Tetrahedron 67 (2011) 8918–8924

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A convenient and efficient protocol for the synthesis of 4(1*H*)-cinnolones, 1,4-dihydrocinnolines, and cinnolines in aqueous medium: application for detection of nitrite ions

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ARTICLE INFO

Article history:
Received 29 April 2011
Received in revised form 5 September 2011
Accepted 7 September 2011
Available online 17 September 2011

Keywords:
Cinnolone
Dihydrocinnoline
Cinnoline
Richter cyclization
Detection of nitrite ion

ABSTRACT

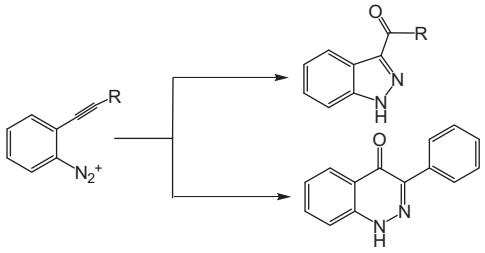
3-Aryl/alkyl-4(1*H*)-cinnolones are obtained in one step from 2-aryl/alkylethynyl aniline by reaction with sodium nitrite and dilute hydrochloric acid via Richter cyclization. The alkyl cinnolones on reduction with Sn/HCl furnish 1,4-dihydro-3-alkylcinnolines, which are converted to 3-alkylcinnolines by treatment with $NaNO_2$/HCl/KI. The whole process is carried out in aqueous medium at ambient temperature within a short reaction period. The reaction of 2-phenylethynyl aniline exhibits yellow color with UV absorbance at 391 nm and has been successfully tested for the detection of nitrite ions in water at parts per million concentration.

1. Introduction

The cinnolines, dihydrocinnolines, and cinnolones have received considerable attention in recent times because of their promising biological activities against several diseases as shown below.[1]

Several methods have been developed for their synthesis[2] and most of them are based on Richter cyclization of *ortho*-ethynyldiazonium salts.[3–8] However, cyclization of *ortho*-ethynyldiazonium salts led to five-membered pyrazole ring or a six-membered pyridazine system (cinnoline) or a mixture with little variation of the reaction conditions and nature of substituents present in the alkynyl moiety[6,9–12] (Scheme 1). Thus, an efficient, reliable, and general method for the synthesis of cinnolines is highly desirable. The synthesis of 4(1*H*)-cinnolones, which are also pharmaceutically very important[1] is not addressed adequately. We found only two reports for their synthesis in the literature.[6,13] These are also not very convenient and efficient. Thus, a direct and convenient route to cinnolones is also appreciated.

In the context of diverse applications and importance of these compounds we considered it worthwhile to investigate this synthetic problem. Our primary interest is to develop a general and efficient method for the synthesis of both cinnolones and cinnolines by the same protocol. We chose commercially available 2-iodo aniline as the starting material. Sonogashira coupling with substituted acetylenes[14] followed by treatment with $NaNO_2$/HCl provided 3-aryl/alkyl-4(*H*)-cinnolones via Richter cyclization (Scheme 2).



Scheme 1. Richter cyclization of 2-arylethynyl diazonium compound.

A further two-step transformation of 3-alkyl-cinnolones led to 3-alkylcinnolines (Scheme 3).

2. Results and discussion

The experimental procedures are very simple. The Sonogashira coupling of 2-iodoanilines and alkyl/aryl acetylenes was carried out in water by standard procedure[14] using $Pd(PPh_3)_4$ as catalyst. The 2-amino phenyl acetylenes were then treated with $NaNO_2$/HCl

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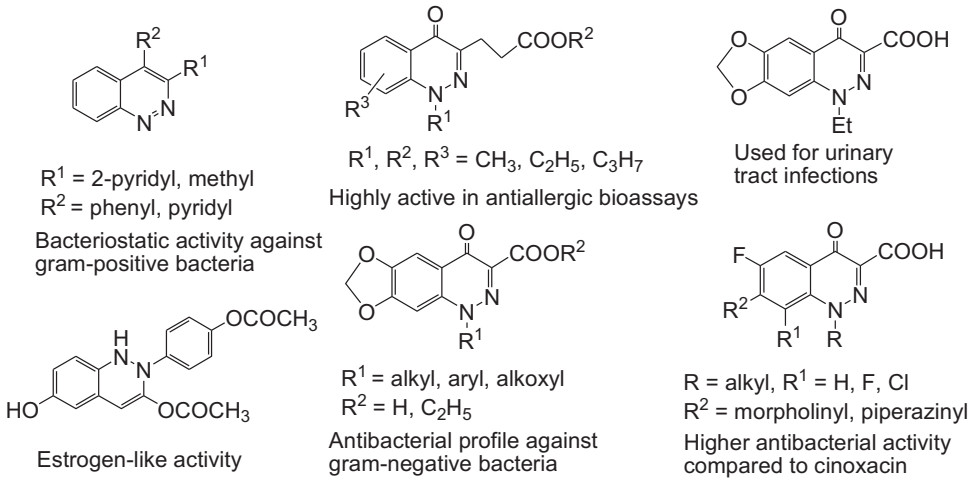
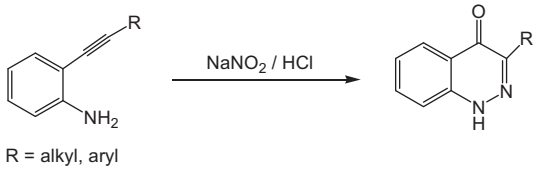
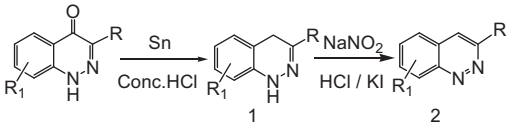
doi:10.1016/j.tet.2011.09.016





Scheme 2. Cyclization to 3-substituted cinnolones.



Scheme 3. Synthesis of 3-substituted 1,2-dihydrocinnoline and cinnolines.

(2 N) at 0–5 °C to produce 3-substituted 4(1*H*)-cinnolones. The results are summarized in Table 1 for aryl-substituted cinnolones and Table 2 reports alkyl-substituted ones. A variety of substituted phenyl and naphthyl-ethynyl anilines participate in this reaction to produce the corresponding cinnolones and several functional groups, such as Cl, CN, OMe are compatible with the reaction conditions. The formation of 3-phenyl-4(1*H*)-cinnolones shows an immediate change of color to yellow from colorless. The change of color is clearly visible up to as less as 10 ppm concentration of nitrite ions.

One of the products, 3-phenyl-4(1*H*)-cinnolone shows a characteristic UV absorption at 391 nm (Fig. 1). On fluorescence studies it was found that starting compound, 2-phenylethynyl aniline as well as the product, 3-phenyl-4(1*H*) cinnolone are not fluorescence active. However, we discovered that 6-methoxy-2-naphthylethynyl aniline shows strong fluorescence emission at 401 nm (excitation at λ_{max} 315 nm), whereas the corresponding cinnolone obtained by reaction with nitrite, was completely fluorescence inactive (Fig. 2).

This property was successfully utilized for the detection of nitrite ions at a very low concentration (<1 ppm). The effect of a wide variety of other ions including F^-, Cl^-, Br^-, I^-, N_3^-, PO_4^{3-}, OAc^-, SCN^-, SO_4^{2-}, NO_3^-, have also been investigated in the sensing process of nitrite by this reaction. Remarkably, in an experiment in absence of nitrite ion none of these ions even at a higher concentration (1000 ppm) shows any change of color (Fig. 3) or UV absorption at 391 nm (Fig. 1) or quenching of fluorescence emission at 401 nm (Fig. 2). The presence of these ions in the test sample containing nitrite ion also does not interfere in the detection process. For an on-the-spot survey when a paper strip (1 cm^2) soaked with ethanolic solution of 2-phenylethynyl aniline (0.05 mg) and aqueous HCl (2 N, 1 drop) was quenched with a drop of sample containing nitrite ion, the presence of nitrite was immediately reflected by a change of color to yellow. The presence of other ions has absolutely no effect. Thus, 2-phenylethynyl aniline serves as a chemodosimeter.

This part dealing with the preliminary results of reactions of 2-arylethynyl anilines has been recently reported by us in a communication.[15] We include here the results of further investigations with detailed experimental procedure and characterization data of all products.

The aryl-substituted alkynyl anilines provided the corresponding cinnolones as sole products, whereas the products formed from alkyl-substituted alkynyl anilines remain in tautomeric mixture of 3-alkyl-cinnolones and 4-hydroxy-3-alkylcinnolines. Thus after the reaction was over, the reaction mixture was further stirred for another 4 h to provide cinnolone as exclusive product. To carry out further derivatization of cinnolones, these compounds are then reduced with Sn/HCl to give 3-alkyl-1,4-dihydrocinnolines. The dihydrocinnolines are aromatized by $NaNO_2$/HCl/KI to furnish 3-alkylcinnolines (Table 3). Interestingly, the aryl-substituted cinnolones remain inert during this derivatization process as outlined in Table 3.

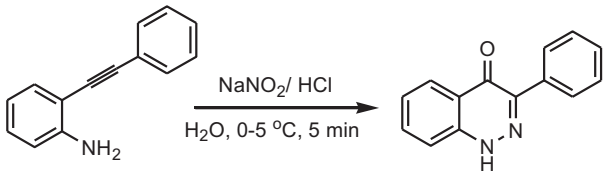
The entire process from iodoanilines to 3-alkylcinnolines was carried out in aqueous medium at ambient temperatures and minimum amount of ethyl acetate was used for extraction in certain steps to maintain a low environmental impact for the process. All the products were characterized adequately by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and HRMS).

A few of these cinnolones are known compounds and were identified by comparison of their spectroscopic data with those reported earlier.[13] The structure of 3-hexyl-1,4-dihydrocinnoline was also established by X-ray crystal data[16] (Fig. 4).

Regarding the reaction pathway, the *O*-ethynyl aniline undergoes diazotization followed by hydration of ethynyl moiety and cyclization to give the cinnolone, which is further transformed to dihydrocinnolone by Sn/HCl reduction. The oxidation–aromatization was accomplished by $NaNO_2$/HCl/KI as outlined in Scheme 4 although we do not have a clear understanding of this step, particularly the role of KI. Nevertheless, the reaction did not proceed in absence of KI.

In general, the reactions are very fast, clean, and high yielding. The 4(1*H*)-cinnolones (Tables 1 and 2) are obtained pure by simple crystallization of the crude products from ethyl acetate. The 4(1*H*)-

Table 1
Synthesis of 3-aryl-cinnolones



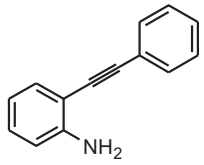
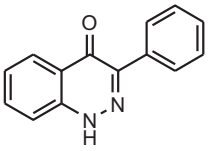
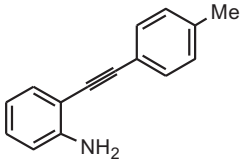
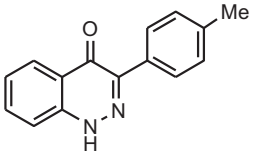
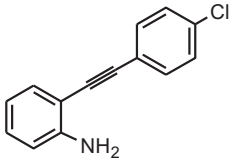
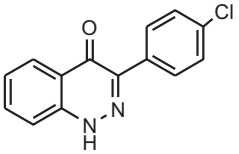
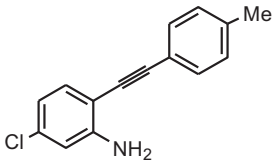
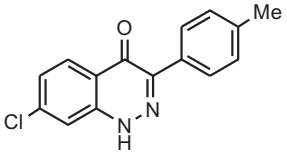
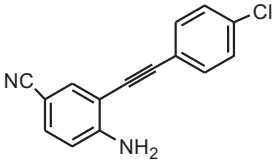
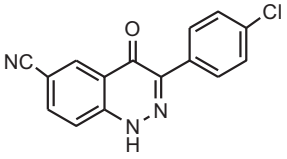
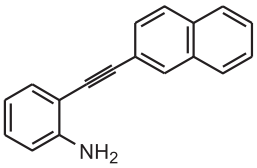
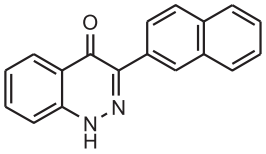
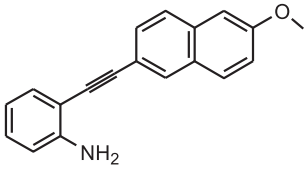
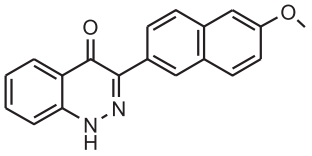
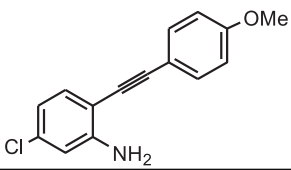
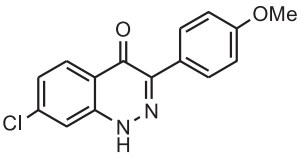
Entry	Substrate	Product	Yield
1			92
2			90
3			95
4			92
5			95
6			91
7			90
8			92

Table 2
Synthesis of 3-alkyl-cinnolones

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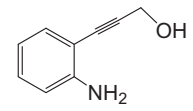
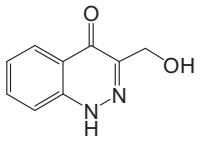
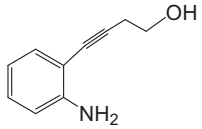
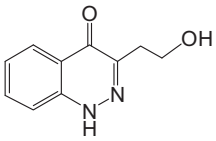
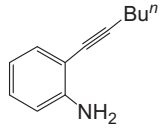
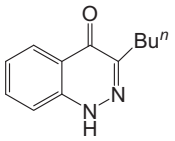
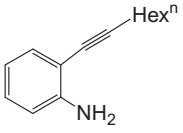
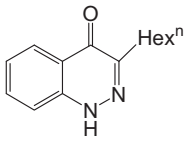
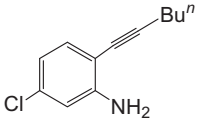
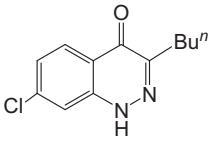
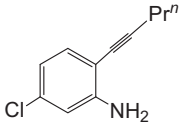
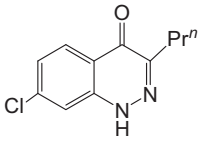
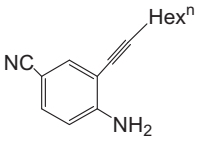
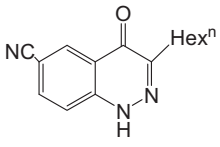
1			80
2			80
3			85
4			83
5			86
6			83
7			80

[a] Yields refer to those of pure isolated products characterized by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and HRMS).

cinnolones are easily converted to 1,4-dihydrocinnolines and cinnolines by simple operations.

3. Conclusion

We have developed a general and green protocol for the synthesis of 4(1*H*)-cinnolones, 1,4-dihydrocinnolines, and cinnolines starting from commercially available 2-iodoanilines through simple operations. To the best of our knowledge, we are not aware of any efficient, direct, and general method for the synthesis of 4(1*H*)-cinnolones and 1,4-dihydrocinnolines, which have demonstrated a variety of biological activities.[1] The reaction in aqueous medium at ambient temperature in open air, easy separation of product with minimum use of organic solvent (ethyl acetate), chromatographic purification only in one step of the reactions and high yield of products make this approach very attractive for an access to

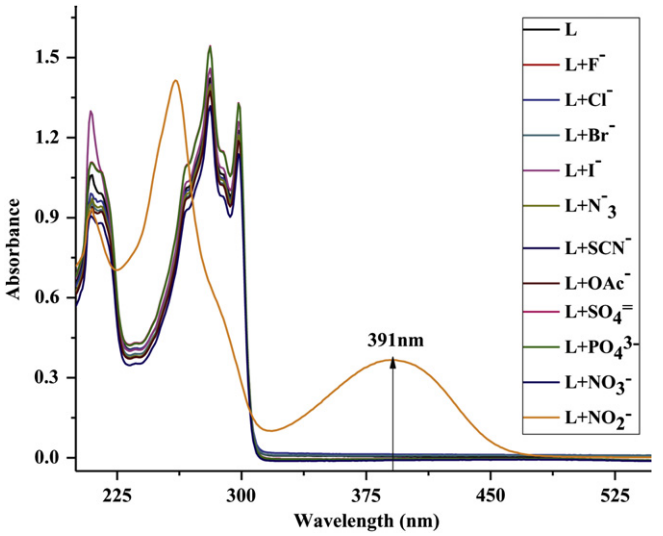


Fig. 1. UV spectroscopic studies for nitrite sensing (L=6-methoxy-2-naphthylethynyl aniline, 10^{-6} M in H_2O).

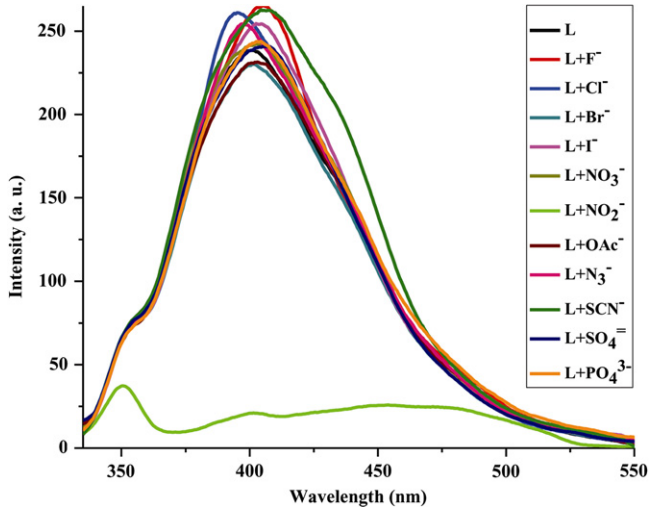


Fig. 2. Fluorescence studies for nitrite sensing (L=2-phenylethynyl aniline, 10^{-4} M in H_2O).

substituted 4(1*H*)-cinnolones, 1,4-dihydrocinnolines, and cinnolines. In addition, the reaction of 2-phenylethynyl aniline and nitrite in acidic aqueous medium provides a simple tool for sensing nitrite ions selectively in presence of other ion contaminants by visual color change, UV absorption, and fluorescence emission.

4. Experimental section

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker instrument at 300 and 75 MHz, respectively. The chemical shifts (δ) are reported in parts per million, using TMS as an internal standard and $CDCl_3$ as the solvent. HRMS were recorded on a Microtek Qtof Micro YA263 spectrometer. IR spectra were recorded on a Shimadzu 8300 FTIR spectrometer. UV studies were carried out in a Carry Bio 100 spectrometer. Luminescence spectra were carried out in a Perkin–Elmer LS-55 instrument. Melting points of the products cannot be determined as these compounds have very high melting and prone to decompose beyond 200 °C.

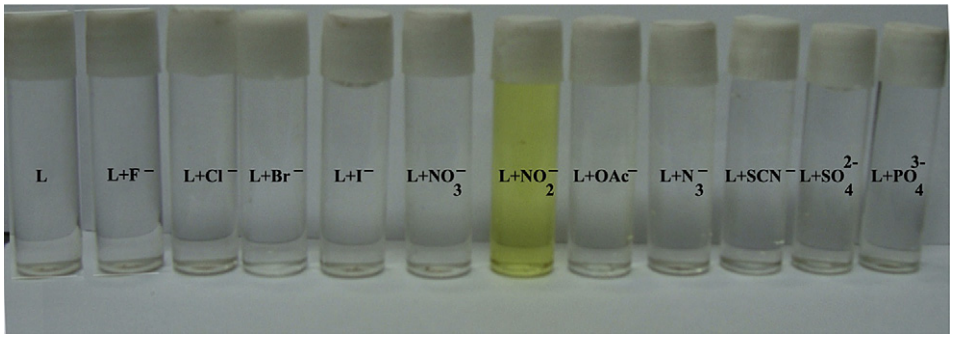
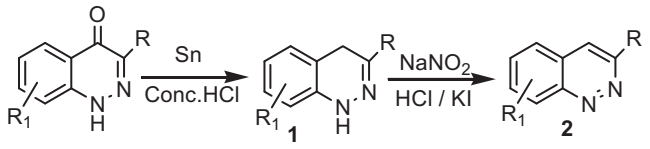


Fig. 3. Colorimetric studies for nitrite sensing (L=2-phenylethynyl aniline, 10^{-4} M in H_2O).

Table 3
Synthesis of 1,4-dihydrocinnolines and cinnolines



Entry	R	R_1	Yield[a] of	
			1	**2**
1	Hexyl	H	70	75
2	Butyl	4-Cl	75	70
3	Butyl	H	72	76

[a] Yields refer to those of pure isolated products characterized by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and HRMS).

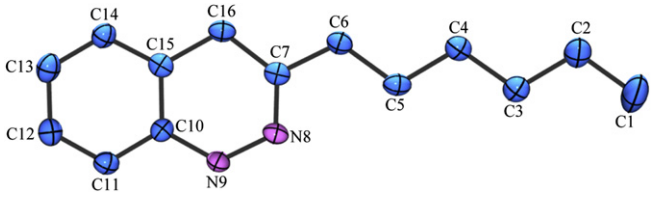
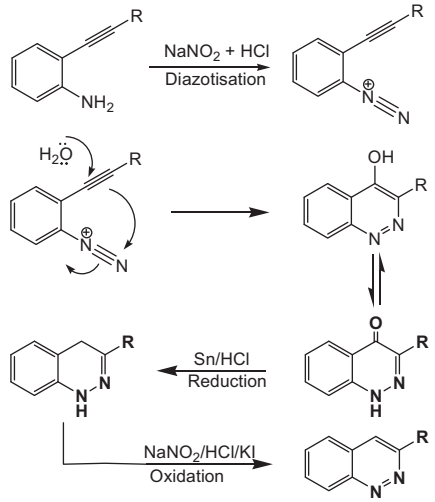


Fig. 4. ORTEP diagram of 3-hexyl-1,4-dihydrocinnoline.



Scheme 4. Possible reaction pathway.

4.2. General experimental procedure for the synthesis of 4(1*H*)-cinnolones. Representative procedure for 3-phenyl-1*H*-cinnolin-4-one (entry 1, Table 1)

To 2 N-acidic suspension (2 mL) of 2-phenylethynyl-phenylamine (193 mg, 1 mmol), $NaNO_2$ (103 mg, 1.5 mmol) was added in portions at 0–5 °C. The reaction mixture was stirred at 0–5 °C for 5 min followed by further 5 min at room temperature. The reaction mixture was extracted with EtOAc (2×5 mL), dried, concentrated and was left at room temperature to give 3-phenyl-1*H*-cinnolin-4-one as a pale yellow solid (204 mg, 92%), IR (KBr): 756, 1305, 1477, 1546, 2860, 2929 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.36–7.46 (m, 4H), 7.63 (d, J=8.4 Hz, 1H), 7.77 (t, J=7 Hz, 1H), 8.09–8.17 (m, 3H), 13.70 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 117.0, 124.0, 125.2, 125.3, 128.4 (2C), 128.8 (2C), 134.1, 135.5, 141.3, 146.0, 169.8; HRMS calcd for $C_{14}H_{10}N_2O$ (M^++H): 223.0871, Found: 223.0868.

The reactions of alkyl-substituted alkynes, the crude products were further stirred in water for another 4 h to allow the tautomeric mixture of cinnolones and hydroxy cinnolines to furnish only 3-alkyl-4(1*H*)-cinnolones.

These procedures were followed for all the reactions listed in Tables 1 and 2. A few of these products are known compounds and were identified by comparison of their spectra with those reported earlier.[13] The products, which were not reported earlier were characterized by their spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and HRMS). These data are provided below in order of their entries in Tables 1 and 2.

4.2.1. 3-p-Tolyl-1H-cinnolin-4-one (entry 2, Table 1). Yield 90%, pale yellow solid, IR (KBr): 667, 754, 821, 1301, 1477, 1545, 2841, 2887 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.33 (S, 3H), 7.23 (d, J=8 Hz, 2H), 7.41 (t, J=7.5 Hz, 1H), 7.61 (d, J=8 Hz, 1H), 7.77 (t, J=7.5 Hz, 1H), 7.99 (d, J=8 Hz, 2H), 8.13 (d, J=8 Hz, 1H), 13.62 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 21.4, 116.9, 123.8, 125.1, 125.2, 128.6 (2C), 128.9 (2C), 132.6, 134.0, 138.3, 141.2, 145.9, 169.7; HRMS calcd for $C_{15}H_{13}N_2O$ (M^++H): 237.101, Found: 237.101.

4.2.2. 7-Chloro-3-p-tolyl-1H-cinnolin-4-one (entry 4, Table 1). Yield 92%; pale yellow solid; IR (KBr): 819, 1051, 1454, 1537, 1560, 2825, 2885, 2982, 3051 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.32 (s, 3H), 7.22 (d, J=8 Hz, 2H), 7.40 (d, J=8.5 Hz, 1H), 7.65 (s, 1H), 7.96 (d, J=8 Hz, 2H), 8.11 (d, J=8.5 Hz, 1H), 13.74 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 21.4, 116.0, 122.3, 125.6, 127.8, 128.7 (2C), 129.0 (3C), 132.2, 138.6, 141.8, 146.5, 169.3; HRMS calcd for $C_{15}H_{12}ClN_2O$ (M^++H): 271.0638, Found: 271.0633.

4.2.3. 3-(4-Chloro-phenyl)-4-oxo-1,4-dihydro-cinnoline-6-carbonitrile (entry 5, Table 1). Yield 95%; pale yellow solid; IR (KBr): 823, 1091, 1300, 1487, 1585, 2231, 3027, 3277 cm^{-1}; ^{1}H NMR

(DMSO-d_6, 500 MHz) δ 7.37 (d, J=8.5 Hz, 2H), 7.68 (d, J=8.5 Hz, 1H), 7.94 (d, J=8.5 Hz, 1H), 8.0 (d, J=8 Hz, 2H), 8.3 (s, 1H), 14.1 (s, 1H), ^{13}C NMR (DMSO-d_6, 125 MHz) δ 107.4, 118.8, 123.1, 128.5 (3C), 130.4 (2C), 131.5, 133.4, 134.2, 135.3, 142.6, 145.9, 168.8; HRMS calcd for $C_{15}H_9ClN_3O$ (M^++H): 282.0434, Found: 282.0429.

4.2.4. 7-Chloro-3-(4-methoxy-phenyl)-1H-cinnolin-4-one (entry 7, Table 1). Yield 92%; pale yellow solid; IR (KBr): 827, 1055, 1300, 1556, 2885, 3054 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.7 (s, 3H), 7.0 (d, J=8.5 Hz, 2H), 7.23 (d, J=7.5 Hz, 1H), 7.48 (s, 1H), 7.98 (d, J=8 Hz, 1H), 8.18 (d, J=8.5 Hz, 2H), 13.90 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 55.56, 112.3, 113.9 (2C), 120.7, 121.2, 121.7, 124.1, 128.8, 131.7 (3C), 134.0, 142.8, 161.0; HRMS calcd for $C_{15}H_{12}ClN_2O_2$ (M^++H): 287.0587, Found: 287.0583.

4.2.5. 3-Hydroxymethyl-1H-cinnolin-4-one (entry 1, Table 2). Yield 80%; pale yellow solid; IR (KBr): 763, 1008, 1039, 1357, 1386, 1473, 2870, 2920, 3371 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.5 (s, 1H), 4.52 (s, 2H), 7.39–7.42 (m, 1H), 7.62 (d, J=8.4 Hz, 1H), 7.74–7.77 (m, 1H), 8.05 (d, J=8.1 Hz, 1H), 13.45 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 59.2, 116.9, 122.6, 124.4, 124.9, 134.0, 141.7, 149.6, 169.9; HRMS calcd for $C_9H_8N_2O_2Na$ (M^++Na): 199.0483, Found: 199.0483.

4.2.6. 3-(2-Hydroxy-ethyl)-1H-cinnolin-4-one (entry 2, Table 2). Yield 80%; pale yellow solid; IR (KBr): 750, 1012, 1182, 1367, 1548, 1570, 2833, 2879 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.5 (s, 1H), 2.88 (t, J=7 Hz, 2H), 3.72 (t, J=6.5 Hz, 2H), 7.37 (t, J=7 Hz, 1H), 7.55 (d, J=8.5 Hz, 1H), 7.75 (t, J=7.5 Hz, 1H), 8.04 (d, J=8 Hz, 1H), 13.25 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 34.3, 59.4, 116.6, 121.7, 124.5, 124.6, 133.8, 141.6, 148.9, 170.3; HRMS calcd for $C_{10}H_{10}N_2O_2Na$ (M^++Na): 213.0640, Found: 213.064.

4.2.7. 3-Hexyl-1H-cinnolin-4-one (entry 4, Table 2). Yield 83%; pale yellow solid; IR (KBr): 758, 1373, 1546, 2868, 2929 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.90 (t, J=7.2 Hz, 3H), 1.16–1.23 (m, 6H), 1.48–1.54 (m, 2H), 2.58 (t, J=7.5 Hz, 2H), 7.25 (t, J=7.5 Hz, 1H), 7.43 (d, J=8.5 Hz, 1H), 7.62 (t, J=8 Hz, 1H), 7.93 (d, J=8 Hz, 1H), 13.09 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 14.4, 22.5, 27.1, 29.0, 30.0, 31.6, 116.6, 121.6, 124.5, 124.6, 133.7, 141.6, 151.1, 170.0; HRMS calcd for $C_{14}H_{18}N_2ONa$ (M^++Na): 253.1317, Found: 253.1315.

4.2.8. 3-Butyl-7-chloro-1H-cinnolin-4-one (entry 5, Table 2). Yield 86%; pale yellow solid; IR (KBr): 876, 1074, 1180, 1373, 1508, 1543, 2835, 2960 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.87 (t, J=7.5 Hz, 3H), 1.29–1.33 (m, 2H), 1.54–1.60 (m, 2H), 2.64 (t, J=7 Hz, 2H), 7.32 (d, J=9 Hz, 1H), 7.54 (s, 1H), 7.99 (d, J=10 Hz, 1H), 13.24 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 14.3, 22.5, 29.3, 29.6, 115.6, 120.1, 125.0, 127.3, 138.5, 142.2, 151.9, 169.7; HRMS calcd for $C_{12}H_{13}ClN_2O$ (M^++Na): 259.0614, Found: 259.0610.

4.2.9. 7-Chloro-3-propyl-1H-cinnolin-4-one (entry 6, Table 2). Yield 83%; pale yellow solid; IR (KBr): 860, 1094, 1210, 1380, 1502, 1552, 2833, 3010 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.91 (t, J=7 Hz, 3H), 1.60–1.65 (m, 2H), 2.63 (t, J=7.5 Hz, 2H), 7.34 (d, J=9 Hz, 1H), 7.53 (s, 1H), 8.0 (d, J=8.5 Hz, 1H), 13.2 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 14.4, 20.5, 32.1, 115.7, 120.2, 125.1, 127.4, 138.6, 142.3, 151.9, 169.8; HRMS calcd for $C_{11}H_{11}ClN_2ONa$ (M^++Na): 245.0458; Found: 245.0453.

4.2.10. 3-Hexyl-4-oxo-1,4-dihydro-cinnoline-6-carbonitrile (entry 7, Table 2). Yield 80%; pale yellow solid; IR (KBr): 551, 837, 1180, 1381, 1475, 1572, 1629, 2229, 2928, 3130 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.82 (t, J=7.5 Hz, 3H), 1.23–1.32 (m, 6H), 1.56–1.60 (m, 2H), 2.65 (t, J=7.5 Hz, 2H), 7.65 (d, J=9 Hz, 1H), 7.99 (d, J=9 Hz, 1H), 8.37 (s, 1H), 13.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 19.1, 27.2, 31.6, 33.7, 34.7, 36.3, 111.2, 123.1, 123.6, 125.4, 136.0, 139.8, 147.8, 157.9, 174.1; HRMS calcd for $C_{15}H_{17}N_3ONa$ (M^++Na): 278.1269, Found: 278.1269.

4.3. General experimental procedure for the synthesis of 1,4-dihydrocinnolines. Representative procedure for 3-butyl-1,4-dihydrocinnoline (entry 3 [1], Table 3)

To concd HCl suspension (2 mL) of 3-butyl-1*H*-cinnolin-4-one (202 mg, 1 mmol), tin powder (298 mg, 2.5 mmol) was added in portions at 25 °C. The reaction mixture was stirred for 15 min with occasional warming at 50 °C for 2–3 times. The reaction mixture was extracted with EtOAc (2×5 mL) under basic condition (pH 12) to give 3-butyl-1,4-dihydro-cinnoline as a yellow solid (135 mg, 72%), IR (KBr): 709, 746, 1078, 1303, 1462, 1494, 1597, 2866, 2949, 3311 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, J=7 Hz, 3H), 1.34–1.39 (m, 2H), 1.53–1.62 (m, 2H), 2.31 (t, J=7.5 Hz, 2H), 3.25 (s, 2H), 6.69 (d, J=7.5 Hz, 1H), 6.92 (t, J=7 Hz, 1H), 7.02 (d, J=7.5 Hz, 1H), 7.11 (t, J=9.5 Hz, 1H), 7.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 22.6, 28.6, 29.7, 36.5, 111.9, 116.6, 122.2, 127.1, 127.6, 140.7, 147.7; HRMS calcd for $C_{12}H_{17}N_2$ (M^++H): 189.1392, Found: 189.1386.

This procedure was followed for all the reactions listed in Table 3. The products were all new compounds and were characterized by their spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and HRMS). These data are provided below in order of their entries in Table 3.

*4.3.1. 3-Hexyl-1,4-dihydro-cinnoline (entry 1[**1**], Table 3).* Yield 70%; pale yellow solid; IR (KBr): 640, 746, 1303, 1465, 1491, 1597, 2926, 3306 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, J=6 Hz, 3H), 1.25–1.35 (m, 6H), 1.56–1.62 (m, 2H), 2.36 (t, J=8 Hz, 2H), 3.29 (s, 2H), 6.72 (d, J=8 Hz, 1H), 6.93–6.96 (m, 2H), 7.03 (d, J=7.5 Hz, 1H), 7.12–7.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 22.5, 26.2, 29.1, 29.6, 31.7, 36.7, 112.0, 116.4, 122.9, 126.4, 127.1, 140.6, 147.8; HRMS calcd for $C_{14}H_{21}N_2$ (M^++H): 217.1705, Found: 217.1699.

*4.3.2. 3-Butyl-7-chloro-1,4-dihydro-cinnoline (entry 2[**1**], Table 3).* Yield 75%; pale yellow solid; IR (KBr): 669, 1066, 1591, 1741, 2856, 2926, 3421 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, J=7.5 Hz, 3H), 1.35–1.39 (m, 2H), 1.53–1.59 (m, 2H), 2.31 (t, J=7 Hz, 2H), 3.21 (s, 2H), 6.7 (s, 1H), 6.88 (d, J=8 Hz, 1H), 6.92 (d, J=8 Hz, 1H), 7.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 22.5, 28.4, 29.1, 36.4, 111.9, 114.9, 122.1, 128.7, 132.7, 141.4, 148.0; HRMS calcd for $C_{12}H_{15}N_2ClNa$ (M^++Na): 245.0821, Found: 245.0828.

4.4. General experimental procedure for the synthesis of cinnolines. Representative procedure for 3-butyl cinnoline (entry 3[2], Table 3)

To 2(M) HCl suspension (2 mL) of 3-butyl-1,4-dihydro-cinnoline (188 mg, 1 mmol), $NaNO_2$ was added (103 mg, 1.5 mmol) in portions at 5–10 °C. The reaction mixture was stirred for 15 min at this temperature and extracted with EtOAc (2×5 mL) and dried. Evaporation of solvent followed by column chromatography (R_f value: 0.7, hexane/EtOAc: 9:1) of the crude product gave 3-butyl-cinnoline as a yellow liquid (139 mg, 76%), IR (neat): 752, 1066, 1109, 1456, 1587, 1622, 2858, 2929, 2956, 3412 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (t, J=7.5 Hz, 3H), 1.38–1.42 (m, 2H), 1.81–1.87 (m, 2H), 3.19 (t, J=8 Hz, 2H), 7.60 (s, 1H), 7.63–7.66 (m, 1H), 7.70–7.73 (m, 2H), 8.45 (d, J=9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 22.4, 32.3, 35.8, 120.8, 126.3, 126.6, 129.6, 129.7, 131.0, 149.6, 158.0; HRMS calcd for $C_{12}H_{15}N_2$ (M^++H): 187.1235, Found: 187.1239.

This procedure was followed for all the reactions listed in Table 3. All of these products are new compounds and were characterized by their spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, and HRMS). These data are provided below in order of their entries in Table 3.

*4.4.1. 3-Hexyl-cinnoline (entry 1[**2**], Table 3).* Yield 75%; pale yellow liquid (R_f value: 0.7, hexane/EtOAc: 9:1); IR (neat): 731, 752, 1458, 1587, 2856, 2926, 3419 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.83 (t, J=7 Hz, 3H), 1.20–1.28 (m, 4H), 1.35–1.40 (m, 2H), 1.80–1.86 (m, 2H), 3.16 (t, J=8 Hz, 2H), 7.58 (s, 1H), 7.61–7.64 (m, 1H), 7.68–7.71 (m, 2H), 8.44 (d, J=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3, 22.6, 29.0, 30.2, 31.7, 36.2, 120.8, 126.4, 126.6, 129.6, 129.8, 131.0, 149.6, 158.0; HRMS calcd for $C_{14}H_{19}N_2$ (M^++H): 215.1548, Found: 215.1635.

*4.4.2. 3-Butyl-7-chloro-cinnoline (entry 2[**2**], Table 3).* Yield 70%; pale yellow liquid (R_f value: 0.6, hexane/EtOAc: 9:1); IR (neat): 756, 1245, 1458, 2850, 3450 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98 (t, J=7.5 Hz, 3H), 1.42–1.50 (m, 2H), 1.84–1.91 (m, 2H), 3.24 (t, J=7.5 Hz, 2H), 7.68 (d, J=7 Hz, 1H), 7.72 (s, 1H), 7.76 (d, J=9 Hz, 1H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 22.5, 32.3, 35.5, 121.7, 125.5, 127.9, 128.3, 132.9, 136.0, 149.4, 158.4; HRMS calcd for $C_{12}H_{14}N_2Cl$ (M^++H): 221.0845, Found: 221.0849.

Acknowledgements

We are pleased to acknowledge the financial support from DST, New Delhi through the award of J.C. Bose National Fellowship to B.C.R. (Grant no. SR/S2/JCB-11/2008). R.D. thanks CSIR, New Delhi for his fellowship. We sincerely thank to M. Arunachalam and B. Nisar Ahamed of IACS for their help in solving crystal structure of one of the compounds.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.016.

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