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Synthesis and Characterization of Some New 5-[2,4-di(4-Chlorobenzyloxy)Phenyl]-3-(4-Substituted Phenyl)-2-Pyrazolines

Farouq Emam Hawaiz[1], Faiq Hama Saed Hussain[2] and Hashim Jalal Azeez[1]

1. Chemistry Department, College of Education, University of Salahaddin-Hawler, Erbil, Kurdistan 44001, Iraq

2. Chemistry Department, College of Science, University of Salahaddin-Hawler, Erbil, Kurdistan 44001, Iraq

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Abstract: The prepared starting material 2,4-dibenzyloxy benzaldehyde has been reacted with different substituted acetophenones using green methods, ultrasound, microwave and solvent-free grinding method to give a series of new chalcones. The later reacted with hydrazine hydrate according to the Michael addition reaction to afford a series of new pyrazoline derivatives. The characterization of the newly synthesized compounds elucidated by spectral methods: FT-IR, ^{1}H-NMR and ^{13}C-NMR.

Key words: Chalcones, pyrazoline, ultrasound, microwave, solvent free.

1. Introduction

Condensation reaction takes place between two carbonyl partners and involves a combination of nucleophilic addition and α-substitution steps. One partner (the nucleophilicdonor) is converted into its enolate ion and undergoes α-substitution reaction when it adds as a nucleophile to the secondpartners (the electrophilic acceptors) [1]. A number of the chemical synthetic methods have been reported for the formation of chalcones and their derivatives [2, 3], the most widely method is one based on base catalyzed (Claisen-Schmidt condensation) of substituted benzaldehydes and appropriate substituted acetophenones in polar solvents [4], α, β-unsaturated ketones are versatile and convenient intermediates for the synthesis of a wide variety of organic compounds like pyrazoline [5], pyrimidines [6] and thiazepines [7]. Chalcones and pyrazoline possessa wide spectrum of biological activitieswhich include: antioxidant [8], antipyretic analgesic [9], anti-inflammatory [10] and anti-bacterial activity against *staphylococcus* and *E-coli* [11]. Herein we have described different methods for the synthesis and spectroscopic studies of some new chalcones and their transformations to new pyrazoline derivatives.

2. Experiments

Melting points were determined using an electro thermal melting point apparatus. IR spectra were recorded on a bio-rad Merlin FT-IR spectroscopy Mod FTS 3000, using KBr disc. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker (300 MHz) with tetramethylsilane as internal reference. The Sonication was performed by Telsonic Ultrasonic type Tpc-25-2. A6 CH-9552 Bronschhofen, output (75/150 W, 30 KHz). The Microwave irradiation was carriedout by domestic microwave oven PM-001W pacific, (700 W, 2,450 MHz).

Corresponding author: Farouq Emam Hawaiz, Ph.D., assistance professor, research field: organic chemistry. E-mail: farouqemam@yahoo.com.

2.1 Preparation of 2,4-Bis(4-Chlorobenzyloxy) Benzaldehyde (1)

Compound (1) was prepared according to our reported procedure [12].

2.2 Synthesis of 3-[2,4-Bis(4-chlorobenzyloxy)phenyl] -1-(4-Substitutedphenyl)-2-Propen-1-on(2a-i)

2.2.1 Method (A): Ultrasound-Assisted Synthesis Chalcones [13]

The prepared 2,4-bis(4-chlorobenzyloxy) benzaldehyde (0.02 mol) was dissolved in ethanol (5 mL) and added to the solution of (0.002 mol) of an substituted acetophenones in ethanol (5 mL) and 2 mL of (4% ethanolic NaOH dissolved by ultrasound). The mixture was irradiated in the water bath ultrasonic cleaner at room temperature for (30 s-5 min). The mixture was solidified and the pale yellow chalcones were separated by suction filteration, washed with ethanol and water to neutralize, dried and purified by recrystallization from a suitable solvent (toluene or ethanol). The results were tabulated in Table 1.

2.2.2 Method (B): Solvent-Free Trituration Synthesis of Chalcones [14]

The prepared 2,4-bis(4-chlorobenzyloxy) benzaldehyde (0.02 mol), substituted acetophenones (0.002 mol) and solid NaOH (0.08 g, 0.002 mol) were combined using a mortar and pestle; the pale yellow medium was aggregated as tacky solid and then to eutectic melt and to the powder product about (5-10 min), the products were washed with water to neutralize and recrystallized from appropriate solvents (toluene, ethanol or dioxane). The results were tabulated in Table 1.

2.2.3 Method (C): Microwave-Assisted Synthesis of Chalcones

The prepared 2,4-bis(4-chlorobenzyloxy) benzaldehyde (0.02 mol), substituted acetophenones (0.002 mol) and 2 g of K_2CO_3 were combined using a mortar and pestle. The mixture was transferred to a (50 mL) beaker, and placed vertically in the center of the microwave oven and irradiated at 390 W for (1-4) successive periods of 30 s with mixing by glass rod between the successive periods until the reaction was completed as a yellow powder and worked as method (A).

2a: ^{1}H-NMR: 5.05(s, 2H, CH_2-Bz); 5.10(s, 2H, CH_2-Bz`); 6.61(s, 1H, Ar-H_3); 6.66(d, 1H, Ar-H_5); 7.56(d, 1H, H-α); 7.82(d, 1H, H-β), 7.28-8.02(m, 14H, Ar-H). ^{13}C-NMR: 69.84, 100.55, 106.57, 117.80, 121.17, 128.82, 129.00, 128.98, 128.38, 129.00, 129.31, 132.60, 134.18, 140.56, 159.39, 161.55, 190.84.

2b:^{1}H-NMR: 2.42(s, 3H, $CH_{3\text{-}4'}$); 5.09(s, 2H, CH_2-Bz); 5.11(s, 2H, CH_2-Bz`); 6.61(s, 1H, Ar-H_3); 6.64(d, 1H, Ar-H_5); 7.55(d, 1H, H-α); 7.74(d, 1H, H-β); 7.28-8.02(m, 13H, Ar-H). ^{13}C-NMR 20.90, 69.48, 69.86, 100.56, 105.56, 117.93 121.31, 128.50, 128.90, 129.02, 129.15 129.34, 134.65, 132.50, 132.50, 135.98, 140.08, 159.33, 161.43, 143.17, 190.39.

Table 1 Some physical properties of the synthesized chalcones (2a-i).

Prod	R	Molecular formula	Melting Point (°C)	Yield %		
				A	B	C
2a	H	$C_{29}H_{22}Cl_2O_3$	139-141	83.8	85.8	-
2b	CH_3	$C_{30}H_{24}Cl_2O_3$	125-126	83.4	83.4	-
2c	3,4-di-OCH_3	$C_{31}H_{26}Cl_2O_5$	170-171	80.0	-	78.3
2d	Cl	$C_{29}H_{21}Cl_3O_3$	155-157	74.0	85.2	-
2e	Br	$C_{29}H_{21}BrCl_2O_2$	162-164	86.7	-	80.9
2f	F	$C_{29}H_{21}Cl_2 FO_3$	146-148	86.7	87.7	-
2g	2-Naph.	$C_{33}H_{24}Cl_2O_3$	145-146	83.4	-	81.6
2h	BzO	$C_{38}H_{28}Cl_2O_4$	180-182	87.3	-	87.3
2i	4-ClBzO	$C_{38}H_{27} Cl_3O_4$	158-160	87.4	-	85.8

2c: ^{1}H-NMR: 3.97 (s, 6H, $2OCH_3$-$C_{3'',4''}$); 5.05 (s, 2H, CH_2-Bz); 5.10 (s, 2H, CH_2-Bz`); 6.61(s, 1H, Ar-H_3); 6.65(d, 1H, Ar-H_5); 7.21 (d, 1H, H-α); 7.61 (d, 1H, H-β);6.8-7.45 (m, 12H, Ar-H). ^{13}C-NMR: 56.03, 69.48, 69.87, 100.51, 106.47, 109.72, 110.63, 117.94, 121.03, 122.78, 128.56, 128.91, 129.31, 131.67, 133.11, 134.75, 148.20, 153.42, 159.40, 161.32, 188.98.

2.3 Synthesis of 2-Pyrazolines-5-[2, 4-di(4-Chlorobenzyloxy)Phenyl]3-(4-Substitutedphenyl)-2-Pyrazolines (3a-i)

Hydrazine hydrate 80% (1 mL, 0.025 mol) was added to methanolic suspension (20 mL) of the prepared chalcones (0.002 mol) and sodium hydroxide (0.08 g, 0.002 mol). The mixture was heated under reflux with stirring for an appropriate time to complete the reaction which was monitored by TLC and the color was changed from yellow to white indicating the disappearance of the pale yellow chalcone. The pyrazolines were removed by suction filtrations,washed with water to neutralize and then with ethanol. The products were dried and recrystallized from ethanol [15]. The reaction time, M.P. and the percentage of yields are summarized in Table 2.

3a: ^{1}H-NMR: 3.14(dd, 1H, H_A); 3.47(dd, 1H, H_B); 5.06(s, 4H, $2CH_2$-Bz); 5.26(dd, 1H, $2H_x$); 6.52-7.31 (m, 17H, Ar-H and N-H). ^{13}C-NMR: 39.70, 58.48, 69.38, 69.55, 100.66, 105.61, 126.43, 128.50, 128.56, 128.70, 128.81, 130.8, 131.00, 133.0, 135.35, 157.15, 158.87, 159.55.

3b: ^{1}H-NMR: 2.41 (s, 3H, CH_3-4``); 3.07 (dd, 1H, H_A); 3.42 (dd, 1H, H_B); 5.02(s, 4H, $2CH_2$-Bz); 5.24(dd, 1H, H_x); 6.51-7.56 (m, 16H, Ar-H and N-H). ^{13}C-NMR: 21.44, 39.69, 58.36, 69.32, 69.38, 100.65, 105.51, 126.43, 128.31, 128.73, 128.88, 129.01, 120.20, 129.31, 133.88, 135.25, 139.66, 157.15, 158.86, 159.52.

3c: ^{1}H-NMR: 2.97(dd, 1H, H_A); 3.39(dd,1H, H_B); 3.93 (s, 6H, $2CH_{3\text{-}3'',4''}$); 5.19(dd, 1H, $2H_x$); 6.35-7.56 (m, 15H, Ar-H and N-H). ^{13}C-NMR: 39.08, 55.90, 58.60, 69.32, 69.53, 100.67, 105.66, 108.12, 110.50, 120.06, 123.98, 127.50, 128.87, 129.34, 129.36, 133.94, 135.28, 149.08, 151.88, 156.74, 158.88, 159.05.

3. Results and Discussion

The present work involves the synthesis of some new chalcones containing electron releasing and electron withdrawing groups from the reaction of 2,4-dibenzyloxy benzaldehyde and substituted acetophenones, using different methods like, ultrasound, solvent free and microwave irradiation techniques followed by their transformation to new pyrazoline derivatives (Scheme 1). The results showed that the green methods are fast, clean and efficient, relatively high yields were achieved in very short reaction times (Table 1). Thus indicates that the effect of microwave irradiation is not purely thermal. Microwave irradiation facilitates the polarization of the molecules under irradiation causing rapid reaction

Table 2 Some physical properties ofthe synthesized-pyrazolines (3a-i).

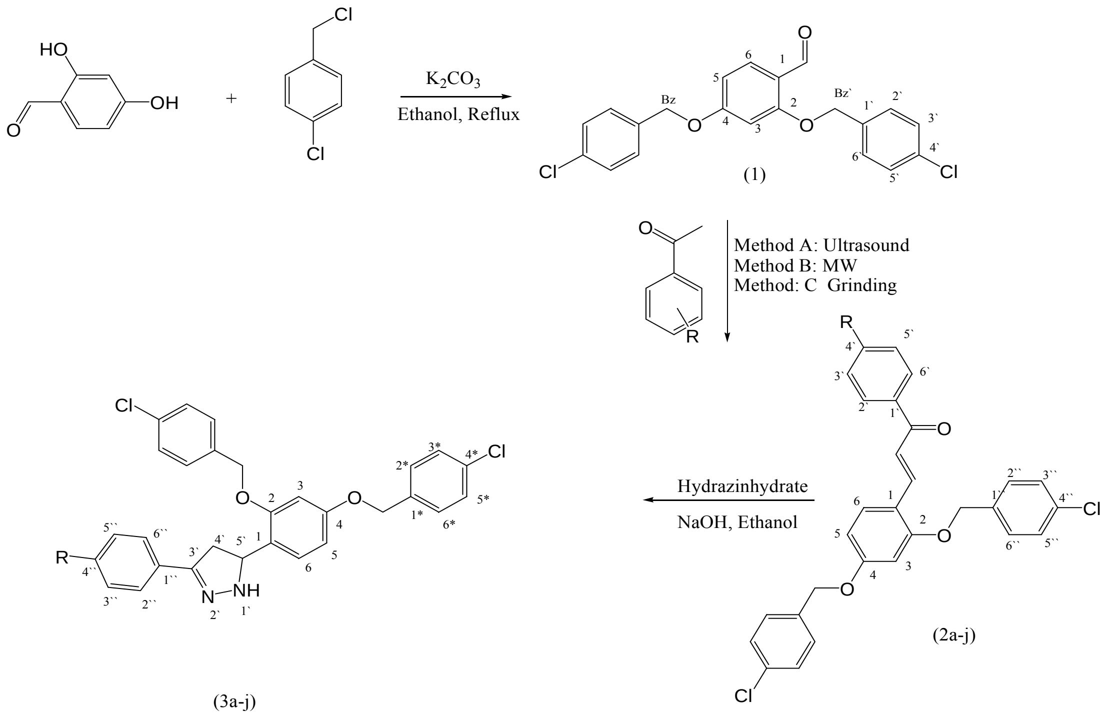
Prod.	R	Molecular formula	M.P. (°C)	Time (h)	Yield (%)
3a	H	$C_{29}H_{24}Cl_2N_2O_2$	135-137	2.0	95.4
3b	CH_3	$C_{30}H_{26}Cl_2N_2O_2$	115-117	3.0	92.8
3f	3,4-di-OCH_3	$C_{31}H_{28}Cl_2N_2O_4$	110-112	4.5	83.4
3d	Cl	$C_{29}H_{23}Cl_3N_2O_2$	150 dec.	3.5	91.2
3e	Br	$C_{29}H_{23}Br_2Cl_2N_2O_2$	156-158	3.5	85.9
3c	F	$C_{29}H_{23}Cl_2F_2N_2O_2$	118-120	3.0	92.0
3g	2-Naph.	$C_{33}H_{26}Cl_2N_2O_2$	145-146	4.0	92.2
3h	BzO	$C_{36}H_{30}Cl_2N_2O_3$	112-114	5.5	83.7
3i	4-ClBzO	$C_{36}H_{29}Cl_3N_2O_3$	132-134	5.0	80.7

to occur [16]. The structure elucidation of the newly synthesized compounds confirmed on the basis of their spectral data FTIR, ^{1}H-NMR, ^{13}C-NMR. The characterization of the starting material 2,4-bis(4-chlorobenzyloxy)benzaldehyde (1) was reported in our previous research [12].

The shifting of thecarbonyl group absorption band in the IR spectra of newly synthesized chalcones (Table 3), to lower wave numbers than the reactants around 1,650cm^{-1} [17] and the appearance of α-H and β-H protons downfield to the aromatic region at 6.0-8.0 ppm due to the resonance and anisotropic effect of the phenyl ring bonded to β-C in the ^{1}H-NMR spectra along with the disappearance of aldehydic protons of the reactants is a strong evidence for the formation of chalcones. Further support is come come from the β-C resonance at δ (140 ppm) in ^{13}C-NMR spectra [18].

Table 3 Assignment of characteristic frequencies (cm^{-1}) of IR spectra for chalcones (2a-i) and pyrazolines(3a-i)

Prod.	2a-i		3a-i	
	C=O	C=C	N-H Str.	C=C;C=N Str.
a	1,652	1,601	3,332	1,610; 1,584
b	1,654	1,608	3,333	1,609; 1,587
c	1,649	1,597	3,327	1,610; 1,599
d	1,649	1,598	3,332	1,609; 1,586
e	1,648	1,595	3,332	1,608; 1,585
f	1,653	1,601	3,334	1,606; 1,585
g	1,653	1,601	3,325	1,607; 1,585
h	1,652	1,604	3,314	1,611; 1,586
i	1,651	1,602	3,318	1,608; 1,587



R: H, Me, Cl, Br, F, 3,4-diMe, 2-Naphth., BzO, ClBzO

Scheme (1)

Scheme 1 Synthesis of some new chalcones containing electron releasing and electron withdrawing grows from the reaction of 2,4-dibenzyloxy benzaldehyde and acetophenones

The IR spectra of the synthesized pyrazolines (Table 3), showed a sharp bandsaround 3,330 cm^{-1} attributed to N-H stretching vibration, and the disappearance of carbonyl group band for conjugated enonesystem [19]. ^{1}H-NMR spectra of pyrazolines observed the ABX spin system for the protons attached to the C-4\` and C-5\` as three doublet to doublets (dd) signals approximately at δ 3, 4, 5 ppm belongs to two geminal and one vicinal protons of pyrazoline rings which unequivocally prove the expected structures [20]. The ^{13}C-NMR chemical shifts of C-3\`, C-4·and C-5\` in pyrazoline rings approximately at 160, 40 and 60 ppm respectively, and the disappearance of two singlets for α-C and β-C of intermediate chalconesis a further confirmation of the expected structures [21].

4. Conclusions

The results presented in this work demonstrate that: there is a substantial enhancing effect in the yield and the rate of the Claisen-Schmidt condensation between substituted benzaldehydes and substituted acetophenones to preparation of chalcones and their transformation to pyrazolines when microwave and ultrasound irradiation were used. The Claisen-Schmidt condensation for synthesis of the chalcones under solvent-free conditions was carried out successfully and found to be inexpensive, efficient, fast, with high yields, and elimination of solvent thereby preventing pollution in organic synthesis.

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