# Synthesis of 3-Chloro-$\Delta^3$-cephem-4-carboxylate by Addition/Cyclization of Allenecarboxylate. Copper(II)-Promoted Aerobic Oxidation of Arenesulfinic Acids

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The selective transformation of allenecarboxylate derived from penicillin into 3-chloro-$\Delta^3$-cephem-4-carboxylate was successfully achieved by an addition/cyclization reaction with chloride salts in aerobic media containing a copper(II) catalysts, in which copper(II)-catalyzed aerobic oxidation of in situ generated benzenesulfinate ion into less nucleophilic sulfonate ion prior to the nucleophilic addition of the former ion to the allenecarboxylate would completely eliminate the formation of undesired 3-phenylsulfonyl-$\Delta^3$-cephem-4-carboxylate. Under similar aerobic conditions, arenesulfinates salts and arenesulfinic acids were smoothly oxidized to the corresponding sulfonate salts and sulfonic acids, respectively.

3-Norcephalosporins **1** bearing heteroatom substituents directly attached to the C(3)-position are an important class of $\beta$-lactam antibiotics particularly as potent orally active drugs.[1—5] So far disclosed synthesis of the 3-norcephalosporins **1** mainly relies upon substitution of the C(3)-hydroxyl group of 3-hydroxy-$\Delta^3$-cephem-4-carboxylates derived from either natural penicillins or cephalosporins.[6—10] These methods, however, involve laborious operations and/or often accompany undesired $\Delta^3/\Delta^2$-migration of the double bond of **1**.

Recently, we and Farina's group have disclosed a conceptually new synthetic route to the C(3)-substituted $\Delta^3$-cephem-4-carboxylates **2** through a sequential addition/cyclization reaction of allenecarboxylates **2** derived from penicillin;[11—15] namely, the construction of the $\Delta^3$-cephem framework as well as introduction of the required C(3)-substituents (Y) have been achieved by addition of nucleophiles ($Y^-$) to **2** and simultaneous cyclization of the adduct **5** to **1** as illustrated in Scheme 1 (path a). The addition/cyclization methodology has been successfully applied to the synthesis of the $\Delta^3$-cephem-4-carboxylates **1** bearing various C(3)-heteroatom substituents, e.g. amino, azido, and sulfenyl groups.[11] In contrast, the addition/cyclization reaction of **2** with chloride salts ($Y^- = Cl^-$), e.g. calcium chloride, afforded only a small amount of 3-chloro-$\Delta^3$-cephem-4-carboxylate **4** (6% yield) together with 3-phenylsulfonyl-$\Delta^3$-cephem-4-carboxylates **3** (69% yield).[11] The disappointing results can be ascribed to the fact the benzenesulfinate anion, formed at the cyclization stage (**2** to **4**), is more nucleophilic than chloride anion; thus the sulfinate anion acts as a predominant nucleophile affording **3** as the major product (Scheme 1, path b).[16] Farina's group also attempted an analogous addition/cyclization reaction with lithium chloride but failed in obtaining the C(3)-chloro-substituted $\Delta^3$-cephem-4-carboxylate derivatives.[15]

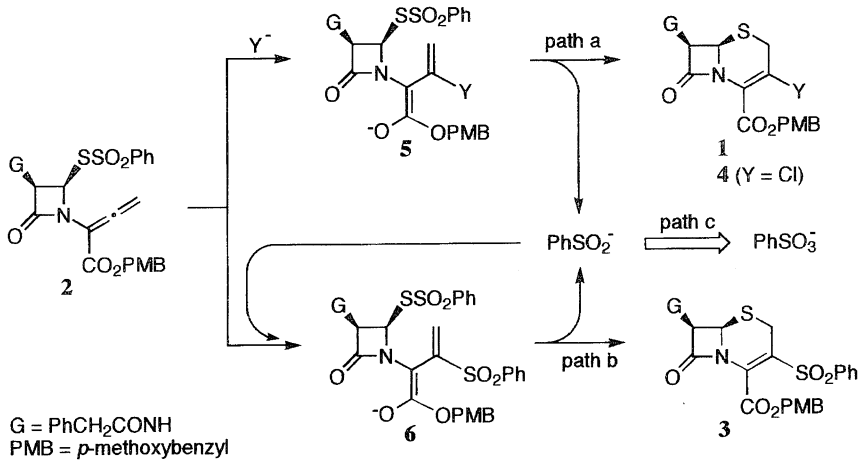
The 3-chloro-$\Delta^3$-cephem-4-carboxylate **4** is well recognized as an essential framework of a potent orally active drug, Cefaclor.[2,17] Our continuing efforts for the construction of the 3-chloro-$\Delta^3$-cephem framework was, therefore, focused on the removal of the sulfinate ion generated in the addition/cyclization reaction of **2**. Consequently, we found that the aerobic oxidation of the in situ generated sulfinate ion into less nucleophilic sulfonate ion (path c) could allow the predominant attack of chloride ion to the allenecarboxylate **2**, leading to the desired 3-chloro-$\Delta^3$-cephem-4-carboxylate **4**.

Herein, we describe a selective transformation of allenecarboxylate **2** into 3-chloro-$\Delta^3$-cephem-4-carboxylate **4** in aerobic media containing a catalytic amount of a copper(I or II) salt and 2—11 folds excess amount of a chloride salt.

## Experimental

**Materials.** The allenecarboxylate **2** was prepared by the reported procedure[11] immediately before use. Lithium chloride was dried by a heat-gun in vacuo immediately before use. *N*-Methyl-2-pyrrolidone (NMP) was distilled over potassium hydride under nitrogen and stored under nitrogen. All other chemicals and solvents were used as supplied without further purification.

**Instrumentation.** NMR spectra were determined with a Varian Gemini-200 (200 MHz for proton and 50 MHz for carbon-13). The $^1$H NMR signals are expressed in ppm downfield from internal tetramethylsilane (0 ppm). The $^{13}$C NMR signals are expressed in ppm using chloroform-*d* as a reference (77 ppm). IR spectra were obtained with a JASCO Valor III FT-IR spectrometer. Mass spectra were recorded with a Hitachi M-80 double focusing mass spectrometer. High-performance liquid chromatography (HPLC) was executed with a Waters HPLC instrument equipped with a 510 LC pump, a 440 UV detector, and a Hitachi D-2500 integrator. The HPLC analysis of **2**, **3**, and **4** was performed under the following conditions: column: Waters $\mu$-Bondasphere C18 (3.9 mm$\phi \times$150 mm), mobile phase: $CH_3CN/H_2O$ 50 : 50, flow rate:




Scheme 1. Addition/cyclization reaction of allenecarboxylate **2**.

1.5 ml min$^{-1}$, detection: UV 254 nm. The HPLC analysis of **7** and **8** was performed under the following conditions: column: Waters $\mu$-Bondapak $NH_2$ (3.9 mm$\phi$ × 300 mm), mobile phase: 0.01 mol dm$^{-3}$ $KH_2PO_4$ containing 1 vol% of $CH_3CN$, flow rate: 1 ml min$^{-1}$, detection: UV 254 nm. External standard method was employed for determination of the products and the substrates by HPLC. UV absorption spectra of peaks on HPLC were obtained with Shimadzu HPLC instrument equipped with an LC-10T pump, an LC-10AV UV detector, and a C-R6A integrator.

**Aerobic Oxidation of Sodium Benzenesulfinate (7a) into Sodium Benzenesulfonate (8a) with Copper(II) Chloride.** A mixture of sodium benzenesulfinate dihydrate (**7a**, 1.006 g, 5 mmol) and copper(II) chloride dihydrate (172 mg, 0.2 molar amount) in NMP (20 ml) was stirred for 1 h at 19—21 °C under bubbling oxygen. An aliquot of the reaction mixture was analyzed by HPLC, showing the presence of sodium benzenesulfonate (**8a**) (95%). After evaopration of most of the solvent, the residue was dissolved in 0.1 mol dm$^{-3}$ hydrochloric acid (10 ml) and, then, the aqueous solution was washed with ethyl acetate. To the aqueous solution was added 20% sodium hydroxide until the pH of the solution was 11—12, while blue-green precipitates appeared. The precipitates were removed by passing through a short celite column (20 mm$\phi$ × 10 mm). To the aqueous solution was added NMP (20 ml) and, then, the solution was concentrated to the volume of 6 ml. A small amount of precipitates was removed by filtration and, then, to the filtrate was added acetonitrile (40 ml), while precipitates were formed. Thus formed solids were collected by filtration and washed with acetonitrile. The solids were dried in vacuo to give sodium benzenesulfonate (**8a**, 560 mg, 62% yield). The IR spectrum of the product **8a** is identical with that of the authentic sample.[18a]

The aerobic oxidations of benzenesulfinic acid (**7b**), sodium *p*-toluenesulfinate (**7c**), sodium *p*-chlorobenzenesulfinate (**7d**), *p*-bromobenzenesulfinic acid (**7e**), and *p*-nitrobenzenesulfinic acid (**7f**) were similarly performed and the yields of the corresponding sulfonic acids and salts **8** were determined by HPLC. The products **8b**—**f** were isolated as the corresponding sodium salts (M = Na) and their IR spectra are identical with those of the authentic samples.[18] The reaction conditions and results and results are summarized in Table 2.

**Transformation of Allenecarboxylate 2 into 3-Chloro-$\Delta^3$-cephem-4-carboxylate 4.** To a mixture of the allenecarboxylate **2** (231 mg, 0.4 mmol) and copper(II) chloride dihydrate (14 mg, 0.2 molar amount) in NMP (5 ml) was added a solution of lithium chloride (184 mg, 11 molar amounts) in NMP (5 ml). The mixture was stirred under bubbling oxygen at 18—22 °C. After most of **2** was consumed (6 h), the reaction mixture was diluted with ethyl acetate and the solution was washed three times with water and once with brine. The organic layer was separated and dried over $MgSO_4$. After evaporation of the solvents, the residue was chromatographed ($SiO_2$, benzene/ethyl acetate: 4/1—1/1) to give 3-chloro-$\Delta^3$-cephem-4-carboxylate **4** (123 mg, 65%): IR (KBr) 3352, 1776, 1727, 1665, 1517, 1248, 1223, 1176 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ = 3.43 (d, $J$ = 18 Hz, 1H), 3.63 (ABq, $J$ = 16 Hz, 2H), 3.74 (d, $J$ = 18 Hz, 1H), 3.80 (s, 3H), 4.97 (d, $J$ = 5 Hz, 1H), 5.22 (s, 2H), 5.81 (dd, $J$ = 5, 9 Hz, 1H), 6.17 (d, $J$ = 9 Hz, 1H), 6.88 (m, 2H), 7.23—7.42 (m, 7H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ = 31.5, 43.6, 55.8, 57.8, 59.4, 68.7, 114.5, 124.7, 125.7, 127.1, 128.0, 129.5, 129.8, 131.2, 134.5, 160.4, 160.6, 165.3, 172.0; Anal. Calcd for $C_{23}H_{21}ClN_2O_5S$: C, 58.41; H, 4.48; N, 5.92%. Found: C, 58.25; H, 4.50; N, 5.84%.

HPLC analysis of the first aqueous washing showed the presence of benzenesulfonate ion (72% yield). The UV absorption spectrum of the peak on HPLC was identical with that of the authentic sample, i.e. sodium benzenesulfonate **8a**.[18a]

## Results and Discussion

**Aerobic Oxidation of Arenesulfinates 7.** The oxidation of benzenesulfinate anion into benzenesulfonate ion can be easily performed with various oxidizing agents, e.g. alkaline sodium permanganate, alkaline hydrogen peroxide, nitric acid, iodine, and hypochlorite.[19] The functional groups of **2** and/or **4**, however, can not survive the oxidation conditions. We therefore investigated transition metal catalyzed aerobic oxidation of the sulfinate anion as an alternate to the conventional oxidations and found that copper(II) chloride could efficiently promote the oxidation of the sulfinate ion into the sulfonate ion.

The aerobic oxidation of sodium benzenesulfinate dihydrate (**7a**) was performed in the presence of copper(II) chloride (0.2 molar amount) in *N*-methylpyrrolidone (NMP) for 1 h at 19—21 °C to give benzenesulfonate **8a** in 96% yield (Scheme 2 and Entry 1 in Table 1).[20] The combination of copper(II) chloride and oxygen is indispensable; thus, in the absence of the copper(II) chloride, most of **7a** was recovered (2 h) (Entry 2 in Table 1), while the reaction with 0.2 molar amount of the copper(II) chloride under argon atmosphere

Table 1. Oxidation of Sodium Benzenesulfinate (**7a**) with Copper(II) Chloride[a]

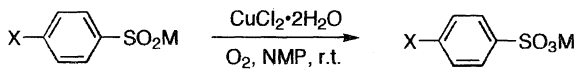
| Entry | $CuCl_2 \cdot 2H_2O$ | LiCl | Atmosphere | Time | **8a** | **7a** |
|---|---|---|---|---|---|---|
| | molar amount | molar amount | | h | Yield/%[b] | Recovery/%[b] |
| 1 | 0.2 | — | $O_2$ | 1 | 96 | 2 |
| 2 | — | — | $O_2$ | 2 | — | 100 |
| 3 | 0.2 | — | Ar | 1 | 18 | 77 |
| 4 | 0.2 | 2 | $O_2$ | 1 | 94 | 5 |

a) Reaction conditions: $PhSO_2Na \cdot 2H_2O$ (**7a**) 0.5 mmol, NMP 2 ml, 19—21 °C. b) Determined by HPLC.

Table 2. Aerobic Oxidation of Benzenesulfinic Acids and Salts **7** with Copper(II) Chloride[a]

| Entry | Substrate **7** | | | Time | Product **8** |
|---|---|---|---|---|---|
| | X | M | | h | Yield/%[b] |
| 1 | H | H | (**b**) | 1 | 81 |
| 2 | $CH_3$[c] | Na | (**c**) | 1 | 96 |
| 3 | Cl[d] | Na | (**d**) | 1 | 97 |
| 4 | Br | H | (**e**) | 1 | 77 |
| 5 | $NO_2$ | H | (**f**) | 6 | 83[e] |

a) Reaction conditions: **7** 0.5 mmol, $CuCl_2 \cdot 2H_2O$ 0.2 molar amount, NMP 2 ml, $O_2$ atmosphere, 20—21 °C. b) Determined by HPLC. c) Tetrahydrate. d) Containing 14 wt% of water. e) 15% of the substrate was recovered.




**7** **8**

**a**: X = H, M = Na; **b**: X = H, M = H; **c**: X = $CH_3$, M = Na; **d**: X = Cl, M = Na; **e**: X=Br, M = H; **f**: X = $NO_2$, M = H.

Scheme 2. Copper(II)-catalyzed aerobic oxidation of benzenesulfinate derivatives **7**.

afforded only 18% yield of the sulfonate **8a** (Entry 3 in Table 1).[21,22] It is worthy to note that the conversion of **7a** to **8a** was not affected by the presence of lithium chloride (2 molar amounts) (Entry 4 in Table 1).[23]

The copper(II)-catalyzed aerobic oxidation can be successfully applied to the oxidation of benzenesulfinic acid (**7b**) and substituted benzenesulfinic acids and salts **7c—f**. The oxidation of benzenesulfinic acid (**7b**) was similarly performed to give the sulfonic acid **8b** in 81% yield (Entry 1 in Table 2). The oxidation of sodium *p*-toluenesulfinate (**7c**), sodium *p*-chlorobenzenesulfinate (**7d**), *p*-bromobenzenesulfinic acid (**7e**), and *p*-nitrobenzenesulfinic acid (**7f**) gave the corresponding sulfonic acids and salts **8c—f** in 81, 96, 97, 77%, and 83% yields, respectively (Table 2).

**Addition/Cyclization Reaction of Allenecarboxylate 2 to 3-Chloro-$\Delta^3$-cephem-4-carboxylate 4.** The success in the copper(II)-catalyzed aerobic oxidation of sodium benzenesulfinate **7a** to the sulfonate **8a**, vide supra, enabled us to investigate the addition/cyclization of the allenecarboxylate **2** with chloride salts in the aerobic media, leading to 3-chloro-$\Delta^3$-cephem-4-carboxylate **4**. A mixture of **2**, copper(II) chloride dihydrate (0.2 molar amount), and lithium chloride (2 molar amounts) in NMP was stirred for 8 h at 19—21 °C under oxygen atmosphere to give **4** in 54% yield (Entry 1 in Table 3).[24] The combination of the three components, i.e. the copper(II) catalyst, chloride salt, and molecular oxygen, was essential for the selective transformation of **2** into **4**. Thus, in the absence of copper(II) chloride, the undesired 3-phenylsulfonyl-$\Delta^3$-cephem-4-carboxylate **3** was obtained as a major product (63%) together with a small amount of **4** (6%) (Entry 2 in Table 3) whereas most of **2** was recovered unchanged in the reaction without lithium chloride (Entry 3 in Table 3). Under argon atmosphere, only 40% yield of **4** together with **3** (11%) was obtained (Entry 4 in Table 3).[25]

The amounts of the copper(II) catalyst and the chloride salt are also important for the efficient transformation of the allenecarboxylate **2** into **4**. Increase of the amount of lithium chloride resulted in increase of the yield of **4**; thus, the reaction of **2** with 11 molar amounts of lithium chloride gave 65% yield of **4** (Entry 1 in Table 4) whereas only 45% yield of **4** was obtained with 1 molar amount of lithium chloride (Entry 2 in Table 4). On the other hand, increase of the amount of the copper(II) chloride brought about the decomposition of **2** and/or **4**; thus, when ca. 1 molar amount of copper(II) chloride was used together with 2.4—12 molar amounts of lithium chloride, the yield of **4** was reduced to 29—50% (Entries 3 and 4 in Table 4). It is interesting to note

Table 3. Transformation of Allenecarboxylate **2** to 3-Chloro-$\Delta^3$-cephem-4-carboxylate **4**[a]

| Entry | $CuCl_2 \cdot 2H_2O$ | LiCl | Atmosphere | Time | Yield/%[b] | | Recovery/%[b] |
|---|---|---|---|---|---|---|---|
| | molar amount | molar amount | | h | **4** | **3** | **2** |
| 1 | 0.2 | 2 | $O_2$ | 8 | 54 | — | 4 |
| 2 | — | 2 | $O_2$ | 5 | 6 | 63 | — |
| 3 | 0.2 | — | $O_2$ | 6 | — | — | 98 |
| 4 | 0.2 | 2 | Ar | 6 | 40 | 11 | — |

a) Reaction conditions: **2** 12—15 mg, NMP 1 ml, 20—24 °C. b) Determined by HPLC.

Table 4. The Amounts of Copper(II) Chloride and Lithium Chloride[a)]

| Entry | $CuCl_2 \cdot 2H_2O$ | LiCl | Time | Yield/%[b)] | | Recovery/%[b)] |
|---|---|---|---|---|---|---|
| | molar amount | molar amount | h | **4** | **3** | **2** |
| 1 | 0.2 | 11 | 3.7 | 65 | Trace | 1 |
| 2 | 0.2 | 1 | 5 | 45 | — | 20 |
| 3 | 1.2 | 12 | 2.5 | 50 | Trace | 4 |
| 4 | 1.1 | 2.4 | 5 | 29 | | 7 |
| 5 | 1.6 | 1.2 | 5 | Trace | — | 95 |

a) Reaction conditions: **2** 12—15 mg, $O_2$ atmosphere, NMP 1 ml, 20—22 °C. b) Determined by HPLC.

that the use of the copper(II) salt (1.6 molar amounts) more than lithium chloride (1.2 molar amounts), no appreciable formation of **4** was observed, resulting in the recovery of most of the starting material **2** (Entry 5 in Table 4). The observation can be reasonably explained by assuming the formation of a poorly nucleophilic complex, e.g. $Li[CuCl_3]$, from lithium chloride and copper(II) chloride.[26)]

Various kinds of copper(II) and copper(I) salts can be used for the transformation of the allenecarboxylate **2** to 3-chloro-$\Delta^3$-cephem-4-carboxylate **4**; thus, anhydrous copper(II) chloride ($CuCl_2$), copper(II) bromide ($CuBr_2$), copper(II) perchlorate ($Cu(ClO_4)_2 \cdot 6H_2O$), copper(II) sulfate ($CuSO_4 \cdot 5H_2O$), copper(II) acetate ($Cu(OAc)_2$), copper(II) acetylacetonate ($Cu(acac)_2$), copper(I) chloride (CuCl), and copper(I) iodide (CuI) appreciably worked to give **4** as a major product (24—49%) (Entries 1, 2, 3, 4, 5, 6, 7, and 8 in Table 5). On the other hand, copper(II) oxide (CuO), copper(I) oxide ($Cu_2O$), and copper metal were not effective since the undesired 3-phenylsulfonyl-$\Delta^3$-cephem-4-carboxylate **3** was obtained as a major product (50—60%) together with a small amount of **4** (6—9%) (Entries 9, 10, and 11 in Table 5), probably because of their low solubility in NMP. In place of copper(II or I) salts, other metal salts were used but so far examined metal salts, e.g. $MnCl_2$, $FeCl_3$, $CoCl_2$, $NiCl_2$, $ZnCl_2$, and $PdCl_2$, did not efficiently work, mainly affording **3** (56—62%) together with small amounts of **4** (<9%).

The addition/cyclization reaction of the allenecarboxylate **2** with various kinds of chloride salts in combination with copper(II) chloride was examined (Table 6). In the presence of calcium chloride ($CaCl_2$), magnesium chloride ($MgCl_2 \cdot 6H_2O$), cerium(III) chloride ($CeCl_3 \cdot 7H_2O$), and tetraethylammonium chloride ($Et_4NCl$), the desired addition/cyclization reaction proceeded to give 3-chloro-$\Delta^3$-cephem-4-carboxylate **4** in 41—59% yields, whereas ammonium chloride ($NH_4Cl$), sodium chloride (NaCl), and potassium chloride (KCl) were not effective (1—12% yields of **4**).

Above all, it is evident that chloride ion works as a predominant nucleophile in the addition/cyclization reaction of the allenecarboxylate **2** under the aerobic conditions. Subsequently, our attention was set on the extension of the present methodology to the synthesis of other halo-substituted $\Delta^3$-cephem-4-carboxylates. Thus, the addition/cyclization of **2** with other halide salts, such as lithium fluoride, lithium bromide, tetrabutylammonium bromide, and potassium iodide, was carried out under similar aerobic conditions. All our attempts, however, failed; the fluoride and the bromide salts did not effect the addition/cyclization reactions at all, resulting in recovery of most of **2**, while with the iodide salt, a complex mixture containing a small amount of 3-phenylsulfonyl-$\Delta^3$-cephem-4-carboxylate **3** (12% yield) was obtained.

**Mechanistic Consideration.** The formation of the 3-chloro-$\Delta^3$-cephem-4-carboxylate **4** in the aerobic conditions containing copper(II) chloride and lithium chloride seems to

Table 5. Activity of Various Copper Catalysts for the Transformation of **2** to **4**[a)]

| Entry | Cu catalyst/molar amount | | Time | Yield/%[b)] | | Recovery/%[b)] |
|---|---|---|---|---|---|---|
| | | | h | **4** | **3** | **2** |
| 1 | $CuCl_2$ | 0.2 | 5 | 57 | — | 3 |
| 2 | $CuBr_2$ | 0.2 | 5 | 53 | — | 7 |
| 3 | $Cu(ClO_4)_2 \cdot 6H_2O$ | 0.2 | 4.8 | 47 | — | 19 |
| 4 | $CuSO_4 \cdot 5H_2O$ | 0.2 | 5 | 49 | — | 7 |
| 5 | $Cu(OAc)_2$ | 0.2 | 3.5 | 33 | — | 18 |
| 6 | $Cu(acac)_2$ | 0.2 | 4 | 29 | 9 | 11 |
| 7 | CuCl | 0.2 | 2 | 37 | — | 13 |
| 8 | CuI | 0.2 | 5 | 24 | 3 | 3 |
| 9 | CuO | 0.4 | 3 | 6 | 60 | Trace |
| 10 | $Cu_2O$ | 0.2 | 5.5 | 9 | 50 | Trace |
| 11 | Cu powder | 0.2 | 3 | 9 | 56 | 1 |

a) Reaction conditions: **2** 12—15 mg, LiCl 2 molar amounts, $O_2$ atmosphere, NMP 1 ml, 20—22 °C.
b) Determined by HPLC.

Table 6. Efficiency of Various Chloride Salts for the Transformation of **2** to **4**[a,b]

| Entry | Chloride/molar amount | | Time | Yield/%[c] | | Recovery/%[c] |
|---|---|---|---|---|---|---|
| | | | h | **4** | **3** | **2** |
| 1 | $CaCl_2$ | 5 | 6 | 59 | — | Trace |
| 2 | $MgCl_2 \cdot 6H_2O$ | 2 | 6.6 | 47 | — | 9 |
| 3 | $CeCl_3 \cdot 7H_2O$ | 2 | 6.3 | 41 | Trace | 37 |
| 4 | $Et_4NCl$[d] | 2.5 | 5 | 49 | Trace | 10 |
| 5 | $NH_4Cl$ | 3 | 5.5 | 12 | — | 75 |
| 6 | NaCl | 8 | 5 | 5 | — | 93 |
| 7 | KCl | 8 | 5.3 | 1 | — | 95 |

a) Reaction conditions: **2** 12—15 mg, $CuCl_2 \cdot 2H_2O$ 0.2 molar amount, NMP 0.5 ml, $O_2$ atmosphere, 20—22 °C. b) Chloride salts were added as solid. c) Determined by HPLC. d) Added as an NMP solution.

proceed in the manner as we expected (Scheme 1); firstly, the conjugate addition of chloride anion to the allenecarboxylate **2** would take place and subsequent cyclization of the adduct **5** would give 3-chloro-$\Delta^3$-cephem-4-carboxylate **4** together with benzenesulfinate anion (path a). Almost complete exclusion of the formation of the undesired 3-phenylsulfonyl-$\Delta^3$-cephem-4-carboxylate **3** can be ascribed to efficient removal of the in situ generated benzenesulfinate anion by the oxidation to the corresponding sulfonate ion in the aerobic media. In fact, HPLC analysis of the first washing in the workup process showed the presence of benzenesulfonate ion (72% yield). In the final stage, the reduced copper species would be oxidized by molecular oxygen to regenerate copper(II).[27] The stoichiometry of the formation of benzenesulfonate with copper(II) chloride under argon atmosphere (Entry 3 in Table 1) indicates that the oxidation of benzenesulfinate ion with copper(II) chloride would proceed through two electron oxidation process. Therefore, it is likely that copper(0) species would be formed and oxidized to copper(II) salt in the aerobic conditions.

## Conclusion

The selective addition/cyclization reaction of the allenecarboxylate **2** into the 3-chloro-$\Delta^3$-cephem-4-carboxylate **4** was achieved by use of 0.2 molar amount of copper(II) chloride and 2—11 molar amounts of lithium chloride under oxygen atmosphere, in which, no appreciable amount of the undesired 3-phenylsulfonyl-$\Delta^3$-cephem-4-carboxylate **3** was obtained. The exclusion of the addition/cyclization reaction of **2** with benzenesulfinate ion, generated from the cyclization stage (the adduct **5** to **4**), into **3** can be ascribed to the copper(II)-catalyzed aerobic oxidation of benzenesulfinate anion into poorly nucleophilic sulfonate ion prior to the nucleophilic attack of the sulfinate ion to the allene moiety of **2**. Indeed, sodium benzenesulfinate **7a** was smoothly oxidized to the corresponding sulfonate **8a** in an aerobic medium containing a catalytic amount of copper(II) chloride. The reduced copper species, generated from the oxidation of the sulfinate ion, would be smoothly oxidized to copper(II) salt in the aerobic condition.

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15) J. Kant, J. A. Roth, C. E. Fuller, D. G. Walker, D. A. Benigni, and V. Farina, *J. Org. Chem.*, **59**, 4956 (1994).
16) Michael addition of the sulfinate anion to 3-chloro-$\Delta^3$-cephem-4-carboxylate **4** followed by elimination of chloride anion is an alternative route to **3**. However, the addition/elimination reaction seems not to occur under these conditions since most of **4**

was recovered upon treatment of **4** with sodium benzenesulfinate (0.5 molar amount) in NMP (20—22 °C, 4 h).

17) R. R. Chauvette and P. A. Pennington, *J. Med. Chem.*, **18**, 403 (1975).

18) a) Sodium benzenesulfonate (**8a**): "Beilsteins Handbuch der Organischen Chemie," ed by B. Prager, P. Jacobson, P. Schmidt, and D. Stern, Verlag von Julius Springer, Berlin (1928), Band 11, p. 26; b) Sodium *p*-toluenesulfonate (**8c**): "Beilsteins Handbuch der Organischen Chemie," ed by B. Prager, P. Jacobson, P. Schmidt, and D. Stern, Verlag von Julius Springer, Berlin (1928), Band 11, p. 97; c) Sodium *p*-chlorobenzenesulfonate (**8d**) and sodium *p*-bromobenzenesulfonate (**8**, X=Br, M=Na): R. R. Baxter and F. D. Chattaway, *J. Chem. Soc.*, **107**, 1815 (1915); d) Sodium *p*-nitrobenzenesulfonate (**8**, X=$NO_2$, M=Na): "Beilsteins Handbuch der Organischen Chemie," ed by B. Prager, P. Jacobson, P. Schmidt, and D. Stern, Verlag von Julius Springer, Berlin (1928), Band 11, p. 67.

19) K. K. Andersen, "Sulphinic Acids and Their Derivatives," in "Comprehensive Organic Chemistry," Vol. 3, ed by D. N. Jones, Pergamon Press, Oxford (1979), Chap. 11.18, pp. 317—329, and the references cited therein.

20) The HPLC analysis of the reaction mixture on the course of the aerobic oxidation showed that the oxidation of the benzenesulfinate **7a** smoothly proceeded to give the sulfonate **8a** in 83% yield within only 5 min.

21) The yield of sodium benzenesulfonate **8a** under argon atmosphere were linearly increased as the increase of the amount of copper(II) chloride up to 0.5 molar amount; namely, oxidation of sodium benzenesulfinate **7a** with 0.5 molar amount of copper(II) chloride gave **8a** in 47% yield (recovery of **7a**: 46%). However, a larger amount of copper(II) chloride, more than 1 molar amount, did not efficiently work since less than 57% yield of **8a** was obtained.

22) Under the argon atmosphere, the oxygen atom incorporated to sulfonate would come mainly from water of crystallization of $CuCl_2 \cdot 2H_2O$.

23) A similar aerobic oxidation of *p*-toluenesulfinic acid in the presence of copper(II) acetylacetonate and tetrabutylammonium chloride in acetonitrile was reported: H. Bredereck, A. Wagner, R. Blaschke, G. Demetriades, and K.-G. Kottenhahn, *Chem. Ber.*, **92**, 2628 (1959).

24) No appreciable amounts of other products (less than 3% each) were detected on HPLC, $^1$H NMR, and the isolation experiments.

25) The reaction of the allenecarboxylate **2** with increased amounts of copper(II) chloride (1 molar amount) under argon atmosphere could completely remove the formation of **3** but did not improve the yield of **4** (42%).

26) In UV-vis spectra of NMP solutions of copper(II) chloride (0.58 mmol $dm^{-3}$) and lithium chloride (0.12—1.5 mmol $dm^{-3}$), an absorption band at 455 nm was observed. The absorbance (455 nm) linearly increased by addition of lithium chloride up to 0.58 mmol $dm^{-3}$ and kept constant by further addition of lithium chloride. These observations suggest that an 1 : 1 complex of the two salts, tentatively formulated as $LiCuCl_3$, was efficiently formed.

27) It can not be ruled out that active oxygen species, generated from molecular oxygen in the aerobic media involving Cu(II) catalysts, work, in part, as an oxidant for the transformation of the sulfinate anion into the sulfonate anion.