DAEHAN HWAHAK HWOEJEE
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REACTION OF NITROUS ACID ON 5-AMINOPYRIMIDINE (IV) THE SYNTHESIS OF 5-CYANO-AND 5-CARBOXYPYRIMIDINES

by

Sae Hee Chang
Department of Chemistry
College of Liberal Arts and Science
Seoul National University

Jae Soon Kim and Tae Soung Huh
Department of Chemistry
Song Sim College for Women
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5-Aminopyrimidine에 대한 아질산의 반응(IV) 5-Cyano 및 5-CarboxyPyrimidine 유도체의 합성

서울대학교 문리과대학 화학과
장 세 희
성심여자대학 화학과
김 재 순 · 허 태 성
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요 약

5-Cyanopyrimidine 유도체를 5-Aminopyrimidine 유도체로부터 Sandmeyer 반응에 의하여 합성하고 이 화합물들을 가수분해하여 Pyrimidine-5-carboxylic acid을 합성하였다.

이 방법에 의하면 불순물 제거의 어려움 없이 5-Cyanopyrimidine 유도체와 Pyrimidine-5-carboxylic acid 유도체를 62%와 65%의 수율로 합성할 수 있었다.

ABSTRACT

5-Cyanopyrimidine derivatives were synthesized starting from 5-aminopyrimidine derivatives through the extended Sandmeyer reaction, and then these compounds were hydrolyzed to obtain pyrimidine-5-carboxylic acids.

According to this procedure, 5-cyanopyrimidine derivatives and pyrimidine-5-carboxylic acid derivatives have been prepared in 62% and 65% yields, respectively, without any difficulties in removing impurities.

INTRODUCTION

As a part of the studies on the reaction of nitrous acid on 5-aminopyrimidine, 5-cyanopyrimidine derivatives and pyrimidine 5-carboxylic acids, which correspond to 5-cyanopyrimidine were synthesized by extended Sandmeyer reactions. Despite their numerous interesting physiological activities, particularly those of importance in potential anticancer activity, only limited work[4,5] has been done on the synthesis of 5-cyanouracil and corresponding uracil-5-carboxylic acid because of the complexity of the reaction.

A general extended Sandmeyer reaction was used; 5-aminopyrimidine derivatives were diazotizated[1,2,3] then treated with cuprous cyanide solution[5,8] to obtain 5-cyanopyrimidine derivatives, the yields were 62%. In order to prevent the formation of hydrogen cyanide[5], the diazotizated solution was neutralized with sodium carbonate. When these compounds were hydrolyzed in an acidic solution[4,7], pyrimidine-5-carboxylic acid derivatives were obtained with 65% yields.

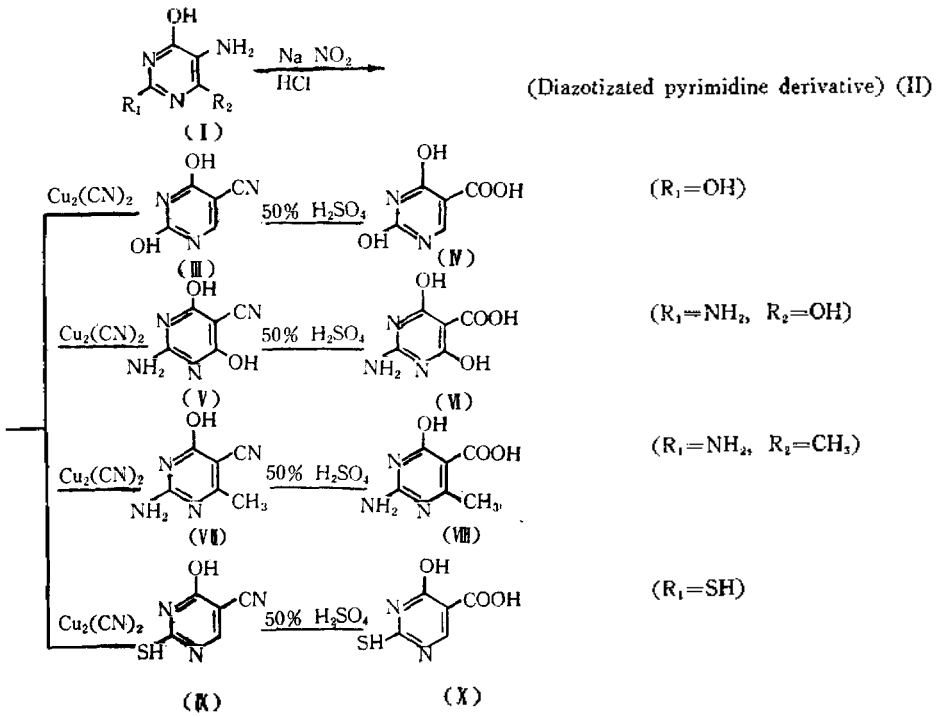
When these 5-carboxylic acids were heated, CO_2 was liberated and the corresponding pyrimidine derivatives remained.

TABLE 1. THE ANALYTICAL AND SPECTRAL DATA OF 5-CYANOPYRIMIDINE DERIVATIVES AND 5-CARBOXYLIC ACID DERIVATIVES.

Designation	m. p., (dec.)	Infrared a) max. (μ)	Analysis b) Calcd	Found	N. E. c) Calcd	N. E. c) Found
5-Cyanouracil $C_5H_3N_3O$	280-282°C	2.8, 3.3, 4.7(2150cm^{-1}), 6.0, 6.6, 6.8, 7.2, 7.5, 8.6, 9.5, 9.5, 10.6, 11.7, 12.3, 12.8, 14.1	C, 49.58; H, 2.48; N, 34.72.	C, 49.67; H, 2.42; N, 34.75.		
Uracil-5-carboxylic acid $C_5H_4N_2O$	283-286°C		C, 42.86; H, 2.86; N, 20.00.	C, 42.82; H, 2.89; N, 20.08.	156.1	157.2
5-Cyano-2-amino-4, 6-dihydroxy-pyrimidine $C_5H_4N_4O_2$	268-270°C	3.2, 3.7, 4.7(2150cm^{-1}), 6.0, 6.3, 6.5, 7.3, 7.7, 8.2, 8.5, 9.0, 9.5, 11.2 13.0, 14.3	C, 39.47; H, 2.63; N, 36.83	C, 39.41; H, 2.56; N, 36.84.		
2-Amino-4, 6-dihydroxypyrimidine-5-carboxylic acid $C_5H_5N_3O_4$	270-275°C		C, 35.10; H, 2.92; N, 24.56.	C, 35.16; H, 2.95; N, 24.51.	171.1	173.8
5-Cyano-2-amino-4-hydroxy-6-methyl-pyrimidine $C_6H_6N_4O$	200-265°C	3.1, 3.3, 4.2, 4.7(2150cm^{-1}) 5.9, 6.8, 7.4, 8.2, 9.5, 9.8, 11.1, 12.5, 13.0, 14.5	C, 48.00; H, 4.00; N, 37.33;	C, 47.94; H, 4.03; N, 37.31.		
2-Amino-4-hydroxy-6-methylpyrimidine-5-carboxylic acid $C_6H_7N_3O_3$	263-265°C		C, 42.60; H, 4.15; N, 24.85.	C, 42.65; H, 4.12; N, 24.87.	169.2	167.7
5-Cyano-2-mercapto-4-hydroxypyrimidine $C_5H_3N_3OS$	280-282°C	3.1, 4.7(2150cm^{-1}), 6.2, 6.5, 7.0, 7.8, 8.3, 8.7, 10.0, 10.5, 11.2, 12.5, 13.2	C, 43.11; H, 3.00; N, 25.15; S, 19.16.	C, 43.15; H, 2.94; N, 25.21; S, 19.19.		
2-Mercapto-4-hydroxypyrimidine-5-carboxylic acid $C_5H_4N_2O_3S$	284-287°C		C, 38.71; H, 3.23; N, 15.05; S, 17.20.	C, 38.68; H, 3.30; N, 14.99; S, 17.16.	172.2	166.5

a) The measurement was done with Perkin Elmer Infracord Model 137.
b) The microanalysis have done at the University of Saskatchewan, Saskatoon, Canada.
c) The neutralization equivalents were determined by potentiometric titration.

The brief chemical formulas are as follow:



According to this procedure, there was no side reaction, and without any difficulty 5-cyanopyrimidine derivatives were hydrolyzed to obtain the corresponding 5-carboxylic acid derivatives.

To identify and estimate the 5-cyanocompounds, corresponding acids were dissolved in an excess alkali solution, then the carboxylic group was quantitatively proved by the acid-back-titration, which are in good agreement with theoretical values. The infrared spectrums of 5-cyanopyrimidine derivatives were examined and the absorption band owing to cyano group were found at 2150 cm^{-1}.

EXPERIMENT

5-Cyanouracil(III), Uracil-5-carboxylic acid(IV)

5-Aminouracil (260 mg.) was mixed with 8 ml. of 3N hydrochloric acid and the temperature of the mixture was brought to 0°C. A solution of 100mg. sodium nitrite in 2ml. of water was added, with stirring, to this mixture, the temperature being kept at 0—5°C. The addition of the nitrite occupied about fifteen minutes. The mixture was then cautiously neutralized by adding dry sodium carbonate with constant stirring, using litmus paper to determine the end-point. The cuprous cyanide solution[5] (180 mg. of cuprous cyanide and 400 mg. potassium cyanide mixture in 10ml. water) was then chilled 0—5°C. To this mixture the cold neutralized diazonium solution was slowly added. After this addition, with constant stirring, the solution gradually attained room temperature. After 2 hrs. the mixture[9,10] was boiled on a water bath for 1 hr., then allowed to stand overnight and the brownish yellow precipitate was filtered off. The product was recrystallized from hot water.

The yield was 165 mg. (64% calculated from 5-aminouracil), pale yellow cryst., m.p., 280-282°C(dec.) [lit., m.p., 282°C (dec.)[4,6]]

The 5-cyanouracil (300mg). was boiled with 5 ml. of 50% sulfuric acid for 1 hr., then was cooled, diluted with 100ml. of water and set aside. Uracil-5-carboxylic acid separated from water as white prisms.

The yield was 195 mg. (65% calculated from 5-cyanouracil), m.p., 283-286°C (dec.) [lit., m.p., 285°C (dec)[4,7]]

2-Amino-5-cyano-4, 6-dihydroxypyrimidine (V), 2-Amino-4, 6-dihydroxypyrimidine-5-carboxylic

acid (VI)

The same procedures described in the precious experiment were adopted. 2, 5-diamino-4, 6-dihydroxypyrimidine was diazotizated, then this cold neutralized diazonium solution was slowly added to the cold cuprous cyanide solution. After this addition, with constant stirring, the solution gradually attained room temperature.

After 2 hrs. the mixture was boiled on a water bath for 1 hr., then allowed to stand overnight and the pale yellow precipitate was filtered off. The product was recrystallized from hot water.

The yield was168 mg. (65%), pale yellow cryst., m. p., 268-270°C (dec). The 2-amino-5-cyano-4, 6-dihydroxypyrimidine (300mg.) was boiled with 5 ml. of 50% sulfuric acid for 1 hr., was then cooled, diluted with 100ml. of water and set aside. Corresponding acid (190mg.) separated from water as prisms.

The yield was 65%, m. p., 270-275°C(dec.).

2-Amino-5-cyano-4-hydroxypyrimidine (VII), 5-carboxylic acid (VIII)

Diazotization of 2, 5-diamino-4-hydroxy-6-methylpyrimidine was carried out as above. This cold neutralized diazonium solution was slowly added to the cold cuprous cyanide solution. After 2 hrs. the mixture was boiled on a water bath for 1 hr., then allowed to stand overnight and the pale yellow precipitate was filtered off. The product was recrystallized from hot water.

The yield: 155mg. (62%), pale yellow cryst., m. p., 260-265°C (dec.) 2-amino-5-cyano-4-hydroxy-6-methylpyrimidine (300mg.) was boiled with 50% sulfuric acid for 1 hr., was then cooled, diluted with 100mg. of water and set aside. Corresponding 5-carboxylic acid (195mg.) separated from water as white prisms. The yield: 65%, m. p., 262-265°C (dec.).

2-Mercapto-4-hydroxy-5-cyanopyrimidine(IX), 5-carboxylic acid(X)

Diazotization of 2-mercapto-4-hydroxy-5-aminopyrimidine was carried out as above. This cold neutralized diazonium solution was slowly added to the cold cuprous cyanide solution. After 2 hrs. the mixture was boiled on a water bath for 1 hr., then allowed to stand overnight and the pale yellow precipitate was filtered off. The product was recrystallized from hot water.

The yield: 156mg. (62%), pale yellow cryst., m. p., 280-282°C (dec.). The 2-mercapto-4-hydroxy 5-cyanopyrimidine (300mg.) was boiled with 50% sulfuric acid for 1 hr., was then cooled, diluted with 100mg. of water and set aside. Corresponding-5-carboxylic acid separated from water as prisms. The yield: 200mg. (66%), m. p., 285-287°C (dec.).

CONCLUSION

Preparation of 5-cyanopyrimidines from 5-aminopyrimidine derivatives by extended Sandmeyer reaction was described. The 5-cyano-derivatives were hydrolyzed to obtain pyrimidine-5-carboxylic acids. According to this procedure, 5-cyanopyrimidine derivatives and pyrimidine-5-carboxylic acid derivatives have been prepared with good yields. This method would give a useful way for the preparation of these compounds.

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