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Deconjugation of Dehydroamino Acids: Stereoselective Synthesis of Racemic (*E*)-Vinylglycines

Paul A. Alexander, Stephen P. Marsden,* Dulce M. Muñoz Subtil, and John C. Reader[†]

School of Chemistry, University of Leeds, Leeds LS2 9JT, United Kingdom

s.p.marsden@leeds.ac.uk

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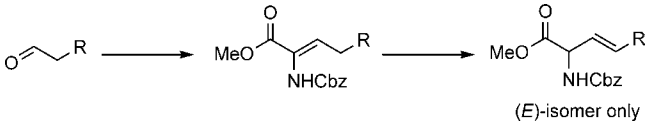
ABSTRACT



A practical and general two-step synthesis of carbamate-protected (*E*)-vinylglycines from aliphatic aldehydes is reported. The key step involves the kinetic α-protonation of dianionic dienolates derived from dehydroamino acids.

New methods for the synthesis of nonproteinogenic amino acids are in constant demand to furnish building blocks for the synthesis of pharmaceutical candidates and biological probes. β,γ-Unsaturated amino acids (also known as vinylglycines) are useful intermediates in the synthesis of polyfunctional amino acids such as the polyoxins[1] and hypermodified nucleosides of phenylalanine ^{t}RNAs[2] and also exhibit desirable biological activity in their own right. The naturally occurring parent compound (α-vinylglycine) inhibits several transaminase[3] and decarboxylase[4] enzymes. Substituted vinylglycines are found in biologically active natural products such as 2-amino-4-methoxy-3-butenoic acid (**1**),[5] rhizobitoxin,[6] and the selective trypsin inhibitor radiosumin.[7] The synthetic vinylglycine (*E*)-2-amino-5-phosphono-3-pentenoic acid (**2**) is also of interest as an inhibitor of cystathionine γ-synthase.[8]

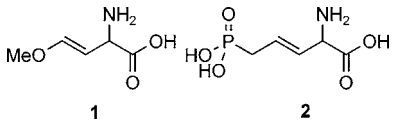


Figure 1. Representative biologically active vinylglycines.

Numerous routes to γ-substituted vinylglycines have been reported in the literature, but these are frequently lengthy and often suffer from a lack of stereocontrol in the generation of the alkene function. A notable exception is the method introduced by Petasis, whereby a three-component condensation of an amine, glyoxylic acid, and an (*E*)-vinylboronic acid gives the (*E*)-vinylglycine directly.[9] This mild and functional group tolerant method has been widely adopted but is still restricted by the need for a nucleophilic amine

[†] Formerly Millennium Pharmaceuticals Inc. Current address: Sareum Ltd., 2 Pampisford Park, Cambridge CB2 4EE, U.K.

(1) Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1993**, *58*, 6990−6995.
(2) Itaya, T.; Kanai, T. *Chem. Pharm. Bull.* **2002**, *50*, 1318−1326.
(3) Soper, T. S.; Manning, J. M.; Marcotte, P. A.; Walsh, C. T. *J. Biol. Chem.* **1977**, *252*, 1571−1575.
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(6) Keith, D. D.; de Bernardo, S.; Weigele, M. *Tetrahedron* **1975**, *31*, 2629−2632.
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component (ruling out direct approaches to *N*-carbamate-protected amino acids) and by the limited commercial availability of (*E*)-vinylboronic acids. Terminal alkyne precursors to vinylboronic acids form a relatively small pool of commercially available starting materials.

An alternative approach to (*E*)-vinylglycines was utilized in Schöllkopf's synthesis of a protected variant of **1** (Figure 2).[10] Treatment of the dehydroamino acid **3** (R = Et, R′ = OMe, P = CHO) with 2 equiv of LDA in the presence of HMPA gave a presumed dianionic dienolate **4**, which upon quenching with TFA yielded the deconjugated compound **5** as a single (*E*)-isomer.[11,12]

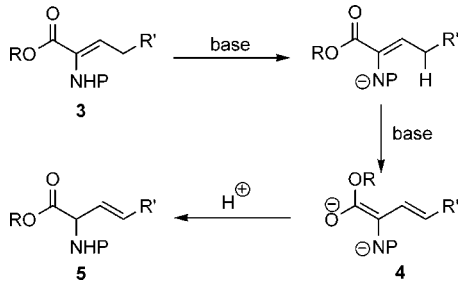
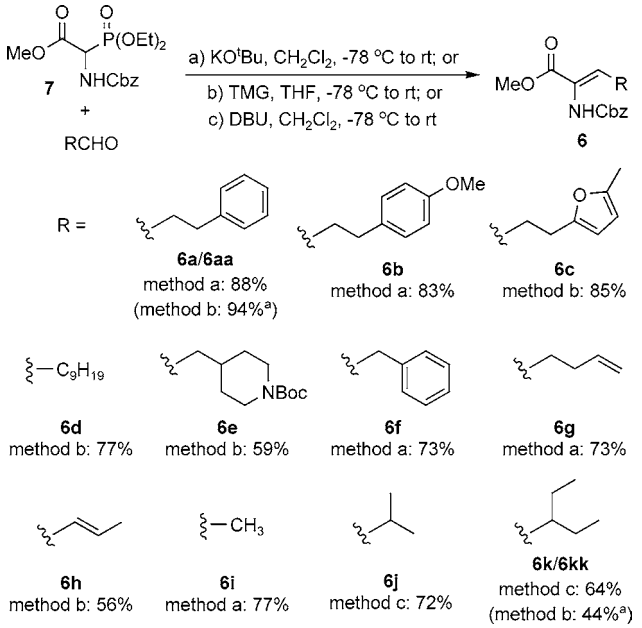


Figure 2. Proposed deconjugative conversion of dehydroamino acids to vinylglycines.

This result suggested a potentially general route to (*E*)-vinylglycines, with some caveats. First, although the stereochemical outcome was presented as arising from a kinetic preference for deprotonation, the potential for facile geometric isomerization of enol ethers could not rule out the possibility of this being a thermodynamic result that would not transfer to more geometrically stable olefins. Second, the *N*-formyl substituent is far from an ideal protecting group for further use in synthesis, and so extension to more useful *N*-carbamoyl derivatives would need to be demonstrated. Third, a general and concise approach to the substrates **3** utilizing widely available and diverse starting materials would need to be demonstrated. We describe herein the successful reduction of this scheme to practice.

The requisite protected dehydroamino acids **6** were synthesized in high yield by condensation of the commercially available phosphonate **7** (or its Boc analogue) with readily available aliphatic aldehydes (Scheme 1). A range of bases were suitable for this transformation, including potassium *tert*-butoxide, tetramethylguanidine, and diazabicycloundecene.[13,14] The *N*-Boc derivatives **6aa** and **6kk** were also accessed by the same chemistry using the Boc-analogue of **7**. In all cases, compounds **6** were isolated as single (*Z*)-isomers following chromatographic purification.

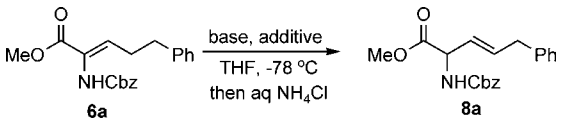
Scheme 1. Synthesis of Dehydroamino Acids from Aldehydes



[a] Yields for formation of *N*-Boc derivatives **6aa**/**6kk**.

Attention then was turned to the deconjugation of the dehydroamino acids. Our optimization studies were carried out on substrate **6a**, and the results are shown in Table 1.

Table 1. Optimizing the Deconjugation of Dehydroamino Acid **8a**



entry	base	additive	yield (%)
1	LiTMP (2.1 equiv)	LiCl	87
2	LiTMP (2.1 equiv)	none	40
3	LDA (2.1 equiv)	LiCl	79
4	LDA (2.1 equiv)	none	58
5	LiHMDS (2.1 equiv)	LiCl	0
6	LiTMP (3 equiv)[a]	LiCl	5
7	LiTMP (3 equiv)[b]	LiCl	82

[a] Substrate/product are the *N*-methyl-*N*-Cbz derivatives. [b] All experiments carried out on a ca. 0.6 mmol scale, except entry 7, which was ca. 3 mmol.

Deprotonation with 2.1 equiv of either lithium tetramethylpiperide (LiTMP) or lithium diisopropylamide (LDA), followed by quenching at low temperature with aqueous ammonium chloride solution, gave cleanly the deconjugated vinylglycine product **8a** as a single geometric isomer (entries 1−4). The stereochemistry of the alkene was assigned as (*E*) on the basis of the olefinic coupling constant (J = 15.4

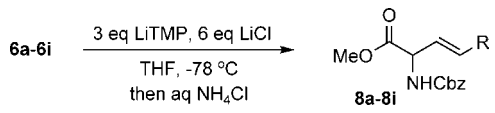
(10) Hoppe, I.; Schöllkopf, U. *Synthesis* **1982**, 129−131.
(11) Regioselective α-protonation of amine-substituted dienolates has also been observed on imidazolidinone templates: Seebach, D.; Buerger, H. M.; Schickli, C. P. *Liebigs Ann. Chem.* **1991**, 669−684.
(12) Deconjugation of 2,2-disubstituted dehydroamino acids during ester saponification has been observed: Nunami, K.; Suzuki, M.; Yoneda, N. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2224−2229.
(13) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53−60.
(14) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487−490.

Hz). While both LiTMP and LDA mediated dienolate formation, the isolated yields of **8a** were found to be higher if anhydrous LiCl (6 equiv) was included in the reaction mixture (entries 1/3, cf. entries 2/4). The role of the LiCl may be to form a more reactive base by deaggregation of the lithium amide,[15] or it may be involved in solvation and stabilization of the dianionic dienolates.[16]

Attempted reaction with lithium hexamethyldisilazide as the base returned only starting material (entry 5), perhaps reflecting the lower basicity of this reagent by comparison with LDA and LiTMP.[17] The crucial need to employ dianionic species to mediate the deconjugation was illustrated by the attempted deconjugation of the *N*-methyl derivative of **6a**, which returned only a 5% yield of the target vinylglycine (entry 6). Mass spectral evidence for the formation of Michael adducts of the lithium amide base to this substrate was observed. Clearly, the initial deprotonation of the secondary carbamate in the parent substrate **6a** generates a metalated enamine, which is resistant to Michael addition and hence an efficient substrate for dienolate formation. Finally, although good results were obtained in the above series using 2.1 equiv of base, to ensure complete deconjugation across a range of substrates, we found that the use of 3 equiv of LiTMP was beneficial and allowed the reactions to be scaled reliably (entry 7).

We next examined the scope and generality of the method (Table 2) with respect to the dehydroamino acid substituents.

Table 2. Scope of the Synthesis of (*E*)-Vinylglycines **8**



entry	product	R	yield (%)
1	**8a**	-CH_2Ph	82
2	**8aa**[a]	-CH_2Ph	70
3	**8b**	-CH_2(*p*-$MeOC_6H_4$)	75
4	**8c**	-CH_2(5-Me-2-furyl)	81
5	**8d**	-C_8H_{19}	99
6	**8e**	-4-*N*-Boc-piperidinyl	71
7	**8f/6f**[b]	-Ph	98
8	**8g**	-$CH_2CH{=}CH_2$	90
9	**8h/9h**[c]	-$CH{=}CH_2$	49
10	**8i/6i**[d]	-H	*e*

[a] Substrate **6aa**/product **8aa** are *N*-Boc derivatives. [b] 6:1 mixture of **8f**/**6f**. [c] 7:1 mixture of **8h**/**9h** plus 39% **6h** isolated. [d] 1:1 mixture of **8i**/**6i** by ^{1}H NMR. [e] Isolated yield not recorded; reaction analyzed by crude ^{1}H NMR.

Under the optimized conditions described (Table 1, entry 7), alkyl-substituted vinylglycines were isolated in excellent yields as single (*E*)-stereoisomers (Table 2, entries 1−6 and 8). Particularly reassuring was the observation that, in products with benzylic, heterobenzylic, or allylic substituents on the vinylglycine, no isomerization of the olefin into conjugation with the adjacent π-system was observed (entries 1−4 and 8). Also noteworthy is the fact that the reaction works for both *N*-Cbz and *N*-Boc carbamates (entries 1 and 2).

Substrate **6f** returned a 6:1 mixture of the deconjugated product **8f** and starting material. This could be a consequence of (a) incomplete deprotonation of **6f**, (b) a mixture of α- and γ-protonations, or (c) isomerization of the initially formed kinetic product on workup or isolation. This was probed by quenching the reaction with H_2O and D_2O. The latter reaction gave 2-deuterated **8f** exclusively, whereas the former gave a ca. 6:1 mixture of **8f**/**6f**. Further, on standing (21 days), the crude NMR samples equilibrated to a ca. 2:3 mixture of **8f**/**6f**. This equilibration could be accelerated by addition of triethylamine (equilibration complete in ca. 2 days). Additionally, treatment of **6f** with triethylamine also resulted in the formation of a final 2:3 mixture of **8f**/**6f**, demonstrating that the process is truly at equilibrium. Taken together, these results suggest that the initial proton quenching occurs exclusively at the α-position, but that base-mediated equilibration through enolization is facilitated by the presence of the phenyl group as an electron-sink (by comparison, no equilibration of **8a** to **6a** was seen on treatment with triethylamine over 3 days). In the case of D_2O quenching, presumably a kinetic isotope effect slows the equilibration sufficiently for the single regioisomer product **8f** to be observed initially. A similar phenomenon was observed in the deconjugation of **6h**, where 49% of a 7:1 mixture of **8h** and the isomerized dehydroamino acid methyl 2-(Cbz-amino)hexa-2,5-dienoate **9h** was isolated, together with 39% of **6h**. The instability of the mixture of **8h**/**9h** prevented investigation of the origin of the isomers, but it is possible that the terminal ethenyl substituent activates initially formed **8h** toward isomerization, analogously to the phenyl substituent in **6f**. Finally, attempted formation of protected vinylglycine itself by deconjugation of **6i** gave a 1:1 mixture of **6i**/**8i**. Quenching with D_2O followed by aqueous workup gave a 2:1 mixture of 2-deuterated **8i** and nondeuterated **6i**, which isomerized to a 1:7 mixture on standing. Again, it seems likely that a completely or largely regioselective protonation at C2 is followed by isomerization.

As stated above, in all cases, a single (*E*)-olefin was formed as the product. This can be rationalized by considering deprotonation of a lithium-coordinated intermediate lithiated carbamate **10** through the transition state **a**, which minimizes $A_{1,3}$-strain by comparison with the alternative transition state **b**, which would give rise to (*Z*)-vinylglycines (Figure 3).

We also attempted to prepare trisubstituted vinylglycines **11** by deconjugation of **6j** and **6k**. Treatment under the standard deconjugation conditions simply returned starting material, and attempts to promote dienolate formation by extended reaction times led to the formation of byproducts.

One of these (from **6k**) was isolated and identified as **12**, apparently arising through a directed metalation of the

(15) De Pue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5518−5524; *ibid.*, 5524−5533.
(16) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654.
(17) pK_a values in THF/HMDS = 29.5; ^{i}Pr$_2$NH = 35.7; TMP = 37.3. Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442−3443.

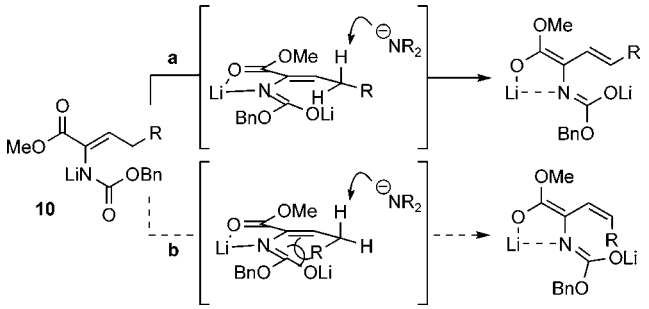
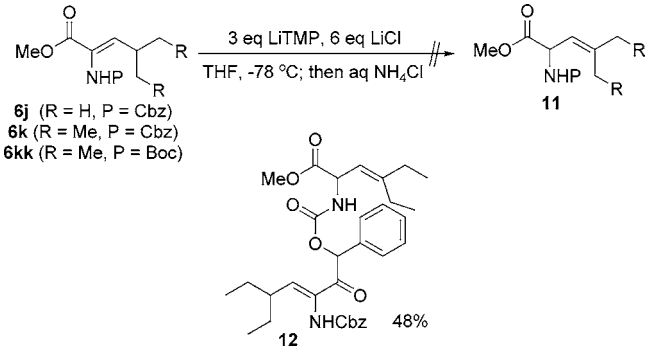


Figure 3. Rationale for selective formation of (*E*)-vinylglycines.

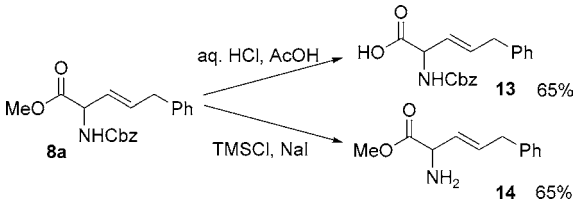
benzylic position of a Cbz group, which is then acylated by a second equivalent of (presumably *N*-lithiated) **6k**. Attempted deconjugation of the *N*-Boc analogue **6kk**, which would not be susceptible to lithiation on the carbamate, again only returned starting material. Seemingly the penalty for placing a non-hydrogen substituent proximal to the lithiated carbamate in the attempted deprotonation is prohibitively high in energy.

Scheme 2. Attempted Formation of Trisubstituted Vinylglycines



Finally, we sought to demonstrate that the protecting groups on the vinylglycines produced by our method could be manipulated without olefin isomerization. Under unoptimized conditions, we were able to orthogonally deprotect both acid and amine functionalities of **8a**, yielding **13** and **14**, respectively, with no trace of dehydroamino acid being formed in either case. This highlights the potential of this method as a route to substituted vinylglycines for incorporation into unnatural peptides and peptidomimetics.

Scheme 3. Orthogonal Deprotection of *N*-Cbz Vinylglycine Esters



In summary, a two-step synthesis of *N*-Cbz-protected (*E*)-vinylglycines starting from aliphatic aldehydes is reported. The key transformation is a stereoselective deconjugation reaction of dehydroamino acids, occurring through kinetic α-protonation of a dianionic dienolate intermediate. Further developments of this chemistry will be reported in due course.

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Supporting Information Available: Experimental procedures for the deconjugation reactions, plus full spectral data and copies of $^{1}H/^{13}C$ NMR spectra for dehydroamino acids **6**, vinylglycines **8**, and compounds **12**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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