Pergamon

Tetrahedron Letters, Vol. 37, No. 30, pp. 5273-5276, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01118-5

The Asymmetric Synthesis of Allylglycine and Other Unnatural α-Amino Acids *via* Zinc-Mediated Allylation of Oximes in Aqueous Media#

Stephen Hanessian* and Rui-Yang Yang

Department of Chemistry, Université de Montréal, C.P.6128, Succursale Centre-ville, Montréal, Québec, H3C 3J7, CANADA

Abstract: Enantiomerically pure or highly enriched allylglycine and its chain-substituted analogs are easily accessible from the reaction of the sultam derivative of O-benzyl glyoxylic acid oxime with allylic bromides in the presence of powdered zinc in aqueous ammonium chloride.

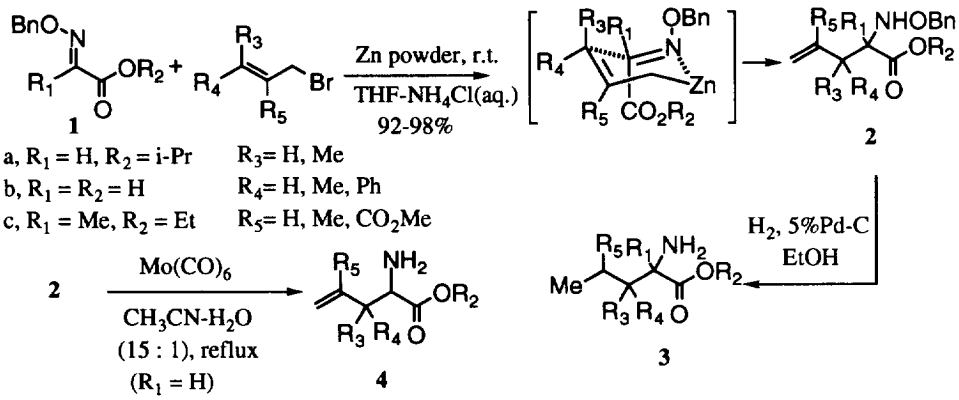
The synthesis of unnatural α-amino acids[1,2] continues to be an area of great interest in conjunction with the design of peptide and peptidomimetic therapeutics.[3] The literature is rich in the variety of methods available for the synthesis of α-amino acids and their analogs. The vast majority of these methods depend on the use of organic solvents and relatively low temperatures, particularly when asymmetric processes are involved. Performing organometallic reactions in aqueous media has attracted a lot of attention in recent years particularly in the quest to promote chemistry in a so-called environmentally benign medium.[4] Metal-mediated allylation of aldehydes and ketones in aqueous media is well documented in the literature, although the scope of these reactions has not been fully exploited with other derivatives.[4,5] Herein, we report zinc-mediated C-allylation additions to O-benzyl glyoxylic acid and ester oximes in aqueous media as a convenient method for the synthesis of enantiomerically pure or highly enriched allylglycines[1,2,6] and a series of related derivatives.

A general protocol for the synthesis of allylglycine and a variety of α, β, and γ-substituted congeners is shown in Scheme 1. In a typical procedure, commercial zinc powder(1.8 mmol) was added slowly to a biphasic solution of **1a** (1.0 mmol) and allyl bromide (1.4 mmol) in THF-NH_4Cl(aq.)[7] (1:5, 5 ml). The allylation proceeded smoothly and was complete in 5 minutes to give a 98% isolated yield of **2** (R_1, R_3-R_5 = H; R_2= *iso*-Pr). Other allylic bromides also reacted well with **1a** to give N-benzyloxy allylglycine derivatives corresponding to the general structure **2**. In each instance the addition took place at the γ-position of the reagent presumably through a six-membered ring transition state as shown in Scheme 1. Interestingly, the reactions were just as efficient with the free carboxylic acid **1b**. Simple hydrogenolysis of compounds represented by expression **2** gave the corresponding saturated α-amino acids **3**. Selective cleavage of the N-O bond in the presence of the carbon-carbon double bond by $Mo(CO)_6$[8] led to allylglycine derivatives expressed as **4**. Allylation also

Dedicated to the memory of Professor Wolfgang Oppolzer, a friend and a distinguished scientist.

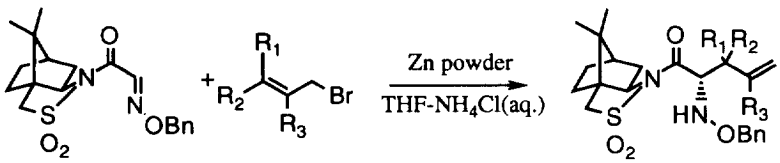
took place with the substituted oxime derived from ethyl pyruvate **1c** in the presence of four equivalents of allyl bromide and zinc to give racemic α-methyl allylglycine in 80% yield.

Scheme 1



Having secured a general method for the synthesis of racemic allylglycine and related structures in aqueous solution, we turned our attention to an asymmetric version of this reaction. After exploring the effects of numerous chiral non-racemic ester and amide derivatives of O-benzyl glyoxylic acid oxime,[9] we found Oppolzer's (1*S*)-(-)-2,10-camphorsultam[10] analog **5** to be the most suitable (Scheme 2). The reaction conditions were identical to the one described earlier, and the results are summarized in Table 1.

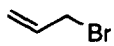
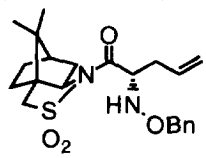
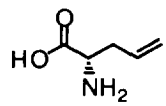
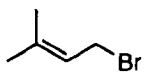
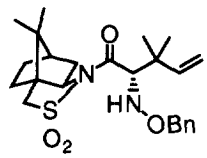
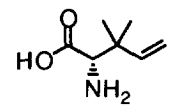
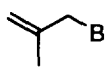
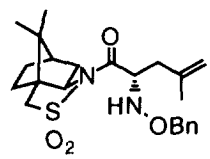
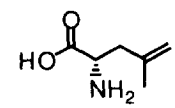
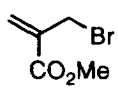
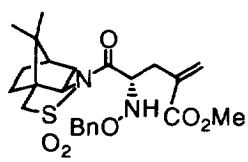
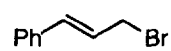
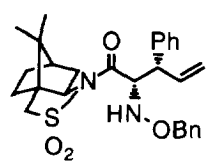
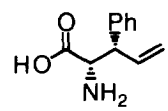
Scheme 2



As in the racemic series, the addition generally took place at the γ-position of the allylic halide with excellent diastereoselectivities. The degree of diastereoselectivity seems to vary depending on the position of the substituent in the allylic moiety. Thus, β-substituents led to a modest decrease in the diastereoselectivity (entries 4, 5), while substituents at the γ-position exhibited an enhancement (entries 3, 6). The reaction of cinnamyl bromide led to a single diastereomer (entry 6), whose structure was unambiguously determined by single crystal X-ray analysis. Yamamoto and co-workers[11] have reported the reaction of allylzinc bromide with the 8-(−)-phenylmenthyl ester of O-methyl glyoxylic acid oxime in anhydrous THF at -78°C which gave allylglycine in 74%d.e.

After selective cleavage of the N-O bond in the presence of $Mo(CO)_6$,[8] the sultam auxiliary in **6a-c, 6e** was removed by treatment with LiOH in THF-H_2O solution[12] to afford the corresponding free allylglycine derivatives without any loss of stereochemical purity compared to the sultam precursor. Alternatively, hydrogenolysis followed by hydrolysis afforded the saturated amino acids. The stereochemistry of **6a** and **6c** was confirmed by comparing the optical rotations of the final α-amino acids with the known values. The e.e's of **7a-7c** and **7e** were further verified by analysis of

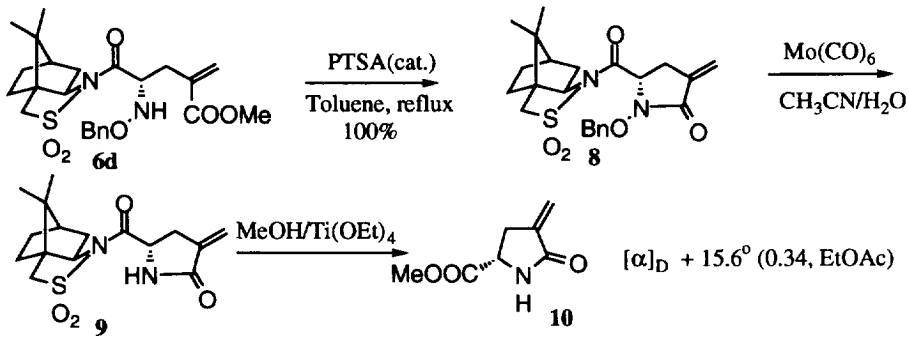
Table 1: Asymmetric Synthesis of N-Benzyloxy (*S*)-Allylglycine Derivatives

Entry	Allylic bromide	Temp.	Product		Yield[a]	d.s[b]	Allylglycines	
1		r.t.		**6a**	95%	91:9		**7a**
2		0°C		**6a**	94%	93:7		
3		r.t.		**6b**	90%	99:1[c]		**7b**
4		0°C		**6c**	93%	81:19		**7c**
5		0°C		**6d**	99%	84:16	see Scheme 3	
6		r.t.		**6e**	88%	99:1		**7e**
			X-ray					

a. Isolated yield. b. Ratio was determined by ^{1}H NMR. c. The stereochemistry was assigned by analogy.

the Mosher amide derivatives.[13] The adduct **6d** could be cyclized in the presence of catalytic PTSA in toluene to give the N-benzyloxy γ-lactam **8**. Cleavage of the N-O bond was achieved by $Mo(CO)_6$,[8] and the resulting lactam derivative **9** was treated with $Ti(OEt)_4$ in methanol[14] to afford the α-methylene pyroglutamate derivative **10** (Scheme 3). This derivative proved to be identical with methyl α-methylene (*S*)-pyroglutamate prepared from (*S*)-pyroglutamic acid.[15]

Scheme 3



We have described a practical method for the expedient synthesis of enantiomerically pure or highly enriched (*S*)-allylglycine and its chain-substituted analogs in aqueous NH_4Cl-THF media at room temperature or 0°C. The resulting α-amino acids can be transformed into versatile chirons for the design and synthesis of pharmacologically important molecules as well as natural products.

Acknowledgment: We thank NSERC and Ciba-Agro for financial support through the University-Industry program.

References

1. Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816.
2. a) Duthaler, R.O. *Tetrahedron* **1994**, *50*, 1539; b) Williams, R.M. *Synthesis of Optically Active α-Amino Acids*, Baldwin, J.E.; Magnus, P.D. eds., Pergamon Press, **1989**, New York, N.Y.
3. For recent reviews on peptidomimetics see: a) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244; b) Kahn, M. *Synlett* **1993**, 821; c) McElroy, A.B. *Current Drugs* **1993**, 1157; d) Hirschmann, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1278; e) Ball, J.B.; Alewood, P.F. *J. Mol. Recogn.* **1990**, *3*, 55; f) Morgan, B.A.; Gainor, J.A.; *Ann. Rep. Med. Chem.* **1989**, *24*, 243.
4. For recent reviews, see: a) Li, C. *Chem. Rev.* **1993**, *93*, 2023; b) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741; c) Chan, T.H.; Li, C.J.; Lee, M.C.; Wei, Z.Y. *Can. J. Chem.* **1994**, 1181.
5. a) Paquette, L.A.; Mitzel, T.M. *J. Am. Chem. Soc.* **1996**, *118*, 1931 and references cited therein; b) Isaac, M.B.; Chan, T.H. *Tetrahedron Lett.* **1995**, *36*, 8957; c) Ahonen, M.; Sjoholm, R. *Chem. Lett.* **1995**, 341; d) Gao, J.; Harter, R.; Gordon, D.M.; Whitesides, G.M. *J. Org. Chem.* **1994**, *59*, 3714; e) Binder, W.H.; Prenner, R.H.; Schmid, W. *Tetrahedron* **1994**, *50*, 749; f) Yanagisawa, A.; Inoue, H.; Morodome, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10356.
6. For selected references on the synthesis of optically active allylglycine and its derivatives, see: a) Katagiri, N.; Okada, M.; Kaneko, C.; Furuya, T. *Tetrahedron Lett.* **1996**, *37*, 1801; b) Voigt, K.; Stolle, A.; Salaun, J.; Meijere, A. *Synlett* **1995**, 226; c) Kitagawa, O.; Hanano, T.; Kikuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1993**, *34*, 2165; d) Hamon, D.P.G.; Massy-Westropp, R.A.; Razzino, P. *J. Chem.Soc., Chem. Commun.* **1991**, 722.
7. a) Petrier, C.; Luche, J.L. *J.Org.Chem.* **1985**, *50*, 910. b) Petrier, C.; Einhorn, J.; Luche, J.L. *Tetrahedron Lett.* **1985**, *26*, 1449.
8. a) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351; b) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Perkin Trans 1* **1985**, 1401.
9. Hanessian, S.; Yang, R.-Y., Park, H. unpublished results.
10. For reviews see: a) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969; b) Kim, B.H.; Curran, D.P. *Tetrahedron* **1993**, *49*, 293.
11. Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415.
12. Oppolzer, W.; Tamura, O.; Deerberg, J. *Helv. Chim. Acta* **1992**, *75*, 1965.
13. Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
14. Oppolzer, W.; Lienard, P. *Helv. Chim. Acta* **1992**, *75*, 2572.
15. a) Ezquerra, J.; Pedregal, C.; Mico, I.; Najera, C. *Tetrahedron: Asymmetry* **1994**, *5*, 921; b) Panday, S.K.; Griffart-Brunet, D.; Langlois, N. *Tetrahedron Lett.* **1994**, *35*, 6673.

(*Received in USA* 6 *May* 1996; *accepted* 31 *May* 1996)