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Copper-free Sonogashira coupling of 2-chloroquinolines with phenyl acetylene and quick annulation to benzo[*b*][1,6]naphthyridine derivatives in aqueous ammonia

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ABSTRACT

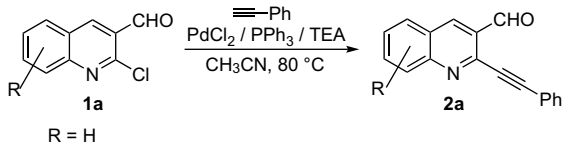
An efficient copper-free Sonogashira coupling of 2-chloroquinolines with phenyl acetylene to 2-ethynylquinolines is described. We further discussed the one pot facile annulation of 2-alkynylquinoline-3-carboxaldehydes to 3-phenylbenzo[*b*][1,6]naphthyridines in aqueous ammonia in excellent yield.

1. Introduction

Among the variety of transition-metal catalyzed coupling reactions, Sonogashira coupling reaction of aryl halides with terminal acetylene, provides an effective route for C–C bond formation, has become useful method for the preparation of arylalkynes and conjugated enynes,[1] and has been widely applied as a key step in natural product synthesis and molecular organic materials.[2,3] Initially, the most common catalytic system for the Sonogashira reaction was palladium–phosphine complexes with CuI as the co-catalyst in excess of amines.[1a–c,4] In recent years significant progress has been made in this reaction and an efficient copper-free catalyst systems has been developed, which avoided the homo-coupling.[4f,5] However, the copper-free Sonogashira reaction has been intensively investigated with aryl/heteroaryl iodide and bromide derivatives[6] and only few examples with aryl chloride are known.[4d,7] Recently, Plenio and co-workers have reported the copper-free coupling reaction of pyridyl chlorides with terminal alkynes in aqueous/organic solvents, but it required bulky phenylphosphine ligand.[8] The 3-cyano-/3-formyl-2-chloroquinolines, easily accessible precursors are in our hand in connection with the studies of new routes for the synthesis of carbo-/hetero-annulatedquinolines.[9] Recently, we have reported the synthesis of cyclopenta-/pyrano-annulatedquinolines via intramolecular cyclization of olefinic bond from their 3-homoallylalcohol analogues.[10] We further anticipated that their 2-alkynyl analogues could also serve as other new route towards annulations. Therefore, with this view our effort is to develop the condition of Sonogashira coupling for the synthesis of 2-alkynylquinolines from 2-chloroquinolines. Thus, in this paper we describe copper-free, palladium-catalyst for the Sonogashira coupling of 3-cyano/formyl-2-quinolinyl chlorides with phenyl acetylene under mild condition.

2. Results and discussion

Initially, we chose 2-chloroquinoline-3-carboxaldehyde (**1a**) with phenyl acetylene as model reaction to investigate the copper-free Sonogashira reaction and optimization of the reaction conditions. Thus, the reaction of **1a** (0.25 mmol) with phenyl acetylene (0.26 mmol) was carried out in the presence of $PdCl_2$ (4 mol %), triphenylphosphine (8 mol %) and triethylamine (2 equiv) in CH_3CN as a solvent at 80 °C under an inert atmosphere for 4 h, the isolated product was characterized as 2-alkynylquinoline-3-carboxaldehyde (**2a**) in 87% yield (Scheme 1, Table 2, entry 1).



Scheme 1.

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Table 1
Optimization of reaction conditions on Sonogashira coupling

Entry	Catalyst	Base	Solvent	Ligand	Time (h)	Yield (%)
1	$PdCl_2$	Et_3N	CH_3CN	PPh_3	4	87
2	$Pd(OAc)_2$	Et_3N	CH_3CN	PPh_3	5	78
3	$PdCl_2$	K_2CO_3	CH_3CN	PPh_3	12	45
4	$PdCl_2$	DABCO	CH_3CN	PPh_3	8	52
5	$PdCl_2$	Cs_2CO_3	CH_3CN	PPh_3	—	Trace
6	$PdCl_2$	Et_3N	CH_3CN	Bu_4NBr	2	77
7	$PdCl_2$/CuI	Et_3N	DMF	PPh_3	15	70

Next, we turned our attention towards the effect of various parameters on the copper-free Sonogashira coupling reaction. The results are reported in Table 1. It was found that amongst four bases such as Et_3N, Cs_2CO_3, K_2CO_3 and DABCO tested, Et_3N was the best (Table 1, entries 1–5). However, Bu_4NBr was found fast in accomplishing the reaction, but yield was poor (Table 1, entry 6). As can be seen from Table 1, $PdCl_2/PPh_3$/TEA was found most effective catalyst for the aforesaid reaction as shorter reaction time and better yield of product (Table 1, entry 1). It is noteworthy that the same coupling reaction was also tried with CuI in longer time with moderate yield of the desired product (Table 1, entry 7).

Table 2
Copper-free Sonogashira reaction of heteroaryl chloride with phenyl acetylene

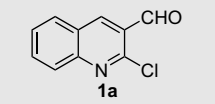
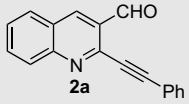
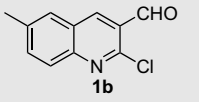
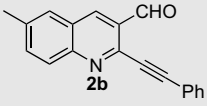
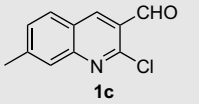
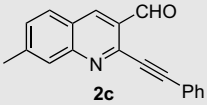
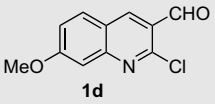
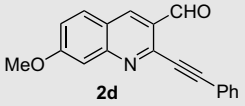
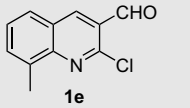
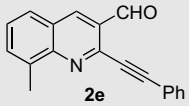
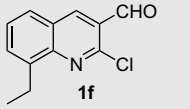
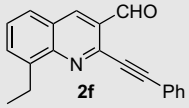
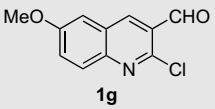
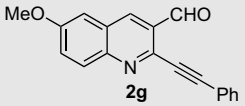
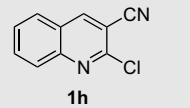
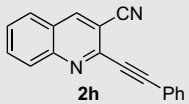
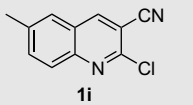
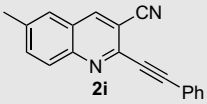
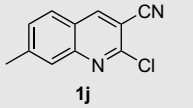
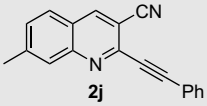
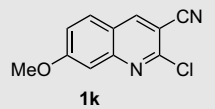
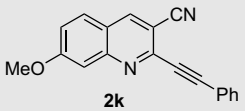
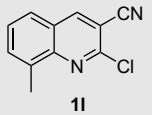
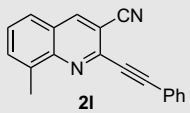
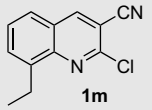
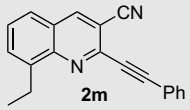
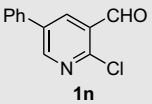
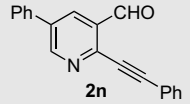
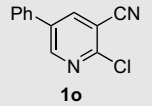
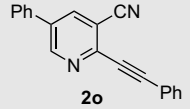
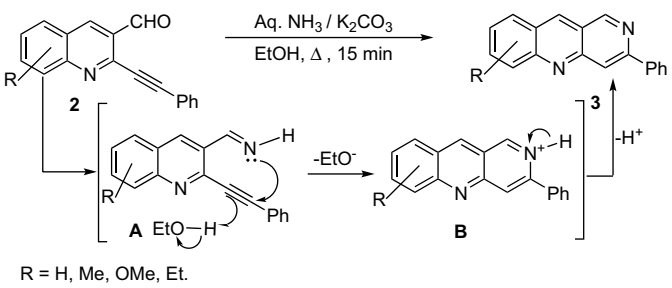
Entry	Substrate	Product	Time (h)	Yield (%)
1	 **1a**	 **2a**	4	87
2	 **1b**	 **2b**	3.5	85
3	 **1c**	 **2c**	3	85
4	 **1d**	 **2d**	3	88
5	 **1e**	 **2e**	4	80
6	 **1f**	 **2f**	4	78
7	 **1g**	 **2g**	3.5	83
8	 **1h**	 **2h**	2	88
9	 **1i**	 **2i**	2	80
10	 **1j**	 **2j**	3.5	82
11	 **1k**	 **2k**	4	84

Table 2 (*continued*)

Entry	Substrate	Product	Time (h)	Yield (%)
12	 **1l**	 **2l**	4	76
13	 **1m**	 **2m**	3	83
14	 **1n**	 **2n**	6	89
15	 **1o**	 **2o**	1.5	92

After optimizing the reaction conditions, we applied the reaction on a series of heteroaryl chlorides (**1a**–**o**), which afforded the corresponding products **2a**–**o**, respectively, in a good yield (Table 2).

Annulation processes have proven powerful methodology for the synthesis of complicated heterocycles. In recent years, synthesis of pyridine-annulated ring system intensively investigated from β-chloroacrolein moiety involving condensation with *N*-*t*-butylamine followed by palladium-catalyzed cyclization with internal alkynes,[11] as well as three-step sequences involving the Sonogashira coupling of terminal alkynes and subsequent condensation to aldimines followed by annulation in the presence of either electrophile or transition metals have been developed.[12] Similarly, analogous synthesis has been reported for naphthyridines but annulation occurred with alcoholic ammonia in a sealed tube.[13] This encouraged us to examine the similar reactions on our substrates **2a**–**g**. In contrast to expensive and foul smelling amines, anhydrous solvents, inert conditions and catalysts, we were delighted to observe that the analogous annulation reaction of substrates **2a**–**g** was occurred, in the absence of catalyst, with aqueous ammonia within 15 min. Thus, the reaction of 2-alkynylquinoline-3-carboxaldehyde (**2a**) (0.5 mmol) and K_2CO_3 (0.75 mmol) in ethanol is refluxed with excess amount of aqueous ammonia. The product was isolated in excellent yield and characterized as 3-phenylbenzo[*b*][1,6]-naphthyridine (**3a**) from spectral data (Scheme 2).



Scheme 2.

Table 3
Representative base mediated annulation of 2-alkynecarbaldehydes

Entry	Alkyne aldehyde	R	Product	Yield (%)
1	**2a**	H	**3a**	89
2	**2b**	6-Me	**3b**	88
3	**2c**	7-Me	**3c**	86
4	**2d**	7-OMe	**3d**	81
5	**2e**	8-Me	**3e**	91
6	**2f**	8-Et	**3f**	93

Table 4
Representative base mediated annulation of oxime

Entry	Oxime	R	Product	Yield (%)
1	**4a**	H	**5a**	91
2	**4b**	6-Me	**5b**	94
3	**4c**	7-Me	**5c**	90
4	**4d**	7-OMe	**5d**	89
5	**4e**	8-Me	**5e**	94
6	**4f**	8-Et	**5f**	96

Thus, after optimizing the reaction conditions of annulation on **2a**, the reaction with other substrates **2a**–**f** afforded corresponding benzo[*b*][1,6]naphthyridines (**3a**–**f**) in excellent yield (Table 3).

Further, the cyclization reaction was attempted with 3-cyanoquinoline derivatives with the view to synthesize 1-amino-3-phenylbenzonaphthyridine. Thus, when 3-cyanoquinoline derivative (**2h**) was treated with aqueous ammonia under similar reaction condition and also by adding more ammonia solution and increasing temperature ranging from 80 to 120 °C, the corresponding desired product could not be isolated at all, starting cyanoquinoline was being recovered. From this observation we speculate that the aldimine **A** initially formed from **2** would be, of short lived, immediately cyclized to naphthyridine derivatives **3** (Scheme 2).

The cyclization reaction was further investigated with their corresponding oximes **4a**–**f** under identical reaction conditions with a view that the base would activate the nucleophilicity of aldoxime nitrogen atom via generating *N*-oxide anion of aldoxime, which accelerate the cyclization to the desired products **5a**–**f**. Thus, when oximes **4a**–**f** (0.5 mmol), prepared by conventional procedure, were refluxed with K_2CO_3 and excess of aqueous ammonia in ethanol, reactions were completed in 5 min and products were characterized as benzo[*b*][1,6]naphthyridine-2-oxides (**5a**–**f**) in excellent yields, which support our speculation (Scheme 3, Table 4).

3. Conclusions

In summary, we optimized copper-free Sonogashira coupling on less explored chlorine of 2-chloroquinoline and 2-chloropyridine derivatives with phenyl acetylene and described their annulations to desired benzo[*b*][1,6]naphthyridines was even more facile in aqueous ammonia. This class of compounds also exhibited, beside biological activity,[14,15] photophysical and photochemical behaviours.[16] Further, the resulting Sonogashira coupling products, 2-ethynequinolines, could be used as key intermediate in area of synthetic organic chemistry.

4. Experimental section

4.1. General

Melting points are measured using Buchi Melting-point apparatus in an open capillary tubes 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 ppm) and coupling constants (Hz) 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). Mass spectra were recorded from SAIF, CDRI, Lucknow and SAIF, Panjab University, Chandigadh. High-resolution mass spectra were recorded using Micromass Q-TOF micro mass spectrometer equipped with a Harvard syringe pump apparatus using electron spray ionization mode at the SAIF, IIT Madras, Chennai. Elemental analyses were carried out using EXTER, CE-440 elemental analyzer at the Department of Chemistry, Faculty of Science, Banaras Hindu University, 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 Copper-free Sonogashira coupling

A mixture of heteroaryl chloride **1** (0.25 mmol), phenyl acetylene (0.26 mmol), $PdCl_2$ (4 mol %), PPh_3 (8 mol %), CH_3CN (4 mL) and TEA (0.5 mmol) was stirred under N_2 at 80 °C for time ranging between 1.5 and 6 h (as monitored by TLC). The reaction mixture was concentrated in vacuo and residue was purified by column chromatography on silica gel using EtOAc/hexane as eluent in different polarity.

*4.2.1. 2-Phenylethynyl-quinoline-3-carbaldehyde (**2a**)*

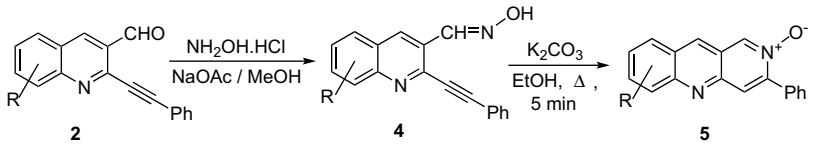
White solid; yield: 87%; mp 118 °C; R_f (11% EtOAc–hexane) 0.54; IR (KBr): 2208, 1693 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (3H, m), 7.62–7.72 (3H, m), 7.88 (1H, t, *J* 7.5 Hz), 7.98 (1H, d, *J* 8.1 Hz), 8.20 (1H, d, *J* 5.7 Hz), 8.76 (1H, s), 10.81 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 85.6, 95.5, 121.4, 126.4, 128.2, 128.6, 128.9, 129.4, 129.7, 129.9, 132.3, 133.0, 137.2, 147.9, 150.2, 190.8. Anal. Calcd for $C_{18}H_{11}NO$: C, 84.03; H, 4.31; N, 5.44. Found: C, 83.37; H, 4.43; N, 5.23.

*4.2.2. 6-Methyl-2-phenylethynyl-quinoline-3-carbaldehyde (**2b**)*

White solid; yield: 85%; mp 132 °C; R_f (11% EtOAc–hexane) 0.61; IR (KBr): 2210, 1691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (3H, s), 7.43 (3H, m), 7.70 (4H, m), 8.08 (1H, d, *J* 8.4 Hz), 8.67 (1H, s), 10.80 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 85.6, 95.0, 121.4, 126.4, 128.2, 128.5, 128.8, 128.9, 129.7, 132.2, 135.4, 136.2, 138.5, 143.0, 148.8, 190.8. Anal. Calcd for $C_{19}H_{13}NO$: C, 84.11; H, 4.83; N, 5.16. Found: C, 83.65; H, 4.98; N, 5.39.

*4.2.3. 7-Methyl-2-phenylethynyl-quinoline-3-carbaldehyde (**2c**)*

Colourless needle; yield: 85%; mp 125 °C; R_f (11% EtOAc–hexane) 0.39; IR (KBr): 2208, 1689 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$):



R = H, Me, OMe, Et.

Scheme 3.

δ 2.62 (3H, s), 7.45 (4H, m), 7.78 (2H, m), 7.83 (1H, d, *J* 9.0 Hz), 8.01 (1H, s), 8.81 (1H, s), 10.82 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3, 85.7, 95.4, 121.5, 124.6, 128.3, 128.4, 128.6, 129.3, 129.8, 130.6, 132.3, 136.7, 144.0, 144.3, 150.4, 190.8; MS: *m*/*z*=272 $(M+H)^+$. HRMS Calcd for $C_{19}H_{14}NO$ $[M+H]^+$ 272.1075; found 272.1082.

*4.2.4. 7-Methoxy-2-phenylethynyl-quinoline-3-carbaldehyde (**2d**)*

White solid; yield: 88%; mp 195 °C; R_f (11% EtOAc–hexane) 0.40; IR (KBr): 2212, 1687 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99 (3H, s), 7.29 (1H, s), 7.41–7.49 (4H, m), 7.69 (2H, m), 7.85 (1H, d, *J* 9.0 Hz), 8.66 (1H, s), 10.76 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8, 85.6, 95.3, 107.1, 121.4, 121.8, 127.3, 128.5, 129.7, 130.7, 132.3, 132.7, 136.4, 144.5, 152.3, 163.7, 190.6. Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.87. Found: C, 79.98; H, 4.41; N, 4.95.

*4.2.5. 8-Methyl-2-phenylethynyl-quinoline-3-carbaldehyde (**2e**)*

Light yellow crystal; yield: 80%; mp 148–150 °C; R_f (11% EtOAc–hexane) 0.54; IR (KBr): 2208, 1689 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.87 (3H, s), 7.42–7.54 (4H, m), 7.72 (3H, m), 7.80 (1H, d, *J* 8.1 Hz), 8.71 (1H, s), 10.82 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.0, 86.0, 94.8, 121.5, 126.4, 127.5, 127.9, 128.5, 129.6, 132.2, 132.4, 133.0, 137.0, 137.5, 142.6, 149.2, 191.1. Anal. Calcd for $C_{19}H_{13}NO$: C, 84.11; H, 4.83; N, 5.16. Found: C, 83.67; H, 5.00; N, 5.31.

*4.2.6. 8-Ethyl-2-phenylethynyl-quinoline-3-carbaldehyde (**2f**)*

Colourless solid; yield: 78%; mp 88 °C; R_f (5% EtOAc–hexane) 0.43; IR (KBr): 2205, 1688 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (3H, t, *J* 7.5 Hz), 3.90 (2H, q, *J* 7.5 Hz), 7.44 (3H, m), 7.56 (1H, t, *J* 7.8 Hz), 7.71 (3H, m), 7.80 (1H, d, *J* 7.8 Hz), 8.71 (1H, s), 10.82 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 24.2, 86.2, 94.6, 125.6, 126.5, 127.5, 128.1, 128.5, 128.6, 128.9, 129.6, 131.3, 132.2, 137.2, 142.7, 143.4, 191.2. Anal. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91. Found: C, 83.75; H, 5.49; N, 4.73.

*4.2.7. 6-Methoxy-2-phenylethynyl-quinoline-3-carbaldehyde (**2g**)*

Light yellow solid; yield: 83%; mp 154 °C; R_f (11% EtOAc–hexane) 0.40; IR (KBr): 2206, 1693 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (3H, s), 7.18 (1H, d, *J* 2.7 Hz), 7.42–7.53 (4H, m), 7.67–7.70 (2H, m), 8.05 (1H, d, *J* 9.3 Hz), 8.63 (1H, s), 10.79 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8, 85.5, 94.7, 106.2, 121.5, 126.3, 127.7, 128.5, 129.0, 129.6, 130.7, 132.2, 135.3, 141.4, 146.6, 159.0, 191.0. Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.87. Found: C, 79.08; H, 4.25; N, 4.96.

*4.2.8. 2-Phenylethynyl-quinoline-3-carbonitrile (**2h**)*

Colourless needle; yield: 88%; mp 165–166 °C; R_f (11% EtOAc–hexane) 0.47; IR (KBr): 2215, 2106 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (3H, m), 7.68–7.90 (5H, m), 8.16 (1H, d, *J* 8.1 Hz), 8.56 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 86.2, 95.6, 109.7, 116.4, 121.1, 125.0, 128.0, 128.5, 129.6, 130.0, 132.6, 133.2, 135.0, 142.0, 142.9, 148.6; MS: *m*/*z*=255 $(M+H)^+$. HRMS Calcd for $C_{18}H_{11}N_2$ $[M+H]^+$ 255.0922; found 255.0919.

*4.2.9. 6-Methyl-2-phenylethynyl-quinoline-3-carbonitrile (**2i**)*

White solid; yield: 80%; mp 118–119 °C; R_f (11% EtOAc–hexane) 0.53; IR (KBr): 2212 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (3H, s), 7.41 (3H, m), 7.63 (1H, s), 7.70–7.76 (3H, m), 8.05 (1H, d, *J* 8.4 Hz), 8.45 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 86.3, 95.1, 109.6, 116.5, 121.2, 125.0, 126.7, 128.5, 129.2, 129.9, 132.6, 135.4, 139.2, 141.2, 142.0, 147.3; MS: *m*/*z*=269 $(M+H)^+$. HRMS Calcd for $C_{19}H_{13}N_2$ $[M+H]^+$ 269.1079; found 269.1076.

*4.2.10. 7-Methyl-2-phenylethynyl-quinoline-3-carbonitrile (**2j**)*

Light yellow crystal; yield: 82%; mp 88 °C; R_f (11% EtOAc–hexane) 0.53; IR (KBr): 2217 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.61 (3H, s), 7.41–7.51 (4H, m), 7.75 (3H, m), 7.94 (1H, s), 8.49 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3, 86.4, 95.4, 108.8, 116.7, 121.2, 123.2, 127.6, 128.5, 128.6, 130.0, 131.0, 132.7, 141.6, 143.0, 144.4. 148.9. Anal. Calcd for $C_{19}H_{12}N_2$: C, 85.05; H, 4.51; N, 10.44. Found: C, 84.41; H, 4.82; N, 10.28.

*4.2.11. 7-Methoxy-2-phenylethynyl-quinoline-3-carbonitrile (**2k**)*

White solid; yield: 84%; mp 122 °C; R_f (11% EtOAc–hexane) 0.38; IR (KBr): 2218 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99 (3H, s), 7.40–7.46 (4H, m), 7.73 (4H, m), 8.42 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8, 86.3, 95.3, 107.2, 107.4, 116.7, 120.4, 121.2, 122.1, 128.5, 129.0, 129.9, 132.6, 141.1, 143.5, 150.8, 163.6. Anal. Calcd for $C_{19}H_{12}N_2O$: C, 80.27; H, 4.25; N, 9.85. Found: C, 79.65; H, 4.16; N, 9.63.

*4.2.12. 8-Methyl-2-phenylethynyl-quinoline-3-carbonitrile (**2l**)*

Light yellow crystal; yield: 76%; mp 93 °C; R_f (5% EtOAc–hexane) 0.38; IR (KBr): 2211 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (3H, s), 7.41 (3H, m), 7.55 (1H, t, *J* 7.8 Hz), 7.68–7.77 (4H, m), 8.49 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9, 86.8, 95.0, 109.5, 116.7, 121.4, 125.0, 125.9, 128.4, 128.5, 129.8, 132.6, 133.2, 137.9, 141.7, 142.1, 147.7. Anal. Calcd for $C_{19}H_{12}N_2$: C, 85.05; H, 4.51; N, 10.44. Found: C, 84.63; H, 4.32; N, 10.54.

*4.2.13. 8-Ethyl-2-phenylethynyl-quinoline-3-carbonitrile (**2m**)*

Colourless solid; yield: 83%; mp 85 °C; R_f (5% EtOAc–hexane) 0.40; IR (KBr): 2223 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (3H, t, *J* 7.5 Hz), 1.34 (2H, q, *J* 7.5 Hz), 7.42 (3H, m), 7.59 (1H, t, *J* 7.2 Hz), 7.68–7.77 (4H, m), 8.50 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 24.1, 86.8, 94.7, 109.4, 116.7, 121.4, 125.0, 125.7, 128.4, 128.5, 129.8, 131.5, 132.6, 141.6, 142.1, 143.6, 147.1. Anal. Calcd for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92. Found: C, 84.70; H, 5.12; N, 9.83.

*4.2.14. 5-Phenyl-2-phenylethynyl-pyridine-3-carbaldehyde (**2n**)*

Colourless solid; yield: 89%; mp 91 °C; R_f (7% EtOAc–hexane) 0.43; IR (KBr): 2209, 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.69 (10H, m), 8.41 (1H, s), 9.07 (1H, s), 10.73 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 84.8, 96.5, 121.4, 127.1, 128.6, 129.0, 129.4, 129.8, 131.6, 132.2, 132.5, 135.9, 136.2, 144.5, 152.8, 190.9. Anal. Calcd for $C_{20}H_{13}NO$: C, 84.78; H, 4.62; N, 4.94. Found: C, 84.31; H, 4.74; N, 5.16.

*4.2.15. 5-Phenyl-2-phenylethynyl-pyridine-3-carbonitrile (**2o**)*

White solid; yield: 92%; mp 121 °C; R_f (7% EtOAc–hexane) 0.42; IR (KBr): 2213 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.61 (8H, m), 7.70 (2H, m), 8.14 (1H, s), 9.00 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 85.7, 96.6, 112.9, 116.1, 121.1, 127.0, 128.5, 129.4, 129.5, 130.0, 132.5, 135.0, 135.3, 137.7, 144.2, 151.3. Anal. Calcd for $C_{20}H_{12}N_2$: C, 85.69; H, 4.31; N, 9.99. Found: C, 85.78; H, 4.45; N, 9.72.

4.3. Transformation of aldehydes (2a–f) to benzo[*b*]-[1,6]naphthyridines (3a–f)

To a solution of **2** (0.5 mmol) in EtOH (7 mL) were added K_2CO_3 (0.75 mmol) and saturated with aq NH_3. The reaction mixture was stirred at refluxed temperature. The reaction completed after 15 min (as monitored by TLC). The reaction mixture allowed to pour in chilled water (7 mL) and precipitate filtered out and dried.

*4.3.1. 3-Phenylbenzo[b][1,6]naphthyridine (**3a**)*

Light green solid; yield: 89%; mp 172 °C; R_f (20% EtOAc–hexane) 0.49; IR (KBr): 3052, 1613, 1441 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.63 (4H, m), 7.90 (1H, t, *J* 7.2 Hz), 8.02 (1H, d, *J* 8.4 Hz), 8.24 (3H, m), 8.45 (1H, s), 8.98 (1H, s), 9.61 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 116.6, 121.1, 126.3, 127.0, 127.2, 128.9, 129.0, 129.2, 129.4, 132.6, 137.2, 138.8, 150.4, 152.1, 153.8, 154.7; MS: *m*/*z*=257 $(M+H)^+$. Anal. Calcd for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93. Found: C, 84.71; H, 4.49; N, 10.74.

*4.3.2. 8-Methyl-3-phenylbenzo[b][1,6]naphthyridine (**3b**)*

Light green solid; yield: 88%; mp 112 °C; R_f (11% EtOAc–hexane) 0.33; IR (KBr): 2922, 1618, 1404 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.61 (3H, s), 7.45–7.54 (3H, m), 7.75 (1H, d, *J* 9.0 Hz), 7.82 (1H, s), 8.15 (1H, d, *J* 9.0 Hz), 8.41 (2H, m), 8.42 (1H, s), 8.84 (1H, s), 9.58 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 116.6, 121.2, 126.9, 127.1, 128.8, 128.9, 129.0, 135.5, 135.9, 136.3, 138.9, 149.8, 150.9, 151.0, 153.4, 154.5; MS: *m*/*z*=271 $(M+H)^+$. Anal. Calcd for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.08; H, 5.13; N, 10.17.

*4.3.3. 7-Methyl-3-phenylbenzo[b][1,6]naphthyridine (**3c**)*

Light green solid; yield: 86%; mp 197 °C; R_f (20% EtOAc–hexane) 0.52; IR (KBr): 2923, 1605, 1436 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.65 (3H, s), 7.43–7.57 (4H, m), 7.99 (2H, m), 8.25 (2H, m), 8.42 (1H, s), 8.90 (1H, s), 9.56 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.5, 116.6, 120.9, 125.5, 127.2, 127.7, 128.6, 128.9, 129.1, 129.2, 136.8, 139.0, 143.6, 150.5, 152.4, 153.8, 154.6. Anal. Calcd for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.03; H, 5.39; N, 10.15.

*4.3.4. 7-Methoxy-3-phenylbenzo[b][1,6]naphthyridine (**3d**)*

Light green solid; yield: 88%; mp 220 °C; R_f (25% EtOAc–hexane) 0.48; IR (KBr): 2925, 1614, 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.04 (3H, s), 7.45–7.60 (5H, m), 7.92 (1H, d, *J* 9.3 Hz), 8.24 (2H, m), 8.36 (1H, s), 8.83 (1H, s), 9.52 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8, 105.1, 116.2, 120.2, 121.9, 123.4, 127.2, 128.9, 129.0, 130.1, 136.6, 139.0, 150.7, 154.0, 154.1, 154.3, 163.3. Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.48; H, 5.15; N, 9.53.

*4.3.5. 6-Methyl-3-phenylbenzo[b][1,6]naphthyridine (**3e**)*

Light green solid; yield: 91%; mp 201 °C; R_f (11% EtOAc–hexane) 0.53; IR (KBr): 2922, 1614, 1443 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.96 (3H, s), 7.45–7.55 (4H, m), 7.72 (1H, d, *J* 7.5 Hz), 7.92 (1H, d, *J* 8.1 Hz), 8.26 (2H, m), 8.50 (1H, s), 8.91 (1H, s), 9.59 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5, 117.3, 121.0, 126.2, 127.0, 127.1, 127.2, 128.9, 129.0, 131.7, 137.0, 137.4, 139.1, 149.7, 151.7, 153.5, 154.5. Anal. Calcd for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 83.95; H, 5.39; N, 10.51.

*4.3.6. 6-Ethyl-3-phenylbenzo[b][1,6]naphthyridine (**3f**)*

Light green solid; yield: 93%; mp 130 °C; R_f (11% EtOAc–hexane) 0.60; IR (KBr): 1610, 1430 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (3H, t), 3.48 (2H, q, *J* 7.5 Hz), 7.45–7.55 (4H, m), 7.72 (1H, d, *J* 6.3 Hz), 7.92 (1H, d, *J* 8.4 Hz), 8.26 (2H, m), 8.48 (1H, s), 8.91 (1H, s), 9.58 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 24.7, 117.4, 121.0, 126.3, 126.9, 127.1, 127.2, 128.8, 129.0, 129.9, 137.0, 139.1, 143.1, 149.7, 151.0, 153.4, 154.5; MS: *m*/*z*=285 $(M+H)^+$. Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 83.75; H, 5.46; N, 9.73.

4.4. Transformation of aldehydes (2a–f) to corresponding oximes (4a–f)

To a solution of **2a–f** (1 mmol) in methanol (5 mL) were added sodium acetate (1.5 mmol) and hydroxylamine hydrochloride (1.2 mmol), the solution allowed to stirred for 5 min, a white precipitate observed. After vacuum evaporation of solvent, reaction mixture poured in water (10 mL), and filtered out. These oximes were pure enough for further use.

4.5. Transformation of oximes (4a–f) to benzo[*b*][1,6]-naphthyridines-2-oxide analogues (5a–f)

To a solution of **4** (0.5 mmol) in EtOH (7 mL) was added K_2CO_3 (0.75 mmol) and the solution was stirred at reflux temperature. The reaction completed after 5 min (as monitored by TLC/green solution appeared). The reaction mixture allowed to pour in chilled water (7 mL) and precipitate filtered out and dried.

*4.5.1. 3-Phenylbenzo[b][1,6]naphthyridine-2-oxide (**5a**)*

Light yellow solid; yield: 91%; mp 175 °C; R_f (60% EtOAc–hexane) 0.36; IR (KBr): 3054, 1620, 1434, 1284, 1189 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53–7.62 (4H, m), 7.87–8.02 (4H, m), 8.17 (2H, m), 8.62 (1H, s), 9.06 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.2, 125.7, 127.6, 127.7, 128.2, 128.3, 129.6, 129.8, 129.9, 131.9, 132.1, 132.2, 136.0, 144.0, 150.3, 150.9; MS: *m*/*z*=273 $(M+H)^+$. Anal. Calcd for $C_{18}H_{12}N_2O$: C, 79.40; H, 4.44; N, 10.29. Found: C, 79.18; H, 4.32; N, 10.55.

*4.5.2. 8-Methyl-3-benzo[b][1,6]naphthyridine-2-oxide (**5b**)*

Light yellow solid; yield: 94%; mp 190 °C; R_f (60% EtOAc–hexane) 0.39; IR (KBr): 2922, 1630, 1414, 1284, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.60 (3H, s), 7.52 (3H, m), 7.67–7.80 (4H, m), 8.07 (1H, d, *J* 8.4 Hz), 8.14 (1H, s), 8.50 (1H, s), 9.03 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8, 122.3, 125.7, 126.4, 127.8, 128.1, 129.3, 129.7, 129.8, 130.8, 132.3, 134.8, 136.0, 137.8, 143.5, 149.3, 150.5; MS: *m*/*z*=287 $(M+H)^+$. Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.93; H, 5.16; N, 9.52.

*4.5.3. 7-Methyl-3-phenylbenzo[b][1,6]naphthyridine-2-oxide (**5c**)*

Light yellow solid; yield: 90%; mp 185 °C; R_f (60% EtOAc–hexane) 0.36; IR (KBr): 2922, 1625, 1447, 1277, 1191 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.63 (3H, s), 7.51 (4H, m), 7.88–7.95 (4H, m), 8.13 (1H, s), 8.56 (1H, s), 9.03 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4, 121.8, 125.6, 126.1, 127.9, 128.0, 128.2, 129.8, 130.5, 131.7, 132.3, 136.1, 142.9, 144.1, 146.8, 150.6, 150.7. Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.39; H, 5.16; N, 9.65.

*4.5.4. 7-Methoxy-3-phenylbenzo[b][1,6]naphthyridine-2-oxide (**5d**)*

Light yellow solid; yield: 89%; mp 188 °C; R_f (60% EtOAc–hexane) 0.41; IR (KBr): 2922, 1619, 1459, 1251, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.03 (3H, s), 7.40 (1H, s), 7.52 (4H, m), 7.85 (3H, m), 8.08 (1H, s), 8.51 (1H, s), 9.02 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8, 105.4, 121.0, 123.1, 124.1, 125.1, 128.2, 129.5, 129.8, 129.9, 131.9, 132.4, 136.4, 144.3, 150.8, 152.4, 162.8; MS: *m*/*z*=303 $(M+H)^+$. Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 74.87; H, 4.51; N, 9.45.

*4.5.5. 6-Methyl-3-phenylbenzo[b][1,6]naphthyridine-2-oxide (**5e**)*

Light yellow solid; yield: 94%; mp 119 °C; R_f (60% EtOAc–hexane) 0.62; IR (KBr): 2921, 1625, 1437, 1286, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.89 (3H, s), 7.51 (4H, m), 7.66 (1H, d, *J* 6.6 Hz), 7.86 (3H, m), 8.22 (1H, s), 8.57 (1H, s), 9.05 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.2, 121.8, 126.3, 127.4, 127.7, 128.2, 129.2, 129.7, 131.2, 132.2, 132.3, 132.4, 136.1, 137.6, 143.2, 149.8, 150.4. Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 80.11; H, 5.14; N, 9.71.

*4.5.6. 6-Ethyl-3-phenylbenzo[b][1,6]naphthyridine-2-oxide (**5f**)*

Light yellow solid; yield: 96%; mp 122 °C; R_f (60% EtOAc–hexane) 0.65; IR (KBr): 2962, 2926, 1436, 1283, 1184 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (3H, t, *J* 7.2 Hz), 3.40 (2H, q, *J* 7.2 Hz), 7.51–7.68 (5H, m), 7.82–7.86 (3H, m), 8.20 (1H, s), 8.57 (1H, s), 9.05 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 24.6, 121.8, 126.2, 126.4, 127.5, 127.8, 128.2, 129.5, 129.7, 129.8, 132.1, 132.4, 136.0, 143.2, 143.4, 149.2, 150.4; MS: *m*/*z*=301 $(M+H)^+$. Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.68; H, 5.21; N, 9.25.

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