Short Note

2-(4-(2-Chloroacetamido)-1-methyl-1H-pyrrole-2-carboxamido)ethyl Acetate

Naim H. Al-Said 1,2

1 Department of Chemistry, Jordan University of Science and Technology, Irbid 22110, Jordan
2 College of Applied Medical Sciences-Al Ahsa, King Saud bin Abdulaziz University for Health Sciences, Al-Ahsa 31982, Kingdom of Saudi Arabia; E-Mail: saidn@ksau-hs.edu.sa; Tel.: +00966-13-562-9000 (Ext. 28057)

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Abstract: The title compound 2-(4-(2-chloroacetamido)-1-methyl-1H-pyrrole-2-carboxamido)ethyl acetate was synthesized. The structure of the compound was fully characterized by 1H-NMR, 13C-NMR and mass spectral analysis.

Keywords: lexitropsins; pyrrole-2-carboxamide; DNA-alkylating agents

Introduction

Lexitropsins, i.e., “information reading molecules”, such as the crescent-shaped naturally occurring antitumor antibiotic netropsin, bind reversibly with the minor groove of double helical DNA to sequences rich with adjacent AT base pairs [1–3]. These pyrrole carboxamide skeletons have been used as vehicles for delivering anticancer drugs to DNA sequences blocking its template function [4,5]. In the course of our work on the synthesis of lexitropsins [6–11], literature search revealed that 1-methyl-1H-pyrrole-2-carboxamides carrying an alkylating unit such as a chloroacetamido group at C-4 have not been prepared. Therefore, 2-(4-(2-chloroacetamido)-1-methyl-1H-pyrrole-2-carboxamido)ethyl acetate (5), a new pyrrole carboxamide possessing an alkylating unit, was prepared as shown in Scheme 1. The product synthesized with a satisfactory yield was fully characterized by nuclear magnetic resonance and mass spectrometry.

Results and Discussion

We have synthesized the amide 3 starting from 2-trichloroacetyl-1-methyl-4-nitropyrole (1) [12,13] according to Scheme 1, in two steps; the first was performed by acyl nucleophilic substitution of the
trichloromethyl leaving group by ethanolamine to afford amide 2 and the second by protecting the hydroxyl group with an acetyl group to furnish ester 3 [14].

Schem 1. Synthesis of 2-(4-(2-chloroacetamido)-1-methyl-1H-pyrrole-2-carboxamido)ethyl acetate (5).

The chloroacetyl group was then introduced by a sequence of two steps. Reduction of the nitro group in the ester 3 to the corresponding amine 4 was best accomplished in MeOH using H₂/Pd(C). It is worth noting that amine 4 decomposes easily. Conducting these reactions without degassing furnished the title compound in low yield after tedious purification by column chromatography. Therefore, the solution of 3 in MeOH in the presence of the catalyst was degassed with N₂ prior to the reduction process. After completion of the reaction (by TLC) the reaction mixture was concentrated and then the residue was dissolved in degassed CH₂Cl₂ containing Et₃N. Finally, the reaction mixture was concentrated and the title compound 5 was then purified by silica gel chromatography. The required compound 5 obtained in 70% overall yield from 3 was characterized by ¹H-NMR, ¹³C-NMR and mass spectral data.

Experimental

2-(4-(2-Chloroacetamido)-1-methyl-1H-pyrrole-2-carboxamido)ethyl Acetate

A solution of 3 (2.55 g, 10.0 mmol) and Pd/C (0.30 g of 3%) in MeOH (200 mL) was degassed with N₂ for 10 min and then the resulting solution was hydrogenated using Shaker Hydrogenation Apparatus for 3 h at 30 psi. After concentration under reduced pressure, the residue was dissolved in degassed CH₂Cl₂ (50 mL) containing Et₃N (2 mL). The resulting mixture was added dropwise to a degassed solution of chloroacetyl chloride (1.68 g, 15 mmol) in CH₂Cl₂ (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was extracted by EtOAc (2 x 100 mL). The combined extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 1:3
hexane/EtOAc) to give the title compound 5 (2.10 g, 70%) as a yellow oil. 

\[ \delta 2.08 (s, 3H), 3.59 (q, J = 5.2 Hz, 2H), 3.89 (s, 3H), 4.15 (s, 2H), 4.22 (t, J = 5.2 Hz, 2H, O-CH2), 6.28 (s, 1H, aromatic-H), 6.56 (d, J = 1.5 Hz, 1H, aromatic-H), 7.11 (t, J = 1.6 Hz, 1H, NH), 8.17 (s, 1H, N-H); \]

\[ \delta 20.6, 36.4, 38.5, 42.3, 63.1, 103.2, 118.9, 119.9, 123.2, 161.2, 162.8, 171.1; MS-ESI m/z \text{calcd for } C_{12}H_{17}N_{3}O_{4}^{35}Cl [M+H]^+ 302.08, \text{found}, 302.06. \]

Anal. Calcd. for C_{12}H_{16}N_{3}O_{4}Cl: C, 47.77%; H, 5.34%; Cl, 11.75%; N, 13.93%. Found: C, 47.83%; H, 5.41%; N, 13.85%.

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Conflict of Interest

The author declares no conflict of interest.

References


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