http://dx.doi.org/10.5012/bkcs.2013.34.2.394

Synthesis of *N*-Azaaryl Anilines: An Efficient Protocol *via* Smiles Rearrangement

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Received September 8, 2012, Accepted November 8, 2012

An efficient process for the synthesis of *N*-azaaryl anilines *via* Smiles rearrangement as a tool. A variety of *N*-azaaryl anilines were generated by the reaction of substituted phenols, substituted anilines, aminopyridines and chloroacetyl chloride or pyridols, under base condition in good to excellent yields.

Key Words : Smiles rearrangement, *N*-Azaaryl anilines, Amine, Phenol, Synthesis

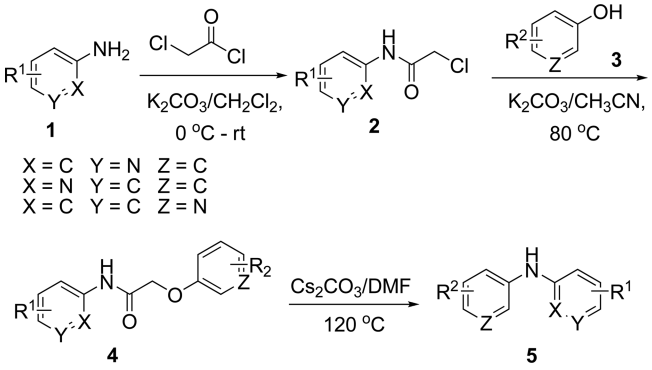
Introduction

The pyridine ring system appears to be indispensable in the structures of various natural products, pharmaceutical compounds, and other commercial substances. With pyridine ring in the structures, *N*-azaaryl anilines have attracted considerable attention owing to their wide range of biological activities, such as antimicrobial,[1] *anti*-inflammatory,[2] antitumor activity,[3] and as Met kinase inhibitor.[3]

As a result, a variety of methods have been described to form C-N bonds for the synthesis of *N*-azaaryl anilines. Traditional Cu-mediated C-N cross-couplings, Ullmann condensation,[4] has been one of the most powerful tools for the formation of C-N bond. Until now, palladium,[5-15] copper,[16-22] rhodium[23] and nickel[24,25] catalyzed cross-coupling reactions have shown great advantages for the construction of aromatic C-N bonds both in industrial and academic settings. And they are presented as the most efficient methods for C-N bond formation. However, in the synthetic processes for metal catalysts, typically an excess amount of ligand is required, which could be a disadvantage if the ligand is expensive. In addition, there are storage and handling difficulties, if the ligand is air sensitive. To point out, the existing methods restrict their use in the synthesis of *N*-azaaryl anilines which contain halogen atom in the structures, due to low yield and selectivity of the reactions. Therefore, the quest for lowering the reaction cost and easy handling reaction still remains greatly challenging.

Smiles rearrangement, an important intramolecular nucleophilic rearrangement reaction, was firstly discovered by Smiles in 1931.[26] With its abundant styles, it extended the diversity of small molecules, allowing the construction of new compounds with different pharmacophore functional groups.[27] We previously found that diarylamines and arylalkylamines were obtained by the reactions of phenols and amines, activated by chloroacetyl chloride in Cs_2CO_3/DMF system, assisted by Smiles rearrangement.[28,29]

Herein, we report an efficient approach to the synthesis of *N*-azaaryl anilines *via* Smiles rearrangement using substituted phenols, aminopyridines and chloroacetyl chloride or pyridols, substituted anilines and chloroacetyl chloride under basic condition (Scheme 1).



Scheme 1. Synthesis of *N*-azaaryl anilines.

Experimental

Chemistry.

General: ^1H and ^{13}C NMR spectra (at 500 MHz or 300 MHz and 125 MHz or 75 MHz, respectively) were recorded in $CDCl_3$ with tetra methylsilane as internal reference on a Bruker Advance 500 FT spectrometer. Chemical shifts were reported in parts per million. MS detection was performed on an Agilent 6510 Q-TOF mass spectrometer with an ESI source. $CDCl_3$ was used as delivered from Adamas (Shanghai, China). Silica gel (80-300 mesh) was used for flash column chromatography. All the reactions were monitored by TLC using 0.25 mm silica gel plates with UV indicator (Shanghai Jiapeng Technology Co., Ltd., China). Unless otherwise noted, other reagents were obtained from commercial suppliers and used without further purification.

Representative Procedure for the Synthesis of Compound (2) 2-Chloro-*N*-(pyridin-3-yl)acetamide. To a magnetically stirred solution of substituted aniline **1** (10.0 mmol, 1.0 equiv) and K_2CO_3 (15.0 mmol, 1.5 equiv) in CH_2Cl_2 (100 mL), cooled in an ice bath, the chloroacetyl chloride (15.0

mmol, 1.5 equiv) was added slowly dropwise. The reaction mixture was stirred at room temperature and monitored by TLC. After the reaction was completed, the solvents were removed under vacuum and ice water (200 mL) was added into the residue. The product was separated out. The precipitate obtained was filtered and washed with water, dried and used for the next step without further purification.

Representative Procedure for the Synthesis of Compound (4). The solution of substituted phenol **3** (6.0 mmol, 1.2 equiv), K_2CO_3 (7.5 mmol, 1.5 equiv), 2-chloro-*N*-(pyridin-3-yl)acetamide **2** (5.0 mmol, 1.0 equiv) in CH_3CN (50 mL) was refluxed and monitored by TLC. After completion of reaction the solution was cooled, solvent was evaporated under reduced pressure. The residue was poured into water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Filtration of $MgSO_4$ and evaporation of solvent under vacuum gave the crude product. The residue obtained was purified by silica gel column chromatography to obtain the corresponding compound **4**.

Representative Procedure for the Synthesis of Compound (5) Substituted *N*-Azaaryl-2-anilines. The solution of compound **4** (5.0 mmol, 1.0 equiv), Cs_2CO_3 (6.0 mmol, 1.2 equiv) in dry DMF (20 mL) was heated to 120 ºC and monitored by TLC. After completion of the reaction, the solution was cooled and was added water; solvent was evaporated under reduced pressure. The residue was poured into water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Filtration of $MgSO_4$ and evaporation of solvent under vacuum gave the the crude product. The residue obtained was purified by silica gel column chromatography to obtain the corresponding compound **5**.

***N*-Phenylpyridin-3-amine (5a)**[17]**:** light-yellow solid, mp 93-95 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.0 Hz, 1H; Ar*H*), 8.16 (d, *J* = 4.0 Hz, 1H; Ar*H*), 7.60-7.27 (m, 4H; Ar*H*), 7.27-6.64 (m, 3H; Ar*H*), 5.88 (s, 1H).

***N*-(*p*-Tolyl)pyridin-3-amine (5b)**[17]**:** yellow solid, mp 98-100 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 1.8 Hz, 1H; Ar*H*), 8.10 (d, *J* = 4.2 Hz, 1H; Ar*H*), 7.36-6.97 (m, 6H; Ar*H*), 5.87 (s, 1H), 2.31 (s, 1H).

***N*-(2-Fluorophenyl)pyridin-3-amine (5c):** yellow liquid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H; Ar*H*), 8.22 (s, 1H; Ar*H*), 7.43 (d, *J* = 8.2 Hz, 1H; Ar*H*), 7.32-6.92 (m, 4H; Ar*H*), 6.92 (d, *J* = 2.9 Hz, 1H; Ar*H*) 5.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.81, 153.19, 144.06, 142.09, 125.89, 125.84, 125.77, 123.34, 119.23, 117.36, 117.11. HRMS (ESI): *m/z* 189.083.

***N*-(2-Chlorophenyl)pyridin-3-amine (5d)**[17]**:** yellow solid, mp 90-92 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.6 Hz, 1H; Ar*H*), 8.21 (dd, *J* = 4.7, 1.2 Hz, 1H; Ar*H*), 7.46-7.26 (m, 5H; Ar*H*), 6.89-6.76 (m, 1H; Ar*H*), 6.50 (s, 1H).

***N*-(2-Nitrophenyl)pyridin-3-amine (5e)**[30]**:** red solid, mp 92-94 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.62 (s, 1H; Ar*H*), 8.49 (d, *J* = 4.0 Hz, 1H; Ar*H*), 8.24 (dd, *J* = 8.6, 1.4 Hz, 1H; Ar*H*), 7.64 (d, *J* = 8.1 Hz, 1H; Ar*H*), 7.49-7.31 (m, 2H; Ar*H*), 7.19 (d, *J* = 8.0 Hz, 1H; Ar*H*), 6.97-6.77 (m, 1H; Ar*H*).

2-(Pyridin-3-ylamino)benzaldehyde (5f): yellow liquid, ^{1}H NMR(500 MHz, $CDCl_3$) δ 10.01 (s, 1H), 9.92 (s, 1H), 8.60 (d, *J* = 2.3 Hz, 1H; Ar*H*), 8.39 (dd, *J* = 4.5, 0.9 Hz, 2H, Ar*H*), 7.61 (dd, *J* = 7.8, 1.3 Hz, 1H; Ar*H*), 7.46-7.35 (m, 1H; Ar*H*), 7.31 (dd, *J* = 8.1, 4.7 Hz, 1H; Ar*H*), 7.19 (d, *J* = 8.5 Hz, 1H; Ar*H*), 6.91 (t, *J* = 7.4 Hz, 1H; Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.47, 146.91, 145.27, 144.88, 136.72, 136.46, 135.72, 129.76, 123.85, 119.89, 118.21, 112.61. HRMS (ESI): *m/z* 199.0868.

1-(2-(Pyridin-3-ylamino)phenyl)ethanone (5g): yellow liquid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.57 (d, *J* = 2.5 Hz, 1H; Ar*H*), 8.35 (dd, *J* = 4.7, 1.3 Hz, 1H; Ar*H*), 7.86 (dd, *J* = 8.1, 1.4 Hz, 1H; Ar*H*), 7.61-7.56 (m, 1H; Ar*H*), 7.39-7.33 (m, 1H; Ar*H*), 7.31-7.25 (m, 1H; Ar*H*), 7.21 (dd, *J* = 8.5, 0.8 Hz, 1H; Ar*H*), 6.82 (m, 1H; Ar*H*), 2.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.60, 147.08, 144.91, 144.79, 137.15, 134.77, 132.66, 129.65, 123.82, 119.70, 117.65, 113.90, 28.19. HRMS (ESI): *m/z* 213.1025.

***N*-(4-Chlorophenyl)pyridin-3-amine (5h)**[17]**:** light-yellow solid, mp 95-97 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H; Ar*H*), 8.18 (d, *J* = 4.5 Hz, 1H; Ar*H*), 7.39 (d, *J* = 7.2 Hz, 1H), 7.26-7.16 (m, 3H; Ar*H*), 7.02-6.99 (m, 2H; Ar*H*), 6.08 (s, 1H).

***N*-(4-Bromophenyl)pyridin-3-amine (5i):** light-yellow solid, mp 90-92 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.6 Hz, 1H; Ar*H*), 8.19 (dd, *J* = 4.6, 1.1 Hz, 1H; Ar*H*), 7.52-7.31 (m, 3H; Ar*H*), 7.19 (dd, *J* = 8.2, 4.7 Hz, 1H; Ar*H*), 7.04-6.86 (m, 2H; Ar*H*), 5.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.69, 142.64, 141.73, 140.71, 133.81, 125.35, 125.23, 121.0, 115.19. HRMS (ESI): *m/z* 249.0037.

4-(Pyridin-3-ylamino)benzonitrile (5j)[17]**:** light-yellow solid, mp 97-99 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.5 Hz, 1H; Ar*H*), 8.33 (dd, *J* = 4.6, 0.9 Hz, 1H; Ar*H*), 7.58 (dd, *J* = 8.2, 0.9 Hz, 1H; Ar*H*), 7.51 (d, *J* = 8.7 Hz, 2H; Ar*H*), 7.30 (dd, *J* = 8.3, 4.8 Hz, 1H; Ar*H*), 7.03 (d, *J* = 8.7 Hz, 2H; Ar*H*), 6.99 (s, 1H).

4-(Pyridin-3-ylamino)benzaldehyde (5k): yellow liquid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.52 (s, 1H; Ar*H*), 8.34 (d, *J* = 4.1 Hz, 1H; Ar*H*), 7.78 (d, *J* = 8.2 Hz, 2H; Ar*H*), 7.62 (d, *J* = 7.5 Hz, 1H; Ar*H*), 7.31 (dd, *J* = 7.9, 4.8 Hz, 1H; Ar*H*), 7.22 (s, 1H), 7.09 (d, *J* = 8.2 Hz, 2H; Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.94 (C=O), 150.43, 145.54, 144.11, 138.85, 133.58, 130.55, 128.82, 125.45, 116.35. HRMS (ESI): *m/z* 199.0867.

1-(4-(Pyridin-3-ylamino)phenyl)ethanone (5l): yellow solid, mp 100-102 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.4 Hz, 1H; Ar*H*), 8.32 (d, *J* = 4.6 Hz, 1H; Ar*H*), 7.90 (d, *J* = 8.7 Hz, 2H; Ar*H*), 7.64-7.50 (m, 1H; Ar*H*), 7.35-7.20 (m, 1H; Ar*H*), 7.03 (d, *J* = 8.7 Hz, 2H; Ar*H*), 6.52 (m, 1H), 2.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.90 (C=O), 148.74, 145.38, 143.80, 139.03, 132.09, 131.32, 128.17, 125.34, 116.33, 27.66 (CH_3). HRMS (ESI): *m/z* 213.1021.

***N*-(4-Nitrophenyl)pyridin-3-amine (5m):** yellow solid, mp 90-92 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H; Ar*H*), 8.42 (d, *J* = 4.6 Hz, 1H; Ar*H*), 8.16 (d, *J* = 9.0 Hz, 2H; Ar*H*), 7.60 (d, *J* = 8.2 Hz, 1H; Ar*H*), 7.34 (dd, *J* = 8.0, 4.8

Hz, 1H; Ar*H*), 6.99 (d, *J* = 9.0 Hz, 2H; Ar*H*), 6.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.54, 146.93, 145.11, 142.15, 137.82, 129.77, 127.62, 125.42, 115.60. HRMS (ESI): *m/z* 216.0765.

***N*-(4-Methoxyphenyl)pyridin-3-amine (5n):** yellow solid, mp 102-104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H; Ar*H*), 8.14-7.96 (m, 1H; Ar*H*), 7.20 (d, *J* = 8.3 Hz, 1H; Ar*H*), 7.09 (dd, *J* = 13.7, 6.6 Hz, 3H; Ar*H*), 6.88 (d, *J* = 7.7 Hz, 2H; Ar*H*), 5.75 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0 (C), 141.9 (C), 140.6 (CH), 138.4 (CH), 134.5 (C), 123.9 (CH), 122.8 (CH), 121.3 (CH), 115.0 (CH), 55.7 (CH_3). HRMS (ESI): *m/z* 201.1023.

***N*-(2-Nitrophenyl)pyridin-2-amine (5o):** red solid, mp 93-95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.75 (d, *J* = 8.7 Hz, 1H; Ar*H*), 8.35 (d, *J* = 4.7 Hz, 1H; Ar*H*), 8.22 (d, *J* = 8.5 Hz, 1H; Ar*H*), 7.64 (t, *J* = 7.8 Hz, 1H; Ar*H*), 7.56 (t, *J* = 7.8 Hz, 1H; Ar*H*), 6.95 (t, *J* = 7.8 Hz, 3H; Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.75, 148.11, 139.12, 138.21, 135.84, 134.94, 126.38, 119.94, 119.80, 118.02, 113.97. HRMS (ESI): *m/z* 216.0781.

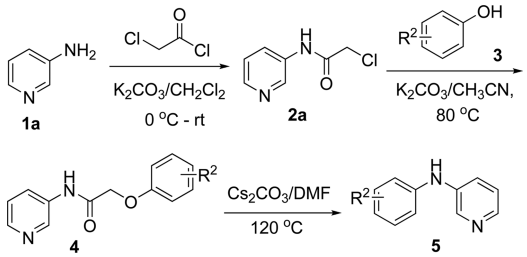
***N*-(2-Fluorophenyl)pyridin-2-amine (5p)[31]:** yellow liquid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, *J* = 4.5 Hz, 1H; Ar*H*), 7.98 (t, *J* = 8.1 Hz, 1H; Ar*H*), 7.57-7.40 (m, 1H; Ar*H*), 7.17-7.03 (m, 2H; Ar*H*), 7.03-6.90 (m, 1H; Ar*H*), 6.86 (s, 1H), 6.82-6.70 (m, 2H; Ar*H*).

***N*-(2-Chlorophenyl)pyridin-2-amine (5q):** brown liquid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31-8.22 (m, 1H; Ar*H*), 8.07 (dd, *J* = 8.2, 1.3 Hz, 1H; Ar*H*), 7.60-7.50 (m, 1H; Ar*H*), 7.39 (dd, *J* = 8.0, 1.3 Hz, 1H; Ar*H*), 7.24 (dd, *J* = 11.1, 3.9 Hz, 1H; Ar*H*), 6.93 (td, *J* = 8.0, 1.4 Hz, 1H; Ar*H*), 6.86 (d, *J* = 8.3 Hz, 2H), 6.81 (dd, *J* = 6.8, 5.4 Hz, 1H; Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.92, 148.25, 137.75, 137.34, 129.55, 127.47, 123.19, 122.44, 119.68, 115.99, 110.04. HRMS (ESI): *m/z* 205.0527.

Results and Discussion

Our work began with the reaction of pyridin-3-amine (**1a**) and substituted phenol (**3**). Initially, the reaction of pyridin-3-amine (**1a**) (1.0 equiv) and chloroacetyl chloride (1.5 equiv) in K_2CO_3/CH_2Cl_2 at room temperature gave 2-chloro-*N*-(pyridine-3-yl)acetamide (**2a**) as the product. The crude amide (**2a**) then reacted with substituted phenol (**3**) (1.2 equiv) in refluxing K_2CO_3/CH_3CN, affording the *O*-alkylated compound (**4**) which then underwent Smiles rearrangement in Cs_2CO_3/DMF system to give *N*-azaaryl-3-anilines (**5a**) as the desired product. A variety of phenols (**3**) and pyridin-3-amine (**1a**) were then studied under the same reaction condition, to explore the range of the reaction, with the results in Table 1. As is seen in Table 1, the reaction of pyridin-3-amine (**1a**) and all the phenols (**3**) afforded the target molecules in good to excellent yields. As pyridine-3-amine was reacted with phenol possessing an electron donating group (**3b**), the yield was moderate (entry 2). The phenols with electron withdrawing group in the *para* position of the hydroxyl did not show significant effect on the yield of the reactions (entries 8-13). It is noteworthy that

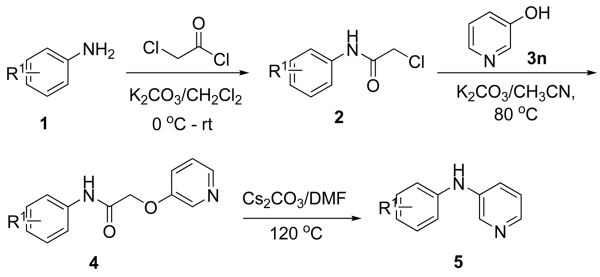
Table 1. Synthesis of *N*-azaaryl-3-anilines



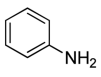
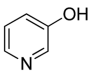
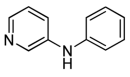
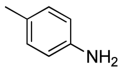
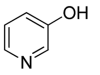
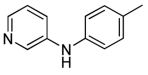
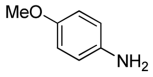
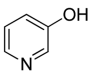
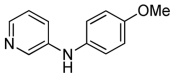
Entry	Amine	Phenol	*N*-azaaryl anilines	Yield (%)[a]
1	**1a**	**3a**	**5a**	75
2	**1a**	**3b**	**5b**	68
3	**1a**	**3c**	**5c**	95
4	**1a**	**3d**	**5d**	90
5	**1a**	**3e**	**5e**	76
6	**1a**	**3f**	**5f**	92
7	**1a**	**3g**	**5g**	65
8	**1a**	**3h**	**5h**	81
9	**1a**	**3i**	**5i**	73
10	**1a**	**3j**	**5j**	78
11	**1a**	**3k**	**5k**	84
12	**1a**	**3l**	**5l**	80
13	**1a**	**3m**	**5m**	85

[a]Isolated yield of the third step. Reaction conditions: *O*-alkylated Compound (**4**) (1.0 mmol), Cs_2CO_3 (1.5 mmol), DMF (25 mL), 120 °C.

Table 2. Synthesis of *N*-azaaryl-3-anilines

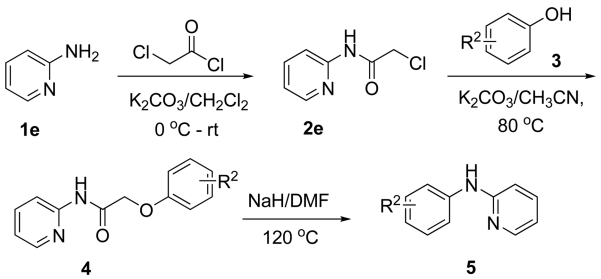


1 2 3n 4 5

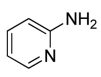
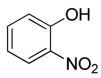
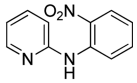
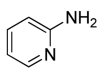
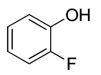
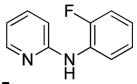
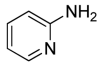
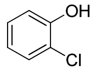
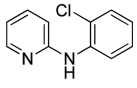
Entry	Amine	Phenol	*N*-azaaryl anilines	Yield (%)[a]
1	 **1b**	 **3n**	 **5a**	88
2	 **1c**	 **3n**	 **5b**	92
3	 **1d**	 **3n**	 **5n**	89

[a]Isolated yield of the third step. Reaction conditions: *O*-alkylated compound (**4**) (1.0 mmol), Cs_2CO_3 (1.5 mmol), DMF (25 mL), 120 °C.

Table 3. Synthesis of *N*-azaaryl-2-anilines



1e 2e 3 4 5

Entry	Amine	Phenol	*N*-azaaryl anilines	Yield (%)[a]
1	 **1e**	 **3e**	 **5o**	54
2	 **1e**	 **3c**	 **5p**	68
3	 **1e**	 **3d**	 **5q**	45

[a]Isolated yield of the third step. Reaction conditions: *O*-alkylated compound (**4**) (1.0 mmol), NaH (1.5 mmol), DMF (25 mL), 120 °C.

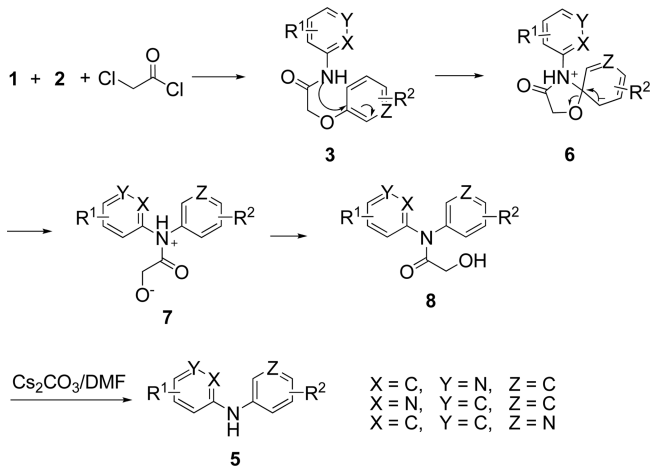
when pyridin-3-amine reacted with phenols containing halogen atom in the *ortho* position of the hydroxyl, the desired products (**5c**) and (**5d**), were generated in excellent yields (entry 3-4).

Encouraged by our findings, we then investigated the reaction of substituted aniline (**1**) and 3-hydroxypyridine (**3n**), with the results shown in Table 2. Similarly, the reaction of anilines (**1**) and chloroacetyl chloride gave the amides (**2**), which was then converted to the *O*-alkylated 3-pyridol (**4**) in MeCN at 80 °C in good yields. Smiles rearrangement of compound (**4**) gave rise to the desired product (**5**). The results indicated that the reaction of aniline (**1b**) and 3-hydroxypyridine (**3n**) gave a product, which has the same physical and chemical properties and NMR spectra with *N*-phenylpyridin-3-amine (**5a**).

On the basis of our experimental results, we explored the reaction of pyridin-2-amine (**1e**), chloroacetyl chloride and substituted phenols (**3**). Considering the Smiles rearrangement was completed in Cs_2CO_3/DMF system, we suspected that the reactions proceeded toward completion in the same condition. However, we found the reaction under Cs_2CO_3/DMF system did not generate *N*-azaaryl-2-anilines, while it gave substituted anilines as the major product, which was hypothesized to be obtained by the decomposition of *N*-azaaryl-2-anilines. Among bases, NaH was found to be the most effective in terms of conversion and price. The reactions with NaH as the base in DMF gave *N*-azaaryl-2-anilines as the major products, while we found the phenols containing electron withdrawing group only afforded the desired products, and the yield was only 45-68% (Table 3).

A survey of pyridin-2-amine (**1e**) and substituted phenols (**3**) performed at 120 °C is provided in Table 3.

On the basis of reported Smiles rearrangement chemistry and our experimental results, a plausible reaction mechanism is presented in Scheme 2. The *O*-alkylated product of phenol (**3**) underwent the Smiles rearrangement by the nucleophilic attack of the nitrogen atom on the carbon of the benzene ring attached to the oxygen atom, which led to the formation of a new C-N bond to give spiro-intermediate (**6**). With the bond breaking of C-O bond, then came the intermediate (**7**). Under alkaline conditions (with Cs_2CO_3 or NaH) in DMF, intermediate (**8**) was decarboxylated to afford the *N*-azaaryl anilines (**5**). Since the transition of compound (**3**) to the intermediate (**6**) proceeded nucleophilic attack of nitrogen atom to benzene ring, the aniline which had higher electronic density with electron donating group R^1 and the



Scheme 2. Plausible mechanism for the formation of *N*-azaaryl anilines **5**.

phenol which had lower electronic density containing electron withdrawing group R^2 would benefit the reaction.

Conclusion

In summary, various *N*-azaaryl anilines were synthesized starting from readily available substituted phenols, aminopyridines and chloroacetyl chloride or pyridols, substituted anilines and chloroacetyl chloride *via* Smiles rearrangement under base condition in good to excellent yields. The application of the reaction and the bioactivity of these compounds will be further investigated in our laboratory.

Acknowledgments. We would like to thank the National Natural Science Foundation of China (21002081), the Korea Ministry of Environment (KME, 412-111-008), the National Research Foundation of Korea (NRF-2010-0029634), the Ministry of Knowledge Economy(MKE, R0000495) and the Fundamental Research Funds for the Central Universities, P.R. China (XDJK2012B012 and XDJK2009C086) for financial support.

References

1. Shetty, R. S.; Lee, Y.; Liu, B.; Husain, A.; Joseph, R. W.; Lu, Y.; Nelson, D.; Mihelcic, J.; Chao, W.; Moffett, K. K.; Schumacher, A.; Flubacher, D.; Stojanovic, A.; Bukhtiyarova, M.; Williams, K.; Lee, K.-J.; Ochman, A. R.; Saporito, M. S.; Moore, W. R.; Flynn, G. A.; Dorsey, B. D.; Springman, E. B.; Fujimoto, T.; Kelly, M. J. *J. Med. Chem.* **2011**, *54*, 179.
2. (a) Lakde, S. K.; Somani, R. R.; Agrawal, A. G.; Shirodkar, P. Y. *Int. J. Chem. Tech. Res.* **2010**, *2*, 780. (b) Du, A.; Zhang, S.; Miao, J.; Zhao, B. *Exp. Lung Res.* **2004**, *30*(6), 419.
3. (a) Williams, D. K.; Chen, X.-T.; Tarby, C.; Kaltenbach, R.; Cai, Z.-W.; Tokarski, J. S.; An, Y.; Sack, J. S.; Wautlet, B.; Gullo-Brown, J.; Henley, B. J.; Jeyaseelan, R.; Kellar, K.; Manne, V.; Trainor, G. L.; Lombardo, L. J.; Fargnoli, J.; Borzilleri, R. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2998. (b) Du, A.; Zhao, B.; Yin, D.; Zhang, S.; Miao, J. *Bioorg. Med. Chem*. **2006**, *16*(1), 81.
4. Sreenivas, D. K.; Ramkumar, N.; Nagarajan, R. *Org. Bio. Chem.* **2012**, *10*, 3417.
5. Chu, J. H.; Lin, P. S.; Lee, Y.-M.; Shen, W. T.; Wu, M. J. *Chem. Eur. J.* **2011**, *17*, 13613.
6. Johansson Seechurn, C. C. C.; Parisel, S. L.; Colacot, T. J. *J. Org. Chem.* **2011**, *76*, 7918.
7. Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 57.
8. Dogan, O.; Demir, S.; Ozdemir, I.; Cetinkaya, B. *Appl. Organometal. Chem.* **2011**, *25*, 163.
9. Demir, S.; Ozdemir, I.; Cetinkaya, B.; Arslan, H.; VanDerveer, D. *Polyhedron* **2011**, *30*, 195.
10. Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc*. **2008**, *130*, 13848.
11. Chen, G. S.; Lam, W. H.; Fok, W. S.; Lee, H. W.; Kwong, F. Y. *Chem. Asian J.* **2007**, *2*, 306.
12. Madrid, P. B.; Polgar, W. E.; Toll, L.; Tanga, M. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3014.
13. Viciu, M. S.; Kelly, R. A.; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479.
14. Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729.
15. Huang, X. H.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.
16. Huang, M. N.; Lin, X. Q.; Zhu, X. H.; Peng, W. L.; Xie, J. W.; Wan, Y. Q. *Eur. J. Org. Chem.* **2011**, *24*, 4523.
17. Mazu, T. K.; Etukala, J. R.; Jacob, M. R.; Khan, S. I.; Walker, L. A.; Ablordeppey, S. Y. *Eur. J. Med. Chem.* **2011**, *46*, 2378.
18. Mazu, T. K.; Etukala, J. R.; Zhu, X. Y.; Jacob, M. R.; Khan, S. I.; Walker, L. A.; Ablordeppey, S. Y. *Bioorg. Med. Chem.* **2011**, *19*, 524.
19. Kim, A. Y.; Lee, H. J.; Park, J. C.; Kang, H.; Yang, H.; Song, H.; Park, K. H. *Molecules* **2009**, *14*, 5169.
20. Lin, B. D.; Liu, M. C.; Ye, Z. S.; Ding, J. C.; Wu, H. Y.; Cheng, J. *Org. Biomol. Chem.* **2009**, *7*, 869.
21. Liu, Y.; Bai, Y.; Zhang, J.; Li, Y.; Jiao, J.; Qi, X. *Eur. J. Org. Chem.* **2007**, *36*, 6084.
22. Xu, Z. L.; Li, H. X.; Ren, Z. G.; Du, W. Y.; Xu, W. C.; Lang, J. P. *Tetrahedron* **2011**, *67*, 5282.
23. Chen, J. L.; Song, G. Y.; Pan, C. L.; Li, X. W. *Org. Lett.* **2012**, *12*, 5426.
24. Horie, H.; Koyama, I.; Kurahashi, T.; Matsubara, S. *Chem. Commun.* **2011**, *47*, 2658.
25. Iglesias, M. J.; Prieto, A.; Nicasio, M. C. *Adv. Synth. Catal.* **2010**, *352*, 1949.
26. Levy, A. A.; Rains, H. C.; Smiles, S. I. *J. Chem. Soc*. **1931**, 3264.
27. Xiang, J. B.; Zhu, T.; Dang, Q.; Bai, X. *J. Org. Chem.* **2010**, *75*, 8147.
28. Yang, H.; Li, Z. B.; Shin, D. S.; Wang, L. Y.; Zhou, J. Z.; Qiao, H. B.; Tian, X.; Ma, X. Y.; Zuo, H. *Synlett* **2010**, *3*, 483.
29. Tian, X.; Wu, R. M.; Liu, G.; Li, Z. B.; Wei, H. L.; Yang, H.; Shin, D. S.; Wang, L. Y.; Zuo, H. *ARKIVOC* **2011**, *10*, 118.
30. Tsaranova, T. V. *Khim. Geterotsikl. Soedin.* **1965**, *6*, 909.
31. Wang, H. G.; Wang, Y.; Peng, C. L.; Zhang, J. C.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, *132*, 13217.