (CH₃), 11.2 (CH₃).

1-(4-Fluoroaryl)-3,5-dimethyl-4-thiocyanato-1H-pyrazole (3i)
Prepared from 1-(4-fluoroaryl)-3,5-dimethyl-1H-pyrazole (11, 95.1 mg). Purification by column chromatography (30% EtOAc/hexanes) afforded 3i (98%, 120.9 mg) as a pale-yellow solid.
Mp 77.0–79.0 °C; Rf = 0.37 (20% EtOAc/hexanes).
IR (neat): 2156 (C=S) cm⁻¹.
1H NMR (400 MHz, CDCl₃): 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).
13C NMR (100 MHz, CDCl₃): 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 (CH₃), 11.2 (CH₃).

1-(2,4-Dinitrophenyl)-3,5-dimethyl-4-thiocyanato-1H-pyrazole (3m)
Prepared from 1-(2,4-dinitrophenyl)-3,5-dimethyl-1H-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; Rf = 0.41 (30% EtOAc/hexanes).
IR (neat): 2160 (CN=) cm⁻¹.
1H NMR (400 MHz, CDCl₃): 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).
13C NMR (100 MHz, CDCl₃): 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 (CH₃), 10.9 (CH₃).

3,5-Diisopropyl-4-thiocyanato-1H-pyrazole (3p)
Prepared from 3,5-diisopropyl-1H-pyrazole (1p, 76.1 mg). Purification by column chromatography (5% EtOAc/CH₂Cl₂) afforded 3p (97%, 101.0 mg) as a colorless oil.
Rf = 0.47 (30% EtOAc/CH₂Cl₂).
IR (neat): 3178 (N–H), 2156 (C=S) cm⁻¹.
1H NMR (400 MHz, CDCl₃): 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).
13C NMR (100 MHz, CDCl₃): δ = 157.6 (2×C), 111.6 (C), 91.2 (C), 26.0 (2×CH), 21.6 (4×CH₃).

1-(2,4-Dinitrophenyl)-3,5-dimethyl-4-thiocyanato-1H-pyrazole (3q)
Prepared from 3,5-di-tert-butyl-1H-pyrazole (1q, 90.1 mg). Purification by column chromatography (5% EtOAc/CH₂Cl₂) afforded 3q (89%, 105.4 mg) as a colorless solid.
Mp 155.5–157.5 °C; Rf = 0.61 (30% EtOAc/CH₂Cl₂).
IR (neat): 3259 (N–H), 2150 (C=S) cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 10.11 (br s, 1 H), 1.51 (s, 18 H).
13C NMR (100 MHz, CDCl₃): δ = 160.3 (2×C), 112.7 (C), 90.6 (C), 33.0 (2×C), 29.3 (6×CH₃).

3,5-Diphenyl-4-thiocyanato-1H-pyrazole (3r)
Prepared from 3,5-diphenyl-1H-pyrazole (1r, 110.1 mg). Purification by column chromatography (10% EtOAc/CH₂Cl₂) afforded 3r (99%, 137.5 mg) as a white solid.
Mp 171.5–174.5 °C; Rf = 0.39 (30% EtOAc/CH₂Cl₂).
IR (neat): 3185 (N–H), 2157 (C=S) cm⁻¹.
1H NMR (400 MHz, CDCl₃): 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).
13C NMR (100 MHz, CDCl₃): 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).

4-Thiocyanato-3,5-di-p-tolyl-1H-pyrazole (3s)
Prepared from 3,5-di-p-tolyl-1H-pyrazole (1s, 124.2 mg). Purification by column chromatography (10% EtOAc/CH₂Cl₂) afforded 3s (99%, 150.5 mg) as a white solid.
Mp 186.5–188.5 °C; Rf = 0.58 (30% EtOAc/CH₂Cl₂).
IR (neat): 3185 (N–H), 2157 (C=S) cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 7.99 (br s, 1 H), 7.56 (dd, J = 8.1 Hz, 4 H), 7.23 (d, J = 7.9 Hz, 4 H), 2.41 (s, 6 H).
13C NMR (100 MHz, CDCl₃): δ = 152.1 (2×C), 139.7 (2×C), 129.6 (4×CH), 128.1 (4×CH), 125.8 (2×CH), 111.9 (C), 92.8 (C), 21.4 (2×CH₃).

3,5-Bis(4-methoxyphenyl)-4-thiocyanato-1H-pyrazole (3t)
Prepared from 3,5-bis(4-methoxyphenyl)-1H-pyrazole (1t, 140.2 mg). Purification by column chromatography (10% EtOAc/CH₂Cl₂) afforded 3t (90%, 152.6 mg) as a white solid.
3-(3-Methoxyphenyl)-5-phenyl-4-thiocyanato-1H-pyrazole (3x)
Prepared from 3-(3-methoxyphenyl)-5-phenyl-1H-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; Rf = 0.55 (40% EtOAc/hexanes).
IR (neat): 2155 (C=O) cm⁻¹.
1H NMR (400 MHz, CDCl₃): 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, 3 H), 1.30–1.21 (m, 6 H), 0.88 (t, J = 6.5 Hz, 3 H).
13C NMR (100 MHz, CDCl3): 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 (CH2), 28.8 (CH3), 25.2 (CH2), 22.3 (CH3), 13.9 (CH3).

HRMS (ESI-TOF): \text{m}/\text{z} [M + Na]^+ calculated for C8H7N3NaOS: 217.0548; found: 217.0548.

5-Benzyl-3-phenyl-4-thiocyanato-1H-pyrazole (3ab)
Prepared from 5-benzyl-3-phenyl-1H-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; \text{Rf} = 0.56 (40% EtOAc/hexanes).

IR (neat): 3211 (N–H), 2154 (C≡N) cm⁻¹.

HRMS (ESI-TOF): \text{m}/\text{z} [M + Na]^+ calculated for C10H7N3NaOS: 240.0208; found: 240.0214.

4-Thiocyanato-1H-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; \text{Rf} = 0.47 (50% EtOAc/hexanes).

IR (neat): 2156 (C≡N) cm⁻¹.

HRMS (ESI-TOF): \text{m}/\text{z} [M + Na]^+ calculated for C4H3N3NaS: 147.995; found: 147.9935.

1-Methyl-4-thiocyanato-1H-pyrazole (3ag)
Prepared from 1-methyl-1H-pyrazole (1ag, 41.0 mg). Product 3ag (57%, 42.6 mg) was afforded as a colorless liquid.

IR (neat): 2156 (C≡N) cm⁻¹.

HRMS (ESI-TOF): \text{m}/\text{z} [M + Na]^+ calculated for C5H5N3NaS: 162.0102; found: 162.0102.

1-Benzyl-4-thiocyanato-1H-pyrazole (3ah)
Prepared from 1-benzyl-1H-pyrazole (1ah, 79.1 mg). Purification by column chromatography (5% acetone/hexanes) afforded 3ah (30%, 29.6 mg) as a colorless oil.

\text{Rf} = 0.40 (30% acetone/hexane).

IR (neat): 2156 (C≡N) cm⁻¹.

HRMS (ESI-TOF): \text{m}/\text{z} [M + Na]^+ calculated for C11H12N3NaOS: 238.0415; found: 248.0414.

Bis(3,5-dimethyl-4-thiocyanato-1H-pyrazol-1-yl)methane (3ai)
Prepared from bis(3,5-dimethyl-1H-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; \text{Rf} = 0.53 (40% EtOAc/hexanes).

IR (neat): 2154 (C≡N) cm⁻¹.

HRMS (ESI-TOF): \text{m}/\text{z} [M + Na]^+ calculated for C13H14N6NaS2: 341.0619; found: 341.0624.
1,3-Bis(3,5-dimethyl-4-thiocyanato-1H-pyrazol-1-yl)propane (3a)
Prepared from 1,3-bis(3,5-dimethyl-1H-pyrazol-1-yl)propane (1aj, 116.2 mg).
Purification by column chromatography (40% EtOAc/hexanes) afforded 3a (86%, 148.3 mg) as a white solid.

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

IR (neat): 2157 (C≡≡) cm–1.

1H NMR (400 MHz, CDCl3): δ = 7.53–7.48 (m, 5 H), 7.47–7.43 (m, 2 H), 7.40–7.38 (m, 1 H), 3.81 (2 H), 7.19 (d, J = 8.2 Hz, 2 H), 3.80 (s, 6 H).

13C NMR (100 MHz, CDCl3): δ = 150.8 (2×C), 143.6 (2×C), 110.7 (2×C), 94.3 (2×C), 46.1 (2×CH2), 28.6 (CH2), 11.6 (2×CH3), 9.7 (2×CH3).


Synthesis of 5-(1-Methyl-3,5-diphenyl-1H-pyrazol-4-yl)tetrazole (5a)30
NaNO3 (39.0 mg, 0.6 mmol) and ZnCl2 (68.2 mg, 0.5 mmol) were added to a solution of 1-methyl-3,5-diphenyl-4-thiocyanato-1H-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 5% HCl (2 × 10 mL) and dried.

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

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

IR (neat): 1476 (C–N) cm–1.

1H NMR (400 MHz, CD3OD): δ = 7.76–7.74 (m, 2 H), 7.48–7.36 (m, 8 H), 3.87 (s, 3 H). 13C NMR (100 MHz, CD3OD): δ = 157.8 (C), 154.2 (C), 151.1 (C), 133.0 (C), 131.1 (C), 131.0 (2×CH), 129.8 (CH), 129.5 (2×CH), 129.3 (C), 129.2 (2×CH), 99.1 (C), 38.5 (CH3).


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