A Convenient Synthesis of L-Proline

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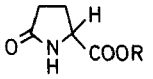
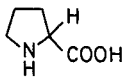
Although many syntheses for proline (**2**) have been described in the literature[1,2], methods for its preparation are still complex and expensive. More recently Buyle[3] described a preparation in which methyl-L-pyroglutamate (**1b**), readily available from L-glutamic acid, was a key intermediate. Although pyroglutamic acid (**1a**) and its simple derivatives seem to constitute the most obvious starting material for a facile proline synthesis, Buyle's[3] method and other synthetic schemes[4,5] using this precursor are not convenient due to the large number of steps and low overall yield.



1a, R = H

1b, R = CH_3



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Recently, in the course of our work on the syntheses of certain proline analogs[6], we found that L-pyroglutamic acid (**1a**) could be directly converted into L-proline (**2**) in a two step-one pot reaction. The conversion, which involves treatment of **1a** with triethyloxonium fluoroborate and reduction of the resulting crude imino ether with sodium borohydride, proceeds in about 75% yield and with no appreciable racemization.

L-Proline (2):

L-Pyroglutamic acid[7] (5.4 g, 0.047 mol) was stirred with freshly prepared[8] triethyloxonium fluoroborate (11.2 g, 0.059 mol) in dichloromethane (100 ml) for 16 hr at room temperature, under exclusion of moisture. The solvent was stripped under vacuum at room temperature and replaced by absolute ethanol (150 ml). The solution was cooled in an ice bath and finely powdered sodium borohydride (4.36 g, 0.115 mol) was added in small portions with stirring, keeping the reaction temperature below 10°. After complete addition, the reaction was stirred at room temperature for 3 hr and acidified with 10% ethanolic hydrogen chloride. After further stirring for 15 min the reaction mixture was filtered, the filter-cake washed with small portions of absolute ethanol, and the collected filtrate evaporated under vacuum. The residue was again dissolved in absolute ethanol (20 ml) and filtered from the inorganic salts. Evaporation of the filtrate left a residue of crude L-proline hydrochloride, which was dissolved in water (10 ml) and poured on an Amberlite IR-120 (H^+) column. After washing with water, the free amino acid was eluted with 2*N* ammonium hydroxide and the eluates evaporated under vacuum. The residue of L-proline (**2**) was finally purified by crystallization from absolute ethanol. Yield: 3.60 g (75%); $[\alpha]_D^{24}$: −85° (c = 1.1, Water; lit.[1]: −86.2).

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