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Synthesis of *N*-(3-Arylpropyl)amino Acid Derivatives by Sonogashira Types of Reaction in Aqueous Media†

M. Pilar López-Deber, Luis Castedo, and Juan R. Granja*

Departamento de Química Orgánica e Unidade Asociada ó C.S.I.C, Facultade de Química, Universidade de Santiago, 15782 Santiago de Compostela, Spain.

qojuangg@usc.es

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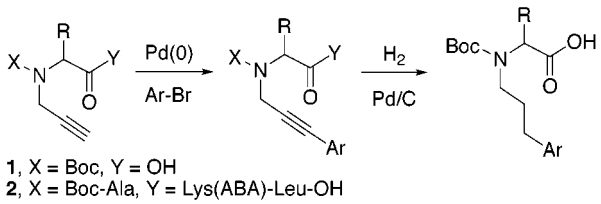
ABSTRACT



1, X = Boc, Y = OH
2, X = Boc-Ala, Y = Lys(ABA)-Leu-OH

***N*-Propargylamino acids and peptides including them can be efficiently derivatized in aqueous media with a wide variety of (hetero)aryl halides by cross-coupling reactions catalyzed by palladium on carbon (10% Pd/C).**

The remarkable structural and functional diversity of protein architecture suggests the enticing goal of constructing synthetic variants. Crucial to the de novo design of functional polypeptides is the availability of synthetic motifs with defined secondary and tertiary structure.[1] For small peptides this generally requires either disulfide bridges or metal binding sites.[2] Alternatively, control of structure can be achieved by modification of a polypeptide with unnatural residues.[3] A particularly interesting modification is N-alkylation.[4] Both designed and naturally occurring peptides are known to form β-turns motifs in the region of any ***N***-alkylamino acid residues.[5] Additionally, the alkyl group can be used to incorporate functions allowing coordination with metals, covalent modification, or the monitoring of design progress.[6] ***N***-Alkylamino acids also possess an increased metabolic stability that makes them potentially useful in drug development.[7]

The synthesis of ***N***-alkylated peptides is usually based on the preparation of ***N***-alkylamino acids followed by their incorporation on solid-phase synthesis.[8−10] Seeking to produce peptides with ***N***-alkyl groups featuring aryl or heteroaryl substituents with useful properties for monitoring or control of peptide structure, we envisaged that ***N***-(3-arylpropyl)-

† Abbreviations used: ABA, 4-acetamidobenzoic amide; 4-DPPBA, 4-diphenylphosphinobenzoic acid; dppe, diphenylphosphinoethane; HATU, *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-***b***]pyridin-1-yl-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; HOAt, 7-aza-1-hydroxybenzotriazole; nd, not detected; SPPS, solid-phase peptide synthesis; TCEP, tris(2-carboxyethyl)phosphine; TIPP, triisopropyl phosphite; TMP, tris(2,4,6-trimethylphenyl)phosphine; TTMPP, tris(2,4,6-trimethoxyphenyl)phosphine.

(1) For research on the design of peptide sequences with a predictable three-dimensional structure, see for example: (a) Struthers, M. D.; Cheng, R. P.; Imperiali, B. *Science* **1996**, *217*, 342−345. (b) Zondlo, N. J.; Schepartz, A. *J. Am. Chem. Soc.* **1999**, *121*, 6938−6939. (c) De Alba, E.; Santoro, J.; Rico, M.; Jiménez, M. A. *Protein Sci.* **1999**, *8*, 854−865.

(2) (a) Handel, T. M.; Williams, S. A.; DeGrado, W. F. *Science* **1993**, *259*, 1288−1293. (b) Ghadiri, M. R.; Case, M. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1594−1597. (c) Barthe, P.; Rochette, S.; Vita, C.; Roumestand, C. *Protein Sci.* **2000**, *9*, 942−955.

(3) (a) Imperiali, B.; Fisher, S. L. *J. Org. Chem.* **1993**, *58*, 1613−1616. (b) Nowick, J. S.; Chung, D. M.; Maitra, K.; Maitra, S.; Stigers, K. D.; Sun, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7654−7661.

(4) Alkylation of the amide nitrogen reduces the energy difference between the ***cis*** and ***trans*** forms to approximately 2.1 kJ/mol compared to ca. 10.9 kJ/mol for conventional amino acids: Stewart, D. E.; Sarkar, A.; Wampler, J. E. *J. Mol. Biol.* **1990**, *214*, 253−260.

(5) (a) Braun, W.; Kallen, J.; Mikol, V.; Walkinshaw, M. D.; Wuthrich, K. *FASEB* **1995**, *9*, 63−72. (b) Fusetani, N.; Matsunaga, S. *Chem. Rev.* **1993**, *93*, 1793−1806. Other effects associated with the presence of *N*-methylamino acids are formation of left-handed α-helical structures, disruption of hydrogen bonding to the amide nitrogen, and increased hydrophobicity.

(6) Bark, S. J.; Kent, S. B. H. *FEBS Lett.* **1999**, *460*, 67−76.

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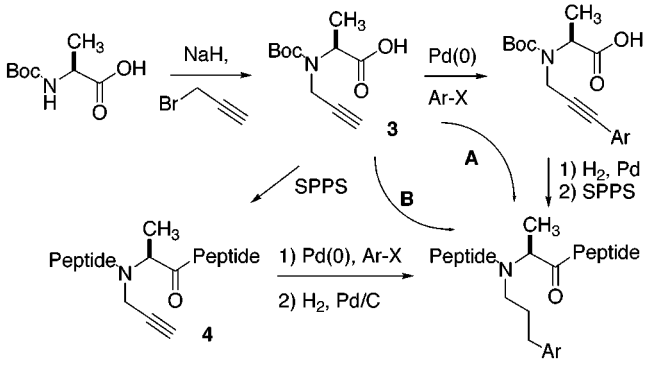
amino acid precursors might be prepared by Sonogashira/Castro-Stephens[11] cross-coupling with appropriated halides and final hydrogenation (Scheme 1, path A). Furthermore,

Scheme 1

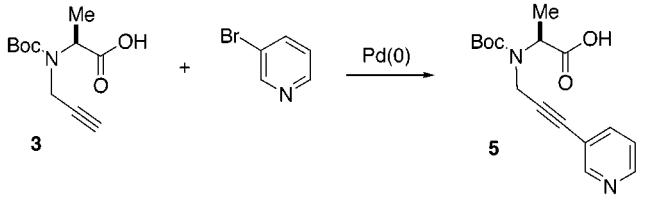


benefits might derive from the possibility of performing SPPS on the ***N***-propargylated amino acids before cross-coupling and hydrogenation (Scheme 1, path B). Here we report the successful development of both paths for construction of peptides with ***N***-(3-aryl)propylated alanine residues.

Initial attempts at propargylation of Boc-Ala-OH using propargyl bromide and NaH in THF mainly gave the propargyl ester, and significant racemization occurred.[13] No epimerization was detected when DMF was used as solvent, which afforded compound **3** in 75% yield.

After unsuccessful attempts at Sonogashira cross-coupling with a variety of heteroaryl bromides and iodides, we undertook a detailed, systematic study of the coupling reaction with 3-bromopyridine. The results are shown in Table 1. None of the typical conditions involving a homogeneous source of Pd(0) afforded the cross-coupling product **5** (entries 1−5). Cross-coupling also did not occur when bromopyridine was replaced by the more reactive triflate (entry 6). Furthermore, the starting amino acid was not recovered in any of these cases, being completely decomposed.

Table 1. Reaction of ***N***-Propargylalanine (**3**) with 3-Bromopyridine



entry	catalyst	ligand	solvent	yield[a] (%)
1	$PdCl_2(Ph_3P)_2$[b]		Et_3N	nd
2	$PdCl_2(Ph_3P)_2$[b]		DMF	nd
3	$PdCl_2(Ph_3P)_2$[b]		THF	nd
4	$Pd(Ph_3P)_4$[b]		CH_3CN	nd
5	$Pd(dba)_2$[b,d]	TTMPP	DMF/DIEA	nd
6	$PdCl_2(Ph_3P)_2$[c]		DMF	nd
7	10% Pd/C[e]	Ph_3P	DME/H_2O	68
8	10% Pd/C[e]	Ph_3P	CH_3CN/H_2O	nd
9	10% Pd/C[e]	Ph_3P	EtOH/H_2O	27
10	10% Pd/C[e]	Ph_3P	ethylene glycol/H_2O	45
11	10% Pd/C[e]	Ph_3P	DMF/H_2O	24
12	10% Pd/C[e]	Ph_3P	DMSO/H_2O	nd
13	10% Pd/C[e]	TCEP	DME/H_2O	10
14	10% Pd/C[e]	dppe	DME/H_2O	nd
15	10% Pd/C[e]	TIPP	DME/H_2O	32
16	10% Pd/C[e]	4-DPPBA	DME/H_2O	75
17	10% Pd/C[e]	TTMPP	DME/H_2O	nd
18	10% Pd/C[e]	TMP	DME/H_2O	nd
19	10% Pd/C[e,f]	Phenol	DME/H_2O	30
20	10% Pd/C[e]	Ph_3P/phenol	DME/H_2O	25
21	10% Pd/C[e,g]	Ph_3P	DME/H_2O	74

[a] All yields are based on **3**. [b] Reactions of 3-bromopyridine (1.1 mmol) with **3** (1.0 mmol) were carried out at 80 °C in 10 mL of solvent using Pd catalyst (0.06 mmol), CuI (0.08 mmol), and Et_3N (0.6 mL). [c] 3-TfOPy was used instead of 3-bromopyridine. [d] DIEA was used instead of Et_3N, 2 equiv of nBu$_4$NI was also added, and the reaction was carried out at −20 °C for 1 h and then heated.[12] [e] Reactions carried out at 80 °C in 60 mL of solvent mixture using 10% Pd/C (0.03 mmol), CuI (0.1 mmol), K_2CO_3 (2.5 mmol), and ligand (0.1 mmol). [f] Two equivalents of nBu$_4$NI was also added. [g] Cs_2CO_3 was used instead of K_2CO_3.

Effective coupling was achieved using palladium on carbon (Pd/C) as the catalyst and DME/H_2O as solvent.[14] Heating of a mixture of 3-bromopyridine and **3** in the presence of 10% Pd/C, PPh_3, CuI, and K_2CO_3 in 1:1 DME−water afforded **5** in 68% yield (entry 7).[15] A systematic study of solvents and ligands with 10% Pd/C as catalyst afforded no significant improvements, but we note the following

(7) For an example, see: Schmidt, R.; Kalman, A.; Chung, N. N.; Lemieux, C.; Horvath, C.; Schiller, P. W. *Int. J. Pept. Protein Res.* **1995**, *46*, 47−55. *N*-Methylation of amino acids has also been used to increase the potency or selectivity of a peptide ligand: Ali, F. E.; Bennett, D. B.; Calvo, R. R.; Elliot, J. D.; Hwang, S.-M.; Ku, T. W.; Lago, M. A.; Nichols, A. J.; Romoff, T. T.; Shah, D. H.; Vasko, J. A.; Wong, A. S.; Yellin, T. O.; Yuan, C.-K.; Samanen, J. M. *J. Med. Chem.* **1994**, *37*, 769−780. Oligomeric ***N***-substituted glycines (peptoids) have emerged as promising tools for drug discovery; for an example, see: Wu, C. W.; Sanborn, T. J.; Zuckermann, R. N.; Barron, A. E. *J. Am. Chem. Soc.* **2001**, *123*, 2958−2963.

(8) Mitsunobu alkylation of *N*-sulfonylamino acid derivatives[a] and reductive amination of amino acids[b] are two of the most commonly methods used for the preparation of *N*-alkylated amino acids: (a) Szardenings, A. K.; Burkoth, T. S.; Look, G. C.; Campbell, D. A. *J. Org. Chem.* **1996**, *61*, 6720−6722. (b) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *33*, 5831−5834. See also ref 10.

(9) Site-selective N-alkylation of peptides by base-promoted alkylation[a] or Mitsunobu reaction[b] on solid phase has recently been reported, although the scope of these methods has not been demonstrated yet: (a) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301−2302. (b) Reichwein, J. F.; Liskamp, R. M. J. *Tetrahedron Lett.* **1998**, *39*, 1243−1246.

(10) *O*-Nitrobenzenesulfonylamino acid has been used in automated solid-phase peptide synthesis: Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1998**, *120*, 2690−2691.

(11) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470. Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313−3315.

(12) Nakamura, K.; Okubo, H.; Yamaguchi, M. *Synlett* **1999**, 549−550.

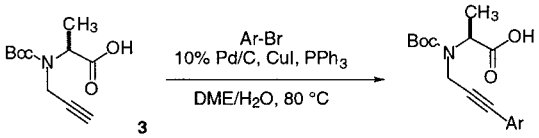
(13) McDermott, J. R.; Benoiton, N. L. *Can. J. Chem.* **1973**, *51*, 1915−1919.

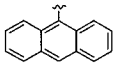
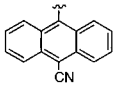
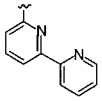
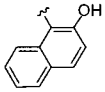
(14) (a) Bleicher, L. S.; Cosford, N.; Herbaut, A.; McCallum, J. S.; McDonald, I. A. *J. Org. Chem.* **1998**, *63*, 1109−1118. (b) De la Rosa, M. A.; Velaverde, E.; Guzmán, A. *Synth. Commun.* **1990**, *20*, 2059−2064. (c) Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277−3280. LeBlond C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R., Jr. *Org. Lett.* **2001**, *3*, 1555−1557.

findings. Although best results were obtained with DME/water, ethanol, ethylene glycol, or DMF can also be used as the organic components of the solvent mixture (entries 9−11). Triphenylphosphine and 4-DPPBA are the best ligands (entries 7 and 16). Yields can be improved by using Cs_2CO_3 instead of K_2CO_3 (entry 21).

To explore the generality of the above conditions we extended these studies to other aryl bromides (Table 2).[16]

Table 2. Reaction of ***N***-Propargylalanine (**3**) with Various (Hetero)aryl Bromides



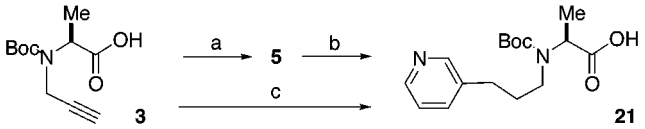
entry	Ar	product (yield %)[a]	entry	Ar	product (yield %)[a]
1		**5** (68)[b] **5** (75)[c]	9		**13** (96)[c]
2		**6** (70)[b]	10		**14** (86)[c]
3		**7** (49)[b] **7** (50)[c]	11		**15** (62)[b]
4		**8** (58)[b] **8** (32)[d]	12		**16** (75)[c]
5		**9** (nd)[f]	13		**17** (81)[b]
6		**10** (62)[b]	14		**18** (35)[b]
7		**11** (nd)[b,g]	15		**19** (12)[b]
8		**12** (15)[b] **12** (71)[e]	16		**20** (18)[b]

[a] Isolated yields. [b] Reactions of X-Ar (1.1 mmol) with **3** (1 mmol) were carried out for 6 h at 80 °C in 60 mL of 1:1 DME/H_2O, using 10% Pd/C (0.03 mmol), CuI (0.1 mmol), PPh_3 (0.1 mmol), and K_2CO_3 (2.5 mmol). [c] 4-Diphenylphosphinobenzoic acid (0.1 mmol) was used instead of PPh_3. [d] Reactions were carried out at 80 °C in 15 mL of 2:1 Et_3N/CH_3CN, using $Pd(PPh_3)_4$ (0.06 mmol) and CuI (0.08 mmol). [e] The reaction was carried out at 80 °C in 10 mL of Et_3N, using $PdCl_2(PPh_3)_2$ (0.025 mmol) and CuI (0.025 mmol). [f] Use of the iodide and of different protecting groups (Ts, Bom, etc.), conditions (b, c, d, e), and solvents was also studied. [g] DMF and EtOH were also tried.

N-Propargylalanine generally coupled in good yields with electron-deficient aryl bromides (entries 1, 2, 6, 9−12),[17] the exception being 6-bromo-2,2′-bipyridine (entry 7).[18] Electron-rich aryl bromides, which are known to be less reactive, also cross-coupled albeit generally in lower yields (entries 3−5, 15−16).

Having optimized the cross-coupling conditions, we proceeded to hydrogenate the triple bond. Treatment of **5** with 10% Pd/C in 5% HOAc/EtOAc under hydrogen afforded compound **21** in 94% yield (Scheme 2). Thiophene

Scheme 2



derivative **7** and anthracene **17** were also hydrogenated under these conditions, likewise in high yields (87% and 92%, respectively). Although in lower overall yield, it was also possible to perform cross-coupling and hydrogenation in one pot. Heating of **3** for 8 h with 3-bromopyridine in the presence of palladium catalyst mixture (Pd/C, CuI, 4-DPPBA, K_2CO_3), followed by stirring of the resulting mixture under hydrogen at room temperature, produced compound **21** in 45% yield without isolation of **5** (Scheme 2).

Encouraged by the success of path A in Scheme 1, we proceeded to examine its application as a new method for backbone modification of peptides (path B). Peptide **22b** was synthesized by SPPS using Boc chemistry on a Pam resin and HF for cleavage from the resin. The resulting unprotected tripeptide was coupled with 3-bromopyridine under the best conditions described above (10% Pd/C, CuI, 4-DPPBA, Cs_2CO_3), but in this case DMF/water was used as solvent, giving peptide **23a** in 44% yield. The reaction yield was improved up to 65% by using the Boc N-protected tripeptide **22c**.

With a view to applying this method to the preparation of diverse peptides with nonterminal ***N***-(3-aryl)propilated residues, especially cyclic peptides,[19] we also studied the acylation of secondary ***N***-propargylamino group and the palladium cross-coupling. Acylation of the secondary amino group was slow, but after trying a variety of standard coupling protocols[20] we found that coupling of **22a** with Boc-Ala-OH using HATU and HOAt proceeded in nearly quantitative yield.[21] Following cleavage with TBAF in DMF,[22] the resulting peptide **24b** was cross-coupled with 3-bromopyridine using the above conditions to give after

(15) (a) For other Sonogashira cross-coupling reactions using water-soluble catalysts, see: Dibowski, H.; Schmidtchen, F. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 476−478. (b) For an example using diaryliodonium salts, see: Radhakrishnan, U.; Stang, P. J. *Org. Lett* **2001**, *3*, 859−860.

(16) No significant improvements in yield were obtained using iodoaryl derivatives, despite the latter being more reactive than bromides: Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-CVH: New York, 1998; Chapter 5.

(17) For cost reasons, triphenylphosphine and potassium carbonate were used in most of the experiments.

(18) We attribute this negative result in base to the low solubility of 6-bromo-2,2′-bipyridine in the solvent mixture.

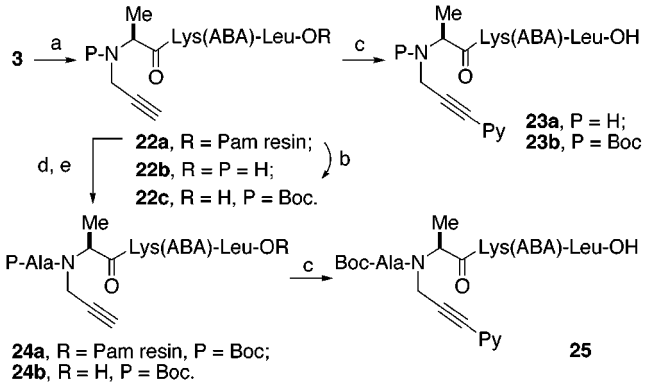
(19) (a) Ghadiri, M. R.; Kobayashi, K.; Granja, J. R.; Chadha, R. K.; McRee, D. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 93−95. (b) Kobayashi, K.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 95−97. (c) Ghadiri, M. R.; Granja, J. R.; Buehler, L. *Nature* **1994**, *369*, 301−304.

(20) For a review of the principal coupling reagents, see: Albericio, F.; Carpino, L. A. *Methods Enzymol.* **1997**, *289*, 104−126.

(21) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398.

(22) Ueki, M.; Kai, K.; Amemiya, M.; Horino, H.; Oyamada, H. *Chem. Commun.* **1988**, 414−415.

Scheme 3



10 h of reaction a 90% yield of a single product that was purified by HPLC and showed by MS to be the expected compound **25** (MS MH^+ 778).[23]

In conclusion, we have developed a new, versatile method for obtaining a variety of ***N***-(3-aryl)propylamino acids by means of a Sonogashira-type reaction and have also established the feasibility of the construction and subsequent cross-coupling of peptides with ***N***-propargylated amino acids at terminal or nonterminal positions. Extension of this work to other functional amino acids and unprotected peptides is currently being pursued. We believe that this new method shows great promise for the simple introduction of novel pharmacologically active functionality into peptides, for the construction of polypeptide species that fold into compact structures upon metal complexation, and for development of new metal ion sensors.

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Supporting Information Available: Experimental procedures for alkylation, cross-coupling, and hydrogenation and ^1H and ^{13}C NMR data and spectra for some of the products illustrated in Table 2 (**3**, **5**−**8**, **10**, **12**, **13**, **16**, **17**, **21**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) The cross-coupling reaction of the unprotected tetrapeptide gave lower yield.