Research Article

An Efficient and Green Method for Synthesis of 2,4,5-Triarylimidazoles without Use of Any Solvent, Catalyst, or Solid Surface

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An efficient and green method for synthesis of 2,4,5-triarylimidazoles without use of any catalyst or solvent has been developed simply by heating (at 130°C) of mixtures of 1,2-diketone, aromatic aldehyde, and ammonium acetate in 1:1:3 mole ratio.

1. Introduction

Multicomponent reactions (MCRs) have emerged as a powerful tool for convergent synthesis of many complex organic molecules [1–6]. They are one-pot processes bringing together three or more components in a particular sequence of reactions and show high atom economy and remarkable selectivity. Because of their operational simplicity, MCRs have occupied a very prominent place in diversity oriented synthesis which is an important requirement for drug discovery. The imidazole nucleus is a rich source for getting biologically important organic molecules. Compounds containing imidazole moiety show a range of pharmacological properties and play important roles in biochemical processes. Various substituted imidazoles act as inhibitors of P38 MAP kinase [7] and B-Raf kinase [8], glucagon receptors [9], pesticides [10], fungicides [10], herbicides [11], and antitumor [12], anti-inflammatory [13], and antithrombotic [14] agents. Moreover, they are used in photography as photosensitive compounds [15]. 2,4,5-Triarylimidazoles (**3**) form an important group of substituted imidazoles having many of the above biological activities and material properties. Retrosynthetic analysis of **3** suggests the readily available compounds aromatic 1,2-diketones, aromatic aldehydes, and ammonia as their precursors. This has led to the development of a large number of synthetic methods for **3** using these simple starting materials. Almost all of these methods use ammonium acetate as the ammonia source. Many of the reported methods

require long reaction time and use of expensive catalysts and organic solvents [16–23]. The current literature shows that there has been a growing trend towards green synthesis of these compounds [24, 25]. However, in such reported green methods, also use of catalysts or organic solvents could not be avoided. The current trend towards development of catalyst-free and solvent-free reaction conditions for organic synthesis [26, 27] encouraged us to study the same reaction under thermal condition without using any solvent or catalyst. The remarkable success in this endeavor is presented herein.

2. Results and Discussion

Our present method involves subjecting of an intimate mixture of 1,2-diketone, aromatic aldehyde, and ammonium acetate in 1:1:3 mole ratio directly to heat (130°C, 3–6 h). A range of structurally diverse aldehydes belonging to the categories aromatic and heterocyclic aldehydes were taken (Scheme 1). To our delight, the target compounds were obtained in good to very good yield in this method for all the combinations. The yields of the products are presented in Table 1.

In the method being reported, it was a common observation that the reactions were very clean and no side product was formed in any run. In fact, the crude products obtained were of high purity and did not require any chromatographic separation. Their crystallization from ethanol provided analytically pure samples. More significantly, the whole operation

SCHEME 1: Synthesis of 2,4,5-triarylimidazoles (**3**) under catalyst-free and solvent-free condition. Ar¹ = C₆H₅; 4-CH₃-C₆H₄; Ar² = C₆H₅; 4-CH₃-C₆H₄; 4-Cl-C₆H₄; 4-Br-C₆H₄; 4-CH₃O-C₆H₄; 3,4-(OCH₂O) C₆H₃; 3-O₂N-C₆H₄; 4-(CH₃)₂N-C₆H₄; 3-CH₃O, 4-HO-C₆H₃; 2-Thienyl; 3-Pyridyl.

did not require any solvent, organic or inorganic, at any stage. Furthermore, the reaction condition has been found to be mild enough to tolerate a variety of functionalities such as NO₂, Cl, OH, and OMe.

3. Conclusion

We report here a very simple and efficient green method for synthesis of 2,4,5-triarylimidazoles avoiding the use of any solvent, catalyst, and solid surface.

4. Experimental

4.1. General. Melting points were recorded on a Kfler block. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer (Spectrum BX II) in KBr pellets. ¹H NMR spectra and ¹³C NMR spectra were recorded in CDCl₃ on a Bruker AV-300 (300 MHz) spectrometer. Analytical samples were routinely dried *in vacuo* at room temperature. Microanalytical data were recorded on two Perkin-Elmer 2400 Series II C, H, N analyzers. Mass spectra were measured in the following ways FAB-MS [Jeol the M Station JMS.700]. TLC was performed with silica gel G made by SRL Pvt. Ltd. Petroleum ether had the boiling range 60–80C.

4.2. General Method for Synthesis of 2,4,5-Triarylimidazoles (3). In a typical experiment, an intimate mixture of benzil (1 mmol), aromatic aldehyde (1 mmol), and ammonium acetate (3 mmol) was taken in a round-bottom flask (50 mL) fitted with a CaCl₂-guard tube and the flask was heated in an oil bath at 130C. Initially, the reaction mixture melted and after some time (*ca.* 1–3 h) it began to solidify. When the reaction mixture solidified totally (time period mentioned in Table 1), it was cooled to room temperature and to it water (20 mL) was added. The resulting solid mass was crushed and it was filtered, and the residue was washed with water and then dried. The crude product so obtained was crystallized from ethanol.

All of the products **3a–n** were known compounds and were identified by comparison of their physical and spectral data with those reported in the literature. The spectral data recorded by us are given below.

4.2.1. Compound 3a. Colorless needles, ¹H NMR (300 MHz, CDCl₃, δ/ppm): and 7.95 (br. d, 2H, *J* = 8.1 Hz), 7.59 (br. d, 4H, *J* = 7.8 Hz), 7.28–7.48 (m, 9H); Anal. Calcd. for C₂₁H₁₆N₂

(296.37): C, 85.11; H, 5.44; N, 9.45. Found: C, 85.26; H, 5.72; N, 9.31.

4.2.2. Compound 3b. Colorless needles, IR (KBr, cm^{–1}): 3414, 3027, 2363, 1654, 1601, 1493, 1449, 1381; ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.86 (d, 2H, *J* = 8.1 Hz), 7.50 (br. d, 4H, *J* ≈ 7.8 Hz), 7.21–7.31 (m, 8H), 2.38 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃, δ/ppm): 146.2, 138.9, 132.9, 129.6, 128.6, 127.8, 127.4, 127.1, 125.2, 21.3; FAB MS (*M* + *H*)⁺: Calcd. 311.3. Found 311.3; Anal. Calcd. for C₂₂H₁₈N₂ (310.39): C, 85.13; H, 5.85; N, 9.03. Found: C, 84.86; H, 5.75; N, 8.82.

4.2.3. Compound 3c. Colorless needles, ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.83 (d, 2H, *J* = 8.7 Hz), 7.53 (br. d, 4H, *J* ≈ 7.0 Hz), 7.28–7.40 (m, 8H).

4.2.4. Compound 3d. Colorless needles, ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.78 (d, 2H, *J* = 8.5 Hz), 7.54–7.58 (m, 6H), 7.28–7.38 (m, 6H).

4.2.5. Compound 3e. Colorless needles, ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.88 (br. d, 2H, *J* = 8.4 Hz), 7.49 (br. d, 4H, *J* ≈ 6.6 Hz), 7.24–7.30 (m, 6H), 6.93 (d, 2H, *J* = 9 Hz), 3.82 (s, 3H).

4.2.6. Compound 3f. Colorless needles, ¹H NMR (300 MHz, d₆-DMSO, δ/ppm): 12.49 (s, 1H, NH), 7.21–7.63 (m, 12H), 7.03 (d, 1H, *J* = 8.4), 6.08 (s, 2H, –OCH₂O–); ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.52 (br. d, 4H, *J* ≈ 7.2 Hz), 7.39 (d, 1H, *J* = 8.2 Hz), 7.46 (br. s, 1H), 7.26–7.33 (m, 5H), 6.83 (d, 1H, *J* = 8.0 Hz), 6.00 (s, 2H, –OCH₂O–).

4.2.7. Compound 3g. Yellow needles, ¹H NMR (300 MHz, d₆-DMSO, δ/ppm): 13.08 (s, 1H), 8.94 (s, 1H), 8.50 (d, 1H, *J* = 7.8 Hz), 8.19 (d, 1H, *J* = 8.1 Hz), 7.76 (t, 1H, *J* = 7.8 Hz), 7.32–7.53 (m, 10H).

4.2.8. Compound 3h. Colorless needles, ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.82 (d, 2H, *J* = 7.7 Hz), 7.52–7.54 (m, 4H), 7.26–7.33 (m, 6H), 6.74 (d, 2H, *J* = 7.8 Hz), 2.99 (s, 6H, NMe₂).

4.2.9. Compound 3i. Colorless needles, ¹H NMR (300 MHz, CDCl₃, δ/ppm): 12.40 (br. s, 1H, NH), 9.24 (br. s, 1H, OH), 7.19–7.54 (m, 11H), 7.61 (br. s, 1H), 6.84 (d, 1H, *J* = 8.2 Hz), 3.84 (s, 3H, OCH₃).

TABLE I: Synthesis of 2,4,5-triarylimidazoles (**3**) under catalyst-free and solvent-free conditions.

Entry	Starting materials 1 with Ar ¹ =	2 with Ar ² =	Product	Time (h)	Yield (%)	M. P. (Lit.) reference
1	C ₆ H ₅	C ₆ H ₅	3a	3	80	272-273 (272-274) [19]
2	C ₆ H ₅	4-CH ₃ -C ₆ H ₄	3b	3	75	227-228 (227-228) [19]
3	C ₆ H ₅	4-Cl-C ₆ H ₄	3c	3	78	261-262 (261-262) [19]
4	C ₆ H ₅	4-Br-C ₆ H ₄	3d	3	81	245-246 (244-246) [19]
5	C ₆ H ₅	4-CH ₃ O-C ₆ H ₄	3e	3	76	226-227 (227-228) [19]
6	C ₆ H ₅	3,4-(OCH ₂ O)C ₆ H ₃	3f	3	73	248-250 (248-250) [19]
7	C ₆ H ₅	3-O ₂ N-C ₆ H ₄	3g	3	90	>300 (>290) [19]
8	C ₆ H ₅	4-(CH ₃) ₂ N-C ₆ H ₄ -	3h	3	45	256-258 (257-258) [19]
9	C ₆ H ₅	3-CH ₃ O,4-HO-C ₆ H ₃ -	3i	5	67	165-167 (166) [28]
10	C ₆ H ₅	2-Thienyl	3j	4	67	261-263 (260-262) [29]
11	C ₆ H ₅	3-Pyridyl	3k	3	66	245-247 (244-246) [30]
12	4-CH ₃ -C ₆ H ₄ -	C ₆ H ₅	3l	5	59	252-253 (254) [31]
13	4-CH ₃ -C ₆ H ₄ -	4-Cl-C ₆ H ₄	3m	5	64	262-263 (263-264) [32]
14	4-CH ₃ -C ₆ H ₄ -	4-CH ₃ O-C ₆ H ₄	3n	6	61	250-251 (250-251) [33]

4.2.10. *Compound 3j*. Colorless needles, ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.70 (br. d, 1H, *J* ≈ 3 Hz), 7.43–7.46 (m, 4H), 7.31 (dd, 1H, *J* = 5.1 and 1.0 Hz), 7.24–7.28 (m, 6H), 7.04 (dd, 1H, *J* = 4.8 and 3.7 Hz).

4.2.11. *Compound 3k*. Colorless needles, IR (KBr, cm⁻¹): 3376, 3052, 2200, 1663, 1604, 1563, 1469, 1438, 1382; ¹H NMR (300 MHz, CDCl₃, δ/ppm): 9.28 (br. s, 1H, H-2 of 3-pyridyl), 8.50 (d, 1H, *J* = 8.0 Hz, H-4 of 3-pyridyl), 8.43 (d, 1H, *J* = 4.6 Hz, H-6 of 3-pyridyl), 7.54–7.56 (m, 4H, *o*-proton of 2 × C₆H₅), 7.28–7.39 (m, 7H, *m*- and *p*-protons of 2 × C₆H₅ and H-5 of 3-pyridyl); ¹³C NMR (75 MHz, CDCl₃, δ/ppm) 148.9, 145.9, 143.1, 133.5, 132.6, 128.6, 128.0, 127.6, 126.7, 123.9; FAB MS (*M* + *H*)⁺: Calcd. 298.3. Found 298.3, Anal. Calcd. for C₂₀H₁₅N₃ (297.35): C, 80.78; H, 5.08; N, 14.13. Found: C, 80.56; H, 5.31; N, 13.92.

4.2.12. *Compound 3l*. Colorless needles, ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.90 (d, 2H, *J* = 7.8 Hz), 7.42–7.48 (m, 6H), 7.36 (t, 1H, *J* = 7.5), 7.16 (d, 4H, *J* = 7.8 Hz), 2.36 (s, 6H, 2 × -CH₃).

4.2.13. *Compound 3m*. Colorless needles, ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.83 (2H, d, *J* = 8.1 Hz), 7.43 (d, 4H, *J* = 7.8 Hz), 7.40 (2H, d, *J* = 8.1 Hz), 7.14 (d, 4H, *J* = 7.6 Hz), 2.36 (s, 6H, 2 × -CH₃).

4.2.14. *Compound 3n*. Colorless needles, ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.83 (d, 2H, *J* = 8.4 Hz), 7.43 (br. d, 4H, *J* = 7.2 Hz), 7.13 (br. d, 4H, *J* = 7.6 Hz), 6.96 (d, 2H, *J* = 8.5 Hz), 3.85 (s, 3H, -OCH₃), 2.36 (s, 6H, 2 × -CH₃).

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