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Tosylhydrazine mediated conjugate reduction and sequential reductive coupling cyclization: synthesis of 2-arylchromans

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ABSTRACT

Tosylhydrazine mediated conjugate reduction of 2-hydroxyl chalcones and sequential reductive coupling cyclization is described. This is an unprecedented protocol and an extremely efficient method for a one-pot domino synthesis of 2-arylchromans in good to excellent yields from commercially available, cheap starting materials. More importantly, the two-step reactions can be easily controlled to afford dihydrochalcones or 2-arylchromans by the mole amounts of tosylhydrazine. Furthermore, the operational simplicity of the process and the high functional group tolerance are remarkable.

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1. Introduction

Chromans constitute the core of numerous natural products and synthetic analogs[1], which have been shown an extensive array of biological and pharmacological activities (Fig. 1). As such, chromans **1** have played an important role in various therapeutic areas including cardiovascular diseases, diabetes, obesity, hypertension, cancer, and infectious diseases.[2] The most well-known chroman is α-tocopherol **2**, which is the most significant member of the vitamin E family serving as a natural lipophilic antioxidant and radical scavenger.[3] Moreover, some synthetic 2-arylchromans show significant biological activity, For example, racemic 4′,6-dichloroflavan (BW683C) **3** is a potent in vitro inhibitor of rhinovirus replication.[4] Furthermore, among the several classes of flavanoids, dihydrochalcones (DHCs) **4** have been reported to demonstrate antifungal, antibacterial,[5] anticancer,[6] and antioxidant[7] properties and have received considerable attention as food sweeteners.[8] DHCs are also useful key synthetic intermediates toward flavenes[9] and anthocyanin-type dyes.[10]

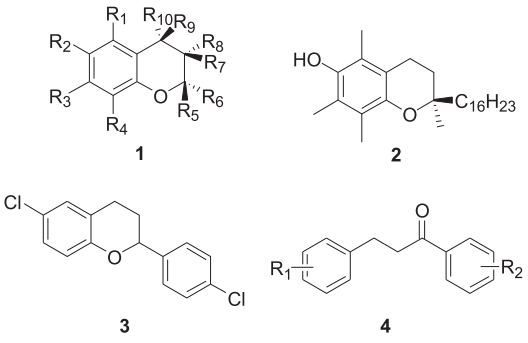

Fig. 1. Chroman and dihydrochalcone derivatives.

Various approaches to the construction of the chromans core have been developed; the traditional methods include intramolecular Mitsunobu reaction,[11] cyclization of chalcones[12] and the reduction of flavanones,[13] flav-2-enes[14] and flavones.[15] Most of these procedures suffer from long reactions times, poor yields and harsh conditions. Recently, Knight has reported an approach to 2-substituted chromans based on the intramolecular trapping by alcohols with benzynes generated from 7-substituted-1-aminobenzotriazoles[16] and Ohwada has developed a method based on hetero-Diels–Alder reaction of the in situ formed *o*-quinone methides with dienophiles.[17] More recently, Sames has reported $RuCl_3$/AgOTf as an efficient intramolecular hydroarylation catalyst, a variety of chromans are accessible under mild conditions using this method.[18] Yamamoto has developed an elegant method for synthesis of chromans based on the molybdenum complex/*o*-chloranil-catalyzed formal [3+3] cyclocoupling of phenol derivatives with allylic alcohols under microwave heating conditions.[19]

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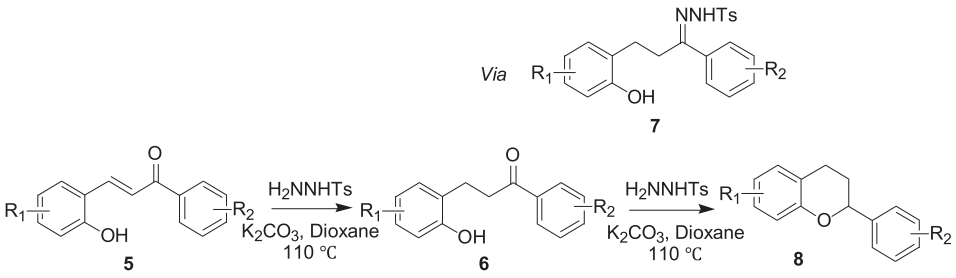
However, these versatile procedures suffer some drawback, such as methodologies based on hetero-Diels–Alder reactions require multistep routes to synthesize *4H*-1,2-benzoxazines,[17] while routes based on cyclocoupling reactions usually feature selectivity problems, and are limited to the availability of *ortho*/*para* substituted phenols.[18,19] The transition metal-catalyzed routes via intramolecular C–O bond coupling reactions have been successfully developed for the synthesis of chromans derivatives.[20] Nevertheless, the efficient preparation of chromans and derivatives is still a challenging task, which involves low-yielding, harsh reaction conditions, limited substrate scope, and several synthetic steps. Therefore, the development of alternative and general protocols for the preparation of chromans and derivatives, which operate under simple and mild reaction conditions, is still desirable.

In recent years, tosylhydrazones have attracted extensive attention because of their various useful applications in organic synthesis. In particular, they are valuable and readily available reagents in C–C,[21] C–N,[22] C–O,[23] and C–S[24] bond-forming reactions through metal-catalyzed and metal-free processes. As part of our ongoing efforts to employ tosylhydrazine as a hydride donor in metal-free chemoselective conjugate reduction of α,β-unsaturated ketones,[25] combined with the C–O bond forming reactions through reductive coupling of tosylhydrazones with alcohols or phenols.[23] Herein, we report a novel protocol for the synthesis of 2-aryl substituted chromans **8** (Scheme 1) from readily available 2-hydroxylchalcones **5** and tosylhydrizine. The corresponding chromans were obtained with unprecedented regioselectivity under mild reaction conditions. The reaction involves conjugate reduction of 2-hydroxylchalcones **5** and sequential reductive coupling cyclization via tosylhydrazones **7** as both a hydride donor and a coupling partner precursor.



Scheme 1. Conjugate reduction of 2-hydroxylchalcones **5** and sequential reductive coupling cyclization using tosylhydrazine.

2. Results and discussion

The 2-hydroxylchalcones **5** substrates were obtained quite conveniently from commercially available acetophenone and salicylaldehyde through an aldol condensation in a mixture of 40% NaOH (aq) and ethanol at 60 °C for 2 h[12] With compounds **5** in hand, we first studied the conjugate reduction of 2-hydroxyl chalcones **5** using tosylhydrazine as a hydride donor. In our initial study, 2-hydroxylchalcones **5a** and tosylhydrazine were chosen as model substrates for the conjugate reduction, the reaction was first investigated according to our previously reported conditions (K_2CO_3/dioxane, 110 °C for 24 h). Gratifyingly, the reaction of model substrate **5a** proceeded in a chemoselective manner to give exclusively the 1,4-adduct **6a** in 76% yield (Table 1, entry 1).

To furthermore optimize the reaction conditions, an extensive screening of various reaction parameters (base, solvent, time, temperature, and ratio of substrates) was conducted. We found that the best yields were achieved by employing a 1:1 chalcone and tosylhydrazine ratio and 3 equiv of K_2CO_3, in 1,4-dioxane as solvent at 110 °C for 3 h (83%, Table 1, entry 1). It should be noted that excessive amounts of tosylhydrazine were detrimental and small amounts of reductive coupling cyclization products **8a** were formed. To further evaluate the scope of the reaction, we next investigated the transformation of a range of 2-hydroxylchalcones **5b–p** with diverse substitution patterns, and the results are summarized in Table 1. The reaction system displayed good tolerance toward a range of functional groups. For example, various substituents on the *para* positions of the phenyl rings, bearing electron-donating (Table 1, entries 2 and 3) or electron-withdrawing substituents (Table 1, entries 4–6) were all tolerated. For example, substrates bearing electron-donating group such as 4-methyl, and 4-methoxyl groups underwent this transformation to form the corresponding products in 79%, and 77% yields, respectively. Substrates with halogen atoms in *para* positions including fluorine, chlorine, and bromine were tolerated under the employed reaction conditions and afforded the corresponding products in 72–80% yields. Notably, steric hindrance had little effect on this transformation, *ortho* and *meta* substituted chalcones presented good reactivity. For example, substrates with methoxyl or boromo group at *meta*-position afforded 74% and 76% yields, respectively (Table 1, entries 7 and 8), and substrates with a same group at *para* position obtained 79% and 80% yields, respectively (Table 1, entries 2 and 6). Remarkably, *ortho* substituted substrate **5i** can smoothly give the corresponding product in 63% yield (Table 1, entry 9). Disubstituted substrate such as **5j** and **5k** participated in the reaction smoothly to afford the desired products **6j** and **6k** in good yields (Table 1, entries 10 and 11). Substrate derived from 1-naphthyl aldehyde **5l** was good substrate for this transformation, which gave the desired product **6l** smoothly (Table 1, entry 12). Interestingly, the reaction of substrate **5m**, bearing a thienyl ring proceeded smoothly to afford the desired product **6m** in 76% yield (Table 1, entry 13). Furthermore, substrates **5n** and **5o** were suitable substrates under the same conditions, giving the conjugate reduction products (Table 2, entries 14 and 15). Notablely, substrate **5p** with two hydroxyl groups was compatible under the modified reaction conditions and was converted into the desired product in 57% yield (Table 1, entry 16). It was worth to note that substrates derived from aliphatic ketones were unsuitable in the present protocol, giving the corresponding pyrazoles.[26]

Recently, Valdés and co-workers reported a new protocol for the synthesis of ethers via a metal-free reductive coupling of tosylhydrazones with phenols and alcohols. This metal-free C–O bond-forming reaction proceeds through the base-promoted decomposition of tosylhydrazones in the presence of phenols or alcohols, and results in the insertion reaction of the carbene into the O–H bond.[23] We hypothesized that the hydroxy group of the resulting intermediate **7** could be a nucleophile to intramolecularly attack the diazo intermediate to afford correspondingly 2-aryl substituted chromans **8** (Scheme 2).

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