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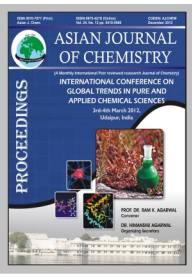

Synthesis and Biological Evaluation of Novel of 6-(Substituted Phenyl)-2*H*-imidazo[1,2-α]imidazol-3-one†

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One of the most attractive concept in chemistry for sustainability is green chemistry, which is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and applications of chemical product. Microwave heating has attracted the attention of today's research worker. Reactions in microwave are currently in use for synthesis of medicinally important compounds. Within the framework of green chemistry we had synthesized 6-(substituted phenyl)-2*H*-imidazo[1,2-α] imidazol-3-one by cyclocondensation of 4-(substituted phenyl)-1*H*-imidazol-2(5H)-one/thione/imine with amino acids using PTC and triethyl benzyl ammonium chloride. Synthesized compounds have been tested for antimicrobial activity against *Staphylococcus aureus, Escherichia coli, Salmonella typhi, Proteus vulgaris* using cup-plate methodand their minimum inhibitory concentration (MICs) were determined using broth macrodilution method.

Key Words: Microwave, TEBA catalyst, Antimicrobial activity, Cup plate method.

INTRODUCTION

Imidazoles are probably the most well-known heterocycle, which is common and important feature of a variety of natural products and medicinal agents. Derivatives of imidazole were reported for antiinflammatory[1-4], analgesic[5], anticonvulsant[6-7], tuberculostatic[8], antimicrobial[9] and anticancer[10] activities. Prompted by the broad spectrum activities of imidazole derivatives, it was decided to synthesize various 6-(substituted phenyl)-2*H*-imidazo[1,2-a]imidazol-3-one and studied for biological activities.

EXPERIMENTAL

All the synthesized compounds have been characterized on the basis of chemical properties, elemental and spectral analysis. The melting points were measured in a open glass capillary and are uncorrected. IR spectra in KBr were recorded on instrument Shimadzu FT-IR. ^{1}H NMR spectra were recorded on varian mercury YH-300, 400 MHz ($CDCl_3$ and DMSO-d_6) spectrophotometer using TMS as an internal standard. All reactions were monitored by TLC using silica gel 60-f 254 plates. The reactions were carried out in scientific microwave oven (scientific microwave system model RG31L1, 700 w, 2450 MHz). Satisfactory C, H, N analyses were carried out for most of the compounds.

Synthesis of 6-(substituted phenyl)-2*H*-imidazo[1,2-a]-imidazol-3-one (VIa-f): Dissolve 4-(substituted phenyl)-1*H*-imidazol-2(5*H*)-one (0.02 M) in ethanol (5 mL) and amino acid (0.02 M) in lukewarm water and to it add TEBA (0.05 M) as catalyst. Irradiate the reaction mixture for 2 min at 700 W. Allow the reaction mixture to cool at room temperature and triturate till solid separate out. The product thus obtained was filtered, washed with water and recrystallized from ethanol to get 6-(substituted phenyl)-2*H*-imidazo[1,2-a] imidazol-2(5*H*)-one in 60 to 70 % yield.

RESULTS AND DISCUSSION

Such type of cycloaddition is novel for the preparation of imido-imidazole system. The present investigation gives the importance of such type of cycloaddition in one step preparation of imidazole derivative with high yield in presence of microwave irradiation. The structures of prepared novel compound were confirmed by using IR and NMR spectroscopic data and elemental analysis.

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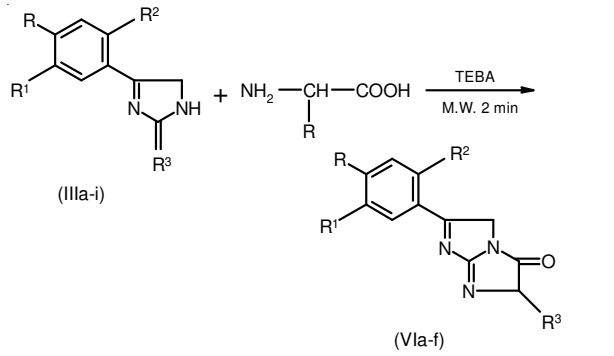
TABLE-1
ANTIMICROBIAL ACTIVITY OF 6-(SUBSTITUTED PHENYL)-2*H*-IMIDAZO[1,2-a]IMIDAZOL-3-[5*H*]-ONE (**VIc-d**)

Compd. No.	Compounds	Inhibition zone in mm (MIC in µg/mL)			
		P. vulgaris	*S. aureus*	*E. coli*	*S. typhi*
VIc	6-(4'-Chlorophenyl)-2H-imidazo [1,2-a] imidazol-3[5H]-one	23 (125)	7 (125)	20 (250)	18 (125)
Vid	6-(4'-Chlorophenyl)-2-methyl imidazo [1,2-a] imidazol-3[5H]-one	26 (125)	15 (250)	17 (250)	19 (125)
	Chloramphenicol	28 (6)	27 (25)	29 (25)	28 (50)

Spectral data of principal compound

6-(4'-Chloro phenyl)-2-methyl-imidazo[1,2-a]imidazol-3-[5*H*]-one (VId): IR (KBr, ν_{max}, cm^{-1}): 3361 (s, -NH), 3136 (s, -Ar-H), 1693 (s,-C=O), 1300-1200 (s, -C=C, -C=N), 781 (s, -C-Cl).

The ^{1}H NMR $CDCl_3$, 300 MHz, δ ppm 1.25 (s, 3H, $-CH_3$ (ketoform), 1.48 (s, 3H, $-CH_3$ (enolic form), 1.75 (s, 1H, -NH), 3.44 (s, 1H, -OH (enolform), 4.6 (s, 2H, $-CH_2$)), 7.49 (d, 2H, -Ar-H), 7.2 (s, 1H, =CH (hetero aromatic tautomeric), 7.92 (d, 2H, -Ar-H).

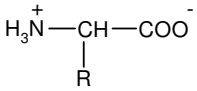


Expt. No.	Compound (VIa-f)	R	R^1	R^2	R^3	m.p. (°C)
1	a	H	CH_3	OH	H	110
2	b	H	CH_3	OH	CH_3	85
3	c	Cl	H	H	H	98
4	d	Cl	H	H	CH_3	74
5	e	NO_2	H	H	H	72
6	f	NO_2	H	H	CH_3	123

Screening for antimicrobial activity: The antimicrobial activity of the synthesized 6-(substituted phenyl)-2*H*-imidazo[1,2-a]imidazol-3-one heterocyclic compounds have been tested against *Staphylococcus aureus, Escherichia coli, Salmonella typhi, Proteus vulgaris* using cup-plate method[11] and their minimum inhibitory concentration (MICs) were determined using broth macrodilution method.

The sterilized nutrient agar medium was poured into the petridishes and allowed to solidify. The lawn of the culture was prepared by spreading the microbial suspension on the surface of the medium with the help of sterilized triangular loop. Petridishes were allowed to remain for 10 min, after which excess of nutrient broth cultures were taken out aseptically using pasture pipettes. Standard 8 mm size cups were prepared in the solidified medium with the help of per-sterilized steel cylinder of 8 mm diameter. The wells were then filled with the 0.5 mL stock solution of the test compounds and standard drug chloramphenicol (200 µg/mL). Controls were run using only DMF solvent. All the plates were incubated at 37 ± 2 ºC 24 ± 2 h. The zones of inhibition were recorded by using vernier calipers. The zone of inhibition is recorded including the well diameters of 8 mm. MIC values of all the synthesized compounds against various organisms have been recorded. The test compounds were dissolved in DMF.

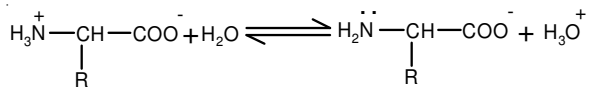
Probable mechanism: This is 1,3-addition of amino acid to the O=C-NH moiety of imidazole derivatives. Amino acid has both basic $-NH_2$ and acidic -COOH group. There is an internal transfer of a hydrogen from the -COOH to the $-NH_2$ group to leave an amphoteric ion with both negative and positive ion called as zwitter ion.



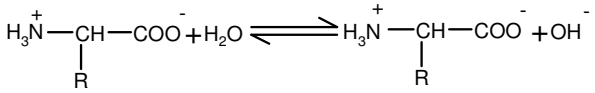
This is the form that amino acid exits even in the solid state and in solution. A zwitter ion is a compound with no overall electrical charge but, which contain separate parts which are positively and negatively charged.

When an amino acid dissolve in water the zwitter ion interact with water molecule and act as a both weak acid and weak base.

As an acid-



As an base-



This tendency facilitate the cyclodehydration process in the reaction. The addition of amino acid to a carboyl group involves nulceophilic attack by the nitrogen of amino acid to carbonyl carbon. This reaction is carried out in TEBA which act as a catalyst facilitate the protonation of carbonyl carbon in the reactant, leading to the formation of an intermediate. This undergo cyclization with elimination of water molecule.

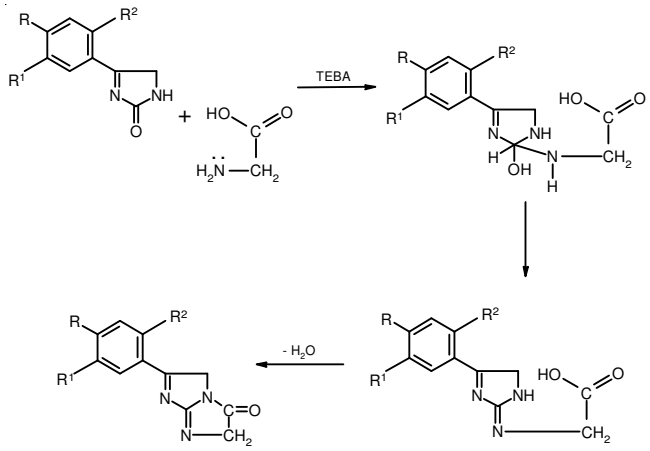


TABLE-2
SYNTHESIS OF 6-(substituted phenyl)-2*H*-imidazo[1,2-a] imidazol-3-one

Expt. No	4-(substituted phenyl)-1H-imidazol-2(5H)-one/thione/imine	6-(substituted phenyl)-2H-imidazo[1,2-a] imidazol-3-one	m.p. (°C)	m.f.	Yield (%)
1	4-(2-Hydroxy-5-methyl phenyl)-1*H*-imidazol-2(5*H*)-one/thione (**IIIa/IIIb**)	6-(2'-Hydroxy-5-methyl phenyl)-2*H*-imidazo[1,2-a]-imidazol-3[5*H*]-one (**VIa**)	110	$C_{12}H_{11}N_3O_2$	62
2		6-(2'-Hydroxy-5-methyl phenyl)-2-methyl-imidazo-[1,2-a]imidazol-3[5*H*]-one (**VIb**)	85	$C_{13}H_{13}N_3O_2$	65
3	4-(4-chloro phenyl)-1*H*-imidazol-2(5*H*)-one/thione (**IIId/IIIe**)	6-(4'-Chloro phenyl)-2H-imidazo[1,2-a]imidazol-3[5*H*]-one (**VIc**)	98	$C_{11}H_{18}ClN_3O$	70
4		6-(4'-Chloro phenyl)-2-methyl-imidazo[1,2-a]imidazol-3[5*H*]-one (**VId**)	74	$C_{12}H_{10}ClN_3O$	69
5	4-(4-nitro phenyl)-1*H*-imidazol-2(5*H*)-one/thione (**IIIg/IIIh**)	6-(4'-Nitro phenyl)-2*H*-imidazo[1,2-a]imidazol-3[5*H*]-one (**VIe**)	72	$C_{11}H_8N_4O_3$	65
6		6-(4'-Nitro phenyl)-2-methyl-imidazo[1,2-a]imidazol-3[5*H*]-one (**VIf**)	123	$C_{12}H_{10}N_4O_3$	68

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