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RESEARCH ARTICLE

Papain Catalyzed: Multicomponent Synthesis of Trisubstituted Imidazoles

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ABSTRACT:

A reliable synthetic method has been developed for 2, 4, 5-trisubstituted imidazole from benzil, ammonium acetate, and aromatic aldehyde by using papain a non toxic and inexpensive catalyst. The Structural features have been arrived at from their analytical data, IR, Mass, 1H NMR. The antibacterial activity of all synthesized compound has been performed by using filter paper disc method against gram positive and gram negative bacteria.We observed that 4a –compound is more active against gram +ve S. Typhi at lower concentration 4f less active against gram +ve S. Typhi and gram –ve E. Coli

Keywords: Multi component reaction, one pot synthesis, substituted imidazole, papain.

1. INTRODUCTION

Over last three decade, enzymes as practical catalyst have been exploited for organic synthesis for their simple processing requirement and mild reaction condition[1-2].Therefore, the development of environmentally benign and cost –efficient catalyst for condensation aldehyde, benzil, ammonium acetate reaction.

Multi-substituted imidazole have received significant attention as a result of their diverse medical use[3].Compounds with an imidazole moiety have biological activity such as therapeutic agent t[4] .it also reduces the platelet in animal and human species. Triaryl imidazole are used in photography as photosensitive compound.[5]In addition they are of interest because of their herbicidal [6] Analgesis[7]fungicididal [8] and antithrombotic activitity[9].

The synthesis of tri substituted imidazole by the condensation of aldehyde, bezil, ammonium acetate in refluxing acetic acid for few hours is a well-established procedure. However, this method suffers so many drawbacks like low yield, longer time .Recently some methods for synthesis of substituted imidazole have been reported. some of the methods have resorted to harsh condition (for example. the formamide synthesis, which requires excess reagent ,H_2SO_4 as a condensing agent [10-11]various synthetic protocol have been developed for synthesis of imidazole such a scope rearrangement, diketone, aldehyde ,amine and ammonium acetate in phosphoric acid and acetic acid ,catalyst in acetic acid as well as H_2SO_4 ,silica gel Al_2o_3 ,$Zrcl_4$ $Nicl_2.6H_20$[12-13]

In continuation of our ongoing research here in we wish to report a simple ,economic and efficient method for synthesis of 2,4,5,tri substituted imidazole from bezil ,ammonium acetate ,and aromatic aldehyde using papain a non toxic and inexpensive catalyst. Also showen the antibacterial activity of these synthesized compound against gram +ve and gram-ve bacteria.

2. RESULTS AND DISCUSSION

The synthesis of tri substituted imidazole by condensation of,benzil ,ammonium acetate and amine in refluxing acetic acid for few hour is well known procedure.But in this method have some draw backs like longer time ,drastic reaction condition. An improved methodology for the synthesis of 2,4,5-tri substituted imidazole using papain catalyst these draw backs minimized.

We have made this reaction environmentally friendly, reaction is carried out in water solvent of and various

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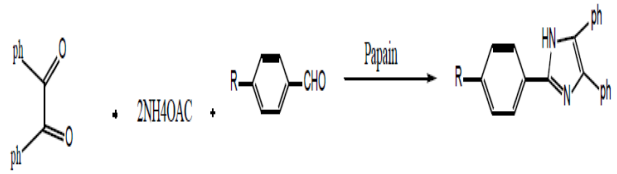
mol% papain, mild reaction conditions operational simplicity and excellent yield make the catalyst more versatile. We also used other solvents for this condensation reaction but results were not satisfactory. It was obvious that papain was the most effective catalyst among the tested enzymes. Therefore, we chose papain as the catalyst for this condensation.

Effect of solvents

We investigated the effect of different solvents on reaction .We found that the catalytic activity of papain was remarkable influenced by solvents. The reaction in water at room temperature gave best yield of 80% . The other tested solvents ethanol, methanol, THF, DCM, gave the low yield. Based on the result, water was chosen as the optimum solvent for the papain catalysed condensation.

Scheme 1



1 2 3a-3h 4a-4h

Entry	Aldehyde	Solvent	Yield%
a	Benzaldehyde	Ethanol	54
		Methanol	50
		THF	49
		DCM	45
		Water	80

Table 1: Catalytic activities in different Solvents

	Aldehyde	Mol.Formula	Yield%	Mp/°C
a	Benzaldehyde	$C_{12}H_{16}N_2$	80	273
b	4-methoxy Benzaldehyde	$C_{22}H_{18}N_2O$	75	321
c	4-hydroxy Benzaldehyde	$C_{21}H_{16}N_2O$	82	256
d	4- chloro Benzaldehyde	$C_{27}H_{19}N_2Cl$	75	160
e	4-(dimethylamino) Benzaldehyde	$C_{23}H_{21}N_3$	75	257
f	Furan -2-carbaldehyde	$C_{19}H_{14}O_2N_2$	80	200
g	3,4,5 tri methoxy Benzaldehyde	$C_{24}H_{13}O_3N_2$	80	257
h	4- Nitobenzaldehyde	$C_{21}H_{15}N_3O_2$	75	234

Table 2 Synthesis of Trisubstituted Imidazole Using papain catalyst in water

3. EXPERIMENTAL SECTION

All reagents were purchased from Merck and Aldrich and papain catalyst were prepared from latex of papaya. Treatment of latex of papaya with sodium meta-bisulphite at 50-55°C and dry. Spectra IR and H ^{1}NMR and ^{13}C NMR Spectra were recorded on SHIMADZU FT-IR-8400S and Bruker spectrophotometers respectively. Progress of reaction was checked on TLC and melting points were determined in capillary tubes.

General procedure for synthesis of 2, 4, 5-triaryl imidazole. (4a-4h)A mixture of benzil 1(10mmol)ammonium acetate 2(20mmol)aromatic aldehyde 3a-3h(20mmol)and papain (150mg)stirred at room temperature in water for mentioned time in table 1and poured in cold water. Washed with excess of water and dried re-crystallized by using ethanol. Melting point were matched with literature melting point results a pure compound of 2,4,5-triarylimidazole(4a-4h) scheme -1.all synthesized compound were characterized with Spectra IR and H ^{1}NMR and ^{13}C NMR Spectra.

Antibacterial activity.

Nutrient agar of the requisite composition viz. peptone (2.5g) beef extract (0.5g) agar –agar (10g) and distilled water (500ml) was prepared and pH of the medium was adjusted to 6 .6 for preparation of media. All the above ingredients (except-agar-agar) were weighed and dissolved in distilled water (250ml) by application of gentle heating. After dissolving the ingredients completely more distilled water and weighed quantity of agar-agar were added. Then it was filtered through cotton to obtain a clear solution.

The mixture was autoclaved for 30 min at a pressure of 1-5 kg/cm^2. All the glass apparatus were cleaned with chromic acid and then sterilized by keeping in oven and cooled to 37±1°C and homogeneous suspension was prepared by transferring aseptically, a loop full of all the corresponding microorganism from fresh sub culture into agar medium followed by vigorous shaking 20 ml of this medium was poured into each sterilized petridish under aseptic condition and allowed to set.

Test solution and streptomycin having con. 40mg/ml and 20mg/ml were prepared in DMF. The paper disc (6mm) was immersed in seeded agar containing petridishs. The solution was dropped into the filter paper disc. The inhibition zone for each test solution was measured in mm. The synthesized compound were tested for antibacterial activity against S.Typhi E.coli Using streptomycine as a standard drug.

Spectroscopic Data of the Synthesized Compounds: (4a-4h)2,4,5 –triphenyl 1H-Imidazole

M.P.274°C 1HNMR (DMSO-d6) δ=12.32 (s ,1H), 7.21-8.10 (M,15H) ppm ^{13}C NMR(DMSO)

δ 123.2, 126.7, 128.2, 129.0, 135.6ppm

Entry	Concetration (mg/ml)	Zone of Inhibition in mm* Gram+ ve *S.Typhi*	Gram -ve *E.coli*
4a	20	16	14
	40	14	12
4b	20	10	13
	40	14	14
4c	20	13	14
	40	12	14
4d	20	14	15
	40	15	11
4e	20	12	10
	40	11	14
4f	20	10	8
	40	12	13
4g	20	14	13
	40	11	10
4h	20	10	12
	40	12	8
Streptomycin	20	18	17
	40	20	22

*Average of three determinations.

Table 3: Antibactirial acivity of tri substituted Imidazole 4a-4h

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Conflict of Interest: None Declared

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