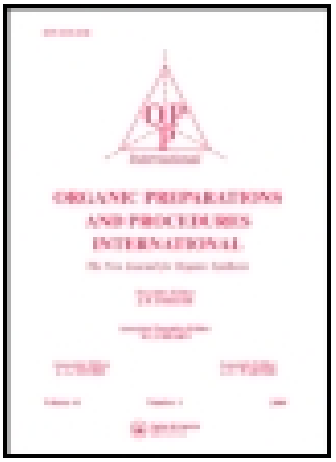

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SYNTHESIS OF N-PROTECTED 2-AMINOHEXANESULFONIC ACID

Violetta Constantinou-Kokotou [a]

[a] Chemical Laboratories , Agricultural University of Athens , Iera Odos 75, Athens, 11855, GREECE

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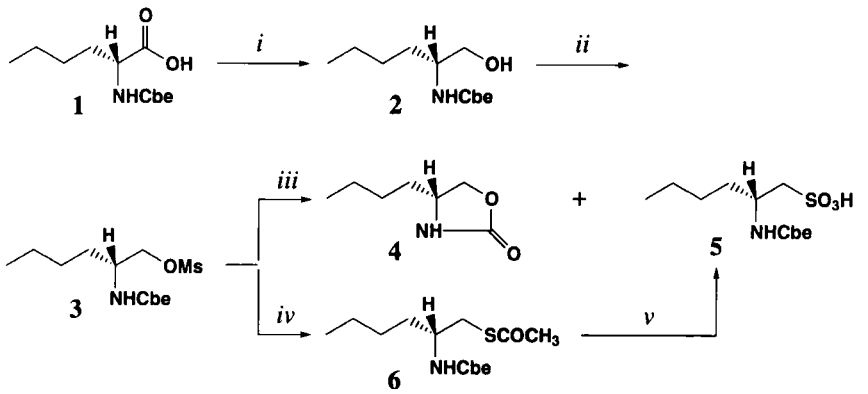
SYNTHESIS OF *N*-PROTECTED 2-AMINOHEXANESULFONIC ACID

Submitted by Violetta Constantinou-Kokotou
(10/13/98)

Chemical Laboratories, Agricultural University of Athens
Iera Odos 75, Athens 11855, GREECE

Taurine (2-aminoethanesulfonic acid) and cysteic acid (2-amino-3-sulfopropionic acid) are endogenous amino acids involved in various important physiological processes in mammals.[1] As a consequence taurine derivatives and analogs of taurine are of interest for biological studies. *N*-protected 2-amino alcohols, which are easily obtained from α-amino acids[2,3] have been used recently as starting materials for the synthesis of optically active compounds of interest, such as 1,2-diamines,[4,5] 1,3-diamines,[6] triamines.[7] In this paper the synthesis of 2-ethoxycarbonylaminohexanesulfonic acid (**5**) starting from the non-proteinogenic amino acid norleucine, is described.

(*R*)-*N*-Carbethoxynorleucine (**1**) was converted into the alcohol **2** by chemoselective reduction of its corresponding mixed anhydride with sodium borohydride[2] and the hydroxyl group of **2** was activated as the mesylate. Although the displacement of the mesylate group by the sulfite group has been reported in the case of various free amino methanesulfonates,[8-10] in our case such a reaction led to a mixture of oxazolidinone **4** (60%) and 2-ethoxycarbonylaminohexanesulfonic acid **5** (40%). Replacement of the carbethoxy (Cbe) group used for the protection of the amino group with *tert*-butoxycarbonyl (Boc) group led to the cyclic derivative **4** as the main product (90%). Since this substitution pattern appeared to be unsuitable for the preparation of the target compound, the methanesulfonate group of **3** was replaced by the thioacetyl group; this was accomplished by treatment of **3** with potassium thioacetate. Performic acid, prepared by mixing 30% hydrogen peroxide and 98% formic acid in a 1:10 ratio at rt,[11] was then used to oxidize the thioacetyl group of **6** to the sulfonic acid group (**5**). Under these oxidative conditions, the carbethoxy group was not affected, permitting the synthesis of *N*-protected taurine analogs which can not be obtained by the already reported in literature.[8-11]



i) Ethyl chloroformate, N-methylmorpholine, $NaBH_4$, MeOH *ii*) Methanesulfonyl chloride, Et_3N
iii) Na_2SO_3 *iv*) Thiolacetic acid, KOH *v*) HCOOH, H_2O_2

EXPERIMENTAL SECTION

Mps were determined on a Buchi apparatus and are uncorrected. Specific optical rotations were measured on a Perkin-Elmer 141 polarimeter using a 10-cm cell. ^{1}H NMR spectra were recorded on a Varian Mercury 200 spectrometer at 200 MHz; chemical shifts (δ) are expressed in ppm.

(R)-2-Ethoxycarbonylaminohexanol (2).- To a stirred solution of (*R*)-*N*-carbethoxy-norleucine (0.118 g, 0.62 mmol) in dry THF (3 mL), *N*-methylmorpholine (0.068 mL, 0.62 mmol) and ethyl chloroformate (0.059 mL, 0.62 mmol) were added at -10°. After 15 min, sodium borohydride (0.070 g, 1.8 mmol) was added in one portion, followed by addition of MeOH (12 mL) over a period of 1 h. Water (3 mL) was then added and the reaction mixture was acidified with 1 *N* H_2SO_4 to pH 6. The organic solvents were evaporated under reduced pressure and the residue was extracted with AcOEt (2x5 mL). The extract was concentrated to small volume and purified on a silica gel column by flash chromatography using hexane:AcOEt (7:3) to afford 0.094 g (80%) of colorless solid, mp 32°, $[\alpha]_D^{20}$ = +19.6° (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 4.80 (bs, 1H, OCONH), 4.14 (q, *J* = 7 Hz, 2H, CH_3CH_2OCO), 3.70 (m, 2H, CH_2OH), 3.58 (m, 1H, α-CH), 2.40 (b, 1H, OH), 1.62-1.31 (m, 6H, 3xCH_2), 1.28 (t, *J* = 7 Hz, 3H, CH_3CH_2OCO), 0.93 (m, 3H, CH_3).

Anal. Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.12; N, 7.40. Found: C, 56.97; H, 10.33; N, 7.25

(R)-2-Ethoxycarbonylaminohexyl Methanesulfonate (3).- To an ice-cooled solution of **2** (0.189 g, 1 mmol) in dichloromethane (10 mL), triethylamine (0.21 mL, 1.5 mmol) and methanesulfonyl chloride (0.12 mL, 1.5 mmol) were added together dropwise. The reaction mixture was stirred for 30 min at 0°, then 30 min at rt. The organic phase was washed consecutively with brine (10 mL), 1 *N* HCl (10 mL), brine (10 mL), 5% aqueous $NaHCO_3$ (10 mL), dried (anhydrous Na_2SO_4), concentrated under reduced pressure and purified by flash column chromatography using hexane:AcOEt (8:2) as eluent to afford 0.209 g (89%) of colorless solid, mp 62-64°, $[\alpha]_D^{20}$ = +34.5° (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 4.72 (d, *J* = 7.5 Hz, 1H, OCONH), 4.28 (dd, *J* = 4 Hz, *J* = 8 Hz, 1H, $CHHSO_2CH_3$), 4.18 (dd, *J* = 4 Hz, *J* = 8 Hz, 1H, $CHHSO_2CH_3$), 4.10 (q, *J* = 7 Hz, 2H, CH_3CH_2OCO), 3.85 (m, 2H, α-CH), 2.99 (s, 3H, SO_2CH_3), 1.62-1.28 [m, 6H, $(CH_2)_3$], 1.24 (t, *J* = 7 Hz, 3H, CH_3CH_2OCO), 0.88 (m, 3H, CH_3).

Anal. Calcd for $C_{10}H_{21}NO_5S$: C, 51.05; H, 9.00; N, 5.95. Found: C, 50.96; H, 9.18; N 5.99

4-Butyl-2-oxazolidinone (4).- A mixture of **3** (0.118 g, 0.5 mmol) and sodium sulfite (0.189 g, 1.5 mmol) in 1,4-dioxane:water (1:1) (10 mL) was stirred for 6 h at 50°. Dioxane was removed and AcOEt (10 mL) and water (10 mL) was added. The AcOEt phase was washed with brine (5 mL), dried (anhydrous Na_2SO_4) and evaporated under reduced pressure giving 0.043 g (60%) of pure **4**, $[a]_D^{20}$ = +9.5° (*c* 1, $CHCl_3$) (*lit.*[12] $[\alpha]_D^{20}$ = +9.2° (*c* 2.62, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 6.35 (b, 1H, OCONH), 4.43 (t, *J* = 8 Hz, 1H, $CHHOCO$), 3.97 (dd, *J* = 6 Hz, *J* = 8 Hz, $CHHOCO$), 3.80 (m, 1H, α-CH), 1.56 (m, 2H, CH_2CHCH_2OCO), 1.25 (m, 4H, $CH_2CH_2CH_3$), 0.87 (t, *J* = 7 Hz, 3H, CH_3).

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.79; H, 9.09; N, 9.82

(R)-2-Ethoxycarbonylaminohexanesulfonic Acid (5).- a) By substitution of 3.- The aqueous phase from the above preparation of **4**, was passed through a column of Amberlite IR-120 (H^+ form). The

eluate was evaporated to dryness under reduced pressure to give 0.051 g (40%) of **5** as an oil, $[\alpha]_D^{20}$ = -3.0° (*c* 0.5, EtOH). ^{1}H NMR (CD_3OD): δ 4.12 (q, *J* = 7 Hz, 2H, CH_3CH_2OCO), 4.00 (m, 1H, CH), 3.63 (m, 1H, $CHHSO_3H$), 2.98 (m, 1H, $CHHSO_3H$), 1.46-1.20 (m, 9H, 3xCH_2, CH_3CH_2OCO), 0.86 (t, *J* = 7 Hz, 3H, CH_3).

Anal. Calcd for $C_9H_{19}NO_5S$: C, 42.67; H, 7.56; N, 5.53. Found: C, 42.60; H, 7.52; N, 5.68

b) By oxidation of 6.- To a performic acid solution, prepared by mixing 30% H_2O_2 (1 mL) and 98% HCOOH (9 mL) at rt (17°) for 1 h, thioacetyl derivative **6** (0.247 g, 1 mmol) in 98% HCOOH (4 mL) was added dropwise, keeping the temperature at 0°. After the mixture was stirred at 0° for additional 2 h and at rt for 20 h, 10% Pd/C (0.04 g) was added in order to decompose the remaining peroxide. After the mixture was stirred for additional 3-4 h at rt, the catalyst was removed by filtration and the filtrate was evaporated in vacuo. The residue was dissolved in ethanol (8 mL) and concentrated to dryness to afford 0.182 g (72%) of a product, identical to that obtained by substitution of **3** by means of spectroscopic data.

(R)-2-Ethoxycarbonylaminohexyl Ethanethioate (6).- Thiolacetic acid (0.08 mL, 1.1 mmol) was mixed with KOH (0.062 g, 1.1 mmol) in dry DMF (1 mL). A solution of **3** (0.235 g, 1 mmol) in DMF (3 mL) was added under cooling at 0-3°. After overnight incubation at rt, DMF was evaporated, the reaction mixture was poured into water (15 mL) and extracted with AcOEt (10 mL). The extract was washed with water (5 mL), 5% aqueous $NaHCO_3$ (5 mL), dried (Na_2SO_4), concentrated under reduced pressure and purified on a silica gel column using hexane:AcOEt (9:1) as eluent to afford 0.228 g (92%) of yellow solid, mp 47-49°, $[\alpha]_D^{20}$ = +23.0° (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 4.59 (d, *J* = 8 Hz, 1H, OCONH), 4.10 (q, *J* = 7Hz, 2H, CH_3CH_2OCO), 3.62 (m, 2H, α-CH), 3.09 (dd, *J* = 4.7 Hz, *J* = 14 Hz, $CHHSCO$), 2.96 (dd, *J* = 7 Hz, *J* = 14 Hz, $CHHSCO$), 2.32 (s, 3H, $SCOCH_3$), 1.58-1.12 (m, 9H, 3xCH_2, CH_3CH_2OCO), 0.86 (t, *J* = 7 Hz, 3H, CH_3).

Anal. Calcd for $C_{11}H_{21}NO_3S$: C, 53.41; H, 8.56; N, 5.66. Found: C, 53.28; H, 8.66; N, 5.63

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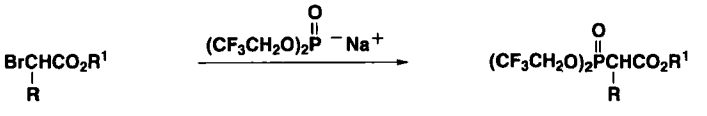
MICHAELIS-BECKER SYNTHESIS OF *bis*(2,2,2-TRIFLUOROETHYL)PHOSPHONO ESTERS

Submitted by (12/16/98)

Gregory M. Ciszewski and John A. Jackson*

Department of Chemistry, Youngstown State University
Youngstown, OH 44555, USA

The Michaelis-Becker reaction is a well known method for the synthesis of alkylphosphonates,[1] although the yields of phosphono esters tend to be relatively low.[1c] Although the Arbuzov reaction generally provides phosphono esters in significantly higher yields,[1c] *bis*(2,2,2-trifluoroethyl)phosphono esters are inaccessible *via* the Arbuzov reaction due to the non-nucleophilic nature of $(CF_3CH_2O)_3P$. *bis*(2,2,2-Trifluoroethyl)phosphono esters have found widespread use in the synthesis of Z-α,β-unsaturated esters in the Horner-Wadsworth-Emmons condensation.[1b,2a] The two principal literature methods for synthesis of *bis*(2,2,2-trifluoroethyl)phosphono esters have involved variations of Still's procedure of phosphonate ester interchange,[2] or modifications of that reported by Patois and Savignac *et al.* of acylation of an alkylphosphonate anion,[3] both of which rely upon an existing phosphonate starting material. This paper describes the use of the Michaelis-Becker reaction to prepare *bis*(2,2,2-trifluoroethyl)phosphono esters **2a-d**.



1a-d **2a-d**

a) R = H, $R^1 = CH_2CH_3$ b) R = CH_3, $R^1 = CH_2CH_3$ c) R = CH_2CH_3, $R^1 = CH_2CH_3$ d) R = CH_3, R^1 = Cl