

Short Note

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

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Abstract: The title compound 2-(4-(2-chloroacetamido)-1-methyl-1*H*-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

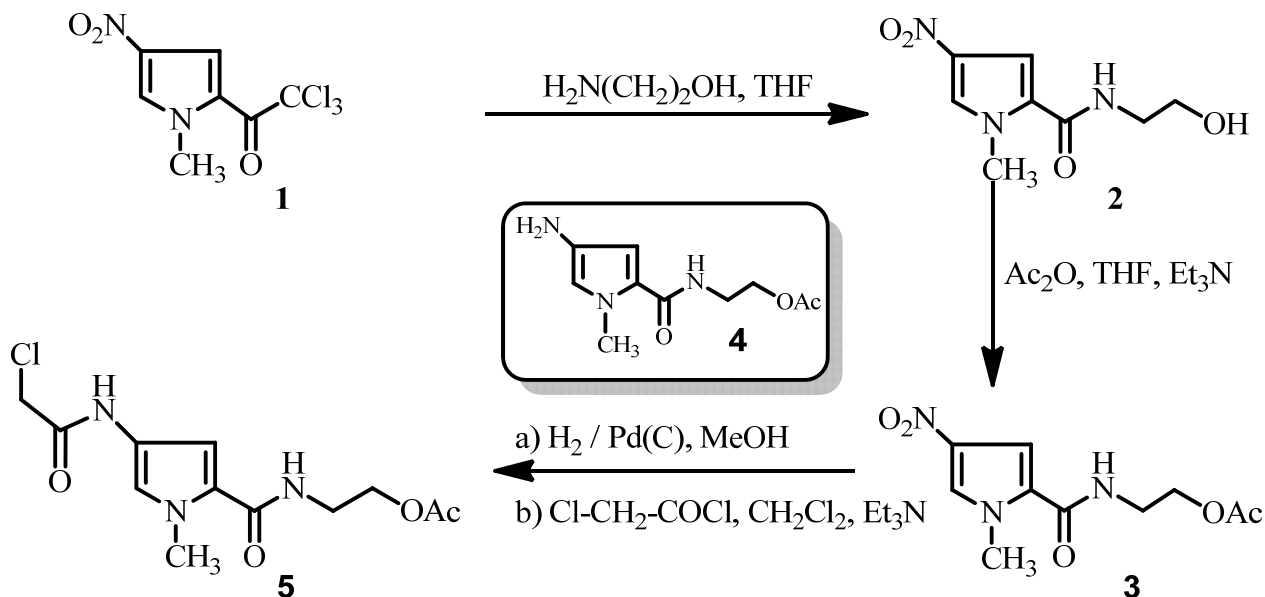
Lexitropsins, *i.e.*, “information reading molecules”, such as the crescent-shaped naturally occurring antitumor antibiotic netropsin, bind reversibly with the minor groove of double helical *DNA* to sequences rich with adjacent *AT* base pairs [1–3]. These pyrrole carboxamide skeletons have been used 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-1*H*-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-1*H*-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-nitropyrrole (**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-1*H*-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 $\text{H}_2/\text{Pd}(\text{C})$. 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 N_2 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 CH_2Cl_2 containing Et_3N . 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, ^{13}C -NMR and mass spectral data.

Experimental

2-(4-(2-Chloroacetamido)-1-methyl-1*H*-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 N_2 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 CH_2Cl_2 (50 mL) containing Et_3N (2 mL). The resulting mixture was added dropwise to a degassed solution of chloroacetyl chloride (1.68 g, 15 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was extracted by EtOAc (2×100 mL). The combined extracts were dried (Na_2SO_4), 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. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 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); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 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 calcd for $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_4^{35}\text{Cl}$ $[\text{M}+\text{H}]^+$ 302.08, found, 302.06. Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_3\text{O}_4\text{Cl}$: C, 47.77%; H, 5.34%; Cl, 11.75%; N, 13.93%. Found: C, 47.83%; H, 5.41%; N, 13.85%.

Acknowledgments

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Conflict of Interest

The author declares no conflict of interest.

References

1. Zimmer, C. Effects of the antibiotics netropsin and distamycin A on the structure and function of nucleic acids. *Prog. Nucleic Acid Res. Mol. Biol.* **1975**, *15*, 285–291.
2. Lown, J.W. Lexitropsins in antiviral drug development. *Antiviral Res.* **1992**, *17*, 179–185.
3. Arcamone, F.; Penco, S.; Orezzi, P.; Nicoletta, V.; Pirelli, A. Structure and synthesis of distamycin. *Nature* **1964**, *203*, 1064–1065.
4. Khan, G.S.; Shah, A.; Rehman, Z.U.; Barker, D. Chemistry of DNA minor groove binding agents. *J. Photochem. Photobiol. B* **2012**, *115*, 105–118.
5. Romagnoli, R.; Baraldi, P.G.; Iaconinoto, M.A.; Carrion, M.D.; Tabrizi, M.; A. Gambari, R.; Borgatti, M.; Heilmann, J. Synthesis and biological activity of alpha-bromoacryloyl lexitropsin conjugates. *Eur. J. Med. Chem.* **2005**, *40*, 1123–1128.
6. Al-Said, N.H.; Shawakfeh, K.Q. Synthetic studies towards bis-heterodimeric netropsin analogs. *Jordan J. Chem.* **2007**, *2*, 125–132.
7. Al-Said, N.H.; Klaib, S. Synthesis of a C-2 stapled bis-lexitropsin. *Monatsh. Chem.* **2007**, *138*, 573–577.
8. Al-Said, N.H. Synthesis of a terminally linked homodimeric bis-distamycin analog. *Monatsh. Chem.* **2006**, *137*, 1535–1541.
9. Zhao, R.; Al-Said, N.H.; Sternbach, D.L.; Lown, J.W. Camptothecin and minor-groove binder hybrid molecules: Synthesis, inhibition of topoisomerase I, and anticancer cytotoxicity *in vitro*. *J. Med. Chem.* **1997**, *40*, 216–225.
10. Gupta, R.; Al-Said, N.H.; Oreski, B.; Lown, J.W. Design, synthesis and topoisomerase II inhibition activity of 4'-demethylepipodopyllotoxine-lexitropsin conjugate. *Anticancer Drug Des.* **1996**, *11*, 325–338.
11. Al-Said, N.H.; Lown, J.W. A convenient synthesis of cross-linked homodimeric lexitropsins. *Synth. Comm.* **1995**, *25*, 1059–1070.

12. Belanger, P. Electrophilic substitutions on 2-trichloroacetylpyrrole. *Tetrahedron Lett.* **1979**, *27*, 2505–2508.
13. Rahman, K.M.; Jackson, P.J.M.; James, C.J.; Basu, P.; Hartley, J.A.; de la Fuente, M.; Schatzlein, A.; Robson, M.; Pedley, R.B.; Pepper, C.; *et al.* GC-Targeted C8-linked pyrrolobenzodiazepine-biaryl conjugates with femtomolar *in vitro* cytotoxicity and *in vivo* antitumor activity in mouse models. *J. Med. Chem.* **2013**, *56*, 2911–2935.
14. Breen, D.; Kennedy, A.R.; Suckling, C.J. A divergent synthesis of minor groove binders with tail group variation. *Org. Biomol. Chem.* **2009**, *7*, 178–186.

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