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Ultrasound assisted green one pot synthesis of bound type bis-heterocyclic furan-2-yl imidazo [1,2-*a*] pyridines via GBBR

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Abstract: A series of six new 3-imidazo[1,2-*a*] pyridine furan bound type *tris*-heterocycles were synthesized by Ultrasound Irradiation (USI) assisted Groebke-Blackburn-Bienaymé reaction (GBBR), by employing ammonium chloride (10 mol%) as a catalyst in excellent yields (80-93%) under green conditions. This efficient and mild protocol has silent features such as green inexpensive and easily available catalyst and solvent at room temperature.

Keywords: Ultrasound-GBBR; *tris*-heterocycles; green catalyst and green one pot process

1. Introduction

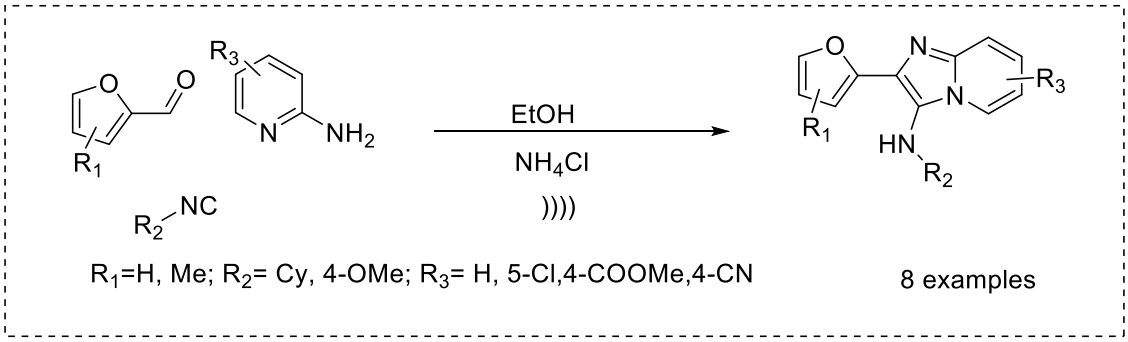
Multicomponent reactions (MCR's) have been considered as a powerful tool for the construction of novel and complex molecular structures from simple materials due to their advantages over conventional multistep synthesis. The major advantages of MCR's over multistep synthesis include cheap and readily available reagents, convergent or high atom economy; they exhibit a very high bond-forming-index (BFI) [1]. The GBBR in the synthesis of fused heterocycles imidazo[1,2-*a*] pyridines is an important synthetic strategy as these scaffolds are found to form a very important core in numerous synthetic, pharmaceuticals and a wide variety of biologically active compounds [2]. Imidazo [1.2-*a*] pyridine scaffolds are present in many commercially available drugs including, alpidem (anxiolytic), minodronic acid (to treat anxiety, heart failure and osteoporosis), olprinone (cardiotonic agent), optically active GSK 812397 candidate (HIV infection), saripidem (sedative and anxiolytic), zolimidine (an antiulcer drug) and zolpidem (a hypnotic drug) are derived from imidazo[1,2-*a*] pyridine core entities [3-4]. Besides Imidazo[1,2-*a*] pyridine moieties have applications in the field of optics such as OLED's, fluorescentlabeling, fluorescent dyes, because of their luminescent properties [5]. Recently furan bound to Imidazo[1,2-*a*] pyridine has been reported as chemo-sensor for Cu^{2+} [6].

The most important approaches are: (i) condensation of 2-aminopyridine with α-halocarbonyl compounds [7], (ii) one pot condensations of aldehydes, isonitriles and 2-aminopyridines well know as Groebke-Blackburn-Bienayme reaction (GBBR) [8], (iii) copper-catalyzed three component reactions of 2-aminopyridines, aldehydes and alkynes [9]. Other methods have also been developed within the last three decades [10]. Fused bicyclic imidazo[1,2-*a*] pyridines via GBBR methodologies using various green catalysts, such as Lewis acids, Bronsted acids, solid supported, organic bases and inorganic salts have been reported**.** However, these methods have limitations in terms of the use of expensive and excess amount of catalysts, long reaction times, high temperatures, less yields and

non-readily available catalysts [11]. Hence, in modern synthetic chemistry there is a necessity of development of a simple, high yielding and ecofriendly protocols for the one pot synthesis of molecules with potential applications in optic field like fused bicyclic imidazo[1,2-*a*] pyridine scaffolds.

As a part of our research program to develop eco-friendly and green methodologies based on IMCRs, we recently reported the efficient ultrasound assisted synthesis of imidazopyridine analogues via GBBR [12-14].

Herein, we report a USI assisted, mild and greener GBB protocol to synthesize bound type *tr*is-heterocycles containing furane, imidazole and pyridine aromatic heterocycles. from 2-amino-pyridines, substituted furan carbaldehyde, and isocyanides using NH_4Cl as a green catalyst and EtOH as a green solvent (**Scheme 1**).

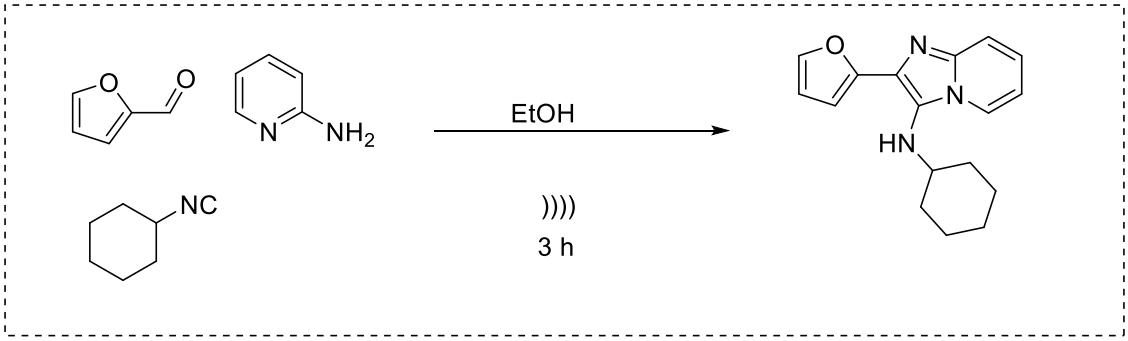


Scheme 1. Strategy for the synthesis of furan-2-yl imidazo [1,2-a] pyridines.

2. Results and Discussion

To develop green conditions for GBBR, we started the synthesis of furan-2yl-imidazo[1,2-*a*] pyridine-3-amine analogue **4a** by reacting 9-octyl-9H-carbazole-3-aldehyde **1a** (1 mmol), 2-aminopyridine **2a** (1mmol), cyclohexyl isonitrile **3a** (1mmol) in EtOH as a solvent and green catalyst such as *p*-toluene sulfonic acid (*P*TSA), L-proline and ammonium chloride under USI conditions (Table 1). Initially, we performed the GGBR at room temperature without catalyst no reaction was observed. (Table1, entry 1). Also, on heating, the product **4a** was obtained in 30% yield (Table1, entry 2). Then we switched to solvent system and considered EtOH as green solvent and performed the reaction. At room temperature in absence of catalyst the product **4a** was observed in traces (Table1, entry 3). On heating at 60 ° without catalyst gives 40% of product **4a** (Table1, entry 4). Then we switched to another green catalyst *P*TSA at room temperature and heating conditions gave product **4a** in 68 and 75% yield respectly (Table1, entry 4 and 5). Then we switched to another catalytic system L-proline as catalyst and carried out the reaction at room temperature and heating conditions and isolated product **4a** in 46 and 56 % yield respectively (Table1, entry 6 and 7). Then we tried NH_4Cl as catalyst and carried out the reaction at different conditions in room temperature the product **4a** was isolated in 83 % yield (Table1, entry 8) while that at 60 ° the product yield of **4a** was tremendously increased to 93% (Table1, entry 9). Screening various catalysts in this reaction revealed that NH_4Cl is the most efficient catalyst for good conversion and utilized for the synthesis of different analogues of imidazopyridines (**4a-h)**.

Table 1. Screening Conditions



Entry	*Solvent*	*Catalyst*	*Temperature (°C)*	*Time (h)*	*Yield (%)*
1	-----	-----	t.a	3	-----
2	-----	-----	60	3	30
2	EtOH	-----	t.a	3	Traces
3	EtOH	-----	60	3	40
4	EtOH	PTSA*H_2O (10%)	t.a	3	68
5	EtOH	PTSA*H_2O (10%)	60	3	75
6	EtOH	L-Proline (10%)	t.a	3	46
7	EtOH	L-Proline (10%)	60	3	56
8	EtOH	NH_4Cl (10%)	t.a	3	83
9	EtOH	NH_4Cl (10%)	60	3	93

3. *Experimental section*

General Information: ^{1}H and ^{13}C NMR spectra were acquired on a 500 MHz spectrometer. The solvent for the NMR samples was $CDCl_3$. Chemical shifts are reported in parts per million (δ/ppm). The internal reference for the NMR spectra is tetramethylsilane at 0.00 ppm. Coupling constants are reported in hertz (J/Hz). Multiplicities of the signals are reported using standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). IR spectra were recorded by the attenuated total reflection (ATR) method, using neat compounds. The wavelengths are reported in reciprocal centimeters (ν_{max}/cm^{-1}). High-resolution mass spectrometry (HRMS) spectra were acquired via electrospray ionization ESI (+) and recorded via the time-of-flight (TOF) method. Reactions at reflux were performed in round-bottomed flasks, using a recirculation system mounted on a sand bath, with an electronic temperature control. Ultrasound irradiated reactions were performed in sealed vials (10 mL) placed into a water bath of a Branson 1510 sonicator cleaner working at 42 kHz ± 6% frequencies. The reaction progress was monitored by TLC, and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230–400

mesh) and mixtures in different proportions of hexanes, with ethyl acetate as mobile phase. Melting points were determined on a Fisher−Johns apparatus and were uncorrected.

General method: In a vial (10mL) containing a solution of furan carbaldehyde (1.0 equiv.) in EtOH [0.5 M] were added sequentially 2-aminopyridine (1.0 equiv.), ammonium chloride (0.1 equiv.) and the corresponding isocyanide (1.0 equiv.). The vial was closed, and the reaction mixture was sonicated (42 kHz ± 6%) at room temperature for 3 hours The solid products obtained from the reaction was filtered and washed with deionized water (10 mL) and used as such for analytical characterization.

Spectral data

***N*-cyclohexyl-2-(furan-2-yl)imidazo[1,2-*a*]pyridin-3-amine**.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 6.9, 0.8 Hz, 1H), 7.41 (dd, *J* = 6.5, 0.7 Hz, 2H), 7.02 (dd, *J* = 8.4, 7.3 Hz, 1H), 3.53 (s, 1H), 2.91 – 2.85 (m, 1H), 1.83 – 1.79 (m, 2H), 1.67 – 1.63 (m, 2H), 1.54 – 1.50 (m, 1H), 1.23 – 1.10 (m, 5H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 141.8, 141.3, 128.1, 125.5, 123.8, 122.7, 117.2, 111.5, 111.4, 106.3, 57.0, 34.1, 25.7, 24.9 ppm. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ Calcd for $C_{17}H_{19}N_3O$ 282.1601, found 282.1619.

4. Conclusions

We have developed the first efficient and mild USI assisted GBB based methodology for the green synthesis of new *tris*-heterocyclic furan-2yl-imidazo[1,2-*a*] pyridine-3-amines in excellent overall yields. To the best of our knowledge, this is the first ultrasound assisted GBBR using green, readily available, inexpensive catalyst in mild conditions. Compared to the previously reported green expensive or non-readily available catalyzed GBBRs, herein we are the first to report the efficient catalytic use of inexpensive NH_4Cl as a green catalyst in GBBR using furfural as component.

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Conflicts of Interest: "The authors declare no conflict of interest."

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