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An efficient method for the synthesis of sulbactam pivoxil

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Abstract

Sulbactam pivoxil, a prodrug of the β-lactamase inhibitor sulbactam, was prepared in high yield by reacting the sodium salt of sulbactam with chloromethyl pivalate in a polar solvent, then diluting the reaction mixture with water and isolating the product by filtration. Dimethyl sulfoxide was found to be the solvent of choice among several aprotic organic solvents.

Keywords: Sulbactam; β-Lactamase inhibitor; Prodrug; Chloromethyl pivalate

1. Introduction

Sulbactam pivoxil **2** (pivsulbactam, CP-47,904) [1] is a prodrug of sulbactam **1** [2], the latter being a β-lactamase inhibitor, poorly absorbed from the gastrointestinal tract (Scheme 1). In contrast, pivsulbactam has a better absorption than the parent drug and provides high serum levels after oral administration [3].

Until now sulbactam pivoxil was prepared by reacting chloromethyl pivalate with sulbactam free acid [4,5] in DMF or with its sodium salt [6] in acetone. In the former case, pivsulbactam was obtained after extraction with ethyl acetate and evaporation of the solvent under reduced pressure, and in the latter, after concentration of the reaction mixture and column chromatography. There are also methods in which the esterification of the carboxyl group was accomplished at an early stage (prior to oxidation or dehalogenation) in the synthesis of sulbactam [4,5,7–9].

In all these cases however, the purity and the yields of the isolated sulbactam pivoxil were unsatisfactory. We report here a simple method for preparing sulbactam pivoxil by reacting the sodium salt of sulbactam with chloromethyl pivalate in a polar aprotic solvent for 18 h at room temperature, then diluting the reaction mixture with water and isolating the product by filtration (Scheme 1).

2. Results and discussion

A number of aprotic solvents were used, with or without sodium iodide as a catalyst (10% from the weight of the sulbactam), added as a 25% solution in water (Table 1). In all cases the sodium salt of sulbactam was insoluble in the corresponding solvent and the reaction seemed to be heterogeneous, between the solid sulbactam and the chloromethyl pivalate in the solution.

As can be seen the best results were obtained in DMSO. The presence of NaI in this case did not affect the yield of pivsulbactam. The use of 18-crown-6 as a catalyst (10% from the weight of the sulbactam) in DMSO as a solvent also did not affect the yield. In our opinion the best yields of sulbactam pivoxil in DMSO were due to its higher polarity, compared with the other solvents (Table 1). Good yields were also obtained in *N*,*N*-dimethylacetamide and in 1-methyl-2-pyrrolidone in the presence of NaI. In less polar solvents (acetone, THF, dioxan) the reaction did not proceed without a catalyst, while in the presence of NaI the yields were

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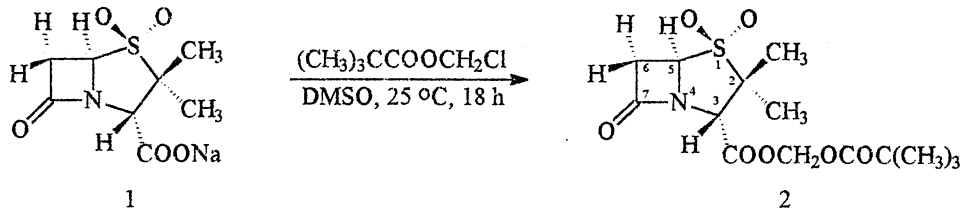

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Scheme 1. Synthesis of pivsulbactam from sulbactam sodium salt.

Table 1
Yields of sulbactam pivoxil in different solvents

Solvent	ε [a]	Yields of pivsulbactam (%)	
		Without catalyst	With catalyst NaI
Dimethyl sulfoxide	48.9	85	85
Sulfolane	44.0	3	58
N,*N*-Dimethyl-acetamide	37.0	62	83
Acetonitrile	37.5	traces (TLC)	7
N,*N*-Dimethyl-formamide	36.7	35	64
1-Methyl-2-pyrrolidone	33	25	83
Hexamethylphosphoric triamide	29.6	59	61
Acetone	20.7	traces (TLC)	11
Tetrahydrofuran	7.4		oil
1,4-Dioxan	2.2		oil

[a] ε, dielectric constant.

poor. DMSO was also the solvent of choice in the synthesis of pivsulbactam because of its low toxicity, which is important for large-scale operations.

In all cases the isolated pivsulbactam had a high purity (at least 98% by HPLC).

3. Experimental

Melting points were determined on Büchi 512 apparatus and are uncorrected. IR spectra (ν_{max}, cm^{-1}) in KBr were recorded on a Schimadzu 435 spectrophotometer. ^1H NMR spectra (δ, ppm; J, Hz) were determined on Bruker WM 250 spectrometer, using 3-trimethylsilylpropionic acid-d_4 sodium salt (TSPA) as an internal standard (for the numbering of the protons see Scheme 1). The elemental analysis was carried out on Perkin–Elmer 240 apparatus.

3.1. Sulbactam pivaloiloxymethyl ester

Sulbactam sodium salt (20.0 g, 0.08 mol) was suspended in DMSO (200 ml) and chloromethyl pivalate (13.4 ml, 13.6 g, 0.09 mol) was added at one portion. The mixture was stirred at 20–25°C for 18 h, than cooled to 5°C and water (400 ml) was added dropwise. After stirring for another 30 min the crystals were filtered off and dried. Yield: 23.1 g sulbactam pivoxil (85%).

To recrystallize the product, 96% ethanol (60 ml) was heated to 60°C and sulbactam pivoxil (12.0 g) was added portionwise. To the resulting clear solution was added activated carbon (0.12 g), the mixture was stirred 5 min at 60°C and quickly filtered. The filtrate was stirred for 30 min at room temperature and 1 h at 0°C. The obtained crystals were collected by filtration, washed with cold ethanol and dried. Yield: 10.7 g pivsulbactam (90%), m.p. 90–92°C.

IR (KBr): ν 2980, 1810–1745, 1320 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.23 (s, 9H, $-C(CH_3)_3$), 1.43 (s, 3H, 2-CH_3), 1.59 (s, 3H, 2-CH_3), 3.48 (m, 2H, $J = 16.3$, $J = 4.0$, $J = 2.4$ Hz, 6α- and 6β-H), 4.42 (s, 1H, 3-H), 4.64 (dd, 1H, $J = 2.4$, $J = 4.0$ Hz, 5-H), 5.72 (d, 1H, $J = 5.5$ Hz, $-CH_2-$), 5.96 (d, 1H, $J = 5.5$ Hz, $-CH_2-$). Anal. ($C_{14}H_{21}NO_7S$) C, H, N.

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