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Aqueous 2-Methoxyethanol Reaction Media: Synthesis of Some 4, 5-Dihydro-Pyrazole-1-Carbaldehyde Derivative

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Abstract

A novel N-formyl-2-pyrazoline derivative was synthesized by reaction of an α,β- unsaturated ketone with hydrazine hydrate and formic acid in aqueous 2-methoxyethanol reaction media. The Clean reaction conditions, simple workup procedure and short reaction time giving high yields of product are notable advantages of method. The structure of the title compound was established by IR, ^{1}H NMR, ^{13}C NMR and analytical data.

Keywords: Aqueous 2-methoxyethanol; N-formyl-2-pyrazoline; α,β- unsaturated ketone; hydrazine hydrate.

1. Introduction

Pyrazolines constitute an important heterocyclic class of organic compounds with diverse chemical and pharmacological applications [1] and therefore they are useful in drug research. Pyrazolines with a phenyl group at 5-position possess good film-forming properties, exhibit excellent characteristics of blue photoluminescence and electroluminescence [2].

2. Review of Literature

Pyrazolines are extensively useful synthons in organic chemistry and also important in the development of theory in heterocyclic chemistry. These compounds are also well known for their pronounced biological activities including antimicrobial [3], antitubercular [4], antiamoebic activity and cytotoxicity[5], anti-inflammatory [6], anticancer [7], antitumor [8], antiamoebic [9], anticonvulsant [10], anti-infective [11] andantidiabetic [12] properties.

Synthesis of bicyclic pyrazolines were reported by condensation of 2,6-diarylidenecyclohexanones with hydrazine hydrate [13]. Acetone and acetophenones on base catalyzed condensation with substituted aldehyde affords α,β-unsaturated carbonyl compound which on treatment with hydrazine hydrate and formic acid yielded a 2-pyrazoline [14]. In view of these observations; it was thought worthwhile to synthesize some new different substituted pyrazolines **3a-d** by reacting chalcones with hydrazine hydrate and formic acid in aqueous 2-methoxyethanol as an alternative reaction media.

3. Material and Methodology

3.1 Chemical

All chemicals, solvents and reagents used in the present study were of analytical grade purchased from Sigma, SD Fine, or Spectrochem.

3.2 Physical Measurement

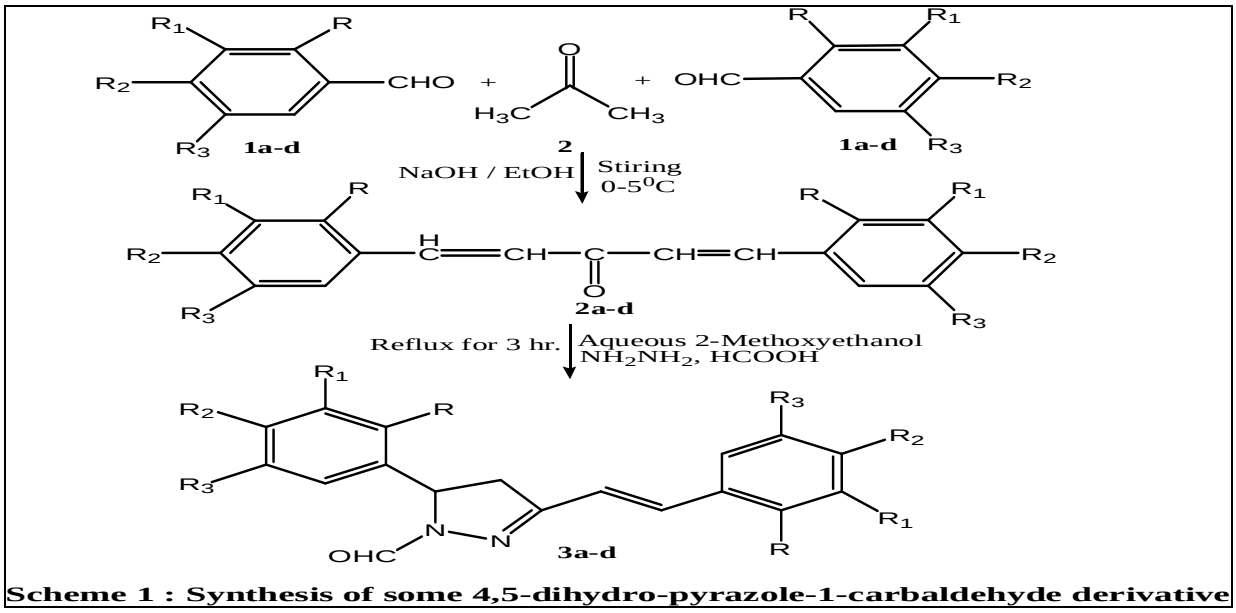
Melting points were determined in an open capillary tube and are uncorrected. The reactions were carried out in aqueous 2-methoxyethanol solvent (10 mL: 10 mL, v/v). Purification of the compounds was indicated using TLC (mixture of ethyl acetate and hexane, 0.20 mL : 0.20 Ml, vv). IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. ^{1}H NMR spectra were recorded on a Gemini 300-MHZ instrument in DMSO as solvent and TMS as an internal standard. The mass spectra were recorded on EISHIMADZU-GC-MS spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer.

3.3 Typical Procedure for Synthesis of Chalcones 2a-d

To a mixture of different substituted benzaldehyde **1a-d** (0.02 mol) and acetone **2** (0.01 mol) in ethanol, 10 % aqueous sodium hydroxide (10 ml) was added drop by drop with constant stirring at 0-5 ^{0}C. After complete addition of NaOH solution, the reaction mixture left to stand in ice bath for 20 min. Then obtained light yellow coloured solid was filtered washed with cold water and crystallized from ethanol to give the corresponding chalcones derivative **2a-d**. The physical data of synthesized chalcones are given in Table-**1**.

3.4 Typical Procedure for Synthesis of 4, 5-dihydro-pyrazole-1-carbaldehyde.

A mixture of Chalcones **2a-d** (0.01 mol) hydrazine hydrate (0.02 mol) and formic acid (2ml) was dissolved in aqueous 2-methoxyethanol (20 ml). The reaction mixture was refluxed for 3 hours. The progress of reaction was monitored by TLC. After completion, reaction solution get cooled to room temperature and poured into crushed ice, obtained crude product was filtered washed with cold water and recrystallized from mixture of ethanol: dioxane to give the product **3a-d**. The physical data of synthesized chalcones are given in Table-**2**.



Scheme 1 : Synthesis of some 4,5-dihydro-pyrazole-1-carbaldehyde derivative

1,5-Bis-(4-fluoro-phenyl)-penta-1,4-dien-3-one. (2a): IR (KBr): 1655 (C=O), 1618 (C=C), 2940 (CH) Cm^{-1}. ^{1}H NMR (300 MH_Z, DMSO) δ 6.78 (d, *J* = 16.5 H_Z, 2H, H_α), δ 7.36 (d, *J* = 16.5 HZ, 2H, H_β), δ 7.20-7.80 (m, 8H, Ar-H). MS m/z: 270 (M+). Anal. Cacld for $C_{17}H_{12}OF_2$: C, 75.55; H, 4.44. Found: C, 75.67; H, 4.46.

1,5-Bis-(4-chloro-phenyl)-penta-1,4-dien-3-one. (2b): IR (KBr): 1655 (C=O), 1615 (C=C), 2946 (CH) Cm^{-1}. ^{1}H NMR (300 MH_Z, DMSO) δ 6.75 (d, *J* = 16.5 H_Z, 2H, H_α), δ 7.38 (d, *J* = 16.5 HZ, 2H, H_β), δ 7.13-7.73 (m, 8H, Ar-H). MS m/z: 303 (M+). Anal. Cacld for $C_{17}H_{12}OCl_2$: C, 67.32; H, 3.96. Found: C, 67.41; H, 4.02.

1,5-Bis-(5-chloro-2-hydroxy-phenyl)-penta-1,4-dien-3-one. (2c): IR (KBr): 3360 (OH), 1653 (C=O), 1620 (C=C), 2964 (CH) Cm^{-1}. ^{1}H NMR (300 MH_Z, DMSO) δ 6.72 (d, *J* = 16.5 H_Z, 2H, H_α), δ 7.35 (d, *J* = 16.5 HZ, 2H, H_β), δ 7.17-7.59 (m, 6H, Ar-H), δ 12.15 (s, 2H, OH). MS m/z: 335 (M+). Anal. Cacld for $C_{17}H_{12}O_3Cl_2$: C, 60.89; H, 3.58. Found: C, 60.92; H, 3.60.

1,5-Bis-(3-iodo-4,5-dimethoxy-phenyl)-penta-1,4-dien-3-one. (2d): IR (KBr): 1654 (C=O), 1623 (C=C), 2978 (CH) Cm^{-1}. ^{1}H NMR (300 MH_Z, DMSO) δ 3.8 (s, 12H, four OCH_3), δ 6.70 (d, *J* = 16.5 H_Z, 2H, H_α), δ 7.33 (d, *J* = 16.5 HZ, 2H, H_β), δ 7.23-7.68 (m, 4H, Ar-H). MS m/z: 606 (M+). Anal. Cacld for $C_{21}H_{20}O_5I_2$: C, 41.58; H, 3.30. Found: C, 41.64; H, 3.34.

5-(4-Fluoro-phenyl)-3-[2-(4-fluoro-phenyl)-vinyl]-4,5-dihydro-pyrazole-1-carbaldehyde. (3a): IR (KBr): 1628 (C=O), 1578 (C=N) Cm^{-1}. ^{1}H NMR (300 MHZ, DMSO) δ 3.25 (dd, J = 5.0, 17.8 HZ, 1H, H_A), δ 3.65 (dd, J = 12.0, 17.8 HZ, 1H, H_B), δ 5.49 (dd, J = 5.1, 12.1 HZ, 1H, H_X), δ 6.78 (d, J = 16.2 HZ, 1H, H_α), δ 7.17 (d, J = 16.2 HZ, 1H, H_β), δ 7.31-7.68 (m, 8H, Ar-H), δ 8.90 (s, 1H, CHO). ^{13}C NMR (DMSO) 160.42 (C=O), 143.70 (C=N), 135.28 (C_β, C=C double bond), 137.88 (C, Ar-C), 135.57 (C, Ar-C) 134.74 (2CH, of two Ar-C), 130.53 (2CH, of two Ar-C), 128.50 (2CH, of two Ar-C), 120.42 (2CH, of two Ar-C) 118.32 (Cα, C=C double bond), 50.47 (-CH), 38.42 (-CH2). MS m/z: 312 (M+). Anal.Cacld for $C_{18}H_{14}F_2N_2O$: C, 69.23; H, 4.48. Found: C, 69.35; H, 5.53.

5-(4-Chloro-phenyl)-3-[2-(4-chloro-phenyl)-vinyl]-4,5-dihydro-pyrazole-1-carbaldehyde. (3b): IR (KBr): 1630 (C=O), 1581 (C=N) Cm^{-1}. ^1H NMR (300 MHZ, DMSO) δ 3.23 (dd, J = 5.0, 17.8 HZ, 1H, H_A), δ 3.64 (dd, J = 12.0, 17.8 HZ, 1H, H_B), δ 5.50 (dd, J = 5.1, 12.1 HZ, 1H, H_X), δ 6.78 (d, J = 16.2 HZ, 1H, H_α), δ 7.17 (d, J = 16.2 HZ, 1H, H_β), δ 7.29-7.69 (m, 8H, Ar-H), δ 8.90 (s, 1H, CHO). ^{13}C NMR (DMSO) 160.47 (C=O), 143.68 (C=N), 135.26 (C_β, C=C double bond), 137.84 (C, Ar-C), 135.55 (C, Ar-C) 134.76 (2CH, of two Ar-C), 130.51 (2CH, of two Ar-C), 128.53 (2CH, of two Ar-C), 120.46 (2CH, of two Ar-C) 118.34 (Cα, C=C double bond), 50.42 (-CH), 38.40 (-CH2). MS m/z: 344 (M+). Anal.Cacld for $C_{18}H_{14}Cl_2N_2O$: C, 62.79; H, 4.06. Found: C, 62.75; H, 4.12.

5-(5-Chloro-2-hydroxy-phenyl)-3-[2-(5-chloro-2-hydroxy-phenyl)-vinyl]-4,5-dihydro-pyrazole-1-carbaldehyde. (3c): IR (KBr): 3385 (OH), 1632 (C=O), 1585 (C=N) Cm^{-1}. ^1H NMR (300 MHZ, DMSO) δ 3.28 (dd, J = 5.0, 17.8 HZ, 1H, H_A), δ 3.64 (dd, J = 12.0, 17.8 HZ, 1H, H_B), δ 5.51 (dd, J = 5.1, 12.1 HZ, 1H, H_X), δ 6.78 (d, J = 16.2 HZ, 1H, H_α), δ 7.17 (d, J = 16.2 HZ, 1H, H_β), δ 7.25-7.71 (m, 6H, Ar-H), δ 8.90 (s, 1H, CHO), 10.78 (s, 2H, two OH). ^{13}C NMR (DMSO) 160.45 (C=O), 143.70 (C=N), 135.28 (C_β, C=C double bond), 137.80 (C, Ar-C), 135.57 (C, Ar-C) 134.79 (2CH, of two Ar-C), 130.48 (2CH, of two Ar-C), 128.59 (2CH, of two Ar-C), 120.42 (2CH, of two Ar-C) 118.36 (Cα, C=C double bond), 50.40 (-CH), 38.43 (-CH2). MS m/z: 376 (M+). Anal.Cacld for $C_{18}H_{14}O_3Cl_2N_2$: C, 57.44; H, 3.72. Found: C, 57.50; H, 3.75.

5-(3-Iodo-4,5-dimethoxy-phenyl)-3-[2-(3-iodo-4,5-dimethoxy-phenyl)-vinyl]-4,5-dihydro-pyrazole-1-carbaldehyde. (3d): IR (KBr): 1632 (C=O), 1585 (C=N) Cm^{-1}. ^1H NMR (300 MHZ, DMSO) δ 3.76 (s, 12H, fourOCH_3), δ 3.27 (dd, J = 5.0, 17.8 HZ, 1H, H_A), δ 3.62 (dd, J = 12.0, 17.8 HZ, 1H, H_B), δ 5.50 (dd, J = 5.1, 12.1 HZ, 1H, H_X), δ 6.78 (d, J = 16.2 HZ, 1H, H_α), δ 7.17 (d, J = 16.2 HZ, 1H, H_β), δ 7.29-7.74 (m, 4H, Ar-H), δ 8.90 (s, 1H, CHO). ^{13}C NMR (DMSO) 167.12 (4C of two paraAr-ome) 160.47 (C=O), 143.77 (C=N), 135.30 (C_β, C=C double bond), 137.67 (C, Ar-C), 135.61 (C, Ar-C) 134.75 (2CH, of two Ar-C), 130.50 (2CH, of two Ar-C), 128.55 (2CH, of two Ar-C), 120.48 (2CH, of two Ar-C) 118.32 (Cα, C=C double bond), 50.43 (-CH), 38.48 (-CH2). MS m/z: 648 (M+). Anal.Cacld for $C_{22}H_{22}O_5I_2N_2$: C, 40.74; H, 3.39. Found: C, 40.81; H, 3.43.

4. Table 1: Physical data of synthesized Chalcones (2a-d)

Table 1: Physical data of synthesized Chalcones (2a-d)						
Product	**R**	**R_1**	**R_2**	**R_3**	**Yield (%)**	**Melting Point (^0C)**
2a	H	H	F	H	78	129-131
2b	H	H	Cl	H	82	137-139
2c	OH	H	H	Cl	84	152-155
2d	H	I	OCH_3	OCH_3	75	160-162

5. Table 2: Physical Data of Newly Synthesized 4.5-dihydro-pyrazole-1-carbaldehyde derivatives (3a-d)

Table 2: Physical Data of Newly Synthesized 4.5-dihydro-pyrazole-1-carbaldehyde derivatives (3a-d)						
Product	**R**	**R_1**	**R_2**	**R_3**	**Yield (%)**	**Melting Point (^0C)**
3a	H	H	F	H	79	138-140
3b	H	H	Cl	H	80	118-120
3c	OH	H	H	Cl	76	135-137
3d	H	I	OCH_3	OCH_3	83	147-149

6. Results and Discussion

In continuation of earlier research work [14-18], in present investigation here, reported the synthesis of new series of 4, 5-dihydro-pyrazole-1-carbaldehyde derivatives. The starting chalcones **2a-d** were prepared by classical Claisen-Schmidt condensation involving base-catalyzed condensation of the desired carbonyl compounds followed by dehydration forming α,β-unsaturated carbonyl compounds. Synthesis of 4, 5-dihydro-pyrazole-1-carbaldehyde were attempted by reacting α,β-unsaturated carbonyl compounds (chalcones) with hydrazine hydrate and formic acid in presence of 2-methoxyethanol as solvent (Scheme-1). Recently the formation of 2-pyrazoline was reported by the reaction of chalcones with hydrazine hydrate take place in various conditions using acetic acid [19], formic acid [20], or pyridine [21] as solvent. However,

many of these reported procedures have one or more disadvantages such as use of expensive catalyst, low selectivity, harsh reaction conditions, low yield, relatively long reaction time and environmental concern. After some preliminary observation we found that aqueous 2-methoxyethanol as an efficient reaction medium in terms of clean reaction conditions, not expensive, decreasing reaction time giving high yields of desired product.

The formation of chalcones **2a-d** was confirmed by IR spectra, absence of a band around 1710-1720 Cm^{-1}due to the ketonic C=O stretch and the appearance of characteristic band near 1655 $Cm^{-1}$and near 1620 Cm^{-1}due to α,β-unsaturated carbonyl group and ν (C=C) respectively. In ^{1}H NMR spectrum of chalcones two doublet in range at δ 6.75 (H-α, J = 16.5 HZ) and δ 7.35 (H-β, J = 16.5 HZ) suggested the presence of olefin protons at α,β-position to the carbonyl group. The IR spectrum of newly synthesized 2-pyrazolines **3a-d** showed a strong band for carbonyl group near 1632 $Cm^{-1}$and band at 1585 Cm^{-1}due to C=N. In the ^{1}H NMR spectra, an ABX pattern was observed for H_A, H_B and H_X proton which appear as pair of doublets near δ 3.28, 3.65 and 5.50 ppm. Trans olefin proton appears asdoublets near δ 6.85 and 7.14 ppm with J = 16 HZ. The singlet of CHO appeared at δ 8.90 ppm which conforms the N-H of 2-pyrazoline replaced by N-CHO group. This also conforms on the basis of silver mirror test [22].

7. Conclusion

In summary, we have synthesized of some new series of 4, 5-dihydro-pyrazole-1-carbaldehyde derivative by condensation of chalcones with hydrazine hydrate and formic acid in aqueous 2-methoxyethanol as efficient and alternative reaction solvent. The advantages of present protocol are simplicity of operation, high yields of products and avoidance of expensive catalyst and usage of volatile organic solvent.

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