A Facile and Novel Synthesis of 5-Phenylimidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-ones

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A convenient and regioselective synthesis of a new heterocycle, 5-phenyl-1*H* or 3*H*-imidazo[4,5-*c*][1,8]-naphthyridin-4(5*H*)-one **1-a** or **1-b**, is described. Methyl 2-anilinonicotinate **15** was transformed into the valuable intermediate, *N*-phenyl-3-azaisatoic anhydride **4** using trichloromethyl chloroformate (TCF). Treatment of **4** with the anion of ethyl nitroacetate gave 4-hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-4(5*H*)-one **3**. Compound **3** was chlorinated, aminated, reduced, and cyclized to afford 5-phenylimidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-one **1**. Regioselective substitution at the 1 or 3-position in the imidazole moiety of **1** was achieved by minor changes of the above scheme.

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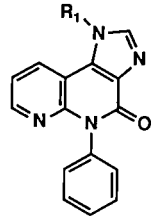
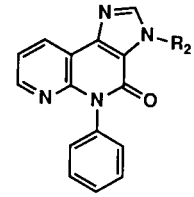
5-Phenyl-1*H* or 3*H*-imidazo[4,5-*c*][1,8]naphthyridin-4-(5*H*)-one derivatives **1a** and **1b** have been shown to exhibit extremely potent antiinflammatory or antiasthmatic activities where 5-phenyl substitution is pivotal [1]. These results will be published elsewhere. We are interested in the structure-activity relationship of these compounds, particularly with regard to certain 1, or 3 substitution. This paper describes a facile and regioselective synthesis of 5-phenyl-1*H* or 3*H*-imidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-one, **1-a** or **1-b**.



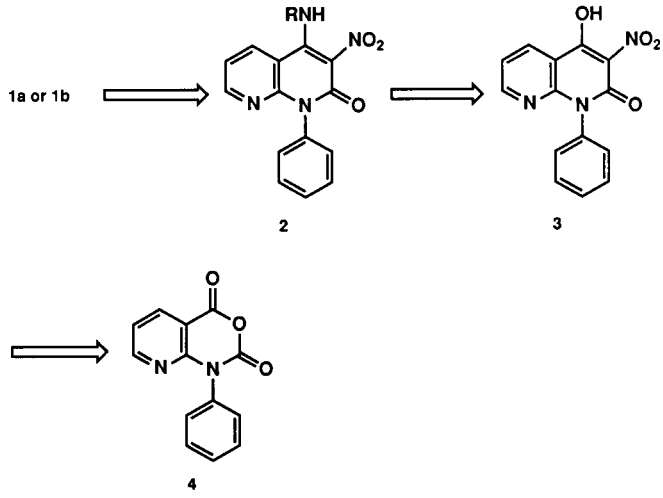
1a



1b

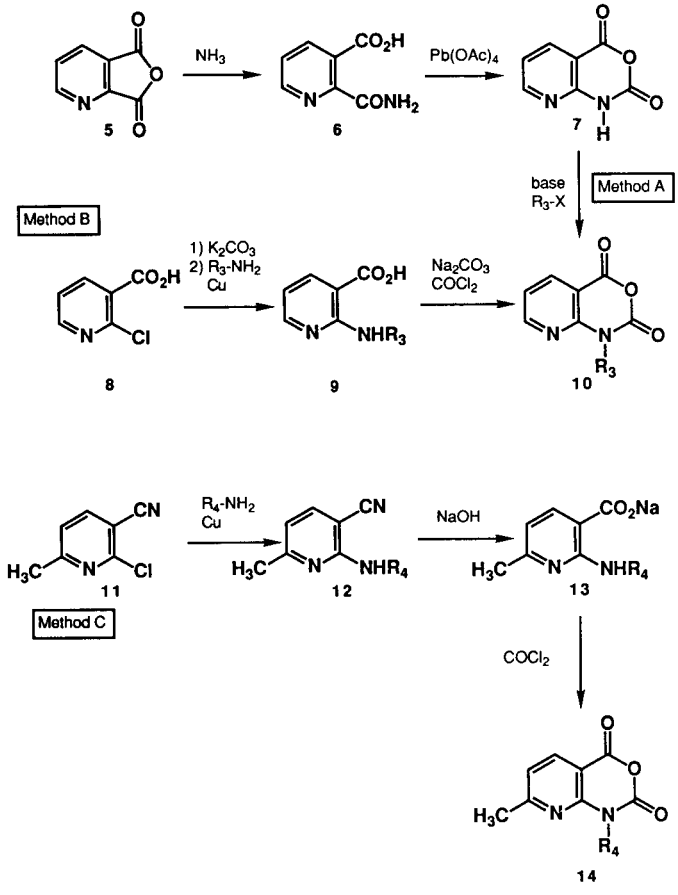
Retrosynthetic analysis suggested that 4-hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-4(5*H*)-one **3** might be an appropriate synthetic intermediate (Scheme 1). These types of heterocycles have been prepared *via* the particular reaction which is opening of the heterocyclic ring of an 3-azaisatoic anhydride by the anion of active methylene compounds [2,3]. Although a *N*-phenyl-3-azaisatoic anhydride **4** is not known, 1-alkyl substituted derivatives **10** and **14** have been prepared with three methods as shown in Scheme 2 [3,4]. The direct substitution on the nitrogen of **7** with a phenyl moiety is not possible [5] (Method A, Scheme 2). Consequently, the phenyl group must be introduced prior to the formation of the 3-azaisatoic anhydride ring by use of Methods B and C (Scheme 2). Both approaches use phosgene which is not easily available in Japan. This situation caused us to develop a more convenient synthesis of an 3-azaisatoic anhydride. In peptide chemistry, the *N*-carboxy-α-amino acid anhydride has been prepared by the treatment of an alkyl α-amino acid ester with trichloromethyl chloroformate (TCF) [6]. We applied this reaction to methyl 2-anilinonicotinate **15** which was prepared from 2-chloronicotinic acid **8** [7]. Compound **15** was treated with trichloromethyl chloroformate (TCF) in 1,2-dichloroethane at 80° for 3 hours. The reaction occurred cleanly to give *N*-phenyl-3-azaisatoic anhydride **4** in a 87% yield (Scheme 3).

Scheme 1

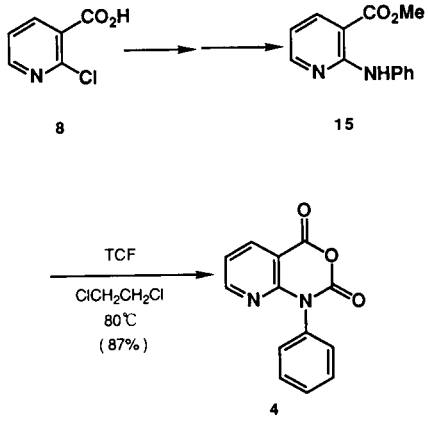


Compound **4** was reacted with the sodium anion of ethyl nitroacetate in *N*,*N*-dimethylacetamide (DMA) to afford 4-hydroxy-3-nitro-1-phenyl-1,8-naphthyridin-4(5*H*)-one **3** in a 75% yield (Scheme 4). It was reported that *N*-methyl-3-azaisatoic anhydride was transformed to 4-hydroxy-1-methyl-3-nitro-1,8-naphthyridin-4(5*H*)-one under the same conditions in a low yield (22%) [3]. *N*-Phenyl substitution in **4**

Scheme 2



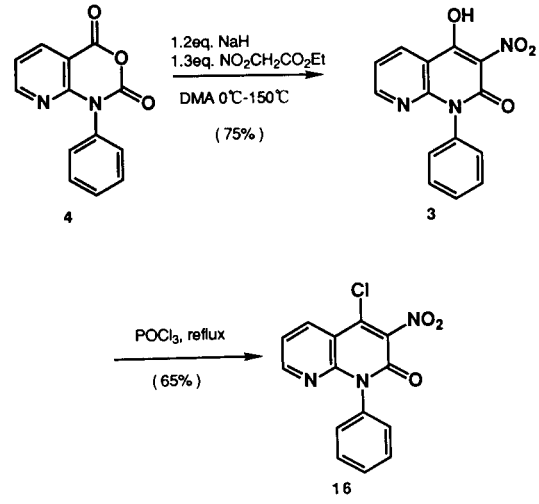
Scheme 3



improves the yield of this reaction dramatically. Chlorination of **3** was achieved by phosphorus oxychloride in reflux to afford **16**.

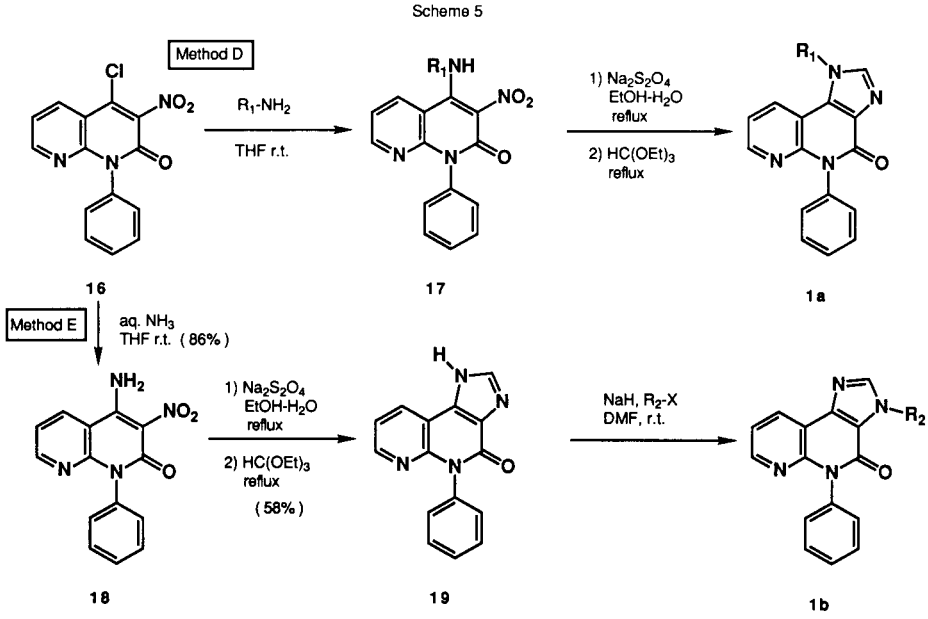
Regioselective introduction of a substituent at the 1 or 3-position in the imidazole moiety of **1** was outlined in Scheme 5. 1-Substituted products **1a** were prepared according to Method D. The chloride **16** was readily displaced by the primary amine in tetrahydrofuran (THF) at room temperature to provide **17** (Table 1). Reduction of the nitro group of **17** was carried out by sodium hydrosulfite in a mixture of ethanol and water at 80°. Without purification, the imidazole moiety was constructed with refluxing triethyl orthoformate to give **1a** (Table 2). The chemical structure of **1a** was confirmed by spectroscopic analysis. Observation of the NOEs of **1a-a** between 1-Me and 2-H, and between 1-Me and 9-H (enhancement of 28.5% and 28.6% respectively) indicated that the methyl group was located as illustrated in **1a-a** (Scheme 6). On the other hand, 3-substituted products **1b** were prepared according to Method E. Compound **19** was obtained by ammonolysis, reduction and cyclization from **16** by the same procedure as Method D. Regioselective introduction of the substituent at the 3-position was achieved by the treatment of the sodium salt of **19** with appropriate electrophiles to afford **1b** (Table 3). In this reaction, none of **1a** was observed. Steric interaction between the 1-substituent and 9-H, and the linear conjugation of the double bonds in imidazole with the carbonyl group presumably favour 3-substitution of the compound **19** under the present alkylation conditions.

Scheme 4



In summary, we have described a convenient synthesis of the valuable intermediate, *N*-phenyl-3-azaisatoic anhydride **4** and a regioselective synthesis of 1 or 3-substituted-5-phenylimidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-one derivatives. Further extensions and applications of our methods to syntheses of other heterocycles are currently under study in our laboratory.

Scheme 5



Scheme 6

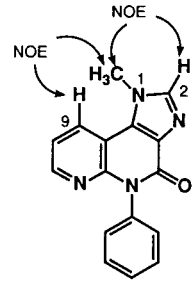
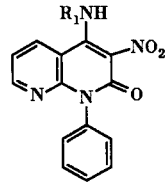


Table 1

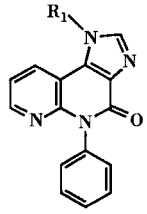
4-Alkylamino-3-nitro-1-phenyl-1,8-naphthyridin-2(1*H*)-ones



Compound No.	R_1	Mp °C	Yield %	Recrystallization solvent	Molecular Formula	Analysis % Calcd. (Found) C	H	N
17-a	CH_3	>300	97	Dimethylformamide/ water	$C_{15}H_{12}N_4O_3$	60.93 (60.81)	3.94 (4.08)	19.07 (18.71)
17-b	CH_3CH_2	189-193	88	Dimethylformamide/ water	$C_{16}H_{14}N_4O_3$	61.79 (61.93)	4.55 (4.55)	18.06 (18.06)
17-c	$(CH_3)_2CH_2$	259-261	91	Ethyl alcohol/ water	$C_{17}H_{16}N_4O_3$	63.19 (62.97)	4.86 (4.97)	17.04 (17.27)
17-d	$C_6H_5CH_2$	192-194	87	Ethyl alcohol/ water	$C_{21}H_{16}N_4O_3$	68.13 (67.73)	4.24 (4.33)	14.91 (15.04)

Table 2

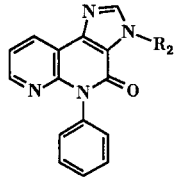
1-Alkyl-5-phenyl-1*H*-imidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-ones



Compound No.	R_1	Mp °C	Yield %	Recrystallization solvent	Molecular Formula	Analysis % Calcd. (Found) C	H	N
1a-a	CH_3	262	58	Isopropyl alcohol/ Isopropyl ether	$C_{16}H_{12}N_4O$	69.55 (69.68)	4.38 (4.27)	20.28 (20.19)
1a-b	CH_3CH_2	>300	34	Methyl alcohol	$C_{17}H_{14}N_4O$	70.33 (70.33)	4.81 (4.86)	19.30 (19.33)
1a-c	$(CH_3)_2CH_2$	>300	56	Ethyl alcohol	$C_{18}H_{16}N_4O$	71.02 (71.04)	5.23 (5.30)	18.41 (18.16)
1a-d	$C_6H_5CH_2$	>300	25	Methyl alcohol	$C_{22}H_{16}N_4O$	74.59 (74.89)	4.58 (4.58)	16.20 (15.90)

Table 3

3-Alkyl-5-phenyl-3*H*-imidazo[4,5-*c*][1,8]naphthyridin-4-(5*H*)-ones



Compound No.	R_2	X	Mp °C	Yield %	Recrystallization solvent	Molecular Formula	Analysis % Calcd. (Found) C	H	N
1b-a	CH_3	I	>300	72	Isopropyl ether/ Ethyl alcohol	$C_{16}H_{12}N_4O$	69.55 (69.85)	4.38 (4.10)	20.28 (20.28)
1b-b	CH_3CH_2	I	233-234	96	Chloroform/ Isopropyl ether	$C_{17}H_{14}N_4O$	70.58 (70.33)	4.82 (4.86)	19.29 (19.50)
1b-c	$(CH_3)_2CH_2$	I	255-257	71	Isopropyl ether	$C_{19}H_{18}N_4O$ 1/10 H_2O	71.15 (71.28)	5.62 (5.73)	17.46 (17.50)
1b-d	$C_6H_5CH_2$	Br	189-192	78	Ethyl alcohol/ water	$C_{22}H_{16}N_4O$	75.13 (74.98)	4.57 (4.57)	15.97 (15.89)

EXPERIMENTAL

Melting points were determined on a Yanagimoto hot plate micro melting point apparatus and are uncorrected. Infrared (ir) spectra were measured on a JASCO IR-810 spectrometer. Proton nuclear magnetic resonance (^{1}H-nmr) spectra were measured on a JEOL JNM GX-270 spectrometer or a Hitachi R-90H spectrometer with tetramethylsirane (TMS) as an internal standard. Mass spectra (ms) were determined on a JEOL JMS-D300 instrument at an ionization potential of 70eV. Elemental analyses were performed of a Perkin-Elmer 2400CHN. For open column chromatography, Silica gel 60 (E. Merck, 0.063-0.200 mm) was used. The reaction was usually carried out under nitrogen. Organic extracts were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator.

1-Phenyl-2*H*-pyrido[2,3-*d*][1,3]oxazine-2,4-(1*H*)dione (*N*-Phenyl-3-azaisatoic Anhydride) (**4**).

To a solution of 7.0 g (0.031 mole) of methyl 2-anilinonicotinate in 150 ml of dry 1,2-dichloroethane was slowly added dropwise 11 ml (0.092 mole) of trichloromethyl chloroformate at 80° [8]. The reaction mixture was stirred for 3 hours at this temperature. After cooling, 0.25 g of activated carbon was added and then the mixture was refluxed for 30 minutes. After cooling, the solvent was evaporated under reduced pressure. The residue was recrystallized from dichloromethane-isopropyl ether to give 6.5 g (87%) of white crystals of **4**, mp 196-198°; ir (potassium bromide): ν 1791, 1728 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): 7.10-7.70 (m, 6H, 6-H and phenyl protons (5H)), 8.47 (dd, 1H, 5-H, J = 6,2 Hz), 8.57 (dd, 1H, 7-H, J = 5,2 Hz); ms: m/e 240 (molecular ion).

Anal. Calcd. for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66. Found: C, 65.11; H, 3.22; N, 11.48.

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

To a solution of 1.9 ml (0.020 mole) of ethyl nitroacetate in 25 ml of dry dimethylacetamide (DMA) was added 0.80 g (0.020 mole) of 60% sodium hydride at 0° in portions. When the evolution of hydrogen ceased, 4.0 g (0.017 mole) of **4** was added. The temperature was raised slowly to 100° and kept there for 30 minutes (carbon dioxide evolved). The solvent was evaporated under reduced pressure and water was added to the residue. The aqueous solution was washed with ethyl acetate and the aqueous phase was acidified with concentrated hydrochloric acid. The resulting precipitate was filtered, washed with water, and recrystallized from isopropyl alcohol-ethyl alcohol to give 3.6 g (77%) of yellow crystals of **3**, mp 296-298°; ir (potassium bromide): ν 1682 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 7.26-7.36 (m, 3H, 6-H and phenyl protons (2H)), 7.41-7.54 (m, 3H, phenyl protons), 8.48 (dd, 1H, J = 5,2 Hz), 8.51 (dd, 1H, J = 8,2 Hz); ms: m/e 283 (molecular ion).

Anal. Calcd. for $C_{14}H_9N_3O_4$: C, 59.37; H, 3.20; N, 14.84. Found: C, 59.57; H, 2.99; N, 14.68.

4-Chloro-3-nitro-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**16**).

A suspension of 10 g (0.038 mole) of **3** in 50 ml (0.54 mole) of phosphorus oxychloride was refluxed for an hour. After cooling, the solvent was evaporated under reduced pressure and water was added to the residue. The mixture was neutralized with 2*N* sodium hydroxide solution. The resulting precipitate was filtered, washed with water, and recrystallized from ethyl acetate-hexane to give 5.2 g (49%) of white crystals **16**, mp 228-232°; ir (potassium bromide): ν 1667 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): 7.25-7.30 (m, 2H, phenyl protons), 7.40 (dd, 1H, 6-H, J = 8,5 Hz), 7.50-7.63 (m, 3H, phenyl protons), 8.44 (dd, 1H, 5-H, J = 8,2 Hz), 8.62 (dd, 1H, 7-H, J = 5,2 Hz); ms: m/e 300, 302 (molecular ion).

Anal. Calcd. for $C_{14}H_8N_3O_3Cl$: C, 55.74; H, 2.67; N, 13.93. Found: C, 55.91; H, 2.68; N, 13.97.

4-Methylamino-3-nitro-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**17-a**).

A mixture of 1.8 g (6.0 mmoles) of **16** and 4.6 ml (60 mmoles) of 40% aqueous methylamine solution in 60 ml of tetrahydrofuran (THF) was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure and water was added to the residue. The resulting precipitate was filtered, washed with water, and recrystallized from dimethylformamide-water to give 1.6 g (97%) of yellow crystals of **17-a**, mp >300°; ir (potassium bromide): ν 1620 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 2.88 (d, 3H, NCH_3, J = 5 Hz), 7.23-7.27 (m, 2H, phenyl protons), 7.37 (dd, 1H, 6-H, J = 8,5 Hz), 7.40-7.53 (m, 3H, phenyl protons), 8.05-8.16 (m, 1H, NH), 8.46 (dd, 1H, 7-H, J = 5,2 Hz), 8.63 (dd, 1H, 5-H, J = 8,2 Hz); ms: m/e 296 (molecular ion).

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.93; H, 3.94; N, 19.07. Found: C, 60.81; H, 4.08; N, 18.71.

1-Methyl-5-phenyl-1*H*-imidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-one (**1a-a**).

A mixture of 1.2 g (4.0 mmoles) of **17-a** and 2.8 g (16 mmoles) of sodium hydrosulfite in 10 ml of ethyl alcohol and 10 ml of water was stirred at 80° for 10 minutes. After cooling, the resulting precipitate was filtered and dried. A suspension of the precipitate in 8.0 ml (48 mmoles) of triethyl orthoformate was stirred under reflux for an hour. After cooling, the resulting precipitate was filtered and recrystallized from isopropyl alcohol-isopropyl ether to give 0.64 g (58%) of yellow crystals **1a-a**, mp 262°; ir (potassium bromide): ν 1667 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 4.22 (s, 3H, 1-CH_3), 7.22-7.25 (m, 2H, phenyl protons), 7.34 (dd, 1H, 6-H, J = 8,5 Hz), 7.41-7.57 (m, 3H, phenyl protons), 8.20 (s, 1H, 2-H), 8.35 (dd, 1H, 7-H, J = 5,2 Hz), 8.60 (dd, 1H, 9-H, J = 8,2 Hz); ms: m/e 276 (molecular ion).

Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.68; H, 4.27; N, 20.19.

4-Amino-3-nitro-1-phenyl-1,8-naphthyridin-2(1*H*)-one (**18**).

A mixture of 1.8 g (6.0 mmoles) of **16** and 3.6 ml (60 mmoles) of 28% aqueous ammonia in 60 ml of tetrahydrofuran (THF) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and water was added to the residue. The resulting precipitate was filtered, washed with water, and recrystallized from dimethylformamide-water to give 1.5 g (86%) of yellow crystals of **18**, mp >300°; ir (potassium bromide): ν 1623 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 7.23-7.50 (m, 6H, 7-H and phenyl protons (5H)), 8.44-8.51 (m, 3H, 5-H and 2H, NH_2), 8.79 (dd, 1H, 5-H, J = 9,2 Hz); ms: m/e 282 (molecular ion).

Anal. Calcd. for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.59; H, 3.61; N, 19.71.

5-Phenyl-1*H*-imidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-one (**19**).

Compound **19** was prepared from **18** in a 58% yield following the same procedures as for **1a-a**. This compound was obtained as white crystals (dimethylformamide-water), mp >300°; ir (potassium bromide): ν 1668 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 7.23-7.38 (m, 3H, 8-H and phenyl protons (2H)), 7.43-7.58 (m, 3H, phenyl protons), 8.36-8.36 (m, 2H, 2-H and 7-H), 8.49-8.53 (m, 1H, 9-H), 13.84 (br s, 1H, NH); ms: m/e 262 (molecular ion).

Anal. Calcd. for $C_{15}H_{10}N_4O1/5H_2O$: C, 67.76; H, 3.94; N, 21.07. Found: C, 67.92; H, 3.45; N, 21.10.

3-Methyl-5-phenyl-3*H*-imidazo[4,5-*c*][1,8]naphthyridin-4(5*H*)-one (**1b-a**).

To a solution of 0.80 g (3.1 mmoles) of **19** in 30 ml of dry dimethylformamide (DMF) was added 0.18 g (4.6 mmoles) of 60% sodium hydride at 0° in portions. When the evolution of hydrogen ceased, 4.0 ml (6.3 mmoles) of methyl iodide was added. After stirring at room temperature for 5 hours, 2 ml of aqueous saturated ammonium chloride was added with cooling. The solvent was evaporated under reduced pressure and water was added to the residue. The aqueous mixture was extracted with chloroform. The organic phase was washed with water, dried and evaporated under reduced pressure. The residue was chromatographed on silica gel using chloroform/methyl alcohol = 70/1 to elute the product, 0.61 g (72%) of **1b-a**. An analytical sample was recrystallized from isopropyl alcohol-ethyl alcohol, mp >300°; ir (potassium bromide): ν 1663 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 4.06 (s, 3H, 3-CH_3), 7.27-7.36 (m, 3H, 8-H and phenyl protons (2H)), 7.43-7.57 (m, 3H, phenyl protons), 8.33-8.35 (m, 2H, 2-H and 7-H), 8.50 (dd, 1H, 9-H, J = 8,2 Hz); ms: m/e 276 (molecular ion).

Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.85; H, 4.10; N, 20.28.

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* To whom all correspondence should be addressed.

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