ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2016, *61*(11-12), 863-869

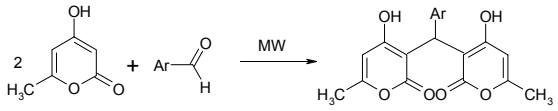
APPLICATION OF MICROWAVE HEATING OF DRY ORGANIC REACTIONS: NEW CONDENSATION PRODUCTS FROM TRIACETIC ACID LACTONE (TAL)

Nassima BENFERRAH,[a,b*] Mohamed HAMMADI[a] and Florian BERTHIOL[c]

[a] URMPE Research Unit for Materials, Processes and Environment, University M'hamed Bougara Boumerdes, Faculty of Engineering Sciences, 35000, Boumerdes, Algeria
[b] Scientific and Technical Research Center in Physical Chemical Analyses (C.R.A.P.C) 35000, Boumerdes, Algeria
[c] Department of Molecular Chemistry (SERCO), UMR-5250, ICMG FR-2607, University Joseph Fourier, 301 Rue de la Chimie, BP 53, 38041 Grenoble Cedex 9, France

Received February 17, 2016

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 whit the pioneering papers of authors.[2-5] As shown by the recent reviews in this field[6-11] 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-pyrones have common products in nature[13,14] and are responsible for a wide range of biological (Anxiolytic, antifongic,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 (PRVIH-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]

* Corresponding author: benferrahnassima@gmail.com

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), (Sheme **1**).

RESULTS AND DISCUSSION

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

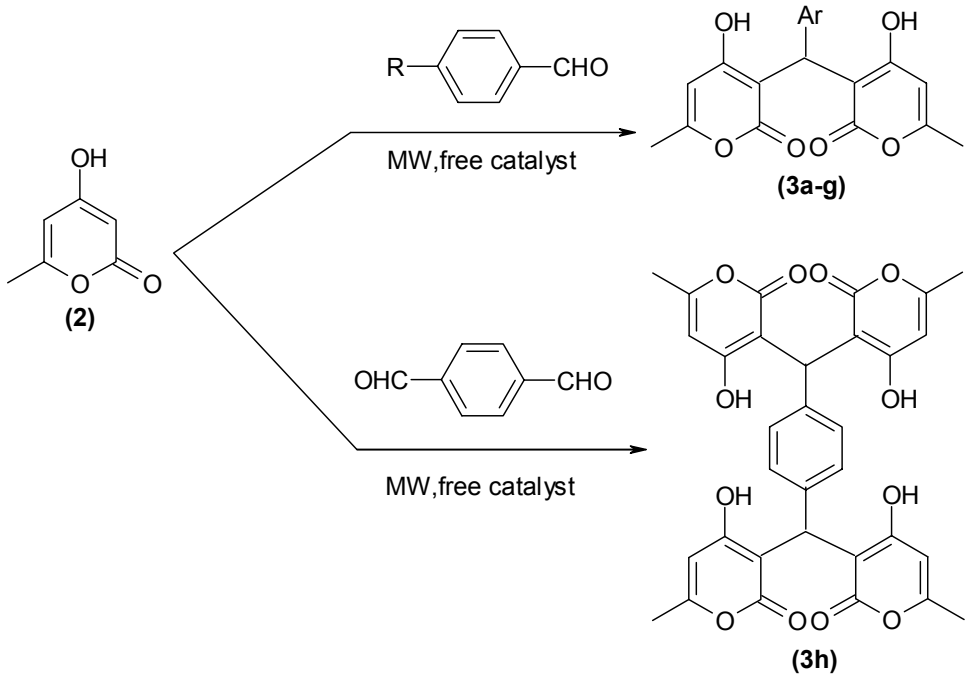
In a preliminary study we were inspired by the literature,[27-31] to access to dehydroacetic acid. The reaction of 2 equivalents of β-ketoester in the presence of sodium bicarbonate leads to the DHA **1** in good yield (83 %). The resulting product is also available commercially. The results were compared with the authentic sample (Scheme **2**).

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

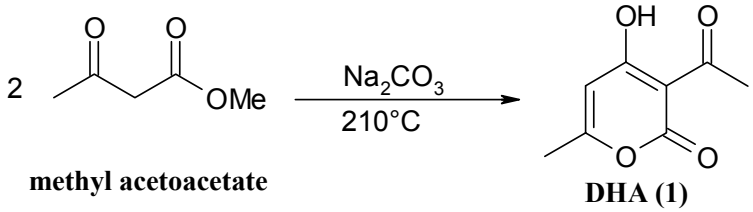
The chain acetyl of position 3 of dehydroacetic acid (CH_3CO) is removed by a heat treatment at sulfuric acid[28,32] (95 %) (Scheme **3**). The white product with yield of 85 % was identified by the following spectroscopic methods: TLC, UV-VIS, IR, ^{1}H NMR and ^{13}C NMR and mass spectrum.

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]



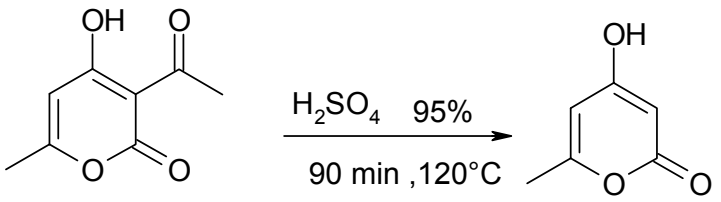
Scheme 1 – Synthesis of bis (4-hydroxy-6-methyl-2-oxo-3-yl)arylmethanes.



Scheme 2

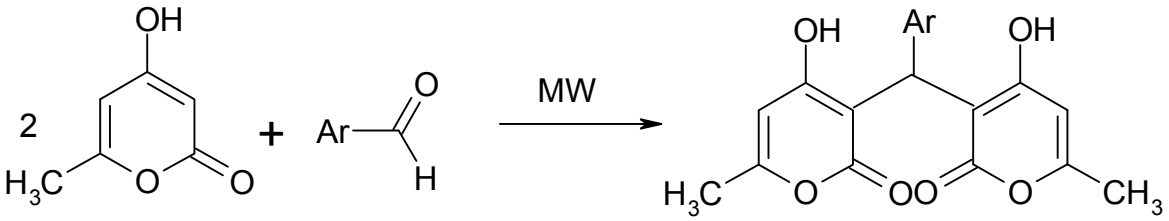
There are journals in literature who described the synthesis of bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)arylmethanes under typical Knoevenagel conditions, at reflux in the presence of AcOH, piperidine in ethanol.[29,33] Hagiwara and his coauthors[34,35] have reported two improved synthesis procedures or by the use of Et $_2$AlCl 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] [BF 4] 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 monofonctional (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 (terephtaldehyde). 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 %).

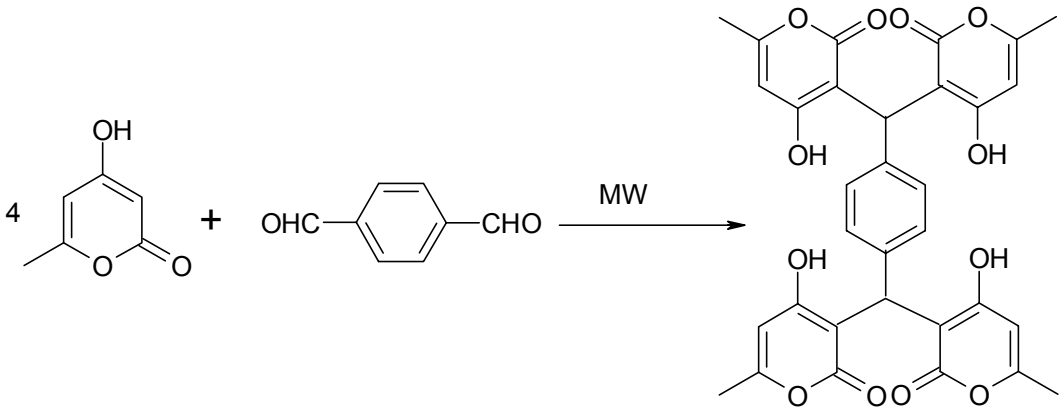


DHA (1) **Triacetic acid lactone (2)**

Scheme 3



Scheme 4



Scheme 5

Table 1

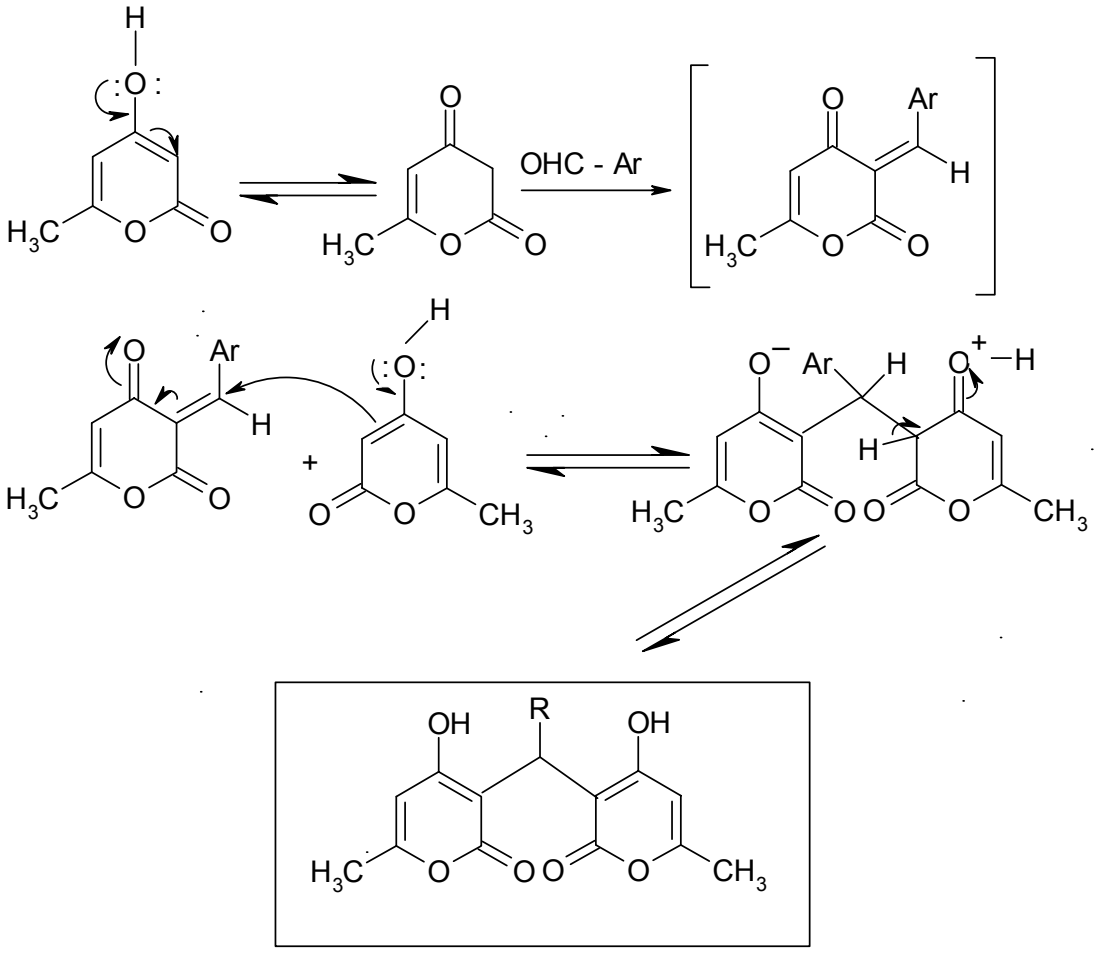
Physical and analytical data of synthesis compounds (3)

Ar	Microwave		Product	Yield (%)	Color	^{1}HNMR δ; ppm	m.p (°C)
	p(W)	t(min)				C_3-CH-C_3'	
C_6H_5-	300	8	**3a**	100	white	5.75	216-218
4-Cl- C_6H_4-		11	**3b**	88		5.69	202-205
4-H_3CO-C_6H_4-		10	**3c**	97		5.71	186-187
4- H_3C-C_6H_4-		10	**3d**	96		5.70	188-190
4-Br -C_6H_4-		11	**3e**	87		5.66	199-121
4-F-C_6H_4-		8	**3f**	100		5. 69	218-220
4-O_2N-C_6H_4-		12	**3g**	88	yellow	5. 76	245-250
-C_6H_4-		13	**3h**	89	Brown	5. 89	225-228

All products were characterized by IR, ^{1}H 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 ^{1}H 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(ε)) 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 clair crystallized in ethylacetate; m.p = 108-110 °C, (lit[28] = 107-108 °C); $C_8H_8O_4$; MM = 168.15 g.mol^{-1}; yield: 83 %; TLC [pentane/ ethyl acetate : 80 /20] : Rf = 0.7; UV (EtOH) λ_{max} (log ε) 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); ^{1}H 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, CDCl3) δ_{ppm} = 20.71 CH3 (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, (lit[28] = 188-190 °C) ; $C_6H_6O_3$; MM = 126.12 g.mol^{-1}; yield : 85% ; TLC [pentane/ ethylacetate : 80 /20] : Rf = 0.65; UV (EtOH) λ_{max} (log ε) 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; ^{1}H 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 (lit[29] = 214-215°C); $C_{19}H_{16}O_6$; MM = 340.32 g. mol^{-1}, yield : 100 %; TLC [pentane/ ethylacetate : 80 /20] : Rf = 0.65 ; UV (EtOH) λ_{max} (log ε) 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); ^{1}H 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, CDCl3) 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 (lit[29] = 202-205 °C); $C_{17}H_{15}ClO_6$; 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) ν/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) ; ^{1}H NMR ($CDCl_3$) δ_{ppm} = 2. 28 (s, 6H, CH_3), 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 (lit[29] = 174-176 °C); UV spectrum (EtOH), λmax : 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; ^{1}H NMR spectrum (400 MHz, CDCl3), δ, ppm : 2.28 (s, 6H,CH_3), 5.69 (s, 1H, CH); 6.02 (s, 2H, CH); 7.07-7.27 (m, 4H, H arom); MS Found, m/z: 370.33 $[M]^+$. $C_{20}H_{18}O_7$. 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 cyistallized 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) ν/cm^{-1} : 3320 (ν OH), 2974 (ν C-CH_3), 1721 (ν C=O), 1626 (ν C=C), 1540, 1303, 1250 (ν COC), 870, 813 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 2.31 (s, 6H ,CH_3), 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; $C_{19}H_{15}BrO_6$; 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) ν/cm^{-1} : 3104 (ν OH), 1721 (ν C=O), 1626 (ν C=C), 1540, 1303, 1250 (ν COC), 870, 813, 738 (ν C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 2. 28 (s, 6H, CH_3), 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; $C_{17}H_{15}FO_6$; MM = 358.32 g.mol^{-1}; yield : 100 %; UV (EtOH) λ_{max} (log ε) nm = 296.22 (3.47); IR (KBr) ν/cm^{-1} = 3100 (ν OH), 1721 (ν C=O), 1626 (ν C=C), 1540, 1303, 1250 (ν COC), 870, 813 (ν C-F); ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 2.28 (s, 6H, CH_3), 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 (lit[29] = 214-217 °C); $C_{19}H_{15}NO_8$; 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) ν/cm^{-1} = 3100 (ν OH), 1721 (ν C=O), 1626 (ν C=C), 1522 (ν NO_2), 1303, 1250 (ν COC), 870, 825 (ν CH, arom disubs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} = 2.31 (s, 6H, CH_3), 5.76 (s, 1H, C H); 6.05 (s, 2H, CH); 7.42 (m, 4H, Harom); ^{13}C 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 terephtalaldehyde (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; $C_{32}H_{26}O_{12}$; 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) ν: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}; ^{1}H NMR (400 MHz,$CDCl_3$) δ_{ppm} = systeme AB 2.36 (s, 6H,

CH3), 5.97 (s, 1H, CH); 6.11 (s, 2H, CH);7.12-7.13 (m, 4H, Harom); ^{13}C NMR (400 MHz, $CDCl_3$) 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

REFERENCES

1. J. Thuery, "Les microondes et leurs effets sur la matière", Technique et Documentation, 2nd edition Lavoisier, 1989.
2. A. Ben Alloum, B. Labiad and D. Villemin, *J. Chem. Soc. Chem. Comm*., **1989**, *7*, 386-387.
3. A. K. Bose, M. S. Manhas, M. Ghosh, M. Shah, V. S. Raju, S. S. Bari, S. N. Newaz, B. K. Banik, K. J. Barakat and A. G. Chaudhury, *J. Org. Chem.*, **1991**, *56*, 6968-6970.
4. R. Gedye, F. Smith, K. Westaway, A. Humera, L. Baldisera, L. Laberge and J. Rousell, *Tetrahedron Lett.*, **1986**, *27*, 279-282.
5. R. J. Giguere, T. L. Bray, S. M. Duncan and G. Majetich, *Tetrahedron Lett*, **1986**, *27*, 4945-4958.
6. P. Lidstrom, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, **2001**, *57*, 9225-9283.
7. A. De La Hoz, A. Diaz-Ortiz and A. Moreno,. *Chem. Soc. Rev*., **2005**, *34*,164-178.
8. I. I. Mangalagiu, *Curr. Org. Chem.*, **2011**, *15*, 730-752.
9. C. O. Kappe, B. Pieber and D. Dallinger, *Angew. Chem. Int. Edit.*, **2013**, *52*, 1088-1094.
10. G. Zbancioc, C. Moldoveanu, A. M. Zbancioc and I. I. Mangalagiu, *Curr. Microwave. Chem.*, **2014**, *1*, 41-46.
11. N. Benferrah, M. Hammadi and F. Berthiol, *Russian J. of Gen. Chem*., **2015**, *85*,1939-1944.
12. A. Loupy, (Edited by K. Smith), Ellis Horwood Chichester, 1992, p. 302-304.
13. G. P. McGlacken and I. J. S. Fairlamb, *Nat. Prod. Rep.,* **2005**, *22,* 369-385.
14. C. Beckert, C. Horn, J. P. Schnitzler, A. Lehning, W. Heller and M. Veit, *Phytochemistry*., **1997**, *44*, 275-283.
15. R. Hansel, *Pacific Sci*., **1968**, *22*, 293-313.
16. R. Kampf,. *Schweiz. Apoth. Ztg*., **1970**, *108*, 520-526.
17. A. T. Shulgin,. *Bull. Narcotics.,* **1973**, *25*, 59-74.
18. W. Emboden, "Narcotic plants", London, Cassell, 1979, p. 206.
19. W. B. Mors, M. T. Magalhaes and O. R. Gottlieb, *Fortsch. Chem. Org. Natur*., **1962**, *20*, 131-138.
20. E. De Clercq, *J. Med Chem*., **1995**, *38*, 2491-517.
21. P. Lasme, F. Davrieux, D. Montet and V. Lebot, *J. Agric Food Chem*., **2008**, *56*, 4976–4981.
22. W. Borsche and B. K. Blount, *Berichte der Deutschen Chemischen Gesellschaft. Abteilung B: Abhandlungen* **1933**, *65*, 803–806.
23. J. L. Douglas and T. Money, *Tetrahedron*, **1967**, *23*, 3545-3555.
24. J. Scherer, *Adv. Ther*., **1998**, *15*, 261-269.
25. A. R. Bilia, S. Gallon and F. F. Vincieri, *Life Sci.*, **2002**, *70*, 2581-97.
26. E. Ernst, *Br. J. Clin. Pharmacol.*, **2007**, *64*, 415-417.
27. U. Seitz, A. Schüle and J. Gleitz, *Planta. Med.,* **1997**, *63*, 548-9.
28. R. R. Nagawade, V. V. Khanna, S. S. Bhagwat and D. B. Shinde, *Eur. J. Med. Chem*., **2005**, *40*, 12, 1325-1330.
29. P. De March, M. Moreno-Manas, P. Pi and A. Trius,. *J. Heterocyclic. Chem.,* **1982**, *19*, 335-336.
30. F. Arndt, B. Eistert, H. Scholz and E. Aron, *Ber.*, **1936**, *62B*, 2373-2380.
31. F. Arndt, *Org. Synth. Coll.*, **1955**, *3*, 231.
32. A. J. Demuner and V. M. M. Valente, *Molecules*, **2009**, *14*, 4973-4986.
33. M. Cervera, M. Moreno-manas and R. Pleixats, *Terahedron.*, **1990**, *46*, 1885-7892.
34. H. Hagiwara, N. Fujimoto, T. Suzuki and M. Ando, *Heterocycles*, **2000**, *53*, 549-552.
35. H. Hagiwara, S. Miya, T. Suzuki, M. Ando, I. Yamamoto and M. Kato, *Heterocycles.*, **1999**, *51*, 497-500.
36. X. Zhang, Y. Qu, X. Fan, X. Wang and J. Wang., *J. Chem. Res.,* **2009**, *8*, 473-477.