iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 5 **Issue:** XII **Month of publication:** December 2017

DOI:

www.ijraset.com

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor :6.887
Volume 5 Issue XII December 2017- Available at www.ijraset.com

Green Approach for the Synthesis of Tetra Substituted Imidazoles Derivatives on $NH_4OAc/NaHSO_4$ Supported onto Silica Gel under Microwave Irradiation

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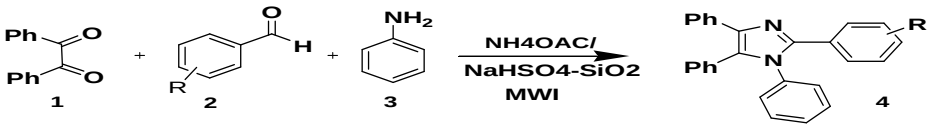
Abstract: ***Imidazole derivatives are reported to be physiologically and medicinally active and find applications in the treatment of several diseases. An efficient synthesis of various Tetra substitute dimidazoles (4a-g) are synthesized in a four component condensation of aldehydes(2), 1,2-diketones(1),amines(3), and ammonium acetate in $NaHSO_4$–SiO_2under microwave irradiation of 600W.***

Keyword: Tetra substituted imidazoles, Silica gel/$NaHSO_4$ support and Microwave irradiation.



Scheme-1

Entry	R
4a	H
4b	2-OH
4c	4-Me
4d	4-Br
4e	4-Cl
4f	3-NO2
4g	2,4,5-$(OMe)_3$

Synthesis of1,2,4,5-tetra substituted imidazoles

I. INTRODUCTION

In recently, organic reaction scan be efficiently catalyzed by these materials, which canbe designed to provide different types of acidity as well as high degrees of reaction selectivity. Solid acids are based on micelle-template silica's and other mesoporous synergize surface area support materials are beginning to play a significant role in the greening of fine and specialty chemicals manufacturing processes, enhanced reaction times, greater selectivity, simple workup, and recoverability of catalysts. Recently, $NaHSO_4$–SiO_2, as an inexpensive and eco friendly catalyst, has been effectively utilized in organic synthesis as an acid catalyst or an accelerator, which is easily separable from the reaction products [3]. The prevalence of imidazoles in natural products and pharmacologically active compounds has instituted adverse array of synthetic approaches to these heterocyclic[4].In continuation of our previous work on the applications of solid supports for development of new synthetic methodologies [6] and heterocyclic compounds containing nitrogen [6-7], and due to the resultant pharmacological interest in compounds which belong to the imidazole family, in this paper, we wish to report the solvent-free synthesis of tetra substitute dimidazoles 4a–l using$NH_4OAc/NaHSO_4$ supported onto silica gel under microwave irradiation or classical heating (Schemes 1).

Imidazole derivatives are a very interesting class of heterocyclic compounds because they are found in many natural products and pharmacologically active compounds such as ant ulcerative agent cimetidine[8], proton pump inhibitor omeprazole[9], and the

benzodiazepine antagonist flumazenil. [10]. Many of the substituted imidazolesactas inhibitors of p-MAP kinase[11], fungicides, herbicides, plant growth regulators and therapeutic agents. [12-14], Medicinal properties of imidazoles include antifungal, anticancer, anticoagulants, anti-inflammatory, antibacterial, antiviral, , ant diabetic and ant malarial[15-19].

II. MATERIALS AND METHOD

The formation of the compounds was checked by thin-layer chromatography and accomplished on 0.2-mm pre coated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. The melting point of all the synthesized compounds was determined in open capillary tubes and was uncorrected.

The characterization of all these compounds was done by NMR, ^{13}C NMR and mass spectral data. The Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR was determined in DMSO solution on a Bruker Ac 400 MHz spectrometer and ^{13}C NMR was determined in MeO Hsolution on 75.46 MHz

A. Experimental procedure for the preparation of desired compound 4a–g

A mixture of $NaHSO_4$–SiO_2 (8.3 g) and ammonium acetate (3.4 g) was ground in a mortar until a fine powder was formed. A solution of 0.01mol of aromatic diketone **(1)**, 0.01mol of aromatic aldehyde **(2)** and 0.01mol of amine **(3)** in 2 ml of methylene chloride was added to 0.2 g of the $NaHSO_4$– SiO_2/ammonium acetate mixture in a 20 ml glass vial. The solvent was allowed to evaporate and the dry residue was irradiated in a microwave oven at 600 W for 12–25 min. The contents were cooled to room temperature and mixed thoroughly with 10 mL of acetone. The solid inorganic material was filtered off. After separation of solid, the solvent was evaporated under reduced pressure and recrystallized from acetone–water.

III. RESULTS AND DISCUSSIONS

Tetra substituted imidazoles(**4a-g**) are synthesized in a four component condensation of aldehydes(**2**), 1,2-diketones(**1**),amines(**3**), and ammonium acetate in $NaHSO_4$ –SiO_2under microwave irradiation. No doubt, these methods are good in terms of reactivity. This catalyst can actas eco-friendly for a variety of organic transformations. It is non-volatile, recyclable, non-explosive, easy to handle. In view of the emerging importance of the heterogeneous catalyst, we wish to explore the use ofsilica gel supported sodium bisulfate as a recyclable catalyst for the synthesis of tetra substituted imidazoles(Scheme1).The synthetic procedure involves impregnating the mixture of solid support, $NaHSO_4$–SiO_2, and ammonium acetate (ammonia source) with a dichloromethane solution of benzil, aldehyde, and amine, evaporating the solvent, and heating the solid residue in a microwave oven. The results were excellent in terms of yields and concentration of catalyst in the presence of$NH_4OAc/NaHSO_4$–$SiO_2$and melting points are shown in Tables 1 and 2.

4,5-dihydro-2-(2,4-dimethoxy-5-methylphenyl)-1,4,5-triphenyl-1H-imidazole (4g)

^{1}H NMR [300 MHz,CDCl3] δ: 5.10 (s, 1H, CH), 6.77-7.91 (m, 19H, Ar).

^{13}C NMR) δ 102.56, 105.75, 113.83, 125.47, 125.83, 126.43,127.01, 127.80, 128.49,128.67, 128.87,129.16, 130.31, 131.16, 134.35, 135.08,136.68, 136.92, 137.50, 137.68, 145.40, 145.70, 152.32, 153.12.Mass Es/Ms = m/z cal. 462.26, m/z obs.(M+.+1) = 463.29.(Shown in Fig:1,2)

IV. CONCLUSION

A convenient and efficient process for the synthesis of tetra substituted imidazoles through the four-components coupling of aromatic diketone, aromatic aldehydes, amine, and ammonium acetate using $NaHSO_4$–SiO_2 as a solid support under MWI have been reported. Present methodology offers very attractive features such as reduced reaction times, higher yields, and economic viability of the catalyst, when compared with conventional method as well as with other catalysts, which will have wide scope in organic synthesis. The simple procedure combined with easy of recovery and reuse of this catalyst make this method benign and a waste-free chemical process for the synthesis of tetra substituted imidazoles.

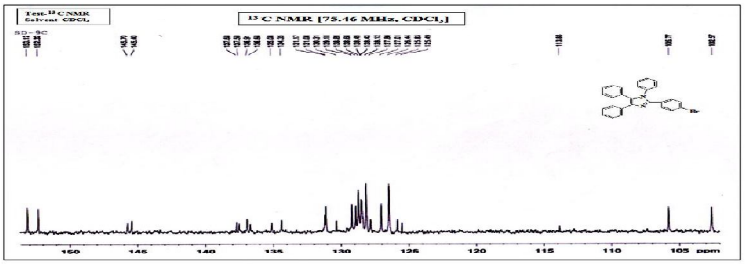


Fig:1^{1}H NMR spectrum of compound 4g

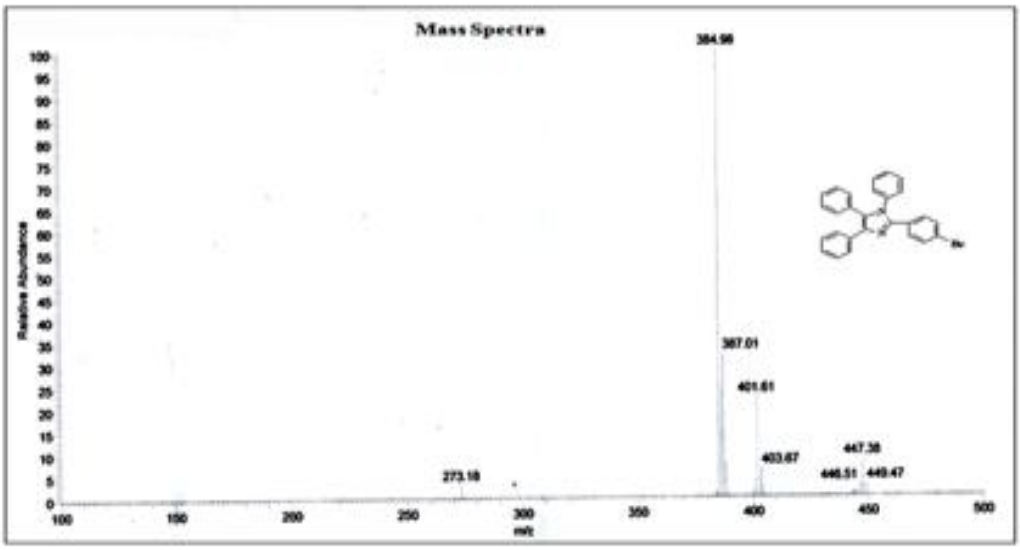


Fig: 2 Mass spectrum of compound 4g

Table-1:Yield(%) and MP(°C)data for products 4a-g

Entry	R	Time(Min)	Yield %	Melting Point (°C)
4a	H	21	92	214-216
4b	2-OH	15	90	140-142
4c	4-Me	20	89	186-188
4d	4-Br	12	90	167-169
4e	4-Cl	17	94	187-189
4f	3-NO2	18	88	150-152
4g	2,4,5-$(OMe)_3$	20	93	260-262

Reaction conditions: 1 (1 mmol) and 2(1 mmol) and 3 (1 mmol) and (1.2mmol) of NH_4OAc .

Table-2:Screening of concentration of catalyst on model reaction

Entry	Catalyst	Catalyst(mol%)	Time (min)	Yield(%)
1	$NaHSO_4$–SiO_2	4	22	78
2	$NaHSO_4$–SiO_2	6	19	79
3	$NaHSO_4$–SiO_2	8	23	82
4	$NaHSO_4$–SiO_2	10	20	86
5	$NaHSO_4$–SiO_2	12	14	>90
6	$NaHSO_4$–SiO_2	14	25	84

Reaction conditions: 1(1 mmol) and 2(1 mmol) and 3 (1 mmol) 4 (1.2 mmol),NH_4OAc using $NaHSO_4$–SiO_2 as a solid support under MWI.

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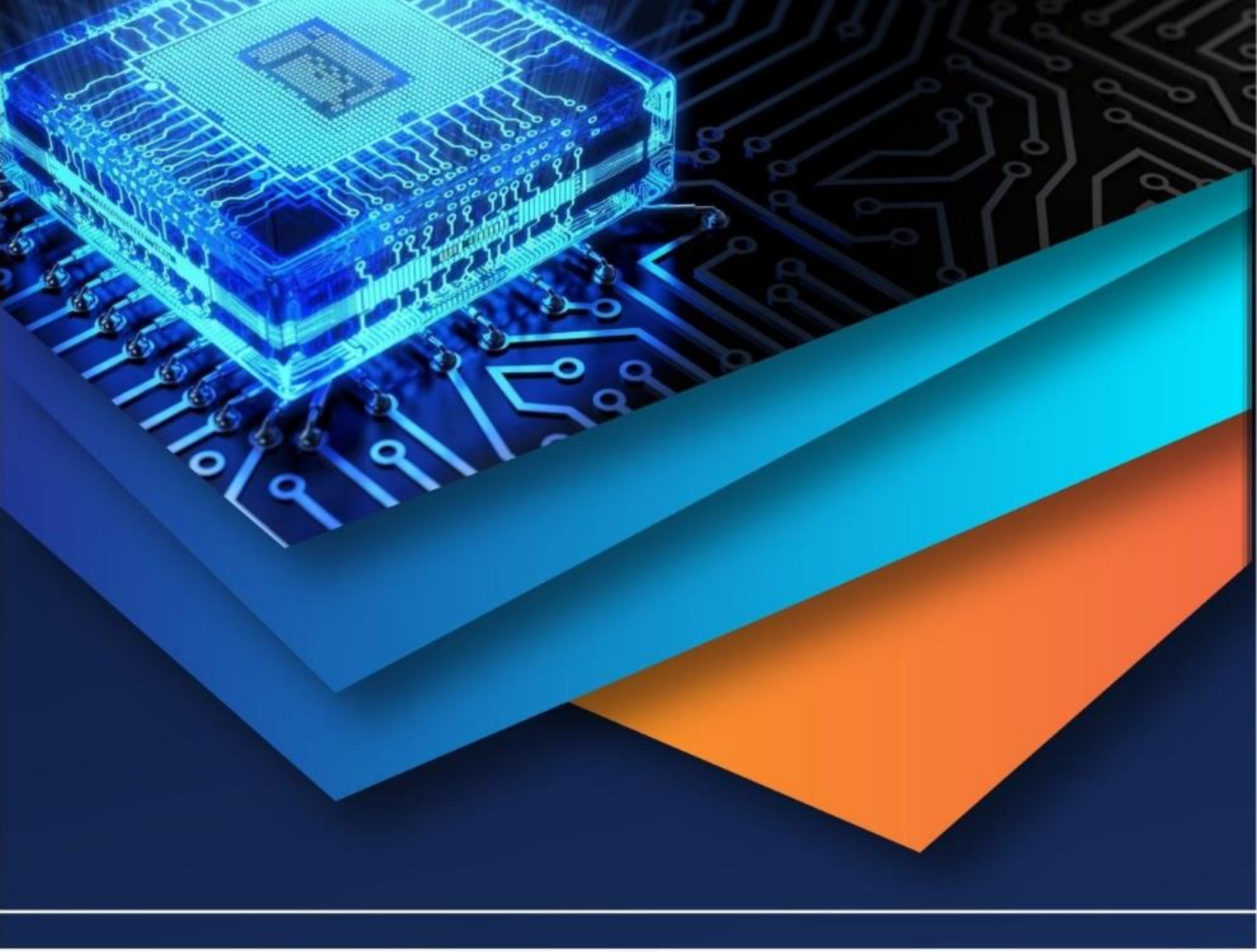

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