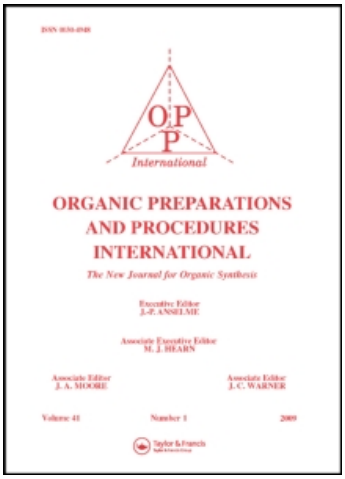

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF R,S-2-(3-BENZO[b]THIENYL)GLYCINE USING IMPROVED AMIDOALKYLATION METHODOLOGY

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To cite this Article Gardner, J. P. and Jackson, B. G.(1987) 'SYNTHESIS OF R,S-2-(3-BENZO[b]THIENYL)GLYCINE USING IMPROVED AMIDOALKYLATION METHODOLOGY', Organic Preparations and Procedures International, 19: 6, 439 — 442
To link to this Article: DOI: 10.1080/00304948709356206
URL: http://dx.doi.org/10.1080/00304948709356206

SYNTHESIS OF R,S-2-(3-BENZO[b]THIENYL)GLYCINE USING IMPROVED AMIDOALKYLATION METHODOLOGY

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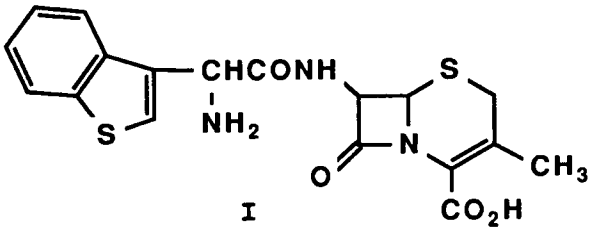
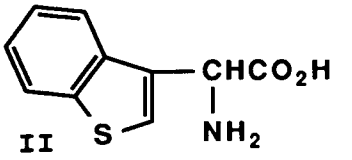
The cephalosporin antibiotic (I) resulting from acylation of 7-amino-deacetoxycephalosporanic acid with R-2-(3-benzo[b]thienyl)glycine (II) possesses desirable biological and pharmacological characteristics.[1] Synthesis of R,S-II using the methodology of Ben-Ishai et al.[2] has been reported by Huffman.[3] We now report a one-pot version of the amidoalkylation reaction. This preparation offers increased yield and a streamlined process for large scale reactions.

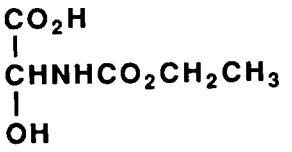


I

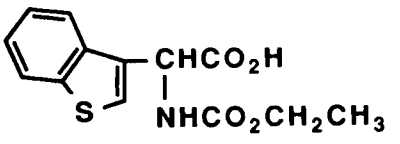


II

Ethyl carbamate was condensed with aqueous glyoxylic acid in refluxing acetic acid. The reaction mixture was concentrated to about one-half its volume by distillation at atmospheric pressure.[4] Treatment of the resulting solution of hydroxycarbamate III with benzo[b]thiopene and concentrated sulfuric acid afforded product IV in 75-82% yield.



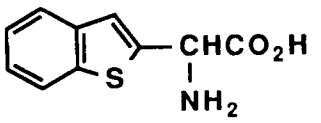
III



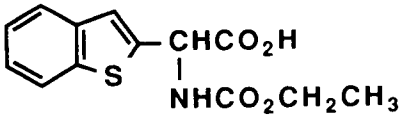
IV

Carbamate IV was examined by HPLC analysis and was found to contain

2% of the 2-substituted regioisomer VI. Authentic VI was prepared by acylation of the amino acid V[5] with ethyl chloroformate.



V



VI

Hydrolysis of IV with aqueous sodium hydroxide afforded R,S-II in 90-98% yield. Overall yield of R,S-II from benzo[b]thiophene was 80%.

EXPERIMENTAL SECTION

Melting points were determined on a Buchi melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 10-MX. Mass spectra were obtained on a Consolidated Electrodynamics Corporation 21-110 mass spectrometer operating at an ionizing voltage of 70eV and a source temperature of 220°C. The ^{1}H NMR spectra were recorded using a Varian T-60 instrument. Ultraviolet spectra were determined on a Cary 219 ultraviolet spectrophotometer. Elemental analyses were obtained using a Perkin-Elmer 240 Elemental Analyzer. HPLC analyses were determined using a system which consisted of a Waters M-45 pump, Waters C_{18} Radial-Pak column, Laboratory Data Control UVIII monitor, and a Linear recorder. The eluent was 50:50 MeOH:H_2O (2% dibutylammonium phosphate buffer) at a flow rate of 2.0 ml/min.

R-S-α-[(Ethoxycarbonyl)amino]benzo[b]thiopene-3-acetic acid (R,S-IV).- Glyoxylic acid (11.12 ml of a 50% solution in water, 100 mmol) was added at room temperature to a solution of ethyl carbamate (8.91 g, 100 mmol) in glacial acetic acid (60 ml). The solution was heated at reflux for two hours then distilled at atmospheric pressure to one-half its volume. The resultant solution was cooled to room temperature and fresh acetic acid (15 ml), concentrated sulfuric acid (12 ml), and benzo[b]thiopene (13.42 g, 100 mmol) were added sequentially while the temperature was maintained at 20-25°C. The reaction mixture was stirred for 21 hours at room temperature. Water (114 ml) was added dropwise to the resultant mixture and the product was collected to give 22.19 g (75%) which was recrystallized from ethyl acetate/hexane, mp. 159-160°C. IR ($CHCl_3$): 1721, 1505, 1428, 1058 cm^{-1}. UV (EtOH): λ_{max}(ε) 298 (3052), 289 (2883),

259 (5499), 227 (26,970)nm. ^{1}H NMR (DMSO-d_6): δ 8.3-7.4 (m,6H, aromatic and amide), 5.74 (d,1H, methine), 4.16 (q,2H, methylene of ester), 1.28 (t,3H, methyl of ester). MS: m/e 279 (M+), 261, 235, 161, 134.

Anal. Calcd. for $C_{13}H_{13}NO_4S$: C,55.90; H,4.69; N,5.01; S,11.48

Found: C,56.19; H,4.77; N,4.85; S,11.25

R,S-2-(3-Benzo[b]thienyl)glycine (R,S-II).- R,S-IV (17.78 g, 64 mmol) was added to a solution of sodium hydroxide (25.5 g, 640 mmol) in water (108 ml) and heated at reflux for one hour. The resulting solution was cooled to room temperature and the pH was adjusted to 11 by dropwise addition of concentrated hydrochloric acid (36 ml). The cloudy solution was filtered through Celite. The pH of the filtrate was adjusted to 7 by addition of concentrated hydrochloric acid (8 ml) causing precipitation of the product, 11.73 g (90%), mp. 200-202°C. IR (KBr): 1643, 1611, 1520, 1508, 1403, 1373, 1334 cm^{-1}. UV (EtOH): $\lambda_{max}(\varepsilon)$ 298 (3127), 289 (3076), 259 (6078), 228 (25,344)nm. ^{1}H NMR (DMSO-d_6 + DCl): δ 8.4-7.5 (m,5H, aromatic), 5.75 (s,1H, methine). MS: m/e 207 (M+), 162 (100), 135, 91.

Anal. Calcd. for $C_{10}H_9NO_2S$: C,57.95; H,4.38; N,6.76; S,15.47

Found: C,57.77; H,4.15; N,6.47; S,15.21

R,S-α-[(Ethoxycarbonyl)amino]benzo[b]thiophene-2-acetic acid (R,S-VI).- R,S-2-(2-benzo[b]thienyl)glycine (R,S-V) (5.00 g, 24 mmol) was added to a solution of water (66 ml) and acetone (20 ml). The pH was adjusted to 10.5 with a 45% solution of tribasic potassium phosphate (0.5 ml). The resulting solution was cooled to 5°C. Ethyl chloroformate (3.00 ml, 31 mmol) was added and the pH was maintained at 10.5 over 75 minutes by addition of tribasic potassium phosphate solution as needed. The resulting solution was warmed to 25°C and stirred an additional 75 minutes. Ethyl acetate (100 ml) was added and the pH of the two-phase mixture was adjusted to 2.0 with 15% sulfuric acid. The layers were separated and the ethyl acetate layer was washed with brine then dried (Na_2SO_4). Evapora-

tion of solvent under reduced pressure afforded a yellow solid which was recrystallized from acetic acid:water (1:1) to yield 3.92 g (58%). IR ($CHCl_3$): 1723, 1504, 1436, 1341, 1303, 1052 cm^{-1}. UV (EtOH): $\lambda_{max}(\varepsilon)$ 299 (2116), 289 (2272), 260 (9298), 228 (27,133)nm. ^1H NMR (DMSO-d_6): δ 8.3-7.3 (m,6H, aromatic and amide), 5.57 (d,1H, methine), 4.12 (q,2H, methylene of ester), 1.23 (t,3H, methyl of ester). MS: m/e 279 (M+), 261, 233, 206, 188, 160 (100), 135.

Anal. Calcd. for $C_{13}H_{13}NO_4S$: C,55.90; H,4.69; N,5.01

Found: C,56.20; H,4.48; N,4.91

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3. G. W. Huffman, U. S. Patent 4,458,085 (1984).

4. Omission of the concentration operation resulted in reduced yields of IV.

5. The authors thank Dr. Paul Pranc, Lilly Research Laboratories, for preparation of R,S-2-(2-benzo[b]thienyl)glycine (R,S-V).

REDUCTIVE DEHALOGENATION OF HALOACETOPHENONES WITH RANEY ALLOYS IN ALKALINE SOLUTION

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Halophenols and halobenzoic acids are reduced with Raney alloys in an