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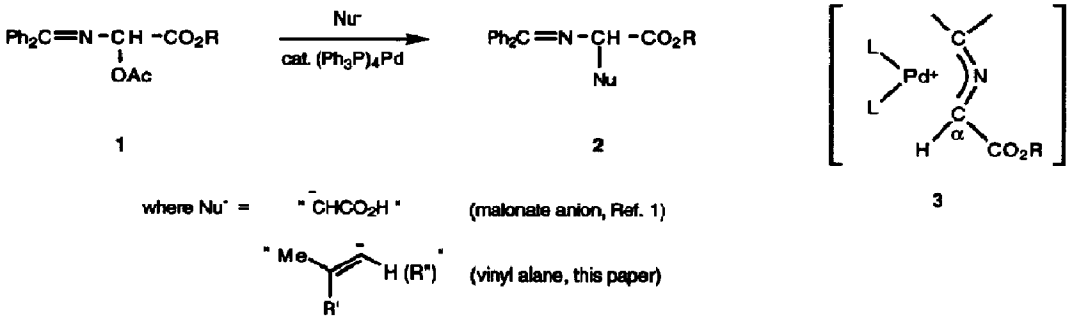
Synthesis of β,γ-Unsaturated Amino Acid Derivatives by Alkyne Carbometalation-Palladium Catalyzed Coupling with 2-Aza-π-Allyl Palladium Complexes

Martin J. O'Donnell,* Min Li, William D. Bennett and Todd Grote

Department of Chemistry, Indiana University-Purdue University at Indianapolis, Indianapolis, IN 46202 USA

Abstract: Zirconium-catalyzed carboalumination of terminal or symmetrical internal alkynes followed by palladium-catalyzed coupling of the resulting vinylalane with Schiff base acetate **1** gives protected β,γ-unsaturated amino acid derivatives (vinylglycines) **6**.

We recently reported the reaction of Schiff base acetate **1** with malonate anions in the presence of a palladium(0) catalyst to form derivatives of γ-carboxyaspartic acid (**2**) which can be deprotected to the parent α-amino acid.[1] This reaction can be considered a coupling reaction between the soft malonate anion and a 2-aza-π-allyl system **3**.

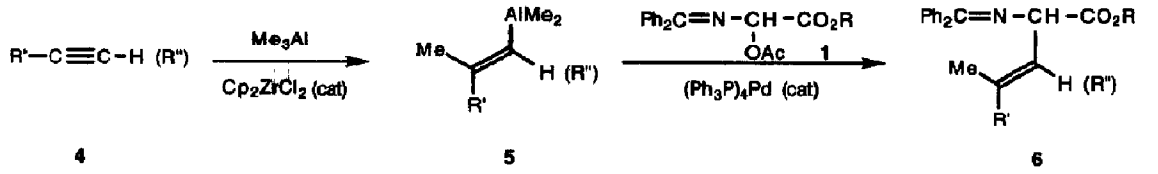


1 **2** **3**

Extension of this chemistry to the coupling of **3** with hard nucleophilic species is of interest as a potential route to a variety of amino acid structural classes by carbon-carbon bond-forming reactions with the glycine cationic precursor **1**.[2-6] In particular, β,γ-unsaturated amino acids (vinylglycines) are of particular current biological and synthetic importance. We report here preliminary studies toward the realization of this chemistry.

Zirconium-catalyzed carboalumination of 1-octyne (**4a**, R' = n-hex) with trimethylaluminum gave the vinylalane **5a** (R' = n-hex)[7] which was then reacted with Schiff base acetate **1** (R = Me) in the presence of a

catalytic amount of tetrakis(triphenylphosphine)palladium(0) in acetonitrile, the solvent of choice in the corresponding coupling with soft nucleophiles,[1] at room temperature to give the vinylated product **6a** (R' = n-hex) in 18% yield. A study of the reaction variables in the coupling step showed a dramatic solvent effect



4 **5** **6**

[solvent, % **6** (R = Me): DMF or DMSO, 0%; CH_3CN, 18%; $ClCH_2CH_2Cl$, 26%; Et_2O, 40%; THF, 42%; dioxane, 63%] As observed in the earlier malonate reactions,[1] the alane couplings are also quite sensitive to steric effects [R in ester **1**, % **6** (R' = n-hex): Me, 63%; Et, 60%; $PhCH_2$, 25%; tBu, 22%]. A minor product in the coupling reactions was the alanine Schiff base (**7**, $Ph_2C{=}NCH(Me)CO_2Me$), formed by reaction of **1** (R = Me) with excess Me_3Al.[8] The formation of this by-product is minimized by removal of excess Me_3Al *in vacuo* following the carboalumination reaction.

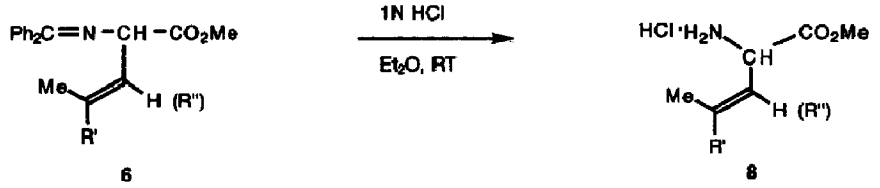
Application of the optimal two-step sequence[9] to various alkynes gave the tri- and tetrasubstituted β,γ-unsaturated derivatives **6a-6d** (see Table) in good yields. While the vinylalanes (**5a-5c**) derived from non-sterically demanding terminal alkynes undergo the coupling smoothly, the vinylalane (**5e**) from t-butylacetylene gave no reaction. Vinylalane **5d**, from a symmetrical internal alkyne, gave a single coupling product (**6d**) in good yield; however, as expected,[7b] products derived from unsymmetrical alkynes (**5f**) gave mixtures of regioisomeric coupling products.

Table. Preparation of derivatives **6** from **1** (R = Me) and hydrolysis to the vinylglycine esters **8**.[a]

Entry	R'	R''	Yield **6**[b]	Yield **8**[b]
a	n-Hex	H	68%	80%
b	Ph	H	50%	80%
c	n-Pr	H	60%	89%
d	Et	Et	54%	75%
e	t-Bu	H	0%	--
f	n-Pr	Me	[c]	--

[a]See footnotes 9 and 10 for typical procedures. [b]Yields of isolated products; all new products gave satisfactory elemental analyses or high resolution mass spectra as well as NMR spectra consistent with the assigned structures. [c]A mixture of regioisomers was formed, see text.

The β,γ-unsaturated Schiff base esters (**6**) are deprotected in good yield by treatment with mild acid in a two-phase system to yield the corresponding vinylglycine ester hydrochlorides **8** (see Table).[10]



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8. While Me_3Al reacts with Schiff base acetates **1** in the absence of a catalyst (W. D. Bennett and M. J. O'Donnell, unpublished results), the vinyl alane **5** gave < 5% of coupling product **6** in the absence of the palladium catalyst.

9. Typical procedure: Synthesis of methyl (E)-2-(N-diphenylmethylene)-4-methyl-3-decylenate (**6a**). A 50 mL three-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septa, and a mineral oil bubbler with calcium chloride drying tube was charged with dichlorobis(η^5-cyclopentadienyl)zirconium (0.058 g, 0.20 mmol) and flushed with argon. To this was added sequentially at 0 °C. 1,2-dichloroethane (2 mL), 1-octyne (0.110 g, 1.00 mmol), and a 2 M solution of trimethylalane in toluene (1.0 mL, 2.00 mmol). The reaction mixture was stirred for 12 hr at room temperature. Before proceeding to the next step, the reaction mixture was evacuated by an oil-pump (~ 5 mm Hg, 1 hr, at room temperature) in order to remove excess trimethylalane.

   To the (E)-(2-methyl-1-octenyl)dimethylalane solution prepared above was added dropwise a solution of methyl N-(diphenylmethylene)-2-acetoxyglycinate **1** (R = Me) (0.208 g, 0.670 mmol) and tetrakis(triphenylphosphine)-palladium(0) (0.008 g, 0.007 mmol) in 1,4-dioxane (4 mL), while the reaction temperature was controlled below 25-30 °C with a water bath. After the reaction mixture was stirred for 6 hr at room temperature, it was quenched by slowly adding 5% $NaHCO_3$ dropwise at 0 °C. The organic layer was separated and the aqueous layer was extracted with pentane (3 x 3 mL). The combined organic layer was washed with water (5 mL), 5% $NaHCO_3$ (5 mL), and water (5 mL). After the organic extract was dried over anhydrous $MgSO_4$, the solvent was removed *in vacuo*. The red-brown residue was then dissolved in methanol (2 mL) and concentrated *in vacuo* again to remove the toluene that was present. The crude product was then purified by chromatotron (hexane/ethyl acetate: 97 : 3) to yield pure **6a** as a yellow oil (0.17 g, 68%). ^1H NMR ($CDCl_3$) δ (ppm): 0.86 (t, 3H), 1.26 (s, 3H), 1.25-1.40 (m, 8H), 1.98 (t, 2H), 3.69 (s, 3H), 4.88 (d, 1H), 5.50 (d, 1H), 7.15-7.66 (m, 10H). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.07, 16.59, 22.62, 27.45, 28.78, 31.68, 39.49, 52.07, 64.83, 121.03, 127.65, 127.90, 127.97, 128.24, 128.46, 128.60, 128.83, 130.00, 130.25, 136.48, 139.43, 139.58, 169.69, 172.41. MS: Calcd. for $C_{25}H_{31}NO_2$: 377.2355. Found: 377.2367.

10. Typical Procedure: Hydrolysis of vinyl Schiff base **6a** to form (E)-α-(2-methyl-1-octenyl)glycine methyl ester hydrochloride (**8a**). To a 50 mL round-bottomed flask, equipped with a rubber septa and magnetic stirring bar, containing 1 N HCl (7 mL) and ethyl ether (10 mL) was added vinyl Schiff base **6a** (0.50 g, 1.32 mmol). The mixture was stirred at room temperature overnight. The ether layer was separated and the aqueous layer was washed with ethyl ether (3 x 10 mL). The aqueous solution was frozen with dry ice and acetone, then freeze dried on the freeze dryer. The product **8a** was a pale-brown powder (0.263 g, 80%); mp 93-95 °C. ^1H NMR ($CDCl_3$) δ (ppm): 0.87 (t, 3H), 1.24-1.40 (m, 8H), 1.83 (s, 3H), 2.05 (t, 2H), 3.77 (s, 3H), 4.94 (d, 1H), 5.36 (d, 1H), 8.72 (bs, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.06, 17.23, 22.61, 27.42, 28.91, 31.66, 39.62, 51.72, 53.20, 114.22, 147.77, 169.55.

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