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# A FACILE SYNTHESIS OF 5-PHENYLIMIDAZO-[4,5-*c*][1,8]NAPHTHYRIDIN-4(5*H*)-ONE

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ABSTRACT: 1-Phenyl-3-nitroso-4-amino-1,8-naphthyridin-2(1*H*)-one (**9**) was prepared on a large scale and was converted to 5-phenylimidazo[4,5-*c*] [1,8]naphthyridin-4(5*H*)-one (KF17625, **1**) which exhibits potent antiasthmatic activity.



Imidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-one derivatives have been reported to exhibit potent branchodilatory activity. Suzuki and Kuroda reported that 5-phenyl substitution was pivotal, and that KF17625 (**1**) showed more potent branchodilatory activity than aminophylline (ethylenediamine salt of theophylline). Furthermore, compound **1** inhibited carbachol-, histamine-, or leucotriene $D_4$-induced contraction and relaxed the spontaneous tone in guinea pig isolated tracheal preparation. [1-3]

For further pharmacological studies, the large-scale preparations of **1** are needed. From the standpoint of safety, we report the facile and novel synthetic preparation of **1**.

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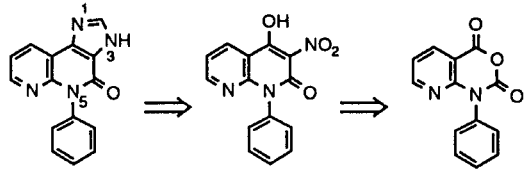
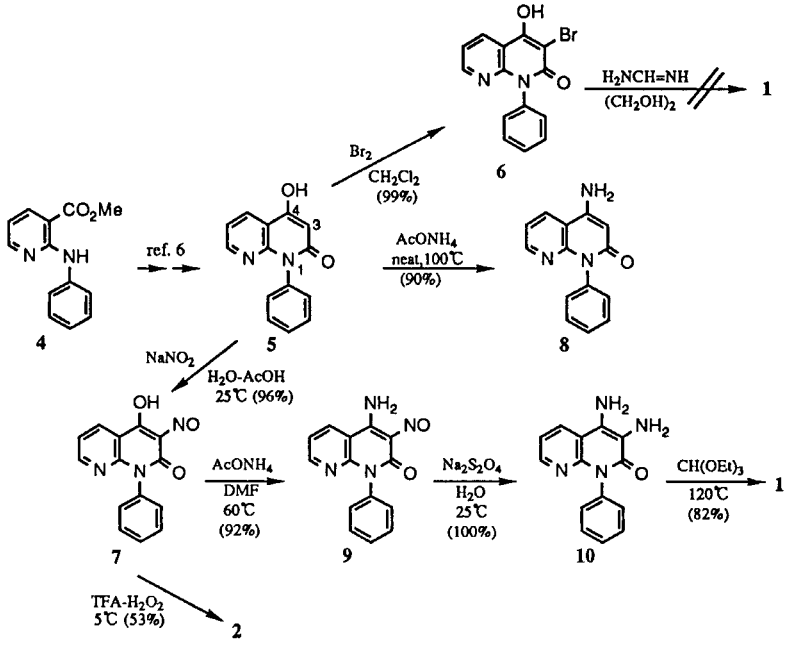
In the preceding paper, [1] the key intermediate, 4-hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**2**) was prepared by the base catalyzed condensation of *N*-phenyl-3-azaisatoic anhydride (**3**) and ethyl nitroacetate. (Scheme 1) This route has several problems for the large-scale preparations. First, compound **3** prepared from methyl 2-anilinonicotinate (**4**) and trichloromethyl chloroformate (TCF), was difficult to obtain in large quantities and released severely poisonous phosgene under the described conditions.[1,4] Second, the condensation reaction to **2** proceeded satisfactorily at a temperature over 150 °C. On the other hand, DSC (Differential Scanning Calorimetry) studies of **2** indicated that severe exothermic decomposition began at 170 °C. It suggested the possibility of an explosion when the reaction temperature exceeded 170 °C during the large-scale preparations of **2**. Therefore, such a high reaction temperature should be avoided.

Sherlock reported the convenient synthesis of 4-hydroxy-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**5**) from **4**. [6] Using this compound **5**, we studied a facile and novel imidazole ring construction to afford **1**. (Scheme 2) Compound **5** was brominated with bromine in methylene chloride to afford 3-bromo-4-hydroxy-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**6**) in almost quantitative yield. [7] However, the known method to construct the imidazole ring skeleton by the condensation of formamidine with α-haloketone [8] could not be applied to **6**. [9] On the other hand, we found that compound **5** could be easily converted to 4-hydroxy-3-nitroso-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**7**) by treatment with sodium nitrite at room temperature in high yield. The mild oxidation of the nitroso group of **7** to the nitro group [10, 11] by treatment with hydrogen peroxide in trifluoroacetic acid at 5 °C also afforded **2**. Here, a novel and practical route for the synthesis of **2** without using TCF was accomplished.

On the other hand, when compound **5** was fused with ammonium acetate at 100 °C (neat, 20 h), the hydroxy group at the C-4 position was slowly substituted




Scheme 1




Scheme 2

for the amino group to afford **8**. [12, 13] We expected that the reaction rate of the amination at C-4 might be accelerated in the presence of an electron-withdrawing group at C-3 and the best candidate was **7**. Since DSC studies of **7** showed that its exothermic pattern was quite similar to that of **2** (exothermic decomposition began at 170 °C), a lower reaction temperature for the amination at C-4 of **7** should have no possibility of exothermic decomposition. As expected, the hydroxy group of **7**

was easily converted to the amino group within 1 h with 3 eq. of ammonium acetate at 60 °C in *N,N*-dimethylformamide (DMF). Thus, 4-amino-3-nitroso-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**9**) was obtained in 90 % yield. These results provide another novel and more practical route to **1** without using TCF and the oxidation of the nitroso group of **7**. Thus, compound **9** was reduced to the diamino compound **10** and finally converted to **1** by the method reported by Kuroda. [1)]

In summary, we have established a convenient, safe and novel synthetic route to KF17625 which has potent antiasthmatic activity.

## EXPERIMENTAL

All the reagents and solvents were commercially available and were used without purification. Melting points (mp) were determined with a Yanagimoto hot-stage microscope and are uncorrected. Microanalyses were measured with a Yanaco MT-3 CHN corder. Infrared (IR) spectra were recorded on a Shimadzu IR-435 spectrometer. Proton nuclear magnetic resonance ($^1$H NMR) spectra were obtained with a Brucker AC-300 spectrometer and signals were given in ppm using tetramethylsilane as an internal standard. Mass (MS) spectra were obtained with a Hitachi M-80B mass spectrometer. Differential Scanning Calorimetry studies (DSC) were performed using a Shimadzu DT-40 thermal analyzer.

**4-Hydroxy-3-nitroso-1-phenyl-1,8-naphthyridin-2(1*H*)-one (7):**

A solution of sodium nitrite (9.4 g, 63 mmol) in water (7 ml) was added in small portions to a suspension of **5** (10.7g, 45 mmol) in a mixture of acetic acid (23 ml) and water (67 ml) at room temperature, and the whole mixture was stirred for 2 h. The precipitate was filtered off to afford **7** as a yellow solid. (11.5 g, 96 %)

$C_{14}H_9N_3O_3$ calcd. C. 62.92 %, H. 3.40 %, N. 15.72 %.

(267.24) found C. 62.89 %, H. 3.61 %, N. 15.45 %.

mp.: 205 - 210 °C (decomp.). $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (ppm): 7.28 - 7.44 (m, 3H), 7.46 - 7.58 (m, 3H), 8.37 (br, 1H), 8.44 (br, 1H). IR (KBr): ν max 1678, 1585, 1437, 1402, 1340, 1057, 783 cm$^{-1}$. MS (EI): m/z 267 ($M^+$, 83), 250 (21), 236 (4), 222 (14), 194 (18), 181 (19), 168 (60), 77 (100).

**4-Hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-2(1*H*)-one (2):**

Compound **7** (3.0 g, 11.23 mmol) was dissolved in trifluoroacetic acid (30 ml) at 5 °C. To this solution, 30 % aqueous hydrogen peroxide solution (2 ml) was added in small portions, and the whole mixture was stirred at 5 °C for 30 h. Then water (60 ml) was added and the precipitate was filtered off to give **2** as trifluoroacetic acid salt. This solid was dissolved in 2N NaOH (20 ml), and the pH of the reaction mixture was adjusted to 7 with 2N HCl. The precipitate was filtered off to give compound **2** as a yellow solid. (1.68 g, 53 %)

$C_{14}H_9N_3O_4$ calcd. C. 59.37 %, H. 3.20 %, N. 14.84 %.

(283.24) found C. 59.57 %, H. 2.99 %, N. 14.68 %.

mp.: 296 - 298 °C (decomp.). $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (ppm): 7.26 - 7.36 (m, 3H), 7.41 - 7.54 (m, 3H), 8.48 (d, 1H, $J$ = 5.2 Hz), 8.51 (d, 1H, $J$ = 8.2 Hz). IR (KBr): ν max 1690, 1612, 1590, 1540, 1497, 1421, 1354, 1220, 1178, 780, 745 cm$^{-1}$.

**4-Amino-1-phenyl-1,8-naphthyridin-2(1*H*)-one (8):**

Compound **5** (1.0 g, 4.20 mmol) was fused with ammonium acetate (20.0 g, 259 mmol) at 100 °C for 20 h. To this reaction mixture, water (20 ml) was added in small portions. After the mixture was stirred for 2 h at room temperature, the precipitate was filtered off, and then dissolved in chloroform (200 ml). The solution was washed with water (100 ml), dried over anhydrous $MgSO_4$. After the solvent was removed *in vacuo*, the residue was purified by column chromatography on $SiO_2$ using chloroform/methanol (100 : 1) as an eluent to give

compound **8** as a yellow solid. (897 mg, 90%)

$C_{14}H_{11}N_3O$ calcd. C. 70.87 %, H. 4.67 %, N. 17.71 %.

(237.26) found C. 71.02 %, H. 4.48 %, N. 17.60 %.

mp.: 246 - 250 °C (decomp.). $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (ppm): 6.02 (s, 1H), 7.29 - 7.39 (m, 3H), 7.52 - 7.64 (m, 3H), 8.36 (d, 1H, $J$ = 7.8 Hz), 8.47 (br, 1H), 13.03 (br, 2H). IR (KBr): ν max 1640, 1610, 1572, 1558, 1485, 1440, 1361, 1300, 1260, 1208, 1156, 1072, 797 cm$^{-1}$.

**4-Amino-3-nitroso-1-phenyl-1,8-naphthyridin-2(1*H*)-one (9):**

A mixture of **7** (5.0 g, 18.7 mmol), ammonium acetate (4.3 g, 56.1 mmol) and DMF (10 ml) was heated at 60 °C for 3 h, then water (50 ml) was added at room temperature and the precipitate was filtered off to afford **9** as a brown solid. (4.6 g, 92 %)

$C_{14}H_{10}N_4O_2$ calcd. C. 63.15 %, H. 3.79 %, N. 21.04 %.

(266.26) found C. 63.30 %, H. 3.88 %, N. 20.78 %.

mp.: 287 - 290 °C (decomp.). $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (ppm): 7.32 - 7.39 (m, 3H), 7.46 - 7.59 (m, 3H), 8.51 (d, 1H, $J$ = 4.6 Hz), 8.95 (d, 1H, $J$ = 7.2 Hz), 12.88 (br, 2H). IR (KBr): ν max 1657, 1630, 1597, 1445, 1348, 1300, 1215, 785 cm$^{-1}$. MS (EI) m/z: 266 ($M^+$, 53), 249 (68), 221 (31), 206 (11), 194 (100), 179 (5), 168 (19), 77 (95).

**5-Phenylimidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-one (1).**

Sodium hydrosulfite (9.0 g, 51.7 mmol) was added in small portions to a suspension of **9** (4.5 g, 16.9 mmol) at room temperature and the mixture was stirred for 4 h. The precipitate was filtered off to afford 3,4-diamino-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**10**). This solid, after drying under reduced pressure, was suspended in triethyl orthoformate (75 ml, 454 mmol) and heated at 120 °C for 2 h. The reaction mixture was then cooled to room temperature. The precipitate

was filtered off to afford **1** as a yellow solid. This was recrystallized from a mixture of DMF and water to give pure **1** as colorless prisms. (3.6 g, 82 %)

$C_{15}H_{10}N_4O$ calcd. C. 68.69 %, H. 3.84 %, N. 21.36 %.

(262.27) found C. 68.88 %, H. 3.77 %, N. 21.31 %.

mp.: > 300 °C (lit. > 300 °C). [1] $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (ppm): 7.31 - 7.41 (m, 3H), 7.49 - 7.59 (m, 3H), 8.37 - 8.40 (m, 2H), 8.53 - 8.56 (m, 1H), 13.80 (br, 1H). IR (KBr): ν max 1668, 1583, 1423 cm$^{-1}$. MS (EI): m/z 262 ($M^+$, 41), 261 (100), 206 (12), 179 (5), 131 (9), 103 (10), 77 (30).

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