

Communication

p-TSA Catalyzed Synthesis of 2,4,5-Triarylimidazoles from Ammonium Heptamolybdate Tetrahydrate in TBAI

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A one-pot synthesis of 2,4,5-trisubstituted imidazoles from 1,2-diketone or α -hydroxy ketone, aldehyde and ammonium heptamolybdate tetrahydrate in an inexpensive and readily available ionic liquid, tetrabutylammonium iodide (TBAI) in molten state using catalytic amounts of *p*-TSA has been described.

Keywords: Trisubstituted imidazoles; 1,2-Diketone; α -Hydroxy ketone; Ammonium heptamolybdate; *p*-TSA; Ionic liquid.

INTRODUCTION

Heterocyclic compounds with imidazole ring systems have many pharmaceutical activities and play important roles in biochemical processes.¹ Imidazole derivatives have antiviral,² antifungal,³ antihelminthic,⁴ pesticidal or herbicidal properties.

Highly substituted imidazoles could potentially have novel therapeutic activities⁵ and thus have rekindled an increased interest in obtaining tri- and tetra-substituted imidazoles via absolute region controlled processes.⁶ Triaryl imidazoles are used in photography⁷ as photosensitive compounds. In addition, they are of interest due to their herbicidal,⁸ analgesic,⁹ fungicidal,¹⁰ antiinflammatory¹¹ and antithrombotic activities.¹² Despite their importance from pharmacological, industrial, and synthetic points of view, comparatively few methods for the preparation of trisubstituted imidazoles have been reported. These include the condensation of 1,2-diketone, aldehyde and ammonium acetate in the presence of H₃PO₄,¹³ H₂SO₄,¹⁴ HOAc,¹⁵ and silica sulfuric acid.¹⁶ Recently, one-pot condensations of an aldehyde and ammonium acetate with α -hydroxy ketone, α -keto-oxime or 1,2-diketone have been performed using solid supports under microwave irradiation.¹⁷ Despite their potential utility, these methods have a number of drawbacks including poor yields, utilization of excessive glacial acetic acid, high temperature (180-200

°C), high cost of most conventional room temperature ionic liquids,¹⁸ use of toxic organic solvent, and requirement of an excess of ammonium acetate.

Recent advances in green chemistry and organometallic chemistry have extended the boundary of imidazoles to the synthesis and application of a large class of imidazoles as ionic liquids and imidazole related N-heterocyclic carbenes (NHC).^{19,20} Ionic liquids are emerging as effective solvents for 'green' processes.²¹ These solvents are non-flammable, non-volatile, easy to handle and possess high thermal stability.²² However, the high cost of most conventional room temperature ionic liquids and apprehension about their toxicity²³ have led us to explore the use of more benign salts in the molten state as practical alternatives.

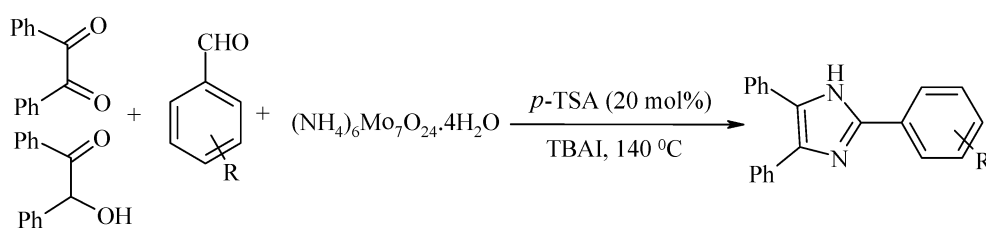
RESULTS AND DISCUSSION

Recently, we used ionic liquids in a number of useful synthetic transformations.²⁴ In this report, a simple and green method for the synthesis of 2,4,5-trisubstituted imidazoles in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) in ionic liquid has been described (Scheme I).

The condensation of 1,2-diketone or α -hydroxy ketone, aldehyde and ammonium acetate in the presence of a strong protic acid, is one of the most frequently used path-

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Scheme 1



ways to 2,4,5-trisubstituted imidazoles. Unfortunately, this method involves the utilization of excessive ammonium acetate such as eight fold^{17a} or ten fold.^{9b} In addition, in most of the methods reported for the synthesis of trisubstituted imidazoles, the use of microwave irradiation conditions is necessary (Table 1).

Thus we decided to use another reagent instead of ammonium acetate and apply ammonium heptamolybdate tetrahydrate for the preparation of 2,4,5-trisubstituted imidazoles. It was found that two equivalents of ammonium heptamolybdate tetrahydrate were enough to perform the reaction.

To explore the scope and limitations of this reaction, we studied the reactions of benzil or benzoin with benzaldehydes bearing either electron-releasing or electron-withdrawing substituents in the *ortho* or *para* positions. The reactions proceeded very efficiently and the results are summarized in Table 2. However, it was observed that aromatic aldehydes carrying strong electron-withdrawing groups like 4-nitrobenzaldehyde and 3-nitrobenzaldehyde afforded no corresponding products and the starting materials remained intact.

These reactions in molten tetrabutylammonium iodide are in general, fast and clean. No reaction was observed using solid tetrabutylammonium iodide at room temperature. Also, the reaction in the absence of tetrabutylammonium iodide at 140-145 °C leads to a mixture of unidentified products. Thus, the presence of molten tetrabutylammonium iodide is essential for an efficient and clean reaction. In addition, the reaction in the absence of *p*-TSA proceeded very slowly.

In conclusion, this paper describes a convenient and efficient process for the synthesis of trisubstituted imidazoles through the three-components coupling of benzil or benzoin, aldehydes, and ammonium heptamolybdate tetrahydrate in ionic liquid in the presence of a catalytic amount of *p*-toluenesulfonic acid. Moreover, the use of inexpensive

Table 1. Comparison of different methods for the synthesis of imidazole derivatives

Entry	Conditions	Yield (%)	Time
1	MW/180 °C ^{9b}	80-99	5 min
2	MW ^{17a}	86-92	4-30 min
3	MW/Silica gel ^{30a}	58-92	8 min
4	Excess of H ₂ SO ₄ /150-200 °C ^{30b}	40-90	4 h
5	AcOH ^{30c}	Low yield	-
6	<i>p</i> -TSA/TBAI	75-95	1-4 h

and easily accessible *p*-TSA and TBAI makes this methodology as a useful procedure for preparation of biologically active trisubstituted imidazoles.


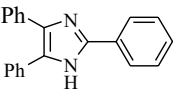
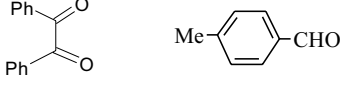
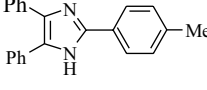
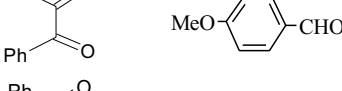
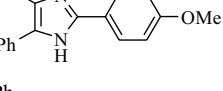
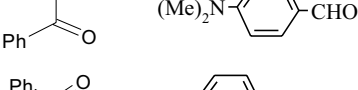
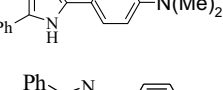

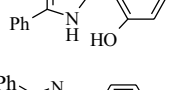
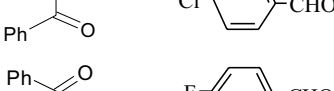
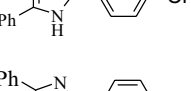

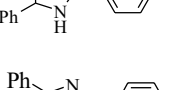

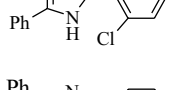

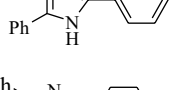
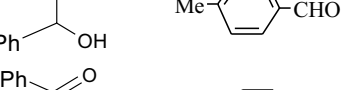
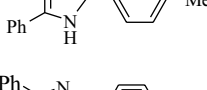

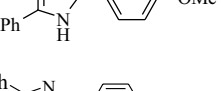
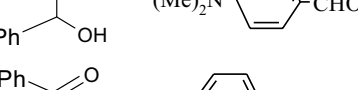
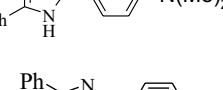

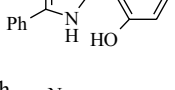
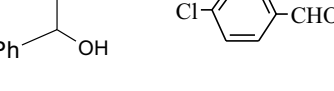
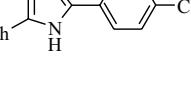
EXPERIMENTAL SECTION

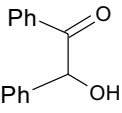
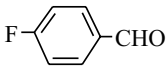
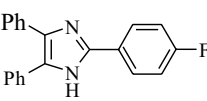
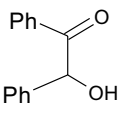
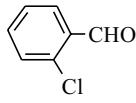
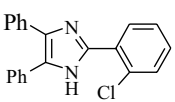
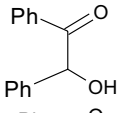
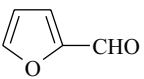
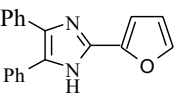
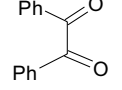
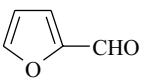
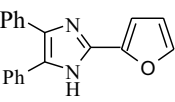
Products are known compounds and were characterized by comparison of their spectral data (¹H NMR, IR) and melting points with those reported in the literature. Monitoring of the reactions was accomplished by TLC on pre-coated silica gel 60 F₂₅₄ sheets. All yields refer to isolated products.

General experimental procedure

A mixture of benzil or benzoin (0.5 mmol), aldehyde (0.5 mmol), ammonium heptamolybdate tetrahydrate (1 mmol), tetrabutylammonium iodide (1 g), and *p*-TSA (0.038 g) were heated at 145 °C with good stirring for the appropriate time as indicated in Table 2. The progress of the reaction was monitored by TLC. After completion of the reaction, hot ethanol (5 mL) was added and the mixture was then filtered. The filtrate was condensed under reduced pressure and it was diluted with water (25 mL). The separated out solid product was filtered, washed with water and dried. For further purification this product was recrystallized from a 9:1 acetone-water solution.

Table 2. One-pot synthesis of trisubstituted imidazoles in TBAI in the presence of *p*-TSA

Entry	Substrates	Products ^a	Time (h)	Yield ^b (%)	Mp/ ^o C (Found)
1			1	88	274-275 ²⁵
2			1	95	233-235 ²⁶
3			1	93	230-233 ²⁷
4			1.5	88	256-257 ²⁷
5			2.5	80	200-203 ²⁰
6			2	80	261-263 ²⁷
7			2	82	260-262 ²⁸
8			3.5	75	183-184 ²⁰
9			1.5	85	274-275 ²⁵
10			1.5	90	233-235 ²⁶
11			2	88	230-233 ²⁷
12			2	85	256-257 ²⁷
13			3	80	200-203 ²⁰
14			3	80	261-263 ²⁷

15				3	80	260-262 ²⁸
16				4	75	183-184 ²⁰
17				2	87	233-235 ²⁹
18				2	90	233-235 ²⁹

^a The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures.

^b Yields refer to pure isolated products.

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