FULL PAPER

Synthesis of 2-Aryl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-ones by Deprotective Cyclization of *N*-{3-[(2*E*)-3-Arylprop-2-enoyl]pyridin-2-yl}-2,2-dimethylpropanamides in Water

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A new and convenient method for the preparation of 2-aryl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-ones **4** has been developed. Thus, *N*-{3-[(2*E*)-3-arylprop-2-enoyl]pyridin-2-yl}-2,2-dimethylpropanamides **3** are synthesized from commercially available pyridin-2-amine using an easily performed three-step sequence and are subjected to cyclization with deprotection under acidic conditions in H_2O to give the desired products. Similarly, 2-aryl-2,3-dihydro-1,7-naphthyridin-4(1*H*)-ones **8** and 2-aryl-2,3-dihydro-1,6-naphthyridin-4(1*H*)-ones **12** can be prepared from pyridin-3-amine and pyridin-4-amine, respectively.

Keywords: 2,3-Dihydro-1,6-naphthyridin-4(1*H*)-ones, 2,3-Dihydro-1,7-naphthyridin-4(1*H*)-ones, 2,3-Dihydro-1,8-naphthyridin-4(1*H*)-ones, Pyridinamines, Lithiated pyridines.

Introduction

Utilization of 2,3-dihydro-1,8-naphthyridin-4(1*H*)-one derivatives as versatile intermediates in the synthesis of biologically useful and structurally more complex compounds has been demonstrated [1]. However, only a limited number of methods for the general preparation of 2,3-dihydro-1,8-naphthyridin-4(1*H*)-one derivatives are known [2]. Recently, an efficient method, involving the reaction of 1-(2-chloropyridin-3-yl)prop-2-en-1-ones with primary amines, has been reported by *Bunce et al.* [3]. However, this method was limited to the preparation of 1-alkylated 2-nonsubstitued (or Me substituted) derivatives. Therefore, we embarked on the research on developing a novel and facile method for the preparation of 2,3-dihydro-1,8-naphthyridin-4(1*H*)-one derivatives. We previously reported that *N*-lithio-*N*-(4-lithiopyridin-3-yl)-2,2-dimethylpropanamide [4] reacted with *N*-methoxy-*N*-methylbenzamides to give *N*-(4-aroylpyridin-3-yl)-2,2-dimethylpropanamide, from which 1,7-naphthyridine [5] and 3-aryl-3*H*-pyrrolo[2,3-*c*]pyridin-3-ol derivatives [6] could be prepared. We envisioned the possibility of preparing *N*-{3-[(2*E*)-3-arylprop-2-enoyl]pyridin-2-yl}-2,2-dimethylpropanamides **3** from *N*-lithio-*N*-(3-lithiopyridin-2-yl)-2,2-dimethylpropanamide [4] *via* reactions with (2*E*)-3-arylprop-2-enals, followed by oxidation. Compound **3** would readily undergo cyclization during acid hydrolysis to give 2-aryl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-ones **4**. In this article, we describe the results of our investigations, which provide a new and convenient approach to obtain not only **4** but also 2-aryl-2,3-dihydro-1,7-naphthyridin-4(1*H*)-ones **8** and 2-aryl-2,3-dihydro-1,6-naphthyridin-4(1*H*)-ones **12**.

Results and Discussion

The synthesis of 2,3-dihydro-1,8-naphthyridin-4(1*H*)-ones **4** was accomplished in three steps from 2,2-dimethyl-*N*-(pyridin-2-yl)propanamide (**1**) as illustrated in *Scheme 1*. Compound **1** was easily prepared by 2,2-dimethylpropanoylation of commercially available pyridin-2-amine with 2,2-dimethylpropanoyl chloride [7]. We first investigated the possibility of the formation of *N*-{3-[(2*E*)-3-aryl-1-hydroxyprop-2-en-1-yl]pyridin-2-yl}-2,2-dimethylpropanamides **2** *via* the reaction of *N*-lithio-*N*-(3-lithiopyridin-2-yl)-2,2-dimethylpropanamide, generated by the treatment of **1** with 2 equiv. of BuLi [4], with (2*E*)-3-arylprop-2-enals[1]). The reactions proceeded smoothly to give **2** in good yields as compiled in the *Table*. The oxidation of **2** was facilitated with activated MnO_2 to give the corresponding enones **3** in good yields as well. These precursors were then subjected to deprotective cyclization under acidic conditions.

The initial attempts at transforming 2,2-dimethyl-*N*-{3-[(2*E*)-3-phenylprop-2-enoyl]pyridin-2-yl}propanamide (**3a**) into 2,3-dihydro-2-phenyl-1,8-naphthyridin-4(1*H*)-one (**4a**) were carried out in 3M HCl under reflux.

[1]) We first used *tert*-butyl pyridin-2-ylcarbamate to take advantage of the mild conditions for deprotection of the *N*-Boc group. However, it did not perform well in the dilithiation and the subsequent reaction with (2*E*)-PhCH=CHCHO.

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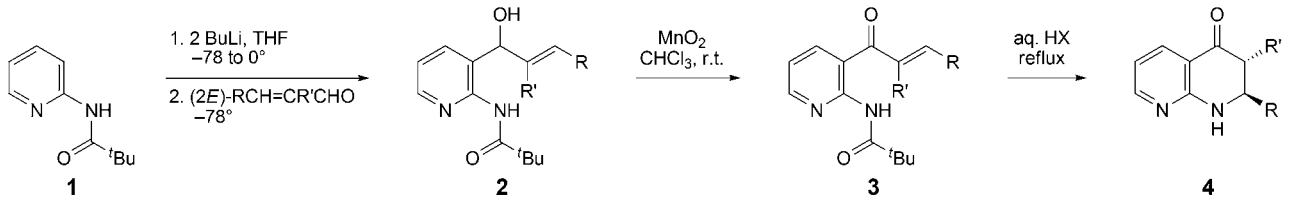
Table. Preparation of 2,3-dihydro-1,8-naphthyridin-4(1*H*)-ones **4**

Entry	R	R′	**2**	Yield [%][a])	**3**	Yield [%][a])	Acid[b])	**4**	Yield [%][a])
1	Ph	H	**2a**	87	**3a**	83	A	**4a**	28
2	Ph	H	**2a**	87	**3a**	83	B	**4a**	62
3	4-MeO–C_6H_4	H	**2b**	79	**3b**	85	A	**4b**	75
4	3,4-$(MeO)_2$–C_6H_3	H	**2c**	80	**3c**	79	A	**4c**	74
5	4-Cl–C_6H_4	H	**2d**	89	**3d**	94	B	**4d**	55
6	Ph	Me	**2e**	91	**3e**	90	B	**4e**	59
7	Me	H	**2f**	93	**3f**	59	B	**4f**	16

[a]) Yield of isolated product. [b]) A, 3M HCl; B, concentrated HBr.

Scheme 1



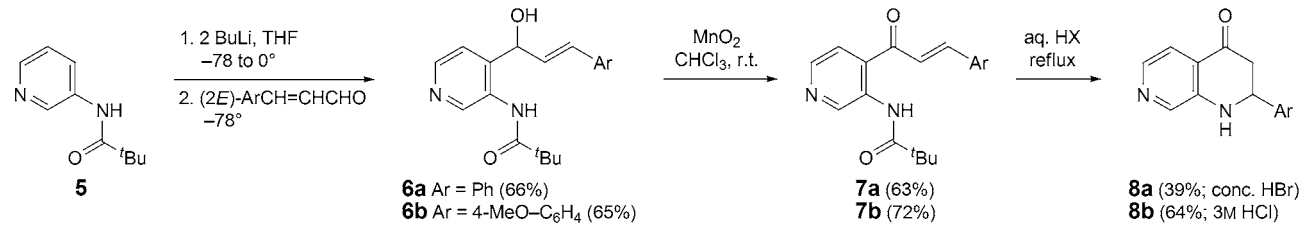
Unfortunately, the reaction resulted in the formation of a rather complex mixture of products and the desired product was isolated in only a disappointing yield (*Table*, *Entry 1*). Then, we conducted the reaction in concentrated HBr under reflux. Fortunately, it proceeded smoothly and led to the isolation of **4a** in a satisfactory yield (*Entry 2*). Substitution of the benzene ring proved to have a large effect on the cyclization. The synthesis of **4b** and **4c** with MeO group(s) as substituent(s) was shown to proceed under less acidic conditions in better yields (*Entries 3* and *4*) than the synthesis of **4a** and **4d** – **4f**, while a Cl-substituent gave only moderate yields of the desired product **4d** even under much more acidic conditions (conc. HBr; *Entry 5*). The precursor **3e**, derived from (2*E*)-2-methyl-3-phenylprop-2-enal, gave exclusively product **4e** with *trans*-configuration. This is probably due to the less steric crowdedness of the *trans*-isomer. In the case of precursor **3f**, derived from (2*E*)-but-2-enal, the reaction under these conditions gave complicated mixtures of products and the desired products could be isolated in a low yield from the reaction in 3M HCl under reflux (*Entry 7*). The cyclization was supposed to proceed *via* deprotection of the 2,2-dimethylpropanoyl group giving aminopyridinyl enones, followed by acid-mediated conjugate addition of the amino group to the enone moiety, as proposed by *Bunce et al.* [8] in the formation of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones by a tandem reduction/conjugate addition of 3-aryl-1-(nitrophenyl)-prop-2-en-1-ones [8].

With the sequence for the preparation of 2,3-dihydro-1,8-naphthyridin-4(1*H*)-one derivatives **4** in hand, attention was turned to its application to the synthesis of 2,3-dihydro-1,7-naphthyridin-4(1*H*)-ones **8** and 2,3-dihydro-1,6-naphthyridin-4(1*H*)-ones **12**. As shown in *Scheme 2*, the precursor enones **7** were obtained by reaction of *N*-lithio-*N*-(4-lithiopyridin-3-yl)-2,2-dimethylpropanamide [4], generated from 2,2-dimethyl-*N*-(pyridin-3-yl) propanamide (**5**) [7], with (2*E*)-3-arylprop-2-enals and subsequent oxidation in fair yields. The precursor **7a**, derived using (2*E*)-3-phenylprop-2-enal, underwent cyclization in concentrated HBr to give the desired product **8a** but in rather diminished yield, while the reaction in 3M HCl did not proceed cleanly and resulted in the formation of an intractable mixture of products. However, the reaction of precursor **7b**, derived from (2*E*)-3-(4-methoxyphenyl)prop-2-enal, proceeded more cleanly in 3M HCl to give the corresponding product **8b** in fair yield.

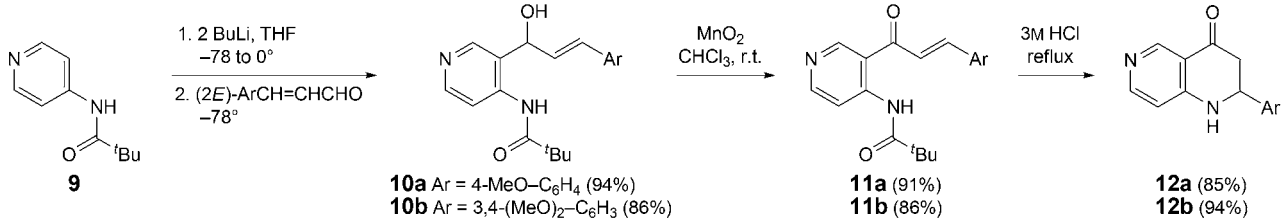
Similarly, *N*-{3-[(2*E*)-3-arylprop-2-enoyl]pyridin-4-yl}-2,2-dimethylpropanamides **11** were obtained from 2,2-dimethyl-*N*-(pyridin-4-yl)propanamide (**9**) [7] and (2*E*)-3-arylprop-2-enals in good yields and were subjected to cyclization. Only precursors **9** with MeO substituent(s) on the benzene ring worked well in 3M HCl under reflux to afford the corresponding 2-aryl-2,3-dihydro-1,6-naphthyridin-4(1*H*)-ones **12** in excellent yields (*Scheme 3*). It should be noted that the precursor derived from (2*E*)-3-phenylprop-2-enals gave only intractable mixtures of products both in 3M HCl and concentrated HBr.

In conclusion, we have demonstrated a three-step sequence from 2,2-dimethyl-*N*-pyridinylpropanamides that provides a new and efficient method for the preparation of three types of 2,3-dihydronaphthyridin-4(1*H*)-one ring systems. It may be valuable in organic synthesis because it can be conducted by easy experimental operations. In addition, this sequence has the advantages of starting with

Scheme 2



Scheme 3



readily available pyridinamine derivatives. Further investigation on the utilization of the dilithium compounds generated from 2,2-dimethyl-*N*-pyridinylpropanamides for the synthesis of other fused heterocyclic ring systems are now under study in our laboratory.

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Experimental Part

General

All org. solvents used in this study were dried over appropriate drying agents and distilled prior to use. (2*E*)-3-(3,4-Dimethoxyphenyl)prop-2-enal [9], 2,2-dimethyl-*N*-(pyridin-2-yl)propanamide (**1**) [7], 2,2-dimethyl-*N*-(pyridin-3-yl)propanamide (**5**) [7], and 2,2-dimethyl-*N*-(pyridin-4-yl)propanamide (**9**) [7] were prepared by the reported procedures. BuLi was supplied by *Asia Lithium Corporation* (Naoshima, Japan). All other chemicals used in this study were commercially available. M.p.: *Laboratory Devices MEL-TEMP II* (Laboratory Devices Company, Plavervile, CA, USA) melting-point apparatus; uncorrected. Thin-Layer Chromatography (TLC): *Merck* (Darmstadt, Germany) silica gel *60 PF*$_{254}$ (SiO_2). Column chromatography (CC): *Wako Gel C-200E* (Wako Pure Chemical Industries, Ltd., Osaka, Japan). IR Spectra: *PerkinElmer Spectrum65* (PerkinElamer, Inc., Waltham, MA, USA) FT-IR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *JEOL ECP500* FT NMR spectrometer (Japan Electron Optics Laboratory, Co., LTD., Akishima, Japan) (500 and 125 MHz for ^{1}H and ^{13}C, resp.) or *JEOL LA400* FT NMR spectrometer (Japan Electron Optics Laboratory, Co., LTD., Akishima, Japan) (400 MHz for ^{1}H); in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-DART-MS (pos.): *Thermo Scientific Exactive* spectrometer (Thermo Fisher Scientific Inc, Waltham, MA, USA); in *m*/*z*. HR-EI-TOF-MS: *JEOL JMS-T100GCV* (Japan Electron Optics Laboratory, Co., LTD., Akishima, Japan) (70 eV) spectrometer; in *m*/*z*. Elemental analyses: *Elementar Vario EL II* instrument (Elementar Analysensysteme GmbH, Hanau, Germany).

***N*-{3-[(2*E*)-1-Hydroxy-3-phenylprop-2-en-1-yl]pyridin-2-yl}-2,2-dimethylpropanamide** (**2a**). *Representative Procedure.* A soln. of **1** (0.20 g, 1.1 mmol) in THF (5 ml) was treated with BuLi (1.6M in hexane; 2.2 mmol) as described in [7] to generate *N*-lithio-*N*-(3-lithiopyridin-2-yl)-2,2-dimethylpropanamide. To this soln. at −78° was added (2*E*)-PhCH=CHCHO (0.15 g, 1.1 mmol) and the temperature was gradually raised to 0°. Sat. aq. NH_4Cl (20 ml) was added and the mixture was extracted with AcOEt (3 × 10 ml). The combined extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by CC (SiO_2; AcOEt/hexane 1:3) to afford **2a** (0.30 g, 87%). Pale-yellow solid. M.p. 154 – 156° (hexane/CH_2Cl_2). IR (KBr): 3319, 1689, 1605. ^{1}H-NMR (400 MHz): 1.35 (*s*, 9 H); 4.28 (br. *s*, 1 H); 5.36 (*dd*, *J* = 4.9, 2.0, 1 H); 6.32 (*dd*, *J* = 15.6, 4.9, 1 H); 6.81 (*dd*, *J* = 15.6, 2.0, 1 H); 7.23 – 7.40 (*m*, 6 H); 7.83 (*dd*, *J* = 7.8, 2.0, 1 H); 8.24 (br. *s*, 1 H); 8.37 (*d*, *J* = 4.5, 1 H). Anal. calc. for $C_{19}H_{22}N_2O_2$ (310.40): C 73.52, H 7.14, N 9.03; found: C 73.43, H 7.22, N 9.13.

***N*-{3-[(2*E*)-1-Hydroxy-3-(4-methoxyphenyl)prop-2-en-1-yl]pyridin-2-yl}-2,2-dimethylpropanamide** (**2b**). Pale-yellow amorphous powder. R_f (AcOEt/hexane 1:3) 0.30. IR (KBr): 3306, 1693, 1607. ^{1}H-NMR (500 MHz): 1.35 (*s*, 9 H); 3.81 (*s*, 3 H); 4.10 (br. *s*, 1 H); 5.36 (br. *d*, *J* = 5.2, 1 H); 6.19 (*dd*, *J* = 16.0, 5.2, 1 H); 6.73 (*dd*, *J* = 16.0, 1.7, 1 H); 6.85 (*d*, *J* = 9.2, 2 H); 7.18 (*dd*, *J* = 7.4, 4.6, 1 H); 7.32 (*d*, *J* = 9.2, 2 H); 7.82 (*dd*, *J* = 7.4, 1.1, 1 H); 8.26 (br. *s*, 1

H); 8.39 (*d*, *J* = 4.6, 1 H). Anal. calc. for $C_{20}H_{24}N_2O_3$ (340.42): C 70.56, H 7.11, N 8.23; found: C 70.50, H 7.28, N 8.06.

***N*-{3-[(2*E*)-3-(3,4-Dimethoxyphenyl)-1-hydroxyprop-2-en-1-yl]pyridin-2-yl}-2,2-dimethylpropanamide** (**2c**). Pale-yellow amorphous powder. R_f (AcOEt/hexane 1:3) 0.24. IR (KBr): 3316, 1687, 1603. ^{1}H-NMR (500 MHz): 1.35 (*s*, 9 H); 3.88 (*s*, 3 H); 3.88 (*s*, 3 H); 4.11 (br., 1 H); 5.38 (*dd*, *J* = 5.2, 1.1, 1 H); 6.20 (*dd*, *J* = 16.0, 5.2, 1 H); 6.71 (*dd*, *J* = 16.0, 1.1, 1 H); 6.81 (*d*, *J* = 8.6, 1 H); 6.92 – 6.93 (*m*, 2 H); 7.19 (*dd*, *J* = 7.4, 4.6, 1 H); 7.83 (*dd*, *J* = 7.4, 1.1, 1 H); 8.25 (br. *s*, 1 H); 8.39 (br. *s*, 1 H). Anal. calc. for $C_{21}H_{26}N_2O_4$ (370.45): C 68.09, H 7.07, N 7.56; found: C 67.98, H 7.11, N 7.50.

***N*-{3-[(2*E*)-3-(4-Chlorophenyl)-1-hydroxyprop-2-en-1-yl]pyridin-2-yl}-2,2-dimethylpropanamide** (**2d**). Pale-yellow amorphous powder. R_f (AcOEt/hexane 1:3) 0.36. IR (KBr): 3287, 1689, 1605. ^{1}H-NMR (500 MHz): 1.35 (*s*, 9 H); 4.38 (br. *s*, 1 H); 5.37 (*d*, *J* = 4.6, 1 H); 6.28 (*dd*, *J* = 16.0, 4.6, 1 H); 6.79 (br. *d*, *J* = 16.0, 1 H); 7.21 (*dd*, *J* = 7.4, 4.0, 1 H); 7.28 (*d*, *J* = 8.0, 2 H); 7.32 (*d*, *J* = 8.0, 2 H); 7.82 (*d*, *J* = 7.4, 1 H); 8.17 (br. *s*, 1 H); 8.39 (*d*, *J* = 4.0, 1 H). Anal. calc. for $C_{19}H_{21}ClN_2O_2$ (344.84): C 66.18, H 6.14, N 8.12; found: C 65.98, H 6.08, N 8.06.

***N*-{3-[(2*E*)-1-Hydroxy-2-methyl-3-phenylprop-2-en-1-yl]pyridin-2-yl}-2,2-dimethylpropanamide** (**2e**). Colorless viscous oil. R_f (AcOEt/hexane 1:3) 0.25. IR (neat): 3281, 1679, 1606. ^{1}H-NMR (500 MHz): 1.35 (*s*, 9 H); 1.61 (*s*, 3 H); 4.41 (*d*, *J* = 2.9, 1 H); 5.18 (br. *s*, 1 H); 6.97 (*s*, 1 H); 7.20 – 7.25 (*m*, 2 H); 7.31 – 7.37 (*m*, 4 H); 7.84 (*dd*, *J* = 7.4, 1.1, 1 H); 8.13 (*s*, 1 H); 8.39 (*dd*, *J* = 4.6, 1.1, 1 H). Anal. calc. for $C_{20}H_{24}N_2O_2$ (324.42): C 74.04, H 7.46, N 8.64; found: C 73.87, H 7.47, N 8.38.

***N*-{3-[(2*E*)-1-Hydroxybut-2-en-1-yl]pyridin-2-yl}-2,2-dimethylpropanamide** (**2f**). Colorless oil. R_f (AcOEt/hexane 1:3) 0.21. IR (neat): 3311, 1694, 1601. ^{1}H-NMR (500 MHz): 1.35 (*s*, 9 H); 1.74 (*d*, *J* = 6.3, 3 H); 3.63 (br. *s*, 1 H); 5.15 (br. *d*, *J* = 5.7, 1 H); 5.68 (*ddd*, *J* = 15.5, 5.7, 1.1, 1 H); 5.80 – 5.87 (*m*, 1 H); 7.16 (*dd*, *J* = 7.4, 5.2, 1 H); 7.74 (*dd*, *J* = 7.4, 1.1, 1 H); 8.31 (br. *s*, 1 H); 8.38 (br. *d*, *J* = 5.2, 1 H). Anal. calc. for $C_{14}H_{20}N_2O_2$ (248.33): C 67.71, H 8.12, N 11.28; found: C 67.50, H 8.27, N 11.00.

***N*-{4-[(2*E*)-1-Hydroxy-3-phenylprop-2-en-1-yl]pyridin-3-yl}-2,2-dimethylpropanamide** (**6a**). Yellow viscous oil. R_f (AcOEt/hexane 1:2) 0.12. IR (neat): 3318, 1686, 1604. ^{1}H-NMR (500 MHz): 1.36 (*s*, 9 H); 4.18 (br. *s*, 1 H); 5.47 (*d*, *J* = 5.7, 1 H); 6.37 (*d*, *J* = 16.0, 5.7, 1 H); 6.69 (*d*, *J* = 16.0, 1 H); 7.13 (*d*, *J* = 4.6, 1 H); 7.27 – 7.36 (*m*, 5 H); 8.31 (*d*, *J* = 4.6, 1 H); 8.87 (*s*, 1 H); 9.11 (br. *s*, 1 H). Anal. calc. for $C_{19}H_{22}N_2O_2$ (310.40): C 73.52, H 7.14, N 9.03; found: C 73.52, H 7.24, N 8.86.

***N*-{4-[(2*E*)-1-Hydroxy-3-(4-methoxyphenyl)prop-2-en-1-yl]pyridin-3-yl}-2,2-dimethylpropanamide** (**6b**). Pale-yellow solid. M.p. 170 – 172° (hexane/CH_2Cl_2). IR (KBr): 3300, 1682, 1607. ^{1}H-NMR (500 MHz): 1.30 (*s*, 9 H); 3.81 (*s*, 3 H); 3.89 (br., 1 H); 5.44 (*d*, *J* = 6.3, 1 H); 6.23 (*dd*, *J* = 16.0, 6.3, 1 H); 6.62 (*d*, *J* = 16.0, 1 H); 6.85 (*d*, *J* = 8.6, 2 H); 7.15 (*d*, *J* = 5.2, 1 H); 7.30 (*d*, *J* = 16.0, 2 H); 8.30 (*d*, *J* = 5.2, 1 H); 9.02 (br. *s*, 1 H); 9.43 (*s*, 1 H). Anal. calc. for $C_{20}H_{24}N_2O_3$ (340.42): C 70.57, H 7.11, N 8.23; found: C 70.57, H 7.18, N 8.10.

***N*-{3-[(2*E*)-1-Hydroxy-3-(4-methoxyphenyl)prop-2-en-1-yl]pyridin-4-yl}-2,2-dimethylpropanamide** (**10a**). Pale-yellow solid. M.p. 118 – 120° (hexane/CH_2Cl_2). IR (KBr): 3305, 1698, 1607. ^{1}H-NMR (500 MHz): 1.25 (*s*, 9 H); 3.80 (*s*, 3 H); 4.35 (br., 1 H); 5.47 (*d*, *J* = 5.2, 1 H); 6.24 (*dd*, *J* = 15.5, 5.1, 1 H); 6.59 (*d*, *J* = 15.5, 1 H); 6.84 (*d*, *J* = 9.2, 2 H); 7.27 (*d*, *J* = 9.2, 2 H); 8.17 (*s*, 1 H); 8.38 – 8.41 (*m*, 2 H); 9.57 (br. *s*, 1 H). Anal. calc. for $C_{20}H_{24}N_2O_3$ (340.42): C 70.57, H 7.11, N 8.23; found: C 70.50, H 7.27, N 8.03.

***N*-{3-[(2*E*)-3-(3,4-Dimethoxyphenyl)-1-hydroxyprop-2-en-1-yl]pyridin-4-yl}-2,2-dimethylpropanamide** (**10b**). Pale-yellow solid. M.p. 170 – 172° (hexane/CH_2Cl_2). IR (KBr): 3310, 1696. ^{1}H-NMR (500 MHz): 1.26 (*s*, 9 H); 3.87 (*s*, 3 H); 3.88 (*s*, 3 H); 4.32 (br., 1 H); 5.49 (*d*, *J* = 5.2, 1 H); 6.24 (*dd*, *J* = 16.0, 5.2, 1 H); 6.58 (*d*, *J* = 16.0, 1 H); 6.80 (*d*, *J* = 8.0, 1 H); 6.87 (*s*, 1 H); 6.88 (*d*, *J* = 8.0, 1 H); 8.19 (*s*, 1 H); 8.40 (*s*, 2 H); 9.55 (br. *s*, 1 H). Anal. calc. for $C_{21}H_{26}N_2O_4$ (370.45): C 68.09, H 7.07, N 7.56; found: C 67.69, H 7.20, N 7.52.

2,2-Dimethyl-*N*-{3-[(2*E*)-3-phenylprop-2-enoyl]pyridin-2-yl}propanamide (**3a**). *Representative Procedure.* A mixture of **2a** (0.30 g, 0.96 mmol) in $CHCl_3$ (5 ml) containing activated MnO_2 (0.42 g, 4.8 mmol) was stirred at room temperature for 5 h. After vacuum filtration through a pad of *Celite 545* (Wako Pure Chemical Industries, Ltd., Osaka, Japan), the filtrate was concentrated by evaporation. The residue was purified by CC (SiO_2; AcOEt/hexane 1:3) to afford **3a** (0.24 g, 83%). White solid. M.p. 118 – 120° (hexane/CH_2Cl_2). IR (KBr): 3261, 1704, 1681, 1646. ^{1}H-NMR (500 MHz): 1.37 (*s*, 9 H); 7.15 (*dd*, *J* = 7.8, 4.6, 1 H); 7.42 – 7.50 (*m*, 6 H); 7.82 (*d*, *J* = 15.6, 1 H); 8.27 (*d*, *J* = 7.8, 1 H); 8.66 (*dd*, *J* = 4.6, 1 H); 11.28 (br. *s*, 1 H). Anal. calc. for $C_{19}H_{20}N_2O_2$ (308.38): C 74.00, H 6.54, N 9.08; found: C 73.81, H 6.68, N 9.01.

***N*-{3-[(2*E*)-3-(4-Methoxyphenyl)prop-2-enoyl]pyridin-2-yl}-2,2-dimethylpropanamide** (**3b**). Yellow solid. M.p. 146 – 148° (hexane/CH_2Cl_2). IR (KBr): 3258, 1705, 1687, 1644. ^{1}H-NMR (500 MHz): 1.37 (*s*, 9 H); 3.87 (*s*, 3 H); 6.95 (*d*, *J* = 9.2, 2 H); 7.14 (*dd*, *J* = 8.0, 4.6, 1 H); 7.36 (*d*, *J* = 15.5, 1 H); 7.61 (*d*, *J* = 9.2, 2 H); 7.81 (*d*, *J* = 15.5, 1 H); 8.26 (*dd*, *J* = 8.0, 1.7, 1 H); 8.66 (*dd*, *J* = 4.6, 1.7, 1 H); 11.41 (br. *s*, 1 H). Anal. calc. for $C_{20}H_{22}N_2O_3$ (338.41): C 70.99, H 6.55, N 8.28; found: C 70.81, H 6.63, N 8.24.

***N*-{3-[(2*E*)-3-(3,4-Dimethoxyphenyl)prop-2-enoyl]pyridin-2-yl}-2,2-dimethylpropanamide** (**3c**). Yellow solid. M.p. 135 – 137° (hexane/CH_2Cl_2). IR (KBr): 3255, 1698, 1645. ^{1}H-NMR (500 MHz): 1.37 (*s*, 9 H); 3.95 (*s*, 3 H); 3.95 (*s*, 3 H); 6.92 (*d*, *J* = 8.0, 1 H); 7.13 – 7.16 (*m*, 2 H); 7.25 (*dd*, *J* = 8.0, 1.7, 1 H); 7.32 (*d*, *J* = 15.5, 1 H); 7.78 (*d*, *J* = 15.5, 1 H); 8.26 (*dd*, *J* = 8.4, 1.7, 1 H); 8.66 (*dd*, *J* = 5.2, 2.3, 1 H); 11.28 (br. *s*, 1 H). Anal. calc. for

$C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.10, H 6.41, N 7.52.

***N*-{3-[(2*E*)-3-(4-Chlorophenyl)prop-2-enoyl]pyridin-2-yl}-2,2-dimethylpropanamide** (**3d**). Pale-yellow solid. M.p. 139 – 141° (hexane/CH_2Cl_2). IR (KBr): 3261, 1703, 1688, 1647. ^{1}H-NMR (500 MHz): 1.37 (*s*, 9 H); 7.16 (*dd*, *J* = 8.0, 5.1, 1 H); 7.42 (*d*, *J* = 8.6, 2 H); 7.44 (*d*, *J* = 16.0, 1 H); 7.58 (*d*, *J* = 8.6, 2 H); 7.77 (*d*, *J* = 16.0, 1 H); 8.25 (*dd*, *J* = 8.0, 1.7, 1 H); 8.67 (*dd*, *J* = 5.1, 1.7, 1 H); 11.17 (br. *s*, 1 H). Anal. calc. for $C_{19}H_{19}ClN_2O_2$ (342.82): C 66.57, H 5.59, N 8.17; found: C 66.29, H 5.49, N 8.19.

2,2-Dimethyl-*N*-{3-[(2*E*)-2-methyl-3-phenylprop-2-enoyl]pyridin-2-yl}propanamide (**3e**). White solid. M.p. 126 – 128° (hexane/CH_2Cl_2). IR (KBr): 3278, 1683, 1653. ^{1}H-NMR (500 MHz): 1.28 (*s*, 9 H); 2.26 (*d*, *J* = 1.7, 3 H); 6.98 (*s*, 1 H); 7.16 (*dd*, *J* = 7.4, 4.6, 1 H); 7.35 – 7.42 (*m*, 5 H); 7.99 (*dd*, *J* = 7.4, 1.7, 1 H); 8.57 (*dd*, *J* = 4.6, 1.7, 1 H); 9.42 (br. *s*, 1 H). Anal. calc. for $C_{20}H_{22}N_2O_2$ (322.41): C 74.51, H 6.88, N 8.69; found: C 74.43, H 6.91, N 8.60.

***N*-{3-[(2*E*)-But-2-enoyl]pyridin-2-yl}-2,2-dimethylpropanamide** (**3f**). White solid. M.p. 91 – 93° (hexane/CH_2Cl_2). IR (KBr): 3264, 1688, 1657. ^{1}H-NMR (500 MHz): 1.36 (*s*, 9 H); 2.03 (*dd*, *J* = 6.9, 1.7, 3 H); 6.87 (*dd*, *J* = 15.5, 1.1, 1 H), 7.07 – 7.14 (*m*, 2 H); 8.15 (*dd*, *J* = 8.0, 1.7, 1 H); 8.64 (*dd*, *J* = 4.5, 1.7, 1 H); 11.23 (br. *s*, 1 H). Anal. calc. for $C_{14}H_{18}N_2O_2$ (246.31): C 68.27, H 7.37, N 11.37; found: C 68.17, H 7.49, N 11.28.

2,2-Dimethyl-*N*-{4-[(2*E*)-3-phenylprop-2-enoyl]pyridin-3-yl}propanamide (**7a**). Pale-yellow solid. M.p. 118 – 120° (hexane/CH_2Cl_2). IR (KBr): 3304, 1689, 1653. ^{1}H-NMR (500 MHz): 1.38 (*s*, 9 H); 7.46 – 7.49 (*m*, 3 H); 7.53 (*d*, *J* = 16.0, 1 H); 7.68 (*dd*, *J* = 7.4, 1.7, 2 H); 7.74 (*d*, *J* = 5.1, 1 H); 7.87 (*d*, *J* = 16.0, 1 H); 8.52 (*d*, *J* = 5.1, 1 H); 10.06 (*s*, 1 H); 11.25 (br. *s*, 1 H). Anal. calc. for $C_{19}H_{20}N_2O_2$ (308.38): C 74.00, H 6.54, N 9.08; found: C 74.11, H 6.53, N 8.91.

***N*-{4-[(2*E*)-3-(4-Methoxyphenyl)prop-2-enoyl]pyridin-3-yl}-2,2-dimethylpropanamide** (**7b**). Yellow solid. M.p. 120 – 122° (hexane/CH_2Cl_2). IR (KBr): 3280, 1687, 1648. ^{1}H-NMR (500 MHz): 1.38 (*s*, 9 H); 3.88 (*s*, 3 H); 6.97 (*d*, *J* = 8.6, 2 H); 7.40 (*d*, *J* = 16.0, 1 H); 7.64 (*d*, *J* = 8.6, 2 H); 7.72 (*d*, *J* = 5.2, 1 H); 7.87 (*d*, *J* = 16.0, 1 H); 8.51 (*d*, *J* = 5.2, 1 H); 10.04 (*s*, 1 H); 11.29 (br. *s*, 1 H). Anal. calc. for $C_{20}H_{22}N_2O_3$ (338.41): C 70.99, H 6.55, N 8.28; found: C 70.93, H 6.59, N 8.04.

***N*-{3-[(2*E*)-3-(4-Methoxyphenyl)prop-2-enoyl]pyridin-4-yl}-2,2-dimethylpropanamide** (**11a**). Yellow solid. M.p. 154 – 156° (hexane/CH_2Cl_2). IR (KBr): 3155, 1699, 1643. ^{1}H-NMR (500 MHz): 1.38 (*s*, 9 H); 3.88 (*s*, 3 H); 6.97 (*d*, *J* = 8.6, 2 H); 7.50 (*d*, *J* = 15.5, 1 H); 7.64 (*d*, *J* = 8.6, 2 H); 7.88 (*d*, *J* = 15.5, 1 H); 8.61 (*d*, *J* = 6.3, 1 H); 8.72 (*d*, *J* = 6.3, 1 H); 9.21 (*s*, 1 H); 12.19 (br. *s*, 1 H). Anal. calc. for $C_{20}H_{22}N_2O_3$ (338.41): C 70.99, H 6.55, N 8.28; found: C 70.97, H 6.61, N 8.21.

***N*-{3-[(2*E*)-3-(3,4-Dimethoxyphenyl)prop-2-enoyl]pyridin-4-yl}-2,2-dimethylpropanamide** (**11b**). Yellow solid. M.p. 206 – 208° (hexane/CH_2Cl_2). IR (KBr): 3134, 1706, 1644. ^{1}H-NMR (500 MHz): 1.38 (*s*, 9 H); 3.96 (*s*, 3 H); 3.97 (*s*, 3 H); 6.93 (*d*, *J* = 8.6, 1 H); 7.18 (*d*, *J* = 2.3, 1 H); 7.27 (*d*, *J* = 8.6, 1 H); 7.48 (*d*, *J* = 15.5, 1 H); 7.85 (*d*, *J* = 15.5, 1 H); 8.61 (*d*, *J* = 5.7, 1 H); 8.72 (*d*, *J* = 5.7, 1 H); 9.23 (*s*, 1 H); 12.16 (br. *s*, 1 H). Anal. calc. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.46, H 6.57, N 7.60; found: C 68.18, H 6.55, N 7.48.

***Preparation of Dihydronaphthyridinones* 4, 8b, *and* 12 *Using 3M HCl*.** *General Procedure.* A mixture of **3**, **7b**, or **11** (0.5 mmol) in 3M HCl (2 ml) was heated under reflux for 10 h. After cooling, the mixture was treated with sat. aq. $NaHCO_3$ (30 ml) and extracted with AcOEt (3 × 10 ml). The combined extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was purified by CC (SiO_2; AcOEt/hexane 1:1) to afford the desired product.

***Preparation of Dihydronaphthyridinones* 4 *and* 8a *Using Conc. HBr*.** *General Procedure.* A mixture of **3** or **7a** (0.5 mmol) in conc. HBr (2 ml) was heated under reflux for 30 min. After cooling, the mixture was worked up and purified as described above to afford the desired product.

2,3-Dihydro-2-phenyl-1,8-naphthyridin-4(1*H*)-one (**4a**). Yellow solid. M.p. 199 – 201° (hexane/CH_2Cl_2). IR (KBr): 3204, 1683, 1603. ^{1}H-NMR (500 MHz): 2.81 (*ddd*, *J* = 16.6, 4.6, 1.1, 1 H); 2.90 (*dd*, *J* = 16.6, 13.7, 1 H); 4.83 (*dd*, *J* = 13.7, 4.6, 1 H); 6.62 (*dd*, *J* = 7.4, 4.6, 1 H); 6.72 (br. *s*, 1 H); 7.37 – 7.44 (*m*, 3 H); 7.48 (*d*, *J* = 7.4, 2 H); 7.67 (*dd*, *J* = 4.6, 1.7, 1 H); 8.06 (*dd*, *J* = 7.4, 1.7, 1 H). ^{13}C-NMR: 45.90; 56.41; 113.45; 114.37; 126.62; 128.54; 129.10; 136.25; 140.44; 154.73; 161.03; 193.01. HR-DART-MS: 225.1028 ($[M + H]^+$, $C_{14}H_{13}N_2O^+$; calc. 225.1022). Anal. calc. for $C_{14}H_{12}N_2O$ (224.26): C 74.98, H 5.39, N 12.49; found: C 74.76, H 5.61, N 12.28.

2,3-Dihydro-2-(4-methoxyphenyl)-1,8-naphthyridin-4(1*H*)-one (**4b**). Yellow solid. M.p. 189 – 191° (hexane/CH_2Cl_2). IR (KBr): 3202, 1684, 1600. ^{1}H-NMR (500 MHz): 2.77 (*ddd*, *J* = 16.0, 4.0, 1.1, 1 H); 2.88 (*dd*, *J* = 16.0, 13.2, 1 H); 3.84 (*s*, 3 H); 4.79 (*dd*, *J* = 13.2, 4.0, 1 H); 6.33 (br. *s*, 1 H); 6.66 (*dd*, *J* = 7.4, 4.6, 1 H); 6.94 (*d*, *J* = 8.6, 2 H); 7.39 (*d*, *J* = 8.6, 2 H); 7.88 (*dd*, *J* = 4.6, 1.7, 1 H); 8.07 (*dd*, *J* = 7.4, 1.7, 1 H). ^{13}C-NMR: 46.03; 55.36; 55.81; 113.47; 114.34; 114.45; 127.75; 132.35; 136.23, 154.81; 159.64; 160.97; 193.25. HR-DART-MS: 255.1130 ($[M + H]^+$, $C_{15}H_{15}N_2O_2^+$; calc. 255.1128). Anal. calc. for $C_{15}H_{14}N_2O_2$ (254.29): C 70.85, H 5.55, N 11.02; found: C 70.69, H 5.66, N 10.81.

2-(3,4-Dimethoxyphenyl)-2,3-dihydro-1,8-naphthyridin-4(1*H*)-one (**4c**). Yellow needles. M.p. 182 – 184° (hexane/CH_2Cl_2). IR (KBr): 3209, 1684, 1600. ^{1}H-NMR (500 MHz): 2.74 (*dd*, *J* = 16.0, 4.0, 1 H); 2.82 (*dd*, *J* = 16.0, 13.1, 1 H); 3.82 (*s*, 3 H); 3.83 (*s*, 3 H); 4.72 (*dd*, *J* = 13.1, 4.0, 1 H); 5.96 (br. *s*, 1 H); 6.64 (*dd*, *J* = 7.4, 4.6, 1 H); 6.81 (*d*, *J* = 8.0, 1 H); 6.91 (*d*, *J* = 8.0, 1 H); 6.92 (*s*, 1 H); 7.97 (*dd*, *J* = 4.6, 1.7, 1 H); 8.01 (*dd*, *J* = 7.4, 1.7, 1 H). ^{13}C-NMR: 46.17; 55.93; 55.98; 56.23; 109.19; 111.29; 113.59; 114.70; 118.81; 132.80; 136.25; 149.09; 149.37; 154.89; 160.93; 193.12. HR-EI-MS: 284.1167 (M^+, $C_{16}H_{16}N_2O_3^+$; calc. 284.1161).

Anal. calc. for $C_{16}H_{16}N_2O_3$ (284.32): C 67.59, H 5.67, N 9.85; found: C 67.44, H 5.87, N 9.66.

2-(4-Chlorophenyl)-2,3-dihydro-1,8-naphthyridin-4(1*H*)-one (**4d**). Yellow solid. M.p. 173 – 175° (hexane/CH_2Cl_2). IR (KBr): 3204, 1683, 1602. ^{1}H-NMR (500 MHz): 2.82 (*ddd*, *J* = 16.0, 4.6, 1.1, 1 H); 2.86 (*dd*, *J* = 16.0, 11.5, 1 H); 4.83 (*dd*, *J* = 14.0, 4.6, 1 H); 6.23 (br. *s*, 1 H); 6.71 (*dd*, *J* = 8.0, 5.1, 1 H); 7.39 (*d*, *J* = 9.2, 2 H); 7.41 (*d*, *J* = 9.2, 2 H); 7.95 (*dd*, *J* = 5.1, 2.3, 1 H); 8.08 (*dd*, *J* = 8.0, 2.3, 1 H). ^{13}C-NMR: 45.84; 55.81; 113.61; 114.87; 127.89; 129.30; 134.32; 136.29; 138.92; 154.84; 160.82; 192.52. HR-EI-MS: 258.0562 (M^+, $C_{14}H_{11}ClN_2O^+$; calc. 258.0560). Anal. calc. for $C_{14}H_{11}ClN_2O$ (258.71): C 65.00, H 4.29, N 10.83; found: C 64.90, H 4.28, N 10.72.

***trans*-2,3-Dihydro-3-methyl-2-phenyl-1,8-naphthyridin-4(1*H*)-one** (**4e**). Yellow solid. M.p. 208 – 210° (hexane/CH_2Cl_2). IR (KBr): 3206, 1686, 1605. ^{1}H-NMR (500 MHz): 1.00 (*d*, *J* = 6.3, 3 H); 2.79 – 2.85 (*m*, 1 H); 4.39 (*d*, *J* = 12.6, 1 H); 6.51 (br. *s*, 1 H); 6.63 (*dd*, *J* = 7.4, 4.6, 1 H); 7.38 – 7.44 (*m*, 3 H); 7.47 (*d*, *J* = 7.4, 2 H); 7.72 (br. *s*, 1 H); 8.08 (*d*, *J* = 7.4, 1 H). ^{13}C-NMR: 10.96; 46.34; 62.84; 113.06; 114.29; 127.64; 128.67; 128.96; 136.55; 139.85; 154.48; 160.26; 195.31. HR-EI-MS: 238.1106 (M^+, $C_{15}H_{14}N_2O^+$; calc. 238.1106). Anal. calc. for $C_{15}H_{14}N_2O$ (238.29): C 75.61, H 5.92, N 11.76; found: C 75.53, H 5.88, N 11.53.

2,3-Dihydro-2-methyl-1,8-naphthyridin-4(1*H*)-one (**4f**). White solid. M.p. 92 – 94° (hexane/CH_2Cl_2). IR (KBr): 3223, 1679, 1653, 1602. ^{1}H-NMR (500 MHz): 1.38 (*d*, *J* = 6.3, 3 H); 2.51 (*dd*, *J* = 16.0, 12.6, 1 H); 2.69 (*ddd*, *J* = 16.0, 4.0, 1.7, 1 H); 3.84 – 3.91 (*m*, 1 H); 5.48 (br. *s*, 1 H); 6.71 (*dd*, *J* = 7.4, 4.6, 1 H); 8.06 (*dd*, *J* = 7.4, 1.7, 1 H); 8.25 (*dd*, *J* = 4.5, 1.7, 1 H). ^{13}C-NMR: 21.08; 45.01; 47.19; 112.23; 114.35; 136.15; 154.79; 160.65; 193.80. HR-DART-MS: 163.0863 ($[M + H]^+$, $C_9H_{11}N_2O^+$; calc. 163.0866). Anal. calc. for $C_9H_{10}N_2O$ (162.19): C 66.65, H 6.21, N 17.27; found: C 66.44, H 6.37, N 17.42.

2,3-Dihydro-2-phenyl-1,7-naphthyridin-4(1*H*)-one (**8a**). Yellow amorphous powder. R_f (AcOEt/hexane 1:2) 0.42. IR (KBr): 3331, 1688, 1602. ^{1}H-NMR (500 MHz): 2.78 (*dd*, *J* = 16.6, 4.0, 1 H); 2.85 (*dd*, *J* = 16.6, 13.2, 1 H); 4.72 (*dd*, *J* = 13.2, 4.0, 1 H); 4.80 (br. *s*, 1 H); 7.30 – 7.39 (*m*, 5 H); 7.54 (*d*, *J* = 4.6, 1 H); 7.98 (*d*, *J* = 4.6, 1 H); 8.33 (*s*, 1 H). ^{13}C-NMR: 46.26; 58.10; 119.08; 122.64; 126.55; 128.80; 129.15; 138.32; 139.92; 140.03; 146.04; 192.92. HR-DART-MS: 225.1024 ($[M + H]^+$, $C_{14}H_{13}N_2O^+$; calc. 225.1022). Anal. calc. for $C_{14}H_{12}N_2O$ (224.26): C 74.98, H 5.39, N 12.49; found: C 74.91, H 5.52, N 12.32.

2,3-Dihydro-2-(4-methoxyphenyl)-1,7-naphthyridin-4(1*H*)-one (**8b**). Yellow viscous oil. R_f (AcOEt/hexane 1:3) 0.44. IR (neat): 3333, 1687, 1603. ^{1}H-NMR (500 MHz): 2.79 (*ddd*, *J* = 16.6, 4.0, 1.7, 1 H); 2.91 (*dd*, *J* = 16.6, 13.7, 1 H); 3.83 (*s*, 3 H); 4.68 (br. *s*, 1 H); 4.74 (*dd*, *J* = 13.7, 4.0, 1 H); 6.94 (*d*, *J* = 8.6, 2 H); 7.38 (*d*, *J* = 8.6, 2 H); 7.58 (*d*, *J* = 5.2, 1 H); 8.07 (*d*, *J* = 5.2, 1 H); 8.29 (*s*, 1 H). ^{13}C-NMR: 46.42; 55.35; 57.62; 114.53; 118.70; 122.38; 125.47; 127.81; 139.09; 140.34; 145.79; 159.78; 193.29. HR-DART-MS: 255.11127 ($[M + H]^+$, $C_{15}H_{15}N_2O_2^+$; calc. 255.1128). Anal. calc. for $C_{15}H_{14}N_2O_2$ (254.29): C 70.85, H 5.55, N 11.02; found: C 70.72, H 5.64, N 10.81.

2,3-Dihydro-2-(4-methoxyphenyl)-1,6-naphthyridin-4(1*H*)-one (**12a**). Yellow solid. M.p. 145 – 147° (hexane/CH_2Cl_2). IR (KBr): 3313, 1682, 1609. ^{1}H-NMR (500 MHz): 2.77 (*ddd*, *J* = 16.0, 4.0, 1.1, 1 H); 2.90 (*dd*, *J* = 16.0, 13.2, 1 H); 3.83 (*s*, 3 H), 4.77 (*dd*, *J* = 13.2, 4.0, 1 H); 5.16 (br. *s*, 1 H); 6.58 (*d*, *J* = 5.7, 1 H); 6.93 (*d*, *J* = 8.6, 2 H); 7.34 (*d*, *J* = 8.6, 2 H); 8.23 (*d*, *J* = 5.7, 1 H); 8.85 (*s*, 1 H). ^{13}C-NMR: 45.79; 55.35; 56.67; 110.06; 114.42; 114.50; 127.76; 131.63; 149.90; 153.34; 155.18; 159.82; 192.57. HR-DART-MS: 255.1126 ($[M + H]^+$, $C_{15}H_{15}N_2O_2^+$; calc. 255.1128). Anal. calc. for $C_{15}H_{14}N_2O_2$ (254.29): C 70.85, H 5.55, N 11.02; found: C 70.88, H 5.58, N 10.96.

2-(3,4-Dimethoxyphenyl)-2,3-dihydro-1,6-naphthyridin-4(1*H*)-one (**12b**). Yellow solid. M.p. 178 – 180° (hexane/CH_2Cl_2). IR (KBr): 3345, 1683, 1607. ^{1}H-NMR (500 MHz): 2.81 (*dd*, *J* = 16.0, 4.0, 1 H); 2.93 (*dd*, *J* = 16.0, 13.2, 1 H); 3.90 (*s*, 6 H); 4.77 (*dd*, *J* = 13.2, 4.0, 1 H); 4.97 (br. *s*, 1 H); 6.59 (*d*, *J* = 5.7, 1 H); 6.88 (*d*, *J* = 8.6, 1 H); 6.93 (*s*, 1 H); 6.96 (*dd*, *J* = 8.6, 1.7, 1 H); 8.27 (*d*, *J* = 5.7, 1 H); 8.89 (*s*, 1 H). ^{13}C-NMR: 45.82; 55.91; 55.93; 57.04; 109.28; 110.12; 111.33; 114.49; 118.91; 132.13; 149.24; 149.35; 149.78; 153.21; 155.26; 192.44. HR-EI-MS: 284.1167 (M^+, $C_{16}H_{16}N_2O_3^+$; calc. 284.1161). Anal. calc. for $C_{16}H_{16}N_2O_3$ (284.32): C 67.59, H 5.67, N 9.85; found: C 67.33, H 5.50, N 9.95.

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