Research Article

Synthesis of Some Novel 1, 5-disubstituted-4-chloro-iH-imidazole Derivatives

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ABSTRACT
The Synthesis of Some Novel 1, 5-Disubstituted-4-Chloro-IH-Imidazole was carried out and was evaluated for anticonvulsant activity. 1, 5-Disubstituted-4-Chloro-IH-Imidazole were obtained from imines and p-tolunesulfonyl methyl cyanide (TOSMIC). Imines were prepared from commercially available amines and aldehydes.

Keywords: 1, 5-Disubstituted-4-chloro-imidazoles.

INTRODUCTION

Medicinal chemistry is the discipline concerned with determing the influence of chemical structure on biological activity and in the practice of medicinal chemistry developed from an empirical one involving organic synthesis of new compound based largely on the modification of structure and then identifies their biological activity.[1,2]Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level.[3]Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures.

Imidazole derivatives have occupied a unique place in the field of medicinal chemistry. It is the constituent of several natural compounds like histamine, histamine, biotin, alkaloids and nucleic acid and a very important class among the medicinal compounds. Large number of imidazole derivatives have been are being developed for different therapeutic actions. Imidazole is an entity which is being synthesized in many of its derivative form from past few years; the entity is major source of interest for many of medicinal chemist to explore its various pharmacological potentials.

Imidazole is an organic compound with the formula C_3H_4N. This aromatic heterocyclic is a "1, 3-diazole" and is classified as an alkaloid[4].

Imidazole moiety have been most frequently studied, many of its analogs are active against various pathological conditions Substitutions are discussed in pharmacological actions as anti neoplastic agent.

On the basis of various literature survey imidazole derivatives show various activity against anthelmentic[5], analgesic[6], anti-inflammatory[7], platelet aggregation inhibitor[8] antitubercular[9] etc. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic imidazole nucleus. Having structural similarity with histidine imidazole compound can bind with protein molecules with ease compared to the some other heterocyclic moieties. Thus imidazole offers better pharmacodynamic characteristics. Furthermore, some imidazoles drugs, at high concentrations, could exert direct inhibitory effects on membranes, without interference with sterols and sterol esters. Various recent new drugs developments in imidazoles derivatives show better effect and less toxicity.

Thus can say Imidazole is a moiety which had been exploited in the past years for synthesizing various compounds having diverse pharmacological activities, and still it can be further utilized for future prospective against various pathological conditions and other uses and therefore the current research focuses on the synthesis of some novel synthesis of 1,5-disubstituted-4-chloro-imidazoles and its derivatives[10].

MATERIAL AND METHODS

Melting points was taken on electrothermal digital melting point apparatus and are

uncorrected. Completion of the reaction was determined by single spotted TLC, structures of the compound were confirmby Infrared (IR), Proton Nuclear magnetic resonance (lHNMR) and **IR** spectra were recorded using KBr disc on a JASCO FTIR-410.1H~NMR spectra were recorded in CDCl3 solution on FTNMR, varian mercury 300Hz and proton chemical shifts are relative to tetramethylsilane as internal standard.
Visualization of the compound on chromatographic plates was done by exposure to iodine vapours.

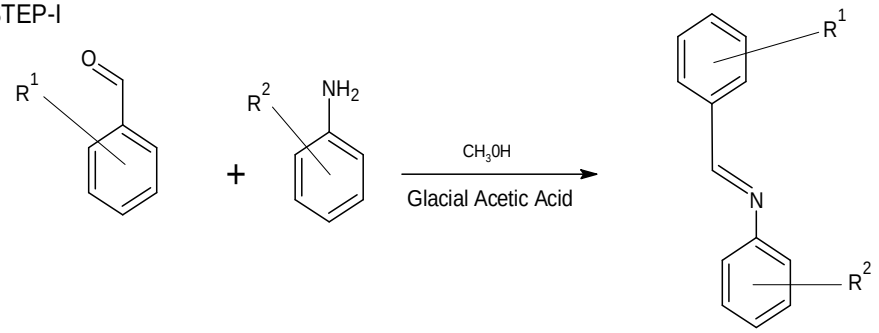
CHEMICALS
All the chemicals and solvents used were mostly of AR grade obtained from LobaChemie Pvt. Ltd, Mumbai, Sigma Aldrich, Rajesh Chemicals and S.D. Fine ChemLtd. The melting points were determined in open glass capillary tubes containing liquid paraffin and are uncorrected. Purity of the compounds was checked on thin layer chromatography (TLC) plates using silica gel G (Research Lab) and the solvent system benzene-acetone (9:1 and 8:2, v/v) and toluene-ethyl acetate-formic acid (TEF) (5:4:1, v/v/v);
The spots were visualized under iodine vapors or UVlight. The IR spectra were obtained in KBr pellets on BIO-RAD FTS FT-IR spectrophotometer. The lH NMR spectra were recorded on DPX-300 NMR spectrometer and BRUKER-400 Ultra Shied^{TM}spectrometer using tetramethylsilane (TMS) as an internal standard in DMSO/$CDCl_3$. Chemical shifts (δ) are expressed in ppm.The physical constants, spectral data and anti-convulsant screening of the synthesized compounds are presented in Tables 1, 2 and 3, respectively.

Experimental
Step I: Preparation of Schiff's Bases
Procedure
The synthesis of Schiff's bases was carried out by the reaction of various derivatives of aniline (0.lM) and aromatic aldehydes (0.lM) in the presence of glacial acetic acid in methanol. The reaction mixture was refluxed for 3-4 hrs, cooled and poured in cold water. The separated solid was filtered off and the residue was recrystallised with methanol.
The melting point and other detailsare given in table No.1

Step II- Preparations of Imidazoles
Procedure
The synthesized Schiff's bases were refluxed with Tosylmethylisocyanide (172 mmol) in presence of K_2C0_3 (229 mmol), methanol (795 ml) and dioxane (340 ml) for 2 hrs. Then the solvent was removed and the residue was dissolved in dichloromethane. The layer was separated and aqueous layer was extracted with dichloromethane. The combined organic phases were dried over magnesium sulphate and concentrated. The crude product was recrystallized which gave respective imidazole. The melting point and other details are given in table No.2

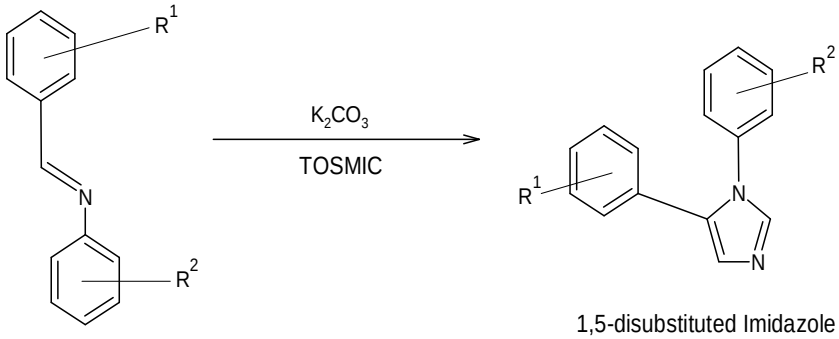
Step III - Preparation of substituted Chloro-derivative of imidazoles
Procedure
The synthesized imidazoles then reacted with N-chlorosuccinamide in presence of chloroform. Refluxed for about 18 hrs. Then the solvent was evaporated and dried using solid magnesium sulphate in dessicator. The crude product was recrystallized using alcohol. The melting point and other details are given in table No.3.

STEP-I



Schiff's Base

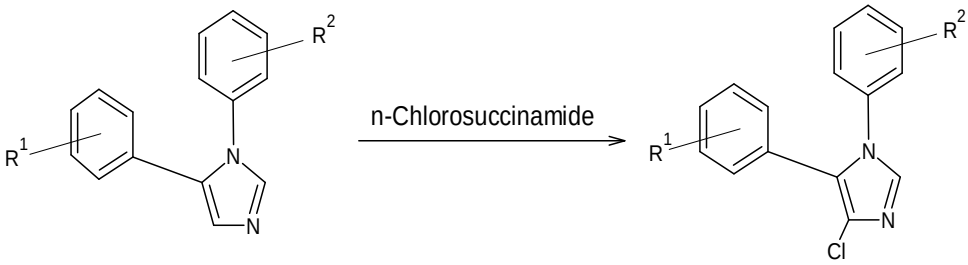
STEP-II



Schiff's Base

1,5-disubstituted Imidazole

STEP-III



1,5-disubstituted Imidazole

1,5-disubstituted-4-chloroimidazole

Table 1: Physical data of the title compounds(1a-f)

Compd	R1	R2	Mol.Formula (Mol. Wt.)	M.P. (o C)	Yield (%)	Rf-Value
1a	4-OH	2-CH_3	$C_{14}H_{13}N_1O_1$	75 ^oC	60 %	0.96
1b	4-OH	2,4-CH_3	$C_{15}H_{15}N_1O_1$	135 ^oC	63 %	0.83
1c	4-OH	2,6-CH_3	$C_{15}H_{15}N_1O_1$	173 ^oC	67 %	0.85
1d	2-NO_2	2,4-CH_3	$C_{15}H_{14}N_2O_2$	75 ^oC	70 %	0.67
1e	2-NO_2	2-CH_3	$C_{14}H_{12}N_2O_2$	66 ^oC	65 %	0.70
1f	4-OCH_3	2,4-CH_3	$C_{16}H_{18}N_1O_1$	60 ^oC	66 %	0.77

Table 2: Physical data of the title compounds (2a-f)

Compd	R1	R2	Mol. Formula (Mol. Wt.)	M.P. (o C)	Yield (%)	Rf-Value
2a	4-OH	2-CH_3	$C_{15}H_{14}N_2O_1$	70 ^oC	60 %	0.6
2b	4-OH	2,4-CH_3	$C_{16}H_{16}N_1O_1$	75 ^oC	66 %	0.8
2c	4-OH	2,6-CH_3	$C_{16}H_{16}N_2O_1$	81 ^oC	63 %	0.5
2d	2-NO_2	2,4-CH_3	$C_{16}H_{15}N_3O_2$	73 ^oC	59 %	0.63
2e	2-NO_2	2-CH_3	$C_{15}H_{13}N_3O_2$	85 ^oC	55 %	0.1
2f	4-OCH_3	2,4-CH_3	$C_{17}H_{18}N_2O_1$	73 ^oC	60 %	0.93

Table 3: Physical data of the title compounds (3a-f)

Compd	R1	R2	Mol. Formula (Mol. Wt.)	M.P. (o C)	Yield (%)	Rf-Value
3a	4-OH	2-CH3	$C_{15}H_{13}N_2O_1Cl$	75 ^oC	59 %	0.6
3b	4-OH	2,4-CH3	$C_{16}H_{15}N_2O_1Cl$	86^o C	65 %	0.53
3c	4-OH	2,6-CH3	$C_{16}H_{15}N_2O_1Cl$	73^o C	60 %	0.5
3d	2-NO2	2,4-CH3	$C_{15}H_{14}N_3O_1Cl$	80^o C	55 %	0.7
3e	2-NO2	2-CH3	$C_{15}H_{12}N_2O_1Cl$	60 ^oC	43 %	0.4
3f	4-OCH3	2,4-CH3	$C_{15}H_{13}N_2O_1Cl$	79^o C	56 %	0.61

Solvent of crystallization - ethanol, 'Melting point of the compounds at their decomposition, Solvent system -toluene:ethylacetate:formic acid (5:4:1, v/v/v) and benzene:acetone (8:2,7:3 v/v).

Table 4: Elemental analysis for C, H, N were within ± 0.4% of the theoretical value

Compd	IR (KBr),cm-1	1H-NMR (DMSO-d6),δ (ppm) /MS data
3a	3443(CH),1631(C=N),1390(C=C),1313(C-N)	2.49(3H,s,CH3),7.633(1H,s,OH),7.705-7.805(14H,m,ArH),8.96(1H,s,imidazole)
3b	2950(CH),1645(C=N),1397(C=C),1316(C-N)	3.682(3H,s,CH3),7.64(1H,s,Ar),7.69-7.98(14H,m,ArH),8.119(1H,s,imidazole)
3c	2922(CH),1680(C=N),1388(C=C),1221(C-N)	2.49(3H,s,CH3),7.533(1H,s,OH),7.705-7.805(14H,m,ArH)8.110(1H,s,imidazole)
3d	3443(CH),1674(C=N),1390(C=C),1313(C-N)	2.74-2-90(3H,s,CH3),7.255(14H,m,ArH),8.90(1H,s,imidazole)
3e	3454(CH),1709(C=N),1371(C=C),1296(C-N)	2.45-2.75(3H,s,CH3),7.32-7.80(14H,m,ArH),7.831(1H,s,imidazole)
3f	3416(CH),1637(C=N),1354(C=C),1296(C-N)	2.71(3H,s,CH3),7.254-7.86(14H,m,ArH),8.96(1H,s,imidazole)

RESULT AND DISCUSSION

The title compounds were synthesized from the reaction of anilines and aromatic aldehydesinyhe presence of glacial acetic acid in methanol. Formed schiff's bases were treated with tosylmethylisocyanide in presence of potassium carbonate,methanol and dioxane which gave respective imidazoles. The formed imidazoles were refluxed with N-chlorosuccinamide in presence of chloroform which formed respective chloro derivatives of imidazoles.

The purity of the starting material has been confirmed by using TLC and melting point.the progress of the reaction was checked by TLC .The structural elucidation of the synthesized compounds were done by IR and 1-H NMR.

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