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 Sin 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
(1968. 5. 7. 접수)

요 약

5-Cyanopyrimidine 유도체를 5-Aminopyrimidine 유도체로부터 Sandmeyer 반응에 의하여 합성하고 이
화합물들은 가수분해하여 Pyrimidine-5-carboxylic acid 을 합성하였다.

이 방법의 의의란 본문을 제거의 아래층 안에 5-Cyanopyrimidine 유도체와 Pyrimidine-5-carboxylic acid
유도체를 62%와 65%의 수율로 합성할 수 있겠다.

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-amino pyrimidine, 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 has been done on the synthesis of 5-cyano uracil and corresponding uracil-5-carboxylic acid because of the complexity of the reaction.

A general extended Sandmeyer reaction was used: 5-amino pyrimidine derivatives were diazotized and then treated with cuprous cyanide solution to obtain 5-cyanopyrimidine derivatives, the yields were 62%. In order to prevent the formation of hydrogen cyanide, the diazotized solution was neutralized with sodium carbonate. When these compounds were hydrolyzed in an acidic solution, pyrimidine-5-carboxylic acid derivatives were obtained with 55% yields.

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

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

<table>
<thead>
<tr>
<th>Designation</th>
<th>m. p. (dec.)</th>
<th>Infrared a)</th>
<th>Analysis b)</th>
<th>Found</th>
<th>N.E. c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Cyanouracil</td>
<td>280-282°C</td>
<td>2.8, 3.3, 4.7(2150cm⁻¹)</td>
<td>C, 49.58; H, 2.48; N, 34.72</td>
<td>49.67; 2.42; 34.75</td>
<td></td>
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<tr>
<td>C₅H₄N₂O</td>
<td></td>
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<tr>
<td>Uracil-5-carboxylic acid</td>
<td>283-285°C</td>
<td>4.28, 4.28, 11.7, 12.3, 12.8, 14.1</td>
<td>C, 42.06; H, 2.86; N, 20.00</td>
<td>157.1; 157.2</td>
<td></td>
</tr>
<tr>
<td>C₅H₄N₂O</td>
<td></td>
<td></td>
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<tr>
<td>5-Cyan-2-amino-4,5-dihydroxy-</td>
<td>258-270°C</td>
<td>3.2, 3.7, 4.7(2150cm⁻¹)</td>
<td>C, 39.47; H, 2.83; N, 36.83</td>
<td>39.41; 2.56; 36.84</td>
<td></td>
</tr>
<tr>
<td>pyrimidine</td>
<td>C₅H₄N₂O</td>
<td>6.0, 6.3, 6.5, 7.2, 7.7</td>
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<td></td>
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<tr>
<td>2-Amino-4,6-dihydroxypyrimidine-</td>
<td>270-275°C</td>
<td>8.2, 8.5, 9.0, 9.5, 11.2, 15.0, 14.3</td>
<td>C, 35.16; H, 2.92; N, 24.56</td>
<td>171.1; 173.8</td>
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<tr>
<td>5-carboxylic acid</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>C₅H₄N₂O</td>
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<tr>
<td>5-Cyan-2-amino-4-hydroxy-6-methyl-</td>
<td>200-265°C</td>
<td>3.1, 3.3, 4.2, 4.7(2150cm⁻¹)</td>
<td>C, 48.00; H, 4.00; N, 37.33</td>
<td>47.94; 4.02; 37.31</td>
<td></td>
</tr>
<tr>
<td>pyrimidine</td>
<td>C₅H₄N₂O</td>
<td>5.9, 6.8, 7.4, 8.2, 9.5</td>
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<tr>
<td>2-Amino-4-hydroxy-6-methylpyrimidine</td>
<td>263-265°C</td>
<td>9.8, 11.1, 12.5, 13.0, 14.5</td>
<td>C, 42.65; H, 4.15; N, 24.85</td>
<td>169.2; 167.7</td>
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<tr>
<td>5-carboxylic acid</td>
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<tr>
<td>C₅H₄N₂O</td>
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<tr>
<td>5-Cyan-2-mercapto-4-</td>
<td>280-282°C</td>
<td>3.1, 4.7(2150cm⁻¹)</td>
<td>C, 43.11; H, 3.00; N, 25.15;</td>
<td>43.15; 2.94; 25.21;</td>
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<tr>
<td>hydroxypyrimidine</td>
<td>C₅H₄N₂OS</td>
<td>6.2, 6.5, 7.0, 7.8, 8.3</td>
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<td>2-Mercapto-4-hydroxypyrimidine-</td>
<td>284-287°C</td>
<td>8.7, 10.6, 10.5, 11.2, 15.5, 16.2</td>
<td>C, 38.71; H, 3.22; N, 15.05;</td>
<td>38.68; 3.22; 14.99;</td>
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<tr>
<td>5-carboxylic acid</td>
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</tr>
<tr>
<td>C₅H₄N₂O</td>
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</table>

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.
Reaction of Nitrous acid on 5-aminopyrimidine

The brief chemical formulas are as follow:

\[
\begin{align*}
&\text{OH} \\
&(\text{Diazotizated pyrimidine derivative}) \ (\text{II}) \\
&\text{(R}_1=\text{OH}) \\
&\text{(R}_1=\text{NH}_2, \ R_2=\text{OH}) \\
&\text{(R}_1=\text{NH}_2, \ R_2=\text{CH}_3) \\
&\text{(R}_1=\text{SH}) \\
\end{align*}
\]

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 cyanocompounds, corresponding acids were dissolved in an excess alkali solution, then the carboxyl 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 nitrate in 2ml. of water was added, with stirring, to this mixture, the temperature being kept at 0−5°C. The addition of the nitrate 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\(^1\) (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\(^1\) 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.).\(^1\)]

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.).\(^1\)]

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

2-Amino-4,6-dihydroxypyrimidine-5-carboxylic acid

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acid (VI)

The same procedures described in the previous experiment were adopted. 2,5-diamino-4,6-dihydroxypyrimidine was diazotized, 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 was 150 mg. (65%), pale yellow cryst., m.p. 250-270°C (dec.). The 2-amino-5-cyano-4,6-dihydroxypyrimidine (300 mg.) was boiled with 5 ml. of 50% sulfuric acid for 1 hr., was then cooled, diluted with 100 ml. of water and set aside. Corresponding acid (190 mg.) 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 was 155 mg. (62%), pale yellow cryst., m.p. 250-265°C (dec.) 2-amino-5-cyano-4-hydroxy-6-methylpyrimidine (300 mg.) was boiled with 50% sulfuric acid for 1 hr., was then cooled, diluted with 100 mg. of water and set aside. Corresponding 5-carboxylic acid (195 mg.) 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: 156 mg. (62%), pale yellow cryst., m.p., 290-292°C (dec.). The 2-mercapto-4-hydroxy 5-cyanopyrimidine (300 mg.) was boiled with 50% sulfuric acid for 1 hr., was then cooled, diluted with 100 mg. of water and set aside. Corresponding 5-carboxylic acid separated from water as prisms. The yield: 200 mg. (68%), 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.

REFERENCE

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