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Hypervalent Iodine Mediated Efficient Solvent-Free Regioselective Halogenation and Thiocyanation of Fused *N*-Heterocycles

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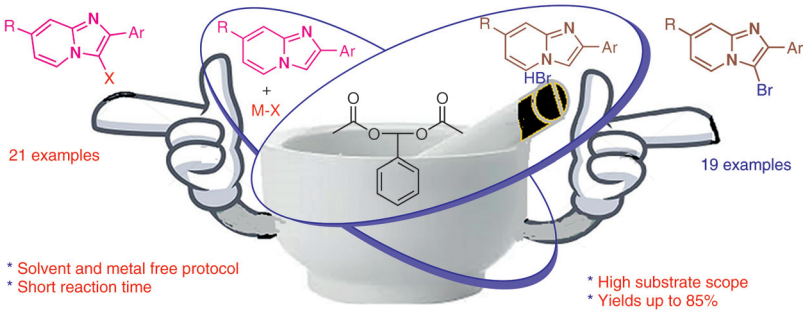

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Abstract A facile, rapid, metal-free regioselective halogenation and thiocyanation of imidazo[1,2-*a*]pyridine/pyrimidine heterocycles has been achieved under solvent-free reaction conditions. Halogenations and thiocyanation of the heterocycles could be accomplished by simple grinding of reactants and hypervalent iodine reagents with the corresponding alkali metal or ammonium salts. The method has been extrapolated to a cleaner synthesis of brominated imidazo[1,2-*a*]pyridine/pyrimidine derivatives, starting from the corresponding heterocyclic amines and substituted α-bromoketones, utilising HBr generated in situ as the source of bromine.

Key words solvent free, grinding, regioselective substitution, in situ bromination, atom economy

Fused *N*-heterocycles are an important class of molecules that exhibit not only unique bioactivities[1] but also interesting chemical properties that lead to broad applications in synthetic[2] and material chemistry.[3] Consequently, the synthesis of fused *N*-heterocycles has received much attention. The utility and activity profile of these molecules, especially imidazo[1,2-*a*]pyridine/pyrimidine has been shown to be greatly influenced by the nature of substitutions on the C-2 and C-3 positions (Figure 1). In these heterocycles the C-3 position is normally an electron-rich centre that is susceptible to electrophilic substitution.[4] Substitutions at C-3 carbon of these key substrates via metal-catalyzed oxidative C–H activation,[5] as well as a few organocatalyst- and organophotocatalyst-mediated[6] oxidative reactions have also been attempted.

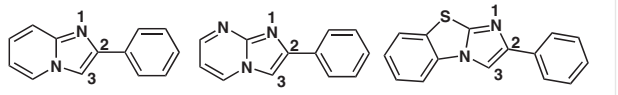

Figure 1 Fused *N*-heterocycles used in this study

A diverse range of substitutions can be introduced on substrates through the reversal of reactivity of reagents and/or synthons. Hypervalent iodine[7] reagents have been reported to promote this reversal of reactivity to facilitate hitherto impossible substitutions on electron-rich substrates. A recent flurry of reports on iodobenzenediacetate (IBD) mediated substitutions on electron-rich aromatic compounds alkenes,[8] carbonyls,[9] and enamines[10] has prompted us to investigate hypervalent iodine mediated functionalisation of the imidazo[1,2-*a*]pyridine/pyrimidine framework. Hypervalent iodine reagents are ambiphilic in nature and behave similar to transition-metal complexes, facilitating ligand exchange[11] and their subsequent transfer via reductive elimination. Though few synthetic protocols[12] have been devised for key substitution on fused *N*-heterocycles, a versatile metal-free oxidative protocol for C-3 substitution, incorporating green chemistry principles, is highly desirable.

The reactivity of fused *N*-heterocycles was assessed with a range of salts in the presence of iodobenzene diacetate (IBD) under various reaction conditions (Table 1, Scheme 1). To begin with, the strategy was tested by subjecting imidazo[1,2-*a*]pyridine to IBD-mediated bromination with NH_4Br in H_2O at room temperature (entry 1). 3-Bromo-2-phenylimidazo[1,2-*a*]pyridine (**3a**) precipitated from the reaction mixture within a short time (30 min) and the product was isolated in 69% yield. Raising the temperature to 80 °C and performing reaction under solvent-free conditions not only improved the yield of the reaction (72%) but also reduced the reaction time by half (entry 2). The conversion yield (71%) was comparable, when the reactants were subjected to simple grinding in a mortar and pestle under neat conditions (entry 3). Optimum product yields were obtained by using 1.5 equivalents of NH_4Br and IBD (entry 4). Having successfully demonstrated the forma-

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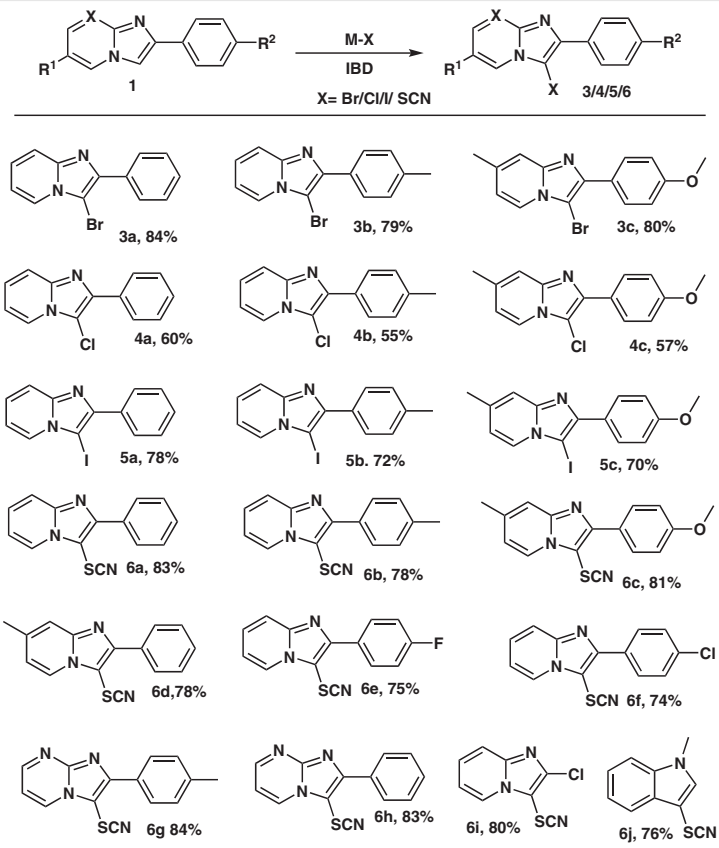

Scheme 1 Substrate scope of C-3 halogenation and thiocyanation of imidazoheterocycles. Reaction conditions for products **3a–c**, **4a–c**, **5a–c** and **6a–j**: compound **1** (1 mmol), **2** (1.5 mmol), IBD (1.5 mmol), grinding at room temperature. General procedure and data for select compounds are provided in References and Notes.[13]

tion of the required product under solvent-free conditions, other oxidising reagents were tested for their utility in the current protocol. Reaction was facile with NH_4Br and [hydroxy(tosyloxy)iodo]benzene (HTIB) (entry 5) by simple grinding of reactants. On the other hand, the reaction was not successful under these conditions with $K_2S_2O_8$ (entry 6). However, heating the reaction at 80 °C in CH_3CN for a longer time (6 h) resulted in 51% conversion into the desired product (entry 7) in the presence of $K_2S_2O_8$. The results establish the superiority of hypervalent iodine reagents, unequivocally. Sodium bromide gave slightly higher yield of **3a** (entry 8). The study was extended to other halide salts. The chloride salts NH_4Cl and NaCl gave the corresponding 3-chloro-2-phenylimidazo[1,2-*a*]pyridine (**4a**; entries 9 and 10), under similar reaction conditions, albeit in much lower yield. Iodination with NaI in the presence of IBD was also successful, yielding 3-iodo-2-phenylimidazo[1,2-*a*]pyridine (**5a**; entry 11). The substrate scope of the protocol, investigated with respect to substitutions on C-2 phenyl group of imidazopyridines, indicated that the unsubstituted phenyl ring gave the best yields in all halogenations. Among the various halogenations attempted, the yields were better for bromination, followed closely by iodination, and chlorination gave lowest yield of products (Scheme 1, 3a–c, 4a–c, and **5a–c**). Interestingly halogenations with aq. HBr (48%) and aq. HCl (36.5%) were also successful, and the corresponding products (**3a** or **4a**, respectively) could be obtained in moderate yields (entries 12 and 13).

Extending the protocol to other reagents was explored in an attempt to further broaden its scope and applicability. Thiocyanation of the above heterocycles was studied under a similar set of optimised conditions (Table 1, entry 4). Gratifyingly, simple grinding of imidazo[1,2-*a*]pyridine and KSCN with IBD gave the corresponding 2-phenyl-3-thiocyanatoimidazo[1,2-*a*]pyridine (**6a**) in 85% yield (entry 14). Comparable results were obtained with NH_4SCN and imidazopyridine as reactants (entry 15). Reaction with alternative hypervalent reagent HTIB was also facile under simple grinding conditions (entry 16). However, when $K_2S_2O_8$ was used, the formation of the product was possible only on refluxing in solution in dichloroethane (DCE) at 80 °C. Thiocyanation failed to progress under simple grinding conditions (entries 17 and 18). The substrate scope of thiocyanation was broad, as evident from the examples depicted in Scheme 1 (**6a–j**) and products were obtained in good yields.

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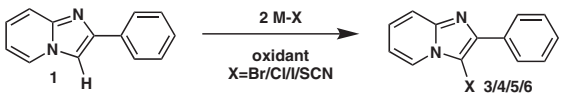
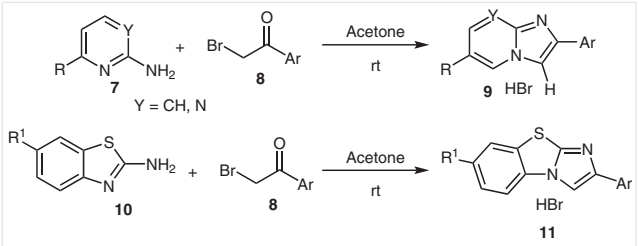
Table 1 Optimization of Conditions for Halogenation and Thiocyanation of 2-Phenylimidazo[1,2-*a*]pyridine (**1a**)[a]



Entry	Reagent	Solvent	Oxidant	Time (min)	Yield (%)[b]
1	NH_4Br	H_2O	IBD (1.2)[f]	30	69
2	NH_4Br	neat (80 °C)	IBD (1.2)[f]	15	72
3	NH_4Br	grinding	IBD (1.2)[f]	15	71
4	NH_4Br	grinding	IBD (1.5)[f]	15	84
5	NH_4Br	grinding	HTIB	15	75
6	NH_4Br	grinding	$K_2S_2O_8$	15	NR[c]
7	NH_4Br	CH_3CN	$K_2S_2O_8$	360	51
8	NaBr	grinding	IBD	15	88
9	NH_4Cl	grinding	IBD	30	60
10	NaCl	grinding	IBD	30	60
11	NaI	grinding	IBD	15	78
12	HBr aq.[d]	H_2O(rt)	IBD	20	55
13	HCl aq.[e]	H_2O(rt)	IBD	20	42
14	KSCN	grinding	IBD	15	85
15	NH_4SCN	grinding	IBD	15	70
16	KSCN	grinding	HTIB	15	80
17	KSCN	grinding	$K_2S_2O_8$	30	NR[c]
18	KSCN	DCE	$K_2S_2O_8$	360	60

[a] Reaction conditions: **1a** (1 mmol), **2** M-X (1.5 mmol), oxidant.
[b] Isolated yields reported.
[c] No reaction.
[d] HBr 48% solution.
[e] HCl 36.5% solution.
[f] Equivalents of halide salt and oxidant used are given in parentheses.

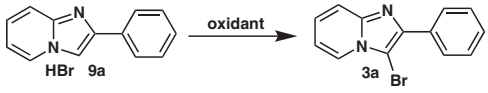
The success of halogenations with aqueous HCl and HBr (Table 1, entries 12 and 13) inspired us to investigate a cleaner and more atom-economical method for the synthesis of 3-bromo-2-phenylimidazo[1,2-*a*]pyridine (**3a**). Construction of these fused rings often involves condensation of a heterocyclic amine and α-bromoketone, resulting in generation of HBr in stoichiometric portions as a by-product. It would be an ideal situation if the HBr generated in situ could be used for bromination. The α-bromoketone and heterocyclic amine were stirred in solvent for the requisite time (Scheme 2) to complete ring formation and subsequently solvent was removed from the reaction mixture. The residue was taken in a mortar and pestle and the mass was thoroughly ground along with IBD. Continuous grinding for 15 minutes resulted in formation of the corresponding brominated product in good yields.



Scheme 2 Synthesis of heterocyclic hydrobromides

A one-pot protocol for the synthesis of **3a** by grinding heterocyclic amine and α-bromoketone under solvent-free, aerobic conditions resulted in hydrolysis of the α-bromoketone. Therefore, a completely solvent-free grinding protocol could not be designed. Suitable conditions for in situ bromination protocol were arrived at by studying various reaction parameters. It was found that bromination yields were good when the reaction residue (**9**/**11**) was heated neat (melt) or by simple grinding with IBD (Table 2, entries 1 and 2). Both these conditions gave brominated products in yields that were comparable to the yields obtained when brominations were performed in refluxing aprotic solvents (entries 3 and 4). Protic solvents (entries 5–7) were not good media for bromination. Brominations in IBD gave better yield of the product compared with other oxidising reagents (entries 8–10).

Table 2 Optimization of Conditions for Bromination of 2-Phenylimidazo[1,2-*a*]pyridine Hydrobromide to 3-Bromo-2-phenylimidazo[1,2-*a*]-pyridine (**3a**)[a]



Entry	Solvent	Oxidant	Time (min)	Yield (%)[b]
1	neat (80 °C)	IBD	15	80
2	grinding	IBD	15	85
3	dioxane	IBD	15	80
4	CH_3CN	IBD	15	78
5	H_2O	IBD	20	65
6	EtOH	IBD	15	50
7	MeOH	IBD	15	45
8	grinding	$K_2S_2O_8$	30	NR[c]
9	CH_3CN	$K_2S_2O_8$	6 h	trace
10	grinding	HTIB	6	54

[a] Reaction Conditions: **9a** (1 mmol), oxidant (1.5 mmol).
[b] Isolated yields were reported.
[c] No reaction.

The established ideal reaction conditions for in situ bromination [hydrobromide salt **9**/**11**, IBD (1.5 equiv), grinding] were extended to other substrates. The substrate scope

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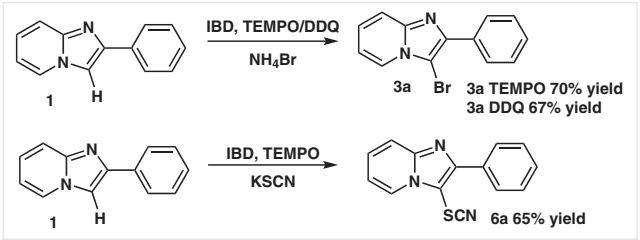
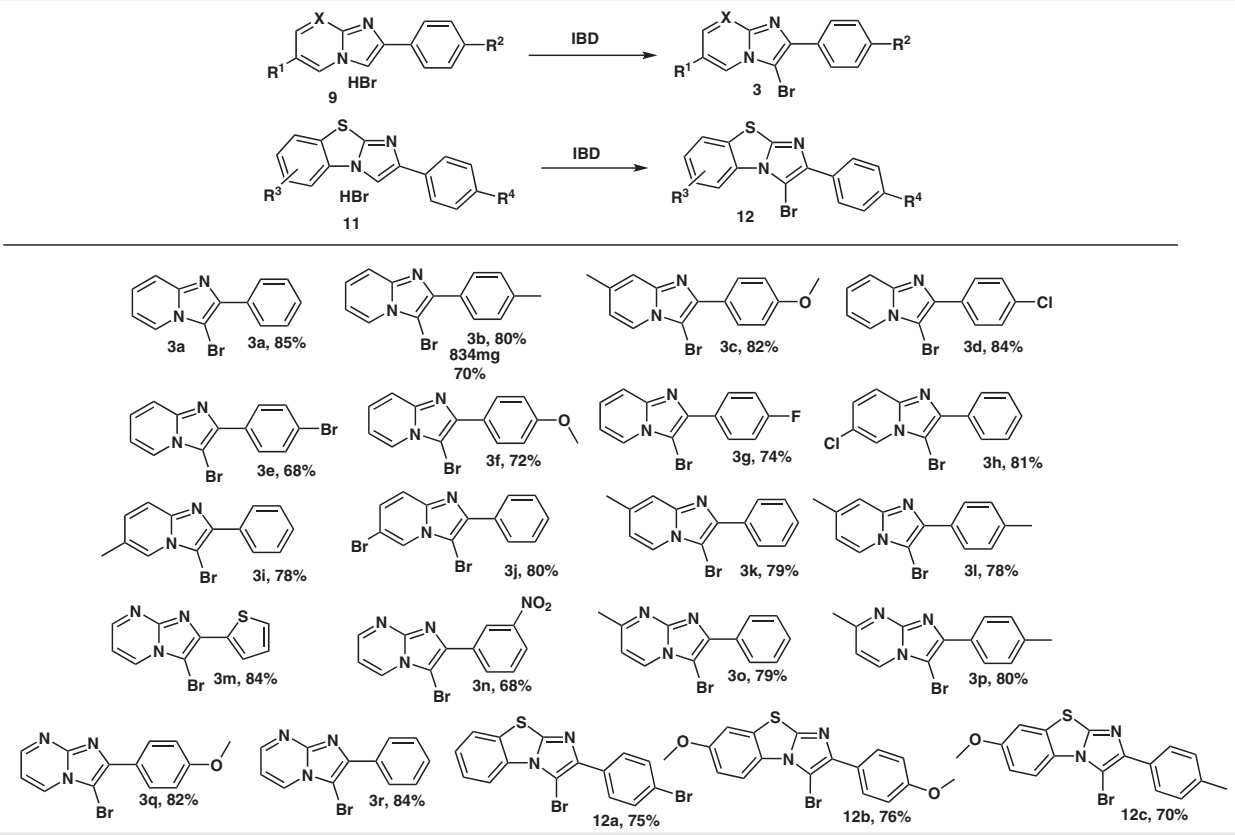
of the protocol is broad, as a wide range of substituents are tolerated. The reaction conditions could be used for bromination of a number of substituted imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrimidine, as well as other fused *N*-heterocycles (Scheme 3; **3a–r**, **12a–c**).

Having established the scope and utility of the reaction, the mechanistic aspects of the transformation attracted our attention. Hypervalent iodine-mediated reactions are known to adopt two pathways: either a radical pathway[15] or ionic pathway.[16] Control experiments carried out in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as radical scavengers were surprisingly successful (Scheme 4). This unambiguously rules out a radical pathway for the reaction. The product yield of the reaction was susceptible to variations in the oxidant quantity and slightly higher than stoichiometric proportions of IBD and halide/thiocaynate salts were essential to obtain good product yields. A simple grinding of the halide salts with IBD resulted in the liberation of distinct acetic acid odour. This indirectly indicates that a ligand exchange mechanism is probably involved. A plausible mechanism therefore involves ligand exchange with acetate to form in situ [acetoxy(halo/thiocyanato)iodo]benzene[17] from IBD and MX (Scheme 5). The species, being labile, serves as a formal X^+ reagent, thereby facilitating substitution on C-3 carbon.



Scheme 4 Control experiments. Reaction conditions: **1** (1 mmol), IBD (1.5 mmol) TEMPO or DDQ (1.5 mmol), NH_4Br or KSCN (1.5 mmol), grinding for 15 min at room temperature.

In summary, a highly efficient, rapid, operationally simple and facile substitution protocol for C–H substitution of fused *N*-heterocycles has been established.[13,14,18] An inexpensive practical halogenation method has been established for imidazo[1,2-*a*]pyridine/ pyrimidine using simple alkali/ammonium halides, aq. HBr / aq. HCl in the presence of IBD. The scope of the protocol has been extended to other reagents, and effective thiocyanation of imidazo[1,2-



Scheme 3 Substrate scope of in situ bromination of fused *N*-heterocycles. Reaction conditions: heterocyclic hydrobromide (**9/11**; 1 mmol), IBD (1.5 mmol), grinding for 15 min at room temperature. General procedure and data for select compounds is given in References and Notes.[14]

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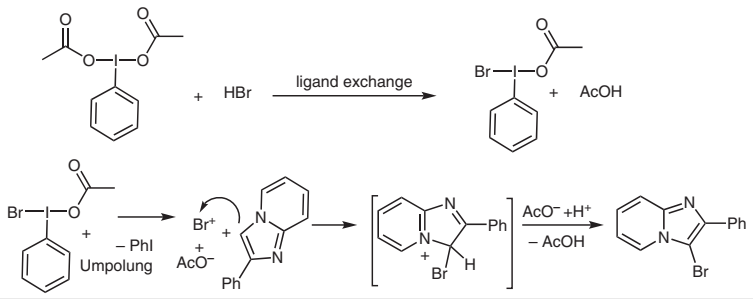

Scheme 5 Plausible route

a]pyridine/ pyrimidine could be achieved under solvent-free conditions. The method has been extrapolated to an atom-economical[17] cleaner synthesis of brominated derivatives of fused *N*-heterocycles starting from heterocyclic amine and α-bromomketone. Additionally, this in situ bromination protocol could be scaled up to a gram level synthesis (Scheme 3, compound **3b**). This hypervalent iodine mediated substitution protocol, which is compatible with a wide range of substrates, substituents and reagents, is a valuable tool for substitution of electron-rich arene centres and *N*-heterocycles.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611856.

References and Notes

(1) (a) Feng, S.; Hong, D.; Wang, B.; Zheng, X.; Miao, K.; Wang, L.; Yun, H.; Gao, L.; Zhao, S.; Shen, H. C. *ACS Med. Chem. Lett.* **2015**, *6*, 359. (b) Gueiffier, E.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888. (c) Dyminska, L. *Bioorg. Med. Chem.* **2015**, *23*, 6087.

(2) (a) Sharma, S.; Saha, B.; Sawant, D.; Kundu, B. *J. Comb. Chem.* **2007**, *9*, 783. (b) Shono, H.; Ohkawa, T.; Tomoda, H.; Mutai, T.; Araki, K. *ACS Appl. Mater. Interfaces* **2011**, *3*, 654.

(3) (a) Stasyuk, A. J.; Banasiewicz, M.; Cyranski, M. K.; Gryko, D. T. *J. Org. Chem.* **2012**, *77*, 5552. (b) Shao, N.; Pang, G.-X.; Yan, C.-X.; Sci, G.-F.; Cheng, Y. *J. Org. Chem.* **2011**, *76*, 7458. (c) Douhal, A.; Amat-Guerri, F.; Acuna, A. U. *J. Phys. Chem.* **1995**, *99*, 76. (d) Douhal, A.; Amat-Guerri, F.; Acuna, A. U. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1514.

(4) (a) Zhang, H.; Wei, Q.; Wei, S.; Qu, J.; Wang, B. *Eur. J. Org. Chem.* **2016**, 3373. (b) Bagdi, A. K.; Hajra, A. *Chem. Rec.* **2016**, *16*, 1868. (c) Xiang, S.; Chen, H.; Liu, Q. *Tetrahedron Lett.* **2016**, *57*, 3870. (d) Dey, A.; Singsardar, M.; Sarkar, R.; Hajira, A. *ACS Omega* **2018**, *3*, 3513. (e) Li, J.; Tang, J.; Wu, Y.; He, Q.; Yu, Y. *RSC Adv.* **2018**, *8*, 5058. (f) Rashmi, S.; Chitrakar, R.; Rahul, K.; Ramavatar, M.; Subbarayappa, A. *J. Org. Chem.* **2019**, *84*, 792.

(5) (a) Xuan, Q.; Song, Q. *Org. Lett.* **2016**, *18*, 4250. (b) Wu, W.; Ding, Y.; Xie, P.; Tang, Q.; Pittman, C. U. Jr.; Zhou, A. *Tetrahedron* **2017**, *73*, 2151. (c) Ravi, C.; Reddy, N. N. K.; Pappula, V.; Samanta, S.; Adimurthy, S. *J. Org. Chem.* **2016**, *81*, 9964. (d) Jiao, J.; Xu, L.; Zheng, W.; Xiong, P.; Hu, M.-L.; Tang, R.-Y. *Synthesis* **2017**, *49*, 1839. (e) Qi, Z.; Yu, S.; Li, X. *J. Org. Chem.* **2015**, *80*, 3471. (f) Sun, K.; Mu, S.; Liu, Z.; Feng, R.; Li, Y.; Panga, K.; Zhang, B. *Org. Biomol. Chem.* **2018**, *16*, 6655.

(6) (a) Wang, S.; Huang, X.; Ge, Z.; Wang, X.; Li, R. *RSC Adv.* **2016**, *6*, 63532. (b) Wang, Y.; Frett, B.; McConnella, N.; Li, H. *Org. Biomol. Chem.* **2015**, *13*, 2958. (c) Zhang, J.-R.; Zhan, L.-Z.; Wei, L.; Ning, Y.-Y.; Zhong, X.-L.; Lai, J.-X.; Xu, L.; Tang, R.-Y. *Adv. Synth. Catal.* **2018**, *360*, 533. (d) Falck, J. R.; Gao, S.; Prasad, R. N.; Koduru, S. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1768. (e) Mitra, S.; Ghosh, M.; Mishra, S.; Hajra, A. *J. Org. Chem.* **2015**, *80*, 8275.

(7) (a) Hari, D. P.; Caramenti, P.; Waser, J. *Acc. Chem. Res.* **2018**, *51*, 3212. (b) Moriyama, K.; Izumisawa, Y.; Togo, H. *J. Org. Chem.* **2011**, *76*, 7249. (c) Huang, Z.-Z.; Yu, X.-C.; Huang, X. *Tetrahedron Lett.* **2002**, *43*, 6823. (d) Shneider, O. S.; Pisarevsky, E.; Fristrup, P.; Szpilman, A. M. *Org. Lett.* **2015**, *17*, 282. (e) Daniel, M.; Blanchard, F.; Nocquet-Thibault, S.; Cariou, K.; Dodd, R. H. *J. Org. Chem.* **2015**, *80*, 10624. (f) Zhao, Z.; Peng, Z.; Zhao, Y.; Liu, H.; Li, C.; Zhao, J. *J. Org. Chem.* **2017**, *82*, 11848. (g) Shen, H.; Li, J.; Liu, Q.; Pan, J.; Huang, R.; Xiong, Y. *J. Org. Chem.* **2015**, *80*, 7212.

(8) (a) Gottam, H.; Vinod, K. T. *J. Org. Chem.* **2011**, *76*, 974. (b) Zhang, J.; Szabó, J. K.; Himo, F. *ACS Catal.* **2017**, *7*, 1093. (c) Kiyokawa, K.; Yahata, S.; Kojima, T.; Minakata, S. *Org. Lett.* **2014**, *16*, 4646. (d) Desjardins, S.; Andrez, J.; Canesi, S. *Org. Lett.* **2011**, *13*, 3406.

(9) (a) Fang, C.; Qian, W.; Bao, W. *Synlett* **2008**, 2529. (b) Moteki, S. A.; Usui, A.; Selvakumar, S.; Zhang, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2014**, *53*, 11060.

(10) (a) Sun, X.; Lyu, Y.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2013**, *15*, 6222. (b) Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782. (c) Mandha, S. R.; Alla, M.; Bommena, V. R.; Nanubolu, J. B.; Lingala, S. K.; Yarasi, S. *J. Org. Chem.* **2012**, *77*, 10648.

(11) (a) Yusubov, M. S.; Wirth, T. *Org. Lett.* **2005**, *7*, 519. (b) Han, H.; Tsarevsky, N. V. *Chem. Sci.* **2014**, *5*, 4599. (c) Ochiai, M.; Sueda, T.; Miyamoto, K.; Kiprof, P.; Zhdankin, V. V. *Angew. Chem. Int. Ed.* **2006**, *45*, 8203. (d) Sajith, P. K.; Suresh, C. H. *Inorg. Chem.* **2012**, *51*, 967.

(12) (a) Shakoor, S. M. A.; Mandal, S. K.; Sakhuja, R. *Eur. J. Org. Chem.* **2017**, 2596. (b) Karade, N. N.; Tiwari, G. B.; Shirodkar, S. G.; Dhoot, B. M. *Synth. Commun.* **2005**, *35*, 1197. (c) Chen, Z.; Cao,

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G.; Zhang, F.; Li, H.; Xu, J.; Miao, M.; Ren, H. *Synlett* **2017**, *28*, 1795. (d) Rahaman, R.; Das, S.; Barman, P. *Green Chem.* **2018**, *20*, 141. (e) Mondal, S.; Samanta, S.; Jana, S.; Hajra, A. *J. Org. Chem.* **2017**, *82*, 4504. (f) Yagyu, T.; Takemoto, Y.; Yoshimura, A.; Zhdankin, V. V.; Saito, A. *Org. Lett.* **2017**, *19*, 2506. (g) Xu, D.; Sun, W.; Xie, Y.; Liu, J.; Liu, B.; Zhou, Y.; Wu, B. *J. Org. Chem.* **2016**, *81*, 11081. (h) Zhang, X.; Hou, W.; Zhang-Negrerie, D.; Zhao, K.; Du, Y. *Org. Lett.* **2015**, *17*, 5252.

(13) **Synthesis of 3-Halo/thiocyanato-2-phenylimidazo[1,2-*a*]pyridine Derivatives; General Procedure**

A mixture of 2-phenylimidazo[1,2-*a*]pyridine (**1**; 1 mmol), M-X (**2a–d**; 1.5 mmol) and IBD (1.5 mmol) were taken in a mortar and the mixture was ground with a pestle until the solids melted (ca. 15 min). A distinction odour of acetic acid was noted. The progress of the reaction was monitored by TLC and grinding was continued until the starting materials disappeared. The reaction mixture was extracted with ethyl acetate (30 mL) and washed with water (10 mL) to remove remnant inorganic salts. The organic layer was separated and dried over Na_2SO_4. Solvent was removed in vacuo. The crude product thus obtained was purified by column chromatography for all halogenations (silicon 60–120 mesh; EtOAc/hexane, 5:95). Thiocyanation products could be obtained in pure form without further purification.

(14) **Synthesis of 3-Bromo-2-phenylimidazo[1,2-*a*]pyridine/pyrimidine/benzo[*d*]imidazo[2,1-*b*]thiazole Derivatives via in Situ Bromination; General Procedure**

A mixture of heterocyclic hydrobromide (**9**/**11**; 1 mmol), and IBD (1.5 mmol) were taken in a mortar and the mixture was ground with a pestle until the solids melted (ca. 15 min). The progress of the reaction was monitored by TLC and grinding was continued until the starting materials disappeared. The solid residue was washed with *n*-pentane and dried under high vacuum to afford the product

(15) (a) Selvakumar, S.; Kang, Q.-K.; Arumugam, N.; Almansour, A. I.; Kumar, R. S.; Maruoka, K. *Tetrahedron* **2017**, *73*, 5841. (b) Zhao, F.; Sun, T.; Sun, H.; Xi, G.; Sun, K. *Tetrahedron Lett.* **2017**, *58*, 3132. (c) Wang, X.; Studer, A. *Acc. Chem. Res.* **2017**, *50*, 1712. (d) Wang, X.; Studer, A. *Acc. Chem. Res.* **2017**, *50*, 1712. (e) Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261.

(16) (a) Yoshimura, A.; Middleton, K. R.; Todora, A. D.; Kastern, B. J.; Koski, S. R.; Maskaev, A. V.; Zhdankin, V. V. *Org. Lett.* **2013**, *15*, 4010. (b) Boye, A. C.; Meyer, D.; Ingison, C. K.; French, A. N.; Wirth, T. *Org. Lett.* **2003**, *5*, 2157.

(17) (a) Tang, S.-Z.; Zhao, W.; Chen, T.; Liu, Y.; Zhang, X.-M.; Zhang, F.-M. *Adv. Synth. Catal.* **2017**, *359*, 4177. (b) Akula, R.; Galligan, M.; Ibrahim, H. *Chem. Commun.* **2009**, 6991.

(18) Analytical data and copies of spectra of all compounds are given in the Supporting Information.

Analytical data of a selection of new compounds are given below.

3-Bromo-2-(4-methoxyphenyl)-7-methylimidazo[1,2-*a*]pyridine (3c)

Yield: 253 mg (80%); yellow solid; mp 92–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08–8.04 (m, 1 H), 8.02 (d, *J* = 7.0 Hz, 1 H), 7.38 (s, 1 H), 7.03–6.99 (m, 2 H), 6.74 (dd, *J* = 7.0, 1.5 Hz, 1 H), 3.86 (s, 3 H), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.57, 145.52, 141.94, 136.15, 129.02, 125.35, 122.96, 115.65, 115.50, 113.81, 89.96, 77.00, 55.24, 21.28. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{15}H_{14}BrN_2O$: 317.0284; found: 317.0290.

3-Bromo-7-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridine (3l)

Yield: 234 mg (78%); white solid; mp 176–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (dd, *J* = 7.5, 5.8 Hz, 3 H), 7.37 (s, 1 H), 7.29–7.25 (m, 2 H), 6.70 (dd, *J* = 7.0, 1.5 Hz, 1 H), 2.40 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.64, 142.27, 137.95, 136.02, 130.04, 129.08, 127.60, 122.98, 115.81, 115.49, 90.41, 77.00, 21.28. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{15}H_{14}BrN_2$: 301.0348; found: 301.0340.

3-Bromo-2-(thiophen-2-yl)imidazo[1,2-*a*]pyrimidine (3m)

Yield: 232 mg (84%); white solid; mp 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (dd, *J* = 4.0, 1.8 Hz, 1 H), 8.40 (dd, *J* = 6.8, 1.8 Hz, 1 H), 7.95 (d, *J* = 3.6 Hz, 1 H), 7.45 (d, *J* = 5.0 Hz, 1 H), 7.20–7.14 (m, 1 H), 6.99 (dd, *J* = 6.8, 4.1 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.23, 147.99, 140.28, 135.12, 131.15, 127.74, 127.28, 126.71, 109.36, 89.31, 77.00. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{10}H_7BrN_3S$: 279.9543; found: 279.9544.

3-Bromo-2-(3-nitrophenyl)imidazo[1,2-*a*]pyrimidine (3n)

Yield: 214 mg (68%); white solid; mp 224–226 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO): δ = 9.12 (s, 1 H), 8.67 (dd, *J* = 4.1, 1.9 Hz, 1 H), 8.65–8.57 (m, 2 H), 8.27 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.72 (t, *J* = 8.0 Hz, 1 H), 7.15 (dd, *J* = 6.8, 4.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO): δ = 150.36, 147.28, 147.06, 139.91, 133.11, 132.40, 131.32, 128.71, 122.07, 121.29, 109.15, 90.40, 77.00. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{12}H_8BrN_4O_2$: 317.9749; found: 317.9752.

3-Bromo-7-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyrimidine (3p)

Yield: 241 mg (80%); brown solid; mp 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 7.0 Hz, 1 H), 8.14–8.10 (m, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 6.85–6.82 (m, 1 H), 2.66 (s, 3 H), 2.41 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.32, 148.05, 143.39, 138.52, 130.58, 129.60, 129.13, 127.73, 110.08, 88.91, 77.00, 24.84, 21.35. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{13}H_{11}BrN_3$: 288.0140; found: 288.0136. HRMS-ESI: *m*/*z* [M + H]$^+$, calcd. for $C_{14}H_{13}BrN_3$: 302.0293; found: 302.0287.

3-Bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyrimidine (3q)

Yield: 249 mg (82%); white solid; mp 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (dd, *J* = 4.1, 2.0 Hz, 1 H), 8.45 (dd, *J* = 6.8, 2.0 Hz, 1 H), 8.22–8.16 (m, 2 H), 7.05–6.96 (m, 3 H), 3.88 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.16, 149.79, 148.14, 144.22, 131.18, 129.44, 124.79, 113.95, 109.14, 89.38, 77.00, 55.33. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{13}H_{10}BrN_3O$: 304.0086; found: 304.0085.

3-Bromo-7-methoxy-2-(4-methoxyphenyl)benzo[*d*]imidazo[2,1-*b*]thiazole (12b)

Yield: 251 mg (65%); white solid; mp 206–208 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 9.1 Hz, 1 H), 7.94 (d, *J* = 8.8 Hz, 2 H), 7.20 (d, *J* = 2.4 Hz, 1 H), 7.05–6.92 (m, 3 H), 3.87 (d, *J* = 4.5 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.34, 157.31, 147.08, 143.31, 131.54, 128.46, 127.18, 125.18, 114.26, 113.87, 113.06, 108.54, 90.89, 77.00, 55.88, 55.31. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{17}H_{14}BrN_2O_2S$: 388.9958; found: 388.9959.

3-Bromo-7-methoxy-2-(*p*-tolyl)benzo[*d*]imidazo[2,1-*b*]thiazole (12c)

Yield: 260 mg (70%); pale-pink solid; mp 204–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 9.1 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 2 H), 7.26 (t, *J* = 4.0 Hz, 2 H), 7.20 (d, *J* = 2.4 Hz, 1 H), 7.01 (dd, *J* = 9.0, 2.4 Hz, 1 H), 3.88 (s, 3 H), 2.40 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.27, 147.20, 143.74, 137.63, 131.56, 129.96, 129.11, 127.22, 126.99, 114.26, 112.96, 108.54, 91.33, 77.00, 55.86, 21.31. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{17}H_{14}BrN_2OS$: 372.9967; found: 372.9954.

3-Chloro-2-(4-methoxyphenyl)-7-methylimidazo[1,2-*a*]pyridine (4c)

Yield: 155 mg (57%); brown solid; mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.04 (m, 2 H), 7.97 (d, *J* = 7.0 Hz,

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1 H), 7.39 (s, 1 H), 7.03–6.98 (m, 2 H), 6.75 (dd, *J* = 7.0, 1.5 Hz, 1 H), 3.87 (s, 3 H), 2.43 (d, *J* = 0.6 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.60, 143.98, 139.23, 135.94, 128.75, 125.19, 121.82, 115.80, 115.45, 113.99, 104.16, 55.34, 21.41. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{15}H_{14}OClN_2$: 273.0792; found: 273.0789.

3-Iodo-2-(4-methoxyphenyl)-7-methylimidazo[1,2-*a*]pyridine (5c)

Eluent: hexane/ethyl acetate, 90:10.

Yield: 254 mg (70%); white solid; mp 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.0 Hz, 1 H), 8.00 (d, *J* = 8.7 Hz, 2 H), 7.35 (s, 1 H), 7.01 (d, *J* = 8.7 Hz, 2 H), 6.73 (d, *J* = 6.9 Hz, 1 H), 3.86 (s, 3 H), 2.43 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.56, 148.23, 147.52, 136.37, 129.59, 126.16, 125.43, 115.71, 115.45, 113.66, 77.00, 57.33, 55.22, 21.19. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{15}H_{14}IN_2O$: 365.0146; found: 365.0151.

3-Thiocyanato-2-(*p*-tolyl)imidazo[1,2-*a*]pyrimidine (6g)

Yield: 223 mg (84%); white solid; mp 208–210 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO): δ = 8.81 (ddd, *J* = 6.1, 5.5, 1.9 Hz, 2 H), 8.07 (d, *J* = 8.2 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.27 (dd, *J* = 6.7, 4.3 Hz, 1 H), 2.46 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO): δ = 151.94, 138.92, 131.87, 128.45, 127.67, 126.76, 109.65, 77.00, 20.38. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{14}H_{11}IN_4S$: 267.0695; found: 267.0699.

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