



Reaction of 1-Carboxymethyluracil with Amino acid alkyl ester hydrochloride

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ABSTRACT

We have synthesized derivatives of uracil **3** by the reaction of 1-carboxymethyluracil **1** and different amino acid alkyl ester hydrochloride **2** in the presence of Et_3N , DCC, HOBt. The structure of synthesized compounds was characterized by IR, ^1H NMR and mass spectroscopy.

Key words: 1-carboxymethyluracil, amino acid alkyl ester hydrochloride

INTRODUCTION

Heterocyclic compounds^{1,2} have received considerable attention due to their wide range of pharmacological activities. Pyrimidine is most important heterocyclic compound with two nitrogen atoms. Different Pyrimidine derivatives³ comprise of interesting medicinal properties. Uracil is among the five nucleobases like adenine, guanine, cytosine, and thymine but is only found in RNA. 5-Fluorouracil⁴ is found to be antimetabolite of uracil and is one of most widely used antineoplastic agents. Antimicrobial properties of various nitro uracil derivatives have been studied. Peter G. Schultz *et al.*,⁵ have reported the preparation of 1-carboxymethyluracil methyl glycinate amide and

1-carboxymethyluracil glycine amide by the photocleavage reaction of uracil dimer.

By considering the above facts we have started our work on the synthesis of uracil derivatives and therefore reporting here a method for the synthesis of uracil derivative **3**.

Chemistry

The first step involves the preparation of 1-carboxymethyluracil by the usual reported method⁵⁻⁷. The synthesis of the 1-carboxymethyluracil alkyl glycinate amide derivatives **3** was carried out by the reaction of 1-carboxymethyluracil **1** and amino acid alkyl ester

hydrochloride **2** at 0°C in the presence of Et₃N, DCC/HOBt as the coupling reagent⁸⁻¹⁰. The desired compounds **3** was isolated as the sole product in good yield. Scheme 1 represents the sequence of reaction for the synthesis of the desired compounds **3**. The structure of all the synthesized compounds were characterized by means of IR, ¹H NMR and mass spectra.

RESULT AND DISCUSSION

The present work describes the synthesis of 1-carboxymethyluracil alkyl glycinate amide derivatives **3** synthesized from 1-carboxymethyluracil **1** and amino acid alkyl ester hydrochloride **2** in the presence of Et₃N, DCC/HOBt. The structure of the synthesized compounds **3** was characterized by means of IR, ¹H NMR, mass spectra and all data are in accordance with the assigned structure **3**.

EXPERIMENTAL

Spectral data were recorded as follows: IR Spectra was run on a Perkin Elmer and Shimadzu 8201 PC, FT Infrared spectrophotometer (ν in cm⁻¹). Mass spectra were recorded on Jeol SX-102 (FAB). ¹H NMR has been recorded on Bruker Avance-300 (300MHz) and chemical shifts (δ in ppm) were reported relative to the solvent peak (CDCl₃+DMSO-d₆) or TMS as internal standard. Signals were designated as follows: s, singlet; bs, broad signal; d, doublet; t, triplet; m, multiplet. Melting points were determined by open capillary method and were uncorrected. All reagents used were of commercial grade and used as received without further purification unless otherwise specified. Dry DMF was used wherever required. Reagent grade solvents were used in all other cases unless

otherwise specified. Organic solutions were dried over anhydrous Na₂SO₄ and concentrated at reduced pressure.

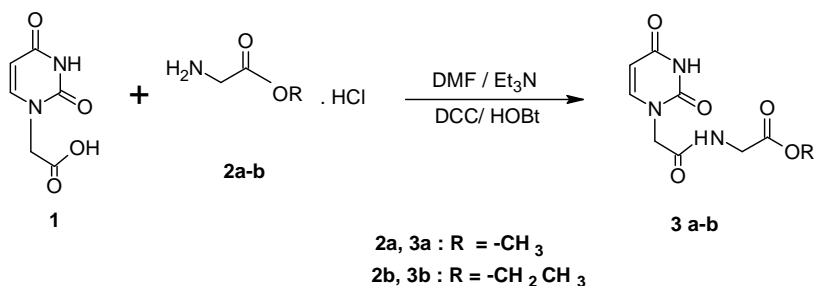
General procedure for synthesis of 1-Carboxymethyluracil Alkyl Glycinate Amide **3 a-b**

To a well stirred solution of amino acid alkyl ester hydrochloride **2** (12 mmol) suspended in anhydrous DMF (12 mL) neutralized with triethylamine in portions (12 mmol) at 0°C, 1-carboxymethyluracil **1** (12 mmol) and 1-hydroxybenzotriazole (12 mmol), dissolved in dry DMF (8 mL) were added consequently in the reaction flask in the small portions. The mixture was stirred at the same temperature for few min and dicyclohexylcarbodiimide (DCC, 12 mmol) dissolved in dry DMF (16 mL) was added drop wise in 30 min under the same condition. Stirring was continued in ice-cold condition for 4 h and left for overnight at the room temperature. The precipitated dicyclohexylurea (DCU) was filtered off and washed with DMF and combined filtrates were evaporated to dryness under reduced pressure. The solid residue was triturated with ethyl acetate and the resulting organic layer was washed with H₂O (2×60 mL), ice-cold 1N HCl (3×60 mL), water (2×60 mL), saturated NaHCO₃ (3×60 mL) and finally with H₂O (3×80 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get the desired product.

Spectral characterization of synthesized compounds **3a** and **3b** are given below

1-Carboxymethyluracil Methyl Glycinate Amide (**3a**)

Yield: 90%; mp: 190 °C; elemental analysis: Anal. Calcd. for C₉H₁₁N₃O₅: C, 44.82, H, 4.60, and N, 17.42, Found: C, 44.70, H, 4.81, and N, 17.11; IR (KBr, cm⁻¹): 3301, 3015, 2825, 1740, 1680, 1550,



Scheme 1

1450, 1225, 1080, 740, 625 cm^{-1} ; $^1\text{H-NMR}$ (300 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$) δ (ppm): 3.52 (s, 3H, $-\text{OCH}_3$), 3.84(d, 2H, $-\text{CH}_2-$), 4.40 (s, 2H, $-\text{CH}_2-$), 5.50 (d, 1H, Ar-H), 7.50 (d, 1H, Ar-H), 8.60 (bs, 1H, NH), 11.10 (s, 1H, NH); MS m/z 241 (M^+).

3.70(d, 2H, $-\text{CH}_2$), 4.15 (q, 2H, $-\text{OCH}_2\text{CH}_3$), 4.40 (s, 2H, $-\text{CH}_2-$), 5.40 (d, 1H, Ar-H), 7.30 (d, 1H, Ar-H), 8.33 (bs, 1H, NH), 10.50(s, 1H, NH); MS m/z 255 (M^+).

1-Carboxymethyluracil Ethyl Glycinate Amide (3b)

Yield: 85%; mp: 210 $^\circ\text{C}$; elemental analysis: Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_5$: C, 47.06, H, 5.13, N, 16.46; found: C, 47.45, H, 5.51, N, 16.23; IR (KBr, cm^{-1}): 3425, 3300, 3125, 2805, 1700, 1665, 1566, 1430, 1228, 1005, 752, 650; $^1\text{H-NMR}$ (300 MHz, $\text{CDCl}_3 + \text{DMSO-d}_6$) δ (ppm): 1.20(t, 3H, $-\text{CH}_2\text{CH}_3$),

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