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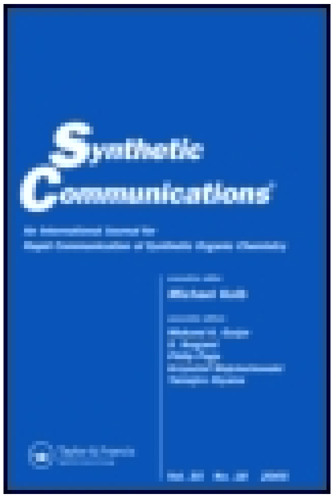

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# An Efficient One-Pot Synthesis of 2,2-Dimethyl-2H-chromenes via Pd(II)-Catalyzed Coupling and $Sio_2$-Promoted Condensation ofo-Halophenols with 2-Methyl-3-buten-2-ol

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# An efficient one-pot synthesis of 2,2-dimethyl-2*H*-chromenes via Pd(II)-catalyzed coupling and $SiO_2$-promoted condensation of *o*-halophenols with 2-methyl-3-buten-2-ol

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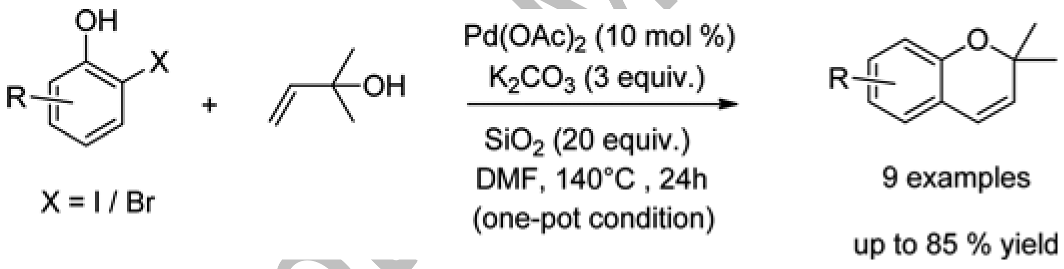
## Abstract

An efficient synthesis of 2,2-dimethyl-2*H*-chromenes was accomplished by Pd(II)-catalysed coupling and $SiO_2$-promoted condensation of *o*-halophenols with 2-methyl-3-buten-2-ol (1,1-dimethyl allyl alcohol) in one-pot condition. The method is very general and can be useful to the synthesis of some natural 2,2-dimethyl-2*H*-chromenes.



**KEYWORDS:** 2,2-dimethyl-2*H*-chromene; palladium; phenol; 2-methyl-3-buten-2-ol

## INTRODUCTION

2,2-Dimethyl-2*H*-chromenes (2,2-dimethyl-2*H*-1-benzopyran) are commonly found as a parent structure in natural products.[1] It is also an important intermediate for the syntheses of numerous pharmaceutical and biologically active compounds.[2] Therefore, a number of methods have been reported for the construction of 2,2-dimethyl-2*H*-chromenes. In particular, the condensation of phenols with *α*,*β*-unsaturated carbonyls (aldehydes or acetals) under different reaction conditions, is the most commonly used method.[3] Other methods include condensation of phenols with 2-methyl-3-butyn-2-ol (1,1-dimethyl propargyl alcohol) catalysed by $ReCl(CO)_5$,[4] catalysed by $BF_3.Et_2O$[5] or other Lewis acids,[6] condensation of phenols with 3-chloro-3-methylbut-1-yne catalysed by $Ph_3PAuNTf_2$,[7] dehydration of chromanols,[8] Pd-catalysed cyclisation of *o*-prenyl phenols,[9] and photocyclisation of 3-aryl-1,1-dimethylprop-2-en-1-ol.[10] Although there are many reports on the preparation of 2,2-dimethyl-2*H*-chromenes, developing an efficient method which uses easily accessible starting materials is still of interest.

Here we describe an efficient route to 2,2-dimethyl-2*H*-chromenes by Pd(II)-catalysed coupling and $SiO_2$-promoted condensation of *o*-halophenols with 2-methyl-3-buten-2-ol (1,1-dimethyl allyl alcohol) in one-pot condition.

## RESULTS AND DISCUSSION

We began investigating the condensation reaction of *o*-iodophenol **1a** and 2-methyl-3-buten-2-ol **2a** using a variety of Pd catalysts ($PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd(TFA)_2$, $Pd(dba)_2$), bases ($Na_2CO_3$, $K_2CO_3$, KOAc), additive (*n*-$Bu_4NCl$, molecular sieve 4Å) and solvents (DMF, DMSO, toluene) and the results are summarised in Table 1. Mixture of **1a** (1.0 mmol), **2a** (10 mmol) and $PdCl_2$ (1 to 10 mol %) in the present of $K_2CO_3$ (3 equiv.) in toluene (1 mL) was heated in a pressure tube under nitrogen atmosphere at 100°C, TLC analysis of the reaction mixture showed that **1a** to be completely consumed after 24 h. As expected, the Heck coupling product **3a** was the major product obtained (35 – 45% yield, entries 1-3). The desired product, 2,2-dimethyl-2*H*-chromene (**4a**), was isolated only in low yield (5 – 10%, entries 1-3). Increasing the reaction temperature to 140°C resulted in a slightly increased yield of **4a** (20%, entry 4 vs entry 3). Presumably, a higher reaction temperature improved the formation of **4a**, most likely due to increase in the rate of condensation of **3a**. Indeed, when the reaction was repeated at 150°C in DMF (entry 5) and DMSO (entry 6), **4a** was obtained in 23% and 25% yields, respectively. Attempts to increase the yield of **4a** using microwave irradiation, however, were unsuccessful (entries, 7-8). It is noteworthy that identical results are observed under both air and nitrogen atmosphere (entries 4 and 5).

We next examined the catalytic activity of other Pd catalysts. Notably, the yields of **3a** and **4a** were slightly increased with catalytic $Pd(OAc)_2$ (entries 9-10). Although three other Pd catalysts, $Pd(PPh_3)_4$, $Pd(TFA)_2$, $Pd(dba)_2$, had activity for the reaction, they were less effective than $Pd(OAc)_2$ (entries 11-13). Adding *n*-$Bu_4NCl$ had no significant effect on formation of **3a** and **4a** (entry 10 vs entry 14). The effect of base on the yield of reaction was also evaluated (entries 15-17). The yields of **3a** and **4a** were reduced when $Et_3N$ was used (entry 17). We also found that both $Na_2CO_3$ and KOAc were less efficient for the Heck coupling reactions (entries 15-16). Amongst the bases, $K_2CO_3$ gave the best result (entries 10 & 14).

Subsequently we investigated the condensation reaction of *o*-iodophenol **1a** with 1,1-dimethyl allylic acetate (2-methylbut-3-en-2-yl acetate) **2b**. Li and co-workers described a selective Heck reaction of 4-iodoanisole with **2b** to give (*E*)-4-(4-methoxyphenyl)-2-methylbut-3-en-2-ol in quantitative yield.[11] Thus we anticipated that the condensation of **1a** with **2b** could enhance the formation of **3** and **4**. However, condensation of **1a** with **2b** under the present optimal reaction condition (Pd(OAc)$_2$ (10 mol%), $K_2CO_3$ (3 equiv.), DMF (1M), 140 °C) significantly decreased the yield of **3a** and **4a** (entry 18), accompanied with the formation of undesired side-product.

Since present condensation reaction of **3a** to **4a** did not proceed well at elevated temperature or under microwave irradiation, we investigated the condensation under acidic condition, *i.e*. AcOH,[12] $H_3PO_4$.[13] Considering sensitivity of some functional groups (*i.e*. ethoxy methoxy group, EOM) in acidic condition, we decided to use a milder reagent such as molecular sieve or silica gel ($SiO_2$). However, the condensation reaction of **3a** to **4a** did not proceed well in present of molecular sieve (entry 8). To our delight, the condensation reaction proceeded extremely good in present of $SiO_2$ to afford **4a** in good yield (76 – 80%, entries 19-20). A controlled experiment was carried out to examine the role of $SiO_2$ as a dehydrating agent (Scheme 1). Treatment of allylic alcohol **3a** in the present of $SiO_2$ afforded chromene **4a** in nearly quantitative yield under the standard conditions.

Consequently, the scope of *o*-halophenols was explored for condensation reaction under the optimised conditions (Table 2). In the presence of Pd(OAc)$_2$ and $K_2CO_3$, a variety of *o*-halophenols **1b-j** were examined by reacting with 2-methyl-3-buten-2-ol **2a** (entries 1-9). The results indicated that both electron-rich and electron-deficient aryl iodides to be suitable for the reaction. Aryl bromide **1b** had similar activity as iodide **1a** (entry 1). However, aryl bromides bearing aldehyde and naphthol moieties gave lower product yield (entries 4 & 8). Aryl chloride had no activity (entry 5). The ethoxy methoxy protecting group (EOM) was cleaved under the optimised conditions (entry 2).

With regards to the synthesis of natural products, isoencecalin **4d** and 2-demethoxymillepachine **4j**, it is noteworthy that the present protocol allows the installation of 2,2-dimethylchromene ring at the late-stage of synthesis. In contrast, the conventional synthesis of millepachine for example, required preparation of 2,2-dimethylchromene ring at earlier stage of the synthesis.[14] The late-stage installation of 2,2-dimethylchromene ring could provide an alternative method for diversity-oriented synthesis of small molecules.

In conclusion, a Pd(II)-catalysed Heck coupling and $SiO_2$-promoted condensation of *o*-halophenols with 2-methyl-3-buten-2-ol has been described for preparing 2,2-dimethyl-2*H*-chromenes in moderate to good yields in one-pot condition. This procedure is simple and efficient. Importantly, this protocol provides a facile synthesis of naturally occurring 2,2-dimethyl-2*H*-chromenes.

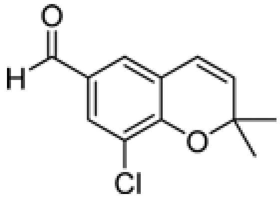
## EXPERIMENTAL

All chemicals were obtained from commercial suppliers and used without further purification. Anhydrous toluene was distilled from calcium hydride under positive pressure of nitrogen. Anhydrous DMSO and DMF were purchased from Aldrich. All reactions were carried out under nitrogen atmosphere unless specified. Pressure tube was purchased from Ace Glassware (USA). NMR spectra were obtained using a Jeol ECA 400 (400 MHz) NMR spectrometer with TMS as the internal standard. All chemical shifts are reported in ppm. Mass spectra were recorded on a Agilent G6530A Accurate-Mass Q-TOF LC/MS spectrometer. Analytical thin layer chromatography (TLC) was carried out on Merck pre-coated aluminum silica gel sheets (Kieselgel 60 F-254). Column chromatography was done with silica gel 60 (230-400 mesh) from Merck. All target compounds were characterized by $^{1}$H, $^{13}$C-NMR and HRMS analysis. Compound **4a** (CAS registration number 2513-25-9),[8b] **4c** (CAS registration number 60986-49-4),[15] **4d** (CAS registration number 30414-95-0),[16] **4e** (CAS registration number 162335-02-6),[17] **4i** (CAS registration number 157495-19-7)[4] were known.

## General Procedure For The Synthesis Of 2,2-Dimethyl-2*h*-Chromenes.

A mixture of *o*-halophenol (1 equiv.), Pd(OAc)$_2$ (10 mol%), K$_2$CO$_3$ (3 equiv.), and 2-methyl-3-buten-2-ol (10 equiv.) in DMF (1 mL per mmol) in a pressure tube was heated to 140°C for 6 ~ 8 h. The reaction was monitored by TLC until the starting material was completely consumed. Then, silica gel (20 equiv.) was added to the reaction mixture, followed by heating at 140°C for another 4 ~ 16 h to give the desired 2,2-dimethyl-2*H*-chromenes.

## 8-Chloro-2,2-Dimethyl-2*H*-Chromene-6-Carbaldehyde (4f)



$^1$H-NMR (400MHz, $CDCl_3$): δ 9.79 (1H, s, CHO), 7.81 (1H, s, phenyl-H), 7.62 (1H, s, phenyl-H), 6.57 (1H, d, $J$ = 9.8 Hz, -CH=), 5.95 (1H, d, $J$ = 10.1 Hz, -CH=), 1.46 (6H, s, 2 x Me); $^{13}$C-NMR (100MHz, $CDCl_3$): δ 190.5, 153.1, 132.5, 131.3, 130.1, 125.8, 122.5, 120.7, 120.6, 79.5, 28.1; HRMS calcd for $C_{12}H_{12}ClO_2$ $[M+H]^+$ = 223.0518. Found: 223.0512

## SUPPLEMENTAL MATERIAL

Full experimental detail and $^1$H and $^{13}$C NMR, and HRMS spectra for this article can be accessed on the publisher's website.

## ACKNOWLEDGMENT

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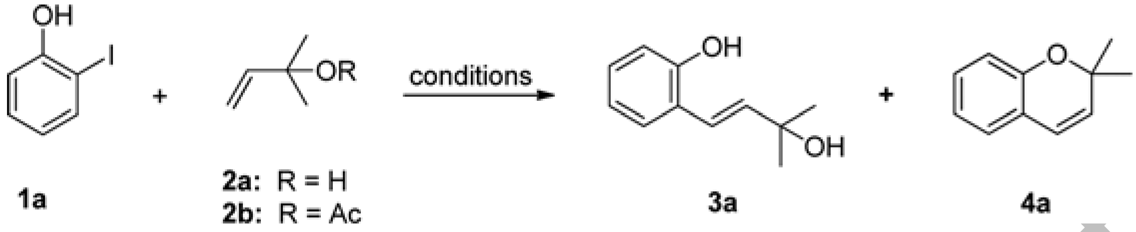
Table 1. Pd(II)-catalysed coupling of o-iodophenol 1a and 2-methyl-3-buten-2-ol 2a.



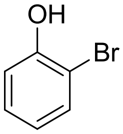
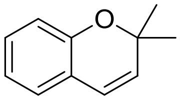
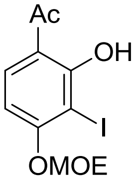
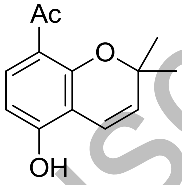
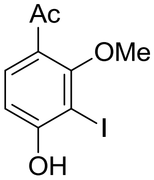
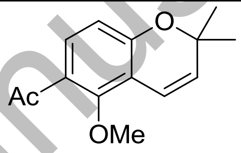
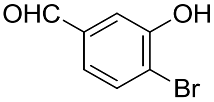
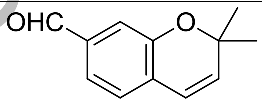
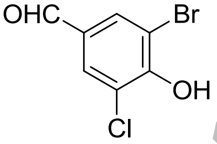
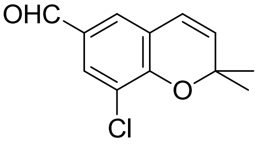
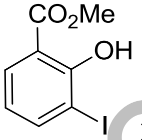
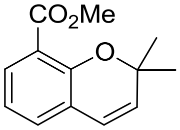
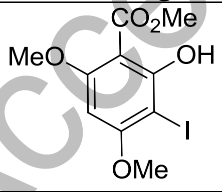
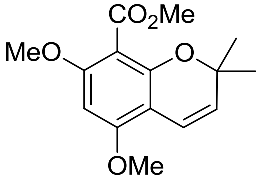
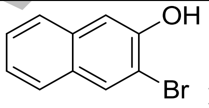
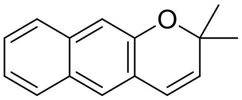
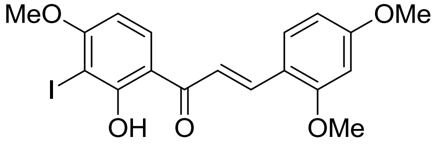
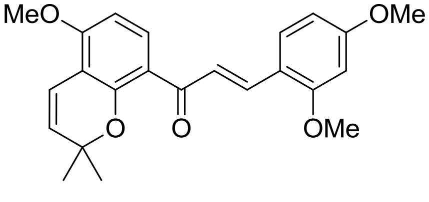
| Entry | Catalyst$^{a}$ (mol %) | **2** | Base | Additive | Solvent | Temp (°C) | Time (h) | Yield (%)$^{d}$ |
|---|---|---|---|---|---|---|---|---|
| | | | (equiv.) | (equiv.) | | | | (**3**:**4**) |
| 1 | $PdCl_2$ (1) | **2a** | $K_2CO_3$ (1.5) | *n*-$Bu_4NCl$ (1.5) | toluene | 100 | 24 | 35:5 |
| 2 | $PdCl_2$ (5) | **2a** | $K_2CO_3$ (2) | *n*-$Bu_4NCl$ (1.5) | toluene | 100 | 24 | 40:10 |
| 3 | $PdCl_2$ (10) | **2a** | $K_2CO_3$ (3) | *n*-$Bu_4NCl$ (1.5) | toluene | 100 | 24 | 45:10 |
| 4 | $PdCl_2$ (10) | **2a** | $K_2CO_3$ (3) | *n*-$Bu_4NCl$ (1.5) | DMF | 140 | 24 | 40:20 |
| 5$^{b}$ | $PdCl_2$ (10) | **2a** | $K_2CO_3$ (3) | *n*-$Bu_4NCl$ (1.5) | DMF | 150 | 24 | 43:23 |
| 6 | $PdCl_2$ (10) | **2a** | $K_2CO_3$ (3) | *n*-$Bu_4NCl$ (1.5) | DMSO | 150 | 24 | 45:25 |
| 7$^{c}$ | $PdCl_2$ (10) | **2a** | $K_2CO_3$ (3) | *n*-$Bu_4NCl$ (1.5) | DMF | 140 | 0.5 | 65:15 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 8[c] | $PdCl_2$ (10) | **2a** | $K_2CO_3$ (3) | MS 4Å (10)[e] | DMF | 140 | 0.5 | 70:10 |
| 9 | $Pd(OAc)_2$ (5) | **2a** | $K_2CO_3$ (3) | *n*-$Bu_4NCl$ (1.5) | DMF | 140 | 24 | 52:15 |
| 10 | $Pd(OAc)_2$ (10) | **2a** | $K_2CO_3$ (3) | *n*-$Bu_4NCl$ (1.5) | DMF | 140 | 24 | 55:20 |
| 11 | $Pd(TFA)_2$ (10) | **2a** | $K_2CO_3$ (3) | - | DMF | 140 | 24 | 40:12 |
| 12 | $Pd(PPh_3)_4$ (10) | **2a** | $K_2CO_3$ (3) | - | DMF | 140 | 24 | 35:5 |
| 13 | $Pd(dba)_2$ (10) | **2a** | $K_2CO_3$ (3) | - | DMF | 140 | 24 | 38:5 |
| 14 | $Pd(OAc)_2$ (10) | **2a** | $K_2CO_3$ (3) | - | DMF | 140 | 24 | 55:15 |
| 15 | $Pd(OAc)_2$ (10) | **2a** | KOAc (3) | - | DMF | 140 | 24 | 40:8 |
| 16 | $Pd(OAc)_2$ (10) | **2a** | $Na_2CO_3$ (3) | - | DMF | 140 | 24 | 35:5 |
| 17 | $Pd(OAc)_2$ (10) | **2a** | $Et_3N$ (3) | - | DMF | 140 | 24 | 25:3 |
| 18[f] | $Pd(OAc)_2$ (10) | **2b** | $K_2CO_3$ (3) | - | DMF | 140 | 24 | 10: - |
| 19 | $Pd(OAc)_2$ | **2a** | $K_2CO_3$ (3) | $SiO_2$ (10)[g] | DMF | 140 | 24 | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (10) | | | | | | | :76 |
| 20 | Pd(OAc)$_2$ (10) | **2a** | K$_2$CO$_3$ (3) | SiO$_2$ (20)[g] | DMF | 140 | 24 | -:80 |

[a]Reaction conditions: **1a** (1.0 equiv.), **2a** (10 equiv.), solvent 1 ml/mmol; [b]Under air condition; [c]Microwave irradiation; [d]Isolated yield after chromatography; [e]In present of molecular sieve 4Å (10 equiv.); [f] Using **2b** (10 equiv.); [g]Silica gel (SiO$_2$, MW=60, size 230-400 mesh) was added to the reaction mixture after heating for 16 h.

**Table 2**. Pd(II)-catalysed coupling and $SiO_2$-promoted condensation of *o*-halophenols **1** and 2-methyl-3-buten-2-ol **2a**.[a]

| Entry | Halide **1** | Time (h) | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  **1b** | 15 |  **4a** | 75 |
| 2 |  **1c** | 15 |  **4c** | 80 |
| 3 |  **1d** | 12 |  **4d** | 60 |
| 4 |  **1e** | 20 |  **4e** | 25 |
| 5 |  **1f** | 20 |  **4f** | 70 |
| 6 |  **1g** | 20 |  **4g** | 15 |
| 7 |  **1h** | 18 |  **4h** | 85 |
| 8 |  **1i** | 30 |  **4i** | 17 |
| 9 |  | 24 |  | 65 |

| | | | | |
|---|---|---|---|---|
| | **1j** | | **4j** | |

[a]Reaction conditions:**1** (1.0 mmol), **2a** (10 mmol), $Pd(OAc)_2$(10 mol %), $K_2CO_3$ (3.0 equiv), and DMF (1 mL) at 140 °C under air for 8 ~ 14 h. The reaction was monitored by TLC until **1** was completely consumed. Silica gel (20 equiv.) then was added to the reaction mixture, followed by heating at 140°C for another 4 ~ 16h to yield desired product. [b]Isolated yield.

**Scheme 1**. Controlled experiment