DOI: 10.1002/adsc.200800447

Efficient Synthesis of γ,δ-Alkynyl-β-amino Acid Derivatives by a New Copper-Catalyzed Amine-Alkyne-Alkyne Addition Reaction

Lei Zhou,[a,b] Huan-feng Jiang,[a,*] and Chao-Jun Li[b,*]

[a] College of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, People's Republic of China
[b] Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal, Quebec, Canada, H3A 2K6
Fax: (+1)-514-398-3797; phone: (+1)-514-398-8457; e-mail: cj.li@mcgill.ca

Received: June 29, 2008; Revised: July 21, 2008; Published online: October 7, 2008

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800447.

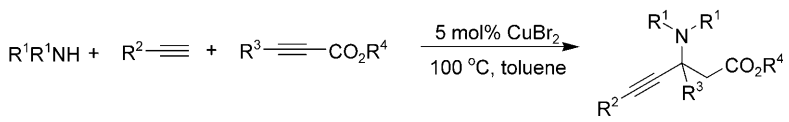
Abstract: A simple and efficient method for the synthesis of γ,δ-alkynyl-β-amino acid derivatives by a new copper-catalyzed amines-alkynes-alkynes addition was developed. Various γ,δ-alkynyl-β-amino acid derivatives were obtained in moderate to good yields in one step.

Keywords: addition reactions; alkynes; β-amino esters; copper catalysis; three-component addition

In recent years, the stereoselective synthesis of β-amino acids has gained increasing attention due to their biological importance, occurrence in various natural products,[1] and as potential precursors for β-lactams[2] and various heterocyclic compounds.[3] Free β-amino acids show interesting biological and pharmacological properties such as antiketogenic,[4] antihelminthic[5] and antitumor properties.[6] Another interesting discovery is that only six β-amino acids were required for the formation of a stable helix,[7] whereas for α-amino acids, 15–20 residues were necessary. Considering their importance, it is of great significance to develop new methods for synthesizing β-amino acids and their derivatives efficiently.

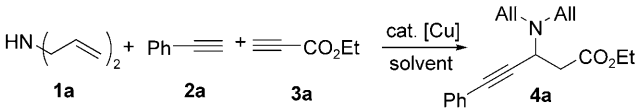
Among the various β-amino acids, γ,δ-alkynyl-β-amino acid derivatives are a special class of non-proteinogenic amino acids. It is now recognized that β-ethynyl-substituted amino acid not only can greatly change the biological properties of some natural amino acids but also is the key intermediate of certain designed drugs, such as Xemilofiban, which is a platelet aggregation inhibitor that can prevent ischemia, heart attacks and other major adverse cardiac events.[8] However, the γ,δ-alkynyl-β-amino acid derivatives are challenging structures to synthesize. Compared with numerous reports about the preparation of alkynyl-β-amino acid,[9] until now only a few reports for the synthesis of alkynyl-β-amino acid derivatives are known.[10] For example, Awasthi and coworker reported the synthesis of such β-amino esters *via* the coupling of a terminal alkyne with a Reformatsky reagent.[10a] Boys reported the synthesis of such compounds from aspartic acid through a four-step precedure.[10b] However, the multi-step synthesis with the use of expensive reagents made these methods both difficult to operate and not atom-economical.[11] Thus, the development of methods to synthesize such compounds in one step would be highly valuable and desirable. Herein, we report a simple and efficient method for the synthesis of γ,δ-alkynyl-β-amino acid derivatives by a Cu-catalyzed three-component addition of amine, alkyne and alkyne (Scheme 1).

To begin our study, we discovered that heating the mixture of diallylamine (**1a**), phenylacetylene (**2a**) and ethyl propiolate (**3a**) with 5 mol% CuBr as the catalyst at 60 °C for 24 h generated a 26% yield of **4a** (Table 1, entry 1). Increasing the reaction temperature increased the yield, giving 47% and 81% yields when carried out at 80 °C and 100 °C, respectively (Table 1, entries 2 and 3). Adding a ligand such as bipyridine



Scheme 1.

Table 1. The coupling of diallylamine, phenylacetylene and ethyl propiolate catalyzed by copper.[a]



1a **2a** **3a** **4a**

Entry	Catalyst	T [°C]	Solvent	Yield [%][b]
1	CuBr	60	toluene	26
2	CuBr	80	toluene	47
3	CuBr	100	toluene	81
4	CuBr/bipyridine	100	toluene	trace
5	CuBr/phenanthroline	100	toluene	<10
6	CuCN	100	toluene	<10
7	CuI	100	toluene	40
8	Cu(IMes)Cl	100	toluene	0
9	$CuBr_2$	100	toluene	84
10	$Cu(CF_3CO_2)_2$	100	toluene	77
11	$Cu(OTf)_2$	100	toluene	27
12	$CuBr_2$	100	DMF	23
13	$CuBr_2$	100	NMP	15
14	$CuBr_2$	100	EtOH	11
15	$CuBr_2$	100	1,4-dioxane	75
16	$CuBr_2$	100	xylene	69
17	$CuBr_2$	100	water	21
18	$CuBr_2$	100	water/TBAB	0

[a] All reactions were carried out by using 0.5 mmol of diallylamine, 0.5 mmol of ethyl propiolate, 0.75 mmol phenylacetylene and 5% mol of copper catalysts in 2 mL solvent for 24 h.

[b] Measured by ^{1}H NMR.

and phenanthroline did not favor the reaction (Table 1, entries 4 and 5). Among the various copper catalysts examined (Table 1, entries 6–11), the relatively common and inexpensive $CuBr_2$ gave the best result (entry 9). The use of solvents also affected the reaction. Toluene is the best choice for the reaction and its use resulted in high conversions to the desired product. Use of polar solvents such as DMF, *N*-methylpyrrolidinone (NMP) and ethanol gave lower yields of the product as compared with the less polar 1,4-dioxane and xylene (Table 1, entries 12–16). The reaction carried out in pure water also resulted in 21% yield while no product was obtained when TBAB was added as phase-transfer reagent (Table 1, entries 17 and 18).

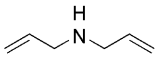
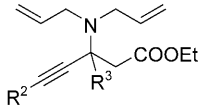
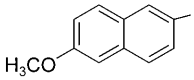
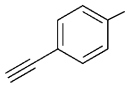
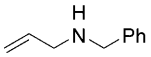
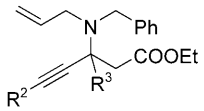
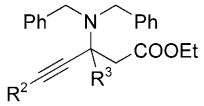
Having optimized the reaction conditions, we explored the scope of the reaction and the results are summarized in Table 2. Treatment of diallylamine and ethyl propiolate with different terminal alkynes **2a**–**h** furnished the corresponding γ,δ-alkynyl-β-amino ester **4a**–**h** in moderate to good yields (Table 2, entries 1–9). The reaction can tolerate various functional groups including bromide, acetylene and protected alcohols present in alkyne **2**. In the reaction of diallylamine, ethyl propiolate and 1,4-diethynylbenzene, only a mono-addition adduct was obtained as the sole product (Table 2, entry 9) in 60% yield. By increasing the steric hindrance of the protecting groups, the yields of the addition decreased [$(All)_2 > (All)Bn > Bn_2$]. Treatment of ethyl propiolate and phenylacetylene with allylbenzylamine (**1b**) or dibenzylamine (**1c**) gave the corresponding γ,δ-alkynyl-β-amino ester derivatives **4k** or **4m** in yields of 72% or 70%, respectively (Table 2, entries 11 and 13). It is noteworthy that the yield of this addition reaction is substantially affected by the substituted group in alkyne **3**. 2-Butynoate gave a lower yield relative to ethyl propiolate (Table 2, entries 9 and 16). When ethyl propiolate was switched to diethyl acetylenedicarboxylate as the substrate, none of desired product was detected (Table 2, entry 10).

Free β-amino esters can be obtained selectively by the removal of the diallyl or dibenzyl residues according to the known methods.[12,13] Treatment of γ,δ-alkynyl-β-amino acid derivatives **4a** with thiosalicylic acid (**5**) in the presence of a palladium(0) catalyst {[$Pd(dba)_2$] (5 mol%) and DPPB (10 mol%)} at room temperature for 1 hour leads to the monoallylate β-amino ester **6** in 85% yield (Scheme 2). Free β-amino ester **7** can be obtained in 68% yield by increasing the temperature and the loading of thiosalicylic acid. Primary amines can also be obtained by hydrogenation of the γ,δ-alkynyl-β-amino acid derivatives **4**. For example, hydrogenation of **4m** in the presence of Pd on charcoal in methanol under a hydrogen atmosphere (1 bar) afforded β-amino ester **8** in 55% yield. To demonstrate further synthetic applications, the allyl-protected amino ester **4a** was employed for cyclization to produce the α-chloromethylene-pyrrolidine derivatives. In the presence of $Pd(PhCN)_2Cl_2$, $CuCl_2$ and LiCl, cyclic product **9** was obtained as a single product in 92% yield.

A plausible mechanism for the three-component addition of amine, alkyne and alkyne catalyzed by copper is shown in Scheme 3. A copper-catalyzed hydroamination[15] of electron-deficient propiolate **3** by amine **1** generates intermediate **A**. Subsequent reaction of **A** with alkyne **2** results in intermediate **B**, which is protonated to give an iminium intermediate **C**.[16] Subsequently, an intramolecular transfer of the alkyne moiety to the iminium ion produces the γ,δ-alkynyl-β-amino ester **4** and regenerates the copper catalyst. As Cu(I) and Cu(II) generated similar results, the active catalyst is most likely Cu(I) as Cu(II) can be converted into Cu(I) readily by reacting with the enolate, terminal alkyne, or amine.

In conclusion, we have developed a simple and efficient method for γ,δ-alkynyl-β-amino acid derivatives by a new copper-catalyzed amines-alkynes-alkynes

Table 2. Copper-catalyzed addition of amine, alkyne and alkyne in toluene.[a]

Entry	1	R^2	2	R^3	4	Yield [%][b]
						
1	**1a**	Ph-	**2a**	H	**4a**	77
2	**1a**	EtO_2C-	**2b**	H	**4b**	82
3	**1a**	*p*-BrC_6H_4-	**2c**	H	**4c**	75
4	**1a**	*p*-$CH_3C_6H_4$-	**2d**	H	**4d**	66
5	**1a**	*p*-$CH_3OC_6H_4$-	**2e**	H	**4e**	57
6	**1a**		**2f**	H	**4f**	62
7	**1a**	$C_2H_5CO_2CH_2$-	**2g**	H	**4g**	71
8	**1a**		**2h**	H	**4h**	60
9	**1a**		**2a**	CH_3	**4i**	51
10	**1a**		**2a**	CO_2Et	**4j**	0
						
11	**1b**		**2a**	H	**4k**	72
12	**1b**		**2d**	H	**4l**	61
						
13	**1c**		**2a**	H	**4m**	70
14	**1c**		**2b**	H	**4n**	74
15	**1c**		**2f**	H	**4o**	48
16	**1c**		**2d**	CH_3	**4p**	46

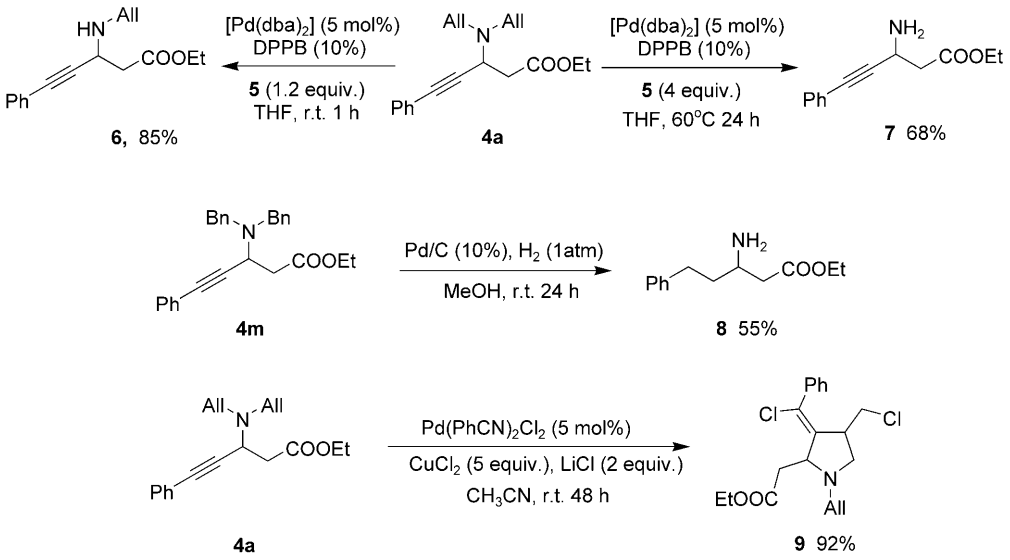
[a] All the reactions were carried out by using 0.5 mmol amine, 0.5 mmol alkyne and 0.75 mmol terminal alkyne with 5 mol% $CuBr_2$ as the catalyst in toluene at 100 °C for 24 h.
[b] Isolated yield.

addition. Various γ,δ-alkynyl-β-amino acid derivatives were obtained in moderate to good yields in one step. The asymmetric addition, mechanism and synthetic applications of this efficient addition reaction are under investigation.

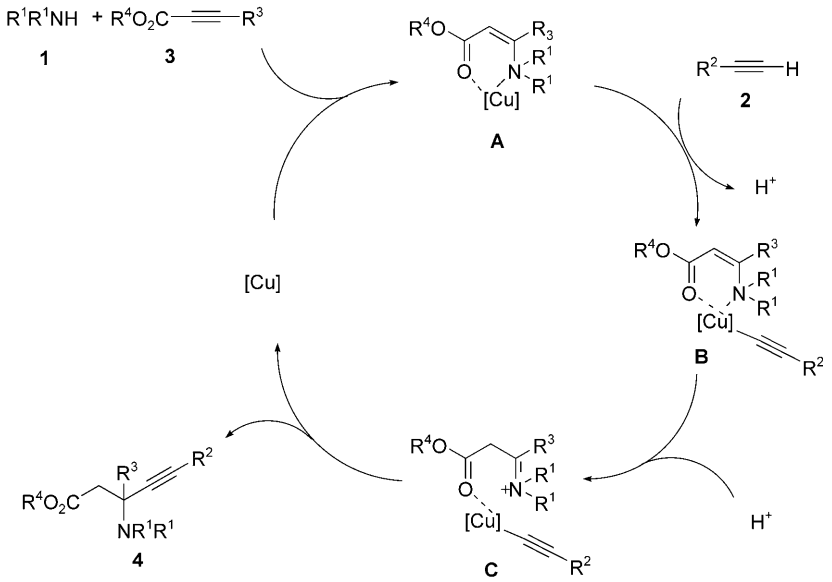
Experimental Section

Representative Experimental Procedure (4a)

$CuBr_2$ (6 mg, 0.025 mmol, 5 mol%) was suspended in toluene (2 mL) in a 10-mL Schlenk tube under nitrogen. Then diallylamine (49 mg, 0.5 mmol), ethyl propiolate (49 mg, 0.5 mmol), and phenylacetylene (76.5 mg, 0.75 mmol) were added. The resulting solution was stirred at 100 °C for 24 h. After cooling to room temperature, the resulting mixture was filtered through a short path of silica gel in a pipette eluting with ethyl acetate. The volatiles were removed under vacuum and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate 10:1) to give **4a** as a pale yellow oil; yield: 114 mg (77%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.44–7.40 (m, 2H), 7.31–7.29 (m, 3H), 5.86–5.77 (m, 2H), 5.23 (d, J = 17.2 Hz, 2H), 5.14 (d, J = 10.0 Hz, 2H), 4.31 (t, J = 8.4 Hz, 1H), 4.17 (q, J = 7.6 Hz, 2H), 3.33(dt, J=14.0, 2.4 Hz, 2H), 2.98 (dd, J = 14.0, 8.0 Hz, 2H); 2.74–2.68 (m, 2H), 1.26 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.8, 136.5, 132.0, 128.5, 128.3, 123.2, 117.5, 86.2, 85.8, 60.7, 54.2, 50.0, 39.9, 14.4; MS (70 eV): m/z = 296 (M^+), 256, 210 (100); HR-MS (EI): m/z = 296.16432, calcd. for $C_{19}H_{23}NO_2$ [M^+]: 296.16505.



Scheme 2. Selective transformations of γ,δ-alkynyl-β-amino acid derivatives.



Scheme 3. Tentative mechanism for the copper-catalyzed amine-alkyne-alkyne addition.

The experiments in Table 2 were carried out analogously. All products were purified by column chromatography and characterized by NMR spectroscopy and standard/high-resolution mass spectrometry.

Generation of Free γ,δ-Alkynyl-β-amino Esters

A mixture of $Pd(dba)_2$ (5 mol%) and DPPB (10 mol%) in THF (0.5 mL) was stirred at room temperature, under a nitrogen atmosphere, for 15 min. The preformed catalyst and 2-mercaptobenzoic acid (1.2 or 4 equiv.) were added to a solution of **4a** in THF and the reaction mixture was stirred under argon atmosphere at 20 or 60 °C. After completion (the reaction was monitored by TLC and GC-MS), the mixture was treated by a solution of 10% HCl and extracted by AcOEt to eliminate the by-product and the catalyst in the organic layer. The aqueous layer containing the protonated amine was basified with 1 M NaOH and extracted by AcOEt. The organic layer was dried over $MgSO_4$ and concentrated under vacuum, affording clean crude products. Further purification was performed by flash chromatography with hexane:AcOEt (3:1) as the elute.

Acknowledgements

We are grateful to the Canada Research Chair (Tier I) foundation (to CJL), the CFI, NSERC and McGill University for

support of our research. LZ thanks the China Scholarship Council for a Visiting Scholarship.

References

[1] For a discussion of the synthesis and biology of β-amino acids, see: a) *Enantioselective Synthesis of* β-*Amino Acids*, (Ed.: E. Juaristi), Wiley-VCH, New York, **1997**; b) N. Kise, N. Ueda, *J. Org. Chem.* **1999**, *64*, 7511; c) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oarbide, *Curr. Med. Chem.* **2004**, *11*, 1837; d) T. Murayama, T. Kobayashi, T. Miura, *Tetrahedron Lett.* **1995**, *36*, 3703; e) M. Liu, M.-P. Sibi, *Tetrahedron* **2002**, *58*, 7991.

[2] a) F. Fülöp, T. A. Martinek, G. K. Tóth, *Chem. Soc. Rev.* **2006**, *35*, 323; b) E. Forró, F. Fülöp, *Tetrahedron: Asymmetry* **2008**, *19*, 1005.

[3] a) G. Guanti, A. Moro, E. Narisano, *Tetrahedron Lett.* **2000**, *41*, 3203; b) S. Gyónfalvi, Z. Szakonyi, F. Fülöp, *Tetrahedron: Asymmetry* **2003**, *14*, 3965; c) P. Kapferer, A. Vasella, *Helv. Chim. Acta* **2004**, *87*, 2764.

[4] S. Shinagawa, T. Kanamaru, S. Harada, M. Asai, H. Okazaki, *J. Med. Chem.* **1987**, *30*, 1458.

[5] a) P. Crews, L. V. Manes, M. Boehler, *Tetrahedron Lett.* **1986**, *27*, 2797; b) R. J. Stonard, R. J. Andersen, *J. Org. Chem.* **1980**, *45*, 3687; c) S. Matsunaga, N. Fusetani, S. Konosu, *Tetrahedron Lett.* **1985**, *26*, 855.

[6] J. L. Hubbs, H. Zhou, A. M. Kral, J. C. Fleming, W. K. Dahlberg, B. L. Hughes, R. E. Middleton, A. Szewczak, J. P. Secrist, T. A. Miller, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 34.

[7] a) D. H. Apella, L. A. Christianson, I. L. Karle, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1996**, *118*, 13071; b) T. A. Martinek, F. Fülöp, *Eur. J. Biochem.* **2003**, *270*, 3657; c) D. Seebach, M. Overhand, F. N. M. Kühnle, B. Martinoni, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1996**, *79*, 913.

[8] a) M. L. Boys, K. J. Cain-Janicki, W. W. Doubleday, P. N. Farid, M. Kar, S. T. Nugent, J. R. Behling, D. R. Pilipauskas, *Org. Process Res. Dev.* **1997**, *1*, 233; b) R. Anders, J. Kleiman, N. Nicholson, B. Wazowicz, D. Burns, *Cardiovascular Drug Reviews* **2001**, *19*, 116; c) J. A. Zablocki, J. G. Rico, R. B. Garland, T. E. Rogers, K. Williams, L. A. Schretzman, S. A. Rao, P. R. Bovy, F. S. Tjoeng, R. J. Lindmark, M. Toth, M. Zupec, D. E. McMackins, S. P. Adams, M. Miyano, C. S. Markos, M. N. Milton, S. Paulson, M. Herin, P. Jacquin, N. Nicholson, S. G. Panzer-Knodle, N. F. Haas, J. D. Page, J. A. Szalony, B. B. Taite, A. K. Salyers, L. W. King, J. G Campion, L. P. Feigen, *J. Med. Chem.* **1995**, *38*, 2378.

[9] a) Y. Yamamoto, H. Hayashi, *Tetrahedron* **2007**, *63*, 10149; b) M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem. Int. Ed.* **2007**, *46*, 6903; c) R. M. Williams, D. J. Aldous, S. C. Aldous, *J. Org. Chem.* **1990**, *55*, 4657; d) J.-X. Ji, J. Wu, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11196.

[10] a) A.-K. Awasthi, M.-L. Boys, K.-J. Cain-Janicki, P.-J Colson, W. Doubleday, J. Duran, P. Farid, *J. Org. Chem.* **2005**, *70*, 5387; b) M. L. Boys, *Tetrahedron Lett.* **1998**, *39*, 3449; c) J. Cossy, A. Schmitt, C. Cinquin, D. Buisson, D. Belotti, *Biorg. Med. Chem. Lett.* **1997**, *7*, 1699; d) R. Topgi, J. S. Ng, B. Landis, P. T. Wang, J. R. Behling, *J. Biorg. Med. Chem.* **1999**, *7*, 2221; e) B. Landis, P. B. Mullins, K. E. Mullins, P. T. Wang, *Org. Proc. Res. Dev.* **2002**, *6*, 539.

[11] a) B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259; b) B. M. Trost, *Science* **1991**, *254*, 1471.

[12] S. Lemaire-Audoire, M. Savignac, J. P. Genêt, *Tetrahedron Lett.* **1995**, *36*, 1267.

[13] N. Gommermann, P. Knochel, *Tetrahedron Lett.* **2005**, *61*, 11418.

[14] S. Ma, X, Lu, *J. Org. Chem.* **1993**, *58*, 1245.

[15] For recent reviews on hydroaminations, see: a) F. Pohlki, S. Doye, *Chem. Soc. Rev.* **2003**, *32*, 104; b) R. Severin, S. Doye, *Chem. Soc. Rev.* **2003**, *32*, 1407; c) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079.

[16] a) C. Koradin, N. Gommermann, K. Polborn, P. Knochel, *Chem. Eur. J.* **2003**, *9*, 2797; b) C. Koradin, K. Polborn, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*,2535; c) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584; d) C. Wei, Z. Li, C.-J. Li, *Org. Lett.* **2003**, *5*, 4473; e) L. Zani, T. Eichhorn, C. Bolm, *Chem. Eur. J.* **2007**, *13*, 2587; P. Aschwanden, C. R. J. Stephenson, E. M. Carreira, *Org. Lett.* **2006**, *8*, 2437.

