

## Synthesis and Fluorescence Studies of 5-chlorothiazolo[5,4-*d*]pyrimidine

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**Abstract** : 5-Aminouracil was used as the precursor in the synthesis of 5-chlorothiazolo[5,4-*d*]pyrimidine. Treatment of 5-aminouracil with phosphorous pentasulfide gave 5-amino-4-thiouracil. Cyclisation of 5-amino-4-thiouracil with acid methanoic gave thiazolo[5,4-*d*]pyrimidin-5-(4H)-one. Reaction of thiazolo[5,4-*d*]pyrimidin-5-(4H)-one with phosphoryl chloride gave 5-chlorothiazolo[5,4-*d*]pyrimidine. 5-Chlorothiazolo[5,4-*d*]pyrimidine showed fluorescence peak at 380 nm when excited at 270 nm in ethanol. The relative fluorescence intensity was reduced in non-polar solvents.

**Abstrak** : 5-Aminourasil diguna sebagai sebatian pemula dalam sintesis 5-klorothiazolo[5,4-*d*]pirimidina. Pengolahan 5-aminourasil dengan phosphorus pentasulfida membentuk 5-amino-4-tiourasil. Pensiklikan 5-amino-4-thiourasil dengan asid metanoik menghasilkan tiazolo[5,4-*d*]pirimidin-5-(4H)-on. Tindak balas tiazolo[5,4-*d*]pirimidin-5-(4H)-on dengan fosforil klorida membentuk 5-klorotiazolo[5,4-*d*]pirimidina. 5-Klorotiazolo[5,4-*d*]pirimidina menunjukkan puncak pendafluoran pada 380 nm apabila diuja pada 270 nm dalam etanol. Kadar pendafluoran relatif menurun dalam pelarut tidak berkutub.

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### Introduction

It is known that some of the heterocyclic compounds are fluorescent but the fluorescence-structure relationship is less investigated. Investigations on the fluorescence of these compounds are made difficult because their fluorescence characteristics are often dependent on the nature of the solvents used. In general, compounds tend to be fluorescent in polar solvents. Under these condition, the lone pair of electrons are bonded and the longest absorption wavelength is due to  $\pi \rightarrow \pi^*$  transition, instead of  $n \rightarrow \pi^*$ .

The fluorescence characteristic of nitrogen and sulphur containing heterocycles are not very well investigated. However, some fluorescence studies of selected quinoline [1, 2], 2-substituted pyrimidines [3], 2-substituted purines [4] and 5-substituted thiadiazolo[3,4-*d*]pyrimidines [5] have been reported. This paper reports on the synthesis and the fluorescence studies of 5-chlorothiazolo[5,4-*d*]pyrimidine in various solvents.

### Experimental

#### General

5-Chlorothiazolopyrimidine was obtained as described below. The fluorescence studies of 5-chlorothiazolopyrimidine in ethanol, methanol, ether, ethyl acetate and dichloromethane were carried out at room temperature in a quartz cell using a Perkin-Elmer MPF-3 Fluorescence Spectrometer. Quinine

sulphate was used as the standard. <sup>1</sup>HNMR spectra were recorded for CDCl<sub>3</sub> solution using JEOL 60MHx-JNM-PMX60SI, Bruker WP-80 and Bruker AM250. Mass spectra were recorded using a Kratos MS 50TC and infrared spectra were recorded using Perkin Elmer 298 Infrared Spectrometer and FTIR Perkin-Elmer-1600 Series.

#### Synthesis

##### 5-Amino-4-thiouracil (2) [6].

5 Aminouracil (5 g), phosphorous pentasulphide (15 g) and pyridine (175 ml) were refluxed with stirring for 2 hours. The green-black suspension was evaporated to dryness under reduced pressure and the residue was boiled with water (100 ml) for one hour. After overnight refrigeration, greenish solid was obtained. Recrystallization from 10% sulphuric acid gave yellow crystals. m.pt:decomposed above 183°,  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 3330, 1665, 1620, 1085; <sup>1</sup>HNMR (CDCl<sub>3</sub>),  $\delta$ : 8.60, br, 1H, N1; 7.70, br, 1H, N3; 6.83, s, 1H, H-6; 5.50, br, 2H, NH<sub>2</sub>.

##### Thiazolo[5,4-*d*]pyrimidin-5-(4H)-one (3)

A mixture of 5-amino-4-thiouracil (0.43 g) and methanoic acid (20 ml) was heated on steam bath for 30 minutes. After hot filtration, the filtrate was cooled and evaporated. The residue was washed with ethanol and dried at room temperature. m.p: decomposed above 300°,  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 3315, 1710, 1670, 1620, 1110; <sup>1</sup>HNMR (CDCl<sub>3</sub>)  $\delta$ : 9.15, s, 1H, N-1; 9.48, s, 1H, H-2; 8.10, s, 1H, H-7; Mass spect: M<sup>+</sup> = 152.997, C<sub>5</sub>H<sub>3</sub>N<sub>3</sub>OS requires M<sup>+</sup> = 153.000

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**5-Chlorothiazolo[5,4-*d*]pyrimidine (4)**

Thiazolo[5,4-*d*]pyrimidin-5-(4H)-one (2.0 g), phosphoryl chloride (40 ml) and *N,N*-diethylaniline (5.2 ml) were refluxed for one and half hour. The mixture was cooled and phosphoryl chloride was removed under *vacuo*. The residue was poured onto ice, stirred vigorously and extracted with ether (120 ml). The ethereal layer washed with water and dried. Evaporation of ether gave the product which was recrystallised from ethanol. m.p 110-112°,  $\nu_{\text{max}}$  (cm<sup>-1</sup>) 1660, 1625, 1075, 790; <sup>1</sup>HNMR (CDCl<sub>3</sub>)  $\delta$ : 9.15, s, 1H, H-7; 9.32, s, 1H, H-2; Mass spect: M<sup>+</sup>: 170.966, C<sub>5</sub>N<sub>3</sub>H<sub>2</sub>SCl requires M<sup>+</sup> = 170.966.

**Fluorescence Measurements**

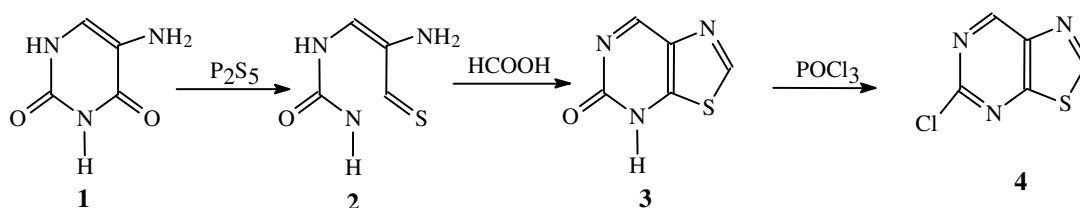
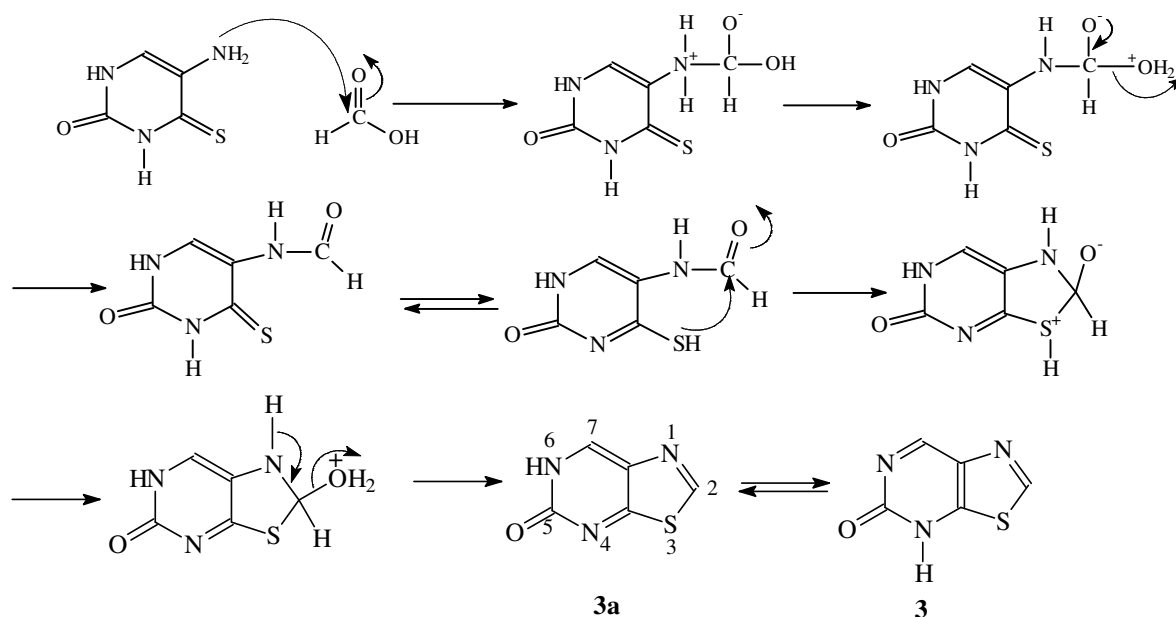
The compound (2 mg) was dissolved in ethanol (10 ml) and a standard solution of quinine sulphate of the same concentration was also prepared. The measurements were taken using Perkin-Elmer MFP-3, Fluorescence Spectroscopy, using 'sensitivity' at 3. All the measurements were taken at room temperature in a quartz cell. The fluorescence of quinine sulphate was taken as 1.00. The procedure was repeated with other solvents.

**Results and Discussion**

The preparation of 4, 5-chlorothiazolo[5,4-*d*]pyrimidine was carried out using 1, 5-aminouracil as the starting material. The synthesis route is as shown in the scheme 1.

Treatment of 1 with phosphorous pentasulphide gave compound 2, 5-amino-4-thiouracil. This method is the normal method used in the direct conversion of 2- and 4- hydroxyl group to mercapto group [7]. The alternative route for the above transformation is via the chloro derivative [7], but in this work, direct transformation was preferred due to better yield of the product. The thio compound obtained was unstable and the subsequent step was carried out immediately.

Compound 3, thiazolo[5,4-*d*]pyrimidin-5-(4H)-one was formed when compound 2 was refluxed with formic acid. In this reaction, formic acid was used as the cyclisation reagent [8], and 84.5% of thiazolo[5,4-*d*]pyrimidin-5-(4H)-one was obtained. The formation of five-membered ring in the thiazolo[5,4-*d*]pyrimidine system is suggested in scheme 2.

**Scheme 1****Scheme 2**

The formation of the five membered ring by the action of formic acid is similar to the route for the preparation of the purine [8], except that the reaction was carried for 30 minutes instead of one hour. The shorter reaction period for the cyclisation process is believed to be due to the presence of sulphur which facilitates the cyclisation process, thus lower temperature and shorter reaction period were used. Better percentage yield was also obtained. There was no increase in percentage yield when the reaction mixture was allowed to react more than one hour.

The  $^1\text{H}$ NMR spectrum of compound **3** showed singlets at  $\delta$  8.10 and 9.48, which were due to the proton resonance of H-7 and H-2 respectively. A one proton broad peak was recorded at  $\delta$  9.15 was due to the proton resonance of N-H group N-4 (structure **3**) or on N-6 (structure **3a**). The infrared analysis showed a strong absorption at  $1690\text{ cm}^{-1}$  which was due to the stretching frequency of a carbonyl group. There was no absorption peak at  $3350\text{ cm}^{-1}$ , and this suggested that the compound obtained was in its keto

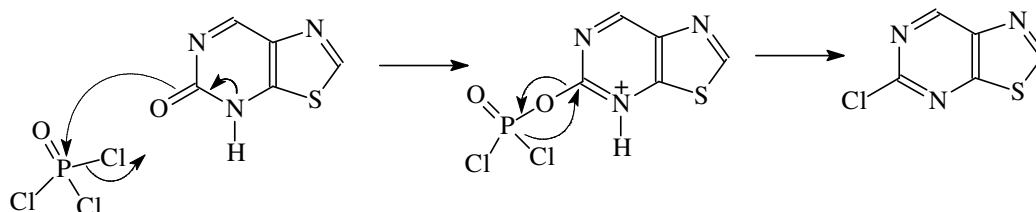
form rather than the hydroxyl form. The N-H stretching and C-S stretching were recorded as weak absorption peak at  $3315\text{ cm}^{-1}$  and  $1110\text{ cm}^{-1}$  respectively. The molecular ion of thiazolo[5,4-*d*]pyrimidin-5-(4H)-one was recorded at 152.997.

Compound **4**, 5-chlorothiazolo[5,4-*d*]pyrimidine, was obtained when an equimolar of **3** was reacted with phosphoryl chloride in the presence of N,N-dimethylaniline as a base. The formation of 5-chlorothiazolo[5,4-*d*]pyrimidine is as suggested in scheme 3.

The  $^1\text{H}$ NMR of **4** showed singlets at  $\delta$  9.32 and  $\delta$  9.15 which were due to a proton at H-2 and H-7 respectively. The presence of -Cl was recorded in the infrared spectrum as a medium absorption at  $790\text{ cm}^{-1}$ . The molecular ion of **4** was recorded at 170.966.

Table 1 shows the fluorescence characteristics of 5-chlorothiazolo[5,4-*d*]pyrimidine in various solvents, using quinine sulphate as the standard.

Scheme 3

Table 1: Fluorescence characteristic of 5-chlorothiazolo[5,4-*d*]pyrimidine

Compound	Solvent	Excitation wavelength/nm	Fluorescence peak/nm	Relative intensity
Quinine	0.1 M H <sub>2</sub> SO <sub>4</sub>	365	440	1.00
Thiazolo[5,4- <i>d</i> ] pyrimidin-5-(4H)-one	Ethanol/ chloroform	-	-	-
5-Chlorothiazolo[5,4- <i>d</i> ] pyrimidine	Ethanol	270	380	0.1520
5-Chlorothiazolo[5,4- <i>d</i> ] pyrimidine	Methanol	272	382	0.1480
5-Chlorothiazolo[5,4- <i>d</i> ] pyrimidine	Diethyl ether	260	385	0.0083
5-Chlorothiazolo[5,4- <i>d</i> ] pyrimidine	Ethyl acetate	275	390	0.0763
5-Chlorothiazolo[5,4- <i>d</i> ] pyrimidine	Dichloromethane	270	385	0.0756

Thiazolo[5,4-*d*]pyrimidin-5-(4H)-one did not show any fluorescence characteristic in either ethanol or chloroform. 5-Chlorothiazolo[5,4-*d*]pyrimidine showed fluorescence peak at 380 nm in ethanol when excited at 270 nm, and the relative fluorescence intensity was reduced when non polar solvents were used. The fluorescence peaks of 5-chlorothiazolo[5,4-*d*]pyrimidine in various solvents were recorded at a shorter wavelength compared to quinine.

The fluorescence peaks observed at a shorter wavelength compared to quinine is probably due a lower degree of conjugation in the thiazolo[5,4-*d*]pyrimidine system compared to quinine. The high degree of conjugation in quinine results in the free mobility  $\pi$  electrons in the system which results in shifting of the fluorescence peaks to a higher wavelength as shown in the table 1.

The relative fluorescence intensity of 5-chlorothiazolo[5,4-*d*]pyrimidine is less than quinine at the same concentration is probably due to the presence of more nitrogen atoms and a sulphur atom in the thiazolo[5,4-*d*]pyrimidine ring. The sulphur atoms in the thiazolo[5,4-*d*]pyrimidine ring may also contributed to the low fluorescence intensity observed. The presence of nitrogen and sulphur atoms normally favours  $n \rightarrow \pi^*$  intermediate rather than  $\pi \rightarrow \pi^*$  intermediate. The low lying  $n \rightarrow \pi^*$  intermediate favours phosphorescence to occur, and as the result low fluorescence intensity was recorded.

The higher fluorescence intensity recorded in ethanol and methanol as compared to diethyl ether and other non-polar solvents was probably due the formation of complex between 5-chlorothiazolo[5,4-*d*]pyrimidine and the solvents. This complex is probably formed through the non-bonding electron of the solute, that is 5-chlorothiazolo[5,4-*d*]pyrimidine, which bonded to the hydrogen atom of the solvent, forming a stable hydrogen-bonded complex [10].

The hydrogen-bonded complex stabilizes the ground state as well as the excited state of  $n \rightarrow \pi^*$  transition. However, the ground state of 5-chlorothiazolopyrimidine has two electrons in the non-bonding orbital whereas the excited state has only one, therefore the stabilisation of the ground state is greater. As the result, the energy of  $n$  to  $\pi^*$  transition increases, thus favouring the low lying  $\pi \rightarrow \pi^*$  transition which is responsible for higher fluorescence intensity.

Low fluorescence intensity observed when non polar solvents was used probably due to in non polar solvents, such as diethyl ether, diethyl ether cannot formed a hydrogen-bonded complex with the solute. The longest absorption wavelength was due to  $n \rightarrow \pi^*$  transition, which favours phosphorescence to occur. As the result, low fluorescence intensity was recorded. However, at this point, it is very difficult to generalize the effect of solvents on the fluorescence characteristic of 5-chlorothiazolo [5,4-*d*]pyrimidine. More work is under progress to understand the solvent-structure-fluorescence relationship of nitrogen and sulphur containing heterocycles.

### Conclusion

5-Chlorothiazolo[5,4-*d*]pyrimidine was successfully prepared using 5-aminouracil as the precursor. 5-Chlorothiazolo[5,4-*d*]pyrimidine showed weak fluorescence intensity in alcohols and its fluorescence intensity was reduced in non-polar solvents.

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