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An Improved Procedure for Preparation of Carbapenem Antibiotic: Meropenem

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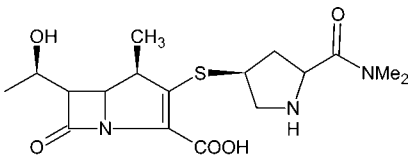
Abstract:
An efficient synthesis of a 1β-methyl carbapenem antibiotic, meropenem, is described. The present process does not involve cryogenic temperatures, chromatographic purification, or reverse osmosis and is amenable to large scale synthesis.

Introduction

Meropenem (**1**) is a semisynthetic, broad spectrum 1β-methyl carbapenem antibiotic for parenteral administration.[1,2] It is used in the treatment of a wide range of serious infections such as intra-abdominal infections, urinary tract infections, and lower respiratory tract infections.[3,4]

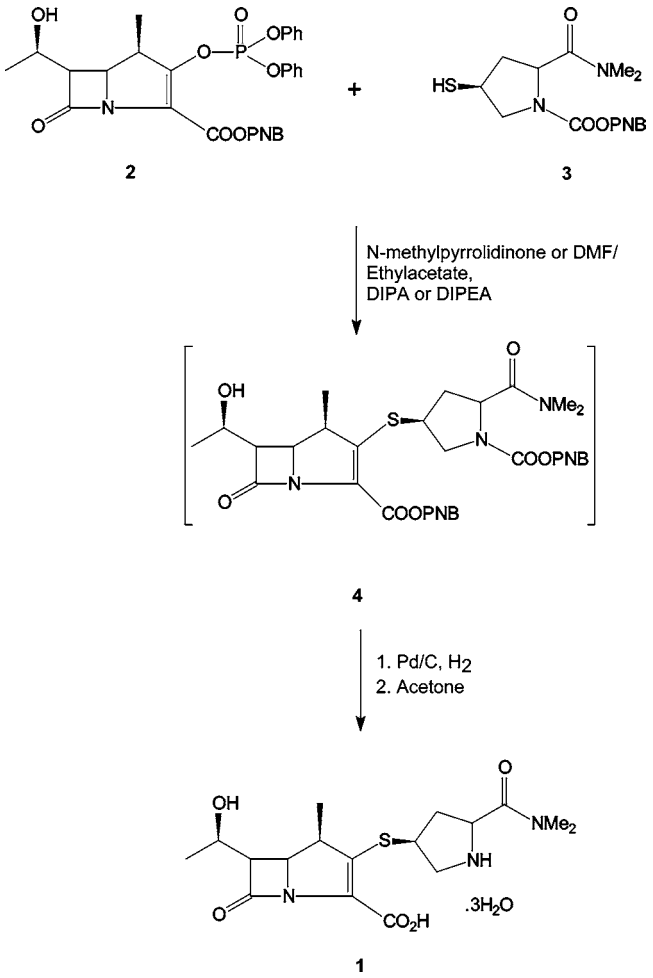


1

There are several methods reported in literature for the preparation of **1**.[5] In all these reported methods, synthesis of meropenem (**1**) involves condensation of commercially available 4-nitrobenzyl (4*R*,5*S*,6*S*)-3-[(diphenylphosphono)-oxy]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3,2,0] hept-2-ene-2-carboxylate (**2**, enol phosphate) with (2*S*,4*S*)-2-dimethylaminocarbonyl-4-mercapto-1-(4-nitrobenzyloxycarbonyl) pyrrolidine (**3**, side chain) in the presence of base to give diprotected meropenem **4**. Hydrogenolysis of **4** with Pd/C in the presence of buffer provides meropenem (**1**) (Scheme 1).

In reported methods[5a,b] diprotected meropenem **4** is isolated as a solid and then subjected to hydrogenolysis to give **1**. Further, this process required chromatographic purification on an Diaion HP-20 and concentration of the aqueous solution by reverse osmosis to give **1**, in an overall yield of 28−43% from **4**. In one of our publications,[6] we have reported an efficient process for the preparation and isolation of meropenem in an overall yield of 59% directly from intermediate **2**. The method does not involve the isolation of intermediate **4**, chromatographic purification, or reverse osmosis.

Scheme 1



In the course of our ongoing efforts to increase the yield and further simplify the process from a commercial aspect, improvements have been made in the existing process of **1**. In this communication we report an efficient and practical one-step synthesis of meropenem (**1**) from intermediates **2** and **3**.

Results and Discussion

The present method involves condensation of enol phosphate **2** with side chain **3** in the presence of base to give **4**,

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Table 1. **Preparation of meropenem (1) under different conditions**

entry	solvent (volume w.r.t. input 2)[a]	base[a]	reaction time (h)	yield (%)
1	EtOAc/DMF (6:1)	DIPA	3	60
2	EtOAc/DMF (6:1)	DIPEA	6	52
3	EtOAc/N-methylpyrrolidinone (6:1)	DIPA	3	63
4	EtOAc/N-methylpyrrolidinone (6:1)	DIPEA	5	53
5	THF/DMF (6:1)	DIPA	3	41
6	THF/*N*-methylpyrrolidinone (6:1)	DIPEA	incomplete reaction	
7	EtOAc/DMF (6:0.5)	DIPA	incomplete reaction	
8	EtOAc/*N*-methylpyrrolidinone (6:0.5)	DIPA	incomplete reaction	

[a] Solvent and base used in the condensation step.

which is directly taken up for deprotection on Pd/C in the presence of buffer under biphasic conditions to provide **1**. In reported methods,[5] condensation of **2** with **3** is carried out in dimethyl formamide (DMF) or acetonitrile to give diprotected meropenem **4** in ~92% yield. Hydrogenolysis of **4** using 10% Pd/C in a mixture of tetrahydrofuran (THF) and water in the presence of buffer (3-[*N*-morpholino]-propanesulfonic acid) provided **1**. This process requires additional solvents for workup and isolation of **4**. Deprotection of **4** requires a different solvent system and expensive buffer, and isolation of **1** involves chromatographic purification and reverse osmosis.

We have also reported the synthesis of meropenem (**1**)[6] without isolation of diprotected meropenem **4** using DMF as a solvent for condensation of **2** and **3**. The resulting intermediate **4** is extracted with ethyl acetate and subjected to deprotection under biphasic conditions in the presence of *N*-methylmorpholine−acetic acid buffer (pH 6.0).

In the present communication, we are reporting a further improved process with respect to consumption of solvents and simplicity in terms of operations on a commercial scale. In this process the condensation of **2** and **3** are carried out in a mixture of ethyl acetate and *N*-methyl pyrrolidinone (6: 1 v/w with respect to input **2**) in presence of base at 0−5 °C. The reaction mixture is subjected to hydrogenolysis on 5% Pd/C in water (5 v/w with respect to input **2**) in the presence of *N*-methylmorpholine−acetic acid buffer at pH 6.0. After hydrogenation the reaction mixture is filtered, and the layers are separated. The aqueous layer so obtained is treated with acetone to give crystalline meropenem (**1**) in an overall yield of 63%.

During the process optimization, we have studied the effects of different solvents and role of the base (diisopropylamine (DIPA) vs diisopropylethylamine (DIPEA)) in the formation of **4**. The results are tabulated in Table 1. The use of ethyl acetate and *N*-methylpyrrolidinone (6:1, v/w) as solvent for condensation results in maximum yield (63%) (entry 3). The condensation reaction time is shorter in the case of DIPA in comparison with DIPEA.[7] The use of THF instead of ethyl acetate results in low yield and inferior quality of the product. Reducing the quantity of DMF and *N*-methylpyrrolidinone from 1 to 0.5 v/w results in an incomplete condensation reaction (entries 2 and 7, 3 and 8).

(7) Williams, J. M.; Jobson, R. B. (Merck) U.S. Patent 5,872,250, 1999.

The advantages of this method over the existing methods are the drastic reduction of the quantity of DMF or *N*-methylpyrrolidinone which eliminates exhaustive workup and does not affect the crystallization of **1**. In the reported methods where DMF is used as the reaction solvent in condensation step, it is essential to remove DMF by aqueous workup at an intermediate step due to the solubility of meropenem (**1**) in DMF. Since the preparation of **4** is carried out at 0−5 °C the present process does not require any cryogenic temperatures. Ethyl acetate and acetone used in the process are easily recyclable and the consumption of solvents is minimized, thereby making the process more cost-effective and environment friendly.

In conclusion, a cost-effective and commercial process for preparation of meropenem (**1**) with improved yield and shorter reaction time is reported. This process does not involve isolation of diprotected meropenem **4**, cryogenic temperatures, and chromatographic purification.

Experimental Section

General. Reagents are used as such without purification. ^{1}H NMR spectra are recorded using a Bruker 300 MHz spectrometer. The chemical shift data are reported as δ (ppm) downfield from tetramethylsilane which is used as an internal standard. HPLC analysis is performed on a Waters instrument with a UV detector (220 nm) using a Hyprsil ODS (250 mm × 4.6 mm, 5μ) column (oven temperature 40 °C) and mobile phase (water, 900 mL + acetonitrile, 70 mL + TEA 1 mL and adjusting the pH 5.0 ± 1 with diluted phosphoric acid) with a flow rate of 1.6 mL/min.

Preparation of (4*R*,5*S*,6*S*)-3-[{(3*S*,5*S*)-5-(Dimethylaminocarbonyl)-3-pyrrolidinyl]thio]-6-[(1*R*)-1-(hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo-[3,2,0]-hept-2-ene-2-carboxylic Acid Trihydrate (Meropenem Trihydrate 1). Enolphosphate 2 (200 g, 0.336 mol) was suspended in a mixture of ethyl acetate (1.2 L) and *N*-methylpyrrolidone (200 mL) and cooled to 0−5 °C. Side chain **3** (130.5 g, 0.369 mol) was added followed by dropwise addition of DIPA (44.2 g, 0.436 mol) at 0−5 °C. The reaction mixture was stirred for 3.0 h, and the progress of the reaction was monitored by TLC (EtOAc/hexane, 8:2). After completion of reaction, it was poured into an aqueous buffer (1.0 L) containing *N*-methylmorpholine (34 g) and acetic acid (14 g) (pH 6.0). The resulting biphasic reaction mixture was hydrogenated over 5% Pd/C (200 g, dry) at 20−25 °C for

3.0 h (~70 psi of H_2 gas). The reaction mixture was filtered and washed with deionized water (400 mL), and the layers were separated. To the aqueous layer activated carbon (10 g) was added, which was stirred for 15 min at 15−20 °C and filtered. To the aqueous layer acetone (5.0 L) and seed sample of meropenem (200 mg) were added at 5−10 °C. The suspension was stirred for 2 h, and additional acetone (2.5 L) was added and stirred for 5−6 h at 0−5 °C. The precipitate was collected by filtration and washed with acetone (400 mL) and dried to give **1** (93 g, 63%) as a nonsterile solid. Chromatographic purity, by HPLC ≥ 98% ^{1}H /NMR (D_2O): δ 1.13 (d, 3H, 4C-C*H*$_3$), 1.21 (d, 3H, C*H*$_3$-CHOH), 1.90 (m, 1H, CH_3-C*H*-4), 2.92 (s, 3H, -CON(C*H*$_3$)$_2$), 2.99, (m, 4H, -CON(C*H*$_3$)$_2$ and S-C*H*-CH_2), 3.33 (m, 1H, N-C*H*-), 3.40 (m, 2H, S-CH-C*H*$_2$) 3.69 (dd, 1H, -C*H*), 3.97 (m, 1H, C*H*-8), 4.16 (m, 2H, S-CH-C*H*$_2$), 4.73 (m, 1H, C*H*CON). MS (*m*/*e*): 384.

Acknowledgment

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Supporting Information Available

Spectral data of meropenem. This material is available free of charge via the Internet at http://pubs.acs.org.

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