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Research article

FACILE ANDGREEN SOLVENT APPROACH FOR THE SYNTHESIS OF NITROGEN BRIDGEHEAD-FUSED HETEROCYCLIC NUCLEUS

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ABSTRACT: Green Chemistry is defined as environmentally benign chemistry. The revolution in green chemistry provides enormous scopes for discovery and even application for new synthetic approaches. An efficient and general method has been described for the formation of imidazo[1,2-*a*]pyridine from 2-amino pyridine with substituted α-haloketones in the presence of water and acidic additives in efficient yields.

Key words: Acidic Additives; 2-amino pyridine; Green Chemistry; Imidazo[1,2-*a*]pyridine; Water

INTRODUCTION

In recent years, water has emerged as a multifarious solvent in organic chemistry. Water as a solvent is not only economical and environmentally affable, but also shows good reactivity. Even one of the principles of green chemistry promotes the idea of using GREENER solvents. Many efforts have been carried out for finding of sustainable reaction media and precisely the use of water as solvent [a) Chavan, H.V., et.al., 2011, b) Li, C. and Trost, B.M., 2008, c) Rostami-Charati, F.,et.al., 2012, d) Reddy, S.M., et.al., 2014, e) Tundo, P., et.al., 2000]. Indeed, water offers many advantages because it is inexpensive, readily available, non-toxic and non-flammable solvent; in short water is captivating solvent. Many organic compounds have least solubility in water and therefore the use of water as medium of solvent in organic reactions is the latest challenge for synthetic organic chemist. A newer apprehensive perception has been developed by carrying out chemical synthesis in water.

Nitrogen bridgehead-fused heterocycles containing an imidazole ring are pharmacologically important molecules as they have a diversified activity on various targets. In comparison to classical benzodiazepines, non-benzodiazepines show less inimical effects and are generally used as sedatives, anticonvulsants, hypnotics, and anxiolytics and muscle relaxants(Li, M., et.al., 2012). The imidazo[1,2-*a*]pyridine ring can be considered a biosimilar "aza-indole" analogue. Functionalized imidazo[1,2-*a*]pyridines and other imidazo-fused heterocycles are prevalent structural motifs in biologically active and pharmaceutically important compounds[a) Koubachi, J., et.al., 2007, b) Shotwell, J.B.,et.al., 2012, c) Tomczuk, B.E.,et.al., 1991, d) Yan, R-L.,et.al., 2012]. Several non-benzodiazepines which act upon various Central Nervous Systems (CNS) disorders include expansive imidazo pyridine derivatives. Zolpidem, Alpidem, Saripidem, etc. exhibit potency against pentylenetetrazole (PTZ) induced seizures are marketed drugs that possess imidazo[1,2-*a*]pyridine as a parent nucleus(Zhuan, F.,et.al., 2013).

The bridgrhead nitrogen heterocycles are synthesised by solution-phase reaction of corresponding heteroaromatic amidines with α-haloketones or equalents in moderate yield. There are innumerable appropriate methods for the synthesis of fused imidazoles. Newer methods of synthesis of these bioactive heterocycles continue to attract attention to attain experimental simplicity and effectiveness.Taken in consideration the aspects of *Green Chemistry* we have developed environmentally benign *water-mediated*syntheses of imidazo[1,2-*a*]pyridine derivatives. The core structure of imidazo[1,2-*a*] pyridine has been synthesized in the most cheapest, non-toxic and safest solvent water. The synthesis has been carried out by the reaction of 2-amino-5-bromo pyridine (1), substituted α-haloketones (2) in presence of water and acidic additives. The schematic representation is shown below Figure 1.

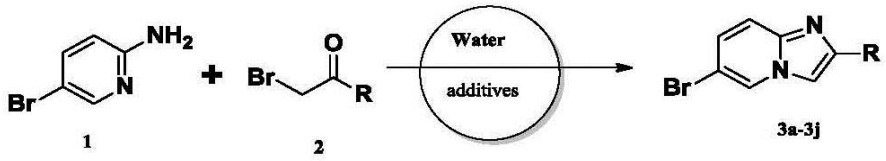


Figure 1. Reaction of Scheme

Figure**1.**Synthesis of Imidazo [1,2-*a*]pyridine
*Note given at end of references

MATERIALS AND METHODS

All the chemicals and solvents were ofAR grade and used without further purification. Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were identified by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique.^{1}H NMR and ^{13}C NMR was determined in DMSO-d_6 solvent on a Bruker AC 400 MHz Spectrometer. Single Crystal X-ray was carried out using Rigaku-SCX Mini Single Crystal X-RayDiffractometer.

Procedure for synthesis of 6-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine*(3c):*

A mixture of 2-amino-5-bromopyridine (**1**) (1gm, 58mmol), 2-bromo-1-(4-methoxyphenyl)ethanone(**2**) (1.6 gm, 70mmol) in water and acidic additive silica gel (solid support) were refluxed for 6-8h. The completion of reaction was monitored by TLC. After completion of the reaction, the resulting mixture was cooled at room temperature and the precipitated solid was filtered.

Another synthesis of the same reaction was carried out where the mixture of 2-amino-5-bromopyridine (**1**) (1 gm, 58mmol), 2-bromo-1-(4-methoxyphenyl)ethanone(**2**) (1.6 gm, 70mmol) in water and acidic additive acetic acid (AcOH)(0.33ml, 58mmol) were refluxed for 4-6h. The completion of reaction was monitored by TLC. After completion of the reaction, the resulting mixture was cooled at room temperature and the precipitated solid was filtered.

Compounds ***3a, 3b, 3d-3j*** were prepared by same procedure using AcOH as an additive and use of substituted α-haloketones was done for obtaining the desired product. Characterization of compounds prepared is shown in Table **1**.

The analytical data of compoundssynthesized Imidazo[1,2-*a*]pyridine ***(3a-3j)*** are given as below:

* **NOTE:** word file of all compounds labelled in numbers is provided separately.

6-bromo-2-phenylimidazo[1,2-*a*]pyridine*(3a)*:

Yield, 83%, m.p. 210-212 ºC;^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.55-7.53 (d, 1H, J= 8.0 *Hz*, ArH), 7.62-7.58 (t, 2H, J= 8.0 *Hz*, ArH), 7.88-7.68 (d, 1H, J= 8.0 *Hz*, ArH), 7.96-7.99 (m, 3H, ArH), 8.66 (s, 1H, ArH), 9.22 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.64 (C1), 111.98 (C7), 114.89 (C3), 126.15 (C2), 127.50 (C9), 128.10 (C6), 128.63 (C11), 129.39 (C10), 130.10 (C8), 133.58 (C5), 139.99 (C4); MS(EI) m/z calculated for $C_{13}H_9BrN_2$ $[M]^+$ = 272.02

6-bromo-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine*(3b):*

Yield, 89%, m.p. 216-220 ºC; IR (KBr) cm^{-1}: 769, 820, 1259, 1450, 1530, 1630, 2987, 3105; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.67-7.65 (d, 2H, J= 8.0 *Hz*, ArH), 7.91-7.89 (d, 2H, J= 8.0 *Hz*, ArH), 8.02-7.99 (d, 2H, J= 12.0 *Hz*, ArH), 8.75 (s, 1H, ArH), 9.28 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 110.17 (C1), 111.43 (C7), 113.80 (C3), 125.97 (C2), 127.94 (C9), 128.80 (C6), 129.47 (C10), 134.84 (C8), 135.03 (C5), 136.10 (C11), 139.66 (C4); MS(EI) m/z calculated for $C_{13}H_8BrClN_2$ $[M]^+$ = 305.99

6-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine*(3c):*

Yield, 90%, m.p. 267-270 ºC; IR (KBr) cm^{-1}: 825, 1259, 1275, 1455, 1534, 1629, 3010, 3100; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.80 (s. 3H, -OCH_3), 7.03-7.00 (d, 2H, J= 12.0 *Hz*, ArH), 7.36-7.34 (d, 1H, J= 8.0 *Hz*, ArH), 7.56-7.54 (d, 1H, J= 8.0 *Hz*, ArH), 7.90-7.88 (d, 2H, J= 8.0 *Hz*, ArH), 8.26 (s, 1H, ArH), 8.86 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.12 (C12), 110.64 (C1), 112.18 (C7), 114.21 (C10), 114.89 (C3), 124.97 (C2), 125.94 (C8), 127.48 (C9), 128.32 (C6), 132.44 (C5), 145.21 (C4), 159.21 (C11); MS(EI) m/z calculated for $C_{14}H_{11}BrN_2O[M]^+$= 302.05

6-bromo-2-(4-bromophenyl)imidazo[1,2-*a*]pyridine*(3d)*:

Yield, 87%, m.p. 252-255 ºC; IR (KBr) cm^{-1}: 685, 830, 1270, 1469, 1531, 1627, 2998, 3095; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.34-7.32 (d, 1H, J= 8.0 *Hz*, ArH), 7.55-7.53 (d, 1H, J= 8.0 *Hz*, ArH), 7.66-7.69 (d, 2H, J= 12.0 *Hz*, ArH), 7.82-7.80 (d, 2H, J= 8.0 *Hz*, ArH), 8.25 (s, 1H, ArH), 8.86 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 110.21 (C1), 112.03 (C7), 113.61 (C3), 124.30 (C11), 126.17 (C2), 127.80 (C9), 128.43 (C6), 130.79 (C10), 134.50 (C8), 135.56 (C5), 140.11 (C4); MS(EI) m/z calculated for $C_{13}H_8Br_2N_2$ $[M]^+$= 349.99

6-bromo-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine*(3e):*
Yield, 92%, m.p. 280-252 ºC; IR (KBr) cm^{-1}: 820, 1264, 1452, 1540, 1589, 1631, 2985, 3100; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.34-7.32 (d, 1H, J= 8.0 *Hz*, ArH), 7.55-7.53 (d, 1H, J= 8.0 *Hz*, ArH), 8.08-8.05 (d, 2H, J= 12.0 *Hz*, ArH), 8.26 (s, 1H, ArH), 8.36-8.32 (d, 2H, J= 16.0 *Hz*, ArH), 8.86 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 110.22 (C1), 111.43 (C7), 114.32 (C3), 126.22 (C2), 125.40 (C10), 127.39 (C9), 127.91 (C6), 135.36 (C5), 136.13 (C8), 139.66 (C4), 146.90 (C11); MS(EI) m/z calculated for $C_{13}H_8BrN_3O_2$ $[M]^+$= 316.98

6-bromo-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine *(3f):*
Yield, 86%, m.p. 220-225 ºC; IR (KBr) cm^{-1}: 825, 1240, 1450, 1530, 1645, 2850, 3075 ; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.36 (s. 3H, CH_3), 7.30-7.28 (d, 2H, J= 8.0 *Hz*, ArH), 7.34-7.32 (d, 1H, J= 8.0 *Hz*, ArH), 7.55-7.53 (d, 1H, J= 8.0 *Hz*, ArH), 7.70-7.68 (d, 2H, J= 8.0 *Hz*, ArH), 8.26 (s, 1H, ArH), 8.86 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.12 (C12), 110.17 (C1), 112.04 (C7), 113.99 (C3), 125.99 (C2), 124.17 (C9), 127.45 (C8), 128.50 (C10), 129.18 (C6), 130.70 (C11), 134.81 (C5), 138.99 (C4); MS(EI) m/z calculated for $C_{14}H_{11}BrN_2$ $[M]^+$= 286.01

6-bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine*(3g):*
Yield, 85%, m.p. 232-235 ºC; IR (KBr) cm^{-1}: 830, 950, 1256, 1465, 1545, 1650, 2865, 3090; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.30-7.29 (m, 2H, ArH), 7.34-7.32 (d, 1H, J= 8.0 *Hz*, ArH), 7.55-7.53 (d, 1H, J= 8.0 *Hz*, ArH), 8.18-8.15 (d, 2H, J= 12.0 *Hz*, ArH), 8.26 (s, 1H, ArH), 8.86 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.87 (C1), 111.43 (C7), 113.80 (C3), 114.70 (C10), 126.22 (C2), 127.50 (C9), 129.02 (C6), 135.63 (C5), 140.23 (C4), 140.82 (C8), 159.69 (C11); MS(EI) m/z calculated for $C_{13}H_8BrFN_2$ $[M]^+$= 290.08

6-bromo-2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridine*(3h)*:
Yield, 80%, m.p. 236-240 ºC; IR (KBr) cm^{-1}: 680, 725, 1256, 1472, 1558, 1656, 3004, 3090; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.34-7.32 (d, 1H, J= 8.0 *Hz*, ArH), 7.43-7.41 (d, 1H, J= 8.0 *Hz*, ArH), 7.55-7.50 (m, 2H, ArH), 8.05-8.03 (d, 1H, ArH), 8.26 (s, 1H, ArH), 8.86 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 110.45 (C1), 112.28 (C7), 113.85 (C3), 126.52 (C2), 127.23 (C12), 128.17 (C8), 128.84 (C6), 130.31 (C13), 131.70 (C10), 132.63 (C9), 135.03 (C5), 135.37 (C11), 139.66 (C4); MS(EI) m/z calculated for $C_{13}H_7BrCl_2N_2$ $[M]^+$= 339.92

6-bromo-2-(3-bromophenyl)imidazo[1,2-*a*]pyridine*(3i):*
Yield, 89%, m.p. 238-245 ºC; IR (KBr) cm^{-1}: 740, 815, 850, 1260, 1452, 1555, 1648, 2903, 3100; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.34-7.32 (d, 1H, J= 8.0 *Hz*, ArH), 7.46-7.40 (m, 2H, ArH), 7.55 (m, 2H, ArH), 7.73-7.71(d, 1H, J= 8.0 *Hz*, ArH), 8.26 (s, 1H, ArH), 8.86 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.95 (C1), 112.18 (C7), 114.31 (C3), 122.20 (C10), 124.57 (C13), 126.52 (C2), 127.09 (C11), 129.18 (C9), 129.94 (C12), 131.36 (C8), 128.84 (C6), 135.03 (C5), 139.66 (C4); MS(EI) m/z calculated for $C_{13}H_8Br_2N_2$ $[M]^+$= 349.91

6-bromo-2-(3-nitrophenyl)imidazo[1,2-*a*]pyridine*(3j):*
Yield, 80%, m.p. 227-230 ºC; IR (KBr) cm^{-1}: 750, 835, 820, 1269, 1460, 1578, 1592, 1678, 3050, 33110; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 7.34-7.32 (d, 1H, J= 8.0 *Hz*, ArH), 7.55-7.53 (d, 1H, J= 8.0 *Hz*, ArH), 8.20-7.75 (m, 3H, ArH), 8.26 (s, 1H, ArH), 8.65(s, 1H, ArH), 8.86 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 110.20 (C1), 111.88 (C7), 114.25 (C3), 122.78 (C12), 123.98 (C11), 125.88 (C2), 129.04 (C6), 130.67 (C9), 132.15 (C8), 133.61 (C13), 134.83 (C5), 140.66 (C4), 148.43 (C10); MS(EI) m/z calculated for $C_{13}H_8BrN_3O_2$ $[M]^+$=316.98

The structure of the synthesized compounds was confirmed by Mass, FT-IR, ^{1}H and ^{13}C-NMR spectroscopic data and further it has also been supported by single crystal X-Ray.

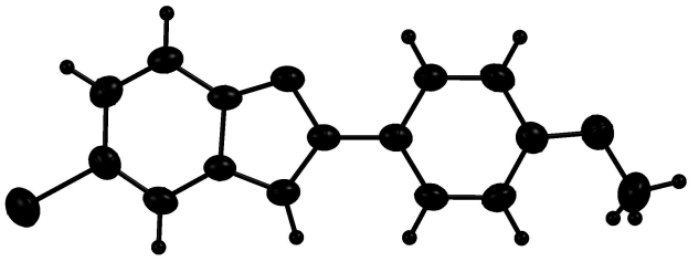
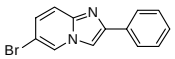
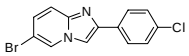
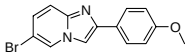
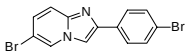
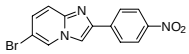
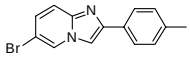
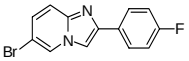
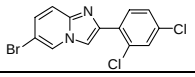
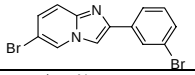
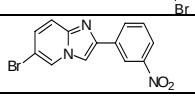


Figure 2. ORTEP diagram of Compound 3c is shown above. Displacement ellipsoids are drawn at the 50% probability level

Table1. Characterization of compounds prepared.[a]

Compound	R	Structure	Temp.°C	Reaction Time (h)	Yield (%)	M.P. °C
3a	C_6H_5		90	4h	83	210-212
3b	4-ClC_6H_4		90	4h	89	216-220
3c	4-$MeOC_6H_4$		90	4h	90	267-270
3d	4-BrC_6H_4		90	4h	87	252-255
3e	4-$NO_2C_6H_4$		90	5h	92	280-282
3f	4-MeC_6H_4		90	4h	86	220-225
3g	4-FC_6H_4		90	4h	85	232-235
3h	2,4-$Cl_2C_6H_4$		90	5h	80	236-240
3i	3-Br C_6H_4		90	4h	89	238-245
3j	3-$NO_2C_6H_4$		90	6h	80	227-230

[a]**Reaction conditions:** (1) 2-amino pyridine (1 mmol), (2) α-haloketones (1.5mmol), acidic additive (1.5mmol), water (6 mL)

RESULT AND DISCUSSION

In concern with the use of green solvents in organic synthesis, we report herein the use of water and n-butanol as greener solvents for the synthesis of imidazo pyridine. The method reported for the synthesis of imidazo pyridine was refluxing of 2-amino pyridines and α-haloketones in ethanol or in some organic solvents and acidic/basic additives. The problem associated with the above reported methods of synthesis was longer reaction times and/or poor yields [a) Dossetter, A., et.al.,2002, b) Hooshyar, Y.B., et.al., 2012, c) Hiebel, M-A., et.al., 2014, d) János, G., et.al., 2005].The condensation of 2-amino pyridine with α-haloketone is most favorable due to the attack of the nitrogen ring of pyridine due to the formation of very stable pyridinium ion intermediate. The plausible mechanism of the reaction carried out is same as that proposed earlier (Hand, E.S. and Paudler, W.W. 1982)and shown in Figure 3.

*Note given at end of references

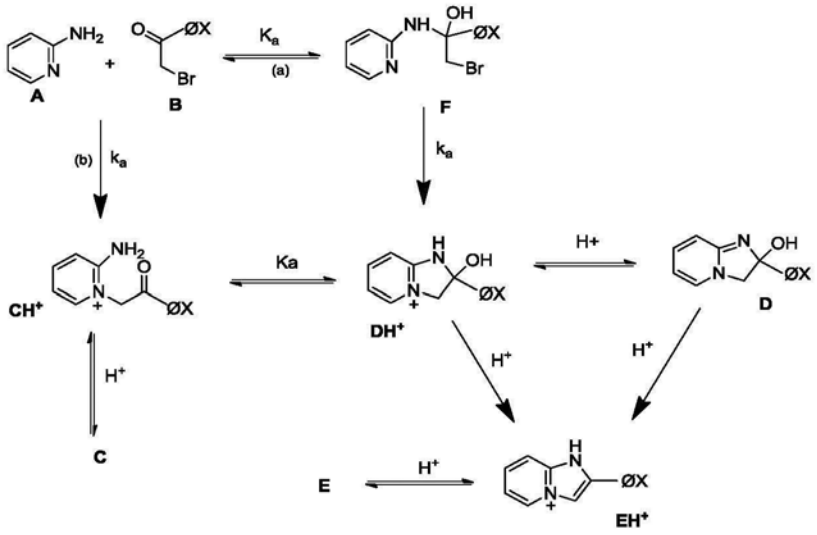


Figure 3. Mechanism of the reaction

In the current developed method, Imidazo pyridines were synthesized in water and acidic additives in high yields and less reaction time compared to previous reported methods. Another trial of the same reaction was carried out in another greener solvent n-butanol and acidic additive and it was quite surprising that yield obtained was high as well as reaction time was less compared to that when the reaction was carried out in ethanol or in some organic solvent and acidic/basic additives. When same experiment with two different acidic additives (silica gel/acetic acid) was carried out it was concluded that acetic acid as an additive showed better result than silica gel in terms of reaction time and yield. Optimization of reaction conditions for the synthesis of 6-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine ***(3c)***is given in Table 2.

Table 2. Optimization of reaction conditions for the synthesis of *3c*.

Entry	Additives	Solvent	Reaction time(hours)	Yield %
1	-	EtOH	12	51
2	NaOH	DMF	2	77
3	Na_2CO_3	EtOH	1-16	84
4	Silica gel	n-BuOH	8-9	60
5	Silica gel	Water	6-7	65
6	AcOH	n-BuOH	4	82
7	AcOH	Water	3	89

CONCLUSION

We have developed a facile and coherent reaction for the synthesis of 2-phenyl imidazo[1,2-*a*]pyridine under green condition. The advantages of this current developed method over other prevailing methods are reduced milder conditions, higher yields, low costs and environmental safety. The simple, economical and potentially viable reaction method makes it useful and captivating process for commercial application.

CONFLICT OF INTEREST

Authors have no conflict of interest for publication of the present work.

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SUPPORTING/ SUPPLEMENTARY MATERIAL

1. X-Ray Structure Report of Compound

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