

Microwave-Assisted Solid-Phase Synthesis of 2,4,5-Triaryl Imidazoles in Solventless System: An Improved Protocol

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ABSTRACT: *The solventless microwave-assisted synthesis of 2,4,5-triaryl imidazoles from 1,2-diphenylethandione or 2-hydroxy-1,2-diphenylethanone in the presence of $\text{NH}_4\text{OAc}/\text{NaHSO}_4$ supported onto silica gel under microwave irradiation is reported.*

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INTRODUCTION

The synthesis, reactions, and biological properties of substituted imidazole constitute a significant part of modern heterocyclic chemistry [1]. Compounds with the imidazole ring system have many pharmacological properties and play important roles in biochemical processes [2]. Many of the substituted diaryl imidazoles are known as inhibitors of P38 MAP kinase [3].

Research into imidazole chemistry has been quite comprehensive, single-site functionalizations and substitution as well as various annulation strategies have been well documented [4]. Recently, the interest in this heterocyclic system has been widened as it is a precursor to a class of compounds, called room temperature ionic liquids [5].

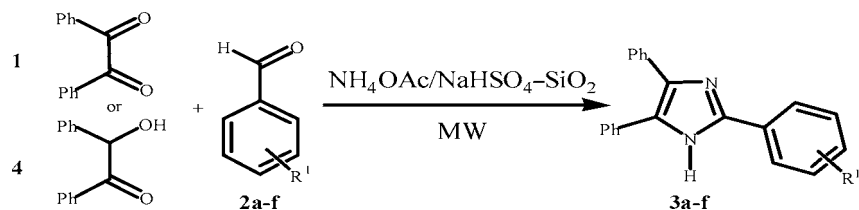
Microwave-assisted synthesis of the substituted imidazoles on a solid support under solvent-free conditions in a three-component reaction [6] and efficient synthesis of imidazoles from aldehydes, 1,2-diketones, and ammonium acetate in acetic acid have been reported [7].

Khmelnitsky and co-worker [6a] were tested several support for synthesis of 2,4,5-trisubstituted imidazoles by a three-component reaction of 1,2-diketones, aldehydes, and ammonium acetate, which makes use of various supports such as acidic, basic, and neutral alumina, bentonite, montmorillonite K10, montmorillonite KSF, silica gel, and florisil. It was found that the addition of a small amount (several drops) of acetic acid was required for the reaction to occur on neutral and basic supports, such as basic and neutral alumina, silica gel, or florisil. On the other hand, when acidic supports were used (bentonite, montmorillonite K10, montmorillonite KSF, or acidic alumina), the reaction was successful without additional acid. No doubt, these methods are good in terms of reactivity; however, these methods suffer from the drawbacks of longer reaction time and moderate yield. Among the reported methods, the use of acidic alumina deserves mention here as a convenient laboratory method for the synthesis of these compounds in moderate to high yields, but on longer time.

Recently, $\text{NaHSO}_4\text{-SiO}_2$, 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 [8]. Among the various heterogeneous

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SCHEME 1

catalysts, particularly, silica gel impregnated with sodium bisulfate has advantages of low cost, ease of preparation [8a], and catalyst recycling.

In continuation of our previous work on the applications of solid supports for development of new synthetic methodologies [9], and heterocyclic compounds containing nitrogen [10], and due to the resultant pharmacological interest in compounds that belong to the imidazole family, in this paper we report the microwave-assisted solvent-free synthesis of 2,4,5-trisubstituted imidazoles using $\text{NH}_4\text{OAc}/\text{NaHSO}_4$ supported onto silica gel (Scheme 1).

Solvent-free reactions using organic or inorganic solid media have been known for some time, and the environmentally friendly goal of making organic compounds without using solvents has come several steps closer in recent years [11].

RESULTS AND DISCUSSIONS

The results were excellent in terms of yields and product purity in the presence of $\text{NaHSO}_4\text{-SiO}_2$, while with NaHSO_4 in pure form only 60% yield was obtained after 6 min. On the other hand, when the silica gel is employed as support in lieu of $\text{NaHSO}_4\text{-SiO}_2$, the reaction was not successful.

Comparison of different supports showed that $\text{NaHSO}_4\text{-SiO}_2$ was the most suitable support for the synthesis of **3a-f** and, therefore, it was used in all subsequent experiments (Table 1).

Generally, the synthetic procedure involves impregnating the mixture of solid support, $\text{NaHSO}_4\text{-SiO}_2$, and ammonium acetate (ammonia source) with dichloromethane solution of benzil and

appropriate aldehyde, evaporating the solvent, and heating the solid residue in a microwave oven (Scheme 1). The results were excellent in terms of yields and product purity in the presence of $\text{NH}_4\text{OAc}/\text{NaHSO}_4\text{-SiO}_2$ as shown in Table 2.

Under the same conditions, this approach can be repeated for synthesis of these imidazoles **3a-f** when 2-hydroxy-1,2-diphenylethanone **4** is used as a starting material. Thus, 2-hydroxy-1,2-diphenylethanone effectively participated in the condensation with aldehyde and ammonium acetate to give the corresponding 2,4,5-substituted imidazoles **3a-f** (Table 1).

The identity of imidazoles **3a-e** was confirmed by analytical comparison (melting points and mass spectra) with authentic standards prepared according to the established procedure [12]. The structure of **3f** was confirmed by NMR and mass spectral analysis.

In summary, microwave-assisted solvent-free (under conditions of the so-called 'Green Chemistry') reactions were employed to synthesize substituted imidazole derivatives. The method not only offers substantial improvement in yield over conventional heating but also eliminates the use of hazardous solvents and excess of expensive acidic catalyst. Advantages of this method include the fact that it is environmentally benign, being an economical procedure, has a short reaction times and the simplicity of the performance with nonaqueous work-up. This method not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety, and pollution. This catalyst can act as eco-friendly for a variety of organic transformations, nonvolatile, recyclable, non-explosive, easy to handle, and thermally robust.

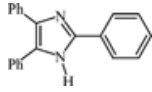
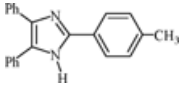
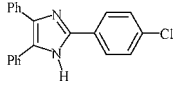
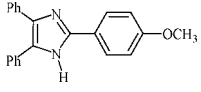
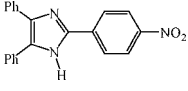
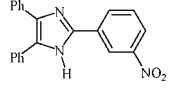
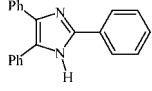
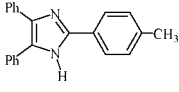
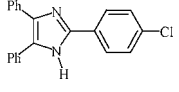
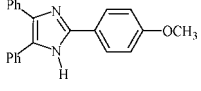
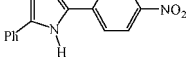
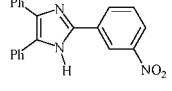
EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-470 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were determined on Bruker 300 DRX AVNCE instrument at 300 and 75 MHz, respectively. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer.

TABLE 1 Comparison of Different Conditions on Synthesis of **3a**

Conditions	Time	Yield (%)
SiO_2 (MW)	6 min	25
NaHSO_4 (MW)	6 min	60
$\text{NaHSO}_4\text{-SiO}_2$ (MW)	6 min	90
$\text{NaHSO}_4\text{-SiO}_2$ (reflux in CH_3CN)	2 h	40

TABLE 2 Synthesis of 2,4,5-Triaryl Imidazoles on Solid Support $\text{NH}_4\text{OAc}/\text{NaHSO}_4\text{-SiO}_2$

Entry	1/4	Time (min)	Product (3a-f)	Yield (%)	M.p. (°C)	Literature m.p. (°C)
1		6	 3a	90	275–276	275 [12a]
2		5	 3b	93	227–229	233 [12b]
3		6	 3c	91	258–260	261–263 [12c]
4		6	 3d	92	226–228	230–232 [12c]
5		8	 3e	84	235–238	240 [12b]
6		7	 3f	85	313–315	–
7		8	 3a	89	275–276	275 [12a]
8		8	 3b	92	227–229	233 [12b]
9		8	 3c	90	258–260	261–263 [12c]
10		8	 3d	93	226–228	230–32 [12c]
11		10	 3e	83	235–238	240 [12b]
12		9	 3f	85	313–315	–

General Procedure

In a typical reaction, a mixture of $\text{NaHSO}_4\text{-SiO}_2$ (9.3 g) and ammonium acetate (4.4 g) was ground in a mortar until a fine powder was formed. A solution of 0.5 mmol of 1,2-dicarbonyl compound and 0.5 mmol of aldehyde in 2 mL of methylene chloride was added to 1 g of the $\text{NaHSO}_4\text{-SiO}_2$ /ammonium acetate mixture in a 20 mL glass vial. The solvent was allowed to evaporate and the dry residue was irradiated in a domestic microwave oven at 600 W for 6–9 min in the open vial. The contents were cooled to room temperature and mixed thoroughly with 3×10 mL of acetone. The solid inorganic material was filtered off. After separation of the solid, the solvent

was evaporated under reduced pressure. The resulting solid residue was purified by recrystallization from acetone–water (15:1 v/v) for **3a–e** or ethanol for **3f**.

3f. M.p. 313–315°C; IR (KBr) (ν_{max} , cm^{-1}): 3415, 3050, 1535, 1517, 1344; ^1H NMR (DMSO-d_6 , 500 MHz) δ_{H} : 7.34–8.95 (14H, m, H_{arom}), 12.99 (1H, bs, NH); ^{13}C NMR (DMSO-d_6 , 75 MHz) δ_{C} : 119.85, 123.07, 127.63, 128.84, 129.69, 129.98, 130.89, 131.63, 132.26, 135.17, 138.18, 143.83, 148.80 (C_{arom}); MS (m/z , %): 341 (M^+ , 80), 294 (30), 190 (35), 89 (75). Anal. Calcd for $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.70; H, 4.40; N, 12.25.

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