A FACILE ACCESS TO 3-CEPHEMS BY EMPLOYING NOVEL LEWIS ACID MEDIATED REACTION†

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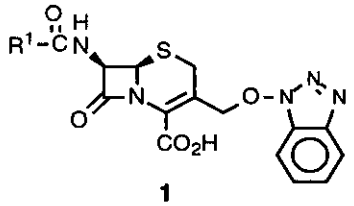
Abstract —— A novel and efficient process to afford 3-cephem Δ^3 derivatives was established by employing ZnI_2 - $NaHCO_3$ - DMF system.

In recent years, considerable interest has been focused on altering the C-3 substituent of the cephem nucleus to obtain a variety of analogues with enhanced biological activities.[1] And it has long been known that electron-withdrawing groups on the 3-position of cephems enhance antibacterial activity.[2]

In the course of our continuous chemical studies on cephalosporins, we designed novel 3-methyloxy-benzotriazole derivative (**1**), as a new lead compound having potent antibacterial activity. First, nucleophilic addition at the allylic C-3' position of 3-chloromethyl-3-cephem (**2**) was performed. This route was considered short and convenient to synthesize our target molecule. However, the reaction of **2** with 1-hydroxybenzotriazole (HOBT) and sodium bicarbonate ($NaHCO_3$) in *N*,*N*-dimethylformamide (DMF) afforded the undesired Δ^3/Δ^2 -migration product (**4a**) as a major product. In the field of the cephalosporin chemisty, this well-known Δ^3 / Δ^2 isomerization[1, 3] represents one of the major obstacle



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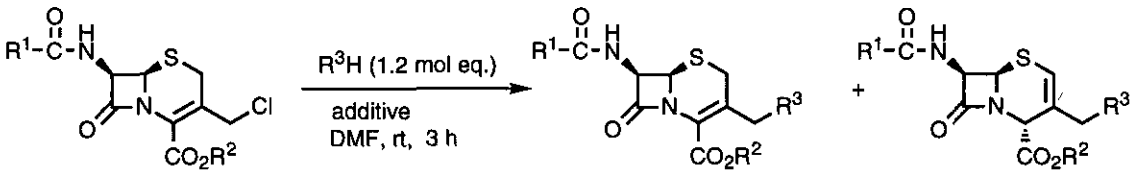
† This paper is dedicated to Dr. Koji Nakanishi, Professor of Columbia University, on the occasion of his 75th birthday, and with gratitude for his many contributions in organic chemistry.

toward the production of the desired product.

Here, we wish to report the novel method to prepare specifically the Δ^3 product (**3**) without the formation of isomer (**4**). We have already reported that mild Lewis acids such as $SnBr_2$ and $ZnBr_2$ were found to exhibit excellent catalytic activity for *cis*-opening of the epoxide with thiols[4] and regioselective ring-opening of aryl orthoacetates with acetyl bromide.[5] Thus an appropriate Lewis acid would activate the allylic position of **2**, bearing the chlorine atom to be substituted under acidic or neutral conditions. Then, we investigated several conditions including using Lewis acid as shown in **Table 1**.[6] The enhancement of nucleophilicity of the oxybenzotriazole anion did not improve the Δ^3 / Δ^2 ratio (Entry **2**). Next, ZnI_2 was added to the reaction mixture (**2** and HOBT in DMF) as an activating agent of the allylic position of **2**, **3a** was obtained in 11% yield along with the starting material (**2**) (63% yield) without detecting the side product (**4a**). This ZnI_2-mediated process generated HCl which would interrupt the reaction proceeding. Therefore, we added $NaHCO_3$ powder as an acid scavenger to the reaction in the presence of ZnI_2, the reaction proceeded smoothly and the selectivity was dramatically improved and the desired isomer (**3a**) was obtained in excellent yield (Entry **4**). $ZnCl_2$ and NaI were ineffective on the reaction which suggested that ZnI_2 was a suitable Lewis acid catalyst for this reaction (Entries **5** and **6**). Furthermore, by using the process, desired succinimide derivative (**3b**) was obtained as a sole product (Entry **7**). We now established more efficient process to afford 3-cephem Δ^3 derivatives by employing ZnI_2 - $NaHCO_3$ - DMF system.

Scheme 1



2 **3** **4**

R^1 = Benzyl
R^2 = *p*-Methoxybenzyl

a : R^3 = OBT
b : R^3 = OSU

Table 1. Substitution Reaction of 3-Chloromethyl-3-cephem by Nucleophiles.

Entry	R^3H	Additive (mol %)	Products yield[a] (3+4) %	Ratio[b] 3/4
1	HOBT[c]	$NaHCO_3$ (150)	71	0.6
2	NaOBT[d]	15-Crown-5 (10)	100	0.3
3	HOBT	ZnI_2 (40)	11	>100[e]
4	HOBT	ZnI_2 (40), $NaHCO_3$ (150)	93	>100[e]
5	HOBT	NaI (40), $NaHCO_3$ (150)	63	1.7
6	HOBT	$ZnCl_2$ (40), $NaHCO_3$ (150)	100	1.2
7	HOSU[f]	ZnI_2 (40), $NaHCO_3$ (150)	70	>100[e]

a) Isolated yield.
b) Isomers were separated by column chromatography on SiO_2 and determined the ratio.
c) HOBT : 1-Hydroxybenzotriazole
d) NaOBT : Sodium 1-oxybenzotriazole
e) Regio isomer (**4**) was not detected in 300 MHz ^{1}H-NMR spectrum.
f) HOSU : *N*-Hydroxysuccinimide

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6. A typical procedure is as follows : To a solution of **2** (250 mg, 0.51 mmol) and 1-hydroxybenzotriazole (83 mg, 0.61 mmol) in DMF (8 mL) were successively added ZnI_2 (65 mg, 0.2 mmol) and $NaHCO_3$ (63 mg, 0.77 mmol) at rt and the reaction mixture was continued to stir for 2 h.

The reaction mixture was poured into ice-water and extracted with AcOEt. The extract was washed with water, sat. aq. $NaHCO_3$, dil. HCl and brine, dried over $MgSO_4$, and the solvent was removed in *vacuo*. The resulting solid was triturated with Et_2O to give **3a** (280 mg) in 93% yield, mp 162-163 ℃ ($CHCl_3$-Et_2O) Anal. Calcd for $C_{30}H_{27}N_5O_6S$: C, 61.53; H, 4.65; N, 1196; S, 5.47. Found: C, 61.89; H, 4.56; N, 12.20; S, 5.56. IR (Nujol): 1785, 1720, 1655 cm^{-1}. FAB-MS m/z 586 (MH^+). ^{1}H-NMR ($CDCl_3$) δ 3.62 (2H, s, 2-H), 3.66 (1H, d, J = 19 Hz, CH_2CON), 3.78 (3H, s, OMe), 3.91 (1H, d, J = 19 Hz, CH_2CON), 4.95 (1H, d, J = 5 Hz, 6-H), 5.01 (2H, s, CO_2CH_2), 5.18 (1H, d, J = 11 Hz 3'-H), 5.44 (1H, d, J = 11 Hz, 3'-H), 5.82 (1H, dd, J = 5 and 10 Hz, 7-H), 6.19 (1H, d, J = 10 Hz, NH), 6.8 ~ 8.0 (13H, m, Ar-H).

4a: ^{1}H-NMR ($CDCl_3$) , δ 3.63 (2H, s, CH_2CON), 3.79 (3H, s, OMe), 4.88 (1H, d, J = 11 Hz, 3'-H), 5.10 (1H, d, J = 11 Hz, 3'-H), 5.16 (2H, s, CO_2CH_2), 5.20 (1H, d, J = 4 Hz, 6-H), 5.35 (1H, d, J= 2 Hz, 2-H), 5.59 (1H, dd, J = 4 and 8 Hz, 7-H), 6.14 (1H, d, J = 2 Hz, 4-H), 6.34 (1H, d, J = 8 Hz, NH), 6.7 ~ 8.0 (13H, m, Ar-H).

3b : IR (Nujol): 1785, 1730, 1715, 1650 cm^{-1}. FAB-MS m/z 566 (MH^+). ^{1}H-NMR ($CDCl_3$), δ 2.54 (4H, s, CH_2CH_2), 3.50 (2H, s, CH_2CON), 3.72 (3H, s, OMe), 3.74 (2H, s, 2-H), 4.66 (1H, d, J = 13 Hz, 3'-H), 4.81 (1H, d, J = 13 Hz, 3'-H), 5.02 (1H, d, J= 5 Hz, 6-H), 5.03 (1H, d, J= 5 Hz, CO_2CH_2), 5.22 (1H, d, J = 5 Hz, CO_2CH_2), 5.70 (1H, dd, J = 5 and 9 Hz, 7-H), 6.8 ~ 7.4 (9H, m, Ar- H, 9.15 (1H, d, J= 9 Hz, NH).

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