Pergamon

Tetrahedron Letters, Vol. 38, No. 8, pp. 1309-1312, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00065-8

A Convenient Cross-Coupling Route to α,β,γ,δ–Unsaturated Amino Acids

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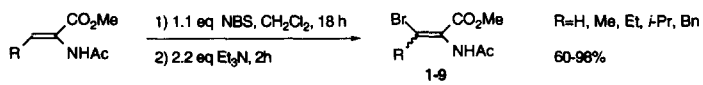
Abstract - β-Bromoenamide esters are coupled stereospecifically to vinylboronic acids *via* a palladium-catalyzed Suzuki reaction. This cross-coupling proceeds under mild conditions with $Pd(OAc)_2$ in 95% EtOH at 50 °C and produces amino acids with 1,3-diene side chains in high yields.

Unsaturated or didehydroamino acids possess interesting biological properties yet synthetically remain a challenging class of targets.[1] As constituents of peptides, they impart increased resistance from enzymatic degradation[2] and have been shown to induce conformational changes in the secondary structure of polypeptides.[3] Unsaturated amino acids are found in a family of polycyclic peptide antibiotics known as the lantibiotics[4] and have also served as intermediates in the construction of highly functionalized and rigidified amino acids. Importantly, didehydroamino acids are valuable substrates for enantioselective asymmetric hydrogenation reactions catalyzed by chiral transition-metal complexes.[5]

Danion *et al.* [6] previously reported the coupling of β-bromodidehydroalinate with alkynes mediated by $Pd(PPh_3)_4$ and CuI to produce amino acids with 1,3-enyne side chains. We surmised that Suzuki-type conditions[7] could be employed to couple β-bromoenamide esters with vinylboronic acids to produce amino acids with 1,3-diene side chains. Herein, we introduce the stereospecific palladium-catalyzed Suzuki cross-coupling of β-bromoenamide esters with vinylboronic acids as a general and high yielding route to unsaturated amino acids.

The synthesis of the required starting materials was straightforward. Bromination of methyl-2-acetamidoacrylate by successive treatment with NBS and NEt_3 in CH_2Cl_2 afforded only the *Z* product (**1**) (Scheme 1).[6,8] Under similar conditions, (*Z*)-β-alkylenamide esters (R = Me, Et, *i*-Pr, Bn) gave mixtures of *E* and *Z* products (**2-9**) which were easily separated by column chromatography.[9] Configurations of the β-bromoenamide esters were assigned by NOE experiments[10] and agreed with precedent.[6] Hydroboration of substituted alkynes by Brown's procedure[11] gave *B*-alkenylcatecholboranes which upon hydrolysis yielded the required *E* vinylboronic acids (**10**).[12]



Scheme 1

The characteristic reactivity of the β-bromoenamide esters required that: (*i*) we choose a weak base *i.e.*, Na_2CO_3 to protect the ester functionality from hydrolysis (common bases such as NaOH and $Ba(OH)_2$ could not be used), (*ii*) the reactions be performed at temperatures lower than that normally employed for Suzuki couplings (typically 80 °C) to avoid the threat of isomerization about the enamide double bond.

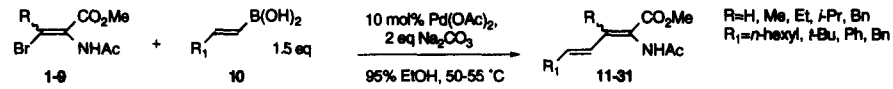
Treatment of the β-bromoenamide esters with 1.5 equiv. boronic acid, 2 equiv. solid Na_2CO_3, 10 mol% $Pd(OAc)_2$ in 95% EtOH at 50-55 °C gave high yields of the diene products in 2-4 hours.[13] The mild reaction conditions not only left the ester intact but also gave the cross-coupling product with complete retention of configuration. [8,14,15] The results of the coupling reactions are summarized in Table 1. The yields of the unsaturated amino acids where R = H, Me, Et and Bn ranged from good to excellent (55-94%). Both *E* and *Z* β-bromoenamide esters gave similar yields of cross-coupling product. In the case where R = H (entries 1-4), the unavailability of the *E* bromide precluded its study in this reaction (*vide supra*). Small amounts of the homocoupling product of the boronic acids were observed as side products in all of the cross-coupling reactions. These compounds may be byproducts of the reduction of $Pd(OAc)_2$ to the catalytically active Pd(0) species.[16]

Interesting results were obtained in the case of the *i*-propyl substituted bromoenamide esters, compounds **6** and **7** (entries 13-16). *E* Bromide **6** reacted sluggishly but stereoselectively with **10** (R_1 = Ph and *n*-hexyl) giving 40% of **23** and 44% of **24,** respectively. The *Z* bromide **7** on the other hand gave, none of the desired cross-coupling product with **10** (R_1 = Ph) (entry 15). Instead a large amount of homocoupling product, 17% of the *E* bromide **6**, and traces of protodebrominated *i*-propyl enamide were found. The reaction of the *Z* bromide **7** with **10** (R_1 = *n*-hexyl) (entry 16) did not proceed stereoselectively and gave a 1:1 mixture of the *E* and *Z* products (**24** and **25**).

With respect to the observed reactions of the *i*-propyl bromides, the steric bulk of the *i*-propyl group may adversly effect the normal cross-coupling pathway and allow alternative reactions to dominate. The detection of *E* bromide in the reaction mixture for entry 15 and the mixture of products resulting from the cross-coupling of **7** with **10** (R_1 = *n*-hexyl) (entry 16) may be explained by the isomerization of *Z* bromide **7**. Isomerization of **7** to **6** could take place through a π-allyl complex after Pd(0) insertion into the *i*-propyl methine C-H bond.[16]

In conclusion, we have demonstrated for a variety of β-bromoenamide esters that the Suzuki cross-coupling is a high yielding and general route to unsaturated amino acids. The investigation of this method in the preparation of γ,δ-unsaturated amino acids *via* regio- and enantioselective asymmetric catalytic hydrogenations is underway.

Table 1. Suzuki Cross-Coupling of β–Bromoenamide Esters With Vinylboronic Acids



entry	R	bromide (config.)[a]	**10** (R_1)	% yield[b]	product (config.)[a]
1	H	**1** (*Z*)	Bn	94	**11** (2*Z*, 4*E*)
2		**1** (*Z*)	Ph	55	**12** (2*Z*, 4*E*)
3		**1** (*Z*)	*t*-Bu	71	**13** (2*Z*, 4*E*)
4		**1** (*Z*)	*n*-hexyl	88	**14** (2*Z*, 4*E*)
5	Me	**2** (*E*)	Ph	66	**15** (2*E*, 4*E*)
6		**2** (*E*)	*n*-hexyl	80	**16** (2*E*, 4*E*)
7		**3** (*Z*)	Ph	67	**17** (2*Z*, 4*E*)
8		**3** (*Z*)	*n*-hexyl	82	**18** (2*Z*, 4*E*)
9	*Et*	**4** (*E*)	Ph	78	**19** (2*E*, 4*E*)
10		**4** (*E*)	*n*-hexyl	76	**20** (2*E*, 4*E*)
11		**5** (*Z*)	Ph	73	**21** (2*Z*, 4*E*)
12		**5** (*Z*)	*n*-hexyl	88	**22** (2*Z*, 4*E*)
13	*i*-Pr	**6** (*E*)	Ph	40	**23** (2*E*, 4*E*)
14		**6** (*E*)	*n*-hexyl	44[c]	**24** (2*E*, 4*E*)[d]
15		**7** (*Z*)	Ph	0[e]	--
16		**7** (*Z*)	*n*-hexyl	37[f]	**25** (2*Z*, 4*E*)
17	Bn	**8** (*E*)	Ph	83	**26** (2*E*, 4*E*)
18		**8** (*E*)	*t*-Bu	85	**27** (2*E*, 4*E*)
19		**8** (*E*)	*n*-hexyl	85	**28** (2*E*, 4*E*)
20		**9** (*Z*)	Bn	63[g]	**29** (2*Z*, 4*E*)
21		**9** (*Z*)	Ph	84	**30** (2*Z*, 4*E*)
22		**9** (*Z*)	*n*-hexyl	88	**31** (2*Z*, 4*E*)

[a] Configurations were assigned by NOE experiments. [b] Yields of isolated product: all compounds gave satisfactory ^1H and ^{13}C NMR spectra as well as HRMS. [c] Yield determined by ^1H NMR. [d] Inseparable mixture of **6** and **24**. [e] Obtained 82% of 1,4-diphenylbutadiene and 17% of **6**. [f] Also obtained 37% of **24**. [g] The reaction performed with 20 mol% $Pd(OAc)_2$ gave **29** in 70% yield.

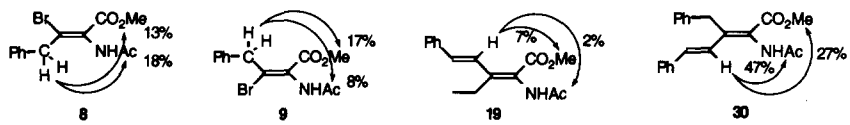
Acknowledgment

We are grateful to the National Institutes of Health for financial support of this work (GM51342).

REFERENCES AND NOTES

1. Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53-61; Schmidt, O.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159-172; Nunami, K.; Hiramatsu, K.; Hayashi, K.; Matsumoto, K. *Tetrahedron* **1988**, *44*, 5467-5478; Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487-490.
2. Shimohigashi, Y.; English, M. L.; Stammer, C. H.; Costa, T. *Biochem. Biophys. Res. Commun.* **1982**, *104*, 583-590.
3. Jain, R.; Chauhan, V. S. *Biopolymers* **1996**, *40*, 105-119.
4. Jung, G. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1051-1068; Freud, S.; Jung, G.; Gutbrod, O.; Folkers, G.; Gibbons, W. A.; Allgaier, H.; Werner, R. *Biopolymers* **1991**, *31*, 803-811.

5. Burk, M. J.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure & Appl. Chem.* **1996**, *68*, 37-44 and references cited therein.
6. Miossec, B.; Danion-Bougot, R.; Danion, D. *Synthesis* **1994**, 1171-1174.
7. Suzuki, A. *Pure & Appl. Chem.* **1985**, *57*, 1749-1758; Suzuki, A. *Pure & Appl. Chem.* **1991**, *63*, 419-422; Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, G. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2395.
8. Danion-Bougot, R.; Danion, D.; Francis, G. *Tetrahedron Lett.* **1990**, *31*, 3739-3742.
9. The *E/Z* ratios of the starting bromoenamide esters were as follows: R = H: *Z* exclusively; R = Me: 40/60; R = Et, *i*-Pr, Bn: 50/50. The *E* and *Z* bromoenamide esters were easily separated by flash chromatography (SiO_2, 1:1 EtOAc/PE).
10. Representative NOE experiments on examples of starting materials and products:



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11. Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370-4371; Lane, C. F.; Kabalka, G. W. *Tetrahedron* **1976**, *32*, 981-990.
12. The boronic acids were all colorless crystalline solids which *in vacuo* became oily semisolids.
13. Typical Experimental Procedure: All reagents were degassed and manipulations were performed under an inert atmoshere. In a 50-mL round-bottom flask were combined bromoenamide **4** (0.300 g, 1.20 mmol), *E* octenylboronic acid (0.283 g, 1.80 mmol), Na_2CO_3 (0.254 g, 2.40 mmol), $Pd(OAc)_2$ (0.027 g, 0.10 mmol), and a magnetic stir bar. The reaction vessel was charged with 25 mL of degassed 95% EtOH and stirred in an oil bath at 50 °C. The reaction was monitored by tlc. After complete consumption of the bromoenamide (2h) the reaction mixture was diluted with 1:1 EtOAc/PE, passed through a plug of $NaHCO_3$ and silica, and concentrated. Chromatography (SiO_2, EtOAc/PE, 1:1) of the crude material gave coupling product **20** (0.259 g, 76%) as white needles. ^1H NMR ($CDCl_3$, 300MHz) δ 0.76 (t, 3H, *J* = 12.9 Hz), 0.90 (t, 3H, *J* = 15 Hz), 1.14-1.33 (m, 6H), 1.95 (s, 3H), 2.03 (q, 2H, *J* = 6.6 Hz), 2.25 (q, 2H, *J* = 7.5 Hz), 3.64 (s, 3H), 5.86 (dt, 1H, *J* = 6.3, 15.3 Hz), 6.67 (d, 1H, *J* = 15.6 Hz), 7.92 (s, 1H); ^{13}C NMR (74.5 MHz) δ 12.96, 13.90, 13.80, 21.44, 22.32, 28.63, 28.89, 31.42, 33.22, 51.58, 121,72, 125.44, 136.29, 143.19, 165.55, 169.88. HRMS $C_{16}H_{27}NO_3$ calcd 281.1991, found (M^+) 281.1991.
14. Preliminary work at 70 °C with the catalyst system described in Burk, M. J.; Lee, J. R.; Martinez, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 10847 gave mixtures of *E* and *Z* products.
15. Extended reaction times (>24 h) under these conditions lead to isomerization of the product.
16. Hegedus, L. S.; Palladium in Organic Synthesis. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: New York, 1994; Chapter 5.

(*Received in USA* 6 *December* 1996; *revised* 7 *January* 1997; *accepted* 8 *January* 1997)