DIRECT LINKAGE OF CHLOROACETAMIDES OF AMINO ACIDS TO THEOPHYLLINE

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Summary: Acetamides of theophylline-7-acetic acid (7-TAA) with amino acids were synthesized via a cost effective method directly from theophylline. The synthetic protocols involve: first the synthesis of N-chloroacetyl amino acid methyl ester, and second, its consequent interaction with deprotonated theophylline to give the corresponding acetamide. The described method is characterized with cost effectiveness and good yields.

Key words: Theophylline, chloroacetyl chloride, amino acid, amides

Introduction

The biological properties of various purine based structures [1] as well as methylxanthines[2] are extensively reviewed. Methylxanthines are central nervous system stimulants. Theophylline is used in the management of asthma [3] and COPD [4]. Theophylline-based structures comprise an attractive scaffold for structural modification and efforts have been undertaken into the synthesis and development of new antimicrobial [5], pro-coagulant [6], hypoglycemic [7], anti-HIV-1[8], antitussieve[9], and anti-cancer [10, 11] derivatives.

Recently, we became interested in the synthesis and anti-mycobacterial activity evaluation of theophylline acetamides with a variety of amino acids [12]. Herein, we continue our study towards optimization and upscaling of the synthetic procedures.

Materials and Methods

Synthesis of *N*-chloroacetyl valine methyl ester (1a).

L-Valine methyl ester hydrochloride (1 eq, 5.97 mmol, 1.00 g) was mixed with K_2CO_3 (4 eq, 3.30 g) and water (20 ml), and after 5 min, chloroacetyl chloride (1.5 eq, 8.95 mmol, 0.71 ml) was added dropwise while vigorously stirring. The reaction was stirred for another 30 min at r.t. and diluted with CH_2Cl_2. Extraction with CH_2Cl_2 was followed by washing with water and 1N HCl, drying over Na_2SO_4 and concentration under reduced pressure. The product was isolated in good yield (0.94 g, 76%) as colorless oil. The spectral data correspond to these in the literature [13].

Synthesis of *N*-chloroacetyl leucine methyl ester (1b).

L-Leucine methyl ester hydrochloride (1 eq, 5.50 mmol, 1.00 g) was mixed with K_2CO_3 (4 eq, 3.04 g) and water (20 ml) and after 5 min, chloroacetyl chloride (1.5 eq, 8.26 mmol, 0.66 ml) was added dropwise while vigorously stirring. The reaction was stirred for another 30 min at r.t. and diluted with CH_2Cl_2. Extraction with CH_2Cl_2 was followed by washing with water and 1N HCl, drying over Na_2SO_4 and concentration under reduced pressure. The product was isolated in good yield (0.94 g, 82%) as colorless oil. The spectral data correspond to these in the literature [13].

Synthesis of *N*-(2-(theophylline-7-yl)acetyl)valine methyl ester (2a).

To theophylline (1.5 eq, 1.5 mmol, 0.270 g) in DMF (5 ml) was added NaH (55% in mineral oil; 1.5 eq, 1.5 mmol, 0.065 g) and the solution was stirred for 10 min at r.t. *N*-Chloroacetyl valine methyl ester **1a** (1 eq, 1 mmol,0.208 g) was added and the mixture was stirred overnight at r.t. The reaction was separated between CH_2Cl_2 (20 ml) and water (20 ml). The aqueous layer was acidified with 1N HCl and extracted with CH_2Cl_2 (2 x 25 ml). The combined organic extracts were washed with water (3 x 100 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The product was achieved in 76% yield after recrystallization from methanol. The spectral data correspond to these in the literature [12].

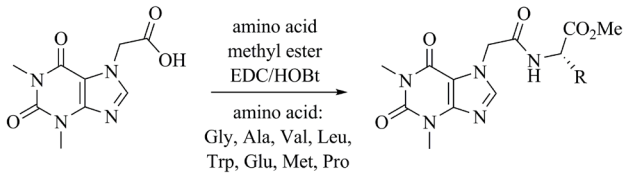
Synthesis of *N*-(2-(theophylline-7-yl)acetyl)leucine methyl ester (2b).

To theophylline (1.5 eq, 1.5 mmol, 0.270 g) in DMF (5 ml) was added NaH (55% in mineral oil; 1.5 eq, 1.5 mmol, 0.065 g) and the solution was stirred for 10 min at r.t. *N*-Chloroacetyl leucine methyl ester

1b (1 eq, 1 mmol,0.221 g) was added and the mixture was stirred overnight at r.t. The reaction was separated between CH_2Cl_2 (20 ml) and water (20 ml). The water was acidified with 1N HCl and extracted with CH_2Cl_2 (2 x 25 ml). The combined organic extracts were washed with water (3 x 100 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The product was achieved in 82% yield after recrystallization from methanol. The spectral data correspond to these in the literature [12].

Results and Discussion

The synthesis and characterization of the 7-TAA derivatives with amino acids have been described in our earlier work [12]. The amide bond was created *via* coupling reactions carried out using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide and hydroxybenzotriazole (EDC/HOBt) in dichloromethane (Scheme 1).



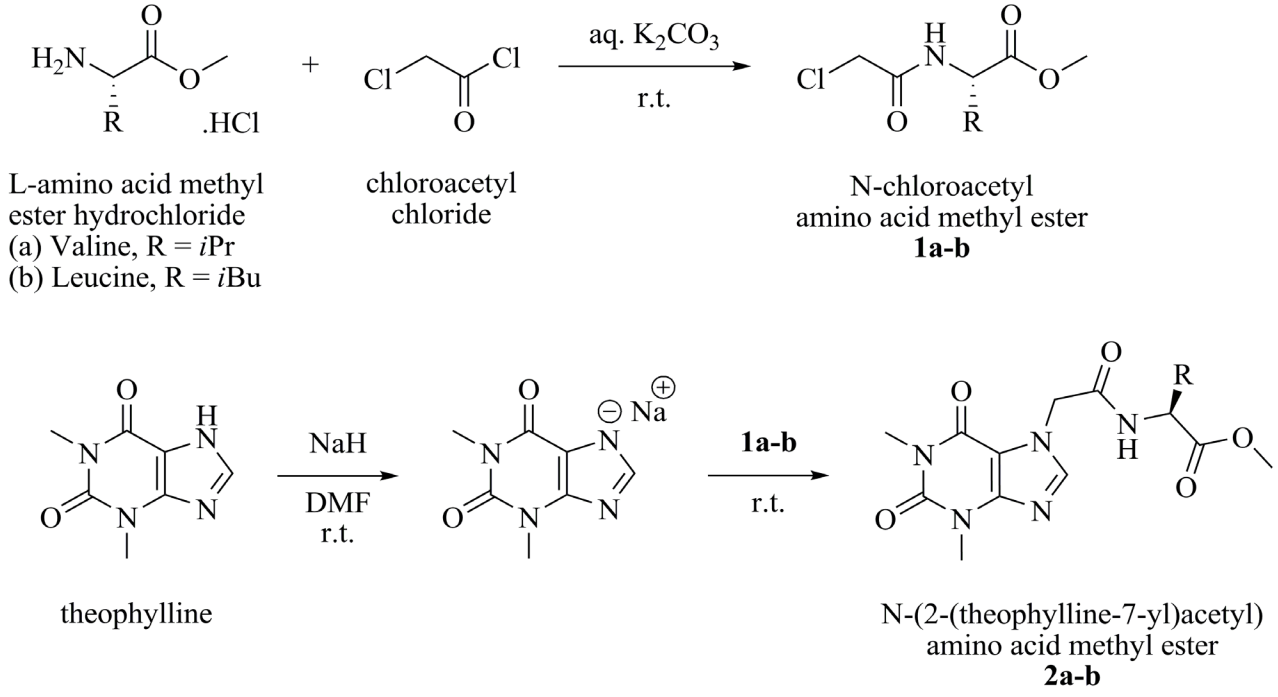
Scheme 1.Synthesis of amino acid methyl ester derivatives of theophylline using EDC/HOBt protocol.

Although coupling reagents are effective and extensively utilized for the formation of amide bonds, especially in peptide synthesis, they are associated with considerable cost. In this current work we describe a much more cost effective method for the synthesis of amino acid derivatives of theophylline (Scheme 2). The amino group at the 7th position in the theophylline ring possesses weak acidic properties and can be deprotonated with strong metallic hydrides like sodium hydride (NaH). The resulting conjugate base is strongly nucleophilic and can be easily functionalized *via* nucleophilic substitutions.

For our purposes we initially synthesized amides of amino acid methyl esters with chloroacetyl chloride. Commercially available amino acid methyl ester hydrochloride was dissolved in aqueous K_2CO_3 and transformed into free amino base. The latter reacted vigorously with chloroacetyl chloride to give the desired amides **1a-b** in good yields and excellent purity. The reactions were performed in aquous media, thus additionally fulfilling the criteria for green and sustainable synthesis.

In a separate pot, theophylline was deprotonated to give the conjugate base, which was allowed to react with **1a-b** to the corresponding theophylline acetamide**2a-b**.

The starting theophylline, which was used in excess, and the resulting from the reaction sodium salts are considerably more hydrophilic than the desired products, and were easily removed by water washings. The products were additionally purified by recrystallization from methanol to give **2a-b** in good yields and excellent purity.



Scheme 2. Two step synthesis of theophylline acetamide derivatives with valine or leucine methyl ester.

Conclusion

Theophylline-7-acetamides derived from valine and leucine were synthesized directly from theophylline by its initial deprotonation and consequent nucleophilic substitution of cloroacetamides. The method is considerably cost effective in comparison to the reaction of theophylline-7-acetic acid with amino acids using coupling reagents, and allows upscaling of the synthesis of theophylline-7-acetamides.

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