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An easy and efficient synthesis of 3-nitrochromans

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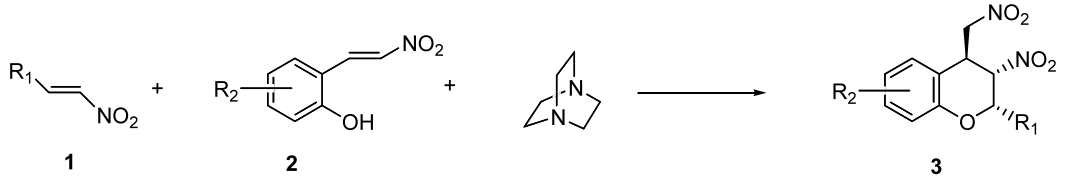
Abstract—The reaction of nitro olefins reacted with (*E*)-(2-hydroxyphenyl)-1-nitroethylene in the presence of DABCO generates 3-nitrochroman with a high stereoselectivity. A possible reaction mechanism for the reaction and the transition states involved in producing the final product are proposed. The treatment of 3-nitrochromans with *t*-BuOK give alkenes.

Chromans are important and interesting heterocyclic compounds in that they are biologically active and have therapeutic use.[1] Our interest in structurally diverse chromans such as the NADH cytochrome c reductase inhibitor polyalthidin[2] and the helicase inhibitor heliquinomycin[3] (Fig. 1) promoted us to consider methods for rapidly preparing chromans that contain a variety of functional groups. A number of methods are available for the preparation of specific chromans as well as some general methods. Chromans can be synthesized using phenol derivatives as the starting materials.[4] For example, the condensation of salicylaldehyde derivatives with alkenes yields chromans.[4b] Another example is the preparation of chroman derivatives under Baylis–Hillman conditions.[4f,g] Chromans can also be prepared via the reaction of phenol ether derivatives with a variety of reactants.[5] The reduction of coumarins, chromenes, chromanones, and chromones also give chromans.[6] Another important method involves the reaction of *o*-quinone methides with alkenes to give chromans.[7] Based on our previous study concerning the synthesis of 3-nitrochromenes,[8] we conclude that salicylaldehyde and its derivatives represent highly potential starting materials for the synthesis of chromans. Herein, we describe an easy and efficient method that involves the condensation of various nitro olefins **1** with (*E*)-(2-hydroxyphenyl)-1-nitroethylene **2**, a salicylaldehyde derivative, to give 3-nitro-4-nitromethylchromans **3** (Eq. (1)) as the final product. The resulting products can be further derived to give a variety of functionalities.

In order to determine the optimum conditions for the reaction, similar reactions were conducted under different conditions and the experimental results are shown in Table 1. First, 2 mmol of **1a**, 1 mmol of **2a**, and 0.1 mmol of DABCO were added to 15 mL THF and the solution was then refluxed for 24 h. As expected, 24% of **3a** and unreacted **1a** and **2a** were observed in the solution (entry 1). Although it is possible to increase the yield of **3a** by increasing the reaction time under similar conditions, mild reaction conditions would be highly desirable. Only traces of product were formed when the reaction was conducted at room temperature for 2 days in a THF solution using **1a** as a limiting reagent (entry 2). To increase the yield of **3a**, the



1 **2** **3** (1)

1 a: R_1 = phenyl, **b**: R_1 = 4-methoxyphenyl, **c**: R_1 = 4-chlorophenyl, **d**: R_1 = 4-fluorophenyl, **e**: R_1 = 4-nitrophenyl, **f**: R_1 = butyl, **g**: R_1 = *iso*-propyl, **h**: R_1 = propyl

2 a: R_2 = H, **b**: R_2 = 3-methoxy, **c**: R_2 = 5-bromo

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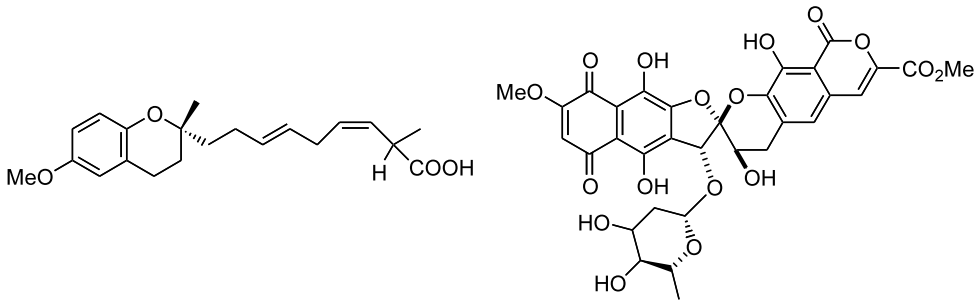


Figure 1. Biologically active chromans.

Table 1. Reaction of **1a** with **2a** in the presence of DABCO under different conditions to generate **3a**

Entry	**1a** (mmol)	**2a** (mmol)	Solvent (mL)	Reaction condition[a]	**3a** (%)[b]
1	2	1	THF (15 mL)	Reflux, 24 h	24
2	1	1.5	THF (1 mL)	rt, 2 days	Trace
3	2	1	CH_2Cl_2 (10 mL)	rt, 2 days	Trace
4	2	1	CH_2Cl_2 (1 mL)	rt, 2 days	51
5	1	1.5	CH_2Cl_2 (1 mL)	rt, 2 days	90

[a] In all entries, 0.1 mmol DABCO was added to the reaction solution.
[b] All yields were measured by ^{1}H NMR with a known amount of DMF as an internal standard.

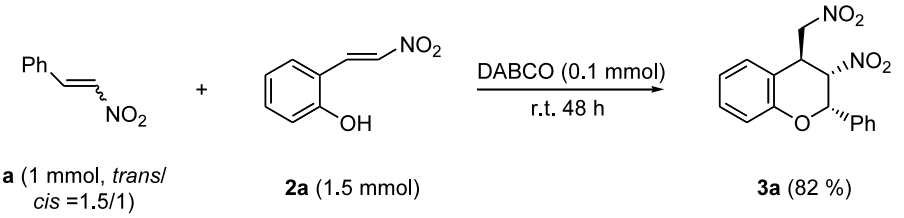
reaction was carried out using a different solvent (CH_2Cl_2) due to the low solubility of the starting material in THF. When the methylene chloride solution was stirred at room temperature for 2 days, traces of **3a** were generated (entry 3). However, when the volume of CH_2Cl_2 was decreased to 1 mL, the yield of **3a** was increased to 51% and only a small amount of **2a** was found in the solution (entry 4). Comparing entry 4 to entry 3, an increase in the concentration of the reactants leads to an efficient increase in the yield of **3a**. Based on conditions used in entry 2, we were also surprised to find that changing the limiting reagent from **2a** to **1a** also leads to a dramatically increased yield of **3a** to 90% (entry 5).

Based on the results of Table 1, it appears that the experimental procedures and conditions shown for entry 5 is the best choice for other similar reactions and all the experimental results shown in Table 2 were conducted under these conditions. Fortunately, high yields of **3a**–**h** except the product **3b** and trace of **3i** were generated when aryl nitro olefins **1a**–**e** or alkyl nitro olefins **1f**–**h** were reacted with **2** under similar conditions (entry 1–8). Concerning the low yield of product **3b**, it seems that the presence of an electron-donating 4-methoxy, in **1b** decreases its electrophilicity to **2a** so that a large amount of **3i** was also generated (entry 2). On the contrary, the presence of an electron-withdrawing halogen or nitro group at the *para* position of reactant **1** not only accelerates the reaction but also leads to increase yields of chroman **3** (entries 3–5). The generation of product **3i** is proposed from the self condensation of **2a** and can be verified by using **2a** only under similar conditions (entry 9). Not only for the starting material **1** but also for the reactant **2**, the presence of the different substituents on the benzene ring also simultaneously affects the nucleophilicity of the 2-hydroxyl group and the electrophilicity of the 1-nitroethylene group. In entry 10, although the presence of a 3-methoxy group on **2b** increases the nucleophilicity of the 2-hydroxyl group, it also increases the steric hindrance between the hydroxyl group and the 3-methoxy group of **2b** and/or between reactants **2b** and **1c** so that a yield of only 21% of **3j** was obtained (entry 10). These assumptions were verified by using the sterically less hindered substrate nitro olefin **1h** to form chroman **3k** in 76% yield (entry 11). When **2c** was reacted with **1c**, **1f**, and **1h**, respectively, 24–84% of **3l**–**n** were obtained but it was necessary to increase the reaction time to 3 days (entries 12–14).

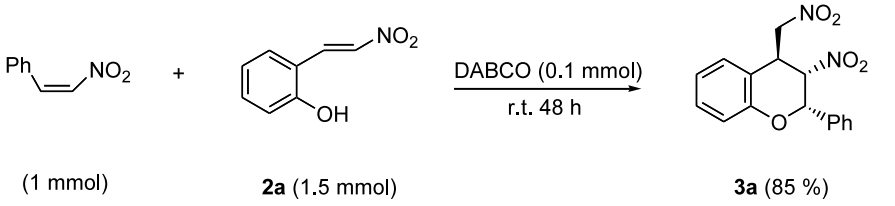
Table 2. The condensation of **2a**–**c** with various nitro olefins **1a**–**h**

Entry	**1**	**2**	Reaction time	**3** (%)[a]
1	**1a**	**2a**	2 days	**3a** (98)
2	**1b**	**2a**	5 days	**3b** (38)
3	**1c**	**2a**	30 h	**3c** (91)
4	**1d**	**2a**	1 day	**3d** (99)
5	**1e**	**2a**	1 day	**3e** (99)
6	**1f**	**2a**	1 day	**3f** (72)
7	**1g**	**2a**	1 day	**3g** (68)
8	**1h**	**2a**	1 day	**3h** (99)
9	–	**2a**	4 days	**3i** (90)
10	**1c**	**2b**	4 days	**3j** (21)
11	**1h**	**2b**	2 days	**3k** (76)
12	**1c**	**2c**	3 days	**3l** (24)
13	**1f**	**2c**	3 days	**3m** (84)
14	**1h**	**2c**	3 days	**3n** (88)

[a] All yields were obtained from ^{1}H NMR with a known amount of DMF as an internal standard.



1a (1 mmol, *trans*/*cis* =1.5/1) **2a** (1.5 mmol) **3a** (82 %) (2)



(1 mmol) **2a** (1.5 mmol) **3a** (85 %) (3)

A possible mechanism for the reaction involves a reaction that proceeds through an intermolecular and intramolecular sequential Michael addition to form 3-nitrochroman **3**. According to the Baldwin rules, six-*exo*-trig is a favored process. This enhances the second nucleophilic attack following the Michael addition. However, an alternate mechanism involving the initial formation of an *o*-quinone methide followed by a stereoselective [4+2] cycloaddition cannot be excluded. If these reactions proceed through a concerted [4+2] cycloaddition of *o*-quinone methide and different dienophiles, the stereochemistry of the R_1 and the nitro groups in compound **3** should be *trans* relative to each other.[7b,c] However, the actual relationship is *cis*. Additional evidence to support the above assumption is that the use of a mixture of *cis*- and *trans*-nitrostyrene **1a** (Eq. (2)) or pure *cis*-**1a** (Eq. (3)) in a reaction with **2a** also generated high yields of 3-nitrochroman **3a** only and these results were almost the same as the result of Eq. (1). In addition to this evidence that supports a stepwise mechanism, the intermolecular [4+2] cycloaddition of *o*-quinone methides (an electron-poor diene) with different electron-rich alkenes is usually favored.[7c] However, nitro olefin **1** is an electron-poor alkene and is also used as a limiting reagent in Eq. (1). According to literature reports,[7b] the formation of *o*-quinone methides to react with different highly reactive dipolarphile via [4+2] intermolecular cycloaddition are usually conducted at high reaction temperatures. However, the reaction conditions outlined in Eq. (1) are mild. Based on these observations, we conclude that a highly stereospecific cycloaddition of *o*-quinone methides and alkenes can be ruled out.

To explain the high diastereoselectivity found in the formation of 3-nitrochroman **3**, four possible transition states that lead to different diastereomers were examined (Fig. 2). Transition states **C** and **D** are not favored due to steric hindrance between the nitro and nitromethylene groups but this effect disappears in the case of transition state **A** or **B**. Although transition state **A** seems to be less sterically hindered than **B**, the stereochemical relationships between R_1 and the nitro and nitromethyl groups are all *cis* to each other. Based on these assumptions, only transition state **B** explains the stereochemistry of the final products.

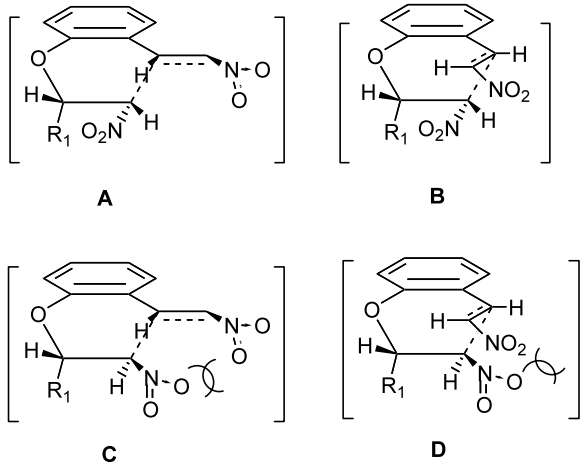
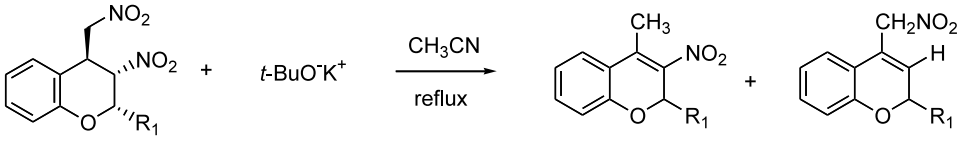


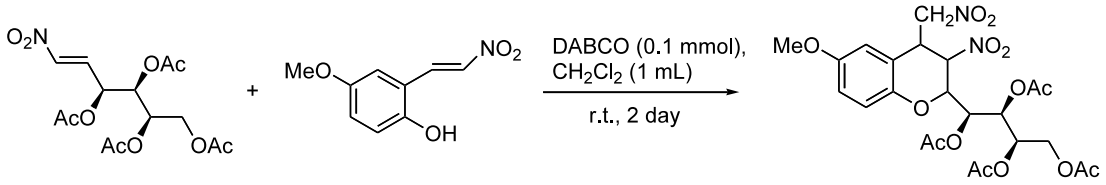
Figure 2. The four possible transition states of the reaction of Eq. (1).

Nitro compounds are very useful precursors for preparing amines, aldehydes, carboxylic acids, nitrile oxides, alkenes, nitro alcohols, etc.[9] From this point of view, 3-nitrochromans **3** represent useful precursors in the



3a: R_1 = Ph	5 h	**4a** (29 %)	**5a** (22%)
3c: R_1 = 4-chlorophenyl	5 h	**4c** (40 %)	**5c** (34 %)
3h: R_1 = propyl	4 h	**4h** (39 %)	**5h** (33%)

(4)



(5)

1i (2 mmol) **2d** (2.2 mmol) **3o** (Two isomers. The conversion yield of major isomer is 84% and trace of minor isomer was isloated)

preparation of a variety of chromans with diverse functional groups. For example, alkenes **4** and **5** were obtained when 3-nitrochroman **3** was treated with base (Eq. (4)).

It has been reported that **1i** can be prepared from D-(+)-xylose.[10] When **1i** was reacted with **2d** (Eq. (5)), 3-nitrochroman **3o** was obtained. The use of the optical active nitro alkene **1i** not only resulted in good diastereoselectivity but permits the generation of optical active **3o**. The separation of two isomers of **3o** can be accomplished by flash chromatography and there is no need for an optical active column. Product **3o** is an analog of polyalthidin (Fig. 1). With the nitro group attached on **3o**, **3o** could be modified by various methods[9] to give ample functionality.

Herein, we provide an easy and efficient method for the synthesis of 3-nitrochromans. The reaction conditions are mild and the yields are high with high diastereoselectivity in most cases. Various R_1 and R_2 can give ample functionality of 3-nitrochromans **3**. In addition, the nitro and nitromethyl groups can be transformed into other compounds **4** and **5** and this transformation demonstrates the potential of 3-nitrochromans **3** in organic synthesis. During the preparation **3**, there are some limitations of the R_1 group in the starting material **1** and R_2 group in the starting material **2**. An asymmetric synthesis of 3-nitrochromans **3** was our goal and is currently under investigation.

Acknowledgements

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