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Design and synthesis of 2-pyrazoline derivatives

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ABSTRACT

Some substituted pyrazoline -1-carbothiamides have been synthesized using cyclization reaction of chalcones and thiosemicarbazide. Some acetophenone derivatives were treated with appropriate substituted benzaldehydes in the presence of ethanol as solvent and sodium hydroxide as basic medium to furnish some substituted chalcones. These chalcones were treated with thiosemicarbazide yielding substituted 3,5-diphenyl-4,5-dihydro-1-H-pyrazole-1-carbothioamides which are named as 2-pyrazoline derivative. The reaction progress for all synthesized compounds was checked by thin layer chromatography (TLC) and melting point techniques, the structure of synthesized compounds were confirmed using IR, [1]HNMR, and GCMS.

Keywords: Acetophenone, Benzaldehydes, Chalcones, Thiosemicarbozide.

INTRODUCTION

Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings or one aromatic and other alkyl group are linked by a three carbon α, β-unsaturated carbonyl system. There is variety of methods used for the synthesis of chalcones, the commonly used one is Claisen-Schmdit condensation reaction between benzaldehydes and ketones[1].Pyrazolines are five member heterocyclic compounds containing two adjacent nitrogen atoms with one double bond C=N. Pyrazoline and their derivatives have been found to possess a variety of significant and diverse chemical and pharmacological activities such as antibacterial, antifungal, antiviral, antitubercular, antidepressant, antiamoebic, anti-inflammatory, anticonvulsant, analgesic and anticancer activities[2,3].Cyclization reaction of chalcones with thiosemicarbazide in the presence of basic medium and ethanol under reflux for some hours form pyrazoline-1-carbotrhiamide derivatives,[4-8].

The present work aimed to synthesize certain designed 2-pyrazolines and to investigate and correlate their spectroscopic data.

MATERIALS AND METHODS

All chemicals used in this work were of analytical grade and obtained from LOBA company (India) and were used without further purification, melting points were recorded with Gallenkamp melting point apparatus and were uncorrected, IR spectrum (in KBr disk) is recorded using FTIR-8400s instrument (Shimadzu, Japan) and frequencies are expressed in cm^{-1}. The ^{1}HNMR recorded on Ultrashield-500 plus instrument (BRUKER, Germany) using DMSO as solvent, the values is expressed in δ ppm. GCMS spectra performed on QP 2010 GC instrument (Shimadzu, Japan).

a) **General procedure for synthesis of α,β-unsaturated carbonyl compounds.**
To 0.01mol of alkyl or aryl methyl ketone and 0.01 mol of benzaldehyde in a 10 ml of 95% ethanol,10ml of sodium hydroxide (2M) was added dropwise and the reaction mixture was stirred under room temperature for 24 hours. The reaction mixture was allowed to stand overnight, powered into cold water 30ml and acidified with diluted hydrochloric acid (10%).The precipitate was filtered, washed with cold water, air dried and recrystallized from ethanol.

I:1,3-diphenyl-prop-2-en-1-one:Yield: 76.30%, **mp**, 53-56C̊. **IR (KBr, cm^{-1})** 1664.14 (C=O), 1607.84 (olefin C=C), 1575.37, 1495.88 (arom C=C). **^{1}H-NMR(DMSO, mpp)**: 7.59,(***d***,1H α) ,8.03(***d***,1Hβ) ,7.33-7.50 (m, 10H).

II:3-(3-nitrophenyl)-1-phenylprop-2-en-1-one: Yield: 69%, mp, 136-138C̊, **IR (KBr, cm^{-1})**1661.92 (C=O), 1608.59 (olefin C=C), 1576.58, 1458.10,(arom C=C), 2366.29

(C-H aliphatic), 2344.25(arom C-H), 1527.18, 1350.37 (NO_2).**^{1}H-NMR(DMSO, mpp)**: 7.80,(d,1H α), 8.13(d,1Hβ), 7.60 -8.24 (m, 9H.Ar).

III:3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one: Yield, 62%, **mp**, 86-88C̊, **IR (KBr,cm^{-1})**1654.19(C=O), 1560.03(olefinC=C),1508.27, 1458.22(aromC=C),1262.95, 1211.98(OCH_3). **^{1}H-NMR(DMSO, mpp)**: 7.59, (d,1H α), 8.02(d,1Hβ), 6.64-7.60 (m, 9H-Ar), 3.50(s, 3H, OCH_3).

IV:**1-(4-aminophenyl)-3-(3-nitrophenyl)prop-2-en-1-one**: **Yield:**55%, mp, 146-148C̊, **IR (KBr, cm^{-1})**1684.26, (C=O), 1635.99 (olefin C=C), 1558.32, 1442.61,(arom C=C),2368.25 (C-H aliphatic), 2344.38(arom C-H), 1528.14, 1341.50, (NO_2), 3422.35 (NH_2). **^{1}H-NMR(DMSO, mpp)**: 6.786,(d,1H α),6.682(d,1Hβ),6.80-7.5 (m, 8H),5.25(s, 2H, NH_2).

V:(4-nitrophenyl)-3-phenylprop-2-en-1-one: **Yield**:57%, **mp**, 145-147C̊, **IR (KBr, cm^{-1})** 1675.62 (C=O), 1613.91 (olefin C=C), 1558.00, 1475.75,(arom C=C),2360.27 (C-H aliphatic), 2344.87 (arom C-H), 1508.73, 1325.01 (NO_2).

VI:1-(4-bromophenyl)-3-phenylprop-2-en-1-one: **Yield**:77%, **mp**, 108-110C̊, **IR (KBr, cm^{-1})** 1670.62 (C=O), 1600.01 (olefin C=C), 1580.00, 1458.00,(arom C=C),2368.00 (C-H aliphatic), 2344.50 (arom C-H), 780.0 (Br).

VII:1-(4-aminophenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one: **Yield**:75%, **mp**, 96-98C̊, **IR (KBr, cm^{-1})** 1685.62 (C=O), 1615.91 (olefin C=C), 1582.80, 1481.97,(arom C=C),2672.27 (C-H aliphatic), 2555.87 (arom C-H), 1528.31, 1355.25 (NO2).

VIII:1-(4-bromophenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one:**Yield**:79%, **mp**, 139-142C̊, **IR (KBr, cm^{-1})**1665.00 (C=O), 1600.09 (olefin C=C), 1557.00, 1440.00,(arom C=C),2352.90 (C-H aliphatic), 2344.19 (arom C-H), 2880.0 (CH_3)1190.0 (C-N)812.0 (Br).

b): **General procedure for Synthesis of 3,5-diaryl and 3-alkyl-5-aryl-4,5-dihydro-1H-pyrazole-1-carbothioamides.**
A solution of sodium hydroxide (1 g, 0.025 mol) and the required Chalcone (0.01 mol) in ethanol 25 ml, thiosemicarbazide (0.92 g, 0.01mol) was added slowly under stirring. After addition completed, the reaction mixture was refluxed for one hour and the solution was added to crush ice. The resulting solid was washed with ether and cold water, filtered. The crystals were washed thoroughly with ice-cold water, air dried and recrystallized from ethanol.

IX. 3,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide: **Yield**:65%, **mp**, 121-123C̊, **IR (KBr, cm^{-1})** 1585.48 arom(C=C), 1635.09 (C=N), 1093.97 (N-N), 1351.59,(st.v,N-C),1383.89(st,v C=S), 3143.55, 2923.98 (C-H), 3420.42 (NH_2).**^{1}H-NMR (DMSO, mpp)**: 7.27-7.63,(m,10H,Ar-H),3.482(m,2H, CH_2),3.951(m,1H, CH),8.02 (s,2H,NH_2).

X.5-(3-nitrophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide:**Yield**:55%, **mp**, 167-169C̊, **IR (KBr, cm^{-1})** 1530.89arom (C=C), 1638.81 (C=N), 1095.42 (N-N), 1345.00,(st.v,N-C), 1384.25 (st,v C=S), 2852.02, 2921.42 (C-H), 3116.61 (NH_2). **^{1}H-NMR (DMSO, mpp)**: 7.10-8.10,(m,9H,Ar-H),3.36,2.95(m,2H, CH_2),3.95(m,1H, CH), 8.95 (s,2H,NH_2). **MS (m/z):** 265.14, 281.15.

XI.5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide:**Yield**:61%, **mp**, 126-128C̊, **IR (KBr, cm^{-1})** 1510.60arom (C=C), 1603.10 (C=N), 1028.98 (N-N), 1304.55,(st.v,N-C), 1383.50 (st,v C=S), 2838.28,

2929.73 (C-H), 3422.46 (NH_2), 1248.82 (OCH3). **^{1}H-NMR (DMSO, mpp)**:7.10-7.62,(m,9H,Ar-H),3.42,3.55(s,2H, CH_2),3.91 (s,1H, CH), 10.12 (s,2H,NH2), 3.83 (s,3H,OCH_3).

XII.3-(4`-aminophenyl)-5-(3-nitrophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide:**Yield**:63%, **mp**, 166-168Ċ, **IR (KBr, cm^{-1})**1556.60arom (C=C), 1620.00 (C=N), 1100.92 (N-N), 1350.67,(st.v,N-C), 1384.07 (st,v C=S), 2921.59, 2852.02(C-H),3366.56,(NH_2),1526.91,(NO_2).**^{1}H-NMR(DMSO,mpp)**:6.68-7.58 (m,4H,Ar-H), 7.68-8.18 (m,4H,Ar-H),3.89, (s,3H, OCH_3), 3.22 (m,2H,CH2), 5.73(m,1H, CH), 9.65 (s,2H,NH_2).**MS (m/z):** 268.16, 341.16.

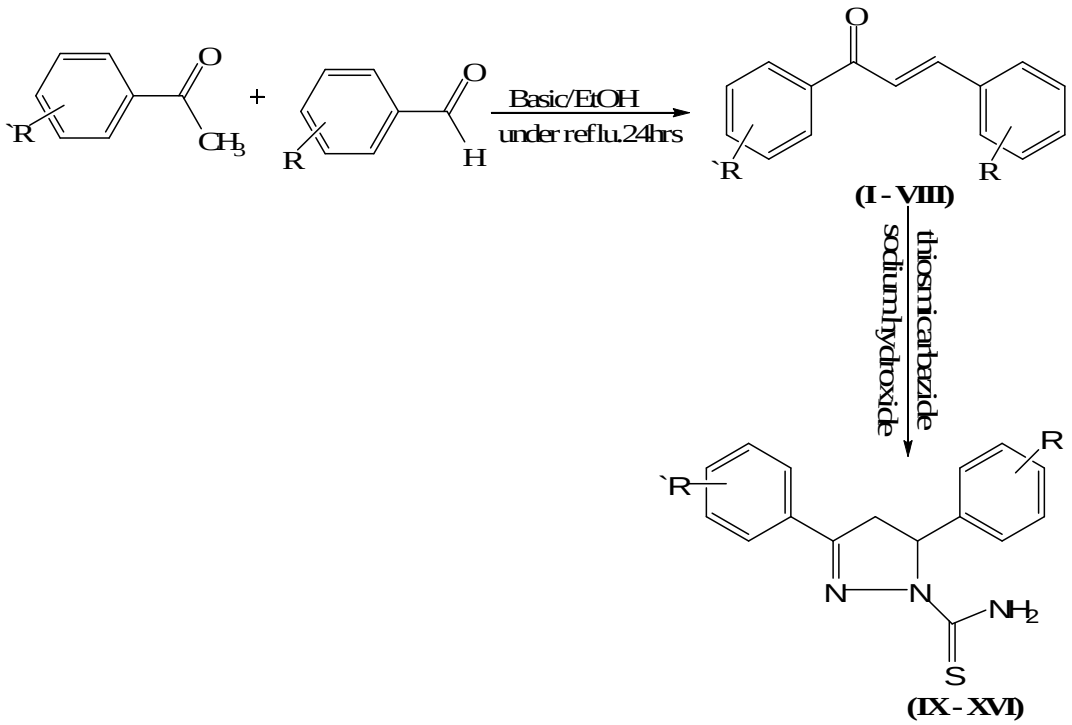
XIII.3-(4`-nitrophenyl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide:Yield:66%,**mp**, 133-136Ċ, **IR (KBr, cm^{-1})**1522.21arom (C=C), 1621.12 (C=N),1093.00 (N-N), 1345.48,(st.v,N-C), 1384.58 (st,v C=S), 2919.23, 2850.20 (C-H), 3115.50(NH_2),1178.87,(NO2). **^{1}H-NMR (DMSO, mpp)**: 7.29-8.33,(m,9H,Ar-H),3.38,3.69(s,2H, CH_2),3.95 (s,1H, CH), 9.55 (s,2H,NH_2). **MS (m/z):** 255.09, 326.22.

XIV.3-(4`-Bromophenyl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide:Yield:73%,**mp**, 116-118Ċ, **IR (KBr, cm^{-1})**1568.98arom (C=C), 1636.00 (C=N),1093.90 (N-N), 1304.07,(st.v,N-C), 1384.15 (st,v C=S), 2919.54, 2850.54(C-H), 3419.54 (NH_2),827.08,(Br). **^{1}H-NMR (DMSO, mpp)**: 7.29-7.72(m,9H,Ar-H),3.69,3.90 (s,2H, CH_2),3.95 (s,1H, CH), 9.55 (s,2H,NH_2). **MS (m/z):** 255.05, 361.06.

XV.3-(4`-aminophenyl)-5-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide:Yield:80%,**mp**, 155-157 Ċ, **IR (KBr, cm^{-1})**1549.90arom (C=C), 1639.68(C=N),1059.99(N-N), 1334.94,(st.v,N-C), 1383.98 (st,v C=S), 2920.00, 2812.51 (C-H), 3412.38(NH_2),3030.00 (CH3). **^{1}H-NMR (DMSO, mpp)**: 6.71-7.58 (m,8H,Ar-H),3.44,3.65(s,2H, CH_2),3.95 (s,1H, CH),2.513(s, 6H,2CH_3)9.57 (s,2H,NH_2).

XVI.3-(4`-Bromophenyl)-5-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide:Yield:82%,**mp**, 162-164Ċ, **IR (KBr, cm^{-1})**1554.20arom (C=C), 1600.91(C=N),1058.22(N-N), 1344.89,(st.v,N-C), 1384.06(st,v C=S), 2904.28, 2818.16(C-H), 3410.27 (NH_2), 3000.17,(CH_3), 815.11,(Br). **^{1}H-NMR (DMSO, mpp)**: 6.71-7.58(m,8H,Ar-H),3.69,3.78(s,2H, CH_2),3.95 (s,1H,CH), 2.513,(s, 6H,2CH_3), 9.87 (s,2H,NH_2).

SCHEME 1



Where R and R` groups are as following:
R = H,3-NO_2, 4-OCH_3 and 4-N,N(CH_3)$_2$
R` = H, 4-NH_2, 4-NO_2 and 4-Br
Chemical Structures of Synthesized Chalcones and 2-pyrazolines.

RESULTS AND DISCUSSION

Chalcones (**I-VIII**) were prepared by Claisen-SchemditAldol condensation reactions between aromatic aldehydes (benzaldehyde derivatives) and aromatic ketones (acetophenone derivatives), in the presence of basic medium and ethanol, with stirring under room temperature for 24hours. The synthesized chalcones were reacted with thiosemicarbazide to furnish the target compounds which are 2-pyrazoline derivatives (3,5-diaryl and 3-alkyl-5-aryl-4,5-dihydro-1H-pyrazole-1-carbothioamides(**IX-XVIII**).The structure of newly synthesized compounds were identified by performing **TLC**, melting points, and elucidated on the basis of spectral data by IR, ^{1}HNMRand MS, for some 2-pyrazoline derivatives (**X, XII, XIII** and **XIV**).The IR spectra of compounds (**I -VIII**) show the characteristic band in the region of (1700-1650 cm^{-1}) which indicate presence of C=O group and band in the region (1640-1560cm^{-1}) indicate for olefin C=C for Chalcones. The IR spectra of compounds (**IX-XVI**) show characteristic band in region (1600-1580cm^{-1}) due to –C=N bond and the band show in region (3400 – 3550 cm^{-1}) which indicate the presence of amino group. The IR spectra of compounds (**IX-XVI**) do not show any absorption band in the region of (1700-1650 cm^{-1}) which indicate the absence of carbonyl group. ^{1}H-NMR spectra of some Chalcones (**I, II, III** and **IV**) show doublet of –CO-CH= near about δ 7.50 – 8.15 confirmed the presence of Chalcones moiety. The ^{1}H-NMR spectra of compounds (**IX-XVI**) show multiple of –CH2 close to δ 3.35 confirmed the cyclization in pyrazoline moiety. The reaction sequence for the synthesis of the compounds is outlined in Scheme1.

CONCLUSION

In conclusion, substituted pyrazoline -1-carbothiamides have been synthesized using cyclization reaction of chalcones and thiosemicarbazide. These chalcones were treated with thiosemicarbazide and the new substituted 3,5-diphenyl-4,5-dihydro-1-H-pyrazole-1-carbothioamides which are named as 2-pyrazoline derivatives were obtained which have avariety of significant and the present synthetic method is a low cost approach.

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