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Research Article

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Improved One-Pot Synthesis of Acetylsalol, Benorilate and Guacetisal: Prodrugs of Aspirin

ZHI-ZHONG WANG*, JIANG-YUAN MA

School of Pharmacy, Ningxia Medical University, Yinchuan, Ningxia, 750004, P. R. China

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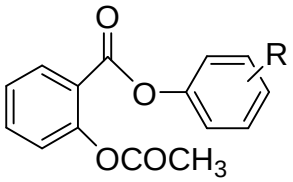
ABSTRACT

Improved, cost-effective and one-pot methods for the synthesis of three aspirin prodrugs (Acetylsalol, Benorilate, Guacetisal) were achieved by using N,N′-carbonyldiimidazole as a coupling reagent. Moreover, the byproduct imidazole as the catalyst promoted the reactions. The procedures are simple and suitable to large-scale manufactures.

Keywords: *N,N′*-Carbonyldiimidazole, Acetylsalol, Benorilate, Guacetisal, Prodrugs.

INTRODUCTION

To date, aspirin, also known as acetylsalicylic acid, is the most effective drug in the treatment for inflammatory and fever diseases, and new uses are being discovered all the time [1,2]. However, the use of aspirin is limited by the gastric ulceration that results from cyclooxygenase inhibition in the mucosa [3-5]. Therefore, many prodrugs of aspirin based on non-acidic latentiated derivatives are synthesized and extensively used [6-10], such as acetylsalol (**1**), benorilate (**2**) and guacetisal (**3**) (Figure 1).



1 Acetylsalol, R=H

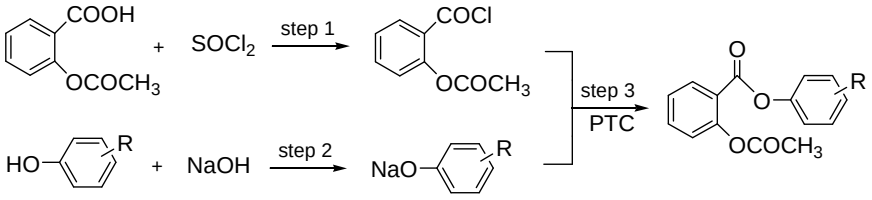
2 Benorilate, R=4′-CH_3CONH

3 Guacetisal, R=2′-CH_3O

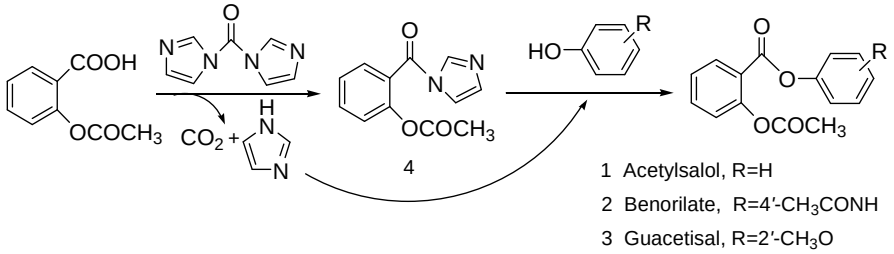
Figure 1. The chemical structure of three aspirin prodrugs

The conventional routes for synthesis of above prodrugs were the three-step synthesis as shown in Scheme 1, which required the preparation of acetylsalicylic acid chloride and the reaction required strict anhydrous conditions [11]. In addition, in the combination of acetylsalicylic acid chloride and sodium substituted phenolate, the phase transfer catalyst (PTC) was needed to promote the reaction [12]. *N*,*N*′-carbonyldiimidazole (CDI) is one of several commonly used reagents for activating carboxyl groups. It is relatively cheap, and the only byproducts are carbon dioxide and imidazole which, being relatively benign, are unlikely to cause problems on scale up [13]. Herein, we report improved procedures for the preparations of above aspirin prodrugs in one pot by using *N*,*N*′-carbonyldiimidazole as a coupling reagent, which are simple and suitable to large-scale manufactures (Scheme 2).

Scheme 1. The conventional routes



Scheme 2. The improved one-pot procedures



EXPERIMENTAL SECTION

The HPLC assays for the purity of three aspirin prodrugs were performed on a Perkin-Elmer Series 200 HPLC system using a Kromasil 100-10-C18 column (4.6 mm×250 mm) at 35□; flow rate: 1.0 cm^3/min; detection wavelength: 240 nm; the mobile phase: 56:44 MeOH-H_2O (pH adjusted to 3.5 with phosphoric acid). The melting point determinations were carried out on a XRC-I melting point apparatus. The progresses of the reactions were monitored by TLC on 0.25-mm thick layers of silica gel GF_{254} developed with solvent system, AcOEt:petroleum ether (1:1 *v/v*). All other chemicals were of commercial grade without further purification.

General Experimental Procedure

To a solution of 500 mmol aspirin in 500 cm^3 anhydrous DMF, 600 mmol *N*,*N*′-carbonyldiimidazole was added at room temperature. After stirred for 2 h, 550 mmol phenol was added. The resulting solution was maintained at room temperature for 24 h. Then the reaction mixture was evaporated in vacuo to dryness. The residual solid was then dissolved in 300 cm^3 AcOEt, and the organic layer was washed sequentially with saturated aqueous sodium bicarbonate (2×100 cm^3) and water (100 cm^3), dried over anhydrous sodium sulphate and concentrated in vacuo. Finally, the concentrate was crystallized and recrystallized from 95% ethanol to afford the pure products.

*phenyl 2-acetoxybenzoate (**1**, acetylsalol)*

Yield 81%; M.p.: 96-97°C(Ref. [6] 97°C). Purity 98.7% by HPLC (UV).

*4′-Acetaminophenyl 2-acetoxybenzoate (**2**, benorilate)*

Yield 84%; M.p.: 175-177°C (Ref. [6] 174-177°C). Purity 99.2% by HPLC (UV).

*2′-Methoxyphenyl 2-acetoxybenzoate (**3**, guacetisal)*

Yield 88%; M.p.: 73-74°C (Ref. [6] 72-74.5°C). Purity 99.0% by HPLC (UV).

RESULTS AND DISCUSSION

In our work, we found that simply mixing *N*-(2-acetoxybenzoyl)imidazole (**4**) with paracetamol in DMF did not result in an obvious reaction in 24 h at room temperature. Imidazole can efficiently promote the reaction. Furthermore, the stronger bases such as Na_2CO_3 or Et_3N did not distinctly enhance the reaction rate.

N,N′-carbonyldiimidazole is a useful, general carboxylic acid activating reagent, and imidazole as byproduct can serve as the catalyst. Therefore, benorilate (**2**) was prepared in a simple, two-step sequence in just one reactor. In the first step, based on TLC analysis, the reaction between aspirin and *N,N′*-carbonyldiimidazole was quantitative within 2 h at room temperature. In the second step, the coupling of paracetamol to the 2-acetoxybenzoyl group was accomplished in 24 h at room temperature.

The optimized conditions for the synthesis of benorilate are aspirin/*N,N′*-carbonyldiimidazole/paracetamol = 1/1.2/1.1 (mol/mol). The purity and structure were confirmed by TLC, HPLC and Melting point.

Moreover, the method works equally well for preparing acetylsalol (**1**) and guacetisal (**3**), accordingly using phenol and guaiacol as reaction reagents.

CONCLUSION

Improved methods for the preparations of three aspirin prodrugs via a one-pot reaction were developed by using *N,N′*-carbonyldiimidazole as a coupling reagent, which do not require extra catalysts. Compared with routine synthetic methods, these procedures may become efficient routes for the synthesis of them on a large scale.

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