

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

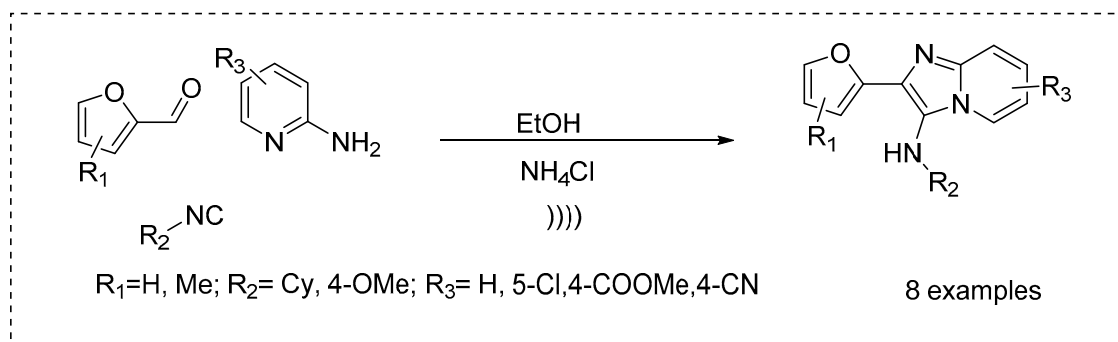
Multicomponent reactions (MCR's) have been considered as a powerful tool for the construction of novel and complex molecular structures from simple materials due to their advantages over conventional multistep synthesis. The major advantages of MCR's over multistep synthesis include cheap and readily 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-aminopyridine with α -halocarbonyl compounds [13,14], (ii) one pot condensations of aldehydes, isonitriles and 2-aminopyridines, which are well known as Groebke-Blackburn-Bienayme 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 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).

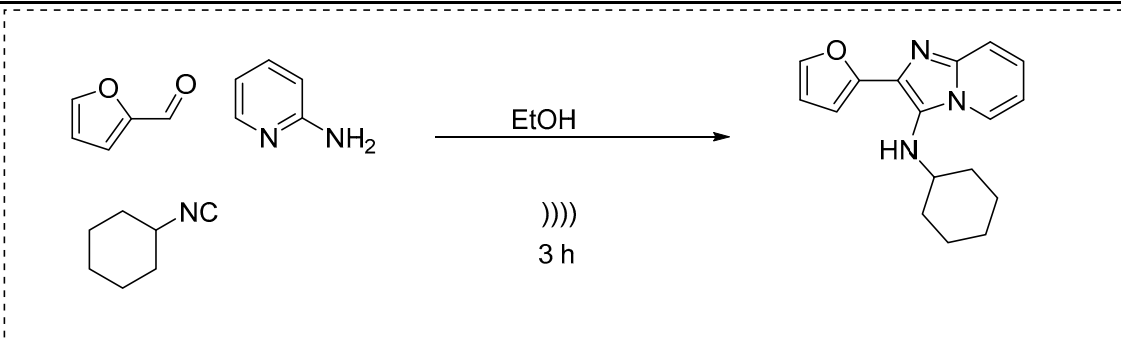


Scheme 1. Strategy for the synthesis of furan-2-yl imidazo [1,2-*a*] pyridines.

2. Results and Discussion

To develop green conditions for GBBR, we started the synthesis of furan-2-yl-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 GBBR 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 46 and 56% yield respectively (Table 1, entry 6 and 7). Then we tried NH_4Cl as 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 NH_4Cl 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	-----	-----	60	3	30
2	EtOH	-----	t.a	3	Traces
3	EtOH	-----	60	3	40
4	EtOH	PTSA*H ₂ O (10%)	t.a	3	68
5	EtOH	PTSA*H ₂ O (10%)	60	3	75
6	EtOH	L-Proline (10%)	t.a	3	46
7	EtOH	L-Proline (10%)	60	3	56
8	EtOH	NH ₄ Cl (10%)	t.a	3	83
9	EtOH	NH ₄ Cl (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 (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 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-2-yl-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.

References

- Goutam, B.; Suvankar, D.; Bismuth nitrate-catalyzed multicomponent reaction for efficient and one-pot synthesis of densely functionalized piperidine scaffolds at room temperature. *Tetrahedron Lett.* **2012**, *53*, 1479–1484, doi:10.1016/j.tetlet.2012.01.042.
- Chennan, R.; Young, W.K. Tetrachlorosilane catalyzed multicomponent one-step fusion of bio-pertinent pyrimidine heterocycles. *Tetrahedron* **2008**, *64*, 5023–5031, doi:10.1016/j.tet.2008.03.078.
- Domiling, A.; Wei, W.; Kan, W. Chemistry and Biology of Multicomponent Reactions. *Chem. Rev.* **2012**, *112*, 3083–3135, doi:10.1021/cr100233r.
- Christopher, H.; Yeon, S.L. Emerging approaches for the syntheses of bicyclic imidazo[1,2-*x*]-heterocycles. *Mol. Divers.* **2008**, *12*, 1–15, doi:10.1007/s11030-008-9072-1.
- Byth, K.F.; Culshaw, J.D.; Green, S.; Oakes, S.E.; Thomas, A.P. Imidazo[1,2-*a*]pyridines. Part 2: SAR and optimisation of a potent and selective class of cyclin-dependent kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2245–2248, doi:10.1016/j.bmcl.2004.02.015.
- Kishino, H.; Moriya, M.; Sakuraba, S.; Sakamoto, T.; Takahashi, H.; Suzuki, T.; Moriya, R.; Ito, M.; Iwaasa, H.; Takenaga, N.; et al. Discovery of imidazo[1,2-*a*]pyridines as potent MCH1R antagonists. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4589–4593, doi:10.1016/j.bmcl.2009.06.101.
- Warshakoon, N.C.; Wu, S.; Boyer, A.; Kawamoto, R.; Sheville, J.; Renock, S.; Xu, K.; Pokross, M.; Evdokimov, A.G.; Walter, R.; et al. A novel series of imidazo[1,2-*a*] pyridine derivatives as HIF-1 α prolyl hydroxylase inhibitors. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5598–5601, doi:10.1016/j.bmcl.2006.08.089.
- Zhuang, Z.-P.; Kung, M.-P.; Wilson, A.; Lee, C.-W.; Plössl, K.; Hou, C.; Holtzman, D.M.; Kung, H.F. Structure-Activity Relationship of Imidazo[1,2-*a*]pyridines as Ligands for Detecting β -Amyloid Plaques in the Brain. *J. Med. Chem.* **2003**, *46*, 237–243, doi:10.1021/jm020351j.
- Firmansyah, D.; Ciuciu, A.I.; Hugues, V.; Blanchard-Desce, M.; Flamigni, L.; Gryko, D.T. Bright, Fluorescent Dyes Based on Imidazo[1,2-*a*] pyridines that are Capable of Two-Photon Absorption. *Chem. Asian J.* **2013**, *8*, 1279–1294, doi:10.1002/asia.201300058.
- Nagarajan, N.; Velmurugan, G.; Prakash, A.; Shakti, N.; Katiyar, M.; Venuvanalilingam, P.; Renganathan, R. Highly Emissive Luminogens Based on Imidazo[1,2-*a*]pyridine for Electroluminescent Applications. *Chem. Asian J.* **2014**, *9*, 294–304, doi:10.1002/asia.201301061.
- Burchak, O.N.; Mugherli, L.; Ostuni, M.; Lacapere, J.J.; Balakirev, M.Y. Combinatorial Discovery of Fluorescent Pharmacophores by Multicomponent Reactions in Droplet Arrays. *J. Am. Chem. Soc.* **2011**, *133*, 10058–10061, doi:10.1021/ja204016e.
- Kumawat, L.K.; Kumar, M.; Bhatt, P.; Sharma, A.; Asif, M.; Gupta, V.K. An easily accessible optical chemosensor for Cu²⁺ based on novel imidazoazine framework, its performance characteristics and potential applications. *Sens. Actuators B* **2017**, *240*, 365–375, doi:10.1016/j.snb.2016.08.184.
- Pericherla, K.; Kaswan, P.; Pandey, K.; Kumar, A. Recent Developments in the Synthesis of Imidazo[1,2-*a*] pyridines. *Synthesis* **2015**, *47*, 887–912, doi:10.1055/s-0034-1380182.
- Bagdi, A.K.; Santra, S.; Monir, K.; Hajra, A. Synthesis of imidazo[1,2-*a*] pyridines: A decade update. *Chem. Commun.* **2015**, *51*, 1555–1575, doi:10.1039/c4cc08495k.

15. Groebke, K.; Weber, L.; Mehlin, F. Synthesis of Imidazo[1,2-*a*] annulated Pyridines, Pyrazines and Pyrimidines by a Novel Three-Component Condensation. *Synlett* **1998**, *6*, 661–663, doi:10.1055/s-1998-1721
16. Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. Parallel Synthesis of 3-Aminoimidazo[1,2-*a*] pyridines and pyrazines by a New Three-Component Condensation. *Tetrahedron Lett.* **1998**, *39*, 3635–3638, doi:10.1016/S0040-4039(98)00653-4.
17. Bienaymé, H.; Bouzid, K. A New Heterocyclic Multicomponent Reaction for the Combinatorial Synthesis of Fused 3-Aminoimidazole. *Angew. Chem.* **1998**, *110*, 2349–2352, doi:10.1002/(SICI)1521-3773(19980904)37:16.
18. Chernyak, N.; Gevorgyan, V. General and Efficient Copper-Catalyzed Three-Component Coupling Reaction towards Imidazoheterocycles: One-Pot Synthesis of Alpidem and Zolpidem. *Angew. Chem. Int. Ed.* **2010**, *49*, 2743–2746, doi:10.1002/anie.200907291.
19. Mishra, S.; Ghosh, R.; Mechanistic studies on a new catalyst system (CuI-NaHSO₄·SiO₂) leading to the one-pot synthesis of imidazo [1,2-*a*] pyridines from reactions of 2-aminopyridines. *Synthesis* **2011**, 3463–3470, doi:10.1055/s-0030-1260255.
20. Reddy, B.V.S.; Reddy, P. S.; Reddy, Y.J.; Yadav, J.S. InBr₃-catalyzed three-component, one-pot synthesis of imidazo [1,2-*a*] pyridines. *Tetrahedron Lett.* **2011**, *52*, 5789–5793, doi:10.1016/j.tetlet.2011.08.110.
21. Ebrahim, K.; Mohammad, G.; Mehri, N.N.; Reza, F. Novel One-Pot Three Component Reaction for the Synthesis of [2-(Alkylsulfanyl)imidazo[1,2-*a*]pyridin-3-yl](aryl)methanone. *J. Comb. Chem.* **2010**, *12*, 41–44, doi:10.1021/cc900103r.
22. Devi, N.; Rawal, R.K.; Singh, V. Diversity-oriented synthesis of fused-imidazole derivatives via Groebke-Blackburne-Bienayme reaction: *Tetrahedron* **2015**, *71*, 183–232, doi:10.1016/j.tet.2014.10.032;
23. Shaaban, S.; Abdel-Wahab, B.F. Groebke–Blackburn–Bienaymé multicomponent reaction: Emerging chemistry for drug discovery. *Mol. Divers.* **2016**, *20*, 233–254, doi:10.1007/s11030-015-9602-6.
24. Kurva, M.; Pharande, S.G.; Quezada-Soto, A.; Gámez-Montaña. R. Ultrasound assisted green synthesis of bound type bis-heterocyclic carbazolyl imidazo[1,2-*a*] pyridines via Groebke-Blackburn-Bienayme reaction. *Tetrahedron Lett.* **2018**, *59*, 1596–1599, doi:10.1016/j.tetlet.2018.03.031.
25. Claudio-Catalan, M.A.; Pharande, S.G.; Quezada-Soto, A.; Kishore, K.G.; Renteria-Gomez, A.; Padilla-Vaca, F.; Gamez-Montano, R. Solvent-and Catalyst-Free One-Pot Green Bound-Type Fused Bis-Heterocycles Synthesis via Groebke-Blackburn-Bienayme Reaction/SNAr/Ring-Chain Azido-Tautomerization Strategy. *ACS Omega* **2018**, *3*, 5177–5186, doi:10.1021/acsomega.8b00170.
26. Unnamatla, M.V.B.; Islas-Jácome, A.; Quezada-Soto, A.; Ramírez-López, S.C.; Flores-Álamo, M.; Gámez-Montaña, R. Multicomponent One-Pot Synthesis of 3-Tetrazolyl and 3-Imidazo[1,2-*a*]pyridin Tetrazolo[1,5-*a*]quinoline. *J. Org. Chem.* **2016**, *81*, 10576–10583, doi:10.1021/acs.joc.6b01576.

