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Practical One-Pot Synthesis of *N*-(*tert*-Butoxycarbonyl)sulfamide from Chlorosulfonyl Isocyanate via *N*-(*tert*-Butoxycarbonyl)aminosulfonylpyridinium Salt

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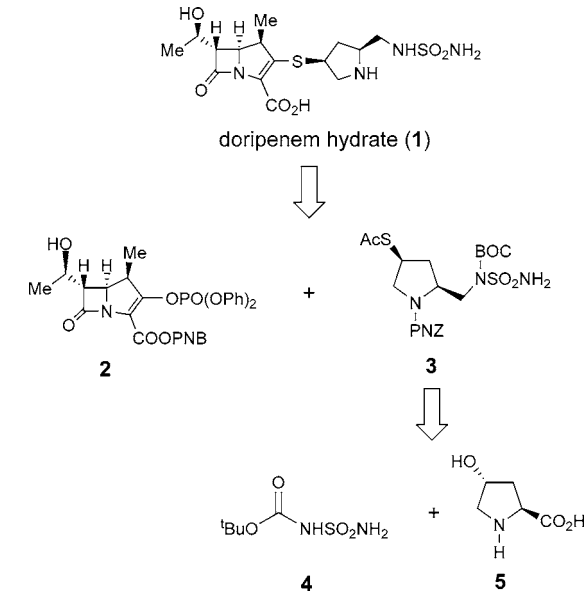
Abstract:

An efficient and practical process for the one-pot synthesis of *N*-(*tert*-butoxycarbonyl)sulfamide (4), a raw material for the aminosulfamoyl-containing side chain 3 of a novel carbapenem antibiotic doripenem hydrate (S-4661: 1), is described. In the previous process, chlorosulfonyl isocyanate was converted to *N*-(*tert*-butoxycarbonyl)aminosulfonyl chloride (7), an extremely unstable intermediate against moisture, which afforded the target compound 4 using liquid ammonia at cryogenic temperatures in 90% isolated yield. The use of liquid ammonia required cryogenic reaction temperatures because of heat generated from the highly exothermic reaction and the low boiling point of ammonia. In the improved process, the deactivation of the sulfonyl chloride 7 with pyridine at 0 °C afforded water-resistant *N*-(*tert*-butoxycarbonyl)aminosulfonylpyridinium salt (8) which was converted in situ to the target compound 4 in the presence of water at 0 °C in 90−96% isolated yields. Aqueous ammonia can be used, and no cryogenic temperatures are necessary for this new one-pot process.

Scheme 1



Introduction

Doripenem hydrate (S-4661: **1**),[1] which was discovered by Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka, Japan, is a novel parenteral 1β-methylcarbapenem antibiotic. In our previous reports,[1,2] its synthesis, biology, and structure−activity relationships (SAR) have been reported. Compound **1** exhibited potent, broad, and well-balanced antibacterial activity against a wide range of both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*. Following conventional carbapenem retrosynthetic analysis of a carbapenem (Scheme 1), doripenem can be assembled from 4-nitrobenzyl-protected 1β-methylcarbapenem enolphosphate **2**[3] and the aminosulfamoyl-containing side chain **3**.[4,5] Enolphosphate **2** is also used for the synthesis of ertapenem as a starting material.[6] Both the enolphophate **2** and the side chain **3** are now commercially available. Both *N*-(*tert*-butoxycarbonyl)sulfamide (**4**)[2,4] and *trans*-4-hydroxy-L-proline (**5**) are raw materials for the side chain **3**.

Alcohols or phenols react with chlorosulfonyl isocyanate (CSI: **6**) to form alkyl or aryl *N*-(chlorosulfonyl)carbamates,[7,8] which react with amines containing a reactive

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Scheme 2. **Original process**

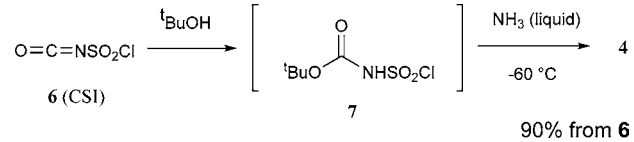

Table 1. **One-pot synthesis of compound 4 from CSI**

entry	amine (equiv) for deactivation of sulfonyl chloride **7**	ammonia (equiv)	isolated yield (%)
1[a]	pyridine (2.2 equiv)	25 wt % aqueous (6.0 equiv)	96
2[b]	pyridine (2.2 equiv)	25 wt % aqueous (6.0 equiv)	94
3	triethylamine (2.2 equiv)	25 wt % aqueous (6.0 equiv)	83
4	none	25 wt % aqueous (6.0 equiv)	9
5[c]	none	liquid ammonia (6.0 equiv)	90

[a] Reaction conditions and procedures are described in the Experimental Section. *tert*-Butyl alcohol was added dropwise to a solution of CSI in toluene. [b] CSI was added dropwise to a solution of *tert*-butyl alcohol in toluene. [c] The reaction was carried out at −60 °C.

hydrogen to give stable *N*-acyl-substituted sulfamides.[8,9] According to this conventional procedure, we established the previous process as shown in Scheme 2. The results of a 78.4 kg-scale preparation of *N*-acylsulfamide **4** were described in our previous paper.[4b] In the previous process (Scheme 2), CSI (62.5 kg, 442 mol) was converted in situ to *N*-(*tert*-butoxycarbonyl)aminosulfonyl chloride (**7**), an extremely instable intermediate against moisture, which afforded the target compound **4** (78.4 kg) by its reaction with liquid ammonia at cryogenic temperatures in 90% isolated yield on a pilot scale.[4] The use of liquid ammonia required cryogenic reaction temperatures because of the highly exothermic reaction and low boiling point of ammonia. A cryogenic reaction temperature confines equipment and significantly increases the cost of production. In our previous report,[10] we described a one-pot preparation of *N*-(aryloxycarbonyl)- and *N*-(alkoxycarbonyl)sulfamides via the corresponding aminosulfonylammonium salts (Burgess-type intermediates[11]). We then developed an improved process according to the previous paper.[10] In this contribution,[4a] we describe an efficient and practical process for the synthesis of *N*-acylsulfamide **4**, which replaces the use of liquid ammonia with aqueous ammonia and requires no cryogenic temperatures.

Results and Discussion

First, we investigated the reaction conditions for the one-pot synthesis of *N*-acylsulfamide **4**. The representative results are summarized in Table 1. The solvent, which must not react with CSI at 0 °C, must be chosen. According to our previous paper,[10] we chose toluene as a solvent. The reaction carried out by the addition of *tert*-butyl alcohol to a solution of CSI gave *N*-acylsulfamide **4** in 96% isolated yield (Table 1, entry 1). It gave the similar yield to the reaction by the addition of CSI to a solution of *tert*-butyl alcohol (94%, Table 1, entry 2). Tertiary amines to afford the Burgess-type intermediate **8** by the deactivation of sulfonyl chloride **7** influenced the yields for the reaction (Scheme 3). According to our previous paper,[10] pyridine and triethylamine are preferable for deactivation of isopropyl *N*-(chlorosulfonyl)-carbamate (**9**) obtained from CSI and 2-propanol. Therefore, we compared these two amines (Table 1, entries 1 and 3) and chose pyridine (96%) because it gave a higher yield than triethylamine (83%). When no tertiary amine was used, the use of aqueous ammonia dramatically decreased the yield of *N*-acylsulfamide **4** (9% yield, Table 1, entry 4) because intermediate **7** is extremely water-sensitive. Dry liquid ammonia gave *N*-acylsulfamide **4** in 90% yield (Table 1, entry 5).

Table 2. **Reaction heats[a]**

step		reaction heat, kJ/mol: improved process[b]	reaction heat, kJ/mol: previous process[c]
1	reaction between CSI and *tert*-BuOH	105	94
2	reaction between intermediate **7** and pyridine	117	−
3	reaction between intermediate **7** and liq. NH_3	−	255
4	reaction between intermediate **8** and aq NH_3	99	−
	total reaction heat	321	349

[a] Reaction heats were measured on a RC1 reaction calorimetor (Mettler Toledo). The procedures are described in the Supporting Information. [b] The reaction was carried out at −4 °C. [c] The reaction was carried out at −35 °C.

The reaction heats of the improved and previous processes were measured on an RC1 reaction calorimeter. The results are shown in Table 2. Total reaction heat of the previous process (349 kJ/mol) was larger than that of the improved one (321 kJ/mol). However, this difference (28 kJ/mol) was not significant for industrial manufacture of *N*-acylsulfamide **4**. In the improved process, three exothermic reactions were observed (formation of intermediate **7** by the addition of *tert*-BuOH to CSI: 105 kJ/mol, formation of intermediate **8** from intermediate **7** and pyridine: 117 kJ/mol, and formation of *N*-acylsulfamide **4** from intermediate **8** and aqueous ammonia: 99 kJ/mol). The previous process contains two exothermic reactions (formation of intermediate **7** by the addition of *tert*-BuOH to CSI: 94 kJ/mol, and formation of *N*-acylsulfamide **4** from intermediate **7** and liquid ammonia: 255 kJ/mol). The improved process was carried out at −4 °C. The reaction temperature of the improved process can be more easily controlled by normal coolant systems than that of the previous process because the maximum reaction heat in the improved process (117 kJ/mol) was dramatically smaller than that of the previous one (255 kJ/mol). The previous process requires cryogenic reaction conditions because of the low boiling point of liquid ammonia. In addition to the advantage of the improved process, it was difficult to scale-up the previous process,

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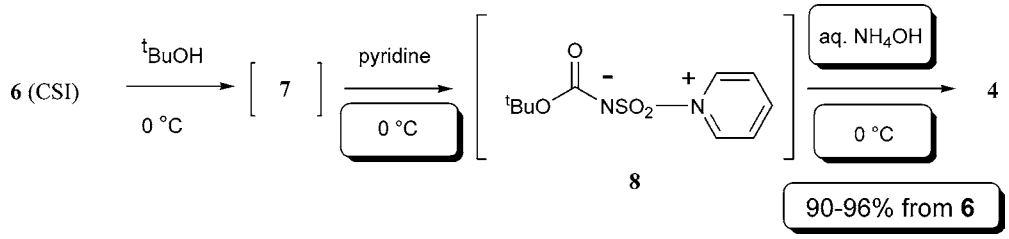
Scheme 3. **Improved process**



because the reaction mixture contained ammonium chloride as sticky, adhesive precipitates. The improved process can be easily scaled up because ammonium chloride is dissolved in the aqueous medium.

We then developed an efficient process for the synthesis of *N*-acylsulfamide **4** which is shown in Scheme 3. Significant improvements have been made in the reaction conditions. In the improved process, the deactivation of intermediate **7** with pyridine at 0 °C afforded water-resistant intermediate **8** which was converted in situ to the target compound **4** in the presence of water at 0 °C in 90−96% isolated yields. Aqueous ammonia can be used, and no cryogenic temperatures are necessary for this new one-pot process.

The improved process is a practical and efficient process since it requires no cryogenic temperatures, uses one-pot reactions, and is scalable because of the disappearance of problematical ammonium chloride in the reaction mixture. In view of green chemistry, the use of pyridine for the deactivation of intermediate **7** is a disadvantage. However, pyridine can be easily recovered from the waste for reuse.

Conclusions

We describe the practical one-pot synthesis of *N*-(*tert*-butoxycarbonyl)sulfamide (**4**), a raw material for the sulfamoyl-containing side chain **3** of a novel carbapenem antibiotic doripenem hydrate (**1**). Chlorosulfonyl isocyanate (CSI) was converted to *N*-(*tert*-butoxycarbonyl)aminosulfonyl chloride (**7**), which is an extremely unstable intermediate against moisuture. The deactivation of intermediate **7** with pyridine afforded *N*-(*tert*-butoxycarbonyl)aminosulfonylpyridinium salt (**8**) which was converted to the target compound **4** in the presence of water at 0 °C in 90−96% isolated yields. Aqueous ammonia can be used, and no cryogenic temperatures are necessary for this one-pot process.

Experimental Section

Materials and Instrumentation. All commercially available materials and solvents were used as received. NMR experiments were conducted by using a Mercury 300 NMR spectrometer (Varian). Reaction heats were measured on a RC1 reaction calorimeter (Mettler Toledo).

The Improved Process (Scheme 3). *Preparation of Compound **4** via Intermediate **8** Using Aqueous Ammonia.* *tert*-Butyl alcohol (21.0 g, 1.0 equiv) was added dropwise to a solution of chlorosulfonyl isocyanate (**6**) (40.0 g, 283 mmol) in toluene (387 mL) below 0 °C. The reaction mixture was stirred at 0 °C for 20 min. After pyridine (49.2 g, 2.2 equiv) was added dropwise to the reaction mixture below 0 °C, the reaction mixture was stirred at 0 °C for 40 min. Aqueous ammonia (25%, 114 g, 5.9 equiv) was added dropwise to the reaction mixture below 0 °C. After water (32 mL) was added at 0 °C, the reaction mixture was stirred at 0 °C for 2.5 h. Each layer was separated. The aqueous layer was washed with toluene (150 mL). Each organic layer was back-extracted with water (128 mL). The combined aqueous extracts were acidified with sulfuric acid (22%, 271 g) to adjust the pH to 2. The resulting precipitate was collected by filtration, washed with water, and dried to give compound **4**[2,4] (53.4 g, 96%) as a colorless crystalline powder: mp 131−133 °C (lit. 130−131 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.43 (s, 9H, *tert*-Bu-), 7.27 (s, 2H, -NH_2), 10.79 (s, 1H, -NH-).

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Supporting Information Available

The procedures and heat-flow charts of the measurement with a RC1 reaction calorimeter (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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