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3-Methylene-2,4-chromandione *in situ* trapping : Introducing molecular diversity on 4-hydroxycoumarin

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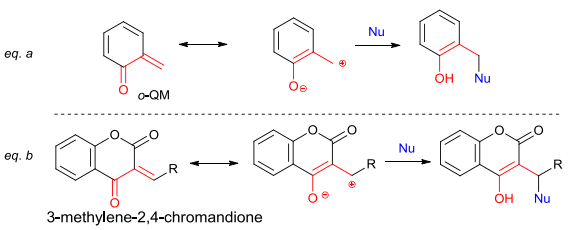
Abstract. 3-Methylene-2,4-chromandione trapped in a solid-state stable Mannich adduct, is released in solution. In the presence of different nucleophiles, this highly reactive intermediate allows the introduction of molecular diversity on C-3 position of 4-hydroxycoumarin.

The reactivity of *ortho*-quinone methides (*o*-QMs) has been largely exploited in natural product, total synthesis, medicinal chemistry and biochemistry. And yet, for a long time, *o*-QMs have been underused, mainly due to their transient nature.[1] Quinone methides have been hardly ever isolated, due to fast reactions favored by rearomatization into phenol, acting as the driving force (Scheme 1, *eq. a*). Gardner[2] detected their existence in 1963 by spectroscopy at -100°C, even if more than fifty years before, in 1907, Fries got preliminary suspicion of the reality of such molecular species.[3] Their high reactivity makes it attractive, in particular for multi-component reactions.[4] Over the past years, they have regained a new interest for drug targeting or fluorescent probe.[5] Biomimetic synthesis of Schefflone, a monoterpenoid was recently performed by oxidative trimerization of *o*-QM.[6] A large spectrum for their biological activities was highlighted with the understanding of DNA alkylation, anti-tumoral or anti-bacterial properties and so on.[7] As a notorious example, anti-diabetic Troglitazone was withdrawn in 2000 due to *in vivo* formation of *o*-QM metabolite displaying prejudicial secondary effects.[8]



Scheme 1. Structural and reactivity analogy of *ortho*-quinone methide and 3-methylene-2,4-chromandione.

Recently, our laboratory reported an effective procedure for C-3 reductive alkylation of 4-hydroxycoumarin by a dehydrogenative oxidation of benzylic alcohols in the presence of $RuCl_2(PPh_3)_2$ (5 mol%), KOH (0.2 eq) in ^{tert}amyl alcohol under microwave irradiation at 140°C in 2 hours.[9] Supposed mechanism is described as a first step of activation of the alcoholic substrate by metallo-catalyzed dehydrogenative oxidation, followed by a Knoevenagel condensation / reduction sequence, under one pot conditions. The Knoevenagel adduct (3-methylene-2,4-chromandione) displaying similar structural analogy (Scheme 1, *eq. b*) with classical *o*-QM, is a versatile substrate for cycloaddition reactions.[10] To a larger extent, 3-methylene-2,4-chromandione have been reported as *in situ* generated partner for multi-component reactions (MCRs), providing a powerful platform to access diversity as well as complexity. Following this strategy, pyranocoumarins were obtained by Knoevenagel-electrocyclic reaction starting from 4-hydroxycoumarin, an enal and an amine.[11] *o*-QMs analogs have been involved in numerous cycloadditions ([4+2][12] or [4+1][13]) and other multi-component or domino reactions.[14] The common points of this strategy were to access the high added value molecules in a linear synthetic strategy.

The approach developed in the laboratory is to trap the 3-methylene-2,4-chromandione highly reactive intermediate in a solid-state stable Mannich adduct. In solution, the equilibrium

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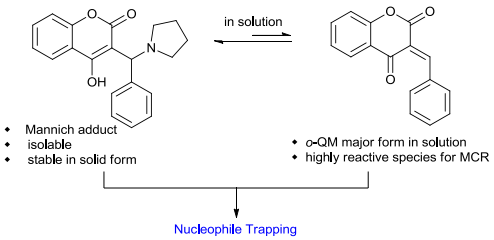
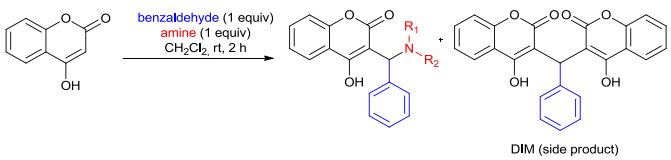
is more favourable for the *o*-QM adduct which upon treatment with various nucleophilic species can react in excellent yields (Scheme 2). Therefore, we decided to focus on an elegant approach to trap this intermediate by different methods including simple reduction methods. The methodology deviced should also limit the percentage of undesired DIM, which is often observable in all the synthesis reported in literature (Table 1).[15]



Scheme 2. Equilibrium between Mannich adduct and methylene chromandione.

Preliminary study began with the choice of the amine partner involved in the Mannich reaction (Table 1). A set of primary and secondary amines were screened and pyrrolidine was the sole amine affording the desired Mannich adduct without any trace of dimer. Other amines (piperidine, morpholine and isopropylamine) led to 10% of undesired dimer adduct (entries 2, 4, 7). Dimethylamine, diethylamine (entries 3, 5) were less efficient with almost 40% of dimer. Aniline and proline (entries 6, 8) led to partial conversion in favour of expected product with in both cases, dimer as the major product. These results were almost in accordance with the nucleophilicity scale developed by Mayr and co-workers in 2009.[16]

Table 1. Nature of nucleophilic amine

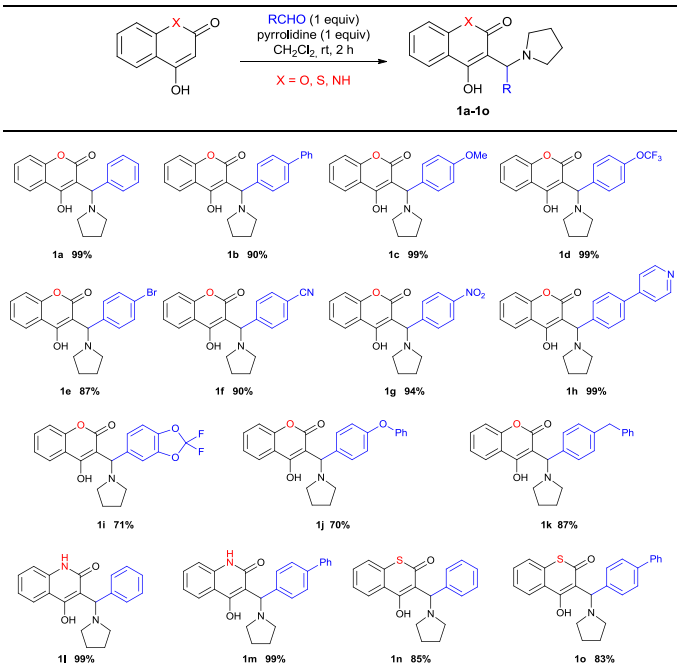


Entry	Amine	Ratio	
		Product	**DIM**
1	pyrrolidine	100	0
2	piperidine	90	10[17]
3	dimethylamine	69	31
4	morpholine	91	9
5	diethylamine	60	40
6	aniline	27	73
7	isopropylamine	93	7
8	proline	15	85

Using the conditions outlined in entry 1 (Table 1), we tested the scope of this procedure with a range of aromatic aldehydes. The three-component reaction of 4-hydroxycoumarin, pyrrolidine and a set of benzaldehydes was effective in good to excellent yields, regarding the stoichiometric ratio of each partner (Table 2). No trace of bis-coumarin product was detected for compounds **1a-k**. Dichloromethane was the best solvent, allowing the precipitation of the Mannich adduct at the end of the reaction and thus facilitating its isolation, by simple filtration.

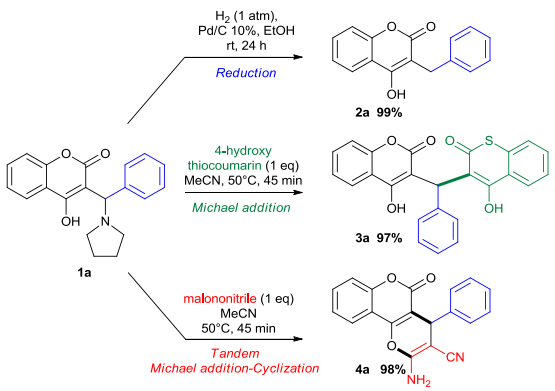
The electronic nature of the substituent on aromatic ring did not affect the reaction and excellent yields were obtained for all substrates described in Table 2. Electronic effects (electron-donating group such as **1c, 1d** or electron-withdrawing group for **1f, 1g**) on aryl aldehyde do not affect the issue of the reaction. Halogen was also well tolerated (**1e**). Other substituted benzaldehydes such as 4-(pyridin-4-yl)benzaldehyde, 2,2-difluorobenzo[*d*][1,3]dioxole-5-carbaldehyde, 4-phenoxybenzaldehyde or 4-benzylbenzaldehyde were coupled with good to excellent yields (**1h-1k**). Replacement of 4-hydroxycoumarin scaffold either by quinolone-2,4-diol (**1l**, **1m**) or by 4-hydroxythiocoumarin (**1n**, **1o**) resulted in similar yields.

Table 2. Mannich reaction of 4-hydroxycoumarin (and analogs) with aldehydes



[a] Conditions : 4-hydroxycoumarin (1 mmol), aldehyde (1 mmol), pyrrolidine (1 mmol), CH_2Cl_2 (2 ml), rt, 2 h.

To our delight, the reaction could be performed on 10 gram scale for compound **1a**, our benchmark compound for the following studies. Three reactions were selected for evaluation of the reactivity of the Mannich adduct, as pointed out in Scheme 3: hydrogenation, Michael addition or tandem Michael addition-cyclization (Scheme 3). Hydrogenation allows the formation of linear C-3 alkylated compounds, which are not so obvious to obtain.[18] Treating Mannich adduct **1a** under H_2 atmosphere (1 bar) in anhydrous ethanol with 10% Pd/C (5 mol%) afforded compound **2a** quantitatively.

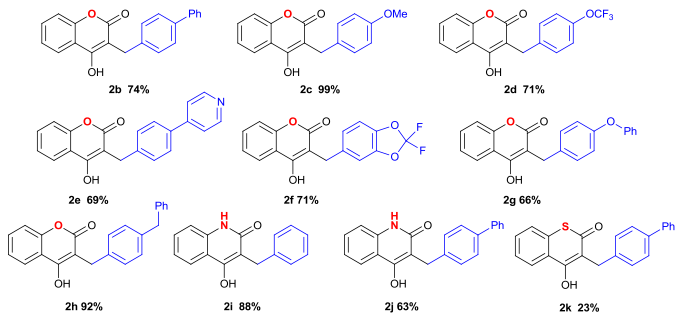


Scheme 3. Overview of the reactivity of intermediate **1a**

Non-symmetrical dimer **3a** was obtained in an excellent 97% yield by reaction of **1a** with stoichiometric quantity of 4-hydroxythiocoumarin in acetonitrile at 50°C during 3 hours. In this case, the mechanism reaction is supposed to be assimilated to Michael addition with nucleophilic 4-hydroxythiocoumarin reacting on *o*-QM liberated in solution. The last reaction explored is the MCR tandem reaction of Michael addition followed by cyclization to provide dihydropyrano[2,3-*c*]chromene skeleton. The reaction of **1a** with malononitrile (1 eq) in MeCN at 50°C during 3 hours furnished derivative **4a** in 98% yield. Thermal stability of compound **1a** supplied important information on the equilibrium between Mannich adduct and *o*-QM. Heating a solution of **1a** in MeCN [0.25M] at 50°C during 15 min only led to recovery of the starting material. After 15 min at 90°C, a significant ratio of dimer could be quantified by ^{1}H NMR at a level of 10%. The 1/9 mixture of dimer/**1a** was heating at 15 min at 110°C leading to a displacement of the equilibrium in favour of a more important ratio of the dimer: 33% of DIM and 67% of substrate **1a**. The stability experiments were run under microwave irradiation to speed up the kinetics and evaluate the stability of **1a**. In regard with these observations, to limit the formation of the dimer, classic thermal activation was selected to the detriment of microwave irradiation.

All the Mannich adducts **1** (obtained in table 2) were submitted to hydrogenation in conditions described in Scheme 3 to allow the formation of C-3 alkylated coumarins (Figure 1). Excellent yields were obtained for most of the cases engaged in the reduction (11 successful reactions on 15 compounds) with isolation by simple filtration (no need to additional column chromatography for increasing the compounds purity).

Figure 1. Hydrogenation scope[a]

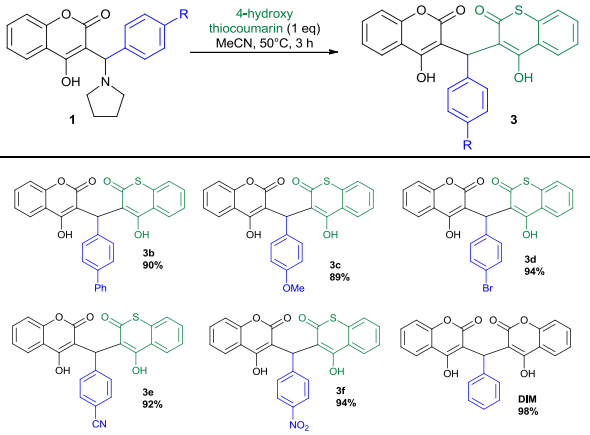


[a] Conditions : **1a**, H_2, Pd/C, EtOH, rt, 24 h.

As expected, derivatives **1e-1g** could not be reduced with good chemoselectivity and complete reduction of para substituent was observed. In the case of **1f**, nitrile group was reduced into CH_3 within 13% yield. Substrates with quinolone diol skeleton were reduced successfully into **2i** and **2j**, whereas compound **2k** bearing 4-hydroxythiocoumarin, was obtained in poor yield of 23%, probably due to poisoning of the catalyst. Same observation was reported for the reduction for **1n** and thus was not reported.

As in solution, Mannich adduct and *o*-QM intermediate are in equilibrium, any nucleophile could be selected to perform Michael addition and trap irreversibly the conjugated enone, with recovery of the aromaticity. Litterature has reported many conditions for the formation of dicoumarols such as DIM. To our delight, no reference was found concerning the formation of unsymmetrical dimers. Pyrrolidinyl derivatives **1** were dissolved in acetonitrile, in the presence of a stoichiometric quantity of 4-hydroxythiocoumarin, at 50°C. In 3 hours, the reaction ran to completion in all cases with excellent isolated yields higher than 89%. Symmetrical DIM could be also obtained successfully in these conditions in 98% yield.

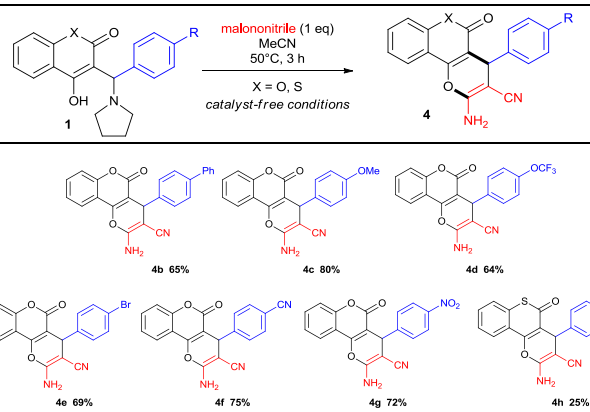
Table 3. Formation of non-symmetrical dimers[a]



[a] Conditions : **1** (1 mmol), 4-hydroxythiocoumarin (1 mmol), CH_3CN (2.5 ml), 50°C, 3 h

We decided to apply our methodology to the synthesis of 2-amino-4*H*-pyrans prepared by a tandem Michael addition-cyclization sequence (Table 4). The access to functionalized 2-amino-3-cyano-4*H*-pyrans annulated heterocycle **4** has been already published by simple multi-component reaction between aldehydes, malononitriles and 4-hydroxycoumarin in the presence of a wide range of catalysts such as $(NH_4)_2HPO_4$,[19] proline,[15] TBAB,[20] meglumine,[21] fermented Baker's yeast,[22] $ZnFe_2O_4$,[23] urea.[24] Simple aqueous conditions[25] were also efficient due to the hydrophobic effect as the driving force. Catalyst-free conditions in recyclable glycerol were recently developed.[26] In a direct comparison to the above cited strategies, our approach is a stepwise process, based on the isolation of the *o*-QM intermediate and benefits from catalyst free conditions. With the optimized conditions, the scope and generality of this protocol was next examined by employing various *o*-QM intermediates **1**.

Table 4. Tandem Michael addition / Cyclization[a]

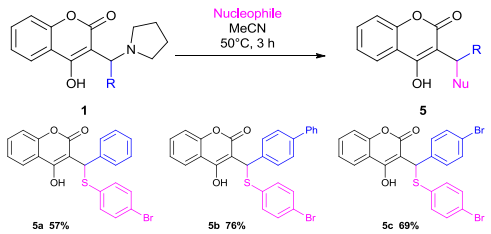


[a] Conditions : **1** (1 mmol), malononitrile (1 mmol), CH_3CN (2.5 ml), 50°C, 3 h

A family of eight new 2-amino-4*H*-pyran compounds **4** was synthesized using this protocol (Table 4). Good to excellent yields were obtained when 4-hydroxycoumarin skeleton was involved, whereas in the presence of 4-hydroxythiocoumarin, compound **4h** was prepared with a poor yield of 25% due to problems in the solubility of the starting material, resulting in a low kinetics in this set of experimental conditions. In some cases such as **4b** or **4e**, the decrease of the yield could be also

associated to the formation of the dimer present in significant quantities. As a perspective of these preliminary studies on the *o*-QM intermediates, we decided to study simple thiophenol nucleophiles and examine their reactivity towards *o*-QM intermediate **1**.[27]

Scheme 4. Introduction of simple nucleophiles



Compounds **5a**-**5c** were obtained in moderate yield of 57-76% and conditions are under optimisation due do the problems of separation and the requirement of additional step of purification by column chromatography. Addition of acetophenone (4 eq) was performed in a modest 50% yield under microwave activation (80°C, 1 h).[28]

Conclusions

An efficient synthesis of 4-hydroxycoumarin derivatives in C-3 position has been developed by taking advantage of *o*-QM intermediate. A wide range of reagents H_2, malononitrile, 4-hydroxythiocoumarin, thiophenols were used and broadened the scope. Due to the easily scalable step to generate derivatives **1**, the challenging point is to generalize the second step of the reaction to any nucleophilic species. Aliphatic aldehydes were not tested in the first stage of the reaction and will deserve also some attention in the future.

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