Efficient synthesis of a novel imine from *L*-methionine and pyrrole

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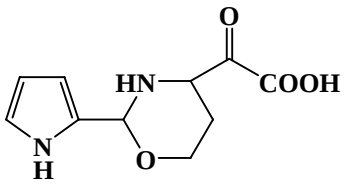
Abstract: Starting from readily available amino acid *L*-methionine and pyrrole, a novel imine was efficiently synthesized. This is the first report about the imine with pyrrole structure. The synthetic route has the advantages of mild conditions, good yield and easy manipulation.

Key words: *L-methionine; L-homoserine; imine; condensation reaction*

1. Introduction

As we know, the imine is an intermediate in the synthesis of a variety of complex chemical compounds. In this paper, the synthesis of a novel imine is described, it is an intermediate in the process of the total synthesis of chinese bittersweeter (I) **1** [1], which is a new structural compound found in 1999[2] and has good biological activity and anticancer ability. We used lithium hydroxide as a catalyst and an intermediate imine **5** was obtained successfully.



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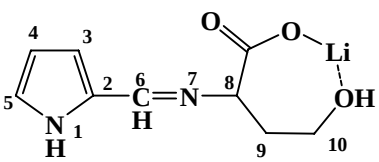

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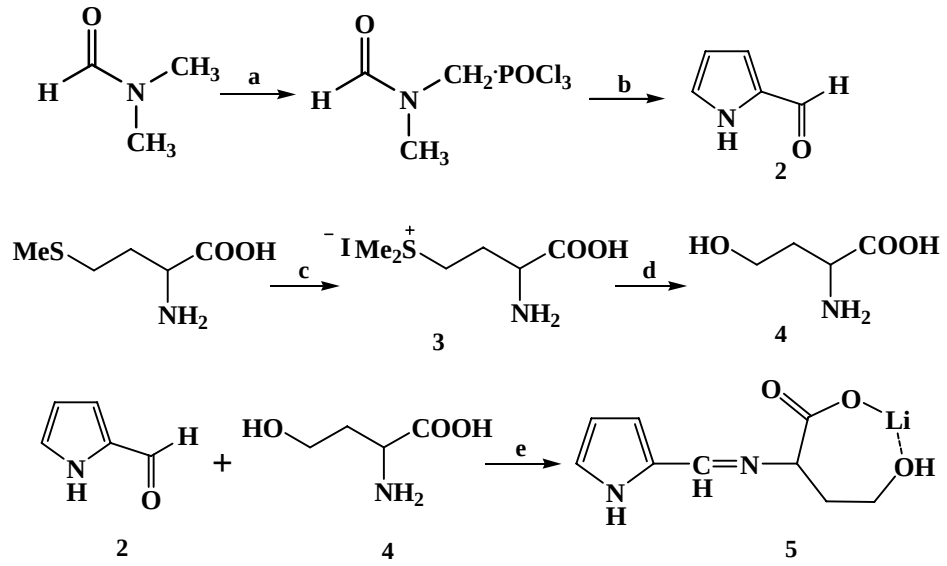
As shown in Scheme **1**, 2-pyrrolealdehyde was synthesized using DMF, $POCl_3$ and pyrrole after a series of reaction. After *L*-methionine and methyl iodide reacted in water, $NaHCO_3$ was added, and refluxed until Sulfuric acid dimethyl ester was eliminated, *L*-homoserine was obtained. The new structural compound of imine was synthesized by the condensation reaction of 2-pyrrolealdealdehyde with *L*-homoserine.

Scheme 1



a) 0°C $POCl_3$, stir; **b)** 0 °C, Pyrrole, stir; $CH_3COONa{\cdot}H_2O$; **c)** 40 °C, stir, 24 h; **d)** $NaHCO_3$, reflux; **e)** 40 °C, LiOH, dried methanol, stir for18 h.

2. Experimental

2.1. Materials and instruments

Methanol was freshly distilled from magnesium powder under argon before use. Other solvents were purified and dried as described in literature before use. Iodomethane, $POCl_3$ and lithium hydroxide were purchased from Chinese Tianjin Chemical Reagent Co. *L*-methionine and pyrrole were purchased from Aldrich and used as received.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker 500 MHz spectrometer in $CDCl_3$, MeOH and D_2O as internal standard.

2.2. Preparation of 2-pyrrolealdehyde (2)

To a stirred solution of DMF (8.5mL, 0.11mol), $POCl_3$ was added dropwise (10.3mL, 0.11 mol) in an ice bath. After stirring for 15 min at room temperature, the mixture was added to a solution of freshly distilled pyrrole(6.92mL, 0.11mol) in CH_2Cl_2 (25 mL) in ice bath for 1 h. The ice bath was removed, and heated to reflux for 15 min, and the temperature was cooled to room temperature, $CH_3COONa{\cdot}3H_2O$ (75 g, 0.55 mol) in 100 mL water was added, The mixture was again refluxed for 15 min. Then cooled to room temperature, the reaction mixture was partitioned between water and CH_2Cl_2 layer. The aqueous phase was extracted with ether (3 × 25 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3, dried over anhydrous Na_2SO_3. The solvents were concentrated and eliminated in vacuo, obtained crude 2-pyrrolealdehyde (8.5 g, 89%), m.p. 45-46 °C [lit.[3] m.p. 44–45 °C]. ^{1}HNMR(500 MHz, $CDCl_3$, ppm), 6.36 (t, 1H, -CHCN), 7.01 (t, 1H, -CHN-), 7.17 (t, 1H, =CH-C-CHO), 9.43 (s, 1H, -CHO), 10.33 (s, 2H, $-NH_2$).

2.3. Preparation of L-Methionine methylsulphonium Iodide (3)

L-Methionine(7.697 g, 0.0516 mol)was suspended in distilled water (50 mL). Iodomethane(8.2 mL, 0.132 mmol)

was added, and the mixture was stirred at 35~40 °C for 24 h. No suspended solid remained, and TLC indicated completion of reaction. The mixture was evaporated to dryness and the resulting solid was dissolved in water (20 mL). Ethanol (75 mL) was added, causing the precipitation of a white crystalline solid. The mixture was allowed to stand overnight to allow further precipitation. *L*-Methionine methylsulphonium Iodide **3**[4] (14.17 g, 94%), collected by filtration, was obtained as a white solid, m.p. 149~150 °C [lit. [5] m.p. 150 °C].

2.4. Preparation of L-Homoserine (4)

L-Methionine methylsulphonium Iodide (4.0 g, 13.2 mmol) was dissolved in water (10 mL) and heated under reflux. A solution of sodium hydrogen carbonate (1.1 g, 13.2 mmol) in water (10 mL) was placed in a dropping funnel, and added drop wise until the pH of the solution rose to 6.0. The reaction was allowed to proceed until the pH dropped to 3.0, whereupon base was added as previously. This cycle was repeated until the reaction was complete (TLC analysis), then the mixture was evaporated under reduced pressure to yield a thick syrup. This residue was dissolved in a minimum quantity of water (4 mL). Addition of acetone (10 mL) followed by ethanol (80 mL) caused immediate precipitation of *L*-homoserine[6] as a white solid (1.08 g, 68%), m.p. 202~203 °C [lit.[7] m.p. 203 °C] ^{1}HNMR(500MHz, D_2O,δppm), 2.03(m, 1H, -$CH_2C(NH_2)$-), 2.16(m,1H, -$CH_2C(NH_2)$-), 3.78 (m, 2H, -CH_2O-), 3.86 (m, 1H, -CH-N-).

2.5. Preparation of the imine (5)

A mixture of 2-pyrrolealdehyde (1.32 g, 11.2 mmol), *L*-homoserine (1.22 g, 11.2 mmol) ,LiOH(0.27 g, 11.2 mmol)in dried methanol was stirred at 40 °C for 18 h under an nitrogen atmosphere, diluted with water(5 mL), and extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_3. The solvents were concentrated and eliminated in vacuo, obtained imine(2.06 g, yield 85%) as a colorless powder. m.p.142□. ^{1}HNMR (500MHz, DMSO, δppm), 6.45(d, J=6.8 1H, H-3), 6.07 (d, J=6.8 1H, H-4), 6.89 (d, J=1.6, 1H, H-5), 7.93 (d,1H, H-6), 3.69 (m, 1H, H-8), 1.78 (m,1H,H-9a), 1.94 (m, 1H, H-9b), 3.35 (m, 1H, H-10a), 3.44(m, 1H, H-10b); ^{13}CNMR(500MHz, DMSO, δppm), 130.3 (C-2), 115.3 (C-3), 108.9 (C-4), 118.9 (C-5), 152.2 (-CH=N-), 73.5 (-CH-COO^-), 39.5 (-CH_2-), 59.2 (-CH_2-O-).

3. Results and discussion

To our knowledge, this is the first report on the imine with pyrrole structure. The synthetic route has the advantages of mild conditions, good yield and easy manipulation. At the process of condensation reaction of 2-pyrrolealdehyde with *L*-homoserine, we have used some other alkali such as NaOH, KOH, $NaHCO_3$, K_2CO_3 as catalysts [8], but the reaction couldn't take place with the anticipated route. We use lithium hydroxide as catalyst after many experiments. The reaction temperature is crucial. Low or high temperature decreased the catalytic activity of the reaction considerably. The best result was obtained when the reaction was carried out at 40 °C. We will continue completing the synthesis of Chinese bittersweet (I) using the imine.

Acknowledgment

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