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Catalyst-Free Regioselective C-3 Thiocyanation of Imidazopyridines

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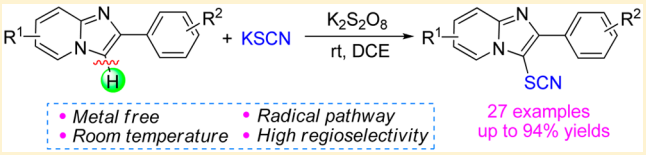
Supporting Information

ABSTRACT: A direct and straightforward approach for highly regioselective thiocyanation of imidazoheterocycles through sp^2 C−H functionalization has been realized at room temperature. Various C-3 thiocyanated imidazopyridines are formed in moderate to good yield. The present method exhibits a mild and selective access to a variety of imidazopyridine derivatives of pharmacological interest.



Aryl thiocyanates have shown diverse biological and pharmacological activities, including antifungal, antiviral, antibacterial, and so forth.[1] Additionally, aryl thiocyanates are also versatile precursors for the synthesis of many sulfur-containing aromatic compounds, such as sulfonic acids,[2] sulfonyl chlorides,[3] thiocarbamates,[4] thioesters,[5] and sulfonyl cyanides.[6] Despite their potentially wide applications, unfortunately, synthetic methods remain rare. The traditional methods for the synthesis of aryl thiocyanates typically involve coupling of diazonium salt with metal thiocyanates under Sandmeyer-type conditions,[7] or the cyanation of organometallic[8] and organosulfur compounds.[9] Although these methods have made various synthesis contributions, the toxic and high cost of the reagent, unavailable starting materials, and undesired by-products could impede their wide applications. As an alternative, the direct thiocyanation of readily available aryl halides is an appealing approach to aryl thiocyanates. In 1996, Suzuki and co-workers developed an elegant method for the synthesis of arylthiocyanates from cross-coupling of $KCu(SCN)_2$ with aryl iodides.[10] In 2006, Guo et al. reported the coupling of aryl iodides with KSCN using CuI catalysis to provide the corresponding thiocyanation products.[11] However, the yields of these methods were low, and the substrates were mainly focused on aryl iodides.

Recently, exploring efficient, practical, and highly selective metal-free approaches for the direct functionalization of C−H bonds has become a hot topic of intensive studies.[12] Thus, the direct thiocyanation of $C(sp^2)$−H bonds would be more economical and practical. Recently, a few direct thiocyanation transformations have been reported, but these examples are mainly concentrated on indoles.[13] As a consequence, it is of great significance and highly desirable to develop more efficient and selective methods to prepare SCN-containing aryls or heterocycles that utilize inexpensive thiocyanation reagents through direct C−H functionalization under metal-free conditions.

Imidazoheterocycle motifs are well-known to possess various useful biological and medicinal activities. For example, they can be used as antibacterial,[14] antiviral,[15] antitumor,[16] anti-inflammatory,[17] and antimicrobial agents.[18] Additionally, some commercially available drugs contain this core structure (Figure 1), such as **A** (Zolimidin; to treat peptic ulcers),[19] **B** (minodronic acid; to treat osteoporosis),[20] **C** (Alpidem; a peripheral benzodiazepine receptor ligand),[21] and **D** (GSK812397; a potent noncompetitive CXCR4 receptor antagonist).[22] Consequently, extensive efforts have been devoted to the discovery of efficient and useful methods for imidazoheterocycle synthesis and functionalization.[23] Furthermore, the exploration of new methods for C-3 functionalization of imidazopyridines has made significant progress but unfortunately examples remain rather limited.[24] In 2015, Hajra and co-workers developed a silver-catalyzed regioselective trifluoromethylation of imidazopyridines under mild conditions.[25] Recently, direct C-3 thiolation of imidazoheterocycles has been extensively studied because of the importance of the 3-thio-substituted imidazopyridines.[26] For example, as shown in Figure 1, compounds **E** and **F** have been considered as important intermediates for the synthesis of enviroxime analogues, which possess potent broad spectrum antiviral activities.[27] In 2011, Zhou and co-workers developed an efficient CuI-catalyzed C-3 thiolation of imidazopyridines using alkyl/aryl disulfides as the thiol source.[26a] In 2013, Roychowdhury et al. reported a metal-free method for methylthiolation of imidazo[1,2-*a*]pyridines using a DMSO/$POCl_3$ complex.[26b] In 2014, Adimurthy's group described an *N*-chlorosuccinimide-promoted C-3 thiolation of imidazoheterocycles at room temperature.[24a] In 2015, Hiebel et al. demonstrated an iodine-catalyzed regioselective sulfenylation of imidazoheterocycles in PEG400.[26c] Subsequently, Tang and Chen's group demonstrated an iodine-catalyzed thiolation of imidazoheterocycles with disulfides in the presence of hydrogen peroxide.[26d] It is well-known that the biological activity is mainly dependent on the nature of the functional groups. Incorporation of thiocyanate into bioactive compounds could increases their medicinal activity. Thus, the synthesis of new 3-

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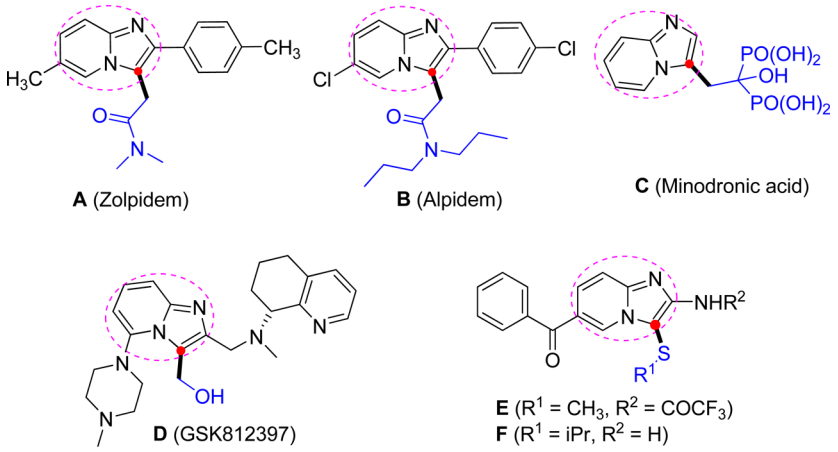
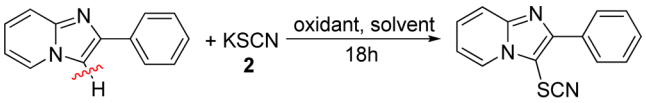


Figure 1. Representative examples of C-3-substituted imidazopyridine compounds.

thiocyanatoimidazopyridines is highly desirable. Herein, we report a novel, efficient, and direct catalyst-free C-3 thiocyanation of imidazopyridines with simple and readily available KSCN as the sulfur source under mild condtions.

First, 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and KSCN were used as the model substrates to optimize the reaction conditions, including the oxidant, solvent, and temperature under ambient air. As shown in Table 1, seven oxidants, oxone, TBHP, O_2, $(NH_4)_2S_2O_8$, $Na_2S_2O_8$, H_2O_2, and $K_2S_2O_8$ were investigated at 25 °C in 2 mL of HOAc, and $K_2S_2O_8$ was found to be the most effective oxidant (72%) (entries 1−7). Furthermore, the solvents, including HOAc, DCE, CH_3CN, H_2O, DMF, and 1,4-dioxane were tested using $K_2S_2O_8$ as the oxidant at 25 °C, and DCE provided the highest yield (entries 6, 8−12). Additionally, different amounts of $K_2S_2O_8$ were attempted, and 1.5 equiv of $K_2S_2O_8$ was found to be more suitable for the present reaction (compare entries 8, 13, and 14). Interestingly, the yield decreased when the temperature was elevated to 40 °C (entry 15). We also investigated reactivity of other thiocyanates, such as NaSCN and NH_4SCN, and KSCN showed the most effective activity in the transformation (compare entries 8, 16, and 17). Notably, no target product was observed in the absence of $K_2S_2O_8$. After the optimization process for oxidant, solvent, and temperature, the various 3-thiocyanatoimidazo[1,2-*a*]pyridines were synthesized under our standard conditions: 1.5 equiv of $K_2S_2O_8$ as the oxidant, 2 equiv of KSCN as the SCN source, and DCE as the solvent under air atmosphere at room temperature.

Table 1. Optimization of the Reaction Conditions[a]



1a **3a**

entry	oxidant	solvent	yield[b] (%)
1	oxone (1.5)	HOAc	63
2	TBHP (1.5)	HOAc	trace
3	O_2 (1.5)	HOAc	0
4	$Na_2S_2O_8$ (1.5)	HOAc	68
5	$(NH_4)_2S_2O_8$ (1.5)	HOAc	65
6	$K_2S_2O_8$ (1.5)	HOAc	72
7	H_2O_2	HOAc	trace
8	**$K_2S_2O_8$ (1.5)**	**DCE**	**83**
9	$K_2S_2O_8$ (1.5)	CH_3CN	74
10	$K_2S_2O_8$ (1.5)	H_2O	trace
11	$K_2S_2O_8$ (1.5)	DMF	76
12	$K_2S_2O_8$ (1.5)	1,4-dioxane	66
13	$K_2S_2O_8$ (1.0)	CH_3CN	72
14	$K_2S_2O_8$ (2.0)	CH_3CN	80
15	$K_2S_2O_8$ (1.5)	CH_3CN	58[c]
16	$K_2S_2O_8$ (1.5)	CH_3CN	78[d]
17	$K_2S_2O_8$ (1.5)	CH_3CN	74[e]
18	none	CH_3CN	0

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (2 equiv), oxidant (1.5 equiv), solvent (2 mL), rt, 18 h. TBHP = *tert*-butyl hydroperoxide solution 5.5 M in decane. [b]Isolated yield. [c]Reaction temperature (40 °C). [d]NaSCN was used. [e]NH_4SCN was used.

The scope and generality of substrates for the metal-free regioselective C-3 thiocyanation of imidazopyridines was investigated under the optimized conditions, and the results are summarized in Table 2. To our delight, most of the tested substrates afforded moderate to good yields. A variety of electron-donating and -withdrawing groups at any aryl ring of imidazopyridines could be well tolerated, showing no obvious electronic effect in this transformation. Additionally, the hindrance effect of this reaction was also not obvious, imidazopyridines bearing a methyl group at different positions could efficiently reacted with KSCN to give the corresponding products in good yields (**3d**, **3e**, **3f**, **3h**, **3j**, **3m**, and **3n**). Notably, when 2-furan imidazo[1,2-*a*]pyridines were used, desired products **3t** and **3u** were obtained in 69 and 76% isolated yields, respectively. Furthermore, the application of our present protocol for thiocyanation of other heterocyclic and aromatic compounds, including imidazo[2,1-*b*]thiazoles, indole, and *N*,*N*-dimethylaniline were explored (Table 3). Satisfactorily, these substrates also gave good yields of thiocyanated products **5a**−**5f** in 72−87% yield. Some functional groups were compatible in the present reaction, including methyl, methoxy, C−Cl bond, and C−Br bond, which could be further transformed to other useful functional groups. The structure of **3n** was confirmed by X-ray crystallographic analysis (see Supporting Information for details).

Gram-scale applications for the present method were also explored. As shown in Scheme 1, the proposed reaction between **1a** and **2** was investigated under the standard conditions, which could give 1.2 g of **3a** in 80% yield without any significant loss of reactive efficiency. Thus, this simple, metal-free protocol could be extended as an efficient and

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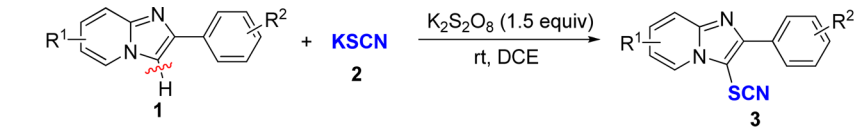
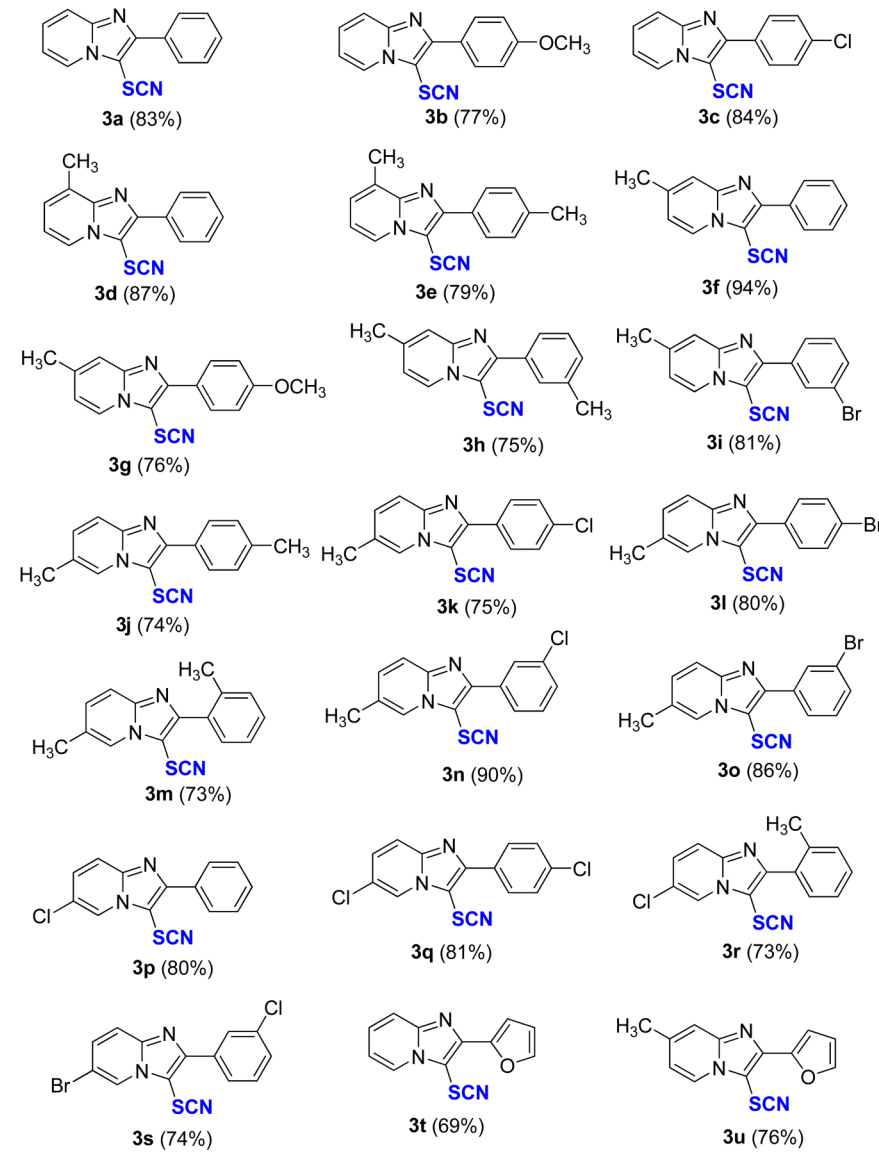
Table 2. Direct C-3 Thiocyanation of Different Imidazopyridines[a]





[a]Reaction conditions: substituted imidazopyridines (0.4 mmol), KSCN (0.8 mmol), $K_2S_2O_8$ (0.6 mmol), DCE (2 mL), reaction time (18 h). Isolated yield.

practical method to construct various potentially bioactive C-3-substituted imidazopyridines.

To gain further insight into the reaction mechanism, we added the well-known radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) to the reaction system; the thiocyanation reaction was suppressed, which indicated that a free radical pathway might be involved in the present reaction.

On the basis of the priliminary results above and previous related literature,[25,28] two plausible pathways for this present reaction were proposed (Scheme 2). In path I, SCN radical **A** was first generated by the oxidation of KSCN. Subsequently, the radical **A** reacted with imidazopyridines **1** to give alkyl radical intermediate **C**, which could be stabilized by the adjacent nitrogen atom and phenyl. Subsequently, the radical intermediate **C** was further oxidized to the carbocation **D** by $K_2S_2O_8$. Finally, elimination of H^+ from the intermediate carbocation **D** afforded desired product **3**. As a complementary mechanism, oxidation of KSCN by $K_2S_2O_8$ generated electrophile thiocyanogen $(SCN)_2$ **B**. Subsequently, electrophilic addition of electrophile **B** to **1** also gave the same intermediate carbocation **D** as shown in path II (Scheme 2). Further investigations on the more detailed mechanism are in progress in our laboratory.

In summary, we have disclosed the first example of catalyst-free highly regioselective C-3 thiocyanation of imidazopyridines under mild conditions. The transformation proceeded in good

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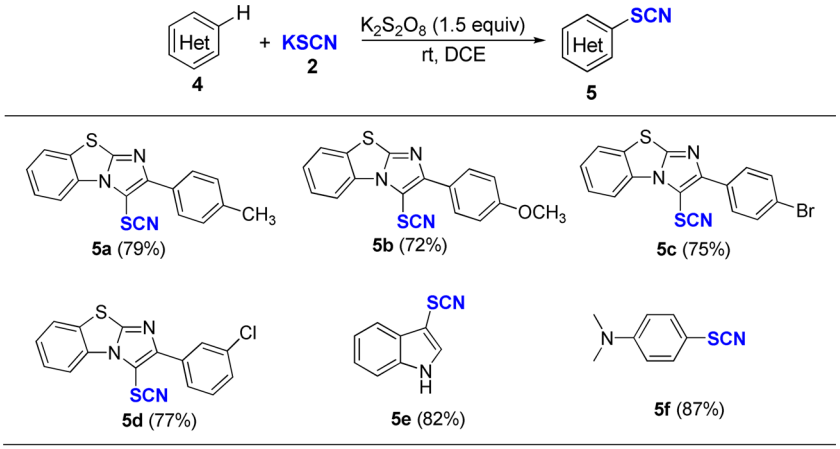
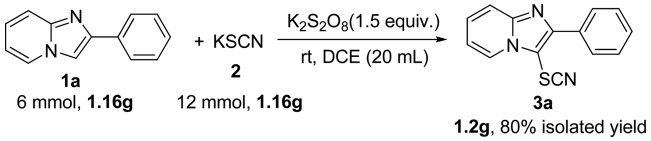
Table 3. Substrate Scope of Heterocyclic and Aromatic Compounds[a]

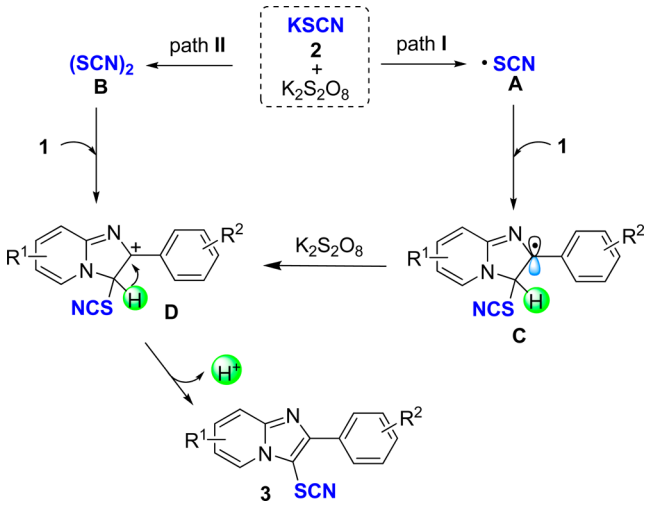


[a]Reaction conditions: substituted heterocyclic and aromatic compounds (0.4 mmol), KSCN (0.8 mmol), $K_2S_2O_8$ (0.6 mmol), DCE (2 mL), reaction time (18 h). Isolated yield.

Scheme 1. Synthesis of 3a on a Gram Scale



Scheme 2. Proposed Mechanism for Direct Transformation



yields and tolerated a wide range of functional groups. Tentative experiments suggested that this reaction was likely to proceed via a radical pathway. The present protocol provided a new avenue to formation of potentially bioactive imidazopyridine derivatives, and it would gain much more attention in synthetic and pharmaceutical chemistry.

EXPERIMENTAL SECTION

General. All commercially available reagents and chemicals were purchased from chemical suppliers and used as received without further purification. Mass analyses and HRMS were obtained by ESI on a TOF mass analyzer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as internal standard (400 MHz ^{1}H, 100 MHz ^{13}C) at room temperature. Column chromatography was performed on silica gel (200−300 mesh).

General Experimental Procedures. A 25 mL Schlenk tube was charged with imidazopyridines (0.4 mmol), KSCN (77.5 mg, 0.8 mmol), $K_2S_2O_8$ (161.9 mg, 0.6 mmol), and DCE (2 mL). The tube was sealed, and then the mixture was stirred under air at room temperature for 18 h. After completion of the reaction (TLC), H_2O (5 mL) was added; the mixture was extracted with ethyl acetate or dichloromethane (3 × 4 mL). The combined organic layers were concentrated by a rotary evaporator, and the residue was purified by column chromatography on silica gel to provide the desired products (**3**). The same procedure starting from imidazothiazoles led to compounds **5**.

*2-Phenyl-3-thiocyanatoimidazo[1,2-a]pyridine (**3a**).* Eluent petroleum ether/ethyl acetate (5:1). White solid, 83 mg, 83% yield, mp 121−122 °C (2:1 petroleum ether/ethyl acetate, R_f = 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.48 (d, 1H, J = 8.0 Hz), 8.08 (d, 2H, J = 8.0 Hz), 7.79 (d, 1H, J = 8.0 Hz), 7.56 (t, 2H, J = 8.0 Hz), 7.49 (t, 2H, J = 8.0 Hz), 7.16 (t, 1H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.1, 148.0, 132.0, 129.5, 128.8, 128.7, 128.0, 124.4, 118.3, 114.4, 108.1, 94.7. HRMS m/z: calcd for $C_{14}H_{10}N_3S$ $[M + H]^+$, 252.0595; found, 252.0597. IR (KBr): 3068, 2154, 1633, 1496, 1469, 1443 cm^{-1}.

*2-(4-Methoxyphenyl)-3-thiocyanatoimidazo[1,2-a]pyridine (**3b**).* Eluent petroleum ether/ethyl acetate (5:1). White solid, 87 mg, 77% yield, mp 160−162 °C (2:1 petroleum ether/ethyl acetate, R_f = 0.4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.43 (d, 1H, J = 8.0 Hz), 8.05 (d, 2H, J = 8.0 Hz), 7.74 (d, 1H, J = 8.0 Hz), 7.45 (t, 1H, J = 8.0 Hz), 7.12−7.05 (m, 3H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.7, 152.9, 147.9, 130.1, 127.9, 124.5, 124.3, 118.0, 114.2, 114.1, 108.2, 93.7, 55.4. HRMS m/z: calcd for $C_{15}H_{12}N_3OS$ $[M + H]^+$, 282.0701; found, 282.0705. IR (KBr): 2901, 2152, 1608, 1534, 1454, 1406 cm^{-1}.

*2-(4-Chlorophenyl)-3-thiocyanatoimidazo[1,2-a]pyridine (**3c**).* Eluent petroleum ether/ethyl acetate (5:1). White solid, 96 mg, 84% yield, mp 158−161 °C (2:1 petroleum ether/ethyl acetate, R_f = 0.4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45 (d, 1H, J = 8.0 Hz), 8.03 (d, 2H, J = 8.0 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.52−7.48 (m, 3H), 7.15 (t, 1H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.8, 147.9, 135.6, 130.5, 130.0, 129.0, 128.2, 124.4, 118.3, 114.6, 107.8, 94.8. HRMS m/z: calcd for $C_{14}H_9ClN_3S$ $[M + H]^+$, 286.0206; found, 286.0202. IR (KBr): 3029, 2151, 1634, 1515, 1497, 1459 cm^{-1}.

*8-Methyl-2-phenyl-3-thiocyanatoimidazo[1,2-a]pyridine (**3d**).* Eluent petroleum ether/ethyl acetate (10:1). White solid, 92 mg, 87% yield, mp 131−133 °C (5:1 petroleum ether/ethyl acetate, R_f = 0.6). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31 (d, 1H, J = 8.0 Hz), 8.10 (d, 2H, J = 8.0 Hz), 7.56 (t, 2H, J = 8.0 Hz), 7.48 (d, 1H, J = 8.0 Hz), 7.27 (d, 1H, J = 8.0 Hz), 7.05 (t, 1H, J = 8.0 Hz), 2.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.6, 148.3, 132.3, 129.3, 128.9, 128.7, 128.6, 126.7, 122.1, 114.4, 108.3, 94.9, 16.7. HRMS m/z: calcd for $C_{15}H_{12}N_3S$ $[M + H]^+$, 266.0752; found, 266.0741. IR (KBr): 2919, 2153, 1627, 1559, 1490, 1463 cm^{-1}.

*8-Methyl-3-thiocyanato-2-p-tolylimidazo[1,2-a]pyridine (**3e**).* Eluent petroleum ether/ethyl acetate (10:1). White solid, 88 mg,

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79% yield, mp 137−139 °C (5:1 petroleum ether/ethyl acetate, R_f = 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31 (d, 1H, J = 8.0 Hz), 7.99 (d, 2H, J = 8.0 Hz), 7.36 (d, 2H, J = 8.0 Hz), 7.25 (d, 1H, J = 8.0 Hz), 7.02 (t, 1H, J = 8.0 Hz), 2.71 (s, 3H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.7, 148.2, 139.3, 129.6, 129.4, 128.8, 128.4, 126.6, 122.1, 114.2, 108.4, 94.5, 21.4, 16.7. HRMS m/z: calcd for $C_{16}H_{14}N_3S$ $[M + H]^+$, 280.0908; found, 280.0911. IR (KBr): 2964, 2143, 1631, 1488, 1473 cm^{-1}.

7-Methyl-2-phenyl-3-thiocyanatoimidazo[1,2-a]pyridine (**3f**). Eluent petroleum ether/ethyl acetate (5:1). White solid, 100 mg, 94% yield, mp 123−124 °C (2:1 petroleum ether/ethyl acetate, R_f = 0.4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (d, 1H, J = 8.0 Hz), 8.07 (d, 2H, J = 8.0 Hz), 7.58−7.54 (m, 3H), 7.50 (d, 1H, J = 8.0 Hz), 7.00 (d, 1H, J = 8.0 Hz), 2.53 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.3, 148.6, 139.8, 132.3, 129.4, 128.8, 128.7, 123.5, 117.0, 116.9, 108.2, 21.5. HRMS m/z: calcd for $C_{15}H_{12}N_3S$ $[M + H]^+$, 266.0752; found, 266.0741. IR (KBr): 2949, 2157, 1644, 1465, 1440, 1463 cm^{-1}.

2-(4-Methoxyphenyl)-7-methyl-3-thiocyanatoimidazo[1,2-a]pyridine (**3g**). Eluent petroleum ether/ethyl acetate (5:1). White solid, 90 mg, 76% yield, mp 126−128 °C (3:1 petroleum ether/ethyl acetate, R_f = 0.4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (d, 1H, J = 8.0 Hz), 8.04 (d, 2H, J = 8.0 Hz), 7.52 (s, 1H), 7.08 (d, 1H, J = 8.0 Hz), 6.98 (d, 1H, J = 8.0 Hz), 3.91 (s, 3H), 2.52 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.6, 153.1, 148.4, 139.4, 130.1, 124.7, 123.5, 116.7, 116.6, 114.2, 108.4, 92.9, 55.4, 21.4. HRMS m/z: calcd for $C_{16}H_{14}N_3OS$ $[M + H]^+$, 296.0858; found, 296.0852. IR (KBr): 2953, 2154, 1665, 1608, 1471, 1439 cm^{-1}.

7-Methyl-3-thiocyanato-2-m-tolylimidazo[1,2-a]pyridine (**3h**). Eluent petroleum ether/ethyl acetate (5:1). White solid, 84 mg, 75% yield, mp 153−155 °C (2:1 petroleum ether/ethyl acetate, R_f = 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.34 (d, 1H, J = 8.0 Hz), 7.87−7.85 (m, 2H), 7.54 (s, 1H), 7.44 (t, 1H, J = 8.0 Hz), 7.29 (d, 1H, J = 8.0 Hz), 6.97 (d, 1H, J = 8.0 Hz), 2.52 (s, 3H), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.3, 148.3, 139.4, 138.5, 132.0, 130.1, 129.4, 128.6, 125.9, 123.5, 116.9, 116.8, 108.3, 93.7, 21.5, 21.4. HRMS m/z: calcd for $C_{16}H_{14}N_3S$ $[M + H]^+$, 280.0908; found, 280.0911. IR (KBr): 2973, 2151, 1645, 1453, 1406 cm^{-1}.

2-(3-Bromophenyl)-7-methyl-3-thiocyanatoimidazo[1,2-a]pyridine (**3i**). Eluent petroleum ether/ethyl acetate (5:1). White solid, 111 mg, 81% yield, mp 165−167 °C (2:1 petroleum ether/ethyl acetate, R_f = 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.34 (d, 1H, J = 8.0 Hz), 8.23 (s, 1H), 8.02 (d, 1H, J = 8.0 Hz), 7.61 (d, 1H, J = 8.0 Hz), 7.54 (s, 1H), 7.41 (t, 1H, J = 8.0 Hz), 7.01 (d, 1H, J = 8.0 Hz), 2.53 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.4, 148.3, 139.8, 134.2, 132.3, 131.6, 130.2, 127.2, 123.5, 122.9, 117.3, 116.9, 107.9, 94.2, 21.5. HRMS m/z: calcd for $C_{15}H_{11}BrN_3S$ $[M + H]^+$, 343.9857; found, 343.9855, 345.9833. IR (KBr): 2961, 2162, 1638, 1594, 1561, 1489 cm^{-1}.

6-Methyl-3-thiocyanato-2-p-tolylimidazo[1,2-a]pyridine (**3j**). Eluent petroleum ether/ethyl acetate (5:1). White solid, 83 mg, 74% yield, mp 164−165 °C (2:1 petroleum ether/ethyl acetate, R_f = 0.6). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25 (s, 1H), 7.97 (d, 2H, J = 8.0 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.37−7.32 (m, 3H), 2.50 (s, 3H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.0, 147.0, 139.4, 130.9, 129.4, 129.3, 128.6, 124.4, 122.2, 117.5, 108.3, 93.7, 21.4, 18.6. HRMS m/z: calcd for $C_{16}H_{14}N_3S$ $[M + H]^+$, 280.0908; found, 280.0911. IR (KBr): 2962, 2154, 1640, 1613, 1507, 1462 cm^{-1}.

2-(4-Chlorophenyl)-6-methyl-3-thiocyanatoimidazo[1,2-a]pyridine (**3k**). Eluent petroleum ether/ethyl acetate (5:1). White solid, 90 mg, 75% yield, mp 151−153 °C (2:1 petroleum ether/ethyl acetate, R_f = 0.4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25 (s, 1H), 8.03 (d, 2H, J = 8.0 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.52 (d, 2H, J = 8.0 Hz), 7.36 (d, 1H, J = 8.0 Hz), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.6, 147.0, 135.5, 131.3, 130.6, 129.9, 129.0, 124.8, 122.2, 117.6, 108.0, 94.2, 18.5. HRMS m/z: calcd for $C_{15}H_{11}ClN_3S$ $[M + H]^+$, 300.0362; found, 300.0361. IR (KBr): 2970, 2155, 1598, 1539, 1503, 1407 cm^{-1}.

2-(4-Bromophenyl)-6-methyl-3-thiocyanatoimidazo[1,2-a]pyridine (**3l**). Eluent petroleum ether/ethyl acetate (5:1). White solid, 110 mg, 80% yield, mp 183−185 °C (3:1 petroleum ether/ethyl acetate, R_f = 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (s, 1H), 7.95 (d, 2H, J = 8.0 Hz), 7.68−7.65 (m, 3H), 7.35 (d, 1H, J = 8.0 Hz), 2.50 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.6, 147.0, 131.9, 131.3, 131.1, 130.1, 124.8, 123.8, 122.2, 117.6, 108.0, 94.2, 18.5. HRMS m/z: calcd for $C_{15}H_{11}BrN_3S$ $[M + H]^+$, 343.9857; found, 343.9855 and 345.9833. IR (KBr): 2924, 2155, 1537, 1502, 1455, 1402 cm^{-1}.

6-Methyl-3-thiocyanato-2-o-tolylimidazo[1,2-a]pyridine (**3m**). Eluent petroleum ether/ethyl acetate (5:1). White solid, 82 mg, 73% yield, mp 113−115 °C (2:1 petroleum ether/ethyl acetate, R_f = 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25 (s, 1H), 7.69 (d, 2H, J = 8.0 Hz), 7.43−7.33 (m, 5H), 2.52 (s, 3H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.7, 146.8, 137.6, 131.6, 130.8, 130.7, 130.6, 129.2, 125.6, 124.5, 122.3, 117.7, 108.3, 96.1, 20.2, 18.4. HRMS m/z: calcd for $C_{16}H_{14}N_3S$ $[M + H]^+$, 280.0908; found, 280.0911. IR (KBr): 2929, 2151, 1536, 1502, 1458, 1414 cm^{-1}.

2-(3-Chlorophenyl)-6-methyl-3-thiocyanatoimidazo[1,2-a]pyridine (**3n**). Eluent petroleum ether/ethyl acetate (5:1). White solid, 108 mg, 90% yield, mp 187−188 °C (2:1 petroleum ether/ethyl acetate, R_f = 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (s, 1H), 8.08 (s, 1H), 7.99 (d, 1H, J = 8.0 Hz), 7.69 (d, 1H, J = 8.0 Hz), 7.51−7.45 (m, 2H), 7.37 (d, 1H, J = 8.0 Hz), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.2, 147.0, 134.8, 133.9, 131.3, 129.9, 129.4, 128.7, 126.7, 124.9, 122.3, 117.7, 107.9, 94.5, 18.5. HRMS m/z: calcd for $C_{15}H_{11}ClN_3S$ $[M + H]^+$, 300.0362; found, 300.0361. IR (KBr): 2971, 2154, 1539, 1502, 1406 cm^{-1}.

2-(3-Bromophenyl)-6-methyl-3-thiocyanatoimidazo[1,2-a]pyridine (**3o**). Eluent petroleum ether/ethyl acetate (5:1). White solid, 118 mg, 86% yield, mp 169−171 °C (2:1 petroleum ether/ethyl acetate, R_f = 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26−8.24 (m, 2H), 8.03 (d, 1H, J = 8.0 Hz), 7.69 (d, 1H, J = 8.0 Hz), 7.61 (d, 1H, J = 8.0 Hz), 7.42 (t, 1H, J = 8.0 Hz), 7.37 (d, 1H, J = 8.0 Hz), 2.52 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.1, 147.0, 134.2, 132.3, 131.6, 131.3, 130.2, 127.2, 124.9, 122.9, 122.2, 117.7, 107.8, 94.6, 18.5. HRMS m/z: calcd for $C_{15}H_{11}BrN_3S$ $[M + H]^+$, 343.9857; found, 343.9855 and 345.9833. IR (KBr): 2922, 2159, 1593, 1561, 1499, 1466 cm^{-1}.

6-Chloro-2-phenyl-3-thiocyanatoimidazo[1,2-a]pyridine (**3p**). Eluent petroleum ether/ethyl acetate (10:1). White solid, 91 mg, 80% yield, mp 183−184 °C (4:1 petroleum ether/ethyl acetate, R_f = 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (s, 1H), 8.07 (d, 2H, J = 8.0 Hz), 7.74 (d, 1H, J = 8.0 Hz), 7.59−7.51 (m, 3H), 7.47 (d, 1H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7, 146.3, 131.6, 129.7, 129.5, 128.8, 128.7, 123.0, 122.5, 118.7, 107.6, 95.7. HRMS m/z: calcd for $C_{14}H_9ClN_3S$ $[M + H]^+$, 286.0206; found, 286.0201. IR (KBr): 3018, 2156, 1519, 1493, 1466, 1443 cm^{-1}.

6-Chloro-2-(4-chlorophenyl)-3-thiocyanatoimidazo[1,2-a]pyridine (**3q**). Eluent petroleum ether/ethyl acetate (10:1). White solid, 103 mg, 81% yield, mp 201−203 °C (5:1 petroleum ether/ethyl acetate, R_f = 0.4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.50 (s, 1H), 8.03 (d, 2H, J = 8.0 Hz), 7.72 (d, 1H, J = 8.0 Hz), 7.53 (d, 2H, J = 8.0 Hz), 7.48 (d, 1H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.5, 146.3, 136.0, 130.0, 129.9, 129.7, 129.1, 123.2, 122.5, 118.7, 107.3, 95.7. HRMS m/z: calcd for $C_{14}H_8Cl_2N_3S$ $[M + H]^+$, 319.9816; found, 319.9821. IR (KBr): 2987, 2164, 1523, 1489, 1405 cm^{-1}.

6-Chloro-3-thiocyanato-2-o-tolylimidazo[1,2-a]pyridine (**3r**). Eluent petroleum ether/ethyl acetate (10:1). White solid, 87 mg, 73% yield, mp 149−152 °C (5:1 petroleum ether/ethyl acetate, R_f = 0.4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (s, 1H), 7.74 (d, 1H, J = 8.0 Hz), 7.49 (d, 1H, J = 8.0 Hz), 7.43−7.35 (m, 4H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.7, 146.2, 137.6, 131.0, 130.8, 130.6, 129.6, 129.3, 125.7, 123.0, 122.5, 118.8, 107.6, 97.8, 20.1. HRMS m/z: calcd for $C_{15}H_{11}ClN_3S$ $[M + H]^+$, 300.0362; found, 300.0361. IR (KBr): 3018, 2154, 1518, 1489, 1460, 1415 cm^{-1}.

6-Bromo-2-(3-chlorophenyl)-3-thiocyanatoimidazo[1,2-a]pyridine (**3s**). Eluent petroleum ether/ethyl acetate (10:1). White solid, 107 mg, 74% yield, mp 177−178 °C (5:1 petroleum ether/ethyl acetate, R_f = 0.3). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.61 (s, 1H), 8.09 (s, 1H), 8.00−7.97 (m, 1H), 7.69 (d, 1H, J = 8.0 Hz), 7.59 (d, 1H, J = 8.0 Hz), 7.51−7.49 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.9, 146.4, 135.0, 133.3, 131.9, 130.1, 129.8, 128.8, 126.8, 124.6, 119.0, 109.7, 107.2, 95.9. HRMS m/z: calcd for $C_{14}H_8BrClN_3S$ $[M + H]^+$,

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363.9311; found, 363.9315, 365.9291. IR (KBr): 2988, 2160, 1595, 1566, 1492, 1405 cm^{-1}.

*2-(Furan-2-yl)-3-thiocyanatoimidazo[1,2-a]pyridine (**3t**).* Eluent petroleum ether/ethyl acetate (5:1). White solid, 67 mg, 69% yield, mp 174−176 °C (1:1 petroleum ether/ethyl acetate, R_f = 0.4). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.43 (d, 1H, J = 4.0 Hz), 7.35 (d, 1H, J = 8.0 Hz), 7.67 (s, 1H), 7.48 (t, 1H, J = 8.0 Hz), 7.24 (d, 1H, J = 4.0 Hz), 7.13 (t, 1H, J = 8.0 Hz), 6.62 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.2, 147.1, 144.1, 128.2, 124.2, 118.2, 114.5, 111.9, 111.4, 107.7, 93.5. HRMS m/z: calcd for $C_{12}H_8N_3OS$ $[M + H]^+$, 242.0388; found, 242.0391. IR (KBr): 2959, 2156, 1633, 1512, 1494, 1429 cm^{-1}.

*2-(Furan-2-yl)-7-methyl-3-thiocyanatoimidazo[1,2-a]pyridine (**3u**).* Eluent petroleum ether/ethyl acetate (5:1). White solid, 78 mg, 76% yield, mp 178−180 °C (1:1 petroleum ether/ethyl acetate, R_f = 0.3). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.27 (d, 1H, J = 8.0 Hz), 7.65 (s, 1H), 7.67 (s, 1H), 7.47 (s, 1H), 7.19 (d, 1H, J = 4.0 Hz), 6.94 (d, 1H, J = 8.0 Hz), 6.61 (dd, 1H, J = 4.0 Hz), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.5, 147.2, 144.3, 143.9, 139.8, 123.3, 117.1, 116.6, 111.8, 111.2, 107.9, 92.6, 21.4. HRMS m/z: calcd for $C_{13}H_{10}N_3OS$ $[M + H]^+$, 256.0545; found, 256.0544. IR (KBr): 3094, 2151, 1644, 1611, 1515, 1432 cm^{-1}.

*2-(p-Tolyl)-3-(thiocyanato)benzo[d]imidazo[2,1-b]thiazole (**5a**).* Eluent petroleum ether/ethyl acetate (10:1). White solid, 101 mg, 79% yield, mp 126−128 °C (5:1 petroleum ether/ethyl acetate, R_f = 0.5). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.48 (d, 1H, J = 8.0 Hz), 7.90 (d, 2H, J = 8.0 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.58 (t, 1H, J = 8.0 Hz), 7.45 (t, 1H, J = 4.0 Hz), 7.32 (d, 2H, J = 8.0 Hz), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.7, 152.6, 139.4, 132.9, 130.2, 129.4, 128.3, 126.9, 125.6, 124.5, 113.8, 112.6, 108.9, 97.6, 21.4. HRMS m/z: calcd for $C_{17}H_{12}N_3S_2$ $[M + H]^+$, 322.0473; found, 322.0479. IR (KBr): 2963, 2157, 1478, 1408 cm^{-1}.

*2-(4-Methoxyphenyl)-3-(thiocyanato)benzo[d]imidazo[2,1-b]thiazole (**5b**).* Eluent petroleum ether/ethyl acetate (10:1). White solid, 97 mg, 72% yield, 186−188 °C (5:1 petroleum ether/ethyl acetate, R_f = 0.4). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.50 (d, 1H, J = 8.0 Hz), 7.97 (d, 2H, J = 8.0 Hz), 7.79 (d, 1H, J = 8.0 Hz), 7.60 (t, 1H, J = 8.0 Hz), 7.47 (t, 1H, J = 4.0 Hz), 7.06 (d, 2H, J = 8.0 Hz), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.5, 155.6, 152.6, 132.9, 130.1, 129.8, 126.9, 125.6, 124.5, 124.3, 114.2, 113.8, 109.0, 97.0, 55.4. HRMS m/z: calcd for $C_{17}H_{12}N_3OS_2$ $[M + H]^+$, 338.0422; found, 338.0426. IR (KBr): 2934, 2159, 1608, 1574, 1526, 1453 cm^{-1}.

*2-(4-Bromophenyl)-3-(thiocyanato)benzo[d]imidazo[2,1-b]thiazole (**5c**).* Eluent petroleum ether/ethyl acetate (10:1). White solid, 115 mg, 75% yield, mp 173−175 °C (5:1 petroleum ether/ethyl acetate, R_f = 0.6). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.50 (d, 1H, J = 8.0 Hz), 7.89 (d, 2H, J = 8.0 Hz), 7.81 (d, 1H, J = 8.0 Hz), 7.66 (d, 2H, J = 8.0 Hz), 7.60 (t, 1H, J = 8.0 Hz), 7.49 (t, 1H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.3, 152.9, 132.6, 132.0, 130.7, 130.2, 129.8, 127.1, 126.0, 124.6, 123.8, 113.9, 108.4, 98.2. HRMS m/z: calcd for $C_{16}H_9BrN_3S_2$ $[M + H]^+$, 385.9421; found, 385.9419 and 387.9400. IR (KBr): 2962, 2158, 1478, 1396 cm^{-1}.

*2-(3-Chlorophenyl)-3-(thiocyanato)benzo[d]imidazo[2,1-b]thiazole (**5d**).* Eluent petroleum ether/ethyl acetate (10:1). White solid, 105 mg, 77% yield, mp 176−177 °C (5:1 petroleum ether/ethyl acetate, R_f = 0.4). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.52 (d, 1H, J = 8.0 Hz), 8.01 (s, 1H), 7.92 (d, 1H, J = 8.0 Hz), 7.81 (d, 1H, J = 8.0 Hz), 7.61 (t, 1H, J = 8.0 Hz), 7.52−7.43 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.8, 152.9, 134.8, 133.5, 132.8, 130.3, 130.0, 129.3, 128.4, 127.1, 126.3, 126.0, 124.6, 114.0, 108.4, 98.6. HRMS m/z: calcd for $C_{16}H_9ClN_3S_2$ $[M + H]^+$, 341.9926; found, 341.9921. IR (KBr): 3067, 2157, 1569, 1479, 1465, 1409 cm^{-1}.

*3-Thiocyanato-1H-indole (**5e**).*[13a] Eluent petroleum ether/ethyl acetate (10:1). White solid, 57 mg, 82% yield, mp 72−74. (3:1 petroleum ether/ethyl acetate, R_f = 0.2). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.81 (br, 1H), 7.83 (dd, 1H, J = 8.0 Hz), 7.46 (d, 1H, J = 8.0 Hz), 7.45−7.43 (m, 1H), 7.35−7.32 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.1, 131.1, 127.7, 123.9, 121.9, 118.7, 112.2, 112.1, 92.0. HRMS m/z: calcd for $C_9H_7N_2S$ $[M + H]^+$, 175.0330; found, 175.0321.

*N,N-Dimethyl-4-thiocyanatoaniline (**5f**).*[29] Eluent petroleum ether/ethyl acetate (10:1). White solid, 62 mg, 87% yield, mp 73−75 °C (3:1 petroleum ether/ethyl acetate, R_f = 0.5). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.44 (d, 2H, J = 8.0 Hz), 6.70 (d, 2H, J = 4.0 Hz), 3.01 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.7, 134.4, 113.2, 112.6, 106.5, 40.1. HRMS m/z: calcd for $C_9H_{11}N_2S$ $[M + H]^+$, 179.0643; found, 179.0631.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01637.

CIF file of **3n** (CIF)

^1H and ^{13}C NMR spectra for all compounds and ORTEP structures and spectroscopic data of compound **3n** (PDF)

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Notes

The authors declare no competing financial interest.

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