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P-TOLUENESULFONIC ACID (*P*-TSA) CATALYZED EFFICIENT SYNTHESIS OF BENZIMIDAZOLES AND IMIDAZOLINES UNDER THERMAL CONDITION

Amreen Khanum and Mohamed Afzal Pasha*

Department of Studies in Chemistry, Jnanabharathi Campus, Bangalore University, Bangaluru-560056, India.

***Corresponding Author: Mohamed Afzal Pasha**

Department of Studies in Chemistry, Jnanabharathi Campus, Bangalore University, Bangaluru-560056, India.

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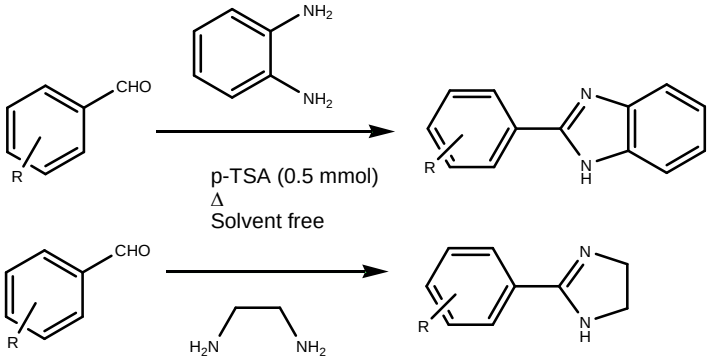
ABSTRACT

Synthesis of some important and functionalized benzimidazoles and imidazolines from aromatic aldehydes and *o*-phenylenediamine or ethylenediamine using catalytic *p*-TSA under neat thermal condition is reported. The method is simple, efficient and the products are obtained in excellent yield in very short durations.

KEYWORDS: Benzimidazoles; imidazolines; araldehydes; *p*-TSA; thermal condition.



R= H,CH_3, OMe, NO_2, $N(CH_3)_2$, Cl, F

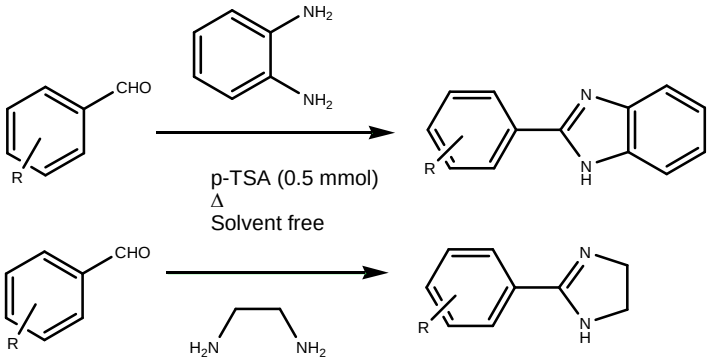
1. INTRODUCTION

Synthesis of substituted benzimidazole and imidazoline units arises because they are found in many pharmaceutical products and display a broad spectrum of biological activities including anti-ulcer, anti-tumor and anti-viral activity.[1] Benzimidazole derivatives are shown to be active against several viruses such as HIV and human cytomegalovirus (HCMV),[2] herpes (HSV-1),[3] RNA,[4] influenza virus.[5] In the light of the affinity which they display towards a variety of enzymes and protein receptors; medicinal and pharmaceutical chemists would certainly qualify them as 'privileged sub-structures' for the drug design.[6] In organic synthesis, imidazole derivatives are also used as synthetic intermediates,[7] chiral auxiliaries,[8] chiral catalysts[9] and ligands for asymmetric catalysis.[10] The *bis*-benzimidazole class of fluorescent dyes, such as Hoechst 33258 {chemical name: 2-(4-hydroxyphenyl)-5-[5-(4-methyl-1-piperazinyl)-1*H*-benzimidazol-2-yl]-1*H*-benzimidazole} are well established in molecular genetics and cytofluorimetry studies.[11] Owing to the fact that, such type of compounds bind to selected DNA subsequences with high affinity and an accompanying large enhancement of the observed fluorescence quantum yield,[12] synthesis of benzimidazole and imidazoline derivatives has gained acceptance and popularity among the synthetic chemist community. Thus, the preparation of this type of molecules is of much importance; consequently, a few methods which have been reported are either direct or indirect methods, such as: the conversion of esters using an aluminium reagent,[13] the reaction between *N*-ethoxycarbonylthioamides with 1,2-diamines,[14] and the reaction of aldehydes with 1,2-diamines followed by reaction with *N*-halosuccinimides (halogen = -Cl, -Br, -I).[15] Methods have been developed, where azalactones,[16] 2-aryl-1,1-dibromoethanes,[17] nitriles[18] and amino amides[19] are used as starting materials for their synthesis. The preparation of benzimidazole derivatives from carboxylic acids and 1,2-aminophenol using PS-PPh_3/CCl_3CN,[20] oxone,[21] by the reduction of *N*-2-nitrophenylimidate using $(NH_4)_2SO_4$-Mg/MeOH,[22] by the condensation of

o-phenylenediamine with fatty acids in the presence of *p*-toluenesulfonic acid[23a] and synthesis of 2-substituted benzimidazole from OPDA and an organic acid or urea using polyphosphoric acid (PPA)[23b] or by the reaction of alkylcyanides with diamines in CS_2 under microwave irradiation[24] are also known. Recently, condensation of diamines and arylaldehyde in the presence of $KHSO_4$,[25] $I_2/KI/K_2CO_3/H_2O$,[26] iodine/potassium carbonate[27], pyridinium hydrobromide perbromide in water,[28] NBS in CH_2Cl_2 or TBME,[29] *tert*-butyl hypochlorite,[30] CAN,[31] hydrogen peroxide/sodium iodide/anhydrous magnesium sulfate,[32] $K_4[Fe(CN)_6]$,[33] molecular iodine/potassium carbonate under ultrasonication,[34] and N-iodosaccharin[35] is also documented in the literature for the synthesis of imidazolines and/or banzimidazoles.

2. RESULTS AND DISCUSSION

In continuation of our investigation on the use of *p*-TSA for chemical transformations,[36] we have been able to use *p*-TSA as a catalyst for the synthesis of benzimidazoles and imidazolines (**3**) under thermal condition from arylaldehyde (**1**), OPDA or ethylenediamine (**2**) by heating for about 5–10 min as shown in the **Scheme 1**.

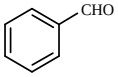
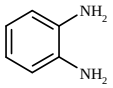
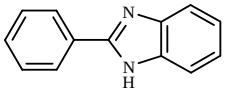
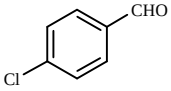
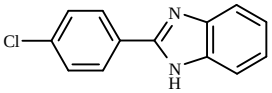
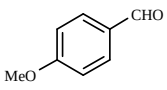
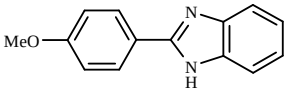
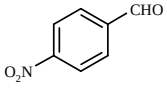
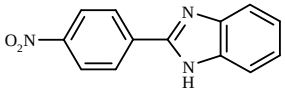


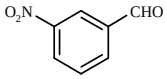
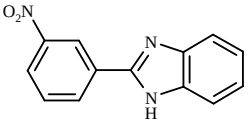
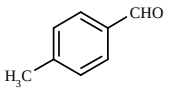
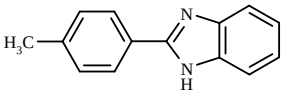
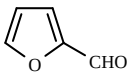
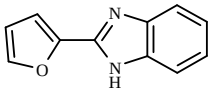
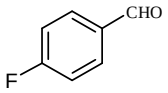
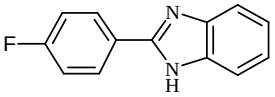
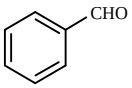
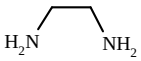
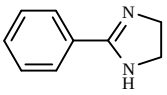
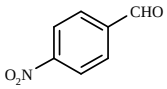
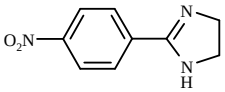
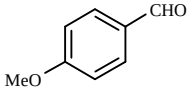
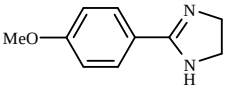
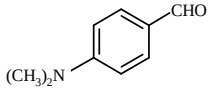
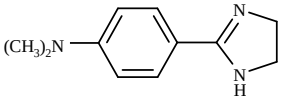
R= H,CH_3, OMe, NO_2, $N(CH_3)_2$, Cl, F

Scheme 1: Synthesis of benzimidazoles and imidazolines.

To demonstrate the protocol, we selected *p*-anisaldehyde (1 mmol) as the model substrate and treated it with OPDA (1 mmol) in the presence of *p*-TSA (0.5 mmol). The reactants were heated on a hot-plate for 8 min. to get the desired benzimidazole in 85% yield. The method was extended to the preparation of a variety of benzimidazoles and imidazolines and the results of this study are presented in the **Table 1**; and several interesting features of the preparation of benzimidazoles and imidazolines are apparent from **Table 1**; more importantly, the substituents such as -OCH_3, -Cl, -F, Me_2N- and -NO_2 bear any noticeable effect on either the rate of the reaction or yield of the products under the present reaction condition.

Table 1: Synthesis of benzimidazoles and imidazolines from aldehydes and diamines in the presence of catalytic *p*-TSA under thermal condition.

Entry	Aldehyde	Diamine	Product[a]	Time (min)	Yield[b] (%)	Mp (°C)[c]
a				5	90	294 (290–93)[24]
b		,,		8	88	290 (288–91)[25]
c		,,		8	85	225–326(223–26)[25]
d		,,		10	82	309–310(308–10)[24]

e		,,		10	85	205 (204–06)[25]
f		,,		8	86	264–265(261–63)[24]
g		,,		8	70	284 (284–86)[25]
h		,,		10	94	241[†]
i				6	92	101–102 (101)[25]
j		,,		6	85	230–232 (231)[25]
k		,,		7	94	138–139 (140)[25]
l		,,		6	86	259–261(258–60)[25]

[a]Products **a-g** and **i-l** are known, and the new compound **h** is characterized by IR, NMR, GC-Mass Spectral and CHN analysis and spectra of all the other products are compared with the authentic samples. [†]Novel compound.

The data presented in the **Table 1** also clearly indicates the scope of the reaction with respect to various substituted aldehydes. Comparison of existing catalysts and different reported methodologies is shown in the **Table 2**.

Table 2: Comparison of the reported and present method for the condensation of OPDA with RCHO/RCOOH in the presence of different catalysts.

Entry	Reactant	Catalyst	Time	Temp (ºC)	Yield(%)[b]
1	OPDA + RCHO	Oxone/DMF[21]	0.5–24 h	r.t	59–90
2	OPDA + RCHO	Fe(III)/Fe(II)/DMF[11]	1h	90–120	68–94
3	OPDA or $C_2H_8N_2$ + RCHO	I_2/KI/K_2CO_3[25]	30–50 min	90	75–90
4	OPDA + RCHO	$KHSO_4$/DMF[24]	10–45 min	80	58–87
5	OPDA + RCOOH	PS-PPH_3/CCl_3CN[20]	15 min	MW	76–85
6	OPDA + RCOOH	PPA[23b]	8 min	MW	39–88
7	**OPDA/Diamine + RCHO**	***p*-TSA**[a]	**5–10 min**	**Heat (Neat)**	**70–94**

[a]Present method: Reaction condition: *p*-Anisaldehyde (1 mmol), OPDA (1 mmol)/ethylenediamine (1.5 mmol) and *p*-TSA (0.5 mmol) were heated on a hot plate to afford the products **c/k**. [b]Isolated yield.

When compared with the other reported methods, we have found that, *p*-TSA under solvent-free condition is an efficient catalyst for the preparation of benzimidazoles and imidazolines. The reactions proceed smoothly just by heating a mixture of the substrates and catalyst on a hot plate to afford the corresponding products in high yield in a short duration.

3. Experimental

Aldehydes, diamine and *p*-TSA were all commercial products. Melting points were determined on a RAAGA melting point apparatus. IR spectra were recorded on Nicolet 400D FT-IR spectrophotometer; ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz Bruker spectrophotometers respectively. GC-MS using Shimadzu GC-MS QP 5050A spectrometer and elemental analysis was performed on Thermo Finnigan FLASH EA 1112 CHNS analyzer.

3.1 *General experimental procedure for the synthesis of imidazolines/benzimidazoles*: A mixture of OPDA (1.0 mmol) /diamine (1.5 mmol), aldehyde (1.0 mmol) and *p*-TSA (0.5 mmol) were taken in a 50 mL RB flask fitted with a water cooled condenser, heated on a hot plate at 50-70 ℃ for 25 min, the syrupy reaction mixture got solidified within a min after removing the condenser. After the completion of the reaction (monitored by TLC), the resulting suspension was washed with 1N NaOH and the solid product was filtered and washed with water and extracted with ethyl acetate (3 × 5 mL). The combined ethyl acetate extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by crystallization/column chromatography (silica gel) using hexane and ethyl acetate as an eluent.

3.2 Spectral Data of the Novel compound 2-(4´-Fluorophenyl)-2,3-dihydro-1*H*-benzimidazole (3h)

FT-IR (KBr): ν 3188, 2945, 1683 cm^{-1};
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (t, *J* = 4.0 Hz, 2H), 7.64–7.69 (m, 2H), **7.**24–7.31 (m, 2H), 7.16 (t, *J* = 8.0 Hz, 2H) ppm;
^{13}C NMR (DMSO-d_6, 100 MHz): 113.25, 113.85, 116.00, 123.48, 127.34, 127.45, 127.48, 127.50, 127.67, 139.85, 152.10, 162.01, 168.64 ppm;
MS: *m/z* = 212.7 (M^+);
Anal. calculated for $C_{13}H_9FN_2$ (212.23): C, 73.57; H, 4.27; N, 13.20; Found: C, 73.54; H, 4.31; N, 13.18.

4. CONCLUSIONS

In conclusion, we have developed a simple, efficient and high yielding method and demonstrated an efficient synthesis of benzimidazoles and imidazolines using catalytic amount of *p*-TSA under thermal condition.

5. Acknowledgement

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