New Thiazole[3,2 - b][1,2,4]triazole Derivatives

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

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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, R₁ = NH₂
b, R₁ = H
c, R₁ = CH₃   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
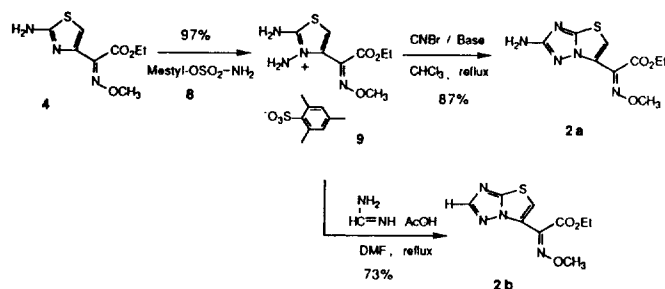
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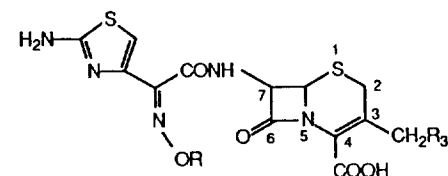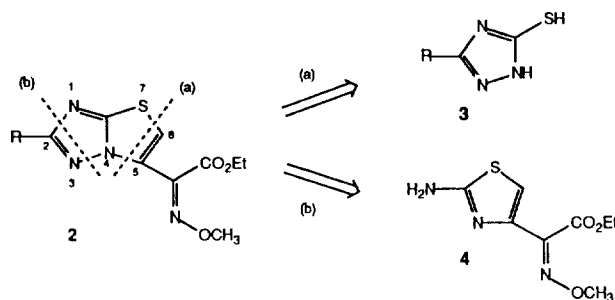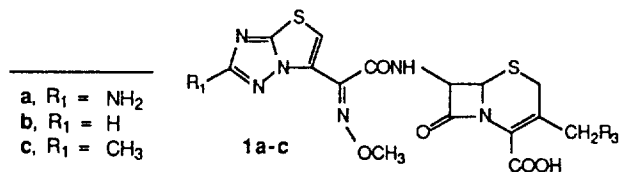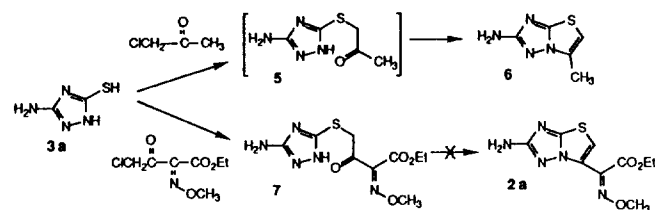
Scheme 2

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.
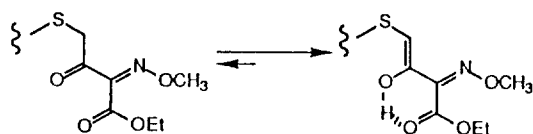

Alternated route (b) was performed (Scheme 3). The key intermediate diamino thiazolium mesitylenesulfonate 9 was prepared by the treatment of aminothiazole derivative 4 and *O*-mesitylenesulfonyl hydroxylamine 8 (MSH)[4] in high yield (97%). For the synthesis of amino derivative 2a, cyanogen bromide 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-*e*][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.
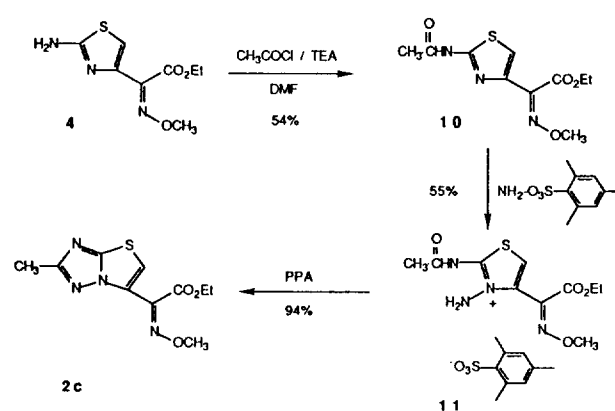
Scheme 4
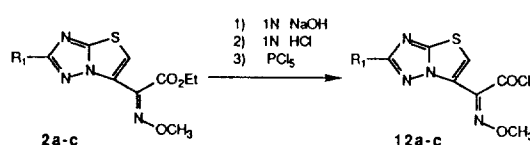
a, R₁ = NH₂
b, R₁ = H
c, R₁ = CH₃

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 (Na₂SO₄) and evaporated, providing thiazolo[3,2-*b*][1,2,4]triazole 6 (3.86g, 89%) as ivory solid: ^{1}H NMR (60 MHz, DMSO-d₆) δ 2.34 (d, 3, J = 2.0 Hz, CH₃), 4.82-5.81 (bs, 2, NH₂), 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 (MgSO₄) 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-d₆) δ 1.31 (t, 3, J = 7.2 Hz, CH₂CH₃), 4.11 (s, 3, OCH₃), 4.25 (q, 2, J = 7.2 Hz, CH₂CH₃), 4.29 (s, 2, SCH₂), 5.51 (bs, 2, NH₂); IR (KBr, cm⁻¹) 3456 (N-H), 3296-3207 (NH₂), 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-d₆) δ 1.23 (t, 3, J = 7.2 Hz, CH₂CH₃), 2.19 (s, 3, CH₃), 2.59 (s, 6, 2CH₃), 4.01 (s, 3, OCH₃), 4.36 (q, 2, J = 7.2 Hz, CH₂CH₃), 6.10 (s, 2, NH₂), 6.80 (s, 2, aromatic H), 7.12 (s, 1, aromatic H), 9.78 (s, 2, NH₂).

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 (Na₂SO₄). Evaporation afforded an yellow solid 2a (528 mg, 87%): mp. 112-114 °C; ^{1}H NMR (60 MHz, DMSO-d₆) δ 1.33 (t, 3, J = 7.2 Hz, CH₂CH₃), 4.10 (s, 3, OCH₃), 4.43 (q, 2, J = 7.2 Hz, CH₂CH₃), 5.91 (bs, 2, NH₂), 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 (MgSO₄). Evaporation afforded an yellow solid 2b (230 mg, 73%): ^{1}H NMR (60 MHz, CDCl₃) δ 1.38 (t, 3, J = 7.2 Hz, CH₂CH₃), 4.18 (s, 3, OCH₃), 4.51 (q, 2, J = 7.2 Hz, CH₂CH₃), 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, CDCl₃) δ 1.33 (t, 3, J = 7.2 Hz, CH₂CH₃), 2.13 (s, 3, CH₃CO), 3.94 (s, 3, OCH₃), 4.34 (q, 2, J = 7.2 Hz, CH₂CH₃), 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-d₆) δ 1.32 (t, 3, J = 7.2 Hz, CH₂CH₃), 2.24 (s, 3, CH₃), 2.43 (s, 3, CH₃CO), 2.60 (s, 6, 2CH₃), 4.11 (s, 3, OCH₃), 4.37 (q, 2, J = 7.2 Hz, CH₂CH₃), 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 (MgSO₄). Removal of solvent and column chromatography afforded an yellow oil 2c (500 mg, 94%): ^{1}H NMR (60 MHz, CDCl₃) δ 1.31 (t, 3, J = 7.2 Hz, CH₂CH₃), 2.45 (s, 3, CH₃), 4.13 (s, 3, OCH₃), 4.39 (q, 2, J = 7.2 Hz, CH₂CH₃), 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.); ¹H NMR (60 MHz, DMSO-d₆) δ 4.01 (s, 3, OCH₃), 6.29 (bs, 2), 7.56 (s, 1). To phosphorus pentachloride (660 mg, 3.2 mmol) in dried CH₂Cl₂ (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 CH₂Cl₂ (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 (Na₂SO₄) and evaporation of organic layer afforded a yellow solid 1a–c. 1a: 284 mg, 29%, mp. 149–151°C; ¹H NMR (60 MHz, DMSO-d₆) δ 2.15 (s, 3, CH₃), 3.43–3.62 (m, 2, CH₂), 4.15 (s, 3, OCH₃), 4.78–5.25 (m, 4, NHCHCH + CH₂), 5.83(dd, 2, J = 8.2, 4.8 Hz, CH₂), 7.15(s, 2, NH₂), 8.74 (s, 1, CH), 9.28 (d, 1, J = 8.0 Hz, NH). 1b: 35%, mp. 158–161°C; ¹H NMR (200 MHz, DMSO-d₆) δ 2.07 (s, 3, CH₃), 3.41 (d, 1, J = 18.2 Hz, CH₂), 3.62 (d, 1, J = 18.2 Hz, CH₂), 4.14 (s, 3, OCH₃), 4.84 (d, 1, J = 13.2 Hz, CH₂), 5.09 (d, 1, J = 13.2 Hz, CH₂), 5.13 (d, 1, J = 4.8 Hz, CH), 5.85 (dd, 1, J = 8.0, 4.8 Hz, CH₂), 7.57 (s, 1, CH), 8.21 (s, 1, CH), 9.82 (d, 1, J = 8.0 Hz, NH). 1c: 12%; ¹H NMR (200 MHz, DMSO-d₆) 2.10 (s, 3, CH₃), 2.53 (s, 3, CH₃), 3.44 (d, 1, J = 18.5 Hz, CH₂), 3.65 (d, 1, J = 18.5 Hz, CH₂), 4.09 (s, 3, OCH₃), 4.96 (d, 1, J = 13.4 Hz, CH₂), 5.12 (d, 1, J = 4.8 Hz, CH), 5.20 (d, 1, J = 13.4 Hz, CH₂), 5.95 (dd, 1, J = 9.0, 4.8 Hz, CH₂), 7.35 (s,

1, CH), 7.78 (d, 1, J = 9.0 Hz, NH).

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Formation Process of a Red Phosphor, Y₂O₂S:Eu³⁺

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Yttrium oxysulfide incoporated with europium has been prepared by direct heating the mixture of Y₂O₃, Eu₂O₃, NaOH(or Na₂CO₃), and S. The reaction of the mixture at low temperatures and treatment at higher temperatures are studied. The formation of Y₂O₂S is completed at lower temperature (*ca.* 500°C) and incorporation of Eu³⁺ into Y₂O₂S lattice proceeds at higher temperature (above 1000°C) along with crystal growth. Small amount of the unknown phase considered to be Y₂O₂S₂ is formed along with Y₂O₂S in the temperature range from 400°C to 460°C.

Introduction

Yttrium oxysulfide incorporated with europium, Y₂O₂S: Eu³⁺, 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 Y₂O₃ (neat or 3~4 at % Eu₂O₃ added),

Na₂CO₃ (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, Y₂O₂S, and incorporation process of Eu³⁺ into it.

Experimental

Europium-incorporated yttrium oxysulfide phosphors,