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Molybdate sulfuric acid (MSA) an efficient catalyst for the one-pot synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles

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ABSTRACT

A simple highly versatile and efficient synthesis of 2,4,5-trisubstituted imidazoles is achieved by three-component cyclo condensation of 1,2-dicarbonyl compound, aldehyde and ammonium acetate using molybdate sulfuric acid (MSA) as a catalyst in methanol at moderate temperature. To explore the utility of this method 1,2,4,5-tetra-substitute imidazoles were also synthesized. The key advantages of this process are high yields, cost effectiveness of catalyst.

KEYWORDS

2,4,5-trisubstitutedand imidazoles;
1,2,4,5-tetrasubstituted imidazoles;
Three-component;
Molybdate sulfuric acid (MSA).

INTRODUCTION

Multicomponent reactions (MCRs) have been proven to be a very elegant and rapid way to access complex structures in a single synthetic operation from simple building blocks, and show high atom-economy, high selectivity and procedural simplicity due to the formation of carbon-carbon and carbon-heteroatom bonds in one-pot[1]. As a one-pot reaction, MCRs generally afford good yields and are fundamentally different from the two-component reactions in several aspects[2] and permitted rapid access to combinatorial libraries of organic molecules for an efficient lead structure identification and optimization in drug discovery[3,4]. In addition, the implementation of several transformations in a single manipulation is highly compatible with the goals of sustainable and green chemistry[5].

Imidazoles are commonly utilized substructures within the pharmaceutical industry, as these heterocycles impart unique physical and biological properties to compounds of interest[6-9]. Trisubstituted imidazole derivatives are widely used as organic materials, such as to resist composition on textile[10], fluorescent whiteners on textile[11], photographic materials[12], electroluminescent materials[13] and optical materials[14]. Meantime, it was found that these compounds play roles in many kinds of biological activities[15]. 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[16]. 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[17], ionic liquids[18], refluxing in acetic acid[19], silica sulfuric acid[20], $NiCl_2 \cdot 6H_2O/Al_2O_3$[21], $Yb(OTf)_3$[22], $Zr(acac)_4$[23], $InCl_3 \cdot 3H_2O$[24], heteropoly acid[25], sodium bisulfate[26], potassium aluminum sulfate (alum)[27], ceric ammonium nitrate (CAN)[28], and

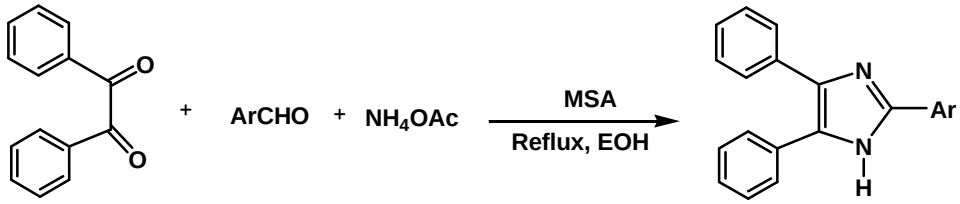
L-proline[29]. Most of these synthetic methods suffer from one or more serious drawbacks, such as laborious and complex work-up and purification, significant amounts of waste materials, strongly acidic conditions, and occurrence of side reactions, low yields and the use of expensive reagents.

RESULTS AND DISCUSSION

In continuation with the search for simple non-hazardous methods for the transformations in organic synthesis using various reagents[30-37], we wish, herein, to report on the use of MSA as a more robust and efficient catalyst in the one-pot synthesis of 2,4,5-trisubstituted imidazoles from cyclo-condensation of benzyl, aldehyde and ammonium acetate under neutral conditions in ethanol at moderate temperature., Initially, we sought a mild and convenient method for the synthesis of trisubstituted imidazoles at room temperature. Our investigation began with the condensation of benzyl (1mmol), benzaldehyde (1 mmol) and ammonium acetate (2 mmol) in ethanol at room temperature for 24 h in the absence of catalyst, which led to very poor yield (21%) of 2,4,5-trisubstituted imidazole. To enhance the yield of the desired product the temperature of the reaction was increased to 80 °C but no appreciable increment in the product yield was observed. We also evaluated the amount of catalyst required for this transformation and it was found that using 5 mol % and 10 mol % catalyst for product **(1a)**, we obtained 77% and 96% yields, respectively. Maximum yield was obtained when the reaction was loaded with 10 mol % of the catalyst (Scheme 1, TABLE 1).

The same reaction conditions were applied for the synthesis of 1,2,4,5-tetrasubstituted imidazoles via the one-pot, four component condensation of benzyl, an aldehyde, a primary amine and ammonium acetate (Scheme 2, TABLE 2).

Plausible mechanism for the molybdate sulfuric acid (MSA) synthesis of substituted imidazoles (Scheme 3) has been proposed. In the case of 2,4,5-trisubstituted imidazole the reaction proceeds through diamine intermediate A, the oxygen of the carbonyl group in step 1 may easily influence [H^+] the catalyst molybdate sulfuric acid (MSA) through intermolecular hydrogen bonding to give the activated aldehyde which may attack



(1) (2) (4)

Scheme 1

TABLE 1 : Synthesis of 2,4,5-trisubstituted with MSA

Entry	Product[a]	Ar	Time (h)	Yields (%)[b]	M.P. (°C)
1	4a	C_6H_5	6.5	96	273
2	4b	4-ClC_6H_4	7	94	262-264
3	4c	4-MeC_6H_4	7	93	235
4	4d	4-$OMeC_6H_4$	9	90	222-224
5	4e	4-OHC_6H_4	8	89	233-232
6	4f	4-$NO_2C_6H_4$	8	91	199-201
7	4h	2-$NO_2C_6H_4$	8.5	87	230-231
8	4g	4-BrC_6H_4	8.5	87	254-256
9	4i	3-$NO_2C_6H_4$	8.5	89	>300
10	4j	2-OHC_6H_4	9	84	202-205

[a] **Isolated yields;** [b] **All the products are known, characterized by IR, NMR spectral analysis and compared with the authentic samples**

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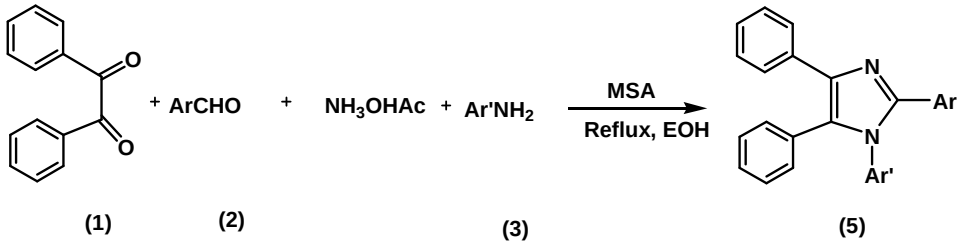


Scheme 2

TABLE 2 : Synthesis of 1,2,4,5-trisubstituted with MSA

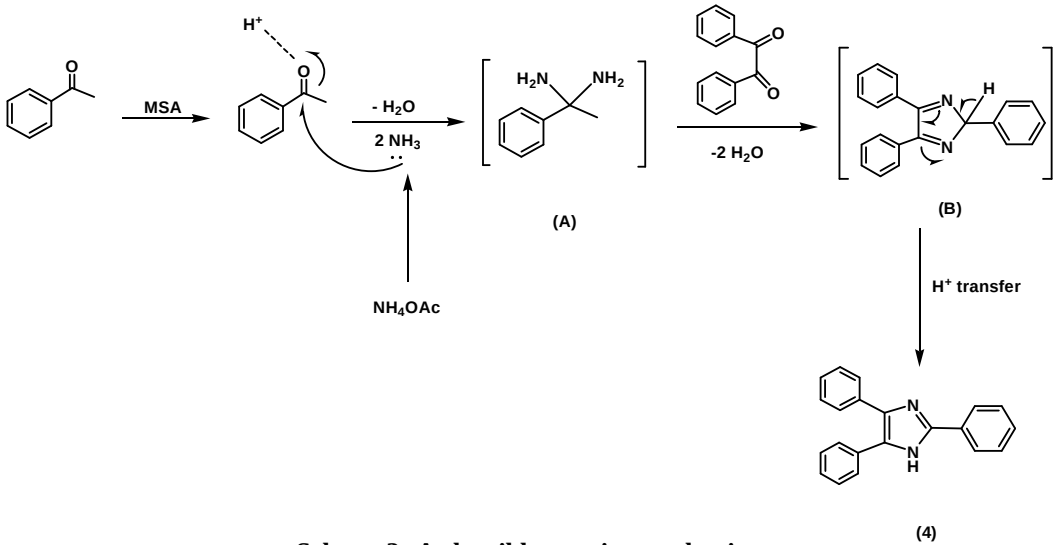
Entry	Product[a]	Ar	Ar'	Time (h)	Yields (%)[b]	M.P. (°C)
1	4a	C_6H_5	C_6H_5	7	94	218-220
2	4b	4-ClC_6H_4	C_6H_5	7.5	93	160-161
3	4c	4-MeC_6H_4	C_6H_5	8	91	180-181
4	4d	4-$OMeC_6H_4$	C_6H_5	8.5	90	183-185
5	4e	4-OHC_6H_4	C_6H_5	9	88	281-282
6	4f	4-$NO_2C_6H_4$	C_6H_5	8.5	90	190-191
7	4h	2-$NO_2C_6H_4$	C_6H_5	9	87	253-255
8	4g	4-BrC_6H_4	C_6H_5	8	91	167-169
9	4i	3-$NO_2C_6H_4$	4-ClC_6H_4	8.5	88	188-189
10	4j	2-OHC_6H_4	4-ClC_6H_4	7	94	218-220

[a] **Isolated yields;** [b] **All the products are known, characterized by IR, NMR spectral analysis and compared with the authentic samples**

1,2-diketone to give diamine intermediate **(A)**. which condenses with the carbonyl carbons of the 1,2-diketone followed by dehydration to afford the imino intermediate **(B)**, which rearranges to the required trisubstituted imidazoles **(4)**. In the case of tetrasubstituted imidazoles **(5)** reaction proceeds in the same fashion as above except the intermediate **(B)** undergoes dehydration rather isomerization Scheme 3.

General procedure for the synthesis of 2,4,5-triarylimidazole (4a-j)

A mixture of benzil **(1)** (10 mmol), ammonium acetate (20 mmol), aromatic aldehyde **(2)** (20 mmol) and MSA (10 mol%) stirred at 80 ºC in ethanol (7 ml) for the appropriate time as mentioned in TABLE 1. The completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled



Scheme 3 : A plausible reaction mechanism

to room temperature and diluted with excess of cold water. The solid imidazole products that separated out, were filtered, washed with excess of water and was further recrystallized with 9:1 acetone-water to result a pure compound of 2,4,5-triarylimidazole **(4a-j)**.

General procedure for the synthesis of 1,2,4,5-tetraarylimidazole (5a–j)

A mixture of benzil **(1)** (10 mmol),ammonium acetate (10 mmol), aniline **(3)** (10 mmol), aromatic aldehyde **(2)** (10 mmol), and MSA (10 mol %) stirred at 80°C in ethanol (7 ml) for the appropriate time as mentioned in TABLE 2. The completion of reaction was monitored by TLC. To obtain pure compounds of 1,2,4,5-tetraarylimidazole **(5a–j)** after completion of reaction, work-up procedure followed was similar to the synthesis of 2,4,5-triarylimidazole.

CONCLUSION

In conclusion, a new strategy has been developed for the convenient synthesis of tri-substituted imidazoles using MSA as a highly efficient catalyst. In the presence of this solid acid a series of tandem condensation and dehydration reactions occurred and resulted in the formation of tri-substituted imidazoles in high yields

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