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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

Kenta Tanaka, Mami Kishimoto, Yujiro Hoshino *, Kiyoshi Honda *

Graduate School of Environment and Information Sciences, Yokohama National University, Tokiwadai, Hodogaya-ku, Yokohama 240-8501, Japan

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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 °C 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.

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.[9b] In this context, we performed the acid catalyzed generation of *o*-QM from salicylaldehyde in the presence of trimethyl orthoformate under mild conditions.[10] In addition, inverse-electron-demand [4+2] cycloaddition reaction of electron-rich arylalkynes with salicylaldehydes to give 2*H*-chromene were investigated.[11] Although arylalkynes known to have low reactivity for inverse-electron-demand [4+2] cycloaddition,[12] the reaction smoothly proceeded to afford the desired products in good yields. Recently, when we examined the 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 (Fig. 1).[13]

Result and discussion

We initially investigated the reaction of 5-nitrosalicylaldehyde (**1a**) with 1,1-diphenylethylene (**2a**) using a variety of acid

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* Corresponding authors.

E-mail address: k-honda@ynu.ac.jp (K. Honda).

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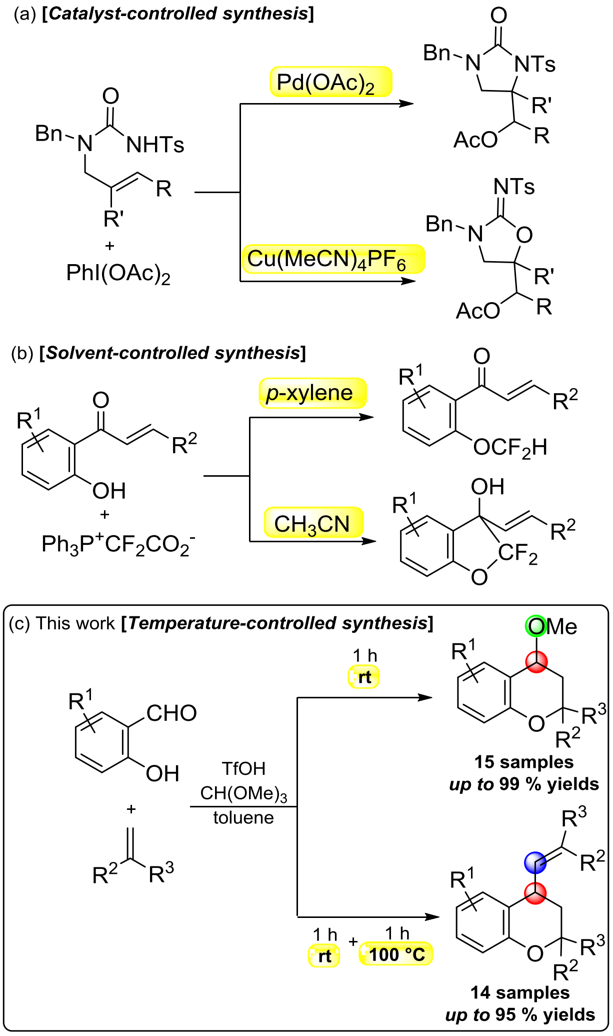


Scheme 1. Selected example of reaction condition-controlled divergent synthesis.

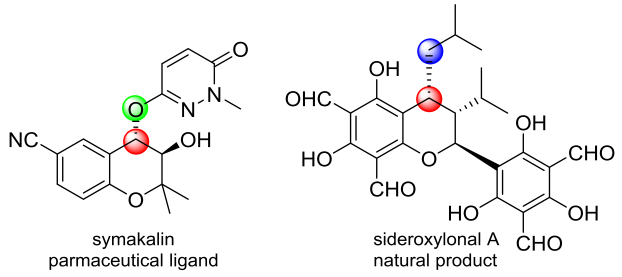
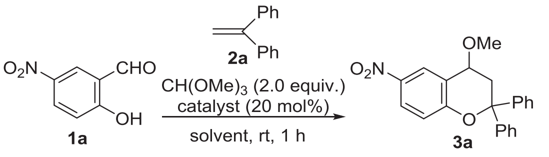


Fig. 1. Selective examples of bioactive compound and natural product of chromanes.

Table 1
Optimization of the reaction conditions[a].



Entry	Solvent	Catalyst	Yield (%)
1	Toluene	$Pd(OAc)_2$	N.R
2	Toluene	$BF_3{\cdot}OEt_2$	trace
3	Toluene	$Sc(OTf)_3$	15
4	Toluene	p-TsOH·H_2O	8
5	Toluene	$HBF_4{\cdot}OEt_2$	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%.

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 $HBF_4{\cdot}OEt_2$ 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.[11] 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 °C (**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** (Fig. 2) as an inseparable mixture in 33% and 32% yields, respectively. When the ratio of amounts of the starting materials was changed, chromene **4 m** was selectively obtained in 66% yield. Chromene **4 m** is known as photochromic materials,[14] and it means that the present method might be a facile method for the one-pot synthesis of chromene-based photochromic materials