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A Synthetic Approach to PW2-Like Compounds

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The 9H-xanthene derivatives, like PW2, displayed a wide spectrum of bioactivities. Herein, we reported a rapid and simple synthetic route for compounds containing the xanthenic moiety in their structure and amides. The efficient preparation of novel 1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1-xanthen-9-yl-acetic acid alkyl esters by multicomponent tandem Michael-cyclization reactions starting from cyclohexanediones and alkynes is described. Iodine and cerium (IV) ammonium nitrate were used for the oxidative aromatization step proving a series of 1,8-mono and dialkoxy-alkyl-xanthenyl-9-yl acetic acid esters in good yields. The proposed mechanism for the oxidative aromatization involves several organic transformations. The final step was the incorporation of an amide to mimic the PW2 structure that was prepared by hydrolysis of the esters, followed by the amide formation using *N,N*-dimethyl-1,3-propandiamine, and benzylamine.

1. Introduction

Molecules containing linear tricycles are ideal skeletons to produce a wide range of drugs for diverse clinical applications. Interconnected ring systems, orientation, aromaticity and heteroatoms are responsible of the ability to bind different receptors that provide a wide spectrum of bioactivities.[1–4] Between them, xanthene derivatives present different activities including antibacterial,[5] antiviral,[6] antimalarial[7] and anti-inflammatory.[8]

9*H*-xanthene derivatives, like PW2, PW3, WU5 and WU6 (Figure 1), are interesting examples of this scaffold displaying antiparasitic activity, in particular, toward *Plasmodium falciparum*, the malaria etiological agent.[7]

9,9-Dimethylxanthene derivatives recently reported by Chibale *et al* have shown antikinetoplastid activity against *Trypanosoma cruzi*, *Trypanosoma brucei*, and *Leishmania donovani*, Figure 1.[9]

We previously reported the synthesis of several octahydroxanthenodiones by a *tandem* Michael-Michael-Cyclization reaction of 1,3-cyclohexanediones, methyl propiolate, L-proline and iodine, either in solution or in solid phase.[10–13]

Molecular iodine has played an important role in organic synthesis,[14] being an expedient old reagent for different chemical transformations.[15,16] Among its numerous applications, we found the systematic functionalization of Hagemann's ester derivatives that permitted the preparation of highly substituted phenols and benzenes according to Kotnis method.[17] Likewise, the reaction of iodine in methanol was extended to prepare substituted resorcinols (olivetol) from 1,3-cyclohexanedione, and cyclohexane-1,3-diones with electron withdrawing substituents at the 2-position. Mono-methoxy resorcinol derivatives were obtained as the major products,[18] or the substituted 2-iodomethyl-tetrahydrobenzofuran-4-ones from α-allyl-cyclohexane-1,3-diones ones.[19]

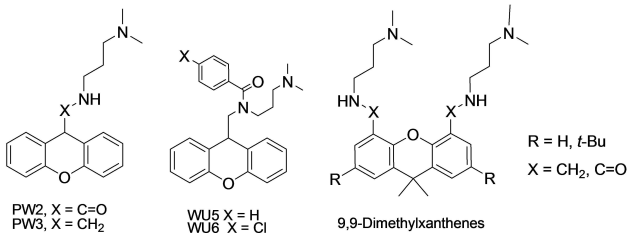

Figure 1. Synthetic 9*H*-xanthenes, chloroquine resistance-reversing agents.

Their synthetic utility can also be illustrated by the reactions of 2-cyclohexenones holding electron withdrawing group at the 4-position or *N*-alkyl-1,3-cyclohexadien-1-amines with iodine and sodium alkoxide, that produce the regioselective iodination and aromatization.[20]

With those precedents in mind, herein we present the synthesis of a new series of non-symmetric hydro-xanthenodiones. The oxidative aromatization of the lateral rings of the heterocyclic core was also studied, being an efficient, user-friendly procedure to generate structurally diverse compounds.[21,22] Moreover, the collection of derivatives was extended preparing different amides, of high incidence in modern pharmaceuticals and biologically active compounds,[23] by reaction of the xanthenic precursors with different amines.

2. Results and Discussion

First, we looked to expand the scope of the Michael reaction focusing on non-symmetric structures. Different 1,3-cyclohexanediones were combined to introduce structural diversity in the tricycle by means of multicomponent reactions (MCR) in solution. The reaction of 1,3-cyclohexanediones **1**–**4**, methyl

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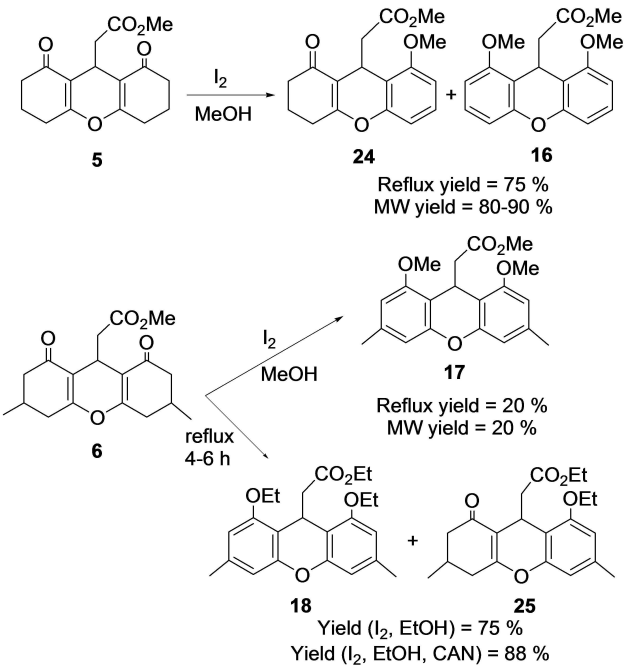
propiolate and L-proline in DMSO at room temperature and subsequent I_2/EtOH addition afforded the symmetric and the non-symmetric esters **5**–**15** in 69–77% overall yields. (Scheme 1) The 1,3-cyclohexanedione **4**, that has a non-symmetrical substitution, leads to more products than the rest of the diones.

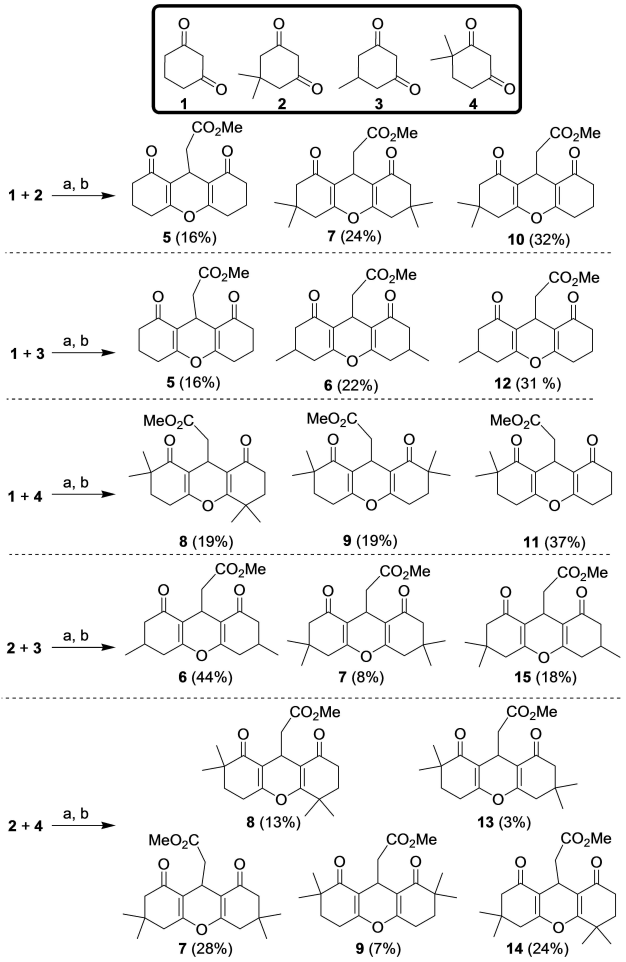
Then, the oxidative aromatization of the lateral rings of the heterocyclic core of **5**–**15** using molecular iodine in an alcohol solution was evaluated.

The cyclohexenone portions of ester **5** undergone aromatization with iodine in refluxing methanol, being the di-oxidized ester **16** the major product, along with small amount of **24** in 75% overall yield. (Scheme 2) Alternatively, a one-pot reaction of **5** with iodine in methanol under microwave heating for 15–30 minutes provided a mixture of **24**:**16** in a 1:2 ratio with high yields (80-90%). The reaction of the mono-substituted cyclic ketone **6** in methanol, which was less reactive than **5**, provides the dimethoxy-methyl ester **17** as only isolated product, but in low yields.

The oxidative aromatization in ethanol also produce the concomitant transesterification of the methyl acetate side chain. The addition of a catalyst, such as the cerium (IV) ammonium nitrate (CAN),[24,25] to the iodine increased the overall yield of ethyl esters **18** and **25**. (Scheme 2).



Scheme 2. Oxidative reactions on **5** and **6** with iodine.



Scheme 1. Three-component synthesis of xanthenedione esters **5**–**15**. a) Methyl propiolate, DMSO, RT, 13 days; b) I_2, MeOH or EtOH, 5 h.

In order to carried out the oxidation of the *gem*-dimethyl-ester **7**, the reaction with iodine in methanol or ethanol needed CAN as catalysis, due to the lower reactivity of this substrate. Consequently, mixtures of methoxy-methyl-esters **19** (20%) and **26** (64%) and the corresponding ethoxy-ethyl-esters **20** (25%) and **27** (52%) were successfully separated during the purification by column chromatoghraphy. (Scheme 3)

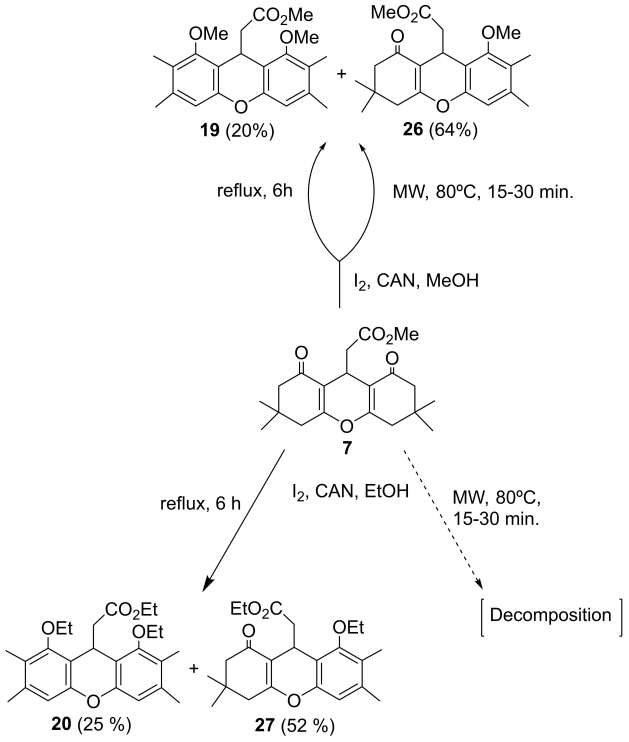
A possible mechanism for the oxidation of compound **7** is shown on Scheme 4. The addition of iodine gives a product of α-halogenation which undergoes a 1,2-migration of a methyl group with addition of the catalyst, generating a double cross-conjugation in both cyclohexanone portions by the loss of hydrogen iodide.

Water is then removed, after addition of methanol (or ethanol) to the carbonyl group, and thus emerging the aromatic products.[24]

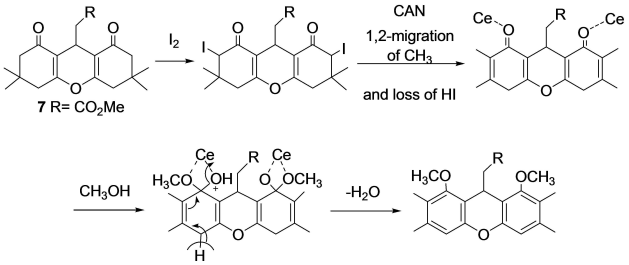
When same oxidative aromatization condition was applied on *gem*-dimethyl-ester **8** and **9**, the reaction do not provide the expected products. That was not unexpected based on the proposed reaction mechanism, where the α-halogenation and water loss are not possible. (Scheme 5)

As is shown in Scheme 6, the oxidation of the non-symmetric compounds **10**–**15** has also been studied. These reactions gave different mixtures of products depending on the particular ring substitution and if the aromatization occurs in one ring or both.

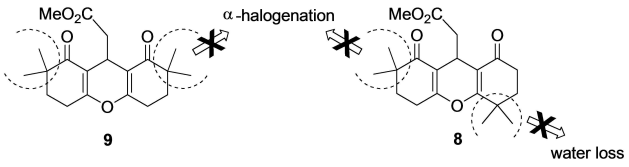
Reactions carried out on compounds **11** and **13** give only products of mono-oxidation on the annular portion because one of the α-position to the carbonyl groups is blocked. Unfortunately, after different attempts, the isolation of the



Scheme 3. Reactions of **7** with iodine, CAN, MeOH or EtOH.



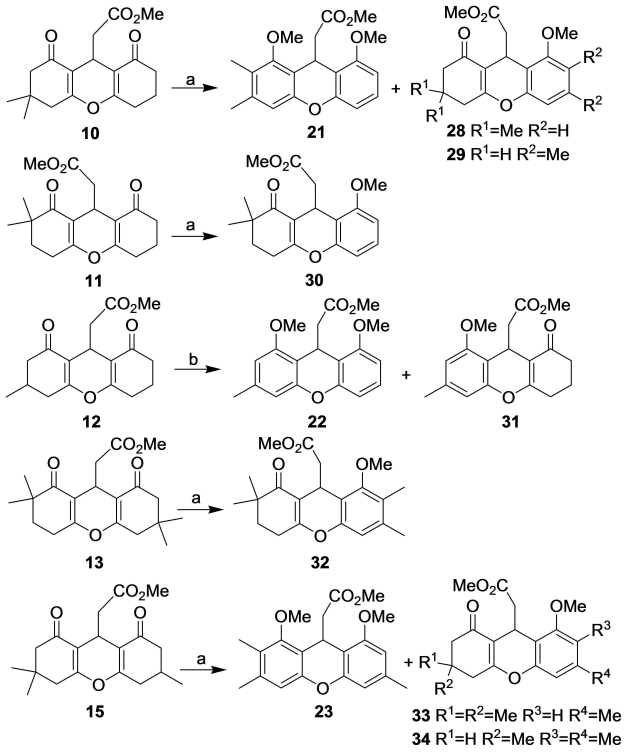
Scheme 4. Reaction mechanism of the compound **7** with iodine-cerium (IV) ammonium nitrate in methanol.



Scheme 5. Impeded reaction positions for α-halogenation and water loss.

oxidation product of compound **14**, that was expected to produce a mono-oxidized derivative, was unsuccessful.

As was mentioned before, we aim to prepare xanthenic amides derivatives that mimic PW2. Based on the previous experience of our group, the esters were transformed in carboxylic acids followed by amides formation using *N*-(3-(dimethylamino)propyl)amine and benzylamine. Esters **5**–**8** showed a low reactivity with standard reagents like aqueous



Scheme 6. Oxidation reactions of non-symmetric compounds **10**–**15** with iodine-cerium (IV) ammonium nitrate in methanol. a) I_2, CAN, MeOH; b) I_2, MeOH

LiOH, NaOH or KOH. To surpass that problem, the esters **5**–**8** were demethylated with LiI in EtOAc under reflux.[26] Thus, **35**–**38** were transformed into the *N*-benzyl amides **41**–**44** and *N*-(3-(dimethylamino)propyl) amides **45**–**48** by reaction with the amines with the corresponding acids, HOBt, and diisopropylcarbodiimide in dichloromethane. The mixture was maintained at 0 °C over 1.5 hours and them warm up to room temperature, (Scheme 7) and the purification by column chromatography provides the amides with 53–95 % yield.

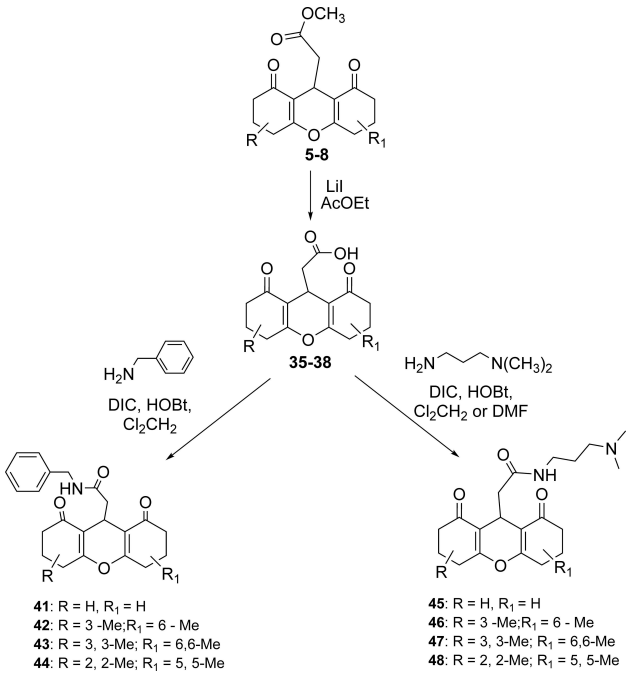
All the attempts of oxidative aromatization of amides were unsuccessful. Therefore, we decided to prepare the aromatic amides **49** and **50** starting from the aromatic esters **16** and **20** through the corresponding carboxylic acids. (Scheme 8)

The acid **39** was obtained by hydrolysis, using LiOH as a base, on the other hand, to hydrolyze the ester **20**, the base had to be exchange to KOH since the ethyl ester did not react with LiOH.

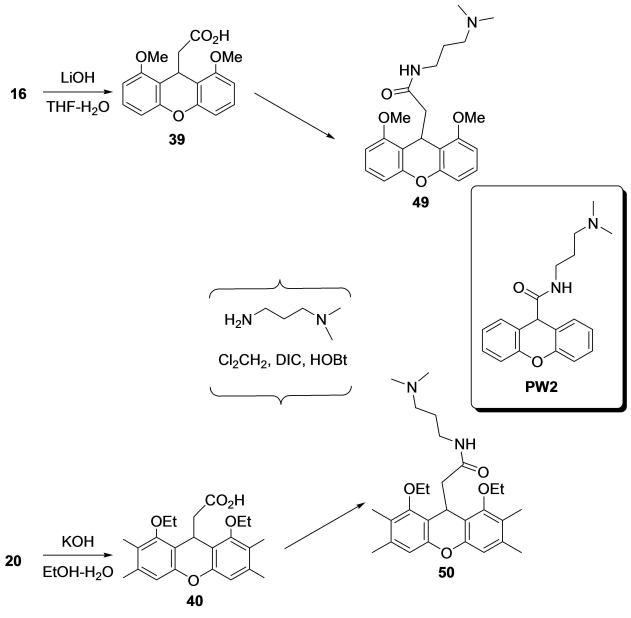
The amides **49** and **50** were prepared and purified in a similar way than the amides **45**–**48** with a global yield of 50–60 %.

3. Conclusions

We have successfully developed a rapid and simple synthetic route for the efficient preparation of a series of 1,8-dioxo-2, 3, 4, 5, 6, 7, 8, 9-octahydro-1H-xanthene −9-yl acetic acid esters **5**–**15** by multicomponent Michael-Michael-cyclization reactions.



Scheme 7. Formation of amides **41**–**48** from the carboxylic acid **35**–**38**



Scheme 8. Formation of amides **49** and **50** from the esters **16** and **20**

Molecular iodine promotes both cyclization and aromatization reactions contributing to an extension of the iodine methodology towards the formation of more complex structures.

Iodine-mediated oxidative aromatization of 1,8-dioxo-hydroxanthene scaffold is a simple synthetic procedure for obtaining mono- and dialkoxy-xanthenyl-9-yl acetic acid esters **16**–**34**. This oxidative aromatization involves different transformations including α-iodination, transesterification, etherification, elimination and alkyl rearrangement when it was required. Applying the reaction on non-symmetric tricycles was crucial to validate the proposed mechanism.

The final approach was to incorporate amides on the structure to mimic PW2. Compounds **49** and **50** were prepared from the corresponding acids **39** and **40** applying the same methodology used to prepare the amides **45**–**48**.

This diversity oriented synthesis strategy will be used as the starting point of a medicinal chemistry program targeting Neglected Tropical Diseases.

Supporting Information Summary

Supporting information file contains details of the experimental procedure, ^{1}H and ^{13}C NMR spectroscopy, high-resolution mass spectrometry, IR spectroscopy, and physical state. Specific rotation and melting point were included when necessary. In addition, it also contains copies of the ^{1}H and ^{13}C NMR spectra of all final products.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: 1,8-alkoxy-9H-Xanthen-9-yl-acetic acid alkyl estersamides · iodine oxidative aromatization · multicomponent reactions · PW2

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