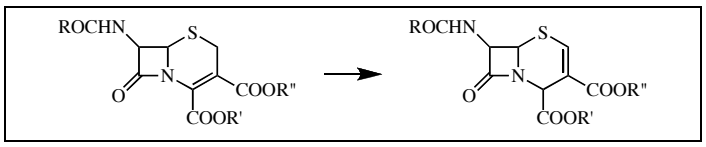
Novel Approach for the Conversion of Natural Δ^3 Cephalosporin Derivatives into Corresponding Δ^2 Cephalosporin Derivatives

Korrapati. V. V. Prasada Rao[a], Ramesh Dandala[a], Vijay. K. Handa[a], Anand. G. Kamat[a], Inti. V. Subramanyeswara Rao[a], Ananta Rani[a] and Andra Naidu[b]

[a] Chemical Research Department, APL Research Center, A division of Aurobindo Pharma ltd, Hyderabad-500 072, Andhra Pradesh, India
[b] Jawaharlal Nehru Technological University, Kukatpally, Hyderabad-500 072, India
E-mail: rdandala@aurobindo.com
Received December 15, 2007



A simple one pot synthetic method for the isomerization of cephem double bond from the natural 3-position to 2-cephem positions is affected by silylation. Thus cephalosporin acids are treated with N-trimethylsilylacetamide (MSA) or *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and the resulting silyl esters are treated with triethylamine at ambient temperature in the same pot to afford Δ^2-cephalosporins, which are potentially related compounds in cephalosporin antibacterial compounds.

J. Heterocyclic Chem., **44**, 1513 (2007).

INTRODUCTION

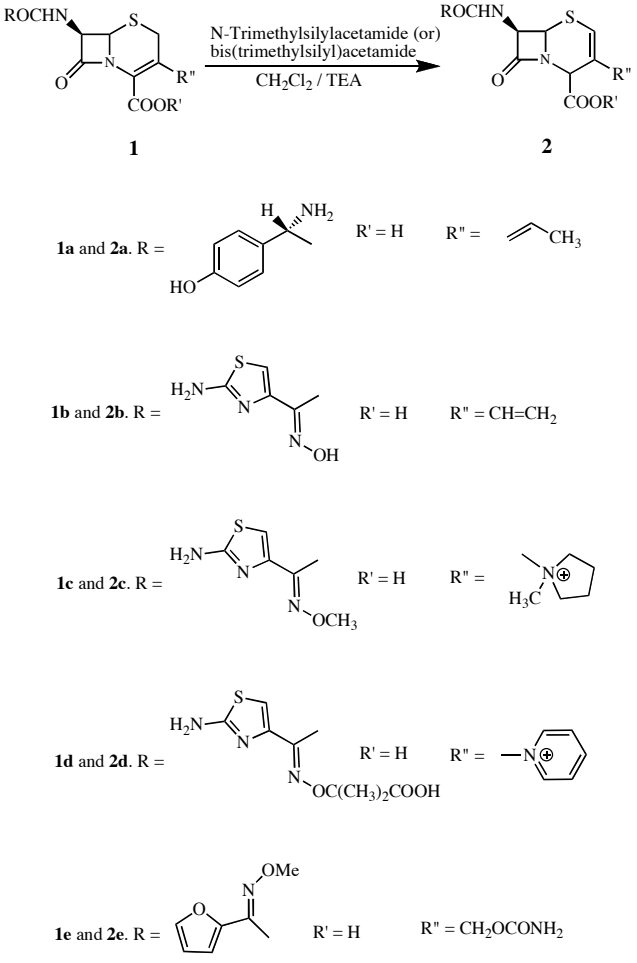
In the synthesis of cephalosporin derivatives, Δ^2-isomers are found to be potential related substances. Therefore, it is necessary to isolate these compounds in pure form for the analytical method developments and validation of the finished products. Δ^2- cephem compounds are particularly useful for the preparation of 3-cephem sulphoxides [1,2] in the conversion of penicillins into corresponding cephem derivatives. Very few synthetic methods are reported in literature for the synthesis of Δ^2-isomers. The isomerization of the naturally occurring 3-cephem double bond to the 2-cephem positions was first reported by Green *et al.* in 1965 [3] and Cocker *et al.* in 1966 [1]. They stated that the cephalosporin acids undergo a slow isomerization in pyridine [1]. Chavutte and Flynn stated that, a facile double bond isomerization occurs with an amine base when the carboxyl group is converted into the methyl ester or otherwise blocked with mixed anhydride or chloride [4]. The cephalosporanic acid, 3-acetoxy-methyl-7-phenylacetamido-3-cephem-4-carboxylic acid was converted to the 2-cephem analogs in 50 % yield in presence of acetic anhydride and pyridine. 7-Acetylamido-3-acetoxymethyl-3-cephem-4-carboxylic-acid methyl ester was isomerized in presence of acetic anhydride and pyridine to an equilibrium mixture, composed of 7:3 ratios of 2-cephem to 3-cephem isomers. Morin *et al.* in 1969 conjectured that the equilibrium composition is largely determined by the size of the 3-methyl substituents [5]. Later Sugioka *et al.* reported a method for the conversion of Δ^3- isomers into corresponding Δ^2-isomers by the treatment with potassium hydroxide in water and the products were isolated by preparative column chromatography [6]. In another report [7] pivaloyloxymethyliodide has been used for the isomerization. The disadvantages of the reported methods are the use of expensive reagents, difficulties in the preparation of methyl esters, acid chlorides and mixed anhydrides and treatment with strong base that leads to beta lactam cleavages and needs very low temperatures -50 to -40°C. These drawbacks have led us to develop a new process for the preparation of Δ^2-cephem compounds in one-pot.

RESULTS AND DISCUSSION

The main objective of the present invention is the use of *N*-trimethylsilylacetamide (MSA) or *N*,*O*-bis(trimethyl-silyl)acetamide (BSA) for the silylation of compound **1,** which on treatment with TEA affords the corresponding 2-cephem derivatives **2** in one-pot. We have tried the silylation reaction with many silylating agents like HMDS, trimethylchlorosilane, *N*-trimethylsilylacetamide and *N*,*O*-bis(trimethylsil)ylacetamide. We have also tried the silylation reaction with catalytic amount of ammonium chloride and with acetamide along with HMDS, however reactions have not gone to completion and great numbers of unidentified impurities have been formed. *N*-Trimethylsilylacetamide (MSA) and *N*,*O*-bis (trimethylsilyl)acetamide were found to be the best options for the silylation of Cefprozil **(1a)**, cefdinir (**1b**), Cefipime (**1c**), ceftazidime (**1d**) and cefuroxime acid (**1e**) in methylene chloride and their conversion to corresponding Δ^2-isomers by adding triethylamine in one-pot. All these reactions were carried out at room temperature. Cephalosporin acids as well as solvates were

also effectively converted to the corresponding Δ^2-isomers by the present method.

Scheme 1



EXPERIMENTAL

All melting points were determined with Polmon melting point apparatus. ^{1}H-NMR spectra were recorded on a Bruker 300 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard. Mass spectra are recorded in units of mass (*m/z*) and were recorded on Perkin Elmer PE SCIEX-API 2000 mass spectrometer. Elemental analyses were performed using a Heraeus CHN-O-Rapid instrument.

7β-[[(2*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-propenyl-2-cephem-4-carboxylic acid (2a). 10 g (0.0216 mol) Of 7β-[[(*2R*)-2-amino-2-(4-hydroxyphenyl)acetamido]-3-propenyl-3-cephem-4-carboxylic acid *N*,*N*-dimethylformamide solvate (**1a)** was suspended in 100 ml of anhydrous methylene chloride at 25-30°C under nitrogen atmosphere. 8.2 g, (0.04 mol) *N*,*O*-Bis(trimethylsilyl)acetamide was added and the suspension was stirred for 30 min to get a clear solution. Thereafter, 7 g (0.0693 mol) of triethylamine was added in 5 min at 20-25°C. The reaction mass was stirred at the same temperature for 30 min. Thereafter, the pH of the reaction mass was lowered to 6.8-7.0 by adding 6 *N* hydrochloric acid at 20-25°C. Thereafter, 40 ml of water was added and stirred for 30 min at a temperature below 25°C. Thereafter, layers were separated and the organic layer was extracted with 20 ml water. The combined aqueous layers were adjusted to pH 4.5 with 6 *N* hydrochloric acid and stirred for 1 h at 20-25°C. The precipitated solid was collected by filtration and washed with acetone (10 ml) and dried to obtain the title compound (**2a),** 4 g (40%) as an off white crystalline powder. ^{1}H nmr (dimethyl sulfoxide-d_6); 1.67-1.68 (d, 3H), 4.38 (s, 1H), 4.79 (s, 1H), 5.25 (d, 1H), 5.40 (brs, 1H), 5.44-5.52 (m, 1H), 5.92 (d, 1H), 6.03 (s, 1H), 6.76 and 7.27 (2d, 4H), 9.26 (brs, 1H), ir: 1755, 1683, 1518, 1365, 1178, 840cm^{-1}; ms: m/z 388.2 $[(M-H)]^-$. Anal. Calcd. For C_{18} $H_{19}N_3O_5S$: C, 55.52; H, 4.92; N, 10.79; Found: C, 55.12; H, 4.90; N, 10.72.

7β-[2-(2-Amino-4-thiazolyl)-2-(*Z*)-hydroxyimino)acetamido]-3-vinyl-2-cephem-4-carboxylicacid (2b). 19.90 g, (0.152 mol) of *N*-trimethylsilylacetamide was added to a suspension of 7β-[2-(2-amino-4-thiazolyl)-2-(*Z*)-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid **1b**, 20 g (0.0506 mol) in 200 ml methylene chloride and stirred for 30 min to get a clear solution. The resulting solution was cooled to 2-5°C and 5.63 g (0.0557 mol) triethylamine was added in 30 min at 2-5°C. Thereafter the reaction mass was stirred for 24 h at 25-30°C temperature. Water 200 ml was added and stirred for 10 min. The aqueous layer was separated and washed with 50 ml methylene chloride. The aqueous layer was cooled to 2-5°C and pH adjusted to 3.0 with 10 ml of 10 % w/w sulfuric acid. The resulting slurry was stirred for 2 h. The solid was collected by filtration and washed with water It was suspended in 200 ml water and pH adjusted to 7.5-8.0 with aqueous sodium bicarbonate at 20-25°C to get a clear solution. Carbon 1 g was added and stirred for 30 min. Carbon was filtered washed with 25 ml water. The filtrate was cooled to 5-10°C and pH adjusted to 3.0 with 10% w/w sulfuric acid. The solid was collected by filtration, washed with 50 ml water and dried to yield the title compound **2b**, 6 g, (48%) as an off-white solid. mp 255-260°C (decompose); ^{1}Hnmr (dimethyl sulfoxide-d_6); 4.73 (s, 1H), 4.89 & 5.35 and 5.36 (2d, 1H each), 5.45 (dd, 1H), 6.27 (dd, 1H), 6.44 s, 1H), 6.70 (s, 1H), 7.38 (s, 2H), 9.42 (d, 1H), 11.61 (brs, 1H); ir: 3300, 3196, 3000, 1760, 1674, 1614, 1401, 1533, 1370, 1310,1113, 1046 cm^{-1}; ^{13}C nmr (dimethyl sulfoxide-d_6); 3.02, 54.30, 60.20, 107.80, 111.40, 121.10, 126.60, 137.0, 144.60, 149.50, 163.40, 164.60, 169.0, 169.90; ms: m/z 396.2 $[(M+H)]^+$. *Anal*. Calcd. For $C_{14}H_{13}N_5O_5S_2$: C, 42.49; H, 3.29; N, 17.70; S, 16.19. Found: C, 42.60; H, 3.32, N, 17.70, S, 16.25.

7β-[2-(2-Amino-4-thiazolyl)-2-(*Z*)-methoxyimino)acetamido]-3-(1-methyl-1-pyrrolidinium)-methyl]-2-cephem-4-carboxylate (2c). 27.30 g, (0.208 mol) *N*-Trimethylsilylacetamide was added to a suspension of 7β-[2-(2-amino-4-thiazolyl)-2-(*Z*)-(methoxyimino)acetamido]-3-(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate **1c**, 10 g (0.021 mol) in 100 ml methylene chloride and stirred for 30 min to get a clear solution. The resulting solution was cooled to 2-5°C and 6.73 g (0.0666 mol) triethylamine was added in 30 min at 2-5°C. Thereafter the reaction mass was stirred for 24 h at 25-30°C temperature. 50 ml Water was added and stirred for 10 min. The aqueous layer was separated and washed with 50 ml methylene chloride. The aqueous layer was cooled to 2-5°C and 2.6 ml of 35% w/w hydrochloric acid was added followed by 500 ml of acetone. The gummy mass obtained was subjected to preparative column chromatography to afford the title compound **2c** 4 g (40%) as a white amorphous powder. ^{1}Hnmr (dimethyl sulfoxide-d_6); 2.08

(brs, 4H), 2.92 (s, 3H), 3.41-3.65 (m, 4H), 3.84 (s, 3H), 3.94 and 4.60 (ABq, 2H), 4.50 (s, 1H), 5.32 d, 1H), 5.40 (dd, 1H), 6.63 (s, 1H), 7.22 (brs, 2H), 9.42 (d, 1H); ir: 3399, 2980, 1759, 1621, 1534, 1359, 1034 cm^{-1}; ms: m/z 481.1 $[(M+H)]^+$. *Anal.* Calcd. For $C_{19}H_{24}N_6O_5S_2$: C, 47.49; H, 5.03; N, 17.49;. Found: C, 46.79; H, 5.00; N, 17.51.

7β-[[2-(2-Amino-4-thiazolyl)-2-(*Z*)-(2,2-dimethylacetoxyimino)acetamido]-3-(pyridinium)methyl]-2-cephem-2-carboxylate (2d). It was synthesized as per the method described for the preparation of compound **2c** from compound **1d** with 30% yield as an off-white powder. ^{1}Hnmr (dimethyl sulfoxide-d_6); 1.38 and 1.45 (2s, 6H), 4.07 (s, 1H), 5.31 (d, 1H), 5.39 (m, 1H), 5.36 and 5.63 (ABq, 2H), 6.67 (s, 2H), 7.26 (s, 2H), 8.15 (m, 2H), 9.16 (m, 1H), 10.55 (brs, 1H); ir: 3399, 2980, 1759, 1621, 1534, 1359, 1034 cm^{-1}; ms: m/z 546.9 $[(M+H)]^+$. *Anal.* Calcd. For $C_{22}H_{22}N_6O_7S_2$: C, 48.37; H, 4.06; N, 15.38; Found: C, 48.66; H, 4.05; N, 15.39.

7β-[(*Z*)-2-(2-Furyl)-2-methoxyiminoacetamido]-3-carbomoyloxymethyl-2-cephem-4-carboxylic acid (2e). It was prepared as per the method described for the preparation of compound **2b** from compound **1e** in 40% yield as white amorphous powder. ^{1}Hnmr (dimethyl sulfoxide-d_6); 3.90 (s, 3H), 4.54 and 4.59 (s, 2H), 4.90 (s, 1H), 5.24 (d, 1H), 5.59 (dd, 1H), 6.63-6.73 (m, 5H), 7.84 (s, 1H), 9.85 (d, 1H), 13.66 (brs, 1H); ir: 3459, 3341, 1759, 1732, 1698, 1681, 1607, 1531, 1414, cm^{-1}; ms: m/z 423.0 $[(M-H)]^-$. *Anal.* Calcd. For $C_{16}H_{16}N_4O_8S$: C, 45.28; H, 3.80; N, 13.20;. Found: C, 45.55; H, 3.80; N, 13.23.

Acknowledgement. Authors thank the management of Aurobindo Pharma Limited for allowing us to carry out the work. The authors also thankful to the colleagues of Chemical Research Department for their support.

REFERENCES AND NOTES

[1] Cocker, J. D.; Eardly, S.; Gregory, G. 1.; Hall. M. E.; Long, A. G. *J. Chem. Soc*. **1966**, 1142.

[2] Cooper, R. D.; Demarko, P. V.; Murphy, C. F.; Spangle, L. *A. J. Chem. Soc*, **1970**, 340.

[3] Green, G. F. H.; Page, J. E.; Staniforth, S. E. *J. Chem. Soc*, **1965**, 1595.

[4] Chavette, R. R.; Flynn, E. H. *J. Med. Chem*, **1966**, *9*, 741.

[5] Morin, R. B.; Jackson, G. B.; Muller, R. A.; Lavanginine, E. R.; Scanlon, W. B.; Andrecos, S. L. *J. Am. Chem. Soc*. **1965**, *91*, 1401.

[6] Sugioka, T.; Asano, T.; Chikaraishi, Y.; Suzuki, E..; Sano, A.; Kuriki, T.; Shirotsuka, M. *Chem. Pharm. Bull*. . **1990**, *38(7)*, 1998.

[7] Miyouchi, M.; Nakayama, E.; Fujimotor, K.; Kawamoto, I.; Ide, *J. Chem. Pharm. Bull*. . **1990**, *38(7)*, 1906.

[8] Clark, J. C.; Newall, C. E.; Looker, B. E. GB Patent 2,218,094, 1989, *Chem. Abstr*. **1990**, 112, 235057.