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THE BISMUTH (III) CHLORIDE MEDIATED *N*-DERIVATIZATION OF *L*-PROLINE AND PIPECOLINIC ESTERS IN AQUEOUS MEDIA

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ABSTRACT. An efficient method for the *N*-derivatization, in aqueous media, of *L*-proline and pipecolinic esters is reported, using benzotriazole as a synthetic auxiliary.

Our laboratory recently reported the bismuth (III) chloride/aluminum promoted alkylation of immonium cations, derived from 1-(aminoalkyl)benzotriazoles, to amines in aqueous media.[1,2] We have now extended and developed this methodology to include the *N*-derivatization of the protected optically pure α-amino acid, *L*-proline benzyl ester **1**, and of the ethyl ester of pipecolinic acid.

N-Substituted α-amino acids are important due to their use in the preparation and conformational studies of peptide analogs;[3] some *N*-alkyl α-amino acids also display considerable inherent biological activity.[4-7] Indeed, as reported by others,

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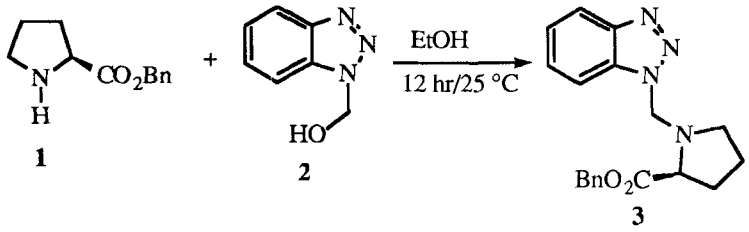
the synthesis of many proline derivatives has been undertaken over recent years to study a wide variety of problems in peptide chemistry and drug design.[8]

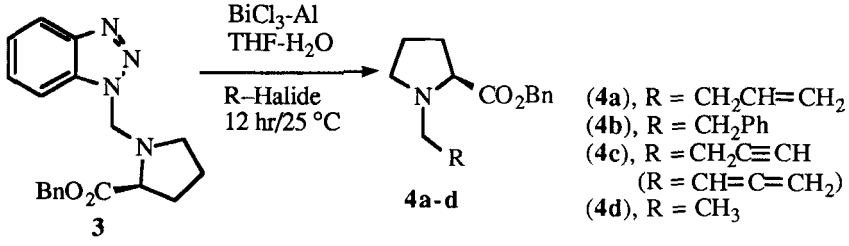
In this communication we report a procedure in which *L*-proline benzyl ester is first converted to its *N*-(benzotriazol-1-yl) adduct, followed by derivatization in aqueous solution mediated by a bismuth (III) chloride-aluminum system. Such C–C bond forming processes involving unstabilized carbanions in aqueous media are extremely rare, but are useful in cases where the substrate may be sensitive to commonly used organometallic reagents such as Grignard reagents, for example if the substrate contains an acidic hydrogen atom; or if the substrate is poorly soluble in organic solvents but readily soluble in aqueous solutions. In the latter case, the use of many organometallic systems would be impractical since strictly anhydrous conditions are usually necessary due to the moisture sensitivity of the reagents.



Scheme 1

We have chosen to examine the derivatization of *L*-proline benzyl ester **1**, commercially available as its hydrochloride salt, or readily synthesized in optically pure form from *L*-proline.[9] Compound **1** was efficiently converted to *N*-(benzotriazol-1-ylmethyl)proline benzyl ester **3** by simply stirring the free amino acid ester with an equimolar quantity of 1-(hydroxymethyl)benzotriazole **2** in ethanol for 12 hr at room temperature (Scheme 1). Evaporation of the solvent under reduced pressure yielded the crude product which was sufficiently pure by ^{1}H

NMR spectroscopy to be used directly in subsequent steps without further treatment. 300 MHz ^{1}H NMR spectroscopy also revealed that **3** existed in chloroform solution as an isomeric mixture of 1- and 2-substituted benzotriazoles in a ratio of 3 : 1 respectively, as expected.[10–12] Compound **3** was subjected to alkylation by the bismuth system developed by Wada (Scheme 2).[13] This procedure utilizes bismuth (III) chloride-aluminum in THF-water at room temperature.[2] The results for the general reaction shown in Scheme 2 are summarized in Table 1. Products **4a-d** were determined to be ≥98% enantiomerically pure by 300 MHz ^{1}H NMR spectroscopy using tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato], europium (III) derivative as chiral shift reagent.



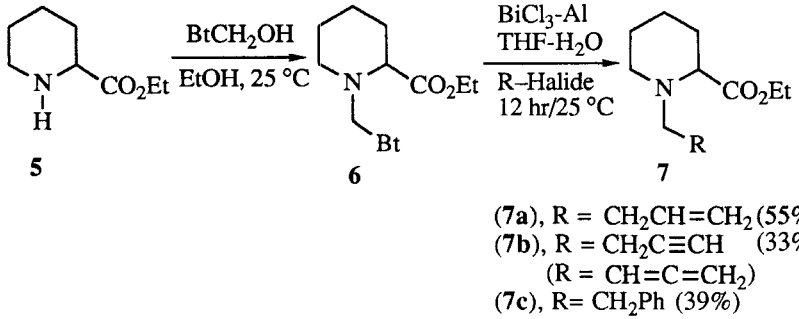
Scheme 2

As described above, benzotriazole derivatives such as **3** are expected to dissociate to the corresponding iminium species readily in solution[10–12] and interestingly a titanium (0) induced allylation of imines has previously been reported by other researchers.[14]

Table 1. *N*-Derivatization of 3 Using $BiCl_3$-Al in THF-Water

R–Halide	Product (**4a-d**)	Yield (%)
allyl bromide	**4a**	70
benzyl bromide	**4b**	65
propargyl bromide	**4c**[15]	52
methyl iodide	**4d**	18[17]

Our methodology was further extended to include the *N*-derivatization of racemic pipecolinic acid ethyl ester **5**. The benzotriazole derivative **6** was readily synthesized as described above and was also found to exist as an isomeric mixture of 1- and 2-substituted benzotriazoles (2.5 : 1 respectively) in choroform solution. Compound **6** was subjected to alkylation with allyl, propargyl and benzyl bromides (Scheme 3). Lower product yields were observed on alkylation of **6** than with the corresponding proline derivative **3**. We believe that this may be due to an increase in steric crowding of the reactive site in **6** by the ethyl ester moiety caused by the inherent decrease in ring strain on moving from the five membered to the six membered heterocyclic series. Product **7b** was formed along with its allenic isomer as an inseparable mixture (1:1.5 respectively).



Scheme 3

In conclusion, we report an efficient method for the *N*-derivatization of two cyclic α-amino acid derivatives in aqueous solution using benzotriazole as a synthetic auxiliary. The introduction of multiple bond functionality provides an interesting handle for further synthetic transformations of this interesting class of compound.

Experimental Section.

Melting points were determined on a Thomas Hoover Capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian VXR 300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument. Chemical shifts (δ) are reported in parts per million downfield of tetramethylsilane (TMS) as internal standard. Coupling constants (J values) are reported in Hertz (Hz). Elemental analyses and high resolution mass spectra were performed on site at the analytical facility.

Benzotriazole was purchased from Fischer and used as supplied. *L*-Proline benzyl ester, pipecolinic acid ethyl ester, bismuth (III) chloride and aluminum powder were purchased from Aldrich and used as supplied.

Thin layer chromatography was performed on pre-coated silica gel F254 plates which were developed using ethyl acetate/hexanes solutions and visualized with UV light and iodine.

***N*-[(Benzotriazolyl)methyl]-*L*-proline benzyl ester 3.**

1-(Hydroxymethyl)benzotriazole (0.52 g, 3.49 mmol) was dissolved in 5 ml ethanol and stirred overnight at room temperature with *L*-proline benzyl ester (0.72 g, 3.51 mmol). Removal of the solvent under reduced pressure gave the title compound as a yellow oil in quantitative yield. ^{1}H NMR spectroscopy revealed that **3** existed in chloroform solution as a 2.2:1 mixture of the 1- and 2-substituted benzotriazole isomers respectively. Purification was unnecessary and the product was used directly in further steps. ^{1}H NMR for major (Bt-1) isomer (300 MHz, $CDCl_3$): δ = 1.56-1.74 (1H, m), 1.74-1.94 (1H, m), 1.94-2.06 (2H, m), 2.78 (1H, q, J = 8.73), 3.20-3.28 (1H, m), 3.57 (1H, dd, J = 7.8, 7.8), 5.22 (2H, m), 5.65 (1H, d, J = 13.98), 5.74 (1H, d, J = 14.01), 7.32-7.42 (7H, m), 7.53 (1H,

d, J = 7.38), 8.05 (1H, d, J = 7.26). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.27, 29.42, 51.02, 60.78, 63.46, 66.69, 109.63, 118.25, 119.74, 123.85, 127.54, 128.29 (2C), 128.50 (2C), 133.95, 135.63, 145.57, 173.15. $C_{19}H_{20}N_4O_2$ requires: C, 67.84; H, 5.99; N, 16.66. Found: C, 67.48; H, 6.01; N, 16.76. High resolution MS (CI, CH_4): $C_{19}H_{19}N_4O_2$ (M^+ - H) requires: 335.1508. Found: 335.1508.

***N*-[(Benzotriazolyl)methyl]-pipecolinic acid ethyl ester 6.**

1-(Hydroxymethyl)benzotriazole (1.24 g, 8.38 mmol) was dissolved in 5 ml ethanol and stirred overnight at room temperature with an equimolar amount of pipecolinic acid ethyl ester (1.31 ml, 8.38 mmol). Removal of the solvent under reduced pressure gave the title compound as a white crystalline solid in quantitative yield. ^1H NMR spectroscopy revealed that **6** existed in chloroform solution as a 2.5:1 mixture of the 1- and 2-substituted benzotriazole isomers respectively. Purification was unnecessary and the product was used directly in further steps. M.p. 72-74°C (Et_2O). ^1H NMR for major (Bt-1) isomer (300 MHz, $CDCl_3$): δ = 1.29 (3H, t, J = 7.1) 1.40-1.70 (4H, m), 1.70-1.90 (2H, m), 2.48-2.60 (1H, m), 3.05-3.22 (1H, m), 3.34 (1H, dd, J = 10, 10), 4.10-4.30 (2H, m), 5.49 (1H, d, J = 13.7), 5.66 (1H, d, J = 13.7), 7.38 (1H, t, J = 8), 7.49 (1H, t, J = 8), 7.66 (1H, d, J = 8), 8.06 (1H, d, J = 7.26). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.15, 21.99, 25.03, 29.54, 49.23, 60.77, 60.86, 67.80, 110.19, 119.76, 123.78, 127.26, 133.59, 145.96, 172.96. $C_{15}H_{20}N_4O_2$ requires: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.36; H, 7.05; N, 19.61. High resolution MS (FAB): $C_{15}H_{21}N_4O_2$ (M^+ + H) requires: 289.1664. Found: 289.1664.

General Procedure for the *N*-Derivatization of Compounds 3 and 6. *N*-(But-3-enyl)-*L*-proline benzyl ester 4a.

Water (0.50 ml) was cautiously added to an ice-cooled, stirred solution of bismuth (III) chloride (0.94 g, 2.98 mmol) and aluminum powder (0.16 g, 5.93 mmol) in 5 ml THF. After the exotherm had subsided, allyl bromide (0.26 ml, 3 mmol) was added dropwise *via* syringe and stirring continued for a further 10 min prior to addition of the benzotriazole derivative **3** (0.50 g, 1.49 mmol) as a solution in 2 ml THF. The reaction mixture was stirred at room temperature overnight. The inorganic precipitate was then removed by filtration and washed well with chloroform (3 x 10 ml). The chloroform washings were combined, washed with saturated aqueous sodium bicarbonate (10 ml) and water (10 ml), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to yield the title compound as a yellow oil. Flash column chromatography on silica gel using ethyl acetate:hexanes (15:85) as eluent furnished the desired product as a yellow oil (0.27 g, 70%). $[\alpha]_D^{20} = -55.34°$ (c = 2.53, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.74-2.00 (3H, m), 2.07-2.18 (1H, m), 2.22 (2H, q, J = 6.9), 2.29-2.51 (2H, m), 2.72-2.81 (1H, m), 3.16-3.26 (2H, m), 4.96-5.06 (2H, m), 5.17 (2H, s), 5.73-5.85 (1H, m), 7.30-7.40 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.19, 29.29, 33.14, 53.35, 54.23, 65.87, 66.25, 115.57, 128.18 (2C), 128.21 (2C), 128.50, 135.00, 136.44, 174.03. $C_{16}H_{21}NO_2$ requires: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.74; H, 8.25; N, 5.36. High resolution MS (FAB): $C_{16}H_{22}NO_2$ (M^+ + H) requires: 260.1650. Found: 260.1650.

N-(2-Phenyl)ethyl-*L*-proline benzyl ester 4b.

Treatment of **3** (0.32 g, 0.95 mmol) as described above with bismuth (III) chloride (0.60 g, 1.90 mmol), aluminum powder (0.10 g, 3.78 mmol), water (0.40 ml) and

benzyl bromide (0.22 ml, 1.88 mmol) gave the title compound as a yellow oil (0.19 g, 65%) after flash column chromatography on silica gel using ethyl acetate:hexanes (15:85) as eluent. $[\alpha]_D^{20} = -73.17°$ (c = 1.64, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.77-2.21 (4H, m), 2.40-2.52 (1H, q, J = 8.58), 2.60-2.72 (1H, m), 2.73-2.85 (2H, m), 2.86-3.02 (1H, m), 3.22-3.32 (2H, m), 5.16 (2H, m), 7.12-7.37 (10H, series m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.26, 29.26, 35.31, 53.39, 56.47, 65.75, 66.23, 125.93 (2C), 128.24 (4C), 128.56 (4C), 135.95, 140.10, 173.91. $C_{20}H_{23}NO_2$ requires: C, 77.64; H, 7.49; N, 4.33. Found: C, 77.37; H, 7.54; N, 4.33. High resolution MS (FAB): $C_{20}H_{24}NO_2$ (M^+ + H) requires: 310.1807. Found: 310.1807.

***N*-(But-3-ynyl)-*L*-proline benzyl ester 4c.**

Treatment of **3** (0.42 g, 1.25 mmol) as described above with bismuth (III) chloride (0.79 g, 2.50 mmol), aluminum powder (0.14 g, 5.20 mmol), water (0.50 ml) and propargyl bromide (0.28 ml, 3.14 mmol) gave the title compound after flash column chromatography on silica gel using ethyl acetate:hexanes (15:85) as eluent, as a yellow oil (0.16 g, 52%) which was found to be an inseparable 1:1 mixture of **4c** and its allenic isomer, *N*-(2,3-butadienyl)-*L*-proline benzyl ester. Analytical samples of the alkyne and allene were obtained by preparative scale gas chromatography. For alkyne, **4c**: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.75-2.02 (4H, m), 2.04-2.19 (1H, m), 2.34-2.52 (3H, m), 2.62-2.72 (1H, m), 2.80-2.98 (1H, m), 3.14-3.24 (1H, m), 3.28-3.34 (1H, dd, J = 9, 9), 5.13-5.23 (2H, m), 7.30-7.40 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.54, 23.29, 29.33, 53.29, 65.52, 66.38, 69.02, 82.60, 128.22 (2C), 128.57 (2C), 135.91, 173.86 (4° alkyne signal and 4° aromatic signal not observed). For allenic isomer, *N*-(2,3-butadienyl)-*L*-proline benzyl ester: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.72-2.02

(1H, m), 2.06-2.22 (3H, m), 2.49 (1H, q, J = 8.9), 3.14-3.38 (4H, m), 4.65 (2H, dt, J = 2.4, 2.3), 5.15-5.25 (3H, m), 7.35 (5H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.27, 29.64, 52.90, 53.15, 64.50, 66.35, 74.90, 86.81, 128.22 (2C), 128.55 (2C), 136.00, 174.02, 209.36 (4° aromatic signal not observed). IR (neat mixture): ν (cm^{-1}) 3305 (CC alkyne), 2152 (CC alkyne), 1960 (C=C allene), 1769 (C=O). $C_{16}H_{19}NO_2$ (mixture) requires: C, 74.62; H, 7.44; N, 5.44. Found: C, 74.35; H, 7.45; N, 5.41. High resolution MS (FAB): $C_{16}H_{20}NO_2$ (M^+ + H) requires: 258.1494. Found: 258.1494.

_N_-(Ethyl)-_L_-proline benzyl ester 4d.

Treatment of **3** (0.40 g, 1.19 mmol) as described above with bismuth (III) chloride (0.75 g, 2.38 mmol), aluminum powder (0.13 g, 4.75 mmol), water (0.50 ml) and methyl iodide (0.15 ml, 2.37 mmol) gave the title compound as a yellow oil (0.049 g, 18%) after flash column chromatography on silica gel using ethyl acetate:hexanes (10:90) as eluent. $[\alpha]_D^{20}$ = –114.25° (c = 0.35, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (3H, t, J = 7.65), 1.73-2.02 (3H, m), 2.04-2.19 (1H, m), 2.31 (1H, q, J = 8), 2.39-2.50 (1H, dq, J = 7, 7), 2.69-2.82 (1H, dq, J = 7, 7), 3.15-3.24 (2H, m), 5.18 (2H, s), 7.30-7.40 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.63, 23.08, 29.37, 40.68, 53.04, 65.71, 66.20, 128.14 (2C), 128.47 (2C), 136.00, 174.00, (4° aromatic signal not observed). $C_{14}H_{19}NO_2$ requires: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.42; H, 8.37; N, 5.85. High resolution MS (FAB): $C_{14}H_{20}NO_2$ (M^+ + H) requires: 234.1494. Found: 234.1494.

_N_-(But-3-enyl)pipecolinic acid ethyl ester 7a.

Treatment of **6** (0.40 g, 1.38 mmol) as described above with bismuth (III) chloride (0.88 g, 2.79 mmol), aluminum powder (0.15 g, 5.56 mmol), water (0.50 ml) and

allyl bromide (0.24 ml, 2.77 mmol) gave the title compound as a yellow oil (0.16 g, 55%) after flash column chromatography on silica gel using ethyl acetate:hexanes (20:80) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (3H, t, J = 7.1), 1.30-1.42 (1H, m), 1.58-1.88 (5H, m), 2.14-2.42 (4H, m), 2.56-2.66 (1H, m), 3.03-3.12 (2H, m), 4.40 (2H, q, J = 6.8), 4.95-5.05 (2H, m), 5.70-5.85 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.26, 22.65, 25.25, 29.61, 31.05, 50.57, 55.86, 60.31, 65.18, 115.27, 136.50, 173.72. $C_{12}H_{21}NO_2$ requires: C, 68.21; H, 10.02; N, 6.63. Found: C, 67.89; H, 9.94; N, 6.68. High resolution MS (FAB): $C_{12}H_{22}NO_2$ (M^+ + H) requires: 212.1650. Found: 212.1650.

***N*-(But-3-ynyl)pipecolinic acid ethyl ester 7b.**

Treatment of **6** (0.40 g, 1.38 mmol) as described above with bismuth (III) chloride (0.88 g, 2.79 mmol), aluminum powder (0.15 g, 5.56 mmol), water (0.50 ml) and propargyl bromide (0.31 ml, 3.48 mmol) gave the title compound, a yellow oil (0.095 g, 33%) after flash column chromatography on silica gel using ethyl acetate:hexanes (15:85) as eluent, as an inseparable 1:1.5 mixture of **7b** and its allenic isomer, *N*-(2,3-butadienyl)-pipecolinic acid ethyl ester, respectively. ^{1}H NMR of mixture (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.2), 1.28 (t, J = 7.2), 1.30-1.52 (m), 1.57-1.91 (series m), 2.22-2.33 (m), 2.35-2.42 (m), 2.54-2.64 (m, alkyne), 2.73-2.84 (m, alkyne), 3.00-3.17 (m), 3.22-3.31 (m), 4.20 (q, J = 7.2), 4.64-4.71 (dt, J = 2.1, 2.0, allene), 5.12-5.23 (dq, J = 11, 11). ^{13}C NMR of mixture (75 MHz, $CDCl_3$): δ = 14.28, 16.79, 22.46, 22.83, 25.23, 29.57, 29.77, 50.48, 50.74, 55.10, 60.45, 64.26, 64.60, 68.99, 74.53, 85.60, 126.56, 173.53, 209.58. High resolution MS (FAB): $C_{12}H_{20}NO_2$ (M^+ + H) requires: 210.1494. Found: 210.1494. IR (neat): ν (cm^{-1}) 3275 (CC alkyne), 2325 (CC alkyne), 1950 (C=C allene), 1725 (C=O).

_N_-(2-Phenyl)ethyl pipecolinic acid ethyl ester 7c.

Treatment of **6** (0.40 g, 1.38 mmol) as described above with bismuth (III) chloride (0.88 g, 2.79 mmol), aluminum powder (0.15 g, 5.56 mmol), water (0.50 ml) and benzyl bromide (0.33 ml, 2.77 mmol) gave the title compound as a yellow oil (0.14 g, 39%) after flash column chromatography on silica gel using ethyl acetate:hexanes (15:85) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (3H, t, J = 7), 1.32-1.42 (1H, m), 1.62-1.92 (5H, m), 2.25-2.35 (1H, m), 2.50-2.65 (1H, m), 2.74-2.88 (3H, m), 3.10-3.22 (2H, m), 4.20 (2H, dq, J = 7, 7), 7.15-7.40 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.34, 22.68, 25.34, 29.70, 33.25, 50.73, 58.48, 60.43, 65.13, 125.99, 128.37 (2C), 128.72 (2C), 140.37, 173.70. $C_{16}H_{23}NO_2$ requires: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.85; H, 8.84; N, 5.01. High resolution MS (FAB): $C_{16}H_{24}NO_2$ (M^+ + H) requires: 262.1807. Found: 262.1807.

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15. Product isolated as a 1:1 mixture of (**4c**) and its allenic isomer, inseparable by column chromatography.[16]

16. Analytical samples of both the desired alkyne and its allenic isomer were obtained by preparative scale gas chromatography.

17. Isolated yield quoted in Table 1; crude yield *ca.* 50% by 300 MHz ^{1}H NMR spectroscopy.

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