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Evaluation of Effect of Microwave Irradiation on Synthesis and Reactions of Some New 3-Acyl-2-R-methylchromones

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Abstract: The study of preparation by classic and microwave irradiation methods, spectroscopic characterization of 3-Acyl-2-R-methylchromone derivatives(R = H, C_6H_5, ArO). Some subsequent reactions of these products with hydroxylamine and by aldol condensation with 3-formylchromones have been studied.

Keywords: 4-oxo-4*H*-[1]-benzopyran-derivatives,aldol reaction, rearrengement of chromones

- 1. Introduction
- 2. Results and Discussion
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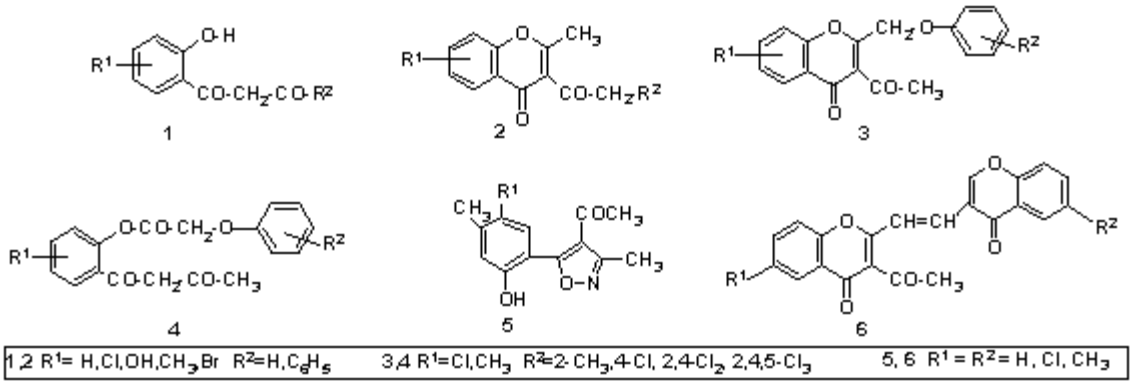
Introduction

The 3-Acyl-2-R-methylchromones as several functional compounds are useful building-blocks in organic synthesis. The chromones are attractive for ability to form of new nitrogen heterocycles after nucleophilic opening of -pyrone ring [1,2]. Methyl groups at position 2 and at carbonyl group of study compounds can be active in aldol type reactions. Carbonyl groups and carbon at position 2 as electronodeficit centers are very effective in reactions with nucleophile reagents. Synthesized compounds **2-6** are useful for are ability to transform in different ways and at versatile steps of the synthetic sequence. For this work we have chosen some method for preparation of compounds **2-4**. As we showed before [6,7]. microwave irradiation is a suitable method for condensation reactions.

Results and Discussion

The main goal of the study was the preparation of new 3-acyl-2-R-methylchromones and comparison of the reactions results obtained by classic method and microwave irradiation. Structural formules of prepared compounds are depicted in scheme.



For preparation of compounds **2** are known two methods. One of them is Kostanecki-Robinson acetylation of 2-hydroxyacetophenone derivatives with acetic anhydride and sodium acetate [3]. This cyclocondensation reaction is known yet only in a classic modification by heating of react mixture. The another more general method of preparation of 3-acyl-2-methylchromones , can be used the rearrangement of 2-acyloxy-1-acetoarones after treating with metallic sodium. Rearranged intermediates - 2-hydroxyaroylacetones **1** were formed. They afforded of 3-acyl-2-methylchromones or 2-methylchromones by acid-catalyzed cyclization.

In our study is reported preparation of the 3-acetyl-2-methylchromone derivatives **2** in good yield (72 - 98 %) by treating under classic reaction conditions of 2-hydroxy- aroyl acetone derivati-ves **1** with freshly fused sodium acetate and acetic anhydride to give the desired products **2** after 2 hours refluxing. The using microwave irradiation products **2** were prepared from the same compo-nents, but react time was shortened to 3 - 8 minutes.

The structure of compounds **2(R=H)** were confirmed by IR, ^{1}H-NMR, and ^{13}C-NMR spectra. IR-spectra (in nujol) showed an acetyl carbonyl stretching frequencies as strong band at 1699 -1677 cm^{-1} and - pyrone at 1648 - 1636 cm^{-1}. In the ^{1}H-NMR spectra of the CH_3 acetyl signals occurred at 2.70 - 2.62 ppm, on the other hand the signals of CH_2-CH_3 occurred at 2.66 - 2.52 ppm , other protone signals and the ^{13}C-NMR spectra are listing in Experimental Part.

3-Benzoyl-2-methylchromone derivatives **2($R=C_6H_5$)** were prepared by treatment of 2-hydro-xybenzoylacetophenones with acetic anhydride and sodium acetate at 110^{o} C for 3 hours. On the other hand by focused microwave irradiation yield 80 % were produced after 6 minutes .

The preparation of compounds **3** and **4** imagines a new route to synthesis of the title compounds. Reaction of compounds **1** with acid chlorides and potassium carbonate in acetone reflux for 3 hours yielded 3-acetyl-2-aryloxymethylchromone derivatives **3** in about 47 % yields. Intermediates **4** were isolated from cold water hydrogen carbonate solution after acidification with CH_3COOH in about 30 % yields. The cyclocondensation of intermediates **4** on compounds **3** is very easy by heating in benzene medium.. The heating of starting compounds **1** in refluxing (dry toluene 3 hs.) were isolated only cyclic products **3** (in 80% yields). In the microwave oven the condensation reaction of components **1** with acylchlorides, potassium carbonate and acetone required only 2 minutes time for 85 % yield of compounds **3.** No any intermediates **4** there were isolated.

Compounds **2** contain two active CH_3 groups which can react at aldol reaction. Aldol conden-sation product **6** was obtained by reaction **2** with 3-formyl chromones in acetylanhydride medium by classic and also microwave irradiation methods respectively. In every attempts , the reaction was realized only at 2-position-methyl group of -pyrone ring .The classic arrangement of method required 2h of react time. Beneficial effect of microwave irradiation on the reaction shortened the react time into 40 sec.

It is known that reaction of 3-acetyl-2,6-dimethylchromone with hydroxylamine in acetic acid gave monoxime and dioxime [4], but reaction of 3-acetyl-2-methyl-chromone with hydroxylamine hydrochloride and sodium acetate in ethanol gave 4-acetyl-5-(2-hydroxyphenyl)-3-methylisoxazole [5].

Conclusion

In the present study we have found that 3-acetyl-2-methyl-chromones and 3-benzoyl-2-methyl-chromones gave products **5** which were separated by crystallisation from cyclohexane**.** The reaction was carried out at the boiling point of pyridine with hydroxylamine hydrochloride. The isoxazole derivatives **5** gave deep red color with alcoholic ferric chloride, soluble in aqueous sodium hydroxide confirming the presence of phenolic hydroxyl group. Their IR spectra confirmed the structure by broad band centered at 3100 cm^{-1} for OH group and band at 1683 - 1680 cm^{-1} for C=O acetyl group. Also, the structure of isoxazoles were confirmed by ^{1}H-NMR spectra . Product of subsequent reactions (**5,6**) of compounds **2** were obtained by both methods.

Experimental Part

The melting points were determined on a Kofler block.

Infrared spectra were recorded on a Specord IR 75 spectrometer (Zeiss, Jena), in 400 - 4000 cm^{-1} region in nujol. ^{1}H-NMR spectra were measured on Tesla BS 487 A (80 MHz). ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra for compounds **2a** - **2i** were measured on FT NMR spectrometer Bruker AM 300 at 300^{o} K in solution of $CDCl_3$ with TMS as internal standard. The ^{1}H NMR spectra were measured for all publicated compounds. The signals of protons were corresponding to their surroundings and confirmed their structures.

Elemental analyses for C, H, N, halogene were within 0.3 % of the theoretical values.

All microwave assisted reactions were carried out in a microwave oven type of Lavis - 1000 multi Quant. The apparatus is adapted for laboratory application with external reflux condenser.

3-Acetyl-2-methylchromone derivatives 2

Method A(classic) A mixture of 2-hydroxyaroylacetones **1** (1g), acetic anhydride (8 ml) and freshly fused sodium acetate (1g) was refluxed for 6h and left to cool. The mixture was diluted with cooled water (50 ml) and stirred at room temperature for 30 min. The solid products filtered off, washed with water and recrystallized from the proper solvent (Table 1).

Method B (microwave irradiation)

The similar mixture as in procedure A was irradiated in microwave oven at 270 W for the 8 minutes. Compounds are in table 1.

Table 1 : Characteristic data of the prepared compounds.

Comp.	Formula	M.P.,^{o}C		Calc/	Found		[nu](C=O)[c]	[nu](C=O)[c]	[nu](C=N)[c]	[nu](O-H)[c]
Yield, %	M.W.	Solvent	%C	%H	%N	%X	pyrone	acetyl		
2a	$C_{12}H_{10}O_3$	86-87	71.28	4.98			1637	1687		
72	202.21	P.Ether[b]	71.56	5.07						
2b	$C_{13}H_{12}O_3$	116-118	72.21	5.59			1639	1691		
85	216.24	Cyclohex[a]	72.45	5.64						

2c	$C_{12}H_9ClO_3$	129-131	60.90	3.83		14.98	1639	1691		
82	236.65	Cyclohex[a]	60.77	3.84		14.98				
2d	$C_{12}H_9BrO_3$	124-125	51.27	3.23		28.42	1640	1692		
82	281.11	Cyclohex[a]	51.31	3.17		28.63				
2e	$C_{12}H_8Cl_2O_3$	132-134	53.17	2.97		26.15	1643	1680		
98	271.10	Cyclohex[a]	53.40	3.01		26.18				
2f	$C_{13}H_{11}ClO_3$	152-153	62.29	4.42		14.14	1637	1687		
91	250.68	Cyclohex[a]	62.56	4.45		14.29				
2g	$C_{14}H_{14}O_3$	112-114	73.03	6.13			1636	1677		
84	230.26	Cyclohex[a]	73.31	6.14						
2h	$C_{16}H_{12}O_3$	154-156	76.18	4.79			1637	1685		
91	252.27	Cyclohex[a]	76.22	4.81						
2i	$C_{16}H_{12}O_3$	136-138	76.18	4.79			1648	1699		
95	252.27	Cyclohex[a]	76.24	4.79						
3a	$C_{13}H_{12}ClNO_3$	114-115	58.77	4.55	5.27	13.34		1683	1612	3100
57	265.70	Cyclohex[a]	58.46	4.55	5.06	13.58				(br)
3b	$C_{14}H_{15}NO_3$	119-121	68.56	6.16	5.71			1680	1613	3100
62	245.28	Cyclohex[a]	68.55	6.19	5.52					(br)
4a	$C_{13}H_{12}ClNO_3$	150-151	58.77	4.55	5.27	13.34		1681	1620	3120
20	265.70	Benzene	58.35	4.60	5.02	13.61				
4b	$C_{14}H_{15}NO_3$	142-144	68.56	6.16	5.71			1675	1620	3127
28	245.28	Benzene	68.61	6.16	5.74					

[a] solvent is cyklohexane, [b] 40-60, [c] in cm^{-1}

Table 2: ^{1}H-NMR spectra of the prepared substances

Compound	^{1}H-NMR spectrum[a]
2a	8.14(1H, dd, J=8.4 and 1.6, H-5), 7.64(1H, ddd, J=7.1, 8.2 and 1.6, H-7), 7.39(1H, dd, J=8.2 and 1.1, H-8), 7.37(1H, ddd, J=8.4, 7.1 and 1.1, H-6), 2.63(3H, s, CH_3 acetyl), and 2.52(3H, s, C_2-CH_3).
2b	7.99(1H, d, J=2.3, H-5), 7.50(1H, dd, J=8.7 and 2.3, H-7), 7.34(1H, d, J=8.7, H-8), 2.67(3H, s, CH_3 acetyl), 2.55(3H, s, C_2-CH_3), and 2.45(3H, s, C_6-CH_3).
2c	8.14(1H, d, J=2.6, H-5), 7.60(1H, dd, J=8.8 and 2.6, H-7), 7.38(1H, d, J=8.8, H-8), 2.64(3H, s, CH_3 acetyl), and 2.54(3H, s, C_2-CH_3).
2d	8.30(1H, d,J=2.4, H-5), 7.76(1H, dd, J=8.8 and 2.4, H-7), 7.33(1H, d, J=8.8, H-8), 2.64(3H, s, CH_3 acetyl), and 2.53(3H, s, C_2-CH_3).
2e	8.04(1H, d, J=2.2, H-5), 7.70(1H, d, J=2.2, H-7), 2.62(3H, s, CH_3 acetyl), and 2.60(3H, s, C_2-CH_3).
2f	8.12(1H, s, H-5), 7.33(1H, s, H-8), 2.65(3H, s, CH_3 acetyl), 2.52(3H, s, C_2-CH_3), and 2.49(3H, s, C_7-CH_3).
2g	7.89(1H, s, H-5), 7.18(1H, s, H-8), 2.66(3H, s, CH_3 acetyl), 2.52(3H, s, C_2-CH_3), 2.42(3H, s, C_7-CH_3), and 2.35(3H, s, C_6-CH_3).
2h	9.97(1H, d, J=8.6, H-9), 8.06(1H, d, J=8.9, H-7), 7.85(1H, d, J=9.5, H-12), 7.68(1H, dd, J=8.6 and 6.9, H-10), 7.61(1H, dd, J=6.9 and 9.5, H-11), 7.45(1H, d, J=8.9, H-8), 2.70(3H, s, CH_3 acetyl), and 2.52(3H, s, C_2-CH_3).
2i[b]	8.45(1H, d, J=7.5, H-9), 8.12(1H, d, J=8.7, H-5), 7.92(1H, d, J=6.8, H-12), 7.76(1H, d, J=8.7, H-6), 7.72(1H, d, J=7.5, H-10), 7.67(1H, d, J=6.8, H-11), 2.70(3H, s, CH_3 acetyl), and 2.66(3H, s, C_2-CH_3).
9a	7.38(1H, s, H-6), 6.96(1H, s, H-3), 11.58(1H, s, OH), 2.44(3H, s, CH_3), 2.41(3H, s, CH_3), and 2.32(3H, s, CH_3).
9b	7.19(1H, s, H-6), 6.86(1H, s, H-3), 11.63(1H, s, OH), 2.32(3H, s, CH_3), 2.30(3H, s, CH_3), 2.28(3H, s, CH_3), and 2.24(3H, s, CH_3).
10a	7.43(1H, s, H-5), 6.98(1H, s, H-8), 2.54(3H, s, CH_3 acetyl), and 2.41(6H, brs, C_2-CH_3 and C_7-CH_3).
10b	7.18(1H, s, H-5), 6.85(1H, s, H-8), 2.50(3H, s, CH3 acetyl), 2.32(3H, s, C_2-CH_3), 2.27(3H, s, C_7-CH_3), and 2.22(3H, s, C_6-CH_3).

[a] J in Hz, [b] $J_{10,11}$ not resolved

Table 3: ^{13}C-NMR spectra of the compound **2a - 2i**

Comp.	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	CO	CH_3	CH_3
										ace-tyl	ace-tyl	
2a	168.5	123.6[a]	175.7	123.8[a]	125.5	125.8	133.9	117.6	155.2	200.3	32.1	19.7
2b	168.3	123.3[a]	175.9	123.4[a]	125.1	135.5	135.2	117.4	153.5	200.5	32.1	20.9 19.7
2c	168.8	123.6	174.7	124.7	125.3	131.5	134.2	119.5	153.6	200.0	32.2	19.8
2d	168.7	123.6	174.4	125.0	128.5	118.9	136.9	119.6	154.0	199.8	32.0	19.7

2e	168.9	124.0[a]	174.0	125.6	124.0	131.2	134.0	123.6[a]	149.7	199.3	32.0	19.7
2f	168.6	123.4	174.6	122.7	125.5	132.2	143.3	119.5	153.5	200.1	32.1	20.8 19.8
2g	168.0	123.3	175.7	121.4	125.3	134.7	144.4	117.7	153.7	200.7	32.1	20.3 19.7 19.2
2h[b]	164.7	126.4	177.8	117.0	130.2	130.6	135.8	117.0	156.6	201.1	32.0	19.0
2i[c]	167.4	124.6	175.7	123.5	120.5	125.6	135.9	120.1	152.7	200.5	32.2	19.7

[a] J in Hz, [b] $J_{10,11}$ not resolved

Table 3: ^{13}C-NMR spectra of the compound 2a - 2i

Comp.	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	CO	CH_3	CH_3
										ace-tyl	ace-tyl	
2a	168.5	123.6[a]	175.7	123.8[a]	125.5	125.8	133.9	117.6	155.2	200.3	32.1	19.7
2b	168.3	123.3[a]	175.9	123.4[a]	125.1	135.5	135.2	117.4	153.5	200.5	32.1	20.9 19.7
2c	168.8	123.6	174.7	124.7	125.3	131.5	134.2	119.5	153.6	200.0	32.2	19.8
2d	168.7	123.6	174.4	125.0	128.5	118.9	136.9	119.6	154.0	199.8	32.0	19.7
2e	168.9	124.0[a]	174.0	125.6	124.0	131.2	134.0	123.6[a]	149.7	199.3	32.0	19.7
2f	168.6	123.4	174.6	122.7	125.5	132.2	143.3	119.5	153.5	200.1	32.1	20.8 19.8
2g	168.0	123.3	175.7	121.4	125.3	134.7	144.4	117.7	153.7	200.7	32.1	20.3 19.7 19.2
2h[b]	164.7	126.4	177.8	117.0	130.2	130.6	135.8	117.0	156.6	201.1	32.0	19.0
2i[c]	167.4	124.6	175.7	123.5	120.5	125.6	135.9	120.1	152.7	200.5	32.2	19.7

[a] The assignment can be interchanged, [b] values C-9 126.8, C-10 129.4, C-11 126.7, C-12 128.3,

[c] values C-9 122.0, C-10 127.3, C-11 129.4, C-12 128.1

2-Aryloxymethyl-3-acetylchromone derivatives *3* **and Intermediates** *4*

To a mixture of 2-hydroxyaroylacetones 1 (1g), K_2CO_3 (0.5g) in dry acetone after 2 h stirring at reflux the aryloxyacetyl chlorides were added. The reaction mixture was stirred and heated under reflux for 2h and left overnight at room temperature. The mixture was poured over crushed ice (50g) and solid product was separated. The product was diluted in 5 % cold $NaHCO_3$. The insoluble part was separated and recrystalized from ethanole. From $NaHCO_3$ solution which contained compounds 4, they were separated after acetic acid acidification and recrystalized from cyclohexane.

Prepared compounds:

1. *3-Acetyl- 2-(2,4-dichlorophenyloxymethyl)-6-metylchromone* **3a**

M.p. 150 - 151^{o} C

^{1}H-NMR($CDCl_3$)(ppm): 7.97(1H,brs, H-5), 7.49 - 6.95(m, 5H, Ar-H), 5.40(s, 2H.CH_2), 2.60(s, 3H,$COCH_3$), 2.47(s, 3H, Ar-CH_3)

2. *3-Acetyl-2-(2,4,5-trichlorophenoxymethyl)-6-metylchromone* **3b**

M.p.187 - 189^{o} C

3. *2-(2,4-dichlorophenyloxyacetyloxy)-5-methylbenzoylacetone* **4a**

M.p. 116 - 118^{o} C

4. *2-(2,4,5-trichlorophenyloxyacetyloxy)-5-methylbenzoylacetone* **4b**

M.p.94 - 95^{o} C

4-Acetyl-5-(2-hydroxyaryl)-3-methylisoxazoles 5

A mixture of 2 (0.0022 mole) in pyridine (3 ml) and hydroxylamine hydrochloride (0.15g, 0.0022 mole) in water (1 ml) was refluxed for 4h. The cooled mixture was poured over crushed ice and acidified with acetic acid and the solid that separated was filtered off and recrystallized from cyclohexane to give 5..

1. *4-Acetyl-5(2-hydroxy-4methyl-5-chlorophenyl)-3-methylisoxazole* **5a**

M. p. 114 - 115^{o} C

2. *4-acetyl-4,5-dimethylphenyl)-3-methylisoxazole* **5b**

M. p. 119 - 121^{o} C

Condensation products of 2 with 3-formylchromones 6

Method A(classic)

A mixture of compounds 2 (0.01 mole),3-formylchromones (0.01 mole),acetic anhydride (5 ml) and freshly fused potassium acetate (0.5g) was heated at 120 -130^{o} C for 2h. The cooled mixture was diluted with cooled water and the solid was separated and recrystallized from acetic acid.

Method B **A mixture of the same composition as in method A was irradiated in microwave oven for 3 minutes. Isolation of compounds are similar to method A.**

1. 6,6'-dimethyl derivative 6a

M.p. 222-224^{o} C

$C_{24}H_{18}O_5$ (386.4).

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