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An efficient green synthesis of novel 1*H*-imidazo[1,2-*a*]imidazole-3-amine and imidazo[2,1-*c*][1,2,4]triazole-5-amine derivatives via Strecker reaction under controlled microwave heating

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Abstract: A highly efficient multi-component one-pot synthesis of novel 1*H*-imidazo[1,2-*a*]imidazole-3-amine and imidazo[2,1-*c*][1,2,4]triazole-5-amine derivatives has been developed through the reaction of easily available aromatic aldehydes, benzoyl cyanide and either 2-aminoimidazole-4,5-dicarbonitrile or 3-amino-1,2,4-triazole in pyridine under controlled microwave heating. The process is environmentally friendly, is operationally simple, with short reaction time and with high yields.

Keywords: catalyst free; imidazo [1,2-*a*]imidazoles; imidazo[2,1-*c*][1,2,4]triazoles; microwave heating; multi-component reaction; Strecker reaction.

1 Introduction

Nitrogen containing heterocycles widely occur in synthetic drugs and natural products. A privileged theme of such heterocycles is the ability to act as bond donor and/or acceptor that effectively influences the medicinal scaffold and its target interaction [1–3]. *1H*-imidazo[1,2-*a*]imidazoles as [5+5] bicyclic guanidines exhibit a wide range of applications in fields related to pharmaceuticals and material science. Imidazo[1,2-*a*]imidazoles serve as lymphocyte function-associated nitrogen (LFA-1) inhibitors [4, 5], specifically inhibiting [3*H*] diazepam binding [6]. In addition, guanidinium cations are extensively utilized as sensors for anion recognition [7]. Chiral imidazo[1,2-*a*]imidazoles act as a asymmetric catalyst in enantio-selective synthesis of α-amino nitriles and α-amino acids in Strecker reaction [8, 9]. Very limited reported strategies for the synthesis of imidazo[1,2-*a*]imidazoles are known. It mainly involves the construction of a α-bicyclic scaffold starting from a monocyclic guanidine. Thus, Langer et al. [10] reported an interesting synthesis of imidazo[1,2-*a*]imidazoles via the [3+2] cyclization of oxaldiimidoyl chlorides and 2-aminoimidazoles in dimethylformamide (DMF) and catalytic amount of triethylamine and heating under reflux for 4 h with moderate yields (47%–77%). Aerobic oxidative intramolecular C-H amination of substituted 2(1-*H*-imidazol-1-yl)-*N*-alkyl benzene amines utilizing cupper acetate in the presence of 1,10-phenanthroline (phen) as ligand using dioxygen as an oxidant in m-xylene and heating under reflux at 155°C for 24–55 h has been recently reported by Wang et al., which afforded the target molecule with a variety of molecular diversity and excellent yields [11]. Although these methods have their specific merits, they require long reaction times, harsh reaction conditions and, sometimes, low yields.

Imidazo[2,1-*c*][1,2,4]triazole derivatives have received considerable interest due to their potential biological activities. For instance, they have applications as anti-inflammatory [12], antimicrobial [13], anti-fungicidal [12, 14, 15] and analgesic agents [12]. To the best of our knowledge, few articles describe the synthesis of imidazo[2,1-*c*][1,2,4]triazole derivatives. The different approaches for the synthesis of such scaffold consist of construction of a bicyclic system starting from 3-amino-1,2,4-triazole. These approaches mainly involve coupling of 5-diazoimidazoles with nitro, chloro, bromo and acetyl amino malonic acid diethyl ester and subsequent cyclization of the coupling product via heating under reflux in DMF [16]. The Groebke reaction of 3-amino-1,2,4-triazole, aldehydes and aliphatic isonitriles in methanol in the presence of ammonium chloride under reflux for 15 h afforded the corresponding *N*-alkylidene-4-imidazotriazole-6-amine in moderate yields. Though these protocols are quite useful, they require harsh reaction conditions, use of hazardous and expensive reagents and long reaction times [17, 18]. Although there are several reports on the utility of trimethylsilyl cyanide (TMSCN), cyanamide (NH_2CN) or cyanohydrin as cyanide source of Strecker reaction, it is well documented that such reagents are toxic and hazardous. This prompted us to develop an efficient catalyst-free multi-component reaction for the synthesis of imidazo[1,2-*a*]imidazole-3-amine and imidazo[2,1-*c*][1,2,4]triazole-5-amine derivatives by

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the reaction of 2-aminoimidazole-4,5-dicarbonitrile **1a** and 3-amino-1,2,4-triazole with aromatic aldehydes **2** and benzoyl cyanide **3** in pyridine under controlled microwave heating. The use of microwave technology has advantageous features of operational simplicity, enhanced reaction rates with short reaction times, high yields and purity of products [19].

In conjunction to our interest in performing green, general and efficient synthesis of biologically relevant heterocycles utilizing controlled microwave heating [20–24], we have developed convenient multi-component reaction for the synthesis of imidazo[1,2-*a*]imidazole-3-amine and imidazo[2,1-*c*][1,2,4]triazole-5-amine derivatives.

2 Materials and methods

2.1 General information

All the reactions were carried out in a Milestone START Microwave Lab Station (temperature controlled by infrared sensor). Melting points are uncorrected and were determined with a Gallenkamp instrument. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were carried out using a Bruker DPX instrument (Billerica, MA, USA) at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR using DMSO-d_6 as solvent and TMS as internal standard. Chemical shifts are expressed in δ ppm. Mass spectra were made using a GCMS DFS Thermo spectrometer with the EI (70 ev) mode. Analytical thin-layer chromatography was performed with silica gel plates using silica gel 60 PF_{254} (Merck). Starting materials were obtained from Aldrich (Mumbai, India) and used directly.

2.2 General procedure for the synthesis of imidazo[1,2-*a*]imidazole-3-amine and imidazo[2,1-*c*][1,2,4]triazole-5-amine derivatives (4, 5, 8, 9)

A mixture of 2-aminoimidazole-1,3-dicarbonitrile **1** or 3-amino-1,2,4-triazole **6** (1 mmol), aromatic aldehydes **2** (2 mmol) and benzoyl cyanide **3** (1 mmol) in pyridine (10 ml) was heated under reflux in a Milestone Microwave Lab Station at 120°C for 30 minutes. After concentration under reduced pressure and cooling to room temperature, addition of 10 ml H_2O and acidification with HCl, the resulting solid product was collected by filtration, washed with EtOH, dried and recrystallized from appropriate solvent.

2.2.1 (*E*)-3-((4-methoxybenzylidene)amino)-2-(4-methoxyphenyl)-1*H*-imidazo[1,2-*a*]imidazole-5,6-dicarbonitrile (4a): Dark yellow crystals from DMF, yield 90%, mp: 332–334°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.35 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 7.04–7.07 (m, 4H, Ar-H), 7.73 (d, 2H, J = 8.4 Hz, Ar-H), 7.88 (d, 2H, J = 8.4 Hz, Ar-H), 8.83 (d, 1H, J = 14.8 Hz, arylidene CH), (NH imidazole, not seen, [25]). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.83, 56.01, 99.39, 114.92, 115.22, 128.86, 129.56, 130.68, 160.30, 162.85. Anal. Calcd. For $C_{22}H_{16}N_6O_2$: C, 66.66; H, 4.07; N, 21.20; Found: C, 66.71; H, 4.18; N, 21.37.

2.2.2 (*E*)-3-((4-chlorobenzylidene)amino)-2-(4-chlorophenyl)-1*H*-imidazo[1,2-*a*]imidazole-5,6-dicarbonitrile (4b): Yellow crystals from DMF, yield 82%; mp: 357–359°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.36–7.40 (m, 4H, Ar-H), 7.50 (d, 2H, J = 8.4 Hz, Ar-H), 7.76 (d, 2H, J = 8.4 Hz, Ar-H), 8.57 (s, 1H, arylidene CH), 13.15 (s, 1H, imidazole NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.74, 113.37, 114.01, 120.50, 123.09, 124.97, 125.34, 126.74, 127.89, 128.19, 129.07, 129.22, 129.50, 129.77, 129.77, 129.3, 131.57, 134.21, 135.22, 136.96. Anal. Calcd. For $C_{20}H_{10}Cl_2N_6$: C, 59.28; H, 2.49; Cl, 17.50; N, 20.74; Found: C, 59.43; H, 2.61; Cl, 17.63, N, 20.89.

2.2.3 (*E*)-3-((3-nitrobenzylidene)amino)-2-(3-nitrophenyl)-1*H*-imidazo[1,2-*a*]imidazole-5,6-dicarbonitrile (4c): Dark orange crystals from DMF; yield 83%; mp: 257–259°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.46–7.56 (m, 2H, Ar-H), 7.84 (d, 1H, J = 7.6 Hz, Ar-H), 7.94 (d, 1H, J = 7.2 Hz, Ar-H), 8.04 (s, 1H, Ar-H), 8.08 (d, 1H, J = 8.4 Hz, Ar-H), 8.23 (d, 1H, J = 8 Hz, Ar-H), 8.40 (s, 1H, Ar-H), 8.90 (d, 1H, J = 14.8 Hz, arylidene CH), (NH imidazole, not seen [25]). ^{13}C NMR (100 MHz, DMSO-d_6): δ 97.18, 113.50, 114.38, 121.64, 122.37, 122.45, 124.72, 124.76, 125.67, 129.98, 130.80, 133.09, 133.31, 133.87, 138.44, 148.07, 148.63, 151.65. Anal. Calcd. For $C_{20}H_{10}N_8O_4$: C, 56.34; H, 2.36; N, 26.28; Found: C, 56.50; H, 2.19; N, 26.32.

2.2.4 (*E*)-3-((3,4-dimethoxybenzylidene)amino)-2-(3,4-dimethoxyphenyl)-1*H*-imidazo[1,2-*a*]imidazole-5,6-dicarbonitrile (4d): Greenish yellow crystals from DMF, yield 86%; mp: 328–330°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.74 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.94 (d, 1H, J = 7.6 Hz, Ar-H), 7.00 (d, 1H, J = 8 Hz, Ar-H), 7.16 (d, 1H, J = 6.4 Hz, Ar-H), 7.29 (s, 1H, Ar-H), 7.46 (d, 1H, J = 8.4 Hz, Ar-H), 7.54 (s, 1H, Ar-H), 8.64 (s, 1H, arylidene CH), 13.22 (s, 1H, imidazole NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.93, 56.07, 56.38, 117.10, 120.95, 121.03, 121.26, 123.52, 124.24, 126.22, 126.87, 128.14, 132.02, 132.17, 133.89, 136.91, 144.64, 153.52, 156.99, 159.70. Anal. Calcd. For $C_{24}H_{20}N_6O_4$: C, 63.15; H, 4.42; N, 18.41; Found: C, 63.22; H, 4.38; N, 18.29.

2.2.5 (*E*)-3-((2-methoxybenzylidene)amino)-2-(2-methoxyphenyl)-1*H*-imidazo[1,2-*a*]imidazole-5,6-dicarbonitrile (4e): Bright yellow crystals from DMF, yield 58%; mp: 298–300°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.74 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 7.01–7.96 (m, 8H, Ar-H), 8.67 (s, 1H, arylidene CH), 13.17 (s, 1H, imidazole NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.10, 56.35, 112.48, 113.10, 114.13, 117.07, 121.05, 121.25, 123.42, 124.34, 126.79, 128.14, 132.04, 132.17, 133.98, 136.90, 144.62, 153.49, 157.01, 159.64. Anal. Calcd. For $C_{22}H_{16}N_6O_2$: C, 66.66; H, 4.07; N, 21.20; Found: C, 66.57; H, 3.97; N, 21.06.

2.2.6 3-Amino-2-phenyl-1*H*-imidazo[1,2-*a*]imidazole-5,6-dicarbonitrile (5): Light purple from DMF, yield 84%; mp: 282–284°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.54–8.06 (m, 5H, Ar-H), (NH_2, not seen [25]), 12.34 (s, 1H, imidazole NH).^{13}C NMR (100 MHz, DMSO-d_6): δ 111.70, 128.67, 128.79, 129.08, 132.34, 133.39, 145.15, 150.12, 166.36. Anal. Calcd. For $C_{13}H_8N_6$: C, 62.90; H, 3.25; N, 33.85; Found: C, 62.71; H, 3.17; N, 33.97.

2.2.7 6–(4-Methoxyphenyl)-7*H*-imidazo[2,1-*c*][1,2,4]triazole-5-amine (8a): Yellow crystals from ethanol; yield 82%; mp: 282–285°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H, OCH_3), 7.02–7.12 (m, 3H, Ar-H), 7.39–7.60 (m, 3H, 1 ArH, 2H NH_2), 7.61 (s, 1H, triazole),

8.04 (brs, 1H, imidazole NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.83, 111.40, 119.51, 120.59, 122.47, 128.06, 130.46, 150.03, 156.13. MS: m/z (%) 229 (M^+) (45), 198 (25), 171 (85), 146 (100), 116 (44), 91 (30), 71 (12). Anal. Calcd. For $C_{11}H_{11}N_5O$: C, 57.63; H, 4.84; N, 30.55; Found: C, 57.75; H, 4.76; N, 30.36.

2.2.8 (*E*)-*N*-(4-chlorobenzylidene)-6-(4-chlorophenyl)-7*H*-imidazo[2,1-*c*][1,2,4]triazol-5-amine (9b): Yellow crystals from ethanol; yield 80%; mp: 212–214°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.58–7.63 (m, 5H, Ar-H), 7.95–7.97 (m, 2H, ArH), 8.12–8.14 (m, 3H, 1 ArH, 1H arylidene, 1H triazole), 9.45 (s, 1H, imidazole NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 120.08, 120.18, 129.28, 129.30, 129.63, 130.18, 133.40, 136.16, 139.04, 141.13, 146.03, 150.16, 152.14. MS: m/z (%) 356 (M+1, 65), 355 (M^+, 100), 328 (28), 191 (18), 156 (43), 138 (55), 111 (18), 89 (15), 75 (12). Anal. Calcd. For $C_{17}H_{11}Cl_2N_5$: C, 57.32, H, 3.11, Cl, 19.91, N, 19.66; Found: C, 57.40, H, 3.20, Cl, 19.86, N, 19.57.

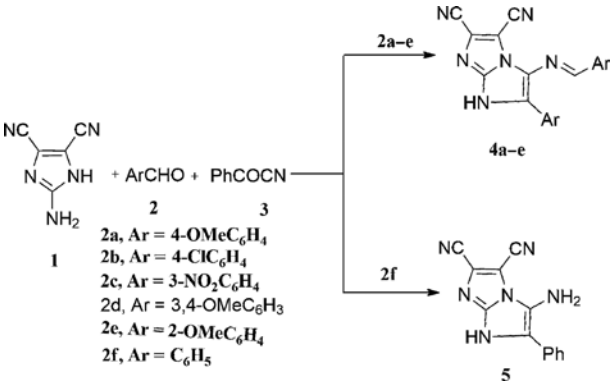
2.2.9 (*E*)-*N*-(3-nitrobenzylidene)-6-(3-nitrophenyl)-7*H*-imidazo[2,1-*c*][1,2,4]triazol-5-amine (9c): Yellowish crystals from ethanol; yield 84%; mp: 252–254°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.67–8.74 (m, 10H, 8 Ar-H, 1 arylidene, 1H triazole), 9.30 (s, 1H, imidazole NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 126.29, 126.62, 129.39, 129.55, 129.59, 130.25, 130.45, 130.49, 131.01, 131.53, 132.04, 132.19, 143.28, 143.34, 143.39, 147.57, 147.62. MS: m/z (%) 377 (M^+, 22), 314 (15), 300 (30), 286 (10), 241 (5), 213 (5), 163 (7), 135 (35), 121 (100), 93 (15), 76 (20). Anal. Calcd. For $C_{17}H_{11}N_7O_4$: C, 54.11, H, 2.94, N, 25.99; Found: C, 54.32, H, 3.01, N, 26.12.

2.2.10 (*E*)-*N*-benzylidene-6-phenyl-7*H*-imidazo[2,1-*c*][1,2,4]triazol-5-amine (9f): Yellow crystals from ethanol; yield 85%; mp: 262–264°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.50–7.53 (m, 4H, Ar-H), 7.56–7.61 (m, 4H, Ar-H), 7.70–7.72 (m, 2H, Ar-H), 7.96 (s, 1H arylidene), 7.99 (s, 1H triazole), 8.21 (brs, 1H, imidazole NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 119.43, 128.70, 129.17, 129.64, 130.83, 131.17, 131.66, 133.26, 134.36, 140.60, 142.85, 152.66, 162.34. MS: m/z (%) 287 (M^+, 28), 185 (16), 171 (12), 129 (42), 83 (46), 73 (92), 57 (100). Anal. Calcd. For $C_{17}H_{13}N_5$: C, 71.06, H, 4.56, N, 24.37; Found: C, 71.18, H, 4.63, N, 24.50.

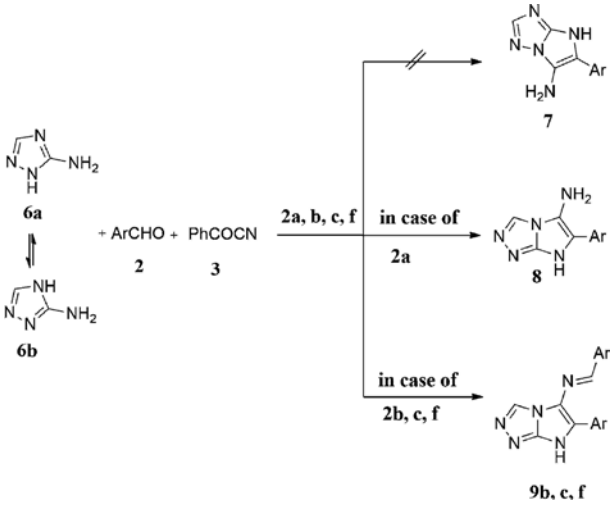
3 Results and discussion

With the initial aim of optimizing the reaction conditions, we explored the reaction of equimolar amounts of **1**, **2a** and **3** in ethanol in the presence of three drops of piperidine, and the reaction was promoted by microwave heating at 70°C over 30 minutes. The process led to the formation of a low yield (35%) of the reaction product **4a**. Pyridine was also examined and found to be convenient for such reaction, and higher yields were obtained. The structure of **4a** could be established based on analytical and spectral data. ^{1}H NMR showed arylidine CH at δ = 8.83 ppm (J = 14.8 Hz, which is characteristic for *E* configuration), aromatic protons and two methoxy functions. ^{13}C NMR spectrum was in support of the proposed structure. We noticed that the yield was increased to 90% when two equivalents of aldehyde **2a** were utilized. Similarly multi-component reaction of **1** two equivalents of **2b–e** and **3** under the same reaction conditions afforded **4b–e** in excellent yields. However, the reactions of **1a, 2f** and **3** afford **5** without further condensation with another molecule of aldehyde **2f**. The proposed structures for the reaction products were established on spectral and analytical data (Scheme 1).

The same reaction protocol was applied to the reaction of 3-amino-1,2,4-triazole **6** with aromatic aldehyde **2b** and benzoyl cyanide **3** (Scheme 2). A product **9b** of molecular formula was obtained, which showed M^+ 355 (100%). ^{1}H NMR spectra of the product showed signals for aromatic protons, arylidene CH as well as imidazole NH at δ = 9.45 ppm. Structure **9b** was established for the reaction product via formation of the corresponding imidazo[2,1-*c*][1,2,4]triazole and subsequent reaction of another molecule of aldehyde **2b**. The energy difference for **6a,b** was computed and found to be 4.2 kcal/mol in favor of **6b** [26].



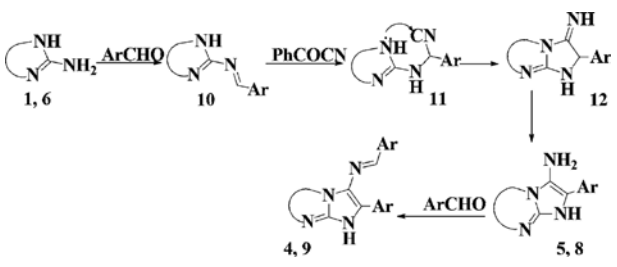
Scheme 1: Synthesis of imidazo[1,2-*a*]imidazole derivatives.



Scheme 2: Synthesis of imidazo[2,1-*c*][1,2,4]triazole derivatives.

Moreover, the NH group of **6b** renders more nucleophilic than the NH group of **6a** due to the presence of adjacent electron-withdrawing endocyclic nitrogen atom. In addition, the regioselectivity for the reaction of 3-amino-1,2,4-triazole with nucleophilic reagents has been reported to be solvent dependent. It includes the initial reaction with exocyclic amino function and subsequent cyclization with endocyclic NH of **6a** in acidic medium or NH of **6b** in protic or basic medium [25]. This ruled out the possible formation of **7** and its subsequent reaction with another molecule of **2b**. If the reaction product was **7**, the imidazole NH will appear at downfield shift (≈12.43 ppm) [27, 28]. Similarly, compound **6b** reacted with **2a,c,f** to afford the corresponding **8a** and **9b,c,f**.

A proposed mechanism for the formation of the reaction products displayed involves the formation of Schiff base **10** from the reaction of 2-aminoimidazole -1,3-dicarbonitriles **1** or 3-amino-1,2,4 triazole **6** with aromatic aldehydes and subsequent Strecker reaction with benzoyl cyanide to afford the corresponding aminonitrile **11.** Attack of the imidazole or triazole ring nitrogen ion pair to the CN function would result in the formation of the bicyclic imine product **12.** 1,3-Proton shift followed by aromatization led to the formation of the corresponding imidazo[1,2-b]imidazole-3-amine **5** or imidazo[2,1-*c*]-1,2,4-triazole -5-amine **8.** Further reaction with another molecule of aldehyde **2** affords the corresponding N-arylidine derivatives **4** and **9.** The enhancement of the reaction under microwave heating can be rationalized based on medium effects and mechanistic effects. As a result of the material-wave interaction, the greater the polarity of a molecule of either the solvent or reactant with the rise of temperature resulted in a more pronounced microwave effect. Concerning mechanistic effects, when the polarity is increased during the reaction proceeding from the ground state to the transition state leading to intermediates **10, 11,** stabilization of such transition will decrease the activation energy and reactivity will be enhanced (Scheme 3).



Scheme 3: Proposed mechanism for the formation of imidazo[1,2-*a*] imidazole derivatives and imidazo[2,1-*c*][1,2,4]triazole derivatives.

4 Conclusion

In conclusion, we have developed a convenient synthesis of novel imidazo[1,2-*a*]imidazole-3-amine and imidazo[2,1-*c*][1,2,4]triazole-5-amine derivatives from three component reactions of 2-aminoimidazole-1,3- dicarbonitril or 3-amino-1,2,4-triazole with aromatic aldehyde and benzoyl cyanide in pyridine under controlled microwave heating. The process proved to be a simple, green and efficient methodology for the synthesis of target molecules. To the best of our knowledge, very limited methodologies for the synthesis of these scaffolds have been reported in the literature.

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