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Chloral-2-acetothienone과 Trichloroethylidene-2-acetothienone의 합성 및 Trichloroethylidene-2-acetothienone과 Hydrazine들과의 반응

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Synthesis of Chloral-2-acetothienone and Trichloroethylidene-2-acetothienone, and Reaction of Trichloroethylidene-2-acetothienone with Hydrazines

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요 약 2-Acetothienone과 chloral을 축합시켜 chloral-2-acetothienone을 합성하였으며 이것을 탈수하여 trichloroethylidene-2-acetothienone을 합성하였다. Trichloroethylidene-2-acetothienone과 phenylhydrazine 또는 치환된 phenylhydrazine들과의 반응으로 2-aryl-6-(2-thienyl)-3(2*H*)-pyridazinone들을 얻었으며 hydrazine과의 반응에서는 3-(2-thienyl)-5-trichloromethyl-2-pyrazoline이 합성되었다.

Abstract Chloral-2-acetothienone was synthesized from the condensation of 2-acetothienone with chloral, and trichloroethylidene-2-acetothienone was obtained from the dehydration of chloral-2-acetothienone.

From the reaction of trichloroethylidene-2-acetothienone with phenylhydrazine or substituted phenylhydrazines 2-aryl-6-(2-thienyl)-3(2*H*)-pyridazinones were obtained. 3-(2-Thienyl)-5-trichloromethyl-2-pyrazoline was synthesized from the reaction of trichloroethylidene-2-acetothienone with hydrazine hydrate.

Introduction

Pyridazine ring system has not been found to occur in natural products, a sharp distinction from the other diazines. Accordingly this heterocyclic type has been investigated much less than the pyrimidines and pyrazines. However, 3(2*H*)-pyridazinones have been found to have a pharmaceutical potential and there have recently appeared many literatures on the synthesis of 3(2*H*)-pyridazinones.

2, 6-Disubstituted 3(2*H*)-pyridazinones are commonly synthesized from the reaction of a γ-keto-α, β-unsaturated acid or ester with hydrazine or substituted hydrazines.[1] Otherwise, several methods have been employed to dehydrogenate 4, 5-dihydro-3 (2*H*) -pyridazinones. Treatment with bromine in acetic acid has been the most satisfactory and gives almost quantitative yield under anhydrous conditions.[2]

In the previous communications[3,4] it was reported that 2, 6-disubstituted 3(2*H*)-pyridazinones

were synthesized from the reaction of trichloroethylideneacetophenone with phenylhydrazine or substituted phenylhydrazines. This paper reports an investigation on the sysnthesis of chloral-2-acetothienone and trichloroethylidene-2-acetothienone, and the reacthion of trichloroethylidene-2-acetothienone with hydrazines.

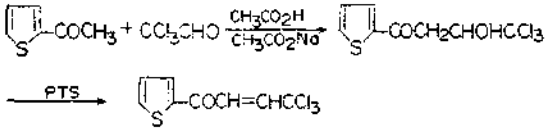
Results and Discussion

Chloral condensation products are usually prepared according to König's metod.[5,6] This method utilize the acetic acid as an acidic catalyst.

But Reeve and Kiehlmann[7] used sodium acetate and acetic acid mixture to improve the yield, and found that reducing the acidity of the acidic catalyst gives better yield.

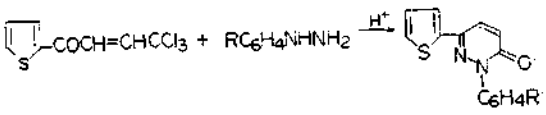
The condesation of chloral with 2-acetothienone[8] in glacial acetic acid over a period of 50 hrs at 130° C gave about 30% yield of chloral-2-acetothienone. Heating for much longer periods is undesirable because of the formation of dark-colored side products. Using sodium acetate as a basic catalyst improved the yield about to 50%. Slight excess of ketone reduced the dark side products. Water inhibited the reaction by forming chloral hydrate, but not significantly.

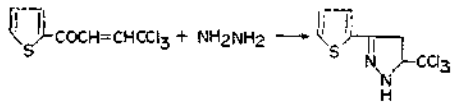
To dehydrate the chloral condensation product König used concentrated sulfuric acid as a dehydrating agent. But chloral-2-actothienone was found to be destroyed when concentrated sulfuric acid was used. Dehydration of chloral-2-acetothienone to trichloroethylidene-2-acetothienone was accomplished by *p*-toluenesulphonic acid(PTS)



as a dehydrating agent.

Trichloroethylidene-2-acetothienone reacted with phenylhydrazine or substituted phenylhydrazine hydrochlorides in ethanol to form 2-aryl-6-(2-thienyl)-3(2*H*)-pyridazinones. In a series of reaction with substituted phenylhydrazines, phenylhydrazines containing electron-withdrawing group reacted more readily than those containing electron-releasing group. The reaction with *o*-nitrophenylhydrazine required more reaction time relative to that with *m*- or *p*-nitrophenylhydrazine. These results are consistent with those obtained from the reaction of trichloroethylideneacetophenone with phenylhydrazines, and support previous suggestion on the effect of substitituents[4]. From the reaction of trichloroethylidene-2-acetothienone with hydrazine hydrate 3-(2-thienlyl)-5-trichloromethyl-2-pyrazoline was obtained instead of pyridazinone derivative.





The characteristic absorption bands for O—H and C=O at 3370 and 1626 cm^{-1}, respectively, were observed in the infrared spectrum of chloral-2-acetothienone. The absorption bands for C=O and C=C in trichloroethylidene-2-acetothienone were found at 1666 and 1650 cm^{-1}, respectively. The pattern of infrared spectra of synthesized 2-aryl-6-(2-thienyl)-3(2*H*)-pyridazinones was similar to that of corresponding 2-aryl-6-phenyl-3(2*H*)-pyridazinones with strong amide carbonyl band at 1650~1680 cm^{-1}. The absorption band for N—H in 3-(2-thienyl)-5-trichloromethyl-2-pyrazoline was found at 3240 cm^{-1}.

Experimental

Infrared spectra were taken on Jasco IR-G spectrophotometer using KBr pellet. Carbon, hydrogen, and nitrogen were analyzed by F & M CHN Analyzer Model 180.

Chloral-2-acetothienone In a 500 m*l* two necked round-bottomed flask fitted with a thermometer and reflux condenser were placed 63 g of 2-acethienone, 74 g of freshly prepared chloral, 100 g of acetic acid and 40 g of sodium acetate. A calcium chloride tube was attached to the condenser to protect from moisture. The mixture was heated under reflux for 45 hrs at 130~135 °C.

The reaction mixture was cooled and washed with 10% sodium bicarbonate solution until neutral for litmus paper test, and the aqueous solution was removed by filtration. The solid mixture obtained was dissolved in hote thanol, and sodium acetate was removed by filtration. The activated carbon was added to the solution and filtered on a Büchner funnel. This process was repeated several times until the solution was colorless. It was allowed to stand overnight in a refrigerator, and the product was separated as white leaf-like crystals. The yield was 71 g(52 %); m. p., 105~106 °C. IR(KBr); 3370(O—H), 1626(C=O), 1507, 1410, and 1354(aromatic C=C of thiophene).

Anal. Calcd. for $C_8H_7Cl_3O_2S$: C, 35.1; H, 2.58. Found C, 35.8; H, 2.63.

Trichloroethylidene-2-acetothienone In a 500m*l* round-bottomed flask attached to a Dean-Stark distillation trap which is connected to a reflux condenser were placed 30 g of chloral-2-acetothienone, 5 g of *p*-toluenesulphonic acid and 200 m*l* of benzene. The mixture was heated under reflux until 2 m*l* of water was collected in the trap. The reaction mixture was washed with warm water sevreal times, and then again with 5 % sodium carbonate solution until neutral for litmus paper test. After solution was dried with anhydrous sodium sulfate, the solvent was removed by distillation under reduced pressure. The crude product was dissolved in hot ethanol. The activated carbon was added to the solution and filtered on a Büchner funnel. This process was repeated several times until the solution was colorless. It was allowed to stand overnight in a refrigerator, and the product was separated as white needles. The yield was 15 g(53 %); m. p., 73~74 °C. IR(KBr); 1666(C=O), 1650(C=C), 1513, 1410 and 1354(aromatic C=C of thiophene ring).

Anal. Calcd. for $C_8H_5Cl_3OS$: C, 37.6; H, 1.97. Found C, 37.7; H, 2.33.

2-(*o*-Nitrophenyl)-6-(2-thienyl)-3(2*H*)-pyridazinone A mixture of 0.50 g of trichloroethylidene-2-acetothienone and 0.40 g of *o*-nitrophenylhydrazine hydrochloride in 20 m*l* of 95 % ethanol was heated under reflux for 2 hrs. Water was added to the solution until it became turbid. After cooling the solution in a refrigerator the crude product was obtained. It was recrystallized from acetone to give yellow crystals. The yield was 0.14 g(23 %); m. p., 175~176 °C. IR (KBr); 1675(C=O), 1525(asymm. NO_2), 1360 (symm. NO_2).

Anal. Calcd. for $C_{14}H_9N_3O_3S$: C, 56.2; H, 3.03; N, 14.0. Found C, 55.6; H, 2.85; N, 13.7.

2-(*m*-Nitrophenyl)-6-(2-thienyl)-3(2*H*)-pyridazinone A mixture of 0.50 g of trichloroethylidene-2-acetothienone and 0.40 g of *m*-nitrophenylhydrazine hydrochlide in 20 m*l* of 95 % ethanol was heated under reflux for 1 hr. The reaction mixture was allowed to stand overnight at room temperature. The crude product separated was recrystallized from *N*, *N*-dimethylformamide(DMF) to give pale yellow crystals. The yield was 0.13 g(22 %); m. p., 231~232 °C. IR (KBr); 1670(C=O), 1535(asymm. NO_2), 1355 (symm. NO_2).

Anal. Calcd. for $C_{14}H_9N_3O_3S$: C, 56.2; H, 3.03; N, 14.0. Found C, 55.8; H, 3.07; N, 14.2

2-(*p*-Nitrophenyl)-6-(2-thienyl)-3(2*H*)-pyridazinone A mixture of 0.50 g of trichloroethylidene-2-acetothienone and 0.40g of *p*-nitrophenylhydrazine hydrochloride in 20 m*l* of 95 % ethanol was heated under reflux for 40 minutes. The reaction mixture was allowed to stand overnight at room temperature. The crude product obtained was recrystallized from DMF to give pale yellow crystals. The yield was 0.13 g(22%); m.p., 216~217 °C. IR(KBr); 1673(C=O), 1517 (asymm. NO_2), 1346(symm. NO_2).

Anal. Calcd. for $C_{14}H_9N_3O_3S$: C, 56.2; H, 3.03; N, 14.0. Found C, 56.5. H, 3.01; N, 13.7.

2-(*m*-Chlorophenyl)-6-(2-thienyl) -3 (2 *H*)-pyridazinone A mixture of 0.50 g of trichloroethylidene-2-acetothienone and 0.48 g of *m*-chlorophenylhydrazine sulfate in 20m*l* of 95% ethanol was heated under reflux for 3 hrs. After water was added to the solution until it became turbid, it was allowed to stand overnight in a refrigerator. The crude product separated was recrystallized from acetone to give colorless crystals. The yield was 0.18 g(32 %); m.p., 166~167 °C. IR (KBr); 1665(C=O), 1585(aromatic C=C).

Anal. Calcd. for $C_{14}H_9ClN_2OS$: C, 58.2; H, 3.14; N, 9.70. Found C, 59.1; H, 3.21; N, 9.90.

2-(*p*-Chlorophenyl)-6-(2-thienyl) -3 (2 *H*)-pyridazinone A mixture of 0.50 g of trichloroethylidene-2-acetothienone and 0.36 g of *p*-chlorophenylhydrazine hydrochloride in 20 m*l* of 95% ethanol was heated under reflux for 3 hrs. After water was added to the solution until it became turbid, it was allowed stand overnight in a refrigerator. The crude product separated was recrystallized from acetone to give pale yellow needles. The yield was 0.12 g(21 %); m.p., 180~181 °C. IR(KBr); 1650(C=O), 1600 and 1583 (aromatic C=C).

Anal. Calcd. for $C_{14}H_9ClN_2OS$: C, 58.2; H, 3.14; N, 9.70. Found C, 58.0; H, 3.30; N, 9.96.

2-(*o*-Tolyl)-6-(2-thienyl)-3-(2*H*)-pyridazinone A mixture of 0.50 g of trichloroethylidene-2-acetothienone and 0.32 g of *o*-tolylhydrazine hydrochloride in 20 m*l* of 95 % ethanol was heated under reflux for 4 hrs. Water was added to the solution until it became turbid. It was allowed to stand overnight in a refrigerator. The crude product separated was recrystallized from acetone to give colorless needles. The yield was 0.20 g(38%); m.p., 188~189 °C. IR(KBr); 1680(C=O), 1593 and 1493(aromatic C=C).

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.1; H, 4.51; N, 10.4. Found C, 67.7; H, 4.64; N, 11.1.

2-(*m*-Tolyl)-6-(2-thienyl)- (2 *H*) -pyridazinone. A mixture of 0.50 g of trichloroethylidne-2-acetothienone and 0.32 g of *m*-tolylhydrazine hydrochloride in 20 m*l* of 95 % ethanol was heated under reflux for 4 hrs. Water was added to the solution until it became turbid. It was allowed to stand overnight in a refrigerator. The crude product separated was recrystallized from acetone. The yield was 0.12 g(23%); (m.p., 127~128 °C. IR(KBr); 1665(C=O), 1585 (aromatic C=C).

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.1; H, 4.51; N, 10.4. Found C, 66.6; H, 4.75; N, 10.5.

2-(*p*-Tolyl)-6-(2-thienyl)-3-(2*H*)-pyridazinone A mixture of 0.50g of trichloroethylidene -2-acetothienone and 0.32 g of *o*-tolylhydrazine hydrochloride in 20 m*l* of 95 % ethanol was heated under reflux for 4 hrs. Water was added to the solution until it became turbid. It was allowed to stand overnight in a refrigerator. The crude product separated was recrystallized from acetone. The yield was 0.20 g(38 %); m.p., 165~166 °C. IR(KBr); 1652(C=O), 1592 and 1508(aromatic C=C).

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.1; H, 4.51; N, 10.4. Found C, 67.4; H, 4.77; N, 10.9.

2-Phenyl-6-(2-thienyl) -3 (2 *H*) -pyridazin-

one A mixture of 0.50 g of trichloroethylidene-2-acetothienone and 0.30 g of phenylhydrazine hydrochloride was heated under reflux for 4 hrs. After water was added to the solution until it became turbid, it was allowed to stand overnight in a refrigerator. The crude product separated was recrystallized from acetone. The yield was 0.12 g(24%); m.p., 172~173 °C. IR (KBr); 1663(C=O), 1600 and 1585(aromatic C=C).

Anal. Calcd. for $C_{14}H_{10}N_2OS$: C, 66.1; H, 3.96; N, 11.0. Found C. 65.8; H, 3.82; N, 10.1.

3-(2-Thienyl)-5-trichloromethyl-2-pyrazoline A mixture of 0.50 g of trichloroethylidene-2-acetothienone and 0.50 m*l* of hydrazine hydrate was warmed for 30 minutes. The reaction mixture was allowed to stand at room temperature for 7 hrs. The product separated was recrystallized from ethanol to give colorless needles. The yield was 0.40 g(78 %); m.p., 166~167 °C. IR (KBr); 3240(N—H).

Anal. Calcd. for $C_8H_6Cl_3N_2S$: C, 35.8; H, 2.25; N, 10.4. Found C, 35.2; H, 2.49; N, 10.7.

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