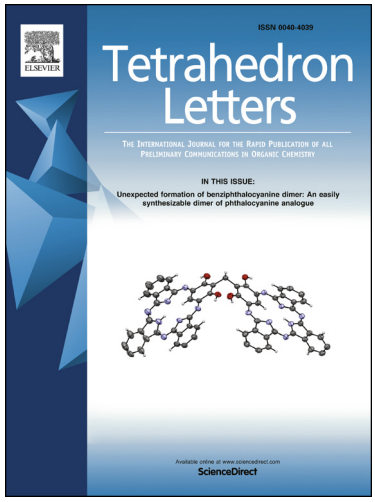


NBS mediated protocol for the synthesis of *N*-bridged fused heterocycles in water

Saket B. Bhagat, Vikas N. Telvekar

PII: S0040-4039(17)31006-7
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.08.017
Reference: TETL 49207

To appear in: *Tetrahedron Letters*

Received Date: 28 June 2017
Revised Date: 3 August 2017
Accepted Date: 7 August 2017

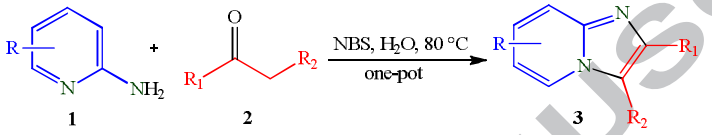
Please cite this article as: Bhagat, S.B., Telvekar, V.N., NBS mediated protocol for the synthesis of *N*-bridged fused heterocycles in water, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.08.017

Graphical Abstract

NBS mediated protocol for the synthesis of *N*-bridged fused heterocycles in water

Leave this area blank for abstract info.

Saket B. Bhagat, Vikas N. Telvekar*



ELSEVIER

Tetrahedron Letters

journal homepage: www.elsevier.com

NBS mediated protocol for the synthesis of *N*-bridged fused heterocycles in water

Saket B. Bhagat, Vikas N. Telvekar*

Department of Pharmaceutical Sciences & Technology, Institute of Chemical Technology, Matunga, Mumbai-400 019, India

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Heterocycle
diketone
NBS
-Water

ABSTRACT

A facile and environmental friendly protocol for the synthesis of *N*-bridged fused bicyclic compounds such as imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines, and imidazo[2,1-*b*]thiazole, from commercially available starting materials has been developed. The reaction proceeds via NBS mediated *in situ* formation of *α*-brominated intermediate of corresponding aromatic ketones, 1,3-diketones, *β*-keto esters, followed by trapping with suitable nucleophiles to provide these versatile imidazole fused bicyclic heterocycles in good yields under metal-free conditions.

The bridgehead nitrogen heterocycles, especially the fused imidazoles like imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines, and imidazo[2,1-*b*]thiazole, are an important class of privileged structural motifs in bioactive compounds, pharmaceuticals and organic functional materials. Amongst them, imidazo[1,2-*a*]pyridines exhibit a plethora of biological properties displayed over a broad range of therapeutic classes; including antibacterial, antifungal, antiviral, antiulcer, anti-inflammatory, β-amyloid formation inhibitors, immunosuppressive, GABA receptor agonists, cardiotonic agents, and nonpeptide B_2 receptor antagonists.[1] This structural motif imidazo[1,2-*a*]pyridine is an important ring system that has been successfully developed into commercially marketed drugs such as Alpidem, Zolpidem etc (Fig 1).[2]

Another fused imidazoles heterocycle which has gained much focus is imidazo[2,1-*b*]thiazole. The imidazo[2,1-*b*]thiazole is an attractive scaffold found in many natural products and biologically active compounds as antibacterial, antitubercular, antifungal, anthelmintic, antiinflammatory, and antitumor agents.[3] The imidazo[2,1-*b*]thiazole system constitutes the main part of the well-known antihelmintic-immuno modulatory agent such as Levamisole. Also, YM-201627, benzo[*d*]imidazo[2,1-*b*]thiazoles derivative, has been reported as a potent orally active antitumor agent.[4] The versatility of these *N*-heterocycles has prompted great interest in the development of novel and efficient methodologies to gain an easy access to these bicyclic ring systems.[5] The most widely used approach for the synthesis of imidazo[1,2-*a*]pyridines involves the construction of imidazole rings by cyclocondensation of suitably substituted pyridine precursors

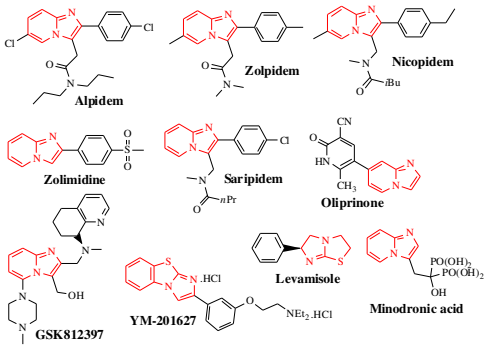


Figure 1. Commercial drugs on imidazo[1,2-*a*]pyridine/imidazo[2,1-*b*]thiazole

such as 2-aminopyridines with various compounds, such as *α*-halocarbonyl,[6] 1,3-dicarbonyl,[7] nitroolefins,[8] alkynes,[9] diazoketones,[10] 1,2-diols,[11] 1-chloromethyl-benzotriazole,[12] 1,2-bis (benzotriazolyl)-1,2-(dialkylamino)-ethanes.[13] Also, 2-halo-1-phenacyl/alkyl pyridinium salts, pyridinium azomethine ylides, and other derivatives have been explored as precursors for construction of these heterocycles.[14] The imidazopyridine nucleus have reportedly been synthesized from substituted imidazoles too.[15] A multi-component approach involving one-pot condensations of 2-aminopyridines, aldehydes, and isonitriles, also referred as Groebke-Blackburn-Bienayme reaction.[16] Recently, this ring system has also been synthesized from 2-aminopyridine and 1,3-dicarbonyl compounds using reagents such as CBr_4 and $CBrCl_3$, however, these polyhalogenated reagents are known environmental hazards and the reaction requires a strong base, organic solvent, long reaction time, thus limiting the utility of these protocols.[17]

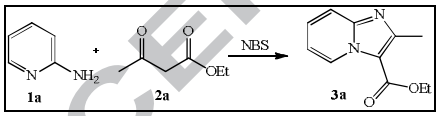
* Corresponding author. Tel.: +91 22 3361 2213; fax: +91 22 3361 1020.
E-mail address: vikastelvekar@rediffmail.com (V.N. Telvekar).

Although elegant processes have been reported, the traditional method for the construction of this scaffold involves condensation of 2-aminopyridines with α-halocarbonyl compounds both at laboratory and industrial scale. However, the commercial availability of only small variety of α-halocarbonyl compounds, their stability and their lachrymatory properties severely restrict the utility of this process. Thus, there is an intrinsic need to develop a simpler, practical and atom-economical synthesis of these significant bioactive motifs from simple precursors. Compared to pre-activated ketones, the use of unactivated ketones as starting substrates for imidazo[1,2-*a*]pyridine synthesis is highly desirable.

Our approach is to activate the ketones, followed by their reaction with appropriate nucleophiles to provide a diverse range of these heterocycles in one step. Thus, in continuation of our interest on the exploration of novel environment friendly approaches in synthetic organic chemistry, we report herein a NBS mediated, method for the construction of *N*-bridged fused heterocycles from readily available starting material using water as a solvent.

The study was initiated by using 2-aminopyridine (**1a**) and ethyl acetoacetate (**2a**) as model substrates in presence of NBS to optimize the reaction conditions. No reaction was observed in water at room temperature even after 24h (Table 1, entry 1), but, when the reaction was performed at elevated temperature (80 °C), the product **3a** was obtained in 35% yield within 6 h (Table 1, entry 2). Furthermore, the use of other solvent such as EtOH, MeOH, MeCN and CCl_4, did not have any noteworthy impact on the yield of **3a** (Table 1, entries 3-6). However, the yield of the desired product **3a** was significantly improved when ethyl acetoacetate (**2a**) was first reacted with NBS at 80 °C in water for 30 min, followed by the addition of 2-aminopyridine (**1a**) and heating at 80 °C for another 30 min (Table 1, entry 7). A further decrease in the temperature to 60 °C had detrimental impact on the yield of **3a** (Table 1, entry 8), while bringing the temperature to reflux did not advance the yield of **3a** (Table 1, entry 9). Thus, it was determined that NBS (1.2 equiv) at 80 °C in water were the optimal reaction conditions for this transformation (Table 1, entry 7).

Table 1. Screening of the reaction conditions[a]

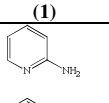
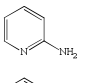
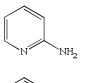
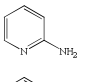
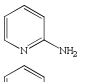
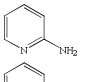
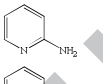
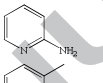
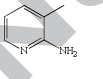
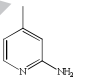
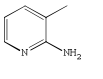
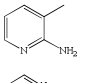
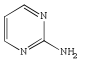
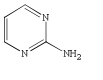
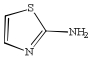
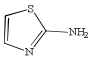
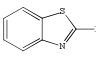


Entry	Solvent	Temperature	Yield (%)[c]
1	H_2O	RT	NR
2	H_2O	80 °C	35
3	EtOH	Reflux	30
4	MeOH	Reflux	25
5	CH_3CN	Reflux	15
6	CCl_4	Reflux	40
7[b]	H_2O	80 °C	91
8[b]	H_2O	60 °C	60
9[b]	H_2O	Reflux	88

[a]Reaction conditions: 2-aminopyridine (**1a**, 1.0 mmol), ethyl acetoacetate (**2a**, 1.05 mmol), NBS (1.2 mmol) in water (5.0 mL). [b]Ethyl acetoacetate (**2a**, 1.05 mmol), NBS (1.2 mmol) in water (5.0 mL) heated for 30 min. Subsequently, 2-aminopyridine (**1a**, 1.0 mmol) was added to this reaction mixture, heated until the disappearance of **2a**, monitored by TLC. [c]Isolated yield. NR: no reaction.

With the above optimized reaction condition in hand, the scope of the methodology was investigated and the results are summarized in Table 2.[18]

Table 2. Synthesis of *N*-bridged fused heterocycles[a]

Entry	Amine (1)	Ketone (2)	Product (3)	Yield (%)
1				91
2				86
3				94
4				89
5				84
6				78
7				81
8				83
9				94
10				92
11				87
12				80
13				71
14				67
15				70
16				64
17				61

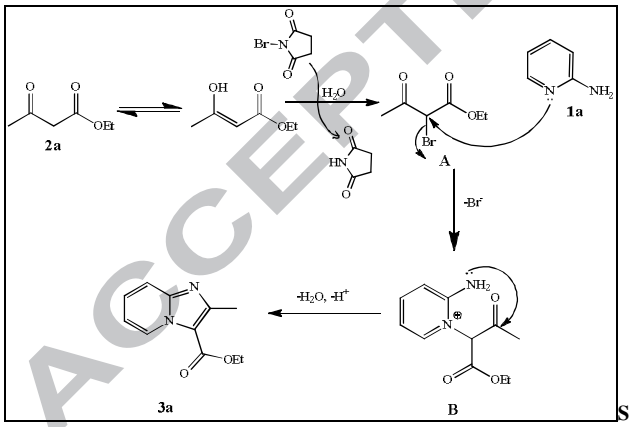
[a]Reaction conditions: 1.05 mmol of β-diketones/β-keto esters/aryl ketones, 1.2 mmol of NBS in water at 80 °C for 30 min, followed by addition of 1.0 mmol of appropriate nucleophile and heating at 80 °C. [b]Isolated yields after column chromatography and the structures were confirmed by comparison of IR, ^{1}H NMR and M.P. with literature.

The reaction of 2-aminopyridine (**2a**) with various β–keto esters and 1,3-diketones, gave the corresponding products smoothly in good to excellent yields (Table 2, entries 1-4). Next, 2-aminopyridine was reacted with aryl methyl ketones bearing an electron withdrawing or an electron donating substituent on the phenyl ring, the corresponding product was obtained in good yield in all the cases (Table 2, entries 5-7). Encouraged by this

result, 2-aminopyridine was reacted with heteroaryl ketone, *viz* 2-acetylthiophene, which also furnished the desired product in good yield (Table 2, entry 8). To further expand the substrate scope, substituted 2-aminopyridine were subjected to the reaction condition. Reaction of 3-methyl and 4-methyl-2-aminopyridines with *β*–keto esters, 1,3-diketones and aryl methyl ketones, afforded the corresponding imidazo[1,2-*a*]pyridines in good to moderate yield (Table 2, entries 9-12). Next, we shifted to investigate the scope of other nucleophiles, such as 2-aminopyrimidine, 2-aminothiazole and 2-aminobenzothiazole. These heterocycles did not affect the overall efficiency of the reaction and the corresponding products **3m–3q** were furnished in good to moderate yields (Table 2, entries 13-17).

To gain an insight into the mechanism of this transformation, control experiments were carried out. Initially, ethyl acetoacetate **2a** was reacted with NBS under the present optimised reaction conditions for 30 min and the intermediate **A** was isolated in a quantitative yield. Further, the reaction of this isolated intermediate **A** with 2-aminopyridine **2a** gave the corresponding product **3a** in excellent yield. These results indicated that **A** is the intermediate formed in this transformation. Based on the above results, a tentative mechanism of the reactions is shown in Scheme 1, taking the reaction of 2-aminopyridine **1a** and ethyl acetoacetate **2a** for the synthesis of imidazo[1,2-*a*]pyridine **3a** as an example. As depicted in Scheme 1, **2a** is first brominated with NBS in water to give intermediate **A**. The *in situ* generated intermediate **A** underwent an intermolecular nucleophilic substitution reaction with 2-aminopyridine **2a** to obtain intermediate **B**. Finally, intermediate **B** further underwent an intramolecular cyclization to afford the desired product imidazo[1,2-*a*]pyridine **3a**.

Further, to demonstrate the scalability of this process, a multigram preparation of imidazo[1,2-*a*]pyridine **3a** was attempted. The reaction of 2-aminopyridine (**1a**) with ethyl acetoacetate (**2a**) performed on a 10 g scale, under the optimal reaction conditions, furnished the desired imidazo[1,2-*a*]pyridine **3a** in a comparable yield (82%).



Scheme 1. Plausible reaction mechanism

In conclusion, an NBS-mediated one-pot strategy in water has been proposed for the synthesis of *N*-bridged fused bicyclic heterocycles. The process involves the reaction of 2-aminopyridines, or 2-aminopyrimidines, or 2-aminothiazole, with *β*-keto esters, or 1,3-diones, or aryl ketones, to construct imidazo[1,2-*a*]pyridines, or imidazo[1,2-*a*]pyrimidines, or imidazo[2,1-*b*]thiazole, respectively. It is notable that the present protocol has a broad scope of substrates owing to the generality of the reaction and the commercial availability of the starting materials and the promoter. The method is advantageous in terms of its high efficiency, mild reaction conditions, operational simplicity, absence of expensive transition metal catalyst or toxic solvents, the ease of product isolation, and the higher yield.

Acknowledgment

SBB is thankful to the University Grants Commission (UGC, New Delhi, India) for providing fellowship and VNT is thankful for financial support under UGC major research scheme.

References

1. (a) Lacerda, R. B.; De Lima, C. K.; Da Silva, L. L. *Bioorg. Med. Chem. Lett*. **2009**, *17*, 74; (b) Rupert, K. C.; Henry, J. R.; Dodd, J. H.; Wadsworth, S. A.; Cavender, D. E.; Olini, G. C.; Fahmy, B.; Siekierka, J. J. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 347; (c) Zhuang, Z. P.; Kung, M. P.; Wilson, A.; Lee, C. W.; Plossl, K.; Hou, C.; Holtzman, D. M.; Kung, H. F. *J. Med. Chem*. **2003**, *46*, 237; (d) Goodacre, S. C.; Street, L. J.; Hallett, D. J.; Crawforth, J. M.; Kelly, S.; Owens, A. P.; Blackaby, W. P.; Lewis, R. T.; Stanley, J.; Smith, A. J.; Ferris, P.; Sohal, B.; Cook, S. M.; Pike, A.; Brown, N.; Wafford, K. A.; Marshall, G.; Castro, J. L.; Atack, J. R. *J. Med. Chem*. **2006**, *49*, 35; (e) Humphries, A. C.; Gancia, E.; Gilligan, M. T.; Goodacre, S.; Hallett, D.; Marchant, K. J.; Thomas, S. R. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 1518; (f) Fookes, C. J. R.; Pham, T. Q.; Mattner, F.; Greguric, I.; Loc'h, C.; Liu, X.; Berghofer, P.; Shepherd, R.; Gregoire, M.-C.; Katsifis, A. *J. Med. Chem*. **2008**, *51*, 3700; (g) Abe, Y.; Kayakiri, H.; Satoh, S.; Inoue, T.; Sawada, Y.; Imai, K.; Inamura, N.; Asano, M.; Hatori, C.; Katayama, A.; Oku, T.; Tanaka, H. *J. Med. Chem*. **1998**, *41*, 564.
2. (a) Okubo, T.; Yoshikawa, R.; Chaki, S.; Okuyama, S.; Nakazato, A. *Bioorg. Med. Chem*. **2004**, *12*, 423; (b) Mori, H.; Tanaka, M.; Kayasuga, R.; Masuda, T.; Ochi, Y.; Yamada, H.; Kishikawa, K.; Ito, M.; Nakamura, T. *Bone* **2008**, *43*, 840; (c) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem*. **2007**, *7*, 888.
3. (a) Güzeldemirci, N. U.; Küçükbasmacı, Ö. *Eur. J. Med. Chem*. **2010**, *45*, 63; (b) Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Lenaz, G.; Fato, R.; Bergamini, C.; Farruggia, G. *J. Med. Chem*. **2005**, *48*, 3085; (c) Gürsoy, E.; Güzeldemirci, N. U. *Eur. J. Med. Chem*. **2007**, *42*, 320; (d) Andreani, A.; Burnelli, S.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Calonghi, N.; Cappadone, C.; Farruggia, G.; Zini, M.; Stefanelli, C.; Masotti, L.; Radin, N. S.; Shoemaker, R. H. *J. Med. Chem*. **2008**, *51*, 809; (e) Park, J.-H.; El-Gamal, M. I.; Lee, Y. S.; Oh, C.-H. *Eur. J. Med. Chem*. **2011**, *46*, 5769.
4. (a) Raeymaekers, A. H. M.; Allewijn, F. T. N. *J. Med. Chem*. **1966**, *9*, 545; (b) Furlan, A.; Colombo, F.; Kover, A.; Issaly, N. *Eur. J. Med. Chem*. **2012**, *47*, 239.
5. Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A. *Chem. Commun*. **2015**, *51*, 1555.
6. (a) Herath, A.; Dahl, R.; Cosford, N. D. P. *Org. Lett*. **2010**, *12*, 412; (b) Denora, N.; Laquintana, V.; Pisu, M. G.; Dore, R.; Murru, L.; Latrofa, A.; Trapani, G.; Sanna, E. *J. Med. Chem*. **2008**, *51*, 6876.; (c) Paudler W. W.; Kuder, J. E. *J. Org. Chem*. **1966**, *31*, 809; (d) Chunavala, K. C.; Joshi, G.; Suresh, E.; Adimurthy, S. *Synthesis* **2011**, *42*, 635; (e) Hand, E. S.; Paudler, W. W. *Tetrahedron* **1982**, *38*, 49.
7. (a) Wang, X.; Ma, L.; Yu, W. *Synthesis* **2011**, *15*, 2445; (b) Ma, L.; Wang, X.; Yu W.; Han, B. *Chem. Commun*. **2011**, *47*, 11333.
8. (a) Santra, S.; Bagdi, A. K.; Majee A.; Hajra, A. *Adv. Synth. Catal*. **2013**, *355*, 1065; (b) Nair, D. K.; Mobin S. M.; Namboothiri, I. N. N. *Org. Lett*. **2012**, *14*, 4580; (c) Yan, R.-L.; Yan, H.; Ma, C.; Ren, Z.-Y.; Gao, X.-A.; Huang, G.-S.; Liang, Y.-M. *J. Org. Chem*. **2012**, *77*, 2024.

9. (a) He, C.; Hao, J.; Xu, H.; Mo, Y.; Liu, H.; Han J.; Lei, A. *Chem. Commun.* **2012**, *48*, 11073; (b) Zeng, J.; Tan, Y. J.; Leow M. L.; Liu, X.-W. *Org. Lett.* **2012**, *14*, 4386.
10. Yadav, J. S.; Reddy, B. V. S.; Rao, Y. G.; Srinivas, M.; Narsaiah, A. V. *Tetrahedron Lett*. **2007**, *48*, 7717.
11. Kondo, T.; Kotachi, S.; Ogino, S.-I.; Watanabe, Y. *Chem. Lett.* **1993**, *22*, 1317.
12. Katritzky, A. R.; Qiu, G.; Long, Q.; He, H.; Steel, P. J. *J. Org. Chem*. **2000**, *65*, 9201.
13. Katritzky, A. R.; Xu, Y.-J.; Tu, H. *J. Org. Chem.* **2003**, *68*, 4935.
14. (a) Alcock, N. W.; Golding, B. T.; Hall, D. R.; Horn, U.; Watson, W. P. *J. Chem. Soc., Perkin Trans. 1* **1975**, 386; (b) Hand, E. S.; Paudler, W. W. *J. Org. Chem*. **1978**, *43*, 658; (c) Tominaga, Y.; Hosomi, A. *J. Heterocycl. Chem.* **1988**, *25*, 1449; (d) Artyomov, V. A.; Shestopalov, A. M.; Livinov, V. P. *Synthesis* **1996**, *8*, 927; (e) Vega, J. A.; Vaquero, J. J.; Alvarez-Builla, J.; Ezquerra, J.; Hamdouchi, C. *Tetrahedron* **1999**, *55*, 2317.
15. (a) Potts, K. T.; Kanamasa, S. *J. Org. Chem.* **1979**, *44*, 3803; (b) Knolker, H.-J.; Boese, R. *J. Chem. Soc., Chem. Commun.* **1988**, 1151; (c) Knolker, H.-J.; Boese, R.; Hitzemann, R. *Heterocycles* **1989**, *29*, 1551; (d) Knolker, H.-J.; Boese, R.; Hitzemann, R. *Chem. Ber.* **1990**, *123*, 327; (e) Knolker, H.-J.; Hitzemann, R. *Tetrahedron Lett*. **1994**, *35*, 2157.
16. (a) Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett*. **1998**, *39*, 3635; (b) Bienaymé, H.; Bouzid, K. *Angew. Chem., Int. Ed*. **1998**, *37*, 2234; (c) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661; (d) Lyon, M. A.; Kercher, T. S. *Org. Lett*. **2004**, *6*, 4989; (e) Masquelin, T.; Bui, H.; Brickley, B.; Stephenson, G.; Schwerkoske, J.; Hulme, C. *Tetrahedron Lett*. **2006**, *47*, 2989; (f) Rousseau, A. L.; Matlaba, P.; Parkinson, C. J. *Tetrahedron Lett*. **2007**, *48*, 4079; (g) DiMauro, E. F.; Kennedy, J. M. *J. Org. Chem*. **2007**, *72*, 1013; (h) Adib, M.; Sheikhi, E.; Rezaei, N. *Tetrahedron Lett*. **2011**, *52*, 3191; (i) Burchak, O. N.; Mugherli, L.; Ostuni, M.; Lacape`re, J. J.; Balakirev, M. Y. *J. Am. Chem. Soc*. **2011**, *133*, 10058; (j) Tyagi, V.; Khan, S.; Bajpai, V.; Gauniyal, H. M.; Kumar, B.; Chauhan, P. M. S. *J. Org. Chem*. **2012**, *77*, 1414; (k) Khan, A. T.; Basha, R. S.; Lal, M. *Tetrahedron Lett*. **2012**, *53*, 2211; (l) Sun, H.; Zhou, H.; Khorev, O.; Jiang, R.; Yu, T.; Wang, X.; Du, Y.; Ma, Y.; Meng, T.; Shen, J. *J. Org. Chem.* **2012**, *77*, 10745; (m) Kishore, K. G.; Basavanag, U. M. V.; Islas-Ja´come, A.; Ga´mez-Montan˜o, R. *Tetrahedron Lett*. **2015**, *56*, 155; (n) Chernyak, N.; Gevorgyan, V. *Angew. Chem. Int. Ed*. **2010**, *49*, 2743; (o) Palani, T.; Park, K.; Kumar, M. R.; Jung, H. M.; Lee, S. *Eur. J. Org. Chem.* **2012**, 5038.
17. (a) Huo, C.; Tang, J.; Xie, H.; Wang, Y.; Dong, J. *Org. Lett.* **2016**, *18,* 1016; (b) Roslan, I. I.; Ng, K.-H.; Chuah, G.-K.; Jaenicke, S. *Adv. Synth. Catal*. **2016**, *358*, 364.

18. **Typical Procedure for the Synthesis of imidazo[1,2-*a*]pyridine/imidazo[1,2-*a*]pyrimidine/imidazo[2,1-*b*]thiazole (3):** To a round bottom flask containing 1,3-diketones/*β*-keto esters/aryl ketones (1.05 mmol) and water (5 mL) was added NBS (1.2 mmol) and mixture was allowed to stir at 80 °C for 30 min. Subsequently, 2-aminopyridine/2-aminopyrimidine/2-aminothiazole (1.0 mmol) was added and reaction mixture was further heated to 80 °C for 30 min. After completion of reaction (checked by TLC), it was allowed to cool to room temperature and then the mixture was poured into 10 mL of sodium carbonate solution. The reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with water, saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated *in vaccuo*. The resulting crude product was purified by silica gel column chromatography with petroleum ether–ethyl acetate to give corresponding imidazo[1,2-*a*]pyridine/imidazo[1,2-*a*]pyrimidine/imidazo[2,1-*b*]thiazole.

Ethyl 2-methylimidazo[1,2-*a*]pyridine-3-carboxylate 3a (Table 2, entry 1):[17] White solid, mp 66-68 °C (lit. mp 68-70 °C). IR (KBr, cm^{-1}) ν_{max} 3410, 3145, 2999, 1678, 1595, 1490, 1411, 1296, 1222, 1094, 850, 761. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.29 (d, *J* = 6.9 Hz, 1H), 7.59 (d, *J* = 8.9 Hz, 1H), 7.36 – 7.33 (m, 1H), 6.94 (t, *J* = 6.7 Hz, 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 2.70 (s, 3H), 1.42 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.7, 152.0, 146.1, 127.2, 126.7, 115.9, 112.6, 111.4, 59.5, 16.0, 13.5. MS (ESI) m/z: 205 $[M+H]^+$.

2-Phenylimidazo[1,2-*a*]pyridine 3e (Table 2, entry 5):[19] Yellowish white solid, mp 134-136 °C (lit.mp 135–137 °C). IR (KBr, cm^{-1}) ν_{max} 2930, 1634, 1370, 1246, 739. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.09 (d, *J* = 6.8 Hz, 1H), 7.96 (d, *J* = 7.4 Hz, 2H), 7.85 (s, 1H), 7.63 (d, *J* = 9.1 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.18 – 7.11 (m, 1H), 6.77 (t, *J* = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 145.7, 145.5, 133.6, 128.7, 127.9, 125.9, 125.5, 124.6, 117.3, 112.4, 108.0. MS (ESI) m/z: 195 $[M+H]^+$.

2-(Thiophen-2-yl)imidazo[1,2-*a*]pyridine 3h (Table 2, entry 8):[12] Yellowish white solid, mp 136-138 °C (lit.mp 137-139 °C). IR (KBr, cm^{-1}) ν_{max} 2927, 1739, 1496, 1242, 746. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.02 (d, *J* = 6.8 Hz, 1H), 7.71 (s, 1H), 7.60 (d, *J* = 9.1 Hz, 1H), 7.46 (dd, *J* = 3.9, 1.0 Hz, 1H), 7.27 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.15–7.12 (m, 1H), 7.10-7.06 (m, 1H), 6.72 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 145.3, 140.7, 137.4, 127.9, 125.4, 124.9, 124.7, 123.6, 117.2, 112.4, 107.3. MS (ESI) m/z: 201 $[M+H]^+$.

Ethyl 2-methylimidazo[1,2-*a*]pyrimidine-3-carboxylate 3m (Table 2, entry 13):[17] Yellow solid, mp 99-101 °C (lit. mp 98-100 °C). IR (KBr, cm^{-1}) ν_{max} 3397, 3163, 2991, 1692, 1466, 1221, 1098, 758. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.57 (dd, *J* = 6.9, 2.0 Hz, 1H), 8.67 (dd, *J* = 4.2, 2.0 Hz, 1H), 7.06 (dd, *J* = 6.8, 4.2 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 2.78 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.2, 154.7, 151.6, 149.5, 135.5, 111.2, 109.9, 60.5, 16.6, 14.3. MS (ESI) m/z: 206 $[M+H]^+$.

6-Phenylimidazo[2,1-*b*]thiazole 3p (Table 2, entry 16):[19] Yellow solid, mp 147-149 °C (lit. mp 148-149 °C). IR (KBr, cm^{-1}) ν_{max} 1554, 1536, 1466, 1191, 772, 724. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.21 (s, 1H), 7.93 (d, *J* = 4.2 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 4.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.2, 147.8, 134.0, 128.4, 127.3, 125.1, 118.4, 112.4, 107.9. MS (ESI) m/z: 201 $[M+H]^+$.

19. (a) Zhu, D.-J.; Chen, J.-X.; Liu, M.-C.; Ding, J.-C.; Wu, H.-Y. *J. Braz. Chem. Soc.* **2009**, *20*, 482; (b) Cai, Z.-J.; Wang, S.-Y.; Ji, S.-J. *Adv. Synth. Catal*. **2013**, *355*, 2686.

- Synthesis of *N*-bridged fused bicyclic compounds from commercially available starting materials has been developed
- The reaction is performed with readily available starting materials with broad substrate scope
- This reaction proceeds via NBS mediation bromination of ketones and *β*-ketoesters
- Reaction is metal free and water is used as a green solvent