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Efficient One-Pot Microwave Synthesis of 2,4,5trisubstituted Imidazoles Using Catalyst

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Abstract: Microwave assisted one pot synthesis organic is a new and quickly growing area in synthetic organic chemistry. A rapid and efficient microwave-induced one-pot synthesis of 2,4,5-trisubstituted imidazoles has been developed. This protocol involves the reaction of aldehydes, 1,2-diketones, and ammonium acetate in a single step, using microwave irradiation as the energy source. The reaction proceeds rapidly, affording the desired tri substituted imidazoles in excellent yield. The key advantages of this process are reaction proceeded smoothly and products obtained in excellent yield with high purity, cost effectiveness of catalyst .The synthesized compounds were fully characterized by spectroscopic methods, including 1HNMR and IR.

Keywords: Imidazole synthesis, Microwave-assisted

I. INTRODUCTION

Chemists specialize in one-pot multicomponent reactions (MCRs) that directly transform more than two reactants into their products because they preserve atom economy and promote the safe synthesis of organic molecules. These reactions are effective and practical methods for creating a small number of chemical molecules that have biological and pharmacological activity. It was discovered that substituted imidazole structures were present in a large number of naturally occurring physiologically active compounds.

Since several of these chemical frameworks exhibit interesting biological activity and are frequently included in different pharmacological formulations, imidazole is one of the most well-known heterocyclic scaffolds.2 It is commonly recognized that imidazole derivatives are fungicides, herbicides, anti-inflammatory, antithrombotic, plant growth regulators, and inhibitors of P38MAP kinase.5-6 Numerous techniques for the synthesis of imidazole derivatives has been described in the literature in recent years.[1] As pharmacological drugs with anticancer [3], anti-inflammatory [4], antibacterial [5], herbicide [6], fungicide [7], P38 MAP kinase [8], and mammalian 15-LOX [9] inhibitors, substituted imidazoles have become remarkably important. Furthermore, imidazoles play a significant role in the production of ionic liquids [10]. As photosensitive substances, they are also employed in photography [11]. As a result of their significance, numerous artificial tactics have been created. The first imidazole synthesis from 1,2-dicarbonyl molecule, several aldehydes, and ammonia to produce 2,4,5-triphenylimidazoles was described by Radziszewski and Japp in 1882 [12].

Multiple synthesis methods to produce 2,4,5-trisubstituted imidazole derivatives have been documented in the literature. A popular technique for this purpose is the cyclo-condensation of 1,2-diketone or α -hydroxyketone with an aldehyde using ammonium acetate. ZnO nanorods [13], silica sulfuric acid [14], sulfated tin oxide [15], ytterbium trifluoromethanesulfonate, Yb(OTf)3 [16], and diethyl ammonium hydrogen phosphate [17] were among the several catalysts and conditions that were investigated. However, a couple of the earlier methods require a high temperature, use hazardous solvents or chemicals, take a long time, and require a lot of catalyst. Thus, it is necessary to investigate a novel catalytic material for the clean and effective synthesis of imidazoles. This study presents the use of a CoFe2O4 magnetic catalyst in the synthesis of imidazoles. (Fig. 1) Many of these approaches, however, have one or more

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drawbacks, including low yields, a high temperature requirement, a lengthy reaction time, extremely acidic conditions, the need for an excess of catalysts, and solvent usage. Therefore, a straightforward, extremely effective, safe for the environment, and adaptable approach for the one-pot synthesis of 2,4,5-triphenylimidazoles (Fig. 2) derivatives is highly desired [4]. As a result, they weren't suitable for creating imidazoles with different structures. There is still a strong desire for the development of environmentally friendly, high-yielding, and clean methods.

Microwave assisted synthesis is an important tool for green chemistry. Microwave assisted synthesis has emerged as a new lead in organic synthesis which makes the synthetic chemistry to go green. Debus – Radiziszewski imidazole synthesis is a simple and highly efficient method for synthesis of 2, 4, 5- triphenyl imidazoles. The use of microwave for the synthesis of organic compounds under solvent-free conditions proved to be efficient, safe and environmentally benign technique, with shorter reaction time, high yields, and easier manipulation. Additionally, it can also avoid the use of hazardous and expensive solvents and can be environmentally benign to make manipulations much easier [5]. In this work, we present an intriguing method for creating 2,4,5-trisubstituted imidazoles using a multicomponent reaction using CoFe2O4 magnetic nanoparticles as a novel, effective, and environmentally friendly magnetically separable catalyst.

II. EXPERIMENTAL

Materials and Method

An 800W microwave oven (IFB-3way system, 23sc1, 2450 MHz) was used for the microwave irradiation. Thin layer chromatography, or TLC, was used to track the reaction's development. The open capillary method was used to estimate the melting points of the produced compounds. Using a KBr disc, IR spectra were captured using a Perkin-Elmer FT spectrophotometer. A Bruker 400 ultra-shield NMR spectrometer running at 400MHz was used to record 1 H NMR spectra.DMSO is employed as a solvent for FT-NMR, and chemical shift values were measured in ppm units. For compound synthesis, analytical-grade chemicals were employed.

General Procedure:



General procedure for the synthesis of 2,4,5 - triphenyl-1H- Imidazole (5s1-5s4)

Ammonium acetate (2.5 mmol), $COFe_2O_4$ (20mg), ethanol (2ml), benzil (1 mmol), and aldehyde (1 mmol), such as 4flourobenzaldehyde, 4-methylbenzaldehyde, 4-chlorobenzaldehyde, and 4-nitrobenzaldehyde, were combined in a 50 ml borosil beaker. A glass rod was used to appropriately mix the reaction mixture. It was subjected to radiation for 15 seconds at 180 watts of power in a microwave oven. The reaction mixture was taken out of the microwave oven to shake after each irradiation. The microwave irradiation lasted between one and three milliseconds. Following this procedure, the TLC revealed that the initial benzil and aldehyde components disappeared. When cooling to room

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temperature, the catalyst was separated using an external magnet, washed several times with water: ethanol solution and dried under vacuum at room temperature to be ready for a later run. The solvent was evaporated, and then the solid residue was recrystallized from ethanol to afford pure 2, 4, 5-trisubstituted imidazole derivatives.

Spectra Data

Spectral Data for 2,4,5-Tri Substituted Imidazoles

Compound and Spectral data

2-(3-Bromo phenyl)-4, 5, diphenyl-1-H Imidazole: (4a)

M.P. 299°C - 301°C; ¹HNMR (Bruker) (399 MHz, CDCl3/DMSO-d6): δ = 7.21 - 7.49 (m, 10H), 7.64 (s, 1H), 7.41 (d, 1H), 7.38 (d, 1H), 7.20(t, 1H); ¹³CNMR (101 MHz, CDCl3/DMSO-d6); δ = 123.5, 126.4, 127.4, 128.7, 129.2, 132.8, 147. 5 ppm; FTIR (KBr, cm–1); 3433 (N-H), 1601 (C=C), 1481 (C=N), 728 (C-Br): NCMS (m/z) (M+ +1) 366

2-(4-Flouro phenyl)-4, 5, diphenyl-1-H Imidazole: (4b)

M.P.187°C - 191°C^{: 1}HNMR (Bruker) (401 MHz CDCl3/DMSO-d6): $\delta = 7.21 - 7.47$ (m, 10H), 7.45 - 7.41 (d, J = 8.0 Hz, 2H), 7.04 - 6.70 (d, J = 8.6 Hz, 2H); ¹³CNMR (101 MHz, CDCl3/DMSO-d6); $\delta = 126.2$, 127.6, 128.8, 129.2, 129.2, 162.8, 133.2 ppm; FTIR(KBr, cm-1); 3431 (N-H), 1601 (C=C), 14821(C=N), 693 (C-F): NCMS (m/z) 314(M+ + 1)

2-(3-Nitro phenyl)-4, 5, diphenyl-1-H Imidazole: (4c)

M.P: 299°C. FTIR (KBr, cm–1): 3447, 3067, 1525, 1351^{; 1}HNMR (Bruker) (401 MHz, CDCl3/DMSO-d6): δ = 13.11 (s, 1H), 8.94 (s, 1H), 8.54 (d, J1/4 7.4 Hz, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.80(d, J1/4 7.8 Hz, 1H), 7.55 - 7.32 (m, 10H); ¹³C NMR (101 MHz, CDCl3/DMSO-d6): δ = 148.5, 143.3, 131.7, 131.1, 130.5, 128.6, 128.3,127.2, 122.5, 119.5; NCMS (m/z): 342.2(M++1)

2-(4-Nitro phenyl)-4, 5, diphenyl-1-H Imidazole: (4d)

M.P: 200°C - 202°C. FTIR (KBr, cm–1): 3403, 2927, 1597, 1518, 1345, 855; ¹H NMR (Bruker) (401 MHz, CDCl3/DMSO-d6): δ = 12.82(s, 1H), 8.02 - 7.43 (m, 14H); ¹³C NMR (101 MHz, CDCl3/DMSO-d6): δ = 148.8, 143.6, 131.5, 130.5, 129.6, 128.3, 127.7, 127.3, 126.8, 126.2, 125.5, 124.2, 122.3, 118.6; NCMS (m/z): 342.3 (M++1).

2-(4-Methyl phenyl)-4, 5, diphenyl-1-H Imidazole: (4e)

M.P: 185° C - 187° C. FTIR (KBr, cm–1): 3451 (N-H), 1601 (C=C), 1584 (C=N). ¹HNMR (Bruker) (401 MHz, CDCl3/DMSO-d6): 2.31 (s, CH3), 7.11 - 7.61 (m, 10H), 7.71 (d, 2H, J = 10 Hz), 7.31 (d, 2H, J = 10 Hz). ¹³CNMR (101 MHz, CDCl3/DMSO-d6), 55.6, 113.5, 122.5, 126.2, 126.5, 128.3, 128.2, 133.3, 145.6, 159.7 ppm: NCMS (m/z):312 (M + 1)

2-(4-chlorophenyl)-4, 5-diphenyl-1H-imidazole (4f):

¹H NMR (301 MHz, CDCl3): 7.05 (d, 2H, J = 8.0 Hz), 7.22-7.72 (m, 10 H), 8.03 (d, 2H, J = 7.6 Hz), 12.42 (s, 1H); ¹³C NMR (101 MHz, CDCl3): 123.3, 125.., 126.1, 127.4, 128.0, 129.5, 129.9, 131.3, 133.7, 136.6, 138.6, 145.2, and 146.7.

2-(2,4-dichlorophenyl)-4,5-diphenyl-1H-imidazole (4g):

¹H NMR (301 MHz, CDCl3): 7.32-7.37 (m, 6H), 7.46-7.56 (m, 5H), 7.68 (d, 1H, J = 7.7 Hz), 7.77 (d, 1H, J = 7.6 Hz), 12.35 (s, 1H); ¹³C NMR (101 MHz, CDCl3): 125.1, 126.4, 127.2, 127.3, 128.1, 128.8, 129.6, 130.8, 131.7, 134.1, 136.2, 138.3, 144.8.



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III. RESULTS AND DISCUSSION

3.1 Catalytic Study

The probably mechanism involving the copper and cobalt catalyst in the reaction may be illustrated in the scheme, as may be understood from similar research that have been published in the literature. Ferrite nanoparticles (Fe3+) first activate the aldehyde and 1,2-diketone to produce imine intermediate and 1,2 diketone imine , respectively. Imoimidazole is produced by further condensing the imine intermediate with the carbonyl carbon or 1, 2 diketone imine, forming a carbocation , attacking the imine nitrogen to the positive center, and dehydrating it. The imo-imidazole then rearranges via a 1,5 sigmatropic shift and deprotonation to yield wd imidazole.

3.1a Comparison of effect of the present catalysts with other catalysts on synthesis of 2,4,5, tri-substituted imidazoles:

An important contribution to this technique is the observation that cobalt ferrites exhibit comparable effective yields to iodine and TCCA with the shortest reaction durations.

3.1b Effect of solvent on synthesis of 2,4,5, trisubstituted imidazoles:

An analysis of the process's reaction medium showed that solvents were important for the reaction being studied. Polar solvents like acetic acid, CH3CN, and C2H5OH were discovered to be much superior to non-polar solvents. When H2O was employed as a solvent, trace levels of yield were seen, most likely as a result of the hydrophobic catalyst aggregating. Despite its effectiveness, acetic acid had a low yield when the catalyst was repeated. For this reason, we decided to use ethanol as the solvent.

3.2 Recycling of the catalyst

One of the primary concerns with heterogeneous catalysis is catalyst reusability. In this reaction with benzaldehyde, the catalyst's recovery and reusability were examined (4a). By using a powerful magnet to secure the catalyst magnetically at the flask's bottom, the solution was removed using a pipette, the solid was twice cleaned with dichloromethane (DCM), and then the new substrate, dissolved in the same solvent, was added to the flask to enable the reaction to continue for the subsequent run. Five repeated reuses of the catalyst were made without any noticeable decrease in catalytic activity. These extremely magnetic catalysts have saturation magnetization values of 32.45 and 35.56 emu/g, which are significantly higher than those of previous magnetic catalysts that have been described. Hence, an external magnet may easily and nearly totally separate them, which is very advantageous for a heterogeneous catalyst.

IV. CONCLUSION

Using CoFe2O4 magnetic nanoparticles as an effective and ecologically safe catalyst, we have created a straightforward and incredibly effective process for the synthesis of 2,4,5-trisubstituted imidazoles. Simple magnetic decantation may readily recover the cobalt ferrite catalyst, which could then be employed five times without seeing a noticeable decrease in activity. This process offers a highly quick, environmentally friendly, and inexpensive way to synthesize imidazoles.

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