Monatsh Chem (2012) 143:1067–1073
DOI 10.1007/s00706-011-0694-0

ORIGINAL PAPER

Synthesis of 3-iodopyrrolocoumarins via iodine-induced 5-*endo-dig* electrophilic cyclization

K. C. Majumdar · Nirupam De · Biswajit Sinha · B. Roy

Received: 4 July 2011 / Accepted: 22 November 2011 / Published online: 13 December 2011

Abstract An efficient synthesis of 3-iodopyrrolocoumarins has been achieved by a simple and straightforward strategy involving palladium–copper-catalyzed Sonogashira coupling followed by iodocyclization at ambient temperature using molecular iodine as the electrophilic source. In addition, functionalization at the 3-position of the iodocyclized product is performed via Sonogashira reaction.

Keywords Molecular iodine · Electrophilic cyclization · 3-Iodopyrrolocoumarins · 5-*endo-dig* Cyclization

Introduction

Coumarin derivatives are important subunits present in a number of natural products showing a broad spectrum of biological activity such as antibacterial, antiviral, antifungal, and antimicrobial properties [1–7]. In particular, pyrrolocoumarin derivatives exhibit photobiological activity [8], photophysical properties [9], and antiproliferative [10], anti-inflammatory, and antioxidant activities [11]. Pyrrolocoumarins can act as monofunctional DNA-photobinding agents [12]. These are also used as ideal dyes for various modern fluorescent imaging technologies such as fluorescence resonance energy transfer (FRET) [13]. The pyrrolocoumarin subunit is present in various bioactive marine alkaloids, e.g., ningalin B and lamellarin D [14, 15]. Both alkaloids possess potential biological activity, e.g., cytotoxicity, HIV-1 integrase inhibition, multi-drug resistance reversal activity, and immunomodulatory activity [16–19]. Therefore, the development of a strategy for the synthesis of libraries of coumarin compounds, particularly pyrrolocoumarins, has been the subject of continued interest in recent years.

Several methods [11, 20, 21] including our methodologies [22–25] have been employed for their synthesis, but most of them require harsh conditions, expensive catalytic systems, complicated work-up and purification procedures, etc. Moreover, functionalization at the 3-position of the pyrrole unit may be useful for some target syntheses [21]. Considering these aspects we have selected iodocyclization of the key intermediate 5-alkynyl-6-aminocoumarin because it proceeds under very mild reaction conditions and offers a wide scope in terms of functional group compatibility. In recent years, molecular iodine has received considerable attention as it is an economic, non-toxic, and readily available reagent for effective iodocyclization reactions [26–30]. The iodocyclization of carbon–carbon multiple bonds with an intramolecular nucleophilic center plays an important role in the stereoselective construction of cyclic compounds [31, 32]. Synthesis of various heterocyclic compounds of biological importance by iodocyclization has been explored with a wide variety of nucleophiles, including N, O, S, Se, etc., and it has become a powerful tool for the construction of different heterocycles [33–41]. The cyclized products are ideal substrates for further functionalization as they contain an iodo group. Herein we report our approach for the straightforward synthesis of 3-iodopyrrolocoumarins.

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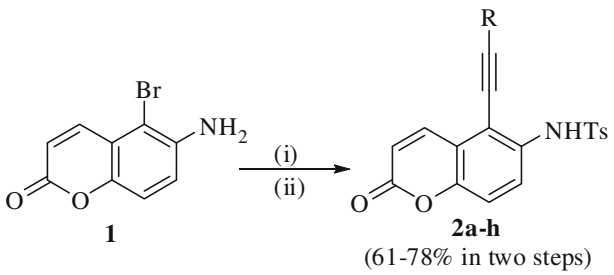
Results and discussion

The requisite precursors **2a–2h** were prepared in good yields via Sonogashira coupling reactions of 5-bromo-6-aminocoumarin (**1**) [22] with different alkynes followed by tosylation of the amino group with *p*-toluenesulfonyl chloride in pyridine (Scheme 1).

In our initial study we used substrate **2a** for the investigation of the cyclization reaction. When compound **2a** was subjected to iodocyclization reaction under usual conditions using I_2 (3 equiv.) and $NaHCO_3$ (3 equiv.) in acetonitrile at room temperature pyrrolocoumarin derivative **3a** was formed in 58% yield through 5-*endo-dig* mode of cyclization. The starting material was consumed in 6 h as checked by TLC. To improve the yield of the product we studied the cyclization reaction under several reaction conditions (Table 1) by varying the base, solvent, and amount of molecular iodine.

The cyclization reaction did not occur in the absence of any base. Among the bases used ($NaHCO_3$, K_2CO_3, Cs_2CO_3) K_2CO_3 gave the best result by shortening the reaction time to 3 h and increasing the yield to 86% when acetonitrile was used as solvent. Reduction of the amount of iodine from 3 to 1.5 equiv. lowered the yield to 39%. Acetonitrile was found to be most effective among the different solvents (nitromethane, dichloromethane, methanol, and acetonitrile) examined for this reaction. Thus the optimal reaction conditions developed for the reaction are iodine (3 equiv.), K_2CO_3 (3 equiv.), acetonitrile, r.t., 3 h (Scheme 2). After optimizing the reaction parameters, all other precursors **2b–2g** were subjected to the optimized conditions to explore the scope and generality of the reaction. Cyclized products **3b–3g** were obtained in 53–96% yield (Table 2).

The cyclization reaction is assumed to occur via the initial formation of the iodonium intermediate by the attack of iodine electrophile on the triple bond followed by the nucleophilic attack of the amine nitrogen atom. The mode of cyclization is 5-*endo-dig* in accordance with Baldwin's rules [42–44].



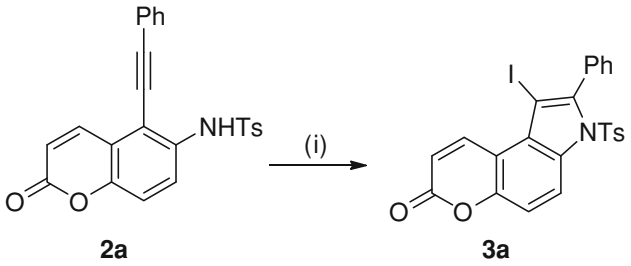
(i) $Pd(PPh_3)_2Cl_2$ (0.05eq.), alkyne (1.2 eq.) CuI (0.05eq.) DMF, Et_3N, 80 °C, 2.5-5 h
(ii) Tosyl chloride (1.2eq.), pyridine, 80 °C, 3-4h

Scheme 1

Table 1 Optimization of iodocyclization reaction

Entry	Base[a]	Solvent	Equiv. I_2	Time/h	Yield[b]/%
1	$NaHCO_3$	Acetonitrile	3	6	58
2	K_2CO_3	Acetonitrile	3	3	86
3	–	Acetonitrile	3	24	NR
4	K_2CO_3	Nitromethane	3	10	<15
5	K_2CO_3	Dichloromethane	3	6	56
6	K_2CO_3	Acetonitrile	1.5	3	39
7	Cs_2CO_3	Acetonitrile	3	10	NR
8	K_2CO_3	Methanol	3	10	NR

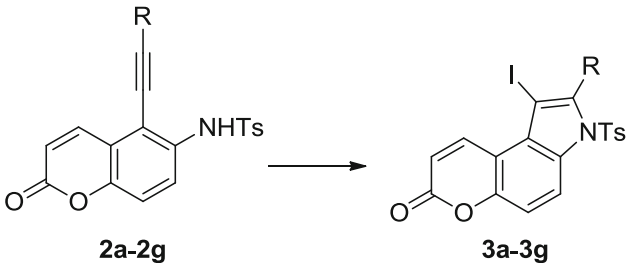
NR no reaction
[a] 3 equiv. base were used in all reactions
[b] Isolated yield



(i) I_2 (3eq.), K_2CO_3 (3 eq.), acetonitrile, r.t., 3 h

Scheme 2

Table 2 Summarized results of the iodocyclization reactions



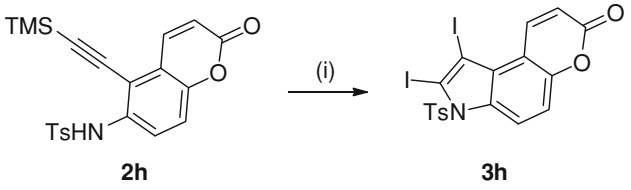
Entry	R	Substrate	Product	Time/h	Yield/%
1	C_6H_5	**2a**	**3a**	3	86
2	4-CH_3O–C_6H_4	**2b**	**3b**	3.5	81
3	4-Cl–C_6H_4	**2c**	**3c**	4	53
4	*n*-C_3H_7	**2d**	**3d**	2.5	93
5	*n*-C_4H_9	**2e**	**3e**	2.5	90
6	*n*-C_5H_{11}	**2f**	**3f**	2	95
7	*n*-C_6H_{13}	**2g**	**3g**	2	96

The nature of the substituents at the terminal position of the alkyne had a considerable effect on the reaction yield. Substrates containing alkyl chain substituents gave good product yields, whereas the substrate containing an aromatic ring with a chlorine atom (electron-withdrawing group) at the *para* position afforded a relatively poor yield. It was also notable that alkyl-chain-containing precursors required shorter reaction times for the completion of the reaction.

It is interesting to note that compound **2h**, possessing a trimethylsilyl (TMS) group as substituent at the terminal position of the alkyne, gave 2,3-diiodo cyclized product **3h** in 38% yield when treated under optimized reaction conditions (Scheme 3). Perhaps the iodide ion, generated during the formation of the iodonium intermediate replaced the TMS to produce the product **3h**.

The interesting aspect of this type of iodocyclization chemistry is that one iodine atom is incorporated in the final product that may be functionalized when required. For instance, when compound **3a** was treated under Sonogashira reaction conditions product **4a** was obtained in 95% yield (Scheme 4).

In conclusion, we have developed an easy and efficient method for the regioselective synthesis of pyrrolocoumarin derivatives. The procedure is mild, economic, and gave the products in good to excellent yields. Moreover, an iodine atom is introduced in the final product that offers scope for further functionalization. The application of this methodology to the synthesis of a target compound is in progress in our laboratory.



2h **3h**

(i) I_2 (3 eq.), K_2CO_3, (3 eq.), acetonitrile, r.t., 3.5 h, 38%

Scheme 3

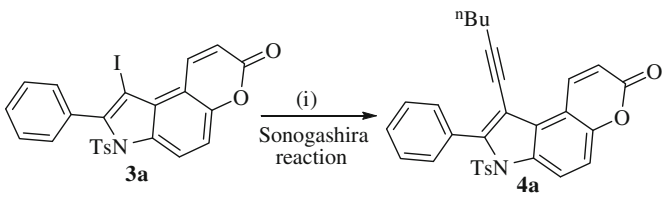
Experimental

Melting points were determined in an open capillary. IR spectra were recorded on a Perkin-Elmer L 120-000A spectrometer from KBr disks. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-400 and Bruker DPX-500 spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as internal standard. EI-MS was recorded on a Qtof-Micro^{TM} instrument, ESI-MS was recorded on Qwattro micro mass instrument, LC–MS was recorded on SIL-HTC Shimadzu API-2000 LC/MS-Applied Biosystems instrument, and HRMS was recorded on a Qtof-Micro YA263 instrument. CHN was recorded on a Perkin-Elmer 2400 series II CHN analyzer. *N*,*N*-Dimethylformamide (DMF) was sequentially dried (3×) over freshly activated 4 Å molecular sieves and Et_3N was dried overnight over anhydrous CaH_2 and then distilled after 2 h reflux. Silica gel (60–120 mesh and 230–400 mesh, Spectrochem, India) was used for chromatographic separation. Silica gel G and silica gel GF-254 (Spectrochem, India) were used for TLC. Petroleum ether (PE) refers to the fraction boiling between 60 and 80 °C.

*General procedure for the synthesis of compounds **2a–2h***

A mixture of 500 mg compound **1** (2.08 mmol), alkyne (2.5 mmol), 2 cm^3 dry Et_3N, 73 mg $Pd(PPh_3)_2Cl_2$ (5 mol%), and 20 mg CuI (5 mol%) in 8 cm^3 dry DMF was stirred in a sealed tube at 80 °C for 2.5–5 h (indicated by TLC). Then the reaction mixture was cooled and diluted to 50 cm^3 with chloroform. The organic phase was washed successively with water (3 × 25 cm^3), brine (25 cm^3), and then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude mass which was used for tosylation without further purification. Tosylation was performed by heating the crude acetylenic amine with *p*-toluenesulfonyl chloride (1.2 equiv.) in 2 cm^3 pyridine at 80 °C for 3–4 h (indicated by TLC). The reaction mixture was then allowed to cool to room temperature, ice-water was added, and the mixture was extracted with chloroform (3 × 15 cm^3). The combined organic layer was washed with 25 cm^3 water and 25 cm^3 brine and then dried over

Scheme 4



3a **4a**

(i) 1-hexyne (1.3 eq.), $Pd(PPh_3)_2Cl_2$ (0.01eq.), CuI (0.01eq.), THF/Et_3N (3:2), r.t., 2 h, 95%

anhydrous Na_2SO_4 and evaporated under reduced pressure to furnish a crude mass, which was purified by column chromatography over silica gel to afford compounds **2a–2h**.

4-Methyl-N-[2-oxo-5-(phenylethynyl)-2H-chromen-6-yl]benzenesulfonamide (**2a**, $C_{24}H_{17}NO_4S$)
Isolated yield: 73%; eluent PE/EtOAc (7:3); yellow solid, recrystallized from PE/EtOAc (3:1, 2 cm^3/100 mg). M.p.: 177–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.34$ (s, 3H), 6.47 (d, $J = 9.6$ Hz, 1H), 7.18 (d, $J = 8.4$ Hz, 2H), 7.26–7.29 (m, 3H), 7.46–7.52 (m, 4H), 7.65 (d, $J = 8.4$ Hz, 2H), 7.83 (d, $J = 9.2$ Hz, 1H), 8.01 (d, $J = 9.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 20.9$, 110.8, 111.5, 113.5, 116.1, 119.3, 126.3, 127.6, 127.7, 129.1, 129.9, 130.1, 131.4, 133.3, 140.7, 143.9, 145.5, 151.2, 160.0 ppm; IR (KBr): $\bar{\nu}$ = 1,163, 1,728, 2,204, 3,327 cm^{-1}.

N-[5-(4-Methoxyphenylethynyl)-2-oxo-2H-chromen-6-yl]-4-methylbenzenesulfonamide (**2b**, $C_{25}H_{19}NO_5S$)
Isolated yield: 77%; eluent PE/EtOAc (6:4); yellow solid, recrystallized from PE/EtOAc (3:1, 2 cm^3/100 mg). M.p.: 158–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H), 3.89 (s, 3H), 6.46 (d, $J = 9.6$ Hz, 1H), 6.96 (d, $J = 7.2$ Hz, 2H), 7.18 (d, $J = 6.8$ Hz, 2H), 7.25 (s, 1H), 7.26 (d, $J = 9.2$ Hz, 1H), 7.45 (d, $J = 6.8$ Hz, 2H), 7.65 (d, $J = 7.2$ Hz, 2H), 7.82 (d, $J = 9.2$ Hz, 1H), 8.00 (d, $J = 9.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.6$, 55.5, 102.5, 112.9, 113.6, 114.2, 114.4, 117.4, 117.6, 119.4, 124.5, 127.2, 129.8, 133.4, 134.3, 135.7, 141.4, 144.4, 151.2, 160.0, 160.9 ppm; IR (KBr): $\bar{\nu}$ = 1,164, 1,724, 2,203, 3,235 cm^{-1}.

N-[5-(4-Chlorophenylethynyl)-2-oxo-2H-chromen-6-yl]-4-methylbenzenesulfonamide (**2c**, $C_{24}H_{16}ClNO_4S$)
Isolated yield: 61%; eluent PE/EtOAc (7:3); yellow solid, recrystallized from PE/EtOAc (3:1, 2 cm^3/100 mg). M.p.: 176–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H), 6.48 (d, $J = 9.6$ Hz, 1H), 7.12 (s, 1H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 9.2$ Hz, 1H), 7.40–7.43 (m, 4H), 7.64 (d, $J = 8.0$ Hz, 2H), 7.81 (d, $J = 9.2$ Hz, 1H), 7.97 (d, $J = 9.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.1$, 99.5, 103.4, 106.1, 116.7, 117.1, 117.6, 118.2, 118.6, 119.2, 120.8, 129.0, 132.7, 135.1, 141.5, 141.7, 142.3, 145.2, 147.0, 160.9 ppm; IR (KBr): $\bar{\nu}$ = 1,166, 1,711, 2,213, 3,225 cm^{-1}.

4-Methyl-N-[2-oxo-5-(1-pentynyl)-2H-chromen-6-yl]-benzenesulfonamide (**2d**, $C_{21}H_{19}NO_4S$)
Isolated yield: 71%; eluent: PE/EtOAc (8:2); yellow solid, recrystallized from PE/EtOAc (3:1, 2 cm^3/100 mg). M.p.: 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.00$ (t, $J = 7.6$ Hz, 3H), 1.65–1.72 (m, 2H), 2.37 (s, 3H), 2.48 (t, $J = 7.0$ Hz, 2H), 6.42 (d, $J = 9.6$ Hz, 1H), 7.14 (s, 1H), 7.20 (d, $J = 9.2$ Hz, 1H), 7.22 (d, $J = 8.0$ Hz, 2H), 7.64 (d, $J = 8.0$ Hz, 2H), 7.77 (d, $J = 9.2$ Hz, 1H), 7.91 (d, $J = 9.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.8$, 21.7, 22.6, 30.2, 71.6, 105.3, 112.9, 116.9, 117.4, 119.7, 124.0, 128.1, 129.9, 134.3, 136.1, 141.1, 143.9, 150.6, 160.1 ppm; IR (KBr): $\bar{\nu}$ = 1,165, 1,713, 2,226, 3,212 cm^{-1}.

N-[5-(1-Hexynyl)-2-oxo-2H-chromen-6-yl]-4-methylbenzenesulfonamide (**2e**, $C_{22}H_{21}NO_4S$)
Isolated yield: 78%; eluent PE/EtOAc (8:2); yellow solid, recrystallized from PE/EtOAc (4:1, 2 cm^3/100 mg). M.p.: 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.00$ (t, $J = 7.2$ Hz, 3H), 1.45–1.51 (m, 2H), 1.60-1.64 (m, 2H), 2.38 (s, 3H), 2.51 (t, $J = 7.0$ Hz, 2H), 6.43 (d, $J = 10.0$ Hz, 1H), 7.14 (s, 1H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.24 (d, $J = 9.2$ Hz, 1H), 7.64 (d, $J = 8.0$ Hz, 2H), 7.78 (d, $J = 9.2$ Hz, 1H), 7.90 (d, $J = 10.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.6$, 19.5, 21.6, 22.2, 30.5, 71.9, 104.5, 113.4, 117.0, 117.5, 119.6, 123.7, 127.2, 129.7, 134.6, 135.8, 141.5, 144.3, 151.0, 160.0 ppm; IR (KBr): $\bar{\nu}$ = 1,168, 1,716, 2,232, 3,208 cm^{-1}.

N-[5-(1-Heptynyl)-2-oxo-2H-chromen-6-yl]-4-methylbenzenesulfonamide (**2f**, $C_{23}H_{23}NO_4S$)
Isolated yield: 75%; eluent PE/EtOAc (9:1); yellow solid, recrystallized from PE/EtOAc (4:1, 2 cm^3/100 mg). M.p.: 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (t, $J = 7.0$ Hz, 3H), 1.36-1.50 (m, 4H), 1.62–1.66 (m, 2H), 2.37 (s, 3H), 2.49 (t, $J = 7.0$ Hz, 2H), 6.42 (d, $J = 9.6$ Hz, 1H), 7.15 (s, 1H), 7.19 (d, $J = 9.2$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.64 (d, $J = 8.0$ Hz, 2H), 7.76 (d, $J = 9.2$ Hz, 1H), 7.90 (d, $J = 9.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$, 19.8, 21.6, 22.5, 28.6, 31.2, 73.4, 102.5, 112.6, 116.9, 118.3, 119.7, 126.3, 126.7, 130.0, 133.0, 135.8, 142.1, 144.9, 151.4, 161.1 ppm; IR (KBr): $\bar{\nu}$ = 1,165, 1,714, 2,229, 3,212 cm^{-1}.

4-Methyl-N-[5-(1-octynyl)-2-oxo-2H-chromen-6-yl]-benzenesulfonamide (**2g**, $C_{24}H_{25}NO_4S$)
Isolated yield: 67%; eluent PE/EtOAc (9:1); yellow solid, recrystallized from PE/EtOAc (5:1, 2 cm^3/100 mg). M.p.: 78–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (t, $J = 7.0$ Hz, 3H), 1.34–1.37 (m, 4H), 1.42-1.49 (m, 2H), 1.60–1.63 (m, 2H), 2.37 (s, 3H), 2.50 (t, $J = 7.2$ Hz, 2H), 6.42 (d, $J = 9.6$ Hz, 1H), 7.14 (s, 1H), 7.20 (d, $J = 9.2$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 2H), 7.64 (d, $J = 8.4$ Hz, 2H), 7.77 (d, $J = 9.2$ Hz, 1H), 7.90 (d, $J = 9.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.9$, 19.5, 21.6, 22.3, 28.6, 30.8, 31.2, 73.8, 101.1, 112.7, 116.9, 118.1, 119.7, 124.5, 126.8, 130.0, 132.9, 135.6, 142.0, 144.9, 151.6, 161.2 ppm; IR (KBr): $\bar{\nu}$ = 1,167, 1,714, 2,228, 3,216 cm^{-1}.

4-Methyl-N-[2-oxo-5-(trimethylsilylethynyl)-2H-chromen-6-yl]benzenesulfonamide (**2h**, $C_{21}H_{21}NO_4SSi$)
Isolated yield: 63%; eluent PE/EtOAc (8:2); yellow solid, recrystallized from PE/EtOAc (3:1, 2 cm^3/100 mg). M.p.: 145–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.50$ (s, 9H), 2.34 (s, 3H), 6.49 (d, $J = 9.6$ Hz, 1H), 7.14 (s, 1H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 9.2$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 2H), 8.01 (d, $J = 9.2$ Hz, 1H), 8.05 (d, $J = 9.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 0.5$, 21.7, 97.8, 103.1, 108.0, 114.2, 117.5, 118.3, 120.0, 127.8, 129.9, 133.1, 135.8, 141.9, 145.8, 147.7, 161.2 ppm; IR (KBr): $\bar{\nu} = 1{,}167$, 1,737, 2,154, 3,321 cm^{-1}.

General procedure for the synthesis of compounds ***3a–3h***

To a solution of compound **2** (0.48 mmol) in 5 cm^3 acetonitrile, 200 mg K_2CO_3 (1.44 mmol) and 365 mg I_2 (1.44 mmol) were added. The reaction mixture was stirred at room temperature for 2–4 h (monitored by TLC). The reaction mixture was then quenched with 20 cm^3 saturated $Na_2S_2O_3$ solution and extracted with chloroform (3 × 15 cm^3). The combined organic layer was washed with 30 cm^3 water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to furnish a crude mass, which was purified by column chromatography over silica gel to afford compounds **3a–3h**.

1-Iodo-3-(4-methylphenylsulfonyl)-2-phenylpyrano-[3,2-e]indol-7(3H)-one (**3a**, $C_{24}H_{16}INO_4S$)
Isolated yield: 86%; eluent PE/EtOAc (9.5:0.5); colorless solid, recrystallized from PE/$CHCl_3$ (3:1, 2 cm^3/100 mg). M.p.: 191–192 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H), 6.52 (d, $J = 9.9$ Hz, 1H), 7.14 (d, $J = 8.1$ Hz, 2H), 7.27 (d, $J = 7.8$ Hz, 2H), 7.33 (d, $J = 8.3$ Hz, 2H), 7.41 (d, $J = 9.3$ Hz, 1H), 7.47 (t ≈ dd, $J = 7.4$ Hz, 2H), 7.53 (t ≈ dd, $J = 7.4$ Hz, 1H), 8.60 (d, $J = 9.3$ Hz, 1H), 9.45 (d, $J = 9.9$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.7$, 68.8, 111.8, 114.7, 115.1, 119.1, 124.9, 127.0, 127.8, 129.7, 129.8, 131.3, 131.9, 133.2, 134.9, 137.9, 144.2, 145.7, 152.5, 160.5 ppm; IR (KBr): $\bar{\nu} = 1{,}171$, 1,726 cm^{-1}; LC–MS: $m/z = 542$ [M^+].

1-Iodo-2-(4-methoxyphenyl)-3-(4-methylphenylsulfonyl)-pyrano[3,2-e]indol-7(3H)-one (**3b**, $C_{25}H_{18}INO_5S$)
Isolated yield: 81%; eluent PE/EtOAc (9:1); yellow solid, recrystallized from PE/$CHCl_3$ (3:1, 2 cm^3/100 mg). M.p.: 204–205 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H), 3.92 (s, 3H), 6.52 (d, $J = 10.0$ Hz, 1H), 6.99 (d, $J = 8.4$ Hz, 2H), 7.14 (d, $J = 8.0$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.40 (d, $J = 9.2$ Hz, 1H), 8.60 (d, $J = 9.6$ Hz, 1H), 9.46 (d, $J = 10.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.7$, 55.4, 69.0, 111.7, 113.2, 114.5, 115.0, 119.3, 123.2, 125.0, 127.0, 129.7, 133.3, 133.4, 134.9, 138.0, 144.3, 145.6, 152.5, 160.5, 160.7 ppm; IR (KBr): $\bar{\nu} = 1{,}166$, 1,724 cm^{-1}; HRMS (TOF, ES^+): m/z $[M + Na]^+$ calcd for $C_{25}H_{18}INO_5S$ 593.9848, found 593.9846.

2-(4-Chlorophenyl)-1-iodo-3-(4-methylphenylsulfonyl)-pyrano[3,2-e]indol-7(3H)-one (**3c**, $C_{24}H_{15}ClINO_4S$)
Isolated yield: 53%; eluent PE/EtOAc (9:1); yellow solid, recrystallized from PE/ACN (3:1, 2 cm^3/100 mg). M.p.: 216–217 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.36$ (s, 3H), 6.54 (d, $J = 9.6$ Hz, 1H), 7.16 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 8.4$ Hz, 2H), 7.43 (d, $J = 9.2$ Hz, 1H), 7.46 (d, $J = 8.4$ Hz, 2H), 8.59 (d, $J = 9.2$ Hz, 1H), 9.43 (d, $J = 9.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.7$, 69.1, 111.9, 115.0, 115.3, 119.2, 124.9, 126.9, 128.2, 129.8, 129.9, 133.2, 133.3, 134.8, 136.1, 137.7, 142.9, 146.0, 152.6, 160.4 ppm; IR (KBr): $\bar{\nu} = 1{,}168$, 1,726 cm^{-1}; EI-MS: $m/z = 359.43$ (62.0%), 576.25 ([M + H]$^+$, 100%), 598.24 ([M + Na]$^+$, 93.7%).

1-Iodo-3-(4-methylphenylsulfonyl)-2-propylpyrano-[3,2-e]indol-7(3H)-one (**3d**, $C_{21}H_{18}INO_4S$)
Isolated yield: 93%; eluent PE/EtOAc (9.5:0.5); light yellow solid, recrystallized from PE/EtOAc (3:1, 2 cm^3/100 mg). M.p.: 165–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.07$ (t, $J = 7.4$ Hz, 3H), 1.72-1.78 (m, 2H), 2.36 (s, 3H), 3.17 (t, $J = 7.8$ Hz, 2H), 6.51 (d, $J = 9.6$ Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 9.2$ Hz, 1H), 7.61 (d, $J = 8.4$ Hz, 2H), 8.42 (d, $J = 9.2$ Hz, 1H), 9.44 (d, $J = 9.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 21.7, 23.5, 31.9, 67.0, 111.4, 113.7, 114.9, 118.4, 124.9, 126.3, 130.2, 132.8, 135.3, 137.9, 145.1, 145.7, 152.3, 160.5 ppm; IR (KBr): $\bar{\nu} = 1{,}171$, 1,730 cm^{-1}.

2-Butyl-1-iodo-3-(4-methylphenylsulfonyl)pyrano-[3,2-e]indol-7(3H)-one (**3e**, $C_{22}H_{20}INO_4S$)
Isolated yield: 90%; eluent PE/EtOAc (9.5:0.5); colorless solid, recrystallized from PE/EtOAc (3:1, 2 cm^3/100 mg). M.p.: 143–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$ (t, $J = 7.4$ Hz, 3H), 1.47-1.54 (m, 2H), 1.66–1.71 (m, 2H), 2.36 (s, 3H), 3.19 (t, $J = 8.0$ Hz, 2H), 6.52 (d, $J = 10.0$ Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 9.2$ Hz, 1H), 7.61 (d, $J = 8.4$ Hz, 2H), 8.43 (d, $J = 9.2$ Hz, 1H), 9.44 (d, $J = 10.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.8$, 21.6, 22.8, 29.9, 32.0, 66.8, 111.3, 113.7, 114.9, 118.4, 124.8, 126.4, 130.2, 132.8, 135.3, 137.9, 145.3, 145.7, 152.3, 160.5 ppm; IR (KBr): $\bar{\nu} = 1{,}170$, 1,729 cm^{-1}.

1-Iodo-3-(4-methylphenylsulfonyl)-2-pentylpyrano-[3,2-e]indol-7(3H)-one (**3f**, $C_{23}H_{22}INO_4S$)
Isolated yield: 95%; eluent PE/EtOAc (9.6:0.4); colorless solid, recrystallized from PE/EtOAc (4:1, 2 cm^3/100 mg). M.p.: 137–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$

(t, $J = 7.2$ Hz, 3H), 1.35–1.45 (m, 4H), 1.69 (m, 2H), 2.36 (s, 3H), 3.18 (t, $J = 8.0$ Hz, 2H), 6.51 (d, $J = 10.0$ Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 9.2$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 2H), 8.42 (d, $J = 9.2$ Hz, 1H), 9.44 (d, $J = 10.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0, 21.6, 22.5, 28.6, 29.1, 31.6, 105.3, 110.3, 112.6, 115.9, 118.3, 126.3, 126.8, 130.0, 133.0, 135.8, 140.0, 145.3, 145.5, 151.4, 161.1$ ppm; IR (KBr): $\bar{\nu} = 1{,}169, 1{,}731$ cm^{-1}; ESI-MS: $m/z = 536$ [M$^+$].

2-Hexyl-1-iodo-3-(4-methylphenylsulfonyl)pyrano-[3,2-e]indol-7(3H)-one (**3g**, $C_{24}H_{24}INO_4S$)

Isolated yield: 96%; eluent PE/EtOAc (9.6:0.4); colorless solid, recrystallized from PE/EtOAc (4:1, 2 cm^3/100 mg). M.p.: 149–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 6.8$ Hz, 3H), 1.34-1.35 (m, 4H), 1.47–1.49 (m, 2H), 1.66-1.70 (m, 2H), 2.36 (s, 3H), 3.18 (t, $J = 7.8$ Hz, 2H), 6.41 (d, $J = 10.0$ Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 9.2$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 2H), 8.42 (d, $J = 9.2$ Hz, 1H), 9.44 (d, $J = 10.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1, 21.7, 22.6, 29.4, 29.9, 30.2, 31.4, 66.8, 111.4, 113.7, 114.9, 118.4, 124.8, 126.4, 130.2, 132.8, 135.4, 137.9, 145.3, 145.7, 152.3, 160.5$ ppm; IR (KBr): $\bar{\nu} = 1{,}163, 1{,}732$ cm^{-1}.

1,2-Diiodo-3-(4-methylphenylsulfonyl)pyrano[3,2-e]indol-7(3H)-one (**3h**, $C_{18}H_{11}I_2NO_4S$)

Isolated yield: 38%; eluent PE/EtOAc (9.5:0.5); light yellow solid, recrystallized from PE/EtOAc (4:1, 2 cm^3/100 mg). M.p.: 244–245 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.38$ (s, 3H), 6.55 (d, $J = 9.6$ Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 9.2$ Hz, 1H), 7.78 (d, $J = 8.4$ Hz, 2H), 8.59 (d, $J = 9.2$ Hz, 1H), 9.43 (d, $J = 9.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.7, 87.8, 90.1, 113.6, 114.9, 118.1, 119.4, 124.9, 127.1, 129.9, 134.3, 137.6, 143.3, 144.4, 151.6, 160.3$ ppm; IR (KBr): $\bar{\nu} = 1{,}159, 1{,}730$ cm^{-1}; EI-MS: $m/z = 359.44$ (100%), 592.17 ([M + H]$^+$, 13.3%), 614.15 ([M + Na]$^+$, 47.5%).

1-(1-Hexynyl)-3-(4-methylphenylsulfonyl)-2-phenylpyrano-[3,2-e]indol-7(3H)-one (**4a**, $C_{30}H_{25}NO_4S$)

A mixture of 300 mg of compound **1** (0.54 mmol), 60 mg 1-hexyne (0.72 mmol), 2 cm^3 dry Et_3N, 4 mg $Pd(PPh_3)_2Cl_2$ (1 mol%), and 1 mg CuI (1 mol%) in 3 cm^3 dry THF was stirred at room temperature for 2 h. Then the reaction mixture was cooled and diluted to 30 cm^3 with chloroform. The organic phase was washed successively with water (3 × 10 cm^3), 10 cm^3 brine, and then dried (Na_2SO_4). The solvent was removed under reduced pressure to give a crude mass which was purified by column chromatography over silica gel (PE/EtOAc, 9.7:0.3) to give compound **4a** in 95% yield as a colorless solid, which was recrystallized from PE/EtOAc (4:1, 2 cm^3/100 mg). M.p.: 117–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 7.2$ Hz, 3H), 1.28 (m, 2H), 1.45 (m, 2H), 2.32 (s, 3H), 2.34 (t, $J = 6.8$ Hz, 2H), 6.44 (d, $J = 10.0$ Hz, 1H), 7.09 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 9.2$ Hz, 1H), 7.43–7.52 (m, 5H), 8.50 (d, $J = 9.2$ Hz, 1H), 9.03 (d, $J = 10.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.5, 19.3, 21.6, 22.1, 30.5, 83.4, 95.3, 109.7, 111.7, 114.8, 115.1, 119.2, 125.0, 126.9, 127.7, 129.8, 129.9, 131.3, 131.9, 133.2, 134.9, 137.7, 144.1, 145.8, 152.5, 160.5$ ppm; IR (KBr): $\bar{\nu} = 1{,}169, 1{,}732, 2{,}234$ cm^{-1}.

Acknowledgments We thank the CSIR (New Delhi) and DST (New Delhi) for financial assistance. N. D. and B. S. thank the UGC (New Delhi) and the CSIR (New Delhi) respectively for their fellowships. We also thank the DST (New Delhi) for providing the Perkin-Elmer L 120-000A IR spectrometer, Bruker DPX-400 NMR spectrometer, and 2400 series II CHN analyzer under its FIST programme.

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