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Thiocyanation

Highly Efficient and Practical Thiocyanation of Imidazopyridines Using an *N*-Chlorosuccinimide/NaSCN Combination

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Abstract: A direct C–H thiocyanation of imidazo[1,2-*a*]pyridines, and a practical sequential one-pot condensation/C–H thiocyanation process, using a combination of *N*-chlorosuccinimide/NaSCN for the synthesis of 3-thiocyanatoimidazo[1,2-*a*]pyridines have been developed. The reactions are environmentally friendly, and easy to carry out. They use readily available starting materials and mild reaction conditions, show a wide functional group tolerance, and give good to excellent yields.

Introduction

Imidazo[1,2-*a*]pyridines are significant members of the family of fused polyheterocycles. The great importance of these compounds can be seen by their occurrence and application in several fields, including materials science, natural products chemistry, and medicinal chemistry.[1] Several imidazopyridines have recently been reported to have remarkable therapeutic value, showing antifungal, antibacterial, antiviral, antiparasitic, antiinflammatory, antiulcer, and antiprotozoal properties.[2] Consequently, some products with imidazo[1,2-*a*]pyridine skeletons have progressed to the market, including alpidem (anxiolytic),[3a] saripidem (anxiolytic),[3b] zolpidem (insomnia),[3a] zolimidine (antiulcer),[2a] olprinone (cardiotonic),[3c] minodronic acid (antiosteoporosis),[3d] and many others. In addition, considerable attention has recently been given to some unusual proton-transfer reagents and N-heterocyclic carbenes, which are synthesized based on imidazo[1,2-*a*]pyridines.[4]

The biological profile of privileged imidazo[1,2-*a*]pyridines has been shown to be mainly dependent on the nature of the substituents at the C-2 and C-3 positions; the introduction of sulfur-containing groups onto the N-heterocyclic rings may also impart significant biological properties. As a result, extensive effort has been put into the discovery of efficient and practical approaches for the synthesis and functionalization of imidazopyridine cores from readily available starting materials.[5] Organic thiocyanates are an important class of sulfur-containing organic compounds. They occur in biologically important compounds such as the anticancer natural products formed by deglycosylation of glucosinolates derived from cruciferous vegetables,[6] but they can also be used as masked mercapto compounds, or as versatile precursors for the construction of new sulfur-containing derivatives, such as thiazolidines or cyclic thioureas.[7] The literature on thiocyanate-substituted arenes and heterocycles such as indoles and pyrroles is ever growing,[8] however, examples of imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyrimidines incorporating a thiocyanate group remain comparatively infrequent. In 2015, Hajra et al. developed the first example of a direct and environmentally benign system for the thiocyanation of imidazopyridines using eosin Y as a photoredox catalyst under ambient conditions.[9] Subsequently, Wang's group independently disclosed a catalyst-free highly regioselective C-3 thiocyanation of imidazopyridines in the presence of $K_2S_2O_8$, proceeding by a radical pathway.[10]

Due to the importance of step, atom, and redox economy in industrial and green chemistry, and especially due to the low threshold residual tolerance in the synthesis of pharmaceuticals,[11] the exploration of efficient, practical, and highly selective metal-free methods for the direct functionalization of C–H bonds has been the subject of intense research for decades.[12] One-pot sequential transformations, which represent a valuable way of introducing complexity and diversity into industrially and medically important compounds while avoiding the need for the isolation of intermediates and for purification steps, have risen to prominence.[11d,13] In connection with our interest in accessing biologically active molecules containing C–X through cheap, green, and sustainable methods,[14] in this paper we report a generally applicable method for the construction of diversely SCN-substituted imidazopyridines. The method has a broad substrate scope, gives excellent yields, and proceeds under simple reaction conditions. Notably, the use of EtOH as a green and efficient reaction solvent to synthesize and functionalize the imidazopyridine moiety in a one-pot condensation and direct C–H functionalization process allowed us to dispense with the use of metal salts, the preformation of imidazo[1,2-*a*]pyridines, and the exclusion of air and moisture.

Results and Discussion

We began our investigation using the reaction of 2-phenylimidazo[1,2-*a*]pyridine (**3a**) and NaSCN as a model system. We

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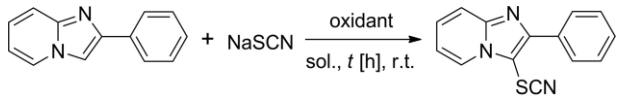
Table 1. Optimization of reaction conditions.[a]



3aa **4aa**

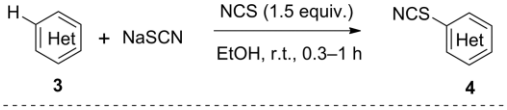
Entry	Oxidant (equiv.)	Solvent	*t* [h]	Yield[b] [%]
1	I_2 (2.0)	MeCN	6	31
2	NBS (1.5)	MeCN	0.5	88
3	NCS (1.5)	MeCN	0.5	89
4	NCS (1.5)	Et_2O	6	trace
5	NCS (1.5)	CH_2Cl_2	6	61
6	NCS (1.5)	DMSO	0.5	83
7	NCS (1.5)	DMF	0.5	84
8	NCS (1.5)	MeOH	0.5	90
9	NCS (1.5)	EtOH	0.5	93
10	NCS (1.5)	EtOAc	0.5	93
11[c]	NCS (1.5)	EtOH	0.5	92
12[d]	NCS (1.5)	EtOH	0.5	83
13	NCS (1.2)	EtOH	2	67
14	–	EtOH	6	n.r.

[a] Reaction conditions: imidazopyridine **3a** (0.50 mmol), NaSCN (1.0 mmol), oxidant, solvent (2.0 mL), open to air. [b] Isolated yield; n.r.: no reaction. [c] NH_4SCN (1.0 mmol) was used. [d] KSCN (1.0 mmol) was used.

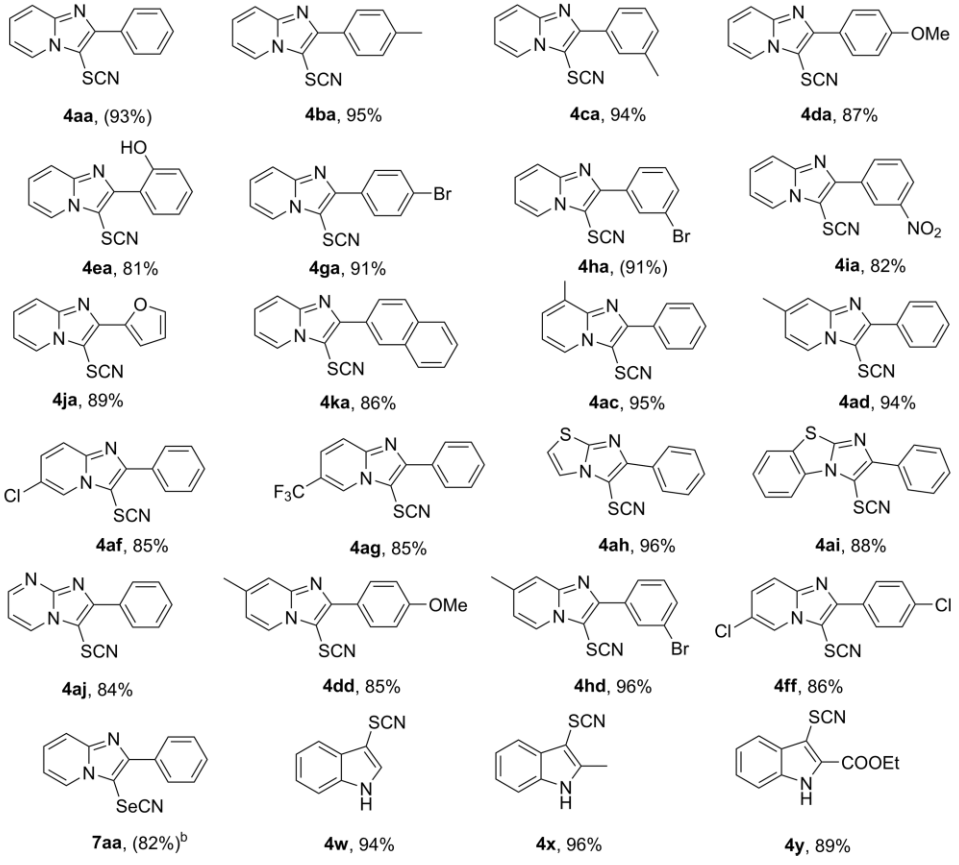
tested various oxidants and solvents to optimize the reaction conditions. As summarized in Table 1, in the preliminary investigation we screened various oxidants, and *N*-chlorosuccinimide (NCS) showed the best performance, giving the corresponding product (i.e., **4aa**) in 89 % yield at room temperature under air (Table 1, entry 3). Encouraged by the initial results, we tested other common solvents, including Et_2O, CH_2Cl_2, DMSO, DMF, MeOH, EtOH, and EtOAc (Table 1, entries 4–10). The best results (93 %) were obtained using EtOH and EtOAc (Table 1, entries 9 and 10). When NaSCN was replaced by other readily available thiocyanates, such as NH_4SCN or KSCN, a slight decrease in the product yield was observed (Table 1, entries 11 and 12). The influence on the reaction outcome of the amount of oxidant was then assessed. A decrease in yield was observed when the amount of oxidant decreased, and notably, none of the target product was formed in the absence of NCS (Table 1, entries 13 and 14).

Having established optimal reaction conditions, the generality of the transformation was investigated. As outlined in Table 2, imidazo[1,2-*a*]pyridine derivatives bearing a variety of functional groups on any of the aryl rings tolerated the thiocyanation reaction with NaSCN, and structurally diverse prod-

Table 2. Direct thiocyanation of imidazopyridines and indoles.[a]



3 **4**

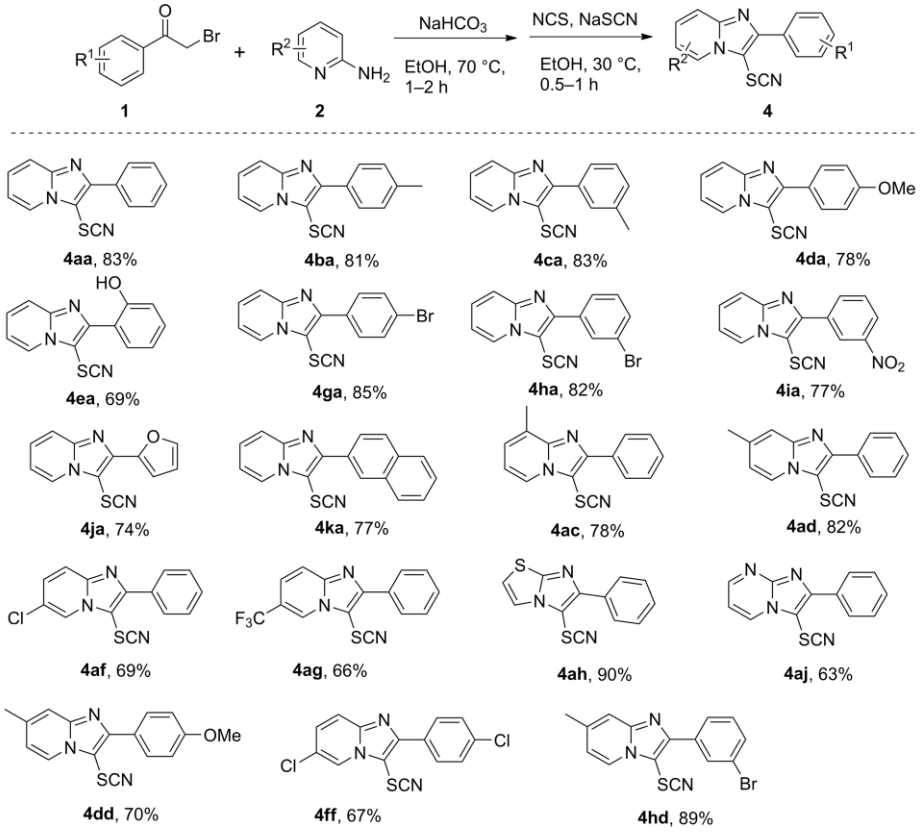


[a] Reaction conditions: imidazopyridine **3** (0.5 mmol), NaSCN (1.0 mmol), NCS (0.75 mmol), EtOH (2 mL) under air. Isolated yield. [b] KSeCN was used.

ucts were formed smoothly in high yields with extremely high regioselectivity. Satisfyingly, imidazopyridines bearing functional groups such as –OH, –Cl, –Br, $–NO_2$, and $–CF_3$ were well tolerated under the established reaction conditions and gave the desired products in good yields (Table 2, **4ea**, **4ga**, **4ia**, **4ag**, and **4ff**). In addition, steric and electronic effects were also assessed, and turned out to be insignificant (Table 2, **4ea**, **4ia**, and **4ag**). It is worth noting that the thiocyanation reaction of 2-furyl and naphthyl-substituted imidazopyridines successfully took place under these conditions (Table 2, **4ja** and **4ka**). We were delighted to find that gratifying yields were also obtained from imidazoheterocycles like imidazopyrimidine, imidazo[2,1-*b*]thiazole, and benzo[*d*] imidazo[2,1-*b*]thiazole (Table 2, **4ah**, **4ai**, and **4aj**). Moreover, imidazopyridine (**3aa**) reacted effectively with KSeCN to give the corresponding selenocyanated product in 82 % yield (Table 2, **7aa**). The extension of our protocol to the thiocyanation of indoles was also explored. Gratifyingly, indoles with functional groups like a methyl group and an ester group also gave the thiocyanated products in excellent yields of 89–96 % (Table 2, **4w**–**4y**).

One-pot reaction sequences offer economic and environmental benefits through eliminating the need for time-consuming intermediate work-ups, and decreasing the use of organic solvents for extraction and purification, as well as energy for evaporation. They generally have increased atom efficiency and potentially lower environmental impact.[11d,13] However, to the best of our knowledge, there is no literature precedent for the preparation of 3-thiocyanatoimidazopyridines by one-pot sequences using commercially available α-bromo ketones and 2-aminopyridines as starting materials. With this in mind, our optimized reaction conditions were further validated by using them for a sequential one-pot condensation and C–H thiocyanation procedure. 2-Pphenyl-3-thiocyanato imidazopyridine (**4aa**) was obtained by the one-pot reaction in 83 % yield (Table 3). The first step involves the formation of the 2-phenylimidazo[1,2-*a*]pyridine core by condensation of 2-aminopyridine and α-bromoacetophenone in the presence of $NaHCO_3$; this is then followed by C–H thiocyanation at C-3. In an attempt to expand the scope of the method, the one-pot procedure was applied to different α-bromo ketones and 2-aminopyridines, and the results are shown in Table 3. Strikingly, the reaction tolerated a variety of functional groups such as methyl, alkoxy, hydroxy, halogen, trifluoromethyl, and nitryl, and the expected products were formed exclusively in moderate to high yields (Table 3, **4ba**–**4ia** and **4ag**). It is worth noting that 2-furyl and naphthyl-substituted imidazopyridines as well as imidazoheterocycles were compatible with our reaction conditions, and gave the relevant derivatives in good yields (Table 3, **4ja**, **4ka**,

Table 3. Thiocyanation of imidazopyridines in a sequential one-pot process.[a]



[a] Reaction conditions: α-bromo ketones **1** (0.55 mmol), 2-aminopyridines **2** (0.5 mmol), $NaHCO_3$ (0.6 mmol), NaSCN (1.0 mmol), NCS (0.75 mmol), EtOH (4 mL) under air. Isolated yield.

4ah, and **4aj**). By comparing with previously reported results, it can clearly be seen that the new method significantly decreased the reaction time and eliminated work-up procedures for intermediates. But above all, it also successfully eliminated the use of detrimental solvents, and was environmentally friendly, with a high atom economy.

Control experiments were carried out to get a better insight into the probable mechanism, as shown in Figure 1. Firstly, 3-chloro-2-phenylimidazo[1,2-*a*]pyridine (**5aa**), which was prepared from NCS and **3aa**, was treated with NaSCN (2 equiv.) in EtOH at room temperature for a period of 8 h to determine whether **5aa** could be transformed into the final product (i.e., **4aa**) by nucleophilic substitution (Figure 1, a). Notably, although the thiocyanation reaction did occur in the presence of NaSCN, **4aa** was obtained in only 17 % yield, which indicates that the reaction is less likely to proceed by nucleophilic substitution. In a further experiment, preprepared *N*-thiocyanatosuccinimide[15] and **3aa** were mixed in EtOH at room temperature, and this immediately led to the formation of **4aa** in 96 % yield. This strongly suggests that direct C–H thiocyanation is completely predominant over nucleophilic substitution in the reaction (Figure 1, b).

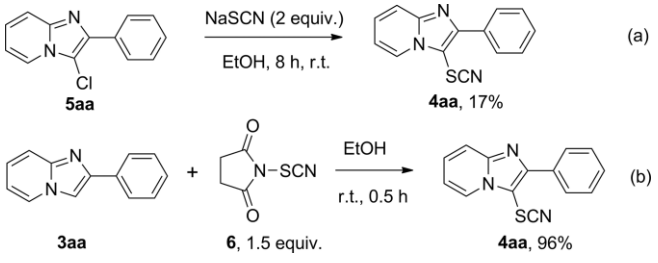


Figure 1. Control experiments.

On the basis of the above experimental results, along with previously published examples,[15] a plausible reaction mechanism for the thiocyanation of imidazo[1,2-*a*]pyridines by the *N*-chlorosuccinimide/NaSCN combination is shown in Figure 2. In the predominant mechanism, *N*-thiocyanatosuccinimide is formed by the reaction of NCS with NaSCN. This is followed by regioselective electrophilic attack on the C-3 position of **3aa** to generate imidazolenium intermediate **A**. Loss of a proton from **A** gives the desired product (i.e., **4aa**) and succinimide. Alternatively, but less likely, electrophilic substitution of **3aa** with NCS results in the formation of **5aa**, and then nucleophilic substitution of **5aa** with NaSCN would deliver product **4aa**. Further investigations of the detailed mechanism are in progress in our laboratory.

To demonstrate the practical applicability of the one-pot process on a larger scale, a gram-scale synthesis of **4aa** was attempted using this protocol. To our delight, the reaction proceeded smoothly, and the expected product (i.e., **4aa**) was isolated in 85 % yield (Figure 3, a). Furthermore, we also investigated the selenocyanation of imidazopyridines in one pot (Figure 3, b). Selenocyanated product **7aa** was prepared in good yield under our developed reaction conditions.

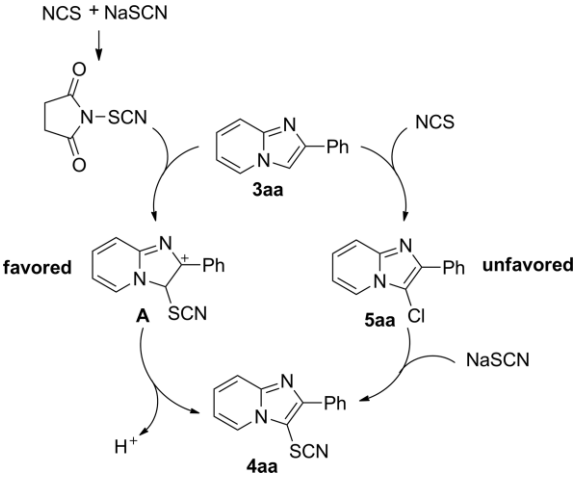


Figure 2. Proposed mechanism.

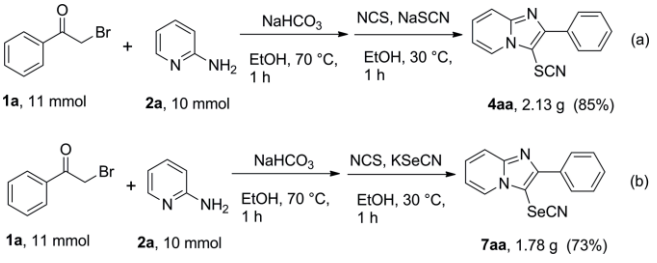


Figure 3. Gram-scale reactions.

Conclusions

In summary, a simple, green, and versatile oxidative system for the selective thiocyanation of imidazopyridines to give the corresponding thiocyanated product has been developed. The reaction takes place in the presence of NCS using NaSCN as thiocyanato-transfer reagent in EtOH under mild conditions. Compared with reported procedures, this method is environmentally friendly and practical, and has the advantages of short reaction times and high yields. Moreover, the use of EtOH as an efficient solvent for the synthesis and functionalization of the imidazo[1,2-*a*]pyridine moiety in a one-pot sequential condensation/C–H functionalization process has been shown to be reliable. Both transformations proceeded in good yields, and tolerated a wide range of functional groups. Last but not least, this study paves the way for the synthesis of thiocyanated and selenocyanated imidazopyridines and other imidazo-heterocycles through the addition of NCS in EtOH. The reaction should gain much attention in multidisciplinary fields for the preparation of potentially biologically active imidazopyridine derivatives.

Experimental Section

General Remarks: Unless otherwise noted, all reagents and chemicals (AR grade) were purchased from commercial suppliers and used without further purification. Petroleum ether (PE) refers to the fraction boiling in the 60–90 °C range. Unless otherwise noted, all reactions were carried out under air in oven-dried glassware with magnetic stirring. The progress of the reactions was monitored by

TLC (silica gel, Polygram SILG/UV 254 plates). Column chromatography was carried out on silica gel (100–200 mesh). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance II 400 MHz instrument, and ^{19}F NMR spectra were recorded with a Bruker Avance III 471 MHz instrument. $CDCl_3$ and [D_6]DMSO were used for NMR spectroscopy, and tetramethylsilane was used as an internal reference. Data for ^{1}H NMR spectra are recorded as follows: chemical shift (δ, ppm), multiplicity (s singlet, d doublet, t triplet, m multiplet or unresolved, br. broad, dd doublet of doublets), coupling constants in Hz, integration. Data for ^{13}C and ^{19}F NMR spectra are reported in terms of chemical shift (δ, ppm). HRMS (ESI) measurements were made with an HRMS/MS instrument (LTQ Orbitrap XL TM).

General Procedure for the Direct C–H Thiocyanation of Imidazopyridines: A mixture of imidazopyridine **3** (0.5 mmol) and NaSCN (1.0 mmol) was dissolved in EtOH (2.0 mL) at room temperature in an oven-dried flask, then NCS (0.75 mmol) was added immediately. The reaction proceeded under an air atmosphere for 0.5–1.0 h until TLC indicated the complete consumption of starting material. The reaction mixture was concentrated under vacuum, and the crude product was purified by column chromatography using petroleum ether/ethyl acetate as eluent to give the product (i.e., **4**).

General Procedure for the Thiocyanation of Imidazopyridines in One-pot Process: 2-Aminopyridine (0.5 mmol), α-bromo ketone (0.55 mmol), and $NaHCO_3$ (0.6 mmol) were dissolved in EtOH (2.0 mL). The resulting mixture was stirred at 70 °C under air for 1–2 h until TLC indicated the complete consumption of starting material. When the reaction was complete, the mixture was cooled to room temperature.

NaSCN (1.0 mmol) and NCS (0.75 mmol) were added immediately, and the reaction mixture was stirred under an air atmosphere for 0.5–1.0 h until TLC indicated the complete consumption of starting material. The resulting mixture was concentrated under vacuum, and the crude product was purified by column chromatography using petroleum ether/ethyl acetate as eluent to give the product (i.e., **4**).

2-Phenyl-3-thiocyanatoimidazo[1,2-*a*]pyridine (4aa):[9] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, J = 4.4 Hz, 1 H), 8.06 (d, J = 8.0 Hz, 2 H), 7.74 (d, J = 8.8 Hz, 1 H), 7.54–7.44 (m, 4 H), 7.09 (d, J = 5.2 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.0, 147.9, 132.0, 129.5, 128.8, 128.1, 124.4, 118.2, 114.4, 108.2, 94.7 ppm.

3-Thiocyanato-2-(*p*-tolyl)imidazo[1,2-*a*]pyridine (4ba):[9] Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, J = 4.8 Hz, 1 H), 7.95 (d, J = 7.6 Hz, 2 H), 7.73 (d, J = 7.2 Hz, 1 H), 7.42 (s, 1 H), 7.32 (d, J = 7.2 Hz, 2 H), 7.07 (s, 1 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.0, 147.8, 139.6, 129.5, 129.0, 128.7, 128.0, 124.4, 118.1, 114.3, 108.3, 94.4, 21.5 ppm.

3-Thiocyanato-2-(*m*-tolyl)imidazo[1,2-*a*]pyridine (4ca): White solid, m.p. 170.5–171.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, J = 6.8 Hz, 1 H), 7.87–7.84 (m, 2 H), 7.74 (d, J = 9.2 Hz, 1 H), 7.46–7.39 (m, 2 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.11–7.08 (m, 1 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.2, 147.9, 138.6, 131.8, 130.3, 129.4, 128.6, 128.0, 125.9, 124.4, 118.2, 114.4, 108.2, 94.7, 21.6 ppm. HRMS (ESI): calcd. for $C_{15}H_{12}N_3S$ [M + H]$^+$ 266.0746; found 266.0750.

2-(4-Methoxyphenyl)-3-thiocyanatoimidazo[1,2-*a*]pyridine (4da):[10] Brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, J = 6.4 Hz, 1 H), 8.03 (d, J = 8.8 Hz, 2 H), 7.74 (d, J = 8.8 Hz, 1 H), 7.47–7.43 (m, 1 H), 7.12–7.04 (m, 3 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.7, 152.9, 147.9, 130.2, 127.9, 124.5, 124.3, 118.0, 114.2, 108.2, 93.7, 55.4 ppm.

3-Thiocyanato-1*H*-indole (4w):[10] White solid (94 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (br. s, 1 H), 7.74–7.72 (m, 1 H), 7.31–7.29 (m, 2 H), 7.24–7.20 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.2, 131.5, 127.7, 123.8, 121.9, 118.5, 112.9, 112.5, 91.2 ppm.

2-Methyl-3-thiocyanato-1*H*-indole (4x):[16] Brown solid (96 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (br. s, 1 H), 7.67 (d, J = 6.8 Hz, 1 H), 7.31–7.29 (m, 1 H), 7.25–7.20 (m, 2 H), 2.51 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.3, 135.2, 128.7, 123.0, 121.5, 118.0, 112.5, 111.4, 88.5, 12.0 ppm.

Ethyl 3-Thiocyanato-1*H*-indole-2-carboxylate (4y):[16] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.89 (br. s, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.46 (d, J = 8.0 Hz, 1 H), 7.42–7.39 (m, 1 H), 7.32–7.29 (m, 1 H), 4.53–4.48 (m, 2 H), 1.51–1.47 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.6, 135.6, 128.6, 128.3, 126.8, 122.7, 120.5, 112.8, 110.8, 98.4, 62.4, 14.3 ppm.

2-(3-Thiocyanatoimidazo[1,2-*a*]pyridin-2-yl)phenol (4ea):[9] Pale yellow solid. ^{1}H NMR (400 MHz, DMSO): δ = 11.56 (s, 1 H), 8.78 (d, J = 6.0 Hz, 1 H), 8.07 (d, J = 7.6 Hz, 1 H), 7.90 (d, J = 8.8 Hz, 1 H), 7.68–7.64 (m, 1 H), 7.37 (d, J = 7.2 Hz, 2 H), 7.08–7.03 (m, 2 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 157.0, 149.3, 146.1, 131.4, 129.6, 129.2, 125.6, 119.6, 117.4, 115.4, 110.3, 98.0 ppm.

2-(4-Bromophenyl)-3-thiocyanatoimidazo[1,2-*a*]pyridine (4ga): Pale yellow solid, m.p. 175.5–177.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, J = 6.4 Hz, 1 H), 7.94 (d, J = 8.0 Hz, 2 H), 7.74 (d, J = 8.8 Hz, 1 H), 7.64 (d, J = 8.4 Hz, 2 H), 7.49–7.45 (m, 1 H), 7.15–7.12 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.7, 147.9, 132.0, 130.9, 130.2, 128.3, 124.4, 124.0, 118.3, 114.7, 107.9, 94.8 ppm. HRMS (ESI): calcd. for $C_{14}H_9BrN_3S$ [M + H]$^+$ 331.9680; found 331.9677.

2-(3-Bromophenyl)-3-thiocyanatoimidazo[1,2-*a*]pyridine (4ha): White solid, m.p. 159.7–160.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, J = 6.8 Hz, 1 H), 8.22 (s, 1 H), 8.00 (d, J = 7.6 Hz, 1 H), 7.74 (d, J = 8.8 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.49–7.45 (m, 1 H), 7.40–7.36 (m, 1 H), 7.14–7.11 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.2, 147.9, 134.0, 132.4, 131.6, 130.3, 128.3, 127.2, 124.4, 122.9, 118.3, 114.7, 107.8, 95.2 ppm. HRMS (ESI): calcd. for $C_{14}H_9BrN_3S$ [M + H]$^+$ 329.9695; found 329.9700.

2-(3-Nitrophenyl)-3-thiocyanatoimidazo[1,2-*a*]pyridine (4ia):[9] Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.99 (s, 1 H), 8.50–8.45 (m, 2 H), 8.33–8.32 (m, 1 H), 7.81 (d, J = 7.2 Hz, 1 H), 7.76–7.72 (m, 1 H), 7.57–7.53 (m, 1 H), 7.29–7.21 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.3, 148.6, 148.1, 134.3, 133.8, 129.8, 128.6, 124.5, 124.0, 123.6, 118.6, 115.1, 107.3, 95.7 ppm.

2-(Furan-2-yl)-3-thiocyanatoimidazo[1,2-*a*]pyridine (4ja):[10] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, J = 6.4 Hz, 1 H), 7.76 (d, J = 8.8 Hz, 1 H), 7.66 (s, 1 H), 7.47–7.43 (t, 1 H), 7.23 (s, 1 H), 7.12–7.09 (t, 1 H), 6.60 (s, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.1, 147.0, 144.2, 144.1, 128.3, 124.2, 118.1, 114.5, 111.9, 111.5, 107.8, 93.5 ppm.

2-(Naphthalen-2-yl)-3-thiocyanatoimidazo[1,2-*a*]pyridine (4ka): Yellow solid, m.p. 138.6–141.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (s, 1 H), 8.36 (d, J = 6.4 Hz, 1 H), 8.16 (d, J = 8.4 Hz, 1 H), 7.95–7.93 (m, 2 H), 7.84 (d, J = 4.8 Hz, 1 H), 7.73 (d, J = 8.8 Hz, 1 H), 7.52–7.50 (m, 2 H), 7.41–7.38 (m, 1 H), 7.05–7.02 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.8, 148.0, 133.6, 133.2, 129.3, 128.7, 128.6, 128.4, 128.1, 127.8, 127.0, 126.6, 125.8, 124.4, 118.2, 114.4, 108.2, 94.9 ppm. HRMS (ESI): calcd. for $C_{14}H_9BrN_3S$ [M + H]$^+$ 302.0746; found 302.0753.

8-Methyl-2-phenyl-3-thiocyanatoimidazo[1,2-*a*]pyridine (4ac):[9] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J =

4.4 Hz, 1 H), 8.05 (d, *J* = 6.0 Hz, 2 H), 7.51–7.44 (m, 3 H), 7.19 (s, 1 H), 6.97 (m, 1 H), 2.66 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.5, 148.2, 132.3, 129.3, 128.9, 128.7, 128.5, 126.8, 122.1, 114.4, 108.4, 94.8, 16.8 ppm.

7-Methyl-2-phenyl-3-thiocyanatoimidazo[1,2-*a*]pyridine (4ad):[9] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 7.2 Hz, 1 H), 8.04 (d, *J* = 7.2 Hz, 2 H), 7.53–7.43 (m, 4 H), 7.19 (s, 1 H), 6.92 (d, *J* = 6.8 Hz, 1 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.9, 148.3, 139.5, 132.1, 129.3, 128.7, 123.5, 116.9, 116.7, 108.5, 93.7, 21.5 ppm.

6-Chloro-2-phenyl-3-thiocyanatoimidazo[1,2-*a*]pyridine (3af):[10] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1 H), 8.02 (d, *J* = 6.8 Hz, 2 H), 7.65 (d, *J* = 8.8 Hz, 1 H), 7.51–7.38 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.5, 146.3, 131.5, 129.7, 129.5, 128.8, 128.7, 122.9, 122.5, 118.6, 107.8, 95.7 ppm.

2-Phenyl-3-thiocyanato-6-(trifluoromethyl)imidazo[1,2-*a*]pyridine (4ag): White solid, m.p. 172.3–174.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (s, 1 H), 8.04 (d, *J* = 6.8 Hz, 2 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.59 (d, *J* = 8.8 Hz, 1 H), 7.50 (d, *J* = 7.2 Hz, 3 H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.0 (s, 3 F) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.5, 147.8, 131.2, 130.0, 128.9, 128.8, 120.4 (q, *J* = 273.0 Hz), 124.0, 123.3 (q, *J* = 5.9 Hz), 119.0, 118.9 (q, *J* = 34.9 Hz), 118.7, 107.4, 97.1 ppm. HRMS (ESI): calcd. for $C_{15}H_8F_3N_3S$ [M + H]$^+$ 320.0464; found 320.0469.

6-Phenyl-5-thiocyanatoimidazo[2,1-*b*]thiazole (4ah):[9] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 2 H), 7.64–7.06 (m, 5 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.4, 153.3, 132.1, 129.2, 128.8, 128.1, 117.8, 114.8, 108.4, 95.8 ppm.

2-Phenyl-3-thiocyanatobenzo[*d*]imidazo[2,1-*b*]thiazole (4ai):[10] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.55–7.42 (m, 2 H), 7.02 (d, *J* = 8.0 Hz, 2 H), 3.91 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.5, 155.5, 152.6, 144.1, 132.9, 130.1, 129.7, 126.9, 125.6, 124.5, 114.2, 113.7, 109.0, 96.9, 55.4 ppm.

2-Phenyl-3-thiocyanatoimidazo[1,2-*a*]pyrimidine (4aj): Pale yellow solid, m.p. 198.2–201.3 °C. ^{1}H NMR (400 MHz, DMSO): δ = 9.23–9.21 (m, 1 H), 8.84–8.82 (m, 1 H), 8.16 (d, *J* = 7.2 Hz, 2 H), 7.64–7.60 (m, 2 H), 7.56–7.53 (m, 1 H), 7.43–7.40 (m, 1 H) ppm. ^{13}C NMR (101 MHz, DMSO): δ = 153.9, 151.8, 150.1, 134.7, 132.3, 130.0, 129.3, 128.9, 111.3, 110.6, 97.5 ppm. HRMS (ESI): calcd. for $C_{13}H_8N_4S$ [M + H]$^+$ 253.0542; found 253.0546.

2-(4-Methoxyphenyl)-7-methyl-3-thiocyanatoimidazo[1,2-*a*]pyridine (4dd):[10] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 6.8 Hz, 1 H), 8.01 (d, *J* = 8.4 Hz, 2 H), 7.47 (s, 1 H), 7.03 (d, *J* = 8.4 Hz, 2 H), 6.90 (d, *J* = 6.8 Hz, 1 H), 3.87 (s, 3 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.5, 152.8, 148.2, 139.5, 130.1, 124.5, 123.5, 116.7, 116.5, 114.1, 108.5, 92.8, 55.4, 21.5 ppm.

6-Chloro-2-(4-chlorophenyl)-3-thiocyanatoimidazo[1,2-*a*]pyridine (4ff):[10] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (s, 1 H), 7.99 (d, *J* = 8.4 Hz, 2 H), 7.68 (d, *J* = 9.6 Hz, 1 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 7.45–7.43 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.4, 146.3, 135.9, 130.0, 129.9, 129.7, 129.1, 123.2, 122.4, 118.7, 107.4, 95.7 ppm.

2-(3-Bromophenyl)-7-methyl-3-thiocyanatoimidazo[1,2-*a*]pyridine (4hd):[10] Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 7.2 Hz, 1 H), 8.19 (s, 1 H), 7.98 (d, *J* = 7.6 Hz, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.47 (s, 1 H), 7.38–7.34 (m, 1 H), 6.94 (d, *J* = 6.8 Hz, 1 H), 2.47 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.1, 148.2, 139.8, 134.1, 132.2, 131.5, 130.2, 127.1, 123.5, 122.9, 117.3, 116.8, 108.0, 94.2, 21.5 ppm.

2-Phenyl-3-selenocyanatoimidazo[1,2-*a*]pyridine (7aa):[9] Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 6.8 Hz, 1 H), 7.97–7.95 (m, 2 H), 7.71 (d, *J* = 8.8 Hz, 1 H), 7.52–7.48 (m, 2 H), 7.46–7.40 (m, 2 H), 7.09–7.05 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.5, 148.5, 132.5, 129.3, 129.1, 128.6, 127.8, 125.5, 118.1, 114.2, 99.0, 93.6 ppm.

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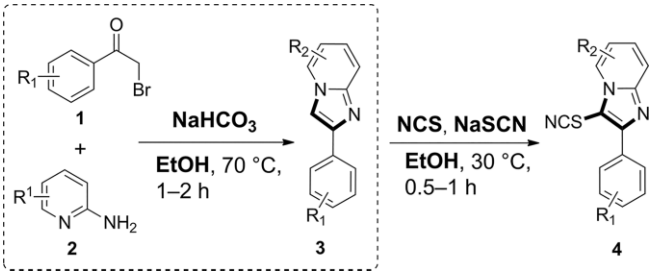

A direct C–H thiocyanation of imidazopyridines, and a practical sequential one-pot condensation/C–H thiocyanation process, using a combination of NCS/NaSCN have been developed. The reactions are environmentally friendly, and easy to carry out. They use readily available starting materials and mild reaction conditions, show a wide functional-group tolerance, and give good to excellent yields.

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