A Convenient Synthesis of Amino Acid Arylamides Utilizing Methanesulfonyl Chloride and *N*-Methylimidazole

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Abstract: *N*-Cbz-protected amino acids reacted with various arylamines in the presence of methanesulfonyl chloride and *N*-methylimidazole in dichloromethane to give the corresponding arylamides in high yields. No obvious racemization was observed under the mild conditions.

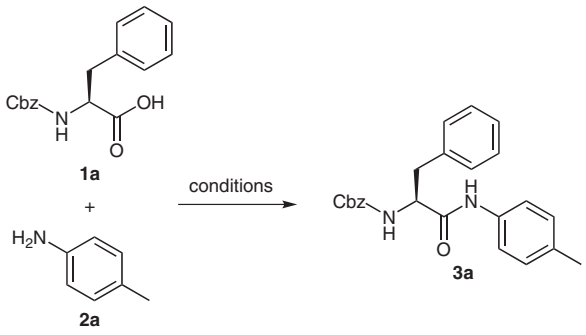
Key words: amino acid arylamides, *N*-Cbz-protected amino acids, condensation, steric hindrance, enantioretention

Amino acid arylamides are compounds of great interest and are widely used in polymers, dendrimers, peptidomimetics, and pharmaceuticals.[1] For example, amino acid *p*-nitroanilides are often used as chromogenic substrates for the determination of the activity of proteolytic enzymes present in body fluids.[2] However, the preparative methods appeared to be rather troublesome since free arylamines used in the reactions are very weak nucleophiles. As a consequence, much effort has been invested in the development of efficient synthesis.

In general, amino acid arylamides are prepared from the amino acids and arylamines in the presence of the coupling agents. The commonly used coupling agents, e.g., DCC,[3] DCC–HOBt[4] and the mixed anhydride,[5] rarely result in satisfactory yields. Other methods based on reactive condensing agents, e.g., phosphorous or boron derivatives, often lead to significant racemization.[6] Acid chlorides[7] and thermal activation[8] have been recommended to cope with the reaction using the arylamine with low nucleophilicity, but they also afford products of questionable optical purity. Recently, a three-step protocol for the preparation of amino acid and peptide *C*-terminal electron-deficient arylamides was described, based on the reaction of an azide with selenocarboxylates. Although high yields were obtained, some racemization proved to be inevitable.[9] In conclusion, each of the known methods for the preparation of amino acid arylamides suffers from some drawbacks such as low yields, racemization, hazardous and expensive condensing reagents.

In the context of developing peptidomimetic inhibitors in our ongoing research, we needed some *C*-terminal arylamides of *N*-Cbz-protected leucine (*N*-Cbz-Leu), isoleucine (*N*-Cbz-Ile) and phenylalanine (*N*-Cbz-Phe) as the building blocks. Our initial experiment to convert *N*-Cbz-phenylalanine (**1a**) with *p*-methylaniline (**2a**) into **3a** using several procedures gave disappointing results

Table 1 Optimization of Reaction Conditions



Entry	Conditions	Solvent	Time (h)	Yield (%)[a]
1	DCC–Et_3N (3.0 equiv)	THF	7	47
2	DCC–Et_3N (3.0 equiv)	CH_2Cl_2	7	41
3	EDCI–Et_3N (3.0 equiv)	THF	6	61
4	EDCI–Et_3N (3.0 equiv)	THF	6	51
5	isobutyl chloroformate–Et_3N (3.0 equiv)	CH_2Cl_2	2	complex
6[b]	MsCl–pyridine (3.0 equiv)	THF	2	complex
7[b]	MsCl–Et_3N (3.0 equiv)	THF	2	36
8[c]	MsCl–Et_3N (3.0 equiv)	THF	2	46
9[b]	MsCl–MeIm (3.0 equiv)	THF	2	70
10[b]	MsCl–MeIm (3.0 equiv)	CH_2Cl_2	2	89
11[b]	MsCl–MeIm (2.5 equiv)	CH_2Cl_2	2	89
12[b]	MsCl–MeIm (2.0 equiv)	CH_2Cl_2	2	80
13[b]	MsCl–MeIm (1.5 equiv)	CH_2Cl_2	2	63
14[b]	MsCl–MeIm (2.5 equiv)	CH_2Cl_2	3	87

[a] Isolated yield based on **2a**.
[b] To a solution of **1a** (1 equiv) and base in the given solvent was added MsCl (1 equiv) below –5 °C. After stirring for 20 min, **2a** (0.9 equiv) was added and the solution was stirred at r.t.

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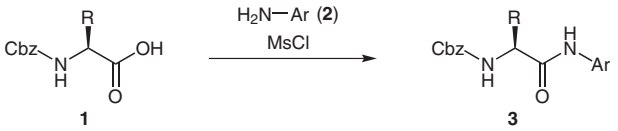
(Table 1, entries 1–5). This seemingly trivial transformation to produce **3a** was plagued with poor isolated yields.

We speculated that the poor yield resulted from not only the weak nucleophilicity of *p*-methylaniline, but also the steric encumbrance around the carboxyl group. Nicolaou had published a method for the formation of hindered α-diazoketones that was presumed to proceed through a mixed anhydride of carboxylic acid with methanesulfonyl chloride (MsCl).[10] Later, Woo adopted this method in his preparation of Weinreb amides from hindered carboxylic acids.[11] Both Nicolaou and Woo obtained their target compounds in reasonable yields. This method, using methanesulfonic acid as a counter acid moiety is a promising candidate for an efficient arylamidation (Scheme 1) from sterically hindered amino acid. In this paper, we report a convenient synthesis of amino acid arylamides from *N*-Cbz-protected amino acids and arylamines utilizing methanesulfonyl chloride and *N*-methylimidazole (MeIm).

We investigated the effect of different bases and solvents on the arylamidation with the model reaction between **1a** and **2a** using MsCl. Preliminary experiments using triethylamine or pyridine as the base gave rather disappointing results (Table 1, entries 6 and 7). Further attempt by increasing the ratio of **1a**:**2a** to 1:3 from 1:0.9 only gave a slight improvement of the yield (Table 1, entry 8). To improve the conversion of **1a** into **3a**, we decided to use *N*-methylimidazole (MeIm) as the base, which was shown to be an efficient promoter in sulfonate formation.[12] To our delight, a noticeable increase in yield was observed (Table 1, entry 9). Furthermore, using dichloromethane as the solvent gave the better result (Table 1, entry 10). In a successive series of experiments, decreasing the amount of MeIm to 2.5 equivalents maintained the yield but a further decrease led to a significant loss of the product (Table 1, entries 11–13). Prolonging the reaction time from two hours to three hours had little effect on the yield (Table 1, entry 14).



Scheme 1 Synthesis of arylamides from *N*-Cbz-protected amino

Encouraged by these results, the conditions used in Table 1, entry 11 were applied to prepare other building blocks in our research of developing peptidomimetic inhibitors. The results are presented in Table 2.[13]

Table 2 Synthesis of Arylamides from *N*-Cbz-Protected Amino Acids and Arylamines with MsCl and MeIm[a]

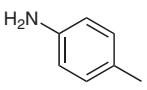
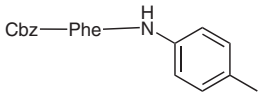
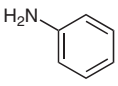
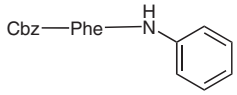
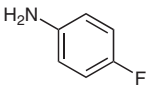
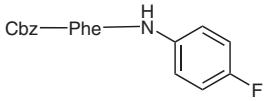
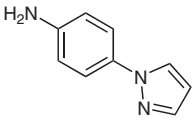
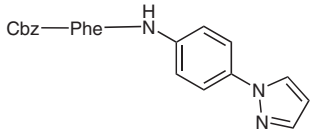
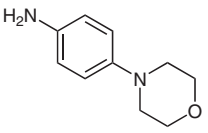
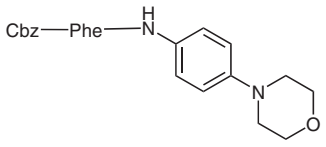
Entry	Amino acid	Arylamine	Product	Yield (%)[b]
1	*N*-Cbz-Phe (**1a**)	 **2a**	 **3a**	89
2	**1a**	 **2b**	 **3b**	90
3	**1a**	 **2c**	 **3c**	87
4	**1a**	 **2d**	 **3d**	90
5	**1a**	 **2e**	 **3e**	87

Table 2 Synthesis of Arylamides from *N*-Cbz-Protected Amino Acids and Arylamines with MsCl and MeIm[a] (continued)

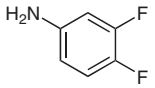
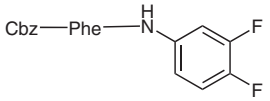
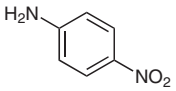
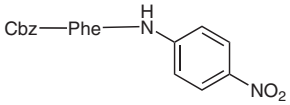
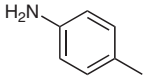
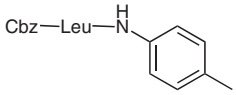
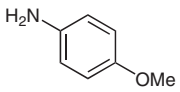
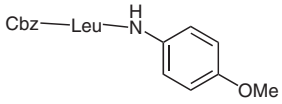
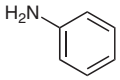
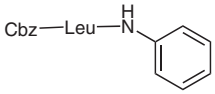
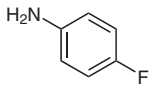
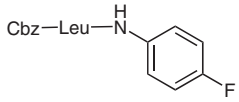
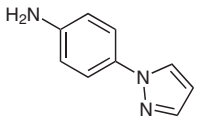
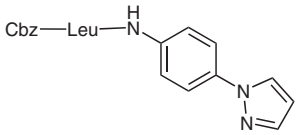
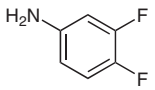
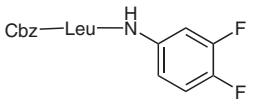
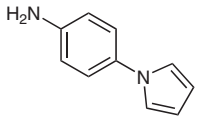
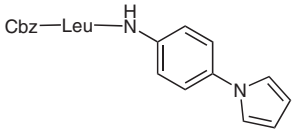
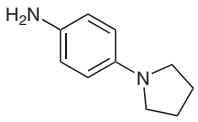
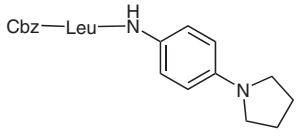
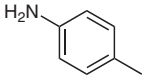
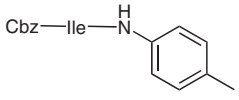
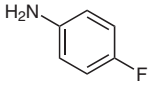
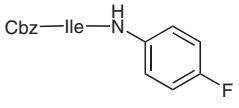
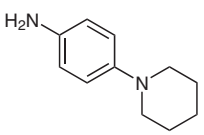
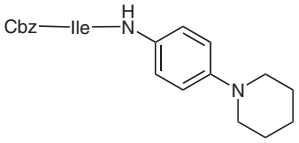
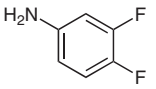
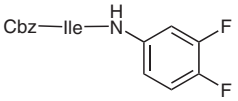
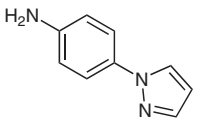
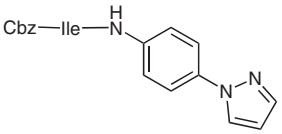
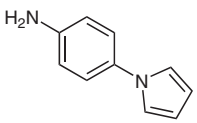
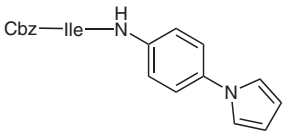
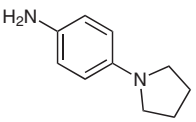
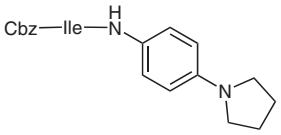
Entry	Amino acid	Arylamine	Product	Yield (%)[b]
6	**1a**	 **2f**	 **3f**	77
7	**1a**	 **2g**	 **3g**	80
8	*N*-Cbz-Leu (**1b**)	 **2a**	 **3h**	89
9	**1b**	 **2i**	 **3i**	88
10	**1b**	 **2b**	 **3j**	83
11	**1b**	 **2c**	 **3k**	89
12	**1b**	 **2d**	 **3l**	81
13	**1b**	 **2f**	 **3m**	83
14	**1b**	 **2g**	 **3n**	82
15	**1b**	 **2h**	 **3o**	89
16	*N*-Cbz-Ile (**1c**)	 **2a**	 **3p**	86
17	**1c**	 **2c**	 **3q**	83

Table 2 Synthesis of Arylamides from *N*-Cbz-Protected Amino Acids and Arylamines with MsCl and MeIm[a] (continued)

Entry	Amino acid	Arylamine	Product	Yield (%)[b]
18	**1c**	 **2i**	 **3r**	86
19	**1c**	 **2f**	 **3s**	84
20	**1c**	 **2d**	 **3t**	87
21	**1c**	 **2g**	 **3u**	87
22	**1c**	 **2h**	 **3v**	89

[a] To a solution of *N*-Cbz-protected amino acid (1.0 equiv) and MeIm (2.5equiv) in CH_2Cl_2 (5 mL/g) was added MsCl (1.0 equiv) below –5 °C and stirred for additional 20 min, then the arylamine (0.9 equiv) was added to this mixture and stirred for 2 h at r.t.
[b] Isolated yield based on arylamines.

Arylamides generated from *N*-Cbz-protected amino acids and arylamines were obtained in reasonable yields using MsCl and MeIm in dichloromethane (Table 2). A range of 4-methyl-, 4-methoxy-, 4-fluoro-, 3,4-difluoro-, 4-pyrazolyl-, 4-pyrrolyl-, 4-pyrrolidinyl-, 4-morpholinyl-, 4-piperidyl- and 4-nitro-substituted anilines were readily condensed with *N*-Cbz-protected amino acids (*N*-Cbz-protected Phe, Leu and Ile) under the mild conditions. Both electron-donating and electron-withdrawing arylamines worked well. It was noted that the weakly nucleophilic *p*-nitroaniline (*p*-NA) (pK_a 1.0 vs pK_a 5.2 for aniline) and 3,4-difluoroaniline (pK_a 1.4) also gave satisfying yields under the reaction conditions (Table 2, entries 6, 7, 13 and 19).

To determine whether the reaction conditions caused racemization in this procedure, the enantiomeric excess (ee) of both **3b** and **3g** were measured by chiral HPLC. As shown in Figure 1 (**3b**, for example), racemates of Cbz-Phe-anilide were baseline separated with retention time of 31.2 min and 38.9 min, respectively, in the chiral HPLC system (chromatogram A, Figure 1). Using this analytical method, we determined that ee of **3b** was more than 99.5% (chromatogram B, Figure 1). The same method was applied to **3g** and the ee of more than 99.5% was also observed. These results indicate that there is no significant racemization in the synthesis.

In summary, we have demonstrated that *N*-terminal-protected amino acids could be readily converted in high yields into various *C*-arylamides utilizing methanesulfonyl chloride and *N*-methylimidazole in dichloromethane even if the arlyamines have extremely low nucleophilicity and the amino acids are sterically hindered. It is also noteworthy that under the mild conditions, no significant race-

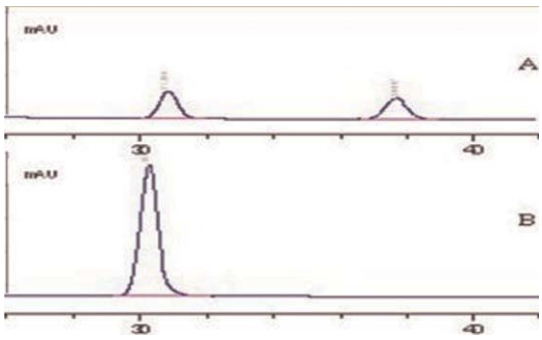


Figure 1 Enantiomeric excess determination of L-Cbz-Phe-anilide (**3b**) by chiral HPLC. The chromatograms shown are (A) recemate of Cbz-Phe-anilide, and (B) L-Cbz-Phe-anilide (**3b**). Chromatographic condition: CHIRAL, AD-H column (250 × 4.6 mm, 5μm); hexane–*i*-PrOH–TFA (90:10:0.1); 0.8 mL/min; 30 °C

mization occurred at the *C*-terminal position. Thus, this method is a promising way for the synthesis of this important class of compounds.

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

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(13) **Typical Procedure for the Preparation of Amino Acid Arylamides**: MeIm (25.0 mmol) was added to a stirred solution of Cbz-Phe (10.0 mmol) in CH_2Cl_2 (15 mL) at 0–5 °C, and the mixture was stirred for 10 min. MsCl (10.0 mmol) in CH_2Cl_2 (1.0 mL) was added to the mixture under –5 °C. After the mixture was stirred under that temperature for 20 min, aniline (9.0 mmol) was added. Then the mixture was stirred at r.t. for 2 h. H_2O (100 mL) was added to the mixture, which was extracted with additional CH_2Cl_2 (100 mL). The organic layer was washed with sat. NaCl solution (3×50 mL) and dried with anhyd Na_2SO_4. The solvent was removed by evaporation under reduced pressure. Purification by chromatography on silica gel (CH_2Cl_2–MeOH) gave **3b** as a white solid; mp 169–170 °C; $[\alpha]_D^{25}$ 46.0 (c = 0.2, DMSO); ee >99.5%. ^{1}H NMR (400 MHz, DMSO): δ = 2.88 (dd, 1 H), 3.03 (dd, 1 H), 4.43 (m, 1 H), 4.99 (s, 2 H), 5.43 (br s, 1 H), 7.00–7.60 (m, 15 H), 10.04 (br s, 1 H). HRMS (ESI$^+$): m/z [M + Na$^+$] calcd for $C_{23}H_{22}N_2O_3$: 397.1528; found: 397.1530.