

APPLICATION OF MICROWAVE HEATING OF DRY ORGANIC REACTIONS: NEW CONDENSATION PRODUCTS FROM TRIACETIC ACID LACTONE (TAL)

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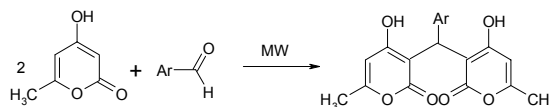
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The work undertaken resides in the development of new methods of synthesis respectful of the environment. A convenient synthesis of bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl) arylmethanes are obtained by condensation of triacetic acid lactone (4-hydroxy-6-methyl-2H-pyran-2-one) with aromatic aldehydes, in absence of the catalyst, without solvent by activation under microwave irradiation. This method has environmentally friendly advantages, short reaction time, high yields and easy preparation. We report here the synthesis of new heterocyclic compounds (dilactones) from TAL providing evidence for the particular reactivity of the position 3 of these compounds.



INTRODUCTION

Microwave heating has long been in polymer chemistry and is used at an industrial scale in vulcanization processes.¹⁻³ But curiously, application of microwaves in molecular chemistry (organic synthesis) appeared only at the end of 1985 with the pioneering papers of authors.²⁻⁵ As shown by the recent reviews in this field⁶⁻¹¹ there is now a growing interest in microwaves chemistry and a question has rapidly been addressed; does microwave irradiation of a reaction of mixture result in a non thermal effect, or in other words, is this molecular activation.

As a matter of fact, from many reported results, several statements could be made: microwave

irradiation results in rate enhancements, higher yields, and improved selectivity.¹²

The 2-pyrone has common products in nature^{13,14} and are responsible for a wide range of biological (Anxiolytic, antifungal, cytotoxic and neurotoxic).¹⁵⁻¹⁹

The structure of triacetic lactone (4-hydroxy-2H-2-pyran-2-one) is a pattern of inhibition of the protease-type 1 virus of Sida (PRVH-1).²⁰⁻²⁴ The best-known representatives of this class of compounds are kavalactone lactone (4-methoxy-6-styryl-pyran-2-ones) that display various and important pharmacological properties (sedative, sleeping pills, local anesthetic, analgesic, anti-inflammatory, anticonvulsants, antimalarial and antituberculosis).²⁴⁻²⁶

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The powerful pharmacological effect (inhibition)²¹ unsaturated γ -lactones to six members on the central nervous system has attracted the attention of organic chemists seeking new strategies for the synthesis of these bioactive compounds.²⁷

We herein report the synthesis of bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)arylmethanes **3** by condensation aromatic aldehyde and 4-hydroxy-6-methyl-2H-pyran-2-one **2** without solvent takes place rapidly under focussed microwave irradiation (MW), (Scheme 1).

RESULTS AND DISCUSSION

Preparation of 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one **1**:

In a preliminary study we were inspired by the literature,²⁷⁻³¹ to access to dehydroacetic acid. The reaction of 2 equivalents of β -ketoester in the presence of sodium bicarbonate leads to the DHA

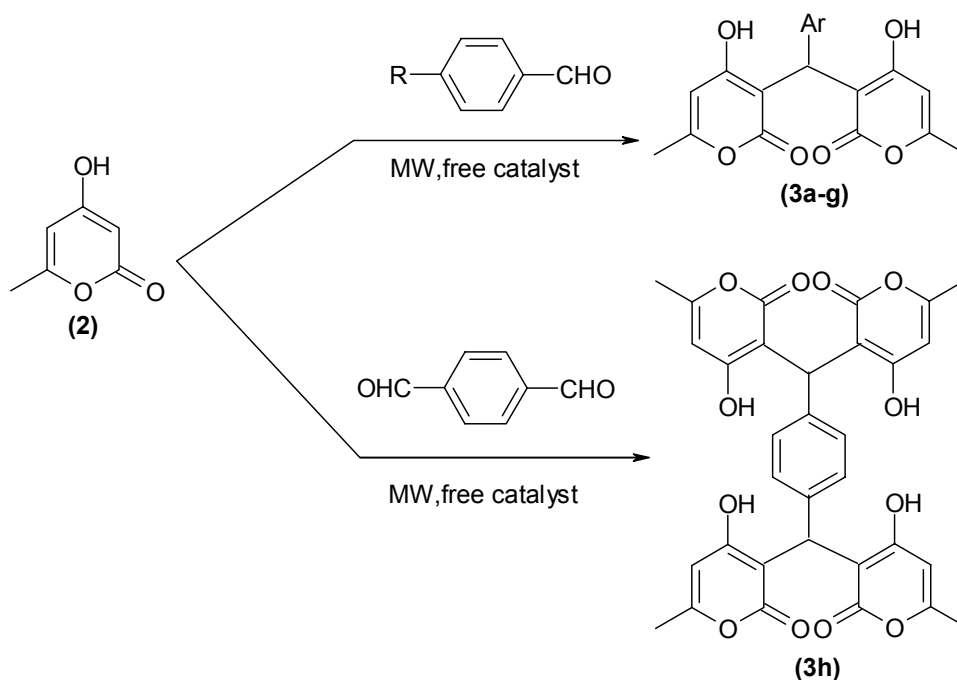
1 in good yield (83 %). The resulting product is also available commercially. The results were compared with the authentic sample (Scheme 2).

Synthesis of 4-hydroxy-6-methyl-2H-pyran-2-one (TAL) **2**:

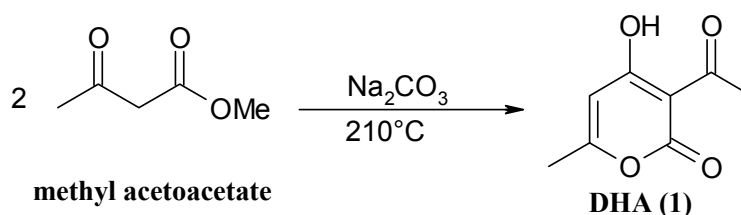
The chain acetyl of position 3 of dehydroacetic acid (CH_3CO) is removed by a heat treatment at sulfuric acid^{28,32} (95 %) (Scheme 3). The white product with yield of 85 % was identified by the following spectroscopic methods: TLC, UV-VIS, IR, ^1H NMR and ^{13}C NMR and mass spectrum.

Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl) aryl methanes: **3**_(a-h):

The chemistry of 4-hydroxy-6-methyl-2-pyrone (Triacetic Acid Lactone) at the C-3 position is well known. However reaction with aldehydes have been only exceptionally described.^{22,23}



Scheme 1 – Synthesis of bis (4-hydroxy-6-methyl-2-oxo-3-yl)arylmethanes.

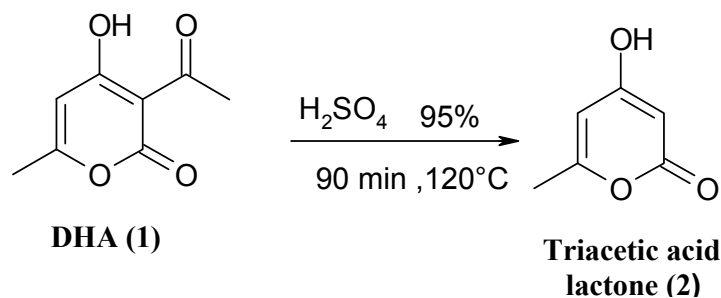


Scheme 2

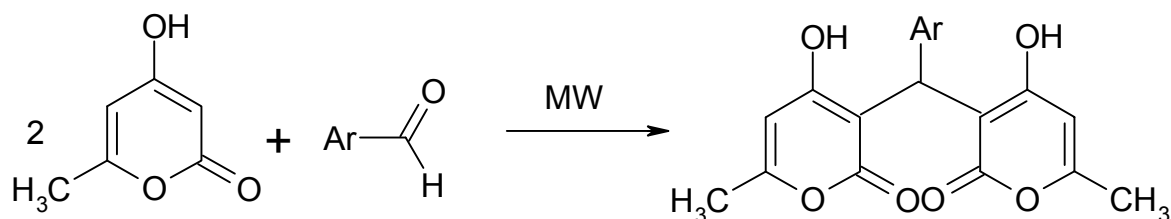
There are journals in literature who described the synthesis of bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)arylmethanes under typical Knoevenagel conditions, at reflux in the presence of AcOH, piperidine in ethanol.^{29,33} Hagiwara and his coauthors^{34,35} have reported two improved synthesis procedures or by the use of Et₂AlCl or the use of DBU at room temperature for 9h. As part of green chemistry and the development of new more environmentally friendly method for the synthesis of various biologically important heterocyclic compounds. Zhang *et al.*³⁶ are preparing the arylbismethanes using the ionic liquid [bmim] [BF₄] at 80 °C for about 4 hours. Although these methods mentioned above, the pyrone reacts with all the aldehydes used with a donor group or electron withdrawing group, are easily and effectively react to give the compound

(3). Our interest in this work draws attention that arylbismethane molecules are easily obtained solvent-free catalysis and in a shorter time. We have used this methodology to prepare the condensation reaction between aromatic aldehyde monofunctional (01 equivalent) and 4-hydroxy-6-methyl-2H-pyran-2-one (02 equivalents) in the absence of solvent under microwaves irradiation with power to 300 W (Scheme 4). The products were obtained in good yields (Table 1).

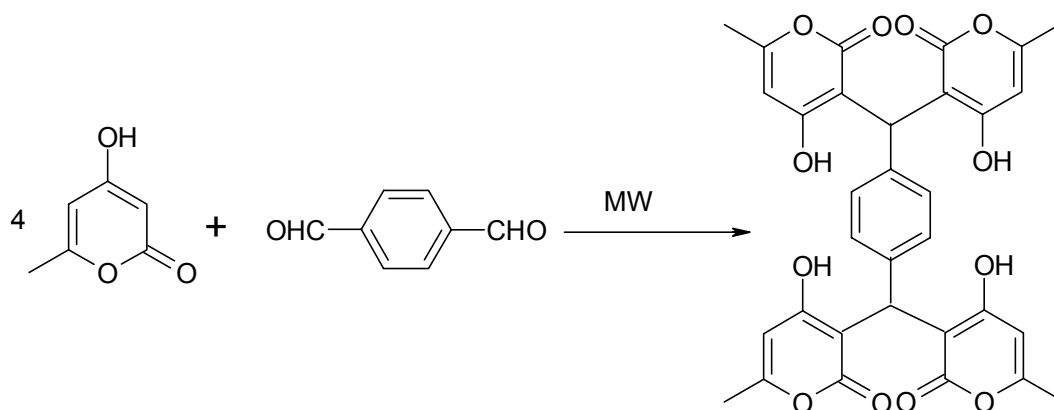
We have also tested this type of reaction with aromatic aldehyde bifunctional (terephthalaldehyde). The triacetic acid lactone (04 equivalents) treated with aromatic aldehyde (01 equivalent) in the absence of catalyst and solvent converts into 1,4-Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)methylbenzene (3) (Scheme 5). Yield of new product (3_h) is good (89 %).



Scheme 3



Scheme 4



Scheme 5

Table 1

Physical and analytical data of synthesis compounds (3)

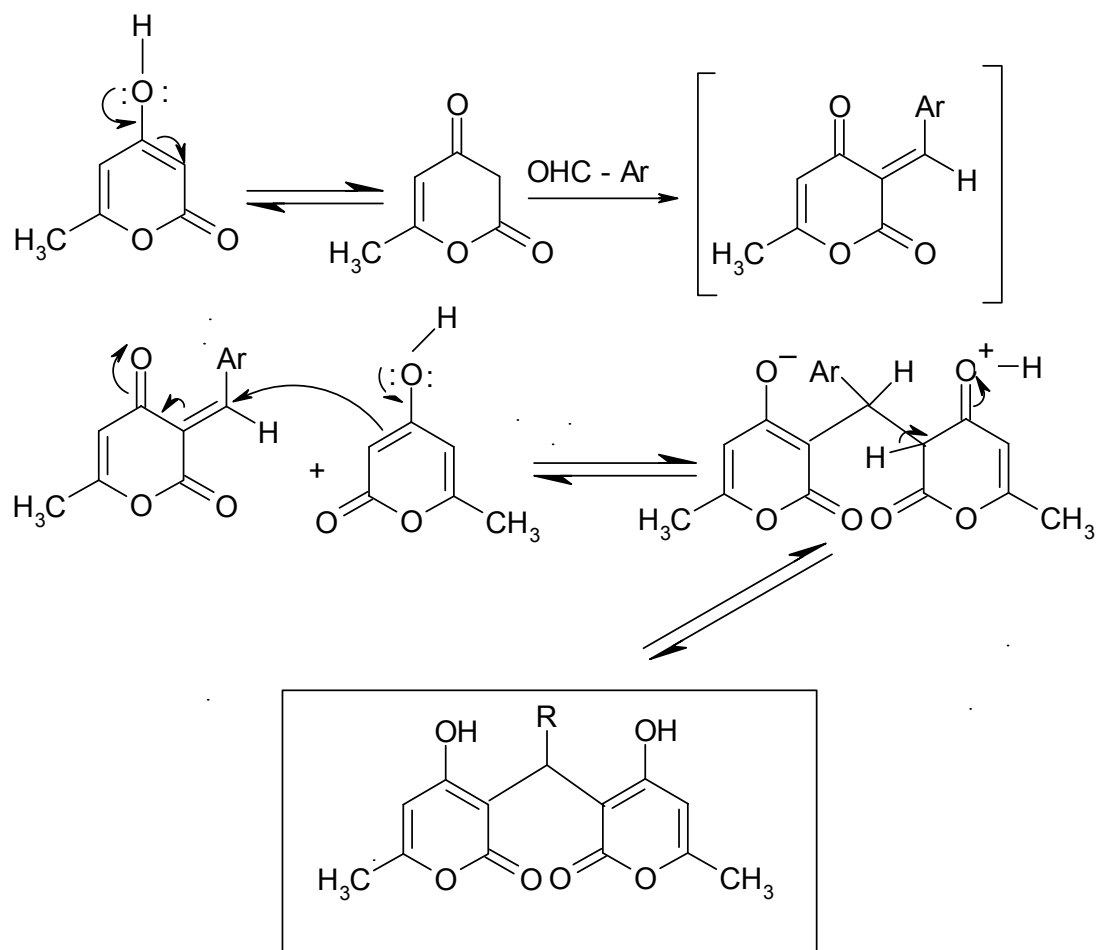
Ar	Microwave		Product	Yield (%)	Color	¹ HNMR δ; ppm	m.p (°C)
	p(W)	t(min)				C ₃ -CH-C ₃ '	
C ₆ H ₅ -	300	8	3a	100	white	5.75	216-218
4-Cl- C ₆ H ₄ -		11	3b	88		5.69	202-205
4-H ₃ CO-C ₆ H ₄ -		10	3c	97		5.71	186-187
4- H ₃ C-C ₆ H ₄ -		10	3d	96		5.70	188-190
4-Br- C ₆ H ₄ -		11	3e	87	yellow Brown	5.66	199-121
4-F-C ₆ H ₄ -		8	3f	100		5.69	218-220
4-O ₂ N-C ₆ H ₄ -		12	3g	88		5.76	245-250
-C ₆ H ₄ -		13	3h	89		5.89	225-228

All products were characterized by IR, ¹H NMR, Mass spectra and by comparison of physical characteristics with authentic samples.

Mechanism:

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation

of 3, 3'-arylidenebis[4-hydroxy-6-methyl-2H-3-pyrone] could be explained by a reaction sequence presented in (Scheme 6). The observed reaction was interpreted in terms of a conjugated Michael addition of several molecule of TAL.



Scheme 6

MATERIALS AND METHODS

NMR spectra were recorded using an Avance III 400 Brüker spectrometer at 293 K at 400 MHz. Chemical shifts are reported in ppm with the solvent as internal reference. All coupling constants are reported in Hz. The following abbreviations are used to describe signal multiplicity for ^1H NMR: s singlet; d doublet, t triplet; dd doublet of doublets; m multiplet; br broad. High Resolution Mass Spectra were recorded on an Orbitrap apparatus with an electrospray ionization (ESI). Reactions were monitored by thin layer chromatography (TLC) using commercial aluminium-backed silica gel plates. Melting points were obtained using a heating rate of 10 °C/min and are uncorrected. Infrared spectra (IR) were recorded as KBr pellets on JASCO FTIR-4100 and the data are reported in reciprocal centimeters (cm^{-1}). Spectrometer UV-visible spectra (λ_{max} $\log(\epsilon)$) were obtained with Spectrophotometer of UV-Force of T60U. Microwave irradiation were carried out with a commercial microwave oven (CEM Discover monomode microwave oven).

3-Acetyl-4-hydroxy-6-methyl-2H-pyran-2-one (1)

Procedure: Methyl acetoacetate (50 mL) and 3 g of sodium bicarbonate (Na_2CO_3) are heated until the liquid has reached 190 °C-200 °C. The time for heating was usually 10 h, during which period 12.5 mL of distillate boiling at 72 °C (methanol) was collected and the color of the reaction mixture becomes dark brown. The resulting dehydroacetic acid was distilled under reduced pressure (the dehydroacetic acid was collected at 140 °C, 12 mm). By recrystallization from ethyl acetate, the clear white solid obtained is then identified by the appropriate spectroscopic methods.

White solid clear crystallized in ethylacetate; m.p = 108-110 °C, (lit²⁸ = 107-108 °C); $\text{C}_8\text{H}_8\text{O}_4$; MM = 168.15 $\text{g}\cdot\text{mol}^{-1}$; yield: 83 %; TLC [pentane/ethyl acetate : 80 /20] : Rf = 0.7; UV (EtOH) λ_{max} ($\log \epsilon$) nm = 303 (3.23), 228 (3.27); IR (KBr) ν/cm^{-1} = 1710 (ν C=O cycle pyrone) 1610 (ν C=O), 1570 (ν C=C), 1186 (ν OCO); ^1H NMR (400 MHz, CDCl_3) δ_{ppm} = 2.26 (s, 3H, CH_3); 2.66 (s, 3H, CH_3); 5.92 (s, H, CH); ^{13}C NMR (400 MHz, CDCl_3) δ_{ppm} = 20.71 CH_3 (C_7), 29.97 CH_3 (C_4), 99.94 (C_3), 101.19 (C_5), 161.17 (C_2), 169.40 (C_6), 181.24 (C_4), 205.25 (C_3); MS m/z (%): 169 (M^+ , 100).

2. 4-Hydroxy-6-methyl-2H-pyran-2-one (2)

Procedure: (1.5 mol, 222 g) of dehydroacetic acid **1** was dissolved in 500 ml of dilute 95% H_2SO_4 . The mixture was then heated up to 120 °C and maintained at the same temperature for about 90 min. The flask was then rapidly cooled and the contents were poured into of ice-cold water. The precipitated solid was collected by filtration, after filtration and washing with water to reduce the acidity, the product is recrystallized from water.

White solid recrystallized in water m.p = 186-188 °C, (lit²⁸ = 188-190 °C); $\text{C}_6\text{H}_6\text{O}_3$; MM = 126.12 $\text{g}\cdot\text{mol}^{-1}$; yield : 85%; TLC [pentane/ethylacetate : 80 /20] : Rf = 0.65; UV (EtOH) λ_{max} ($\log \epsilon$) nm = 390 (3.38), 278 (3.45), 215 (3.30); IR (KBr) ν/cm^{-1} = 3320 (ν OH), 1721 (ν C=O), 1626 (ν C=C), 1540, 1303, 1250 (ν COC), 870, 813; ^1H NMR (400 MHz, CDCl_3) δ_{ppm} = 2.15 (s, 3H, CH_3), 5.21 (s, 1H, H_3), 5.95 (s, 1H, H_5); ^{13}C NMR (400 MHz, CDCl_3) δ_{ppm} = 19.58 (C_7), 88.30 (C_3), 100.32 (C_5), 163.42 (C_6), 164.07 (C_4), 170.70 (C_2), MS, m/z (%): 126 (M^+ , 33).

Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)aryl methanes (3_{a-h})

General Procedure: To a mixture of 4-hydroxy-6-methyl-2H-pyran-2-one **2** (4 mmol ; 0.25 g) and aromatic aldehydes (2 mmol). This mixture was heated by microwaves for 10 min, a power of 300 Watts and temperature 80 °C. The solid is crystallized from ethanol. The solid obtained is then identified by the appropriated spectroscopic methods.

Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)phenyl methane (3a)

Product obtained from benzaldehyde (2 mmol, 0.208 g); Microwaves [power = 300 W, time = 8 min]; white solid crystallized in ethanol; m.p = 216-218 °C (lit²⁹ = 214-215 °C); $\text{C}_{19}\text{H}_{16}\text{O}_6$; MM = 340.32 $\text{g}\cdot\text{mol}^{-1}$, yield : 100 %; TLC [pentane/ethylacetate : 80 /20] : Rf = 0.65 ; UV (EtOH) λ_{max} ($\log \epsilon$) nm = 284 (2.56), 211 (2.78); IR (KBr) ν/cm^{-1} : 3121 (ν OH), 1684 (ν C=O), 1636 (ν C=C), 1573 (ν C=C), 1343, 1199 (ν COC), 870, 841(CH, arom monosubs); ^1H NMR (400 MHz, CDCl_3) δ_{ppm} = 2.28 (s, 6H, CH_3), 5.75 (s, 1H, CH); 6.05 (s, 2H, CH); 7.14-7.32 (m, 5H, Harom); ^{13}C NMR (400 MHz, CDCl_3) δ_{ppm} = 20.06, 36.9, 101.20, 125.83, 128.02, 128.72, 144.4, 162.23, 172.1; MS, m/z (%): 340 (M^+ , 46).

Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-4-chloro phenylmethane (3b)

Product obtained from parachlorobenzaldehyde (2 mmol, 0.228 g); Microwaves [power = 300 W, time = 11 min]; white solid crystallized in ethanol m.p = 202-205 °C (lit²⁹ = 202-205 °C); C₁₇H₁₅ClO₆; MM = 374.77 g.mol⁻¹; yield : 88 %; TLC [pentane/ ethylacetate : 80 /20] : Rf = 0.71; UV-visible : λ max (log ε) (EtOH) nm : 274 (3.48); IR (KBr) v/cm⁻¹ = 3113 (ν OH), 1681 (ν C=O), 1614 (ν C=C), 1575, 1421, 1309, 1201 (ν COC), 868 (ν CH, arom disubs); 771 (C-Cl); ¹H NMR (CDCl₃) δ_{ppm} = 2.28 (s, 6H, CH₃), 5.69 (s, 1H, CH); 6.02 (s, 2H, CH); 7.07-7.27 (m, 4H, H arom); MS, m/z (%) : 374 (M⁺. 34).

Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-4-methoxy phenylmethane (3c)

Product obtained from paramethoxybenzaldehyde (2 mmol, 0.275 g); Microwaves [power = 300 W, time = 10 min]; white solid crystallized in ethanol m.p = 186-187 °C (lit²⁹ = 174-176 °C); UV spectrum (EtOH), λ_{max} : 303.38, 234.94; IR spectrum (KBr), ν, cm⁻¹: 3100 (ν OH), 2836 (ν C-OCH₃), 1721 (ν C=O), 1626 (ν C=C), 1540, 1303, 1250 (ν COC), 870, 813; ¹H NMR spectrum (400 MHz, CDCl₃), δ, ppm : 2.28 (s, 6H, CH₃), 5.69 (s, 1H, CH); 6.02 (s, 2H, CH); 7.07-7.27 (m, 4H, H arom); MS Found, m/z: 370.33 [M]⁺. C₂₀H₁₈O₇. Calculated, m/z: 370.13.

Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-4-methyl phenylmethane (3d)

Product obtained from paramethylbenzaldehyde (2 mmol, 0.372 g); Microwaves [power = 300 W, time = 10 min]; yellow solid crystallized in ethanol m.p = 188-190 °C; C₂₀H₁₈O₆; MM = 354.12 g.mol⁻¹; yield : 96 %; TLC [pentane/ ethylacetate : 80 /20] : Rf = 0.51; UV (EtOH) λ_{max} (log ε) nm : 292 (3.08), 217 (3.12); IR (KBr) v/cm⁻¹ : 3320 (ν OH), 2974 (ν C-CH₃), 1721 (ν C=O), 1626 (ν C=C), 1540, 1303, 1250 (ν COC), 870, 813; ¹H NMR (400 MHz, CDCl₃) δ_{ppm} = 2.31 (s, 6H, CH₃), 5.70 (s, 1H, CH); 6.04 (s, 2H, CH); 7.02-7.77 (m, 4H, H arom).

Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-4-bromo phenylmethane (3e)

Product obtained from parabromobenzaldehyde (2 mmol, 0.351 g); Microwaves [power = 300W, time = 11 min]; white solid crystallized in ethanol m.p = 197-199 °C; C₁₉H₁₅BrO₆; MM = 411.9 g.mol⁻¹; yield : 87 %; TLC [pentane/ ethylacetate :

80 /20] : Rf = 0.68 ; UV (EtOH) λ_{max} (log ε) nm = 290 (2.94), 210 (2.94); IR (KBr) v/cm⁻¹ : 3104 (ν OH), 1721 (ν C=O), 1626 (ν C=C), 1540, 1303, 1250 (ν COC), 870, 813, 738 (ν C-Br); ¹H NMR (400 MHz, CDCl₃) δ_{ppm} = 2.28 (s, 6H, CH₃), 5.66 (s, 1H, CH); 6.02 (s, 2H, CH); 7.01-7.42 (m, 4H, H arom).

Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-4-fluoro phenylmethane (3f)

Product obtained from parafluorobenzaldehyde (2 mmol, 0.247 g); Microwaves [power = 300 W, time = 8 min]; white solid crystallized in ethanol m.p = 218-220 °C; C₁₇H₁₅FO₆; MM = 358.32 g.mol⁻¹; yield : 100 %; UV (EtOH) λ_{max} (log ε) nm = 296.22 (3.47); IR (KBr) v/cm⁻¹ = 3100 (ν OH), 1721 (ν C=O), 1626 (ν C=C), 1540, 1303, 1250 (ν COC), 870, 813 (ν C-F); ¹H NMR (400 MHz, CDCl₃) δ_{ppm} = 2.28 (s, 6H, CH₃), 5.69 (s, 1H, CH); 6.03 (s, 2H, CH); 6.96- 7.12 (m, 4H, H arom).

Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-4-nitro phenylmethane (3g)

Product obtained from paranitrobenzaldehyde (2 mmol, 0.302 g); Microwaves [power = 300 W, time = 12 min]; yellow solid recrystallized in ethanol m.p = 245-250 °C (lit²⁹ = 214-217 °C); C₁₉H₁₅NO₈; MM = 385.32 g.mol⁻¹; yield: 88 %; TLC [pentane/ ethylacetate : 80 /20] : Rf = 0.39; UV (EtOH) λ_{max} (log ε) nm = 287.86 (3.44), 215.37 (3.12); IR (KBr) v/cm⁻¹ = 3100 (ν OH), 1721 (ν C=O), 1626 (ν C=C), 1522 (ν NO₂), 1303, 1250 (ν COC), 870, 825 (ν CH, arom disubs) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ_{ppm} = 2.31 (s, 6H, CH₃), 5.76 (s, 1H, CH); 6.05 (s, 2H, CH); 7.42 (m, 4H, H arom); ¹³C NMR (400 MHz, CDCl₃) δ_{ppm} = 20.9, 37.4, 95.0, 100.9, 123.8, 126.9, 144.9, 150.5, 162.6, 164.2, 172.1.

1, 4-Bis(4-hydroxy-6-methyl-2-oxo-2 H-pyran-3-yl) methyl benzene (3h)

Product obtained from terephthalaldehyde (2 mmol, 0.28 g) and TAL 2 (4 mmol, 0.492 g); Microwaves [power = 300 W, time = 13 min]; Brown clear solid crystallized in ethanol m.p = 225-228 °C; C₃₂H₂₆O₁₂; MM = 602.54 g.mol⁻¹; yield : 89 %; TLC [pentane/ ethylacetate : 80 /20]: Rf = 0.42; UV (EtOH) λ_{max} (log ε) nm = 310 (4, 10), 224 (4, 05); IR (KBr) v:cm⁻¹ = 3100 (ν OH), 1680 (ν C=O), 1636 (ν C=C), 1570 (ν C=C), 1343, 1199 (ν COC), 870, 841(ν CH, arom disubs) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ_{ppm} = système AB 2.36 (s, 6H,

CH₃), 5.97 (s, 1H, CH); 6.11 (s, 2H, CH); 7.12-7.13 (m, 4H, Harom); ¹³C NMR (400 MHz, CDCl₃) δ_{ppm} = 21.10, 37.9, 96.10, 101.1, 129.2, 141.3, 163.2, 165.1, 171.8.

CONCLUSION

In conclusion we have developed a simple approach to synthesis of new products (Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)arylmethanes) from Triacetic Acid Lactone **2**, carbonyl compounds. A study on reaction without solvent and under microwave irradiation. This method (without using catalyst) is very efficient and much more rapid than classical methods.

Compounds with potential synthetic and biological interest are synthesized.

ABBREVIATIONS

DAH = dehydroacetic acid
 TAL = Triacetic acid lactone
 IR = Infrared
 MW = Microwave
 NMR = Nuclear Magnetic Resonance
 TLC = Thin layer chromatography

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