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Preliminary communication

One-pot synthesis and radical scavenging activity of novel polyhydroxylated 3-arylcoumarins

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ABSTRACT

An unexpected domino rearrangement brought about the development of a novel one-pot procedure for synthesis of coumarins. This protocol allowed the gram-scale synthesis of a variety of polyhydroxylated derivatives **3a**–**p**, from readily available starting materials at a low cost. Based on two proven intermediates, a probable mechanism consisting of boron tribromide induced demethylation/lactone ring opening/elimination/isomerization/lactone ring closure reaction sequence of *in situ* formed 3-aryl-3,4-dihydroisocoumarin-4-carboxylic acids was deduced. Compared to the common methods, used for the synthesis of coumarins, the proposed herein possesses great advantages, such as mild conditions, good yields for short reaction time, simple work-up procedure and easy isolation of the final products. The structure of the newly synthesized compounds **3a**–**p** was established by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, MS and HRMS) and their radical scavenging activity was evaluated *in vitro* against 1,1-diphenyl-2-picrylhydrazyl free radical (DPPH$^\bullet$). The results obtained show that compounds **3g**–**p** posses higher radical scavenging activity ($3.16 \leq SC_{50}$ [μM] ≤ 6.82) than well-known antioxidants such as trolox, protocatechuic acid, caffeic acid and gallic acid (SC_{50} [μM] = 9.34, 8.83, 9.48, 5.33, respectively), which is a precondition for promising antioxidant activity of these compounds to be expected.

1. Introduction

Coumarins are a large class of oxygenated heterocyclic secondary metabolites, that are biosynthesized by plants and fruits *de novo* [1]. They serve as phytoalexins which are directly formed as a defence response to stress (drought and cold), wound, viral infection or invasion by bacterial or fungal pathogens [2,3]. Natural coumarins display a wide range of biological activities [4–7] such as anti-inflammatory, anticoagulant, anticancer, vasorelaxant, and antiviral, to name just a few. In addition, several synthetic coumarin derivatives, particularly 3-aryl substituted ones (see Fig. 1), proved to be efficient antioxidants [8–11], that inhibit variety of enzymes [12–20], possess anti-HIV [21], anticancer [22–24] and vasorelaxant activities [25], and are antagonists of certain receptors [26]. Thus, due to their widespread pharmacological properties, coumarins occupy an important place in the realm of medicinal chemistry. Despite their remarkable medical benefits, it is noteworthy that the coumarins bioavailability is dependent to a large extent on the environmental conditions and seasonal changes, and thus their large scale production from natural sources is unreliable. To overcome this, various synthetic approaches for the synthesis of coumarins have been developed [27–49]. One of the main strategies is based on condensation–cyclization-type transformations employing the well-known Perkin, Pechmann or Knoevenagel reactions [27–35] as a key step for the coumarin backbone formation. An alternative strategy consists in the direct 3-arylation of the coumarin scaffold by metal cross-coupling reactions [36–42] leading to diversely substituted coumarin derivatives. All these methods, however, possess some drawbacks that hinder their benefits from an applied standpoint. In particular, the requirement of strong acids, high temperatures and prolonged reaction times in the classical condensation methods and the expensive, toxic, and sensitive to moisture catalysts in the case of metal cross-coupling reactions. Furthermore, these methods are of limited applicability for the direct synthesis of hydroxylated coumarins, and thus, in order polyhydroxylated derivatives to be synthesized, one should follow multistep approach including sequential protection, condensation, and deprotection steps. This sequence is necessary due to the extreme susceptibility of the hydroxyl function towards oxidation and polymerization, but results in a low overall product yields. Therefore, the need for improved methodologies for the synthesis of coumarin derivatives can be put forward [43–51]. In

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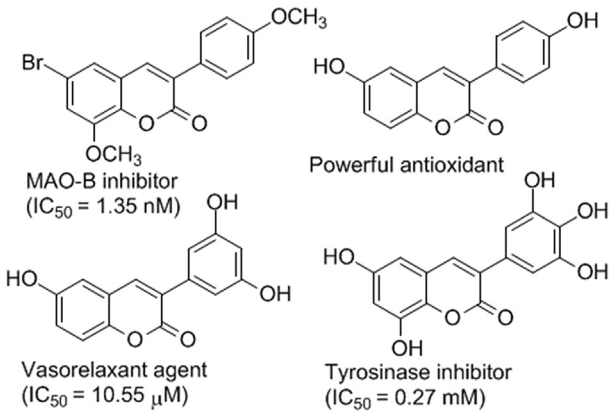


Fig. 1. Structure of some biologically active 3-arylcoumarins.

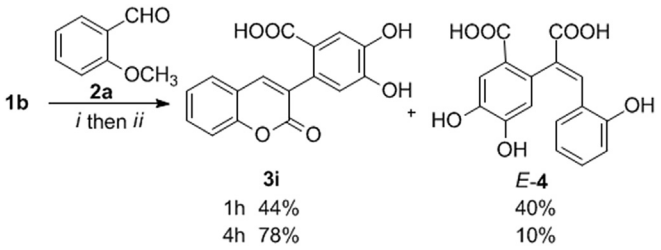
this context, in continuation of an ongoing in our laboratory project on anhydride-based syntheses of biologically active compounds [52–59], herein we report the synthesis of a series of 3-arylcoumarins by means of a novel one-pot procedure, including initial Perkin-like reaction between commercially available homophthalic anhydrides and 2-methoxybenzaldehydes, followed by treatment with BBr_3. This straightforward procedure allows the room-temperature gram-scale production of polyhydroxylated coumarins in good yields for short reaction times, and provides an easy isolation of the final products. Furthermore, in order for the influence of the number and position of the hydroxyl groups in the 3-arylcoumarin scaffold on the radical scavenging activity of the synthesized compounds to be established, an *in vitro* differentiating screening against 1,1-diphenyl-2-picrylhydrazyl free radical (DPPH•) was performed.

2. Results and discussion

2.1. Chemistry

In a recent article of ours [52], we have demonstrated that diastereomeric mixture of methoxylated *cis*- and *trans*-3-aryl-3,4-dihydroisocoumarin-4-carboxylic acids undergoes simultaneous demethylation and lactone-ring opening reaction in presence of BBr_3. This finding resulted in the development of a novel one-pot procedure for the synthesis of polyhydroxylated *cis*-restricted stilbenes possessing a triple biological action as potent antioxidants, antifungal agents and tyrosinase inhibitors. The proposed method consists of sequential reaction between homophthalic anhydrides and aromatic aldehydes to produce diastereomeric mixture of the corresponding 3-aryl-3,4-dihydroisocoumarin-4-carboxylic acids, which, after treatment with BBr_3, give the target polyhydroxylated stilbenes in short reaction times (10–60 min) [52]. In continuation of this study, in order a more complete series of compounds to be synthesized, we were interested to perform reactions between homophthalic anhydrides and a series of 2-methoxybenzaldehydes.

Surprisingly, when 3,4-dimethoxyhomophthalic anhydride (**1b**) and 2-methoxybenzaldehyde (**2a**) were subjected to the reaction conditions depicted in Scheme 1, a by-product, whose structure was latter established as the coumarin **3i**, was isolated in quantity comparable with that of the desired at this stage stilbene *E*-**4a**. This result intrigued us, since, to the best of our knowledge, the synthesis of coumarins according such a protocol is not known. Moreover, a short retrospection of the literature showed that 3-



Scheme 1. Initial synthesis of coumarins. *Reagents and conditions*: (*i*) DMAP/CH_2Cl_2, 10 min, rt, then (*ii*) BBr_3/CH_2Cl_2, rt, 1 or 4 h.

arylcoumarins are normally synthesized under harsh conditions, and that the common methods used for the coumarin scaffold formation are of limited applicability for the direct synthesis of hydroxylated derivatives. So, the above transformation can be considered as attractive for further investigation. We were further delighted to find that the yield of **3i** increases with the time, reaching its maximum in 4 h, and then staying intact even after 12 h. Thus **3i** was obtained in nearly twofold higher yield (78%) compared to the initial conditions (44%). It is noteworthy, that **3i** was isolated as a crystalline product in a high purity, simply by filtration of the worked up reaction mixture, and that some quantities of *E*-**4a** were always present in the filtrate. This shows, on the one hand, that *E*-**4a** could be considered as an intermediate for the synthesis of **3i**, and on the other, that equilibrium between **3i** and *E*-**4a**, in favour of the target coumarin could be assumed. To check this, an isolated *E*-**4a** was reacted at the same conditions and the reaction outcome was monitored by means of TLC. As a result, the expected transformation of *E*-**4a** into **3i** was observed, thus proving the participation of *E*-**4a** as an intermediate in the reaction scheme to **3i** and suggesting some hints regarding the probable reaction mechanism (see below). In addition, when *E*-**4a** was put to crystallize in ethyl acetate, a spontaneous reaction occurs and precipitates of **3i** appear with the time, showing that the lactonization is the thermodynamically favoured process, which proceeds spontaneously to give the more stable product **3i**. In contrary, when **3i** was put under the reaction conditions, no formation of the stilbene *E*-**4a** was observed, thus rejecting the hypothesis for the existing equilibrium between both compounds. The above reasoning, however, suggests the promising potential of the approach under study for the facile synthesis of hydroxylated coumarins in a one-pot manner, from commercially available reagents. Considering this as a great advantage, we were further interested to check the applicability of our methodology by reacting two homophthalic anhydrides with a series of 2-methoxybenzaldehydes. The reaction scheme and conditions are depicted in Scheme 2, and yields and products substitution pattern are given in Table 1. In brief, the obtained by a reaction of the corresponding anhydrides **1a**,**b** and aldehydes **2a**–**h** in presence of DMAP/CH_2Cl_2 diastereomeric mixtures of *cis*- and *trans*-**5** [52–54,59] were further successfully converted without isolation into **3a**–**p** by direct addition of BBr_3/CH_2Cl_2 solution at room temperature. After 4 h, the reaction was terminated by pouring over ice, stirred for additional 30 min for hydrolysis of the boron esters formed, and the target coumarins **3a**–**p** were then isolated simply by filtration. It is noteworthy that the obtained in this way compounds do not need further chromatographic purification, which is a necessary step for isolation of other polyhydroxylated derivatives [12,16,25]. Furthermore, as mentioned above, additional quantities of **3** could be obtained by slow precipitation of the corresponding filtrates, mainly containing stilbenes of type **4**. The structures of **3a**–**p** were elucidated by means of spectral methods. In case of ^1H NMR, ^{13}C NMR and IR methods, the spectra were taken for the