Efficient Synthesis of 6-Aryl-2-chloronicotinic Acids via Pd Catalyzed Regioselective Suzuki Coupling of 2,6-Dichloronicotinic Acid

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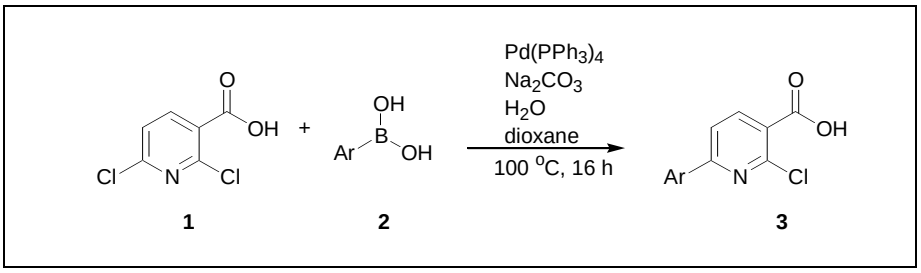

A regioselective Suzuki coupling of 2,6-dichloronicotinic acid with aryl boronic acids to synthesize 6-aryl-2-chloronicotinic acids is described. Regioselectivity was achieved in aqueous dioxane using the routinely used catalyst $Pd(PPh_3)_4$.

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INTRODUCTION

Pyridine derivatives appear as important motifs in biological active compounds as well as therapeutic agents [1]. 2,6-Dichloronicotinic acid and its derivatives are readily accessible and can serve as useful starting materials in the preparation of pyridino-containing biologically active small molecules [2]. Selectively replacing one of the two chloride atoms at the 2- or 6-position of these compounds by different functional groups will lead to access of a pool of diversified pyridines [3]. Although progress has been made on the selective substitution of the 2- or 6-chloro atoms of the 2,6-dichloronicotinic acid and its derivatives by alkoxy and amino groups *via* nucleophilic S_NAr reaction, there are very rare examples of selective substitution of the chloride atoms by aryl groups. Herein we report a method of selective substitution of 6-Cl of 2,6-dichloronicotinic acid.

RESULTS AND DISCUSSION

During the course of our medicinal chemistry research, we encountered a need for introducing aryl group at the position 6 of 2,6-dichloronicotinic acid, its ester and amide derivatives. The only one example of such reactions (a patent) is a substitution of 6-Cl of ethyl 2,6-dichloronicotinate with a phenyl group *via* the Suzuki coupling reaction [4]. The Suzuki reaction conducted in DME by employing $Pd(PPh_3)_4$ as catalyst afforded the 6-phenyl product in 34% yield with a 6:1 ratio of the 6-phenyl product to the 2,6-diphenyl product. Besides this patent, there is only one literature report on the selective substitution of the chlorine atoms of 2,6-dichloronicotinic acid derivatives with aryl groups *via* the Suzuki coupling reaction [5]. In this report [5], Yang *et al.* focused on the selective introduction of aryl groups at position 2 of 2,6-dichloronicotinamide as well as methyl 2,6-dichloro-nicotinate by employing a special Pd catalyst ($PXPd_2$). Regioselectivity at position 2 over position 6 was achieved with best ratio of 9 to 1 in the case of an amide and 2.5 to 1 in the case of methyl ester. Yang *et al* also found that the ratio of 6-phenyl product to 2-phenyl product of Suzuki reaction of phenyl boronic acid with methyl dichloronicotinate has been between 1:1.7 and 5:1 with using broadly diversified Pd catalysts. At the beginning of our study, we tried to explore region-selective Suzuki coupling on methyl 2,6-dichloro-nicotinate. There was not much success in finding reaction conditions with decent regioselectivity. Considering the difficulties we encountered and what was reported by Yang *et al*., we believed that it would not be feasible to achieve good selectivity by playing different catalysts, bases or solvents. We were inclined to explore a different approach to improve selectivity. Because there was no report about introduction of aryl group to the simplest substrate in the series, 2,6-dichloronicotinic acid, we decided to carry out the Suzuki reaction on 2,6-dichloronicotinic acid under one of the most commonly employed conditions. Actually, according to Yang and co-workers, the best selectivity of 6-phenyl product over 2-phenyl product was 5 to 1 when the reaction was conducted in THF with using $Pd(PPh_3)_4$ as catalyst and K_2CO_3 as base [5]. In our study, Suzuki coupling of arylboronic acids with 2,6-dichloronicotinic

Table 1

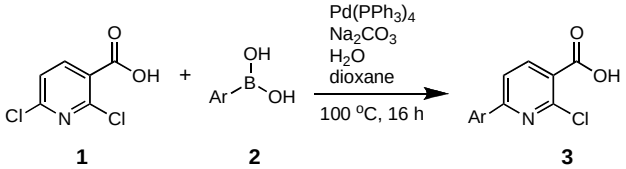
6-Aryl-2-chloronicotinic acids (**3**) from Regioselective Suzuki Coupling of 2,6-dichloronicotinic acid with aryl boronic acids (**2**).

3	Ar	Yield [a] %	^{1}H NMR ($CDCl_3$) δ	ESI-MS *m/z* (MH^+)	Molecular Formula	Analysis % [b] Calcd./Found		
						C	H	N
3a	phenyl	81	7.49-7.53 (3H), 7.92 (d, *J* = 8.1 Hz, 1H), 8.09 (m, 2H), 8.28 (d, *J* = 8.1 Hz, 1H)	234	$C_{12}H_8ClNO_2$	61.69 61.94	3.45 3.46	5.99 5.97
3b	3,4-dimethylphenyl	72	2.31 (s, 3H), 2.34 (s, 3H), 7.20 (d, *J* = 10.3 Hz, 1H), 7.73 (m, 1H), 7.83 (d, *J* = 8.1Hz, 1H), 7.85 (s, 1H), 8.25 (d, *J* = 8.1 Hz, 1H)	262	$C_{14}H_{12}ClNO_2$	64.25 64.45	4.62 4.64	5.35 5.33
3c	3-chlorophenyl	69	7.42-7.49 (2H), 7.95 (d, *J* = 8.1 Hz, 1H), 8.01 (m, 1H), 8.12 (s, 1H), 8.32 (d, *J* = 8.1 Hz, 1H)	268	$C_{12}H_7Cl_2NO_2$	53.76 53.87	2.63 2.63	5.22 5.21
3d	3-methoxyphenyl	79	3.88 (s, 3H), 7.05 (m, 1H), 7.41 (m, 1H), 7.63 (m, 1H), 7.64 (s, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 8.30 (d, *J* = 8.1 Hz, 1H)	264	$C1_3H_{10}ClNO_3$	59.22 59.38	3.82 3.83	5.31 5.29
3e	4-fluoro-2-methoxyphenyl	65	3.90 (s, 3H), 6.83 (m, 1H), 6.95 (m, 1H), 7.90 (m, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 8.25 (d, *J* = 8.1 Hz, 1H)	282	$C1_3H_9ClFNO_3$	55.43 55.62	3.22 3.24	4.97 4.95
3f	2,3-dimethoxylphenyl	78	3.75 (s, 3H), 3.91 (s, 3H), 7.18-7.20 (2H), 7.13 (m, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 8.29 (d, *J* = 8.1 Hz, 1H)	294	$C_{14}H_{12}ClNO_4$	57.25 57.36	4.12 4.14	4.77 4.74
3g	3,5-difluoro-2-methoxyphenyl	63	4.04 (s, 3H), 7.37 (m, 1H), 7.63 (m, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.52 (d, *J* = 8.0 Hz, 1H)	300	$C1_3H_8ClF_2NO_3$	52.11 52.31	2.69 2.72	4.67 4.65
3h	2-naphthalenyl	70	7.53-7.57 (2H), 7.89 (m, 1H), 7.94-8.02 (2H), 8.06 (d, *J* = 8.1 Hz, 1H), 8.18 (dd, *J* = 8.7 and 1.8 Hz, 1H), 8.33 (d, *J* = 8.1 Hz, 1H), 8.61 (s, 1H)	284	$C_{16}H_{10}ClNO_2$	67.74 67.85	3.55 3.57	4.94 4.92

[a] Calculated on the basis of the re-crystallized solid products. [b] Performed with re-crystallized solid products.

acid was conducted in the common solvent dioxane together with water. Inexpensive Na_2CO_3 was used as the base and the catalyst was the most commonly used $Pd(PPh_3)_4$. To our delight, only the desired 6-aryl regioisomers were obtained as exclusive products (Scheme 1). Eight arylboronic acids were examined and the results are listed in Table 1. The yields of the reactions are from good to excellent. All products were pure enough for further coupling reactions with amines to make amides or for esterification. They could also be crystallized easily from a mixed solvent of EtOAc and methanol if special purity is required.

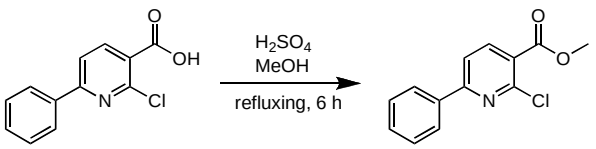
Scheme 1



1 **2** **3**

The structural assignment was clearly supported by chemical shifts in ^{1}H NMR of ~7.9 ppm (d, *J* = 8.1 Hz, 1H) and ~8.3 ppm (d, *J* = 8.1 Hz, 1H) which stand for two protons H4 and H5 of the pyridine core [5]. Because there is no reported NMR data for acid **3a**, we transformed **3a** into the methyl ester **4a** in order to do a direct comparison of **4a**'s NMR data to the reported ones. Therefore, methyl ester **4a** was made from **3a** by refluxing in MeOH in the presence of H_2SO_4 (Scheme 2). The chemical shifts observed in the H^1 NMR spectrum of compound **4a** was found to be identical with what was reported [5].

Scheme 2



3a **4a**

Although the structural elucidation based on ^{1}H NMR of **4a** was persuasive, unambiguous evidence for such assignment was still needed. Hence, single crystals of **3a** with X-ray diffraction quality were grown by slow evaporation from a mixed solvent of EtOAc and MeOH.

As expected, the single-crystal structure of **3a** clearly shows the phenyl group at position 6 of this compound (Figure 1).

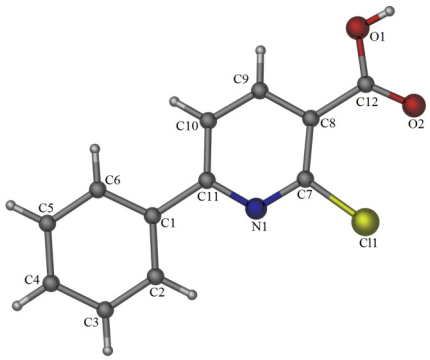


Figure 1. Crystal structure of 2-chloro-6-phenyl-nicotinic acid (**3a**).

In summary, we have described a simple regioselective method for generation of 6-aryl-2-chloro-nicotinic acids starting from commercially available 2,6-dichloro nicotinic acid and arylboronic acids under Suzuki coupling condition catalyzed by $Pd(PPh_3)_4$. This method could be easily adapted in the synthesis of 6-aryl substituted nicotinic acids, from which their amide or ester derivatives could be readily made.

EXPERIMENTAL

General Remarks. ^{1}H NMR spectra were recorded on a 300 MHz Bruker spectrometer and are reported in ppm. 2,6-Dichloronicotinic acid (97%) was obtained from Aldrich. All other commercially available solvents and reagents were used without further purification. Brine refers to a saturated aqueous sodium chloride solution. Solvent removal was accomplished by a rotary evaporator operating at vacuum (40-50 Torr).

Representative Procedure: **6-(3,4-Dimethylphenyl)-2-chloronicotinic acid (3b).** A mixture of 2,6-dichloronicotinic acid (**1**) (198 mg, 97%, 1 mmol), 3,4-dimethylphenylboronic acid (**2**) (178.8 mg, 1.2 mmol), $Pd(PPh_3)_4$ (53 mg, 0.05 mmol) and Na_2CO_3 (318 mg, 3 mol) in a mixed solvent of dioxane (15 mL) and H_2O (5 mL) was purged with N_2 and heated at 100 °C for 16 h. After cooling to room temperature, the reaction mixture was poured into Na_2CO_3 solution (10%, 100 mL) and the aqueous phase was washed with EtOAc (2 × 20 mL), acidified to pH = 1 with concentrated HCl (12 *N*) and extracted with EtOAc (3 × 30 mL). The organic extracts were combined, washed with brine (10 mL), dried over Na_2SO_4 and evaporated to afford **3b** (220.8 mg, 84%). Compound **3b** was crystallized in mixed solvent of EtOAc /MeOH (5:1) to result in crystalline solid (198 mg, 72%).

Esterification of 3a into methyl 2-chloro-6-phenyl-nicotinate (4a). To solution of 2-chloro-6-phenylnicotinic acid (**3a**) (58.4 mg, 0.25 mmol) in methanol (50 mL) was added concentrated sulfuric acid (98%, 0.2 mL) resulting in a mixture which was refluxed for 6 h and then concentrated. The residue was partitioned between aqueous Na_2CO_3 solution (80 mL) and EtOAc (40 mL) and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (10 mL) and dried over Na_2SO_4, evaporated to afford **4a** (37.8 mg, 61%). ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 1H), 7.47-7.53 (3H), 7.73 (d, *J* = 8.1 Hz, 1H), 8.04-8.07 (2H), 8.24 (d, *J* = 8.1 Hz, 1H); ESI-MS *m*/*z* 248 (MH^+).

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