A CONTRIBUTION TO THE SYNTHESIS OF NEW CEPHALOSPORINS: 1-AZACEPHEM

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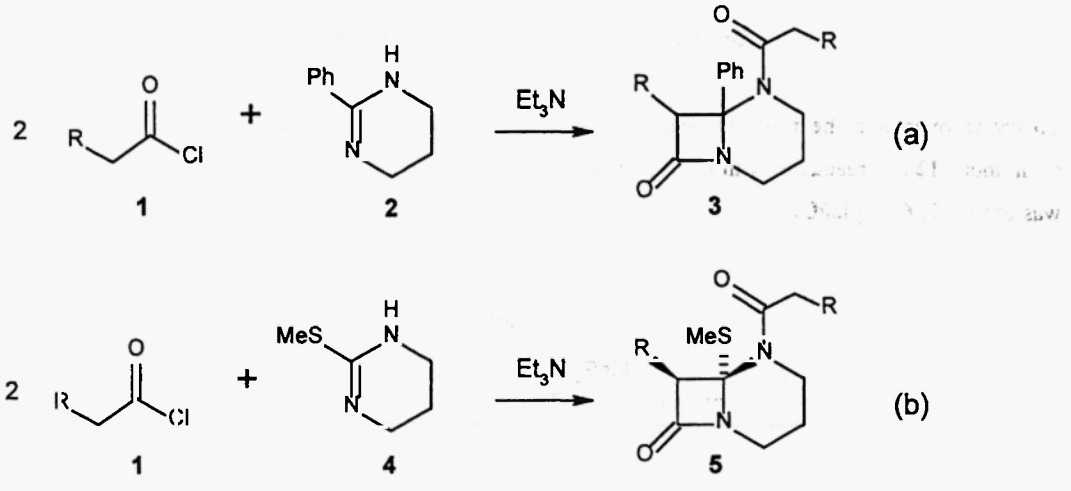
Abstract

The bycyclic β-lactam 1-benzyl-7-phtalimido-4-methyl-6-methylthio-2-oxo-3-cephem was prepared from *N*-phthaloyl glycine chloride and 1-benzyl-4-methyl-2-methylthio-6-oxo-pyrimidine in 61% yield via a Staudinger reaction.

Introduction

The reaction of an acid chloride with a Schiff's base has been the most usual procedure to obtain the 1-azacepham system. Bose and co-workers prepared several compounds using 2-phenyl-1,4,5,6-tetrahydropyrimidine **2** as the Schiff's base (1, 2). Stereoselectivity in the ring-junction was obtained with 2-methylthio-1,4,5,6-tetrahydropyrimidine **3** (Scheme 1). The methylthio group was removed by using Raney-Ni in acetone (3).



R = PhO, N_3, $PhOCH_2CONH$

Scheme 1 – Synthesis of cepham via Staudinger reaction

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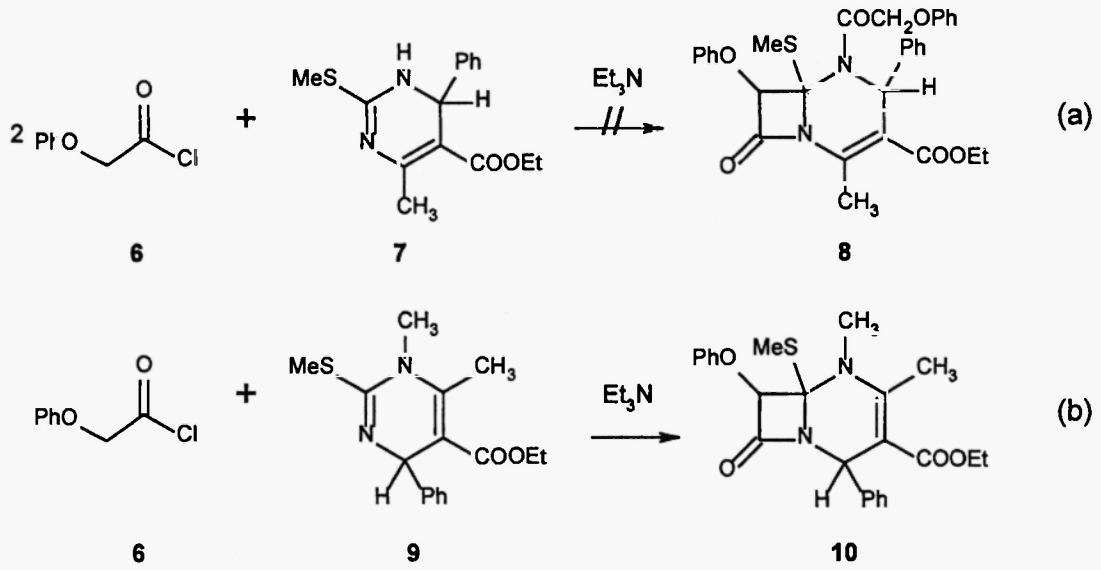
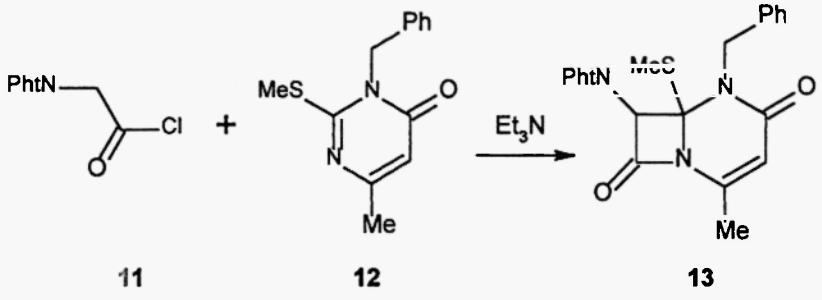
Sharma and co-workers tried to use conjugated dihydro-5-substituted pyrimidines in order to prepare 3,4-cephems (Scheme 2a), but the β-lactams were not formed (4). It was suggested that the lack of reactivity might be related to a "reduced double-bond character in the C=N bond due to a strong conjugation with the substituent in the position 5" (4). When a non-conjugated dihydropyrimidine was used, they succeeded in synthesizing the bycyclic cephem system (Scheme 2b).



Scheme 2 – Synthesis of a non-conjugated cephem ring.

To try to overcome the possible deactivation of the C=N bond in the Schiff's base, we prepared the 4-methyl-pyrimidone **12** and reacted it with the *N*-protected glycine derivative **11** (Scheme 3). The conjugated 1-aza-cephem **13** was formed in 61% yield.



Scheme 3 – Synthesis of 1-aza-cephem

Experimental

NMR spectra were recorded on a Brucker Advance DPX using a magnetic field of 4,70 Tesla and resonance frequencies of 200.13 MHz (^{1}H) and 50.3 MHz (^{13}C). Chemical shifts (δ) are in ppm using tetramethylsilane as reference. FTIR

analyses were carried out on a Nicolet 760 using KBr disks. Melting points were obtained in a Koefler apparatus and are uncorrected. Dichloromethane and triethylamine were dried over CaH_2 and distilled before use. THF was dried with sodium/benzophenone. The Staudinger reactions were conducted under an argon atmosphere.

Synthesis of 4-methyl-2-methylthio-6-oxo-pyrimidine (5): To a 1000 mL round bottom flask with a magnetic stirring bar were added 55.6 g (200 mmol) of *S*-methylthiourea sulphate and 300 mL of distilled water. After dissolution, the flask was immersed in a water/ice bath and a solution of 14.4 g of KOH in 50 mL of water was added slowly. Then 30 mL (230 mmol) of ethyl acetoacetate and 100 mL of distilled water were added. The ice bath was removed and the flask was left in the dark, at room temperature, and stirred for 2 days. The solid formed was filtered under vacuum, washed with 300 mL of distilled water and dried over P_2O_5. Yield: 25.3 g (64%). Melting point: 223-225°C (lit.(5): 218-221°C). FTIR (ν, cm^{-1}): 3001, 1642. ^{1}HNMR ($DMSOd_6$, δ in ppm): 2.14 (s, 3H), 2.44 (s, 3H, CH_3S), 5.93 (s, 1H), 12.4 (s, large, 1H). ^{13}CNMR ($DMSOd_6$, δ in ppm): 13.2, 23.9, 162.9, 163.9, 164.8.

Synthesis of 1*-benzyl-4-methyl-2-methylthio-6-oxo-pyrimidine* **12** (6): to a 100 mL round bottom flask with a magnetic stirring bar were added 1.72 g (10 mmol) of 4-methyl-2-methylthio-6-oxo-pyrimidine and 1.72 g of a 35% suspension of KH in mineral oil (ca. 15 mmol). 40 mL of anhydrous THF were added to the flask under argon atmosphere. *Warning: exothermic*! Then 10 mL of triethylamine and 1.78 mL (15 mmol) of benzyl bromide were added to the flask. After twelve hours at 25°C, the solvent was removed by evaporation under vacuum. 50 mL of ethyl ether were added and the reaction mixture was added to crushed ice. After extraction with ethyl ether (5 X 50 mL) the organic phase was dried over anhydrous sodium sulphate and the solvent was removed under vacuum. After flash chromatography (hexane-ethyl acetate, 9:1), a white solid was isolated. Yield: 870 mg (33%). Melting point: 104-105°C. FTIR (ν, cm^{-1}): 1676, 1494, 1454, 1431. ^{1}HNMR ($CDCl_3$, δ in ppm): 2.21 (s, 3H), 2.52 (s, 3H, CH_3S), 5.29 (s, 2H, $C\underline{H}_2Ph$), 6.13 (s, 1H), 7.32 (s, 5H). ^{13}CNMR ($CDCl_3$, δ in ppm): 15.3 ($\underline{C}H_3S$), 23.9 ($NC\underline{C}H_3C{=}C$), 46.9 ($N\underline{C}H_2Ph$), 107.8 ($C{=}C\underline{C}HC$), 127.7-135.2 (phenyl), 162.1 (C=O), 162.6 (2 signals, $H_3C\underline{C}{=}C$ and $H_3CS\underline{C}{=}N$).

Synthesis of 1-benzyl-4-methyl-6-methylthio-2-oxo-7-phtalimido-1-azaceph-3-em **13** (7): To a 50 mL round bottom flask with a magnetic stirring bar were added 410 mg (2 mmol) of N-phtaloylglycine. 10 mL of dichloromethane were added under an argon atmosphere. The mixture was cooled to –78°C and 0.45 mL (ca. 5 mmol) of oxalyl chloride and one drop of DMF were added. The cooling bath was removed and, after complete dissolution, the solvent was evaporated to dryness under vacuum. The yellow solid was dissolved with 10 mL of dichloromethane, cooled to –78°C and 2.0 mL of triethylamine were added. (The reaction mixture became orange, denoting ketene formation.) In another round bottom flask, 524 mg of 1-benzyl-4-methyl-2-methylthio-6-oxo-pyrimidine **12** were dissolved in 4 mL of dichloromethane. The latter solution was slowly added to the flask with the ketene. The flask was washed twice with 1 mL of dichloromethane. After 10 min, the cooling bath was removed and the mixture stirred at room temperature during twelve hours. The clear solution obtained was washed with 1M HCl, water and dried with anhydrous sodium sulphate. The solvent was removed under vacuum and the oil was dissolved in hot 95% ethyl alcohol. After cooling, a yellowish solid was formed. Yield: 553 mg (61%). FTIR (ν, cm^{-1}): 1775. ^{1}HNMR ($CDCl_3$, δ in ppm): 2.21 (s, 3H), 2.51 (s, 3H, CH_3S), 5.28 (s, 2H, $C\underline{H}_2Ph$), 6.17 (s, 1H), 7.30 (s, 5H, phenyl), 7.71-7.90 (m, 4H, phtaloyl). ^{13}CNMR ($CDCl_3$, δ in ppm): 15.3 ($\underline{C}H_3S$), 23.9 ($NC\underline{C}H_3C{=}C$), 47.0 ($N\underline{C}H_2Ph$), 58.5 ($H_3CS\underline{C}{=}N$), 107.8 ($C{=}C\underline{C}HC$), 123.6,

132.2, 134.2 (phtaloyl), 127.7, 127.8, 128.7, 134.6, 135.1 (phenyl), 162.1 ($NCH_3\underline{C}$=C), 163.0 (C=O), 167.7 (C=O phtaloyl), 169.6 (C=O).

Results and Discussion

The synthesis of a 1-aza-ceph-3-em bicyclic β-lactam **13** via a Staudinger reaction between the acid chloride **11** and the pyrimidine **12** was achieved. Pyrimidine **12** was obtained by benzylation of 4-methyl-2-methylthio-6-oxo-pyrimidine which, in turn, was produced according a published procedure (5). ^1H and ^{13}C spectra of **13** strongly indicated a diastereoisomeric pure compound. No nuclear Overhauser effect was observed between β-lactamic hydrogen and MeS. The absence of such effect suggested, although not conclusively, that the stereochemical relationship between PhtN and MeS groups can be stated as *cis*.

In order to eliminate a synthetic step, we tried the synthesis without the benzylation of N_1 of the pyrimidine, using two equivalents of the acid chloride. However, no β-lactam was formed. In another attempt, the use of two equivalents of ethyl chloroformate, to form a mixed anhydride with *N*-phtaloylglycine and to protect the pyrimidine N_1 position, did not lead to the desired β-lactam. In both cases, only *N*-substituted pyrimidines were formed (**8**). These *N*-substituted pyrimidines are *N*-acylated derivatives, and, according to Sharma and collaborators (4), it is to be expected that the C=N double bond character would be reduced and no ring closure should be observed.

The synthesis of 1-aza-ceph-3-em via a Staudinger reaction was achieved when an alkyl group was used to protect the N_1 position in the pyrimidine ring and no deactivating, i.e., electron withdrawing group, is present in position 5. Further investigation is needed to evaluate the reactivity of a 4-carboxyl substituted pyrimidine. This building block is important since most of the biologically active β-lactams present a carboxyl in this position.

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