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Synthesis And Antimicrobial Activity Of Imidazolo-Pyrazole Compounds Using Silver Triflate As Catalyst.

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Abstract: An effort to develop antimicrobial agents, a series of novel heterocyclic Pyrazoles derivatives were synthesized using silver triflate as catalyst from chalcones by Claisen-Schmidt condensation of appropriate acetophenones with Imidazole aldehydes in the presence of aqueous solution of potassium hydroxide and ethanol at room temperature. The synthesized compounds were characterized by means of their IR, ^{1}H, ^{13}C NMR and MS spectral data. All the synthesized compounds were tested for their antibacterial and antifungal activities by the disc diffusion method.
Key words: Imidazole pyrazole, Silver triflate, Heterocyclic compounds, Anti Bacterial, Anti fungal.

Introduction

Imidazole and Pyrazole nuclei are important structures present in numerous natural and synthetic compounds and have application in medicinal chemistry. Imidazole-pyrazole compounds are reported to have broad pharmacological activities. The Pyrazole function is quite stable and prominent structural motif found in numerous pharmaceutically active compounds. This has inspired chemists to utilize this stable unit in bioactive moieties to synthesize new compounds possessing biological activities [1-6]. The diversity of the structures encountered, as well as their biological and pharmaceutical relevance, have motivated the researchers aimed at the development of new economical, efficient synthesis of imidazole substituted pyrazole compounds using a catalyst.

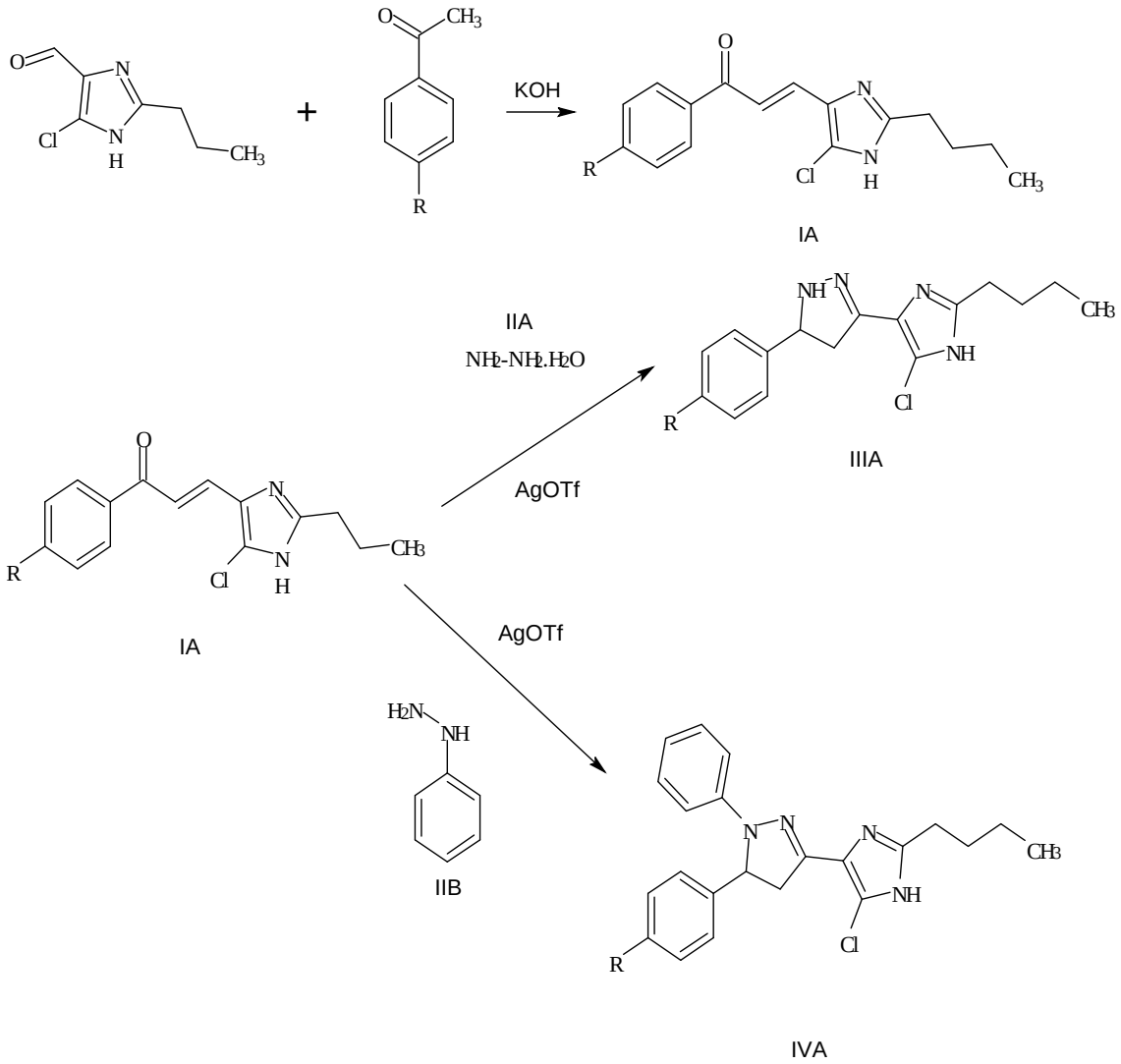
Silver triflate Ag (I) used as Lewis acid catalyst in organic reactions for effective and novel transformations in organic synthesis [7-9]. Although the exact mechanism remains unknown silver activates the carbonyl carbon of the chalcone and add hydrazine hydrate or phenyl hydrazine followed by cyclocoreversion to provide product, these reactions are very rapid and easy workup to isolate the product when compared to conventional method [10-11].Therefore, the synthesis and selective functionalization of pyrazoles has been focus of active research area over the years [12]. In addition to, imidazole moiety having hypertension and ACE Inhibitory activity [13]. This prompted us to synthesize various imidazole pyrazole derivatives and tested their Antimicrobial activity.

Materials and Methods

Melting points were measured in open glass capillaries on a perfit melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR were recorded on a Bruker 400 MHz (^{1}H) & 100MHz (^{13}C) NMR

spectrometer with multinuclear broad band observed probe in DMSO-d_6 with TMS as reference signal. MS data were acquired on API-MS 3000 Mass spectrometer. IR spectra were recorded in a FT-IR spectrometer (Shizamdzu). The chemicals and solvents used were of laboratory grade and were purified and used. The completion of the reaction was monitored by thin layer chromatography on precoated sheets of silica gel-G (Merck, Germany). The synthetic pathway is presented in Scheme 1 and physicochemical data and spectroscopic data for the synthesized compounds are listed below.

Synthetic protocol for the target compound



General procedure for chalcone synthesis [IA-IJ]

A solution of acetophenone (0.02 mol) and aldehyde (0.02 mol) were dissolved in 15mL of ethanol, and aqeous NaOH (50% 12mL) was added in dropwise [14]. The reaction mixture was stirred at room temperature and the completion of the reaction was monitored by TLC. Then the mixture was poured slowly into 400 ml of water with constant stirring and kept overnight in refrigerator for 24 hours. The precipitate obtained was filtered, washed and recrystallized from ethanol. The compound thus purified was subjected to various spectral analysis and from the data the compound obtained is named as (2E)-3-(2-butyl-5-chloro-1H-imidazol-4-yl)-1-phenyl) prop-2-en-1-one respectively.

General procedure for the synthesis of pyrazole [IIIA- IIID] & [IVA- IVE]

To a solution of Chalcone (10 mmol) in 10mL of ethanol, 1.0 mL of hydrazine hydrate or 10 mmol of phenyl hydrazine and catalytic amount of silver triflate (20mg) was added and the reaction mixture refluxed for less than an hour. Then the reaction mixture was cooled and pH of the solution adjusted to 7.0 using and dilute NaOH The solid mass separated out was filtered, washed with cold water and recrystallized from ethanol to obtain Imidazole-pyrazole derivative. The completion of the reaction was monitored by TLC. The compound thus purified was subjected to various spectral analysis and the data given below.

3-(2-butyl-5-chloro-1H-imidazol-4-yl)-5-(4-methylphenyl)-4,5-dihydro-1H-pyrazole (3a)
Pale yellow solid; yield 81%; m.p 108°C; IR ν_{max}: 3428, 2958, 2926, 1722, 1607, 1353,1036; ^{1}H NMR (400MHz, DMSO): δ 1.07 (t,3H) J=7.3Hz, 1.25 (s,2H) J=7.4Hz, 1.56 (q,2H) J=7.4Hz, 2.31 (s,3H), 2.37 (m,1H), 4.77 (m,1H), 4.35 (s,1H), 7.19 (m,2H) 7.52 (m,2H), 12.17 (bs,1H); ^{13}C–NMR (100MHz, DMSO):δ 13.9, 21.3, 22.1, 27.6, 30.5, 39.1, 53.5, 116.8, 120.9, 122.1, 122.3, 125.2, 128.9, 129.5,136.5, 140.2, 143.9, 148.2, 165.6; MS m/z 317 $(M+H)^+$.

3-(2-butyl-5-chloro-1H-imidazol-4-yl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole(3b)
Yellow solid; yield 78%; m.p 108°C; IR ν_{max}: 3434, 2957, 2919, 1641, 1363, 700; ^{1}H–NMR (400MHz, DMSO):δ 0.89 (t,3H) J=7.4Hz, 1.24 (s,2H) J=7.4Hz, 1.54 (q,2H) J=7.4Hz, 2.86(m,1H), 3.38 (m,1H), 4.77 (m,1H), 7.51(d,2H), 7.65(d,2H), 12.15(bs,1H) ^{13}C–NMR (100MHz, DMSO): δ 14.1, 22.3, 27.5,3 0.5, 39.2, 53.5, 115.4, 116.8, 120.9, 122.1, 122.4, 128.6, 129.3, 139.1, 143.9, 148.1, 155.7, 160.9 163.4; MS m/z 321 $(M+H)^+$.

5-(4-bromophenyl)-3-(2-butyl-5-chloro-1H-imidazol-4-yl)-4,5-dihydro-1H-pyrazole (3c)
White powder; yield 65%; m.p 218°C; IR ν_{max}: 3434, 2957, 2919, 1641, 1363, 700, ^{1}H–NMR (400MHz, DMSO):δ 0.85 (t,3H) J=7.3Hz, 1.23, (s,2H) J=7.2Hz, 1.52(q,2H) J=7.3Hz, 2.25,(t,2H), 3.18, (dd,1H) J=18.1Hz&6.0Hz; 3.76,(dd,1H) J=18.1&12.7, 7.54 (d,2H)J=8.5Hz, 7.79 (d,2H) J=8.5Hz, 12.14(bs,1H); ^{13}C–NMR(100MHz, DMSO): δ13.7, 21.7, 21.8, 27.5, 29.9, 50.8, 123.5, 123.6, 128.3, 130.1, 134.8, 146.4,152.9, 167.7; MS m/z 382 $(M+H)^+$.

3-(2-butyl-5-chloro-1H-imidazol-4-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (3d)
Off white powder; yield 73%; m.p 153°C; IR ν_{max}: 3433, 2956, 2920, 1637, 1363, 700; ^{1}H-NMR (400MHz, DMSO): δ 0.91(t3H) J=7.1Hz, 1.32(s,2H) J=7.2Hz, 1.59 (q,2H) J=7.0Hz, 2.89,(s,2H) J=7.0Hz, 3.69(m,2H), 3.83(s, 3H) 3.91 (m,1H), 6.96(m,2H), 7.19(m,2H), 12.91(bs, 1H); ^{13}C–NMR(100MHz, DMSO): δ14.1, 22.1, 27.6, 30.7, 41.9, 49.8, 55.9, 114.2, 122.1, 122.4, 126.9, 135.8, 148.2,155.8, 158.9; MS m/z 333 $(M+H)^+$.

3-(2-butyl-5-chloro-1H-imidazol-4-yl)-5-(3-methylphenyl)-4,5-dihydro-1H-pyrazole (3e)
Pale yellow solid; yield 81%; m.p 108°C; IR ν_{max} : 3428, 2958, 2926, 1722, 1607, 1353, 1036; ^{1}H-NMR (400MHz, DMSO):δ 1.07(t,3H) J=7.3Hz, 1.25(s,2H) J=7.4Hz 1.56(q,2H) J=7.4Hz, 2.31,(s,3H), 2.37(m,1H) 4.77(m,1H), 4.35 (s,1H) 7.19(m,2H), 7.52 (s,2H), 12.17(bs,1H); ^{13}C–NMR(100MHz, DMSO):δ13.9, 21.3, 22.1, 27.6, 30.5, 39.1, 53.5, 116.8, 120.9, 122.1, 122.3, 125.2, 128.9, 129.5,136.5, 140.2, 143.9, 148.2, 165.6; MS m/z 317 $(M+H)^+$.

3-(2-butyl-5-chloro-1H-imidazol-4-yl)-5-(4-methylphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (4a) Off white powder; yield 85%; m.p 180°C; IR ν_{max}: 3430, 2957, 2925, 1598, 1498, 1321, 816; ^{1}H-NMR (400MHz, DMSO): δ 0.81(t,3H) J=7.4Hz, 1.17(s,2H) J=7.2Hz, 1.49(q,2H) J=7.4.1Hz, 2.35(s,3H), 2.47(t.1H), 3.14(dd, 1H) J=17.4.& 8.8Hz, 3.80(dd,1H) J=17.4 & 12.4 Hz, 5.28(dd,1H) J=12.4& 8.8Hz, 6.75(t,1H) J=7.2Hz, 7.03 (d,2H) J=7.9Hz, 7.18(t,2H) J=7.4Hz, 7.69(d, 2H)J=8.0Hz, 12.28 (bs,1H); ^{13}C–NMR (100MHz, DMSO): δ 13.6, 21.0, 21.6, 27.5, 29.8, 54.7,113.1,119.2,125.8, 128.9,129.5, 138.4,145.1,147.7,147.8; MS m/z 393 $(M+H)^+$.

5-(4-bromophenyl)-3-(2-butyl-5-chloro-1H-imidazol-4-yl)-1-phenyl-4,5-dihydro-1H-pyrazole (4b) White solid; yield 73%; m.p 196°C; IR ν_{max} : 3432, 2951, 2922, 1596, 1495, 1321 816; ^{1}H-NMR(400MHz, DMSO): δ 0.90 (t,3H) J=7.2Hz, 1.31(s,2H) J=7.1Hz, 1.60(q,2H) J=6.9Hz, 2.88(t,3H) J=7.0Hz, 3.66& 3.91, (dd,,2H) J=12.4.& 8.0Hz, 5.19(d,1H) J=8.0Hz, 6.80(m,3H), 7.23(m,3H), 7.92(m,2H), 12.92 (bs,1H); ^{13}C–NMR (100MHz, DMSO):δ 14.2, 22.4 27.5, 30.7, 39.1, 53.9, 116.8, 121.0, 121.7, 122.1, 122.4, 127.2, 129.2, 131.5, 142.6, 143.8, 148.1, 155.6; MS m/z 458 $(M+H)^{+}$.

3-(2-butyl-5-chloro-1H-imidazol-4-yl)-5-(4-fluorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (4c) Pale yellow solid; yield 84%; m.p 212°C; IR ν_{max}: 3434, 2958, 2930, 2871, 1599, 1499, 1384, 834; ^{1}H-NMR(400MHz, DMSO): δ 0.81(t,3H) J=7.3Hz, 1.19(s,2H) J=7.3Hz, 1.51.(q,2H) J=7.4Hz, 2.47(t, 3H), 3.17(dd,1H) J=17.4.& 8.6Hz, 3.86(dd,1H), 5.28(dd, 1H) J=12.5& 8.6Hz, 6.77(t,1H) J=7.2Hz, 7.04(d,2H) J=8.0Hz, 7.18(t,2H) J=8.0Hz, 7.27(d,2H) J=8.0Hz, 12.27(bs,1H); ^{13}C–NMR (100MHz, DMSO): δ13.7, 21.7, 27.6, 29.8, 54.9, 113.2, 115.7 & 115.9, 119.4, 123.4, 127.9, 128.0, 129.0, 144.9, 146.9, 148.0, 161.3 & 163.7; 178.2; MS m/z 397 $(M+H)^{+}$.

3-(2-butyl-5-chloro-1H-imidazol-4-yl)-5-(3-methylphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (4d) White powder; yield 86%; m.p 182°C; IR ν_{max}: 3433, 2954, 2931, 2867, 1595, 1494, 1381, 827; ^{1}H-NMR(400MHz, DMSO):δ 0.79(t,3H) J=7.3Hz, 1.14(s,24) J=7.3Hz, 1.44.(q,2H) J=7.4Hz, 2.45(t, 3H), 3.14(dd,1H) J=17.7.& 8.5Hz, 3.84(dd,1H) 5.27(dd,1H) J=12.4& 8.5Hz, 6.74(t,1H) J=7.1Hz, 7.04(d,2H) J=8.0Hz, 7.12(t,2H) J=8.0Hz, 7.27(d,2H)J=8.0Hz, 12.27(bs,1H); ^{13}C–NMR (100MHz, DMSO): 13.7, 21.7, 27.6, 29.8, 54.9, 113.2, 115.7,& 115.9, 119.4, 123.4; 127.9 &128.0; 129.0, 144.9, 146.9, 148.0, 161.3 & 163.7, 178.2; MS m/z 393 $(M+H)^{+}$.

3-(2-butyl-5-chloro-1H-imidazol-4-yl)-5-(3-methoxylphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (4e) Pale yellow powder; yield 76%; m.p 194°C; IR ν_{max}: 3430, 2954, 2933, 2866, 1549,1439, 1384, 834; 1H–NMR(400MHz, DMSO):δ 0.90(t,3H) J=7.1Hz, 1.31(s,2H) J=7.0Hz, 1.60(q,2H) J=7.1Hz, 2.67(t,2H) J=7.0Hz, 3.91(m,2H), 3.90,(s,3H), 5.19(q,2H) J=8.0Hz; 6.83(m,3H) 6.88(m,2H) 7.19(m,4H), 12.91(bs,1H); ^{13}C–NMR (100MHz, DMSO): 14.1, 22.3, 27.6, 30.5, 39.1, 53.5, 55.9, 114.1, 120.9, 122.1, 122.4, 126.7, 135.8, 143.8, 148.2, 155.7 & 159.2; MS m/z 409 $(M+H)^{+}$.

In vitro anti –microbial screening

The synthesized compounds were screened for their antimicrobial activity against test microorganism by Disc Diffusion Technique (Indian Pharmacopoeia 1996, vol. II A-105.). The test microorganisms of staphylococcus aureus, Bacillus subtilis, E.coli, Pseudomonas aeruginosa, Candida albicans and Aspergillus niger were obtained from National Chemical Laboratory (NCL) Pune, India and maintained by periodical sub culturing on nutrient agar and sabouraud dextrose agar medium for bacteria and fungi respectively [15-17]. The effect produced by the sample was compared with the effect produced by the Positive control (Reference standard ciprofloxacin 5 µg/disc for bacteria; Nystatin 100 units/ disc for fungi. The results were recorded in **the Table-1&2.**

Std- Standard; S.C – Solvent Control –DMF

Results and Discussion

A series of Imidazole-pyrazole compounds were synthesized in good yields in short reaction time and easy to work up. To study the generality this process, variety of examples were illustrated for the synthesis of imidazole-pyrazole compounds and the reaction is compatible for various substitutents such as CH_3, OCH_3, F, and Br. The formation of desired product was confirmed by determining their melting points, IR spectra, Mass spectra, ^{1}H NMR and ^{13}C NMR. In-vitro evaluation of some of the synthezied imidazole-pyrazole derivatives exhibit moderate antimicrobial activity at lower concentration and show a significant antimicrobical activity at higher concentrations. Methyl substituted derivatives of imidazole pyrazole IIIA, IVA showed sensitivity at higher concentration to Aspergillus niger fungi. Compound IVA show a significant sensitivity to both Gram positive and Gram negative bacteria than other compounds. In conclusion, Imidazole pyrazole derivatives analogues showed comparable activity. We may say that their pharmacophoric groups are similar and the possible structure of suitable fused heterocyclic could be accepted to give antibacterial activity and may have various pharmacological activities.

Table-1

		Zone of Inhibition (mm)					
		Gram Positive		**Gram Negative**		**Antifungal**	
S.No	Conc (µg)	**Staphylococcus aureus** (NCIM 2079)	**Bacillus subtilis** (NCIM 2063)	**E.coli** (NCIM 2065)	**Pseudomonas aeruginosa** (NCIM 2036)	**Candida albicans** (NCIM 3102)	**Aspergillus niger** (NCIM 105)
III-A	100	16	16	12	12	15	14
	150	16	16	16	14	16	16
	250	18	20	16	18	18	22
	500	22	20	16	18	22	27
III-B	100	14	16	12	18	20	13
	150	14	20	12	16	18	16
	250	16	20	16	18	20	14
	500	22	24	16	20	20	16
III-C	100	14	18	14	14	12	14
	150	16	18	16	14	20	20
	250	14	19	18	20	20	20
	500	18	22	20	20	20	22
III-D	100	14	15	12	14	18	16
	150	16	18	14	18	15	18
	250	22	15	18	16	20	16
	500	24	16	14	26	24	22
III-E	100	16	14	15	18	15	22
	150	14	16	17	16	18	15
	250	18	20	16	18	20	20
	500	20	22	18	14	18	22
	S.C	--	--	--	--	--	--
	Std	35	40	38	40	25	30

Table-2

		Zone of Inhibition (mm)					
		Gram Positive		Gram Negative		Antifungal	
S.No	Conc (µg)	**Staphylococcus aureus** (NCIM 2079)	**Bacillus subtilis** (NCIM 2063)	**E.coli** (NCIM 2065)	**Pseudomonas aeruginosa** (NCIM 2036)	**Candida albicans** (NCIM 3102)	**Aspergillus niger** (NCIM 105)
IV-A	100	14	15	17	16	13	18
	150	18	16	12	20	18	15
	250	20	18	20	20	20	20
	500	20	26	22	28	22	25
IV-B	100	16	22	14	18	15	16
	150	18	18	16	18	16	13
	250	14	18	14	22	18	14
	500	20	22	18	20	18	18
IV-C	100	14	15	17	16	13	18
	150	16	18	15	14	16	16
	250	16	18	15	16	16	16
	500	22	20	18	20	16	20
IV-D	100	18	14	16	18	16	18
	150	16	12	14	22	18	14
	250	18	16	20	20	22	22
	500	18	26	20	28	20	25
IV-E	100	16	14	16	18	15	16
	150	18	16	14	16	18	18
	250	20	16	14	20	18	18
	500	20	22	20	22	18	22
	S.C	--	--	--	--	--	--
	Std	35	40	38	40	25	30

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