Intramolecular Heck reaction: A facile sequential one-pot synthesis of 1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines

P. Bharath Kumar Reddy, K. Ravi, K. Mahesh, P. Leelavathi

PII: S0040-4039(18)31181-X
DOI: https://doi.org/10.1016/j.tetlet.2018.09.068
Reference: TETL 50307

To appear in: *Tetrahedron Letters*

Received Date: 25 June 2018
Revised Date: 21 September 2018
Accepted Date: 27 September 2018

Please cite this article as: Bharath Kumar Reddy, P., Ravi, K., Mahesh, K., Leelavathi, P., Intramolecular Heck reaction: A facile sequential one-pot synthesis of 1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.09.068

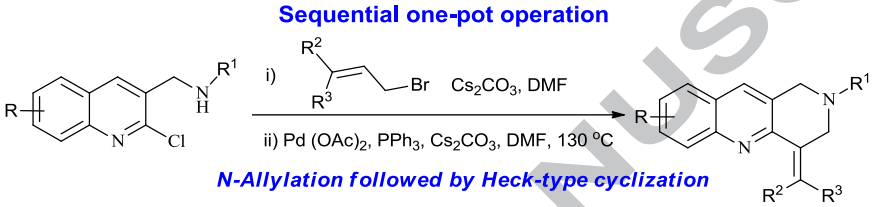
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Leave this area blank for abstract info.

Intramolecular Heck reaction: A facile sequential one-pot synthesis of 1,2,3,4-tetrahydro benzo[*b*][1,6]naphthyridines

P. Bharath Kumar Reddy, K. Ravi, K. Mahesh and P. Leelavathi*



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Intramolecular Heck reaction: A facile sequential one-pot synthesis of 1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines

P. Bharath Kumar Reddy, K. Ravi, K. Mahesh and P. Leelavathi*

Department of Chemistry, Osmania University, Hyderabad 500 007, India. E-mail: leelaou@gmail.com

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Keyword_1 1,6-Naphthyridines
Keyword_2 2-Chloro-3-formylquinolines
Keyword_3 Reductive amination
Keyword_4 Heck reaction
Keyword_5 Sequential one-pot synthesis

ABSTRACT

A simple and convenient sequential one-pot synthesis of 1,2,3,4-tetrahydrobenzo[*b*][1,6] naphthyridines has been developed. The reductive amination of 2-chloro-3-formylquinolines with various amines in the presence of sodium borohydride provided the corresponding secondary amines in high yields. Further, a sequential one-pot reaction involving *N*-allylation and intramolecular Heck type 6-*exo*-trig cyclization was performed on the secondary amines to afford a range of desired 1,2,3,4-tetrahydrobenzo[*b*][1,6]-naphthyridine derivatives in good to high yields.

Among various naphthyridines, 1,6-naphthyridines and their fused analogues are of interest as they showed exceptionally broad spectrum of biological activities[1] includinganti-inflammatory,[2] anticancer,[3] anti-HIV,[4] anti-HSV[5] antimicrobial,[6] cytotoxic[7] and adrenoceptor blocking[8] activities. Additionally, these are also reported as allosteric inhibitors[9] of Akt1 and Akt2, and antagonists of 5-HT4 receptors.[10] Lophocladine-A and Aaptamine are the naphthyridine alkaloids[11,12] found to be d-opioid receptor antagonist and cytotoxic respectively. The synthetic bronchodilator drugs,[13a] such as Benafentrine, Tolafentrine are developed based on benzo[*b*][1,6]naphthyridine derivatives, which are phosphopdiesterase inhibitors. As shown in the Fig. 1, the other interesting benzene fused 1,6-naphthyridines (**A** and **B**) displayed anti-proliferative activity[13b] in human tumor cells, **C** exhibited in vitro cytotoxicity against colon adenocarcinoma, ovarian carcinoma cell lines[13c] and **D** showed anti HSV-1 activity.[5]

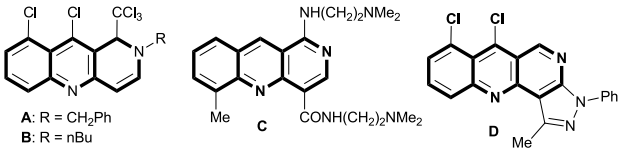
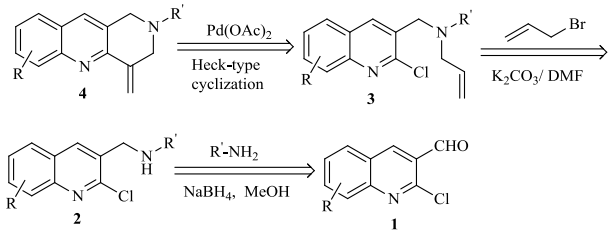


Fig. 1 Bioactive compounds with 1,6-naphthyridine skeleton.

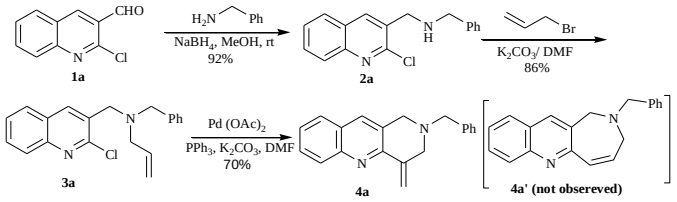
A number of synthetic strategies[14] have been reported for synthesis of 1,6-naphthyridines, however, their benzo-analogues are little explored. Recently, the groups of Verma[15] and Nagarajan[16] have reported independently the synthesis of benzo[*b*][1,6]naphthyridines from 2-alkynyl-quinoline-3-carbox-aldehydes *via* silver-catalyzed multicomponent reactions and copper(II)triflate-catalyzed heteroannulation, respectively. Singh and co-workers[17] described the synthesis of benzo[*b*]-[1,6]naphthyridines by annulation of 2-alkynyl-quinoline-3-carboxaldehydes[17a,b] with aqueous ammonia and also from 2-chloroquinoline-3-carbonitriles using elemental sulfur and amines as nucleophiles.[17c] The interesting pharmacological properties of 1,6-naphthyridines, stimulated us to make considerable efforts towards their synthesis. Not many methods[18] appear in the literature for the synthesis of fused naphthyridines as their pharmacological properties demand. With this pretext, we felt that it is still desirable to explore efficient methods for the synthesis of fused naphthyridines.

We envisioned that benzo[*b*]naphthyridines (**4**) can be synthesized by intramolecular Heck-type 6-*exo*-cyclization of corresponding *N*-allyl amines (**3**). The precursors (**2**) could be prepared from 2-chloro-3-formylquinolines (**1**) by reductive amination (Scheme 1). One-pot sequential or one-pot synthesis[19] are one of the most powerful synthetic strategies in the modern era of organic chemistry for being step-economy and environmentally benign. They avoid the tedious work-up procedure and purification of the intermediate, which would save time, energy, minimize waste and increase the efficiency. Herein, we wish to report a sequential one-pot synthesis of 1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines *via* *N*-allylation followed by intramolecular Heck-type cyclization.



Scheme 1: Retrosynthetic analysis of tetrahydronaphthyridines

Initially, we attempted the synthesis of tetrahydronaphthyridines (**4a**) in a step-wise manner as described in Scheme 2. The compound (**2a**) easily obtained from 2-chloro-3-formylquinoline[20] (**1a**) *via* reductive amination[21] with benzyl amine. The compound **2a** was treated with allylbromide/K_2CO_3 in DMF at room temperature for 15 h and the desired *N*-allyl product (**3a**) was obtained in 86% yield. The *N*-allyl derivative (**3a**) is then subjected to intramolecular Heck reaction with 5 mol% $Pd(OAc)_2$, tripenylphosphine (10 mol%) and potassium carbonate (2 eq.) in DMF at 130ºC under nitrogen atmosphere. The reaction is found clean and afforded the desired product in 70% yield. Exclusively one isomer of (**4a**) formed *via* 6-*exo*-trig cyclization, which was confirmed from the appearance of characteristic signals for *exo*-cyclic methylene protons in ^{1}H-NMR spectrum as a pair of doublets at δ 5.2 and 6.6 with *J*= 1.5 Hz. To our surprise, the other possible isomer (**4a'**) has not been observed *via* 7-*endo*-trig cyclization.

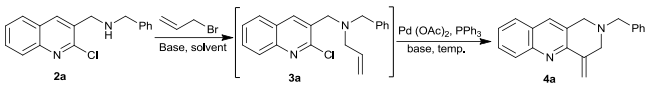


Scheme 2: Synthesis of tetrahydronaphthyridine (**4a**).

Encouraged by the result, we next explored the possibility of sequential one-pot synthesis of the compound (**4a**), as both reactions that is allylation and cyclization are being done in a common solvent and base. Our next investigation is to optimize the reaction conditions (Table 1) for sequential one-pot reaction. A mixture of **2a,** allyl bromide and potassium carbonate in DMF is stirred at room temperature for 15 h (till TLC indicated completion). Without isolation of **3a**, we performed the reaction with 5mol% $Pd(OAc)_2$, PPh_3(10 mol%) and K_2CO_3(2eq) in DMF at 100ºC for 3 h. This procedure afforded the desired product in 60 % yield (entry 1). Increasing the reaction temperature from 100 to 130ºC resulted in marginal increase in the yield of the product (entry 2). Changing the base K_2CO_3 to Et_3N decreased the efficiency of the reaction (entry 3). However, the use of Cs_2CO_3 provided a better yield of the product in less time (entries 4 and 5), the best result achieved at 130 ºC and the desired product in 82% yield (entry 5). On decreasing the catalyst loading to 2.5% of $Pd(OAc)_2$, the yield decreased (entry 6). Keeping the catalyst loading to 5 mol%, changing the solvent to toluene, 1,4-dioxane, THF and acetonitrile afforded the product only in moderate yields (entries 6-10). Therefore, we have continued with the sequential one-pot procedure for synthesis a variety of tetrahydronaphthyridine derivatives under optimized reaction conditions.

Having optimized the reaction conditions, we next focused our attention on the exploration of the substrate scope with sequential one-pot procedure. The results are summarized in Table 2. A variety of *N*-benzyl-quinoline-3-carbaldehydes (**2a-e)** were subjected *N*-allylation followed by intramolecular Heck-type reaction under optimized reaction conditions**.** The reaction proceeded smoothly with **2a-e** afforded the desired products (**4a-q**) in good to high yields. Substitution on the quinoline ring and benzyl amines has not played any important role on the outcome. Compared to benzyl amines, aniline were found to be less efficient. However, the efficiency increased with anilines having electron releasing groups like methyl and methoxy groups. Overall, all the reactions proceeded smoothly to afford the corresponding1,2,3,4-tetrahydrobenzo[*b*][1,6]naphthyridines in moderate to high yields.

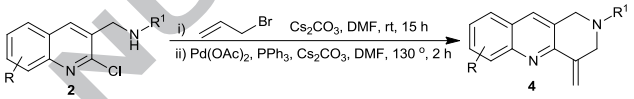
Table 1. Optimization of the reaction conditions for the synthesis of **4a**.[a]

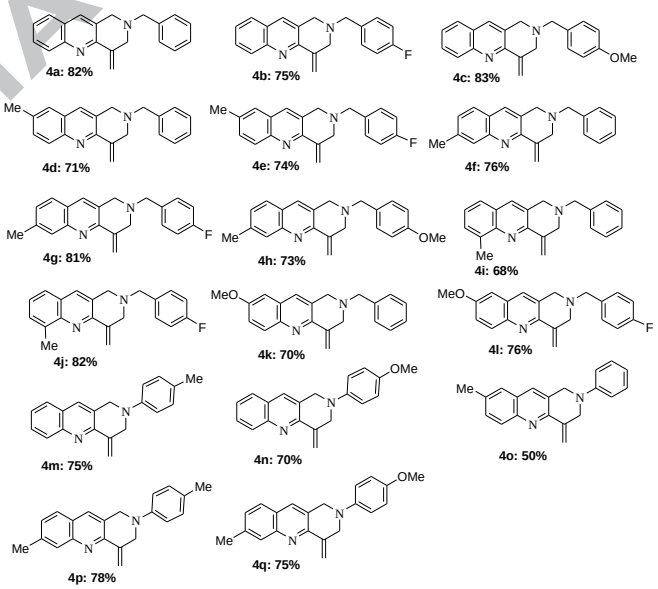


Entry	$Pd(OAc)_2$ mol%	Base	Solvent	Temp (ºC)	Time (h)	Yield[b] (%)
1	5	K_2CO_3	DMF	100	3	60
2	5	K_2CO_3	DMF	130	2	66
3	5	Et_3N	DMF	130	3	51
4	5	Cs_2CO_3	DMF	100	2	75
5	**5**	**Cs_2CO_3**	**DMF**	**130**	**2**	**84**
6	2.5	Cs_2CO_3	DMF	130	3	61
7	5	Cs_2CO_3	$PhCH_3$	120	5	45
8	5	Cs_2CO_3	Dioxane	100	5	46
9	5	Cs_2CO_3	THF	70	10	63
10	5	Cs_2CO_3	CH_3CN	85	10	65

Reaction conditions: [a]All reactions were carried out on a 0.25 mmol of 2-chloro-quinoline-3-ylmethyl)-aryl amines (**2a**, 1 eq.), allyl bromide (1 eq.), base (1.5 eq.), in solvent (2.5 mL). After 15 h, added $Pd(OAc)_2$, PPh_3 (10 mol%), and base (2 eq.). [b] Isolated yields after column chromatography.

Table 2. Sequential one-pot operation for synthesis of tetrahydro-naphthyridines (**4**).[a,b]

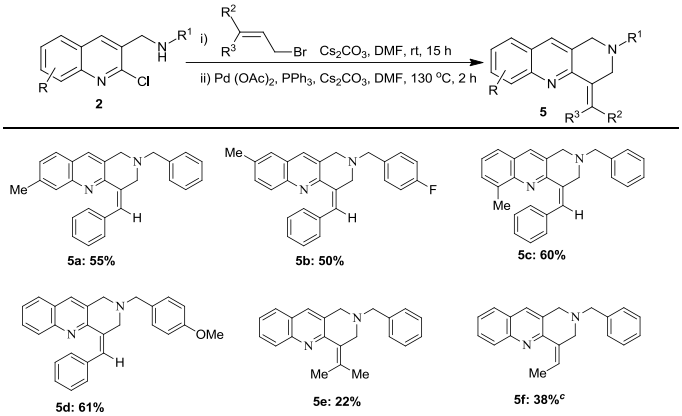




Reaction conditions: [a]All reactions were carried out on a 0.5 mmol of 2-chloro-quinoline-3-ylmethyl)-aryl amines (1 eq.), allyl bromide (1 eq.), Cs_2CO_3 (1.5 eq.) in DMF (5 mL). After 15 h, added $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), and Cs_2CO_3 (2 eq.); [b] Isolated yields after column chromatography.

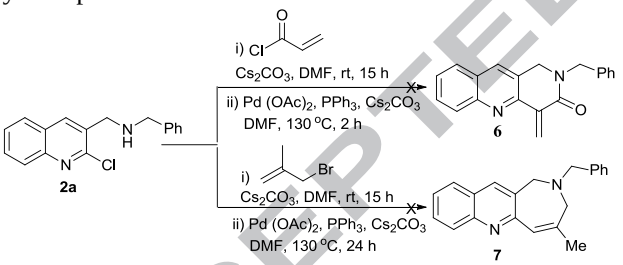
To demonstrate the efficiency and practicality**,** further we explored the generality and scope of this approach (Table 3), by extending our investigation to other allyl bromides such as cinnamyl bromide, crotyl bromide and 3,3-dimethylallyl bromide. A variety of *N*-benzyl-quinoline-3-carbaldehydes with cinnamyl bromide afforded corresponding 1,6-naphthyridines (**5a-d**) in moderate yields under optimized reaction conditions. Disappointingly, we could get only 22% yield of **5e** with 3,3-dimethylallyl bromide and formed a trace amount of the product **5f** with crotyl bromide. However, by loading another 5 mol% $Pd(OAc)_2$ after 1 h, the desired product **5f** afford in 38% yield.

Table 3. Sequential one-pot operation for synthesis of tetrahydro-naphthyridines (**5**).[a,b]



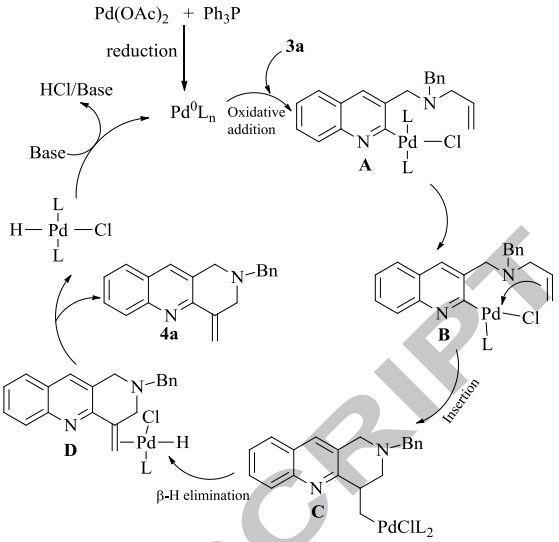
Reaction conditions: [a]All reactions were carried out on a 0.5 mmol of 2-chloro-quinoline-3-ylmethyl)aryl amines (1 eq.), corresponding allylbromides (1 eq.), Cs_2CO_3 (1.5 eq.) in DMF (5 mL). After 15 h, added $Pd(OAc)_2$ (5 mol%), PPh_3(10 mol%), and Cs_2CO_3 (2 eq.); [b] Isolated yields after column chromatography. [c] After 1 h added further 5 mol% of $Pd(OAc)_2$.

With a view to understand the generality, we next explored reaction of **2a** with acryloyl chloride for the synthesis of benzo[*b*][1,6]naphthyrid-3-one (**6**). Unfortunately, desired product (**6)** did not formed under the standard reaction conditions (Scheme 3). Further, we have also tried to get (**6)** in step-wise manner, but we could not succeed in getting the amide itself. We also extended the reaction to methallyl bromide to get the corresponding cyclised product **(**7**)** *via* 7-*endo*-trig cyclisation, but at the end of the sequential one pot reaction we could recover only the corresponding *N*-allylated product.



Scheme 3: Synthesis of tetrahydronaphthyridine derivative (**6** and **7**).

Based on the literature precedence,[22] a plausible mechanism for the Pd(0)-catalyzed intramolecular Heck cyclization of allyl-benzyl-(2- chloro-quinoline-3yl-methyl)-amine (**3a**) to benzo[*b*]-[1,6]napthyridines (**4a**) is given in Scheme 4. The first step in catalytic cycle is the oxidative addition of **3a** with Pd(0) species to form quinoline-palladium intermediate (**A**). Intermediate (**A**) then coordinates intramolecularly with double bond resulting in complex (**B**) followed by the insertion of double bond to give cyclized palladium intermediate (**C**), which further undergoes elimination of β-hydrogen to yield complex (**D**). Subsequent dissociation of **D** furnished the product **4a** and hydridopalladium(II) halide, which undergoes reductive elimination to regenerate the active Pd(0) complex.



Scheme 4: Plausible mechanism

Conclusions

In summary, we have successfully developed a sequential one-pot approach for the synthesis of benzo[*b*][1,6]naphthyridine derivatives from the 2-chloro-3-formyl quinolines *via* reductive amination followed by *N*-allylation and intramolecular Heck-type cyclization. The developed methodology is operationally simple, step-economical and efficient for synthesis of 1,6-naphthyridine derivatives. The generality and ready availability of the starting materials should make this an attractive method for the synthesis of biologically important benzo-naphthyridine motifs.

Acknowledgments

We thank UPE-FAR and OUDST-PURSE program for the financial assistance. PBKR thanks CSIR, New Delhi and KR and KM thank UGC, New Delhi for their fellowship. We also thank Department of Chemistry, OU for laboratory infrastructure under SAP (DRS-I) and DST-FIST programmes.

References and notes

1. (a) Yu, H.-B.; Yang, F.; Sun, F.; Ma, G.-Y.; Gan, J.-H.; Hu, W.-Z.; Han, B.-N.; Jiao, W.-H.; Lin, H.-W.*J. Nat. Prod*., **2014**, 77, 2124; (b) Pham, C.-D.; Hartmann, R.; Müller, W. E. G.; Voogd, N. D. ; Lai , D.; Proksch, P. *J. Nat. Prod*., **2013**, 76, 103; (c) Liu, C.; Tang, X.; Li , P.; Li, G.*Org. Lett*., **2012**,14, 1994.
2. (a) Srivastava, S. K.; Jaggi, M.; Singh, A.T.; Madan, A.; Rani, N.; Vishnoi, M.; Agarwal, S.K.; Mukherjee, R.; Burman, A. C.*Bioorg. Med. Chem. Lett*., **2007**, 17, 6660;(b)Insuasty, B.; Becerra, D.; Quiroga, J.; Abonia, R.; Nogueras, M.; Cobo. J. *Eur.J. Med. Chem*.,**2013**, 60,1.
3. (a)Gangjee, A.; Zeng, Y.; McGuire, J. J.; Kisliuk, R. L. *J. Med. Chem*.,**2002**, 45, 5173; (b) Tsuzuki, Y.; Tomita, K.; Sato,Y.; Kashimoto, S.; Chiba, K., *Bioorg. Med. Chem. Lett*., **2004**, 14, 3189.
4. Johns, B. A.; Weatherhead, J. G.; Allen, S. H.; Thompson, J. B.; Garvey, E. P.; Foster, S. A.; Jeffrey, J. L.; Miller, W. H. *Bioorg. Med. Chem. Lett*.,**2009**, 19, 1802.
5. Bernardino, A. M. R.; Castro, H. C.; Frugulhetti, I. C. P. P.; Loureiro, N. I.V.;Azevedo, A.R.; Pi nheiro, L. C. S.; Souza, T. M. L.; Giongo, V.; Passamani, F.;Magalhaes, U. O.; Albuquerque, M. G.; Cabral, L. M.; Rodrigues, C. R. *Bioorg. Med. Chem*., **2008**, 16, 313.
6. Ferrarini, P. L.; Manera, C.; Mori, C.; Badawneh, M.; Saccomanni, G. *Farmaco*, **1998**, 53,741.
7. Zeng, L.-F.; Wang, Y.; Kazemi, R.; Xu, S.; Xu, Z.-L.; Sanchez, T. W.; Yang, L.-M.;Debnath, B.; Odde, S.; Xie, H.; Zheng, Y.-T.; Ding, J.; Neamati, N.; Long, Y.-Q, *J. Med. Chem*.,**2012**, *55*, 9492.

8. Clark, R. D.; Repke, D. B. A.; Kilpatrick, T.; Brown, C. M.; MacKinnon, A.C.;Clague, R.U.; Spedding, M. *J. Med. Chem*.,**1989**, 32, 2034.
9. Li, Y.; Liang, J.; Siu, T.; Hu, E.; Rossi, M. A.; Barnett, S. F.; Jones, D. D.; Jones, R. E.; Robinson, R.G.; Leander, K.; Huber, H. E.; Mittal, S.; Cosford, N.; Prasit, P.,*Bioorg. Med. Chem. Lett.*,**2009,** 19, 834.
10. Ghotekar, B. K.; Ghagare, M. G.; Toche, R. B.; Jachak, M.N.,*Monatsh. Chem*.,**2010**, 141, 169.
11. Gross, H.; Goeger, D. E.; Hills, P.; Mooberry, S. L.; Ballantine, D. L.; Murray, T. F.;Valeriote, F. A.; Gerwick, W. H. *J. Nat. Prod*.,**2006**, 69, 640.
12. (a) Ohizumi, Y.; Kajiwara, A.; Nakamura, H.; Kobayashi, J. *J. Pharm. Pharmacol*.,**1984**, 36, 785; (b)Nakamura, H.; Kobayashi, J.; Ohizumi, Y.; Hirata, Y. *Tetrahedron Lett*., **1982**, 23, 5555.
13. (a) Freitag, A.; Wessler, I.; Racke, K. *Eur. J. Pharmacol*.,**1998**,354, 67; (b) Rudys, S,;Luci, C. R.; Roth, E. P.; Cikotiene, I, Padron, J. M. *Bioorg. Med. Chem. Lett*., **2010**, 20, 1504; (c)Deady, L. W.; Rodemann, T.; Zhuang, L.; Baguley, B, C.; Denny, W, A. *J. Med. Chem*., **2003**, 46, 1049.
14. (a) Okuma, K.; Koga, T.; Ozaki, S.; Suzuki, Y.; Horigami,K.; Nagahora, N.; Shioji, K.; Fukuda, M.; Deshimaru, M. *Chem. Commun*.,**2014**,50, 15525;(b) Tu, M.-S.; Li, Y.;Wang, X.; Jiang, B.;Wang, S.-L.; Tu, S.-J. *RSC Adv*.,**2013**, 3, 3877.
15. Verma, A. K.; Kotla, S. K. R.; Choudhary, D.; Patel, M.; Tiwari, R. K. *J. Org. Chem*., **2013**, 78, 4386.
16. Prakash, K. S.; Nagarajan, R. *Tetrahedron Lett*., **2013**, 54, 3635.
17. (a) Asthana, M.; Sharma, N.; Singh, R. M. *Tetrahedron*, **2014,** 70, 7996;(b) Chandra,,A.; Singh, B.; Upadhyay, S.; Singh, R. M. *Tetrahedron*,**2008,** 64,11680; (c) Asthana, M.; Kumar, R. ; Singh, R. M.,*J. Org. Chem*.,**2017**,82, 11531.
18. (a) Feng, B. -B.; Zhang, M. -M.; Wang, X. -S. *Polycyclic Aromatic Compounds*, **2016,** 36, 47; (b) Kumar, A. M. M. S.; Dhivya. P.;Rajendran,S. P. *J. Chin. Chem. Soc*., **2017,** 64, 138.
19. (a) Liu, W.; Jiang, H.; Huang, L. *Org. Lett*. **2010,** 12, 312; (b) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, 129, 2762; (c) Hayashi, Y, *Chem. Sci*.,**2016**, **7**, 866.
20. (a) Meth-Cohn, O.; Narine, B.; Tarnowiski. B., *J. Chem. Soc*., *Perkin Trans I*, **1981**, 1520;(b) Srivastava, A.; Singh, R. M. *Indian J. Chem*.,**2005**, 44B, 1868; (c) Srihari, E.; Siva Kumar, G.; Sai Kumar, CHNS.; Ratnesh Kumar, S.; Sukla, B.; Sridhar, B.; Rao, V. J., *Het. Commun*.,**2011**, 17, 111.
21. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, D. R., *J. Org. Chem*.,**1996,** 61, 3849.
22. (a) Shiri, M.; Fathollahi-Lahroud, M.; Zahra Yasaei, Z.; *Tetrahedron*, **2017**, 73, 2501; (b) Singh, R. M.; Chandra, A.; Sharma, N.; Singh, B.; Kumar, R.; *Tetrahedron*, **2012**, 68 9206.

Highlights

- Sequential one-pot approach for synthesis of benzo[*b*][1,6]naphthyridines is developed.

- A variety of naphthyridines have been accessed *via N*-allylation and Heck-type cyclization.

- This method is a simple, straightforward and broad substrate scope compatibility.