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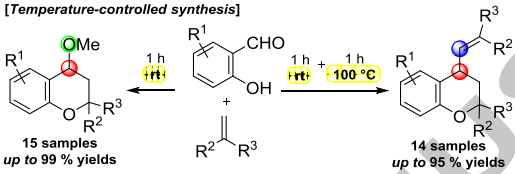

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Temperature-controlled divergent synthesis of 4-alkoxy- or 4-alkenyl-chromanes via inverse electron-demand cycloaddition with *in situ* generated *ortho*-quinone methides

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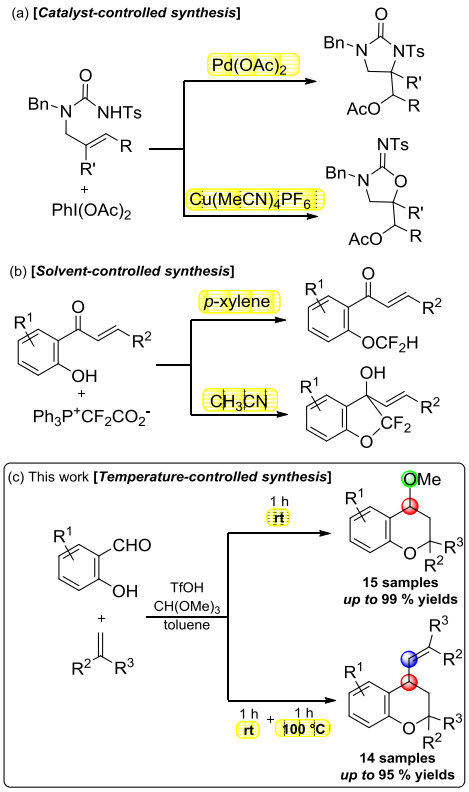
ABSTRACT

The temperature-controlled divergent synthesis of 4-alkoxy- or 4-alkenyl-chromanes via inverse electron-demand cycloaddition with *in situ* generated *ortho*-quinone methides under identical reaction conditions except for thermal condition has been developed. At room temperature, the reaction generated 4-methoxychromanes, whereas the reaction performed at room temperature to 100 ºC gave 4-alkenylchromanes. Trifluoromethanesulfonic acid was efficiently suitable in the reaction to give the 4-substituted chromanes. This divergent synthetic strategy exhibits a new method giving carbon-carbon or carbon-oxygen bond by controlling the reaction temperature.

1. Introduction

Divergent synthesis is one of useful synthetic methods in organic chemistry. One such protocol involves the use of substrate- and/or reaction condition-controlled divergent synthesis, in which two different products are obtained by only changing operations such as catalyst (Scheme 1a),[1] solvent (Scheme 1b),[2] substrate,[3] and the loading amount of catalyst.[4] More recently, temperature-controlled divergent synthesis has been emerging. The approaches include selective synthesis of isoxazoline N-oxides and isoxazoles under ultrasonication,[5] redox-neutral Rh-catalyzed C−H bond annulation of N-methoxybenzamides affording hydrophenanthridone and dibenzo[b,d]pyran-6-one,[6] $BF_3{\cdot}OEt_2$ catalyzed divergent synthesis of sulfinate esters and sulfones via C-O and C-S bond formation from alcohols and TosMIC,[7] and oxidation of α-hydroxy amides in the presence of IBX, giving isatins and α-formyl amides.[8] Despite the availability of these methods, to the best our knowledge, few reports have been reported on temperature-controlled methods and it has been still desirable.

ortho-Quinone methides (*o*-QM) are key reactive intermediates with wide range of applications in organic synthesis.[9] In recent years, catalytic asymmetric reactions including *o*-QM are rapidly growing areas and have been investigated by many researchers.[10] In this context, we performed the acid catalyzed generation of *o*-QM from salicylaldehyde in the presence of trimethyl orthoformate under mild conditions.[11] In addition, inverse-electron-demand [4+2] cycloaddition reaction of electron-rich arylalkynes with salicylaldehydes to give 2*H*-chromene were investigated.[12] Although arylalkynes known to have low reactivity for inverse-electron-demand [4+2] cycloaddition,[13] the reaction smoothly proceeded to afford the desired products in good yields. Recently, when we examined the



Scheme 1. Selected example of reaction condition-controlled divergent synthesis

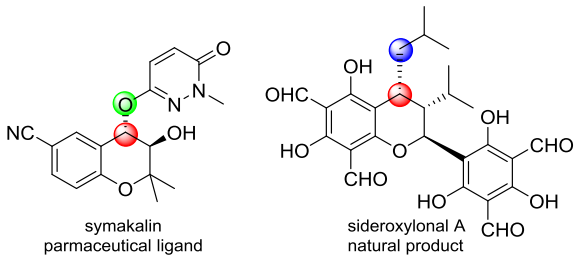


Figure 1. Selective examples of bioactive compound and natural product of chromanes

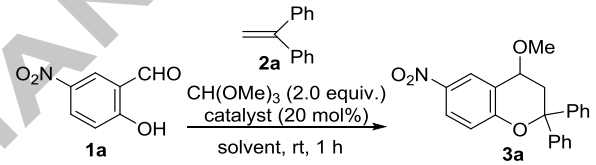
reaction of salicylaldehydes with alkenes, an unexpected reaction was observed, which afforded 4-alkoxy or 4-alkenylchromanes, depended on temperature. The reaction prompted us to investigate a new method giving carbon-carbon or carbon-oxygen bond by controlling the reaction temperature. Herein, we report the temperature-controlled divergent synthesis of 4-alkoxy- or 4-alkenyl-chromanes using 1,1-disubstituted ethylenes with various salicylaldehydes under identical conditions except for the reaction temperature via inverse electron-demand cycloaddition with *in situ* generated *o*-QM (Scheme 1c). This synthetic strategy exhibits a new method giving carbon-carbon or carbon-oxygen bond by controlling only the reaction temperature. The chromanes having carbon-carbon or carbon-oxygen bond of 4-position represent important structural motifs in natural compounds and medicinal chemistry (Figure 1).[14]

2. Result and discussion

We initially investigated the reaction of 5-nitrosalicylaldehyde (**1a**) with 1,1-diphenylethylene (**2a**) using a variety of acid catalysts and solvents at room temperature. While soft Lewis acid catalyst gave no product (Table 1, entry 1), the use of $Sc(OTf)_3$, which is a hard Lewis acid catalyst and is used in [4+2] cycloaddition of salicylaldehydes with ethylenes by Yadav and coworkers in 2002,[9d] afforded the desired chromane **3a** (entry 3). Although *p*-TsOH·H_2O and HBF_4·OEt_2 gave the product in low yields, a more strong Brønsted acid, TfOH, smoothly led to the formation of the desired product in high yield (entry 6). TfOH is an inexpensive organic catalyst, the use of which is much easier than that of $Sc(OTf)_3$ While high polar solvents such as DMF and DMSO were crucial for this reaction (entries 7 and 8), CH_3CN gave the product in 69% yield (entry 9). In addition, the reaction in medium polar solvent, CH_2Cl_2, afforded a good yield (entries 11). Decreasing the amount of **2a** or catalyst did not improve the yields (entry 12 and 13). The best yield of the desired product was achieved by 5-nitrosalicylaldehyde (1.0 equiv.), 1,1-diphenylethylene (3.0 equiv.), $CH(OMe)_3$ (2.0 equiv.), TfOH (20 mol%) in toluene at room temperature (entry 6).

With the optimal conditions in hand, a variety of salicylaldehydes and 1,1-disubstituted ethylenes were examined to evaluate the generality of the reaction (Scheme 2). The parent salicylaldehyde gave the product **3b** in good yield. Moreover, the substrates bearing electron withdrawing groups also efficiently proceeded to afford products **3c**-**3g** in excellent yields. Importantly, 5-methoxysalicylaldehyde was found to be suitable for this transformation **3h**. In our previous work, electron donating groups was not suitable substituents for the reaction with alkynes.[12] In addition, when the ratio of equivalents of starting materials was changed, the yield of the product was increased to 87% yield. However, when the 4-methoxysalicylaldehyde was conducted, the starting material was consumed within 1 h. But the complex mixture was generated, and no trace of the product was detected. While 1,1-diphenylethylene containing *p*-chloro groups afforded the corresponding product in good yield, the reaction with bis(*m*-fluorophenyl)ethylene did not proceed but recovered the starting materials at room temperature or 60 ºC (**3k**). Because meta-substituted fluoride groups on benzene ring are good electron withdrawing groups, the latter substrate would be an unfavorable dienophile for inverse-electron-demand cycloaddition reaction. On the other hand, ethylene bearing electron donating group was well tolerated to give the corresponding product in high yield **3l**. 2-Hydroxy-1-naphthoaldehyde gave the desired product **3m** and chromene **4m** (Figure 2) as an inseparable mixture in 33% and 32% yields, respectively. When the ratio of amounts of the starting materials was changed, chromene **4m** was selectively obtained in 66% yield. Chromene **4m** is known as photochromic materials,[15] and it means that the present method might be a facile method for the one-pot synthesis of chromene-based photochromic materials from easily available starting materials in good yields. A high yield was obtained with the use of 2-phenylpropene as a substrate **3n**. Ethylene having dialkyl groups afforded the product in low yield **3o**.

Table 1. Optimization of the reaction conditions[a]

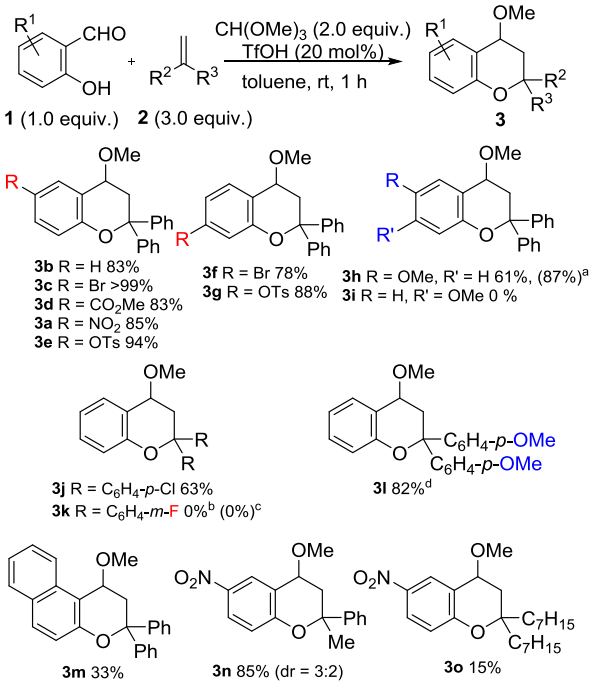


entry	solvent	catalyst	yield (%)
1	toluene	$Pd(OAc)_2$	N.R
2	toluene	BF_3·OEt_2	trace
3	toluene	$Sc(OTf)_3$	15
4	toluene	*p*-TsOH·H_2O	8
5	toluene	HBF_4·OEt_2	18
6	toluene	TfOH	**85**
7	MeOH	TfOH	N.R
8	DMF	TfOH	N.R
9	CH_3CN	TfOH	69
10	THF	TfOH	25
11	CH_2Cl_2	TfOH	79
12[b]	toluene	TfOH	71
13[c]	toluene	TfOH	63

[a] All reactions were carried out with **1a** (0.5 mmol), **2a** (1.5 mmol), $CH(OMe)_3$ (1.0 mmol), catalyst (20 mol%) in solvent (5.0 mL) at room temperature for 1 h.

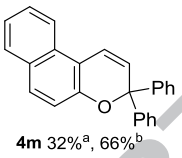
[b] The amount of **2a** was 1.0 mmol.

[c] The amount of TfOH was 10 mol%.



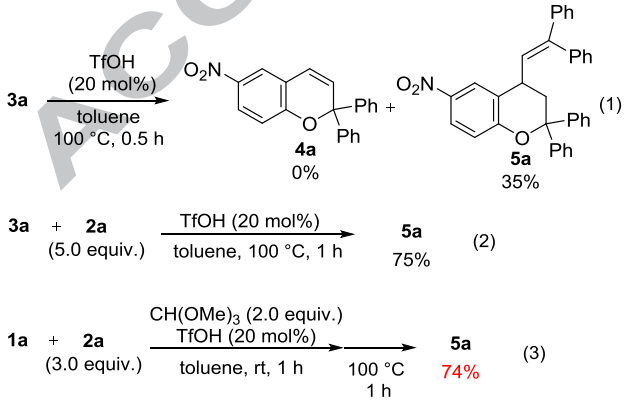
[a] Salicylaldehyde (2.0 mmol) and ethylene (1.0 mmol) were used for 2.5 h. The yield of product was decided basis on ethylene. [b] 3 h. [c] 3 h at 60 ºC. [d] 0 ºC.

Scheme 2. The reaction of salicylaldehydes with 1,1-disubstituted ethylenes at room temperature

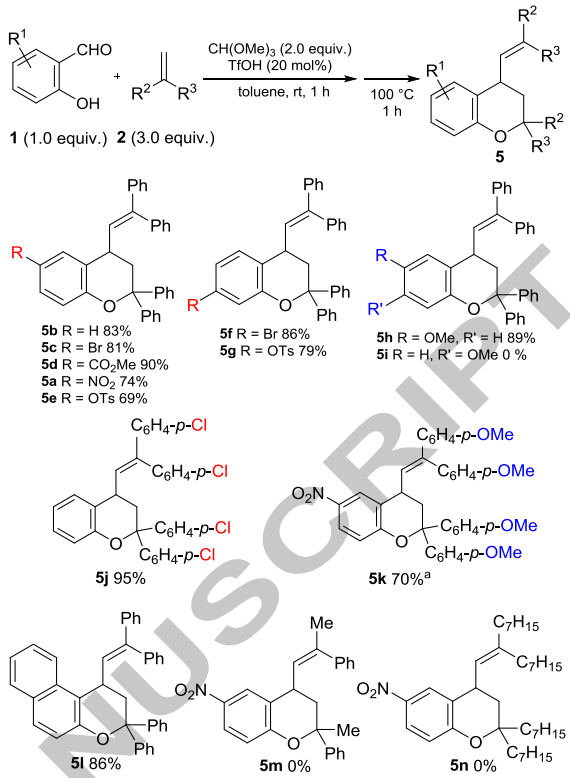


[a] ^{1}H-NMR yield. [b] 2-Hydroxy-1-naphthoaldehyde (2.0 equiv.) and ethylene (1.0 equiv.) were used for 6 h. The yield of product was decided basis on ethylene.

Figure 2. The by-product of the reaction of 2-hydroxy-1-naphthoaldehyde



Scheme 3. The reaction of 4-methoxychromane 3a



[a] The reaction was carried out from 0 ºC (1 h) to 100 ºC (1 h).

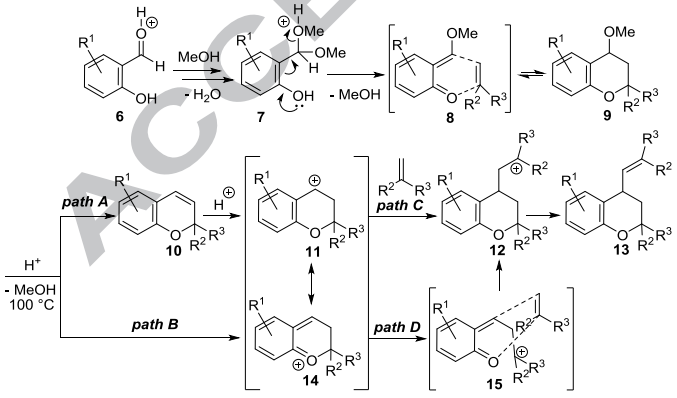
Scheme 4. The synthesis of 4-alkenylchromanes

Next we examined the transformation of chromane. As mentioned above, some 2,2-disubstituted chromens are intriguing compounds, which can display photochromic property. Therefore, we examined the transformations of 4-methoxychromane to chromene, as shown in Scheme 3. When the treatment of 4-methoxychromane with TfOH was carried out at 100 ºC, 4-alkenyl chromane **5a** was unexpectedly obtained in 35% yield instead of chromene **4a** (eq 1). It implies that the elimination of methoxy group from chromane **3a** would be occurred to afford chromene, which, then, would be attacked at the 4 position by 1,1-diphenylethylene, derived from retro-Diels-Alder reaction of **3a**, to give 4-alkenyl chromane **5a**. To confirm this working hypothesis, the reaction of 4-methoxy chromane with 1,1-diphenylethylene was performed under acidic conditions. Expectedly, 4-alkenyl product **5a** was obtained in good yield (eq 2). For this reason, it is anticipated that one-pot synthesis of 4-alkenylchromanes from salicylaldehydes could proceed. Thus, the reaction of 5-nitrosalicylaldehyde with 1,1-diphenylethylene at room temperature to 100 ºC was carried out in one-pot, and the desired product was obtained in good yield (eq 3). These process present a useful synthetic method of selective direct synthesis of 4-alkoxy and 4-alkenyl chromanes by only controlling temperature.

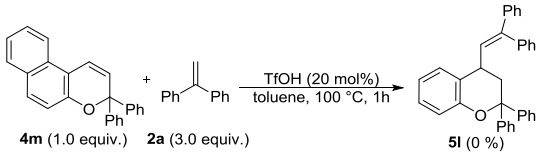
The generality of the formation of 4-alkenylchromanes was evaluated in Scheme 4. When the parent salicylaldehyde was used, the product **5b** was obtained in good yield. Moreover, the substrates having various electron withdrawing group gave chromanes **5c**-**5g** in high yields. 5-Methoxy group was well tolerated to give 89% yield (**5h**). In contrast, the complex mixture was generated, and no desired product was observed in the reaction of 4-methoxysalicylaldehyde (**5i**). We also demonstrated the reactions with some 1,1-diphenylethylene derivatives. An excellent yield was obtained when bis(*p*-dichlorophenyl)ethylene was used (**5j**). In addition, the substrates possessing methoxy groups were also accommodated to this transformation (**5k**). 2-

Hydroxy-1-naphthoaldehyde afforded the desired product in high yield (**5l**). A complex mixture was obtained when 1-Methyl-1-phenylethylene and 1,1-dialkylethylene were used (**5m** and **5n**). While the reactions were suitable both electron donating and electron withdrawing groups, ethylenes need to possess two benzyl groups. It is well known that phenyl group can stabilize benzyl cation,[16] and its effect may need the reaction (vide infra).

A plausible reaction mechanism for the reaction of salicylaldehydes with disubstituted ethylenes is depicted in Scheme 5. First, salicylaldehyde dimethylacetal **7** would be formed by the reaction of salicylaldehyde **6** with $CH(OMe)_3$ in the presence of TfOH. Subsequently, *o*-QM is generated by elimination of methanol from salicylaldehyde dimethylacetal **7**. *o*-QM would react with 1,1-disubstituted ethylene via invers-electron-demand Diels-Alder reaction to give the cyclic product **9**. On the basis of the formation of 4-alkenylchroman **5a** from 4-methoxychromane **3a** under reaction conditions (Scheme 3, eq 1), it is thought that retro-Diels-Alder reaction should occurred when the reaction temperature increased to 100 °C. Elimination of methoxy group in the presence of TfOH afforded chromene **10**. Protonation of the olefinic double bond of the chromene **10** gave intermediate **11** (path A). On the other hand, dihydropyrylium **14** was a resonance structure of intermediate **11**, which would be directly generated from 4-methoxy chromane **9** (path B). It is suggested that **12** would be obtained via path C or path D. 1,1-Disubstituted ethylene attacked to Intermediate **11** to yield stable dibenzyl cation **12** (path C).[17] The formation of dihydropyrylium **14** would induce ring-opening via cleavage of C-O single bond to produce stable dibenzyl cation intermediate, which would react with 1,1-disubstituted ethylene via inverse-electron-demand Diels-Alder reaction to afford **12** (path D).[18] Finally, the loss of a proton from **12** then furnished the desired product **13**. When the reaction of chromene **4m** with ethylene **2a** was carried out, the staring material **4m** was consumed. But the complex mixture was generated, and no trace of chromane **5l** was detected (Scheme 6). Based on the result, path B and path C or path D may be more probable than path A. The scope and mechanism are currently under investigation and will be reported in due course.



Scheme 5. The proposal reaction mechanism



Scheme 6. The reaction of chromene **4m** with ethylene **2a**

Conclusion

In conclusion, we have developed the temperature-controlled divergent synthesis of 4-alkoxy- or 4-alkenyl-chromanes via inverse electron-demand cycloaddition with *in situ* generated *ortho*-quinone methides in the presence of Brønsted acid catalyst. While, at room temperature, the reaction generated 4-methoxychromanes, the reaction at 100 ºC gave 4-alkenylchromanes. The salicylaldehydes having electron withdrawing groups were well-tolerated. In addition, 5-methoxy salicylaldehyde was good suitable in these reaction conditions. Ethylene bearing electron donating group afforded the desired products in good yield. The strategy exhibits a new method giving carbon-carbon or carbon-oxygen bond by controlling the reaction temperature. The present reaction provides versatile access to functionalized 4-substituted chromanes that would be a useful tool for the synthesis of natural product and biologically active molecules.

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Highlights

- The temperature-controlled synthesis of 4-substituted chromanes has been developed.
- The strategy affords a new method giving C-C or C-O bond by controlling temperature.
- The present reaction provides versatile access to functionalized chromanes.