Exploration of versatile reactions on 2-chloro-3-nitroimidazo[1,2-*a*]pyridine: expanding structural diversity of C2- and C3-functionalized imidazo[1,2-*a*]pyridines

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Graphical Abstract

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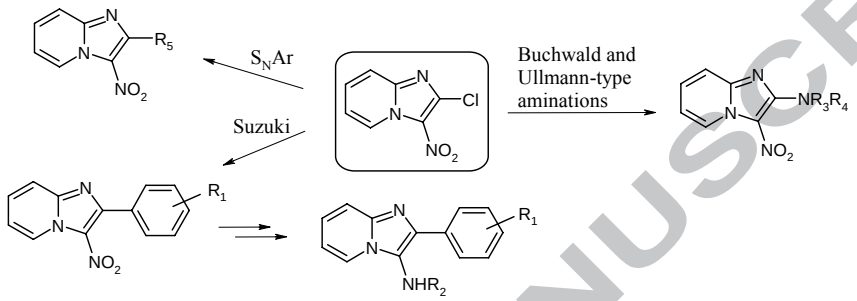

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Exploration of versatile reactions on 2-chloro-3-nitroimidazo[1,2-*a*]pyridine: expanding structural diversity of C2- and C3-functionalized imidazo[1,2-*a*]pyridines

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ABSTRACT

Alternative strategies for functionalizing 2-chloro-3-nitroimidazo[1,2-*a*]pyridine have been developed. Suzuki-Miyaura cross-coupling reaction provided easily the corresponding 2-arylated compounds, and herefrom the nitro group was reduced into amine which afforded amides, anilines and ureas in the 3-position. The amination of the key compound using metal-catalyzed reaction was reported. This study highlighted the importance of nitro group to facilitate the chlorine displacement. Other nucleophilic aromatic substitutions open a route to various products derived from imidazo[1,2-*a*]pyridine.

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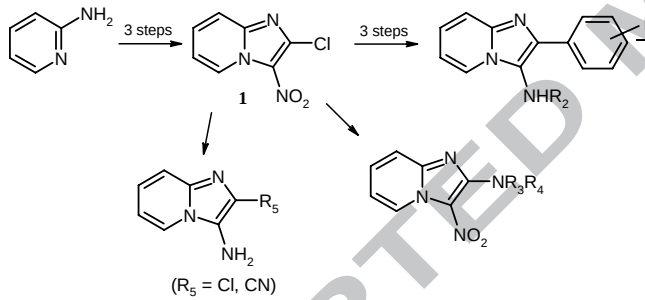
2,3-Disubstituted imidazo[1,2-*a*]pyridines represent the structural motif of various substances possessing relevant biological and pharmacological properties[1] including antinfective,[2] anti-inflammatory,[3] hypnotic,[4] antipsychotic,[5] and gastric antisecretory properties.[6] Besides, imidazo[1,2-*a*]pyridines display photophysical properties of great interest.[7]

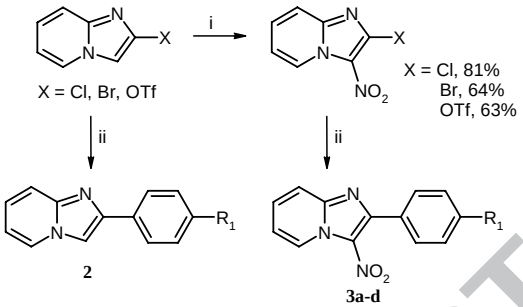
As part of our studies towards the synthesis of biologically active compounds,[8] we were interested in functionalizing 2-chloro-3-nitroimidazo[1,2-*a*]pyridine **1**, a key compound leading to a great diversity of 2,3-disubstituted imidazo[1,2-*a*]pyridines (Scheme 1). In particular, we set out to develop a convenient synthesis of 3-amino-2-arylimidazo[1,2-*a*]pyridines derivatives and useful reactions such as nucleophilic aromatic substitutions (S_NAr) and metal-catalyzed cross-coupling reactions starting from **1**. A few examples of functionalizations of 2-chloro-3-nitroimidazo[1,2-*a*]pyridine **1** are reported in the literature, including only S_NAr in the 2-position with amines,[9] heterocycles,[10] phenols[11] and alcohols.[12] Azaheterocycles bearing such *ortho*-nitro chloro system are efficient scaffolds to introduce amines or amides.[13] Thus we envisaged an extended methodology based on metal-catalyzed reactions exploiting nitro group in the 3-position to provide a wide range of novel 2,3-disubstituted imidazo[1,2-*a*]pyridines.

We first explored the preparation of 3-aminoimidazo[1,2-*a*]pyridines. Such compounds are usually synthesized using multi-component reaction (MCR) Groebke-Blackburn-Bienaymé reaction.[14] Moreover we thought that compound **1** could be an alternative and that a sequence including a Suzuki cross-coupling reaction and a reduction of the nitro group could easily provide the target compounds.



Scheme 1. Reactivity of 2-chloro-3-nitroimidazo[1,2-*a*]pyridine **1** in this study.

Initial trials were carried out on 2-halogenoimidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyridin-2-yl triflate[15] which were subjected to a nitration to afford corresponding 3-nitro derivatives (Scheme 2).[16] Suzuki-Miyaura couplings furnished the required 3-nitro-2-phenylimidazo[1,2-*a*]pyridine[17] **3a** from 2-chloro- and 2-bromo- derivatives in good yields, respectively 68% and 72% (Table 1, entries 4 and 5). The reaction with 2-chloro-3-nitroimidazo[1,2-*a*]pyridine **1** was complete when 2 equivalents of phenyl boronic acid were used (entry 4). Surprisingly, only traces were detected for this reaction with triflate derivative (entry 6). The yield of the reaction was clearly improved due to electron withdrawing effect of the nitro group in the 3-position (entries 1–2 *vs* 4–5), except for triflate derivative. Further, we focused on the use of 2-chloro-3-nitroimidazo[1,2-*a*]pyridine **1** because 2-bromoimidazo[1,2-*a*]pyridine was obtained in poor yield (i.e. 9%) from commercially available 2-aminopyridine.[15]



Scheme 2. Reagents and conditions: (i) HNO_3, H_2SO_4, -5 °C→r.t., 3 h, 63–81%; (ii) $ArB(OH)_2$ 1.2 equiv., $Pd(PPh_3)_4$ 5% mol, Na_2CO_3 2.5 equiv., DME/H_2O (2:1), reflux, 3 h–20 h.

Table 1. Attempts for Suzuki cross-coupling in the 2-position.

Entry	Substrate	Product		Time (h)	Yield[a] (%)
1	X = Cl	R_1 = H	**2**	6	25
2	X = Br	R_1 = H	**2**	6	51
3	X = OTf	R_1 = H	**2**	7	43
4	X = Cl	R_1 = H	**3a**	6	68 (90[b])
5	X = Br	R_1 = H	**3a**	6	72
6	X = OTf	R_1 = H	**3a**	6	traces
7	X = Cl	R_1 = OMe	**3b**	3	96
8	X = Cl	R_1 = F	**3c**	3	97
9	X = Cl	R_1 = NO_2	**3d**	4	72

[a] Isolated yield.
[b] Reaction carried out with $C_6H_5B(OH)_2$: 2.0 equiv, Na_2CO_3: 4.0 equiv.

Moreover, nitration of 2-phenylimidazo[1,2-*a*]pyridine **2** was envisaged to obtain **3a** but a nitration of the phenyl ring was observed as a side reaction, as Hand and Paudler had previously mentioned.[18] To examine briefly the scope of Suzuki-Miyaura reaction with **1**,[19] we carried out other couplings starting from boron reagents bearing either an electron donating group (i.e. methoxy) or an electron withdrawing group (i.e. fluor or nitro) (Table 1, entries 7–9). Products **3b–3d** were obtained in good to excellent yields in a short reaction time. These results suggest that Suzuki coupling on 2-chloro-3-nitroimidazo[1,2-*a*]pyridine **1** in the position 2 could be extended to a greater variety of boron reagents.

Subsequent reduction of the nitro group with H-Cube® afforded easily amine **4** (96% yield) (Scheme 3). This amine was obtained in an excellent 44% overall yield from 2-aminopyridine over 5 steps. Thus we synthesized amides, anilines and ureas to scope the reactivity of the amine in the 3-position. First, acetylation of **4** with acetic anhydride provided acetamide **5a** in a good yield (Table 2, entry 1). Thus this amine **4** was enough reactive towards other electrophilic reagents such as benzoyl chloride (entry 2). Given the success of these reactions we expanded the scope of electrophiles to obtain ureas **6a-f** from amine **4** and various isocyanates. Classical conditions[20,21] were used to afford firstly product **6a** in 55% yield (Table 2, entry 3). This method was subsequently applied to a wide range of isocyanates furnishing corresponding ureas. To our delight, ureas were formed in yields ranging from 41–70% (Table 2, entries 4, 6–8) while compound **6c** was surprisingly obtained in a lower yield (16%) due to purification problems (entry 5).

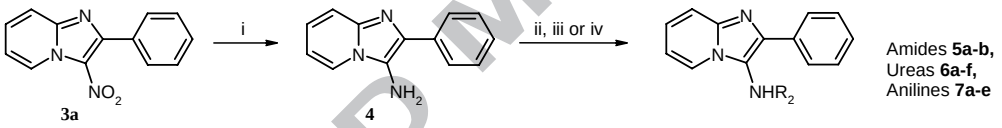
We next envisaged to arylate amine **4** with halogenoarenes in a Pd-catalyzed Buchwald-Hartwig reaction.[22] Indeed, *N*,2-diarylimidazo[1,2-*a*]pyridin-3-amines have attracted growing interest due to their biological applications.[2d,23] The reaction was

performed as described in the general procedure.[24] Conditions used in the first attempt with bromobenzene were found to be acceptable and provided **7a** in 70% yield (Table 2, entry 9). The reaction took place with various haloarenes to provide the corresponding products in low to moderate yields (Table 2, entries 10–12) whereas the reaction with 4-bromoanisole failed, likely due to electron-donor effect of methoxy group (entry 13).

To investigate the behavior of 2-chloro-3-nitroimidazo[1,2-*a*]pyridine **1**, we reasoned that amines would favour S_NAr displacement of the chlorine as previously described.[9-10,25] Such substitution was recently achieved by Salgado-Zamora and co-workers on 2-cyano-3-nitroimidazo[1,2-*a*]pyridine.[26] We carried out a reaction between **1** and benzylamine, aniline and *n*-propylamine in the presence of *t*-BuOK in tetrahydrofurane (Scheme 4, Table 3). As expected, the substitution occurred in a good yield for benzylamine (56%) and in a lower yield for aniline (35%) even heating at 50 °C and adding double quantity of reagents. Surprisingly, the conversion was decreased when *n*-propylamine was used even in harsher conditions (15%). With these initial trials in hand, we were keen to enhance the performance of the substitution implementing metal-catalyzed reactions. It is well-known that Buchwald-Hartwig[27] and Ullmann-type[28] aminations can improve such coupling through transition-metal-mediated processes. Standard conditions of Pd-catalyzed amination were used with benzylamine, Pd_2dba_3, BINAP and *t*-BuONa in toluene to provide **8a** in a higher yield (76%). Microwave-promoted reaction (monomode CEM Discover® SP) allowed a similar yield (84%). Microwave-promoted Buchwald amination with *n*-propylamine afforded the desired product in an acceptable yield (56%). Performing same reaction with the less nucleophilic aniline provided **8b** in 37% yield but the use of microwave heating for 1 hour enhanced the yield to 83%. It is noteworthy that Pd-catalyzed amination of 2-chloroimidazo[1,2-*a*]pyridine with benzylamine and aniline in the same conditions did not afford the corresponding amine in the 2-position. These results confirmed once again the influence of nitro group to carry out the chlorine displacement with an amine. Microwave heating allowed convenient yields in Buchwald coupling with primary amines in a short heating time (1 h). In contrast, reaction of **1** with a less nucleophilic reagent such as benzophenone imine led to **8d** in a very low yield (5%).

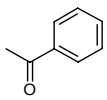
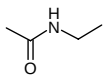
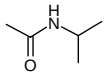
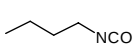
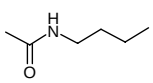
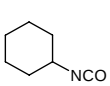
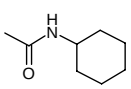
In another set of experiments, a copper-catalyzed amination with CuI, DMEDA and K_3PO_4 in toluene afforded **8a** and **8b** in lower yields than Pd-catalyzed aminations and no reaction occurred with benzophenone imine. Thus the use of palladium in Buchwald-Hartwig conditions seemed to improve the yield of such substitution in the 2-position rather than copper-catalyzed reaction. Finally, the reduction of nitro group of compounds **8a** and **8b** was envisaged. The conversion occurred with H-Cube® (about 50% conversion from LC–MS) but the purification failed on neither alumina nor silica gel (data not reported).

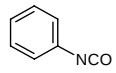
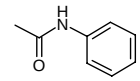
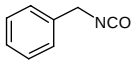
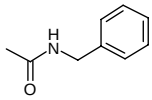
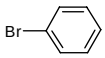
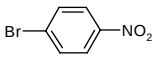
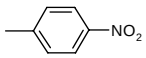
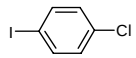
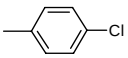
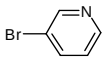
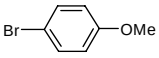
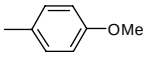
Other functionalizations of 2-chloro-3-nitroimidazo[1,2-*a*]pyridine **1** were explored and are reported in Scheme 5. Compound **9** was synthesized *via* cyanation using copper(I) cyanide in NMP at 170 °C for 4 days. Subsequent reduction of nitro group with Sn/HBr afforded easily 3-amino-2-cyanoimidazo[1,2-*a*]pyridine **10** which would be subjected to further cyclization.[29] In addition, chemical reduction of nitro group of **1** provided amine **11** in 87% yield, and such compound seemed to show a significant interest in heteroannulation of imidazo[1,2-*a*]pyridines.[30]



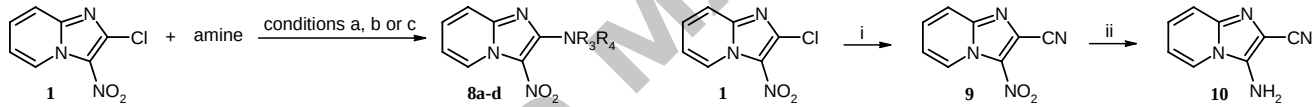
Scheme 3. Synthesis of 3-aminoimidazo[1,2-*a*]pyridines derivatives **5a-b**, **6a-f** and **7a-e**. Reagents and conditions: (i) H-Cube®, Raney Ni cartridge, Full H_2, flow rate 1 mL/min, EtOH/THF (9:1), 40 °C, overnight, 96%; (ii) Cpd **5a**: Ac_2O, toluene, reflux, 16 h, 65%; Cpd **5b**: benzoyl chloride, THF, Et_3N, r.t., 48 h, 43%; (iii) Cpds **6a-f**: isocyanate, DMF, 80 °C, 16 h–24 h, 16–70%.; (iv) Cpds **7a-e**: (het)ArBr or ArI, $Pd_2(dba)_3$, BINAP, *t*-BuONa, toluene, sealed tube, 110 °C, 4 h–16 h, 29–70%.

Table 2. Synthesis of **5a-b**, **6a-f** and **7a-e** from 3-amino-2-phenylimidazo[1,2-*a*]pyridine **4**.

Entry	Reagent	Compd	R_2	Time	Yield[a] (%)
1	Ac_2O	**5a**		16 h	65
2	PhCOCl	**5b**		48 h	43
3		**6a**		16 h	55
4[b]		**6b**		24 h	41
5		**6c**		16 h	16
6		**6d**		16 h	45

7		**6e**		24 h	70
8		**6f**		16 h	54
9		**7a**		4 h	70
10		**7b**		16 h	66
11[c]		**7c**		1.5 h	40
12		**7d**		16 h	29
13		**7e**		24 h	0[d]

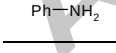
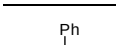
[a] Isolated yield.
[b] 3 Equiv. of isopropylisocyanate.
[c] Conditions: 1-chloro-4-iodobenzene, sealed tube, MW, 125 °C, 1.5 h.
[d] No product was detected on UPLC/MS chromatogram.



Scheme 4. Synthesis of compounds **8a-d**. Reagents and conditions: (a) S_NAr: amine (1.2 equiv.), *t*-BuOK (1.3 equiv.), THF, r.t., 18 h; (b) Buchwald amination: amine (2.0 equiv.), Pd_2dba_3 (0.1 equiv.), BINAP (0.3 equiv.), *t*-BuONa (1.0 equiv.), toluene, sealed tube, 110 °C, 20 h under classical heating; 120 °C, 1 h, microwave heating (P = 75 W); (c) Ullmann-type amination: amine (2.0 equiv.), CuI (0.1 equiv.), DMEDA, (0.3 equiv.), K_3PO_4 (2.0 equiv.), toluene, sealed tube, 110 °C, 20 h.

Scheme 5. Synthesis of compounds **9–11**. Reagents and conditions: (i) CuCN, NMP, sealed tube, 170 °C, 96 h, 39%; (ii) Sn/HBr, 0°C→r.t., 1 h, 81%; (iii) Sn/HCl, 0°C→r.t., 2 h, 87%.

Table 3. Amination of **1** *via* S_NAr, Buchwald or Ullmann-type reactions in the 2-position.

Amine	Product	S_NAr (yield %)	Buchwald (yield %)		Ullmann (yield %)
			Classical heating	MW heating	
	**8a**	56	76	84	62
	**8b**	35[a]	37	83	10
	**8c**	15[b]	–	56	–
	8d	–	5	–	0

–: not implemented.
[a] Aniline: 2.4 equiv, *t*-BuOK: 2.6 equiv, 50 °C.
[b] *n*-Propylamine: 2.0 equiv, *t*-BuOK: 2.0 equiv, sealed tube, 80 °C.

In summary, we have reported new synthetic methods from 2-chloro-3-nitroimidazo[1,2-*a*]pyridine **1** as a valuable scaffold to perform metal-catalyzed reactions. The presence of the nitro group in the 3-position was essential to develop functionalization in the 2-position with aryles and amines. In particular, the obtention of 2-arylimidazo[1,2-*a*]pyridin-3-amine derivatives is an alternative to the multi-component reaction (MCR) Groebke-Blackburn-Bienaymé reaction. Moreover, a broad range of transformations of 2-chloro-3-nitroimidazo[1,2-*a*]pyridine **1** could offer highly diverse products derived from imidazo[1,2-*a*]pyridine scaffold for medicinal chemistry.

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C), 128.13, 128.82 (2 C), 133.33, 139.37, 143.10, 154.30 (C=O); IR (KBr) 3254, 2970, 1722, 1634, 1501, 1485 cm^{-1}; MS (ESI) m/z (%): 281.1 (100) $[M+H]^+$; Anal. Calcd for $C_{16}H_{16}N_4O$: C 68.55; H 5.75; N 19.99. Found: C 68.88; H 5.96; N 19.78%.

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Graphical Abstract

Exploration of versatile reactions on 2-chloro-3-nitroimidazo[1,2-*a*]pyridine: expanding structural diversity of C2- and C3-functionalized imidazo[1,2-*a*]pyridines

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