Research Article

Improved Convenient Synthesis of Benzoyl Metronidazole: A Nitroimidazole Antibiotics

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An improved, cost-effective, and one-pot method for the synthesis of benzoyl metronidazole was achieved by using $N,N'$-carbonyldiimidazole as a coupling reagent. Moreover, the byproduct imidazole as the catalyst promoted the reaction. These processes are simple and suitable to large-scale manufactures.

1. Introduction

Metronidazole (MTZ), 1-hydroxyethyl-2-methyl-5-nitroimidazole, is known to be a powerful antiprotazoal and antibacterial drug. It is clinically effective in trichomoniasis, amoebic colitis, and giardiasis [1]. However, it has a bitter taste, and it is not acceptable to some young patients. Benzoyl metronidazole, the benzoyl ester of metronidazole, is tasteless and has also been widely used because of its greater palatability [2].

The conventional routes for synthesis of benzoyl metronidazole were the two-step synthesis as shown in Scheme 1, which required the preparation of benzoyl chloride, the reaction required strict anhydrous conditions [3, 4], and the reactor should be corrosion resistant. In addition, in the combination of benzoyl chloride and metronidazole, the deacid reagent such as pyridine was needed to promote the reaction. $N,N'$-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 [5]. Herein, we report an improved procedure for the preparation of benzoyl metronidazole in one pot by using $N,N'$-carbonyldiimidazole as a coupling reagent, and the byproduct imidazole as the catalyst can promote the reaction. These processes are simple and suitable to large-scale manufactures (Scheme 2).

2. Experimental

The HPLC assays for the purity of benzoyl metronidazole were performed on a Perkin-Elmer Series 200 HPLC system using a Kromasil 100-10-C18 column (4.6 mm × 250 mm) at room temperature; flow rate: 1.0 mL/min; detection wavelength: 310 nm; the mobile phase: 35:65 MeOH-KH$_2$PO$_4$ (0.02 M). The melting point determinations were carried out on an XRC-1 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:petroleumether (1:1 v/v). Dichloromethane (DCM) was dried by CaCl$_2$ for 12 h and distilled prior to use. All other chemicals were of commercial grade and used without further purification.

2.1. General Experimental Procedure. To a solution of benzoic acid (100.0 g, 820 mmol) in 4 L anhydrous DCM, $N,N'$-carbonyldiimidazole (160.0 g, 984 mmol) was added at room temperature. After stirred for 8 h, metronidazole (140 g, 820 mmol) in 10 L anhydrous DCM was added. Then, the resulting solution was refluxed for 16 h and concentrated. The residue was dissolved in 8 L DCM, and sequently washed with 1 M sodium carbonate solution (2×1.5 L), 10% HCl (2×1.0 L), distilled water (3 × 1.5 L). The organic layer was separated, dried over anhydrous sodium sulphate, and concentrated in vacuo. Finally, the concentrate was crystallized from ethanol...
to give 1 (190.2 g). Yield 84.3%; M.p.: 99.6–100.8°C ([6] 99–102°C). Purity 98.7% by HPLC (UV).

3. Results and Discussion

In our work, we found that simply mixing benzoylimidazole (2) with metronidazole in DCM did not result in an obvious reaction in 24 h. Imidazole can efficiently promote the reaction. Furthermore, the stronger bases such as Na₂CO₃ or Et₃N did not distinctly enhance the reaction rate.

\(N, N'-\text{carbonyldiimidazole is a useful, general carboxylic acid activating reagent, and its byproduct imidazole can serve as the catalyst.}

The optimized conditions for the synthesis of benzoyl metronidazole are benzoic acid/\(N, N'-\text{carbonyldiimidazole/metronidazole} = 1/1.2/1\) (mol/mol). The purity and structure were confirmed by TLC, HPLC, and Melting point.

4. Conclusions

An improved method for the preparation of benzoyl metronidazole via a one-pot reaction was developed by using \(N, N'-\text{carbonyldiimidazole as a coupling reagent, which do not require extra catalysts. Compared with routine synthetic methods, these procedures may become an efficient route for the synthesis of benzoyl metronidazole on a large scale.}

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References

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