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Aqueous phase synthesis of substituted imidazo[1,2-a]pyridine in the presence of β -cyclodextrin

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ABSTRACT

A simple and practical procedure for aqueous phase reaction of various α -tosyloxy ketones with 2- amino pyridine and their derivatives in the presence of β -Cyclodextrin has been developed to furnish bridgehead azaheterocycles 3a-h & 4a-d in good to excellent yields.

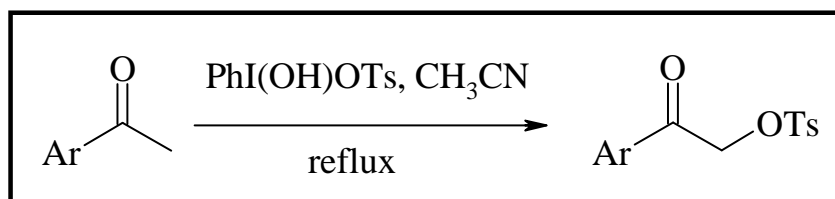
Keywords: Heterocyclic, β -Cyclodextrin, and azaindolizines, green chemistry.

INTRODUCTION

Imidazo[1,2-*a*]pyridines and their derivatives with anodal nitrogen atom, an important class of ring fused heterocyclic compounds exhibit a wide spectrum of biological activities[1]. Therefore development of new and efficient synthetic method for the synthesis of these compounds is of importance in both synthetic organic chemistry and medicinal chemistry[2]. In addition, other applications of these compound imidazo[1,2-*a*]pyridinium salts are also used to prepare styryl dyes[3]. The classical method for synthesis of imidazo[1,2-*a*]pyridines mainly involves the either solution phase[4] or solid phase[5] coupling reaction of α -haloketones or equivalents with corresponding hetero aromatic amidines, or through multicomponent reaction by microwave-assisted reactions[6]. The members of these ring systems have several valuable biological properties and are used as antimicrobial[7] antiasthmatic[8] hypotensive[9] antiulcer[10].

Cyclodextrins[11], which are cyclic oligosaccharides, have generated interest as enzyme due to their ability to bind substrates selectively and catalyze chemical reactions on the basis of supramolecular catalysis. Involving the formation of reversible host-guest complex by non-covalent bonding as seen in enzyme complexation processes. Complexation depends on the size, shape and hydrophobicity of the guest molecule. Cyclodextrins have been utilized for biomimetic modeling of the synthesis of azaindolizines in water.

The reactions of [hydroxyl (tosyloxy) iodo] benzene (HTIB) with enolizable ketone are very efficient and rewarding to generate α -tosyloxy ketone in excellent yields[12].



α -Tosyloxy ketone is a versatile building block for the synthesis of heterocyclic compounds because of following important features: Doubly electrophilic molecule, Non-lachramatory analog of α -halo ketone, a most important feature, More reactivity and stability than α -halo ketone, Easily accessible from the range of substituted acetophenones by the reaction with HTIB (1-2 h reaction time, 72-95% yield), Within this context we have developed a biomimetic and green chemistry approach to synthesize fused imidazoles under aqueous condition through the supramolecular catalysis mediated by β -cyclodextrins. Herein, we described a simple and convenient supramolecular synthesis of some azaindolizines 3a-h the present method seems to overcome all of the above mentioned drawbacks.

MATERIALS AND METHODS

All melting points were taken on an electrothermal capillary melting point apparatus and are uncorrected. Thin layer chromatography was performed on 0.5 mm \times 20 cm \times 20 cm E. Merck silica gel plates (60 F-254) The infrared spectra (wave numbers in cm^{-1}) were taken on a Nexus 670 FT-IR spectrometer. ^{13}C and ^1H NMR spectra were recorded at room temperature using a Bruker Advance DXP250 at 62.9 and 250 MHz, respectively. HMQC and HMBC data were recorded at 400 Hz (Varian-Unity 400). Chemical shifts (δ) are given in parts per million downfield from tetramethylsilane as internal standard. LC/MS Agilent Technologies (ESI+) instrument. Column chromatography was performed on Merck grade 60 silica gel (0.063-0.2 mm).

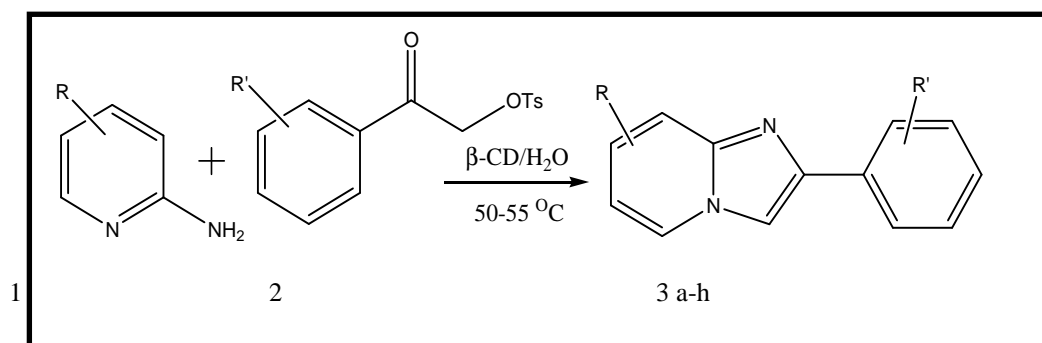
General procedure for preparation of substituted H-imidazo[1,2-a]pyridine :

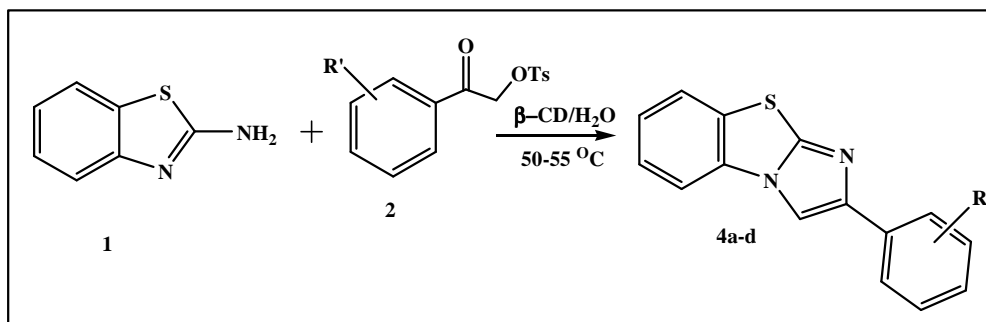
β -Cyclodextrin (1mmol) was dissolved in 10 mL distilled water by heating at 50-55 $^{\circ}\text{C}$, to it was added drop wise, α -Tosyloxy ketone (1mmol). After five minutes of continuous stirring at same temperature, 2-aminopyridine (1mmol) was added and the mixture was stirred at same temperature. After completion of the reaction, the crude products were isolated by extracting with ethylacetate (5mL \times 3). The organic phase were separated and washed with brine, dried over sodiumsulphate and evaporated under vacuum. The product was further purified by column chromatography using 2% methanol/chloroform.

RESULTS AND DISCUSSION

Development of new method of azaindolizines and benzo[d]imidazo[2,1-b]thiazole derivatives have been synthesized, and the results are shown in Table-1. All their actions were carried out with one equivalent of each reactant in the aqueous solution of one equivalent of β -cyclodextrin. The reactions were carried out by dissolving β -cyclodextrin in water warmed to 50-55 $^{\circ}\text{C}$. To resulting clear solution, α -Tosyloxy ketone was added. A milky suspension of β -CD and α -Tosyloxy ketone complex was formed, to which the amino compounds were added and stirred. The progress of reactions was monitored by TLC (10% methanol/chloroform). There action of various α -Tosyloxy ketone with 2-aminopyridines (entry 1, Table 1), furnished the azaindolizines 3a-h. Similarly, the benzo[d]imidazo[2,1-b]thiazole 4a-c were also synthesized in good to excellent yield. The method describes an easy and convenient route to furnish a number of azaheterocycles. The superiority of this procedure over existing protocol could be established while comparing the results obtained with few methods employed previously for the synthesis of 2-arylimidazo[1,2-a] pyridines as these methods [2, 18] needed refluxing in organic solvents for 6 hours. The formation of 2-substituted benzo[d]imidazo[2,1-b]thiazole 20 needed 8 hours refluxing in dry ethanol, but the method given in this report is quite simple and the products were formed within a few minutes in very good yields under the similar reaction.

Reactions :

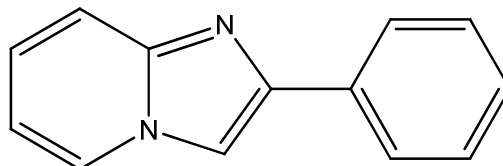


Table-1: Synthesis of bridgehead azaheterocycles in the presence of β -cyclodextrin

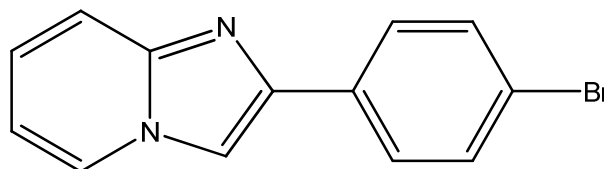
Entry	R	R'	Product	Time (Min)	Yield %	M.P. ($^{\circ}$ C)	Lit.MP ($^{\circ}$ C)
1	H	H	3a	11	82	131-133	134 ¹²
2	H	4-Br	3b	05	89	214-216	215-216 ¹²
3	H	4-OCH ₃	3c	10	83	133-135	132 ¹²
4	H	4-CH ₃	3d	10	82	134-136	137 ¹⁹
5	H	4-Cl	3e	08	85	206-208	208 ¹²
6	H	3,4-Cl	3f	12	80	173-174	172 ¹⁹
7	CH ₃	4-CH ₃	3g	18	76	230-231	227-229 ²¹
8	5-Br	3-NO ₂	3h	14	81	235-236	234-236 ²²
9	H	H	4a	18	75	103-105	102-104 ²¹
10	H	4-OCH ₃	4b	19	72	178-180	175-177 ²¹
11	H	4-Cl	4c	18	74	158-161	157-159 ²¹
12	5-Cl	4-OCH ₃	4d	19	73	225-226	227-228 ²¹

Characterization of the products:

The structures of all the products were established from IR, NMR and Mass spectral analysis.

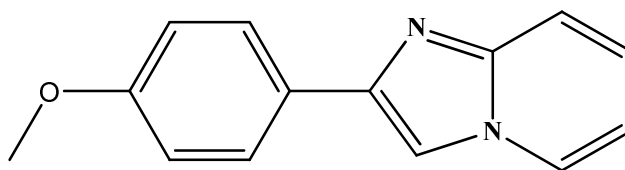
1. 2-Phenylimidazo[1,2-a]pyridine(3a)

Nature : Solid.
 IR (KBr) : 3101, 1666, 1579 1483,736 cm⁻¹.
¹H NMR 400 MHz(CDCl₃) : δ 6.83 (t, 1H, J = 6.9 Hz), 7.13 (t, 1H, J = 7.8 Hz), 7.36 (d, 1H, J = 9.0 Hz), 7.52-7.77 (m, 3H, J = 12.00 Hz), 7.6 (d, 2H) 7.89 (s, 1H), 8.06 (d, 1H, J = 7.8 Hz).
¹³C NMR 400 MHz (CDCl₃) : δ 108.31,113.40,116.79,125.69,126.73,127.21,127.92,130.01,133.10,143.92.
 LCMS : (M+1) = 195

2. 2-(4-Bromophenyl)-imidazo[1,2-a]pyridine(3b).

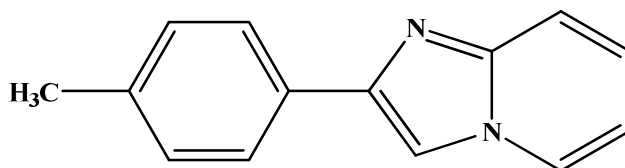
Nature : Solid.
 IR KBr) : 3052, 1637, 1602, 1502,1373,810, 760, 506 cm⁻¹.
¹H NMR 400 MHz(CDCl₃) : δ 6.65 (t, 1H, J = 6.9 Hz), 7.21 (t, 1H, J = 7.8 Hz), 7.36 (d, 2H), 7.49 (d, 2H), 7.51 (d, 1H, J = 9.0 Hz), 7.81 (s, 1H), 8.02 (d, 1H, J = 7.8 Hz).
¹³C NMR 400 MHz (CDCl₃) : δ 109.33,113.26,117.94,125.57,127.23,130.32,132.01, 134.32,134.45,144.69,146.82.
 LCMS : (M+1) = 272.

3. 2-(4-Methoxyphenyl)-imidazo[1,2-a]pyridine(3c).



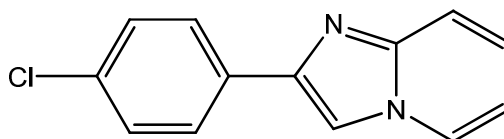
Nature	: Solid.
IR (KBr)	: 3100, 2958, 2832, 1653, 1591, 1485, 1276, 1176, 815, 736 cm^{-1} .
^1H NMR 400 MHz (CDCl ₃)	: δ 3.78 (s, 3H), 6.75 (t, 1H), 6.89 (d, 2H, J = 12.4 Hz, ArH), 7.11 (t, 1H), 7.21 (d, 2H, J = 12.4 Hz, ArH), 7.25 (d, 1H), 7.49 (s, 1H), 7.58 (d, 1H).
^{13}C NMR 400 MHz (CDCl ₃)	: δ 56.05, 105.65, 115.11, 117.75, 122.82, 124.05, 126.15, 128.82, 131.65, 137.51, 144.15, 162.00.
LCMS	: (M+1) = 225.

4. 2-(4-Methylphenyl)imidazo[1,2-a]pyridine (3d).



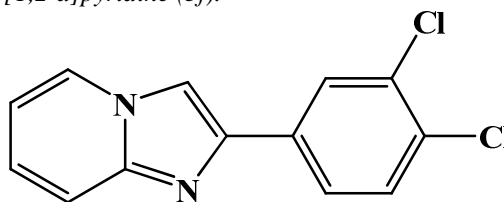
Nature	: Solid.
IR (KBr)	: 3122, 2926, 2852, 1665, 1610, 1485, 817, 771 cm^{-1} .
^1H NMR 400 MHz (CDCl ₃)	: δ 2.22 (s, 3H), 6.73 (t, 1H, J = 6.9 Hz), 7.07 (t, 1H, J = 6.9 Hz), 7.44 (d, 2H, J = 8.4 Hz), 7.56 (d, 1H, J = 9.0 Hz), 7.79 (s, 1H), 7.84 (d, 2H, J = 8.4 Hz), 8.06 (d, 1H, J = 7.8 Hz).
^{13}C NMR 400 MHz (CDCl ₃)	: δ 24.24, 110.53, 113.24, 116.14, 124.15, 126.13, 130.75, 132.01, 134.57, 136.65, 144.69, 146.82.
LCMS	: (M+1) = 209.

5. 2-(4-Chlorophenyl)-imidazo[1,2-a]pyridine(3e).



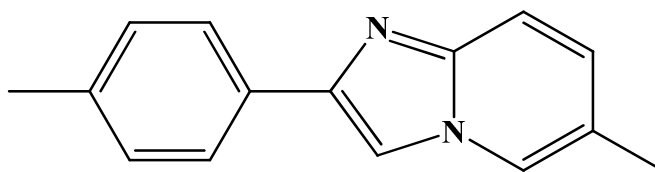
Nature	: Solid.
IR (KBr)	: 3035, 1648, 1502, 1465, 836 cm^{-1} .
^1H NMR 400 MHz (CDCl ₃)	: δ 6.62 (t, 1H), 7.11 (t, 1H), 7.34 (d, 2H), 7.46 (d, 2H), 7.64 (d, 1H), 7.85 (s, 1H), 8.06 (d, 1H).
^{13}C NMR 400 MHz (CDCl ₃)	: δ 109.33, 113.26, 117.94, 125.57, 127.23, 130.32, 132.01, 134.32, 134.45, 144.69, 146.82.
LCMS	: (M+1) = 229.

6. 2-(3,4-Dichlorophenyl)-imidazo[1,2-a]pyridine (3f).



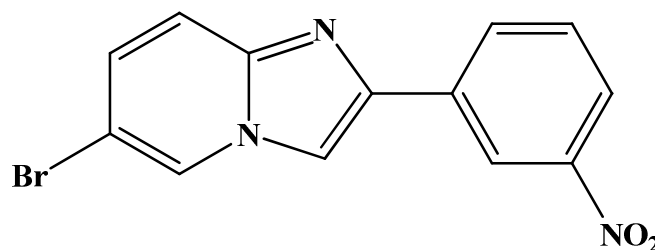
Nature	: Solid.
IR (KBr)	: 3035, 1648, 1602, 1502, 1465, 735, 710 cm^{-1} .
^1H NMR 400 MHz (CDCl ₃)	: δ 6.79 (t, 1H), 7.01 (t, 1H), 7.30 (d, 1H), 7.36 (d, 1H), 7.51 (s, 1H), 7.77 (s, 1H), 7.85 (d, 1H), 8.08 (d, 1H).
^{13}C NMR 400 MHz (CDCl ₃)	: δ 110.02, 113.99, 114.68, 124.88, 126.95, 127.30, 129.09, 129.84, 130.58, 132.69, 133.70, 143.91.
LCMS	: (M+1) = 264.

6-Methyl-2-p-tolylimidazo[1,2-a]pyridine(3g).



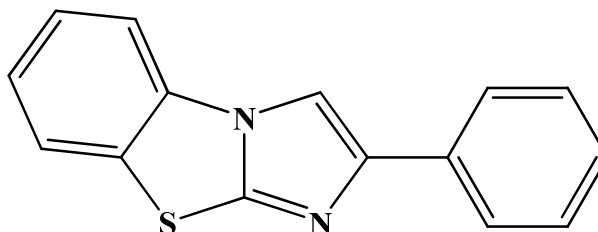
Nature	: Solid.
IR (KBr)	: 3030, 2922, 2832, 1648, 1602, 1502, 1465, 811, 735, 710 cm^{-1} .
^1H NMR 400 MHz(CDCl_3)	: δ 2.44(s,3H),2.50(s,3H),7.42(d,2H,J8.2Hz),7.76(d,2H,J =8.3Hz),7.77-7.87(m,2H),8.42(s,1H),8.59 (s,1H);
^{13}C NMR 400 MHz (CDCl_3)	: δ 16.97,20.44,110.54,111.09,123.65,126.28,126.89,128.64,130.30,136.58,136.68,139.46,141.55;
LCMS	: (M+1) = 223.

7. 6-Bromo-2-(3-nitro-phenyl)-imidazo[1,2-a]pyridine(3h)



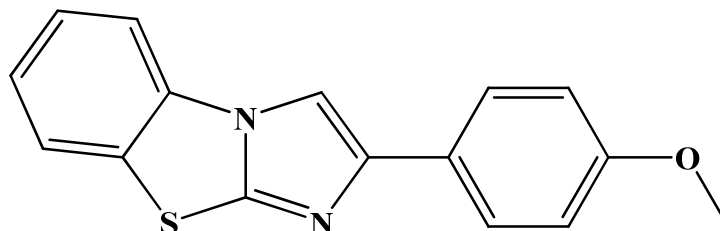
Nature	: Solid.
IR (KBr)	: 3030, 2922, 2832, 1648, 1602, 1502, 1465, 811, 735, 710 cm^{-1} .
^1H NMR 400 MHz(CDCl_3)	: δ 7.75(1H, m),7.43(1H, m),7.62 (1H, d, J = 9.9 Hz),8.18 (1H, d, J = 7.8 Hz),8.39 (1H, d, J = 7.5 Hz),8.58(1H, d, J = 2.4 Hz),8.76 (1H, m),8.91 (1H, s).
^{13}C NMR 400 MHz (CDCl_3)	: δ 110.54,113.09,119.65,123.28,124.89,128.64,130.30,131.58,133.68,134.46,135.55, 146.41, 149.24;
LCMS	: (M+1) = 319.

8. 2-Phenyl-benzo[d]imidazo[2,1-b]thiazole(4a).



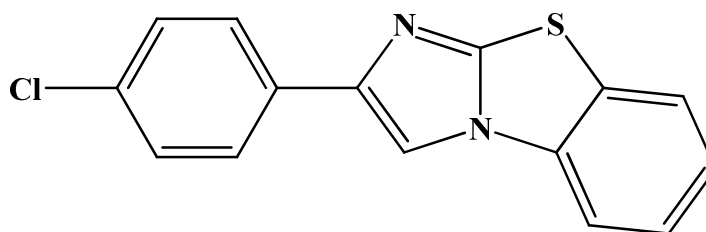
Nature	: Solid.
IR (KBr)	: 3032, 1641, 1605, 1508, 735, 710 cm^{-1} .
^1H NMR 400 MHz(CDCl_3)	: δ 6.45-6.97(m,6H),7.57-7.58(m,1H),7.64-7.66(m,1H),7.88-7.89(m,1H),7.95(s,1H);
^{13}C NMR 400 MHz (CDCl_3)	: δ 107.26, 113.07, 123.95, 124.85, 125.32, 125.67, 126.63, 127.99, 128.11, 129.15,129.39,140.12,148.80;
LCMS	: (M+1) = 251.

9. 2-(4-Methoxyphenyl)-benzo[d]imidazo[2,1-b]thiazole(4b).



Nature	: Solid.
IR (KBr)	: 3066, 2924, 2856, 1656, 1595,1508, 1433, 1155,833,732 cm^{-1} .
^1H NMR 400 MHz (CDCl_3)	: δ 3.75(s,3H),6.93(d,2H),7.15-7.18(m,4H), 7.53(d,2H),7.85(s,1H);
^{13}C NMR 400 MHz (CDCl_3)	: δ 55.83,107.36,113.13,122.91, 125.01, 125.14, 126.12,128.55,129.31,130.21, 139.01, 139.11,152.41,160.43;
LCMS	: (M+1) = 281.

10. 2-(4-Chlorophenyl)-benzo[d]imidazo[2,1-b]thiazole(4c).



Nature	: Solid.
IR (KBr)	: 3032, 1641, 1607, 1518, 1487, 812 cm ⁻¹ .
¹ H NMR 400 MHz(CDCl ₃)	: δ7.13-7.17 (m, 4H), 7.43(d,2H),7.51 (d, 2H),7.89(s,1H);
¹³ C NMR 400 MHz (CDCl ₃)	: δ107.13,112.97,123.80,124.65,125.73,126.68,126.70,127.89,128.90,129.32,132.10,139.31,148.62;
LCMS	: (M+1) = 285.

CONCLUSION

In Summary, We have demonstrated for the First time that bridgehead azaheterocycles formation can be promoted by β -cyclodextrin in water. This methodology also overcomes the formation of unwanted by-products, low yields, slow reaction times, high temperatures and hazardous solvents, thus making it a more user-friendly procedure.

Acknowledgements

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