Thiocyanation of Pyrazoles Using KSCN/K₂S₂O₈ Combination

T. Songsichan
P. Katrun
O. Khaikate
D. Sooruakram
M. Pohmakotr
V. Reutrakul
C. Kuhakarn*

Department of Chemistry and Center of Excellence for Innovation in Chemistry (PERCH-CIC), Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand
chutima.kon@mahidol.ac.th

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, thiocarbamates, thiosters, 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 trimethylsilyliothiocyanate (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, anticancer, anti-inflammatory, antiviral, antioxidant, cytotoxic, antihypertensive, antitubercular, analgesic, antipyretic, anticongulants, and A3 adenosine receptor antagonistic activities. Additionally, pyrazole derivatives are also important in agricultural chemistry. Although thiocyanation of arenes and heterocyclic compounds such as indoles, pyrroles, carboxazoles, 8-aminoquinolines and imidazopyridines 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,
Optimal solvent, thiocyanate source and oxidizing agent was excluded from the reaction (entry 20). After the reaction, no desired product 3a was observed when the oxidizing agent was tert-butyl hydroperoxide (TBHP) and cerium(IV) ammonium nitrate (CAN) (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$_2$CO$_3$ (1 equiv) significantly lowered the yield of 3a (entry 23). Finally, no improvement was observed when the stoichiometry of KSCN or K$_2$S$_2$O$_8$ was increased. After extensive experimentation, the optimum reaction conditions were chosen as: 1a (0.5 mmol), KSCN (1.5 equiv) and K$_2$S$_2$O$_8$ (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-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 produce the corresponding product 3g in 95% yield. On the other hand, the reaction of N-(1-propanyl)-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-(2-fluorophenyl)-3,5-dimethylpyrazole (1i) 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 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–ab 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$_2$S$_2$O$_8$, 3.0 equiv each) to yield the corresponding

<table>
<thead>
<tr>
<th>Entry</th>
<th>SCN source (2)</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>1a (%)</th>
<th>3a (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>H$_2$O</td>
<td>98</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>1,4-dioxane</td>
<td>93</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>THF</td>
<td>98</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>DMF</td>
<td>91</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>CH$_3$Cl</td>
<td>85</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>EtOH</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>CH$_3$OH</td>
<td>15</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>EtOAc</td>
<td>80</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>CH$_3$CN</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>10</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>DCE</td>
<td>54</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>DMSO</td>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td>12</td>
<td>NaSCN (2b)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>DMSO</td>
<td>7</td>
<td>91</td>
</tr>
<tr>
<td>13</td>
<td>NH$_4$SCN (2c)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>DMSO</td>
<td>12</td>
<td>86</td>
</tr>
<tr>
<td>14</td>
<td>KSCN (2a)</td>
<td>OXONE$^a$</td>
<td>DMSO</td>
<td>31</td>
<td>66</td>
</tr>
<tr>
<td>15</td>
<td>KSCN (2a)</td>
<td>Na$_2$S$_2$O$_8$</td>
<td>DMSO</td>
<td>2</td>
<td>95</td>
</tr>
<tr>
<td>16</td>
<td>KSCN (2a)</td>
<td>DB</td>
<td>DMSO</td>
<td>85</td>
<td>14</td>
</tr>
<tr>
<td>17</td>
<td>KSCN (2a)</td>
<td>IBX</td>
<td>DMSO</td>
<td>90</td>
<td>8</td>
</tr>
<tr>
<td>18</td>
<td>KSCN (2a)</td>
<td>TBHP</td>
<td>DMSO</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>19</td>
<td>KSCN (2a)</td>
<td>CAN</td>
<td>DMSO</td>
<td>53</td>
<td>43</td>
</tr>
<tr>
<td>20</td>
<td>KSCN (2a)</td>
<td>–</td>
<td>DMSO</td>
<td>98</td>
<td>–</td>
</tr>
<tr>
<td>21$^a$</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>DMSO</td>
<td>0</td>
<td>99</td>
</tr>
<tr>
<td>22$^a$</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>DMSO</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>23$^a$</td>
<td>KSCN (2a)</td>
<td>K$_2$S$_2$O$_8$</td>
<td>DMSO</td>
<td>19</td>
<td>79</td>
</tr>
</tbody>
</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 K$_2$CO$_3$ (1 equiv).

$^d$ Reaction conditions: entry 21 and in the presence of TsOH (1 equiv).

$^e$ Reaction conditions: entry 21 and in the presence of K$_2$CO$_3$ (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 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-methylyphenol (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 as the 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 light. 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 light. 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 light. 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 light. 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 light. Infrared spectra were recorded with a Bruker ALPHA FT-IR spectrometer.

**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; Rf = 0.57 (30% EtOAc/hexanes).

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 = 153.1 (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 (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 a pale-yellow solid.

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

1H NMR (400 MHz, CDCl₃): δ = 8.14 (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 = 153.0 (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; Rf = 0.61 (30% EtOAc/hexanes).

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 (CH₂), 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; Rf = 0.40 (40% EtOAc/hexanes).
2-(2-(3,5-Diphenyl-1H-pyrazol-1-yl)ethoxy)ethanol (3e)
Prepared from 2-(2-(3,5-diphenyl-1H-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 75.0–76.5 °C; Rf = 0.57 (20% EtOAc/hexanes).

13C NMR (100 MHz, CDCl3): 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 (CH2), 69.0 (CH2), 61.4 (CH2), 50.1 (CH2).

3.5-Dimethyl-1-(prop-1-en-1-yl)-4-thiocyanato-1H-pyrazole (3h)
Prepared from 3,5-dimethyl-1-(prop-1-en-1-yl)-1H-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; Rf = 0.48 (20% EtOAc/hexanes).
IR (neat): 3400 (O–H), 2155 (C≡N) cm–1.
1-(4-Fluorophenyl)-3,5-dimethyl-4-thiocyanato-1H-pyrazole (1l)
Prepared from 1-(4-fluorophenyl)-3,5-dimethyl-1H-pyrazole (1i) (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).

$\text{IR (neat): } 3272 \text{ (N–H), 2163 \text{ (C=O) cm}^{-1}}$.

$[M + H]^+$ calcd for C$_{12}$H$_{11}$FN$_3$S: 248.0658; found: 248.0658.

1-(2,4-Dinitrophenyl)-3,5-dimethyl-4-thiocyanato-1H-pyrazole (1m)
Prepared from 1-(2,4-dinitrophenyl)-3,5-dimethyl-1H-pyrazole (1n) (79.9 mg) as a white solid.
Mp 171.5–174.5 °C; $R_f$ = 0.39 (30% EtOAc/CH$_2$Cl$_2$).

$\text{IR (neat): } 3185 \text{ (N–H), 2157 \text{ (C=O) cm}^{-1}}$.

$[M + H]^+$ calcd for C$_{16}$H$_{12}$N$_3$S: 278.0752; found: 278.0752.

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/CH$_2$Cl$_2$) afforded 3p (97%, 101.0 mg) as a colorless oil.
$R_f$ = 0.47 (30% EtOAc/CH$_2$Cl$_2$).


3,5-Di-tert-butyl-4-thiocyanato-1H-pyrazole (3q)
Prepared from 3,5-di-tert-butyl-1H-pyrazole (1q) (90.1 mg). Purification by column chromatography (5% EtOAc/CH$_2$Cl$_2$) afforded 3q (89%, 105.4 mg) as a colorless solid.
Mp 155.5–157.5 °C; $R_f$ = 0.61 (30% EtOAc/CH$_2$Cl$_2$).

$[M + H]^+$ calcd for C$_{18}$H$_{16}$N$_3$S: 306.1065; found: 306.1060.

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/CH$_2$Cl$_2$) afforded 3r (99%, 137.5 mg) as a white solid.
Mp 171.5–174.5 °C; $R_f$ = 0.39 (30% EtOAc/CH$_2$Cl$_2$).

$[M + H]^+$ calcd for C$_{18}$H$_{16}$N$_3$S: 306.1065; found: 306.1060.

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/CH$_2$Cl$_2$) afforded 3s (99%, 150.5 mg) as a white solid.
Mp 186.5–188.5 °C; $R_f$ = 0.58 (30% EtOAc/CH$_2$Cl$_2$).


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/CH$_2$Cl$_2$) afforded 3t (90%, 152.6 mg) as a white solid.
3-Phenyl-4-thiocyanato-1H-pyrazole (3a)
Prepared from 3-phenyl-4-thiocyanato-1H-pyrazole (1a, 114.2 mg). Purification by column chromatography (5% EtOAc/CH2Cl2) afforded 3a (94%, 134.2 mg) as a colorless oil.
IR (neat): 3165 (N-H), 2165 (C=N) 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).

3-Methylthio-phenyl-4-thiocyanato-1H-pyrazole (3aa)
Prepared from 3-(3-methylthio)-phenyl-1H-pyrazole (1aa, 114.2 mg). Purification by column chromatography (5% EtOAc/CH2Cl2) afforded 3aa (94%, 134.2 mg) as a colorless oil.
IR (neat): 3165 (N-H), 2165 (C=N) 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).
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 146.5–150.0 °C; IR (neat): 3282 (N–H), 2157 (C≡N) cm–1.


1H NMR (500 MHz, CD3OD): δ = 7.65–7.63 (m, 2 H), 7.40–7.37 (m, 2 H), 7.32–7.29 (m, 1 H).

13C NMR (100 MHz, CD3OD): δ = 152.3 (2×C), 145.5 (2×C), 110.3 (2×C), 129.1 (2×CH), 128.7 (2×CH), 129.1 (2×CH), 125.0 (CH), 86.9 (C).


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


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): 3156 (N–H), 2155 (C≡N) cm–1.


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.

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


13C NMR (125 MHz, CD3OD): δ = 153.8 (146.4 (2×C), 131.0 (C), 128.4 (2×CH), 127.8 (2×CH), 126.8 (C), 125.2 (CH), 88.8 (C).


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; IR (neat): 3084 (C≡N) cm–1.

1,3-Bis(3,5-dimethyl-4-thiocyanato-1H-pyrazol-1-yl)propane (3aj)
Prepared from 1,3-bis(3,5-dimethyl-1H-pyrazol-1-yl)propane (1aj, 116.2 mg).
Furification by column chromatography (40% EtOAc/hexanes) afforded 3aj (86%, 148.3 mg) as a white solid.

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

IR (neat): 2157 (C≡N) cm⁻¹.

1H NMR (400 MHz, DMSO-d6): δ = 3.95 (t, J = 6.7 Hz, 4 H), 2.31 (quint, J = 6.7 Hz, 2 H), 2.254 (s, 6 H), 2.249 (s, 6 H).

13C NMR (100 MHz, DMSO-d6): δ = 132.8 (C), 129.9 (2×CH), 129.3 (CH), 128.8 (C), 128.6 (2×CH), 128.3 (2CH), 128.0 (CH), 127.7 (2CH), 127.2 (2CH), 101.1 (C), 38.0 (CH3).


4,4’-[1E,1′E-(4-Thiocyanato-1H-pyrazole-3,5-diyl)]bis(ethene-2,1-diyli)bis(2-methoxyphenol) (3ak)
Prepared from 4,4’-[1E,1′E-(1H-pyrazole-3,5-diyl)]bis(ethene-2,1-diyli)bis(2-methoxyphenol) (1ak, 182.2 mg).
Furification by column chromatography (4% MeOH/CH2Cl2) afforded 3ak (28%, 51.6 mg) as a yellow solid.

Mp 197.0–198.0 °C; Rf = 0.30 (10% MeOH/CH2Cl2).

IR (neat): 3239 (O–H), 2158 (C≡N) cm⁻¹.

1H NMR (400 MHz, acetone-d6): δ = 7.76 (dd, J = 7.9, 2.1 Hz, 2 H), 7.36–7.34 (m, 3 H), 7.10 (dd, J = 7.5, 2.0 Hz, 2 H), 3.64 (s, 3 H).

13C NMR (100 MHz, acetone-d6): δ = 147.5 (2×C), 147.0 (C), 133.3 (C), 128.5 (C), 121.1 (2CH), 119.4 (4CH), 112.0 (C), 110.8 (C), 109.5 (4CH), 92.5 (C), 55.4 (2×CH3).

HRMS (ESI-TOF): m/z [M + H]+ calcld for C22H20N3O4S: 422.1175; found: 422.1165.

Synthesis of 5-(1-Methyl-3,5-diphenyl-1H-pyrazol-4-yl)carbamothioate (4a)³⁰
A solution of 1-methyl-3,5-diphenyl-4-thiocyanato-1H-pyrazole (3a, 145.7 mg, 0.5 mmol) in CH2Cl2 (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 then diluted with water and 1.0 M HCl, which caused the product to form. The product was filtered, washed with 5% NaCl (2 × 10 mL) and dried.

Product 4a (51.6 mg) was obtained as a white solid.

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

IR (neat): 1461 (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 (CH), 131.0 (2CH), 129.8 (CH), 129.5 (2CH), 129.3 (C), 129.2 (2CH), 99.1 (C), 38.5 (CH3).

HRMS (ESI-TOF): m/z [M + Na]+ calcld for C15H15N3S: 293.0898; found: 293.0905.

Synthesis of 1,2-Bis(1-methyl-3,5-diphenyl-1H-pyrazol-4-yl)disulfane (6a)³⁰
A solution of 1-methyl-3,5-diphenyl-4-thiocyanato-1H-pyrazole (3a, 145.7 mg, 0.5 mmol) in anhydrous THF (2 mL) was added to a suspension of LiAlH4 (20.9 mg, 0.55 mmol) in anhydrous THF (4 mL) at 0 °C. The resulting mixture was stirred at 0 °C 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 MgSO4, 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; Rf = 0.57 (60% EtOAc/hexanes).

IR (neat): 1461 (C–N) cm⁻¹.

1H NMR (400 MHz, CD3OD): 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).

13C NMR (100 MHz, CD3OD): δ = 152.7 (2C), 148.7 (2C), 132.1 (2C), 130.1 (4CH), 128.9 (2CH), 128.15 (2C), 128.13 (6CH), 128.0 (4CH), 127.9 (2CH), 107.5 (2CH), 37.6 (2CH2).

HRMS (ESI-TOF): m/z [M + H]+ calcld for C15H15N2S: 553.1497; found: 553.1579.

Funding Information
We thank the Thailand Research Fund (BRG5880012 and IRNS8W0005), the Center of Excellence for Innovation in Chemistry (PERCH-CIC), Postgraduate Education Research Development Office, Office of the Higher Education Commission, Ministry of Education, Mahidol University under the National Research Universities Initiative, PICS6663 ISMA (France/Thailand), and the Franco–Thai Cooperation Program in Higher Education and Research (PHC Siam 2017) for financial support.

Acknowledgment
We also acknowledge the Institute for the Promotion of Teaching Science and Technology through the Development and Promotion of Science and Technology Talents Project (DPST), and Science Achievement
Scholarship of Thailand (SAST) for student scholarships to T.S. and O.K., respectively and the National Research Council of Thailand (NRCT) for a postdoctoral research assistantship to P.K.

Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591891.

References


