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BENZYLOXYPHENYL-BASED SYNTHESES OF SOME NOVEL N-ACETYLPYRAZOLINES

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Abstract

Substituted benzyloxyphenyl chalcones **1a-j** on reaction with hydrazine hydrate **2** and glacial acetic acid **3** in 2-methoxyethanol as reaction medium gave novel substituted N-acetylpyrazolines **4a-j**. Newly obtained N-acetylpyrazolines were characterized on the basis of FT-IR, ^{1}H-NMR, GC-MS, and elemental analysis.

Keywords: Benzyloxyphenyl chalcones, N-acetylpyrazolines, 2-methoxyethanol.

1. Introduction

Pyrazolines are well known, and important nitrogen-containing 5-membered heterocyclic compounds and various methods have been adopted for their synthesis. Numerous pyrazoline derivatives have been found to possess notable biological activities, which stimulated the research activity in this field. They have several prominent effects, such as antimicrobial, anti-mycobacterial, anti-inflammatory, analgesic and antidepressant activities [1-5]. Pyrazolines also exhibit excellent film-forming, fluorescent and luminescent properties [6-8]. After the pioneering work of Fischer and Knoevenagel in the late nineteenth century, the reaction of α, β-unsaturated aldehydes and ketones with hydrazines have become one of the most popular methods for the preparation of 2-pyrazolines [9]. In view of these observations, we wish to synthesize some novel benzyloxyphenyl based N-acetylpyrazolines by the condensation of substituted benzyloxyphenyl chalcones with hydrazine hydrate and glacial acetic acid in 2-methoxyethanol (Scheme 1).

2. Material and Methods

2.1 Chemicals and apparatus

Melting points were determined in an open capillary tube and are uncorrected. FT-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-d_6 as solvent and TMS as an internal standard. The mass spectra were recorded on a Shimadzu EI-GC-MS spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. The purity of the compounds was confirmed using TLC (petroleum ether / ethyl acetate / n-hexane in 1: 1: 1 volume proportion as mobile phase).

a. Typical procedure for synthesis of N-acetylpyrazolines

A mixture of 3-[2-benzyloxyphenyl]-1-[3,5-dichloro-2-hydroxyphenyl]-propenone (0.01 mole), hydrazine hydrate (0.02 mole) and glacial acetic acid (0.01 mole) in 2-methoxyethanol (15 mL) were refluxed for 3 hours. The progress of reaction was monitored with TLC. The reaction mixture was cooled and poured into ice-cold water. The separated solid was filtered, washed with ethanol and then with water, dried and crystallized from ethanol to give a pure sample of N-acetylpyrazoline.

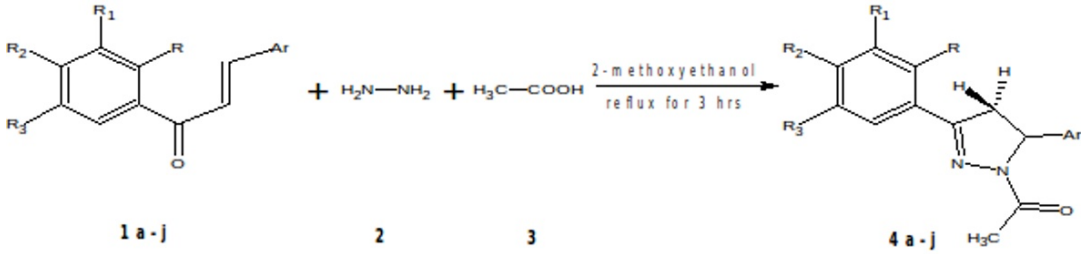
Similar other substituted derivatives were prepared by using the same reaction procedure. The physical and analytical data of **4a-j** N-acetylpyrazolines are reported in Table 1.

Table 1. Physical and analytical data of N-acetyl pyrazolines **4a-j**.

Entry	Mol. formula	Melting point (°C)	Yield (%)		Elemental analysis	
				C %	H%	N%
4a	$C_{24}H_{20}O_3N_2Cl_2$	110	76	63.33 (63.29)	4.21 (4.39)	6.21 (6.15)
4b	$C_{26}H_{25}O_4N_2Br$	198	78	61.41 (61.20)	4.80 (4.91)	5.60 (5.20)
4c	$C_{26}H_{25}O_4N_2Cl_2$	64	67	62.51 (62.40)	5.12 (5.00)	5.55 (5.60)
4d	$C_{25}H_{22}O_4Cl_2N_2$	142	80	61.68 (61.85)	4.41 (4.53)	5.61 (5.77)
4e	$C_{25}H_{21}O_3N_2Cl_3$	137	66	59.41 (59.58)	4.07 (4.17)	5.32 (5.56)
4f	$C_{26}H_{24}O_4N_2ClBr$	206	77	57.51 (57.40)	4.43 (4.41)	5.25 (5.15)
4g	$C_{25}H_{22}O_3N_2Cl_2$	153	72	63.88 (63.96)	4.56 (4.69)	5.93 (5.97)
4h	$C_{25}H_{22}O_4Cl_2N_2$	152	68	61.68 (61.85)	4.41 (4.53)	5.61 (5.77)
4i	$C_{26}H_{25}O_4N_2Cl$	181	71	67.30 (67.16)	5.41 (5.38)	6.18 (6.02)
4j	$C_{26}H_{24}O_5N_2$	140	73	70.38 (70.27)	5.34 (5.40)	6.44 (6.30)

Table 2. Explanations to the substituents used in the compounds **4a-j**.

		Substituents		
Entry	**R**	**R_1**	**R_2**	**R_3**
4a	OH	Cl	H	Cl
4b	OH	Br	H	CH_3
4c	OH	H	CH_3	Cl
4d	OH	Cl	H	Cl
4e	Cl	Cl	Cl	H
4f	OH	Br	CH_3	Cl
4g	Cl	H	Cl	H
4h	OH	Cl	H	Cl
4i	OH	H	CH_3	Cl
4j	H	$H_2C(O^-)_2$		H



Scheme 1. Synthesis of some novel N-acetylpyrazolines.

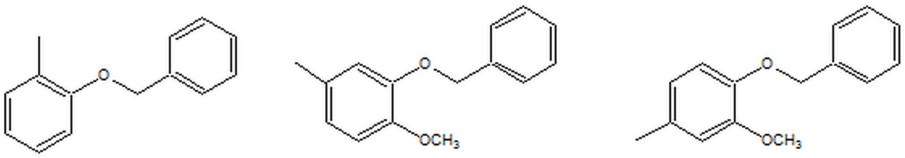


Figure 1. Designation of Ar groups in Scheme 1.

4a. 1-[5-(2-Benzyloxyphenyl)-3-(3,5-dichloro-2-hydroxyphenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone. FT-IR (KBr pellets): 1670 (C=O), 1590 (C=N), 1477, 1540 (C=C), 1232 (C-N) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.8 (s, 1H, OH), 6.8-7.6 (m, 11H, Ar-H), 5.1 (s, 2H, OCH_2), 3.2 (dd, J = 5.0, 17.2 Hz, 1H, H_A), 3.4 (s, 3H, CH_3), 3.6 (dd, J = 12.0, 17.3 Hz, 1H, H_B), 4.8 (dd, J = 5.1, 12.0 Hz, 1H, H_X). MS (EI, m/z: 454 [M^+, 60%].

4b. 1-[5-(3-Benzyloxy-4-methoxyphenyl)-3-(3-bromo-2-hydroxy-5-methylphenyl)-4,5-dihydropyrazol-1-yl]-ethanone. FT-IR (KBr pellets): 1674 (C=O), 1592 (C=N), 1457, 1544 (C=C), 1235 (C-N) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.8 (s, 1H, OH), 6.7-7.5 (m, 10H, Ar-H), 5.2 (s, 2H, OCH_2), 3.2 (dd, J = 5.0, 17.1 Hz, 1H, H_A), 3.2 (s, 3H, CH_3), 3.5 (dd, J = 12.0, 17.2 Hz, 1H, H_B), 3.1 (s, 3H, Ar-CH_3), 3.8 (s, 3H, OCH_3), 4.8 (dd, J = 5.1, 12.2 Hz, 1H, H_X). MS (EI, m/z: 509 [M^+, 48%].

4c. 1-[5-(4-Benzyloxy-3-methoxyphenyl)-3-(5-chloro-2-hydroxy-4-methylphenyl)-4,5-dihydropyrazol-1-yl]-ethanone. FT-IR (KBr pellets): 1672 (C=O), 1590 (C=N), 1480, 1552 (C=C), 1233 (C-N) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.8 (s, 1H, OH), 6.7-7.6 (m, 10H, Ar-H), 5.2 (s, 2H, OCH_2), 3.2 (dd, J = 5.0, 17.1 Hz, 1H, H_A), 3.2 (s, 3H, CH_3), 3.5 (dd, J = 12.0, 17.2 Hz, 1H, H_B), 3.1 (s, 3H, Ar-CH_3), 3.7 (s, 3H, OCH^3), 4.8 (dd, J = 5.1, 12.2 Hz, 1H, H^X). MS (EI, m/z: 464 [M^+, 42%].

4d. 1-[5-(3-Benzyloxy-4-methoxyphenyl)-3-(3,5-dichloro-2-hydroxyphenyl)-4,5-dihydropyrazol-1-yl]-ethanone. FT-IR (KBr pellets): 1670 (C=O), 1591 (C=N), 1465, 1543 (C=C), 1232 (C-N) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.8 (s, 1H, OH), 6.6-7.6 (m, 10H, Ar-H), 5.2 (s, 2H, OCH_2), 3.2 (dd, J = 5.0, 17.1 Hz, 1H, H_A), 3.2 (s, 3H, CH_3), 3.5 (dd, J = 12.0, 17.2 Hz, 1H, H_B), 3.7 (s, 3H, OCH_3), 4.8 (dd, J = 5.1, 12.2 Hz, 1H, H_X). MS (EI, m/z: 464 [M^+, 80%].

4e. 1-[5-(3-Benzyloxy-4-methoxyphenyl)-3-(2,3,4-trichlorophenyl)-4,5-dihydro-pyrazol-1-yl]-ethanone. FT-IR (KBr pellets): 1674 (C=O), 1592 (C=N), 1480, 1554 (C=C), 1232 (C-N) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) 6.7-7.7 (m, 10H, Ar-H), 5.2 (s, 2H, OCH_2), 3.2 (dd, J = 5.1, 17.1 Hz, 1H, H_A), 3.5 (dd, J = 12.0, 17.2 Hz, 1H, H_B), 3.7 (s, 3H, OCH_3), 3.2 (s, 3H, CH_3), 4.9 (dd, J = 5.1, 12.2 Hz, 1H, H_X). MS (EI), m/z: [M^+, 55%].

4f. 1-[5-(3-Benzyloxy-4-methoxyphenyl)-3-(3-bromo-5-chloro-2-hydroxy-4-methyl-phenyl)-4,5-dihydropyrazol-1-yl]-ethanone. FT-IR (KBr pellets): 1672 (C=O), 1590 (C=N), 1470, 1565 (C=C), 1233 (C-N) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.8 (s, 1H, OH), 6.7-7.6 (m, 9H, Ar-H), 5.2 (s, 2H, OCH_2), 3.2 (dd, J = 5.0, 17.1 Hz, 1H, H_A), 3.2 (s, 3H, CH_3), 3.5 (dd, J = 12.0, 17.2 Hz, 1H, H_B), 3.1 (s, 3H, Ar-CH_3), 3.7 (s, 3H, OCH_3), 4.8 (dd, J = 5.1, 12.2 Hz, 1H, HX). MS (EI), m/z: 543 [M_+, 60%].

4g. 1-[5-(3-Benzyloxy-4-methoxyphenyl)-3-(2,4-dichlorophenyl)-4,5-dihydropyrazol-1-yl]-ethanone. FT-IR (KBr pellets): 1670 (C=O), 1591 (C=N), 1476, 1564 (C=C), 1233 (C-N) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) 6.6-7.5 (m, 11H, Ar-H), 5.2 (s, 2H, OCH_2), 3.2 (dd, J = 5.1, 17.1 Hz, 1H, H_A), 3.2 (s, 3H, CH_3), 3.5 (dd, J = 12.1, 17.2 Hz, 1H, H_B), 3.7 (s, 3H, OCH_3), 4.8 (dd, J = 5.1, 12.2 Hz, 1H, H_X). MS (EI), m/z: 468 [M^+, 86%].

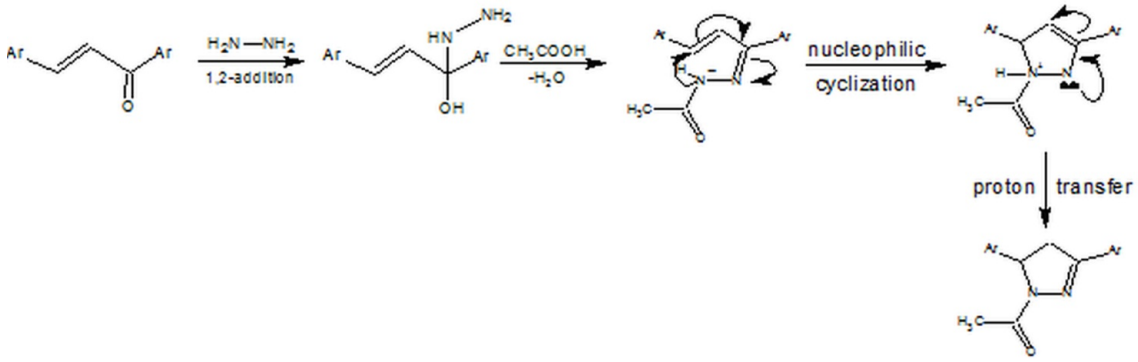
4h. 1-[5-(4-Benzyloxy-3-methoxyphenyl)-3-(3,5-dichloro-2-hydroxyphenyl)-4,5-dihydropyrazol-1-yl]-ethanone. FT-IR (KBr pellets): 1672 (C=O), 1592 (C=N), 1480, 1558 (C=C), 1230 (C-N) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.8 (s, 1H, OH), 6.6-7.5 (m, 10H, Ar-H), 5.2 (s, 2H, OCH_2), 3.2 (dd, J = 5.1, 17.1 Hz, 1H, H_A), 3.2 (s, 3H, CH_3), 3.5 (dd, J = 12.1, 17.2 Hz, 1H, H_B), 3.7 (s, 3H, OCH_3), 4.8 (dd, J = 5.1, 12.2 Hz, 1H, H_X). MS (EI), m/z: 484 [M^+, 38%].

4i. 1-[5-(3-Benzyloxy-4-methoxyphenyl)-3-(5-chloro-2-hydroxy-4-methylphenyl)-4,5-dihydropyrazol-1-yl]-ethanone. FT-IR (KBr pellets): 1672 (C=O), 1590 (C=N), 1474, 1562 (C=C), 1233 (C-N) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.8 (s, 1H, OH), 6.7-7.6 (m, 10H, Ar-H), 5.2 (s, 2H, OCH_2), 3.2 (dd, J = 5.0, 17.1 Hz, 1H, H_A), 3.2 (s, 3H, CH_3), 3.5 (dd, J = 12.0, 17.2 Hz, 1H, H_B), 3.1 (s, 3H, Ar-CH_3), 3.8 (s, 3H, OCH_3), 4.8 (dd, J = 5.1, 12.2 Hz, 1H, H_X). MS (EI), m/z: 464 [M^+, 65%].

4j. 1-[3-Benzo[1,3]dioxol-5-yl-5-(4-benzyloxy-3-methoxyphenyl)-4,5-dihydropyrazol-1-yl]-ethanone. FT-IR (KBr pellets): 1673 (C=O), 1590 (C=N), 1467, 1541 (C=C), 1232 (C-N) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 6.8-7.6 (m, 11H, Ar-H), 5.1 (s, 2H, OCH_2), 3.2 (dd, J = 5.0, 17.2 Hz, 1H, H_A), 3.4 (s, 3H, CH_3), 3.6 (dd, J = 12.0, 17.3 Hz, 1H, H_B), 3.8 (s, 3H, OCH_3), 4.3 (s, 2H, ring OCH_2), 4.8 (dd, J = 5.1, 12.0 Hz, 1H, H_X). MS (EI), m/z: 444 [M^+, 47%].

3. Results and Discussion

A classical synthesis of these compounds involves the condensation of α, β-unsaturated carbonyl compounds with hydrazines. Pyrazoline is also synthesized by using microwave irradiation [10], tungsten light irradiation [11], and ultrasound irradiation [12]. Recently, various modified methods have been reported for synthesis of 2-pyrazolines by using different catalysts such as $KHSO_4.H_2O/SiO_2$, porous calcium hydroxyapatite, mercury(II) acetate, $Bi(NO_3)_3.5H_2O$, Zn, $H_3PW_{12}O_{40}$, and Lewis acid / Lewis bases [13-19]. Greener and environmentally benign syntheses of 2-pyrazolines using solvent-free grindstone technique were reported [20]. In keeping with these observations, we focus towards the reactivity of various substituted benzyloxyphenyl chalcones for the synthesis of novel N-acetyl pyrazolines. The experimental procedure for the syntheses of the compounds **4a-j** involves refluxing the mixture of substituted benzyloxyphenyl chalcones **1a-j**, hydrazine hydrate **2** and glacial acetic acid **3** in 2-methoxyethanol as the reaction medium for 3 hrs.



Scheme 2. Proposed mechanism for the conversion of chalcones into N-acetylpyrazolines.

The obtained 2-pyrazolines were characterized using spectroscopic techniques, their FT-IR spectra showed the absence of carbonyl absorption band and the appearance of characteristic absorption band for ν C=N at 1592-1588 cm^{-1} and a band at 1130 cm^{-1} for C-N. In the ^{1}H-NMR spectrum, an ABX pattern was observable, H_A, H_B and H_X appear as double doublets at δ 3.10–3.30, 3.75–3.80 and 4.90–5.0 ppm with J_{AB} = 17.1 Hz, J_{AX} = 5.1 Hz, and J_{BX} = 12.0 Hz. The appearance of ABX pattern and disappearance of chalcone peaks in ^{1}H-NMR spectrum reveal the cyclization of α, β-unsaturated carbonyl compounds into five membered rings. The singlet of OH and OCH_3 observed at δ 11.8 and 3.8 ppm, respectively. Aromatic protons appear near the region δ 6.7-7.6 ppm.

4. Conclusion

In summary we have synthesized a series of novel benzyloxyphenyl based N-acetylpyrazolines, **4a-j**, by the condensation of substituted benzyloxyphenyl chalcones **1a-j** with hydrazine hydrate **2** and glacial acetic acid **3** in 2-methoxyethanol.

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