

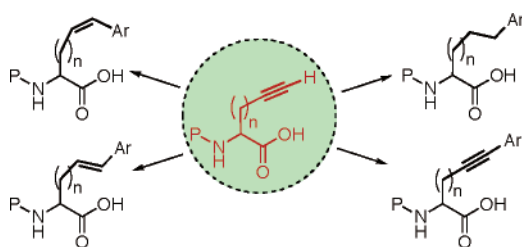
Synthesis of ω -(Hetero)arylalkynylated α -Amino Acid by Sonogashira-Type Reactions in Aqueous Media

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Mild conditions are described that allow the palladium-catalyzed cross-coupling of C_{α} -alkynylated glycine with a wide variety of electron-rich and electron-poor aryl and heteroaryl halides in aqueous media.

Introduction

The main goal of the de novo design of polypeptides is the preparation of short synthetic motifs with defined secondary and tertiary structure that are able to perform functions similar to those of large natural proteins.¹ For small peptides, this generally requires conformational restriction by either disulfide bridges or metal binding,² which in some cases can be achieved by the introduction of nonnatural amino acids.³ For instance,

the use of simple peptides in sensors requires the incorporation of high-affinity metal-binding sites into peptides with defined structures. Nonstandard amino acids can also be used to integrate additional functionality or allow performance monitoring.⁴ Moreover, the incorporation of nonproteinogenic α -amino acids has been found to improve the medical properties of numerous peptide and peptidomimetic drugs.⁵ Finally, a number of nonnatural amino acids are themselves biologically active,⁶ and others can act as organocatalysts in chemical synthesis.⁷ For all these reasons, the development of new synthetic routes to enantiopure nonproteinogenic α -amino acids is of great current chemical interest.^{8,9} Although they can be obtained by a number of methods, including biotransformation, the use of chiral auxiliaries, and asymmetric catalysis, there is a continuing need for mild procedures that are compatible with a wide range of functionalities and are well-suited for library synthesis. Perhaps the most powerful method is the modification of available amino acids equivalents, such as radical, cationic, and anionic alanine and homoalanine or bishomoalanine equivalents, by means of transition metal mediated cross-couplings.¹⁰ Specifically, since Pd(0)-catalyzed cross-couplings are both selective and compatible with a wide range of functional groups, and since the Suzuki reaction has the drawback of requiring prior preparation of the appropriate organoborane,¹¹ we decided to employ Sonogashira-type reactions for the crucial cross-coupling step.^{12,13}

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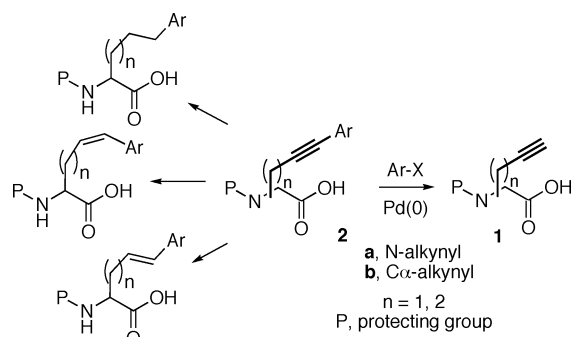


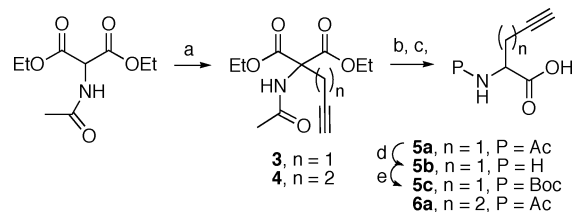
FIGURE 1. General strategy for synthesis of novel amino acids.

Results and Discussion

Recently we have described a highly efficient Sonogashira-type cross-coupling reaction of *N*-propargyl amino acids (1a) or peptide with different (hetero)aryl halides (Figure 1).¹⁴ The optimized condition used palladium on carbon (10% Pd/C) as the catalyst and DME/H₂O as solvent in the presence of PPh₃, CuI, and K₂CO₃.¹⁵ This was especially pleasing because Pd/C allows easy recovery and recycling of Pd and causes little Pd contamination of the product¹⁶ and because reactions in aqueous conditions are both environmentally and economically attractive.¹⁷ Here in this work we improve these conditions and apply them to the preparation of α -amino acids with C α -side chains terminating in aryl or heteroaryl units. The strategy would be based, as before, on equipping the amino acid with an alkyne-terminated C α -chain (1b) that would then be linked to the (hetero)aryl unit, after which the triple bond could be reduced as required (Figure 1). These C α -functionalized amino acids with potential utility for metal binding or monitoring would retain all the hydrogen-bonding properties required for formation of the usual secondary structures by polypeptides containing them (α -helices, β -sheets, etc.) and complement properties of polypeptides containing previously reported N-modified amino acids.¹⁸

Application of the previously reported cross-coupling procedure to the preparation of C α -(ω -aryl)alkynylated glycine was initially frustrated by the failure of attempts to obtain the required C α -propargylated and -homopropargylated glycines by treating *N*-Boc-glycine methyl ester with propargyl or homopropargyl bromide in the presence of 2 equiv of LDA. Contrary to

SCHEME 1. Synthesis of Propargyl- and Homopropargylglycines



(a) *t*-BuOK, dioxane, 100 °C, X-(CH₂)_nC \equiv CH (*n* = 1, X = OTs, 93%; *n* = 1, X = Br, 89%; *n* = 2, X = OTs, 70%); (b) NaOH, H₂O, Δ ; (c) H₂O, Δ (*n* = 1, 91%; *n* = 2, 71%, two steps); (d) HCl, H₂O, Δ , 91%; (e) (Boc)₂O, DIEA, dioxane/H₂O, 97%.

the method originally reported,¹⁹ no significant yields were obtained starting from diethyl *N*-acetylaminomalonate when the alkyne was tosylated and the solvent was THF. After trials with various solvents (THF, dioxane, DMF), bases (NaH, *t*BuOK, EtONa, LDA) and alkyne derivatives (tosylates, bromides, iodides, triflates), reasonable yields of intermediates 3 and 4 were finally obtained using the tosylates in dioxane with potassium tertbutoxide as base (Scheme 1). Basic hydrolysis of compounds 3 and 4, followed by decarboxylation, afforded *N*-acetyl-C α -alkynyl amino acids 5a and 6a. Then, protecting group exchange of 5a by hydrolysis and treatment with Boc anhydride provided the desired propargylglycine 5c. In view to future work, we also obtained enantiopure products by enantioselective hydrolysis of the *N*-acetyl-C α -alkynyl amino acids (ee > 99%) using a *Pseudomonas putita* aminopeptidase,²⁰ followed by Boc protection as before, but in the remainder of the present study only the racemates were used.

Compounds 5a and 6a failed to undergo cross-coupling with 3-bromopyridine under conventional Sonogashira conditions (Table 1, entries 1–5), but with Pd/C, like their *N*-propargylated analogues,¹⁴ the cross-coupling of 6a proceeded in 58% yield using PPh₃, cesium carbonate, and DME/H₂O. Remarkably, the replacement of the combination PPh₃/DME by 4-diphenylphosphinebenzoic acid (4-DPPBA) and DMF raised the coupling yield from 58% to 86% (entries 6 and 7).²¹ To explore the generality of the above conditions, we extended these studies to other aryl halides (Table 1), finding that with both electron-deficient aryl bromides (entries 7, 8, 10, 13, and

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TABLE 1. Reactions of Propargyl (5a and 5c) and Homopropargyl (6a) Glycines with Various (Hetero)aryl Halides

5a, $n = 1$, $P = \text{Ac}$;
5c, $n = 1$, $P = \text{Boc}$;
6a, $n = 2$, $P = \text{Ac}$.

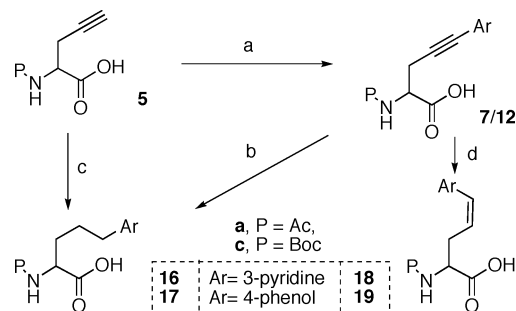
Entry	P	n	Catalyst	Ligand	Solvent	X	Ar	Product (%) ^a
1	Ac	2	$\text{PdCl}_2(\text{Ph}_3\text{P})_2$ ^b	-	Et_3N	Br		8a (nd ^c)
2	Ac	2	$\text{PdCl}_2(\text{Ph}_3\text{P})_2$ ^b	-	DMF	Br		8a (nd ^c)
3	Ac	2	$\text{PdCl}_2(\text{Ph}_3\text{P})_2$ ^b	-	THF	Br		8a (nd ^c)
4	Ac	2	$\text{Pd}(\text{Ph}_3\text{P})_4$ ^b	-	CH_3CN	Br		8a (nd ^c)
5	Ac	1	$\text{PdCl}_2(\text{Ph}_3\text{P})_2$ ^b	-	Et_3N	Br		7a (nd ^c)
6	Ac	2	10% Pd/C ^d	Ph_3P	DME/ H_2O	Br		8a (58)
7	Ac	2	10% Pd/C ^d	4-DPPBA	DMF/ H_2O	Br		8a (86)
8	Ac	1	10% Pd/C ^d	4-DPPBA	DMF/ H_2O	Br		7a (96)
9	Ac	1	10% Pd/C ^d	4-DPPBA	DMF/ H_2O	Br		9a (88)
10	Ac	1	10% Pd/C ^d	4-DPPBA	DMF/ H_2O	Br		10a (94)
11	Ac	1	10% Pd/C ^d	4-DPPBA	DMF/ H_2O	I		11a (92)
12	Ac	1	10% Pd/C ^d	4-DPPBA	DMF/ H_2O	I		12a (93)
13	Ac	2	10% Pd/C ^d	4-DPPBA	DMF/ H_2O	Br		13a (82)
14	Ac	2	10% Pd/C ^d	4-DPPBA	DMF/ H_2O	I		14a (90)
15	Ac	2	10% Pd/C ^d	4-DPPBA	DMF/ H_2O	Br		15a (87)
16	Boc	1	10% Pd/C ^d	4-DPPBA	DMF/ H_2O	Br		7c (93)
17	Boc	1	10% Pd/C ^d	4-DPPBA	DMF/ H_2O	I		12c (91)

^a Isolated yields. ^b Reactions of 3-bromopyridine (1.1 mmol) with **5a/6a** (1.0 mmol) were carried out at 80 °C in 10 mL of solvent using 5% Pd catalyst, 7.5% CuI, and Et_3N (0.6 mL). ^c nd, not detected in reaction crude by ¹H NMR. ^d Reactions of X-Ar (1.1 mmol) with **5a**, **5c**, or **6a** (1.0 mmol) carried out at 80 °C in 9 mL of solvent mixture using 10% Pd/C (0.05 mmol), CuI (0.2 mmol), Cs_2CO_3 (2.5 mmol), and ligand (0.2 mmol).

16) or electron-rich aryl halides (entries 9, 11, 12, 14, 15, and 17), despite their lesser reactivity, cross-couple to propargyl (**5a**, **5c**) and homopropargyl (**6a**) glycines in good yields under these latter conditions. Moreover, similar high yields are also obtained, regardless of whether the bromide or the iodide was used, or whether the N-protecting group on the amino acid was Ac or Boc.

Reduction of the triple bonds of ω -arylalkynylated amino acids prepared as above encountered no problems. Treatment of the C_α -(ω -arylalkynylated) compounds **7a** or **12c** with 10% Pd/C in 5% AcOH/ EtOAc under hydrogen afforded the pyridyl-amino acids **16c** in 98% yield and the bishomotyrosine analogue **17c** in 96% yield (Scheme 2, route b). Moreover, it was in both cases possible to carry out the cross-coupling and hydrogenation reactions in one-pot, albeit in lower yield: When a mixture of propargylglycine (**5a** or **5c**), 3-bromopyridine, Pd/C, CuI, 4-DPPBA, and Cs_2CO_3 in DMF/water was heated for 8 h and then stirred under hydrogen at room temperature, compound **16a** and **16c** were obtained in 57% and 63% yield, respectively

SCHEME 2. Alkyne Reduction Studies



(a) See Table 1; (b) H_2 , 10% Pd/C, 5% AcOH, MeOH (87% for **16a**, 98% for **16c**, and 96% for **17c**); (c) 3-BrPy, 10% Pd/C, CuI, 4-DPPBA, Cs_2CO_3 , DMF/ H_2O , 80 °C and then H_2 , rt (57% for **16a**, 63% for **16c**); (d) H_2 , 10% Lindlar, quinoline, MeOH (82% for **18c**, 86% for **19c**).

(Scheme 2, route c). Semi-hydrogenation was also successful: Treatment of **7c** or **12c** with Lindlar catalyst and quinoline in

methanol under balloon pressure hydrogen afforded **18c** and *cis*-dehydrobishomotyrosine derivative **19c** in yields of 82% and 86%, respectively (Scheme 2, route d).

In conclusion, we have developed a versatile method for the preparation of C α -(*o*-arylalkynyl)glycines by means of Sonogashira-type reactions in mixtures of water with an organic solvent. We envisage that this new method will be widely applicable to the assembly of modified peptides that are of pharmacological interest, can be exploited for the manufacture of metal ion sensors, or can adopt predefined conformations upon complexation with metals.

Experimental Section

Preparation of 7a. Representative Procedure for Sonogashira Cross-Coupling with Propargylglycine or Homopropargylglycine Derivatives. 3-Bromopyridine (102 μ L, 1.06 mmol), Cs₂CO₃ (788 mg, 2.42 mmol), CuI (37 mg, 0.19 mmol), 4-DPPBA (59 mg, 0.19 mmol), and 10% Pd/C (52 mg, 0.05 mmol) were mixed in 9 mL of 1:1 DMF/H₂O. The resulting suspension was degassed and stirred at room temperature for 30 min, and then amino acid **5a** (150 mg, 0.97 mmol) was added. The mixture was heated at 80 °C for 4 h, allowed to cool to room temperature, filtered through Celite, and concentrated, and this crude product was purified by flash chromatography (0–8% MeOH in EtOAc with 0.5% AcOH), giving

215 mg of **7a** as a yellow foam [96%, *R*_f = 0.61 (50% MeOH in DCM with 1% AcOH)]. ¹H NMR (CD₃OD, 250.13 MHz, δ): 8.62–8.30 (m, 2H), 7.79 (dd, *J*₁ = 1.6 Hz, *J*₂ = 7.9 Hz, 1H), 7.34 (dd, *J*₁ = 4.9 Hz, *J*₂ = 7.8 Hz, 1H), 4.46 (t, *J* = 5.7 Hz, 1H), 2.93 (dd, *J*₁ = 5.8 Hz, *J*₂ = 8.4 Hz, 2H), 1.99 (s, 3H). ¹³C NMR (CD₃-OD, 62.90 MHz, δ): 179.4 (CO), 172.8 (CO), 152.6 (CH), 148.6 (CH), 140.7 (CH), 124.9 (CH), 123.0 (C), 92.1 (C), 79.3 (C), 50.0 (CH), 24.3 (CH₂), 22.9 (CH₃). MS (CI) [*m/z* (%): 233 ([MH]⁺, 7), 215 (17), 174 (61). HRMS (CI) calculated for C₁₂H₁₃N₂O₃ ([MH]⁺), 233.092617; found, 233.092474.

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Supporting Information Available: ¹H and ¹³C NMR data and spectra for some of the products illustrated in Table 1 (**7a**–**15a**, **7c**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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