SYNTHESIS OF PYRIDOPYRANOQUINOLINES BY THE SKRAUP REACTION OF AMINO-5H-BENZOPYRANO[2,3-b]PYRIDIN-5-ONES

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INTRODUCTION

In recent years, a number of heteroaromatic antitumor compounds have been prepared with the hope of increasing their pharmacological effects or to find new derivatives with reduced side effects.1-3 DNA intercalating agents, which are a very important classes of antitumor drugs, usually possess planar aromatic and heteroaromatic polycyclic systems. Some thioxanthene derivatives are effective against tumors.4-6 As an extension of our synthetic studies of xanthene derivatives, we prepared xanthene analogues consisting of a tetracyclic system containing two pyridine rings.7-9 In this note we describe the synthesis of 12H-pyrido[3′,2′:5,6]pyrano[2,3-h]quinolin-12-one (10), 12H-pyrido[3′,2′:5,6]pyrano[3,2-f]-quinolin-12-one (11), 7H-pyrido[3′,2′:5,6]pyrano[2,3-f]quinolin-7-one (12), and 7H-pyrido[3′,2′:5,6]pyrano[3,2-h]quinolin-7-one (13) by the Skraup reaction10,11 of amino-5H-[1]benzopyrano[2,3-b]pyridin-5-ones.
RESULTS AND DISCUSSION

The synthesis of 6-amino-5H-benzopyrano[2,3-b]pyridin-5-one (1) was described previously.\textsuperscript{12}

The synthetic route of 7-amino-5H-benzopyrano[2,3-b]pyridin-5-one (2) is summarized in Scheme 1.

\begin{align*}
\text{COOH} & \quad + \quad \text{NHOCH}_3
\end{align*}

\begin{align*}
\text{Cl} & \quad \text{DMF} & \quad \text{K}_2\text{CO}_3 & \quad \text{PPA} & \quad \text{COOH} & \quad \text{NHOCH}_3
\end{align*}

\begin{align*}
\text{Scheme 1}
\end{align*}

The Ullmann reaction of 2-chloronicotinic acid with 4-hydroxyacetanilide in the presence of K\textsubscript{2}CO\textsubscript{3} in DMF under reflux for 2 h gave 2-(4-acetaminophenoxy)nicotinic acid (5) (yield 74%). This acid (5) was heated with PPA at 120\degree C for 3 h and then hydrolyzed with hydrobromic acid in the presence of phenol for 1 h to give 7-amino-5H-benzopyrano[2,3-b]pyridin-5-one (2) (yield 68% from 5). In a similar way, the reaction of 2-chloronicotinic acid with 3-hydroxyacetanilide afforded 2-(3-acetaminophenoxy)nicotinic acid (7) (yield 69%), which was cyclized with PPA and then hydrolyzed with hydrobromic acid to give a mixture of 6- (1) and 8-amino-5H-benzopyrano[2,3-b]pyridin-5-ones (3) (Scheme 2).

The mixture was separated by column chromatography to give 3 (yield 35% from 7).

Although the Ullmann reaction of 2-chloronicotinic acid with o-hydroxyacetanilide or o-nitrophenol was attempted, it failed. One of synthetic method of amino-9H-xanthen-9-ones is direct amination using sulfuric acid and hydroxylamine.\textsuperscript{13} Thus, this direct amination method was similarly applied to the amination of 5H-benzopyrano[2,3-b]pyridin-5-one to afford a mixture of 6-amino- (1) (yield 22%), 7-amino- (2) (yield 14%), 8-amino- (3) (yield 5%) and 9-amino-5H-benzopyrano[2,3-b]pyridin-5-ones (4) (yield 5%) (Scheme 3).
Skraup reactions of amino-5H-benzopyrano[2,3-b]pyridin-5-ones (1-4) with glycerol, fuming sulfuric acid, and nitrobenzene were conducted in the presence of iron(II) sulfate and boric acid, and all obtained products were found to have the molecular formula $C_{15}H_{8}N_{2}O_{2}$ based on the elemental analytical data and the MS spectra ($m/z$ 248 (M+)). The Skraup reaction products are summarized in Scheme 4. The Skraup reaction of 1 gave 12H-pyrido[3′,2′:5,6]pyrano[2,3-h]quinolin-12-one (10) in 71% yield. The structure of 10 was determined by $^1$H-NMR. The $^1$H-NMR showed proton signals of the new pyridine ring at $\delta$ 7.56 (dd, $J$=4.4, 8.3 Hz, 3-H), 8.25 (dd, $J$=1.9, 8.3 Hz, 4-H) and 9.29 (dd, $J$=1.9, 4.4 Hz, 2-H), and proton signals of the 5H-benzopyrano[2,3-b]pyridin-5-one skeleton at $\delta$ 7.79 (d, $J$=8.3 Hz, 6-H) and 8.16 (d, $J$=8.3 Hz, 5-H). The Skraup reaction of 2 afforded only 12H-pyrido[3′,2′:5,6]pyrano[3,2-f]quinolin-12-one (11) in 82% yield. The $^1$H-NMR spectrum of 11 demonstrated a new pyridine ring and two doublet proton signals of the 5H-benzopyrano[2,3-b]pyridin-5-one skeleton as in the case of 2.
Similarly, the Skraup reaction of 3 produced one product, \(7H\)-pyrido [3', 2':5,6]pyrano[2,3-f]quinolin-7-one (12), in 75 % yield, and the structure of 12 was confirmed by \(^1\)H-NMR spectrum as in the case of 11. Based on the present results, the Skraup reaction of 3 afforded the corresponding angular-type product (12) without the linear-type product. Skraup reaction of 4 gave \(7H\)-pyrido[3',2':5,6]pyrano[3,2-h]quinolin-7-one (13) in 84 % yield.

![Scheme 4](image)

**EXPERIMENTAL**

Melting points were measured on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 260-10
spectrophotometer. $^1$H-NMR spectra were measured on a JEOL FX-400 instrument using CDCl$_3$ as a solvent and tetramethylsilane as an internal standard. MS were taken with a Hitachi M-2500 spectrometer.

2-(4-Acetamidophenoxy)nicotinic acid (5)

A mixture of 2-chloronicotinic acid (7.85 g, 50 mmol), 4-acetamidophenol (7.55 g, 50 mmol), potassium carbonate (13.8 g, 100 mmol), copper (0.7 g), cuprous iodide (0.7 g) and DMF (120 mL) was stirred under reflux for 2 h, cooled and filtered. The filtrate was concentrated. The residue was mixed with hot water, filtered, and the filtrate was acidified with 10% hydrochloric acid. The resulting precipitate was collected. The residue was purified by recrystallization from methanol to give 5 (10.0 g, 74%) as colorless needles. mp 241-242 °C. Anal. Calcd for C$_{14}$H$_{12}$N$_2$O$_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.68; H, 4.65; N, 10.13. $^1$H-NMR (DMSO-d$_6$) δ: 7.03 (1H, dd, J=2.0, 8.8 Hz, 2’-H), 7.20 (1H, dd, J=4.9, 7.3 Hz, 3-H), 7.59 (1H, dd, J=2.0, 8.8 Hz, 3’-H), 8.22 (1H, dd, J=2.0, 7.3 Hz, 4-H), 8.30 (1H, dd, J=2.0, 4.9 Hz, 2-H), 9.96 (1H, s, NH). MS: m/z 272 (M$^+$.).

7-Acetamido-5H-[1]benzopyrano[2,3-b]pyridin-5-one (6)

2-(4-Acetamidophenoxy)benzoic acid (10 g, 40 mmol) was heated with PPA (300 g) at 130°C for 8 h. The hot reaction solution was poured into water, and the resulting precipitate was collected, washed and recrystallized from methanol to give 6 (7.2 g, 76%). mp 225-226 °C. Anal. Calcd for C$_{14}$H$_{10}$N$_2$O$_3$: C, 66.13, H, 3.96, N, 11.02. Found: C, 65.89, H, 4.26, N, 11.03. $^1$H-NMR (CDCl$_3$) δ: 2.10 (3H, s, CH$_3$), 7.63 (1H, dd, J=4.4, 7.8 Hz, 3-H), 7.72 (1H, d, J=8.8 Hz, 9-H), 8.03 (1H, dd, J=2.9, 8.8 Hz, 8-H), 8.48 (1H, d, J=2.9 Hz, 6-H), 8.64 (1H, dd, J=2.0, 7.8 Hz, 4-H), 8.82 (1H, dd, J=2.0, 4.4 Hz, 2-H). MS: m/z 254 (M$^+$.).

7-Amino-5H-[1]benzopyrano[2,3-b]pyridin-5-one (2)

Compound (6, 7.2 g, 30 mmol) heated with 47% hydrobromic acid (100 mL) and phenol (5.6 g, 60 mmol) under reflux for 2 h. After cooling, the mixture was basified with 10% aqueous sodium hydroxide to give a yellow solid which was recrystallized from methanol to afford 2 (4.97 g, 89%) as yellow needles, mp 253-254 °C. Anal. Calcd for C$_{12}$H$_8$N$_2$O$_2$: C, 67.91; H, 3.80;
N, 13.21. Found: C, 67.83; H, 3.89; N, 13.19. IR (KBr): 1600, 1620 cm\(^{-1}\). 

\(^{1}\)H-NMR (CDCl\(_3\)) \(\delta\): 7.16 (1H, dd, \(J\)=3.0, 8.7 Hz, 8-H), 7.41 (1H, dd, \(J\)=4.7, 7.8 Hz, 3-H), 7.47 (1H, d, \(J\)=8.3 Hz, 9-H), 7.50 (1H, d, \(J\)=3.0, 6-H), 8.71 (1H, dd, \(J\)=2.0, Hz, 4-H), 8.73 (1H, dd, \(J\)=2.0, 4.7 Hz, 2-H). MS: \(m/z\) 212 (M\(^{+}\)).

2-(3-Acetamidophenoxy)nicotinic acid (7) 
A mixture of 2-chloronicotinic acid (7.85 g, 50 mmol), 3-acetamidophenol (7.55 g, 50 mmol), potassium carbonate (13.8 g, 100 mmol), copper powder (0.7 g), cuprous iodide (0.7 g) and DMF (120 mL) was stirred under reflux for 2 h, then cooled and filtered. The filtrate was concentrated. The residue was mixed with hot water, filtered, and acidified with 10% hydrochloric acid. The resulting precipitate was collected by filtration and recrystallized from methanol to give 7 (9.33 g, 69%) as colorless needles. mp 283-284 °C. Anal. Calcd for C\(_{14}\)H\(_{12}\)N\(_2\)O\(_4\): C, 61.76; H, 4.44; N, 10.29. Found: C, 61.92; H, 4.59; N, 10.32. \(^{1}\)H-NMR (DMSO-d\(_6\)) \(\delta\): 2.03 (3H, s, CH\(_3\)), 6.77 (1H, dd, \(J\)=2.0, 7.3 Hz, 6\(^{-}\)-H), 7.24 (1H, dd, \(J\)=4.9, 7.3 Hz, 3-H), 7.27-7.88 (2H, m, 4\(^{-}\)-H, 5\(^{-}\)-H), 7.44 (1H, s, 2\(^{-}\)-H), 8.25 (1H, dd, \(J\)=2.0, 7.3 Hz, 4-H), 8.28 (1H, dd, \(J\)=2.0, 4.9 Hz, 2-H), 9.96 (1H, s, NH). MS: \(m/z\) 272 (M\(^{+}\)).

8-Amino-5H-[1]benzopyrano[2,3-b]pyridin-5-one (3) 
Compound (7, 9.33 g, 40 mmol) was heated with PPA (500 g) at 130°C for 6 h. The hot solution was poured into ice-water. The resulting precipitate was collected (a mixture of 8 and 9, 6.60 g, 77%), and then heated with 47% hydrobromic acid (120 mL) and phenol (7.5 g, 80 mmol) under reflux for 2 h. After cooling, the mixture was alkalinized with 10% aqueous sodium hydroxide to give a mixture of 1 and 3 as a yellow solid. This mixture was separated by silica gel column chromatography (CHCl\(_3\)) to afford 1 (1.07 g, 14%) and 3 (1.27 g, 16%). Compound (3): Pale yellow needles (from MeOH); mp 272-273 °C. Anal. Calcd for C\(_{12}\)H\(_{8}\)N\(_2\)O\(_2\): C, 67.91; H, 3.80; N, 13.21. Found: C, 67.95; H, 3.96; N, 13.15. IR (KBr): 1585, 1620 cm\(^{-1}\). \(^{1}\)H-NMR(CDC\(_{3}\)) \(\delta\): 6.69 (1H, dd, \(J\)= 2.0, 8.3 Hz, 7-H), 6.70 (1H, d, \(J\)=2.0 Hz, 9-H), 7.39 (1H, dd, \(J\)=4.8, 7.3 Hz, 3-H), 8.11 (1H, d, \(J\)=8.3 Hz, 6-H), 8.66 (1H, dd, \(J\)=1.9, 4.8 Hz, 2-H), 8.68 (1H, dd, \(J\)=1.9, 7.3 Hz, 4-H). MS: \(m/z\)
9-Amino-5H-[1]benzopyrano[2,3-b]pyridin-5-one (4)

A mixture of 5H-[1]benzopyrano[2,3-b]pyridin-5-one (19.7 g, 100 mmol), hydroxylamine sulfate (10 g, 50 mmol), ferrous sulfate (37 g), and 94% sulfuric acid (400 g) was stirred at 140-150 °C for 7 h. The reaction mixture was poured into water and then filtered. To the filtrate was added potassium hydrogen tartrate and the mixture was basified with 25% ammonium hydroxide. The resulting precipitate was collected by filtration and dried (13.17 g). The products were purified with silica gel (solvent: benzene) and alumina column chromatography (solvent: chloroform) to give 6-amino- (1) (4.57 g, 22%), 7-amino- (2) (2.88 g, 14%), 8-amino- (3) (1.10 g, 5%), and 9-amino-5H-[1]benzopyrano[2,3-b]pyridin-5-one (4) (1.04 g, 5%).

Compound (4): Yellow needles (from methanol), mp 212-213 °C. Anal. Calcd for C_{12}H_{8}N_{2}O_{2}: C, 67.91; H, 3.80; N, 13.21. Found: C, 68.01; H, 3.86; N, 13.32. IR (KBr): 1580, 1650 cm⁻¹. ¹H-NMR (CDCl₃) δ: 7.12 (1H, dd, J = 1.5, 7.8 Hz, 8-H), 7.21 (1H, t, J = 7.8 Hz, 7-H), 7.44 (1H, dd, J = 3.5, 5.4 Hz, 3-H), 7.66 (1H, dd, J = 1.5, 7.8 Hz, 6-H), 8.72 (1H, dd, J = 1.5, 3.5 Hz, 2-H), 8.73 (1H, dd, J = 1.5, 5.4 Hz, 4-H). MS: m/z 212 (M⁺).

General procedure for the Skraup reaction of amino-5H-benzopyrano[2,3-b]-pyridin-5-ones (1-4)

A mixture of H₂SO₄·SO₃ (6.0 g, 50 mmol), nitrobenzene (1.23 g, 10 mmol), FeSO₄·7H₂O (0.28 g, 1.0 mmol) and H₃BO₃ (0.31 g, 5.0 mmol) was chilled to 0-5 °C, and then glycerol (1.84 g, 20 mmol), amino-5H-benzopyrano[2,3-b]-pyridin-5-one (1.06 g, 5 mmol) and water (2.5 mL) were successively added. The mixture was heated at 130°C for 5 h. The reaction mixture was basified with 28% NH₄OH, the resulting precipitate was collected by filtration, and the precipitate was dissolved in CHCl₃. The extract was dried over Na₂SO₄, the solvent was evaporated and the residue was recrystallized from MeOH to give the corresponding pyrido[3′,2′:5,6]-pyranonoquinoline derivative.
12H-Pyrido[3',2':5,6]pyrano[2,3-h]quinolin-12-one (10)

Colorless needles, mp 237-238 °C. Yield 71 %. Anal. Calcd for C_{15}H_{8}N_{2}O_{2}: C, 72.56; H, 3.25; N, 11.29. Found: C, 72.60; H, 3.07; N, 11.26. IR (KBr): 1580, 1600, 1640 cm^{-1}. ^1H-NMR(CDCl₃) δ: 7.51 (1H, dd, J=4.4, 7.8 Hz, 10-H), 7.56 (1H, dd, J=4.4, 8.3 Hz, 3-H), 7.79 (1H, d, J=8.8 Hz, 6-H), 8.14 (1H, d, J=8.8 Hz, 5-H), 8.25 (1H, dd, J=2.0, 8.3 Hz, 4-H), 8.75 (1H, dd, J=2.0, 4.4 Hz, 9-H), 8.85 (1H, dd, J=2.0, 7.8 Hz, 11-H), 9.29 (1H, dd, J=2.0, 4.4 Hz, 2-H). MS: m/z 248 (M⁺).


Colorless needles, mp 190-191 °C. Yield 82 %. Anal. Calcd for C_{15}H_{8}N_{2}O_{2}: C, 72.56; H, 3.25; N, 11.29. Found: C, 72.72; H, 3.33; N, 11.41. IR (KBr): 1580, 1600, 1620 cm^{-1}. ^1H-NMR(CDCl₃) δ: 7.69 (1H, dd, J=4.4, 7.8 Hz, 10-H), 7.79 (1H, dd, J=4.4, 8.7 Hz, 2-H), 8.04 (1H, d, J=9.3 Hz, 6-H), 8.49 (1H, d, J=9.3 Hz, 5-H), 8.79 (1H, dd, J=2.0, 7.8 Hz, 11-H), 8.87 (1H, dd, J=2.0, 4.4 Hz, 9-H), 9.02 (1H, dd, J=1.0, 8.7 Hz, 3-H), 10.27 (1H, dd, J=1.0, 8.7 Hz, 1-H). MS: m/z 248 (M⁺).

7H-Pyrido[3',2':5,6]pyrano[2,3-f]quinolin-7-one (12)

Colorless needles, mp 218-219 °C. Yield 75 %. Anal. Calcd for C_{15}H_{8}N_{2}O_{2}: C, 72.56; H, 3.25; N, 11.29. Found: C, 72.39; H, 3.33; N, 11.22. IR (KBr): 1580, 1600, 1640 cm⁻¹. ^1H-NMR(CDCl₃) δ: 7.54 (1H, dd, J=4.4, 7.8 Hz, 9-H), 7.64 (1H, dd, J=4.4, 8.3 Hz, 2-H), 8.03 (1H, d, J=8.8 Hz, 5-H), 8.45 (1H, d, J=8.8 Hz, 6-H), 8.78 (1H, dd, J=1.9, 7.8 Hz, 8-H), 8.81 (1H, dd, J=1.9, 4.4 Hz, 10-H), 9.08 (1H, dd, J=2.0, 8.3 Hz, 1-H), 9.11 (1H, dd, J=2.0, 4.4 Hz, 3-H). MS: m/z 248 (M⁺).

7H-Pyrido[3',2':5,6]pyrano[3,2-h]quinolin-7-one (13)

Colorless needles, mp 291-292 °C. Yield 84 %. Anal. Calcd for C_{15}H_{8}N_{2}O_{2}: C, 72.56; H, 3.25; N, 11.29. Found: C, 72.72; H, 3.25; N, 11.39. IR (KBr): 1580, 1600, 1630 cm⁻¹. ^1H-NMR (CDCl₃) δ: 7.54 (1H, dd, J=4.4, 7.8 Hz, 9-H), 7.69 (1H, dd, J=4.4, 8.3 Hz, 3-H), 7.80 (1H, d, J=8.8 Hz, 5-H), 8.30 (1H, dd, J=1.5, 8.3 Hz, 4-H), 8.36 (1H, d, J=8.8 Hz, 6-H), 8.80 (1H, dd, J=2.0, 7.8 Hz, 8-H), 8.87 (1H, dd, J=2.0, 4.4 Hz, 10-H), 9.20 (1H, dd, J=1.5, 4.4 Hz, 2-H). MS: m/z 248 (M⁺).
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REFERENCES