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Metal Catalyzed Eco-friendly Synthesis of 2-Substituted-1H-Benzimidazoles in Aqueous medium

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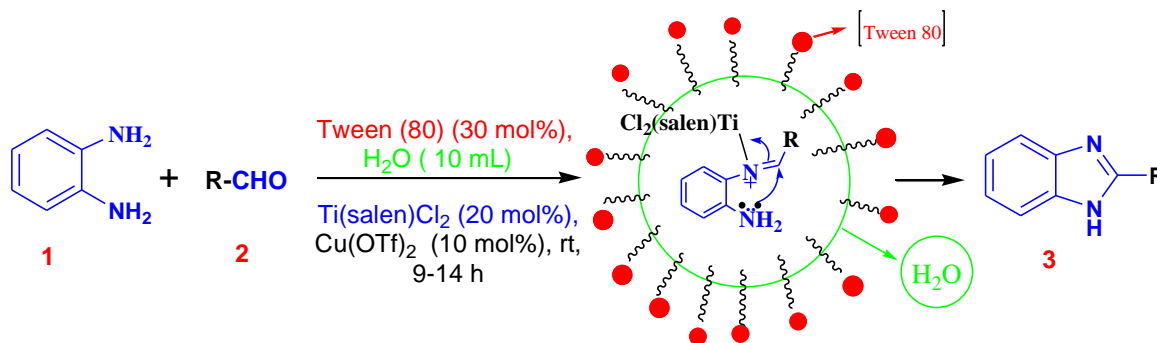
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ABSTRACT

A simple green methodology is explored to synthesized various substituted Benzimidazole derivatives by one pot process of *ortho*-phenylenediamine and variety of different aromatic aldehydes in presence of combination catalyst Ti(salen)Cl₂ and Cu(OTf)₂ at room temperature in aqueous medium. Remarkable influence of neutral phase transfer reagent Tween 80 was observed in aqueous medium. The catalyst was recycled and reused for several times with excellent yield of the product.



KEY WORDS: Phase transfer catalyst, Ti(salen)Cl₂, Cu(OTf)₂, Green methodology, Benzimidazole Derivatives.

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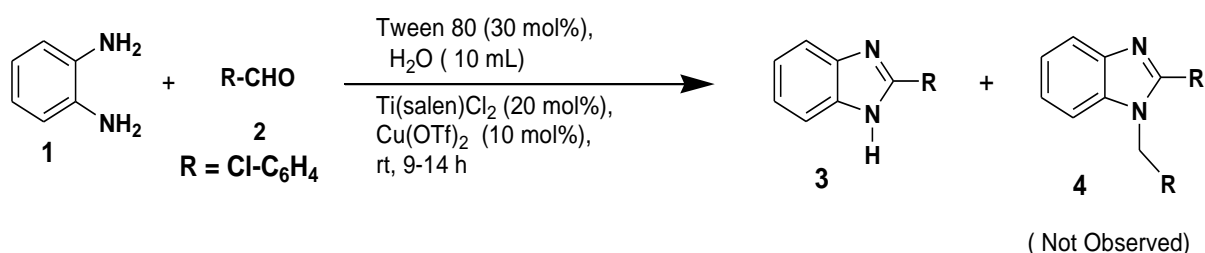
INTRODUCTION

In recent methodology organic solvents are being replaced by either water green solvent¹, Phase transfer catalyst¹, or solvent less technique². Benzimidazole and their analogues has a significant role in organic and also bioorganic chemistry.³ These compounds have a remarkable role in therapeutic function like anticancer⁴, antifungal,⁵ antimicrobial,⁶ anti-inflammatory,⁷ antihistaminic⁸ and antiviral⁹ activities. Green solvent water is used in place of toxic, carcinogenic, hazardous organic solvents and also in place of ionic liquids.¹⁰

Acid derivative such as acid chloride, orthoester, nitriles, imidates were used instead of carboxylic acid to produce 2-substituted benzimidazoles with moderate to high yield.¹¹⁻¹⁴ Most of the cases toxic and problematic by-products are obtained through laborious workup and hectic purifications process that decreases the isolated yield of the products.¹⁵⁻¹⁷ The previous reports have some drawbacks such as high reaction temperatures,^{18,19} low yields,²⁰ and consumption of high power microwave irradiation.^{21,22} So it is very much challenging to the chemist to synthesis biologically active benzimidazole from aldehyde in neutral aqueous medium in presence of mild oxidizing reagent. We examined the method of different benzimidazoles by use of Ti(salen)Cl₂ and Copper (II) triflate combination catalyst in aqueous medium with additional phase transfer reagent Tween 80. Water always acts as a eco-friendly reaction medium.²³ The aqueous organized media is hydrophobic in nature and helps to aggregate organic substances and reagents in water, which enhances the chemical transformations process and for this reason Tween 80 catalyst²⁴ is employed in the reaction medium as a phase transfer catalyst.

RESULTS AND DISCUSSIONS

To explore the synthetic applicability of neutral Tween 80 in aqueous medium towards the synthesis of a variety of heterocycles we carried out an opening examination with 4-chlorobenzaldehyde and orthophenylene diamine as a substrate and reagent (Scheme 1).



Scheme 1. Synthesis of 2-substituted-1H-benzimidazoles catalysed by Ti(salen)Cl₂ and Cu(OTf)₂ in aqueous medium containing Tween 80 phase transfer catalyst

The various reaction conditions have been examined by using *o*-phenylenediamines (**1**) with 4-chlorobenzaldehyde (**1a**, Table 2) for the synthesis of 2-(4'-chlorophenyl)-1*H*-benzimidazole (**3a**, Table 2) in water. We find that the reaction proceeded best in water medium rather than in organic solvents. Using more than 30 mol % of surfactant and also more than 20 mol% and 10 mol% of Ti(salen)Cl₂ and Cu(OTf)₂ did not increase the yield of the product (Table 1, entry 8, 9). It was also observed at the same time; in the absence of Tween 80 surfactant no reaction occurred. No conversion was observed in absence of catalyst (Table 1, entry 11). Since Ti(salen)Cl₂ and Cu(OTf)₂ are not used stoichiometric amount with respect to aldehyde so these reagents act as a catalyst in the reaction medium. A mixture of benzimidazoline and benzimidazole were observed in absence of Cu(OTf)₂ catalyst. So for complete oxidation of intermediate, Cu(OTf)₂ was essential. It was also observed that without Ti(salen)Cl₂ incomplete imine formation raised at room temperature. Thus we can say that not only surfactant or catalyst but both combinations are essential to generate better yield of the products. The best result was obtained with 30 mol% of Tween 80 surfactant, Ti(salen)Cl₂ (20mol%) and Cu(OTf)₂ (10mol%) for 1.2 mmol 4-chlorobenzaldehyde at room temperature (Table 1, entry 7).

Table 1: Optimization of the reaction condition

Entry	Reagents (mol%)	Surfactant (mol%)	Solvent (mL)	Reaction conditions	^a Yield (%) (w.r.t. starting aldehyde)	Conversion (%)
1	^f Ti(salen)Cl ₂ , ^g Cu(OTf) ₂	No	^h CH ₂ Cl ₂	rt, 14 h	45	50
2	^f Ti(salen)Cl ₂ , ^g Cu(OTf) ₂	No	^h CH ₃ CN	rt, 14 h	45	50
3	^b Ti(salen)Cl ₂ , ^f Cu(OTf) ₂	No	^h CH ₃ CN	rt, 14 h	45	50
4	^b Ti(salen)Cl ₂ , ^f Cu(OTf) ₂	No	^h H ₂ O	rt, 14 h	45	50
5	^b Ti(salen)Cl ₂ , ^f Cu(OTf) ₂	^b Tween(80)	^h CH ₂ Cl ₂	rt, 14 h	55	65
6	^b Ti(salen)Cl ₂ , ^f Cu(OTf) ₂	^b Tween(80)	^h H ₂ O	rt, 14 h	75	80
7	^b Ti(salen)Cl ₂ , ^f Cu(OTf) ₂	^c Tween(80)	^h H ₂ O	rt, 12 h	85	100
8	^b Ti(salen)Cl ₂ , ^f Cu(OTf) ₂	^e Tween(80)	^h H ₂ O	rt, 12 h	85	100
9	^c Ti(salen)Cl ₂ , ^b Cu(OTf) ₂	^d Tween(80)	^h H ₂ O	rt, 12 h	85	100
10	^b Ti(salen)Cl ₂ , ^f Cu(OTf) ₂	^c Tween(80)	ⁱ H ₂ O-THF	rt, 14 h	70	80
11	No	^c Tween(80)	^h H ₂ O	rt, 14 h	-	No conversion

^aIsolated yield of the pure compound **3a**. amount of b = (~20 mol%), amount of c = (~30 mol%), amount of d = (~40 mol%), amount of e = (~40 mol%), amount of f = (~10 mol%), amount of g = (~05 mol%), amount of h = (~5 mL), amount of i = (~5 mL H₂O and ~5 mL THF)

With this result, I have studied the catalytic system with *o*-aromaticdiamines (1) and aromatic aldehyde (2) in Tween(80) water media forming the desired substituted benzimidazole derivatives and the results were depicted in Table 2. Electron donating and withdrawing both groups attached to aromatic aldehyde were investigated. Surprisingly I have found that all of the substrates are reacted smoothly under the reaction conditions with excellent yields (74%–85%) (Table 2).

EXPERIMENTAL

Aldehydes, *ortho*-phenylenediamine were purchased from Spectrochem, Pvt. Ltd. and Cu(OTf)₂ and Tween 80 were purchased from Sigma Aldrich. Ti(salen)Cl₂ was prepared by using TiCl₄ from literature study.³¹ ¹H and ¹³C NMR spectra were recorded on Bruker 300 MHz spectrometer using tetramethylsilane (TMS) as an internal standard and CDCl₃ and DMSO-*d*₆ are used as solvents. IR spectra were recorded on a Perkin-Elmerspectrometer as KBr disc. Melting points were measured with a Gallen Kamp electrothermal apparatus.

Procedure of 2-substituted-1*H*-benzimidazoles: A mixture of substituted benzaldehyde (1.2 mmol) with *ortho*-phenylenediamine (1.5 mmol), Ti(Salen)Cl₂ (84.0 mg, 0.2 mmol), Cu(OTf)₂ (42.0 mg, 0.10 mmol), H₂O (5 mL), and Tween 80 (126 mg, 0.30 mmol) were mixed in a rb flask and it was stirred at rt. Reaction monitored by TLC time to time. The reaction completed within 9-14 hrs. The mixture was diluted with ethyl acetate and filtered. Filtrate was concentrated and it was reused for further reaction. Product was directly crystallized from hot ethanol. Known compounds were characterized by comparing their physical and spectral data with the literature value of reported compounds.

Selected Characterization Data for Synthesized Compounds:

2-(4-Chlorophenyl)-1*H*-benzimidazole (3a):

Yield: 85% (582 mg, 0.85 mmol).

Physical appearance: Yellow solid.

Melting point: 302 °C [Lit.²⁶ 303-304 °C].

IR (neat, cm⁻¹): 961, 1011, 1112, 1273, 1318, 1429, 1590, 2782, 3052.

¹H NMR (300 MHz, CDCl₃): □ 7.17-7.21 (2H, m), 7.45 (2H, d, *J* = 8.4 Hz), 7.56-7.62 (2H, m), 8.14 (2H, d, *J* = 7.8 Hz).

¹³C NMR (75 MHz, CDCl₃): □ □ □ 121.9, 127.6, 128.1, 134.8, 150.2

Analytical calculated for C₁₃H₉ClN₂(%); C: 68.28; H: 3.97; N: 12.25 Found; C: 68.30; H: 3.95; N: 12.30%.

Table 2: Synthesis of 2-substituted-1H-benzimidazoles

Entry	<i>o</i> -phenylenediamine (1)	ArCHO (2)	Benzimidazole (3)	Time (h)	Yield (%)	Ref
1.		4-ClC ₆ H ₄ CHO 2a		12	85	25
2.		2-MeC ₆ H ₄ CHO 2b		11	75	26
3.		3-MeC ₆ H ₄ CHO 2c		12	75	26
4.		4-MeC ₆ H ₄ CHO 2d		13	74	27
5.		2-OMeC ₆ H ₄ CHO 2e		12	80	28
6.		4-OMeC ₆ H ₄ CHO 2f		14	78	29
7.		4-CNC ₆ H ₄ CHO 2g		12	85	26
8.		2-CNC ₆ H ₄ CHO 2h		11	82	26
9.		4-NO ₂ C ₆ H ₄ CHO 2i		14	75	30
10.		C ₆ H ₅ CHO 2j		10	75	29
11.		2-ClC ₆ H ₄ CHO 2k		09	85	26
12.		3-ClC ₆ H ₄ CHO 2l		10	82	25
13.		4-BrC ₆ H ₄ CHO 2m		12	85	29

2-(4-Nitrophenyl)-1H-benzimidazole (3i):

Yield: 78% (186 mg, 0.78 mmol).

Physical appearance: Orange solid.

Melting point: 311 °C. [Lit.³⁰ 308-310 °C].

FT-IR (KBr, cm⁻¹): 1100, 1335, 1433, 1513, 1597, 1704, 1933, 2375, 2750, 2854, 2917, 3437.

¹H NMR (300 MHz, DMSO-d₆): δ 7.41(2H, s), 7.54 (1H, d, J = 6.3 Hz), 7.69 (1H, d, J = 6.6 Hz), 8.36 (4H, s), 13.24 (1H, s).

¹³C NMR (75 MHz, CDCl₃): δ 111.8, 119.5, 122.3, 123.6, 124.0, 124.3, 127.4.

CONCLUSION

New and efficient metal catalyzed green methodology for the synthesis of a wide variety of 2-substituted-1H-benzimidazoles using easily available, non toxic and non hazardous combo catalyst in aqueous medium containing PTC is developed. Various 2-substituted-1H-benzimidazoles is prepared with aromatic aldehyde and *o*-phenylenediamine. Green solvent, room temperature, easy purification of wide variety of the isolated products are the main advantages of the process.

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