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One-pot synthesis of *L*-felinine

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Abstract

Conjugate addition of Boc-*L*-Cys-OH to 3-methylcrotonaldehyde, in situ reduction with sodium borohydride, and in situ deprotection with hydrochloric acid, directly followed by chromatography gives *L*-felinine in 73% yield. Similar syntheses may produce acid building blocks for combinatorial libraries.

Keywords: amino acids and derivatives; addition reactions.

Felinine (**1**), an amino acid found in the urine of species of the Felidae family,[1,2] is believed to either possess pheromone activity[3] or give rise to compounds with such activity.[4] Its biosynthesis has been reported to start from cysteine and mevalonate, a member of the isoprenoid pool.[5,6] A number of chemical syntheses have been reported.[7–11] The most recent study[11] led to the conclusion that the preceding procedures give either an isomer of felinine or proceed in low yield. We are interested in synthetic methodologies for the preparation of amino acid derivatives as building blocks for combinatorial libraries. Felinine offers a good example of such a building block accessible through derivatization of cysteine.

The 1,3-relationship between the side chain functional groups suggests conjugate addition as the reaction of choice for construction of felinine. The latest synthetic route, reported by Hendriks and collaborators,[11] involves addition of H_2S to methyl 3,3-dimethylacrylate, reduction of the resulting ester with $LiAlH_4$, and nucleophilic attack of the thiol thus obtained on (±)-β-chloroalanine in the presence of NaH. We sought to avoid the use of hydrogen sulfide and the expensive amino acid analog and to construct the thioether backbone through direct addition of the cysteine thiol to a suitable enal. 3-Methylcrotonaldehyde (**2**) and N-α-Boc protected *L*-cysteine (**3**) were chosen. The latter is an inexpensive optically pure starting material resistant to Schiff base formation with the aldehyde.

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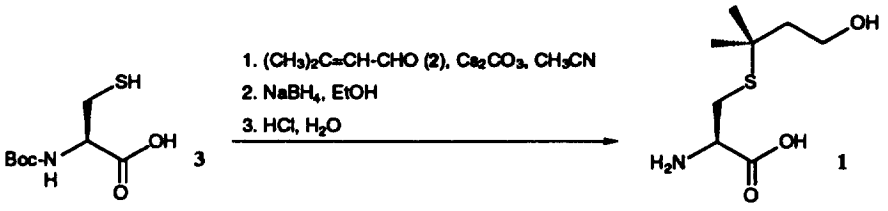

Addition of **3** to **2** in the absence of a catalyst was found to be inefficient, even when **2** was used as solvent and when heating up to 80°C. The reaction proceeds smoothly at room temperature with 1 or 0.5 equivalents of cesium carbonate, whereas 0.1 and 10 equivalents of this base, as well as cesium bicarbonate, gave lower yields. The subsequent $NaBH_4$ reduction to Boc-felinine was first attempted with purified aldehyde intermediate, but was found to be cleanest when $NaBH_4$ was added directly to the reaction mixture at the end of the conjugate addition. Since the carbonate and the hydride can be quenched with acid, and Boc-deprotection is readily accomplished with acid, a convenient one-pot protocol for the preparation of **1** resulted. Initial syntheses used **2** as solvent for the first step and TFA for quenching/deprotection. Subsequent optimization identified CH_3CN and HCl as inexpensive alternatives that allow direct chromatography of the crude product without a time-consuming workup. The resulting reaction sequence proceeds in 73% yield on a 1 g scale.[12]

Our synthesis avoids the possible side reactions under acidic conditions, which apparently generate an isomer of felinine,[11] probably via an oxetane intermediate. The protocol reported here is as short as that reported recently,[11] but produces a single enantiomer at the fraction of the cost, is higher yielding, and more convenient, as it can be performed as a one-pot procedure. The NMR data of felinine agree with those of natural felinine and synthetic materials (amine and ammonium forms are shown in Hendricks, W. et al.[11]). Since other enals are commercially available, derivatives of felinine may be prepared in an analogous fashion. The Boc-protected intermediates of such syntheses may be coupled via standard peptide protocols and may enrich the building block repertoire of combinatorial syntheses. Felinine itself is now more readily available for biological testing.

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12. To a vigorously stirred suspension of Boc-*L*-cysteine (1.05 g, 4.74 mmoles) and Cs_2CO_3 (0.734 g, 2.25 mmoles) in CH_3CN (1.2 mL), was added 3-methyl-2-butenal (0.8 mL, 0.7 g, 8.3 mmoles). After 2 h, the reaction was cooled (0°C) and $NaBH_4$ (0.095 g, 2.5 mmoles) was added. After 0.5 h, Boc-felinine could be either isolated and column purified or directly deprotected with conc. HCl (10 mL) and Dowex-W50X8 resin (10 g, H^+ form). The deprotection mixture was stirred (10 min) and then applied to an ion-exchange column (35 g Dowex-W50X8). Washing to neutrality with H_2O was followed by elution with aqueous NH_3:CH_3CN (95:5, step gradient 0.25–2 M NH_3). Product fractions (TLC: EtOAc:*n*-BuOH:H_2O:AcOH, 2:1:1:1) were lyophilized, yielding 0.721 g (3.48 mmol, 73%) of *L*-felinine, $[\alpha]_D^{20}$ −21±2 (lit[1] $[\alpha]_D^{20}$ −23), whose ^1H NMR spectrum in D_2O is identical to that reported previously[11] for (±)-felinine.