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Base-free NIS promoted electrophilic cyclization of alkynes: an efficient synthesis of iodo substituted pyrano[4,3-*b*]quinolines

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ABSTRACT

A simple and mild procedure for the synthesis of iodo substituted 1*H*-pyrano[4,3-*b*]quinolines has been achieved using NIS reagent in the absence of base from 2-alkynylquinoline-3-carboxaldehydes via intramolecular electrophilic cyclization onto alkynes in good to excellent yields in a short duration of time. The reactions proceeded smoothly in a normal solvent in aerobic atmosphere at room temperature. The presence of substituent at either quinoline or alkyne moieties did not show effect on reaction rate of cyclization. The palladium-catalyzed transformations of iodo group to C–C bond are also discussed.

1. Introduction

Iodocyclization of functionally substituted alkynes has emerged as an important and efficient route for the preparation of a wide variety of carbocyclic and heterocyclic structures.[1] Recently, iodocyclization of alkyne with an aldehyde in *o*-alkynylbenzaldehydes has been explored providing either oxygen heterocycles in the form of the 1,3-disubstituted cyclic alkenyl ether moiety of isochromene[2] or carbocycles, such as the benzene moiety of naphthalene[3] (Fig. 1). The aromatic structure studied in these reactions was typically a benzene ring.

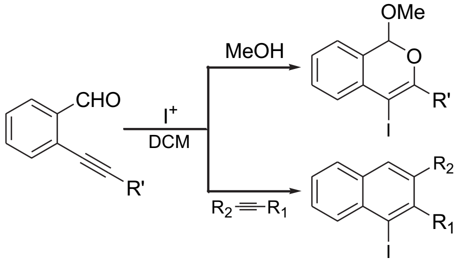

Fig. 1. Iodocyclization of *o*-alkynebenzaldehyde.

In contrast, *o*-alkynyl heterocyclic carboxaldehydes have been less studied, although it could be a facile route to pyrano/benzo annulated heterocycles. Recently, Barluenga et al. have reported iodocyclization of 3-alkynyl-2-carboxaldehyde derivatives of pyrrole, furan, and thiophene using IPy_2BF_4 and HBF_4 reagents and alkene nucleophiles in the synthesis of indole, benzofuran, benzothiophene, and alcohol nucleophiles in the synthesis of 7*H*-thieno [2,3-*c*]pyran.[4] Larock et al. have reported iodocyclization of 2-phenylethynylpyridine-3-carboxaldehydes to the synthesis of 5*H*-pyrano[4,3-*b*]pyridine using I_2/K_2CO_3 and methanol nucleophile.[2b] However, iodocyclization of 2-alkynylquinoline-3-carboxaldehydes **2** using alcohol nucleophiles has not been explored. Although silver and palladium-catalyzed cyclization of alkynylquinoline-3-carboxaldehydes have been reported to the synthesis of furo/pyrano annulated quinolines recently.[5,6] These chemical methods have certain limitations, such as availability of expensive metal catalysts, inert atmosphere, high temperature, and longer reaction time conditions. Hence, it is desirable to search an inexpensive reagent for the cyclization of 2-alkynylquinoline-3-carboxaldehydes to the synthesis of pyranoquinolines that can overcome some of the limitations associated with the existing methodologies. Recently, we have reported an intramolecular iodocyclization of alkene to the synthesis of pyranoquinolines.[7] This observation inspired us to investigate the scope of iodonium reagents for the intramolecular iodocyclization of alkynes of 2-alkynylquinoline-3-carboxaldehydes (**2**). We delighted to observe that NIS is found an effective iodonium reagent for an

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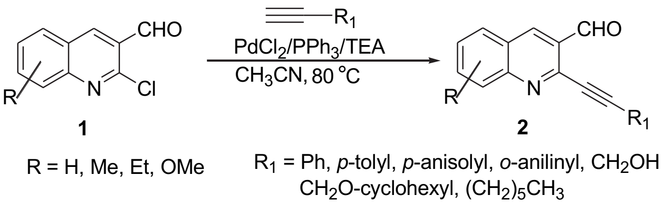
intramolecular cyclization of alkyne providing an alternative route to the synthesis of pyrano annulated quinolines. Herein, we report NIS as an effective reagent for the iodocyclization, providing synthesis of 1-alkoxy-4-iodopyrano[4,3-*b*]quinolines **3** without using base (Scheme 2). Reactions proceeded in mild conditions and very short time providing pyranoquinolines in good to excellent yields. The iodo group at position 4 could be further extended to C–C bond formation by Pd-catalyzed coupling reactions.

The pyranoquinoline moiety constitutes the basic skeleton of a number of alkaloids, such as flindersine, oricine, and verprisine. Derivatives of these alkaloids are widely used as pharmaceuticals and agrochemicals and possess a significant range of biological activity including anti-inflammatory, anti-allergic, psychotropic, and estrogenic effects.[8]

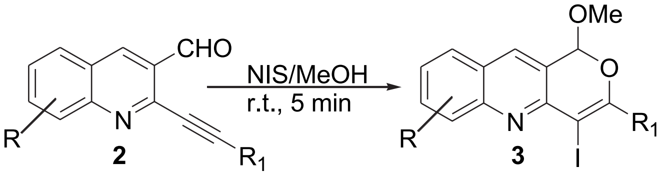
2. Results and discussion

The required 2-alkynylquinoline-3-carboxaldehydes (**2**) were prepared from 2-chloroquinoline-3-carboxaldehydes (**1**) and terminal alkynes under copper-free Sonogashira coupling conditions using our previously reported procedure[9] (Scheme 1).



Scheme 1. Synthesis of 2-alkynylquinoline-3-carboxaldehydes.

The iodocyclization of 6-methyl-2-phenylethynylquinoline-3-carboxaldehyde (**2b**) was examined in methanol using NIS reagent to optimize the reaction conditions for cyclization. We were delighted to observe that the reaction of 0.25 mmol of **2b** with 1.5 equiv of NIS in 4.0 mL methanol was completed at room temperature in 5 min, furnishing the desired cyclized product **3b** in excellent yield (93%, Scheme 2, Table 1, entry 1). Using 1.2 equiv of NIS required much longer reaction time and yield of the product **3b** was substantially dropped (entry 2). Further, increasing the amount of NIS did not improve the yield of **3b** (entries 3 and 4). It is noteworthy that no cyclized product was obtained when K_2CO_3 was added as base in reaction mixture (entry 5). Using Larock's conditions (**2b**, methanol as nucleophile, K_2CO_3 as base in DCM solvent) at room temperature in 5 min furnished the mixture of desired cyclized product **3b** and an ester (6-methyl-2-phenylethynyl-quinoline-3-carboxylic acid methyl ester)[10] **4** in 3:1 ratio (entry 6). Thus, based on above investigations 1.5 equiv of NIS in 4 mL methanol at room temperature in 5 min gave the best yield of the product.



Scheme 2. Synthesis of functionalized pyrano[4,3-*b*]quinolines.

Table 1
Optimization of the reaction conditions for cyclization of **2b**

Entry	Solvent	Electrophile (equiv)	Base (equiv)	Product	Time (min)	Yield of **3b** (%)
1	MeOH	NIS (1.5)	–	**3b**	5	93
2	MeOH	NIS (1.2)	–	**3b**	180	81
3	MeOH	NIS (2.0)	–	**3b**	5	92
4	MeOH	NIS (2.5)	–	**3b**	5	92
5	MeOH	NIS (1.5)	K_2CO_3(1.5)	**4**	5	–
6	DCM	NIS (1.5)	K_2CO_3(1.5)	**3b**+**4** (**3**:**1**)	5	55[a]

[a] MeOH (1.2 equiv) was used.

To further examine the generality of this cyclization, other commercially available electrophiles, such as I_2, Br_2, NBS, and ICl have also been examined in this process under similar reaction conditions. The results are summarized in Table 2. It is noteworthy that the use of I_2 electrophile with **2b** in methanol required overnight reaction time, a 3:2 mixture of acetal **5** and cyclized product **3b** was observed, respectively, from ^{1}H NMR spectroscopic analysis (Table 2, entry 3). While, NBS electrophile with **2b** for 1 h provided a 2.5:1 mixture of cyclized products **3s** (4-bromo-1-methoxy-8-methyl-3-phenyl-1*H*-pyrano[4,3-*b*]quinoline) and **6** (1-(4-bromo-8-methyl-3-phenyl-1*H*-pyrano[4,3-*b*]quinolin-1-yl)-pyrrolidine-2,5-dione) (entry 5), in which succinimidyl ring acts as a nucleophile, was observed by ^{1}H NMR and IR spectroscopic analysis. Undesired mixture was observed when bromine was employed for cyclization. However, ICl electrophile was as efficient as NIS (88%, entry 6).

To examine the generality of this strategy, carbon–carbon triple bond bearing different substituent, such as phenyl, substituted phenyl rings, and alkyl substituent of 2-alkynylquinoline-3-carboxaldehydes were allowed to react under our standard iodocyclization conditions using NIS and methanol to afford the corresponding pyranoquinolines in excellent yields (Table 2, entries 7–12). The presence of a phenyl group and electron donating group on the phenyl ring of the carbon–carbon triple bond enhances the rate of iodocyclization and the yield of the cyclized products (entries 7–9). However, the corresponding alkyl substituted alkynes also cyclized smoothly with slightly lower yield in longer time (entries 10–12).

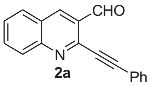
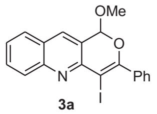
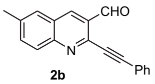
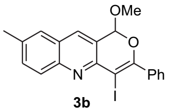
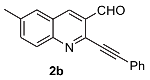
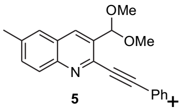
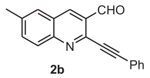
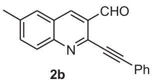
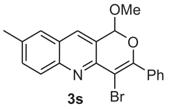
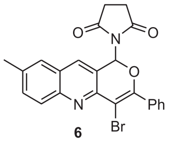
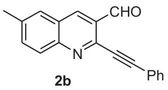
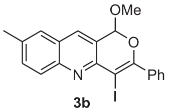
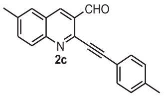
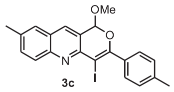
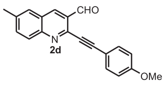
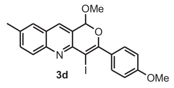
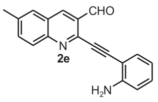
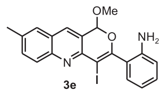
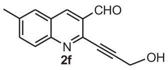
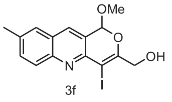
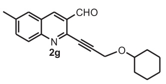
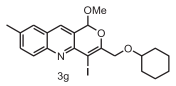
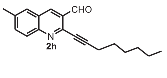
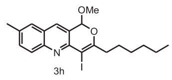
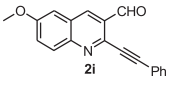
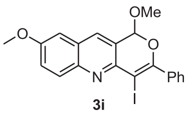
Further, different substituents on quinoline moiety of 2-phenylethynylquinolinyl-3-carboxaldehydes (**2i**–**m**) were allowed to react under our standard reaction conditions for iodocyclization. Reactions proceeded smoothly and provided corresponding pyranoquinolines (**3i**–**m**) in good to excellent yields (Table 2, entries 13–17). Electron donating substituent at position 6 in **2b** and **2i** slightly enhanced the yield of cyclized products corresponding to position 7 in **2j** and **2k**, respectively. Substituents at position 8 in **2l** and **2m** also lowered the yield of the products **3l** and **3m**. Pyridine carboxaldehyde **2n** has also been allowed to react under our standard cyclization condition using NIS and methanol. Cyclization reaction proceeded with the same rate and afforded the product **3n** in excellent yield (entry 18).

The structures of the products were confirmed from the single crystal X-ray data of **3j** (Fig. 2).[11]

It is noteworthy that methanol functioned both as a solvent and as an oxygenated nucleophile in the iodocyclization. This observation prompted us to explore the scope of this chemistry with other alcohols. Various alcohols, such as EtOH, *i*-PrOH, and *n*-BuOH have been tested for cyclization using **2b** and NIS. All alcohols reacted well and provided good to excellent yields of the desired iodocyclized products (Table 2, entries 19–22). Increasing the length or the branching of the alcohol chain had a slight effect on both reaction rate and yield of the products.

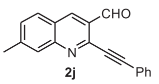
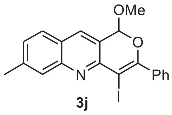
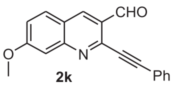
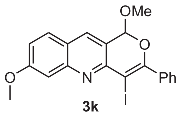
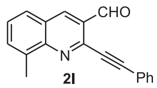
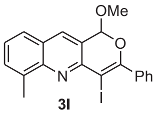
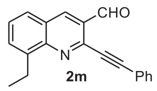
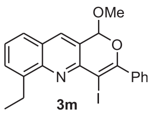
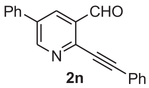
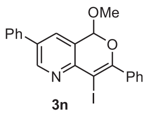
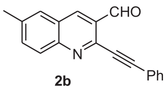
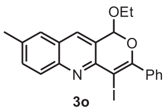
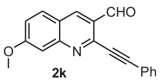
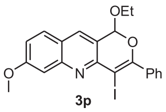
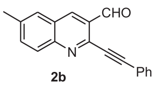
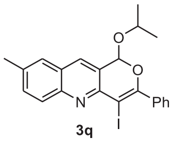
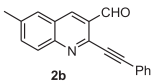
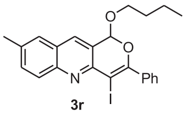
The iodopyranoannulated quinolines synthesized using this approach are very useful intermediates in many palladium-catalyzed

Table 2
Synthesis of functionalized pyrano[4,3-*b*]quinolines

Entry	Substrate	Electrophile	NuH	Product	Time (min)	Yield of **3** (%)
1	 **2a**	NIS	MeOH	 **3a**	5	88
2	 **2b**	NIS	MeOH	 **3b**	5	93
3	 **2b**	I_2	MeOH	 **5**	Overnight	27
4	 **2b**	Br_2	MeOH	–	–	00
5	 **2b**	NBS	MeOH	 **3s**  **6**	60	35[a]
6	 **2b**	ICl	MeOH	 **3b**	5	88
7	 **2c**	NIS	MeOH	 **3c**	5	95
8	 **2d**	NIS	MeOH	 **3d**	5	96
9	 **2e**	NIS	MeOH	 **3e**	5	94
10	 **2f**	NIS	MeOH	 3f	45	83
11	 **2g**	NIS	MeOH	 3g	30	85
12	 **2h**	NIS	MeOH	 3h	20	89
13	 **2i**	NIS	MeOH	 **3i**	5	91

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Electrophile	NuH	Product	Time (min)	Yield of **3** (%)
14	 **2j**	NIS	MeOH	 **3j**	5	88
15	 **2k**	NIS	MeOH	 **3k**	5	85
16	 **2l**	NIS	MeOH	 **3l**	5	82
17	 **2m**	NIS	MeOH	 **3m**	5	82
18	 **2n**	NIS	MeOH	 **3n**	5	87
19	 **2b**	NIS	EtOH	 **3o**	10	89
20	 **2k**	NIS	EtOH	 **3p**	10	82
21	 **2b**	NIS	*i*-PrOH	 **3q**	20	80
22	 **2b**	NIS	*n*-BuOH	 **3r**	20	75

[a] By NMR ratio.

reactions. Thus, when compound **3b** was treated under standard Heck and Sonogashira conditions, the corresponding coupling products **7** and **8** were isolated in 95% and 89% yields, respectively (Scheme 3).

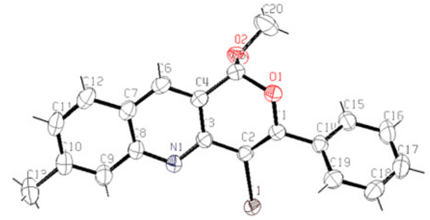
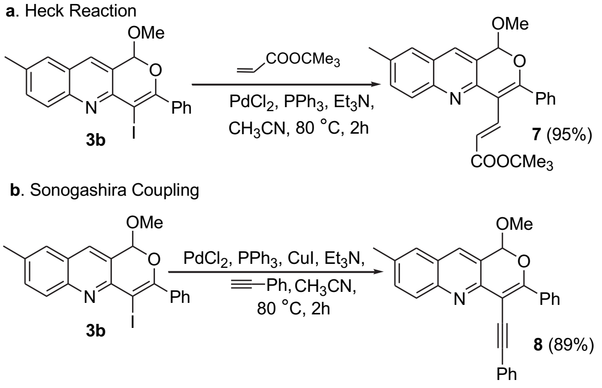


Fig. 2. ORTEP view of **3j**.



Scheme 3. Palladium-catalyzed substitution of iodo group on **3b**.

3. Conclusions

In summary, we have developed a simple and mild procedure for the synthesis of iodo substituted 1*H*-pyrano[4,3-*b*]quinolines using NIS reagent in the absence of base at room temperature. The reactions are completed in a very short duration of time to afford the products in good to excellent yields. Further, the iodo derivatives provide a route to C–C bond formations.

4. Experimental section

4.1. General

Melting points are 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 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). Elemental analyses were performed on Exter Analytical Inc. 'Model CE-400 CHN Analyzer' from Department of chemistry, BHU, Varanasi. Mass spectra were recorded from SAIF, CDRI, Lucknow, and IIT Kanpur. High resolution mass spectra (HRMS) were recorded using Micromass Q-TOF micro mass spectrometer apparatus using electron spray ionization mode from SAIF, IIT Madras, Chennai, IIT Kanpur and SAIF, CDRI Lucknow. 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 the NIS promoted synthesis of pyrano[4,3-*b*]quinolines 3

A mixture of 2-alkynylquinoline-3-carboxaldehyde (**2**) (0.25 mmol) and nucleophile (4–5 mL) was added to NIS (1.5 equiv) stirred at room temperature for 5–45 min. After completion of reaction, the reaction mixture was quenched with saturated solution of aqueous $Na_2S_2O_3$. The resulting solution was extracted using ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (silica gel was neutralized by TEA) using various ratio of EtOAc/hexane as eluent.

*4.2.1. 4-Iodo-1-methoxy-3-phenyl-1H-pyrano[4,3-b]quinoline (**3a**).* Light yellow solid; yield 88%; mp 114 °C; R_f (5% EtOAc/hexane) 0.45; IR (KBr): 1052, 1610, 2923 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.73 (3H, s), 6.24 (1H, s), 7.47–7.54 (4H, m), 7.71–7.76 (3H, m), 7.84 (1H, d, *J* 8.1 Hz), 7.99 (1H, s), 8.20 (1H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 56.4, 77.9, 100.4, 121.8, 126.3, 127.4, 127.5, 127.9, 129.5, 129.8, 129.9, 130.2, 133.1, 136.9, 147.8, 148.8, 157.7; HRMS (EI): *m/z* $[M+H]^+$ found: 416.0123. $C_{19}H_{15}NO_2I$ requires 416.0147.

*4.2.2. 4-Iodo-1-methoxy-8-methyl-3-phenyl-1H-pyrano[4,3-b]quinoline (**3b**).* Light yellow solid; yield: 93%; mp 94 °C; R_f (5% EtOAc/hexane) 0.45; IR (KBr): 1052, 1609, 2922 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.54 (3H, s), 3.72 (3H, s), 6.22 (1H, s), 7.45–7.47 (3H, m), 7.55–7.59 (2H, m), 7.70–7.73 (2H, m), 7.88 (1H, s), 8.09 (1H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 21.5, 56.4, 78.1, 100.4, 121.7, 126.3, 127.5, 127.9, 129.1, 129.7, 129.9, 132.4, 132.5, 136.3, 136.9, 146.9, 147.4, 157.1; HRMS (EI): *m/z* $[M+H]^+$ found: 430.0306. $C_{20}H_{17}NO_2I$ requires 430.0304.

*4.2.3. 4-Iodo-1-methoxy-8-methyl-3-p-tolyl-1H-pyrano[4,3-b]quinoline (**3c**).* Light yellow solid; yield: 95%; mp 102 °C; R_f (5% EtOAc/hexane) 0.45; IR (KBr): 1045, 1610, 2918 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.43 (3H, s), 2.54 (3H, s), 3.71 (3H, s), 6.21 (1H, s), 7.26 (1H, s), 7.54–7.64 (5H, m), 7.87 (1H, s), 8.08 (1H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 21.5, 21.6, 56.3, 77.7, 100.4, 121.8, 126.3, 127.5, 128.6, 129.2, 129.8, 132.3, 132.5, 134.1, 136.2, 139.9, 147.2, 147.4, 157.2; HRMS (EI): *m/z* $[M+H]^+$ found: 444.0322. $C_{21}H_{19}NO_2I$ requires 444.0460.

*4.2.4. 4-Iodo-1-methoxy-3-(4-methoxy-phenyl)-8-methyl-1H-pyrano[4,3-b]quinoline (**3d**).* Light yellow solid; yield: 96%; mp 125 °C; R_f (5% EtOAc/hexane) 0.35; IR (KBr): 1049, 1606, 2934 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.54 (3H, s), 3.72 (3H, s), 3.88 (3H, s), 6.21 (1H, s), 6.97 (2H, d, *J* 8.4 Hz), 7.54–7.58 (2H, m), 7.72 (2H, d, *J* 8.4 Hz), 7.87 (1H, s), 8.08 (1H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 21.5, 55.3, 56.3, 100.4, 113.2, 121.9, 126.3, 127.3, 127.4, 129.1, 129.2, 131.6, 132.2, 132.4, 136.1, 141.9, 147.4, 156.8, 160.6; HRMS (EI): *m/z* $[M+H]^+$ found: 460.0002. $C_{21}H_{19}NO_3I$ requires 460.0409.

*4.2.5. 2-(4-Iodo-1-methoxy-8-methyl-1H-pyrano[4,3-b]quinolin-3-yl)-phenylamine (**3e**).* Light yellow solid; yield: 94%; mp 110 °C; R_f (5% EtOAc/hexane) 0.30; IR (KBr): 1045, 1610, 3341 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.54 (3H, s), 3.64 (3H, s), 4.54 (2H, s), 6.15 (1H, s), 7.48 (1H, s), 7.58–7.61 (3H, m), 7.87 (2H, m), 7.99 (1H, s), 8.10 (1H, d, *J* 8.1 Hz); δ_C (75 MHz, $CDCl_3$) 21.6, 29.6, 56.6, 82.4, 85.5, 100.8, 121.4, 124.1, 126.4, 127.6, 129.3, 132.7, 132.8, 136.8, 138.5, 144.1, 145.5, 147.2, 147.4, 154.2. Anal. Calcd for $C_{20}H_{17}N_2O_2I$: C, 54.07; H, 3.86; N, 6.31. Found: C, 54.16; H, 3.81; N, 6.29.

*4.2.6. (4-Iodo-1-methoxy-8-methyl-1H-pyrano[4,3-b]quinolin-3-yl)-methanol (**3f**).* Light brown solid; yield: 83%; mp 85 °C; R_f (10% EtOAc/hexane) 0.30; IR (KBr): 1086, 1624, 2924, 3412 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.53 (3H, s), 3.39 (3H, s), 3.64 (2H, s), 4.04 (1H, s, D_2O exchangeable), 6.18 (1H, s), 7.55–7.67 (2H, m), 7.85 (1H, s), 8.07 (1H, d, *J* 9.0 Hz); δ_C (75 MHz, $CDCl_3$) 25.7, 51.3, 70.2, 80.3, 99.7, 121.8, 126.2, 126.5, 127.3, 129.1, 129.4, 136.3, 145.6, 147.1, 156.1. Anal. Calcd for $C_{15}H_{14}NO_3I$: C, 47.02; H, 3.68; N, 3.66. Found: C, 46.87; H, 3.74; N, 3.73.

*4.2.7. 3-Cyclohexyloxymethyl-4-iodo-1-methoxy-8-methyl-1H-pyrano[4,3-b]quinoline (**3g**).* Light yellow oil; yield: 85%; R_f (5% EtOAc/hexane) 0.60; IR (KBr): 1084, 1190, 1610, 2930 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.26–1.41 (4H, m), 1.58 (2H, m), 1.76 (2H, m), 2.03 (2H, m), 2.53 (3H, s), 3.50 (1H, m), 3.65 (3H, s), 4.60 and 4.76 (2H, ABq, *J* 12.6 Hz), 6.14 (1H, s), 7.54 (2H, m), 7.83 (1H, s), 8.06 (1H, d, *J* 8.7 Hz); δ_C (75 MHz, $CDCl_3$) 21.4, 24.0, 25.6, 29.5, 51.2, 56.0, 70.1, 80.2, 99.6, 121.9, 126.3, 127.4, 129.0, 132.5, 136.3, 145.7, 147.1, 156.2, 177.9. Anal. Calcd for $C_{21}H_{24}NO_3I$: C, 54.20; H, 5.20; N, 3.01. Found: C, 54.03; H, 5.26; N, 3.03.

*4.2.8. 3-Hexyl-4-iodo-1-methoxy-8-methyl-1H-pyrano[4,3-b]quinoline (**3h**).* Light yellow oil; yield: 89%; R_f (4% EtOAc/hexane) 0.80; IR (KBr): 1079, 1190, 1604, 2929 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.6 Hz), 1.25–1.71 (8H, m), 2.51 (3H, s), 2.83 (2H, m), 3.61 (3H, s), 6.07 (1H, s), 7.54 (2H, m), 7.79 (1H, s), 8.03 (1H, d, *J* 8.7 Hz); δ_C (75 MHz, $CDCl_3$) 14.1, 21.5, 22.6, 27.2, 28.8, 31.7, 38.0, 55.9, 77.7, 99.8, 121.5, 126.3, 127.2, 129.0, 132.3, 132.4, 135.9, 146.5, 147.3, 161.2. Anal. Calcd for $C_{20}H_{24}NO_2I$: C, 54.93; H, 5.53; N, 3.20. Found: C, 55.07; H, 5.45; N, 3.22.

*4.2.9. 4-Iodo-1,8-dimethoxy-3-phenyl-1H-pyrano[4,3-b]quinoline (**3i**).* Light yellow solid; yield: 91%; mp 142 °C; R_f (5% EtOAc/hexane) 0.27; IR (KBr): 1054, 1613, 2925 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.71 (3H, s), 3.94 (3H, s), 6.21(1H, s), 7.10 (1H, d, *J* 2.7 Hz), 7.37–7.47 (4H, m), 7.71–7.73 (2H, m), 7.87 (1H, s), 8.10 (1H, d, *J* 9.0 Hz); δ_C (75 MHz, $CDCl_3$) 55.5, 56.4, 78.0, 100.4, 105.1, 122.1, 122.9, 127.9, 128.5, 129.7, 129.9, 130.9, 131.8, 137.0, 144.9, 145.6, 156.5, 157.7; HRMS (EI): *m*/*z* [M+H]$^+$ found: 446.0255. $C_{20}H_{17}NO_3I$ requires 446.0253.

*4.2.10. 4-Iodo-1-methoxy-7-methyl-3-phenyl-1H-pyrano[4,3-b] quinoline (**3j**).* Light yellow solid; yield: 88%; mp 94 °C; R_f (5% EtOAc/hexane) 0.45; IR (KBr): 1052, 1609, 2922 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.57 (3H, s), 3.72 (3H, s), 6.22 (1H, s), 7.35 (1H, d, *J* 8.1 Hz), 7.45–7.47 (3H, m), 7.70–7.74 (3H, m), 7.93 (1H, s), 8.00 (1H, s); δ_C (75 MHz, $CDCl_3$) 21.8, 56.4, 78.2, 100.5, 120.9, 125.5, 127.1, 127.9, 128.6, 128.7, 129.7, 129.9, 132.8, 137.0, 140.7, 147.7, 149.0, 157.4; HRMS (EI): *m*/*z* [M+H]$^+$ found: 430.0287. $C_{20}H_{17}NO_2I$ requires 430.0304.

*4.2.11. 4-Iodo-1,7-dimethoxy-3-phenyl-1H-pyrano[4,3-b]quinoline (**3k**).* Light yellow solid; yield: 85%; mp 154 °C; R_f (5% EtOAc/hexane) 0.40; IR (KBr): 1048, 1612, 2923 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.71 (3H, s), 3.99 (3H, s), 6.22 (1H, s), 7.17 (1H, dd, *J* 2.4, 9.0 Hz), 7.46–7.52 (4H, m), 7.69–7.72 (3H, m), 7.89 (1H, s); δ_C (75 MHz, $CDCl_3$) 55.7, 56.3, 78.0, 100.5, 107.5, 119.6, 119.8, 122.6, 127.9, 128.4, 129.8, 129.9, 132.9, 137.1, 147.9, 150.7, 157.5, 161.4; HRMS (EI): *m*/*z* [M+H]$^+$ found: 446.0243. $C_{20}H_{17}NO_3I$ requires 446.0253.

*4.2.12. 4-Iodo-1-methoxy-6-methyl-3-phenyl-1H-pyrano[4,3-b] quinoline (**3l**).* Yellow solid; yield: 82%; mp 125 °C; R_f (5% EtOAc/hexane) 0.47; IR (KBr): 1053, 1608, 2924, 1615 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.90 (3H, s), 3.72 (3H, s), 6.26 (1H, s), 7.39–7.48 (4H, m), 7.59–7.75 (4H, m), 7.96 (1H, s); δ_C (75 MHz, $CDCl_3$) 17.9, 56.3, 79.1, 100.4, 121.3, 125.3, 126.1, 127.4, 127.9, 129.7, 129.9, 130.2, 133.2, 136.9, 137.6, 146.4, 147.7, 157.1; HRMS (EI): *m*/*z* [M+H]$^+$ found: 430.0285. $C_{20}H_{17}NO_2I$ requires 430.0304.

*4.2.13. 6-Ethyl-4-iodo-1-methoxy-3-phenyl-1H-pyrano[4,3-b]quinoline (**3m**).* Light brown solid; yield: 82%; mp 135 °C; R_f (5% EtOAc/hexane) 0.57; IR (KBr): 1048, 1606, 2925 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.44 (3H, t, *J* 7.5 Hz), 3.29–3.47 (2H, m), 3.71 (3H, s), 6.25 (1H, s), 7.43–7.48 (4H, m), 7.59 (1H, d, *J* 6.3 Hz), 7.67–7.74 (3H, m), 7.95 (1H, s); δ_C (75 MHz, $CDCl_3$) 15.1, 25.1, 56.3, 79.4, 100.4, 121.2, 125.3, 126.3, 127.5, 127.9, 128.8, 129.7, 129.9, 133.2, 136.9, 143.4, 146.2, 147.2, 156.9; HRMS (EI): *m*/*z* [M+H]$^+$ found 444.0429. $C_{21}H_{19}NO_2I$ requires 444.0460.

*4.2.14. 8-Iodo-5-methoxy-3,7-diphenyl-5H-pyrano[4,3-b]pyridine (**3n**).* Light yellow solid; yield: 87%; mp 107 °C; R_f (5% EtOAc/hexane) 0.50; IR (KBr): 1052, 1623, 2924 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.71 (3H, s), 6.18 (1H, s), 7.41–7.52 (6H, m), 7.60–7.63 (2H, m), 7.70–7.72 (3H, m), 8.95 (1H, s); δ_C (75 MHz, $CDCl_3$) 29.7, 56.3, 100.2, 122.2, 126.9, 127.9, 128.3, 129.2, 129.8, 129.9, 131.7, 135.5, 136.6, 137.0, 146.9, 149.1, 155.9; HRMS (EI): *m*/*z* [M+H]$^+$ found: 442.0309. $C_{21}H_{17}NO_2I$ requires 442.0304.

*4.2.15. 1-Ethoxy-4-iodo-8-methyl-3-phenyl-1H-pyrano[4,3-b]quinoline (**3o**).* Light brown solid; yield: 89%; mp 106 °C; R_f (10% EtOAc/hexane) 0.50; IR (KBr): 1031, 1612, 2923 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.32 (3H, t, *J* 6.9 Hz), 2.54 (3H, s), 3.90 (1H, m), 4.12 (1H, m), 6.31 (1H, s), 7.44–7.46 (3H, m), 7.53–7.59 (2H, m), 7.68–7.70 (2H, m), 7.82 (1H, s), 8.08 (1H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 21.6, 29.7, 64.7, 77.9, 99.2, 122.1, 126.4, 127.6, 127.9, 128.0, 129.1, 129.7, 129.9, 132.3, 132.5, 136.3, 137.1, 147.3, 157.3; HRMS (EI): *m*/*z* [M+H]$^+$ found: 444.0465. $C_{21}H_{19}NO_2I$ requires 444.0460.

*4.2.16. 1-Ethoxy-4-iodo-7-methoxy-3-phenyl-1H-pyrano[4,3-b] quinoline (**3p**).* Light brown solid; yield: 82%; mp 116 °C; R_f (15% EtOAc/hexane) 0.30; IR (KBr): 1051, 1610, 2925 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.32 (3H, t, *J* 6.9 Hz), 3.86–3.94 (1H, m), 3.98 (3H, s), 4.07–4.15 (1H, m), 6.32 (1H, s), 7.15 (1H, dd, *J* 2.4, 9.0 Hz), 7.46–7.52 (4H, m), 7.68–7.72 (3H, m), 7.88 (1H, s); δ_C (75 MHz, $CDCl_3$) 15.1, 55.6, 64.6, 77.9, 99.3, 107.5, 119.7, 119.9, 122.7, 127.9, 128.4, 129.7, 129.9, 132.7, 137.2, 148.1, 150.6, 157.6, 161.3; HRMS (EI): *m*/*z* [M+H]$^+$ found: 460.0384. $C_{21}H_{19}NO_3I$ requires 460.0409.

*4.2.17. 4-Iodo-1-isopropoxy-8-methyl-3-phenyl-1H-pyrano[4,3-b] quinoline (**3q**).* Light brown solid; yield: 80%; mp 81 °C; R_f (5% EtOAc/hexane) 0.30; IR (KBr): 1081, 1619, 2927 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.6 Hz), 1.35 (3H, d, *J* 6.0 Hz), 2.53 (3H, s), 4.35 (1H, m), 6.38 (1H, s), 7.44–7.46 (3H, m), 7.53–7.59 (2H, m), 7.68–7.70 (2H, m), 7.82 (1H, s), 8.07 (1H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 21.8, 29.5, 57.9, 77.9, 99.2, 107.4, 119.6, 122.5, 127.8, 128.1, 128.8, 129.7, 129.9, 130.3, 134.5, 138.3, 148.0, 150.5, 161.3; HRMS (EI): *m*/*z* [M+H]$^+$ found: 458.0564. $C_{22}H_{21}NO_2I$ requires 458.0617.

*4.2.18. 1-Butoxy-4-iodo-8-methyl-3-phenyl-1H-pyrano[4,3-b]quinoline (**3r**).* Colorless oil; yield: 75%; R_f (5% EtOAc/hexane) 0.35; IR (KBr): 1022, 1615, 2926 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.5 Hz), 1.39–1.70 (4H, m), 2.54 (3H, s), 3.80 (1H, m), 4.07 (1H, m), 6.29 (1H, s), 7.45 (3H, m), 7.54–7.60 (2H, m), 7.69–7.71 (2H, m), 7.85 (1H, s), 8.08 (1H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 19.3, 21.6, 29.7, 31.6, 69.1, 77.7, 99.5, 122.2, 126.4, 127.6, 127.9, 129.0, 129.7, 129.9, 132.3, 132.5, 136.3, 137.1, 147.1, 147.2, 157.5; HRMS (EI): *m*/*z* [M+H]$^+$ found: 472.0413. $C_{23}H_{23}NO_2I$ requires 472.0773.

4.3. General procedure for the Heck reaction on 3b

A mixture of **3b** (0.25 mmol), *tert*-butyl acrylate (0.26 mmol), $PdCl_2$ (5 mol %), PPh_3 (10 mol %), and TEA (0.5 mmol) in CH_3CN (4 mL) was stirred under N_2 at 80 °C for 2 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.

*4.3.1. 3-(1-Methoxy-8-methyl-3-phenyl-1H-pyrano[4,3-b]quinolin-4-yl)-acrylic acid tert-butyl ester (**7**).* Yellow solid; yield: 95%; mp 130 °C; R_f (5% EtOAc/hexane) 0.40; IR (KBr): 1068, 1609, 2922 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.48 (9H, s), 2.55 (3H, s), 3.78 (3H, s), 6.21 (1H, s), 7.49–7.71 (9H, m), 7.99 (1H, s), 8.10 (1H, d, *J* 9.0 Hz); δ_C (75 MHz, $CDCl_3$) 21.6, 28.2, 29.7, 56.6, 79.5, 100.7, 111.7, 121.7, 122.8, 126.5, 126.6, 128.3, 129.3, 130.4, 132.1, 132.4, 133.9, 136.2, 137.9, 146.9, 148.1, 161.3, 167.9; HRMS (EI): *m*/*z* [M+H]$^+$ found: 430.2011. $C_{27}H_{28}NO_4$ requires 430.2018.

4.4. General procedure for the Sonogashira coupling on 3b

A mixture of **3b** (0.25 mmol), phenyl acetylene (0.26 mmol), $PdCl_2$ (4 mol %), PPh_3 (8 mol %), CuI (8 mol %), and TEA (0.5 mmol) in CH_3CN (4 mL) was stirred under N_2 at 80 °C for 2 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.

*4.4.1. 1-Methoxy-8-methyl-3-phenyl-4-phenylethynyl-1H-pyrano [4,3-b]quinoline (**8**).* Light brown solid; yield: 89%; mp 98 °C; R_f (5% EtOAc/hexane) 0.30; IR (KBr): 1062, 1611, 2923 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.55 (3H, s), 3.77 (3H, s), 6.34 (1H, s), 7.32–7.36 (1H, m), 7.47–7.48 (8H, m), 7.99 (2H, m), 8.11 (1H, d, *J* 8.4 Hz), 8.27 (m, 2H); δ_C (75 MHz, $CDCl_3$) 21.6, 56.4, 77.6, 88.3, 92.0, 100.5, 121.9, 124.2, 126.9, 127.7, 127.9, 128.2, 128.3, 128.6, 129.5, 129.9, 132.3, 132.4, 132.8, 136.1, 136.6, 147.7, 148.1, 160.0; HRMS (EI): *m*/*z* [M+H]$^+$ found: 404.1656. $C_{28}H_{22}NO_2$ requires 404.1650.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.10.081.

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11. CCDC-790993 (**3j**) contains supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.