32. K. S. Kim, *J. Electron Spectrosc.*, **6**, 71 (1974).
33. H. Watanabe, K. Ikeda, H. Miki, and Ishida, *Jpn. J. Appl. Phys.*, **27**, 783 (1988).
34. H. Ihara, M. Jo, N. Terada, M. Hirabayashi, H. Oyanagi, K. Murata, Y. Kimura, R. Sugise, I. Hayashida, S. Oshashi, and M. Akimoto, *Physica C*, **153-154**, 131 (1988).

New Thiazolo[3,2-*b*][1,2,4]triazole Derivatives: Useful Compounds for the Preparation of 7-Substituted Cephalosporins

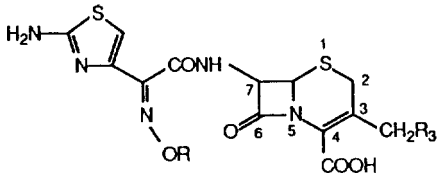
Ghilsoo Nam, Jae Chul Lee, Dae Yoon Chi*, and Joong-Hyup Kim*

Korea Institute of Science and Technology, Seoul 130-650. *Received April 9, 1990*

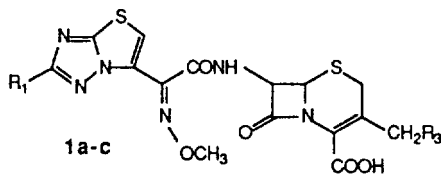
We have synthesized several bicyclic heteroaromatic compounds with bridgehead nitrogen from N-amine salts of heteroaromatic amines. 2-Amino and 2-unsubstituted thiazolo[3,2-*b*][1,2,4]triazole derivatives **2a-b** were prepared by the cyclization reaction from N-amine salts of aminothiazole-5-yl(N-methoxyimino)acetate with cyanogen bromide and formamidine acetic acid salt, respectively. 2-Methylthiazolo[3,2-*b*][1,2,4]triazole **2c** was obtained from N-acetylated N-amine salt of aminothiazole-5-yl(N-methoxyimino)acetate by the cyclization reaction in the presence of polyphosphoric acid (PPA). 2-Substituted and 2-unsubstituted thiazole[3,2-*b*][1,2,4]triazole derivatives **2a-c** were coupled with 7-aminocephalosporanic acid (7-ACA). Coupled cephalosporin derivatives **1a-c** did not have good antibacterial activities *in vitro*.

Introduction

With the discovery of aminothiazole in the 7-side chain of cephalosporin by French workers (Bucourt *et al.*)[1] in 1977, it has been great interest to synthesize new cephalosporins which have better antibacterial activity than those having aminothiazole moiety in the 7-side chain. It has been known that any substituent of amino group of thiazole ring dramatically drops the antibacterial activity. In this report we have described the synthesis of several bicyclic heteroaromatic compounds with bridgehead nitrogen by the cyclization reaction from N-amine salts of aminothiazole-5-yl(N-methoxyimino)acetate with cyanogenbromide, formamidine acetic acid salt, and from N-acetylated N-amine salts of aminothiazole-5-yl(N-methoxyimino)acetate. 2-Substituted and 2-unsubstituted thiazolo[3,2-b][1,2,4]triazole derivatives **2a-c** were coupled with 7-aminocephalosporanic acid (7-ACA).



Aminothiozole Cephalosporin



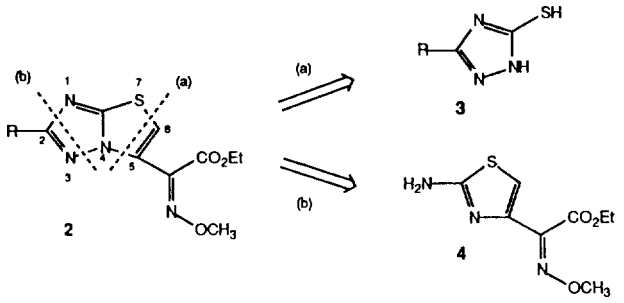
a, R_1 = NH_2
b, R_1 = H
c, R_1 = CH_3

1a-c

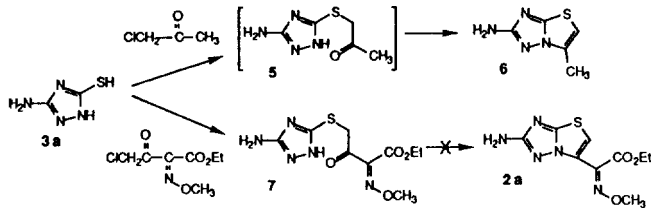
Results and Discussion

As illustrated in Scheme 1, ethyl (Z)-2-(2-substituted-thiazolo[3,2-b][1,2,4]triazol-5-yl)-2-(methoxy-imino)acetate analogues **2** can be synthesized by two different ring formations. By the first (route (a)), 3-mercaptotriazole is alkylated with ethyl 4-chloro-2-methoxyimino-3-oxobutynoate, followed by cyclodehydration. The alternative route (b), thiazolo[3,2-b][1,2,4]triazole ring can be prepared from aminothiazole derivative **4** by N-amination and cyclization of diamino group. Basic ring systems of thiazolo[3,2-b][1,2,4]triazole with simple substituents has been synthesized by several workers and their synthetic methods were one of these two routes.[2,3]

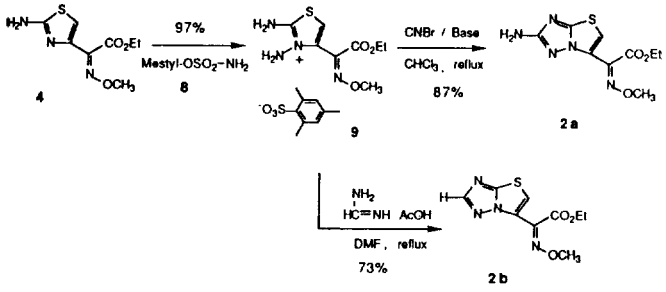
2-Aminothiazolo[3,2-*b*][1,2,4]triazole Derivative. We have great interest for these amino derivatives, since 2-amino functional group in thiazole plays the important role for showing antibacterial activities. With route (a), 3-mercaptotriazole **3a** was reacted with chloroacetone as a model compound of 4-chloro-2-methoxyimino-3-oxobutynoate, providing 2-amino-5-methylthiazolo[3,2-*b*][1,2,4]triazole **6** via alkylated-uncyclized intermediate **5** as shown in Scheme



Scheme 1

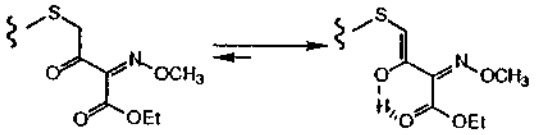


Scheme 2



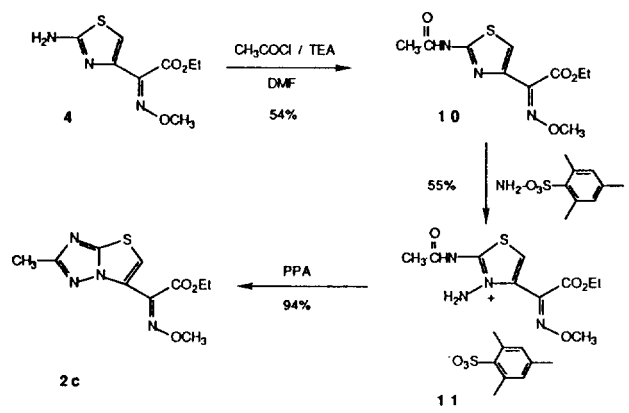
Scheme 3

2. Although Pilgram and Pollard[3] prepared 2-amino-5-methylthiazolo[3,2-*b*][1,2,4]triazole **6** by route (b) using cyanogen bromide, but the yield was low (9%). Unexpectedly, the reaction of 3-mercaptotriazole **3a** with 4-chloro-2-methoxyimino-3-oxobutynoate gave uncyclized product **7** and no desired product **2a**. As illustrated below, formation of hydrogen bond of enol form of uncyclized product **7** prevents alkylated intermediate **7** from undergoing cyclodehydration reaction to desired product **2a**.

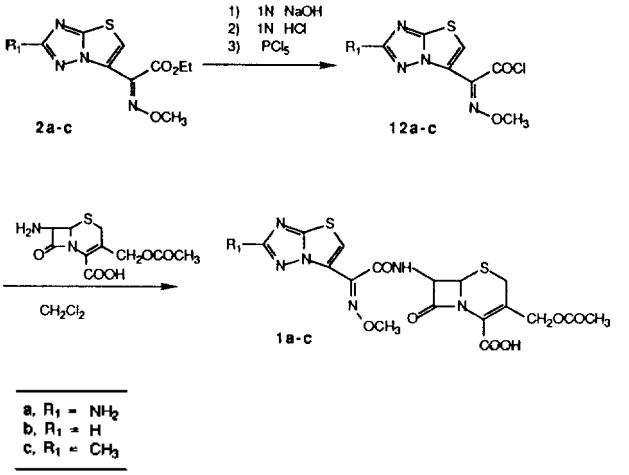


Alternated route (b) was performed (Scheme 3). The key intermediate diamino thiazolium mesitylenesulfonate **9** was prepared by the treatment of aminothiazole derivative **4** and *O*-mesitylenesulfonyl hydroxylamine **8** (MSH)[4] in high yield (97%). For the synthesis of amino derivative **2a**, cyanogen bromide was subjected to ring-closure condition. Very low yield was obtained without triethylamine but amino derivative **2a** was synthesized in high yield (87%) in the presence of triethylamine. The reason that Pilgram and Pollard[3] got a low yield (9%) for the preparation of 2-amino-5-methyl analogue **6** by this route using cyanogen bromide, are due to not using triethyl amine. Potts and Husain[5] also prepared other type thiazolotriazole system, 3-amino-5-phenylthiazolo[2,3-*c*][1,2,4]triazole using cyanogen bromide in low yield (28%).

Thiazolo[3,2-*b*][1,2,4]triazole Derivative. Unsubstituted thiazolotriazole **2b** in 2-position was also prepared from the key intermediate diamino thiazolium mesitylenesulfonate **9** and formamidine acetic acid salt in N,N-dimethylformamide (DMF), as shown in Scheme 3. When formic acid was used in the presence of polyphosphoric acid (PPA) instead of formamidine, ring-closed but decarboxyled product, 5-(1-methoxyiminoethyl)thiazolo[3,2-*b*][1,2,4]triazole, was obtained. Hydrolysis of ester and decarboxylation were occurred in acidic condition, providing 5-(1-methoxyiminoethyl)-thiazolo[3,2-*b*][1,2,4]triazole.



Scheme 4



a, R_1 = NH_2
b, R_1 = H
c, R_1 = CH_3

Scheme 5

2-Methylthiazolo[3,2-*b*][1,2,4]triazole Derivative. As the same manner as 2-amino- or 2-unsubstituted derivatives **2a–b**, the reactions of diamino key intermediate **9** with acethyl chloride or acetic anhydride were performed not to afford cyclized 2-methyl derivative **2c**, but unidentified complexed products. As alternatives, effective procedures were found as shown in Scheme 4. Acetylation of aminothiazole **4**, N-amination with MSH, and cyclization with PPA provided 2-methylthiazolo[3,2-*b*][1,2,4]triazole derivative **2c**.

Coupling of 2-Substituted Thiazolo[3,2-*b*][1,2,4]triazole Derivatives 2a–c with 7-Aminocephalosporanic acid (7-ACA). To exemplify the biological activities of 7-substituted cephalosporin derivatives, 2-substituted and 2-unsubstituted thiazolo[3,2-*b*][1,2,4]triazoles **2a–c** were coupled with 7-ACA. Deesterification of ethyl methoxyiminoacetates **2a–c** and treatment with phosphorus pentachloride gave acid chlorides **12a–c** in high yield (97%). Coupling of acid chlorides **12a–c** with 7-ACA using bis(trimethylsilyl)-acetamide (BSA) afforded new cephalosporins **1a–c** which were substituted in 7 position with bicyclic heteroaromatic compounds with bridgehead nitrogen. The fact that MIC results of **1a–c** are worse than that of cefotaxime means that steric hindrance by extension of bicyclic ring as well as by changing pK value in amino group of thiazole ring seriously affects antibacterial activities. The new thiazolo[3,2-*b*][1,2,4]triazole derivatives, however, will be used by itself or as a part of other systems.

Experimental

Materials and Methods. *O*-Mesitylenesulfonyl hydroxylamine (MSH) 8 was prepared from ethyl *O*-(mesitylenesulfonyl)acetohydroxamate according to literature.[4] Caution MSH could be explosive when it dries. Always keep it wet The latter compound was prepared from ethyl acetohydroxamate and mesitylenesulfonyl chloride. ^{1}H NMR spectra were obtained on a Bruker 200 and Jeol 60 spectrometers and are reported in parts per million downfield from internal tetramethylsilane.

2-Amino-5-methylthiazolo[3,2-*b*][1,2,4]triazole 6. To the solution of 3-amino-5-mercaptotriazole (3.48 g, 27 mmol) in absolute ethanol (60 m*l*) was added 2.5 m*l* (30 mmol) of chloroacetone. The mixture was refluxed for 4 h, and cooled down to room temperature. Triethylamine (3.0 m*l*, 27 mmol) was added dropwise, and then the reaction mixture was refluxed for 1 h. After removal of solvent, the residue was extracted with dichloromethane (25 m*l* × 3). The organic layer was dried (Na_2SO_4) and evaporated, providing thiazolo[3,2-*b*][1,2,4]triazole **6** (3.86g, 89%) as ivory solid: ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.34 (d, 3, J = 2.0 Hz, CH_3), 4.82-5.81 (bs, 2, NH_2), 6.63 (d, 1, J = 2.0 Hz, CH).

(Z)-5-Amino-3-((3-ethyloxycarbonyl-3-methoxyimino-2-oxo)-*n*-propyl)mercapto)[1,2,4]triazole 7. A solution of 3-amino-5-mercaptotriazole **3a** (1 g, 8.6 mmol) in absolute ethanol (80 m*l*) was added ethyl (Z)-4-chloro-2-(methoxyimino)-3-oxobutyrate (1.78 g, 8.6 mmol). The resulting yellow solution was refluxed for 12 h, and turned to brown solution. After removal of solution, the residue was dissolved with saturated sodium acetate solution, and then the solution was extracted with chloroform. The organic layer was dried ($MgSO_4$) and evaporated, providing dark brown viscous solution. Triturating with *n*-hexane gave yellow solid **7** (1.06 g, 43%): mp. 143.5-144 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.31 (t, 3, J = 7.2 Hz, $CH_2C\underline{H}_3$), 4.11 (s, 3, OCH_3), 4.25 (q, 2, J = 7.2 Hz, $C\underline{H}_2CH_3$), 4.29 (s, 2, SCH_2), 5.51 (bs, 2, NH_2); IR (KBr, cm^{-1}) 3456 (N-H), 3296-3207 (NH_2), 1742 (C = O), 1648 (C = N); mass spectrum (70 eV), *m/z* (relative intensity) 287 (M^+, 21), 214 (93), 157 (31), 156 (36), 129 (100).

(Z)-2,3-Diamino-4-(ethyloxycarbonylmethoxyimino)methyl[1,3]-thiazolium 2-mesitylenesulfonate 9. *O*-mesitylenesulfonyl hydroxylamine 8 (MSH, 2.00 g, 5.49 mmol) was dissolved in dichloromethane and the organic layer was dried by passing calcium chloride column. Dried MSH solution was added dropwise to a dried MeOH (1 m*l*) and dichloromethane (15 m*l*) solution of (Z)-2-amino-4-(ethyloxycarbonylmethoxyimino)methyl[1,3]thiazole **4** (1.0 g, 4.57 mmol). After being stirred for 1 h at room temperature, the solution was cooled with ice bath. The reaction mixture was quenched with ether, provided **9** as a white solid. After 15 min, filtration of solid and washing with ether gave **9** (1.98 g, 97%): mp. 198 °C; ^{1}H NMR (60 MHz, DMSO-d_6) δ 1.23 (t, 3, J = 7.2 Hz, $CH_2C\underline{H}_3$), 2.19 (s, 3, CH_3), 2.59 (s, 6, $2CH_3$), 4.01 (s, 3, OCH_3), 4.36 (q, 2, J = 7.2 Hz, $C\underline{H}_2CH_3$), 6.10 (s, 2, NH_2), 6.80 (s, 2, aromatic H), 7.12 (s, 1, aromatic H), 9.78 (s, 2, NH_2).

Ethyl (Z)-2-(2-aminothiazolo[3,2-*b*][1,2,4]triazol-5-yl)-2-(methoxyimino)acetate 2a. A chloroform (40 m*l*) solution of 2,3-diamino thiazolium salt 8 (1.0 g, 2.26 mmol) and triethyl amine (315 m*l*, 2.26 mmol) was added dropwise to a chloroform (10 m*l*) solution of CNBr (263 mg 2.48 mmol). The reaction was refluxed for 20 h. The reaction mixture was extracted with ethyl acetate and water. The organic layer was washed with water 3 times and dried (Na_2SO_4). Evaporation afforded an yellow solid **2a** (528 mg, 87%): mp. 112-114 °C; ^{1}H NMR (60 MHz, DMSO-d_6) δ 1.33 (t, 3, J = 7.2 Hz, $CH_2C\underline{H}_3$), 4.10 (s, 3, OCH_3), 4.43 (q, 2, J = 7.2 Hz, $C\underline{H}_2CH_3$), 5.91 (bs, 2, NH_2), 7.55 (s, 1, aromatic H); mass spectrum (70 eV), *m/z* (relative intensity) 269 (M^+, 22), 166(100), 165 (38), 85 (14), 43 (22), 29 (13).

Ethyl (Z)-2-(thiazolo[3,2-*b*][1,2,4]triazol-5-yl)-2-(methoxyimino)-acetate 2b. Formamidine acetic acid salt (150 mg, 1.36 mmol) was added to a DMF (5 m*l*) solution of 2,3-diamino thiazolium salt **8** (600 mg, 1.35 mmol). The reaction mixture was heated at 110 °C for 1 h. The reaction mixture was neutralized with 10% sodium carbonate solution, and then the mixture was extracted with chloroform. The organic layer was washed with water 3 times and dried ($MgSO_4$). Evaporation afforded an yellow solid **2b** (230 mg, 73%): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.38 (t, 3, J = 7.2 Hz, $CH_2C\underline{H}_3$), 4.18 (s, 3, OCH_3), 4.51 (q, 2, J = 7.2 Hz, $C\underline{H}_2CH_3$), 7.40 (s, 1, aromatic H), 8.23 (s, 1, aromatic H).

(Z)-2-(Acetylamino)-4-(ethyloxycarbonylmethoxyimino)methyl[1,3]thiazole 10. Acetyl chloride (0.5 m*l*, 6.05 mmol) was added dropwise to a DMF (9 m*l*) solution of (Z)-2-amino-4-(ethyloxycarbonylmethoxyimino)methyl[1,3]thiazole **11** (1.0 g, 4.57 mmol) and triethyl amine (630 m*l*, 4.57 mmol) at -15 °C under a stream of nitrogen. After being stirred for 20 min, the reaction was quenched with ice water, provided an yellow solid. Filtration gave **10** (600 mg, 54%): mp. 168-172 °C (dec.); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.33 (t, 3, J = 7.2 Hz, $CH_2C\underline{H}_3$), 2.13 (s, 3, CH_3CO), 3.94 (s, 3, OCH_3), 4.31 (q, 2, J = 7.2 Hz, $CH_2C\underline{H}_3$), 7.33 (s, 1, aromatic H), 12.32 (s, 1, NH).

(Z)-2-(Acetylamino)-3-amino-4-(ethyloxycarbonylmethoxy-imino)methyl[1,3]thiazolium 2-mesitylenesulfonate 11. **11** was prepared by the same method as for **9**: Yield 55%; mp. 162-3 °C; ^{1}H NMR (60 MHz, DMSO-d_6) δ 1.32 (t, 3, J = 7.2 Hz, CH_2CH_3), 2.24 (s, 3, CH_3), 2.43 (s, 3, CH_3CO), 2.60 (s, 6, $2CH_3$), 4.11 (s, 3, OCH_3), 4.37 (q, 2, J = 7.2 Hz, CH_2CH_3), 6.82 (s, 2, aromatic H), 7.34 (s, 3), 7.69 (s, 1).

Ethyl (Z)-2-(2-methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)-2-(methoxyimino)acetate 2c. A mixture of 2,3-diaminothiazolium salt **11** (1.0 g, 2.06 mmol) and polyphosphoric acid (PPA) was heated at 100 °C for 30 min, and then was neutralized with 10% sodium carbonate solution. The mixture was extracted with chloroform and water. The organic layer was washed with water 3 times and dried ($MgSO_4$). Removal of solvent and column chromatography afforded an yellow oil **2c** (500 mg, 94%): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.31 (t, 3, J = 7.2 Hz, $CH_2C\underline{H}_3$), 2.45 (s, 3, CH_3), 4.13 (s, 3, OCH_3), 4.39 (q, 2, J = 7.2 Hz, $CH_2C\underline{H}_3$), 7.49 (s, 1, aromatic H).

General Procedure for Coupling of 2-Substituted Thiazolo[3,2-*b*][1,2,4]triazole Derivatives 2a-c with 7-ACA. 2-Substituted thiazolo[3,2-*b*][1,2,4]triazoles **2a-c** (10.0 mmol) was dissolved in methanol (160 m*l*), aqueous NaOH solution (1 N, 16 m*l*, 16.0 mmol) was added, and the mixture was refluxed for 1 h. The reaction mixture was cool-

ing down with ice bath, and quenched with 8 N HCl (8 m*l*) solution. After removal of solvents, the residue was washed with ethyl ether, providing light-yellow solid, acetic acid of **2a-c** containing NaCl. (Z)-2-(2-Aminothiazolo[3,2-*b*][1,2,4]-triazol-5-yl)-2-(methoxyimino)acetic acid: 2.58 g, 97% (exclude NaCl), mp. 180 °C (dec.); ^{1}H NMR (60 MHz, DMSO-d_6) δ 4.01 (s, 3, OCH_3), 6.29 (bs, 2), 7.56 (s, 1). To phosphorus pentachloride (660 mg, 3.2 mmol) in dried CH_2Cl_2 (10 m*l*) at -20 °C was added crude acetic acid of **2a-c** (2.0 mmol). The mixture was stirred at -20 °C for 2 h. 7-ACA (522 mg, 1.92 mmol) in dried CH_2Cl_2 (5 m*l*) and bis(trimethylsilyl)acetamide (BSA, 1.8 m*l*, 7.28 mmol) was added dropwise, and the mixture was stirred at -20 °C for 50 min and at 0 °C for 2 h. The mixture was poured into cold water. Solid was removed by filtration and the resulting liquid was extracted with EtOAc. Drying (Na_2SO_4) and evaporation of organic layer afforded a yellow solid **1a-c**. **1a**: 284 mg, 29%, mp. 149-151 °C; ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.15 (s, 3, CH_3), 3.43-3.62 (m, 2, CH_2), 4.15 (s, 3, OCH_3), 4.78-5.25 (m, 4, NHC<u>H</u>C<u>H</u> + C<u>H</u>$_2$), 5.83(dd, 2, J = 8.2, 4.8 Hz, CH_2), 7.15(s, 2, NH_2), 8.74 (s, 1, CH), 9.28 (d, 1, J = 8.0 Hz, NH). **1b**: 35%, mp. 158-161 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.07 (s, 3, CH_3), 3.41 (d, 1, J = 18.2 Hz, CH_2), 3.62 (d, 1, J = 18.2 Hz, CH_2), 4.14 (s, 3, OCH_3), 4.84 (d, 1, J = 13.2 Hz, CH_2), 5.09 (d, 1, J = 13.2 Hz, CH_2), 5.13 (d, 1, J = 4.8 Hz, CH), 5.85 (dd, 1, J = 8.0, 4.8 Hz, CH_2), 7.57 (s, 1, CH), 8.21 (s, 1, CH), 9.82 (d, 1, J = 8.0 Hz, NH). **1c**: 12%; ^{1}H NMR (200 MHz, DMSO-d_6) 2.10 (s, 3, CH_3), 2.53 (s, 3, CH_3), 3.44 (d, 1, J = 18.5 Hz, CH_2), 3.65 (d, 1, J = 18.5 Hz, CH_2), 4.09 (s, 3, OCH_3), 4.96 (d, 1, J = 13.4 Hz, CH_2), 5.12 (d, 1, J = 4.8 Hz, CH), 5.20 (d, 1, J = 13.4 Hz, CH_2), 5.95 (dd, 1, J = 9.0, 4.8 Hz, CH_2), 7.35 (s, 1, CH), 7.78 (d, 1, J = 9.0 Hz, NH).

Acknowledgement. This work was supported by MOST grants #2N03881.

References

1. (a) J. A. Webber and W. J. Wheeler in "Chemistry and Biology of m-Lactam Antibiotics", eds. R. B. Morin and M. Gorman, Vol. 1, Academic Press, Chap. 4, 1982; (b) C. E. Newall in "Recent Advences in the Chemistry of m-Lactam Antibiotics", eds. A. G. Brown and S. M. Roberts, the Royal Society of Chemisty, Special Publication, No. 52, 1985.
2. (a) A. Mignot, H. Moskowitz, and M. Miocque, *Synthesis* 52 (1979); (b) A. Singh, R. N. Handa, and H. K. Pujari, *Indian J. Chem.* **16B**, 475 (1978); (c) Y. Tamura, H. Hayashi, E. Saeki, J.-H. Kim, and M. Ikeda, *J. Heterocyclic Chem.* **11**, 459 (1974).
3. K. Pilgram and G. E. Pollard, *J. Heterocyclic Chem.* **13**, 1225 (1976).
4. (a) L. A. Carpino, *J. Am. Chem. Soc.* **82**, 3133 (1960); (b) Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii, and M. Ikeda, *J. Org. Chem.* **38**, 1239 (1973); (c) Y. Tamura, J. Minamikawa, and M. Ikeda, *Synthesis* 1 (1977); (d) Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Teterhedron Lett.* 4133 (1972); (e) Y. Tamura, J.-H. Kim, and M. Ikeda, *J. Heterocyclic Chem.* **12**, 107 (1975); (f) Y. Tamura, J.-H. Kim, Y. Miki, H. Hayashi, and M. Ikeda, *J. Heterocyclic Chem.* **12**, 481 (1975).
5. K. T. Potts and S. Husain, *J. Org. Chem.* **36**, 10 (1971).

Formation Process of a Red Phosphor, $Y_2O_2S:Eu^{3+}$

Sun-Il Mho*

Department of Chemistry, Ajou University, Suwon 441-749

So-Young Chang, Chai-Ik Jeon, Chong-Hong Pyun, Q. Won Choi, and Chang-Hong Kim

Korea Institute of Science and Technology, Seoul 130-650. *Received April 26, 1990*

Yttrium oxysulfide incoporated with europium has been prepared by direct heating the mixture of Y_2O_3, Eu_2O_3, NaOH(or Na_2CO_3), and S. The reaction of the mixture at low temperatures and treatment at higher temperatures are studied. The formation of Y_2O_2S is completed at lower temperature (*ca.* 500 °C) and incorporation of Eu^{3+} into Y_2O_2S lattice proceeds at higher temperature (above 1000 °C) along with crystal growth. Small amount of the unknown phase considered to be $Y_2O_2S_2$ is formed along with Y_2O_2S in the temperature range from 400 °C to 460 °C.

Introduction

Yttrium oxysulfide incorporated with europium, $Y_2O_2S:Eu^{3+}$, is widely used as a red phosphor for color monitors because of its bright luminescence and high energy efficiency.[1-6] It is usually prepared from yttrium oxide coprecipitated with europium oxide.[7] In the present work the reaction of the mixture of Y_2O_3 (neat or 3 ~ 4 at % Eu_2O_3 added), Na_2CO_3 (or NaOH), and S has been studied in a wide range of temperatures in order to understand the formation and particle growing processes of the host material, Y_2O_2S, and incorporation process of Eu^{3+} into it.

Experimental

Europium-incorporated yttrium oxysulfide phosphors,