# Efficient Synthesis of β,γ-Alkynyl α-Amino Acid Derivatives by Ag(I)-Catalyzed Alkynylation of α-Imino Esters

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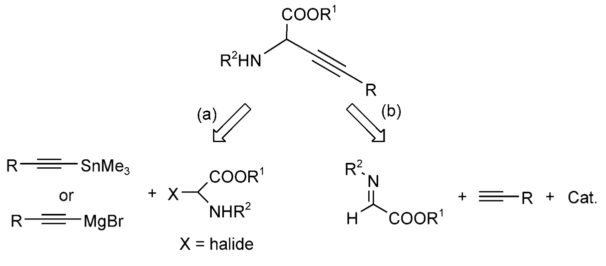
**Abstract:** The first catalytic synthesis of β,γ-alkynyl α-amino acid derivatives was achieved by direct addition of terminal alkynes to α-imino esters in the presence of an Ag(I) salt under mild reaction conditions.

**Keywords:** alkynes; α-amino acids; α-imino ester; catalytic synthesis; silver(I) salt

β,γ-Alkynyl α-amino acid derivatives are a special class of non-proteinogenic amino acids. It is now recognized that α-ethynyl substituents can remarkably change the biological properties of certain natural amino acids, converting them from enzyme substrates to irreversible inhibitors, thereby profoundly altering a number of metabolisms, especially those of microorganisms with potential therapeutic utility.[1] For example, ethynylglycine (FR-900130), a secondary metabolite, displays antimicrobial activity against Gram-positive bacteria and acts synergistically with D-cycloserine, which could be explained by its inhibitory activity on alanine racemase.[2]

However, from a synthetic standpoint, the β,γ-alkynyl α-amino acid derivatives are challenging structures to prepare. Up to now, only a few methods have been found to be successfully used: coupling of α-haloglycinates with either (i) an excess of (environmentally unfriendly) alkynyltin reagents[3] under reflux conditions or (ii) alkynylmagnesium reagents[4] at −78 °C (Scheme 1, path a). These methods are neither straightforward, nor are they catalytic. The alkynilides used were generated from alkynes with an equivalent amount of strong base such as BuLi, EtMgBr as a separate step or by transmetallation. Both for scientific interest and for practical applications, it is highly desirable to develop efficient and convenient methods for the preparation of β,γ-alkynyl α-amino acid derivatives.



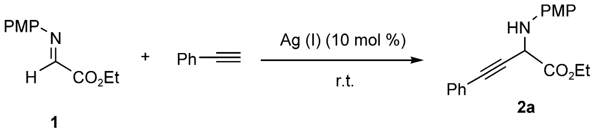
**Scheme 1.** Approaches to β,γ-alkynyl α-amino acid derivatives based on carbon-carbon bond-forming reactions.

An alternative synthon for α-amino acids is an α-imino ester, which has attracted increasing attention. Various nucleophilic reagents such as enol silane, TMS-nitronates, α-protio glyoxyl ketones have been employed in the catalytic addition reaction to α-imino esters.[5] In connection with our recent studies on the alkynylation of carbonyl compounds,[6] we envisioned that the addition of terminal alkynes to α-imino esters using an appropriate metal catalyst should readily provide alkynyl amino acids (Scheme 1, path b).[7] It has been known for a long time that the complexation of alkynes to Ag(I) yields π-complexes, and a large number of Ag-alkyne complexes have been synthesized and characterized.[8] Further, in the presence of weakly basic amines, the corresponding Ag alkynilide can be generated *in situ*.[9] Despite this knowledge, the application of an Ag alkynilide in organic synthesis is very limited. In this paper, we report a successful direct alkynylation of α-imino ester **1** mediated by Ag(I) salts to furnish a variety of β,γ-alkynyl α-amino acid derivatives.

In an initial experiment, *N*-PMP α-iminoethyl glyoxylate **1** was added to a mixture of phenylacetylene (2.0 equiv.) and $AgNO_3$ (10 mol %) in toluene at room temperature to give a solid-liquid two-phase mixture – the silver salt did not appear to be soluble, or at best only sparingly soluble. Much to our delight, despite the absence of a phase-transfer catalyst, TLC analysis showed that the imine was completely consumed after 40 min, and the corresponding product **2** was obtained in 89% yield. To the best of our knowledge, this is the first example of catalytic synthesis of β,γ-alkynyl α-amino acid derivatives.

The screening of a range of solvents under the above conditions showed that solvents have a strong effect on this reaction. The reactions performed in toluene,

**Table 1.** Ag(I)-catalyzed phenylacetylene addition to α-imino ester **1**.[a]

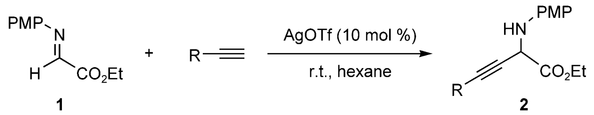


| Entry | Catalyst | Solvent | Time [h] | Yield [%][b] |
|---|---|---|---|---|
| 1 | $AgNO_3$ | Toluene | 1 | 89 |
| 2 | $AgNO_3$ | Hexane | 1 | 92 |
| 3 | $AgNO_3$ | $CH_2Cl_2$ | 1 | 87 |
| 4 | $AgNO_3$ | THF | 3 | 11 |
| 5 | $AgNO_3$ | EtOAc | 3 | 34 |
| 6 | AgOAc | Hexane | 5 | 9 |
| 7 | AgOTf | Hexane | 0.5 | 93 |
| 8 | $AgPF_6$ | Hexane | 0.5 | 90 |
| 9 | $AgClO_4$ | Hexane | 0.5 | 88 |

[a] Reaction conditions: **1** (0.5 mmol) and phenylacetylene (1.0 mmol) in solvent (5 mL).

[b] Isolated yields.

**Table 2.** AgOTf-catalyzed addition of terminal alkynes to α-amino ester **1**.[a]



| Entry | R | Time [h] | Yield [%][b] |
|---|---|---|---|
| 1 | Ph | 0.5 | 93 |
| 2 | $PhCH_2CH_2$ | 0.5 | 87 |
| 3 | *n*-butyl | 0.5 | 84 |
| 4 | *n*-hexyl | 0.5 | 91 |
| 5 | $TMSCH_2$ | 1 | 79 |

[a] Reaction conditions: **1** (0.5 mmol), alkyne (1.0 mmol), AgOTf (10 mol %), hexane (5 mL).

[b] Isolated yields.

hexane and $CH_2Cl_2$ were much faster (Table 1, entries 1–3) than those in THF or EtOAc (Table 1, entries 4 and 5), affording good to high yields within 1 h. In the subsequent study, we investigated the catalytic activity of different Ag(I) salts. As shown in Table 1, AgOAc (entry 6) promoted the reaction slowly and most of the starting material did not react even after 5 h. Other Ag(I) salts (entries 7–9) in this test were demonstrated to possess higher activity than $AgNO_3$, and the reaction catalyzed by AgOTf in hexane gave the highest yield (entry 7).

In order to establish the general utility of this methodology, the AgOTf-catalyzed alkynylations of α-imino ester **1** with an array of terminal alkynes in hexane at r.t. were performed and the results are summarized in Table 2. The addition reactions with 4-phenyl-1-butyne (entry 2), 1-hexyne (entry 3), 1-octyne (entry 4) and propargyltrimethylsilane (entry 5) were similar to that with phenylacetylene (entry 1), all proceeded with a fast reaction rate and gave the corresponding α-amino acid derivatives in good to high yields.

In conclusion, we have not only developed a highly efficient method for the synthesis of β,γ-alkynyl α-amino acid derivatives but also extended the applications of Ag alkinilides in organic synthesis by showing the feasibility of direct addition of terminal alkynes to α-imino ester **1** in the presence of a catalytic amount of Ag(I) salts under mild reaction conditions. The β,γ-alkynyl α-amino acid derivatives thus produced should be useful as building blocks for the burgeoning field of peptide-based drugs. An asymmetric version of this reaction is being developed in our laboratory.

## Experimental Section

### General Remarks

All chemicals and solvents were used as received unless otherwise stated. NMR spectra were recorded in $CDCl_3$ on a Varian AS 500 (500 MHz $^1H$, 125 MHz $^{13}C$) at room temperature, and the chemical shifts (δ) were expressed in ppm and $J$ values are given in Hz. Mass analyses and HRMS were carried out with V.G. MICROMASS, Fisons VG platform or Finnigan Model Mat 95 ST instrument by the ESI method. Column chromatography was performed on silica gel (230–400 mesh).

### Typical Procedure for Alkynylation of α-Imino Ester

To a stirred mixture of phenylacetylene (110 μL, 1.0 mmol) and AgOTf (12 mg, 0.05 mmol) in hexane (5 mL), was the added *N*-PMP-protected α-iminoethyl glyoxylate 1 (104 mg, 0.5 mmol). The reaction mixture was stirred for 0.5 h at room temperature and then was diluted with EtOAc (10 mL) to give a brown solution. The solution was concentrated under vacuum and the purification of the residue by flash chromatography (9:1 hexane-ethyl acetate as eluents) yielded the desired addition products as light yellow oils.

**Ethyl 2-(*p*-Methoxyphenylamino)-4-phenyl-3-butynoate:** $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 7.42-7.40$ (m, 2H), 7.30–7.26 (m, 3H), 6.82–6.80 (m, 2H), 6.76–6.74 (m, 2H), 4.96 (s, 1H), 4.34–4.30 (q, 2H, $J = 7.2$ Hz), 3.76 (s, 3H), 1.35–1.32 (t, 3H, $J = 7.3$ Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 169.1$, 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; MS (ESI): $m/z = 310$ ($M^+ + 1$), 264, 236, 123; HRMS (ESI): calcd. for $C_{19}H_{20}NO_3$ ($M^+ + 1$): 310.1443; found ($M^+ + 1$): 310.1465.

**Ethyl 2-(*p*-Methoxyphenylamino)-6-phenyl-3-hexynoate:** $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 7.28-7.25$ (m, 2H), 7.20–7.16 (m, 3H), 6.80–6.78 (m, 2H), 6.67–6.65 (m, 2H), 4.69 (t, 1H, $J = 2.3$ Hz), 4.27–4.24 (q, 2H, $J = 7.5$ Hz), 3.76 (s, 3H), 2.80–2.77 (t, 2H, $J = 7.3$ Hz), 2.49–2.46 (dt, 2H, $J = 7.3$, 2.0 Hz), 1.31–1.28 (t, 3H, $J = 7.5$ Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta = 169.5$, 153.7, 140.6, 137.6, 128.7, 128.6, 126.6, 116.5, 114.9, 84.8, 75.4, 62.5, 55.9, 50.5, 34.9, 21.1, 14.3; MS (ESI): *m*/

$z = 338$ ($M^+ + 1$), 292, 264, 123; HRMS (ESI): calcd. for $C_{21}H_{24}NO_3$ ($M^+ + 1$): 338.1756; found ($M^+ + 1$): 338.1782.

**Ethyl 2-(*p*-Methoxyphenylamino)-3-octynoate:** $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 6.73-6.70$ (m, 2H), 6.63–6.60 (m, 2H), 4.63 (t, 1H, $J = 2.3$ Hz), 4.22–4.17 (q, 2H, $J = 7.0$), 3.68 (s, 3H), 2.13–2.10 (dt, 2H, $J = 7.0$, 2.3 Hz), 1.40–1.18 (m, 7H), 0.83–0.78 (t, 3H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta = 168.4$, 152.4, 138.2, 115.3, 113.7, 84.6, 73.8, 61.2, 54.6, 49.3, 29.3, 20.8, 17.4, 13.0, 12.5; MS (ESI): $m/z = 290$ ($M^+ + 1$), 244, 216, 123; HRMS (ESI): calcd. for $C_{17}H_{24}NO_3$ ($M^+ + 1$): 290.1756; found ($M^+ + 1$): 290.1779.

**Ethyl 2-(*p*-Methoxyphenylamino)-3-decynoate:** $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 6.79-6.77$ (m, 2H), 6.70–6.68 (m, 2H), 4.70 (t, 1H, $J = 2.3$ Hz 1H), 4.29–4.24 (q, 2H, 7.3 Hz), 3.75 (s, 3H), 2.19–2.15 (dt, 2H, $J = 7.0$, 2.3 Hz), 1.47–1.44 (m, 2H), 1.34–1.20 (m, 9H), 0.89–0.86 (t, 3H, $J = 7.0$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta = 169.6$, 153.7, 139.3, 116.6, 114.9, 86.0, 75.0, 62.4, 55.8, 50.6, 31.5, 28.6, 28.5, 22.8, 18.9, 14.3, 14.2; MS (ESI): $m/z = 318$ ($M^+ + 1$), 272, 244, 164, 123; HRMS (ESI): calcd. for $C_{19}H_{28}NO_3$ ($M^+ + 1$): 318.2069; found ($M^+ + 1$): 318.2091.

**Ethyl 2-(*p*-Methoxyphenylamino)-5-trimethysilyl-3-pentynoate:** $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 6.79-6.72$ (m, 2H), 6.68–6.66 (m, 2H), 4.71 (t, 1H, 2.5 Hz), 4.28–4.24 (q, 2H, $J = 7.2$ Hz), 3.74 (s, 3H), 1.46–1.45 (d, 2H, $J = 3.0$ Hz), 1.32–1.29 (t, 3H, $J = 7.3$ Hz), 0.04 (s, 9H); MS (ESI): $m/z = 320$ ($M^+ + 1$), 274, 202, 174, 169, 123; HRMS (ESI): calcd. for $C_{17}H_{26}NO_3Si$ ($M^+ + 1$): 320.1682; found ($M^+ + 1$): 320.1711.

## Acknowledgements

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