A Facile C–N Bond Formation: One-Pot Reaction of Phenols and Amines via Smiles Rearrangement

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Abstract: Diarylamines and arylalkylamines were synthesized in high yields from 2-chlorophenols and amines, activated by chloroacetyl chloride under microwave irradiation (20–60 min) or conventional thermal conditions (3–6 h). The key transformation is believed to proceed via Smiles rearrangement by initial O-alkylation and subsequent cyclization.

Key words: C–N coupling, one pot, amine, Smiles rearrangement, synthesis

Conventional C–N bond-forming reactions are usually performed via the cross-linking of heteroaryl halides with amines, assisted by metal catalysts, and have importance both in industry and academia.[1] Advances have been made in the development of palladium catalysts, such as **1**–**5**, which have been shown to be efficient ligands for C–N cross-linking reactions (Figure 1).[2–22] Recently, a C–N bond-forming reaction specifically for the synthesis of *N*-arylanilines was developed, proceeding by a two-step sequence of iridium-catalyzed borylation and copper-catalyzed coupling with amines.[23] Amination of aryltriflate (ArOTf) was also achieved via the C–N cross-linking reaction using a palladium catalyst.[24] Processes using other metal catalysts have been developed but notable limitations remain. For example, catalysts are expensive and difficult to prepare and the N-arylation reaction of nitrogen heterocycles is limited in scope with respect to both coupling partners.

Besides the palladium and copper processes, Smiles rearrangement is a valuable alternative method for C–N bond forming to prepare *N*-arylamines. TDA-1 [tris(3,6-dioxaheptylamine)] is used as an efficient solid–liquid phase-transfer catalyst, which activated N-alkylation of chlorinated phenoxyacetamides in the presence of KOH via Smiles rearrangement, while the substrates were limited in trichlorophenol.[25] Smiles rearrangement of substituted aryloxyacetamides in which oxygen and nitrogen are separated by $COCH_2$ group to *N*-alkyl- and *N*-arylamines has been successful at EtONa/EtOH or NaH/DMF conditions, but only for aryloxy ring which carries weak or no electron-withdrawing group.[26] Based on this method, Acemoglu found that K_2CO_3/*i*-PrOH followed by MeONa/MeOH treatment avoided the major side reactions to form *N*-arylamines.[27] Similarly, the Smiles rearrangement was involved in the preparation of alkylarylamines containing a nitro group[28] and *N*-arylamines with a nitro moiety.[29]

In spite of these, C–N bond formation still remains a synthetic challenge, specifically considering the diversity of diarylamines and arylalkylamines. Herein, we report a direct and facile approach that shows excellent reactivity and stability for C–N formation reactions and overcomes many restrictions compared with conventional, metal-catalyzed cross-coupling reactions. The method enables amination of commercially available phenols via a one-pot reaction through Smiles rearrangement. Herein, we present preliminary results of the protocol.

First, we explored the coupling of 2-chlorophenol and 4-methoxyaniline. Various base and solvent systems were investigated for the reaction. The results showed that K_2CO_3/MeCN and K_2CO_3/DMF failed to produce the target transformation. During the course of our optimization studies we found that treatment of amines, chloroacetyl

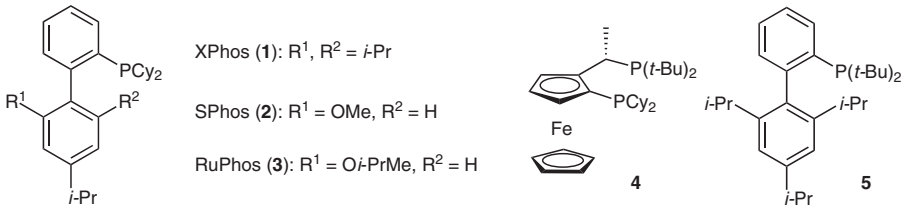

Figure 1

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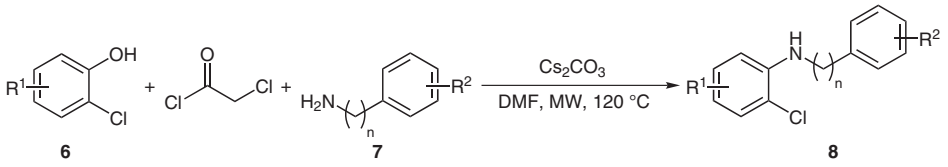
chloride, and phenols in Cs_2CO_3/DMF at 120 °C under conventional heating for 4 hours led to the exclusive formation of 2-chloro-*N*-(4-methoxyphenyl)aniline at 90% yield (Table 1, entry 5). This system was also suitable for the amination of phenol at 150 °C, obtaining the same yield but requiring a shorter time for completion.

To expand the scope of this methodology, we then examined the coupling of a variety of phenols, 2-chlorophenol, 4-methyl-2-chlorophenol, 5-methyl-2-chlorophenol, and 4-fluoro-2-chlorophenol, and a set of amines, which included various alkyl- and aryl-amines containing either methyl or methoxy groups (Table 1). Generally, the major products formed in these reactions are diarylamines **8**, except when alkylamines are used as reaction substrates. According to our previous study,[30] when $PhCH_2NH_2$ (**7a**) and $PhCH_2CH_2NH_2$ (**7b**), which contain the -$(CH_2)_n$- moiety, were used as reactants, the reaction produced to give the corresponding substituted arylalkylamines as minor products (38–48%), while 4-benzyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**9a**), 4-phenethyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**9b**),[36] and 7-methyl-4-phenethyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**9f**) were the major products (entries 1, 2, and 6 in Table 1), which were isolated and identified by their spectral properties.

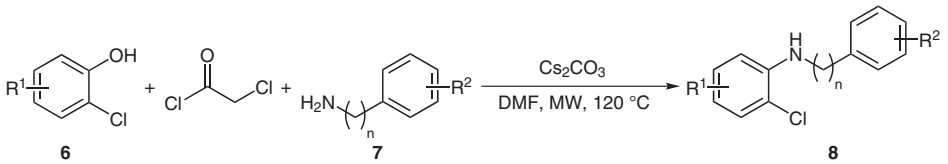
Table 1 One-Pot Synthesis of Diarylamine and Arylalkylamine Derivatives

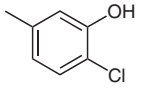
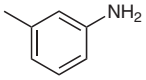
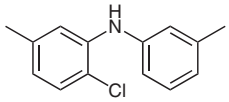
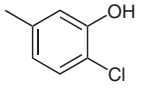
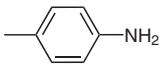
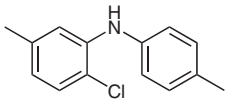
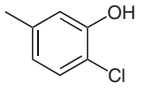
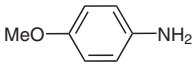
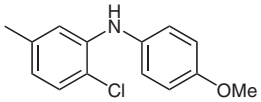
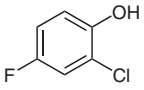
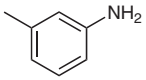
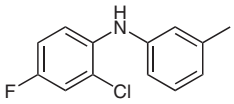
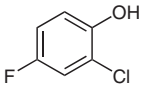
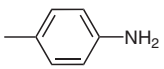
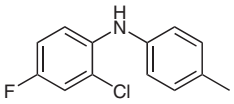
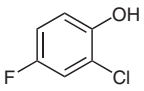
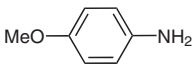
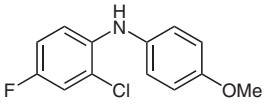


6 **7** **8**

Entry	Phenol	Amine	Product	Yield (%)[a]
1	**6a**	**7a**	**8a**	38
2	**6a**	**7b**	**8b**	48
3	**6a**	**7c**	**8c**	92
4	**6a**	**7d**	**8d**	94
5	**6a**	**7e**	**8e**	90
6	**6b**	**7b**	**8f**	45
7	**6b**	**7c**	**8g**	92
8	**6b**	**7d**	**8h**	90
9	**6b**	**7e**	**8i**	88

Table 1 One-Pot Synthesis of Diarylamine and Arylalkylamine Derivatives (continued)



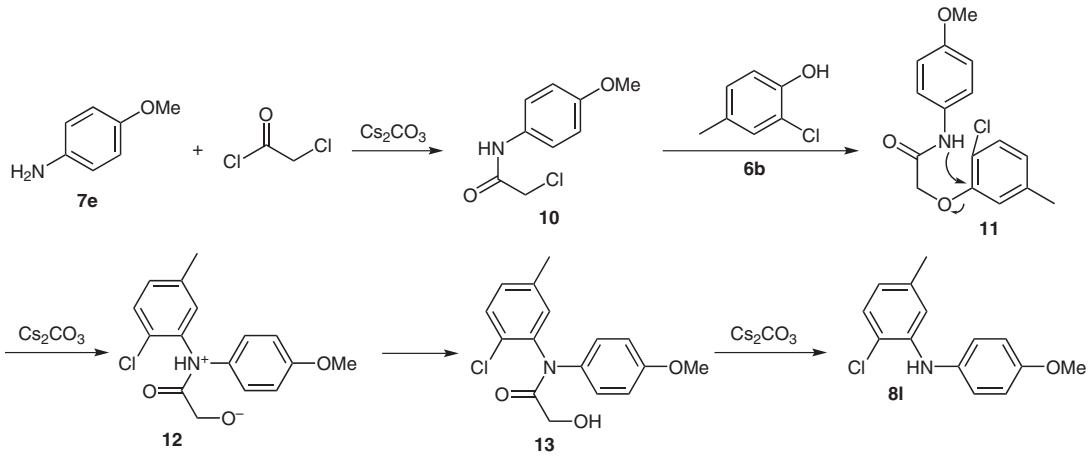
Entry	Phenol	Amine	Product	Yield (%)[a]
10	**6c** 	**7c** 	**8j** 	93
11	**6c** 	**7d** 	**8k** 	86
12	**6c** 	**7e** 	**8l** 	93
13	**6d** 	**7c** 	**8m** 	94
14	**6d** 	**7d** 	**8n** 	90
15	**6d** 	**7e** 	**8o** 	90

[a] Yield of isolated product. Reaction conditions: phenols (1.1 mmol), amines (1.0 mmol), chloroacetyl chloride (1.2 mmol), Cs_2CO_3 (3.2 mmol), DMF (25 mL), 120 °C, under microwave irradiation.

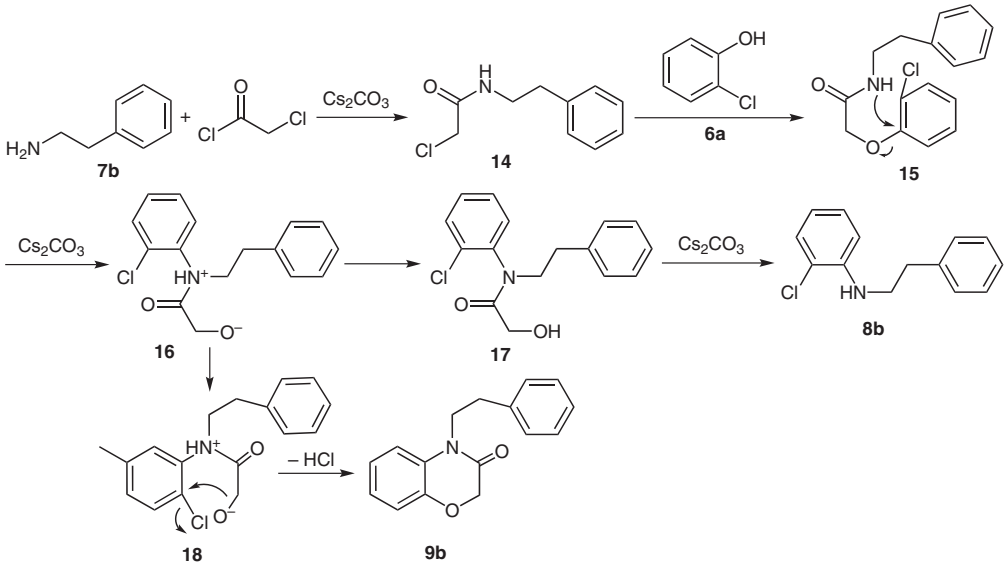
All the reactions proceeded smoothly with substituted 2-chlorophenol **6**, chloroacetyl chloride and aryl/arylalkylamine **7** at a ratio of 1.1:1.2:1 in the presence of Cs_2CO_3 in dry DMF. This mixture underwent a fast 1:1:1 addition reaction at 120 °C under microwave irradiation for 20–60 minutes or conventional thermal conditions for 3–6 hours to produce the corresponding diarylamines or arylalkylamines **8**.[32] The results were excellent in terms of yield for diarylamine formation (83–94%) and reasonable (38–48%) for arylalkylamines (**8a**, **8b**, and **8f**). The spectral and physical data (mp, IR, ^{1}H NMR, ^{13}C NMR, MS) of **8** were in agreement with the predicted structures. To investigate the effect of the electron-withdrawing group like nitro group, experiments were conducted on 4-nitroaniline with 4-methyl-2-chlorophenol and 5-methyl-2-chlorophenol, respectively. Results showed that the reactions gave very complex products.

A proposed explanation for the results is given in Scheme 1. The O-alkylated product **11** was easily formed by nucleophilic attack of compound **6b** on amide **10**.[34] The latter was simply obtained by mixing amine with chloroacetyl chloride. The next step was the conversion of aryloxyacetamide **11**[35] to intermediate **12** via Smiles rearrangement, replacing the oxygen atom on the benzene ring with a nitrogen atom. Finally, hydrolysis of compound **13** led to formation of product **8l**[33] under basic conditions.

For alkylamines as substrates, there were other competition reactions. One was that the intermediate **16** underwent intramolecular proton shift to give *N*-(2-chlorophenyl)-2-hydroxy-*N*-phenethylacetamide (**17**), which subsequently gave 2-chloro-*N*-phenethylaniline (**8b**) as the product. The other reaction was that the alkoxide anion attacked the carbon that was bonded to chlorine atom to form a cyclization product as benzo[*b*][1,4]oxazin-3(4*H*)-one **9b** (Scheme 2). In the case of **7a** and **7b**, formation of benzo[*b*][1,4]oxazin-3(4*H*)-ones was more favorable. As is seen in Table 1, the yields of **8a**, **8b**, and **8f** were lower. To the best of our knowledge, this is the first example describing the synthesis of substituted diarylamines or benzylalkylamines by one-pot reaction of amine, chloroacetyl chloride, and phenols in the absence of any transient metal catalyst via Smiles rearrangement, even though Smiles rearrangement was developed more than 69 years ago.[31]



Scheme 1 Proposed mechanism for formation of **8l** via Smiles rearrangement



Scheme 2 Proposed mechanism for formation of **8a** and **18** via Smiles rearrangement

In summary, we have reported an operationally simple and economical approach to the synthesis of diarylamines from phenols and amines via Smiles rearrangement. Further studies are under way to examine more thoroughly the effect of chlorine atom on benzene ring and expand the scope of diverse substitutions for this reaction system. Our new method holds great promise for industrial processes because of its operational simplicity and lower cost, and because it avoids the use of palladium or iridium.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(31) (a) Warren, L. A.; Smiles, S. *J. Chem. Soc.* **1930**, 956. (b) Warren, L. A.; Smiles, S. *J. Chem. Soc.* **1930**, 1327.
(32) **General Procedure of One-Pot Reaction for the C–N Bond Formation (8)**
To a magnetically stirred solution of the appropriate primary amine **7** (1.0 mmol) and Cs_2CO_3 (3.2 mmol) in dry DMF cooled by ice bath were added chloroacetyl chloride (1.2 mmol) and **6** (1.1 mmol). The reaction mixture was then stirred for 30 min at r.t. and placed into microwave oven (600 W, 120 °C) and irradiated for 20–60 min or under conventional heating for 3–6 h. The solvent was removed under vacuum and H_2O (20 mL) was added into the residue. It was then extracted by EtOAc. The combined organic layers were dried over anhyd $MgSO_4$ and evaporated under vacuum to obtain the crude product. Pure product was obtained by column chromatography on silica gel.
(33) **2-Chloro-*N*-(4-methoxyphenyl)-5-methylaniline (8l)**
Orange oil. IR (KBr): ν = 3402, 3038, 2999, 2952, 2930, 2850, 2834, 1600, 1580, 1513, 1455, 1441, 1398, 1294, 1245, 1180, 1044, 829, 794 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3 H, CH_3), 3.81 (s, 3H, OCH_3), 5.88 (br s , 1 H, NH), 6.53 (d, *J* = 8.1 Hz, 1 H, ArH), 6.89 (d, *J* = 8.7 Hz, 1 H, ArH), 7.12 (d, *J* = 8.7 Hz, 1 H, ArH), 7.17 (d, *J* = 8.1 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 55.5 (OCH_3), 114.4 (CH), 114.7 (CH), 117.1 (C), 120.0 (CH), 124.6 (CH), 129.1 (CH), 134.2 (C), 137.5 (C), 141.7 (C), 156.3 (C) ppm. ESI-MS: *m/z* (%) = 248 (6) [M + 1], 213 (18), 198 (21), 140 (35), 123 (100), 113 (24), 108 (39).
(34) **2-Chloro-*N*-(4-methoxyphenyl)acetamide (10)**[37]
White solid; mp 120–122 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3 H, OCH_3), 4.19 (s, 2 H, CH_2), 6.89 (d, *J* = 8.8 Hz, 2 H, ArH), 7.44 (d, *J* = 8.8 Hz, 2 H, ArH), 8.15 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.8 (OCH_3), 55.5 (CH_2), 114.2 (CH), 122.0 (CH), 129.6 (C), 157.1 (C), 163.6 (C) ppm.
(35) **2-(2-Chloro-5-methylphenoxy)-*N*-(4-methoxyphenyl)acetamide (11)**
White solid; mp 134–136 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 4.64 (s, 2 H, CH_2), 6.78 (s, 1 H, ArH), 6.82 (d, *J* = 8.1 Hz, 1 H, ArH), 6.90 (d, *J* = 8.8 Hz, 2 H, ArH), 7.29 (d, *J* = 14.0 Hz, 1 H, ArH), 7.52 (d, *J* = 8.8 Hz, 2 H, ArH), 8.75 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 55.5 (OCH_3), 68.3 (CH_2), 114.2 (CH), 115.1 (C), 119.8 (C), 121.6 (CH), 123.8 (C), 130.0 (C), 138.6 (C), 152.5 (C), 161.8 (C), 165.3 (C) ppm.
(36) **4-Phenethyl-2*H*-benzo[*b*][1,4]oxazin-3 (4*H*)-one (9b)**
White solid. IR (KBr): ν = 3421, 2930, 1682, 1409, 1058, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.96 (t, *J* = 9.0 Hz, 2 H, CH_2), 4.14 (t, *J* = 9.0 Hz, 2 H, CH_2), 4.58 (s, 2 H, OCH_2CO), 7.00–7.02 (m, 4 H, ArH), 7.25–7.34 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.5 (CH_2), 42.7 (CH_2), 67.7 (OCH_2CO), 114.9 (CH), 117.4 (CH), 123.0 (CH), 124.0 (CH), 126.9 (CH), 128.5 CH), 128.7 (CH), 128.9 (CH), 138.2 (C), 145.5 (C), 164.3 (CO) ppm.
(37) Baraldi, P. G.; Preti, D.; Tabrizi, M. A.; Fruttarolo, F.; Saponaro, G.; Baraldi, S.; Romagnoli, R.; Moorman, A. R.; Gessi, S.; Varani, K.; Borea, P. A. *Bioorg. Med. Chem.* **2007**, *15*, 2514.