Tetrahedron Letters,Vol.29,No.47,pp 6075-6078,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS: COMPARISON OF ENOLATE VS. CATION FUNCTIONALIZATION OF N-BOC-5,6-DIPHENYL-2,3,5,6-TETRAHYDRO-4H-1,4-OXAZIN-2-ONES

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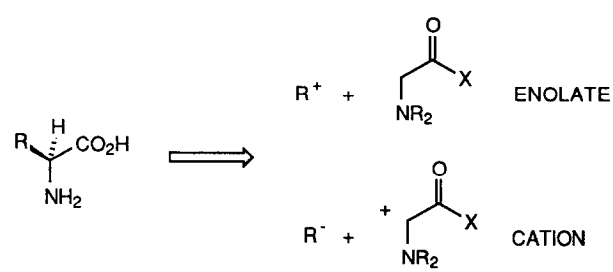
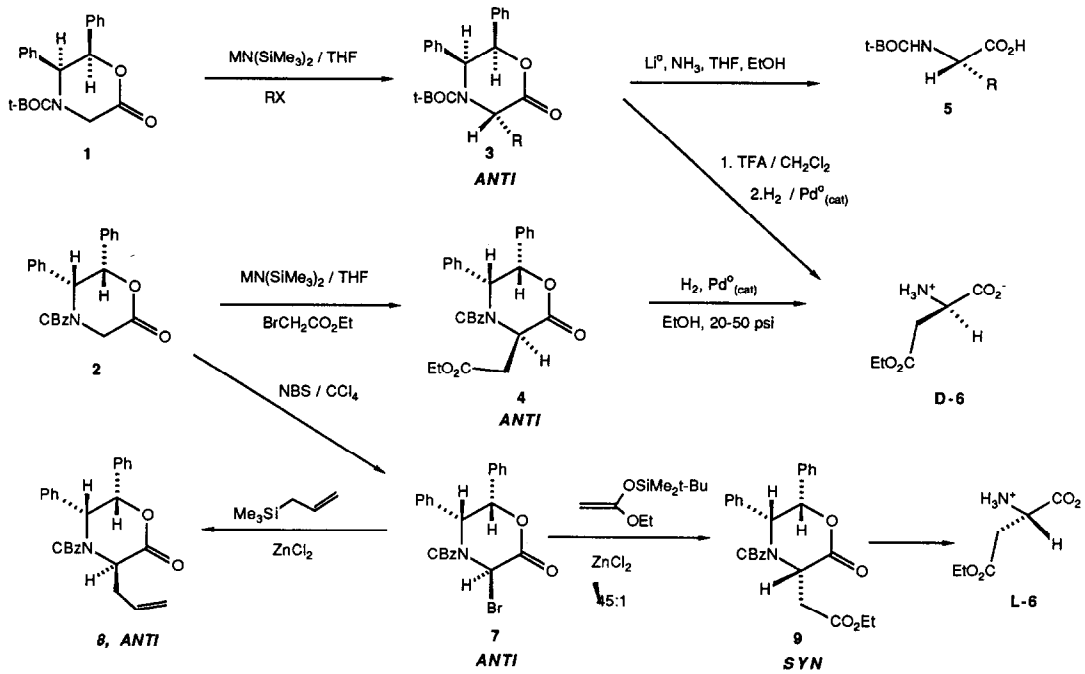
Abstract: Enolate generation and subsequent alkylation of the chiral glycinates **1** and **2** occurs with a high degree of diastereoselectivity. Reduction of the homologation products (**3** and **4**) furnishes with high enantiomeric excess, the N-t-BOC, and free α-amino acid derivatives **5** and **6**, respectively.

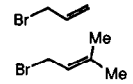
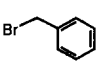
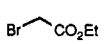
Numerous new and useful approaches to the asymmetric synthesis of α-amino acids have appeared in recent years.[1] Notable amongst these are several chiral, non-racemic glycine enolate equivalents[2] and glycine cation equivalents.[3] The attractiveness of these asymmetric glycine equivalents is the inherent versatility in preparing a diverse array of amino acids from a few common precursors with the appropriate C-C bond-forming technology. Schöllkopf and collaborators[4] have shown that their extensively studied enolate-based bis-lactam ether templates can also serve as glycine cation equivalents.



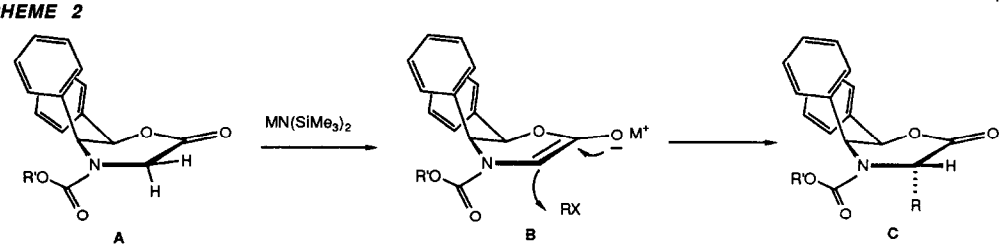
We have published[3] on the utility of the oxazinones **1** and **2** to function as versatile glycine cations *via* NBS bromination to the corresponding electrophilic α-bromo species. Numerous attempts at generating the enolate anions from **1** and **2** (LDA; THF; -100° ~-78°C; NaH; KOt-Bu; etc.) resulted in instantaneous decomposition and no detectable alkylation or deuteration products being isolable.[3] We have now found that the lithium or sodium salts of hexamethyldisilazane in THF at low temperature effects the clean deprotonation of these substrates without the significant decomposition that accompanied the other bases examined. The enolate anions derived from **1** and **2** can be stereoselectively alkylated with a high degree of diastereoselectivity (typically >99%) furnishing the crystalline *anti*-lactones **3** and **4** in good yield. As previously reported,[3] the N-t-BOC

SCHEME 1



ENTRY	LACTONE SUBSTRATE / YIELD 1	2	RX	AMINO ACID DERIVATIVE YIELD 5	6	%ee
1	91		MeI	54		97.2
2	48 (60)			50-70		98
3	68 (85)			52		100
4	70 (77)				76	98.2
5		61 (77)			71	95.9

SCHEME 2



substrates can be directly converted into the corresponding N-t-BOC amino acids (**5**) by dissolving metal reduction (Table, entries 1-3). In the case of dissolving metal-reducible functionality, hydrogenation over a Pd° catalyst directly provides the zwitterions (**6**, Table entries 4 and 5). In all cases, the % ee exceeded 95%.

It is worthwhile to compare the complementary cationic and anionic reactivities of the templates (**1**/**2**) for constructing variously substituted α-amino acids. The amino acids alanine and allyl glycine have been prepared from the electrophilic route by use of CH_3ZnCl and allyltrimethylsilane couplings, respectively. In both cases, the *anti*-oxazinones (**3**) are produced. The same relative stereochemical result is realized with CH_3I and allyl bromide (entries 1, 2) alkylation of the enolate derived from **1**. However, the yield of the CH_3I alkylation (91%) is far superior to the CH_3ZnCl coupling to the α-bromolactone (46%) due to a competing 1-electron reduction pathway observed for the more basic organometallic reagents. The allyl case is more or less equal for either approach. In the case of the bromoethyl acetate alkylation (entry 5) the *anti*-oxazinone (**4**) is obtained as the exclusive product. Amino acid[5] L-**6** was also obtained (in similar yield and % ee) by coupling the ketene silyl acetal of ethyl acetate to the electrophilic system (**7**) and reduction. However, a 45:1 ratio of *syn:anti* products results *via* an S_N2' displacement of the *anti*-α-bromide (**7**) derived from **2** in this coupling. Thus, *either* optical isomer of **6** can be obtained in high enantiomeric excess from the *same* optical antipode of **2** by simply choosing either electrophilic or nucleophilic chemistry. The enolate approach discussed herein, also gives access to the phenylalanine manifold (entry 4) which was not readily achieved from the electrophilic system.

The stereoselectivity of these enolate alkylations can be readily rationalized by considering the conformer **B** that disposes the phenyl ring in a 1,3-relation to the enolate carbon in a pseudoaxial orientation; the electrophile simply approaches from the less hindered face giving the observed *anti*-oxazinones. What is less strightforward, is the observed failure of bases such as LDA and the consistent success of either Li- or $NaN(SiMe_3)_2$ to effect *stable* enolate generation and subsequent alkylation. Several examples[6] of the success of hexamethyldisilazane bases over LDA have been reported, but in the context of cation effects. The underlying reasons for the anomaly in the present case are being investigated.

The present technology nicely complements the electrophilic couplings[3] and should substantially expand the intrinsic versatility of these commercially available templates for amino acid synthesis.

A typical procedure for enolate alkylation is as follows: To a stirred solution of **1** (500 mg, 1.4 mmol, 1.0 eq) in THF (10 mL) at -100°C was added $NaN(SiMe_3)_2$ (1.4 mmol, 1 eq as a 1M THF solution) dropwise. The mixture was stirred for 30 min. at -100°C and 1-bromo-3-methyl-2-butene (500 μL, 4.3 mmol, 3 eq) was added. The solution was stirred an additional 40 min. at -100°C, poured into H_2O and thoroughly extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated and separated by radial PTLC silica gel chromatography (CH_2Cl_2 eluent) to afford 405 mg (68% or 85% based on consumed **1**) of **3** (R = dimethallyl) mp 150-151°C (recryst. Et_2O/hexanes) and 98 mg (19.6%) of unreacted **1**.

^{1}H NMR (200 MHz) (DMSO - d_6, 398°K) δ TMS: 1.18 (9H, s); 1.68 (3H, s); 1.74 (3H, s); 2.73-3.01 (2H, m); 4.82 (1H, dd, J = 5.59 Hz, 5.64 Hz); 5.12 (1H, d, J = 2.75 Hz); 5.30 (1H, t, J = 7.62 Hz); 6.16 (1H, d, J = 3.11 Hz); 6.56 (2H, m); 7.01-7.28 (8H, m). $[\alpha]_D^{25}$ = -19.5° (C = 5.7, CH_2Cl_2). Anal. calcd for $C_{26}H_{31}NO_4$: C, 74.11; H, 7.36; N, 3.33. Found: C, 74.24; H, 7.32; N. 3.28. IR (KBr pellet): 1734, 1692 cm^{-1}.

General experimental conditions for dissolving metal reduction to the corresponding N-t-BOC derivative **5** are provided in ref. 3.

Acknowledgement. We thank the National Science Foundation (CHE-8412055). We also wish to thank Prof. Dave Evans for helpful discussions and communicating their results on enolate alkylations of a related oxazinone prior to publication.

† Fellow of the Alfred P. Sloan Foundation (1986-88). NIH Research Career Development Awardee (1984-89). Eli Lilly Grantee (1986-88).

References and Footnotes

1. For reviews, see: (a) Barrett,G.C., Ed.; *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London 1985. (b) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816. (c) Greenstein, J.P.; Winitz, M. *Chemistry of the Amino Acids*; Robert E. Krieger: FL, 1984; Vols. 1-3.
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(Received in USA 26 April 1988)