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SYNTHESIS AND ANTIBACTERIAL SCREENING OF SOME PYRAZOLE AND CHROMONE DERIVATIVES

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Abstract
A series of pyrazole and chromone analogues were synthesized using silica perchloric acid($HClO_4$-SiO_2) catalyzed condensation of 4-oxo-4H-chromene-3-carbaldehyde (**1**) or 1-phenyl-3-aryl-1H-pyrazole-4-carbaldehyde(**4**) with 3-methyl-1-phenyl-1H-pyrazol-5-(4H)-one (**2**) The synthesized compounds were screened for their antibacterial activity against *E. coli*, *S. albus* and *S. aureus*.

Key word*:* Knoevenagel condensation, silica perchloric acid, heterogeneous catalyst, antibacterial acivity.

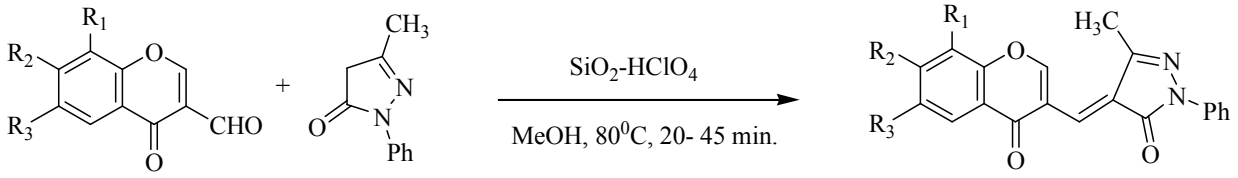
Introduction

Knoevenagel condensation reaction is one of the important C-C bond formation reactions widely used for the synthesis of natural products, biologically active compounds, perfumes and polymers.[i] Various methods are reported in literature which involve use of acid or base catalysts and even neutral media. The methods reported so far using catalysts such as Al_2O_3,[ii] SmI_3,[iii] anionic resin,[iv] clay [v] and calcined hydrotalcites.[vi] Recently, Shingare M S et al [vii] studied the Knoevenagel reaction of 4-oxo-(4*H*)-1-benzopyran-3-carboxaldehyde, 1,3-diphenyl-1*H*-pyrazol-4-carboxaldehyde and aromatic aldehydes with 3-methyl-1-phenyl pyrazolin-5(4*H*)-one under different condition. The reported methods are generally requires drastic reaction conditions, use of strong acid or base catalyst, lack of catalyst reusability and selectivity.[viii]

Pyrazole and its synthetic analogues have gain much attention due to their widespread applications in synthesis of agrochemical and potentially active drug candidates.[ix] Pyrazole derivatives also exhibit a range of biological activities *viz*. antioxidant, antipyretic, antiviral, anti-inflammatory and antidepressant.[ix] Moreover, compounds containing chromene backbone are numerous biological applications.[xi] The synthesis of chromone derivatives can be achieved efficiently by the condensation of active methylene group containing compounds with 4-oxo-4H-chromene-3-carbaldehyde.[xii]

Result and Discussion

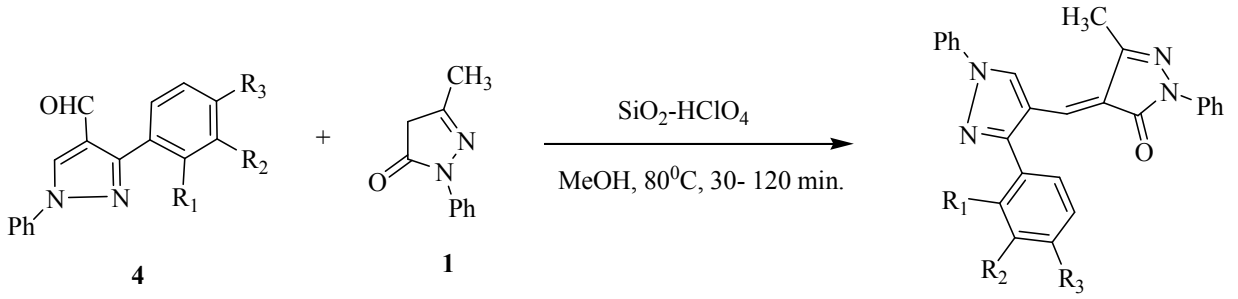
In continuation to our ongoing research programme on the development of novel methodologies for the bioactive compounds,[xiii] the target was to find out an efficient and mild method for the synthesis of bioactive targets. Herein, synthesis of a series of 3-methyl-4-[(4-oxo-4*H*-chromen-3-yl)-methylene]-1-phenyl-1*H*-pyrazol-5-(4*H*)-ones (Scheme 1) and 3-methyl-4-[(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-1-(aryl)-pyrazolin-5(4*H*)-ones using silica supported perchloric acid as a reusable solid acid catalyst (Scheme 2).



1 **2** **3(a-f)**

3a: R_1= R_2 = H; R_3= Cl
3b: R_1=R_3 = H; R_2 = H
3c: R_1= R_3 = Me; R_2= H
3d: R_1= H; R_2 = Me; R_3 = Cl
3e: R_1= R_2 = H; R_3 = Me
3f: R_1= Cl; R_2=R_3 = H

Scheme 1.



4 **1** **5(a-f)**

5a: R_1= R_2 = H; R_3= Cl
5b: R_1=R_3 = H; R_2 = Me
5c: R_1= R_3 = Me; R_2= H
5d: R_1= H; R_2 = Me; R_3 = Cl
5e: R_1= R_2 = R_3 = H
5f: R_1= R_3 =Cl; R_2== H

Scheme2.

For optimization of reaction, condensation of 3-methyl-1-phenyl-1H-pyrazol-5-(4H-one(2) was carried out with chromone aldehyde(1a) or pyrazole aldehyde (**4a**) using silica perchloric acid in various solvents such as methanol, ethanol, dichloromethane, acetonitrile, carbon tetrachloride, THF, 1,4-dioxane and DMF at various temperature range(60-100 ^{0}C). It has been found that methanol is the best solvent and 80 ^{0}C temperature was selected as an optimized temperature and same is used for through study (**Table 1 and 2**).

In order to study the scope and generality of reaction, various pyrazole aldehyde and chromone aldehydes with electron donating as well as electron withdrawing groups were subjected to Knoevenagel condensation. In all cases condensation products are obtained good to excellent

yield with high purity (**4** and **5**). Further reusability study of catalyst for formation of **3a** revealed that silica perchloric acid was reusable for three turns without satisfactory decrease in yield of the product (**3a**: Ist run **Yield = 82%;** IInd turn **Yield = 82 %**; IIIrd turn **Yield = 80** %) Synthesized compounds were evaluated for their antibacterial screening against gram –ve and gram +ve bacteria such as *E. coli*, *S. albus* and *S. aureus*.

Antibacterial activity

The antimicrobial activities of synthesized compounds were determined using cup plate method. The in vitro antibacterial activity was carried out against 24 hour old culture of *Escherichia coli, Staphylcoccus albus and Staphylcoccus aureus*. The compounds were tested at a concentration of 0.001 mole/ml in N, N-dimethyl formamide. Chloramphenicol (0.001 mole/ml) was used as standard for antibacterial activity (**Table 3**).

Experimental Part

All chemicals were of AR grade. The melting points were recorded in the open capillary tube and are uncorrected. The IR spectra were recorded on Bomen FT-IR MB-104 Spectrophotometer with KBr discs. ^{1}H-NMR was recorded on Brucker AC-300 MHz in $CDCl_3$ using TMS as an internal standard.

General procedure for the synthesis of silica perchloric acid($HClO_4$-SiO_2):$HClO_4$ (1.25 gm, 12.5 mmol, as a 70% aqueous solution) was added to the suspension of silica gel (23.75 gms.230-400 mesh) in diethyl ether (75 ml). The mixture was concentrated and residue was dried under vacuum at 100^{0}C for 72 hrs. to afford $HClO_4$-SiO_2(0.5 mmolegm^{-1}) as a free flowing powder.

General procedure for the synthesis of 3-methyl-4-[(chromon-3-yl)methylene]-1-(phenyl)-pyrazolin-5(4H)-ones and 3-methyl-4-[(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-1-(aryl)-pyrazolin-5(4H)-ones: A mixture of 4-oxo-4H-benzopyran-3-carbaldehydes **1(a-f)** or 1,3-diphenyl-1H-pyrazol-4-carboxaldehyde **4(a-f)** (5mmol), 3-methyl-1-phenyl-1Hpyrazol-5 (4H)-ones **2** (5mmol), $HClO_4$-SiO_2 (350 mg) in methanol(10 ml) was heated at 80^{0}C for specified time(Table 1 and 2). After completion of reaction(as indicated by TLC), reaction mixture was filtered when hot. The solvent was removed in reduced pressure. The resultant solid obtained was purified by recrystallization. Catalyst was collected and washed with acetone(5ml), dried and used for subsequent reaction.

Table 1. Synthesis of 3-methyl-4-[(chromon-3-yl)methylene]-1-(phenyl)-pyrazolin-5(4H)-ones (**3**)

Entry	R_1	R_2	R_3	Time(min)	Yield (%)	M.P.(°C) [a]
3a	H	H	Cl	30	82	237-239
3b	H	Me	H	45	75	203-204
3c	Me	H	Me	30	69	283-285
3d	H	Me	Cl	30	77	254-255
3e	H	H	Me	30	89	240-241
3f	Cl	H	H	20	84	219-222

[a]Yield of pure isolated products.

Table 2. Synthesis of 3-methyl-4-[(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-1-(aryl)-pyrazolin-5(4H)-ones(**5**):

Entry	Substituents			Time. (min)	Yield (%)	M.P.(^{0}C)[a,b]
	R_1	R_2	R_3			
5a	H	H	Cl	30	65	110-114
5b	H	Me	H	45	74	247-248
5c	Me	H	Me	30	58	280-283
5d	H	Me	Cl	120	75	256-258
5e	H	H	H	30	88	235-236
5f	Cl	H	Cl	50	62	298-300

[a]Yield of pure isolated products.

Table 3. Antibacterial activities of the synthesized compounds **3(a-f)** and **5(a-f)**

Compounds				Antibacterial activity Zone of inhibition in mm		
Entry	**R_1**	**R_2**	**R_3**	***E. coli***	***S. albus***	***S. aureus***
4a	H	H	Cl	**40**	**33**	**50**
4b	H	Me	H	08	12	18
4c	Me	H	Me	15	24	28
4d	H	Me	Cl	30	15	---
4e	H	H	Me	---	**45**	37
4f	Cl	H	H	**36**	13	---
5a	H	H	Cl	12	---	17
5b	H	Me	H	22	18	31
5c	Me	H	Me	15	06	25
5d	H	Me	Cl	26	10	---
5e	H	H	H	19	32	24
5f	Cl	H	Cl	**39**	**45**	**40**
Chloramphenicol				38	37	44
DMF				+ve	+ve	+ve

+ve indicates growth of microbes
DMF is used as control

Spectral data of representative compounds

3-Methyl-4-[(6-methyl-4-oxo-4H-chromen-3-yl)methylene]-1-phenyl-1H-pyrazol-5 (4H)-one (3c) : Yield: 69%; IR (KBr): 3063, 1790, 1685, 1654, 1460, 2900 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.4 (s, 3H), 2.5 (s, 3H), 7.2-8.2 (m, 9H), 10.8 (s, 1H).

3-Methyl-4-[(6-chloro-7-methyl-4-oxo-4H-chromen-3-yl)methylene]-1-phenyl-1H-pyrazol-5(4H)-one (5d): Yield; 75%; IR (KBr): 3063, 1790, 1685, 1654, 1460, 680, 2885 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 2.3 (s, 3H), 2.4 (s, 3H), 7.2-7.9 (m, 8H), 10.9 (s, 1H).

3-methyl-1-phenyl-4-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)methylene)-1H-pyrazol-5(4H)-one(5e): Yield; 88%; IR (KBr): 3116.7, 2922, 1645; ^{1}H NMR δ= 1.1(s,3H), 2.3(s,3H),7.7(s,1H), 8.0(s,1H), 7.3(d, 2H), 7.5(d, 2H),7.8- 8.1 (m,5H).

Conclusion

In conclusion, a series of structurally diverse analogues of pyrazole and chromone derivatives has been reported under heterogeneous catalysis. The synthesized compounds were screened for there antibacterial activities. Among the tested compound 41, 4e, 4f and 5f shows remarkable activity against gram –ve and gram +ve bacterias.

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