HETEROCYCLES, Vol. 60, No. 4, 2003, pp. 791 - 798
Received, 28th November, 2002, Accepted, 28th January, 2003, Published online, 4th February, 2003

SYNTHESIS OF CHIRAL 3,4-DISUBSTITUTED PYRROLES FROM L-AMINO ACIDS

Jocelyn A. Hover, Charles W. Bock, and Krishna L. Bhat*

Department of Chemistry and Biochemistry, School of Science and Health,
Philadelphia University, Philadelphia, PA 19144, USA
E-mail: BhatK@philau.edu

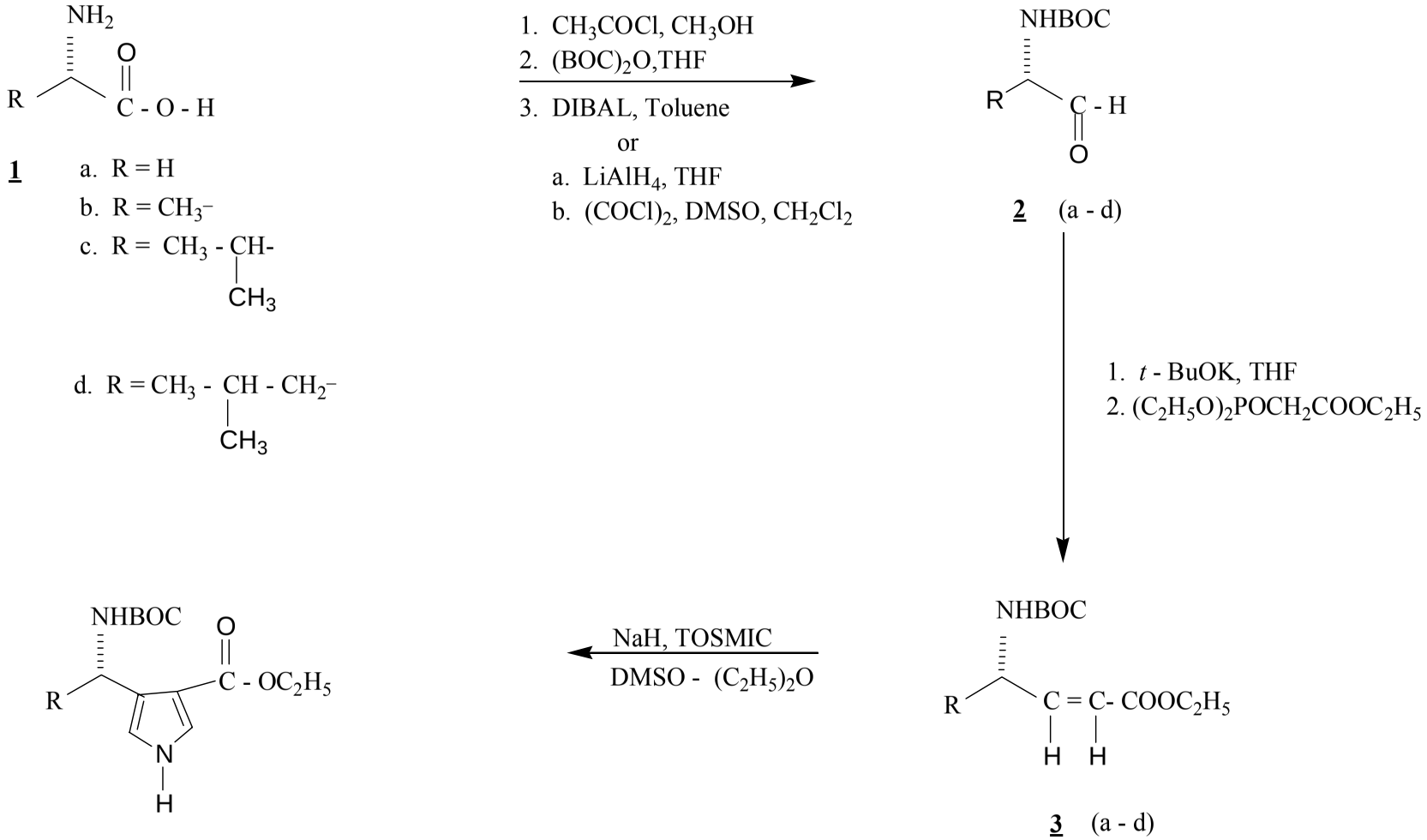
Abstract – A general methodology for the conversion of naturally occurring amino acids to 3,4-disubstituted pyrroles is described. A suitably protected amino acid (**1**) was first converted to the corresponding aldehyde (**2**). Horner-Emmons olefination afforded a facile entry to the corresponding α,β-unsaturated ester (**3**). The construction of the pyrrole ring system was accomplished *in a single step*, using an intramolecular cyclization reaction with tosylmethyl isocyanide (TOSMIC).

INTRODUCTION

Amino acids are one of the most important classes of compounds in the pool of chiral molecules and they have been a source for the preparation of natural products and complex biologically active compounds.[1] The pyrrole ring is an important heterocycle in biological systems being incorporated into the porphyrin ring systems of chlorophyll, heme, vitamin B_{12}, and the bile pigments. Additionally, there are a number of pyrrole-containing small molecules that exhibit useful biological activities.[2] As such, a lot of effort has been spent developing practical methods for the synthesis of pyrrole units that incorporate appropriate functionality.[3] Many of these procedures, however, are limited in terms of substituents and/or substitution patterns.[4] Recently,[5] we reported a facile entry to bicyclic systems from L-glutamic acid, involving the construction of the pyrrole ring *in a single step*, using tosylmethyl isocyanide (TOSMIC) methodology. This paper describes a general synthesis of 3,4-disubstituted chiral pyrroles from naturally occurring amino acids.

RESULTS AND DISCUSSION

Our synthetic reaction sequence is shown in Scheme 1. The carboxylic acid group in **1** was first converted to the corresponding methyl ester and the amine functional group was protected as the *tert*-butyloxycarbonyl derivative. Reduction of the ester functionality to the corresponding aldehydes (**2**) was


NH2
O
R
C - O - H
1. CH3COCl, CH3OH
2. (BOC)2O,THF
3. DIBAL, Toluene
or
a. LiAlH4, THF
b. (COCl)2, DMSO, CH2Cl2
NHBOC
R
C - H
O
1 a. R = H
b. R = CH3–
c. R = CH3 - CH-
CH3
d. R = CH3 - CH - CH2–
CH3
2 (a - d)
1. t - BuOK, THF
2. (C2H5O)2POCH2COOC2H5
NHBOC
R
C = C- COOC2H5
H H
3 (a - d)
NaH, TOSMIC
DMSO - (C2H5)2O
NHBOC
O
R
C - OC2H5
N
H
4 (a - d)

Scheme 1

achieved by using diisobutylaluminum hydride (DIBAL).[6] A somewhat less satisfactory route to the aldehydes (**2**) was the reduction of the ester group to the corresponding alcohols using lithium aluminum hydride in tetrahydrofuran and subsequent Swern oxidation using oxalyl chloride and activated dimethyl sulfoxide.[7] The reaction products in each step were characterized by spectral data (IR and NMR) and comparison with literature values wherever possible. Since α-amino aldehydes are not configurationally stable, they were prepared immediately prior to use.

Reaction of the aldehydes (**2**) with triethyl phosphonoacetate,[8] using potassium *tert*-butoxide as the base, afforded the corresponding α, β-unsaturated esters (**3**) in yields ranging from 91 to 95%; the physical properties of some of the derivatives were compared to reported values.[9] The crucial step in the synthesis is the construction of the pyrrole ring *in one step* using an intramolecular cyclization reaction with tosylmethyl isocyanide (TOSMIC). This methodology developed by Van Leusen *et al.*[10] and subsequently employed by us[5,10] and others,[11] involving the reaction of TOSMIC with Michael acceptors, offers a facile entry to substituted pyrroles. Thus, reaction of **3** with 3.6 equivalents of sodium hydride and 3 equivalents of TOSMIC generated the chiral heterocycles (**4**) in yields ranging from 77 to 98%. The physical properties for compounds (**3**) and (**4**) are listed in Table 1. No effort has been made to establish the stereochemical integrity of the final products or intermediates.

In conclusion, we have developed a simple and convenient preparative method for the synthesis of chiral heterocycles from readily available optically active starting materials *via* conventional transformations of functional groups. Since amino acids are relatively inexpensive and often available commercially in both enantiomeric forms, the approach we have described can easily be extended to the D-series of amino acids. Clearly, this methodology possesses considerable potential in the development of heterocyclic libraries for drug screening, especially in the search for new anti-inflammatory agents.[1]

EXPERIMENTAL

GENERAL METHODS

All reactions were carried out under a nitrogen atmosphere. Glassware was oven dried and cooled to rt under a nitrogen atmosphere. Ether and THF were distilled from sodium benzophenone ketyl. DMSO was distilled under reduced pressure and stored over 4A molecular sieves. ^{1}H NMR spectra were measured at 60 and 500 MHz using acetone-d_6 as solvent. TLC was performed on 0.25 mm precoated silica gel plates (60F-254); the plates were initially examined under UV light and spots were then visualized with iodine and a 7% solution of phosphomolybdic acid in ethanol. Silica gel (70-230 mesh)

was used for column chromatography. Specific rotations were recorded on a Perkin-Elmer Model 241 Polarimeter.

GENERAL PROCEDURE FOR PREPARATION OF ALDEHYDES [2 (a-d)]

Acetyl chloride (20 mL, 281mmol) was added drop wise to methanol (150 mL) over 8 min under nitrogen atmosphere. The solution was stirred for 5 min at rt and compound (**1**) (114 mmol) was added in one portion at rt. The reaction mixture was refluxed for 2 h. Solvent was removed *in vacuo* to yield the corresponding methyl esters. To a cooled solution of this methyl ester (64.3 mmol) in THF (200 mL), under nitrogen atmosphere, triethylamine (19.2 mL, 138 mmol) and di-*tert*-buyl dicarbonate (14.3 g, 363 mmol) in tetrahydrofuran (100 mL) were added over 1 h. The reaction mixture was stirred overnight at rt and at 50˚C for an additional 3 h. The solvent was removed *in vacuo* and the residue was extracted with ether. The ether layer was washed with saturated aqueous $NaHCO_3$ (250 mL). The aqueous phase was extracted with ether (3x150 mL) and the combined organic layers were dried over sodium sulfate and concentrated. The corresponding *tert*-butyloxycarbonylamino acid methyl esters were obtained in good to moderate yields usually as thick oils.

METHOD A

The solution of ester (37.5 mmol) in dry toluene (75 mL) under nitrogen atmosphere was cooled to -78˚C. A solution of DIBAL in toluene (43.75 mL, 1.5 M) was added at an adjustable rate in order to keep the internal temperature of the system below -65˚C (~1 h). The reaction mixture was stirred at -78˚C for 2 h and then quenched with methanol (15 mL). It was then allowed to come to rt and poured into aqueous hydrochloric acid solution (1 N, 250 mL). The aqueous layer was extracted with ethyl acetate (3x250 mL) and the combined organic layers were washed with brine (250 mL) and dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure yielded the aldehydes [**2** (a-d)] as yellowish oils.

METHOD B

The solution of ester (38.2 mmol) in THF (50 mL) was slowly added to lithium aluminum hydride (0.16 g, 57 mmol) in THF (100 mL) under nitrogen atmosphere. The suspension was stirred for an additional 20 min and then cooled to 0˚C. Aqueous potassium hydroxide (10%, 20 mL) was added drop-wise and the reaction mixture was stirred at rt for 1 h. The white precipitate formed was removed by filtration and washed with ether (3x30 mL). The combined organic layers were washed with a phosphate buffer (100 mL, pH=7), dried over sodium sulfate and concentrated under reduced pressure to afford the corresponding alcohols as yellow oils.

Table 1. Physical Data for Compounds in Scheme 1.

Compound	IR cm^{-1}	NMR δ	Elemental Analysis Found (Calculated) C	H	N	Specific Rotation $[\alpha]_D^{25}$
3						
a	1721, 1662	1.24 (3H, t, J=7 Hz), 1.92 (9H, s), 3.50 (2H, m), 4.30 (2H, q, J=7 Hz), 5.90 (1H, d, J=14 Hz), 6.60 (1H, m), 7.20 (1H, br s)	57.58 (57.63)	8.30 (8.35)	6.01 (6.11)	-
b	1724, 1657	1.10 (3H, d, J=7 Hz), 1.30 (3H, t, J=7 Hz), 1.46 (9H, s), 1.80-1.90 (1H, m), 4.28 (2H, q, J=7 Hz), 4.80 (1H, m), 5.95 (1H, d, J=8 Hz) 6.62 (1H, d, J=8 Hz),	59.31 (59.24)	8.62 (8.70)	5.70 (5.76)	-31.75° (c 1.03, CH_3OH)
c	1740, 1710	0.91 (3H, d, J=7 Hz), 0.95 (3H, d, J= 7Hz), 1.25 (3H, t, J=7 Hz), 1.42 (9H, s), 1.70-1.80 (1H, m), 4.20 (2H, q, J=7 Hz), 4.58 (1H, m), 5.87 (1H, dd, J=2 Hz, 15 Hz) 6.51 (1H, dd, J=6 Hz, 15 Hz)	61.86 (61.97)	9.34 (9.29)	5.12 (5.16)	-23.65° (c 1.81, $CHCl_3$)
d	1746, 1720	0.80 (6H, d, J=7 Hz), 1.20 (3H, t, J=7 Hz), 1.38 (9H, s), 1.50 (3H, m), 2.30 (1H, m), 4.20 (2H, q, J=7 Hz), 5.80 (1H, dd, J=6 Hz, 14 Hz), 6.40 (1H, dd, J=6 Hz, 14 Hz), 7.40 (1H, br s)	63.24 (63.13)	9.62 (9.54)	4.98 (4.91)	-36.72° (c 0.89, $CHCl_3$)
4						
a	1743, 1620	1.22 (3H, t, J=7 Hz), 1.90 (9H, s), 3.43 (2H, m), 4.25 (2H, q, J=7 Hz), 6.80 (2H, m), 7.30 (2H, br s)	58.10 (58.19)	7.43 (7.51)	10.37 (10.44)	-

b	1746, 1622	1.18 (3H, d, J=7 Hz), 1.28 (3H, t, J=7 Hz), 1.43 (9H, s), 1.85 (1H, m), 4.30 (2H, q, J=7 Hz), 6.80 (2H, m), 7.40 (2H, br s)	59.47 (59.56)	7.80 (7.85)	9.83 (9.92)	-38.78° (c 1.88, $CHCl_3$)
c	1741, 1635	0.95 (6H, d, J=7 Hz), 1.23 (3H, t, J=7 Hz), 1.42 (9H, s), 1.80 (1H, m), 4.24 (2H, q, J=7 Hz), 4.45 (1H, m), 6.75 (2H, m), 7.20 (1H, br s), 7.70 (1H, br s)	61.82 (61.91)	8.39 (8.44)	9.12 (9.03)	-31.69° (c 0.65, $CHCl_3$)
d	1733, 1597	0.85 (3H, d, J=7 Hz), 0.92 (3H, d, J=7 Hz), 1.20 (3H, t, J=7 Hz), 1.30 (9H, s), 1.40 (2H, m), 2.50 (2H, m), 4.20 (2H, q, J=7 Hz), 6.70 (2H, m), 7.42 (1H, br s), 7.80 (1H, m)	62.85 (62.94)	8.62 (8.70)	8.55 (8.63)	-26.25° (c 0.88, $CHCl_3$)

A flask charged with oxalyl chloride (6.58 g, 51.9 mmol) in methylene chloride (80 mL) was cooled to -78˚C under nitrogen atmosphere. DMSO (8.10 g, 103.71 mmol) in methylene chloride (10 mL) was then added over a period of 25 min. A solution of the alcohol (34.6 mmol) in methylene chloride (60 mL) was added to this reaction mixture. It was stirred at -45˚C for 30 min and quenched by adding *N,N*-diisopropylethylamine (36 mL, 200 mmol) in methylene chloride (5 mL). The solution was warmed to 0˚C and an aqueous solution of hydrochloric acid (1 M, 130 mL) was added. The mixture was extracted with methylene chloride (3x30 mL) and the organic layers were washed with a phosphate buffer (4x80 mL, pH=7), dried over sodium sulfate and concentrated to yield the corresponding aldehydes as thick oils.

GENERAL PROCEDURE FOR PREPARATION OF UNSATURATED ESTERS [3 (a-d)]

Potassium *tert*-butoxide (12 mL, 12 mmol, 1 M in THF) was added to solution of triethyl phosphonoacetate (2.69 g, 13.4 mmol) in THF (50 mL) at 0˚C. The mixture was stirred at rt for 1 h. Compound (**2**) (12 mmol) in THF (20 mL) was added to it at 5˚C and further stirred at rt for 2 h. The solvent was removed under reduced pressure and the residue was extracted with ether (2x100 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was then purified by column chromatography using hexane:ethyl acetate (9:1) as eluant to yield **3** as colorless oil.

GENERAL PROCEDURE FOR PREPARATION OF PYRROLES [4 (a-d)]

Pentane (15 mL) was added to sodium hydride (60% mineral oil, 0.660 g, 16.5 mmol). After stirring for 5 min at 0˚C, the pentane was decanted off. TOSMIC (2.685 g, 13.74 mmol) in dry ether (15 mL) and DMSO (7.5 mL) was added to the dry sodium hydride under a nitrogen atmosphere. Compound (**3**) (4.59 mmol) was then added to the mixture in dry ether (15 mL) and DMSO (7.5 mL) over a period of 15 min. The reaction mixture was stirred at rt for 2 h. The residue was extracted with ether (60 mL) and washed with water (60 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using hexane-ethyl acetate (7:3) as eluant.

REFERENCES

1. G. C. Barret, *Chemistry and Biochemistry of the Amino Acids*, Chapman and Hall, London, 1985; R. M. Williams, *Organic Chemistry Series Volume 7: Synthesis of Optically Active α-Amino Acids*, ed. by J. E. Baldwin and P. D. Magnus, Pergamon Press, Oxford, 1989; R. O. Duthaler, *Tetrahedron,* 1994, **50**, 1539; C. Cativiela, M. D. Diaz-de-Villegas, and J. A. Galvez, *Tetrahedron,* 1994, **50**, 9837; T. Lescrinier, R. Busson, J. Rozenski, G. Janssen, A. V. Aerschot, and P. Herdewijin, *Tetrahedron*, 1996, **52**, 6965.

2. K. Arima, H. Imanaka, M. Kousaka, A. Fukuta, and G. Tamura, *Agr. Biol. Chem.*, 1964, **28**, 575; H.

Nakeno, S. Umio, K. Kariyone, K. Tanaka, T. Kishimpto, H. Noguchi, I. Ueda, H. Nakamura, and Y. Morimoto, *Tetrahedron Lett*., 1966, 737; K. Unverferth, J. Engel, N. Hofgen, A. Rostock, R. Gunther, H. J. Lankau, M. Menzer, A. Rolfs, J. Liebscher, B. Muller, and H. J. Hofmann, *J. Med. Chem*., 1998, **41**, 63; G. Dannhardt, W. Kiefer, G. Kraemer, S. Maehrlein, U. Nowe, and B. Eur. Fiebich, *J. Med. Chem*., 2000, **35**, 499; R. Rango, G. R. Marshall, R. D. Santo, R. Costi, S. Massa, R. Rompei, and M. Artico, *Bioorg. Med. Chem*., 2000, **8**, 1423; M. Artico, R. D. Santo, R. Costi, S. Massa, and A. Metico, *J. Med. Chem*., 1995, **38**, 4223; P. Magnus, T. Gallagher, J. Schultz, Y. S. Or, and T. P. Ananthanarayan, *J. Am. Chem. Soc.,* 1987, **109**, 2706.

3. G. P. Bean, In *The Chemistry of Heterocyclic Compounds*, ed. by A. R. Jones, Wiley, New York, 1990, Vol. 48, Part 1, Chapter 2, p. 105; T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1,* 1998, 615; For the syntheses of 3-pyrrolines, see: V. Breuil-Desvergnes, P. Compain, J. M. Vatèle, and J. Goré, *Tetrahedron Lett*., 1999, **40**, 5009; K. Jayaprakash, C. S. Venkatachalam, and K. K. Balasubramanian, *Tetrahedron Lett*., 1999, **40**, 6493; F. R. Kinder, Jr., M. A. Jarosinski, and W. K. Anderson, *J. Org.Chem.,* 1991, **56**, 6475; A. Padwa and B. H. Norman, *Tetrahedron Lett*., 1988, **29**, 3041; W. K. Anderson and A. S. Milowsky, *J. Org. Chem*., 1985, **50**, 5423.

4. R. Karl Dieter and H. Yu, *Org. Lett*., 2001, **32**, 3855.

5. B. A. Frieman, C. W. Bock, and K. L. Bhat, *Heterocycles*, 2001, **55**, 2099.

6. S. Chandrasekhar, M. Suresh Kumer, and B. Muralidhar, *Tetrahedron Lett.*, 1998, **39**, 909; J. A. Marshall and S. Beaudoin, *J. Org. Chem*., 1996, **61**, 581.

7. Y. Hamada and T. Shioiri, *Tetrahedron Lett*., 1982, 1193; A. J. Manonso and D. Swern, *Synthesis*, 1981, 165.

8. W. V. Murray, S. Sun, I. J. Turchi, F. K. Brown, and A. D. Gauthier, *J. Org. Chem*., 1999, **64**, 5930. M. Van Leusen, H. Siderius, B. E. Hoogenboom, and D. Van Leusen, *Tetrahedron Lett*., 1972, 5337; D. Van Leusen, E. V. Echten, and A. M. Van Leusen, *J. Org. Chem*., 1992, **57**, 2245; H. P. Dijkstra, R. T. Have, and A. M. Van Leusen, *J. Org. Chem*., 1998, **63**, 5332.

9. M. N. Zimmerman, N. H. Nemeroff, C. W. Bock, and K. L. Bhat, *Heterocycles*, 2000, **53**, 205.

10. C. Y. De Leon and B. Ganem, *J. Org. Chem*., 1996, **61**, 8730; N. P. Pavri and M. L. Trudell, *J. Org. Chem*., 1997, **62**, 2649; T. J. Donohoe, P. M. Guyo, R. R. Harji, M. Helliwell, and R. P. C. Cousins, *Tetrahedron Lett*., 1998, **39**, 3075; A. R. Katritzky, D. Cheng, and R. P. Musgrave, *Heterocycles*, 1997, **44**, 67; R. Di Santo, R. Costi, S. Massa, and M. Artico, *Synth. Commun*., 1998, **28**, 1801; N. D. Smith, D. Huang, and N. D. P. Cosford, *Org. Letts*., 2002, **4**, 3537.

11. J. L. Bullington, J. C. Cameron, G. R. Heintzelman, D. E. Cavender, S. A. Wadsworth, G. C. Olini, B. Fahmy, J. H. Dodd, and J. J. Siekierka, 218th ACS National Meeting, New Orleans, LA, USA, Aug. 22-26, 1999, Abstract 429.