

A novel and an efficient catalyst for one-pot synthesis of 2,4,5-trisubstituted imidazoles by using microwave irradiation under solvent-free conditions

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Abstract. $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ has been used as an efficient catalyst for an improved and rapid synthesis of 2,4,5-trisubstituted imidazoles by a three-component, one-pot condensation of benzil, aryl aldehydes and ammonium acetate in good yields under solvent-free conditions using microwave irradiation. The reactions in conventional heating conditions were compared with the microwave-assisted reactions.

Keywords. 2,4,5-Trisubstituted imidazoles; ammonium heptamolybdate tetrahydrate; one-pot condensation; microwave irradiation; solvent-free conditions.

1. Introduction

The toxicity and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in huge amounts for organic reactions have posed a serious threat to the environment.¹ Thus, the design of solvent-free catalytic reaction has received more attention in recent times in the area of green synthesis.^{2,3} The emergence of microwave technology as a tool for increasing reaction rates is well documented.^{4,5} Microwave-assisted reactions are extremely attractive to synthetic organic chemists due to their ability to shorten reaction times and in some cases improve regio- and/or chemoselectivity.^{6,7} Reactions that previously required hours to run for completion can now be finished within minutes.⁸ Imidazoles are commonly utilized substructures within the pharmaceutical industry, as these heterocycles impart unique physical and biological properties to compounds of interest.^{9–13} Trisubstituted imidazole derivatives are widely used as organic materials, such as to resist composition on textile,¹⁴ fluorescent whiteners on textile,¹⁵ photographic materials,^{16–18} electroluminescent materials^{19,20} and optical materials.^{21,22} Meantime, it was found that these compounds play roles in many kinds of biological activities.^{23–25} This versatile

applicability highlights the importance of access to efficient synthetic routes to well-designed and highly substituted imidazole derivatives. There are several methods for the synthesis of highly substituted imidazoles.²⁶ A number of methods have been developed for the synthesis of 2,4,5-trisubstituted imidazoles. 2,4,5-Trisubstituted imidazoles are generally synthesized by three-component cyclocondensation of a 1,2-diketone, α -hydroxyketone or α -ketomonoxime with an aldehyde and ammonium acetate, which comprise the use of microwaves,^{27–30} ionic liquids,^{31–35} refluxing in acetic acid,^{36–38} silica sulfuric acid,^{39,40} $\text{NiCl}_2\cdot 6\text{H}_2\text{O}/\text{Al}_2\text{O}_3$,⁴¹ $\text{Yb}(\text{OTf})_3$,⁴² $\text{Yb}(\text{OPf})_3$,⁴³ iodine,⁴⁴ $\text{Zr}(\text{acac})_4$,⁴⁵ $\text{InCl}_3\cdot 3\text{H}_2\text{O}$,⁴⁶ heteropolyacid,⁴⁷ sodium bisulfite,⁴⁸ potassium aluminum sulfate (alum),⁴⁹ ceric ammonium nitrate (CAN),^{50,51} polymer-supported ZnCl_2 ⁵² and L-proline.⁵³ Moreover, they have also been prepared by the addition of a substituted amino alcohol to a thioamide and subsequent oxidation with PDC⁵⁴ or by the reaction of aryl nitriles and α,α -dilithioarylnitromethanes⁵⁵ or by multistep syntheses^{56,57}. Khodaei and co-workers in 2007 described the synthesis of 2,4,5-trisubstituted imidazoles from 1,2-diketone or α -hydroxyketone, aldehyde and ammonium heptamolybdate tetrahydrate in tetrabutylammonium iodide using catalytic amounts of *p*-TSA.⁵⁸ Despite their potential utility, most of these synthetic methods suffer from one or more serious

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drawbacks, such as laborious and complex work-up and purification, significant amounts of waste materials, strongly acidic conditions, occurrence of side reactions, low yields, high temperature, long reaction time and the use of expensive reagents. We were promoted a facile, mild and efficient method for one-pot synthesis of 2,4,5-trisubstituted imidazole derivatives starting from 1,2-diketone and various aromatic aldehydes under solvent-free and microwave conditions in the presence of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ as catalyst (figure 1).

2. Experimental

2.1 Materials

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

2.2 Apparatus

Melting points were determined in an open capillaries using an Electrothermal Mk3 apparatus. Infrared (IR) spectra were recorded using a Perkin-Elmer FT-IR 550 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded in $\text{DMSO}-d_6$ using Bruker DRX-400 spectrometer at 400 and 100 MHz respectively. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer carried out on Perkin-Elmer 240c analyzer. UV spectra were recorded on a Hitachi 200-20 spectrophotometer using spectrophotometric grade chloroform (Baker). Microwave synthesis was carried out on a ETHOS 1600, Milestone microwave reactor.

2.3 General procedure for synthesis of 2,4,5-trisubstituted imidazoles under conventional heating conditions

Benzil (0.21 g, 1 mmol), ammonium acetate (0.15 g, 2 mmol), aldehyde (1 mmol) and $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$

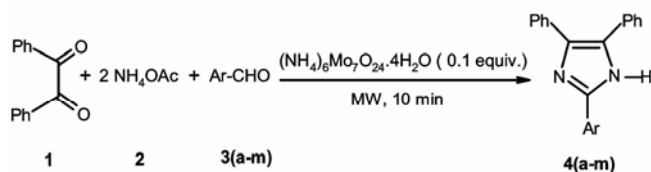


Figure 1. $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ catalysed synthesis of 2,4,5-trisubstituted imidazoles under microwave irradiation.

(0.12 g, 0.1 mmol) were placed in a round bottom flask. The reactants were mixed and heated at 100°C . The progress of the reaction was monitored by TLC (ethyl acetate/petroleum ether = 3 : 7). After completion the reaction mixture was washed with cool water and filtered. The solid residue was then crystallized from 9 : 1 acetone-water solution. Pure product was obtained as crystalline in good yields. Most of the products are known and were identified by comparing with their physical and spectral data with those of authentic samples.

2.4 General procedure for synthesis of 2,4,5-trisubstituted imidazoles under microwave irradiation

A mixture of benzil (0.21 g, 1 mmol), ammonium acetate (0.15 g, 2 mmol), aldehyde (1 mmol) and $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ (0.12 g, 0.1 mmol) put in the hole of the microwave reactor. The mixture was irradiated at 100 W for 10 min. The progress of the reaction was monitored by TLC (ethyl acetate/petroleum ether = 3 : 7). After cooling, the reaction mixture was washed with cool water and filtered. The solid residue was then crystallized from 9 : 1 acetone-water solution. Pure product was obtained in good yields.

2.5 Spectral data for new derivatives of 2,4,5-trisubstituted imidazoles

2.5a 2-(3-methoxyphenyl)-4,5-diphenyl-1H-imidazole (4b): m.p.: $259\text{--}262^\circ\text{C}$; IR (cm^{-1} , KBr): 3431.80, 3058.38, 2926.27, 1591.31, 1482.73, 1241.06, 768.39, 686.84; UV (CDCl_3): $\lambda_{\text{max}} = 314, 240$ nm; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 12.70$ (s, 1H, NH), 6.80–7.80 (m, 14H, Ar-H), 3.80 (s, 3H, OMe) ppm; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): $\delta = 160.00, 145.86, 137.63, 135.60, 132.15, 130.27, 129.20, 128.86, 127.70, 118.13, 114.70, 110.70, 55.70$ ppm; Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.94; H, 5.55; N, 8.57.

2.5b 2-(2-naphthyl)-4,5-diphenyl-1H-imidazole (4g): m.p.: $273\text{--}276^\circ\text{C}$; IR (cm^{-1} , KBr): 3429.00, 3054.16, 1600.50, 1500.35, 1447.26, 752.89, 697.10; UV (CDCl_3): $\lambda_{\text{max}} = 330, 288, 244$ nm; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 12.80$ (s, 1H, NH), 8.61 (s, 1H, Ar-H), 8.25 (d, 1H, $^3J = 8.00$ Hz, Ar-H), 7.92–8.02 (m, 3H, Ar-H), 7.53–7.61 (m, 6H, Ar-H), 7.46 (t, 2H, $^3J = 7.90$ Hz, Ar-H), 7.39 (t, 1H,

Table 1. Synthesis of 2,4,5-trisubstituted imidazoles in the presence of various catalysts^a.

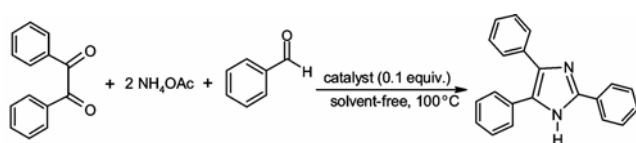
Entry	Catalyst	Time (min)	Temperature (°C)	Yield
1	None	30	100	25
2	(NH ₄) ₆ Mo ₇ O ₂₄ ·4H ₂ O	20	100	80
3	VCl ₃	20	100	45
4	ZrCl ₄	20	100	50
5	WCl ₆	20	100	48
6	AlCl ₃	20	100	42

^aOne equiv. benzil **1**, 1 equiv. benzaldehyde **3a**, 2 equiv. NH₄OAc **2** and 0.1 equiv. catalyst.

Table 2. Optimization of reaction conditions for synthesis of 2,4,5-trisubstituted imidazoles^a.

Entry	(NH ₄) ₆ Mo ₇ O ₂₄ ·4H ₂ O (mmol)	Temperature (°C)	Time (min)	Yield (%)
1	0.0	60	60	10
2	0.05	60	35	35
3	0.1	60	35	50
4	0.2	60	35	50
5	0.0	80	45	20
6	0.05	80	25	47
7	0.1	80	25	60
8	0.2	80	25	60
9	0.0	100	30	25
10	0.05	100	20	58
11	0.1	100	20	80
12	0.2	100	20	80
13	0.0	130	20	40
14	0.05	130	20	60
15	0.1	130	20	80
16	0.2	130	20	80

^aOne equiv. benzil **1**: 1 equiv. benzaldehyde **3a**: 2 equiv. NH₄OAc **2**.

**Figure 2.** Catalysed synthesis of 2,4,5-triphenyl-1H-imidazole under conventional heating conditions.

³J = 7.60 Hz, Ar-H), 7.32 (*t*, 2H, ³J = 7.90 Hz, Ar-H), 7.24 (*t*, 1H, ³J = 7.60 Hz, Ar-H) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 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; Anal. Calcd. for C₂₅H₁₈N₂: C, 86.68; H, 5.24; N, 8.09. Found: C, 86.66; H, 5.22; N, 8.08.

3. Results and discussion

In this study, to choose the appropriate catalyst some of the Lewis acids such as AlCl₃, WCl₆, ZrCl₄, VCl₃ were selected. Then, a comparative study was made by using benzaldehyde, benzil and ammonium acetate in the presence of these materials as catalyst (figure 2). The samples were heated under conventional conditions at 100°C in the presence of each catalysts, separately. The corresponding results are summarized in table 1. The results indicated that (NH₄)₆Mo₇O₂₄·4H₂O was the best catalyst and consequently it was selected for subsequent experiments. In the absence of catalyst, the yield of the product was found to be very low. In the course of this study we found that (NH₄)₆Mo₇O₂₄·4H₂O was the most effective catalyst in obtaining the yield of triphenylimidazole (80%). The catalytic activity of

Table 3. (NH₄)₆Mo₇O₂₄·4H₂O catalysed synthesis of 2,4,5-trisubstituted imidazoles under solvent-free conditions.

Entry	Aldehyde	Ar	Product	Yield (%) ^a Time (min)		M.p. (°C)	
				Δ ^b	MW ^c	Found	Reported
1	3a	C ₆ H ₅	4a	80 (20)	94 (10)	270–272	272–273 ^f
2	3b	<i>m</i> -MeOC ₆ H ₄	4b	78 (15)	93 (10)	259–262	–
3	3c	<i>p</i> -MeC ₆ H ₄	4c	85 (25)	98 (10)	230–233	232–235 ^d
4	3d	<i>p</i> -ClC ₆ H ₄	4d	79 (20)	94 (10)	260–261	262–264 ^d
5	3e	<i>m</i> -ClC ₆ H ₄	4e	78 (20)	94 (10)	282–283	285–287 ^d
6	3f	<i>p</i> -MeOC ₆ H ₄	4f	87 (25)	99 (10)	228–231	230–232 ^d
7	3g	2-Naphthyl	4g	78 (20)	94 (10)	273–276	–
8	3h	2,4-Cl ₂ C ₆ H ₃	4h	77 (30)	93 (10)	170–172	174–176 ^d
9	3i	2-Thienyl	4i	78 (20)	92 (10)	261–264	262–266 ^d
10	3j	<i>p</i> -BrC ₆ H ₄	4j	79 (20)	93 (10)	263–265	261–263 ^d
11	3k	<i>m</i> -O ₂ NC ₆ H ₄	4k	74 (15)	89 (10)	269–271	265–267 ^f
12	3l	<i>o</i> -HOC ₆ H ₄	4l	76 (30)	91 (10)	198–201	203–205 ^f
13	3m	<i>p</i> -(Me) ₂ NC ₆ H ₄	4m	82 (25)	96 (10)	255–257	257–258 ^e

^aIsolated yield based on aldehyde, ^bUnder classical heating conditions at 100°C, ^cUsing microwave irradiation, ^dRef. 24, ^eRef. 42, ^fRef. 44.

(NH₄)₆Mo₇O₂₄·4H₂O is remarkable for both quantitative and qualitative advantages such as cheap availability and non-toxicity.

To optimize the reaction conditions, the reaction of benzaldehyde, benzil and ammonium acetate was used as a model reaction (table 2). In the following study, we examined the reaction at different temperature to find out the effect on the reaction. It was found that at lower temperature, even if the reaction time was prolonged, it gave only low yield, and higher the temperature, higher the yield. The efficiency of the reaction is mainly affected by the amount of catalyst and temperature. As indicated in table 2, the best results have been obtained at 100°C with 0.1 mmol (NH₄)₆Mo₇O₂₄·4H₂O. Increasing the amount of (NH₄)₆Mo₇O₂₄·4H₂O and temperature has not shown in the increase of yield.

For more examination of the influence of microwave irradiation on the reaction, a comparison was made between microwave irradiation and heating conditions. The successful results of (NH₄)₆Mo₇O₂₄·4H₂O catalysed syntheses of 2,4,5-trisubstituted imidazoles under solvent-free classical heating conditions or using microwave irradiation are given in table 3. As shown, microwave irradiation has shown better yields and especially in the reaction times. Also, it is observed that by using a wide range of aromatic aldehydes all imidazoles were obtained in moderate to good yields. Therefore, this is a general method that tolerates both electron-withdrawing and electron-donating constituents. The yield of products for *p*-MeOC₆H₄ and *p*-MeC₆H₄ (table 3, entry 3, 6)

are higher than other aromatic aldehydes. For some of the aromatic aldehydes with high electron-withdrawing and steric effects such as *p*-O₂NC₆H₅ and 2,6-Cl₂C₆H₄, no reaction took place. The structure of the 2,4,5-trisubstituted imidazole products have been confirmed by their spectroscopic data and their melting points compared with literature reports. The presence of signal at 3400–3430 cm⁻¹ in IR spectra and 12.5–12.8 ppm in ¹H NMR spectra, due to NH related to the imidazole ring are observed.

4. Conclusions

In summary, we presented an efficient, mild and rapid approach for the synthesis of 2,4,5-trisubstituted imidazoles via condensation of a representative 1,2-diketone (benzil) with various aromatic aldehydes and ammonium acetate, by using (NH₄)₆Mo₇O₂₄·4H₂O as a new and highly effective catalyst under solvent-free and microwave conditions. Non-corrosiveness, safe, low waste, easy for separation, short time, high yields and environmentally benign are some of the advantages of this methodology.

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