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; 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) [1–3]. The Groebke-Blackburn-Bienaymé reaction (GBBR) in the synthesis of fused heterocycles imidazo[1–4] 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 [4]. 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 [5–8]. Besides Imidazo[1,2-a], pyridine moieties have applications in the field of optics such as organic light-emitting devices (OLED’s), fluorescent labeling, fluorescent dyes, because of their luminescent properties [9–11]. Recently furan bound to Imidazo[1,2-a] pyridine has been reported as a chemo-sensor for Cu²⁺ [12].

The most important approaches are: (i) Condensation of 2-aminoypyridine with α-halocarbonyl compounds [13,14], (ii) one pot condensations of aldehydes, isonitriles and 2-aminopyridines, which are well known as Groebke-Blackburn-Bienaymé reaction (GBBR) [15–17], (iii) copper-catalyzed three component reactions of 2-aminopyridines, aldehydes and alkynes [18–20]. Other methods have also been developed within the last three decades [21]. 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 amounts of catalysts, long reaction times, high temperatures, less yields and non-readily available catalysts [22,23]. 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 fields 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 [24–26].

Herein, we report a ultrasonic irradiation (USI) assisted, mild and greener GBB protocol to
synthesize bound type tris-heterocycles containing furan, imidazole and pyridine aromatic
heterocycles from 2-amino-pyridines, substituted furan carbaldehydes, and isocyanides using NH₄Cl
as a green catalyst and EtOH as a green solvent (Scheme 1).

\[
\begin{align*}
\text{Furan-2-yl imidazo[1,2-a] pyridine-3-amine analogue} & \quad \text{NH₄Cl} \\
\text{4a} & \quad \text{EtOH} \\
\text{R₁=H, Me; R₂=Cy, 4-OMe; R₃= H, 5-Cl, 4-COOMe, 4-CN} \\
\text{8 examples}
\end{align*}
\]

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 (1 mmol), cyclohexyl isonitrile 3a (1mmol) in EtOH as a solvent and green catalyst
such as p-toluene sulfonic acid (PTSA), L-proline and ammonium chloride under USI conditions
(Table 1). Initially, we performed the GGBR at room temperature, however, without a catalyst no
reaction was observed. (Table 1, entry 1). Additionally, on heating, the product 4a was obtained in
30% yield (Table 1, entry 2). Then we switched to the solvent system and considered EtOH as a green
solvent and performed the reaction. At room temperature, in the absence of catalyst the product 4a
was observed in traces (Table 1, entry 3). On heating at 60 °C without catalyst gave 40% of product
4a (Table 1, entry 4). Then we switched to another green catalyst PTSA at room temperature and
heating conditions, which gave product 4a in 68% and 75% yield respectively (Table 1, entry 4 and
5). Then we switched to another catalytic system, where L-proline was the catalyst and carried out the
reaction at room temperature and heating conditions and isolated product 4a in 68% and 75% yield
respectively (Table 1, entry 4 and 5). Then we switched to another catalytic system, where L-proline was the catalyst and carried out the reaction at different conditions at room temperature. The product 4a was isolated in 83% yield (Table 1, entry
8) while at 60 °C the product yield of 4a increased tremendously to 93% (Table 1, entry 9). Screening
various catalysts in this reaction revealed that NH₄Cl was the most efficient catalyst for good
conversion and was 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     | EtOH    | -----    | 60               | 3        | 30        |
| 3     | EtOH    | -----    | 60               | 3        | Traces    |
| 4     | EtOH    | PTSA*H₂O (10%) | t.a    | 3        | 68        |
| 5     | EtOH    | PTSA*H₂O (10%) | 60     | 3        | 75        |
| 6     | EtOH    | L-Proline (10%) | t.a   | 3        | 46        |
| 7     | EtOH    | L-Proline (10%) | 60     | 3        | 56        |
| 8     | EtOH    | NH₄Cl (10%) | t.a             | 3        | 83        |
| 9     | EtOH    | NH₄Cl (10%) | 60              | 3        | 93        |

3. Experimental Section

General Information: ¹H and ¹³C NMR spectra were acquired on a 500 MHz spectrometer. The solvent for the NMR samples was CDCl₃. Chemical shifts were reported in parts per million (δ/ppm). The internal reference for the NMR spectra was tetramethylsilane at 0.00 ppm. Coupling constants were reported in hertz (J/Hz). Multiplicities of the signals were 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 were reported in reciprocal centimeters (νmax/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 the mobile phase. Melting points were determined on a Fisher-Johns apparatus and were uncorrected.

General method: In a vial (10 mL) containing a solution of furan carbaldehyde (1.0 equiv.), EtOH [0.5 M] was added sequentially to 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 h. The solid products obtained from the reaction were 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. ¹H NMR (500 MHz, CDCl₃) 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. ¹³C NMR (126 MHz, CDCl₃) 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 C₁₇H₁₉N₃O 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 NH₄Cl as a green catalyst in GBBR using furfural as a component.

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Conflicts of Interest: The authors declare no conflicts of interest.

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