ORGANIC LETTERS

2001
Vol. 3, No. 16
2583−2586

CuI-Catalyzed Coupling Reaction of β-Amino Acids or Esters with Aryl Halides at Temperature Lower Than That Employed in the Normal Ullmann Reaction. Facile Synthesis of SB-214857

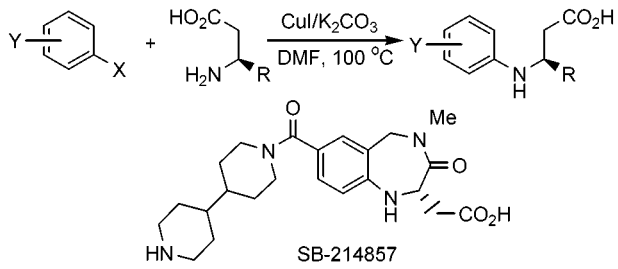
Dawei Ma* and Chengfeng Xia

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, 354 Fenglin Lu, Shanghai 200032, China

madw@pub.sioc.ac.cn

Received June 11, 2001

ABSTRACT



The CuI-catalyzed coupling reaction of aryl halides with β-amino acids or β-amino esters is completed at 100 °C in 48 h, which indicates that the structure of the β-amino acid has an accelerating effect for the Ullmann-type aryl amination reaction. This coupling reaction can be used to prepare enantiopure *N*-aryl β-amino acids. An efficient synthetic route to SB214857, a potent GPIIb/IIIa receptor antagonist, is developed using this method.

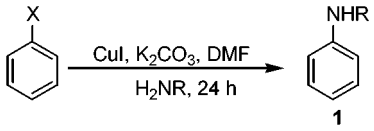
The formation of the carbon−nitrogen bond by the CuI-catalyzed coupling of aryl halides with amines is one of the typical Ullmann coupling reactions.[1] For unsubstituted aryl halides, the reaction is generally carried out at temperature in excess of 150 °C and completed in 3−5 h.[1] Recently, we found that an accelerating effect induced by the structure of α-amino acid existed in the Ullmann reaction and that the coupling of α-amino acids with aryl halides catalyzed by CuI could be carried out at temperature much lower than that employed in the normal Ullmann coupling reaction.[2] To check if the structure of β-amino acid had a similar accelerating effect, we undertook studies to evaluate the coupling reaction of β-amino acids with aryl halides catalyzed by CuI. Herein, we wish to report our results.

As shown in Table 1, CuI-catalyzed coupling of 3-aminobutanoic acid with bromobenzene occurred at 100 °C for 24 h to afford the coupling product in 26% yield (entry 1). This reaction was slightly slower than that of α-amino acid with bromobenzene (compare entries 2 and 3). However, this coupling reaction was still much faster than that of a single amine with bromobenzene, because in a controlled experiment the reaction of benzylamine with bromobenzene only gave less than 4% conversion even at 110 °C after 24 h (entry 6). These results indicated that the structure of β-amino acid also had an accelerating effect for an Ullmann-type aryl amination reaction. Interestingly, γ-amino acid did not show remarkable accelerating effect; no coupling reaction occurred

(1) For a review, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
(2) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459.

10.1021/ol016258r CCC: $20.00
Published on Web 07/14/2001

Table 1. CuI-Catalyzed Coupling Reaction of Various Amines with Aryl Halides[a]



entry	X	H_2NR	temp (°C)	yield (%)[b]
1	Br	3-aminobutanoic acid	100	26
2	Br	3-aminobutanoic acid	90	14
3	Br	(*S*)-valine	90	42
4	Br	4-aminobutanoic acid	90	0
5	Br	4-aminobutanoic acid	110	tr
6	Br	benzylamine	110	<4
7	I	3-aminobutanoic acid	90	69
8	Cl	3-aminobutanoic acid	90	0
9[c]	Br	3-aminobutanoic acid	100	64
10[c]	Br	3-aminobutanoic acid ethyl ester	100	62

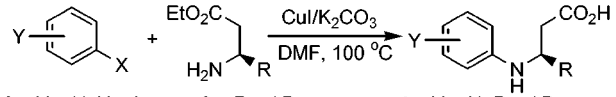
[a] Reaction conditions: ArX (1 mmol), amine (1 mmol), CuI (0.1 mmol), K_2CO_3 (2.5 mmol), DMF (5 mL), and water (0.1 mL). [b] Isolated yield. [c] Reaction time: 48 h.

at 90 °C, and little conversion was determined at 110 °C when 4-aminobutanoic acid was used (entries 4 and 5). Furthermore, it was observed that the reactivity for different aryl halides was ArI > ArBr > ArCl (compare entries 2, 7 and 8), which was the typical character of the Ullmann coupling reaction. In addition, similar to 3-aminobutanoic acid (entry 9), reaction of 3-aminobutanoic acid methyl ester with bromobenzene also worked to give the coupling product in 62% yield (entry 10). Obviously, the coupling reagent here was still a β-amino salt because this ester could be hydrolyzed in situ under the present reaction conditions. (In a controlled reaction without addition of CuI and bromobenzene, it was found that the β-amino ester was hydrolyzed completely in less than 30 min.) Since the enantiopure β-amino esters were conveniently available,[3] we could use it to prepare enantiopure *N*-aryl β-amino acids.

To explore the scope of the coupling reaction of aryl halides with β-amino esters, other β-amino esters and aryl halides were tested under the conditions mentioned above, and the results are summarized in Table 2. It was found that electron-deficient aryl iodides gave the best results (entries 4−6), whereas electron-rich aryl halides showed lower yields or lack of conversion (entries 7−9). Unsubstituted or electron-deficient aryl bromides were also suitable substrates (compare entries 2, 10, and 16). In addition, both aliphatic and aromatic β-amino acids worked well for this reaction. Thus, this method has proven useful for preparing *N*-aryl β-amino acids with considerable diversity in either racemic or enantiopure form.

On the basis of the proposed mechanism of the Cu(I)-catalyzed coupling reaction of aryl halides with α-amino

Table 2. CuI-Catalyzed Coupling Reaction of β-Amino Esters with Aryl Halides[a]



2a: Y = H, X = I
2b: Y = H, X = Br
2c: Y = 4-Me, X = I
2d: Y = 4-I, X = I
2e: Y = 2-Cl, X = I
2f: Y = 4-NO_2, X = I
2g: Y = 4-NH_2, X = I
2h: Y = 4-AcNH, X = I
2i: Y = 4-Br, X = Br
2j: Y = 4-MeO, X = I
2k: Y = 4-MeO, X = Br

3a: R = *i*-Pr
3b: R = Me
3c: R = *n*-C_6H_{13}
3d: R = *n*-Pr
3e: R = *c*-hexyl
3f: R = 4-$MeOC_6H_4$

4a: Y = H, R = *i*-Pr
4b: Y = 4-Me, R = *i*-Pr
4c: Y = 4-I, R = *i*-Pr
4d: Y = 2-Cl, R = *i*-Pr
4e: Y = 4-NO_2, R = *i*-Pr
4f: Y =4-AcNH, R = *i*-Pr
4g: Y = 4-Br, R = *i*-Pr
4h: Y = 4-MeO, R = *i*-Pr
4i: Y = H, R = Me
4j: Y = H, R = *n*-C_6H_{13}
4k: Y = H, R = *n*-Pr
4l: Y = H, R = *c*-hexyl
4m: Y = H, R = 4-$MeOC_6H_4$

entry	ArX	β-amino ester	product	yield (%)[b]
1	**2a**	**3a**	**4a**	74
2	**2b**	**3a**	**4a**	62
3	**2c**	**3a**	**4b**	75
4	**2d**	**3a**	**4c**	83
5	**2e**	**3a**	**4d**	80
6	**2f**	**3a**	**4e**	87
7	**2g**	**3a**		*c*
8	**2h**	**3a**	**4f**	17
9	**2j**	**3a**	**4h**	31
10	**2i**	**3a**	**4g**	72
11	**2a**	**3b**	**4i**	69
12	**2a**	**3c**	**4j**	76
13	**2a**	**3d**	**4k**	74
14	**2a**	**3e**	**4l**	79
15	**2a**	**3f**	**4m**	80
16	**2k**	**3a**		*c*

[a] Reaction conditions: aryl halide (1 mmol), β-amino ester (1 mmol), CuI (0.1 mmol), K_2CO_3 (2.5 mmol) in 5 mL of DMF and 0.1 mL of water, stirred at 100 °C for 48 h. [b] Isolated yield. [c] No coupling product was determined.

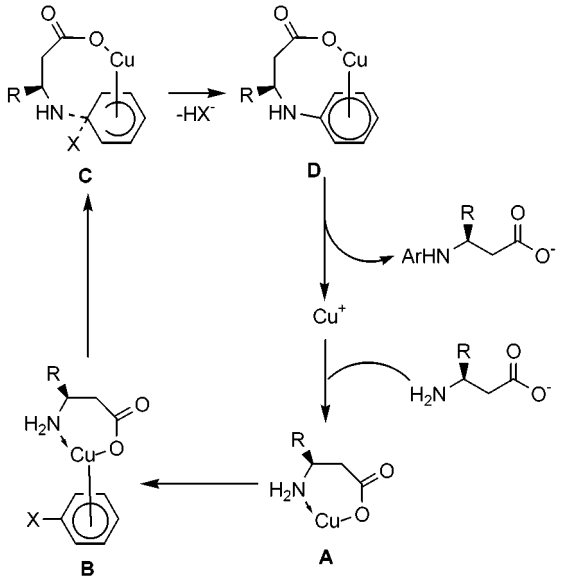
acid,[2] we envisaged that the present coupling reaction might pass through a mechanism as shown in Scheme 1, in which a cuprous ion reacted with a β-amino acid salt to form the chelate A,[5] which coordinated with a suitable aryl halide to provide the π-complex B. Next, intramolecular nucleophilic substitution occurred at the aromatic ring to give intermediate C. This step might be the rate-determining step, and the intramolecular attack would lower the activation energy. With the increase of distance between the amino and carboxylate groups, the ring size in the transition state C became larger and thereby C would be more unstable. This might be the reason the accelerating effect induced by the structure of

(3) (a) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry*, **1991**, *2*, 183. (b) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1141.

(4) **Typical Procedure.** To a solution of aryl halide (1 mmol) and β-amino ester (1 mmol) in 5 mL of DMF were added potassium carbonate (2.5 mmol), 0.1 mL of water, and CuI (0.1 mmol) under nitrogen. After the mixture was stirred at 100 °C for 48 h under nitrogen atmosphere, the cooled solution was concentrated in vacuo. The residue was dissolved in water, acidified to pH 5, and extracted with ethyl acetate. The combined organic layers were concentrated and purified by chromatography to afford the corresponding *N*-aryl β-amino acid.

(5) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961; Vol. 1; p 569.

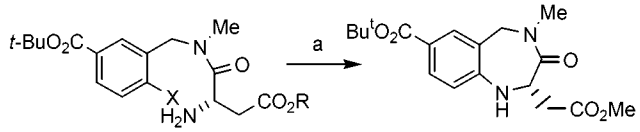
Scheme 1



different amino acids decreased in the following order: α-amino acid > β-amino acid > γ-amino acid. Finally, HX was removed from C with the assistance of potassium carbonate to deliver another π-complex, D, which could decompose to produce the *N*-aryl β-amino acid and regenerate the cuprous ion.

Taking advantage of the present reaction, we developed a very efficient route to SB-214857 (Scheme 3). SB-214857

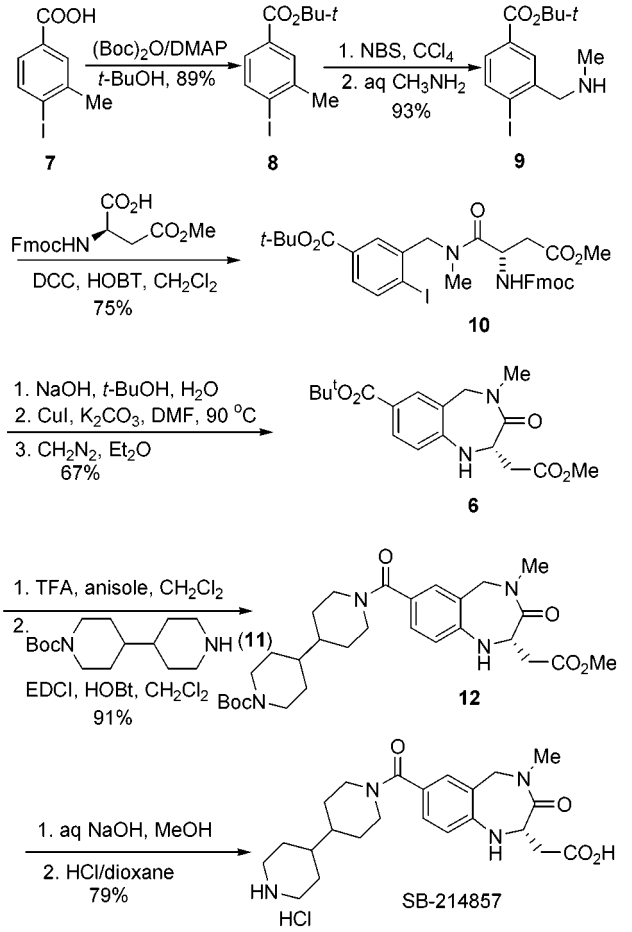
Scheme 2[a]



[a] Reagents and conditions for **5a**: (a) DMSO, 128−130 °C, 22 h, 30−40%, ∼5% racemization.

is a potent GPIIb/IIIa receptor antagonist currently in Phase III clinic trials for the protection of secondary thrombotic events such as heart attack and stroke.[6] Initially, it was synthesized using an intramolecular displacement of the activated aryl fluoride **5a** as a key step.[7] However, this reaction needed to be carried out at 128−130 °C to give the desired cyclization product **6** in 30−40% yield, and unacceptable levels of racemization occurred (Scheme 2).[8] This drawback led to the development of an alternate synthetic protocol in which chemical resolution was applied to get an enantiopure intermediate.[9] Obviously, if a CuI-catalyzed intramolecular aryl amination of the β-amino acid **5b** worked at a reasonable reaction temperature in good yield, we would be able to avoid the drawback of SmithKline's protocol. Thus, esterification of 3-methyl-4-iodobenzoic acid **7** with $(Boc)_2O$/DMAP in *tert*-butyl alcohol provided ester **8** in 89% yield.[10] Bromination of **8** with NBS followed by amination with methylamine gave **9**, which was condensed with Fmoc (*S*)-aspartic acid β-methyl ester to afford amide **10**. Hydrolysis of **10** with aqueous NaOH in *tert*-butyl alcohol produced **5b**, which was heated at 90 °C under the action of 10 mol % CuI and potassium carbonate to provide the desired cyclization product. This product was treated with diazomethane to deliver **6** in 67% overall yield. Its optical rotation value ($[\alpha]^{20}_D$ +267.5 (*c* 0.25, $CHCl_3$)) was almost same as that reported ($[\alpha]^{20}_D$ +267.6 (*c* 1.0, $CHCl_3$)),[7] thus indicating that no racemization occurred in the coupling step. After removal of the *tert*-butyl protecting group, the acid

Scheme 3



(6) For reviews, see: (a) Scarborough, R. M.; Gretler, D. D. *J. Med. Chem.* **2000**, *43*, 3453. (b) Mousa, S. A. *Drug Discovery Today* **1999**, *4*, 552.

(7) Miller, W. H.; Ku, T. W.; Ali, F. E.; Bondinell, W. E.; Calvo, R. R.; Davis, L. D.; Erhard, K. F.; Hall, L. B.; Huffman, W. F.; Keenan, R. M.; Kwon, C.; Newlander, K. A.; Ross, S. T.; Samanen, J. M.; Takata, T. D.; Yuan, C. *Tetrahedron Lett.* **1995**, *36*, 9433.

(8) Hayes, J. F. *Synlett* **1999**, 865.

(9) Etridge, S. K.; Hayes, J. F.; Walsgrove, T. C.; Wells, A. S. *Org. Process Res. Dev.* **1999**, *3*, 60.

(10) Takeda, K.; Akiyama, A.; Nakamura, H. *Synthesis* **1994**, 1063.

generated was condensed with amine **11** to provide amide **12**. Deprotection of **12** with aqueous NaOH and subsequent treatment with 4 N HCl gave SB-214857 as a hydrochloride salt. The overall yield for this total synthesis was about 30%.

In brief, we have demonstrated here that the structure of β-amino acid had an accelerating effect for the Ullmann-type aryl amination reaction, which allowed us to synthesize *N*-aryl β-amino acid by coupling aryl halides with β-amino acids or β-amino esters at relatively low reaction temperature. The synthetic use of this method was demonstrated by an effective preparation of SB214857. Further applications to synthesize other complex molecules are in hand.

Acknowledgment. The authors are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China (grant 29725205) and Qiu Shi Science & Technologies Foundation for their financial support.

Supporting Information Available: Experimental procedures and characterizations for compounds **3**, **6**, and **8**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016258R