Synthesis of α-Amino Acids by Reduction of α-Oximino Esters with Titanium(III) Chloride and Sodium Borohydride

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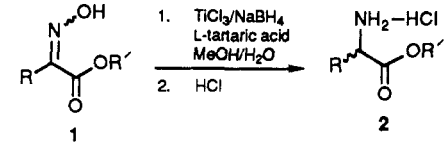
The synthesis of unnatural α-amino acids has been of great interest. Recently, a number of novel racemic and asymmetric approaches to the synthesis of amino acids have been reported.[1-9] α-Oximino acids are particularly useful precursors of α-amino acids. Reduction under a variety of conditions can produce either the corresponding α-*N*-hydroxy amino acid derivative or the parent amino acid itself.[10] Alternatively, *N*-hydroxy amino acids can be first prepared by treatment of the corresponding glyoxylic acid oxime with an alkyllithium reagent and then reduced to the amino acid.[11] Herein, we report that α-amino acids can be prepared directly by reduction of oximino esters with a buffered combination of titanium(III) and sodium borohydride.

Low-valent titanium has been used for a number of reductions. In organic solvents combination of titanium(III) and borohydrides reportedly reduces oximes quite efficiently, but other functional groups, including esters and carboxylic acids, are also reduced.[12] Aqueous solutions of titanium(III) have been used extensively for the reduction of N–O bonds, including those of hydroxamic acids and *N*-hydroxy-2-azetidinones,[13] heterocyclic *N*-oxides,[14] nitro compounds,[15,16] and oximes.[17] The distinct advantage of the use of aqueous solutions of titanium(III) is that the system can easily be buffered to alter the reduction potential and make it compatible with a number of other functional groups, including those which might be acid- or base-sensitive.[13] The fate of the imine produced from the reduction of oximes and nitro compounds depends on the reaction conditions. Usually in the absence of other reducing agents, the imine is simply hydrolyzed. In one instance, a sterically shielded erythromycin derived imine was stable enough to be isolated and reduced to the amine with sodium borohydride in a separate step. The actual combination of titanium(III) chloride and sodium cyanoborohydride in aqueous solution has recently been shown to be effective for the reduction of a sugar-derived oxime to the corresponding amino sugar.[18] That paper prompted our report on our reductions of α-oximino esters to amino acid esters.

Table I. Reduction of α-Oximino Esters



1 2

	R	R′	yield, %
a	Me	Me	73
b	Et	Et	63
c	tBu	Et	68
d	Ph	Me	82
e	$(CH_2)_2CO_2Me$	Me	64

α-Oximino esters are readily available and should be attractive precursors to amino acids. However, it was important to demonstrate that the planned titanium(III)–sodium borohydride reduction would be compatible with the generation of an amino acid ester. If the reduction were to proceed, conditions would need to be employed which would circumvent the tendancy of simple amino acid esters to form diketopiperazines. As shown by the data in Table I, the reaction of sodium borohydride and titanium(III) chloride with α-oximino esters under appropriately buffered aqueous conditions effectively produced the desired amino acid esters even when the unhindered methyl and ethyl esters were employed. The availability of a wide variety of α-keto esters,[19] and consequently, of the corresponding α-oximino esters should make this a useful route for the preparation of a number of unusual amino acids. Based on our previous studies of titanium-mediated reductions,[13] the process should also be compatible with a number of other functional groups.

Although the exact mechanism is unknown, it was thought that a titanium–sodium borohydride complex might be the actual reducing species, effecting loss of the hydroxyl group and concomitant imine reduction. In fact, other titanium–borohydride complexes have recently been characterized.[20] Thus, use of an asymmetric buffer was anticipated to allow formation of an asymmetric complex and perhaps induce asymmetry in the amino acid reduction products. Interestingly, use of the usual[13] acetate or phosphate buffer resulted in no color change of the characteristic dark blue titanium–borohydride mixture, but substitution of L-tartaric acid for the buffer resulted in immediate formation of a green solution. While the color change suggested the formation of an intermediate tartrate complex, the amino acids obtained from reduction of the oximes were all racemic. However, use of the tartrate buffer does facilitate the reaction workup since the apparently coordinated titanium salts remain soluble and the usual emulsion problems are avoided. We are presently

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testing other ligands in order to fully evaluate the potential for any enantiomeric selectivity under the above reaction conditions.

Experimental Section

General Comments. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were obtained in deuterium oxide with 3-(trimethylsilyl)propionic acid sodium salt as a reference on a Varian EM-390, a Chemagnetics A-200, or a General Electric GN-300 spectrometer. Chemical ionization mass spectra (CIMS) were recorded with isobutane by use of a Finnigan MAT Model 8430 spectrometer. Elemental analyses were determined by M-H-W Laboratories, Phoenix, AZ. Aqueous titanium(III) chloride solutions (13%, Fluka) were titrated with cerium(IV) sulfate.[21] Chiral high-pressure liquid chromatography was conducted on a Beckmann/Altex Model 332 chromatograph using a Pirkle covalent D-naphthylalanine column (25 cm, Regis Chemical Co.).[22] TLC was performed on aluminum-backed silica gel 60 F-24, 0.2-mm plates purchased from MCB Reagents. Solvents were dried and purified by standard methods.

α-Keto Esters. Ethyl 2-oxobutylate and ethyl 3,3-dimethyl-2-oxobutyrate were prepared by a literature procedure.[19]

Oximes. Ethyl 2-(hydroxyimino)butyrate and ethyl 2-(hydroxyimino)-3,3-dimethylbutyrate were prepared in 87% and 92% yield, respectively, from the α-keto esters and hydroxylamine hydrochloride. Dimethyl 2-(hydroxyimino)glutarate was prepared in quantitative yield from the corresponding diacid via addition of thionyl chloride to a methanolic solution at −78 °C. The 2-(hydroxyimino)glutaric acid was prepared from 2-oxoglutaric acid and hydroxylamine hydrochloride in 35% yield.

General Procedure for Oxime Reduction. To a solution of 9.24 g (61.6 mmol) of L-tartaric acid and 5.90 g (0.148 mol) of sodium hydroxide in 30 mL of water was added 7.0 mL (6.3 mmol) of 0.9 M aqueous titanium trichloride. The pH of the resulting green solution was adjusted to 7.0 (NaOH/HCl). To the mixture was added 210 mg (5.55 mmol) of solid sodium borohydride, followed quickly by 2.0 mmol of oxime in 5 mL of methanol. The mixture became lighter in color and was stirred for 20 min under nitrogen and then for 17 h in air. The pH of the final white mixture was exactly 7.0 and was adjusted to 8.5 with saturated aqueous dipotassium hydrogen phosphate. The mixture was extracted with dichloromethane (200 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to 10 mL. To the solution was added 3.0 mL of 1.0 M ethereal hydrogen chloride, and the mixture was concentrated in vacuo. The residual solid was rinsed with ether (2 × 10 mL), and residual ether was evaporated to afford the amine hydrochloride as a pale yellow solid. Recrystallization gave pure material as a white solid.

Methyl 2-aminopropionate hydrochloride (2a) (73%, ether/methanol): mp 105–110 °C; ^1H NMR (200 MHz, D_2O) δ 1.55 (d, J = 7, 3 H, CH_3), 3.84 (s, 3 H, CO_2Me), 4.20 (q, J = 7, 1 H, CHN); CIMS (relative intensity) m/e 104 (free amine + 1, 100).

Ethyl 2-aminobutyrate hydrochloride (2b) (63%, ether/ethanol): mp 136–138 °C; ^1H NMR (200 Hz, D_2O) δ 1.01 (t, J = 6, 3 H, CH_2CH_3), 1.30 (t, J = 6, 3 H, $CO_2CH_2CH_3$), 1.99 (m, 2 H, $CHCH_2$), 4.09 (t, J = 6, 1 H, $CHCH_2$), 4.32 (q, J = 6, 2 H, CO_2CH_2); CIMS (relative intensity) m/e 132 (free amine + 1, 100). Anal. Calcd for $C_6H_{14}ClNO_2$: C, 42.99; H, 8.42; N, 8.36. Found: C, 42.79; H, 8.32; N, 8.31.

Ethyl 2-amino-3,3-dimethylbutyrate hydrochloride (2c) (68%, ethyl acetate/hexane): mp 108–110 °C; ^1H NMR (200 MHz, D_2O) δ 1.09 (s, 9 H, tBu), 1.32 (t, J = 6, 3 H, CH_2CH_3), 3.80 (s, 1 H NCHCO$_2$), 4.31 (q, J = 6, 2 H, CH_2CH_3); CIMS (relative intensity) m/e 160 (free amine + 1, 100). Anal. Calcd for $C_8H_{18}ClNO_2$: C, 49.10; H, 9.27; N, 7.16. Found: C, 48.79; H, 9.30; N, 7.14.

Methyl 2-amino-2-phenylacetate hydrochloride (2d) (82%, ether/methanol): mp 197–199 °C; ^1H NMR (200 MHz D_2O) δ 3.85 (s, 3 H, CO_2CH_3), 5.30 (s, 1 H, NCHCO$_2$), 7.50 (m, 5 H, Ph); CIMS (relative intensity) m/e 166 (free amine + 1, 100).

Dimethyl glutamate hydrochloride (2e) (64%, ether/methanol): mp 148–150 °C; ^1H NMR (300 MHz, D_2O) δ 2.10–2.30 (m, 2 H, CH_2CHN), 2.40–280 (m, 2 H, CH_2CO_2), 3.65 (s, 3 H, CO_2CH_3), 3.80 (s, 3 H, NCHCO$_2CH_3$), 4.20 (t, J = 6, 1 H, NCHCO$_2$); CIMS (relative intensity) m/e 176 (free amine + 1, 100).

Derivatives. To further characterize the above amines and in order to determine accurately the percent ee, if any, the 3,5-dinitrobenzoyl derivatives were prepared and analyzed by chiral HPLC.[23] However, no enantiomeric excess was found.

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Registry No. **1a**, 5634-53-7; **1b**, 5339-83-3; **1c**, 120927-14-2; **1d**, 24607-22-5; **1e**, 120927-15-3; **2a**, 13515-97-4; **2b**, 55410-21-4; **2c**, 120927-16-4; **2d**, 15028-40-7; **2e**, 13515-99-6; $H_3CCH_2COCOOEt$, 15933-07-0; $(H_3C)_3CCOCOOEt$, 5333-74-4; NON=C(COOH)CH_2CH_2COOH, 2211-15-6; $HOOCCOCH_2CH_2COOH$, 328-50-7; $NaBH_4$, 16940-66-2; $TiCl_3$, 7705-07-9.

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Reaction of 1,*exo*-5-Dimethyl-3-oxo-*exo*-6-carbomethoxytricyclo[5.2.1.0^{2,6}]dec-8-ene with Ethanedithiol in the Presence of Boron Trifluoride Etherate. A Novel Fragmentation Process

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Introduction

Substituted *endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-ones are of intense current interest as intermediates in the synthesis of polyquinane natural products.[1-4] In this connection,[3,4] reaction of the title compound, **1**, with ethanedithiol in the presence of boron trifluoride etherate catalyst has been investigated. Although this reaction was intended simply to convert the ketone functionality in **1** into the corresponding dithioethylene ketal, it readily became apparent that the reaction had taken a different course. Detailed analysis of the proton and carbon-13 NMR spectra of the reaction product indicates that this material possesses the structure **2** shown in Scheme I.

Results and Discussion

The reaction of **1** with ethanedithiol–$F_3B{\cdot}OEt_2$, performed in methylene chloride solution at −78 °C, afforded **2** (80% yield) as a viscous oil. A control experiment established that no reaction occurred when **1** was mixed with $F_3B{\cdot}OEt_2$ under these conditions in the absence of ethanedithiol.

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