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Novel approach to 3,3-dimethyl-4-morpholino-3,4-dihydrocoumarins via hetero-Diels–Alder reaction

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Dedicated to Professor John M. Roscoe (Acadia University) on the occasion of his 70th birthday

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ABSTRACT

A new four-step synthetic procedure has been developed to prepare 3,3-dimethyl-4-morpholino-3,4-dihydrocoumarins from substituted salicylaldehydes, morpholine, and isobutyraldehyde. It involves aminal formation, deamination, enamine formation, hetero-Diels–Alder reaction, hydrolysis, and oxidation. The aminal formation, subsequent one-pot domino deamination, enamine formation, and hetero-Diels–Alder reaction were achieved in microwave-assisted catalyst-free conditions. The following hydrolysis and oxidation steps, performed conventionally, gave quantitative yields.

1. Introduction

Natural products undoubtedly are rich in chemical diversity, biological specificity, and pharmacological properties inspiring drug development. Among natural products, coumarins and dihydrocoumarins are privileged scaffolds found to possess important biological activities.[1] Their therapeutic potential attracted researchers toward their isolation from natural resources as well as to their chemical synthesis.[2] Dihydrocoumarins are widely prevalent in nature[3] and have received considerable attention due to their interesting biological activities,[4] including inhibition of silent information regulator 2 (sir2)[5] and aldose reductase,[6] antioxidant, immunomodulatory,[7] and antitrypanosomal activities[8] (Fig. 1).

Because of the importance of 3,4-dihydrocoumarins, their syntheses have been widely investigated. Several straightforward processes include cyclocondensation of phenols and cinnamic acids and cyclization of aryl cinnamates,[9] hydrogenation,[10] or enzymatic reduction of corresponding coumarins,[11] redox lactonization of *o*-hydroxycinnamaldehydes,[12] Ir-based oxidative lactonization of 2-(3-hydroxypropyl)phenol,[13] and oxidative cyclization of 3-arylpropionic acids.[14] Another report utilized Au(III)-catalyzed tandem sigmatropic rearrangement/cyclization of (*E*)-2-(aryloxymethyl)

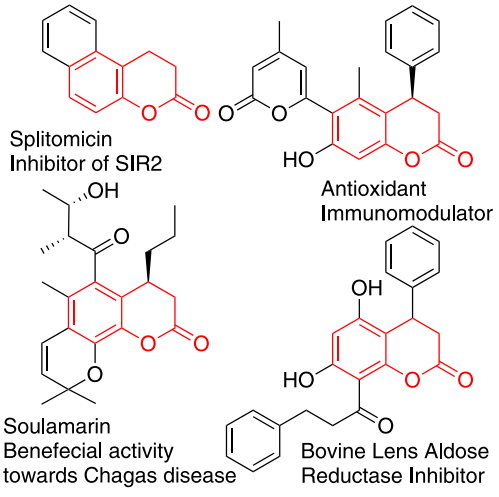

Fig. 1. Molecular structures of several bioactive dihydrocoumarins (highlighted in red).

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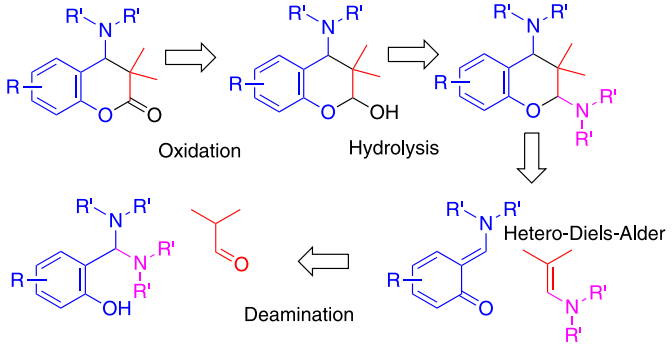
alk-2-enoates to synthesize 3,4-dihydrocoumarin derivatives.[15] [4+2] Cycloaddition reaction of *ortho*-quinone methides with silyl ketene acetals leading to the formation of alkyl- and aryl-substituted dihydrocoumarins is also been documented.[16] Reaction of alkenyl Fischer carbene chromium(0) complexes and ketene acetals are known to furnish 4-aryl-3,4-dihydrocoumarins.[17] Recently, double decarboxylation process has been used for the synthesis of 4-substituted 3,4-dihydrocoumarins.[18] Asymmetric tandem organocatalytic Michael addition–hemiacetalization between aliphatic aldehydes and (*E*)-2-(2-nitrovinyl)phenols has been used to synthesize chroman-2-ols, which were further oxidized to dihydrocoumarins.[19] Asymmetric synthesis of decorated 3,4-dihydrocoumarins has been achieved via a Rh-catalyzed reaction of 3-(2-hydroxyphenyl)cyclobutanones and acrylate analogs.[20] Multi-component reactions using Meldrum's acid, salicylaldehydes, isonitriles, and alcohols have been employed for the synthesis of highly functionalized dihydrocoumarins.[21] A dealkoxycarbonylation–Michael addition sequence for the preparation of 3,4-dihydrocoumarins is also reported.[22]

While many of the reactions described above are efficient and/or mechanistically interesting in producing a variety of 3,4-dihydrocoumarins, some suffer from one of more disadvantages such as harsh reaction conditions, poor yields, expensive transition metal catalysts, corrosive reagents, and/or laborious multistep procedures.[9,13,15,17,20,22] Thus, there is a need to further improve the synthetic procedure and introduce further diversity on the 3,4-dihydrocoumarin core.

In the past decade exploration of the potential of microwave-based synthesis has resulted in many novel synthetically useful transformations including the synthesis of coumarins.[23] With the above mentioned background in view and as part of our on-going research program for the synthesis of biologically active pharmacophores,[24] we delineate herein the synthesis of 3,3-dimethyl-4-morpholino-3,4-dihydrocoumarins via microwave-assisted hetero-Diels–Alder reaction, hydrolysis, and oxidation reaction sequence (Scheme 1).



Scheme 1. Retrosynthetic analysis of 3,3-dimethyl-4-morpholino-3,4-dihydrocoumarins.

2. Results and discussion

We envisioned an approach to construct the benzopyran moiety utilizing [4+2] inverse-demand hetero-Diels–Alder reaction between an *ortho*-quinone methide and an enamine (Scheme 1).[25] The putative *ortho*-quinone methide can be thermally generated in situ from 2-(dimorpholinomethyl)-phenols.[26] Interestingly, reaction between salicylaldehydes and enamines is known to directly afford structurally related 2-dialkylamino-4- chromanols.[27] As depicted in the retrosynthetic analysis (Scheme 1), we initiated our synthetic expedition with the synthesis of an aminal, i.e., 2-(dimorpholinomethyl)-phenol (**1a**) from salicylaldehyde and 2 equiv of morpholine in a solvent-less microwave-assisted reaction (Scheme 2). The purification simply involved addition of hexane, sonication, and vacuum filtration to isolate the pure solid aminal **1a** in 98% yield.

Based on our previous experience from this lab,[25] compound **1a** (1 equiv) was reacted with isobutyraldehyde (1 equiv) and *p*-TSA (5 mol %) as catalyst in the presence of 4 Å activated molecular sieves in toluene at 80 °C in a microwave reactor for 70 min. The desired 3,3-dimethyl-2,4-dimorpholinochroman (**2a**) was obtained in 42% isolated yield along with ~20–25% unreacted aminal **1a**, ~15% chroman-2-ol **3a**, and some unidentified products in trace amounts. Encouraged by the formation of the desired product **2a**, albeit in relatively low yield, we proceeded to optimize the reactions conditions with respect to stoichiometry, catalyst, solvent, temperature, and reaction time. For these experiments, **1a** and isobutyraldehyde were chosen as model substrates for the microwave-assisted reaction (Table 1).

The reaction temperature was maintained at 80 °C or higher because at lower temperatures the reaction was very slow and the desired product was not obtained in reasonable amount. The volatility of isobutyraldehyde (bp 63 °C) was considered responsible for the lower yield of the reaction when 1:1 ratio of isobutyraldehyde and **1a** was used. At the reaction temperature (80 °C), it is likely that isobutyraldehyde is not entirely present in the solution to ensure quantitative in situ generation of 4-(2-methylpropenyl)morpholine from the liberated amine. Increasing the molar equivalent of isobutyraldehyde to 2.5 with respect to **1a** resulted in the formation of **2a** in 48% yield with consumption of the starting material (Table 1, entry 1). Further increase in isobutyraldehyde concentration in the reaction did not affect the yield of **2a**. In order to improve the chemical yield of the desired product, we further investigated the use of Brønsted/Lewis acid catalysts (Table 1). Brønsted acids appeared to work better than Lewis acids with *p*-TSA, TFA, and AcOH furnishing 48, 47, and 43% product yields, respectively (Table 1, entries 1, 3, and 10). Other catalysts resulted in either low yields or virtually no reaction. Interestingly, the control reaction (without any catalyst) resulted in the formation of **2a** in 53% yield (Table 1, entry 11).

Thus, we concluded that acid-catalysis is not a requirement for the reaction and proceeded with the rest of the optimization experiments without using any catalyst in the reaction. Subsequently, a number of common laboratory solvents were screened to assess their effect on the product yield. As indicated in Table 1, the yield of **2a** was found to be the highest in toluene among the solvents tested, followed by chlorobenzene and THF (Table 1, entries 11, 15, and 18). This suggests that non-polar solvents worked better for the cascade process in question. No reaction was observed under solvent-free conditions (Table 1, entry 20).

With the optimized stoichiometry and solvent, the effect of temperature and reaction time was studied simultaneously for this catalyst-free process (Table 1). Experiments were carried out at five temperature points starting at 80 °C with a regular increment of 10 °C. The best result, i.e., 57% isolated yield of **2a** (Table 1, entry 22), was obtained at 100 °C in 50 min. Increasing the temperature to 110 °C with decreased reaction time (45 min) resulted in lower yield (Table 1, entry 23). On further increasing the temperature to 120 °C, the aminal **1a** decomposed with no product formation (Table 1, entry 24). This study indicated that the reaction temperature for this reaction should not be any higher than 100 °C. It is also worth mentioning that when the same reaction was performed in refluxing toluene under conventional heating method for 24 h, product **2a** was formed only in 36% yield. This indicated that the closed-vessel microwave-assisted procedure is a superior option. Thus, microwave irradiation at 100 °C for 50 min in toluene under catalyst-free conditions was established as the optimal condition for the synthesis of compound **2a** from 2-(dimorpholinomethyl)phenol (**1a**) and isobutyraldehyde (Scheme 2).