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Synthesis And Antibacterial Activity Of 1-H-3-Substituted-4,5-(Disubstituted Phenyl)-2-Imidazolone

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ABSTRACT

2-imidazolones are well known for bactericidal as well as insecticidal activity. Though there are several methods for the synthesis of 2-imidazolones, most of them required longer reflux time of 8 to 10 hours. Hence the proposed work was undertaken to workout simple methodology for the synthesis of 2-imidazolones and to improve the yield of the products, by employing Zeolite as a catalyst. The work presented here describes the synthesis of some substituted 2-imidazolones obtained from substituted benzoins and urea in CH_3COOH as a solvent in presence of Zeolite as a catalyst. Substituted benzoins in turn were obtained from aromatic aldehydes by their condensation in presence of aqueous NaCN. The synthesized compounds were characterised on the basis of chemical properties, elemental and spectral analysis. Further these compounds were screened for antibacterial activity against the test organisms *E.coli, S.typhi, P.vulgaris, B.subtilis, S.aureus and S.pneumoniae.*60% of the total samples tested showed antibacterial activity. The compounds containing –N $(CH_3)_2$ $–OCH_3$, -OH as a substituents showed antibacterial activity against maximum number of organisms.

Keywords: Substituted benzoins, Urea, Methyl urea, Phenyl urea, Zeolite catalyst, 2-imidazolones, antibacterial activity.

INTRODUCTION

Imidazolones are believed to be associated with several pharmacological activities. Many natural products are believed to contain imidazolones. The leucetta and oroidin families of alkaloids [1] have been identified which contain either 2-aminoimidazole or 2-imidazolone moiety[2-3]. Jie-Fei Cheng et al.[4] carried out a traceless solid phase synthesis of 2-imidazolones. Polymer-bound glycerol resin was reacted with bromo acetaldehyde diethyl acetal to give the cyclic acetal bromide on the solid support. Tomokazu Katahira et al.[5] studied stereo selective intermolecular radical addition of polyhaloacyl pendant groups to the 1,3-dihydro-2-imidazolone moiety the chiral, synthesis of threo- diamino carboxylic acids. Marie Pascale[6] synthesized several 2-imidazolone derivatives and screened their fungicidal and herbicidal activities. Xue et al[7] synthesized 2,3-Dihydro-*N*,3-bis(3,4,5-trimethoxyphenyl)-4-(substitutedphenyl)-2-oxo-imidazole-1-carboxamides and 1-acetyl-1,3-dihydro-3-(3,4,5trimethoxyphenyl)-4-(substitutedphenyl)-2*H*-imidazol-2-ones and reported their antitumor activities. Glass D et al[8] reported 4-(4-Guanidinobenzoyl)-2-imidazolones and related compounds having phosphodiesterase inhibitors and novel cardio tonics with combined histamine H_2 receptor agonist and PDE 111 inhibitor activity. Butler and Hussain[9] carried out synthesis of 2- imidazolones by the reaction of benzoins or aliphatic acyloins with urea and

methyl urea. Sang-Hyeup Lee and coworkers[10] carried out synthesis of 2-imidazolones by the reaction of substituted urea with 3-hydroxy butanone or 3-iminopentane 2,4-dione in solution or in solid phase. From the review of literature, it was observed that most of the methods of synthesis of 2-imidazolones required longer reflux time of 8-10 hours and the yield of the products was also quite low. Hence, in the context of the above observations, the proposed work was undertaken to reduce the reflux time and to improve the yield of the products by employing Zeolite as a catalyst.Futher in order to know antibacterial activity these compounds, they were screened for antibacterial test against test organisms *E.coli, S.typhi, P.vulgaris, B.subtilis, S.aureus and S.pneumoniae* and their zones of inhibition(mm) were determined.

EXPERIMENTAL

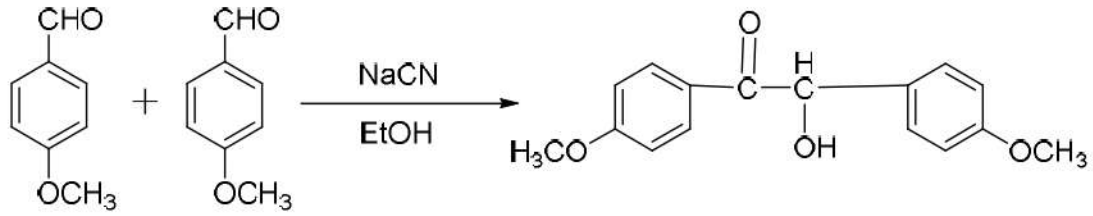
In this work, three substituted benzoins were prepared by the self condensation of 4-dimethyl aminobenzaldehyde, 4-methoxybenzaldehyde and 2-hydroxybenzaldehyde respectively, in presence of aqueous NaCN in ethanolic medium. In the second step, each of above mentioned benzoins was reacted with methyl urea, urea and phenyl urea respectively in CH_3COOH in presence of Zeolite as a catalyst to form 1-H,3-methyl-4-(4-substituted phenyl)-5-(4-substituted phenyl)-2-imidazolones and their methyl and phenyl derivatives respectively. All the synthesized compounds were characterized on the basis of chemical properties, elemental and spectral analysis.

Scheme-1 : Preparation of 4, 4'-dimethoxybenzoin.

Method: In a round bottom flask, took 13.6 gms (0.1 mol) of anisaldehyde, added to it about 50 ml of ethyl alcohol. The mixture was shaken well. To this mixture added 4.9 gms aq. solution of sodium cyanide (0.1 mol). The reaction mixture was refluxed for 30-40 minutes. Cooled reaction mixture and poured it to ice cold water, obtained solid yellow product. Recrystallised it from water-ethanol mixture.

Yield: 65% Melting point: 113°C

Reaction:



(1a)

IR (KBr,cm-[1]) : 3427 (O–H Str) 3066 (Ar,C–H str) 2920 (Aliph, C–H) 1653 (C=O str) 1507 (Ar, C=C str) 1310 (C–O str).

[1]H-NMR (DMSO) (δ): 7.86-7.85 (d,4H,Ar–H); 7.13-7.12 (d,4H,Ar–H); 3.87 (s,1H, CH–OH); 3.37 (s,6H,–OCH_3); 2.50 (s,1H, Aliph, C–H);

Elemental Analysis for $C_{16}H_{16}O_4$ (272.30)

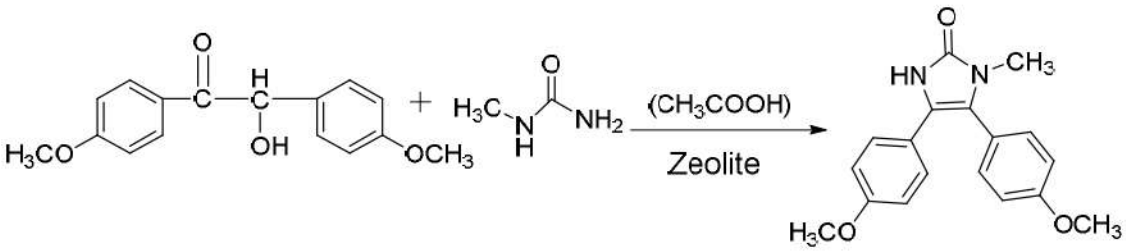
Element (%)	C	H
Calculated	70.58	5.92
Found	70.55	5.90

Scheme 2 : Synthesis of 1-H-3-methyl-4(4-methoxyphenyl)-5-(4-methoxyphenyl)-2-imidazolone

Method: To 4,4'-dimethoxybenzoin (2.72 gms) (0.01 mol) added glacial acetic acid (20ml). The mixture was warmed slightly to dissolve the solute. To this solution, added methyl urea 0.74 gm (0.01mol), followed by zeolite (1gm) as a catalyst. The reaction mixture was refluxed for three hours. Allowed it to cool and poured it to ice cold water. The solid yellow product formed was filtered, washed 2, 3 times with cold water and recrystallized from water-ethanol mixture.

Yield: 62% Melting point: 180°C

Reaction:



(2d)

IR (KBr,cm-[1]) 3650 (N–H str) 3073 (Ar, C–H str) 2922 (Aliph, C–H str) 1678 (C=O str) 1600 (C=N str) 1507 (Ar, C=C str) 1293 (C–N str) 1245 (C–O str)

[1]H-NMR (DMSO) (δ): 7.57 (s,1H,N–H) 7.26-7.22 (m,4H,Ar–H) 7.17-7.05 (m,4H,Ar–H) 3.37 (s,6H, $–OCH_3$) 2.52 (s,3H, $–CH_3$)

Elemental Analysis for $C_{18}H_{18}N_2O_3$ (310.35)

Element (%)	C	H	N
Calculated	69.66	5.85	9.03
Found	69.62	5.82	9.00

Results and Discussion

We synthesized variedly substituted -2-imidzolones by the condensation of each of three substituted benzoins with urea, methyl urea and phenyl urea respectively. The target compounds gave positive tests for Nitrogen as well as for C=O linkage (red coloration with 1% solution of m-dinitrobenzene in ethanol) The IR spectrum showed sharp bands at 3650cm^{-1} (N-H str) and 1678 cm^{-1} (C=O str) and 1507 cm^{-1} (Ar, C=C str) similarly, in ^{1}H-NMR spectrum chemical shifts at 7.57 (s,1H,N–H);7.26-7.22 (m,4H,Ar–H);7.17-7.05 (m,4H,Ar–H);3.37(s,6H,–OCH_3);2.52(s,3H,–CH_3); with elemental analysis further confirmed the formation 2-imidazolones. The synthesized compound along with their percent yield and melting point are given in the following table 1.

Table: 1

List of synthesized compounds along with their % yield and melting point

Sr. No	Compound	Percent Yield (%)	Melting point (°C)
1	1-H-3-methyl-4-(4-dimethylaminophenyl)-5-(4-dimethylaminophenyl)-2-imidazolone (2a)	68	160
2	1,3-dihydro-4-(4-dimethylaminophenyl)-5-(4-dimethylaminophenyl)-2-imidazolone (2b)	65	165
3	1-H-3-phenyl-4-(4-dimethylaminophenyl)-5-(4-dimethylaminophenyl)-2-imidazolone (2c)	70	175
4	1-H-3-methyl-4-(4-methoxyphenyl)-5-(4-methoxyphenyl)-2-imidazolone. (2d)	62	180
5	1, 3,dihydro-4-(4-methoxyphenyl)-5-(4-methoxyphenyl)-2-imidazolone. (2e)	66	145
6	1-H-3-phenyl-4-(4-methoxyphenyl)-5-(4-methoxyphenyl)-2-imidazolone. (2f)	58	138
7	1, 3-dihydro-4-(2-hydroxyphenyl)-5-(2-hydroxyphenyl)-2-imidazolone (2g)	66	190
8	1-methyl-3-H-4-(2-hydroxyphenyl)-5-(2-hydroxyphenyl)-2-imidazolone (2h)	62	168
9	1-H-3-phenyl-4-(2-hydroxyphenyl)-5-(2-hydroxyphenyl)-2-imidazolone (2i)	63	185

ANTIBACTERIAL ACTIVITY

Method for the determination of antimicrobial activity

These newly synthesized compounds were assayed for their antimicrobial activities against some organisms, such as *E.coli (gram+ve), S.typhi (gram+ve), P.vulgaris (gram+ve), B.subtilis(gram-ve), S.aureus (gram-ve) and S.pneumoniae(gram-ve)* at a concentration of 100 µg/ml by disk diffusion method[11]. Each standardized test organism (0.1ml) was spread on the solidified sterile agar plates.

Table: 2

Antibacterial activity of compounds

Sr. No.	Compound (100 µg/ml)	Zone of inhibition (mm)					
		E. coli	*S. typhi*	*P. vulgaris*	*B. subtilis*	*S. aureus*	*S. pneumoniae*
1	1,3-dihydro-4-(4-dimethylaminophenyl)-5-(4-dimethylaminophenyl)-2-imidazolone (2a)	S (11mm)	S (15mm)	R	R	S (12mm)	S (14mm)
2	1-H-3-methyl-4-(4-dimethylaminophenyl)-5-(4-dimethylaminophenyl)-2-imidazolone (2b)	S (14mm)	R	S (10mm)	S (12mm)	R	R
3	1-H-3-phenyl-4-(4zdimethylaminophenyl)-5-(4-dimethylaminophenyl)-2-imidazolone (2c)	R	S (12mm)	S (12mm)	S (15mm)	S (12mm)	R
4	1,3,dihydro-4-(4-methoxyphenyl)-5-(4-methoxyphenyl)-2-imidazolone. (2d)	S (12mm)	R	S (10mm)	S (10mm)	S (10mm)	S (10mm)
5	1-H-3-methyl-4-(4-methoxyphenyl)-5-(4-	R	S	R	S	S	S

	methoxyphenyl)-2-imidazolone. (2e)		(14mm)		(14mm)	(10mm)	(12mm)
6	1-H-3-phenyl-4-(4-methoxyphenyl)-5-(4-methoxyphenyl)-2-imidazolone. (2f)	S (10mm)	S (12mm)	R	R	R	S (12mm)
7	1,3-dihydro-4-(2-hydroxyphenyl)-5-(2-hydroxyphenyl)-2-imidazolone (2g)	S (12mm)	S (15mm)	S (14mm)	R	R	R
8	1-methyl-3-H-4-(2-hydroxyphenyl)-5-(2-hydroxyphenyl)-2-imidazolone (2h)	R	R	S (12mm)	R	S (15mm)	S (12mm)
9	1-H-3-phenyl-4-(2-hydroxyphenyl)-5-(2-hydroxyphenyl)-2-imidazolone (2i)	S (12mm)	R	S (12mm)	S (15mm)	S (12mm)	S (14mm)

The compounds given in Table-5 (from 2a to 2h), were tested for their antimicrobial activity. In the initial screening processes, the 100ug/ml conc. of compound was taken to screen the activity of these compounds against the microorganisms. In these screening processes, the compounds showing the zone against the selected organisms were interpreted in their respective diameter of zone of inhibition. While the compounds having resistance towards the selected organisms were interpreted as R (resistant) whose MIC were not calculated. Most of them showed positive results. All the compounds showed maximum zone against *P. vulgaris* bacterium. Many of these compounds have been found to be moderately active against above-mentioned organisms. Statistically, it can said that 60% of the total samples tested showed antimicrobial activity. The compound 2a shows high zone of inhibition that is 15mm against *S.* typhi. In addition, compounds 2g, 2h and 2i showed maximum zone against *S. typhi, S. aureus, B. subtilis, P. vulgaris and S. typhi* respectively.

Among these, the imidazolones synthesized from 4-hydroxy-benzaldehyde,4-dimethylaminobenzaldehyde,salicylaldehyde,4-methoxybenzaldehyde (2a,2b,2c,2d,2h) showed antibacterial activity against maximum number of organisms which can be attributed to the presence of, $-N(CH_3)_2$, $-OCH_3$ and $-OH$, groups as substituents in these compounds.

Conclusion

Thus we could succeed in synthesizing variedly substituted-2-imidazolone with simple and easy to workout methodology. Use of Zeolite as a catalyst enabled us rapid route for the synthesis of 2-imidazolones which could reduce reflux time to as low as two and half hours. The catalyst is insoluble in solvent due to which isolation of the product became much easy. Most of the synthesized compounds showed antibacterial activity due to presence of $-N(CH_3)_2$, $-OCH_3$ and –OH etc groups as substituent in these compound.

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