Monatsh Chem (2010) 141:1339–1345
DOI 10.1007/s00706-010-0397-y

ORIGINAL PAPER

Nanocrystalline magnesium oxide: a novel and efficient catalyst for facile synthesis of 2,4,5-trisubstituted imidazole derivatives

Javad Safari · Shiva Dehghan Khalili · Mehran Rezaei · Sayed Hossein Banitaba · Fereshteh Meshkani

Received: 18 February 2010 / Accepted: 6 September 2010 / Published online: 7 October 2010

Abstract Nanocrystalline magnesium oxide with high specific surface area has been used as a novel and efficient catalyst for an improved and rapid synthesis of biologically active 2,4,5-trisubstituted imidazoles, by three-component, one-pot condensation of 1,2-diketones and aryl aldehydes, in excellent yields under solvent-free and conventional heating conditions. The method has several advantages, for example excellent yields, shorter reaction time, and use of a non-toxic and recyclable catalyst.

Keywords Nanocrystalline magnesium oxide · 2,4,5-Trisubstituted imidazoles · One-pot condensation · Solvent-free conditions

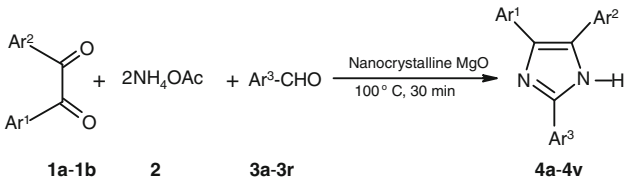
Introduction

The synthesis, reactions, and biological properties of substituted imidazoles constitute a significant part of modern heterocyclic chemistry. Multi-substituted imidazoles, an important class of pharmaceutical compounds, have a wide spectrum of biological activity [1–3]. They have emerged as an integral part of many biological systems [4], viz. histidine, histamine, and biotin [5], and an active backbone in drugs such as losartan, eprosartan [6], and trifenagrel [7]. They also have a variety of bioactive effects, for example fungicidal [8, 9], herbicidal [10], antitumor [11], anti-inflammatory [12], anti-allergic [13], analgesic [14], and antibacterial [15]. Some substituted imidazoles are selective antagonists of the glucagons receptor [16], inhibitors of p38 MAP kinase [17], B-Raf kinase [18], transforming growth factor β1 (TGF-β1) type 1 activin receptor-like kinase (ALK5) [19], cyclooxygenase-2 (COX-2) [20], and biosynthesis of interleukin-1 (IL-1) [21].

Several methods are used for synthesis of multi-substituted imidazoles [22–33]. Recently, one-pot condensations of an aldehyde and ammonium acetate with an α-hydroxy ketone, an α-keto oxime, or a 1,2-diketone have been achieved by using a variety catalysts, for example $Zr(acac)_4$ [34], $Yb(OTf)_3$ [35], $Yb(OPf)_3$ [36], $InCl_3{\cdot}3H_2O$ [37], I_2 [38], $NiCl_2{\cdot}6H_2O/Al_2O_3$ [39], $ZrCl_4$ [40], silica sulfuric acid (SSA) [41, 42], boric acid [43], ionic liquids [44–47], heteropolyacid [48], ceric ammonium nitrate (CAN) [49, 50], sodium bisulfite [51], potassium aluminum sulfate (alum) [52], polymer-supported $ZnCl_2$ [53], phosphomolybdic acid [54], $ZrOCl_2{\cdot}8H_2O$ [55], L-proline [56], PEG-400 medium [57], and scolecite [58]. Despite their potential utility, some of these methods are not environmentally friendly and suffer from one or more disadvantages, for example hazardous reaction conditions, complex work-up and purification, strongly acidic conditions, high temperature, use of toxic metal catalysts, poor yields, occurrence of side reactions, and long reaction time. Therefore, the development of a mild general method to overcome these shortcomings remains a challenge for organic chemists in the synthesis of highly substituted imidazoles. Magnesium oxide (MgO) has many applications as catalyst [59, 60], refractory materials [61], optically transparent ceramic

J. Safari (✉) · S. D. Khalili · S. H. Banitaba
Laboratory of Organic Chemistry Research,
Department of Organic Chemistry, College of Chemistry,
University of Kashan, 87317-51167 Kashan, I.R. Iran
e-mail: Safari@kashanu.ac.ir

M. Rezaei · F. Meshkani
Catalyst and Advanced Materials Research Laboratory,
Chemical Engineering Department, Faculty of Engineering,
University of Kashan, 87317-51167 Kashan, I.R. Iran



Scheme 1

windows [62, 63], etc. Magnesium oxide with large specific surface area is also a potential catalyst support for various reactions and a promising sorbent for chemisorption and destructive adsorption of a variety of pollutants. In the field of catalysis, MgO has strongly basic properties, which are associated with catalysis by bases in many organic reactions [64]. Nanoscale supports create catalysts with more edges and corners, which can lead to higher performance of the catalyst. Herein, we report convenient and facile multi-component, one-pot synthesis of 2,4,5-trisubstituted imidazoles in high yields by using nanocrystalline magnesium oxide with high specific surface area of approximately 116 m^2 g^{-1} and a crystallite size of approximately 12 nm as a novel and efficient catalyst (Scheme 1).

Results and discussion

In an initial study, for examination of catalytic activity of different catalysts such as CaO, BaO, and MgO in this condensation reaction, 1 mmol benzaldehyde was first reacted with 1 mmol benzil and 2 mmol ammonium acetate for 30 min at 100 °C in the presence of each catalyst (2 mol%) separately. In the course of this study we found that MgO was the most effective catalyst (Table 1). In the absence of catalyst, yield of the product was found to be very low. Therefore, we decided to use nanocrystalline MgO with a high specific surface area as a catalyst with higher activity and better controlled selectivity.

The crystallite sizes determined by XRD were between 12.8 and 17.5 nm (determined by use of the Scherrer equation), indicative of the nanocrystalline structure of the prepared MgO. In addition the surface area was approximately 116 m^2 g^{-1}. The pore volume and pore size were also calculated from the N_2 adsorption result; the pore size was approximately 21.1 nm and the pore volume approximately 0.69 cm^3 g^{-1}. The theoretical particle size was also calculated from surface area, assuming spherical particles, from the equation:

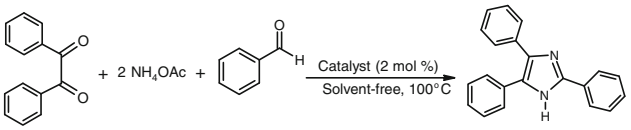
$$D_{BET} = \left(\frac{6,000}{\rho \times S}\right) \quad (1)$$

where D_{BET} is the equivalent particle diameter in nanometers, ρ is the density of the material in g cm^{-3}, and S is the specific surface area in m^2 g^{-1}. The particle size calculated from Eq. 1 was 14.4 nm, which confirmed the nanostructure of the MgO sample [66]. The TEM image of MgO is shown in Fig. 1. As can be seen, the sample has a nanocrystalline structure with a plate-like shape.

Subsequent efforts were focused on optimizing conditions for formation of 2,4,5-triphenylimidazole by using different amounts of nanocrystalline MgO and different temperatures to determine their effects on the reaction (Table 2). As indicated, the best result was obtained at 100 °C with 5 mol% nanocrystalline MgO. The reaction yield with increasing amount of nanocrystalline MgO and temperature was not substantially increased.

Results from nanocrystalline magnesium oxide-catalyzed condensation reaction of 1,2-diketones (benzil, **1a**, 4,4′-difluorobenzil, **1b**) with different aromatic aldehydes and ammonium acetate at 100 °C under solvent-free conditions are given in Table 3. As shown, these conditions proved to be general for the reacting aldehyde. Aldehydes bearing either electron-withdrawing or electron-donating

Table 1 Synthesis of 2,4,5-triphenyl-1*H*-imidazole in the presence of metal oxide catalysts



Entry	Catalyst	Time (min)	Temperature (°C)	Yield (%)
1	None	30	100	15
2	MgO	30	100	55
3	CaO	30	100	20
4	BaO	30	100	50
5	Nano-MgO	30	100	80

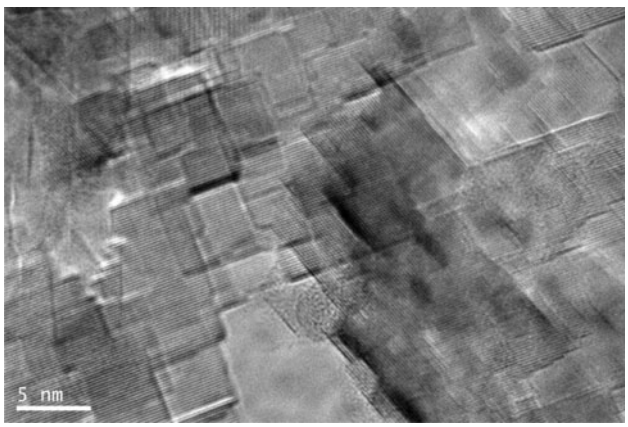
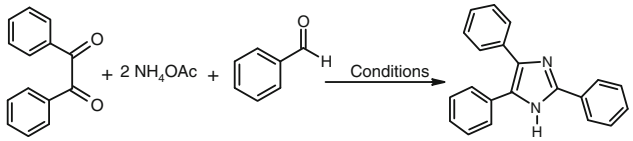


Fig. 1 TEM image of nanocrystalline MgO

Table 2 Optimization of reaction conditions for synthesis of 2,4,5-triphenyl-1*H*-imidazole



Entry	Nanocrystalline MgO (mol%)	Temperature (°C)	Time (min)	Yield (%)
1	2	60	30	35
2	5	60	30	50
3	7	60	30	55
4	11	60	30	55
5	2	100	30	80
6	5	100	30	94
7	7	100	30	93
8	11	100	30	92
9	2	130	30	80
10	5	130	30	95
11	7	130	30	92
12	11	130	30	92

groups perform equally well in the reaction and all imidazoles were obtained in high yields.

The high efficiency of the nanoparticle oxides is caused not only by their high surface area but also by the high concentration of low-coordinated sites and structural defects on their surface. As the particle size is scaled down to a few nanometers, the constituting atoms have highly defective coordination environments. Most of the atoms have unsatisfied valencies and reside at the surface [65]. Nanocrystalline MgO also acts as a mild Lewis acid that catalyzes three-component, one-pot synthesis of 2,4,5-trisubstituted imidazoles.

The structure of compounds **4a**–**4v** was deduced from their high-field ^{1}H NMR, ^{13}C NMR, IR, and UV spectral data. Also, their melting points were compared with literature reports. The ^{1}H NMR spectra of all the products contained a singlet at approximately $\delta = 12.50$–12.80 ppm. IR spectra contained a distinguishing peak at 3,400–3,440 cm^{-1} for NH. In ^{13}C NMR spectra of fluorinated derivatives, C–F couplings were observed with coupling constants of $^{1}J_{C-F} = 241$–244 Hz, $^{2}J_{C-F} = 21$–22 Hz, $^{3}J_{C-F} = 7$–8 Hz, and $^{4}J_{C-F} = 2$ Hz. For example, the ^{13}C NMR spectrum of compound **4t** is indicated in Fig. 2.

In summary, we describe a facile, eco-friendly, and green procedure for synthesis of biologically active 2,4,5-trisubstituted imidazoles via condensation of representative 1,2-diketones with a variety of aromatic aldehydes and ammonium acetate in the presence of nanocrystalline magnesium oxide with high surface area as a novel, efficient, and recyclable catalyst under solvent-free and conventional heating conditions. The approach has several benefits, for example low waste, easy work up, short reaction time, and high yields.

Experimental

Materials

Chemical reagents in high purity were purchased from the Merck Chemical Company. All materials were of commercial reagent grade.

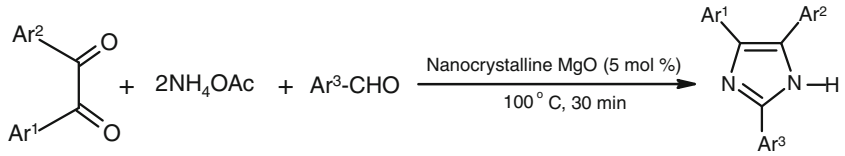
Apparatus

Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus. Infrared spectra were recorded using a Perkin–Elmer FTIR 550 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 and 100 MHz, respectively. NMR spectra were obtained in DMSO-d_6 solutions and are reported as parts per million (ppm) downfield from tetramethylsilane as internal standard. The abbreviations used are: singlet (s), doublet (d), triplet (t), and multiplet (m). Elemental analysis (C, H, N) was performed with a Carlo Erba model EA 1108 analyzer or a Perkin–Elmer 240c analyzer, and results agreed favorably with calculated values. UV spectra were recorded on a Hitachi 200-20 spectrophotometer using spectrophotometric grade chloroform (Baker). The N_2 adsorption/desorption analysis (BET) was performed at −196 °C using an automated gas adsorption analyzer (Tristar 3000, Micromeritics). XRD analysis was performed with an X-ray diffractometer (PANalytical X'Pert-Pro) using a Cu-Kα monochromatic radiation source and an Ni filter. Transmission electron microscopy (TEM) was performed with a Jeol JEM-2100UHR, operated at 200 kV.

Preparation of nanocrystalline MgO

Nanocrystalline MgO was prepared by means of a procedure reported elsewhere [66]. In short, poly(vinyl alcohol) (PVA, MW 70,000) was dissolved in water at 90 °C under vigorous stirring to form a transparent solution. $Mg(NO_3)_2{\cdot}6H_2O$ was dissolved in water containing PVA. The metal ion-to-PVA monomer unit molar ratio (M/PVA) was chosen as 1:3. Aqueous ammonia (25% *w*/*w*) was added dropwise at room temperature to the resulting viscous liquid mixture, with rapid stirring, to achieve careful pH adjustment to 10.5. After precipitation, the slurry was stirred for another 30 min and then heated under reflux at 80 °C for 20 h under continuous

Table 3 Nanocrystalline MgO-catalyzed synthesis of 2,4,5-trisubstituted imidazoles at 100 °C under solvent-free conditions



Entry	Benzil	Ar^1, Ar^2	Aldehyde	Ar^3	Product	Yield (%)[a] Time (min)	M.p. (°C)	
							Found	Reported
1	**1a**	C_6H_5	**3a**	C_6H_5	**4a**	94 (30)	270–272	272–273 [38]
2	**1a**	C_6H_5	**3b**	*p*-MeC_6H_4	**4b**	96 (30)	230–233	232–235 [12]
3	**1a**	C_6H_5	**3c**	*p*-$MeOC_6H_4$	**4c**	97 (30)	228–231	230–232 [12]
4	**1a**	C_6H_5	**3d**	*p*-ClC_6H_4	**4d**	94 (30)	260–261	262–264 [12]
5	**1a**	C_6H_5	**3e**	*p*-BrC_6H_4	**4e**	93 (30)	263–265	261.5–263.5 [12]
6	**1a**	C_6H_5	**3f**	*m*-$MeOC_6H_4$	**4f**	93 (30)	259–262	–
7	**1a**	C_6H_5	**3g**	*O*-HOC_4H_6	**4g**	91 (30)	198–201	203–205 [38]
8	**1a**	C_6H_5	**3h**	*m*-$O_2NC_4H_6$	**4h**	90 (30)	269–271	265–267 [38]
9	**1a**	C_6H_5	**3i**	*m*-ClC_6H_4	**4i**	91 (30)	282–283	285–287 [12]
10	**1a**	C_6H_5	**3j**	*m*-BrC_6H_4	**4j**	92 (30)	301–303	303–304 [12]
11	**1a**	C_6H_5	**3k**	*p*-HOC_4H_6	**4k**	95 (30)	259–260	260–261 [38]
12	**1a**	C_6H_5	**3l**	2-Naphthyl	**4l**	94 (30)	273–276	–
13	**1a**	C_6H_5	**3m**	2-Thienyl	**4m**	94 (30)	261–264	262–266 [12]
14	**1a**	C_6H_5	**3n**	2,4-$Cl_2C_6H_3$	**4n**	92 (30)	170–172	174–176 [12]
15	**1a**	C_6H_5	**3o**	*p*-$(Me)_2NC_6H_4$	**4o**	93 (30)	255–257	257–258 [35]
16	**1a**	C_6H_5	**3p**	3,4-$(MeO)_2C_6H_3$	**4p**	94 (30)	213–216	215–219 [12]
17	**1a**	C_6H_5	**3q**	3,5-$(MeO)_2C_6H_3$	**4q**	94 (30)	254–256	–
18	**1a**	C_6H_5	**3r**	3-HO-4-$MeOC_6H_4$	**4r**	96 (30)	215–216	–
19	**1b**	4-F C_6H_5	**3f**	*m*-$MeOC_6H_4$	**4s**	94 (30)	251–253	–
20	**1b**	4-F C_6H_5	**3j**	*m*-BrC_6H_4	**4t**	95 (30)	287–290	–
21	**1b**	4-F C_6H_5	**3p**	3,4-$(MeO)_2C_6H_3$	**4u**	96 (30)	207–208	–
22	**1b**	4-F C_6H_5	**3r**	3-HO-4-$MeOC_6H_4$	**4v**	97 (30)	218–220	–

[a] Isolated yield based on aldehyde

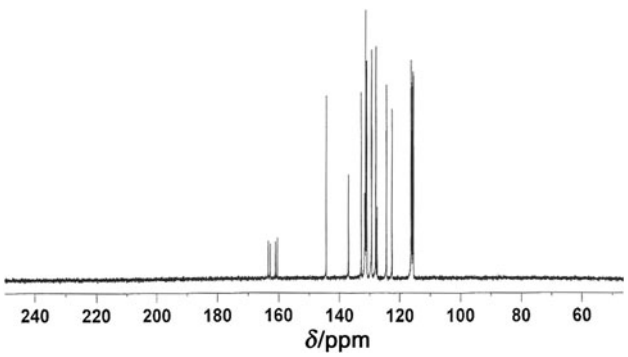


Fig. 2 ^{13}C NMR spectrum of compound **4t**

stirring. The mixture was cooled to room temperature, filtered, and washed with hot deionized water for effective removal of the poly(vinyl alcohol). The final product was dried at 80 °C for 24 h and calcined at 700 °C.

Preparation of 2,4,5-trisubstituted imidazoles by use of nanocrystalline magnesium oxide

A mixture of 1,2-diketone (1 mmol), 0.15 g ammonium acetate (2 mmol), aldehyde (1 mmol), and 0.008 g nanocrystalline magnesium oxide (5 mol%) was stirred at 100 °C for 30 min. The progress of the reaction was monitored by TLC (petroleum ether–ethyl acetate 7:3). After cooling, the reaction mixture was dissolved in acetone and filtered. The filtrate was concentrated on a rotary evaporator under reduced pressure and the solid product obtained was washed with water and recrystallized from acetone–water 9:1 (*v*/*v*). Pure products were obtained in excellent yields, as summarized in Table 3. Most of the products are known and were identified by comparison of their physical and spectral data with those of authentic samples.

2-(3-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (**4f**, $C_{22}H_{18}N_2O$)
Colorless powder; yield 93%; m.p.: 259–262 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.70$ (s, 1H, NH), 6.80–7.80 (m, 14H, Ar–H), 3.80 (s, 3H, OMe) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 160.00$, 145.86, 137.63, 135.60, 132.15, 130.27, 129.20, 128.86, 127.70, 118.13, 114.70, 110.70, 55.70 ppm; IR (KBr): $\bar{\nu} = 3{,}432$ (N–H), 1,591 (C=C), 1,513 (C=N) cm^{-1}; UV ($CDCl_3$): $\lambda_{max} = 314$, 240 nm.

2-(2-Naphthyl)-4,5-diphenyl-1H-imidazole (**4l**, $C_{25}H_{18}N_2$)
Colorless powder; yield 94%; m.p.: 273–276 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.80$ (s, 1H, NH), 8.61 (s, 1H, Ar–H), 8.25 (d, 1H, $^3J = 8.0$ Hz, Ar–H), 7.92–8.02 (m, 3H, Ar–H), 7.53–7.61 (m, 6H, Ar–H), 7.46 (t, 2H, $^3J = 7.9$ Hz, Ar–H), 7.39 (t, 1H, $^3J = 7.6$ Hz, Ar–H), 7.32 (t, 2H, $^3J = 7.9$ Hz, Ar–H), 7.24 (t, 1H, $^3J = 7.6$ Hz, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 146.00$, 137.90, 135.60, 133.50, 132.20, 131.50, 129.10, 129.00, 128.90, 128.70, 128.60, 128.30, 128.20, 127.60, 127.10, 127.00, 126.80, 124.10, 123.90 ppm; IR (KBr): $\bar{\nu} = 3{,}429$ (N–H), 1,601 (C=C), 1,510 (C=N) cm^{-1}; UV ($CDCl_3$): $\lambda_{max} = 330$, 288 nm.

2-(3,5-Dimethoxyphenyl)-4,5-diphenyl-1H-imidazole (**4q**, $C_{23}H_{20}N_2O_2$)
Colorless powder; yield 94%; m.p.: 254–256 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.70$ (s, 1H, NH), 7.30–7.54 (m, 9H, Ar–H), 7.28 (d, 2H, $^4J = 2.0$ Hz, Ar–H), 7.22 (t, 1H, $^3J = 7.8$ Hz, Ar–H), 6.52 (t, 1H, $^4J = 2.0$ Hz, Ar–H), 3.81 (s, 6H, OMe) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 161.21$, 145.76, 137.51, 135.56, 132.59, 131.52, 129.14, 128.98, 128.65, 128.30, 127.56, 127.01, 103.54, 101.10, 55.83 ppm; IR (KBr): $\bar{\nu} = 3{,}429$ (N–H), 1,601 (C=C), 1,533 (C=N) cm^{-1}; UV ($CDCl_3$): $\lambda_{max} = 310$, 245 nm.

5-(4,5-Diphenyl-1H-imidazol-2-yl)-2-methoxyphenol (**4r**, $C_{22}H_{18}N_2O_2$)
Ash-gray powder; yield 96%; m.p.: 215–216 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.50$ (s, 1H, NH), 9.11 (s, 1H, OH), 7.46–7.55 (m, 6H, Ar–H), 7.42 (t, 2H, $^3J = 7.6$ Hz, Ar–H), 7.34 (t, 1H, $^3J = 7.2$ Hz, Ar–H), 7.28 (t, 2H, $^3J = 7.6$ Hz, Ar–H), 7.20 (t, 1H, $^3J = 7.2$ Hz, Ar–H), 7.00 (d, 1H, $^3J = 8.4$ Hz, Ar–H), 3.81 (s, 3H, OMe) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 148.58$, 146.99, 146.31, 137.17, 135.86, 131.71, 129.05, 128.82, 128.62, 128.02, 127.51, 126.84, 123.94, 117.01, 113.31, 112.55, 56.09 ppm; IR (KBr): $\bar{\nu} = 3{,}409$ (N–H), 3,260 (O–H), 1,596 (C=C), 1,510 (C=N) cm^{-1}; UV ($CDCl_3$): $\lambda_{max} = 310$, 244 nm.

2-(3-Methoxyphenyl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4s**, $C_{22}H_{16}F_2N_2O$)
Off-white powder; yield 94%; m.p.: 251–253 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.71$ (s, 1H, NH), 7.65 (d, 1H, $^3J = 7.6$ Hz, Ar–H), 7.62 (s, 1H, Ar–H), 7.50–7.55 (m, 4H, Ar–H), 7.38 (t, 1H, $^3J = 8.0$ Hz, Ar–H), 7.30 (t, 2H, $^3J = 8.8$ Hz, Ar–H), 7.15 (t, 2H, $^3J = 8.8$ Hz, Ar–H), 6.94 (d, 1H, $^3J = 8.0$ Hz, Ar–H), 3.82 (s, 3H, OMe) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 162.20$ (C–F, d, $^1J = 243.0$ Hz), 161.57 (C–F, d, $^1J = 243.0$ Hz), 160.05, 145.90, 136.74, 132.04, 131.94, 131.09 (d, $^3J = 7.0$ Hz), 130.26, 129.37 (d, $^3J = 7.0$ Hz), 127.83, 127.58, 118.11, 116.15 (d, $^2J = 21.0$ Hz), 115.56 (d, $^2J = 22.0$ Hz), 114.68, 110.74, 55.61 ppm; IR (KBr): $\bar{\nu} = 3{,}441$ (N–H), 1,600 (C=C), 1,520 (C=N) cm^{-1}; UV ($CDCl_3$): $\lambda_{max} = 315$, 245 nm.

2-(3-Bromophenyl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4t**, $C_{21}H_{13}BrF_2N_2$)
Colorless powder; yield 95%; m.p.: 287–290 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.70$ (s, 1H, NH), 8.26 (s, 1H, Ar–H), 8.06 (d, 1H, $^3J = 8.0$ Hz, Ar–H), 7.52–7.55 (m, 5H, Ar–H), 7.44 (t, 1H, $^3J = 8.0$ Hz, Ar–H), 7.30 (t, 2H, $^3J = 8.4$ Hz, Ar–H), 7.15 (t, 2H, $^3J = 8.4$ Hz, Ar–H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 162.25$ (C–F, d, $^1J = 244.0$ Hz), 161.62 (C–F, d, $^1J = 242.0$ Hz), 144.34, 137.01, 132.85, 131.69 (d, $^4J = 2.0$ Hz), 131.37 (d, $^3J = 8.0$ Hz), 131.09, 131.01, 129.42 (d, $^3J = 8.0$ Hz), 128.09, 127.98, 127.56 (d, $^4J = 2.0$ Hz), 124.50, 122.62, 116.22 (d, $^2J = 22.0$ Hz), 115.64 (d, $^2J = 21.0$ Hz) ppm; IR (KBr): $\bar{\nu} = 3{,}437$ (N–H), 1,604 (C=C), 1,516 (C=N) cm^{-1}; UV ($CDCl_3$): $\lambda_{max} = 310$, 245 nm.

2-(3,4-Dimethoxyphenyl)-4,5-bis(4-fluorophenyl)-1H-imidazole (**4u**, $C_{23}H_{18}F_2N_2O_2$)
Off-white powder; yield 96%; m.p.: 207–208 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.50$ (s, 1H, NH), 7.48–7.63 (m, 6H, Ar–H), 7.30 (t, 2H, $^3J = 8.0$ Hz, Ar–H), 7.14 (t, 2H, $^3J = 8.0$ Hz, Ar–H), 7.05 (d, 1H, $^3J = 8.0$ Hz, Ar–H), 3.80 (s, 3H, OMe), 3.83 (s, 3H, OMe) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 162.11$ (C–F, d, $^1J = 243.0$ Hz), 161.47 (C–F, d, $^1J = 241.0$ Hz), 149.59, 149.27, 146.17, 136.36, 132.04, 131.06 (d, $^3J = 8.0$ Hz), 129.30 (d, $^3J = 8.0$ Hz), 128.02, 127.00, 123.55, 118.38, 116.18 (d, $^2J = 21.0$ Hz), 115.56 (d, $^2J = 21.0$ Hz), 112.27, 109.26, 56.03, 55.98 ppm; IR (KBr): $\bar{\nu} = 3{,}424$ (N–H), 1,599 (C=C), 1,524 (C=N) cm^{-1}; UV ($CDCl_3$): $\lambda_{max} = 310$, 243 nm.

5-[4,5-Bis(4-fluorophenyl)-1H-imidazol-2-yl]-2-methoxyphenol (**4v**, $C_{22}H_{16}F_2N_2O_2$)
Silver powder; yield 97%; m.p.: 218–220 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.50$ (s, 1H, NH), 9.13 (s, 1H, OH), 7.40–7.60 (m, 6H, Ar–H), 7.27 (t, 2H,

$^{3}J = 8.8$ Hz, Ar–H), 7.13 (t, 2H, $^{3}J = 8.8$ Hz, Ar–H), 7.00 (d, 1H, $^{3}J = 8.4$ Hz, Ar–H), 3.81 (s, 3H, OMe) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 162.06$ (C–F, d, $^{1}J = 244.0$ Hz), 161.47 (C–F, d, $^{1}J = 242.0$ Hz), 148.66, 147.02, 146.34, 136.32, 132.17, 130.96 (d, $^{3}J = 8.0$ Hz), 129.31 (d, $^{3}J = 8.0$ Hz), 128.00, 126.91, 123.84, 117.05, 116.08 (d, $^{2}J = 21.0$ Hz), 115.53 (d, $^{2}J = 21.0$ Hz), 113.32, 112.56, 56.08 ppm; IR (KBr): $\bar{\nu} = 3{,}437$ (N–H), 3,298 (O–H), 1,594 (C=C), 1,521 (C=N) cm^{-1}; UV ($CDCl_3$): $\lambda_{max} = 310$, 242 nm.

Acknowledgments We gratefully acknowledge the financial support from the Research Council of the University of Kashan.

References

1. Lombardino JG, Wiseman EH (1974) J Med Chem 17:1182
2. Heeres J, Back LJJ, Mostmans JH, Vancutsem J (1979) J Med Chem 22:1003
3. Mjalli AMM, Sarshar S (1997) US Patent 570082619 (1998) Chem Abstr 128 88918a
4. Laufer SA, Zimmermann W, Ruff KJ (2004) J Med Chem 47:6311
5. Grimmett MR (1996) In: Katrizky AR, Rees CW, Scriven EFV (eds) Comprehensive heterocyclic chemistry II, Pergamon Press, Oxford, vol 3, p 77
6. Kantevari S, Nair CKS, Pardhasaradhi M (2006) J Heterocycl Chem 43:1353
7. Wolkenberg SE, Wisnoski DD, Leister WH, Wang Y, Zhao Z, Lindsley CW (2004) Org Lett 6:1453
8. Pozherskii AF, Soldatenkov AT, Kareizky AR (1997) Heterocycles in life and society. Wiley, New York, p 179
9. Maier T, Schmierer R, Bauer K, Bieringer H, Buerstell H, Sachse B (1989) US Patent 4820335
10. Liebl R, Handte R, Mildenberger H, Bauer K, Bieringer H (1987) Ger Offen DE 3604042
11. Wang L, Woods KW, Li Q, Barr KJ, McCroskey RW, Hannick SM, Gherke L, Credo RB, Hui YH, Marsh K, Warner R, Lee JY, Zielinsky-Mozng N, Frost D, Rosenberg SH, Sham HL (2002) J Med Chem 45:1697
12. Lombardino JG (1972) DE 2155558 [(1973) US 3772441]
13. Black JW, Durant GJ, Emmett JC, Ganellin CR (1974) Nature 248:65
14. Ucucu U, Karaburun NG, Iskdag I (2001) Il Farmaco 56:285
15. Khan MS, Siddiqui SA, Siddiqui MSR, Goswami U, Srinivasan KV, Khan MI (2008) Chem Biol Drug Des 72:197
16. Chang LL, Sidler KL, Cascieri MA, Laszlo SD, Koch G, Li B, MacCoss M, Mantlo N, O'Keefe S, Pang M, Rolando A, Hagmann WK (2001) Bioorg Med Chem Lett 11:2549
17. Lee JC, Laydon JT, McDonnell PC, Gallagher TF, Kumar S, Green D, McNulty D, Blumenthal MJ, Keys JR, Vatter SWL, Strickler JE, McLaughlin MM, Siemens IR, Fisher SM, Livi GP, White JR, Adams JL, Young PR (1994) Nature 372:739
18. Takle AK, Brown MJB, Davies S, Dean DK, Francis G, Gaiba A, Hird AW, King FD, Lovell PJ, Naylor A, Reith AD, Steadman JG, Wilson DM (2006) Bioorg Med Chem Lett 16:378
19. Khanna IK, Weier RM, Yu Y, Xu XD, Koszyk FJ, Collins PW, Koboldt CM, Veenhuizen AW, Perkins WE, Casler JJ, Masferrer JL, Zhang YY, Gregory SA, Seibert K, Isakson PC (1997) J Med Chem 40:1634
20. Lange JHM, Van Stuivenberg HH, Coolen HKAC, Adolfs TJP, McCreary AC, Keizer HG, Wals HC, Veerman W, Borst AJM, de Looff W, Verveer PC, Kruse CG (2005) J Med Chem 48:1823
21. Gallagher TH, Fier-Thompson SM, Garigipati RS, Sorenson ME, Smietana JM, Lee D, Bender PE, Lee JC, Laydon JT, Griswold DE, Chabot-Fletcher MC, Breton JJ, Adams JL (1995) Bioorg Med Chem Lett 5:1171
22. Sparks RB, Combs AP (2004) Org Lett 6:2473
23. Zaman S, Mitsuru K, Abell AD (2005) Org Lett 7:609
24. Tsuji J, Sakai K, Nemoto H, Nagashima H (1983) J Mol Catal 18:169
25. Evans DA, Lundy KM (1992) J Am Chem Soc 114:1495
26. Radziszewski B (1882) Ber Deut Chem Ges 15:1493
27. Wasserman HH, Long YO, Zhang R, Parr J (2002) Tetrahedron Lett 43:3351
28. Kamitori Y (2001) J Heterocycl Chem 38:773
29. Zhang C, Moran EJ, Woiwade TF, Short KM, Mjalli AMM (1996) Tetrahedron Lett 37:751
30. Lantos I, Zhang WY, Shui Y, Eggleston DS (1993) J Org Chem 58:7092
31. Bleicher KH, Gerber F, Wuthrich Y, Alanine A, Capretta A (2002) Tetrahedron Lett 43:7687
32. Balalaie S, Hashemi MM, Akhbari M (2003) Tetrahedron Lett 44:1709
33. Paone DV, Shaw AW (2008) Tetrahedron Lett 49:6155
34. Khosropour AR (2008) Ultrason Sonochem 15:659
35. Wang L, Wang Y, Tian H, Yao Y, Shao J, Liu B (2006) J Fluorine Chem 127:1570
36. Shen M, Cai C, Yi W (2008) J Fluorine Chem 129:541
37. Sharma SD, Hazarika P, Konwar D (2008) Tetrahedron Lett 49:2216
38. Kidwai M, Mothsra P, Bansal V, Somvanshi RK, Ethayathulla AS, Dey S, Singh TP (2007) J Mol Catal A Chem 265:177
39. Heravi MM, Bakhtiari K, Oskooie HA, Taheri S (2007) J Mol Catal A Chem 263:279
40. Sharma GVM, Jyothi Y, Sree Lakshmi P (2006) Synth Commun 36:2991
41. Shaabani A, Rahmati A (2006) J Mol Catal A Chem 249:246
42. Shaabani A, Rahmati A, Farhangi E, Badri Z (2007) Catal Commun 8:1149
43. Shelke KF, Sapkal SB, Sonar SS, Madje BR, Shingate BB, Shingare MS (2009) Bull Korean Chem Soc 30:1057
44. Siddiqui SA, Narkhede UC, Palimkar SS, Daniel T, Lahoti RJ, Srinivasan KV (2005) Tetrahedron 61:3539
45. Xia M, Lu Y (2007) J Mol Catal A Chem 265:205
46. Khosropour AR (2008) Can J Chem 86:264
47. Chary MV, Keerthysri NC, Vupallapati S, Lingaiah N, Kantevari S (2008) Catal Commun 9:2013
48. Karimi AR, Alimohammadi Z, Amini MM (2009) Mol Diversity. Accessed 29 October 2009
49. Sangshetti JN, Kokare ND, Kotharkara SA, Shinde DB (2008) J Chem Sci 120:463
50. Shaabani A, Maleki A, Behnam M (2009) Synth Commun 39:102
51. Sangshetti JN, Shinde DB, Kokare ND, Kotharkar SA (2008) Monatsh Chem 139:125
52. Mohamadi AA, Mivechi M, Kefayati H (2008) Monatsh Chem 139:935
53. Wang L, Cai C (2009) Monatsh Chem 140:541
54. Jadhave SD, Kokare ND, Jadhave SD (2009) J Heterocycl Chem 45:1461
55. Sangshetti JN, Kokare ND, Kotharkar SA, Shinde DB (2008) Chin Chem Lett 19:762
56. Samai S, Nandi GC, Singh P, Singh MS (2009) Tetrahedron 65:10155
57. Wang XC, Gong HP, Quan ZJ, Li L, Ye HL (2009) Chin Chem Lett 20:44

58. Gadekar LS, Mane SR, Arbad BR, Katkar SS, Lande MK (2009) Cent Eur J Chem 7:550
59. Gulkova D, Solcova O, Zdrazil M (2004) Microporous Mesoporous Mater 76:137
60. Climent MJ, Corma A, Iborra S, Mifsud M (2007) J Catal 247:223
61. Faghihi-Sani MA, Yamaguchi A (2002) Ceram Int 28:835
62. Chaim R, Shen ZJ, Nygren MJ (2004) Mater Res 19:2527
63. Chen D, Jordan EH, Gell M (2008) Scr Mater 59:757
64. Hattori H (1995) Chem Rev 95:537
65. Meshkani F, Rezaei M (2010) Powder Technol 199:144
66. Meshkani F, Rezaei M (2009) Powder Technol 196:85