An efficient and one pot synthesis of polysubstituted imidazoles catalyzed by BiCl₃

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BiCl₃ has been found to be a mild and effective catalyst for the efficient, one-pot, three component synthesis of 2,4,5-trisubstituted imidazoles at RT. Moreover, the utility of this protocol has further been explored conveniently for the one-pot, four component synthesis of 1,2,4,5-tetrasubstituted imidazoles in high yields.

Keywords: Multicomponent reaction, one-pot synthesis, 2,4,5-trisubstituted imidazoles, 1,2,4,5-tetrasubstituted imidazoles

Multicomponent reactions (MCRs) have drawn great interest enjoying an outstanding status in modern organic synthesis and medicinal chemistry because they are one-pot processes bringing together three or more components and show high atom economy and high selectivity[^3]. MCRs have great contribution in convergent synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery[^2]. The synthesis, reactions and biological properties of substituted imidazole constitutes a significant part of modern heterocyclic chemistry[^3]. Compounds with the imidazole ring system have many pharmacological properties and play important roles in biochemical processes[^4]. Many of substituted diaryl imidazoles are known as inhibitors of P38 MAP kinase. There are several methods reported in the literature for the synthesis of imidazoles such as the hetero-Cope rearrangement[^5], four-component condensation of arylglyoxals, primary amines, carboxylic acids and isocyanides on Wang resin[^6], of N-(2-oxo)-amides with ammonium trifluoroacetate, 1,2-aminoalcohols in the presence of PCl₅, diketones, aldehyde, amine and ammonium acetate in phosphoric acid and in acetic acid, organo catalyst in acetic acid as well as H₂SO₄ and DMSO. Several microwave (MW) assisted syntheses of imidazoles from 1,2-diketones and aldehydes in the presence of a variety of catalysts such as silica-gel, silica-gel/HY, Al₂O₃, DMF, acetic acid[^7], ZrCl₄ (Ref 8), NiCl₂.6H₂O (Ref 9) and ionic liquid[^10] have been reported. 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. Additionally, most require elevated temperatures created either by microwave irradiation[^11] at 180-200°C or by refluxing[^12] and heating[^13] the reaction mixture at high temperatures. Therefore, the development of a new catalytic system to overcome these shortcomings and fulfil the criteria of a mild, efficient and environmentally benign protocol for the synthesis of highly substituted imidazoles is an important task for organic chemists.

In recent years, bismuth compounds have been used as catalysts in organic synthesis because these compounds are relatively nontoxic, easy to handle, inexpensive, and possess good stability[^14,15]. Among these, bismuth (III) trichloride has gained special attention because not only is this compound commercially available and cheap, but also has high stability[^16,17] and is an environmentally friendly catalyst[^18]. In this paper is reported a simple, mild and expeditious synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted derivatives of imidazoles in high yields using catalytic amounts of BiCl₃ at ambient temperature.

Results and Discussion

To investigate the catalytic activity of bismuth chloride, a model reaction of benzaldehyde (2 mmol), benzil (2 mmol) and NH₄OAc (10 mmol) in acetonitrile was tested at RT for different molar percentages of catalyst. The reaction did not proceed in the absence of catalyst and was found to be most efficient for 20 mol% of catalyst. Encouraged by this success, the reaction of benzil was examined with a range of other aromatic aldehydes (Table I, Scheme I), which afforded the products in high yields. The present study was then extended to a four-component coupling reaction for the preparation of

Note

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—Contd
tetrasubstituted imidazoles (Scheme I). Accordingly, benzil on reaction with an equimolar quantity of benzaldehyde and excess of \( \text{NH}_4\text{OAc} \) in the presence of benzyl amine in acetonitrile at RT furnished 1,2,4,5-tetrasubstituted imidazole (Table I).

### Experimental Section

\( \text{BiCl}_3 \) was obtained from Thomas Baker. The IR spectra were recorded on Perkin Elmer Spectrum 2000 Fourier transform infrared (FT-IR) spectrometer. Elemental analysis was performed on an Elementar Analysensysteme GmbH VarioEL V3.00. \(^1\text{H} \) NMR spectra for the products were recorded on Bruker 300 MHz instrument using TMS as internal standard. Melting points were recorded on a Buchi R-535 apparatus and are uncorrected.

### Typical Experimental Procedure

**General procedure for the synthesis of trisubstituted imidazoles**

A mixture of aldehyde (2 mmol), benzil (2 mmol), \( \text{NH}_4\text{OAc} \) (10 mmol), and \( \text{BiCl}_3 \) (0.4 mmol) in CH\(_3\)CN

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**Table I — BiCl\(_3\)-catalyzed synthesis of trisubstituted and tetrasubstituted derivatives of imidazoles**

<table>
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<th>Yield (%)(^a)</th>
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<td>2</td>
<td>90</td>
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</table>

\(^a\) Isolated yield
(20 mL) was stirred at RT (Scheme I, Table I). After completion of the reaction (TLC analysis in 9:1, petroleum ether: ethyl acetate), it was diluted with water (10 mL) filtered and washed with water. The crude product was purified by recrystallization from ethanol to give the products in 84-94% yield as solids.

General procedure for the synthesis is of tetra-substituted imidazoles

A mixture of aldehyde (2 mmol), benzil (2 mmol), NH₄OAc (10 mmol), amine (2 mmol), and BiCl₃ (0.4 mmol) in CH₃CN (20 mL) was stirred at RT (Scheme I, Table I). After completion of the reaction (TLC analysis in 9:1, petroleum ether: ethyl acetate), it was diluted with water (10 mL), filtered and washed with water. The crude product was purified by recrystallization from ethanol to give the products in 86-90% yield as solids.

Spectral Data

2,4,5-Triphenyl-1H-imidazole, 1a

m.p. 276°C; IR (KBr): 535.59, 1025.40, 1384.51, 1626, 2925.73, 3402.93 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 7.42-8.12 (m, 15H, Ar), 10.80 (s, 1H). Anal. Calcd for C₂₁H₁₆N₂: C, 85.13; H, 5.40; N, 9.45. Found: C, 85.20; H, 5.44; N, 9.40%.

2-(4-Nitrophenyl)-4,5-diphenyl-1H-imidazole, 2a

m.p. 190°C; IR (KBr): 545.52, 724.47, 855.94, 1345.17, 1522.02, 2924.39, 3411.78 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 7.42-8.12 (m, 15H, Ar), 10.80 (s, 1H). Anal. Calcd for C₂₁H₁₆N₂: C, 85.13; H, 5.40; N, 9.45. Found: C, 85.20; H, 5.44; N, 9.40%.

2-(4-Bromophenyl)-4,5-diphenyl-1H-imidazole, 3a

m.p. 160-64°C; IR (KBr): 535.38, 876.22, 1154.27, 1399.93, 1616.95, 2924.09, 3432.11 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 7.29-7.67 (m, 10H, Ar), 7.97 (d, 2H, Ar), 8.19 (d, 2H, Ar), 10.18 (-NH), 1.98 (s, 3H); LC-MS: m/z 310.2621. Anal. Calcd for C₂₁H₁₈N₂: C, 83.72; H, 6.97; N, 9.30. Found: C, 83.72; H, 6.89; N, 9.29%.

2-Cyclohexyl-4,5-diphenyl-1H-imidazole, 6a

m.p. 190°C; IR (KBr): 535.37, 876.22, 1213.15, 1400.04, 1616.95, 2924.46, 3432.11 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 7.64-7.67 (m, 10H, Ar), 7.92(d, 2H, Ar), 7.95(d, 2H, Ar). Anal. Calcd for C₂₁H₁₈N₂: C, 83.72; H, 6.97; N, 9.30. Found: C, 83.72; H, 6.89; N, 9.29%.

1-Benzyl-2,4,5-triphenyl-1H-imidazole, 7b

m.p. 280°C; IR (KBr): 535.37, 876.22, 1211.98, 1402.70, 1559.80, 1112.31 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ 6.58 (2H, -CH₂), 7.36-7.47 (m, 8H, Ar), 7.61-7.66(m, 8H, Ar), 7.78-7.93(d, 4H, Ar). Anal. Calcd for C₂₃H₂₁N₂: C, 87.10; H, 5.66; N, 7.24%. Found: C, 87.10; H, 5.66; N, 7.24%.
Conclusions

In conclusion, the study describes an efficient, rapid, and convenient synthesis of tri- and tetra-substituted imidazoles in a one-pot, three- and four-component coupling reaction strategy using inexpensive, nontoxic, and easily available BiCl₃ as catalyst in acetonitrile. The present method offers several advantages including shorter reaction times at RT, higher yields, and easy experimental workup besides the tolerability of the conditions to a variety of substrates such as aromatic and aliphatic aldehydes. Thus, this simple method would find wide applicability for the highly substituted imidazole systems.

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References


