Tetrahedron Letters, Vol. 34, No. 43, pp. 6859-6862, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Amination with N-Benzyloxycarbonyl-3-Phenyloxaziridine as a Route to Sensitive Chiral α-Hydrazino Acids: Synthesis of L-Hydrazino Serine[1]

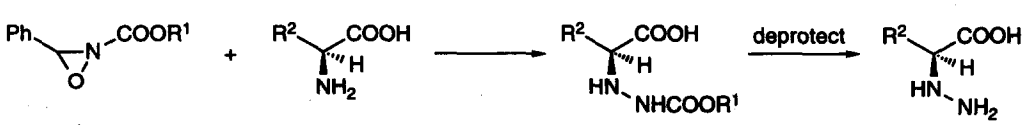
Daniel A. Niederer, James T. Kapron, and John C. Vederas*

Department of Chemistry, University of Alberta
Edmonton, Alberta, Canada T6G 2G2

Abstract: N-Cbz-3-phenyloxaziridine can be generated in a two step process. This is a new reagent for direct electrophilic N-amination of chiral α-amino acids and their derivatives which affords the corresponding hydrazino acids protected with a readily removable N-Cbz group. Application of this methodology to a facile synthesis of L-hydrazino serine, a potentially useful biological tool, is described.

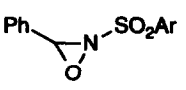
Chiral α-hydrazino acids inhibit a variety of enzymes which metabolize the corresponding α-amino acids,[2] and peptide analogues containing them are often metabolically more stable in mammalian systems.[3] Our group[4] as well as others[5] have developed methods for synthesis of α-hydrazino acids based on electrophilic C-amination of chiral enolates with dialkyl azodicarboxylates. A very attractive alternative approach involving N-amination of the optically pure α-amino acids (as their salts or esters) with N-methoxycarbonyl-3-phenyloxaziridine (**1**) was recently reported by Collet and coworkers.[6,7] In contrast to N-arylsulfonyl-3-phenyloxaziridines **2**, which donate oxygen to nucleophiles,[8] the N-acyl reagent **1** transfers the nitrogen with its N-methoxycarbonyl group (Scheme 1). Unfortunately, the utility of this reagent is limited by the vigorous conditions[9] necessary to remove the N-methoxycarbonyl group from the product, which precludes its use for production of sensitive compounds. Since L-serine occupies a central role in metabolism as a one carbon donor as well as a precursor of other amino

Scheme 1



1 $R^1 = Me$

3 $R^1 = CH_2Ph$



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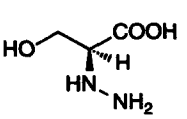
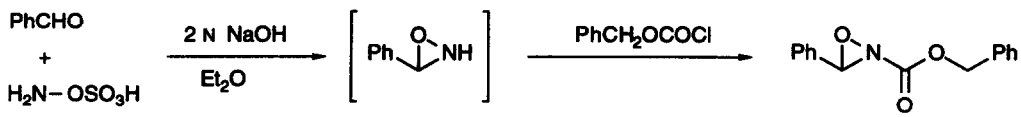


4

acids,[10] it appeared that the previously unreported[11] L-hydrazino serine (**4**) could be a useful inhibitor and biological tool. The present study describes facile production of N-benzyloxycarbonyl(Cbz)-3-phenyloxaziridine (**3**), a reagent for N-amination of α-amino acids, and its use in synthesis of **4**.

Compound **1** is readily prepared by the literature procedure,[6] which involves condensation of benzaldehyde with LHMDS, followed by N-acylation with methyl chloroformate and oxone™ oxidation. However, neither **3** nor other N-acyl oxaziridines with readily removable groups (e.g. *tert*-butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, or 2-(trimethylsilyl)ethoxycarbonyl) could be produced in useful amounts by this method. Oxidation of the intermediate N-acylimines proceeded poorly with a variety of reagents and produced varying amounts of the corresponding N-acyl benzamide as a major product (e.g. 70 % with oxone,™ pyridine, CH_2Cl_2 and N-Cbz-benzaldimine). An older alternative approach developed by Schmitz *et al.* generates 3-phenyloxaziridine by reaction of benzaldehyde with hydroxylamine-O-sulfonic acid (25 % yield).[12] Direct *in situ* acylation (50 % yield) with benzyl chloroformate affords **3**.[13] Although the overall yield of this process is low, the oxaziridine **3** is easily accessible in reasonable amounts from commercially available starting materials.



3 (12 %)

Compound **3**, which exists as a 9:1 mixture of *trans* and *cis* isomers due to slow inversion at the nitrogen, is stable for at least several months at -20 °C under dry conditions.

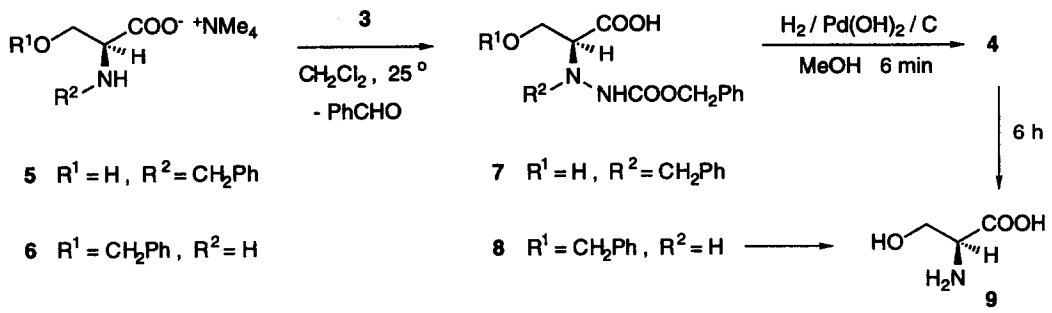
The electrophilic behavior of **3** resembles that of **1** in that it readily aminates a variety of primary and secondary amines, as well as both protected and unprotected α-amino acids, in reasonable yields (Table 1). The main advantage of using **3** instead of **1** is the ease of removal of the Cbz group by hydrogenolysis to produce the

Table 1. Electrophilic Aminations with Oxaziridine **3** and Hydrogenolysis of Cbz Group (Deprotection).

Nucleophile Y:	Yield[a] of Y-NHCOOCH$_2$Ph	Deprotected Product and (Yield[a] of Y-NH$_2$)
N-Benzyl-L-serine (**5**)[b]	41 % (**7**)	**4** (81 %)
O-Benzyl-L-serine (**6**)[b]	55 % (**8**)	**9** (> 99 % of **9**)
L-Phenylalanine[b]	76 %	hydrazino-Phe[c,d] (67 %)
L-Tryptophan[e]	54 %	hydrazino-Trp[d,f] (39 %)
2-Phenylethylamine	63 %	N.D.[g]
Piperidine	90 %	N.D.

[a]Isolated yield of pure product with consistent spectral (α_D, IR, ^{1}H and ^{13}C NMR, MS) characteristics. [b]Amino acids were converted as their Me_4N^+ salts. [c]See ref. 2c. [d]Used Pd/C (5-10 %). [e]Used Et_4N^+ salt in $CHCl_3$ [f]See ref 17. [g]Deprotection not done.

Scheme 2



parent hydrazino compounds, which can bear sensitive functionality. Thus, treatment of the tetramethylammonium salt of either N-benzyl-L-serine (**5**)[14] or O-benzyl-L-serine (**6**) with **3** in methylene chloride gives the corresponding protected hydrazino derivatives **7** and **8** in 41 % and 55 % yield, respectively (Scheme 2). Rapid hydrogenation[15] of **7** with Pd catalyst removes both the Cbz and N-benzyl groups and gives the previously unreported L-hydrazino serine (**4**) in 81 % yield. Deprotections of the hydrazino analogues of L-phenylalanine and L-tryptophan proceed analogously (Table 1). In contrast, hydrogenolysis of **8** results in cleavage of both the O-benzyl group and the N-N bond to afford L-serine (**9**) and only trace amounts of **4**. The hydrazino analogue **4** could also be converted to L-serine (**9**) by prolonged hydrogenation. No racemization was detected during the amination-hydrogenolysis sequence.[16]

Oxaziridine **3** may also prove to be a useful aminating agent for enolates, and may thereby provide a route to α-amino acids. Further studies on electrophilic amination with **3** and related oxaziridines as well as on the biochemical properties of L-hydrazino serine (**4**) are in progress.

Acknowledgements

The authors are grateful to the Natural Sciences and Engineering Research Council of Canada, Merck Frosst Ltd., and the Swiss National Science Foundation for financial support.

References and Notes

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13. To a 4 °C solution of benzaldehyde (5.3 g, 50 mmol) in 50 mL Et_2O was added cold 2N NaOH (50 mL). Cold solutions of hydroxylamine-O-sulfonic acid (6.0 g, 50 mmol) in H_2O (50 mL) and 2N NaOH (25 mL) were added simultaneously with vigorous stirring. Immediately afterwards, benzyl chloroformate (9 g, 50 mmol) was added, and the mixture was stirred for 9 min below 10 °C. The phases were separated, the aqueous phase was extracted twice with 25 mL diethyl ether, and the combined organic phases were stirred at 0 °C for 10 min with hydroxylamine-O-sulfonic acid (2.5 g) in H_2O (25 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 x 25 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to give 10.3 g of an orange oil. This was separated twice by flash chromatography (100 g SiO_2; 40 x 210 mm; first pentane/CH_2Cl_2 1:1, then pentane/AcOEt 9:1) to give **3** (1.5 g, 12 %) as an oil which solidifies below 4 °C: R_f (SiO_2) pentane/ Et_2O/CH_2Cl_2 (8:1:1) 0.25 (**3**), 0.35 (benzaldehyde); IR (CCl_4) 3066, 3035, 1769, 1610, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ *trans* isomer (89 %) 7.48-7.24 (m, 10 H, ArH), 5.28 (d, J = 12 Hz, OC*H*HPh), 5.22 (d, J = 12 Hz, OCH*H*Ph), 5.08 (s, PhC*H*(O)N); *cis* isomer (11 %) 5.3 (s, PhC*H*(O)N), 4.92 (s, OCH_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ *trans* isomer 162.0, 134.2, 131.8, 131.0, 128.8, 128.6, 128.5, 128.4, 127.8, 78.1, 69.8; *cis* isomer: 159.6, 134.3, 130.7, 129.8, 129.6, 128.4, 128.1, 127.0, 126.9, 78.9, 69.1; EI-MS (70 eV) *m/z* 255.0889 (M^+, 0.13), 91.0551 (C_7H_7, 100).
14. N-Benzyl-L-serine (**5**) (244 mg, 1.25 mmol) was dissolved in a solution of $Me_4NOH{\cdot}5H_2O$ (230 mg, 1.27 mmol) in MeOH (3 mL) and then evaporated to dryness. The solid residue was dissolved in CH_2Cl_2 (5 mL), **3** (350 mg, 1.37 mmol) was added, and the mixture was stirred 4 h at 25 °C. The solvent was evaporated, H_2O (10 mL) was added, the pH was adjusted to 2 with 2N HCl, and the mixture was extracted with EtOAc (4 x 10 mL). The dried ($MgSO_4$) extract was evaporated to give a solid (408 mg) which was separated on a Merck Lobar™ RP-8 column (B) with H_2O/MeOH (4:6) to afford **7** (175 mg, 41 %) as a white powder: $[\alpha]_D$ = +22° (c 1.06,$CHCl_3$) IR (KBr) 3362, 3208, 3031, 1708 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.44-7.12 (m, 10 H, ArH), 5.02 (d, J = 11.2 Hz, OC*H*HPh), 4.95 (d, J = 11.2 Hz, OCH*H*Ph), 4.19 (d, J = 12.8 Hz, NC*H*HPh), 4.09 (d, J = 12.8 Hz, NCH*H*Ph), 3.84-3.62 (m, 3 H, $C_\alpha HCH_2OH$); ^{13}C NMR (100 MHz, CD_3OD) δ 173.4, 159.8, 138.2, 137.9, 130.5, 129.5, 129.2, 129.0, 128.6, 68.9, 67.8, 61.9, 61.2; CI-MS (NH_3) *m/z* 362 ($M{\cdot}NH_4^+$, 31.3), 345 (MH^+, 100).
15. A suspension of 36 mg $Pd(OH)_2/C$ in MeOH (2 mL) was presaturated with 1atm H_2 during 10 min. Then a solution of hydrazino derivative **7** (76 mg, 0.22 mmol) in MeOH (8 mL) was added. The mixture was hydrogenated until 90 % of the required amount of H_2 was consumed (6 min). After filtration of the mixture and evaporation of the solvent, the crude product was purified on a cellulose column (130 x 25 mm) with n-BuOH/H_2O/AcOH (4:2:1) to give pure L-hydrazinoserine (**4**) (21.5 mg , 81 %) as a white solid: R_f value (SiO_2) n-BuOH/H_2O/acetone/AcOH (35:23:35:7): 0.5 (**4**), 0.3 (L-serine); $[\alpha]_D$ = -20.4° (c 1.26, 6N HCl); IR 3600-2500 (br), 1733 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.0 (dd, J = 3.7, 12.4 Hz, CHC*H*HO), 3.9 (dd, J = 5.1, 12.4 Hz, CHCH*H*O), 3.75 (dd, J = 3.7, 5.1 Hz, C*H*CHHO); ^{13}C NMR (75 MHz, D_2O) δ 173.6, 65.8, 60.3; FAB-MS (pos., glycerol) 121.09 (M^+, 21 %).
16. The enantiomeric excess of serine can be analyzed by the Marfey procedure (Marfey, P. *Carlsberg Res. Commun.* **1984**, *49*, 591-596) which involves derivatization with N-(2,4-dinitro-5-fluorophenyl)-(*S*)-alaninamide and HPLC separation of the resulting diastereomers. The HPLC analysis employs a Waters™ radial compression reverse phase (RP18) column; flow 1.5 mL/min; 10 % MeCN/triethylammonium phosphate (TEAP) buffer (pH 3.0) linear gradient over 45 min to 50 % MeCN/TEAP buffer; UV detection at 340 nm; retention time for *SS* isomer 17.92 min, for *RS* isomer 18.89 min.
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(Received in USA 20 July 1993; accepted 18 August 1993)