PALLADIUM(0)-CATALYZED COUPLING OF 6-BROMO AND 3-IODO DERIVATIVES OF 7-METHYL-4-OXO-1,4-DIHYDRO[1,8]-NAPHTHYRIDINES

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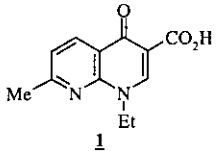
Abstract- Substituted 4-oxo-1,4-dihydro[1,8]naphthyridines were obtained with various substituents (aryl, alkyl, carbonyl chains) by functionalization at positions 6 and 3 using a Suzuki, Heck or Stille reaction.

Since the introduction in 1963 of nalidixic Acid (**1**) as a systemic Gram-negative Antibacterial agent,[1] many related derivatives have been synthesized. These types of compounds have received much attention and interest for their chemical and clinical qualities.



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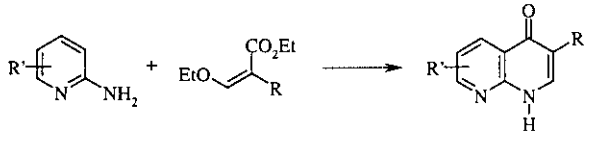
The methods reported in chemical literature for preparing C-6 and C-3 substituted 4-oxo[1,8]naphthyridines are somewhat limited. These methods involve the condensation of substituted 2-aminopyridine with suitable 3-ethoxyacrylate followed by a cyclisation.[2]

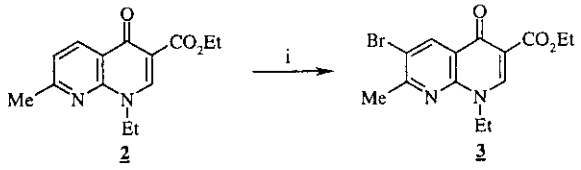


Recently, palladium-catalyzed cross coupling of 7-chloro-1,8-naphthyridine derivatives with organotin reagent has been described.[3] This synthetic approach allows the incorporation of acyclic or cyclic vinyl substituents at the C-7 position.

In this paper, we wish to present a strategy for synthesizing a wide range of C-6 and C-3 substituted 1,8-naphthyridines by palladium-catalysed coupling reactions according to Suzuki's,[4] Heck's,[5] and Stille's,[6] methodologies.

The strategies mentioned above require the preparation of C-6 and C-3 halogenated 1,8-naphthyridines.

First we synthesize ethyl 6-bromo-1-ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (**3**) from nalidixic acid ethyl ester (**2**) by direct bromination, with bromine in acetic acid, in very good yield.

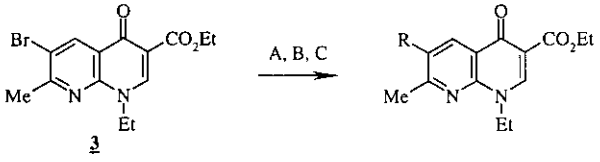


i : Br_2, AcONa, AcOH, reflux

Palladium-catalyzed coupling of compound (**3**) with phenylboronic acid under Suzuki's conditions (Method A) gave the expected 6-phenylnaphthyridine in 80% yield. The naphthyridine (**3**) was treated with phenylboronic acid in presence of 5% tetrakis(triphenylphosphine)palladium(0) in toluene-methanol 4/1 (v/v) with 2M sodium carbonate as base.

Compounds (**4b,c,d**) were prepared according to Heck's protocol (Method B) by using palladium(II) acetate and triphenylphosphine in DMF with triethylamine as a base.

The naphthyridine (**3**) reacts with tetramethylstannane in presence of Pd(0) to give the corresponding 6-methylnaphthyridine (**4e**) in low yield, even in presence of CuBr as co-catalyst (Method C).



Method A: i: $ArB(OH)_2$, $Pd(PPh_3)_4$, 2M Na_2CO_3, Toluene-MeOH

Method B: i: reagent, Et_3N, $Pd(OAc)_2$, Ph_3P, DMF

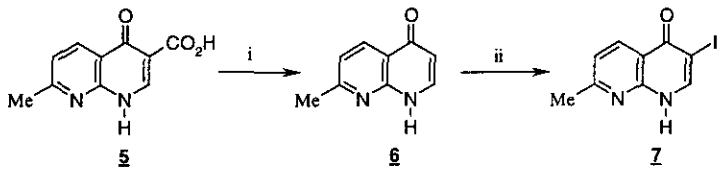
Method C: i: organotin, $Pd(PPh_3)_4$, CuBr, 1,4 Dioxane or Toluene

Compd	Method	Reagent	R	Yield (%)
4a	A	$PhB(OH)_2$	Ph	80
4b	B	CH_2=CH-COOMe	MeOOC	80
4c	B	CH_2=CH-CN	NC	80
4d	B	CH_2=CH-COMe	O, Me	86
4e	C	Me_4Sn	Me	30

We also chose to investigate the palladium-catalyzed cross coupling of 3-halogenonaphthyridine.

The 3-bromo-7-methyl[1,8]naphthyridin-4(1*H*)-one was prepared by decarboxylation of carboxylic acid (**5**),[7] followed by bromination. Decarboxylated product was obtained by heating acid (**5**) at reflux in quinoline in presence of Cu as catalyst. Then the treatment by bromine in DMF with potassium carbonate afforded directly the 3-bromonaphthyridine. But the attempt of coupling reaction was unsuccessful or gave very low yield.

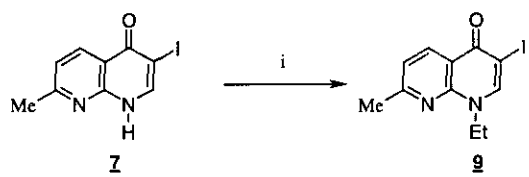
It's for these reasons that we had synthesized, in the same way, the 3-iodonaphthyridine.



i: Cu, Quinoline ; ii : I_2, K_2CO_3, DMF

First, we applied the Heck, Suzuki and Stille methodologies on the 3-iodonaphthyridine (**7**). In fact, only the Suzuki reaction was successful as the other methodologies led to a rapid degradation of the substrate. The reaction between compound (**7**) containing labile hydrogen, and phenylboronic acid in large excess (3 eq.) afforded the desired product in 66% yield.

Consequently we had regioselectively alkylated at position 1 in the naphthyridine structure. The 1-ethyl-3-iodo-7-methyl[1,8]naphthyridin-4(1*H*)-one (**9**), used as starting material, had to be synthesized by treatment of compound (**7**) with iodoethane and potassium carbonate in DMF.



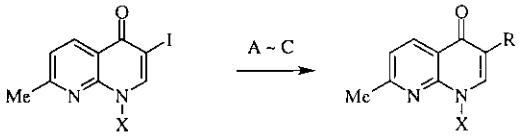
i : EtI, K_2CO_3, DMF

In a first series of experiments, the 3-iodonaphthyridine (**9**) was treated with arylboronic acid under the same conditions as in previous works, except for the addition of catalytic copper(I) iodide (6% mol). Indeed, in most cases higher yields and/or shorter reaction time and cleaner reaction were obtained by the addition of CuI as co-catalyst, as it has been shown in a number of reported palladium-catalyzed couplings. The effect of copper(I) iodide may be explained by its influence as a scavenger of free phosphine ligands similarly to what happens in the Stille reaction. In the latter system the presence of free phosphine was shown to inhibit the transmetallation step and this effect was eliminated by CuI co-catalysis.

Then, naphthyridine (**9**) was coupled with commercially available vinylstannane in the presence of tetrakis(triphenylphosphine)palladium(0) and CuI in toluene under reflux to give the desired 3-

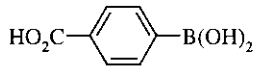
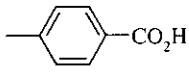
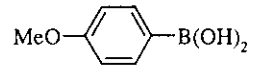
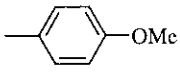
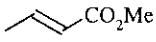
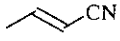
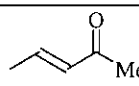
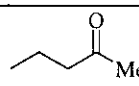
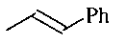
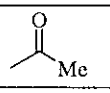
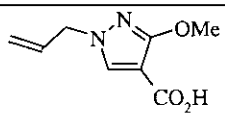
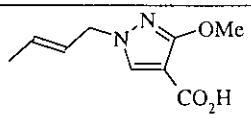
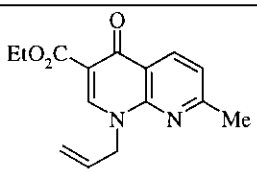
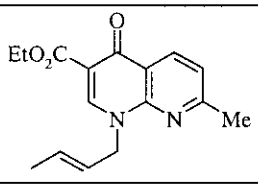
vinylnaphthyridine (**10m**) in 90% yield.

Lastly, heterocyclic halide (**9**) can react with various reagents under Heck's conditions by using palladium(II) acetate, triphenylphosphine, triethylamine, copper(I) iodide in DMF.



7 : X=H
9 : X=Et

8 : X=H
10a-m : X=Et

Subtract	Method	Reagent	—R	Product	Yield (%)
7	A	$PhB(OH)_2$		8	66
9	A	$PhB(OH)_2$		10a	71
9	A			10b	56
9	A			10c	82
9	B	CH_2=CH-CO_2Me		10d	87
9	B	CH_2=CH-CN		10e	86
9	B	CH_2=CH-COMe		10f	93
9	B	CH_2=CH-CHOH-CH_3		10g	50
9	B	CH_2=CH-Ph		10h	51
9	B	CH_2=CH-Obu*		10i	55
9	B			10j	60
9	B			10k	69
9	C	Bu_3Sn-CH=CH_2		10m	90

* Then 2.7M HCl

When coupling with styrene, the expected product (**10h**) was contamined by a small amount (10% in mol) of 1-ethyl-7-methyl-3-(1-phenylvinyl)[1,8]naphthyridin-4(1*H*)-one, a by-product which was difficult to be separated by chromatography or recrystallization.

We have successfully demonstrated that the synthesis of C-6 and C-3 substituted [1,8]naphthyridin-4(1*H*)-one can be performed by use of palladium(0) catalyzed cross coupling reactions.
These methodologies should prove useful to introduce various side chains and aryl into bicyclic *heteroaromatic compounds.*

EXPERIMENTAL

Melting points (uncorrected) were determined on a köfler apparatus. IR spectra were recorded on a Perkin-Elmer Paragon FT-IR 1000 spectrophotometer with 4 cm^{-1} resolution, only the most significant IR absorption's are given. ^1H NMR spectra were recorded at 250 MHz and ^{13}C NMR spectra were recorded at 62.89 MHz on a Brucker AM-250 instrument. Tetramethylsilane was used as the internal standard. MS spectra were recorded on a Perkin-Elmer SCIEX API 3000 spectrometer (ion spray). Separations by column chromatography were performed on silica gel (70-230 mesh).

Starting Materials.

Literature procedure were used for the synthesis of ethyl 1-ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (**2**),[1] 7-methyl[1,8]naphthyridin-4(1*H*)-one (**6**)[7] and 7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine 3-carboxylic acid (**5**).[8]

Ethyl 6-Bromo-1-ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (3)

To a stirred suspension of **2** (20 g, 76.9 mmol), sodium acetate (25 g, 307 mmol) in 90 mL of glacial acetic acid was added dropwise a solution of bromine (10 mL, 192 mmol) in 50 mL of glacial acetic acid. The mixture was refluxed for 30 min and then partitioned between CH_2Cl_2 and an aqueous solution of saturated sodium bisulfite. The organic phase was washed with water and dried over magnesium sulfate. Removal of solvents under reduced pressure followed by recrystallization from acetonitrile gave **3** (24.8 g, 95%); mp 168°C; IR (KBr): 1690, 1629, 810 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.36 (t, *J= 7.0 Hz*, 3H), 1.44 (t, *J= 7.0 Hz*, 3H), 2.71 (s, 3H), 4.45-4.30 (m, 4H), 8.55 (s, 1H), 8.74 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.79, 15.50, 26.12, 47.21, 61.43, 112.76, 118.51, 123.36, 139.92, 147.45, 149.20, 161.70, 165.51, 173.96; MS

m/z 341 (M^++2, 100), 339 (M^+, 100), 295 (38), 293 (38). *Anal.* Calcd for $C_{14}H_{15}N_2O_3Br$: C, 49.57; H, 4.46; N, 8.26. Found: C, 49.63; H, 4.56; N, 8.26.

3-Iodo-7-methyl[1,8]naphthyridin-4(1*H*)-one (7)

To 7-methyl[1,8]naphthyridin-4(1*H*)-one (**6**) (13 g, 81.2 mmol) in 85 mL of DMF was added K_2CO_3 (12.35 g, 89 mmol) and iodine (22.7 g, 89 mmol). The mixture was stirred for 30 min and then poured into an aqueous solution of saturated sodium thiosulfate. The precipitate was filtered off and recrystallized from MeOH (19.0 g, 82%); mp>260°C; IR (KBr): 1598, 1575, 1560, 1524 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.53 (s, 3H), 7.28 (d, *J= 8.0 Hz*, 1H), 7.79 (d, *J= 8.0 Hz*, 1H), 8.37 (s, 1H), 12.46 (br s, 1H exch.); ^{13}C NMR (DMSO-d_6): δ 25.27, 82.39, 115.70, 121.67, 136,20, 145.70, 150.50, 163.73, 174.42; MS *m/z* 287 (M^++1, 100). *Anal.* Calcd for $C_9H_7N_2OI$: C, 37.79; H, 2.47; N, 9.79. Found: C, 37.79; H, 2.51; N, 9.78.

1-Ethyl-3-iodo-7-methyl[1,8]naphthyridin-4(1*H*)-one (9)

The naphthyridine (**7**) (7.6 g, 26.5 mmol) and K_2CO_3 (4.4 g, 92 mmol) were stirred in DMF (50 mL) for 45 min. Then 4.1 mL (40 mmol) of EtI were added. After 1.5 h at 70°C, the mixture was evaporated in *vacuum*. The residue was diluted with water and CH_2Cl_2, the organic layer was separated, dried over $MgSO_4$ and evaporated. Purification by column chromatography (CH_2Cl_2/MeOH 98:2) afforded **9** (7.0 g, 84%); mp 205°C; IR (KBr): 1602, 1588 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.41 (t, *J=7.0 Hz*, 3H), 2.60 (s, 3H), 4.40 (q, *J=7.0 Hz*, 2H), 7.17 (d, *J=8.0 Hz*, 1H), 8.16 (s, 1H), 8.54 (d, *J=8.0 Hz*, 1H); ^{13}C NMR ($CDCl_3$): δ 15.74, 25.62, 46.35, 82.09, 116.75, 121.15, 137.16, 147.35, 149.03, 162.99, 174.95; MS *m/z* 315 (M^++1, 100). CAS Registry Number: [159590-27-9].

<u>Method A</u> : General procedure for Suzuki reactions.

Ethyl 1-Ethyl-7-methyl-4-oxo-6-phenyl-1,4-dihydro[1,8]naphthyridine-3-carboxylate (4a)

To a stirred mixture of heterocyclic halide (**3**) (0.2 g, 0.59 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.02 mmol) in toluene-MeOH (4/1) (3 mL) under nitrogen atmosphere was added a 2M aqueous solution of Na_2CO_3 (0.59 mL) and phenylboronic acid (0.146 g, 1.18 mmol). The vigorously stirred mixture was warmed at reflux during 15 h, then cooled, and partitioned between CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$. Removal of solvents under reduced pressure, followed by purification by chromatography (CH_2Cl_2/MeOH 98:2) afforded the desired product (**4a**) in 80% yield; mp: 144-145°C; IR (KBr): 1678,1653, 1606 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 (t, *J=7.0 Hz*, 3H), 1.50 (t, *J=7.0 Hz*, 3H), 2.58 (s, 3H), 4.37 (q, *J=7.0 Hz*, 2H), 4.47 (q, *J=7.0 Hz*, 2H), 7.46-7.30 (m, 5H), 8.53 (s, 1H), 8.60 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.45, 15.28, 24.30, 46.65, 60.96, 112.02, 121.73, 125.89, 128.42, 128.55 (2C), 129.22 (2C),

135.18, 138.54, 147.45, 148.62, 160.46, 165.63, 174.87; MS . *m/z* 337 (M^++1, 85), 291 (100). *Anal.* Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.34; H, 6.06; N, 8.30.

Method B : General procedure for Heck reactions.

Ethyl 1-Ethyl–6-[(*E*)-3-methoxy-3-oxo-1-propenyl]-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (4b)

To the solution of heterocyclic halide (**3**) (3 g, 8.85 mmol) in DMF (30 mL) were successively added ethyl acrylate (0.915 g, 10.6 mmol), triethylamine (1.6 mL, 11.5 mmol), palladium diacetate (60 mg, 0.27 mmol), and triphenylphosphine (0.298 g, 1.13 mmol). The solution was heated at 130°C in a sealed tube for 17 h. The residue obtained after concentration under reduced pressure was hydrolyzed with water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated. The desired compound (**4b**) were obtained *via* purification by recrystallization from AcOEt. Yield 80%; mp: 140-142°C; IR (KBr): 1713, 1698, 1636, 1606 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 (t, *J=7.2 Hz*, 3H), 1.46 (t, *J=7.2 Hz*, 3H), 2.72 (s, 3H), 3.80 (s, 3H), 4.32-4.49 (m, 4H), 6.52 (d, *J=16.0 Hz*, 1H), 7.89 (d, *J=16.0 Hz*, 1H), 8.56 (s, 1H), 8.82 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.79, 15.55, 23.88, 47.11, 52.35, 61.45, 112.92, 122.30, 127.32, 128.98, 132.55, 134.62, 139.53, 149.20, 161.74, 165.66, 167.20, 174.88; MS *m/z* 345 (M^++1, 100), 299 (80). *Anal.* Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.70; H, 5.91; N, 8.11.

Method C : General procedure for Stille reactions.

1-Ethyl-7-methyl-3-vinyl[1,8]naphthyridin-4(1*H*)-one (10m)

A solution of heterocyclic halide (**9**) (0.4 g, 1.27 mmol), tri-*n*-butylvinyltin (0.402 g, 1.27 mmol), $Pd(PPh_3)_4$ (70 mg, 0.06 mmol) and CuI (14 mg, 0.07 mmol) was refluxed for 30 min in toluene. When the reaction was completed as judged by TLC, the mixture was poured into water and extracted with CH_2Cl_2. Organic layer was dried over $MgSO_4$ and evaporated under vacuum, the residue was chromatographed with CH_2Cl_2/MeOH 98:2 as eluent to afford **10m** in 90% yield; mp: 130-132°C; IR (KBr): 1623, 1607, 1582 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.45 (t, *J=7.2 Hz*, 3H), 2.63 (s, 3H), 4.43 (q, *J=7.2 Hz*, 2H), 5.26 (dd, *J=11.3, 1.9 Hz*, 1H), 6.10 (dd, *J=17.5, 1.9 Hz*, 1H), 6.77 (dd, *J=17.5, 11.3 Hz*, 1H), 7.15 (d, *J=8.2 Hz*, 1H), 7.78 (s, 1H), 8.60 (d, *J=8.2 Hz*, 1H); ^{13}C NMR ($CDCl_3$): δ 15.61, 25.52, 46.20, 114.48, 119.66, 120.14, 120.24, 130.76, 136.62, 140.73, 148.52, 162.35, 176.97; MS *m/z* 215 (M^++1, 100). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.98; H, 6.66; N, 12.99.

Ethyl 6-[(*E*)-2-Cyanoethenyl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine carboxylate (4c)

This compound was prepared according to method B in 80% yield after 17 h. Recrystallization from AcOEt afforded an yellow solid; mp: 214°C; IR (KBr): 2218,1731, 1622 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 (t, *J=7.0 Hz*, 3H), 1.47 (t, *J=7.0 Hz*, 3H), 2.70 (s, 3H), 4.32-4.48 (m, 4H), 5.98 (d, *J=16.4 Hz*, 1H), 7.62 (d, *J=16.4 Hz*, 1H), 8.57 (s, 1H), 8.75 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.40, 15.15, 23.36, 46.83, 61.16, 100.21, 112.88, 117.54, 121.87, 125.98, 133.75, 145.12, 149.04, 149.17 160.75, 165.02, 174.28; MS *m/z* 312 (M^++1, 100), 266 (100).

Ethyl 1-Ethyl-7-methyl-4-oxo-6-[(*E*)-3-oxo-1-butenyl]-1,4-dihydro[1,8]naphthyridine-3-carboxylate (4d)

This compound was prepared according to method B in 86% yield after 17 h. Recrystallization from AcOEt afforded an unbleached solid; mp: 146°C; IR (KBr): 1695, 1642, 1606 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 (t, *J=7.0 Hz*, 3H), 1.47 (t, *J=7.0 Hz*, 3H), 2.37 (s, 3H), 2.73 (s, 3H), 4.35-4.60 (m, 4H), 6.84 (d, *J=15.7 Hz*, 1H), 7.74 (d, *J=15.7 Hz*, 1H), 8.56 (s, 1H), 8.83 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.78, 15.56, 23.87, 29.49, 47.13, 61.46, 112.96, 122.30, 127.39, 129.96, 131.77, 134.57, 137.22, 149.10, 162.08, 165.59, 174.92, 197.64; MS *m/z* 329 (M^++1, 100), 283 (90).

Ethyl 1-Ethyl-6,7-dimethyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (4e)

This compound was prepared according to method C in 30% yield with CuBr as co-catalyst and 1,4-dioxane as solvent after 35 h at 80°C in a sealed tube. Purification by chromatography (CH_2Cl_2/MeOH 98:2) afforded a white solid; mp: 181-183°C; IR (KBr): 1684, 1608 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.36 (t, *J=7.0 Hz*, 3H), 1.43 (t, *J=7.0 Hz*, 3H), 2.35 (s, 3H), 2.54 (s, 3H), 4.30-4.46 (m, 4H), 8.38 (s, 1H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.41, 14.23, 17.71, 22.29, 45.53, 59.81, 110.58, 127.57, 128.71, 131.12, 135.26, 145.77, 147.18, 160.73, 174.2; MS *m/z* 275 (M^++1, 100), 229 (95). CAS Registry Number: [92870-44-5].

7-Methyl-3-phenyl[1,8]naphthyridin-4(1*H*)-one (8)

This compound was prepared according to general procedure A. The mixture was refluxed 17 h, until no further changes in TLC were observed. Then the reaction mixture was evaporated onto silica. Column chromatography (CH_2Cl_2/MeOH 90:10) yielded **8** (66%); mp>260°C; IR (KBr): 3020, 2915, 1610, 1573, 1531 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.60 (s, 3H), 7.30 (d, *J=7.8 Hz*, 2H), 7.36-7.42 (m, 2H), 7.70 (dd, *J=7.8, 1.5 Hz*, 2H), 8.07 (d, *J=6.0 Hz*, 1H), 8.45 (d, *J=7.8 Hz*, 1H), 12.35 (d, *J=6.0 Hz*, $1H_{exch.}$); ^{13}C NMR (DMSO-d_6): δ 24.28, 117.99, 119.98, 120.72, 126.53, 127.82 (2C), 128.25 (2C), 135.36, 135.52, 138.27, 149.31, 162.37, 175.08; MS *m/z* 237 (M^++1, 100).

1-Ethyl-7-methyl-3-phenyl[1,8]naphthyridin-4(1*H*)-one (10a)

This compound was prepared according to general procedure A with CuI as co-catalyst in 71% yield after 1 h. Purification by chromatography (CH_2Cl_2/MeOH 98:2) afforded a white solid; mp: 155°C; IR (KBr): 1622, 1584 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.47 (t, *J=7.2 Hz*, 3H), 2.65 (s, 3H), 4.47 (q, *J=7.2 Hz*, 2H), 7.17 (d, *J=8.1 Hz*, 1H), 7.38-7.43 (m, 3H), 7.67 (dd, *J=8.3, 1.2 Hz*, 2H), 7.83 (s, 1H), 8.66 (d, *J=8.1 Hz*, 1H); ^{13}C NMR ($CDCl_3$): δ 15.65, 25.58, 46.09, 120.09, 120.24, 123.39, 127.55, 128.71 (2C), 128.99 (2C), 135.68, 137.01, 141.49, 148.90, 162.50, 176.58; MS *m/z* 265 (M^++1, 100). *Anal.* Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.33; H, 6.20; N, 10.62.

4-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridin-3-yl)benzoic Acid (10b)

This compound was prepared according to general procedure A from **9** (0.15 g, 0.48 mmol) with 4-carboxyphenylboronic acid (0.12 g, 0.72 mmol), a solution of 2M Na_2CO_3 (0.6 mL, 1.2 mmol) and CuI (6 mg, 0.03 mmol) as co-catalyst in 56% yield after 1 h. A grey solid was obtained by precipitation after dilution with 2.7M HCl; mp>260°C; IR (KBr): 3420, 1689, 1607 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.36 (t, *J=7.0 Hz*, 3H), 2.60 (s, 3H), 4.46 (q, *J=7.0 Hz*, 2H), 7.33 (d, *J=7.1 Hz*, 1H), 7.31-7.94 (m, 4H), 8.46 (d, *J=7.1 Hz*, 1H), 8.53 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 14.89, 24.76, 45.01, 119.07, 119.57, 120.15,128.00, 128.61, 128.84, 135.94, 143.33, 147.89, 162.06, 167.14, 174.44; MS *m/z* 310.5 (M^++1, 100).

1-Ethyl-3-(4-methoxyphenyl)-7-methyl[1,8]naphthyridin-4(1*H*)-one (10c)

This compound was prepared according to general procedure A with CuI as co-catalyst in 82% yield after 1 h. Purification by chromatography (CH_2Cl_2/MeOH 98:2) gave a white solid; mp: 160-162°C; IR (KBr): 1621, 1583, 1543 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.46 (t, *J=7.2 Hz*, 3H), 2.65 (s, 3H), 3.83 (s, 3H), 4.46 (q, *J=7.2 Hz*, 2H), 6.94 (d, *J=8.8 Hz*, 2H), 7.16 (d, *J=7.8 Hz*, 1H), 7.61 (d, *J=8.8 Hz*, 2H), 7.79 (s, 1H), 8.65 (d, *J=7.8 Hz*, 1H); ^{13}C NMR ($CDCl_3$): δ 15.65, 25.56, 46.02, 55.72, 114.18 (2C), 119.93, 120.10, 123.11, 128.08, 130.09 (2C), 136.97, 140.88, 148.82, 159.25, 162.37, 176.70; MS *m/z* 295 (M^++1, 100).

Methyl (*E*)-3-[1-Ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridin-3-yl)]-2-propenoate (10d)

This compound was prepared by using general procedure B with CuI as co-catalyst in 87% after 30 min. Purification by chromatography (CH_2Cl_2/MeOH 98:2) afforded pure product; mp: 202°C; IR (KBr): 1706, 1637, 1612 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (t, *J=7.0 Hz*, 3H), 2.62 (s, 3H), 3.74 (s, 3H), 4.42 (q, *J=7.0 Hz*, 2H), 7.18 (d, *J=8.0 Hz*, 1H), 7.27 (d, *J=16.0 Hz*, 1H), 7.49 (d, *J=16.0 Hz*, 1H), 7.85 (s, 1H), 8.57 (d, *J=8.0 Hz*, 1H); ^{13}C NMR ($CDCl_3$): δ 15.60, 25.52, 46.60, 51.83, 117.01, 118.25, 120.14, 121.05, 136.76,

139.51, 145.64, 148.35, 162.91, 169.18, 176.89; MS *m/z* 273 (M^++1, 100). *Anal.* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.15; H, 5.94; N, 10.25.

(*E*)-3-[1-Ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridin-3-yl)]-2-propenenitrile (10e)

This compound was prepared by using the general procedure B with CuI as co-catalyst in 86% after 30 min. Purification by chromatography (CH_2Cl_2/MeOH 98:2) afforded pure product; mp: 204°C; IR (KBr): 2206, 1634, 1622 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.46 (t, *J=7.0 Hz*, 3H), 2.64 (s, 3H), 4.47 (q, *J=7.0 Hz*, 2H), 7.07-7.10 (m, 2H), 7.23 (d, *J=8.0 Hz*, 1H), 7.80 (s, 1H), 8.56 (d, *J=8.0 Hz*, 1H); ^{13}C NMR ($CDCl_3$): δ 15.66, 25.57, 46.87, 97.13, 115.99, 120.19, 121.48, 130.67, 134.55, 136.57, 145.28, 146.16, 148.12, 163.40, 176.99; MS *m/z* 242 (M^++1, 100).

1-Ethyl-7-methyl-3-[(*E*)-3-oxo-1-butenyl][1,8]naphthyridin-4(1*H*)-one (10f)

This compound was prepared by using general procedure B with CuI as co-catalyst in 93% after 30 min. Purification by chromatography (CH_2Cl_2/MeOH 98:2) afforded pure product; mp: 184-186°C; IR (KBr): 1632, 1602 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.42 (t, *J=7.2 Hz*, 3H), 2.28 (s, 3H), 2.59 (s, 3H), 4.43 (q, *J=7.2 Hz*, 2H), 7.17 (d, *J=8.0 Hz*, 1H), 7.41-7.42 (m, 2H), 7.92 (s, 1H), 8.54 (d, *J=8.0 Hz*, 1H); ^{13}C NMR ($CDCl_3$): δ 15.60, 25.51, 28.82, 46.69, 116.92, 120.04, 121.18, 126.38, 136.71, 137.59, 145.46, 148.40, 163.02, 176.85, 199.63; MS *m/z* 257 (M^++1, 100).

1-Ethyl-7-methyl-3-(3-oxobutyl)[1,8]naphthyridin-4(1*H*)-one (10g)

This compound was prepared by using general procedure B with CuI as co-catalyst in 50% after 30 min. Purification by chromatography (CH_2Cl_2/MeOH 98:2) afforded pure product; mp: 142°C; IR (KBr): 1706, 1624 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (t, *J=7.0 Hz*, 3H), 2.00 (s, 3H), 2.54 (s, 3H), 2.70 (q, *J=5.5 Hz*, 2H), 2.76 (q, *J=5.5 Hz*, 2H), 4.32 (q, *J=7.0 Hz*, 2H), 7.04 (d, *J=8.0 Hz*, 1H), 7.63 (s, 1H), 8.46 (d, *J=8.0 Hz*, 1H); ^{13}C NMR ($CDCl_3$): δ 14.17, 21.77, 24.16, 29.13, 41.08, 44.38, 117.42, 118.43, 120.75, 134.82, 140.27, 147.65, 160.91, 176.72, 207.96; MS *m/z* 259 (M^++1, 100). *Anal.* Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.90; H, 7.09; N, 10.96.

1-Ethyl-7-methyl-3-[(*E*)-2-phenylethenyl][1,8]naphthyridin-4(1*H*)-one (10h)

This compound was prepared by using general procedure B with CuI as co-catalyst in 51% after 30 min. Purification by chromatography (CH_2Cl_2/MeOH 98:2) afforded pure product; mp: 145°C; IR (KBr): 1615 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.46 (t, *J=7.2 Hz*, 3H), 2.62 (s, 3H), 4.45 (q, *J=7.2 Hz*, 2H), 7.08-7.34 (m, 5H), 7.50 (d, *J=7.2 Hz*, 2H), 7.67 (d, *J=16.3 Hz*, 1H), 7.84 (s, 1H), 8.63 (d, *J=8.1 Hz*, 1H); ^{13}C NMR ($CDCl_3$):

δ 15.66, 25.54, 46.98, 119.59, 119.91, 120.34, 122.85, 126.72 (2C), 127.52, 128.42, 128.95 (2C), 136.68, 138.59, 141.07, 148.28, 162.34, 176.95; MS *m/z* 291 (M^++1, 100). *Anal.* Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.55; H, 6.20; N, 9.59.

3-Acetyl-1-ethyl-7-methyl[1,8]naphthyridin-4(1*H*)-one (10i)

This compound was prepared by using general procedure B with CuI as co-catalyst in 55% after 30 min. After removal of solvents, the residue was stirred in 2.7M HCl during 15 h, then extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water , dried over $MgSO_4$ and evaporated in vacum. Purification by chromatography (CH_2Cl_2/MeOH 98:2) afforded pure product; mp: 185-186°C; IR (KBr): 1664, 1626 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.42 (t, *J=7.2 Hz*, 3H), 2.68 (s, 3H), 2.78 (s, 3H), 4.50 (q, *J=7.2 Hz*, 2H), 7.27 (d, *J=8.2 Hz*, 1H), 8.64 (d, *J=8.2 Hz*, 1H), 8.65 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 15.59, 25.45, 31.88, 47.09, 119.75, 121.61, 122.33, 137.04, 148.38, 149.14, 163.18, 176.56, 197.77; MS *m/z* 231 (M^++1, 100). CAS Registry Number: [54756-14-8].

1-[(*E*)-3-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridin-3-yl)-2-propenyl]-3-methoxy-1*H*-pyrazole-4-carboxylic Acid (10j)

To the solution of naphthyridine (**9**) (0.15 g, 0.48 mmol) in DMF (3 mL) were successively added 1-allyl-3-methoxypyrazole-4-carboxylic acid (87 mg, 0.48 mmol), triethylamine (0.15 mL, 1.1 mmol), palladium(II) acetate (6 mg, 0.026 mmol), triphenylphosphine (27 mg, 0.1 mmol), and CuI (6 mg, 0.03 mmol). The solution was heated at 130°C in a sealed tube for 30 min. After usual treatment, the crude product was purified by recrystallization from AcOEt; yield: 60%; mp: 245°C, IR (KBr): 3426, 1684, 1613 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.36 (t, *J=7.2 Hz*, 3H), 2.62 (s, 3H), 3.83 (s, 3H), 4.45 (q, *J=7.2 Hz*, 2H), 4.75 (d, *J=6.2 Hz*, 2H), 6.50 (d, *J=15.7 Hz*, 1H), 6.94 (dt, *J=15.7, 6.2 Hz*, 1H), 7.33 (d, *J=8.0 Hz*, 1H), 8.08 (s, 1H), 8.42 (s, 1H), 8.45 (d, *J=8.0 Hz*, 1H), 11.91 (s, $1H_{exch.}$); ^{13}C NMR (DMSO-d_6): δ 14.89, 24.72, 44.88, 54.20, 55.81, 98.56, 116.84, 118.50, 119.99, 123.40, 127.12, 135.30, 135.63, 143.01, 147.44, 161.60, 161.88, 162.95, 174.93; MS *m/z* 369 (M^++1, 50), 227 (100). *Anal.* Calcd for $C_{19}H_{20}N_4O_4$: C, 61.95; H, 5.47; N, 15.21. Found: C, 62.00; H, 5.48; N, 15.21.

Ethyl 1-[(*E*)-3-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridin-3-yl)-2-propenyl]-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (10k)

To the solution of naphthyridine (**9**) (0.3 g, 0.96 mmol) in DMF (5 mL) were successively added ethyl 1-allyl-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (0.26 g, 0.96 mmol), triethylamine (0.17 mL, 1.24 mmol), palladium(II) acetate (8 mg, 0.035 mmol), triphenylphosphine (37 mg, 0.14

mmol), CuI (11 mg, 0.06 mmol). The solution was heated at 130°C in a sealed tube for 45 min. The residue obtained after concentration under reduced pressure was hydrolyzed and extracted with CH_2Cl_2. Removal of solvent afforded a solid which was washed with hot AcOEt to give a white solid in 69% yield; mp: 233-234°C; IR (KBr): 1735, 1615 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.28 (m, 6H), 2.56 (s, 3H), 2.63 (s, 3H), 4.21 (q, *J=7.0 Hz*, 2H), 4.38 (q, *J=7.0 Hz*, 2H), 5.19 (d, *J=5.5 Hz*, 2H), 6.60 (d, *J=15.1 Hz*, 1H), 6.97 (dt, *J=15.1, 5.5 Hz*, 1H), 7.25 (d, *J=7.3 Hz*, 1H), 7.37 (d, *J=7.3 Hz*, 1H), 8.24 (s, 1H), 8.40 (m, 2H), 8.71 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 14.20, 14.82, 24.67 (2C), 44.87, 51.08, 59.84, 111.34, 116.77, 118.50, 119.99, 120.46, 121.22, 123.32, 127.25, 135.60, 135.99, 143.07, 147.42, 148.32, 149.07, 161.75, 162.46, 164.25, 173.13, 174.90; MS *m/z* 459 (M^++1, 100). *Anal.* Calcd for $C_{26}H_{26}N_4O_4$: C, 68.11; H, 5.72; N, 12.22. Found: C, 68.01; H, 5.57; N, 12.13.

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