A MODIFIED NIEMENTOWSKI REACTION FOR THE SYNTHESIS OF 4-HYDROXYQUINOLINE AND ITS REALTED COMPOUNDS

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Abstract - The iminoketene generated from anthranilic acid and thionyl chloride reacted with ketones to afford 4-hydroxyquinoline derivatives in good yields.

The Friedländer reaction was first introduced in 1882 for the preparation of quinoline from o-aminobenzaldehyde and acetaldehyde\(^1\) and has long been employed for the construction of quinoline nucleus in a variety of polyaza cavity-type molecules,\(^2\) as well as biologically important molecules.\(^3\) Even such a variety of applicability, the scope of the Friedländer reaction is somewhat limited for the preparation of some substituted quinolines such as hydroxyquinolines and quinolinecarboxylic acids.\(^4\) The Niementowski reaction (eq. 1),\(^5\) a reaction of anthranilic acid with a ketone to form a 4-hydroxyquinoline ring, thus introduced to overcome such a limitation. Additionally, the Niementowski reaction can also apply for the construction of quinazoline nucleus by using lactam instead of ketone (eq. 2).

\[
\begin{align*}
\text{NH}_2\text{COOH} + \text{ON} & \rightarrow \text{N} \text{H} \\
\text{NH}_2\text{COOH} + \text{O} & \rightarrow \text{N} \\
\end{align*}
\]

(eq. 1)

(eq. 2)

To extend the applicability of the Niementowski reaction, numerous variations of anthranilic
acid, such as O-acylamino-benzamides, ammonium O-acylamino-benzoates, O-acylamino-benzonitrile, acetanthranils, methyl anthranilates, and isatoic anhydride and reaction conditions, such as in the presence of acetic anhydride and alkaline peroxide, were pursued, the scope of the Niementowski reaction still remained limited presumably due to the severe reaction condition.

As a part of our research for the efficient synthesis of 4-hydroxyquinolines as well as quinazolines, we reinvestigate the Niementowski reaction and herein describe a modified procedure by employing iminoketene as a key intermediate which may undergo cycloaddition to ketone.

RESULTS AND DISCUSSION

The formation of iminoketene (2) by a reaction of anthranilic acid with thionyl chloride and its application to the synthesis were extensively studied by retro mass-spectral analysis. Since such an iminoketene undergoes \([4\pi + 2\pi]\) cycloaddition with imine and amide (via iminol), we expect the iminoketene can undergo the Diels-Alder cycloaddition with ketone.
The iminoketene, generated \textit{in situ} by refluxing anthranilic acid with thionyl chloride in dry benzene,\textsuperscript{12} was neither purified nor identified but rather reacted with cyclohexanone (3a) at room temperature to afford 1,2,3,4-tetrahydro-9-acridone (4) in 82\% yield. Similarly, the reactions of 2 with acetophenone (3b), 2-acetylpyridine (3c), 1-tetralone (3d), and 5,6,7,8-tetrahydroquinol-8-one (3e) afforded corresponding 4-hydroxyquinoline-related compounds (5a, 5b, 6a, and 6b), respectively in 74-87\% yields.

On the other hand, a reaction of 2 with 2,6-diacetylpyridine (3f) afforded bis-(4-hydroxyquinolyl) compound (7) in 85\% yield. The H8' of 7 was resonanced at $\delta$ 7.66 as a two-proton doublet ($J = 8.0$ Hz), H3' and H3'' at $\delta$ 7.35 as a two-proton singlet, and H3 (with H5) at $\delta$ 7.21 as a two-proton doublet of multiplet ($J = 8.4$ Hz) which are characteristic for the 2,6-bis(2'-quinolyl)pyridines.\textsuperscript{13}

![Chemical structure](image)

In conclusion, anthranilic acid was converted to a corresponding iminoketene which was undergone cycloaddition with ketones presumably via enol to afford desired 4-hydroxyquinoline derivatives in good yields. The reaction can be done in one-pot, thus extends the applicability of Niementowski reaction.

**EXPERIMENTAL**

Melting points were determined using a Fischer-Jones melting points apparatus and are not corrected. IR spectra were obtained using a Perkin-Elmer 1330 spectrophotometer. NMR spectra were obtained using a Bruker-250 spectrometer 250 MHz for $^1$H NMR and 62.5 MHz for $^{13}$C NMR and are reported as ppm from the internal standard TMS. The starting 5,6,7,8-tetrahydroquinol-8-one (3e) was prepared by employing previously reported method.\textsuperscript{14} Chemicals and solvents were commercial reagent grade and used without further purification. Elemental analyses were taken on a Hewlett-Packard Model 185B elemental analyzer.
**1,2,3,4-Tetrahydro-9-acridone (4)**

A solution of 1.70 g (12.5 mmol) of o-anthranilic acid and 10 mL (51.6 mmol) of SOCl₂ in 30 mL of dry benzene was refluxed for 2 h. The solvent was removed under reduced pressure at 25 °C to afford iminoketene as a yellow oily liquid, to which a solution of 1.23 g (12.5 mmol) of cyclohexanone in 30 mL of dry benzene was added. After setting aside overnight at rt, the reaction mixture was washed with 10% K₂CO₃ and work-up as usual gave 2.06 g (83%) of a desired product as a white needles after recrystallization from pyridine: mp > 300 °C. (lit.,¹⁵ mp 370 °C). Unreported spectral data are as follows: IR (KBr) ν 3400, 1650, 1630, 1530, 1500, 1340, 1260, 1060, 870 cm⁻¹. ¹H NMR (CD₃OD, 250 MHz) δ 8.21 (dd, J = 8.2, 1.2 Hz, H5), 7.61 (ddd, J = 8.3, 7.0, 1.5 Hz, H6), 7.48 (d, J = 8.3 Hz, H8), 7.32 (ddd, J = 8.3, 7.0, 1.5 Hz, H7), 2.81 (t, J = 5.6, 2H), 2.62 (t, J = 5.6 Hz, 2H), 1.92-1.77 (m, 2H). ¹³C NMR (CD₃OD, 62.5 MHz) δ 179.3, 150.3, 140.6, 132.7, 126.0, 124.6, 124.2, 118.6, 117.9, 28.8, 23.3, 23.0, 22.9.

**4-Hydroxy-2-phenylquinoline (5a)**

The same procedure described above for 4 was employed with 0.68 g (5.0 mmol) of o-anthranilic acid, 10 mL (51.6 mmol) of SOCl₂, and 0.60 g (5.0 mmol) of acetophenone to afford 0.86 g (78%) of a desired compound as white needles after recrystallization from EtOH: mp 256 °C (lit.,¹⁶ mp 255-257 °C). Unreported spectral data are as follows: IR (KBr) ν 3340, 1560, 1500, 1460, 1060, 870 cm⁻¹. ¹H NMR (250 MHz, CD₃OD) δ 8.25 (dd, J = 8.8, 1.0 Hz, H8), 7.81-7.69 (m, 5H), 7.59-7.57 (m, 3H), 7.43 (td, J = 8.4, 1.8 Hz, 1H).

**4-Hydroxy-2-(2'-pyridyl)quinoline (5b)**

The same procedure described above for 4 was employed with 0.68 g (5.0 mmol) of o-anthranilic acid, 10 mL (51.6 mmol) of SOCl₂, and 0.61 g (5.0 mmol) of 2-acetylpyridine to afford 0.92 g (83%) of a desired compound as an pale yellow oil. IR (KBr) ν 3340, 1550, 1510, 1450, 1070, 870 cm⁻¹. ¹H NMR (250 MHz, CDCl₃) δ 9.91 (dd, 1H, J = 8.7, 0.9 Hz, H8), 8.61 (dd, 1H, J = 4.8, 1.4 Hz, H2'), 7.65-7.61(m, 2H), 7.43(dt, J = 8.9, 1.2 Hz, 1H, H3'), 7.17(s, H3), 7.08-7.00(m 1H), 6.81(td, J = 8.6, 1.0 Hz), 6.67 (ddd, J = 7.8, 4.8, 1.3 Hz, 1H, H5'). Anal. Calcd for C₁₄H₁₀N₂O: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.49; H, 4.66; N, 12.76.
5,6-Dihydro-7-hydroxybenz[c]acridine (6a)
The same procedure described above for 4 was employed with 0.68 g (5.0 mmol) of o-anthranilic acid, 10 mL (51.6 mmol) of SOCl₂, and 0.73 g (5.0 mmol) of α-tetralone to afford 0.92 g (74%) of a desired compound as white needles after recrystallization from EtOH: mp 282-283 °C. IR (KBr) ν 3340, 1560, 1500, 1460, 1060, 870 cm⁻¹. ¹H NMR (250 MHz, DMSO-d₆) δ 11.50 (s, OH), 8.11 (dd, 1H, J = 8.3, 1.1 Hz), 8.06 (dm, 1H, J = 8.4 Hz), 7.83 (d, 1H, J = 8.3 Hz), 7.63 (td, 1H, J = 8.3, 1.3 Hz), 7.50-7.37 (m 3H), 7.29 (t, 1H, J = 7.3 Hz), 2.85-2.80 (m, 2H), 2.76-2.70 (m, 2H). Anal. Calcd for C₁₇H₁₃NO: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.54; H, 6.45; N, 6.95.

5,6-Dihydro-7-hydroxy[3,2-c]acridine (6b)
The same procedure described above for 4 was employed with 0.34 g (2.5 mmol) of o-anthranilic acid, 10 mL (51.6 mmol) of SOCl₂, and 0.37 g (2.5 mmol) of 5,6,7,8-tetrahydroquinol-8-one to afford 0.53 g (87%) of a desired compound as white needles after recrystallization from EtOH: mp 249-250 °C. IR (KBr) ν 3350, 1608, 1575, 1450, 975, 880 cm⁻¹. ¹H NMR (250 MHz, DMSO-d₆) δ 10.00 (s, OH), 8.52 (d, 1H, J = 4.8 Hz, H6'), 8.43 (d, 1H, J = 8.0 Hz, H4), 7.58-7.63 (m, 2H), 7.48 (d, 1H, J = 8.0 Hz, H4'), 7.30-7.38 (m, 1H, H2), 7.28 (dd, 1H, J = 8.0, 4.8 Hz, H5'), 3.08 (s, 4H). Anal. Calcd for C₁₆H₁₂N₂O: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.49; H, 5.02; N, 11.19.

2,6-Di(4'-hydroxyquinol-2'-yl)pyridine (7)
The same procedure described above for 4 was employed with 1.16 g (6.25 mmol) of o-anthranilic acid, 10 mL (51.6 mmol) of SOCl₂, and 0.42 g (2.5 mmol) of 2,6-diacetylpyridine to afford 0.73 g (83%) of a desired compound as white needles after recrystallization from EtOH: mp > 300 °C. IR (KBr) ν 3350, 1600, 1500, 1400, 1060, 880 cm⁻¹. ¹H NMR (250 MHz, DMSO-d₆) δ 10.00 (s, OH), 7.68 (d, 1H, J = 8.0 Hz, H8'), 7.36 (s, 2H, H3'), 7.23 (dm, 2H, J = 8.4 Hz, H3 & H5), 6.98 (t, J = 8.4 Hz, H4), 6.86 (d, 2H, J = 8.4 Hz, H5'), 6.48-6.56 (m, 4H). Anal. Calcd for C₂₃H₁₅N₃O₂: C, 75.60; H, 4.14; N, 11.50. Found: C, 75.72; H, 4.12; N, 11.67.

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