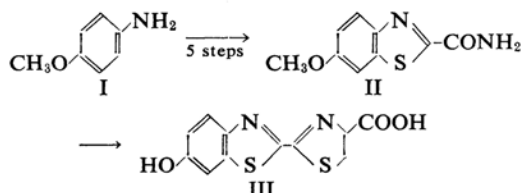


A Convenient Synthetic Method of 2-Carbamoyl-6-methoxybenzothiazole, One of Intermediates for the Synthesis of Firefly Luciferin

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White et al. reported in their short communication¹⁾ that firefly luciferin (III) was synthesized from *p*-anisidine (I) through eight steps. According to them, the preparation of 2-carbamoyl-6-methoxybenzothiazole (II), which is one of intermediates in this synthetic route, requires five steps from the starting material I.



The present authors found a convenient preparative route to II by using carbamoylthiocarbonylthioacetic acid (IV) as a carbamoylthiocarbonylation reagent of *p*-anisidine (I), and II was easily synthesized by two steps from I.

The present paper describes the preparation of the reagent IV and its reactions.

The reagent IV was prepared by the reaction of trichloroacetamide, potassium sulfide and potassium monochloroacetate nearly in the

same manner as in the case of thiobenzoylthioacetic acid²⁾. Being fairly unstable, IV was freshly prepared and used in alkaline solution without being isolated as free acid. Thus obtained alkaline solution which colored deep red reacted various aromatic amines at room temperature to afford corresponding thioamides. Reaction of aniline, *p*-toluidine, α -naphthylamine and β -naphthylamine gave thiooxanilamide (V), 4-methylthiooxanilamide (VI), α -monothiooxal- α' -amide- α (α -naphthylamide) (VII) and α -monothiooxal- α' -amide- α (β -naphthylamide) (VIII) respectively. Compound V, VI and VII are known substances^{3,4)}. Application of the reagent IV to I gave 4-methoxythiooxanilamide (IX), which showed absorptions at 3360, 3200 and 1702 cm^{-1} due to its amide residue. Treatment of IX with a large excess of alkaline potassium ferricyanide afforded II in a fairly good yield. It shows amide bands at 3330, 3200, 1689 and 1661 cm^{-1} .

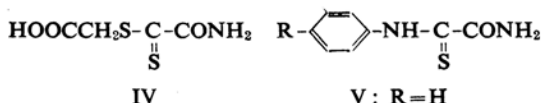
Conversion of the amide II into luciferin (III) by White's method was examined, and 2-cyano-6-methoxy- (X), 2-cyano-6-hydroxybenzothiazole (XI) and III were obtained.

2) J. C. Crawhall et al., *J. Chem. Soc.*, 1951, 2071.

3) A. Reissert and K. Brugemann, *Ber.*, 57, 981 (1924).

4) A. Reissert, *ibid.*, 37, 3708 (1904).

1) E. H. White, F. McCapra, G. F. Field and W. D. McElroy, *J. Am. Chem. Soc.*, 83, 2402 (1961).



IV

V: R=H

VI: R=CH₃IX: R=OCH₃

VII



VIII

Experimental*

Carbamoylthiocarbonylthioacetic Acid (IV).—

A solution of potassium hydroxide (3.0 g.) in ethanol (20 ml.) was divided into halves and one half was saturated with hydrogen sulfide which had been dried through calcium chloride: the other half was then added to the first portion in a 50 ml. flask fitted with nitrogen inlet and dropping funnel. A slow stream of nitrogen was passed and a solution of trichloroacetamide (1.85 g) in ethanol (10 ml.) was added to the mixture with shaking at room temperature. The mixture gradually turned red and the color change from red to brown occurred. As the temperature was raised during this time, the mixture was occasionally cooled with ice-water. A solution of monochloroacetic acid (1.6 g.) in water (10 ml.), neutralized with potassium carbonate, was added to the mixture under nitrogen stream, and the mixture was well shaken. The mixture immediately turned deep red. After being allowed to stand for a few minutes, the mixture was filtered to remove the precipitate of inorganic salt thereby formed. Thus obtained red solution was quickly used for the reaction.

Thiooxanilamide (V).—To a solution of aniline (200 mg.) in 50% ethanol (1 ml.), the solution IV (2 ml.) was added. After the mixture was allowed to stand at room temperature for 3 days, yellow needles that separated out were collected and recrystallized from ethanol to afford yellow needles, m. p. 168~170°C. Yield, 50 mg.

Found: C, 53.61; H, 3.71; N, 14.61. Calcd. for C₈H₉ON₂S: C, 53.33; H, 4.48; N, 15.55%.

4-Methylthiooxanilamide (VI).—To a solution of *p*-toluidine (200 mg.) in 50% ethanol (2 ml.), the solution of IV (2 ml.) was added, and the mixture was allowed to stand at room temperature overnight. Yellow crystals that precipitated were collected and recrystallized from ethanol to form yellow needles, m. p. 166~168°C. Yield, 60 mg.

Found: C, 55.74; H, 5.19; N, 13.94. Calcd. for C₉H₁₀ON₂S: C, 55.66; H, 5.19; N, 14.43%.

α-Monothiooxal-α'-amide-α(α-naphthylamide) (VI).—To a solution of α-naphthylamine (100 mg.) in 70% ethanol (1.5 ml.), the solution of IV (2 ml.) was added. After the mixture was allowed to stand at room temperature overnight, crystals that

separated were collected and recrystallized from ethanol to give yellow needles, m. p. 198~200°C. Yield, 50 mg.

Found: C, 62.41; H, 4.24; N, 12.18. Calcd. for C₁₂H₁₀ON₂S: C, 62.60; H, 4.38; N, 12.17%.

α-Monothiooxal-α'-amide-α(β-naphthylamide) (VIII).—The solution of IV (2 ml.) was added to a solution of β-naphthylamine (100 mg.) in ethanol (3 ml.), and the mixture was allowed to stand at room temperature for 4 days. Crystals that separated were collected by filtration, washed well with water to remove a small amount of inorganic salt. Recrystallization from ethanol afforded yellow needles, m. p. 163~166°C. Yield, 40 mg.

Found: C, 62.38; H, 4.38; N, 12.18. Calcd. for C₁₂H₁₀N₂S: C, 62.60; H, 4.38; N, 12.17%.

4-Methoxythiooxanilamide (IX).—To a solution of I (1 g.) in 50% aqueous ethanol (10 ml.), the solution of IV prepared from 1.85 g. of trichloroacetamide was added. After the mixture was allowed to stand at room temperature, yellow crystals that separated out were collected and recrystallized from ethanol to form yellow needles, m. p. 182~185°C. Yield, 0.5 g. $\lambda_{\text{max}}^{\text{MeOH}}$ mμ (log ε): 228 (4.14), 270 (3.72), 350 (4.00).

Found: C, 51.42; H, 4.80; N, 13.33. Calcd. for C₉H₁₀O₂N₂S: C, 51.16; H, 4.74; N, 13.00%.

2-Carbamoyl-6-methoxybenzothiazole (II).—When a solution of IX (0.5 g) in 10% aqueous sodium hydroxide (40 ml.) was added dropwise into a stirred solution of potassium ferricyanide (9 g.) in water (20 ml.), colorless precipitate separated immediately. After stirring for 30 min., the precipitate was collected by filtration, washed with water and recrystallized from ethanol to form colorless scales, m. p. 246~250°C (decomp.). Yield, 0.4 g. $\lambda_{\text{max}}^{\text{MeOH}}$ mμ (log ε): 260 (3.85), 315 (4.20).

Found: C, 51.17; H, 4.06; N, 13.11. Calcd. for C₉H₈O₂N₂S: C, 51.92; H, 3.87; N, 13.46%.

2-Cyano-6-methoxybenzothiazole (X).—A suspension of II (100 mg.) in phosphorus oxychloride (1.3 ml.) was refluxed for 30 min., and then an excess of phosphorus oxychloride was distilled off under a reduced pressure. Cold water (0.5 ml.) was added to the residue, and the colorless precipitate thereby formed was collected by filtration. The solid was sublimed under a reduced pressure (4 mmHg) at 100°C, and the sublimate was recrystallized from benzene-petroleum ether to afford colorless needles, m. p. 129~130°C. Yield, 80 mg. $\lambda_{\text{max}}^{\text{MeOH}}$ mμ (log ε): 262 (3.87), 320 (4.24). $\nu_{\text{max}}^{\text{KBr}}$ 2230 cm⁻¹.

Found: C, 56.95; H, 3.26; N, 14.91. Calcd. for C₉H₆ON₂S: C, 56.84; H, 3.18; N, 14.73%.

2-Cyano-6-hydroxybenzothiazole (XI).—After a mixture of X (120 mg.) and pyridine hydrochloride (240 mg.) was heated in a sealed tube at 150~160°C for 4 hr., water (1 ml.) was added to the reaction mixture. The precipitate thereby formed was collected, washed with benzene and recrystallized from benzene to form pale yellow needles, m. p. 205~207°C (decomp.). Yield, 45 mg. Evaporation of the benzene filtrate gave colorless crystals, which were recrystallized from methanol to give colorless needles of the starting material (X).

* All melting points were uncorrected. The microanalyses were carried out by Misses Yoko Endo and Yukiko Endo of this Institute, to whom the authors are indebted.

$\lambda_{\text{max}}^{\text{MeOH}}$ $m\mu$ (log ϵ) : 263 (3.88), 323 (4.19). $\nu_{\text{max}}^{\text{KBr}}$ 3220, 2230 cm^{-1} .

Found : C, 54.60; H, 2.14; N, 15.76. Calcd. for $\text{C}_8\text{H}_4\text{ON}_2\text{S}$: C, 54.55; H, 2.29; N, 15.91%.

Firefly Luciferin (III).—A mixture of XI (20 mg.), D-cysteine hydrochloride (20 mg.), potassium carbonate (16 mg.) and 50% aqueous methanol (1 ml.) was stirred under nitrogen stream. After being stirred for 1.5 hr., the mixture was neutralized with diluted hydrochloric acid. The precipitate was collected, washed with water and recrystallized from methanol to afford pale yellow prisms, m. p. 200~202°C. Yield, 25 mg. $\lambda_{\text{max}}^{\text{MeOH}}$ $m\mu$ (log ϵ) : 268

(3.80), 328 (4.24). $\nu_{\text{max}}^{\text{KBr}}$ 3330, 2550, 1700 cm^{-1} .

Found : C, 47.08; H, 3.21; N, 9.60. Calcd. for $\text{C}_{11}\text{H}_8\text{O}_3\text{N}_2\text{S}$: C, 47.14; H, 2.85; N, 10.00%.

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