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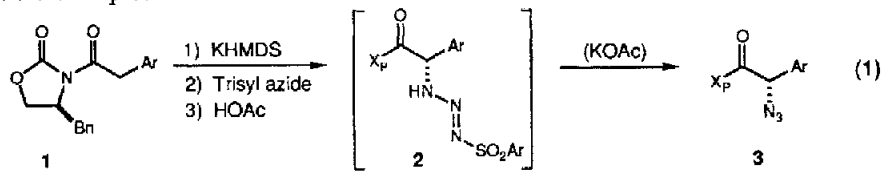
A General Approach to the Asymmetric Synthesis of Vancomycin-Related Arylglycines by Enolate Azidation

David A. Evans,* Deborah A. Evrard, Scott D. Rychnovsky,[1a] Thomas Früh, William G. Whittingham,[1b] and Keith M. DeVries[1c]

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Abstract: The asymmetric synthesis of vancomycin-related α-azido arylglycines by direct azide transfer methodology is reported. Procedures for the conversion of the azides to *N*-protected arylglycines are provided.

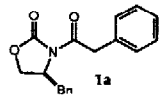
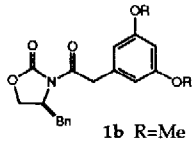
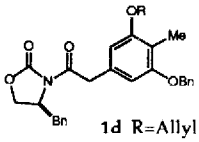
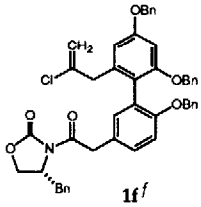
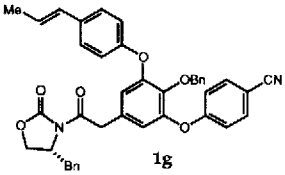
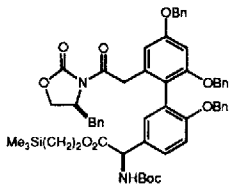
Vancomycin, ristocetin, and related glycopeptide antibiotics[2] contain three to five racemization-prone arylglycines[3] within the heptapeptide aglycones. Accordingly, any attempt to synthesize any member of this family of natural products must incorporate methodology for the construction of these nonproteinogenic arylglycines.[4] In conjunction with our studies directed toward the synthesis of these antibiotics, we have prepared a number of functionalized arylglycines by the asymmetric azidation methodology (eq 1) developed in this laboratory.[4b,c] A recent publication by Williams and co-workers[5] which also described the application of our methodology to the asymmetric synthesis of vancomycin-related arylglycines noted that, in certain instances, the *N*-sulfonyltriazene intermediate **2** could not be decomposed to the azido imide **3**. The purpose of this Letter is to describe our investigations in this area, and to discuss successful procedures for the decomposition of the intermediate triazenes to the azide products.



(1)

N-Arylacetyl oxazolidinones **1** are readily prepared from the corresponding arylacetic acids by reaction of the lithiated phenylalanine-derived oxazolidinone[6] and the mixed pivalic acid anhydride which is generated *in situ*.[7] Enolization of **1** with potassium hexamethyldisilazide (KHMDS, 1.1 equiv, THF, -78 °C 15-45 min) and treatment of the resulting enolate with 2,4,6-triisopropylbenzenesulfonyl azide[8] (trisyl azide, 1.2-1.3 equiv, 1-2 min) followed by acetic acid (5 equiv) affords triazene **2** (eq 1). Generally, this intermediate is not isolated, but decomposes to the azide **3** upon warming the reaction mixture to 25-30 °C. Based on our developmental studies on this reaction,[4c] the effective reagent which is responsible for triazene decomposition under these conditions is the potassium acetate generated as a result of the reaction quench. In the course of our syntheses of functionalized arylglycines, we have noted a substrate dependence on the time required for efficient conversion of the triazene to the desired azide. As shown by the examples provided in the Table, decomposition of the triazene formed by azidation of the unsubstituted substrate **1a** was complete within 30 minutes, while the triazenes derived from imides **1b-f** required longer reaction times for complete conversion (as long as 18 hours for the substrate **1e**). The diastereoselectivities and isolated yields of the azides **3b-3e** are comparable to that of **3a**. The azidation of biaryl imide **1f** (a 1:1 mixture of atropisomers) is noteworthy in that the minor diastereomer of azide **3f** was not detected by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture.

Table. Electrophilic Azidation of Arylacetate-Derived Enolates (eq 1).

Substrate	Azidation Conditions[a]	Triazene Decomposition Conditions	Stereoselection (S)-3:(R)-3	Product (Yield)[b]
 **1a**	A	25-30 °C, 0.5 h	91:9[c]	(*S*)-**3a** (82%)
 **1b** R=Me	A	30 °C, 2 h	90:10[d]	(*S*)-**3b** (78%)
1c R=DCB[e]	A	30 °C, 1 h	88:12[c]	(*S*)-**3c** (76%)
 **1d** R=Allyl	A	25 °C, 3 h	90:10[c]	(*S*)-**3d** (75%)
1e R=Bn	A	25-30 °C, 18 h	88:12[c]	(*S*)-**3e** (81%)
 **1f**[f]	A	25 °C, 2 h	<5:95[d]	(*R*)-**3f**[f] (77%)
 **1g**	B	NaI (5 equiv), NaOAc (3 equiv) Me_2CO, 25 °C, 5 h	8:92[g]	(*R*)-**3g** (61%)
 **1h** Atropisomer A	C	KOAc (10 equiv), THF 25 °C, 16 h	>95:5[d]	(*S*)-**3h** (60%)
1i Atropisomer B	C	KOAc (10 equiv), THF 25 °C, 16 h	93:7[h]	(*S*)-**3i** (60%)[i]

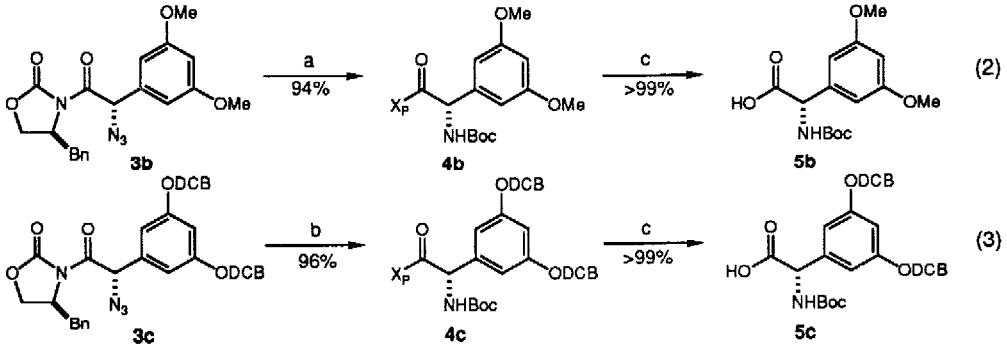
[a]**A:** *i.* 1.1 equiv KHMDS, THF, -78 °C, 15-45 min; *ii.* 1.2-1.3 equiv trisyl azide, -78 °C, 1-2 min; *iii.* 5 equiv HOAc. **B:** *i.* 1.5 equiv LiHMDS, THF, -78 °C, 30 min; *ii.* 2 equiv trisyl azide, -78 °C, 2 min; *iii.* 10 equiv HOAc; *iv.* Extractive workup. **C:** *i.* 2.5 equiv KHMDS, THF, -78 °C, 15 min; *ii.* 3 equiv trisyl azide, -78 °C, 1 min; *iii.* 5 equiv HOAc; *iv.* Extractive workup at 0 °C. [b]Yields refer to diastereomerically pure products unless noted otherwise. [c]Diastereomer ratio determined by HPLC analysis of the unpurified product. [d]Diastereomer ratio determined by ^{1}H NMR analysis of the unpurified product. [e]DCB=3,4-Dichlorobenzyl. [f]Mixture of biaryl atropisomers (1:1). [g]Ratio based on isolated yields. [h]Ratio determined by ^{1}H NMR analysis of the purified product. [i]Combined yield of diastereomers.

In contrast to imides **1a-f**, azidation of imide **1g** under the standard conditions resulted in only low yields (35-40%) of the corresponding azide. Upon close examination, it was found that the intermediate triazene was surprisingly stable and could be isolated in 65% yield after chromatography. However, decomposition to the desired azide could be induced by using sodium iodide in combination with sodium acetate or sodium bicarbonate. When the azide transfer reaction was performed on the lithium enolate of **1g** (1.5 equiv LiHMDS, THF, -78 °C, 30 min) the adduct formation appeared to be cleaner by TLC analysis than the analogous reaction with the potassium enolate. Isolation of the triazene by extractive workup, followed by treatment of the unpurified intermediate with sodium iodide (5 equiv) and sodium acetate (3 equiv) in acetone (25 °C, 5 h) provided the desired product **3g** in 61% overall yield. The diastereoselectivity for this azidation was approximately 93:7, as indicated by the isolated yields of the azide diastereomers. Subsequent to these early experiments, it was found that KOAc is the reagent of choice for this transformation.[4c]

In other studies, initial attempts at the azidation of imides **1h** and **1i** using standard conditions[9] were not successful. Although in each case clean adduct formation was observed by TLC, warming the reaction mixture to room temperature after the acetic acid quench resulted in a complex mixture of unidentified products. Again, optimization of the conditions for triazene decomposition proved successful. In each case, isolation of the triazene by rapid extractive workup at 0 °C, followed by treatment of a THF solution of the adduct with potassium acetate (10 equiv, 25 °C, 16 h) afforded the azide in 60% overall yield for the two steps. While the minor azide diastereomer of **3h** was not detected by ^{1}H NMR analysis of the reaction mixture, the azide **3i** was obtained as an inseparable 93:7 mixture of diastereomeric products.

N-Protected arylglycines can be prepared from the precursor azido carboximides by sequential reduction, *N*-protection, and chiral auxiliary removal.[10] Azide reduction via catalytic hydrogenation and *in situ* *N*-protection in the presence of an acylating reagent, such as *tert*-butylpyrocarbonate ($(Boc)_2O$) is one frequently employed mode of derivatization.[11] We have successfully applied this method to azido imide **3b**: hydrogenation (10% Pd/C, EtOAc, 25 °C, 2 h) in the presence of $(Boc)_2O$ (1.5 equiv) afforded *N*-Boc-imide **4b** in 94% yield (eq 2).[12] Subsequent cleavage of the chiral auxiliary (2 equiv LiOH, 3:1 THF/H_2O, 0 °C, 1 h) provided the *N*-Boc-arylglycine **5b** (≥96% ee)[13] in quantitative yield.

In numerous instances, azide hydrogenation is precluded if sensitive protecting groups such as benzyl ethers are to be retained. An alternative method we have found useful is reduction with $SnCl_2$ in aqueous dioxane. Reduction of azido imide **3c** with $SnCl_2$ (3 equiv, 3:1 dioxane/H_2O, 25 °C, 6-12 h), followed by the addition of Boc_2O (5 equiv) and aqueous bicarbonate (25 °C, 3 h) provided the *N*-Boc-imide **4c** in 96% yield (eq 3).[14] Cleavage of the chiral auxiliary (2 equiv LiOH, 3:1 THF/H_2O, 0 °C, 1 h) afforded the *N*-Boc-arylglycine **5c** (≥96% ee)[15] in quantitative yield. Although methanol is the usual solvent for the reduction of azides with $SnCl_2$,[16] azido imide precursors of arylglycines are unusually prone to methanolysis under these conditions. The use of aqueous dioxane avoids this side reaction, as well as allowing the subsequent *N*-acylation to be accomplished conveniently in the same reaction flask.



(a) H_2, Pd/C, EtOAc, $(Boc)_2O$; (b) *i.* $SnCl_2$, dioxane/H_2O, *ii.* $(Boc)_2O$, aq. $NaHCO_3$; (c) LiOH, THF/H_2O, 0 °C.

In conclusion, these studies extend the general utility of azide transfer methodology for the asymmetric synthesis of arylglycines. As noted, some substrates require modification of the original reaction conditions in order to effect efficient breakdown of the intermediate triazene. By this method we have synthesized eight arylglycines related to the vancomycin family of antibiotics; each of the azidation reactions proceeds with high diastereoselectivity and in good yield. This methodology is being incorporated into syntheses of the vancomycin family of natural products.

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References and Notes

(1) (a) NIH Postdoctoral Fellow, 1985-87. (b) NATO Postdoctoral Fellow, 1988-90. (c) NSF Predoctoral Fellow, 1986-89.

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(7) Experimental procedures for acylation of the oxazolidinone with mixed pivalic acid anhydrides or acid chlorides are provided in ref 4b; see also: Evans, D. A.; Gage, J. R. *Org. Synth.* **1989**, *68*, 83-91.

(8) Harmon, R. E.; Wellman, G.; Gupta, S. K. *J. Org. Chem.* **1973**, *38*, 11-16.

(9) 2.5 equiv KHMDS were used for the enolization and deprotonation of the carbamate.

(10) (a) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141-6144. (b) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123-1126.

(11) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837-838.

(12) A representative general procedure follows: To a solution of the azide (1 mmol) in EtOAc (8 ml) is added $(Boc)_2O$ (1.5 mmol) and 10% Pd/C (25 wt %). The reaction is stirred under a balloon of hydrogen at ambient temperature for 2 h. After purging with nitrogen, the catalyst is removed by filtration through celite. Solvent removal and chromatography provides the pure *N*-Boc-imide.

(13) After conversion of the acid to the *N*-methylamide ($MeNH_4Cl$, DEPC, Et_3N, DMF), Boc removal, and formation of the (+) Mosher amide, the minor diastereomer was undetectable by 500 MHz ^1H NMR analysis.

(14) A representative general procedure follows: To a 0 °C solution of $SnCl_2$ (3 mmol) in 10 ml of dioxane and 5 ml of H_2O, under N_2, is added a solution of the azide (1 mmol) in 5 ml dioxane. The ice bath is removed and the reaction is allowed to stir at ambient temperature for 12 h. $(Boc)_2O$ (5 mmol) and $NaHCO_3$ (5 mmol) in 3 ml of water is added. The resulting heterogenous mixture is stirred for 3 h. Acidification with 1*N* $NaHSO_4$ and extraction with EtOAc, followed by solvent removal and chromatography provides the pure *N*-Boc-imide.

(15) After methylation of the acid (CH_2N_2), Boc removal, and formation of the (-)Mosher amide, HPLC analysis indicated a ≥98:2 ratio of diastereomers.

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