



A Modified Synthesis of 3-Methyl-Flavones Under Microwave Conditions

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3-Methyl flavone, Iodomethane, Phosphorus pentoxide, potassium hydroxide, Grinding technique, Microwave method.

ABSTRACT:

3-Methyl flavones are important members of the flavonoid family which are widely found in nature and are well known for their biological activities. A new, efficient method has been developed for their synthesis using 2-hydroxydibenzoylmethane and iodomethane with potassium carbonate under microwave irradiation for 30 seconds followed by a reaction with phosphorus pentoxide. This protocol offers advantages such as avoiding hazardous chemicals and organic solvents, shorter reaction times, and higher yields than traditional methods.

Introduction: Flavonoids are polyphenolic compounds found in many plants. Most flavonoids have been reported to react selectively with free radicals and exhibit anti-inflammatory activity¹⁻⁷. Flavanols and their derivatives have received special attention from chemists because they prevent various degenerative diseases, such as cardiovascular and cancer⁸⁻⁹. These are also found to possess various pharmacological activities like antidiabetic, hepatoprotective, antidiabetic¹⁰⁻¹⁵, etc. Due to their pharmacological importance, much emphasis has been placed on the synthesis of 3-methyl flavones. One widely used method was the Allan-Robinson method¹⁶. This method involves heating 2-hydroxy ω -methoxy acetophenones with aromatic acid anhydrides in the presence of the potassium salt of the acids. The improved synthetic method involves a novel demethylation process of the 3-methoxy group without the need of hydrogen peroxide. By utilizing a combination of mild demethylation conditions and a catalyst, the 3-methoxy group can be selectively removed, leading to the synthesis of 3-methylflavones with enhanced purity and yield. This novel approach eliminates the challenges posed by the insolubility of 2'-hydroxy chalcones and the use of hazardous substances, thereby aligning with green chemistry principles and the growing demand for sustainable synthetic pathways. These reactions are carried out through grinding and microwave techniques which are successfully employed in several organic transformations¹⁷⁻²⁶. It is well established that the energy produced on the surface of the friction of the molecules caused by grinding and microwave provides the activation energy for the reaction²⁷. Moreover, this technique can be employed on an industrial scale very easily, by using an electric food mixer with stainless steel rotors, or by using a ball mill. Therefore, it was thought worthwhile, to synthesize substituted flavonols, through the grinding and microwave technique.

Methods: Melting points were determined in an open capillary tube. TLC is used to monitor the reactions. A mortar and pestle made of porcelain was used to carry out the reaction. ¹H NMR, ¹³CNMR, and mass spectra were used to characterize the synthesized compound. The IR spectra were recorded on a Perkin Elmer spectrum BX series FT-IR spectrophotometer with KBr pellets.



¹H NMR spectra were recorded on Bruker Avance 400 MHz instrument using TMS as the internal standard. All the chemicals were obtained commercially and used without further purification.

Results The reaction of 2-hydroxydibenzoylmethane with iodomethane and potassium carbonate through grinding followed by microwave irradiation to afford 3-methyl flavones was taken as a model reaction. The compound was extracted by acidifying the reaction mixture in cool, concentrated hydrochloric acid. The reaction of 2-hydroxydibenzoylmethane with iodomethane and potassium carbonate through grinding followed by microwave irradiation to afford 3-methyl flavones was taken as a model reaction. The compound was extracted by acidifying the reaction mixture in cool, concentrated hydrochloric acid.

Conclusions: The protocol for synthesizing 3-methyl flavone using potassium carbonate via oxidative cyclization of 2-hydroxydibenzoylmethane is highly efficient and eco-friendly as it avoids toxic organic solvents. This is the clean, mild, high-yield, and expeditious method that also avoids the formation of any by-products.

1. Introduction:

Flavonoids are polyphenolic compounds found in many plants. Most flavonoids have been reported to react selectively with free radicals and exhibit anti-inflammatory activity¹⁻⁷. Flavanols and their derivatives have received special attention from chemists because they prevent various degenerative diseases, such as cardiovascular and cancer⁸⁻⁹. These are also found to possess various pharmacological activities like antidiabetic, hepatoprotective, antidiabetic¹⁰⁻¹⁵, etc. Due to their pharmacological importance, much emphasis has been placed on the synthesis of 3-methyl flavones. One widely used method was the Allan-Robinson method¹⁶. This method involves heating 2-hydroxy ω -methoxy acetophenones with aromatic acid anhydrides in the presence of the potassium salt of the acids. The improved synthetic method involves a novel demethylation process of the 3-methoxy group without the need of hydrogen peroxide. By utilizing a combination of mild demethylation conditions and a catalyst, the 3-methoxy group can be selectively removed, leading to the synthesis of 3-methylflavones with enhanced purity and yield. This novel approach eliminates the challenges posed by the insolubility of 2'-hydroxy chalcones and the use of hazardous substances, thereby aligning with green chemistry principles and the growing demand for sustainable synthetic pathways. These reactions are carried out through grinding and microwave techniques which are successfully employed in several organic transformations¹⁷⁻²⁶. It is well established that the energy produced on the surface of the friction of the molecules caused by grinding and microwave provides the activation energy for the reaction²⁷. Moreover,

this technique can be employed on an industrial scale very easily, by using an electric food mixer with stainless steel rotors, or by using a ball mill. Therefore, it was thought worthwhile, to synthesize substituted flavonols, through the grinding and microwave technique.

2. Experimental Section

2.1 Materials and Methods

Melting points were determined in an open capillary tube. TLC is used to monitor the reactions. A mortar and pestle made of porcelain was used to carry out the reaction. ¹H NMR, ¹³CNMR, and mass spectra were used to characterize the synthesized compound. The IR spectra were recorded on a Perkin Elmer spectrum BX series FT-IR spectrophotometer with KBr pellets. ¹H NMR spectra were recorded on Bruker Avance 400 MHz instrument using TMS as the internal standard. All the chemicals were obtained commercially and used without further purification.

2.2 General Procedure for the synthesis of 3-methyl flavone:

A mixture of differently substituted 2-hydroxydibenzoylmethane (2 mmol), iodomethane (1ml), and potassium carbonate (1 mmol) was reacted through grinding via mortar & pestle and microwave irradiation for 30 sec. The reaction mixture was cooled at room temperature for 5-10 min and phosphorus pentoxide was added for cyclization. The progress of the reaction was checked by TLC and melting point. The reaction mixture was diluted with ice-cold water and acidified with



concentrated HCl. The colorless solid thus obtained was filtered, and washed with water to obtain 3-methyl flavones in high yield.

3. Spectral data of compounds

3-Methyl-2-phenyl benzopyran-4-one, 3a: IR spectrum (KBr), ν_{\max} , cm^{-1} : 1614 (C=O); $^1\text{H NMR}$ (400MHz, CDCl_3), δ , ppm (J, Hz): 8.2 (s, 3H, CHO), 7.0-7.9 (m, 8H, C_6H_5 , H-6, H-7 and H-8) and 8.10 ppm (d, $J=8.0$ Hz, 1H, H-5).

3-Methyl-2-(4-methylphenyl)benzopyran-4-one 3b: IR spectrum (KBr), ν_{\max} , cm^{-1} : 3178(Ar C-H), 2813(C-H), 1680(C=O), 1570(C=C); $^1\text{H NMR}$ (400MHz, CDCl_3), δ , ppm (J, Hz): 2.1(3H, s, 3- CH_3), 2.5 (3H, s, H-4- CH_3), 7.6 (2H, d), 7.70 (1H, t, H-7), 7.75 (1H, d, H-5), 7.8 (2H, d), 8.0 (1H, t, H-6), 8.1 (1H, d, H-8).

3-Methyl-2-(4-methoxyphenyl) benzopyran-4-one 3c: IR spectrum (KBr), ν_{\max} , cm^{-1} 3080 (Ar C-H), 2716 (C-H), 1637 (C=O), 1467(C=C), 1140 (C-O); $^1\text{HNMR}$ (400 MHz, CDCl_3), δ , ppm (J, Hz): d 8.1 (1H, d, H-8), 7.9 (2H, d, H-30/50), 7.7 (1H, t, H-7), 7.4 (1H, t, H-6), 7.1 (1H, d, H-5), 6.9 (2H, d, H-2'/6'), 3.4 (3H, s, H-4-O CH_3), 2.5 (3H, s, H-3- CH_3).

3-Methyl-7-methoxy-2-phenyl benzopyran 4-one 3d: IR spectrum (KBr), ν_{\max} , cm^{-1} 3110 (Ar C-H), 2750 (C-H), 1658 (C=O), 1460 (C=C), 1200 (C-O); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ , ppm (J, Hz): d 8.1 (2H, d, H-30,50), 8.0 (1H, d, 5H), 7.5 (2H, d, H-20,60), 7.4 (1H, d, 6H), 7.2 (1H, s, H-8), 3.9 (3H, s, H-O CH_3), 2.8 (3H, s, H- CH_3).

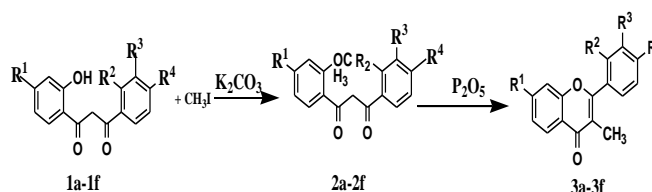
3-Methyl-2-(4'-fluorophenyl) benzopyran-4-one 3e: IR spectrum (KBr), ν_{\max} , cm^{-1} : 3041(Ar C-H), 2762 (C-H), 1639 (C=O), 1467 (C=C), 1014 (C-F); $^1\text{H NMR}$ (400 MHz, CDCl_3), δ , ppm (J, Hz): d 8.26 (2H, d), 7.68 (1H, d, 5H), 7.64 (1H, d, H-8), 7.46 (2H, d, H-20/60), 7.42 (1H, t, H-7), 7.26 (1H, t, H-6), 2.2 (3H, s, CH_3).

4. Results and Discussion:

The reaction of 2-hydroxydibenzoylmethane with iodomethane and potassium carbonate through grinding followed by microwave irradiation to afford 3-methyl flavones was taken as a model reaction. The compound was extracted by acidifying the reaction mixture in cool, concentrated hydrochloric acid.

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Scheme 1. Synthesis of 3-methyl-2-phenyl benzopyran-4-one

After confirming the product by thin-layer chromatography, the next step is to analyze the specific methods and parameters for synthesizing flavonols using the grinding technique under microwave conditions. This method offers the advantage of efficient and rapid heating, allowing for faster reaction times and improved yields. The reaction conditions, such as temperature, time, and the type of grinding material, will play crucial roles in achieving the desired flavonol products. Moreover, using microwave conditions can potentially lead to enhanced product purity and reduced side reactions. Therefore, optimizing these parameters is essential to achieve the best results. The formation of the above-mentioned product was evidenced by a comparison of melting point ($67-68^\circ$) with literature melting point (66°). The IR spectrum of the product formed and showed absorption at 1614 cm^{-1} , and 3178 cm^{-1} due to C=O and (ArC-H) bond stretching respectively, and in the $^1\text{H-NMR}$ spectrum, a singlet at $\delta 2.14$ is due to CH_3 and two multiplets at $\delta 7.0$ to 7.9 and a doublet at 8 is due to aromatic protons which further confirmed the formation of 3-methyl flavone. Encouraged by these results, various substituted 3-methyl flavones were synthesized using the same reaction conditions (Table 1).

Compounds	R ¹	R ₂	R ₃	R ⁴	Time (min)	Yield (%)	Observed MP ($^\circ\text{C}$) (Reported MP in $^\circ\text{C}$)	R _f
3a	H	H	H	H	10	80	67-69-66	0.3
3b	H	H	H	CH ₃	10	83	122-124	0.42



							(125-132)	
3c	H	H	H	OC H ₃	10	85	94-98 (90-95)	0.35
3d	OC H ₃	H	H	H	10	84	89-92 (85-90)	0.43
3e	H	H	H	F	10	92	96-98 (90-95)	0.31

Table 1. Physical data of 3-methyl-2-phenyl benzopyran-4-one

Furthermore, to check the presence of and procedure's efficiency our method's results were compared with the known method (**Table 2**) The current protocol for the synthesis of 3-methyl-2- phenyl benzopyran-4-one is excellent in terms of time and yields and to avoid the use of hazardous and toxic solvents to make the reaction eco-friendly

S.No.	Catalyst	Time	Temp (°C)	Yields	References
1	KOH / Iodine	48- 72h	Reflux ed	65%	[28]
2	LiHMDS	5h	Room temp	80%	[29]
3	K ₂ CO ₃	10 min	Grinding +30 Sec microwave	85%	Present Method

Table 2. Comparison of the results of the reactions carried out with different reagents for the synthesis of 3-methyl-2-phenyl benzopyran-4-one with the present method

Conclusion:

The protocol for synthesizing 3-methyl flavone using potassium carbonate via oxidative cyclization of 2-hydroxydibenzoylmethane is highly efficient and eco-friendly as it avoids toxic organic solvents. This is the clean,

mild, high-yield, and expeditious method that also avoids the formation of any by-products.

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