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Facile Synthesis of 1-(substituted phenyl)-2-phenyl-4-(substituted benzylidine)-imidazole-5-ones and Antifungal Activity Studies against Phytopathogens

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Abstract

A series of five new 1-(substituted phenyl)-2-phenyl-4-(substituted benzylidine)-imidazole-5-one derivatives (or) 5(4*H*)-imidazolones have been synthesised adopting 3 °A Zeolite as catalyst. These compounds were assayed for their antifungal activity on three different selected phytopathogens which disparately affects the Jowar crop (Sorghum Vulgare) of Poaceae family. Among the tested molecules, compound 18 exhibited potent inhibitory activity when compared to the Bavistine (Positive control).

Keywords: 3 °A Zeolite; Phytopathogens; Antifungal activity; Imidazolone

Introduction

Imidazolones have been associated with several pharmacological [1-4] activities such as antimicrobial (antifungal, antibacterial and antiviral), anticancer activity, CNS depressant activity etc. Benzylidene derivatives have been reported to possess anticonvulsant and MAO inhibitory activity. Shaw et al. [5] have reported that certain 5-imidazolones act as cardiotonic agents. Thus construction of these heterocyclic systems using various synthetic methodologies is of great importance is combinatorial organic synthesis [6] and medicinal chemistry.

Attempts have been reported to synthesize these compounds by several methods [7,8] such as condensing glycine ester of acetimidic or phenylacetimidic acid in the presence of benzene, dioxane or acetone. A very few reports are cited in the literature where potent 5(4H)-imidazolones have been synthesized, which in turn acts as good precursors for various organic molecules such as Spiro[4,4]nona-2,8-dien-6-ones [9] and 1,2,6,8-tetra azaspiro [4,4]nona-2,6-dien-9-ones [10].

Though some of the imidazolones have been reported using microwave irradiation, a suitable support or sensitizer is invariable in many of these reactions [11]. Therefore a methodology in synthesizing these potent compounds is still a necessary requirement. To the best of our knowledge, the synthesis of imidazolones adopting zeolites [12] (crystalline aluminosilicates of various metals) were not extensively studied. Motivated by this fact, herein we report the synthesis and yields of imidazolones adopting 3 °A Zeolite [13,14] as catalyst. The application characteristics of this Zeolite include selective and fast adsorption speed, frequent regeneration ability, crushing and pollution resistance. We also investigated the antifungal properties of these imidazolones against specified pathogens *Fusarium oxysporum, Rhizoctonia solani and Curvularia lunata* which destroyed the Jowar plants. The lead molecules (17-21) were synthesised following the procedure described in Scheme 1.

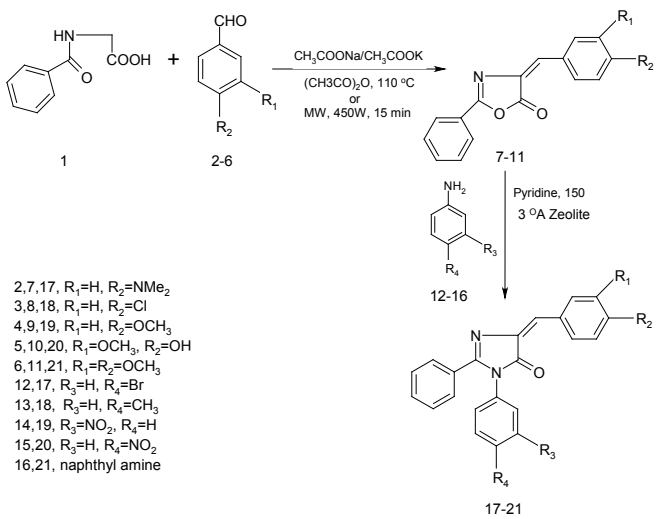
Experimental

All the melting points were recorded on VEB Analytica Dreader, HMK hot plate and are uncorrected. IR spectra (KBr) were recorded on Perkin Elmer IR 841 spectrophotometer.

^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL JNM FTNMR (90 MHz) spectrometer using $CDCl_3$ or DMSO(d6) and TMS as internal reference. GCMS were recorded on QP 5050A, Schimazu spectrometer. All the compounds showed satisfactory elemental analyses.

General procedure for the synthesis of oxazolones [15] (7-11) by conventional and microwave assisted methods

A mixture of different substituted benzaldehydes (2-6) (2.3 mmol), hippuric acid (2.6 mmol), acetic anhydride (7.2 mmol), sodium acetate (2.4 mmol) were refluxed at 110°C with constant stirring for 4 hr. The crude product was separated, filtered and washed with ice cold ethanol,



Scheme 1: The synthesis of lead molecules.

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followed by boiling water and recrystallised from chloroform. All the five oxazolones (7-11) were characterized using advanced spectroscopic data.

In microwave assisted synthesis of oxazolones (7-11) (450 W, 15 min), all the reactants were taken in the same mole ratios as that were taken in the usual conventional method. It was made sure that acetic anhydride was not evaporated from the mixture. The product obtained by this method was identical with that of the conventional method.

General procedure for the synthesis of 5(4H)-imidazolones (17-21) using 3°A Zeolite

Oxazolones (7-11) (0.01 mol) were heated to reflux with substituted anilines (12-16) (0.01 mol) in a solution of slight excess of pyridine (0.01 mol) in an oil bath at 150-170°C with activated 3 °A Zeolite as catalyst (2.5g). The excess of pyridine was distilled off in a Rota vapor, cooled and poured into crushed ice in 10% HCl. The crude imidazolone precipitated was filtered, dried over anhydrous $MgSO_4$, and chromatographed over Silica gel using hexane and ethyl acetate as eluants.

1-(4-bromophenyl)-2-phenyl-4-(4'-*N,N*-dimethyl benzylidene)-imidazol-5-one (17) : Light reddish solid, m.p: 152°C, IR (KBr, $\nu_{max,}$) in cm^{-1}: 2924, 2854, 2373, 2339, 1710, 1649, 1598, 1525, 1381, 1162, 761; ^{1}H NMR (90 MHz, DMSO, δ): 6.61-8.19 (m, 14H), 2.96 (s, 6H); ^{13}C NMR (22.5 MHz, DMSO, δ) : 166.8, 164.6, 132.2, 128.3, 36.7; Mass: m/z (446), 401, 368, 311, 290, 133; Anal. Calcd. for $C_{24}H_{20}N_3OBr$: C 64.57, H 4.48, N 9.41. found: C 64.55, H 4.49, N 9.39.

1-(4-methylphenyl)-2-anisyl-4-(4'-chloro benzylidene)-imidazol-5-one (18): Pale yellow solid; m.p: 174°C; IR (KBr, $\nu_{max,}$) in cm^{-1}: 2960, 2813, 2319, 2390, 1700, 1656, 1620, 1603, 813; ^{1}H NMR (90 MHz, DMSO, δ): 6.68-8.37 (m, 14H), 2.4 (s, 3H); ^{13}C NMR (22.5 MHz, DMSO, δ) : δ 167.1, 164.8, 134.6, 131.5, 26.5; Mass m/z (372), 295, 281, 248, 208, 164, 124; Anal. Calcd. for $C_{23}H_{17}N_2OCl$: C 74.09, H 4.56, N 7.51. found: C 74.01, H 4.56, N 7.49.

1-(3-nitrophenyl)-2-phenyl-4-(4'-methoxy benzylidene)-imidazol-5-one (19) : Lemon yellow solid; m.p: 121°C; IR (KBr, ν_{max}) in cm^{-1} : 3015, 2930, 2882, 2320, 1710, 1635, 1600, 1580, 1215; ^{1}H NMR (90 MHz, DMSO, δ): 7.03-8.35 (m, 14H), 3.86 (s, 3H); ^{13}C NMR (22.5 MHz, DMSO, δ): 167.9, 164.0, 132.1, 128.0, 54.2; Mass: m/z (399), 322, 279, 277, 239, 160, 120; Anal. Calcd. for $C_{23}H_{17}N_3O_4$: C 69.17, H 4.26, N 10.52. found: C 69.15, H 4.27, N 10.49.

1-(4-nitrophenyl)-2-phenyl-4-(3'-methoxy, 4'-hydroxy benzylidene)-imidazol-5-one (20): Yellow solid; m.p: 118 °C; IR (KBr, $\nu_{max,}$) in cm^{-1} : 3420, 3059, 2928, 1720, 1637, 1590, 1452, 1380, 1267, 1134, 813; ^{1}H NMR (90 MHz, DMSO, δ): 9.3 (s, 1H), 8.32 (d, J=8.1Hz, 2H), 7.01-7.92 (m, 11H), 3.98 (s, 3H); ^{13}C NMR (22.5 MHz, DMSO, δ): δ 168.9, 163.8, 131.6, 127.2, 54.1; Mass: m/z (415), 338, 293, 279, 239, 176, 136; Anal. Calcd. for $C_{23}H_{17}N_3O_5$: C 66.50, H 4.09, N 10.12. found : C 66.48, H 4.10, N 10.12.

1-(naphthyl)-2-phenyl-4-(4',5'-dimethoxy benzylidene)-imidazol-5-one (21): Pale yellow solid; m.p: 211 °C; IR (KBr, $\nu_{max,}$) in cm^{-1}: 3017, 2960, 2814, 2760, 2318, 1716, 1660, 1615, 1490, 1316, 1211; ^{1}H NMR (90 MHz, DMSO, δ): 6.82-8.20 (m, 16H), 3.85 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (22.5 MHz, DMSO, δ): 166.5, 160.9, 131.1, 126.5, 54.1, 54.3; Mass: m/z (434), 357, 307, 284, 244, 190, 150; Anal. Calcd. for $C_{28}H_{22}N_2O_3$: C 77.41, H 5.06, N 6.45. found: C 77.39, H 5.06, N 6.43.

Anti fungal activity

The antifungal activity of the synthesized imidazolones (17-21) were tested against three fungal phytopathogens *Viz.*, *Fusarium oxysporum, Rhizoctonia solani* and *Curvularia lunata* which effects Jowar plant (local name: Zonnalu) (Sorghum vulgare) of the family Poaceae. The method adopted for the present study was cup-plate method at 50 µg/mL. For the determination of Minimum Inhibitory Concentration (MIC), the compounds were tested at a concentration of 5, 25, 50, and 100 µg/mL, Bavistine (standard drug) was taken as positive control and DMSO as negative control for comparison of antifungal potency with tested compounds. Potato dextrose agar and Sabourds medium are used as culture media for these fungal phytopathogens.

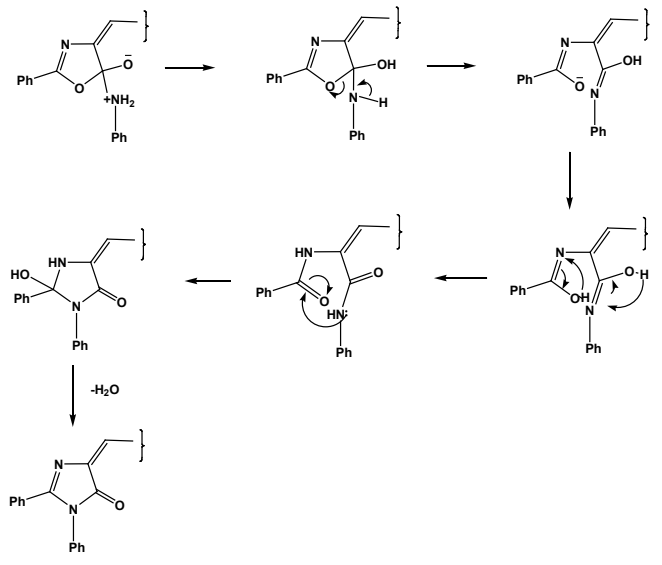
Results and Discussion

The key intermediates i.e., 5(4*H*)-oxazolones (7-11) were synthesised by us in both conventional and microwave assisted methods in good yields. Subsequently the target compounds (17-21) were synthesised using 3 °A zeolite [16,17] as catalysts. 5(4*H*)-oxazolones (7-11) were heated to reflux with various substituted aromatic amines (12-16) containing different electron donating and withdrawing groups is a solution of slight excess of pyridine with this catalyst. Further work up and chromatography over silica gel using hexane and ethyl acetate resulted in the final products. We observed in this study, that the reaction times were drastically less and high yields of the products i.e., 5(4H)-imidazolones were obtained adopting large pored sized 3 °A zeolite as catalyst over conventional method without catalyst as visualized from Table 1.

The structures of the target molecules were characterized using advanced spectroscopic data V.I.Z., FT-IR, FT-NMR, mass and elemental analysis. A plausible mechanism is shown in Scheme 2, refers to that, the large pore sized 3 °A zeolite affected the dehydration effectively, thus paving way for increase in the yield of the products i.e., imidazolones(17-21) (Table 1) in less reaction times.

Antifungal evaluation

Antifungal activity was tested against the fungal phytopathogens i.e., *F. oxysporum, R. solani and C. lunata* which badly affect the Jowar crop. *In vitro* antifungal activity of the target molecules (17-21) was evaluated by cup-plate method at 50 µL of compound concentration [18,19], MIC (minimum inhibitory concentration) was determined by



Scheme 2: A plausible mechanism showing the formation of 5(4*H*)-imidazolone.

Compound	17	18	19	20	21
Catalyst					
Conventional Heating (without catalyst)	22 (14.30 h)[a]	26 (15 h)[a]	20 (15 h)[a]	23 (13 h)[a]	25 (13.30 h)[a]
3 °A Zeolite	69 (6 h)[a]	65 (5.30 h)[a]	60(5 h)[a]	60 (6.30 h)[a]	62 (6 h)[a]

[a]The values inside the brackets indicate the reaction times for the formation of the products

Table 1: Percentage yields of imidazolones(**17-21**) with 3 °A Zeolite as catalyst.

Diameter of Zone of Inhibition(mm)												
	Fusarium oxysporum				*Rhizoctonia solani*				*Curvularia lunata*			
Conc.(µg/mL) Compd.	5	25	50	100	5	25	50	100	5	25	50	100
17	-	13	14	15	15	18	19	19	13	14	16	19
18	-	16	19	19	19	20	22	24	9	10	18	20
19	-	-	-	5	9	11	13	14	7	9	9	10
20	7	9	10	10	10	11	13	15	9	10	10	11
21	-	6	7	7	6	7	8	8	7	8	8	9
Bavistine	-	17	-	-	18	20	22	-	-	15	16	20

(- indicates no activity)
(Solvent DMSO did not have inhibition zone against all the three organisms)

Table 2: Antifungal evaluation of imidazolones (17-21).

assessing the fungal growth at various concentrations of compounds *viz*., 5, 25, 50 and 100 µg/mL for their values. The MIC values and zones of inhibition were comparable with Bavistine a standard antifungal drug. Bavistin [20] is a broad spectrum systemic fungicide containing 50% WP carbendazim and is effective against a wide range of pathogenic fungi and is highly specific in its control of important plant pathogens on a variety of crops such as omamental plants and plantation Crops. DMSO Solvent employed as negative control and which was not showed any effect on the tested fungal strains. The results are presented in Table 2.

All compounds (17-21) showed good antifungal activity against the specified pathogens. Compound 18 showed a comparable activity to that of standard drug used (Bavistine) against *R. solani*. Moreover the least MIC values for compound 18 against *R. solani* and *C. lunata* demonstrated its potency (Table 2) against these fungal strains. Compound 20 showed MIC value at 5 µg/mL against *F. oxysphorum* which proved to be better than the positive control. The MIC values were better for compounds 17-20 against *C. lunata* compared to the standard drug employed. Strong electron withdrawing groups on phenyl ring in compounds 18 and 20 (-Cl & -NO_2) could obviously effect on pharmacological activity and antifungal spectrum.

Conclusion

In conclusion we have developed a new synthetic methodology for a facile synthesis of 5(4H)-imidazolones using 3 °A Zeolite as catalyst. These compounds exhibited potent anti-fungal activity against the specified phytopathogens. The conclusions made were just preliminary, further studies on their synthesis and other pharmacological properties are in progress.

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