A new Strategy for the Synthesis of 3-Cinnamoyl-2-styrylchromones and their Transformation into new Xanthenodione Derivatives

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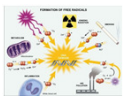
Introduction



"It is difficult these days to open a medical journal and not find some paper on the role of 'reactive oxygen species' or 'free radicals' in human disease."

"These species have been implicated in over 50 diseases. This large number suggests that radicals are not something esoteric, but that they participate as a fundamental component of tissue injury in most, if not all, human disease."

Barry Halliwell, *Am. J. Med.*, 1991, 91, 14

Background:

Chromones are a class of oxygen heterocyclic compounds widely distributed in Nature. 2-Styrylchromones are, however, a small and rare naturally occurring chromones; only three derivatives have been isolated, two from the marine blue green algae Chrysophaeum taylori[1] and one from the rhizomes of Imperata cylindrical.[2] Even so, 2-styrylchromone derivatives are associated with noticeable biological activities.[3] Our group has also been interested in the synthesis[4] and biological evaluation of 3-aroylflavones and found that 3′,4′,5,7-tetrahydroxy-3-(3,4-dihydroxybenzoyl)flavone is a potential antioxidant agent.[5]

Aim:

*As part of our continuing work on the synthesis and antioxidant evaluations of polyhydroxy-2-styrylchromones,[4] we set up a program aiming the synthesis of 3-cinnamoyl-2-styrylchromone (**2**) bearing hydroxyl groups, features considered essential to be good antioxidant and anti-inflammatory agents.*

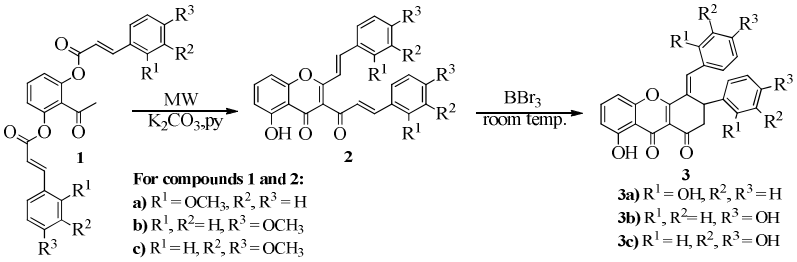
Results and Discussion

Synthesis:

❖*The synthesis was accomplished in a two-step approach, bis-esterification of 2′-hydroxyacetophenone with cinnamoyl chloride derivatives followed by the Baker-Venkataraman rearrangement of the formed diester (**1**), under microwave irradiation conditions;*

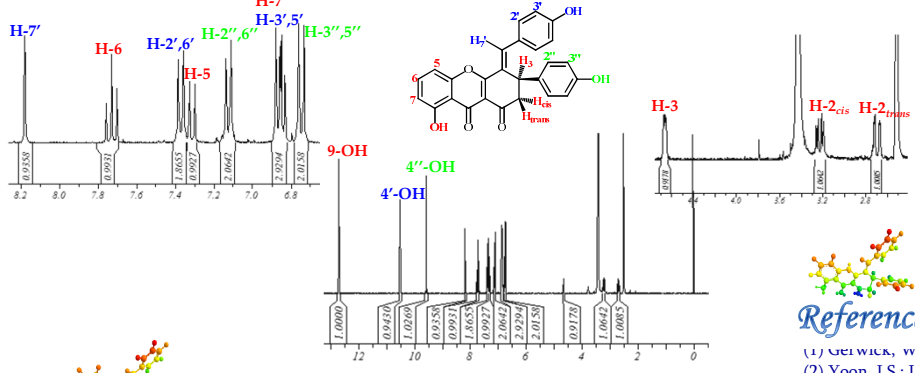
❖*This methodology was employed for the first time with these type of diester derivatives and proved to be efficient in the rearrangement of (E,E)-2-acetyl-1,3-phenylene bis(3-phenylacrylate) (**1a-c**) leading to (E,E)-3-cinnamoyl-5-hydroxy-2-styrylchromones (**2a-c**) in excellent yields (> 85 %);*

❖ *Next, the methoxy groups cleavage with boron tribromide was attempted, and the NMR analysis of the products confirm the demethylation and that an unprecedented cyclization occurred and (E)-4-(benzylidene)-8-hydroxy-3-phenyl-3,4-dihydro-1H-xanthene-1,9(2H)-diones (**3a-c**) were obtained, in moderate to excelent yields (41 to 81 %).*



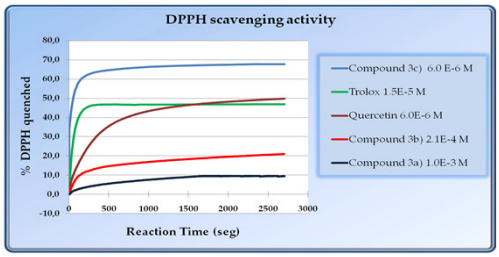
Structural Elucidation:

*The most noticeable features in the ^1H NMR spectra of the (E)-4-(benzylidene)-8-hydroxy-3-phenyl-3,4-dihydro-1H-xanthene-1,9(2H)-diones **3** are the proton resonances of H-2, H-3, H-7′ and 8-OH (Figure shows an example).*



Antioxidant activity:

In recent years, more interest has been paid to protect foods and humans against oxidative damage caused by free radicals such as hydroxyl, peroxyl, and superoxide radicals. It is believed that the ability of a compound to scavenge DPPH radicals is related with their antioxidant activity.



The antioxidant activity was assayed by the DPPH radical scavenging assay.[6]

Compounds	EC_{50} (μM)	T_{EC50}	AE
3a)	> 2080	ND	-
3b)	> 552E-4	ND	-
3c)	3.79 ± 0.06	10 min	0.026
Quercetin	5.97 ± 0.11	40 min	0.0042
Trolox	18.7 ± 0.65	5 min	0.011

*EC_{50} the required concentration of the compound to reduce the DPPH• concentration to 50 % of its original in the reaction mixture. The assays were carried out in triplicate and results expressed as mean ± SD. T_{EC50} the time required to reach the steady state for the EC_{50}. ND – not determinate. AE= 1/(EC_{50} * T_{EC50}).*

The solubility of the compounds 3a) and 3b) not allowed to calculated de respective EC_{50}. At the concentration correspondent to the solubility of the compound 3a) (2.08 mM) the percentage of DPPH remain was 91%, while in the case of compound 3b) at the maximal tested concentration (552 μM) the DPPH remain was 64%.

*The study, by EC_{50} parameter, showed that compound **3c)**, that possesses two cathecol units, exhibit a strong radical scavenging activity, nearly twice more active than quercetin and five fold more than trolox. The monohydroxyl benzyl derivatives not showed significant DPPH scavenging activity.*

Furthermore, T_{EC50} (time required to reach the steady state for the EC_{50}) showed that compound 3c) has a very fast action, most quick than quercetin. So, the antiradical efficiency (AE), a parameter that combines both factors, EC_{50} and T_{EC50}, showed the great potential of the compound 3c) as antioxidant agent.

Acknowledgments

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References

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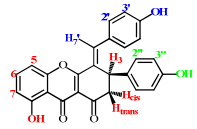
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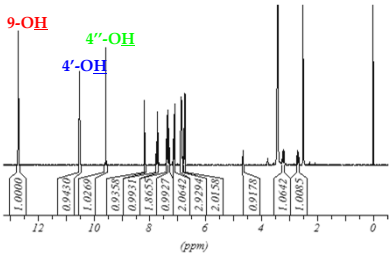
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