Tetrahedron 67 (2011) 2441–2446

Contents lists available at ScienceDirect

Tetrahedron

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

Base-free amination of BH acetates of 2-chloroquinolinyl-3-carboxaldehydes: a facile route to the synthesis of *N*-substituted-1,2-dihydrobenzo[*b*][1,8]-naphthyridines

Bhawana Singh, Atish Chandra, Radhey M. Singh *

Department of Chemistry, Banaras Hindu University, Varanasi 221005, U.P., India

ARTICLE INFO

Article history:
Received 4 December 2010
Received in revised form 22 January 2011
Accepted 25 January 2011
Available online 2 February 2011

Keywords:
Quinoline
Baylis–Hillman
Amination
Naphthyridine
Acridine

ABSTRACT

An efficient base-free one-pot synthesis of 1,2-dihydrobenzo[*b*][1,8]naphthyridines from BH acetates of 2-chloro-3-formylquinolines and activated alkenes followed by their acetylation, with different amines have been reported. These reactions are completed in very short time and provided the products in good to excellent yields. We further explored the scope of BH acetate with carbon nucleophile providing a new route to the synthesis of acridine derivative in excellent yield under mild condition.

1. Introduction

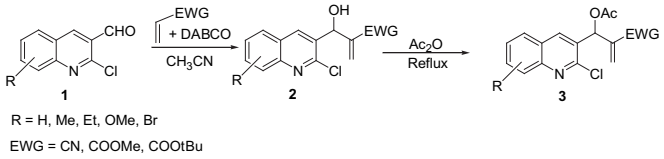
Functionalized quinolines and their annelated analogues have been well recognized by synthetic and medicinal chemists because their structural units are present in several natural products of biological significance.[1] Benzo[*b*]naphthyridines are pyrido-fused quinoline analogues, which possess important biological properties, such as antitumor, trypanocidal and antimicrobial agents.[2] They are also used as potent DNA-intercalating agents, mGlu1 antagonists and Src kinase inhibitors.[3] Although numerous methodologies have been developed for the synthesis of benzo[*b*]naphthyridine derivatives,[4] because of their pharmacological importance, the development of new and facile synthetic routes with wide general applicability is still attracting area for this class of compounds. Among the various available methods, the synthesis of benzo[*b*][1,8]naphthyridine derivatives from the Baylis–Hillman adducts of 2-nitrobenzaldehydes via Johnson–Claisen rearrangement, followed by reduction-double cyclization route have been recently explored.[5] Rao et al. have reported the synthesis of [1,8]naphthyridine-3-carboxylates from the Baylis–Hillman adducts of 2-chloronicotinaldehydes via nucleophilic-addition–elimination reaction followed by S_NAr reaction.[6] Nyerges et al. have reported the synthesis of 1*H*-pyrrolo[2,3-*f*]benzo[*b*][1,8]naphthyridines from 2-chloroquinolinyl-3-carboxaldehydes in multi-step route using intramolecular 1,3-dipolar cycloaddition.[7] However, these methods suffer from some limitations, such as high reaction temperature, longer reaction time and unsatisfactory yields. In our laboratory, our group is engaged in exploring the synthetic utility of easily accessible precursors, 2-chloroquinolinyl-3-carboxaldehydes for annulation reactions and functional group transformations. The easy accessibility of these versatile synthons from *N*-arylacetamides with Vilsmeier reagents[8] make them attractive for their further synthetic applications. We have reported in earlier work the synthesis of carbon and oxygen annulated quinoline derivatives from these precursors by choice of reagents, catalysts and other reactive partners.[9] Recently, we have reported the synthesis of benzo[*b*][1,6]naphthyridines from these precursors via Sonogashira coupling reaction followed by condensation–cyclization with aqueous ammonia.[9b] In continuation of our research interest to annulation reactions, we now report in this paper a facile route to the base-free synthesis of functionalized 1,2-dihydrobenzo[*b*][1,8]naphthyridines from the Baylis–Hillman acetates of 2-chloroquinolinyl-3-carboxaldehydes with aliphatic and aromatic amines in a very short duration of time. The Baylis–Hillman reactions, a well known coupling reaction of aldehydes and activated alkenes provides densely functionalized molecules in simple one-pot procedure, which are normally referred as the Baylis–Hillman adducts, have been considered as a valuable synthons for various organic transformations.[10]

* Corresponding author. Tel.: +91 542 6702482; fax: +91 542 2368127; e-mail address: rmohan@bhu.ac.in (R.M. Singh).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.01.076

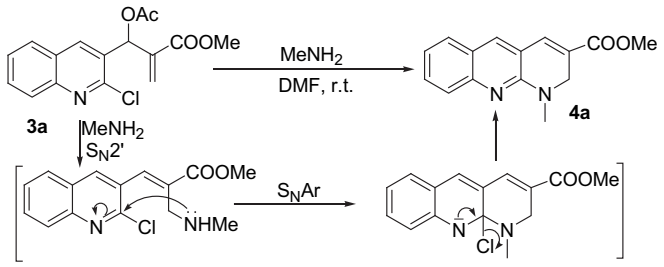
2. Results and discussion

The required Baylis–Hillman acetates were prepared in two steps from the reaction of 2-chloroquinolinyl-3-carboxaldehydes (1 equiv) with activated alkenes (1.2 equiv) in the presence of base DABCO (1.5 equiv) using CH_3CN as solvent (4–5 mL) at room temperature ranging from 4 to 8 h to afford BH adducts in moderate to good yields followed by their acetylation with acetic anhydride at reflux temperature for 2 h afforded the acetates of BH adducts in good to excellent yields (Scheme 1).



Scheme 1. Synthesis of Baylis–Hillman acetate.

Initially, we studied the reaction of BH acetates with methylamine under various conditions to find the optimal reaction condition with a view to obtain *N*-methyl 1,2-dihydrobenzo[*b*][1,8]naphthyridines[11] in one-pot two step protocol via S_N2' followed by S_NAr reactions (Scheme 2, Table 1). Thus, the reaction was first attempted using 1.0 equiv of BH acetate **3a**, 1.5 equiv of methylamine in DMF at room temperature. The reaction was completed in 5 min and provided only one product (91%), which was characterized as desired cyclized product **4a** on the basis of its spectral and analytical data. Lowering the reaction temperature to 0 °C did not show any effect on the chemical yield. Other solvents, such as DCM and EtOH proved to be equally effective. The use of CH_3CN and THF as solvents resulted in a lower yield of the desired product than others (Table 1). Further, the reaction of BH acetates with methylamine was examined under solvent-free condition. The reaction proceeded smoothly and provided the highest yield of desired product as found in DMF. Thus, based on the above optimization reaction conditions with methylamine the use of 1.0 mmol of substrate and 1.5 mmol of methylamine without using base in 4.0 mL of DMF at room temperature gave the best result.



Scheme 2. Synthesis of *N*-methyl 1,2-dihydrobenzo[*b*][1,8]naphthyridine **4a**.

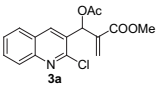
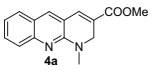
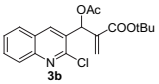
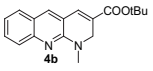
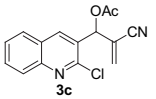
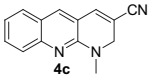
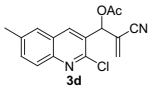
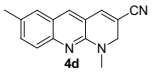
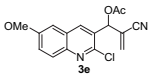
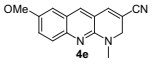
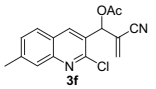
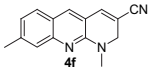
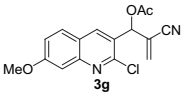
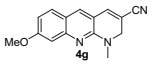
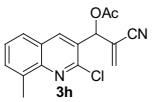
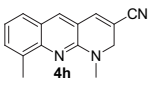
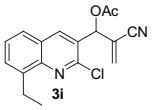
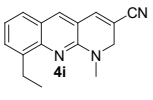
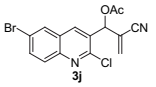
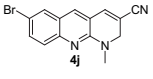
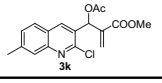
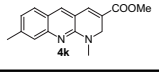
Table 1
Optimization of reaction conditions for the synthesis of *N*-methyl 1,2-dihydrobenzo-[*b*][1,8]naphthyridines **4a**

Entry	Solvent	Amine	Time (min)	Yield (%)	
				rt	0 °C
1	DMF	$MeNH_2$	5	91	90
2	CH_3CN	$MeNH_2$	5	70	68
3	DCM	$MeNH_2$	5	89	86
4	THF	$MeNH_2$	5	68	70
5	EtOH	$MeNH_2$	5	84	86
6	–	$MeNH_2$	5	91	88
7	–	$PhNH_2$	30	91[a]	74

[a] 60 °C.

To examine the generality of this base free reaction, other BH acetates **3b**–**k** were then allowed to react with methylamine under our standard reaction conditions, to afford the desired *N*-methyl 1,2-dihydrobenzo[*b*][1,8]naphthyridine derivatives in good to excellent yields (Table 2, entries 2–11). BH acetates **3b** bearing carbo *tert*-butoxy group and **3c** bearing cyano group, react well under optimized reaction conditions with methylamine to provide the desired cyclized products **4b** and **4c** in good yield, respectively (Table 2, entries 2, 3). The scope of subsituents in benzene ring with cyano group of BH acetates (**3d**–**k**) were further examined with methylamines under optimized reaction condition, BH acetates bearing electron-donating groups as well as electron-withdrawing group reacted smoothly in 5 min providing expected products in good to excellent yields.

Table 2
Base free cyclization of Baylis–Hillman acetates of quinoline with methylamine

Entry	Substrate	Product	Time (min)	Yield (%)
1			5	91
2			5	86
3			5	88
4			5	86
5			5	88
6			5	89
7			5	87
8			5	84
9			5	88
10			5	81
11			5	90

After optimizing reaction conditions for cyclization with methylamine, the generality of this reaction was then tested with variety of aliphatic amines, aromatic amines and hydrazines by using BH acetate **3a** as substrate (Table 3). Primary, secondary,

Table 3
Synthesis of 1,2-dihydrobenzo[*b*][1,8]naphthyridine with different amines

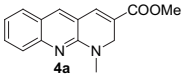
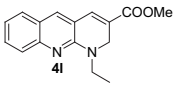
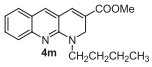
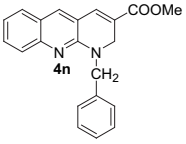
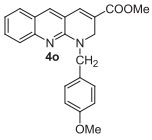
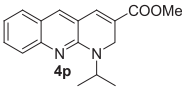
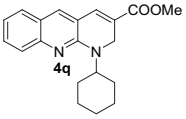
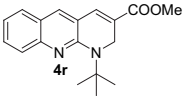
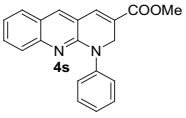
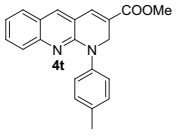
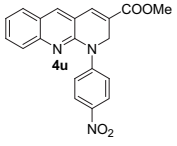
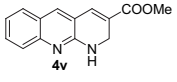
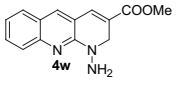
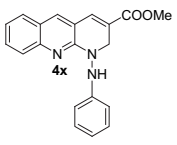
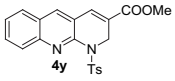
Entry	Substrate	Amines	Product	Time (min)	Yield (%)
1	3a	$MeNH_2$		5	91
2	3a	$EtNH_2$		5	92
3	3a	*n*-$BuNH_2$		5	93
4	3a	$PhCH_2NH_2$		5	93
5	3a	*p*-$OMePhCH_2NH_2$		5	95
6	3a	*i*-$PrNH_2$		5	91
7	3a	cyclohexylamine		5	91
8	3a	*t*-$BuNH_2$		5	85
9	3a	$PhNH_2$		30[a]	91
10	3a	*p*-$MePhNH_2$		20	92
11	3a	*p*-NO_2PhNH_2		30	86
12	3a	NH_3		5	90
13	3a	NH_2NH_2		5	91
14	3a	$PhNHNH_2$		5	94

Table 3 (*continued*)

Entry	Substrate	Amines	Product	Time (min)	Yield (%)
15	3a	$TsNH_2$		5	91[b]

[a] Reaction was incomplete at room temperature till 8 h.
[b] In presence of DMF and K_2CO_3.

tertiary alkyl primary amines, aqueous ammonia/ammonium acetate and hydrazines reacted under our standard conditions with **3a** in 5 min providing expected products in good to excellent yields (Table 3, entries 2–8, 12–14). Increasing the length (entries 2, 3), and branching (entries 6–8) of alkylamines do not show any effect on the rate of reaction. Binucleophilic hydrazines also show similar effect on the reaction rate. In contrast aromatic amines do not react with **3a** under optimized condition and starting material is isolated. However, increasing the temperature of reaction mixture to 60 °C aromatic amines reacted smoothly in 20–30 min (entries 9–11), which may be presumably due to less nucleophilicity of aromatic amines. Also aromatic amine bearing electron releasing group (entry 10) reacts with **3a** in shorter time than unsubstituted aromatic amine and amine bearing electron withdrawing group (entries 9, 11). It is worth mentioning that increasing the temperature of reaction mixture do not affect the yield of cyclized products **4s**–**u** (entries 9–11). Tosylamide is also employed as amine for the reaction with **3a**, but failed to undergo cyclization when varying the optimal reaction condition at room temperature or at 100 °C for longer times, which is presumably due to weak nucleophilicity of amino group of tosylamide. However, adding K_2CO_3 (1.5 mmol) to optimal reaction conditions (1.0 mmol **3a**, 1.5 mmol tosylamide, 4.0 mL DMF), the reaction proceeded smoothly at 90 °C for 5 min and provided the cyclized product **4y** in excellent yield (91%, entry 15) because nucleophile would be an anion of tosylamide.

The success of these reactions in above example led us to extend the applicability of different amines for the synthesis of targeted compounds (Table 3). We have also confirmed structure of the molecule **4o** (Fig. 1) by single-crystal X-ray data.[12]

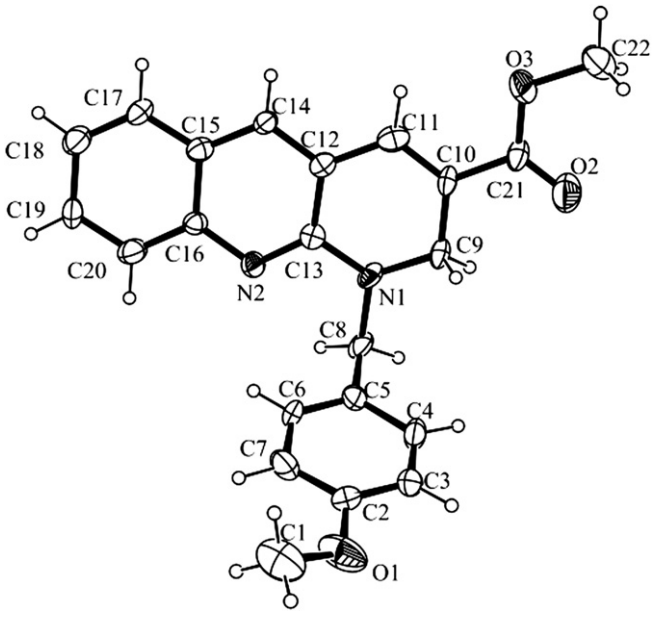
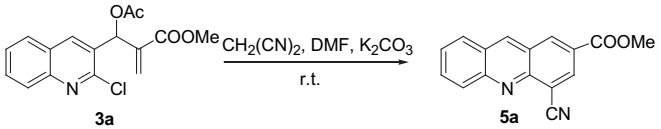


Fig. 1. Single crystal X-ray structure of **4o**.

After establishing the scope of BH acetates **3** with various amines to the synthesis of 1,2-dihydrobenzo[*b*][1,8]naphthyridines, we further explored this reaction for the synthesis of acridine derivatives with active methylene compound instead of amines. Thus, the reaction of **3a** with the conjugate base generated from the reaction of malanonitrile with K_2CO_3 under our optimized reaction condition provided acridine **5a** in excellent yield (95 %, Scheme 3). Further, study with other active methylene compounds is in progress.



Scheme 3. Synthesis of acridine derivative **5a**.

3. Conclusions

In conclusion, we have demonstrated a mild, convenient, one-pot and base-free synthesis of 1,2-dihydrobenzo[*b*][1,8]naphthyridine derivatives from Baylis–Hillman acetates derived from 2-chloro-3-formylquinolines and activated alkenes. The reaction provides products in good to excellent yields. This could also be used as synthons for further annulation reactions with binucleophiles. Further, the BH acetate provided the new and efficient route to the synthesis of acridine derivatives using carbon nucleophile.

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. ^1H (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 ^1H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). Highresolution mass spectra (HRMS) were recorded using Micro mass Q-TOF micro mass spectrometer apparatus using electron spray ionization mode from IIT Kanpur. 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 synthesis of 1,2-dihydrobenzo-[*b*][1,8]naphthyridine derivatives (4)

To a solution of BH acetate (0.25 mmol) and DMF (4.0 mL) added amine (0.37 mmol). The reaction mixture was continually stirred at room temperature for 5–30 min. After completion of the reaction (as monitored by TLC), the reaction mixture was allowed to pour into chilled water, the precipitate was filtered out and dried. The crude product was purified by column chromatography employing hexane–EtOAc (90:10, v/v) as eluent gave pure compounds **4**.

Products 4m, 4n, 4q, 4r, 4s, 4t, 4v and 4y are found in the literature. [Spectroscopic data in agreement with those reported in: Zhong, W.; Lin, F.; Chen, R.; Su, W. *Synthesis* **2009**, 2333.]

*4.2.1. 1-Methyl-1,2-dihydro-benzo[b][1,8] naphthyridine-3-carboxylic acid methyl ester (**4a**).* Yellow solid; yield: 91%; mp 130 °C; R_f (5% EtOAc/Hexane) 0.34; IR (KBr): 2945, 1695, 1616, 1240 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.17 (3H, s), 3.83 (3H, s), 4.55 (2H, s), 7.11 (1H, t, *J* 8.1 Hz), 7.39–7.57 (5H, m); δ_C (75 MHz, $CDCl_3$) 35.3, 51.1, 51.9, 117.0, 122.2, 123.6, 124.6, 126.0, 127.8, 130.4, 134.0, 135.7, 149.4, 154.2, 165.2; HRMS (EI): *m/z* $[M+H]^+$ found: 255.1133. $C_{15}H_{15}N_2O_2$ requires 255.1133.

*4.2.2. 1-Methyl-1,2-dihydro-benzo[b][1,8] naphthyridine-3-carboxylic acid tert-butyl ester (**4b**).* Light brown solid; yield: 86%; mp 70 °C; R_f (5% EtOAc/Hexane) 0.55; IR (KBr): 2976, 1697, 1619, 1254 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.57 (9H, s), 3.16 (3H, s), 4.49 (2H, s), 7.10 (1H, t, *J* 7.2 Hz), 7.29 (1H, s), 7.45 (3H, m), 7.55 (1H, d, *J* 9.0 Hz); HRMS (EI): *m/z* $[M+H]^+$ found: 297.1605. $C_{18}H_{21}N_2O_2$ requires 297.1603.

*4.2.3. 1-Methyl-1,2-dihydro-benzo[b][1,8] naphthyridine-3-carbonitrile (**4c**).* Yellow solid; yield: 88%; mp 170 °C; R_f (5% EtOAc/Hexane) 0.30; IR (KBr): 2922, 2228 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.14 (3H, s), 4.49 (2H, s), 7.09 (1H, s), 7.47–7.60 (5H, m); δ_C (75 MHz, $CDCl_3$) 35.2, 51.8, 106.1, 115.8, 116.9, 122.9, 123.5, 126.4, 128.0, 131.0, 135.8, 139.0, 149.4, 153.3; HRMS (EI): *m/z* $[M+H]^+$ found: 222.1033. $C_{14}H_{12}N_3$ requires 222.1031.

*4.2.4. 1,7-Dimethyl-1,2-dihydro-benzo[b][1,8] naphthyridine-3-carbonitrile (**4d**).* Light yellow solid; yield: 86%; mp 142 °C; R_f (10% EtOAc/Hexane) 0.25; IR (KBr): 2208, 2924 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.39 (3H, s), 3.12 (3H, s), 4.46 (2H, s), 7.07 (1H, s), 7.25–7.50 (4H, m); HRMS (EI): *m/z* $[M+H]^+$ found: 236.1182. $C_{15}H_{14}N_3$ requires 236.1188.

*4.2.5. 7-Methoxy-1-methyl-1,2-dihydro-benzo[b][1,8]naphthyridine-3-carbonitrile (**4e**).* Yellow solid; yield: 88%; mp 140 °C; R_f (10% EtOAc/Hexane) 0.30; IR (KBr): 2920, 2204, 1228 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.10 (3H, s), 3.85 (3H, s), 4.44 (2H, s), 6.85 (1H, s), 7.07 (1H, s), 7.15 (1H, d, *J* 9.0 Hz), 7.40 (1H, s), 7.52 (1H, d, *J* 9.0 Hz); δ_C (75 MHz, $CDCl_3$) 35.1, 51.7, 55.4, 106.3, 106.8, 116.1, 117.0, 122.4, 123.8, 127.8, 134.9, 139.1, 144.9, 152.3, 155.3; HRMS (EI): *m/z* $[M+H]^+$ found: 252.1139. $C_{15}H_{14}N_3O$ requires 252.1136.

*4.2.6. 1,8-Dimethyl-1,2-dihydro-benzo[b][1,8] naphthyridine-3-carbonitrile (**4f**).* Yellow solid; yield: 89%; mp 138 °C; R_f (10% EtOAc/Hexane) 0.60; IR (KBr): 2924, 2202 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.44 (3H, s), 3.13 (3H, s), 4.47 (2H, s), 6.99 (1H, d, *J* 8.4 Hz), 7.07 (1H, s), 7.37–7.43 (3H, m); δ_C (75 MHz, $CDCl_3$) 21.9, 35.2, 51.8, 105.3, 115.0, 117.1, 121.4, 124.9, 125.9, 127.8, 135.6, 139.2, 141.7, 149.5, 153.4; HRMS (EI): *m/z* $[M+H]^+$ found: 236.1187. $C_{15}H_{14}N_3$ requires 236.1188.

*4.2.7. 8-Methoxy-1-methyl-1,2-dihydro-benzo[b][1,8]naphthyridine-3-carbonitrile (**4g**).* Yellow solid; yield: 87%; mp 136 °C; R_f (10% EtOAc/Hexane) 0.26; IR (KBr): 2922, 2204 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.13 (3H, s), 3.90 (3H, s), 4.47 (2H, s), 6.79 (1H, d, *J* 9.0 Hz), 6.98 (1H, s), 7.05 (1H, s), 7.37–7.39 (2H, m); δ_C (75 MHz, $CDCl_3$) 35.1, 51.7, 55.4, 104.0, 105.9, 113.5, 114.9, 117.2, 118.1, 129.2, 135.4, 139.3, 151.3, 153.8, 162.3; HRMS (EI): *m/z* $[M+H]^+$ found: 252.1132. $C_{15}H_{14}N_3O$ requires 252.1136.

*4.2.8. 1,9-Dimethyl-1,2-dihydro-benzo[b][1,8] naphthyridine-3-carbonitrile (**4h**).* Yellow solid; yield: 84%; mp 180 °C; R_f (5% EtOAc/Hexane) 0.60; IR (KBr): 2924, 2202, 1620 cm^{-1}; δ_H (300 MHz,

$CDCl_3$) 2.58 (3H, s), 3.14 (3H, s), 4.49 (2H, s), 7.04–7.09 (2H, m), 7.34–7.38 (2H, m), 7.45 (1H, s); HRMS (EI): *m*/*z* $[M+H]^+$ found: 236.1188. $C_{15}H_{14}N_3$ requires 236.1188.

*4.2.9. 9-Ethyl-1-methyl-1,2-dihydro-benzo[b][1,8] naphthyridine-3-carbonitrile (**4i**).* Light brown solid; yield: 88%; mp 123 °C; R_f (5% EtOAc/Hexane) 0.30; IR (KBr): 2927, 2196, 1617 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.5 Hz), 3.04 (2H, q, *J* 7.5 Hz), 3.14 (3H, s), 4.49 (2H, s), 7.09–7.12 (2H, m), 7.34–7.38 (2H, m), 7.45 (1H, s); δ_C (75 MHz, $CDCl_3$) 14.4, 24.6, 35.0, 51.7, 105.9, 115.4, 122.7, 123.3, 125.9, 129.7, 131.0, 136.1, 139.2, 140.2, 147.5, 153.4; HRMS (EI): *m*/*z* $[M+H]^+$ found: 250.1343. $C_{16}H_{16}N_3$ requires 250.1344.

*4.2.10. 7-Bromo-1-methyl-1,2-dihydro-benzo[b][1,8]naphthyridine-3-carbonitrile (**4j**).* Light brown solid; yield: 81%; mp 124 °C; R_f (5% EtOAc/Hexane) 0.32; IR (KBr): 2925, 2206 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.13 (3H, s), 4.50 (2H, s), 7.06 (1H, s), 7.36–7.62 (4H, m); HRMS (EI): *m*/*z* $[M+H]^+$ found: 300.0134. $C_{14}H_{11}N_3Br$ requires 300.0136.

*4.2.11. 1,8-Dimethyl-1,2-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid methyl ester (**4k**).* Light brown solid; yield: 90%; mp 135 °C; R_f (5% EtOAc/Hexane) 0.33; IR (KBr): 2928, 1625, 1237 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.43 (3H, s), 3.15 (3H, s), 3.82 (3H, s), 4.53 (2H, s), 6.93–6.96 (1H, d, *J* 7.2 Hz), 7.34–7.37 (3H, m), 7.43 (1H, s); HRMS (EI): *m*/*z* $[M+H]^+$ found: 269.1296. $C_{16}H_{17}N_2O_2$ requires 269.1290.

*4.2.12. 1-Ethyl-1,2-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid methyl ester (**4l**).* Yellow solid; yield: 92%; mp 190 °C; R_f (10% EtOAc/Hexane) 0.30; IR (KBr): 2926, 1655, 1256 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.25 (3H, t, *J* 6.6 Hz), 3.72 (2H, q, *J* 6.9 Hz), 3.83 (3H, s), 4.57 (2H, s), 7.09 (1H, t, *J* 6.9 Hz), 7.26–7.54 (5H, m); HRMS (EI): *m*/*z* $[M+H]^+$ found: 269.1292. $C_{16}H_{17}N_2O_2$ requires 269.1290.

*4.2.13. 1-(4-Methoxy-benzyl)-1,2-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid methyl ester (**4o**).* Yellow solid; yield: 95%; mp 130 °C; R_f (5% EtOAc/Hexane) 0.50; IR (KBr): 2934, 1692, 1248 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.78 (3H, s), 3.79 (3H, s), 4.46 (2H, s), 4.90 (2H, s), 6.84–6.87 (2H, m), 7.13 (1H, t, *J* 7.8 Hz), 7.37–7.58 (7H, m); δ_C (75 MHz, $CDCl_3$) 48.3, 49.7, 51.9, 55.2, 113.9, 116.9, 122.3, 123.8, 124.7, 126.2, 127.7, 129.4, 129.8, 130.4, 133.8, 135.9, 149.4, 153.7, 158.9, 165.3; HRMS (EI): *m*/*z* $[M+H]^+$ found: 361.1551. $C_{22}H_{21}N_2O_3$ requires 361.1552.

*4.2.14. 1-Isopropyl-1,2-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid methyl ester (**4p**).* Yellow solid; yield: 91%; mp 135 °C; R_f (5% EtOAc/Hexane) 0.65; IR (KBr): 1709, 1249 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.24 (6H, d, *J* 6.9 Hz), 3.84 (3H, s), 4.46 (2H, s), 5.35–5.47 (1H, m), 7.09 (1H, t, *J* 7.5 Hz), 7.36–7.53 (5H, m); δ_C (75 MHz, $CDCl_3$) 10.3, 41.3, 43.9, 51.9, 117.5, 122.1, 123.3, 124.8, 126.1, 127.6, 130.2, 133.8, 135.7, 149.5, 153.6, 165.5 cm^{-1}; HRMS (EI): *m*/*z* $[M+H]^+$ found: 283.1447. $C_{17}H_{19}N_2O_2$ requires 283.1446.

*4.2.15. 1-(4-Nitro-phenyl)-1,2-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid methyl ester (**4u**).* Brown solid; yield: 86%; mp 135 °C; R_f (10% EtOAc/Hexane) 0.24; IR (KBr): 2922, 1715 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.87 (3H, s), 4.91 (2H, s), 7.56–7.67 (6H, m), 7.83 (2H, s), 8.26–8.29 (2H, m); δ_C (75 MHz, $CDCl_3$) 49.3, 52.3, 123.0, 124.2, 124.6, 125.2, 125.7, 127.2, 127.6, 127.7, 127.8, 127.9, 128.0, 130.9, 133.2, 135.8, 136.8, 164.8; HRMS (EI): *m*/*z* $[M+H]^+$ found: 362.1140. $C_{20}H_{16}N_3O_4$ requires 362.1141.

*4.2.16. 1-Amino-1,2-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid methyl ester (**4w**).* Yellow solid; yield: 91%; mp 96 °C; R_f (15% EtOAc/Hexane) 0.40; IR (KBr): 3512, 1712, 1248 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.83 (3H, s), 4.61 (2H, br s, D_2O exchangeable NH_2 proton), 4.71 (2H, s), 7.16 (1H, t, *J* 7.5 Hz), 7.39 (1H, s), 7.51–7.59 (4H, m); δ_C (75 MHz, $CDCl_3$) 52.0, 52.4, 117.3, 122.8, 124.0, 125.9, 126.0, 127.9, 130.6, 133.3, 135.5, 148.8, 154.7, 165.1; HRMS (EI): *m*/*z* $[M+H]^+$ found: 256.1082. $C_{14}H_{14}N_3O_2$ requires 256.1086.

*4.2.17. 1-Phenylamino-1,2-dihydro-benzo[b][1,8]naphthyridine-3-carboxylic acid methyl ester (**4x**).* Light brown solid; yield: 94%; mp 75 °C; R_f (10% EtOAc/Hexane) 0.30; IR (KBr): 3295, 1719, 1246 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.84 (3H, s), 4.75 (2H, s), 6.82–7.02 (5H, m, 1H D_2O Exchangeable), 7.34–7.62 (7H, m); δ_C (75 MHz, $CDCl_3$) 51.2, 52.0, 113.9, 117.3, 119.3, 120.9, 122.7, 123.3, 127.0, 128.6, 129.2, 130.5, 130.9, 133.4, 136.0, 141.0, 153.8, 165.0; HRMS (EI): *m*/*z* $[M+H]^+$ found: 332.1396. $C_{20}H_{18}N_3O_2$ requires 332.1399.

4.3. General procedure for the synthesis of 4-cyano-acridine-2-carboxylic acid methyl ester (5)

To a solution of BH acetate (0.25 mmol) and DMF (4.0 mL) were added malanonitrile (0.37 mmol) and K_2CO_3 (0.37 mmol). The reaction mixture was continually stirred at room temperature for 5 min. After completion of the reaction (as monitored by TLC), the reaction mixture was allowed to pour into chilled water and the precipitate was filtered out. The crude product was purified via column chromatography using silica gel column chromatography employing hexane–EtOAc (70:30, v/v) as eluent to give pure 5.

*4.3.1. 4-Cyano-acridine-2-carboxylic acid methyl ester (**5a**).* Yellow solid; yield: 95%; mp 145 °C; R_f (20% EtOAc/Hexane) 0.40; IR (KBr): 2201, 1615, 1022 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.06 (3H, s), 7.69 (1H, t, *J* 7.2 Hz), 7.96 (1H, t, *J* 7.2 Hz), 8.09 (1H, d, *J* 8.4 Hz), 8.42 (1H, d, *J* 8.4 Hz), 8.79 (1H, s), 9.00 (1H, s), 9.01 (1H, s); δ_C (75 MHz, $CDCl_3$) 29.7, 52.9, 113.8, 116.8, 124.8, 126.3, 127.6, 128.4, 130.2, 132.9, 136.1, 137.6, 139.0, 147.6, 151.1, 164.9; HRMS (EI): *m*/*z* $[M+H]^+$ found: 263.0823. $C_{16}H_{11}N_2O_2$ requires 263.0820.

Acknowledgements

We thank CSIR (New Delhi) and UGC (New Delhi) for funding. A.C. is thankful to UGC for awarding DSK Postdoc. fellowship, B.S. is thankful to CSIR, New Delhi, for the award of Senior Research Fellowship. We are also thankful to Prof. Y. D. Vankar and Prof. Sandeep Verma, Department Of Chemistry, IIT Kanpur for use of the HRMS facility.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.01.076. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. (a) Sekar, M.; Rajendra Prasad, K. J. *J. Nat. Prod.* **1998**, *61*, 294; (b) Puricelli, L.; Innocenti, G.; Delle Monache, G.; Caniato, R.; Filippini, R.; Cappelletti, E. M. *Nat. Prod. Lett.* **2002**, *16*, 95; (c) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888; (d) Wall, M. E.; Wani, M. C. *J. Ethnopharmacol.* **1996**, *51*, 239.
2. (a) Deady, L. W.; Rodemann, T.; Zhuang, L.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **2003**, *46*, 1049; (b) Deady, L. W.; Rogers, M. L.; Zhuang, L.; Baguley, B. C.; Denny, W. A. *Bioorg. Med. Chem.* **2005**, *13*, 1341; (c) Deady, L. W.; Devine, M. *Tetrahedron* **2006**, *62*, 2313.
3. (a) Chen, Q. P.; Leslie, W. D.; Bruce, C. B.; William, A. D. *J. Med. Chem.* **1994**, *37*, 593; (b) Wissner, A.; Hamann, P.R.; Yamashita, A. WO 0066583, 2000; CAN 133, 350203; (c) Mabire, D.; Coupa, S.; Adelinet, C.; Poncelet, A.; Simonnet, Y.; Venet, M.; Wouters, R.; Lesage, A. S. J.; Beijsterveldt, L. V.; Bischoff, F. *J. Med. Chem.* **2005**, *48*, 2134.
4. (a) Naik, T. R. R.; Naik, H. S. B.; Raghavendra, M.; Naik, S. G. K. *Arkivoc* **2006**, *xv*, 84; (b) Wang, Y. D.; Diane, H.; Boschelli, D. H.; Steven, J.; Erick, H. *Tetrahedron*

2004, *60*, 2937; (c) Nithyadevi, V.; Rajendran, S. P. *J. Heterocycl. Chem.* **2006**, *43*, 755; (d) Elkholy, Y. M. *Molecules* **2007**, *12*, 361.
5. Basavaiah, D.; Reddy, K. R. *Tetrahedron* **2010**, *66*, 1215.
6. Narender, P.; Ravinder, M.; Sadhu, P. S.; Raju, B. C.; Ramesh, C.; Rao, V. J. *Helv. Chim. Acta* **2009**, *92*, 959.
7. Toth, J.; Somfai, B.; Blasko, G.; Dancso, A.; Toke, L.; Nyerges, M. *Synth. Commun.* **2009**, *39*, 2258.
8. Singh, R. M.; Srivatava, A. *Indian J. Chem.* **2005**, *44b*, 1868. Other references therein.
9. (a) Chandra, A.; Singh, B.; Singh, R. M. *J. Org. Chem.* **2009**, *74*, 5664; (b) Singh, R. M.; Chandra, A.; Singh, B.; Upadhyay, S. *Tetrahedron* **2008**, *64*, 11680; (c) Singh, R. M.; Singh, B.; Chandra, A.; Upadhyay, S. *Tetrahedron Lett.* **2008**, *49*, 6423; (d) Singh, R. M.; Singh, M. K.; Chandra, A.; Singh, B. *Tetrahedron Lett.* **2007**, *48*, 5987; (e) Singh, R. M.; Chandra, A.; Singh, M. K. *Synth. Commun.* **2007**, *37*, 1689; (f) Singh, R. M.; Srivastava, A.; Chandra, A. *Indian J. Chem.* **2007**, *46B*, 303; (g) Singh, R. M.; Srivastava, A.; Singh, M. K. *Indian J. Chem.* **2006**, *45B*, 292; (h) Singh, R. M.; Srivastava, A.; Chandra, A. *Indian J. Chem.* **2005**, *44B*, 2077.
10. Hillman, M.E.D.; Baylis, A.B. U.S. Patent 3,743,669, 1973; (b) Baylis, A.B.; Hillman, M.E.D. Ger. Offen. DE 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 434174; (c) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815; (d) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; (e) Kataoka, T.; Kinoshita, H. *Eur. J. Org. Chem.* **2005**, 45.
11. During the course of our synthesis we found that Zhong et al. synthesized the benzo[*b*][1,8]naphthyridines using K_2CO_3 base in 4–5 h. But we have performed base-free synthesis of benzo[*b*][1,8]naphthyridines in very short duration of time. *Synthesis* **2009**, 2333.
12. CCDC-803389 (**4o**) 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.