A Simple and Efficient Procedure for the Synthesis of Benzimidazoles using Trichloroisocyanuric Acid (TCCA) as the Oxidant

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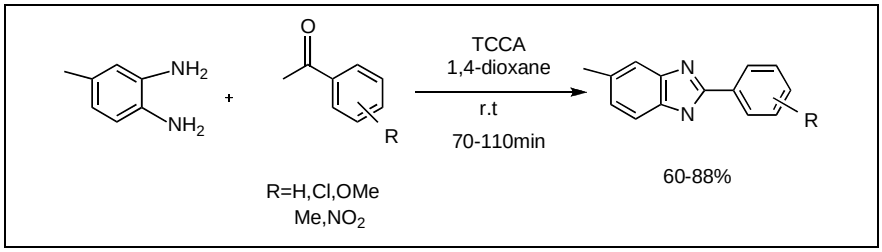

A Direct one step synthesis of various benzimidazoles from 3,4-diaminotoluene and benzaldehydes is described using TCCA as the oxidant. The salient features of this method include simple procedure, mild condition, no waste products, easy separation, low reaction times and generality.

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INTRODUCTION

Benzimidazoles are very useful intermediates for the development of molecules of pharmaceutical and biological interest. Substituted benzimidazoles have found therapeutic applications as antiulcer, antihypertensive, antiviral, antifungal, anticancer, and antihistamine drugs [1-3].

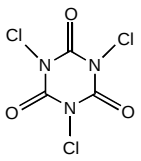
Two general methods for the synthesis of benzimidazoles are reported. One is the coupling of *o*-phenylendiamines and a carboxylic acid or its derivatives under dehydrating conditions [4,5], or the use of microwave irradiation [6]. The other involves a two-step procedure that includes the oxidation and cyclo-dehydrogeneration of aniline Schiff' bases, which are often generated *in situ* from the condensation of phenylendiamines and aldehydes. Various oxidative reagents such as nitrobenzene, 1,4-benzoquinone [7], DDQ [8], tetracyanoethylene [9], benzofuroxan [10], MnO_2 [11], $Pb(OAc)_4$ [12], Oxone® [13], $NaHSO_3$ [14], $Na_2S_2O_5$ [15], air [16], (bromodimethyl) sulfonium bromide [17], $In(OTf)_3$ [18], $Yb(OTf)_3$ [19], and Polyaniline-sulfate salt [20], are also used. Many of these methods produce toxic or environmentally problematic by-products; some of them have long reaction times and low yields. For example, reference [16] uses dioxane in reflux for up to 20 h. We have carried out the reaction in dioxane at RT with reaction times of up to 110 minutes. Several side reactions, tedious workup, use of high temperature and atmosphere sensitive reagents are amongst other limitations.

RESULTS AND DISCUSSION

To the best of our knowledge, the synthesis of benzimidazoles using TCCA has never been explored.

In the context of developing an environmentally friendly preparative method for these compounds, we decided to look at the use of trichloroisocyanuric acid (TCCA) as an oxidant for the synthesis of benzimidazoles. Trichloroisocyanuric acid (TCCA, Scheme 1) is a safe, inexpensive, and efficient oxidant used in oxidation of organic compounds [21]. It is highly soluble in organic solvents, which makes it an ideal oxidant for organic syntheses. Cyanuric acid, which is the waste product of this reaction, is also a non-hazardous substance [22].

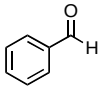
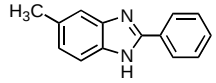
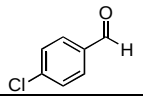
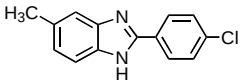
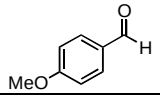
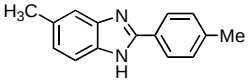
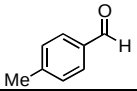
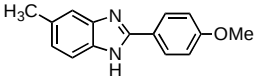
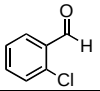
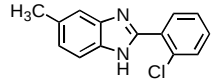
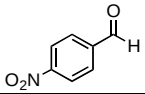
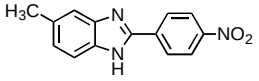
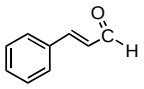
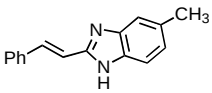
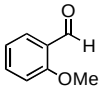
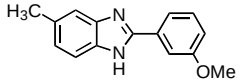
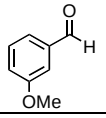
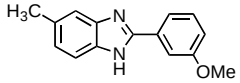
Scheme 1



We have found that benzimidazoles can be synthesized efficiently by treatment of 3,4-diaminotoluene with aldehydes using commercially available TCCA (33% mol) at room temperature (Scheme 2). Several aldehydes underwent the above conversion to form a series of benzimidazoles (Table 1). Aromatic aldehydes containing both electron-donating and electron-withdrawing groups worked well. The reaction conditions were mild. The products were formed in high yields (60-90%).

Table 1

1 Synthesis of benzimidazoles using TCCA.

Entry	Aldehyde	Product [a]	Time (min)	Yield (%) [c]	M.P.°C	M.P.°C [lit.]
1			100	70	[b]	-
2			90	68	189-190	190 [23]
3			85	88	175-177	177 [23]
4			95	75	[b]	-
5			110	80	[b]	-
6			70	60	[b]	-
7			90	66	[b]	-
8			105	68	[b]	-
9			90	80	[b]	-

[a] Products were confirmed by 1H NMR. [b]Decomposed above 260°C. [c] Isolated yields.

To minimize the formation of by-product(s) and to streamline the isolation of desired product, equal molar amounts of benzaldehyde and 3,4-diaminotoluene were dissolved in various commonly used organic solvents (Table 2).

Table 2

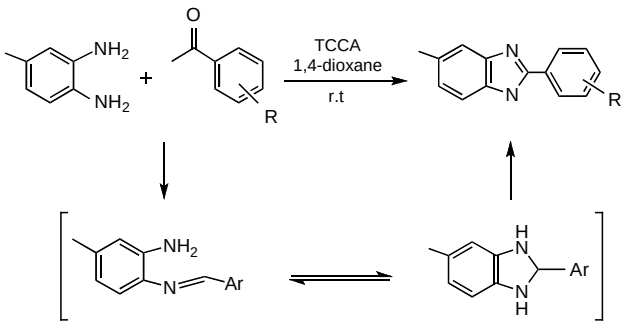
Reaction of benzaldehyde and 3,4-diaminotoluene under different conditions at r. t.

Entry	Solvent	TCCA(mmol)	Yield(%) [a]
1	CH_2Cl_2	0.33	Nr [b]
2	THF	0.33	Nr
3	n-Hexane	0.33	Trace
4	CH_3CN	0.33	40
5	EtOH	0.33	60
6	1,4-Dioxane	0.33	80
7	1,4-Dioxane	0.22	60
8	1,4-Dioxane	0.11	Trace
9	1,4-Dioxane	0.44	70

[a] Isolated yield. [b] No reaction.

1,4-dioxane stood out as the solvent of choice, with fast conversion, high yields and easy separation of products. We believe that the formation of benzimidazoles under these conditions goes through the known intermediate Schiff bases, which exist in equilibrium with the cyclic hydrobenzimidazoles. These are later oxidized to benzimidazoles by TCCA. (Scheme II) [7-16].

Scheme 2



Synthesis of benzimidazoles

In summary, simple work-up procedure, mild reaction condition and high yields make our methodology a significant contribution to the existing processes in the field of synthesis of benzimidazole derivatives.

EXPERIMENTAL

Chemical were purchased from the Fluka, Merck and Aldrich chemical companies. Melting points were determined an Electro thermal 9100, and are not corrected. Thin layer chromatography (TLC), on commercial aluminum-backed plates of silica gel 60 PF254, was used to monitor the progress of the reactions. Yields as reported refer to isolated pure products. ^{1}H NMR spectra were recorded on a Bruker Avance-300 MHz spectrometer with 7–10 m*M* solutions in CD_3OD in the presence of tetramethylsilane as internal standard. IR spectra were recorded using a Perkin-Elmer 843 spectrometer with KBr plates. The products characterized by their spectral data (IR, ^{1}H NMR).

General procedure for synthesis of benzimidazoles. Aldehydes (1 mmol) and 3,4-diaminotouloene (1 mmol) were placed in a round bottomed flask. 1,4-Dioxane (3 mL) as the solvent was added and the mixture was stirred magnetically at room temperature. After complete consumption of diamine (the progress of reaction monitored by TLC), TCCA (0.08 g, 0.33 mmol) dissolved in acetonitrile and was added drop wise over 10 minutes. Reaction mixture was stirred at room temperature for the appropriate time. When the reaction was completed as indicated by TLC, the reaction products were filtered to get crude products. The product was pure enough (single spot on TLC) and was subjected to further purification by recrystallization with ethanol to give the corresponding compounds.

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