ORGANIC LETTERS

2002
Vol. 4, No. 22
3803−3805

Direct Synthesis of Unprotected 4-Aryl Phenylalanines via the Suzuki Reaction under Microwave Irradiation

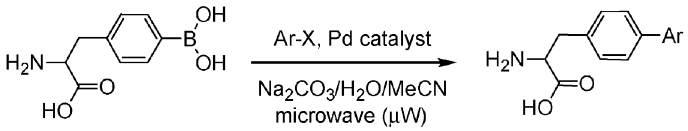
Yong Gong* and Wei He

Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, L.L.C, Welsh & McKean Roads, Spring House, Pennsylvania 19477-0776

ygong@prdus.jnj.com

Received July 23, 2002

ABSTRACT



4-Aryl phenylalanines were prepared as free amino acids from the Suzuki coupling of 4-borono phenylalanine with aryl halides in high yields within 5–10 min under microwave irradiation.

The derivatives of biaryl amino acid possess certain biological activities. *N*-Benzoyl-4-aryl phenylalanines, for example, represent a major class of alpha4 integrin antagonists.[1] The inhibition of other *N*-acyl-4-aryl phenylalanines against endothelin-converting enzyme has also been reported.[2] However, the supply of such biaryl amino acids is very limited. There is a practical need for a versatile and efficient synthetic method, preferably from coupling of readily available and properly functionalized aryl amino acid precursors with suitable coupling partners. The Suzuki reaction has been applied in the preparation of *N*-protected 4-aryl phenylalanine esters[3] from cross couplings of either *N*-protected 4-Br (I or OTf) phenylalanine esters with aryl boronic acids[4] or *N*-protected 4-borono phenylalanine esters with aryl halides (or triflates).[5] However, the direct cross coupling involving free amino acids has not been disclosed. Previously, we reported the synthesis of aryl benzoic acids from the direct coupling of carboxybenzene boronic acids with aryl halides.[6] We envisioned that the direct coupling of unprotected 4-borono phenylalanine with aryl halides under Suzuki conditions would provide structurally diversified 4-aryl phenylalanines without the necessity of protection and deprotection procedures. The free biaryl amino acids can then be selectively protected or derivatized depending on the subsequent chemistry. In addition, the direct coupling of free amino acids under basic conditions might protect the chiral center from racemization, which is often a concern with reactions involved in protected amino acids at elevated temperature.

Microwave heating has been widely applied in the organic synthesis and its advantage over traditional heating has been demonstrated.[7] Moreover, recent advances in the microwave instrumentation have made this technique more accessible and the results more reproducible. The microwave instruments can be readily automated and programmed for screening reaction conditions, as well as for high throughput

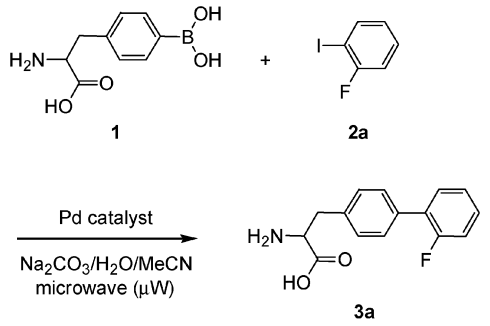
(1) Tilley, J. W.; Sidduri, A. *Drugs Future* **2001**, *26*, 985.
(2) Firooznia, F.; Gude, C.; Chan, K.; Fink, A. C.; Qiao, Y.; Satoh, Y.; Marcopoulos, N.; Savage, P.; Beil, M. E.; Bruseo, C. W.; Trapani, A. J.; Jeng, A. Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 375.
(3) The Stille reaction has also been applied in the synthesis of *N*-Boc-4-aryl phenylalanine methyl esters: Morera, E.; Ortar, G. *Synlett* **1997**, 1403.
(4) (a) Shieh, W. C.; Carlson, J. A. *J. Org. Chem.* **1992**, *57*, 379. (b) Burk, M. J.; Lee, J. R.; Martinez, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 10847. (c) Kotha, S.; Lahiri, K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2887.
(5) (a) Satoh, Y.; Gude, C.; Chan, K.; Firooznia, F. *Tetrahedron Lett.* **1997**, *38*, 7645. (b) Firooznia, F.; Gude, C.; Chan, K.; Satoh, Y. *Tetrahedron Lett.* **1998**, *39*, 3985. (c) Firooznia, F.; Gude, C.; Chan, K.; Marcopulos, N.; Satoh, Y. *Tetrahedron Lett.* **1999**, *40*, 213.
(6) (a) Gong, Y.; Pauls, H. W. *Synlett* **2000**, 829. (b) Gong, Y.; Pauls, H. W.; Spada, A. P.; Czekaj, M.; Liang, G.; Chu, V.; Colussi, D. J.; Brown, K. D.; Gao, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 217.
(7) For recent reviews, see: (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (b) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95. (d) Santagada, V.; Perissutti, E.; Caliendo, G. *Curr. Med. Chem.* **2002**, *9*, 1251.

10.1021/ol026587z CCC: $22.00
Published on Web 10/10/2002

synthesis in a very short period of time. Herein, we report the microwave-assisted direct coupling of 4-borono phenylalanine with aryl halides as a convenient and quick method for the synthesis of 4-aryl phenylalanines.

A set of commonly used palladium catalysts was selected to screen the coupling reaction between racemic 4-borono phenylalanine **1** and 1-fluoro-2-iodobenzene **2a** (Scheme 1)

Scheme 1



under microwave irradiation. In a typical experiment,[8] a mixture of 1 equiv of **1** and **2a** in aqueous acetonitrile (1:1) was microwave heated for 5 min in the presence of 2 equiv of sodium carbonate and a 5 mol % palladium catalyst. The reactions were monitored by HPLC and the results were summarized in Table 1.

Table 1. Reaction Conditions on the Suzuki Coupling via Scheme 1

entry	microwave conditions	convn (%)[a]
1	$Pd(PPh_3)_2Cl_2$, 120 °C, 5 min	58
2	$Pd(PPh_3)_2Cl_2$, 130 °C, 5 min	90
3	$Pd(PPh_3)_2Cl_2$, 140 °C, 5 min	96
4	$Pd(PPh_3)_2Cl_2$, 150 °C, 5 min	99
5	$Pd(PPh_3)_4$, 120 °C, 5 min	35
6	$Pd(PPh_3)_4$, 150 °C, 5 min	83
7	$Pd(dppf)_2Cl_2$, 150 °C, 5 min	93
8	$Pd(PCy_3)_2Cl_2$, 150 °C, 5 min	23
9	$Pd_2(dba)_3$, 150 °C, 5 min	92
10	$Pd(OAc)_2$, 150 °C, 5 min	82

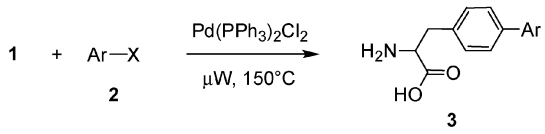
[a] Determined by HPLC at 215 nm. Based on aryl halide **2a**.

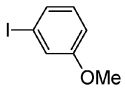
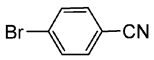
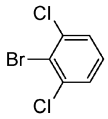
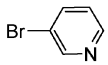
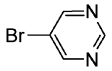
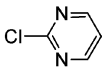
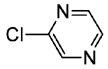
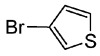
Among the catalysts tested, $Pd(PPh_3)_2Cl_2$ was the most effective one. The conversion of **1** to 4-aryl phenylalanine **3a** was improved from 58% at 120 °C (entry 1) to 90% at 130 °C (entry 2), and reached 99% at 150 °C (entry 4). This result reflected the effect of temperature on the coupling reaction. Several other catalysts were also effective. $Pd(dppf)_2Cl_2$ (entry 7) and $Pd_2(dba)_3$ (entry 9) gave >90% conversion at 150 °C for 5 min. About 80% conversion was achieved with $Pd(PPh_3)_4$ (entry 6) and $Pd(OAc)_2$ (entry 10) under the same conditions. $Pd(PCy_3)_2Cl_2$ (entry 8), however, only gave 23% conversion.

For comparison, the reaction in Scheme 1 was also conducted using a preheated oil bath under otherwise identical conditions as for the microwave reaction, i.e., $Pd(PPh_3)_2Cl_2$, 140 °C, 5 min. As expected, lower conversion (59%) was observed with the traditional thermal conditions as compared to microwave irradiation (96%).

The microwave conditions from entry 4 in Table 1 were identified as the standard reaction conditions, and were utilized for the synthesis of a diverse set of 4-aryl phenylalanines (**3a**−**i**). HPLC analysis of crude mixtures showed nearly complete conversion in most cases. High isolated yields (68−83%) were obtained across the board as summarized in Table 2. For substrate 3-iodoanisole **2b** and

Table 2. Preparation of 4-Aryl Phenylalanines **3**



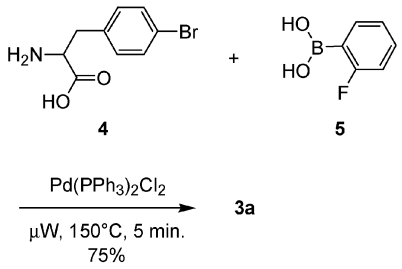
entry	Ar-X (**2**)	time (min)	yield (%)[a]
a		5	86
b		10	73
c		5	84
d		10	75
e		5	72
f		5	76
g		5	74
h		5	68
i		5	83

[a] Isolated by reverse-phase HPLC as TFA salt.

sterically hindered substrate 2-bromo-1,3-dichlorobenzene **2d**,[11] satisfactory results were achieved after the reaction time was prolonged from 5 to 10 min.

Furthermore, the effect of switching positions of boronic acid and halide in the coupling partners was examined. The cross coupling of racemic 4-bromophenylalanine **4** with 2-fluorophenyl boronic acid **5** was carried out under the same conditions as shown in Scheme 2. A high yield (75%) of coupling product **3a** was maintained. This alternative ap-

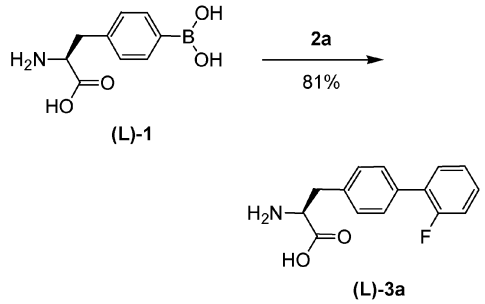
Scheme 2



proach can serve as a complement to the methodology involving 4-borono phenylalanine and aryl halides.

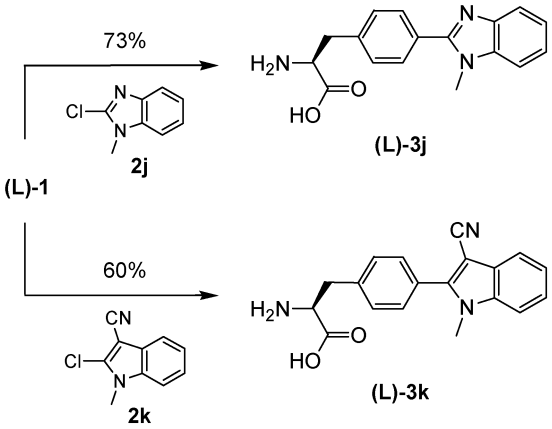
The application in asymmetric synthesis was also investigated. The coupling reaction of 4-borono-L-phenylalanine[12] **(L)-1** with 1-fluoro-2-iodobenzene **2a** (Scheme 3) was

Scheme 3



conducted under the standard conditions. In addition to the excellent conversion as expected, no significant racemization was observed with coupling product **(L)-3a**, according to the analysis of (+)-Mosher's amide of **(L)-3a** and racemic **3a** by HPLC and ^{1}H NMR.[13] This observation is in agreement with the notion that the presence of carboxylate anion and a free amino group in α-amino acid shields α-C−H from deprotonation and thus limits racemization.[14] Similarly, coupling of **(L)-1** with 2-chloro-1-methyl-1*H*-benzoimidazole **2j** and 2-chloro-1-methyl-1*H*-indole-3-carbonitrile **2k** afforded the corresponding coupling products **(L)-3j** and **(L)-3k** in good yields (Scheme 4) within 5 and 10 min, respectively.

Scheme 4



In conclusion, we have described a straightforward approach to the synthesis of unprotected 4-aryl phenylalanines. Microwave irradiation facilitates the coupling reaction to 5−10 min. The amino group and carboxylic group are well tolerated. This method offers an easy access to a variety of free biaryl amino acids.

Acknowledgment. The authors thank Dr. Steven Coats for his initial assistance in the operation of SmithSynthesizer.

OL026587Z

(8) General procedure: A 10-mL SmithPrcess vial containing a magnetic stir bar was charged with 4-borono phenylalanine (0.11 g, 0.50 mmol),[9] aryl halide (0.50 mmol), palladium catalyst (0.025 mmol), 1.0 M Na_2CO_3 (1.0 mL), and acetonitrile (1.0 mL). After vacuum degassing, the vial was sealed and the suspension was heated in the SmithSynthesizer[10] under selected microwave conditions. The conversion was monitored and analyzed by HPLC. The crude reaction mixture was concentrated to dryness, acidified with trifluoroacetic acid (TFA) in MeOH, and purified by reverse phase HPLC, eluted with 0.1% TFA H_2O/MeCN gradient. All products were characterized by NMR and MS. Selected compound **3a** was obtained as a white solid: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.56 (d, J = 6.7 Hz, 2H), 7.54−7.14 (m, 6H), 4.22 (dd, J = 5.2, 7.9 Hz, 1H), 3.38 (dd, J = 5.2, 14.5 Hz, 1H), 3.18 (dd, J = 7.9, 14.5 Hz, 1H); ^{13}C NMR (CD_3OD, 300 MHz) δ 172.05, 163.14, 137.10, 135.84, 132.18, 131.03, 130.20, 126.15, 117.57, 117.27, 55.89, 37.61; MS *m*/*z* 260 (MH^+).

(9) The reaction can be performed at higher concentration to (but not limited to) 2-mmol scale in the same vial, which broadens its preparative usefulness.

(10) For the commentary of SmithSynthesizer, see: Watkins, K. J. *Chem. Eng. News*, **2002**, *80* (6), 17.

(11) 1,3-Dichloro-2-iodobenzene gave similar results to dichloro phenyl product **3d**.

(12) The coupling reaction can also be applied to 4-borono-D-phenylalanine. Both enantiomers are commercially available. For the preparation, see: (a) Malan, C.; Morin, C. *J. Org. Chem.* **1998**, *63*, 8019. (b) Nakamura, H.; Fujiwara, M.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 231.

(13) For the Mosher's amide of (L)-**3a** one set of characteristic ^{1}H NMR ($CDCl_3$, 300 MHz) signals was observed with chemical shifts δ 4.95 (m, 1H) and 3.20 (s, 3H). Two sets of the corresponding signals were obtained at δ 5.05 (m, 1H), 4.95 (m, 1H), 3.40 (S, 3H), and 3.20 (s, 3H) for the Mosher's amides of racemic **3a**.

(14) (a) Bergmeier, S. C.; Ismail, K. A. *Synthesis* **2000**, 1369. (b) Rios, A.; Richard, J. P.; Amyes, T. L. *J. Am. Chem. Soc.* **2002**, *124*, 8251.