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A simple two-step access to diversely substituted imidazo[4,5-*b*]pyridines and benzimidazoles from readily available 2-imidazolines

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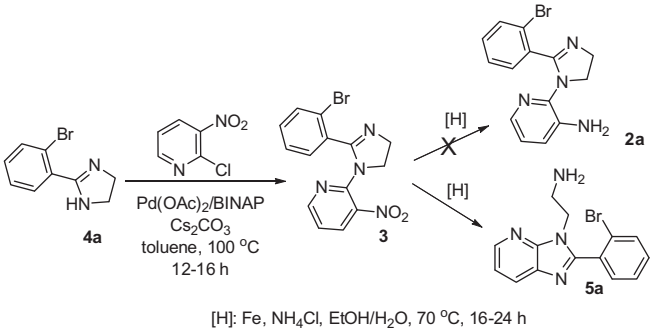
ABSTRACT

We discovered a facile rearrangement of *N*-(hetero)aryl 2-imidazolines into diversely substituted imidazo[4,5-*b*]pyridines and benzimidazoles, under Bechamp reduction conditions. Combined with the earlier reported protocol for Pd-catalyzed (hetero)arylation of 2-imidazolines, it provides a simple two-step access to a range of compounds based on these medicinally important heterocyclic cores.

Discovery of new, non-conventional methods to prepare classical heterocycles broadens the arsenal of synthetic methods and often allows accessing densely functionalized heterocyclic templates more flexibly and in fewer synthetic operations compared to the routes based on the existing methodologies. In this Letter we report on a serendipitous discovery of a straightforward method to prepare two important heterocyclic cores—imidazo[4,5-*b*]pyridines and benzimidazoles—with full control over three elements of diversity.

Recently, we developed an efficient methodology for Pd-catalyzed (hetero)arylation of 2-imidazolines[1] that has allowed us to access a wide range of drug-like compounds belonging to the relatively unexplored[2] *N*-(hetero)aryl-2-imidazoline chemotype (**1**). As the medicinal chemistry potential of the latter began to unravel, we were facing a need to introduce various functionalities in the



Scheme 1. Practical outcome of the Fe/NH_4Cl reduction of **3a** in aqueous ethanol.

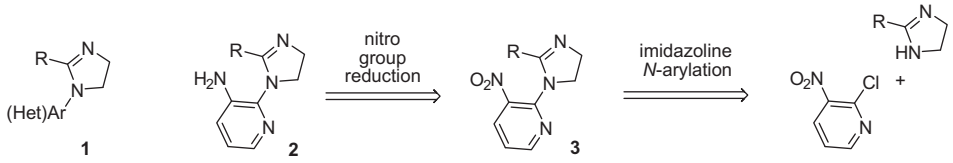


Figure 1. Strategy to access *N*-(3-aminopyrid-2-yl)-2-imidazolines.

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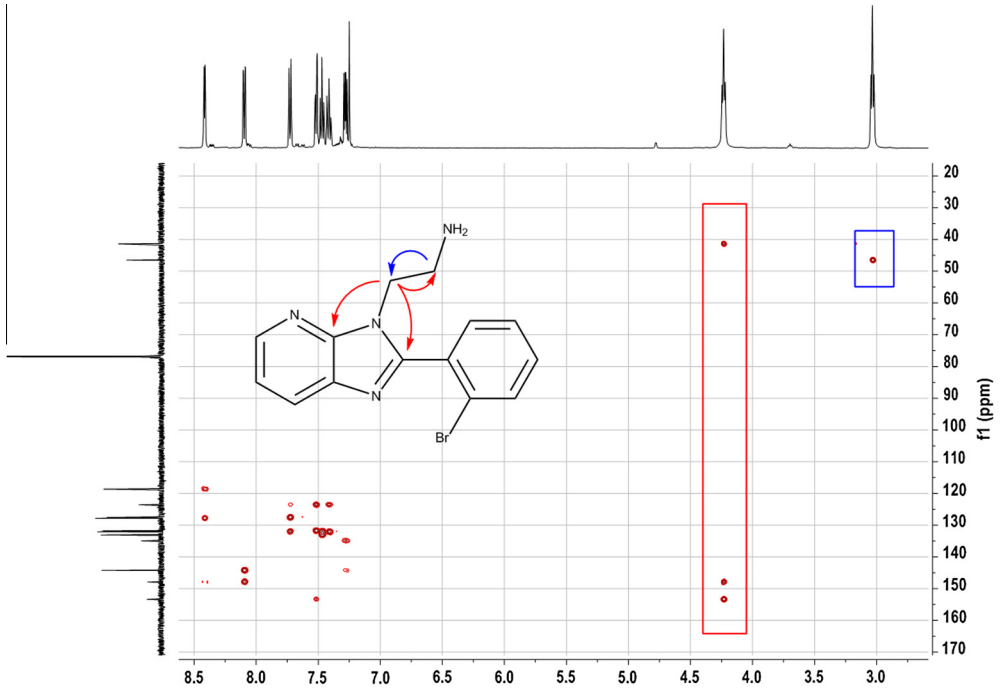
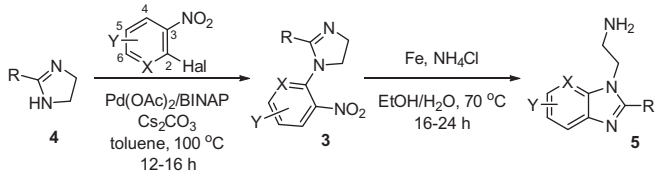


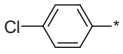
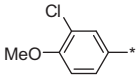
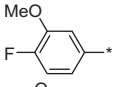
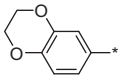
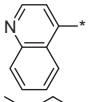
Figure 2. HMBC correlations confirming the imidazo[4,5-*b*]pyridine structure of **5a**.



Scheme 2. General two-step access to imidazo[4,5-*b*]pyridines and benzimidazoles.

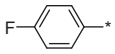
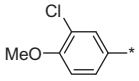
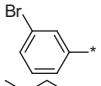
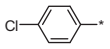
basic core **1**. In particular, we were interested in incorporating an amino group into the *N*-aryl (specifically, 2-pyridyl) substituent (as in **2**), via the use of 2-chloro-3-nitropyridine in the imidazoline arylation step with subsequent reduction of the nitro group in **3** (Fig. 1). We expected 2-chloro-3-nitropyridine to be a reactive partner in imidazoline N-arylation and, indeed, the respective model compound **3a** (R = 2-bromophenyl) was prepared from 2-(2-bromophenyl)imidazoline (**4a**) in 80% yield using the aforementioned protocol. When we subjected **3a** to the modified Bechamp

Table 1
Imidazo[4,5-*b*]pyridines and benzimidazoles prepared in this work

Compound	*R*	*X*	*Y* in **3** (in **5**)	Hal	Yield imidazoline arylation step (%)	Yield reduction–rearrangement step (%)
5a		N	H	Cl	80	71
5b		N	H	Cl	81	79
5c		N	H	Cl	84	77
5d		N	H	Cl	92	62
5e		N	H	Cl	68	81
5f		N	H	Cl	97	81
5g		N	H	Cl	96	63
5h		N	H	Cl	90	28
5i		N	H	Cl	76	60

(*continued on next page*)

Table 1 (*continued*)

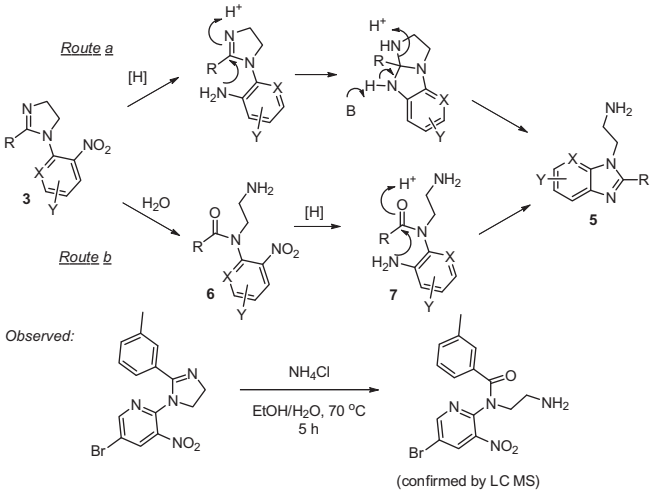
Compound	*R*	*X*	*Y* in **3** (in **5**)	Hal	Yield imidazoline arylation step (%)	Yield reduction–rearrangement step (%)
5j		N	4-Me	Cl	90	83
5k		N	5-Br	Cl	98	73
5l		N	5-Br	Cl	50	74
5m		N	4-Me	Cl	87	74
5n		N	5-Br	Cl	56	56
5o		N	4-Me	Cl	81	75
5p		CH	5-Br	Br	41	52
5q		CH	5-Br	Br	35	55
5r		CH	5-CN	Br	93	91
5s		CH	5-CN	Br	84	65
5t		CH	5-CN	Br	80	69
5u[a]		CH	5-NO_2 (5-NH_2)	Cl	76	92

[a] 6 equiv of Fe and 1.2 equiv of NH_4Cl were used, the 5-aminobenzimidazole product was obtained.

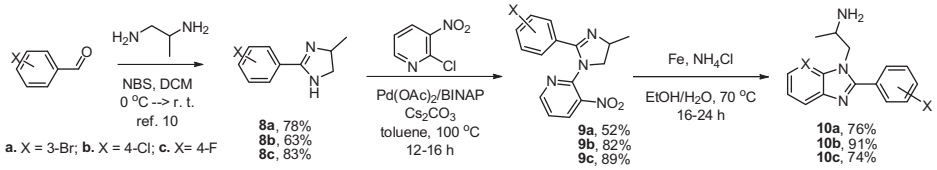
reduction conditions (Fe/NH_4Cl in aqueous EtOH),[3] an efficient conversion to a more polar compound took place. The product was isolated chromatographically and characterized. Although its molecular weight corresponded to the desired amine **2**, close examination of its ^1H NMR spectra revealed the absence of the tightly grouped multiplets around δ_H 4.0 ppm characteristic of the imidazoline bis-methylene bridge. Instead, two triplets at δ_H 4.25 and 3.10 ppm, more characteristic of a 2-aminoethyl side chain were observed. After substantial brainstorming, isomeric imidazo[4,5-*b*]pyridine structure **5a** was proposed for the product obtained (Scheme 1). It was, to our delight, later confirmed by 2D HMBC NMR spectral data (Fig. 2).

Imidazo[4,5-*b*]pyridines containing 2-aminoethyl side chain are somewhat underexplored bioisosteres of the privileged[4] benzimidazoles. To-date, imidazo[4,5-*b*]pyridines have been documented as histamine H3 receptor inverse agonists,[5] histone deacetylase inhibitors[6], and cannabinoid CB2 receptor modulators.[7] We appeared to have identified a conceptually novel and practically simple protocol to prepare these medicinally important compounds from the readily available 2-imidazolines **4**. Therefore we proceeded to investigate the scope of this two-step transformation (Scheme 2) and found it applicable to the preparation of a range of diversely substituted imidazo[4,5-*b*]pyridines **5a**–**o** as well as benzimidazoles **5p**–**u** (Table 1). The methodology[8] is equally workable for 2-alkyl, 2-aryl, and 2-heteroaryl imidazolines and conveniently allows incorporating a range of substituents in the imidazo-fused aromatic nucleus via the use of appropriately substituted (hetero)aryl halides. Particularly noteworthy is the preparation of 5-aminobenzimidazole **5u** via the double reduction of 3,5-dinitrophenyl moiety in the *N*-arylimidazoline precursor.

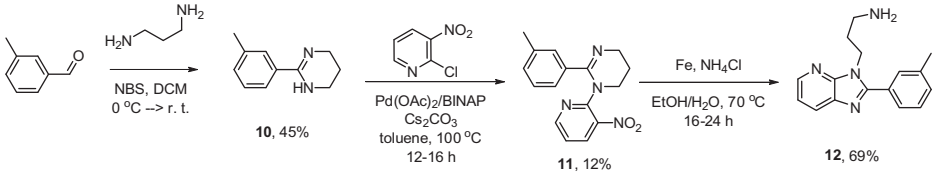
From the mechanistic standpoint, the formation of imidazo[4,5-*b*]pyridines and benzimidazoles in the reduction–rearrangement step could be rationalized as depicted in Scheme 3. The nitro group in **3** may first be reduced to the amino group which would then trigger a 5-*exo*-*trig* attack on the imidazoline's amidine carbon (route a) that would ultimately lead to the formation of the imidazo-fused aromatic core. Alternatively (route b), the imidazoline core could be hydrolyzed, under the mildly acidic reaction conditions, to give amide **6**. The latter would then undergo reduction and dehydrative cyclization (of the amine **7**) to form the observed aromatic nucleus. Based on the abundance of examples of imidazoline hydrolysis in the literature[9] one could a priori conclude that route b would be the preferred reaction course. We further confirmed it by heating a representative compound (**3p**) in aqueous



Scheme 3. Mechanistic rationale for the formation of imidazo-fused compounds **5**.



Scheme 4. Side-chain substitutions in the imidazo-fused aromatic products.



Scheme 5. Synthesis of 3-aminopropyl-substituted imidazo[4,5-*b*]pyridine **12**.

ethanolic solution of NH_4Cl at 70 °C. After 5 h, the starting material underwent a complete conversion into amide **6p** (as confirmed by LC MS analysis). This observation further argues for the formation of imidazo[4,5-*b*]pyridines and benzimidazoles predominantly proceeding via route b.

According to this rationale, the use of additionally substituted imidazolines in the two-step sequence would result in regiospecific incorporation of substituents in the 2-aminoethyl side chain of the resulting imidazo-fused aromatic products. Pd-catalyzed N-arylation of imidazolines **8a–c** (prepared from the respective benzaldehydes and propane-1,2-diamine according to the literature procedure[10]) with 2-chloro-3-nitropyridine proceeded with >90% regiospecificity, as reported by us earlier,[11] to give compounds **9a–c** in good to excellent yields. Treatment of **9a–c** under the Bechamp reduction conditions resulted in excellent yields of compounds **10a–c** (Scheme 4). Regiochemistry of the side chain substitution was unequivocally confirmed by 2D HMBC NMR experiments (see Supplementary data).

Finally, we were curious to see if the present methodology could be extended to the preparation of imidazo[4,5-*b*]pyridines containing 3-aminopropyl side chains, via Pd-catalyzed N-arylation of 1,4,5,6-tetrahydropyrimidines and subsequent reduction-rearrangement. N-Arylation of a model 1,4,5,6-tetrahydropyrimidine **10** provided the desired compound **11** (albeit in disappointingly low yield). The latter, under Bechamp reduction conditions, underwent a smooth and high-yielding transformation into the expected 3-aminopropyl-substituted imidazo[4,5-*b*]pyridine **12** (Scheme 5). Thus, should the yield of *N*-(hetero)arylation of 1,4,5,6-tetrahydropyrimidines be improved,[12] our two-step protocol would be of practical value to access 3-aminopropyl-substituted imidazo-fused aromatic templates as well.

In summary, we discovered a facile rearrangement of *N*-(hetero)aryl 2-imidazolines into diversely substituted imidazo[4,5-*b*]pyridines and benzimidazoles,[13] under Bechamp reduction conditions. Combined with the earlier reported protocol for Pd-catalyzed (hetero)arylation of 2-imidazolines, it provides a simple two-step access to a range of compounds based on these medicinally important heterocyclic cores[14]. Further applications of this methodology to the synthesis of novel, more complex heterocyclic templates are being investigated in our laboratories and the results will be reported in due course.

Acknowledgements

Mikhail Krasavin acknowledges support from Griffith University. Dr. Hoan Vu of Eskitis Institute is thanked for high-resolution mass spectrometry measurements. Mr. Pakornwit Sarnpitak is acknowledged for the preparation of the starting material imidazolines.

Supplementary data

Supplementary data (copies of ^1H and ^{13}C NMR spectra for the newly synthesized compounds **5a-u**, **10a-c**, **12**; copies of 2D HMBC NMR spectra for selected compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.036.

References and notes

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2. According to our literature survey, *N*-(heteroaryl)imidazolines were seldom implicated as central scaffolds in biologically active chemical series. However, they were often reported as essential elements of compound's periphery, e.g., in inhibitors of polo-like kinase (Neitz, R. J.; Troung, A. P.; Galemmo, R. A.; Ye, X. M.; Sealy, J.; Adler, M.; Bowers, S.; Beroza, P.; Anderson, J. P.; Aubele, D. L.; Artis, D. R.; Hom, R. K.; Zhu, Y.-L. PCT Int. Appl. WO 2012048129A2, 408 pp; *Chem. Abstr.* **2012**, *156*, 534299) or MDM2/4 modulators (Bold, G.; Furet, P.; Gessier, F.; Kallen, J.; Hergovich Lisztwan, J.; Masuya, K.; Vaupel, A. PCT Int. Appl. WO2011023677A1, 274 pp *Chem. Abstr.* **2011**, *154*, 310643).
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7. Kon-I, K.; Matsumizu, M.; Shima, A. US Patent Appl. US20060094750A1, 63 pp; *Chem. Abstr.* **2006**, *144*, 409719.
8. Typical procedure for the synthesis of **5**: *N*-(hetero)aryl 2-imidazoline **3** (0.3 mmol), prepared as described earlier, **1** was dissolved in a mixture of EtOH (2.25 mL) and H_2O (0.45 mL). Fe dust (3 equiv, 0.9 mmol, 50 mg) and NH_4Cl (0.6 equiv, 0.18 mmol, 10 mg) were added and the mixture was heated, under vigorous stirring, at 70 °C for 16–24 h. It was then cooled down to rt, filtered through a plug of Celite and the filtrate was evaporated. The residue was absorbed on silica gel, transferred onto a silica gel column and the column was eluted with 8% MeOH in DCM. Fractions containing the product were combined and evaporated to provide the desired imidazo[4,5-*b*]pyridines or benzimidazoles.
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12. N-Arylation of 1,4,5,6-tetrahydropyrimidines is a surprising void in the currently available synthetic methods. Efforts are currently underway in our laboratories to identify optimized conditions to achieve a high-yielding arylation of this special case of cyclic amidines.
13. Characterization data for selected compounds: **5f**: Brown oil; ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.45 (d, *J* = 4.5 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 1.0 Hz, 1H), 7.73–7.76 (m, 1H), 7.60–7.65 (m, 2H), 7.40 (dd, *J* = 7.8, 4.7 Hz, 1H), 4.57 (t, *J* = 6.4 Hz, 2H), 3.25 (s, 2H), NH_2 protons in exchange; ^{13}C NMR (125 MHz, CD_3OD): δ_C 155.6, 150.4, 146.4, 136.9, 136.6, 133.4, 132.7, 132.6, 131.4, 129.7, 129.3, 121.4, 46.3, 42.0; HRMS *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{14}C_lN_4$ 273.0901, found 273.0890. **5g**: 63% yield (10% MeOH in DCM), brown solid, mp = 222–224 °C. ^{1}H NMR (500 MHz, CD_3OD): δ_H 9.07 (d, *J* = 4.4 Hz, 1H), 8.51 (d, *J* = 4.6 Hz, 1H), 8.18 (t, *J* = 8.7 Hz, 2H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 4.3 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 6.8 Hz, 1H), 7.46 (dd, *J* = 8.0, 5.2 Hz, 1H), 4.42 (t, *J* = 5.7 Hz, 2H), 3.22 (t, *J* = 5.6 Hz, 2H), NH_2 protons in exchange; ^{13}C NMR (125 MHz, CD_3OD): δ_C 153.1, 151.9, 150.1, 150.0, 147.0, 137.9, 136.9, 132.8, 131.1, 130.5, 129.9, 128.6, 127.2, 125.2, 121.7, 45.2, 41.6; HRMS *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{16}N_5$ 290.1400, found 290.1390. Compound **10a**: Brown oil; 1H NMR (500 MHz, CD_3OD): δ_H 8.50 (d, *J* = 4.6 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 1.4 Hz, 1H), 7.83 (t, *J* = 9.3 Hz, 2H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 8.1, 4.9 Hz, 1H), 4.60 (dd, *J* = 14.7, 7.2 Hz, 1H), 4.52 (dd, *J* = 14.6, 5.6 Hz, 1H), 3.62–3.72 (m, 1H), 1.10 (d, *J* = 6.5 Hz, 3H), NH2 protons in exchange; ^{13}C NMR (125 MHz, CD_3OD): δ_C 155.6, 150.4, 146.6, 136.6, 135.8, 134.4, 133.7, 132.9, 130.2, 129.5, 124.9, 121.5, 50.7, 48.9, 19.3; HRMS *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{16}BrN_4$ 331.0552, found 331.0551. Compound **10b**: Grayish brown solid; mp = 105–107 °C; 1H NMR (500 MHz, CD_3OD): δ_H 8.42 (d, *J* = 4.5 Hz, 1H), 8.07–8.09 (m, 1H), 7.77 (d, *J* = 8.4, 2H), 7.62 (t, *J* = 8.4 Hz, 2H), 7.37 (dd, *J* = 4.9, 8.0 Hz, 1H), 4.90 (s, 2H), 4.58 (dd, *J* = 14.8, 7.2 Hz, 1H), 4.48 (dd, *J* = 14.8, 5.5 Hz, 1H), 3.67–3.72 (m, 1H), 1.08 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ_C 156.1, 150.5, 146.4, 139.0, 136.6, 133.1, 131.4, 130.1, 129.3, 121.5, 50.3, 49.0, 18.9; HRMS *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{16}C_lN_4$ 287.1058, found 287.1049. Compound **10c**: Brown oil; ^{1}H NMR (500 MHz, CD_3OD): δ_H 8.45 (d, *J* = 7.7 Hz, 1H), 8.10 (d, *J* = 7.9, 1H), 7.86 (dd, *J* = 8.7, 5.3, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.36–7.38 (m, 1H), 4.88 (s, 2H), 4.55 (dd, *J* = 14.8, 7.1 Hz, 1H), 4.47 (dd, *J* = 14.9, 5.6 Hz, 1H), 3.60-3.67 (m, 1H), 1.06 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ_C 166.4 (d, JC-F = 248.8 Hz), 156.4, 150.5, 146.3, 136.6, 133.9 (d, JC-F = 8.8 Hz), 129.2, 127.9 (d, $J_{C\text{-}F}$ = 3.7 Hz), 121.4, 118.1 (d, $J_{C\text{-}F}$ = 22.3 Hz), 50.9, 48.8, 19.6; HRMS *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{16}FN_4$ 271.1353, found 271.1346.
14. All of the compounds synthesized in this work have been deposited with the Queensland Compound Library (Griffith University) and are available for collaborative discovery projects.