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$Pd_2(dba)_3$-promoted synthesis of 3-N-substituted 4-aryl-1,2,3,6-tetrahydropyridine

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ABSTRACT

A novel method for the synthesis of 3-N-substituted 4-aryl-1,2,3,6-tetrahydropyridine **3** is presented. The process is carried out by the allylic bromination of 4-aryl-1,2,3,6-tetrahydropyridines **1** with *N*-bromosuccinimide in propanoic acid and palladium-catalyzed cross coupling of the corresponding bromide **2** with different N-based nucleophiles.

1. Introduction

In the field of substituted piperidine libraries, there is a constant need for new methods for developing medicinal agents. Because the structural skeleton is known as a building partner in the synthesis of related compounds with potential pharmaceutical activities, a number of methods have been developed for the use of these heterocycles along with several applications of these aminopiperidines . The 3-N-substitutent piperidine moiety is a key ingredient in many therapeutic agents and is used as an important bioactive component in pharmaceutical research.[1] For example, alogliptin is used for the treatment of diabetes,[1a,1b] while CP-690550 serves as a Janus kinase 3 (JAK3) inhibitor for autoimmune disease and transplant patients.[1c] In the general preparation of 3-N-substituted piperidines, the common synthetic methods include nucleophilic ring-opening of aziridinopiperidine[2,3] and ring-closing metathesis reaction of diallylamine.[4]

In the preliminary studies, we investigated the interesting rearrangement reaction of 4-aryl-1,2,3,6-tetrahydropyridine **1** which occurred during the preparation of a different framework that included pyrrolidine, piperidine, azepane, benzoisoquinoline, and other substances.[5] Given the synthetic advantages of this initial material, an easy strategy was developed for preparing several N-3-substituted 4-aryl-1,2,3,6-tetrahydropyridines **3a**–**t**. The substituents included sulfonamide, alkenylamide, arylamide, carbamate, and urea. This novel two-step synthesis of **3** from **1** involves an allylic bromination of olefin **1** with *N*-bromosuccinimide (NBS) in propanoic acid, followed by the palladium-catalyzed intermolecular amination of allylic bromide **2** with amine derivatives.

2. Results and discussion

In the NBS-mediated allylic bromination, olefin **1a** was chosen as the model substrate, as shown in Table 1. Initially, treatment of olefin **1a** with NBS in chloroform provided allylic bromide **2a** in low yield (36%). When the reaction solvent was acetic acid, a mixture of allylic bromide **2a** and bromoacetate **4a** was isolated at a nearly 2:1 ratio. After changing the solvent to propanoic acid, the ratio of **2a**/**4b** increased to 10/1.[6] This study suggested that propanoic acid with a slight steric hindrance cannot be easily introduced into the benzylic cation of olefin **1a**, and the main resulting product **2a** can be generated via the abstract hydrogen of olefin **1a**. On the other hand, alcohols (e.g., methanol, ethanol, isopropanol, ethoxyethanol, and water) were introduced into the reaction, while various bromides **4c**–**g** were presented as the major products. As shown in entries 3–6, the resulting ratios of **2a**/**4c**–**2a**/**4f** were: 1/8 (81%), 1/10 (78%), 1/10 (66%), and 1/13 (56%). In particular, the treatment of olefin **1a** with NBS in *t*-butanol generated a sole bromohydrin **4g** (40%) without the formation of **2a** (entry 7). Using the water/dioxane (1/1) as the co-solvent, the yield of **4g** could be increased to a 53% yield under the reaction condition. Determination of the relative ratio of **2a**/**4** was performed through

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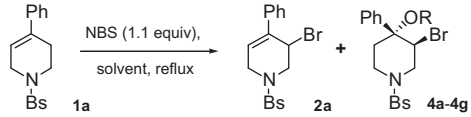
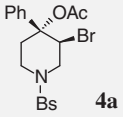
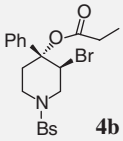
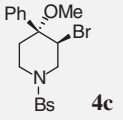
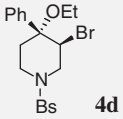
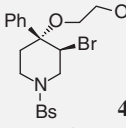
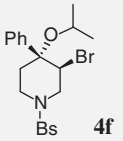
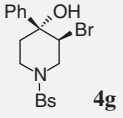
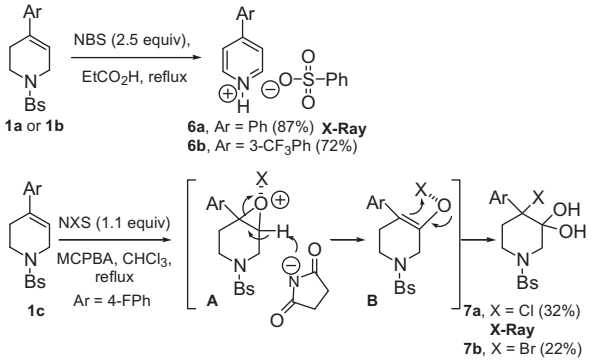
Table 1
NBS-mediated allylic bromination of olefin **1a**[a]



Entry	Solvent (10 mL)	Product **4**	Yield[b] (%), **2a**/**4**
1	$MeCO_2H$	 **4a**	59/30
2	$EtCO_2H$	 **4b**	72/7
3	MeOH	 **4c**	9/72
4	EtOH	 **4d**	7/71
5	$EtOCH_2CH_2OH$	 **4e**	6/60
6	*i*-PrOH	 **4f**	4/52
7	*t*-BuOH	 **4g**	—/40

[a] Reactions were performed in various solvents (5 mL) using the following mole ratios: **1a:**NBS = 1:1.1.
[b] The isolated products are >95% pure as judged by ^{1}H NMR analysis.



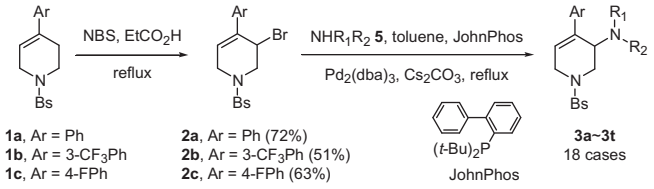
Scheme 1. NBS-mediated reaction of olefin **1**.

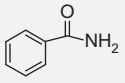
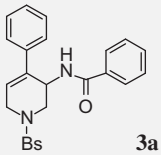
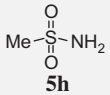
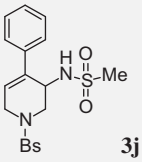
^{1}H NMR experiments and the provided overall yields were adjusted by the isolated products. To determine the allylic bromination of 4-aryl-1,2,3,6-tetrahydropyridine **1**, the optimal condition was an acidic onecondition. Using this protocol, **2b** and **2c** were also provided in 51% and 63% yields.

As shown in Scheme 1, when attempts were made to treat **1a** or **1b** with 2.5 equiv of NBS in propanoic acid at reflux, salt **6a** or **6b** was obtained in 87% or 72% yields without the formation of **2** or **4**. Based on the above results, we examined the reaction between **1c** with *m*-chloroperoxybenzoic acid (MCPBA) and NCS or NBS where the major products **7a** or **7b** were presented in 32% or 22% yields. A possible mechanism is proposed in Scheme 1. The initial event may be regarded as the formation of intermediate **A** with a halide-chelated epoxide. Next, intermediate **B** was generated via succinimide anion-mediated hydrogen abstraction followed by the ring-opening of epoxide. Thus, skeleton **7** was afforded by the intramolecular alkylation, followed by a hydration reaction under the rearrangement process.[7] Although the isolated yield was lower, this proposed method is novel. The structural frameworks of **4a**, **4e**, **6a,** and **7a** were determined using single-crystal X-ray analysis.[8]

Palladium-catalyzed allylic amination reactions have been studied extensively over the past decade.[9] With a useful catalytic system, we envisaged that palladium-catalyzed cross-coupling amination of allylic bromide **2a** with benzamide **5a** would produce the skeleton **3**. In this work, various palladium catalysts and ligands were tested, and the results showed a combination of $Pd_2(dba)_3$ and JohnPhos in toluene at reflux with Cs_2CO_3 as a base, produced

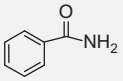
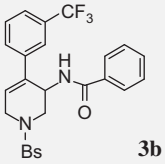
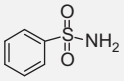
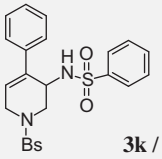
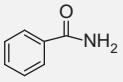
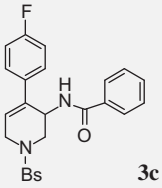
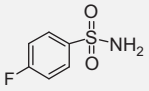
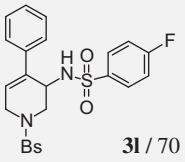
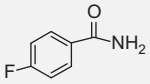
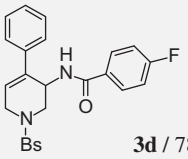
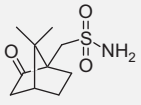
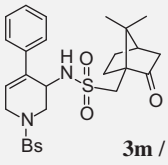
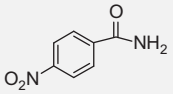
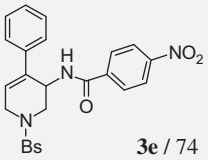
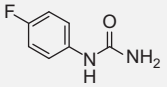
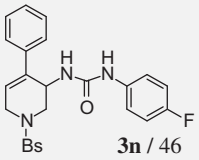
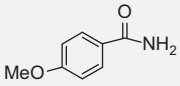
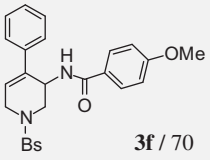
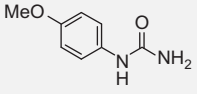
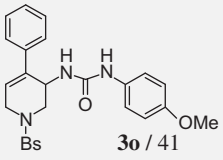
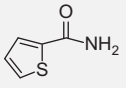
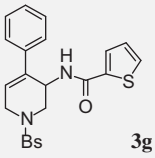
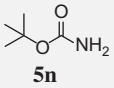
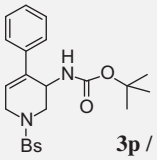
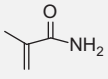
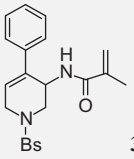
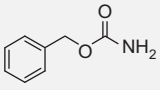
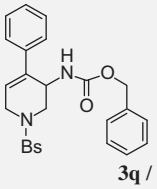
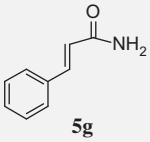
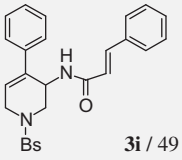
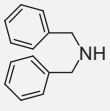
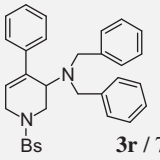
Table 2
Pd-Catalyzed cross-coupling reaction[a]



Entry	Bromide **2**	Nucleophile **5**	Product/Yield[b] (%)	Entry	Bromide **2**	Nucleophile **5**	Product/Yield[b] (%)
1	**2a**	 **5a**	 **3a** / 81	10	**2a**	 **5h**	 **3j** / 76

(*continued on next page*)

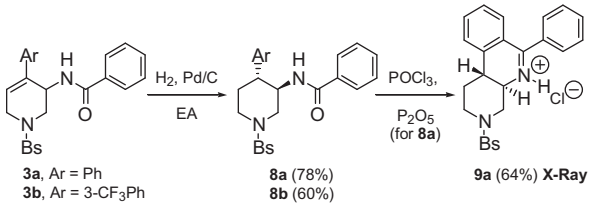
Table 2 (*continued*)

Entry	Bromide **2**	Nucleophile **5**	Product/Yield[b] (%)	Entry	Bromide **2**	Nucleophile **5**	Product/Yield[b] (%)
2	**2b**	 **5a**	 **3b** / 42	11	**2a**	 **5i**	 **3k** / 71
3	**2c**	 **5a**	 **3c** / 63	12	**2a**	 **5j**	 **3l** / 70
4	**2a**	 **5b**	 **3d** / 78	13	**2a**	 (*S*)-**5k**	 **3m** / 68
5	**2a**	 **5c**	 **3e** / 74	14	**2a**	 **5l**	 **3n** / 46
6	**2a**	 **5d**	 **3f** / 70	15	**2a**	 **5m**	 **3o** / 41
7	**2a**	 **5e**	 **3g** / 75	16	**2a**	 **5n**	 **3p** / 48
8	**2a**	 **5f**	 **3h** / 41	17	**2a**	 **5o**	 **3q** / 50
9	**2a**	 **5g**	 **3i** / 49	18	**2a**	 **5p**	 **3r** / 74

[a] Reactions were performed in toluene (2 mL) using the following mole ratios: **2:5:**$Pd_2(dba)_3$:JohnPhos:Cs_2CO_3 = 1:1:0.025:0.05:1.2.
[b] The isolated products **3** are >95% pure as judged by ^1H NMR analysis.

compound **3a** in 81% yield.[10] These conditions were applied to a diverse range of N-based nucleophiles **5**.[11] The dr value of the product **3m** is 53:47 as found by chiral phase HPLC. Each of the resulting **3** obtained was in 41–81% yields, which reflected the reactivity of **5**. A typical procedure offers a general and efficient alternative to the S_N reaction of **2** with various **5**. As shown in Table 2, 16 N-based nucleophiles of **5** included arylamides **5a**–**e**, alkenylamides **5f**–**g**, sulfonamides **5h**–**k**, ureas **5l**–**m**, carbamates **5n**–**o,** and alkylamine **5p**.[12]

This proposed method provides an advantage over the S_N reaction of **2** as it offers the possibility of employing **5** with either electron-donating groups or electron-withdrawing groups. For ani-



Scheme 2. Reaction of compound **3a**.

line, the desired skeleton **3** was isolated in a lower yield (13%). Attempts to perform the reaction with acyclic or cyclic imides (e.g., acetamide, succinimide, phthalimide) failed, which may be due to an insufficient nucleophilicity of imides. Hydrogenation of **3a** and **3b** yielded **8a** and **8b** in 78% and 60% yields (Scheme 2). The results showed that the treatment of **8a** with P_2O_5 in $POCl_3$ at reflux temperature produced benzonaphthyridine **9a** in 52% yield.[13] The structural frameworks of **3d**, **3g**, **3k,** and **9a** were determined by single-crystal X-ray analysis.[14]

3. Conclusion

In summary, we have successfully presented a synthetic methodology for producing novel 3-N-substituted 4-aryl-1,2,3,6-tetrahydropyridines involving NBS-mediated allylic bromination and followed by a palladium-catalyzed cross-coupling amination. Under the $Pd_2(dba)_3$/JohnPhos/Cs_2CO_3 system, the allylic bromides could couple with a wide range of N-based nucleophiles, such as arylamide, alkenylamide, sulfonamide, urea, and carbamate, etc. Several structures of the target products were nicely confirmed by X-ray crystal analysis. The structure–activity studies of desulfonated 3-aminopiperidines **3** and hydrogenated benzonaphthyridine **9a** in the phenylpiperidine selective serotonin reuptake inhibitors (PSSRI)[15] will be investigated in subsequent works.

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11. A representative procedure of skeleton **3** is as follows: A oven-dried sealed tube was charged with $Pd_2(dba)_3$ (2.5 mol %), Johnphos (5.0 mol %), N-based nucleophile **5** (0.5 mmol), allylic bromide **2a** (0.5 mmol), Cs_2CO_3 (0.6 mmol), and degassed toluene (2 mL). The sealed tube was evacuated and back-filled with nitrogen three times and then heated to reflux temperature with stirring for 10 h. The reaction mixture was allowed to cool to rt, diluted with toluene, and filtered through a pad of Celite. 0.5 N HCl (2 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford the crude product. Purification on silica gel (hexane/AcOEt = 3/1–1/1) afforded skeleton **3**. Representative data for compound **3a**: mp = 200–201 °C; HRMS (ESI, M^++1) calcd for $C_{24}H_{23}N_2O_3S$ 419.1429, found 419.1430; ^{1}H NMR (400 MHz): δ 7.84–7.81 (m, 2H), 7.72–7.69 (m, 2H), 7.63–7.24 (m, 11H), 6.50 (d, J = 8.8 Hz, 1H), 6.29 (dd, J = 2.4, 4.8 Hz, 1H), 5.41 (dd, J = 2.0, 8.8 Hz, 1H), 4.32 (dd, J = 4.8, 17.6 Hz, 1H), 4.04 (ddd, J = 1.2, 2.0, 12.0 Hz, 1H), 3.38 (dt, J = 2.4, 17.6 Hz, 1H), 2.79 (dd, J = 2.8, 12.4 Hz, 1H); ^{13}C NMR (100 MHz): δ 167.22, 136.73, 135.74, 135.54, 134.00, 133.14, 131.67, 129.24 (2×), 128.76 (2×), 128.54 (2×), 128.27, 127.66 (2×), 127.10 (2×), 125.32 (2×), 122.85, 49.52, 45.64, 44.77; Anal. Calcd for $C_{24}H_{22}N_2O_3S$: C, 68.88; H, 5.30; N, 6.69. Found: C, 69.02; H, 5.51; N, 6.91.
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