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An economical nucleophilic route toward facile synthesis of pyrano[4,3-*b*]quinolin-1-ones via 6-*endo*-*dig* cyclization of *o*-alkynylquinoline esters

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1-Chloro-benzo[*b*][1,6]naphthyridine

ABSTRACT

Metal-free facile synthesis of pyrano[4,3-*b*]quinoline-1-ones is described from methyl 2-arylethynylquinoline-3-carboxylates via intramolecular cyclization in excellent yields. The cyclization reactions are facilitated using cheap and easily available KOH base in MeOH. The reaction conditions did not require dry solvent, inert atmosphere, and avoid further column chromatography purification of the products. These compounds could be further used as building blocks for the synthesis of 2*H*-benzo[*b*][1,6]naphthyridin-1-one and 1-chloro-benzo[*b*][1,6]naphthyridines.

1. Introduction

Development of new efficient and economical methodology for the synthesis of quinoline and their carbo/hetero annelated analogues have attracted great attention from the synthetic as well as medicinal chemists. Particularly, pyranoquinolines are considered important class of compounds because their structural units are component of many alkaloids isolated from Rutaceae family[1] for example, flindersine, oricine, geibalasine, and verprisine.[2] Their derivatives possess variety of applications as drugs, pharmaceuticals and agrochemicals,[3] and exhibit significant range of biological activities, such as anti-allergic, psychotropic, estrogenic, anti-inflammatory, anticoagulant, coronary constricting, optical brightening, antifungal, and antihistamine activities.[4] Consequently, several methods have been reported for the synthesis of pyranoquinolines.[4e,5] In contrast, the synthesis of pyrano[4,3-*b*]quinolin-1-ones has been less explored. However, the synthesis of 2-pyrone moiety, the core moiety of analogous isocoumarin derivatives, has been recently reported from transition metals Pd(II),[6] Fe(III),[7] Cu(II),[8] electrophiles,[9] and Lewis acid-catalyzed[10] inter/intramolecular cyclization of carboxylic acid and ester derivatives. Recently, Verma et al. have reported the synthesis of similar moiety in pyrano[4,3-*b*]quinolinones from the corresponding *o*-alkynyl esters[11] via intramolecular iodocyclization. Similarly, Ghorai et al. have also reported the synthesis of pyrano[4,3-*b*]quinolinones from corresponding 2-alkynylquinoline-3-carboxaldehydes via oxidation followed by intramolecular cyclization.[12] However, these methods have some limitations, such as use of expensive reagents, anhydrous solvents, longer reaction periods and lower yields.

Recently, our group has been actively engaged in exploring the reactivity and synthetic applications of 2-chloroquinoline-3-carboxaldehydes representing two electrophilic centers for their further reactions. We have demonstrated the synthesis of large variety of *O*, *N*, *S*-annulated quinolines by the choice of appropriate reagents, catalysts, and other reactive partners.[13] The easy accessibility of 3-carboalkoxy[14] and 3-carbonitrile[15] derivatives from 2-chloroquinoline-3-carboxaldehydes via oxidation makes them further attractive intermediates for their synthetic applications. Recently, we have reported the synthesis of pyrimido-fused quinolines via different methodology from 2-chloroquinoline-3-carbonitriles.[16] In continuation of these studies, we now report the facile synthesis of pyrano[4,3-*b*]quinolin-1-ones from methyl 2-arylalkynylquinoline-3-carboxylates using cheap and easily available KOH base in aerobic conditions at room temperature.

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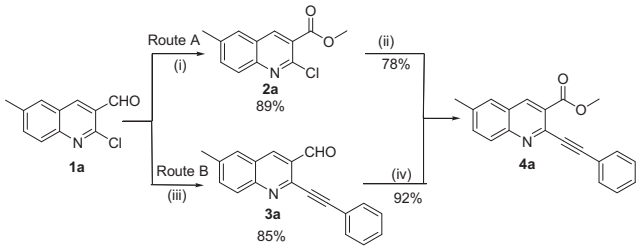
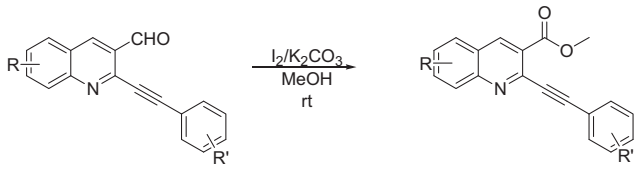
2. Results and discussion

Initially, we attempt to optimize the reaction conditions for the synthesis of methyl 6-methyl-2-phenylethynylquinoline-3-carboxylate from 2-chloroquinoline-3-carbaldehyde through oxidative esterification followed by Sonogashira coupling either route A via intermediate **2** or vice-versa route B via intermediate **3** (Scheme 1). We were delighted that the reaction completed within 10 min at room temperature and afforded **4a** in 92% yield via route B (Table 1, entry 1). We chose route B as our reaction conditions for synthesis of compounds **4a**–**ad** bearing different substituents on the phenyl ring of arylalkyne (Table 1, entries 1–5) and **4b**–**i** bearing different substituents on quinoline nucleus (entries 6–13) and compound **6** (entry 14), respectively.



Scheme 1. Synthesis of methyl 6-methyl-2-phenylethynylquinoline-3-carboxylate (**4**) from 2-choloro-6-methylquinoline-3-carboxaldehyde (**1**). Conditions: route A: (i) 2-chloro-6-methylquinoline-3-carboxaldehyde **1a** (1.0 mmol), iodine (3.0 mmol), K_2CO_3 (3.0 mmol), methanol (3 mL), rt, 10 min (ii) substrate **2a** (1.0 mmol), $PdCl_2$ (5 mol %), PPh_3 (10 mol %), acetonitrile (3 mL), phenyl acetylene (1.1 mmol), Et_3N (2.0 mmol), 80 °C; route B: (iii) substrate **1a** (1.0 mmol), $PdCl_2$ (5 mol %), PPh_3 (10 mol %), acetonitrile (3 mL), phenyl acetylene (1.1 mmol), Et_3N (2.0 mmol) 80 °C; (iv) iodine (2.0 mmol), K_2CO_3 (3.0 mmol), methanol (3 mL), rt, 10 min.

Table 1
Synthesis of methyl 2-arylethynylquinoline-3-carboxylates 4[a]



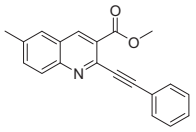
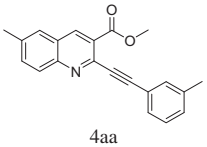
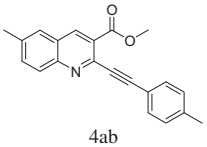
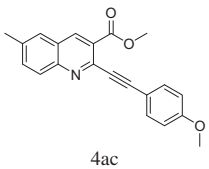
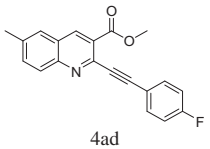
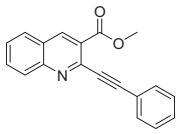
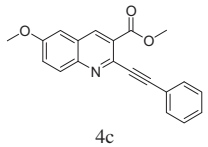
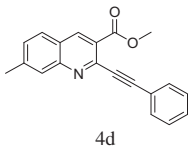
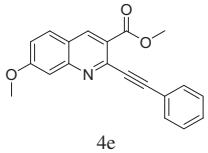
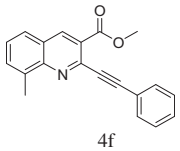
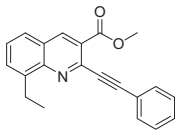
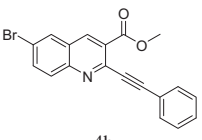
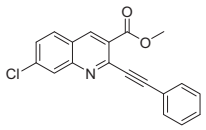
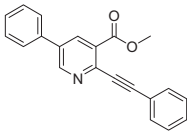
Entry	Substrate		Product	Yield[b] (%)
	R	R′		
1	6-Me	H	 4a	92
2		3-Me	 4aa	91
3		4-Me	 4ab	92
4		4-OMe	 4ac	94

Table 1 (*continued*)

Entry	Substrate		Product	Yield[b] (%)
	R	R′		
5		4-F	 4ad	92
6	H	H	 4b	92
7	6-OMe	H	 4c	89
8	7-Me	H	 4d	87
9	7-OMe	H	 4e	92
10	8-Me	H	 4f	88
11	8-Et	H	 4g	90
12	6-Br	H	 4h	85

(*continued on next page*)

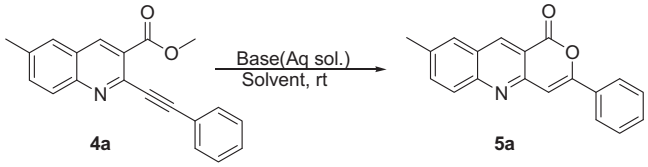
Table 1 (*continued*)

Entry	Substrate		Product	Yield[b] (%)
	R	R′		
13	7-Cl	H	 4i	87
14	Ph	H	 6	85

[a] Conditions: substrate **3** (0.5 mmol), 2.0 equiv of I_2, and 3.0 equiv of K_2CO_3, 3 mL MeOH, rt, 10 min.
[b] Yield of isolated product.

Next, we optimize the reaction conditions for the intramolecular cyclization of methyl 2-arylalkynylquinoline-3-carboxylates affording the synthesis of pyrano[4,3-*b*]quinolin-1-ones. Initially, we examined the cyclization reactions of compound **4a** using different bases and solvents. Results are summarized in Table 2. The reaction of **1a** (1 mmol) with 2 mL of 20% aq KOH in 2 mL methanol at room temperature for 1 h afforded the cyclized product **5a** in 92%, which was characterized as 8-methyl-3-phenyl-pyrano[4,3-*b*] quinolin-1-one from its spectral and analytical data (Table 2, entry 1). Further, decreasing or increasing concentrations of KOH or increasing the temperature of reaction mixture lowered the yield of the cyclized product (entries 2–4). Similarly, using other bases, such as NaOH, K_3PO_4, *t*-BuOK, K_2CO_3, and Cs_2CO_3 did not improve the yield of product **5a** (entries 5–9). No cyclization reaction occurred with organic bases, such as triethylamine and DBU (entries 10, 11). Among the various solvents examined (entries 12–20), ethanol and *t*-BuOH were found equally effective (entries 12 and 13). Other solvents, such as CH_3CN and DMF were found less effective (entries 14, 15). No cyclization reactions occurred in toluene, benzene, DCM, $CHCl_3$, and water (entries 16–20).

Table 2
Optimization of reaction conditions on methyl 6-methyl-2-phenylethynylquinoline-3-carboxylate with different bases and solvents[a] (**4a**)



Entry	Base	Solvent	Time (h)	Yield[b] (%)
1	20% KOH	MeOH	1	92
2	10% KOH	MeOH	6	88
3	30% KOH	MeOH	45 (min)	85
4	20% KOH	MeOH	45 (min)	88[c]
5	20% NaOH	MeOH	2	87
6	20% K_3PO_4	MeOH	3	86
7	20% *t*-BuOK	MeOH	3	85
8	20% K_2CO_3	MeOH	4	85
9	20% Cs_2CO_3	MeOH	12	75
10	Et_3N	MeOH	48	Nr
11	DBU	MeOH	48	Nr
12	20% KOH	EtOH	50 (min)	88
13	20% KOH	*t*-BuOH	55 (min)	86
14	20% KOH	CH_3CN	6	70
15	20% KOH	DMF	2.5	75
16	20% KOH	Toluene	48	Nr
17	20% KOH	Benzene	48	Nr
18	20% KOH	DCM	48	Nr
19	20% KOH	$CHCl_3$	48	Nr
20	20% KOH	H_2O	48	Nr

[a] Conditions: methyl 6-methyl-2-phenylethynylquinoline-3-carboxylate (1 mmol), 20% aq base (2 mL/mmol), solvent (2 mL/mmol), rt.
[b] Isolated yields.
[c] Temp 60 °C.

To examine the scope of the cyclization reactions, other methyl 2-arylethynyl-quinoline-3-carboxylates **4a**–**ad** were allowed to react under the optimized reaction conditions affording the corresponding desired cyclized products **5a**–**ad** in excellent yields (Table 3, entries 1–5). The electron withdrawing and electron donating groups on phenyl ring in arylalkynes do not affect the yields of the cyclized products (entries 2–5). Further, examination of cyclization reactions of ethyl and *n*-butyl 6-methyl-2-phenylethynyl-quinoline-3-carboxylates **4ae**–**af** under the optimized reaction conditions afforded the cyclized product **5a** in 88% and 84% yields, respectively (entries 6, 7). Lengthening the alkyl chain of ester group decreases both reaction rates and yields.

Table 3
Synthesis of pyrano[4,3-*b*]quinolin-1-one[a]

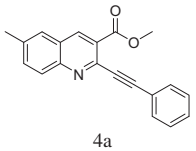
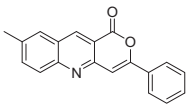
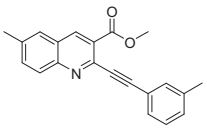
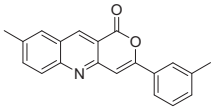
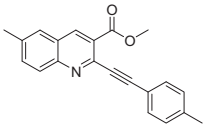
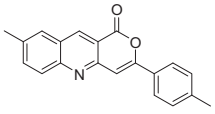
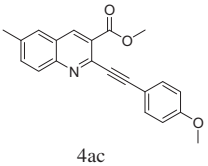
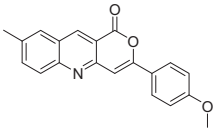
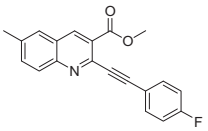
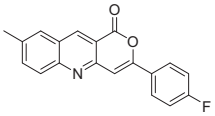
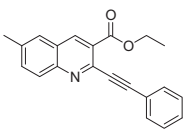
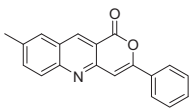
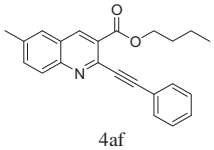
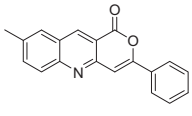
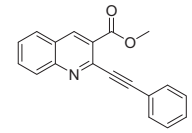
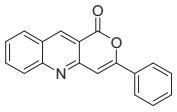
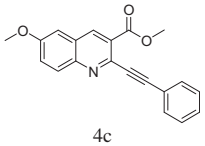
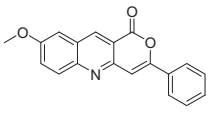
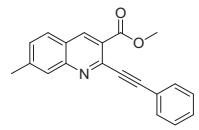
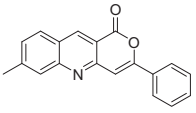
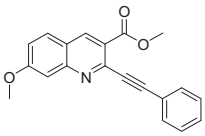
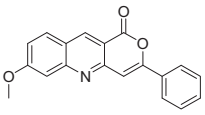
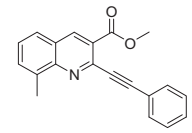
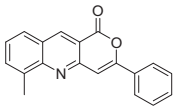
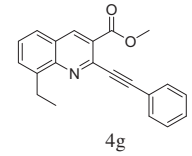
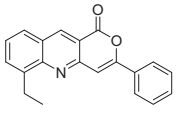
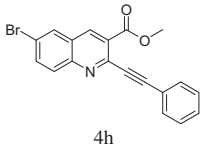
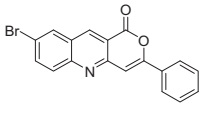
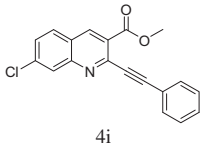
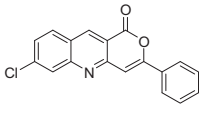
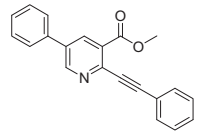
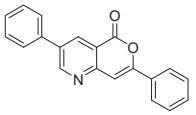
Entry	Substrate	Product	Time (min)	Yield[b] (%)
1	 4a	 5a	60	92%
2	 4aa	 5aa	60	90%
3	 4ab	 5ab	60	92%
4	 4ac	 5ac	60	94%
5	 4ad	 5ad	50	95%
6	 4ae	 5a	65	88%
7	 4af	 5a	70	84%

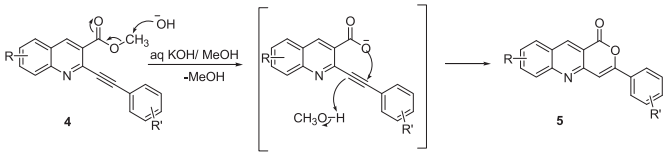
Table 3 (*continued*)

Entry	Substrate	Product	Time (min)	Yield[b] (%)
8	 4b	 5b	60	92%
9	 4c	 5c	55	92%
10	 4d	 5d	60	93%
11	 4e	 5e	55	95%
12	 4f	 5f	60	89%
13	 4g	 5g	60	90%
14	 4h	 5h	50	94%
15	 4i	 5i	50	95%
16	 6	 7	60	92%

[a] Conditions: substrate (1 mmol), 20% aq KOH (2 mL/mmol), MeOH (2 mL/mmol), rt.
[b] Isolated yields.

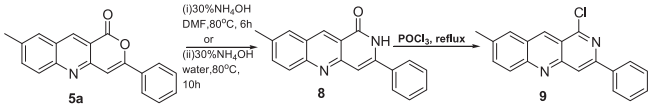
To further examine the generality of cyclization reactions, the reactions of various methyl 2-phenylethynylquinolin-3-carboxylates **4b–i** were tested under the optimized reaction conditions. The reactions proceeded smoothly and afforded the corresponding pyrano[4,3-*b*]quinoline-1-ones **5b–i** in excellent yields (Table 3, entries 8–15). An electron donating and electron withdrawing groups at different positions in benzene ring of quinoline moiety do not show any significant variations in the yields of the products. However, the reaction rates were found enhanced with electron withdrawing halogen groups (entries 14, 15) and electron donating methoxy groups (entries 9, 11), which could be attributed to their –I effects. To further generalize the scope of reactions, pyridine derivative was allowed to react under the optimized reaction conditions and found that the reaction proceeded smoothly affording the cyclized product **7** in good yield (entry 16).

A plausible mechanism for base mediated cyclization is illustrated in Scheme 2.



Scheme 2. Plausible mechanism.

Next, the 2-pyrone moiety present in pyrano[4,3-*b*]quinolin-1-ones **5** undergo further transformation by choice of suitable reagents to afford new class of compounds, providing chemical evidence for the structure of cyclized product **5**. Thus, the reaction of **5a** with excess of 30% NH_4OH in DMF for 6 h or in water for 10 h, at 80 °C afforded compound **8**, which was characterized as 2*H*-benzo[*b*][1,6]naphthyridin-1-one from its spectral and analytical data. The compound **8** was further transformed into 1-chloro-benzo[*b*][1,6]naphthyridine **9** on reaction with $POCl_3$ at reflux temperature for 4 h (Scheme 3).



Scheme 3. Reaction transformations.

Beside spectral data and chemical evidences, single crystal X-ray crystallographic analysis[17] of **5ab** was performed to further support the structure of cyclized products. An ORTEP representation of the molecule **5ab** is given in Fig. 1.

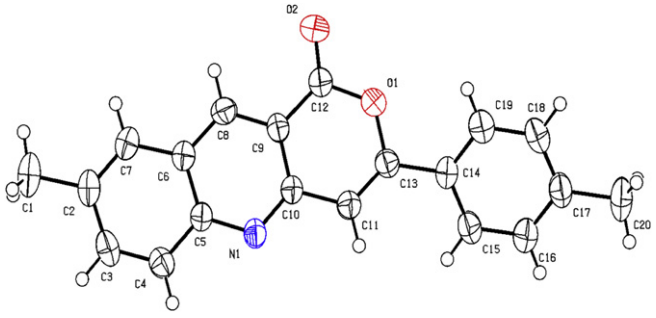


Fig. 1. ORTEP drawing of the X-ray structure of **5ab**.

3. Conclusions

In conclusion we have developed new methodology for facile synthesis of pyrano[4,3-*b*]quinolines using cheap and easily

available KOH base. The procedure is economical avoiding expensive metal catalysts, dry solvent, inert atmosphere, and column chromatography purifications. We have also explored their applications to the synthesis of new class of heterocyclic compounds, such as 1,6-naphthyridone and 1,6-naphthyridine derivatives using easily available inexpensive reagents.

4. Experimental section

4.1. General

Melting points were measured using Buchi Melting-point apparatus in an open capillary tube and are uncorrected. IR spectra were recorded on VARIAN 3300 FTIR spectrophotometers. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on JEOL AL 300 MHz spectrometer. The chemical shifts (δ parts per million) and coupling constants (hertz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). Elemental analyses were performed on Exter Analytical Inc. 'Model CE-400 CHN Analyzer' from Department of Chemistry, BHU, Varanasi. Thin-layer chromatographies (TLC) were performed on glass plates (7.5×2.5 and 7.5×5.0 cm) coated with Loba Chemie's silica gel GF_{254} and various combinations of ethyl acetate and hexane were used as eluent. Visualization of spots was accomplished by exposure to UV light. Qualigen's silica gel (60–120 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product).

4.2. General procedure for synthesis of methyl 2-arylalkynylquinoline-3-carboxylates (4)

Into a solution of 2-arylalkynylquinoline-3-carbaldehydes **3** (0.50 mmol) in methanol (3 mL/mmol) were added I_2 (2 equiv) and K_2CO_3 (3 equiv), stirred at room temperature until total disappearance of the starting material as monitored by TLC. The reaction mixture was then quenched with saturated aq $Na_2S_2O_3$ (5.0 mL) and water (5.0 mL). The solid was filtered and washed with water (3–5 mL) and dried. The crude product was characterized and was pure enough for further use.

*4.2.1. 6-Methyl-2-phenylethynylquinoline-3-carboxylic acid methyl ester (**4a**).* Yellow solid; yield: 92%; mp 90 °C; R_f (10% EtOAc/hexane) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.56 (s, 3H), 4.03 (s, 3H), 7.39–7.41 (m, 3H), 7.64–7.70 (m, 4H), 8.05 (d, J=8.7 Hz, 1H), 8.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.4, 52.5, 87.3, 92.8, 121.4, 122.2, 125.3, 126.0, 127.1, 127.9, 128.4, 129.2, 132.4, 132.9, 139.7, 142.1, 150.9, 165.7. Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65%. Found: C, 79.69; H, 5.01; N, 4.60%.

*4.2.2. 6-Methyl-2-m-tolylethynylquinoline-3-carboxylic acid methyl ester (4**aa**).* Yellow solid; yield: 91%; mp 118 °C; R_f (10% EtOAc/hexane) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.37 (s, 3H), 2.56 (s, 3H), 4.04 (s, 3H), 7.18–7.29 (m, 3H), 7.51 (d, J=8.1 Hz, 1H), 7.63–7.66 (m, 2H), 8.05 (d, J=9.0 Hz, 1H), 8.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.5, 21.6, 52.4, 87.6, 94.0, 121.5, 125.4, 127.2, 128.6, 128.9, 129.1, 129.8, 131.1, 132.4, 133.1, 137.4, 139.8, 142.5, 144.4, 150.1, 165.4. Anal. Calcd for $C_{21}H_{17}NO_2$ C, 79.98; H, 5.43; N, 4.44%. Found: C, 79.90; H, 5.41; N, 4.40%.

*4.2.3. 6-Methyl-2-p-tolylethynylquinoline-3-carboxylic acid methyl ester (4**ab**).* Yellow solid; yield: 94%; mp 128 °C; R_f (10% EtOAc/hexane) 0.42; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.37 (s, 3H), 2.54 (s, 3H), 4.02 (s, 3H), 7.17 (d, J=7.8 Hz, 2H), 7.57–7.64 (m, 4H), 8.03 (d, J=8.7 Hz, 1H), 8.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.5, 22.3, 52.3, 87.4, 94.0, 120.4, 125.5, 128.5, 129.0, 129.3, 130.1, 131.1, 137.5, 138.7, 142.8, 144.1, 148.8, 156.1, 165.4. Anal. Calcd for $C_{21}H_{17}NO_2$ C, 79.98; H, 5.43; N, 4.44%. Found: C, 79.94; H, 5.40; N, 4.39%.

*4.2.4. 2-(4-Methoxy-phenylethynyl)-6-methylquinoline-3-carboxylic acid methyl ester (**4ac**).* Yellow solid; yield: 94%; mp: 136–138 °C (d); R_f (10% EtOAc/hexane) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.59 (s, 3H), 3.84 (s, 3H), 4.04 (s, 3H), 6.90 (d, J=8.1 Hz, 2H), 7.62–7.67 (m, 4H), 8.04 (d, J=8.4 Hz, 1H), 8.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 52.6, 55.3, 87.6, 94.0, 114.1, 118.6, 120.4, 125.4, 127.7, 128.5, 129.1, 132.1, 134.1, 139.9, 142.0, 149.4, 160.4, 165.7. Anal. Calcd for $C_{21}H_{17}NO_3$C, 76.12; H, 5.17; N, 4.23%. Found: C, 76.10; H, 5.14; N, 4.20%.

*4.2.5. 2-(4-Fluoro-phenylethynyl)-6-methylquinoline-3-carboxylic acid methyl ester (**4ad**).* Yellow solid; yield: 92%; mp: 80–82 °C (d); R_f (10% EtOAc/hexane) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.56 (s, 3H), 4.04 (s, 3H), 7.08 (d, J=7.8 Hz, 2H), 7.59–7.73 (m, 4H), 8.17 (d, J=8.4 Hz, 1H), 8.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.6, 52.5, 88.3, 92.3, 115.6, 115.9, 118.4, 125.2, 125.8, 126.4, 127.2, 127.9, 128.5, 129.0, 132.2, 139.7, 148.9, 165.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ=−33.007.Anal. Calcd for $C_{20}H_{14}NO_2$ C, 75.22; H, 4.42; N, 4.39%. Found: C, 75.20; H, 4.38; N, 4.35%.

*4.2.6. 2-Phenylethynylquinoline-3-carboxylic acid methyl ester (**4b**).* Brown solid; yield: 92%; mp 96 °C; R_f (10% EtOAc/hexane) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.03 (s, 3H), 7.39–7.41 (m, 3H), 7.61 (t, J=7.5 Hz, 1H), 7.71–7.73 (m, 2H), 7.83 (t, J=7.2 Hz, 1H), 7.90 (d, J=8.1 Hz, 1H), 8.17 (d, J=8.4 Hz, 1H), 8.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.6, 88.4, 93.4, 122.3, 125.4, 125.9, 127.9, 128.5, 128.7, 129.2, 129.4, 132.2, 132.4, 139.8, 141.7, 149.1, 165.6. Anal. Calcd for $C_{19}H_{13}NO_2$C, 79.43; H, 4.56; N, 4.88%. Found: C, 79.38; H, 4.50; N, 4.84%.

*4.2.7. 6-Methoxy-2-phenylethynylquinoline-3-carboxylic acid methyl ester (**4c**).* Yellow solid; yield: 89%; mp 192 °C; R_f (10% EtOAc/hexane) 0.52; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.96 (s, 3H), 4.04 (s, 3H), 7.12 (s, 1H), 7.37–7.39 (m, 3H), 7.48 (d, J=7.2 Hz, 1H), 7.68–7.71 (m, 2H), 8.05 (d, J=9.0 Hz, 1H), 8.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.5, 55.6, 88.4, 92.5, 105.5, 122.5, 125.2, 125.8, 127.1, 128.3, 129.1, 130.7, 132.3, 138.2, 139.1, 145.3, 158.8, 165.9. Anal. Calcd for $C_{20}H_{15}NO_3$ C, 75.70; H, 4.76; N, 4.41%. Found: C, 75.65; H, 4.72; N, 4.40%.

*4.2.8. 7-Methyl-2-phenylethynylquinoline-3-carboxylic acid methyl ester (**4d**).* Yellow solid; yield: 87%; mp 96–98 °C (d); R_f (10% EtOAc/hexane) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.56 (s, 3H), 4.03 (s, 3H), 7.40–7.41 (m, 3H), 7.64–7.75 (m, 4H), 8.06 (d, J=8.7 Hz, 1H), 8.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.5, 52.2, 87.3, 93.2, 121.1, 122.5, 125.6, 125.9, 126.8, 127.9, 128.1, 129.1, 132.4, 133.9, 139.6, 142.5, 149.9, 165.4. Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65%. Found: C, 79.69; H, 5.01; N, 4.60%.

*4.2.9. 7-Methoxy-2-phenylethynylquinoline-3-carboxylic acid methyl ester (**4e**).* Yellow solid; yield: 92%; mp 150–152 °C (d); R_f (10% EtOAc/hexane) 0.48; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.97 (s, 3H), 4.03 (s, 3H), 7.39–7.47 (m, 4H), 7.71–7.78 (m, 4H), 8.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.4, 55.7, 88.4, 92.6, 105.4, 122.4, 125.6, 125.9, 127.1, 128.5, 129.4, 130.7, 132.3, 138.2, 140.1, 148.3, 160.4, 166.1. Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41%. Found: C, 75.68; H, 4.74; N, 4.40%.

*4.2.10. 8-Methyl-2-phenylethynylquinoline-3-carboxylic acid methyl ester (**4f**).* Yellow solid; yield: 88%; mp 66 °C; R_f (10% EtOAc/hexane) 0.54; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.84 (s, 3H), 4.02 (s, 3H), 7.39–7.52 (m, 4H), 7.64–7.69 (m, 4H), 8.73 (s, 1H); ^{13}C NMR

(75 MHz, $CDCl_3$): δ=18.1, 52.5, 88.1, 93.4, 121.2, 122.5, 125.3, 126.1, 127.5, 127.9, 128.4, 129.9, 132.1, 132.9, 139.7, 143.2, 150.1, 165.6. Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65%. Found: C, 79.70; H, 5.00; N, 4.62%.

*4.2.11. 8-Ethyl-2-phenylethynylquinoline-3-carboxylic acid methyl ester (**4g**).* Yellow solid; yield: 90%; mp 65 °C; R_f (10% EtOAc/hexane) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.38 (t, J=7.2 Hz, 3H), 3.35 (q, J=7.2 Hz, 2H), 4.02 (s, 3H), 7.35–7.38 (m, 3H), 7.51 (t, J=7.5 Hz, 1H), 7.64–7.71 (m, 4H), 8.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.7, 24.0, 52.5, 89.0, 92.4, 122.6, 125.2, 125.8, 126.3, 127.7, 128.3, 129.0, 130.3, 132.3, 139.7, 140.2, 143.1, 147.5, 165.9. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44%. Found: C, 79.96; H, 5.40; N, 4.42%.

*4.2.12. 6-Bromo-2-phenylethynylquinoline-3-carboxylic acid methyl ester (**4h**).* Light green solid; yield: 85%; mp 123–124 °C; R_f (10% EtOAc/hexane) 0.40; ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.05 (s, 3H), 7.39–7.40 (m, 4H), 7.57–8.04 (m, 3H), 8.10 (d, J=8.7 Hz, 1H), 8.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.7, 88.4, 92.0, 94.2, 122.2, 123.0, 125.6, 126.2, 128.4, 129.1, 131.7, 132.3, 134.8, 139.2, 141.9, 148.2, 165.4; Anal. Calcd for $C_{19}H_{12}BrNO_2$: C, 62.32; H, 3.30; N, 3.82%. Found: C, 62.30; H, 3.26; N, 3.80%.

*4.2.13. 7-Chloro-2-phenylethynylquinoline-3-carboxylic acid methyl ester (**4i**).* White solid; yield: 87%; mp 95 °C; R_f (10% EtOAc/hexane) 0.42; ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.03 (s, 3H), 7.37–7.45 (m, 4H), 7.73–7.80 (m, 3H), 8.17 (s, 1H), 8.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.4, 55.7, 88.9, 93.5, 105.1, 122.4, 125.3, 125.9, 127.2, 128.5, 129.4, 130.7, 132.2, 138.3, 141.1, 150.3, 160.9, 165.9. Anal. Calcd for $C_{19}H_{12}ClNO_2$: C, 70.92; H, 3.76; N, 4.35%. Found: C, 70.90; H, 3.72; N, 4.32%.

*4.2.14. 5-Phenyl-2-phenylethynylnicotinic acid methyl ester (**6**).* Yellow solid; yield: 85%; mp 104 °C; R_f (10% EtOAc/hexane) 0.54; ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.00 (s, 3H), 7.36–7.38 (m, 3H), 7.42 (d, J=7.8 Hz, 2H), 7.50–7.52 (m, 2H), 7.64–7.67 (m, 3H), 8.10 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=52.7, 87.4, 93.4, 122.2, 123.4, 126.7, 127.2, 127.6, 128.1, 128.4, 129.1, 132.3, 134.8, 139.2, 141.9, 152.5, 165.4. Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.82; N, 4.47%. Found: C, 80.45; H, 4.80; N 4.44%.

4.3. General synthetic method for synthesis pyrano[4,5-*b*] quinolines-1-one (5)

To a solution of **4** (1 mmol) in 2 mL MeOH was added 20% aq KOH and stirred at room temperature. After completion of the reaction, monitored by TLC, the reaction mixture was cooled to 0 °C and dropwise added 10% HCl solution until pH ≈3, solid product was filtered, washed with water (3–5 mL) and dried. The products were recrystallized from methanol.

*4.3.1. 8-Methyl-3-phenyl-pyrano[4,3-b]quinolin-1-one (**5a**).* Yellow solid; yield: 92%; mp 129–131 °C; R_f (40% EtOAc/hexane) 0.40; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.58 (s, 3H), 7.33–7.36 (m, 4H), 7.62–7.69 (m, 4H), 8.09 (d, J=9.0 Hz, 1H), 8.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.2, 88.5, 92.4, 103.3, 122.3, 125.1, 125.6, 126.2, 126.9, 127.9, 128.7, 131.9, 134.0, 137.6, 138.6, 147.1, 166.7. Anal. Calcd for $C_{19}H_{13}NO_2$: C 79.43, H 4.56, N 4.88%. Found: C 79.40, H 4.52, N 4.86%.

*4.3.2. 8-Methyl-3-m-tolyl-pyrano[4,3-b]quinolin-1-one (**5aa**).* Yellow solid; yield: 90%; mp 133 °C; R_f (40% EtOAc/hexane) 0.28; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.35 (s, 3H), 2.56 (s, 3H), 6.89–7.15 (m, 4H), 7.47–7.49 (m, 3H), 8.04 (d, J=9.0 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.4, 21.6, 101.6, 120.1, 123.2, 126.0, 126.9, 127.2, 128.1, 128.3, 128.4, 133.2, 134.8, 136.3, 137.6, 137.9, 147.4, 148.9, 157.2, 163.0; Anal. Calcd for $C_{20}H_{15}NO_2$: C 79.72, H 5.02, N 4.65%. Found: C 79.70, H 4.98, N 4.63%.

*4.3.3. 8-Methyl-3-p-tolyl-pyrano[4,3-b]quinolin-1-one (**5ab**).* Yellow solid; yield: 92%; mp 142 °C; R_f (40% EtOAc/hexane) 0.26; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.38 (s, 3H), 2.57 (s, 3H), 7.17–7.20 (m, 3H), 7.59–7.69 (m, 4H), 8.06 (d, J=9.0 Hz, 1H), 8.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.5, 21.7, 101.4, 120.0, 123.5, 125.9, 126.4, 127.3, 128.1, 128.7, 134.8, 136.1, 137.6, 138.0, 147.4, 148.9, 157.0, 163.2; Anal. Calcd for $C_{20}H_{15}NO_2$: C 79.72, H 5.02, N 4.65%. Found: C 79.70, H 5.00, N 4.62%.

*4.3.4. 3-(4-Methoxy-phenyl)-8-methyl-pyrano[4,3-b]quinolin-1-one (**5ac**).* Orange solid; yield: 94%; mp 210–212 °C (d); R_f (40% EtOAc/hexane) 0.23; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.57 (s, 3H), 3.82 (s, 3H), 6.87 (d, J=9.1 Hz, 2H), 7.64–7.68 (m, 5H), 8.06 (d, J=9.0 Hz, 1H), 8.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.3, 40.1, 92.9, 102.7, 115.2, 125.2, 125.7, 126.2, 126.7, 127.0, 128.8, 131.9, 134.0, 137.6, 138.7, 140.8, 147.2, 166.0; Anal. Calcd for $C_{20}H_{15}NO_3$: C 75.70, H 4.76,N 4.41. Found: C 75.66, H 4.74, N 4.39.

*4.3.5. 3-(4-Fluoro-phenyl)-8-methyl-pyrano[4,3-b]quinolin-1-one (**5ad**).* Yellow solid; yield: 95%; mp 176 °C; R_f (40% EtOAc/hexane) 0.27; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.57 (s, 3H), 7.06 (d, J=8.4 Hz, 2H), 7.64–7.69 (m, 3H), 7.84–7.94 (m, 2H), 8.18 (d, J=8.1 Hz, 1H), 8.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.0, 101.6, 115.7, 120.8, 126.0, 127.2, 128.0, 130.1, 131.4, 131.7, 133.5, 136.4, 137.9, 147.8, 157.6, 161.1, 165.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ=−32.708. Anal. Calcd for $C_{19}H_{12}FNO_2$: C 74.75, H 3.96, N 4.59. Found: C 74.72, H 3.90, N 4.57.

*4.3.6. 3-Phenyl-pyrano[4,3-b]quinolin-1-one (**5b**).* White solid; yield: 92%; mp 152 °C; R_f (40% EtOAc/hexane) 0.38; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.35 (s, 1H), 7.36–7.40 (m, 3H), 7.64 (t, J=7.2 Hz, 1H), 7.72 (d, J=5.7 Hz, 2H), 7.87 (t, J=7.8 Hz, 1H), 7.94 (d, J=8.1 Hz, 1H), 8.19 (d, J=8.7 Hz, 1H), 8.97 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=103.0, 115.6, 122.2, 125.7, 127.2, 128.3, 129.0, 129.6, 130.9, 132.3, 133.9, 141.2, 149.1, 152.4, 157.4, 167.9; Anal. Calcd for $C_{18}H_{11}NO_2$: C 79.11, H 4.06, N 5.13%. Found: C 79.10, H 4.04, N 5.10%.

*4.3.7. 8-Methoxy-3-phenyl-pyrano[4,3-b]quinolin-1-one (**5c**).* Yellow solid; yield: 92%; mp 180–182 °C (d); R_f (40% EtOAc/hexane) 0.24; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.95 (s, 3H), 7.15 (s, 1H), 7.30–7.39 (m, 4H), 7.48–7.51 (m, 3H), 7.96 (d, J=9.3 Hz, 1H), 8.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=55.5, 105.6, 114.2, 121.0, 126.2, 126.4, 126.7, 127.3, 127.9, 128.1, 129.6, 129.8, 132.1, 140.2, 140.9, 159.0, 166.8. Anal. Calcd for $C_{19}H_{13}NO_3$: C 75.34, H 4.32, N 4.62%. Found: C 75.20, H 4.30, N 4.60%.

*4.3.8. 7-Methyl-3-phenyl-pyrano[4,3-b]quinolin-1-one(**5d**).* Yellow solid; yield: 93%; mp 200 °C; R_f (40% EtOAc/hexane) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.61 (s, 3H), 7.35–7.37 (m, 3H), 7.46–7.52 (m, 2H), 7.72 (m, 2H), 7.83 (d, J=8.1 Hz, 1H), 8.00 (s, 1H), 8.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.6, 88.3, 92.8, 102.2, 121.9, 123.5, 125.1, 127.0, 127.8, 128.6, 129.7, 131.7, 139.0, 140.9, 142.4, 148.2, 166.2. Anal. Calcd for $C_{19}H_{13}NO_2$: C 79.43, H 4.56, N 4.88%. Found: C 79.40, H 4.52, N 4.86%.

*4.3.9. 7-Methoxy-3-phenyl-pyrano[4,3-b]quinolin-1-one (**5e**).* Yellow solid; yield: 95%; mp 205 °C; R_f (40% EtOAc/hexane) 0.44; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.98 (s, 3H), 7.08 (s, 1H), 7.32–7.52 (m, 4H), 7.88–7.93 (m, 3H), 7.81 (s, 1H), 8.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=55.3, 92.8, 102.2, 114.5, 121.7, 124.5, 125.1, 127.0, 127.9, 128.6, 129.7, 131.7, 139.0, 140.7, 141.9, 158.4, 165.0. Anal. Calcd for $C_{19}H_{13}NO_3$: C 75.24, H 4.32, N 4.62%. Found: C 75.20, H 4.30, N 4.59%.

*4.3.10. 6-Methyl-3-phenyl-pyrano[4,3-b]quinolin-1-one (**5f**).* Yellow solid; yield: 89%; mp 145 °C; R_f (40% EtOAc/hexane) 0.38; ^{1}H NMR

(300 MHz, $CDCl_3$): δ=2.87 (s, 3H), 7.39–7.52 (m, 4H), 7.71–7.74 (m, 4H), 7.98 (t, J=7.5 Hz, 1H), 8.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.8, 104.3, 107.4, 115.2, 125.6, 126.7, 127.0, 127.9, 128.7, 128.9, 130.6, 131.6, 133.2, 135.9, 137.1, 140.4, 166.0; Anal. Calcd for $C_{19}H_{13}NO_2$: C 79.43, H 4.56, N 4.88%. Found: C 79.41, H 4.50, N 4.85%.

*4.3.11. 6-Ethyl-3-phenyl-pyrano[4,3-b]quinolin-1-one (**5g**).* Yellow solid; yield: 90%; mp 140–142 °C (d); R_f (40% EtOAc/hexane) 0.25; ^1H NMR (300 MHz, $CDCl_3$): δ=1.40 (t, J=7.2 Hz, 3H), 3.58 (q, J=7.2 Hz, 2H), 7.34–7.56 (m, 5H), 7.69–7.76 (m, 4H), 8.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.7, 24.0, 89.4, 92.9, 122.2, 125.0, 125.8, 126.3, 127.1, 127.9, 129.0, 130.3, 132.5, 139.7, 140.2, 144.1, 149.5, 165.8. Anal. Calcd for $C_{20}H_{15}NO_2$: C 79.72, H 5.02, N 4.65%. Found: C 79.71, H 4.98, N 4.63%.

*4.3.12. 8-Bromo-3-(1-methyl-propenyl)-pyrano[4,3-b]quinolin-1-one (**5h**).* White solid; yield: 94%; mp 148 °C; R_f (40% EtOAc/hexane) 0.42; ^1H NMR (300 MHz, $CDCl_3$): δ=7.39–7.51 (m, 4H), 7.59–7.98 (m, 3H), 8.15 (m, 2H), 8.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=88.8, 92.0, 101.4, 122.2, 123.0, 125.7, 126.2, 128.4, 129.0, 131.8, 132.3, 134.8, 138.9, 142.3, 148.0, 165.6; Anal. Calcd for $C_{18}H_{10}BrNO_2$: C 61.39, H 2.86, N 3.98%. Found: C 61.37, H 2.85, N 3.94%.

*4.3.13. 7-Chloro-3-phenyl-pyrano[4,3-b]quinolin-1-one (**5i**).* White solid; yield: 95%; mp 200 °C; R_f (40% EtOAc/hexane) 0.42; ^1H NMR (300 MHz, $CDCl_3$): δ=7.32–7.40 (m, 4H), 7.57–7.70 (m, 4H), 8.13 (s, 1H), 8.78 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=88.7, 93.8, 102.2, 121.7, 123.5, 125.5, 127.0, 127.8, 128.6, 129.7, 133.7, 139.0, 141.9, 144.4, 150.2, 165.8; Anal. Calcd for $C_{18}H_{10}ClNO_2$: C 70.25, H 3.28, N 4.55%. Found: C 70.22, H 3.25, N 4.50%.

*4.3.14. 3,7-Diphenyl-pyrano[4,3-b]pyridin-5-one (**7**).* White solid; yield: 92%; mp 148 °C; R_f (40% EtOAc/hexane) 0.42; ^1H NMR (300 MHz, $CDCl_3$): δ=7.32–7.40 (m, 3H), 7.44 (d, J=7.8 Hz, 2H), 7.54–7.57 (m, 2H), 7.65–7.70 (m, 3H), 8.05 (s, 1H), 8.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=101.9, 124.4, 126.5, 127.1, 127.6, 128.4, 128.9, 129.2, 132.4, 133.5, 134.9, 136.1, 136.7, 151.4, 152.5, 163.4; Anal. Calcd for $C_{20}H_{13}NO_2$: C 80.25, H 4.38, N 4.68%. Found: C 80.22, H 4.35, N 4.66%.

4.4. Procedure for synthesis 2*H*-benzo[*b*][1,6]naphthyridin-1-one (8)

To a solution of **5a** (1 mmol) in DMF was added excess of 30% NH_4OH 6 h or in water for 10 h and stirred at 80 °C. After completion of the reaction, monitored by TLC, the reaction mixture was poured into ice-cold water, solid product was filtered and washed with water (3–5 mL) and dried. The crude product was characterized as 2*H*-benzo[*b*][1,6]naphthyridin-1-one.

*4.4.1. 8-Methyl-3-phenyl-2H-benzo[b][1,6]naphthyridin-1-one (**8**).* Green solid; yield: 95%; mp 235–238 °C; R_f (40% EtOAc/hexane) 0.35; ^1H NMR (300 MHz, $CDCl_3$): δ=2.57 (s, 3H), 7.10 (s, 1H), 7.52 (d, J=6.6 Hz, 3H), 7.60–7.75 (m, 4H), 8.03 (d, J=8.7 Hz, 1H), 8.82 (s, 1H, D_2O exchangeable), 9.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.6, 103.4, 119.5, 125.8, 126.1, 127.3, 127.8, 128.4, 129.5, 130.2, 135.3, 137.4, 140.1, 143.3, 146.7, 147.2, 157.9. Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78%. Found: C, 79.65; H, 4.90; N, 9.76%.

4.5. Procedure for synthesis 1-chloro-benzo[*b*][1,6]naphthyridine (9)

To a solution of **8** (1 mmol) was added $POCl_3$ (1 mL/mmol) and refluxed. After completion of the reaction, monitored by TLC, the reaction mixture was poured into ice-cold water, solid product was filtered and washed with water (3–5 mL) and dried. The crude product was purified by column chromatography using EtOAc/hexane as eluent to yield pure product as **9**.

*4.5.1. 1-Chloro-benzo[b][1,6]naphthyridine (**9**).* Orange solid; yield: 85%; mp 150–152 °C; R_f (15% EtOAc/hexane) 0.54; ^1H NMR (300 MHz, $CDCl_3$): δ=2.67 (s, 3H), 7.53–7.56 (m, 4H), 7.95–8.00 (m, 2H), 8.29 (d, J=6.6 Hz, 2H), 8.61 (s, 1H), 9.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.7, 110.7, 114.0, 126.8, 127.3, 128.6, 129.8, 132.3, 133.2, 135.1, 135.7, 138.8, 145.6, 146.0, 148.0, 160.3, 164.0. Anal. Calcd for $C_{19}H_{13}ClN_2$: C, 74.88; H, 4.30; N, 9.19%. Found: C, 74.80; H, 4.29; N, 9.16%.

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References and notes

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17. Crystal data for **5ab**: empirical formula, $C_{20}H_{15}NO_2$; formula weight, 301.33; crystal color, habit: colorless, block; crystal system, monoclinic; lattice parameters, *a* 6.794 (5) *b* 7.085 (5) *c* 16.309 (5) Á; *V* 750.1 (8) Á^3; space group *P*–1; Z 2; D_{calcd} 1.334 g/cm^3; F_{000} 316.0; residuals *R* 0.065; *Rw* 0.1714. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 912985. Copies of the data can be obtained free of charge on an application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +441223336033 or e-mail: deposit@ccdc.cam.ac.uk].