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Swati R Jadhav
(A) Department of Chemistry, Modern College of Arts, Science and Commerce, Ganeshkhind, Pune, India
(B) Prof. Ramkrishna More Arts, Commerce and Science College, Akurdi, Pune, Maharashtra, India

Manoj Gayake
Department of Chemistry, Modern College of Arts, Science and Commerce, Ganeshkhind, Pune, Maharashtra, India

Sushma R Katade
Department of Chemistry, Modern College of Arts, Science and Commerce, Ganeshkhind, Pune, Maharashtra, India

Correspondence
Sushma R Katade
Department of Chemistry, Modern College of Arts, Science and Commerce, Ganeshkhind, Pune, Maharashtra, India

Synthesis of series of chalcone and pyrazoline derivatives

Swati R Jadhav, Manoj Gayake and Sushma R Katade

Abstract
Amongst heterocyclic compounds, nitrogen containing five membered heterocycles, Pyrazoline has to be the most useful for biological activities. Pyrazoline refers to the class of simple five member ring organic compounds of the heterocyclic series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature. Literature survey shows, pyrazoline derivatives were found to have potential antipyretic-analgesic, tranquillizing, muscle relaxant, psycho analeptic, antiepileptic, antidepressant, anti-inflammatory, insecticidal and antimicrobial and antihypotensive activities. One of the methods for the synthesis of Pyrazoline derivatives is from α, β-unsaturated carbonyls (chalcone) by cyclization with hydrazine and substituted hydrazines. Chalcone are prepared by condensing Aryl ketones with aromatic aldehydes in presence of suitable condensing agents. In this paper we report the synthesis and characterization by ^{1}H-NMR of series of some chalcone and pyrazoline derivatives were synthesised.

Keywords: Chalcone, Pyrazoline, hydroxyl acetophenone, methoxy benzaldehyde

1. Introduction
Chalcone is a class of compounds, which has many applications in different fields. α, β-unsaturated carbonyls used as a key intermediates for the preparation of number of heterocyclic compounds such as thiazine, oxazines, isoxazoles and pyrazoles. chalcone can be used as an initial compound for synthesis of a lots of compounds [1].
Pyrazoline- categorized as nitrogen- containing heterocycles, are well known for their interminable participation in the field of perpetual research and development of therapeutical active agents. As a consequence pyrazolines became an inevitable core of numerous drugs having diverse activities [2]. 4, 5-dihydro-1H-pyrazolines seem to be the most frequently studied pyrazoline type compounds. As a result, a large number of such pyrazolines using different synthetic methods for their preparation have been described in the chemistry literature [3]. 3-hydroxy-3,4-dihydroxypyrazoles or hydroxyl-pyrazolines are observed as stable isolated intermediates that can be fully characterized prior to loss of second molecule of water that gives rise to pyrazoles [4]. They have considered being important for drug and agricultural chemicals, several prominent effects such as antimicrobial, antimycobacterial, antifungal, antiamoebic, anti-inflammatory, analgesic, antidepressant and anticancer activities [3]

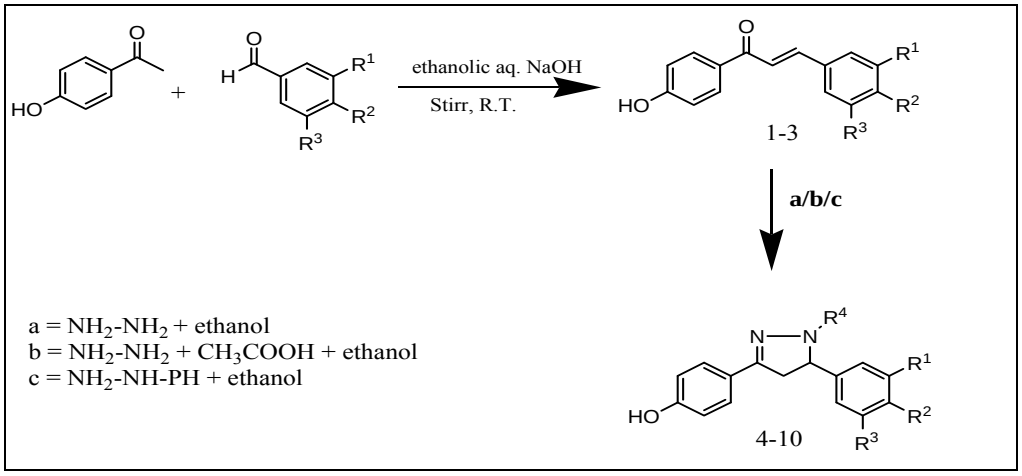
2. Experimental Section
2.1. General Procedure for Synthesis of Chalcone (Compound 1-3)
To a solution of p-hydroxy acetophenone (1 mmol) and substituted methoxy benzaldehyde (1 mmol) dissolves in ethanol (3-5 ml). To that mixture add catalytic amount of NaOH was added and the reaction mixture was stirred for about 8 h at room temperature. The reaction was monitored on Merck pre-coated aluminum TLC plates 60F-254 and product was visualized by UV-light using n-hexane and ethyl acetate as solvent system. After completion of the reaction, the reaction mixture was poured into ice cold water the precipitate was filtered, dried and crystalized from ethanol. (If precipitate has not been obtained, the reaction mixture was neutralized with 1N HCl)

2.2. General Procedure for Preparation of Pyrazoline Derivatives from Chalcone (Compound 4-10)
2.2.1 For hydrazine derivative: To a chalcone (1 mmol) in ethanol (5 ml), hydrazine hydrate (1 mmol) was added drop wise in a round bottom flask. The reaction mixture was heated at

80 ^{0}C under reflux for 5 h on oil bath. The reaction was monitored on Merck pre-coated aluminum TLC plates 60F-254 and product was visualized by UV-light using n-hexane and ethyl acetate as solvent system. After completion of reaction, the reaction mixture poured into ice cold water the precipitate was settle down at a bottom, precipitate filtered, dried and crystalized from ethanol.

2.2.2 For acetyl hydrazine derivative: To a chalcone (1 mmol) in ethanol (5 ml), glacial acetic acid (1 mmol), hydrazine hydrate (1 mmol) was added in a round bottom flask. The reaction mixture was heated at 80 ^{o}C under reflux for 6 h on oil bath. The reaction was monitored on Merck pre-coated aluminum TLC plates 60F-254 and product was visualized by UV-light using n-hexane and ethyl acetate as solvent system. After completion of reaction, the reaction mixture poured into ice cold water the precipitate was filtered, dried and crystalized by ethanol.

2.2.3 For Phenyl hydrazine derivative: To a chalcone (1 mmol) in ethanol (5 ml), phenyl hydrazine hydrate (1 mmol) was added drop wise in a round bottom flask. The reaction mixture was heated at 80 ^{o}C under reflux for 4 h on oil bath. The reaction was monitored on Merck pre-coated aluminum TLC plates 60F-254 and product was visualized by UV-light using n-hexane and ethyl acetate as solvent system. After completion of reaction, the reaction mixture poured into ice cold water the precipitate was filtered, dried and crystallize from ethanol.



Scheme 1.

1	R^1=R^3=H, R^2=OCH_3
2	R^1=H, R^2=R^3=OCH_3
3	R^1=R^2=R^3=OCH_3
4	R^1=R^3=H, R^2=OCH_3, R^4=H
5	R^1=R^3=H, R^2=OCH_3, R^4=$COCH_3$
6	R^1=H, R^2=R^3=OCH_3,R^4=$COCH_3$
7	R^1=H, R^2=R^3=OCH_3, R^4=Ph
8	R^1=R^2=R^3=OCH_3, R^4=H
9	R^1=R^2=R^3=OCH_3, R^4=$COCH_3$
10	R^1=R^2=R^3=OCH_3, R^4=Ph

3. Result and Discussion

Compound (1): ^{1}H NMR spectra of *(E)-1-(4-hydroxyphenyl)-3-(methoxyphenyl)prop-2-en-1-one*, $C_{16}H_{14}O_3$, was purified by recrystallization in ethanol, yellowish solid, m.p. 167 ^{o}C, yield 69.89%. ^{1}H NMR [$CDCl_3$, 500 Mz] spectra shows characteristic signals at 3.91 δ (3H), 6.90 δ (2H), 6.92 δ (2H) 7.03 δ (2H), 7.01 δ (1H), 7.32 δ (1H), 7.85 δ (1H), 7.86 δ (1H).

Compound (2): ^{1}H NMR spectra of*(E)-3-(3*,4-dimethoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one, $C_{17}H_{14}O_4$, was purified by recrystallization in ethanol, yellowish solid, m.p. 195 ^{o}C, yield 87.50%. ^{1}H NMR [$CDCl_3$, 500 Mz] spectra shows characteristic signals at 3.96 δ (3H), 3.98 δ (3H), 6.90 δ (1H), 6.94 δ (2H) 7.17 δ (1H), 7.27 δ (1H), 7.42 δ (1H), 7.76 δ (1H), 8.01 δ (1H).

Compound (3): *(E)-1-(*4-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one,$C_{18}H_{18}O_5$, was purified by recrystallization in ethanol, yellowish solid, m.p. 218 ^{o}C, yield 94.78%. ^{1}H NMR [$CDCl_3$, 500 Mz] spectra shows characteristic signals at 3.94 δ (s 3H), 3.95 δ (s 3H) 3.93 δ (s 3H), 6.86 δ (d, J=8Hz 1H), 6.87 δ (d, J= 8Hz, 1H) 6.92 δ (dd, J= 2 Hz & 8 Hz, 2H), 7.40 δ (d, J= 16Hz, 1H), 7.90 δ (d, J= 16 Hz, 1H), 8.01 δ (dd, J= 2Hz & 8Hz,2H).

Compound (4): 4-(5-(4methoxyphenyl)-4,5-dihydro--1H-pyrazol-3-yl)phenol, $C_{16}H_{16}N_2O_2$, was purified by recrystallization in ethanol, whitish solid, m.p. 128 ^{o}C, yield 73.07%. ^{1}H NMR [$CDCl_3$, 500 Mz] spectra shows characteristic signals at 3.81 δ (3H), 3.04 δ (1H), 3.42 δ (1H), 4.86 δ (1H), 6.84 δ (2H) 6.88 δ (2H), 7.28 δ (2H), 7.52 δ (2H).

Compound (5): 1-(3-(4-hydroxyphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone, $C_{18}H_{18}N_2O_3$was purified by recrystallization in ethanol, solid, m.p. 152 ^{o}C, yield 63.93%. ^{1}H NMR [$CDCl_3$, 500 Mz] spectra shows characteristic signals at 3.87 δ (3H), 6.93 δ (2H), 6.96 δ (1H), 6.86 δ (2H), 7.59 δ (2H).

Compound (6): 4-(5-(4methoxyphenyl)-1-phenyl-4,5-dihydro--1H-pyrazol-3-yl) phenol, $C_{22}H_{20}N_2O_2$, was purified by recrystallization in ethanol, brown solid, m.p. 151 ^{o}C, yield 55.22%. ^{1}H NMR [$CDCl_3$, 500 Mz] spectra shows characteristic signals at 3.81 δ (3H), 3.05δ (1H), 3.42 δ (1H), 4.87 δ (1H), 6.84 δ (2H) 6.88 δ (2H), 6.89 δ (2H), 6.87 δ (1H), 7.56 δ (2H), 7.28 δ (2H), 7.52 δ (2H).

Compound (7): 4-(5-(3,4-dimethoxyphenyl)-4,5-dihydro--1H-pyrazol-3-yl)phenol, $C_{17}H_{18}N_2O_3$ was purified by recrystallization in ethanol, whitish solid, m.p. 192 ^oC, yield 55.76%. ^1H NMR [$CDCl_3$, 500 Mz] spectra shows characteristic signals at 3.88 δ (6H), 3.04 δ (1H), 3.43 δ (1H), 4.867δ (1H), 6.83 δ (1H), 6.84 δ (1H), 8.96 δ (1H), 6.96 δ (2H), 7.56 δ (2H).

Compound (8): 1-(5-(3,4-dimethoxyphenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone, $C_{19}H_{20}N_2O_4$ was purified by recrystallization in ethanol, whitish solid, m.p. 182-183 ^oC, yield 52.54 %. ^1H NMR [$CDCl_3$, 500 Mz] spectra shows characteristic signals at 3.88 δ (6H), 3.02 δ (3H) 3.04 δ (1H), 3.43 δ (1H), 4.87δ (1H), 6.83 δ (1H), 6.84 δ (1H), 8.86 δ (1H), 6.86 δ (2H), 7.59 δ (2H).

Compound (9): 1- (3-(4-hydroxyphenyl) - 5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) ethanone, $C_{20}H_{22}N_2O_5$ was purified by recrystallization in ethanol, whitish solid, m.p. 209 ^oC, yield 53.44%. ^1H NMR [$CDCl_3$, 500 Mz] spectra shows characteristic signals at 3.86 δ (3H), 3.91 δ (3H), 3.94 δ (3H), 2.19 δ (3H) 3.04 δ (1H), 3.45 δ (1H), 4.86 δ (1H), 6.63 δ (1H), 6.42 δ (1H), 8.86 δ (1H), 6.99 δ (2H), 7.56 δ (2H).

Compound (10): 4-(1-phenyl-5-(3, 4, 5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl) phenol, $C_{24}H_{24}N_2O_4$ was purified by recrystallization in ethanol, whitish solid, yield 75%. ^1H NMR [$CDCl_3$, 500 Mz] spectra shows characteristic signals at 3.86 δ (3H), 3.91 δ (3H), 3.94 δ (3H), 2.19 δ (3H) 3.04 δ(1H), 3.45 δ (1H), 4.86 δ (1H), 6.42 δ (2H), 6.86 δ (1H), 6.86 δ (2H), 6.87 δ (1H), 7.71 δ (2H), 6.99 δ (2H), 8.02 δ (2H).

4. Conclusion

We have reported here in the synthesis and characterization of pyrazoline derivatives from α, β-unsaturated chalcone. The chalcone was synthesized by typical Claisen Schmidt condensation from ketone & aldehyde. Here in the ketone is p-hydroxyacetophenone and different methoxy substituted benzaldehyde are used. The reaction was monitored by Thin Layer Chromatography using Merck pre-coated aluminum TLC plate's 60F-254 and melting points. All synthesized derivatives are fully characterized by using NMR spectroscopy. The compounds (1-10) are in good yield.

5. Acknowledgment

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