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MICROWAVE ASSISTED SYNTHESIS AND CHARACTERIZATION OF NEW 2-PYRAZOLINE DERIVATIVES

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ABSTRACT

New pyrazolines were synthesized through cyclocondensation between chalcones derived from acetophenone and substituted benzaldehydes with furan-2-carboxylicacid hydrazide. Cyclocondensation reactions were carried out by refluxing glacial acetic acid solution of reactants with catalytic amount of PPA or subjecting the same reaction mixture to MWI. Both conditions yielded the same product with a similar yield of 65-70%. But refluxing conditions required 18 hours for the completion of the reaction whereas MWI required 1-2 min for the completion of reaction.

Keywords: Pyrazoline, MWI (Microwave irradiation), PPA (Polyphosphoric acid)), Furan-2-carboxylicacid hydrazide.

INTRODUCTION

Pyrazolines are well-known important nitrogen containing five membered heterocyclic bioorganic molecules. The pyrazoline ring protons are bonded with carbon atoms on a spatially different environment. Compounds that contain pyrazoline nucleus are known to possess myriad biological activities [1] like anti-inflammatory [2,3], hypotensive [4], antiamoebic [5], antidepressant [6], antitubercular [7], antimicrobial [8], antiproliferative [9], anticancer [10,11], antibacterial, antifungal [12], antidiabetic [13] and wound healing [14] activities. The stability and broad range promising pharmacological properties [15] inspired chemists to synthesise and study more about pyrazoline derivatives.

Numerous methods have been reported for the preparation of pyrazoline compounds. Fischer and Knoevenagel in the nineteenth century studied the reaction of α,β-unsaturated aldehydes and ketones with phenyl hydrazine in acetic acid by refluxing, which became one of the most popular methods for the preparation of 2-pyrazolines [16]. Powers et al.[17] have reported the reaction of chalcones with phenyl hydrazine hydrochloride in the presence of sodium hydroxide and absolute ethanol at 70°C, where the longer reaction time is the disadvantage of the reaction. K_2CO_3- mediated microwave irradiation has been shown to be an efficient method for the synthesis of pyrazolines [18]. The regioselective formation of pyrazolines has been achieved by the reaction of substituted hydrazine with α,β-unsaturated ketones [19,20]. Recently, many organic reactions in aqueous media have been described in the literature [21].In 2007, Li et al. [22] have synthesized 1, 3, 5-triaryl-2-pyrazoline with chalcones and phenyl hydrazine hydrochloride in sodium acetate-acetic acid aqueous solution under ultrasound irradiation. Encouraged and motivated by the literature reported for the synthesis and biological activities of pyrazoline, it was planned to synthesise new pyrazoline derivatives using furan-2-carboxylicacid hydrazide and chalcones derived from acetophenone and substituted benzaldehydes. Reported biological activities of furan ring prompted for the choice of furan-2-carboxylicacid hydrazide. Chalcones (3a-3c) were synthesized by subjecting acetophenone with substituted benzaldehydes to green chemical [23] method. Furan-2-carboxylicacid hydrazide [24] was prepared by refluxing alcoholic solution of ethyl-2-furoate with hydrazine. Pyrazoline derivatives (7a-7c) were synthesized by cyclocondensation of chalcones (3a-3c) with furan-2-carboxylicacid hydrazide (6) in acetic acid containing catalytic amount of PPA under reflux condition and also by microwave irradiation.

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Chalcones, hydrazide and pyrazolines synthesized were characterized using Mass spectrometry, Fourier Transformed Infrared Spectroscopy (FTIR) and ^{1}H-NMR and ^{13}C-NMR.

EXPERIMENTAL

Synthesis of chalcones

To a mixture of acetophenone (1 eq) and substituted aromatic aldehyde (1.1eq) taken in RB flask, hydroxide ion resin (W/W) was added and the mixture was stirred at room temperature. The reaction was monitored by TLC at an interval of 15 minutes and after the completion of reaction, product was obtained through extraction in organic solvents. The product was recovered after distilling off the solvent under reduced pressure and purified by recrystallization.

Synthesis of furan-2-carboxylicacid hydrazide

Furan-2-carboxylicacid hydrazide (6) was synthesized from 2-furoic acid (4) in two steps. Initially 2-furoic acid was converted to its ethyl ester by stirring 2-furoic acid with ethanol and thionyl chloride at 60^{0}C for 2 hours. After the completion of the reaction excess ethanol was distilled off from the reaction mixture. Ester formed was separated out through solvent extraction using dichloromethane and it was evaporated to get pure ester (5) (Scheme-2).

In the second step, pure ester was refluxed with hydrazine hydrochloride using ethanol as solvent for one hour and then poured the reaction mixture into crushed ice. The hydrazide formed as a solid was filtered, dried and recrystallised using ethanol as solvent (Scheme-2).
[Step-1: 4(1 eq), $SOCl_2$ (2 eq), EtOH, 60^{0}C, 2 h, 78% yield. **Step-2:** 5(1 eq), $NH_2NH_2.H_2O$ (2 eq), EtOH, 60^{0}C, 1 h, 80% yield**]**

Synthesis of pyrazolines

Many syntheses are reported in literature and hence reaction conditions need to be optimised for the synthesis of new pyrazoline derivatives. Pyrazoline formation between the chalcone (3a) derived from acetophenone and 4-methyl benzaldehyde with furan-2-carboxylicacid hydrazide was studied as a model reaction under different experimental conditions. Attempted reactions include refluxing and MW irradiation of ethanolic solution and sodium acetate- acetic acid buffer solution of hydrazide and chalcone; oil bath heating and MW irradiation of reactants - K_2CO_3 admixture and refluxing; and MW irradiation of chalcone and hydrazide in glacial acetic acid containing catalytic amount of PPA. Reactions were monitored through TLC and after completion; reaction mixture was poured into crushed ice. Solid formed was filtered, dried and purified through column chromatography using 60-120 silica gel and using hexane –ethyl acetate as eluent. (Scheme-3)

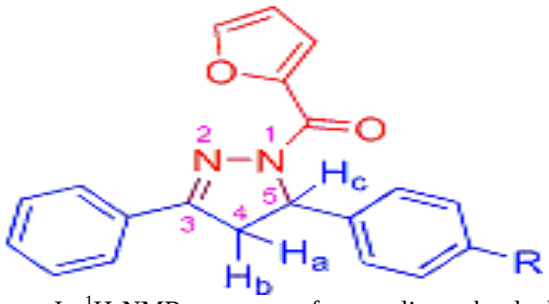
RESULTS AND DISCUSSION

Green chemical method carried out with acetophenone and substituted benzaldehyde in presence hydroxide resin gave higher yield of the respective chalcones. All the compounds gave IR peak for α, β-unsaturated carbonyl group in the range 1650-1670cm^{-1} corresponding to C=O stretching and C=C stretching in the range 1620-1610cm^{-1}. Mass spectra of these chalcones showed molecular ion peaks at the respective molecular masses of the compounds. ^{1}H NMR and ^{13}C NMR also supported the structure proposed for the respective chalcones.

Table-1 presents the structure of the chalcone formed in the respective reactions along with the yield of the reaction and time taken for the completion of reaction.

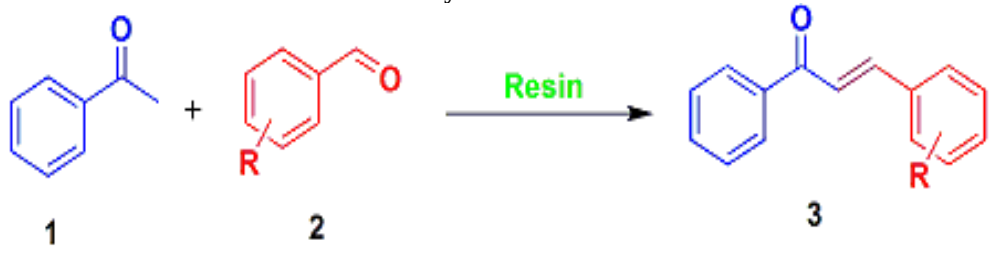
Furan-2-carboxylicacid hydrazide was prepared from 2-furoic acid in two steps. Both the ester formation and hydrazide formation gave higher yield.

Cyclocondensation of chalcone and furan-2-carboxylicacid hydrazide when carried out in glacial acetic acid and catalytic amount of PPA gave higher yield of pyrazoline [7a-7c] both under reflux condition and MW-irradiation compared to other methods. Refluxing of reaction mixture in glacial acetic acid required longer reaction time whereas MW irradiation of reaction mixture gave the same product in lesser time. The yield of cyclocondensation ranges from 65%to 70% both under reflux and microwave heating. (Table-2)



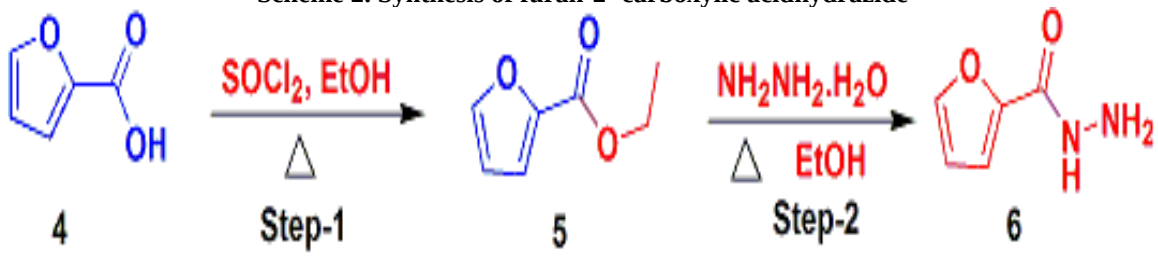
In ^{1}H-NMR spectrum of pyrazolines, the doublet of doublet at δ 3.16 to 3.29 ppm is assigned to H_a proton of C-4 with coupling constants J=18-18.4 Hz corresponding to geminal coupling by H_b proton of C-4 and J = 4.4 - 5.2 Hz for the vicinal coupling by H_c proton of C-5. The doublet of doublet at 3.85 to 4.01 ppm is assigned to H_b proton of C-4 with coupling constants J= 18-18.4 Hz corresponding to geminal coupling by H_a proton of C-4 and J = 11.6-12 Hz for the vicinal coupling by H_c of C-5. Similarly, the doublet of doublet at 5.6 to 5.91 ppm is assigned to H_c proton of C-5 with coupling constants J =11.6-12 Hz corresponding to vicinal coupling by H_b of C-4 and J = 4.4 - 5.2 Hz for the vicinal coupling by H_a of C-4. The aromatic protons appeared in the range of 6.71 to 8.21 ppm. Thus proton NMR confirms the formation of 2-pyrazoline in the cyclocondensation.

Scheme 1. Synthesis of Chalcones



[R → 4-NO_2, 4-CH_3, 4-SCH_3]

Scheme 2. Synthesis of furan-2- carboxylic acidhydrazide



Scheme 3. Synthesis of pyrazolines

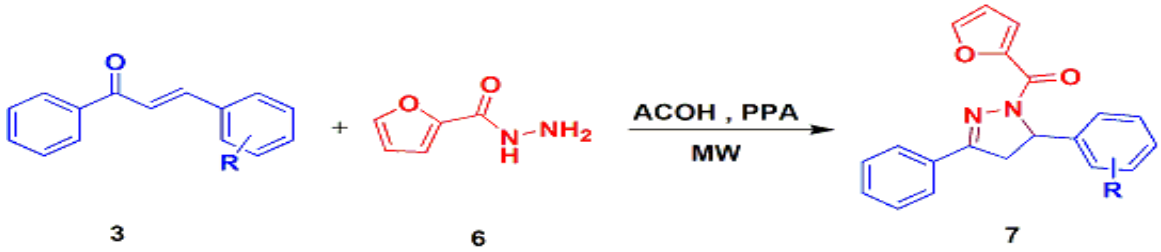


Table 1. Structure and yield of chalcones

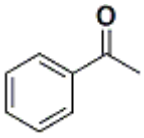
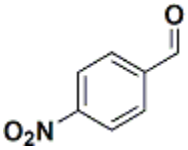
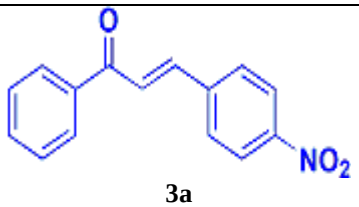
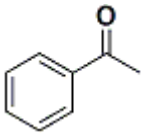
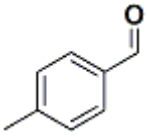
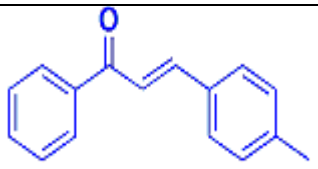
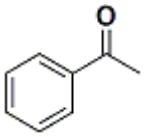
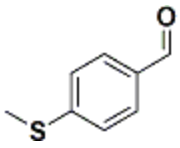
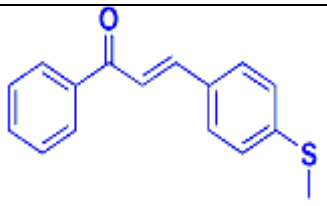
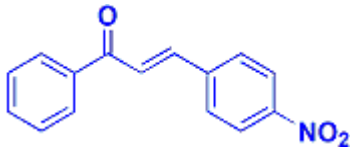
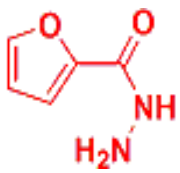
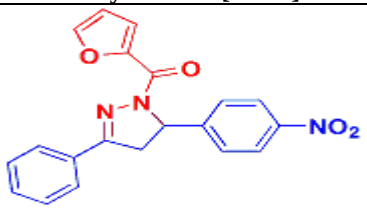
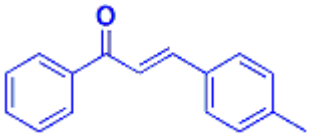
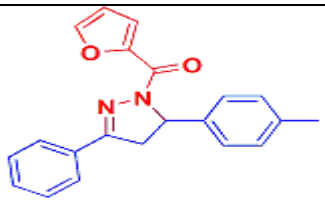
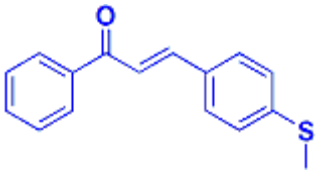
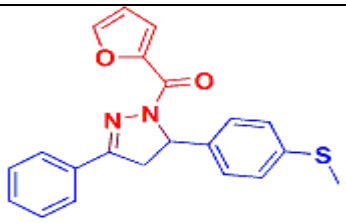
S.No	Ketone	Aldehyde	Chalcone	Time (hour)	%yield
1.			 **3a**	3	70%
2.			 **3b**	7	75
3.			 **3c**	5	70

Table 2. Structure and yield of pyrazolines

Chalcone [3a-3c]	Acid Hydrazides [6]	2-Pyrazoline [7a-7c]	Yield
 **3a**	 **6**	 **7a**	70%
 **3b**		 **7b**	65%
 **3c**		 **7c**	70%

CONCLUSION

Chalcones were synthesized through an eco-friendly Claisen-Schmidt condensation of acetophenone with substituted benzaldehyde in the presence of anion exchange resin at ambient temperature. Furan-2-carboxylicacid hydrazide was prepared from the respective acid by first converting to its ethyl ester and later by refluxing the alcoholic solution of ethyl ester with hydrazine. Solution of chalcones and furan-2-carboxylicacid hydrazide in glacial acetic acid containing catalytic amount of PPA either under reflux condition or MWI yielded the respective pyrazolines with moderate yield. Reactions carried out using MWI required lesser reaction time compared to reflux conditions. Structures of pyrazolines formed were characterized by Mass, ^{1}H-NMR and ^{13}C- NMR.

ACKNOWLEDGEMENT

Financial assistance from University Grants Commission, Hyderabad, India is greatly acknowledged.

Spectral Data

1. 3-(4-Nitro-phenyl)-1-phenyl-propenone (3a)

Pale yellow solid. M. P. 177°C

IR (KBr cm^{-1}): 3057 (Ar-CH stretching), 1667 (C=C conjugation with C=O stretching), 1608(CH=CH stretching); 1577(C-NO_2 asymmetry stretching); 1445 (Aromatic C-C vibration); 1318(C-NO_2symmetry stretching) 698,860 (aromatic five, two adjacent hydrogen wagging)

^{1}HNMR (CDCl3-*d*, 300 MHz, δ, ppm): 7.51-7.56 (m,2H), 7.61-7.65 (m,2H), 7.77-7.85 (m,3H), 8.02-8.05 (d, 7.74 Hz,2H), 8.26-8.29 (d, 8.52Hz, 2H)

^{13}C NMR (CDCl$_3$, 100 MHz): 124.14, 125.66 , 128.52 , 128.75 , 128.86 , 133.29 , 137.46 , 140.98, 141.42 , 148.49, 189.56.

MS (ES+APCI): m/z 254.2 [M+H] $^{+}$.

2. 3-(4-methyl-phenyl)-1-phenyl-propenone (3b)

White solid. M. P. 68°C

IR (KBr cm^{-1}): 3065 (Ar-CH stretching), 1655 (C=C conjugation with C=O stretching), 1599 (CH=CH stretching); 1449 (Aromatic C-C vibration); 693,843 (aromatic five, two adjacent hydrogen wagging)

^{1}HNMR (CDCl3-d, 400 MHz, δ, ppm):8.14 - 8.16 (t,8.48 Hz, 2H) 7.88-7.92 (d, 15.6 Hz, 1H) , 7.78-7.80 (d, 8 Hz, 2H) ,7.65-7.74 (m , 2H),7.55-7.59 (m , 2H),7.27-7.29 (d, 7.96 Hz, 2H), 2.35 (s, 3H).

^{13}C NMR (CDCl3, 100 MHz): 21.3, 124.1, 128.3,131.1,134.5,137.8,145.1,189.7.

MS (ES+APCI): m/z 223.0 [M+H]$^{+}$.

3. 3-(4-methyl sulfanyl-phenyl)-1-phenyl-propenone (3c)

Yellow solid.

IR (KBr cm^{-1}):3065 (Ar-CH stretching), 1650.9 (C=C conjugation with C=O stretching), 1600 (CH=CH stretching); 1444 (Aromatic C-C vibration); 665,868 (aromatic five, two adjacent hydrogen wagging), 688 (C-S stretching).

^{1}HNMR (DMSO-d_6, 400 MHz, δ, ppm):8.14 - 8.16 (d, 7.2 Hz, 2H) 7.89-7.93 (d, 15.6 Hz, 1H), 7.83-7.85 (d, 8.4 Hz, 2H) ,7.65-7.74 (m , 2H) , 7.56-7.59 (t, 8 Hz, 7.2 Hz, 2 H),7.31-7.34 (d ,8.4 Hz, 2H), 2.53(s, 3H).

^{13}C NMR (CDCl3, 100 MHz): 14.6, 121.3, 126.0, 128.9, 129.2, 129.8, 131.5, 133.5, 138.1, 142.5, 144.1, 189.5.

MS (HRMS): m/z 255.07 $[M+H]^+$.

4. Furan-2-carboxylic acid hydrazide (6)

White solid.

IR (KBr cm^{-1}):3267(NH stretching), 3026 (Ar-CH stretching), 1625 (C=O stretching), 1323(CONH stretching); 1121 (C-O-C stretching); 962,983 (N-N stretching); 746,843 (aromatic three, two adjacent hydrogen wagging)

^{1}HNMR (DMSO-d_6, 400 MHz, δ, ppm): 9.63 (s, 1H) 7.8 (t,1H) , 7.07-7.08 (q,1H) ,6.58-6.6 (q , 1H) , 4.42 (s , 2H).

MS (HRMS): m/z 126.67 $[M]^+$.

5. Furan-2-yl-[5-(4-nitro-phenyl)-3-phenyl-4,5-dihydro-pyrazol-1-yl]-methanone (7a)

White solid.

IR (KBr cm^{-1}):3109(aromatic C-H stretching), 1634 (C=Ostrteching), 1596.5(C=Nstretching), 1570, 1317 (C-NO_2Asymmetry and symmetry stretching), 1183 (C-N stretching), 1147(C-O Stretching).

^{1}HNMR (DMSO-d_6, 400 MHz, δ, ppm):8.21 - 8.23 (d, 8.4 Hz, 2H) , 7.96 -7.97 (d,1H) , 7.87 -7.89 (t, 7.2Hz, 3.6 Hz, 2H) , 7.73-7.74 (d , 3.2 Hz,1H) , 7.51-7.55 (m, 5 H), 6.74-6.75 (q ,5.2 Hz, 3.2 Hz, 1.6Hz, 1H), 5.87-5.91(dd, 12Hz, 5.2Hz, 1H), 3.93-4.01(dd, 18Hz, 12Hz, 1H) , 3.23-3.29 (dd, 18Hz, 5.2Hz,1H).

^{13}C NMR (DMSO-d_6, 100 MHz,δ, ppm):39.1, 60.73, 112.5, 119.8, 124.5, 127.51, 127.54, 129.39, 131.16, 131.23, 145.88, 146.85, 147.24, 149.85, 155.3, 156.61.

MS (HRMS): m/z 362.08 $[M+H]^+$.

6. Furan-2-yl-[3-phenyl-5-p-tolyl-4,5-dihydro-pyrazol-1-yl]-methanone (7b)

White solid.

IR (KBr cm^{-1}):3110(aromatic C-H stretching), 1634(C=O strteching),1569(C=N stretching),1081(C-N stretching), 1037(C-O Stretching).

^{1}HNMR (DMSO-d_6, 400 MHz, δ, ppm): 7.94 (s, 1H), 7.86-7.88(q, 8.4Hz ,5.6Hz ,4 Hz, 2H) , 7.68 -7.69 (d,3.6 Hz, 1H) , 7.5 -7.51 (t, 6Hz, 2.4 Hz, 2H) ,7.1-7.15 (q , 20 Hz,11.6 Hz,8.4 Hz, 4H) , 6.72-6.73 (q,4.8 Hz, 3.6Hz, 1.6Hz,1H), 5.67-5.71(dd, 11.6 Hz, 4.4 Hz, 1H), 3.85-3.93 (dd, 18.4 Hz, 12Hz, 1H) , 3.23-3.29 (dd, 18Hz, 4.4 Hz,1H) , 2.26 (s, 3H).

^{13}C NMR (DMSO-d_6, 100 MHz,δ, ppm):21, 39.1, 60.9, 112.4, 119.3, 125.94, 127.3, 129.3, 129.6, 131, 131.4, 136.9, 139.6, 146.2, 146.5, 155.1, 156.4

MS (HRMS): m/z 331 $[M+1]^+$.

7. Furan-2-yl-[5-(4-methylsulfanyl-phenyl)-3-phenyl-4,5-dihydro-pyrazol-1-yl]-methanone (7c)

White solid.

IR (KBr cm^{-1}):3138(aromatic C-H stretching), 1638(C=O stretching), 1567(C=N stretching),1091(C-N stretching), 1081(C-O Stretching), 688 (C-S stretching).

^{1}HNMR (DMSO-d_6, 400 MHz, δ, ppm):7.95 (s, 1H), 7.86-7.88(q, 8.8Hz , 6Hz ,2.4 Hz, 2H) , 7.68 -7.69 (d,3.2 Hz, 1H) , 7.5 -7.52 (t, 5.6 Hz, 2.4 Hz, 2H) , 7.16-7.24 (q , 31.2 Hz,22.8 Hz,8.4 Hz, 4H) , 6.72-6.73 (q,5.2Hz, 3.6Hz, 1.6Hz, 1H), 5.68-5.72(dd, 11.6 Hz, 4.4 Hz, 1H), 3.85-3.93 (dd, 18 Hz, 11.6 Hz, 1H) , 3.22-3.16 (dd, 18.4 Hz, 4.8 Hz,1H) , 2.44 (s, 3H).

^{13}C NMR (DMSO-d_6, 100 MHz,δ, ppm): 15, 39.1, 60.7, 112.4, 119.4, 126.7, 126.8, 127.4, 129.3,131, 131.3, 137.5, 139.2, 146.17, 146.6, 155.1, 156.5 .

MS (HRMS): m/z 363.07 $[M+H]^+$.

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