Copper(I)-Catalyzed Three-Component Coupling Leading to an Efficient Synthesis of β,γ-Alkynyl α-Amino Acid Derivatives

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Abstract: The first copper(I)-catalyzed direct three-component coupling of ethyl glyoxylate, *p*-anisidine, and terminal alkynes has been developed. This protocol provides an efficient method to prepare β,γ-alkynyl α-amino acid derivatives in good yields.

Key words: copper, catalysis, multicomponent reactions, β,γ-alkynyl α-amino acids

Transition-metal-catalyzed multicomponent reaction (MCR) is a powerful synthetic tool for accessing complex structures from simple precursors in a one-pot procedure.[1] The discovery and development of MCRs is an important research field for the advancement of combinatorial chemistry.[2]

β,γ-Alkynyl α-amino acids are an important class of non-proteinogenic α-amino acids. It is recognized that α-ethynyl substituents can profoundly change the biological properties of certain natural amino acids, converting them from enzyme substrates into irreversible inhibitors with potential therapeutic utility.[3] However, methods that provide reliable and convenient access to β,γ-alkynyl α-amino acid derivatives are still limited due to the chemical lability of these substances. The early methods in targeting these compounds involved a two-component coupling of haloglycinates with either alkynyltin reagents[4] under reflux conditions or alkynylmagesium reagents at –78 °C.[5]

Metal-catalyzed addition of terminal alkynes to imines, which are either preformed or generated from aldehydes and amines, represents one of the most convenient methods for obtaining propargylamines.[6] Recently, we extended this reaction to α-imino esters and developed a facile synthesis of β,γ-alkynyl α-amino acid derivatives through silver(I)-catalyzed addition of terminal alkynes to α-imino esters.[7] Based on this method, we realized the first catalytic asymmetric synthesis of β,γ-alkynyl α-amino acid derivatives with 48–91% ee by employing chiral copper(I) complexes.[8] However, these strategies relied on the use of α-imino esters, which needs to be prepared and isolated beforehand. In addition, these substrates are highly moisture-sensitive and inconvenient to handle. For practical purposes, it is highly desirable to develop a more efficient and direct method for the preparation of β,γ-alkynyl α-amino acid derivatives. More recently, Zhao's group reported a silver(I)-catalyzed three-component reaction for the synthesis of α-aminopropargylphosphonates.[6i] Herein, we describe the first copper(I)-catalyzed direct three-component coupling of ethyl glyoxylate, *p*-anisidine, and terminal alkynes. This reaction provides an efficient synthetic approach to *N*-PMP-protected β,γ-alkynyl α-amino acid derivatives.

An investigation on the feasibility of catalytic three-component synthesis of β,γ-alkynyl α-amino acid derivatives was initially conducted by using ethyl glyoxylate (**1**), *p*-anisidine (**2**), and 4-phenylbut-1-yne (**3a**) as the model substrates. Following our findings in the two-component version,[7] we employed silver(I) triflate as a catalyst for the three-component coupling reaction, and found that the desired reaction took place to give the product **4a** in 61% yield after 36 hours using 4 Å molecular sieves as the drying agent.

Encouraged by this result, we screened several transition-metal catalysts for their utility in the transformation (Table 1). As shown in Table 1, silver(I) nitrate and silver(I) acetate proved to be poor catalysts for this reaction (entry 2). Zinc(II) triflate, zinc(II) chloride, scandium(III) triflate, copper(I) bromide, and copper(I) chloride did not catalyze the desired reaction (entries 3–5). In contrast, copper(II) triflate did promote the desired reaction, albeit in low efficiency (entry 6). When benzene complex of copper(I) triflate was employed in the reaction, the product **4a** was obtained in 70% yield (entry 7). Further improvement in yield (75%) was realized using magnesium sulfate as the drying agent (entry 8). The three-component reaction can also occur with a similar chemical yield (77%) in the absence of any additive (entry 9).

To probe the general utility of this newly developed three-component coupling reaction, a variety of different terminal alkynes were examined and the results are summarized in Table 2. To our delight, three-component reaction of alkylacetylenes **1a–e** (entries 1–5) and phenylacetylene (**1g**) (entry 7) afforded the corresponding β,γ-alkynyl α-amino acid derivatives in good yields. Noticeably, the 1-ethynylcyclohexene gave the desired highly functionalized product **4f** in 80% (entry 6).

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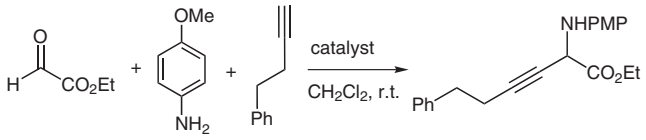
Table 1 Catalysts Screened in the Three-Component Reaction[a]

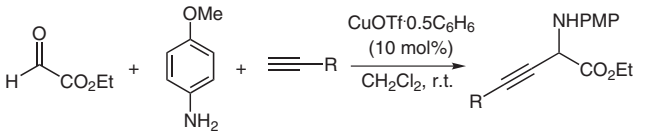


1 2 3a 4a

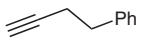
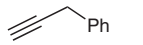
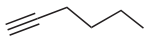
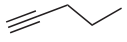
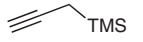
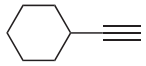
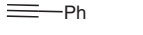
Entry	Metal catalyst	Yield (%)[b]
1	AgOTf	61[c]
2	$AgNO_3$, AgOAc	<5[c]
3	$Zn(OTf)_2$, $ZnCl_2$	0[c]
4	$Sc(OTf)_3$	0[c]
5	CuBr, CuCl	0[c]
6	$Cu(OTf)_2$	44[c]
7	CuOTf·0.5C_6H_6	70[c]
8	CuOTf·0.5C_6H_6	75[d]
9	CuOTf·0.5C_6H_6	77[e]

[a] All reactions were performed with ethyl glyoxylate (0.26 mmol), *p*-anisidine (0.25 mmol), 4-phenylbut-1-yne (0.5 mmol), and catalyst (10 mol%) in anhyd CH_2Cl_2 (1.5 mL) at r.t.
[b] Isolated yield.
[c] 4 Å MS used as additive.
[d] $MgSO_4$ used as additive.
[e] Without any additive.

Table 2 Copper(I)-Catalyzed Three-Component Reaction[a]

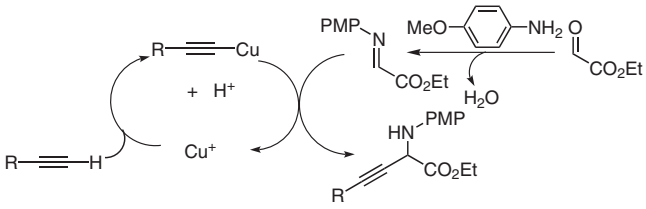


1 2 3 4

Entry	Alkyne	Product	Yield (%)[b]
1		**4a**	77
2		**4b**	74
3		**4c**	71
4		**4d**	73
5		**4e**	61
6		**4f**	80
7		**4g**	81

[a] All reactions were performed with ethyl glyoxylate (0.26 mmol), *p*-anisidine (0.25 mmol), terminal alkyne (0.5 mmol), and CuOTf·0.5C_6H_6 (10 mol%) in anhyd CH_2Cl_2 (1.5 mL) at r.t.
[b] Isolated yield.

On the basis of the above experimental results, together with several related literature reports,[6b–j] a speculative tentative mechanism was proposed involving the activation of the C–H bond of terminal alkyne by copper(I) catalyst (Scheme 1). The copper acetylide intermediate reacted with the α-imino ester generated in situ from the ethyl glyoxylate and *p*-anisidine to give the corresponding β,γ-alkynyl α-amino acid derivative and regenerated the copper(I) catalyst.



Scheme 1 Speculative mechanism for copper(I)-catalyzed three-component coupling

In summary, we have developed a new one-pot, three-component coupling reaction for the synthesis of β,γ-alkynyl α-amino acid derivatives from ethyl glyoxylate, *p*-anisidine, and terminal alkynes in good yields. The asymmetric version of this reaction is presently under active investigation.[9]

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance DPX 400 (400 and 100 MHz, respectively) NMR spectrometer at r.t. Chemical shifts (δ) are expressed in ppm, and *J* values are given in Hz. High-resolution mass spectra (HRMS) were recorded by using the electrospray ionization (ESI) method on a Fisons VG platform or a MAT-95 spectrometer (Finnigan-MAT, San Jose, CA). All reactions were conducted under N_2. All chemicals were used as received without further purification unless otherwise stated. CH_2Cl_2 was distilled from CaH_2. Flash column chromatography was performed on silica gel (230–400 mesh).

β,γ-Alkynyl α-Amino Acid Derivatives 4a–g; Typical Procedure

CuOTf·0.5C_6H_6 (6.3 mg, 0.025 mmol) was added to a dried 5 mL reaction flask. CH_2Cl_2 (1.0 mL) was added under N_2, followed by a solution of ethyl glyoxylate (27 mg, 0.26 mmol), *p*-anisidine (31 mg, 0.25 mmol), and the terminal alkyne (0.5 mmol) in CH_2Cl_2 (0.5 mL). The resulting mixture was stirred at r.t. until TLC monitoring showed the completion of the reaction. The crude mixture was purified by flash chromatography over silica gel using *n*-hexane–EtOAc as eluent to give the products as oils.

2-(4-Methoxyphenylamino)-6-phenylhex-3-ynoic Acid Ethyl Ester (4a)[7]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 5 H), 6.86–6.83 (m, 2 H), 6.72–6.69 (m, 2 H), 4.74 (br s, 1 H), 4.31 (q, 2 H, *J* = 7.0 Hz), 4.22 (br s, 1 H), 3.81 (s, 3 H), 2.85 (t, 2 H, *J* = 7.4 Hz), 2.56–2.51 (m, 2 H), 1.35 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 153.2, 140.4, 139.6, 128.4, 128.3, 126.2, 115.9, 114.7, 84.4, 75.9, 62.1, 55.6, 50.1, 34.7, 20.9, 14.0.

2-(4-Methoxyphenylamino)-5-phenylpent-3-ynoic Acid Ethyl Ester (4b)[8a]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.22 (m, 5 H), 6.82–6.80 (m, 2 H), 6.73–6.71 (m, 2 H), 4.81 (m, 1 H), 4.29 (q, 2 H, *J* = 7.4 Hz), 3.76 (s, 3 H), 3.62 (d, 1 H, *J* = 1.9 Hz), 1.32 (t, 3 H, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 153.3, 139.5, 136.1, 128.4, 127.8, 126.6, 116.1, 114.5, 82.6, 77.6, 62.2, 55.6, 50.2, 25.0, 14.1.

2-(4-Methoxyphenylamino)oct-3-ynoic Acid Ethyl Ester (4c)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81–6.74 (m, 2 H), 6.72–6.62 (m, 2 H), 4.71–4.69 (m, 1 H), 4.26 (q, 2 H, *J* = 7.0 Hz), 4.18–3.16 (m, 1 H), 3.70 (s, 3 H), 2.20–2.16 (m, 2 H), 1.47–1.26 (m, 7 H), 0.87 (t, 3 H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 153.2, 139.7, 115.9, 114.7, 85.3, 75.1, 62.1, 55.6, 50.2, 30.4, 21.8, 18.3, 14.0, 13.5.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{24}NO_3$ $[M + 1]^+$: 290.1756; found: 290.1768.

2-(4-Methoxyphenylamino)hept-3-ynoic Acid Ethyl Ester (4d)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85–6.82 (m, 2 H), 6.74–6.71 (m, 2 H), 4.76 (br s, 1 H), 4.33 (q, 2 H, *J* = 7.2 Hz), 4.24 (br s, 1 H), 3.80 (s, 3 H), 2.23–2.19 (m, 2 H), 1.55 (q, 2 H, *J* = 7.2 Hz), 1.35 (t, 3 H, *J* = 7.2 Hz), 0.98 (t, 3 H, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 153.2, 139.7, 115.9, 114.7, 85.2, 75.2, 62.1, 55.6, 50.1, 21.8, 20.6, 14.0, 13.3.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{22}NO_3$ $[M + 1]^+$: 276.1600; found: 276.1597.

2-(4-Methoxyphenylamino)-5-trimethylsilylpent-3-ynoic Acid Ethyl Ester (4e)[7]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71–6.68 (m, 2 H), 6.60–6.58 (m, 2 H), 4.63 (br s, 1 H), 4.18 (q, 2 H, *J* = 7.0 Hz), 4.09 (br s, 1 H), 3.66 (s, 3 H), 1.37 (d, 2 H, *J* = 2.7 Hz), 1.22 (t, 3 H, *J* = 7.2 Hz), 0.03 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 153.1, 139.7, 115.9, 114.7, 83.2, 73.9, 62.0, 55.7, 50.2, 14.1, 7.1, –2.2.

4-Cyclohex-1-enyl-2-(4-methoxyphenylamino)but-3-ynoic Acid Ethyl Ester (4f)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (d, *J* = 5.6 Hz, 2 H), 6.33 (d, *J* = 5.6 Hz, 2 H), 6.05 (br s, 1 H), 4.78 (br s, 1 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 4.17 (br s, 1 H), 3.72 (s, 3 H), 2.03–1.99 (m, 4 H), 1.56–1.49 (m, 4 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 153.2, 139.6, 136.1, 119.8, 115.9, 114.7, 86.2, 81.3, 62.1, 55.6, 50.5, 28.9, 25.6, 22.1, 21.3, 14.0.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{24}NO_3$ $[M + 1]^+$: 314.1753; found: 314.1756.

2-(4-Methoxyphenylamino)-4-phenylbut-3-ynoic Acid Ethyl Ester (4g)[7]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 2 H), 7.20–7.16 (m, 3 H), 6.80–6.78 (m, 2 H), 6.67–6.65 (m, 2 H), 4.69 (t, 1 H, *J* = 2.3 Hz), 4.27–4.24 (q, 2 H, *J* = 7.5 Hz), 3.76 (s, 3 H), 2.80–2.77 (t, 2 H, *J* = 7.3 Hz), 2.49–2.46 (dt, 2 H, *J* = 7.3, 2.0 Hz), 1.31–1.28 (t, 3 H, *J* = 7.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 153.4, 139.5, 132.0, 128.8, 128.3, 122.2, 116.1, 114.9, 84.4, 84.2, 62.5, 55.7, 50.7, 14.2.

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