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# An efficient and simple method for synthesis of 2,2-disubstituted-2*H*-chromenes by condensation of a phenol with a 1,1-disubstituted propargyl alcohol using $BF_3{\cdot}Et_2O$ as the catalyst

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ABSTRACT

An efficient and simple method for the synthesis of 2,2-disubstituted-2*H*-chromenes by one-step cyclocondensation of a phenol with a variety of 1,1-disubstituted propargyl alcohols using $BF_3{\cdot}Et_2O$ as the catalyst is described.



2,2-Disubstituted-2*H*-chromenes or 2,2-disubstituted-2*H*-1-benzopyrans are found as a parent structure in natural products[1] and also in many biologically active molecules, which include antitumor,[2] anti-HIV,[3] antibacterial,[4] and antifungal agents.[5] In addition, 2,2-dimethyl-2*H*-chromenes have high importance as intermediates for the manufacture of several pharmaceutical compounds[6] and 2,2-diaryl-2*H*-chromenes have applications as photochromic agents.[7] Though several methods are available in literature for the preparation of 2,2-disubstituted-2*H*-chromenes,[8] a simple and straightforward approach is one-step cyclocondensation of a phenol and a propargyl alcohol, which are also easily accessible starting materials. In existing methods, however, formation of 2*H*-chromene from the reaction of a phenol and a propargyl alcohol was often described as a two-step process.[9] The first step is the preparation of aryl propargyl ether by the reaction of a phenol and a propargyl alcohol using an acid catalyst such as *p*-toluene sulfonic acid and in the second step, aryl propargyl ether was converted into 2*H*-chromene via thermal Claisen rearrangement reaction at 180–220 °C. In literature, relatively few methods were described for the preparation of 2*H*-chromenes by one-step condensation of a phenol and a propargyl alcohol using a Lewis acid as the catalyst and the methods are as follows: Carreira et al.,[10] reported the formation of diaryl-benzopyrans and diaryl-naphthopyrans by the reaction of a diaryl propargyl alcohol with a phenol/naphthol using pyridinium *p*-toluenesulfonate(PPTS) as the catalyst and trimethylorthoformate (two equivalents) as an additive. Heron and co-workers,[11] studied the condensation reaction of 2-naphthol and a diaryl propargyl alcohol under the catalysis of acidic alumina to obtain diaryl-naphthopyrans in moderate yields (<45%). In this reaction, propenylidenenapththalenone was formed as the side product. Wang and co-workers,[12] prepared diaryl-naphthopyrans in good yields by condensation of 2-naphthol with a 1,1-diaryl propargyl alcohol using indium(III) chloride as the catalyst. This study was limited to diaryl-naphthopyrans and the reactions were observed only under ball milling conditions. McCubbin et al.,[13] also studied this reaction using perfluorophenylboronic acid ($C_6F_5B(OH)_2$) as the catalyst and obtained naphthopyrans in moderate to good yields. Sartori and co-workers,[14] observed the formation of 2*H*-chromenes by condensation of a phenol with a propargyl alcohol using a zeolite (HSZ-360) as the catalyst. This reaction proceeds only with a 1-methyl substituted propargyl alcohol which undergoes dehydration in the presence of the zeolite and converts into corresponding conjugated enyne in the initial step and the resulting enyne intermediate reacts with phenol to give 2*H*-chromene.

Thus, most of the above methods suffer from a lack of generality as their application was limited to the preparation of either

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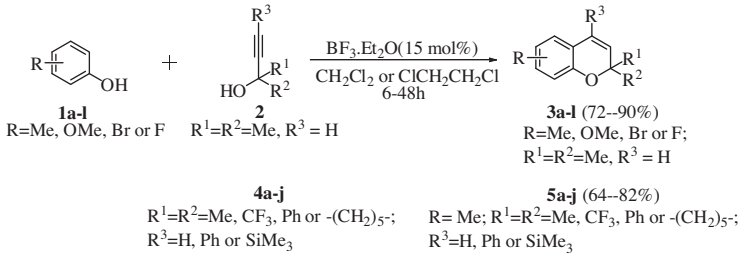
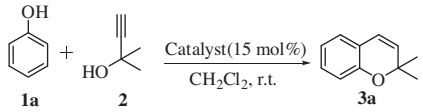



**Scheme 1.** Synthesis of 2,2-disubstituted-2*H*-chromenes.

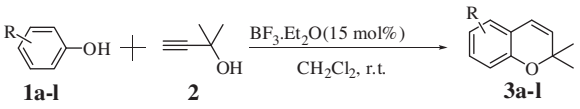
**Table 1**
A study of the formation of 2,2-dimethyl-2*H*-chromene **3a** under acid catalysis




| S.No. | Catalyst | Reaction time (h) | Yield **3a** (%) |
|---|---|---|---|
| 1 | $BF_3{\cdot}Et_2O$ | 6 | 82 |
| 2 | $AlCl_3$ | 24 | 60 |
| 3 | $FeCl_3$ | 24 | 32 |
| 4 | $InCl_3$ | 24 | 12 |
| 5 | $ZnCl_2$ | 24 | 0 |
| 6 | $SbCl_3$ | 24 | 0 |
| 7 | $Yb(OTf)_3$ | 24 | 0 |
| 8 | $Eu(OTf)_3$ | 24 | 0 |
| 9 | $H_2SO_4$ | 24 | 17 |
| 10 | $CF_3COOH$ | 24 | 0 |

benzopyrans or naphthopyrans. Recently, Hua and co-workers,[15] developed a general method for preparation of a variety of 2,2-disubstituted-2*H*-chromenes by condensation of a phenol and a 1,1-disubstituted propargyl alcohol using $ReCl(CO)_5$ as the catalyst. Though this method has a good generality, it involves use of highly expensive catalyst and the reactions were shown to proceed essentially under heating in a sealed tube. Since the existing methods suffer from one or more of the disadvantages such as lack of generality, use of expensive catalyst and poor yields, development of an efficient and simple general method for preparation of 2,2-disubstituted-2*H*-chromenes by condensation of a phenol and 1,1-disubstituted propargyl alcohol is highly desirable. Herein we report an efficient method for the preparation of a variety of 2,2-disubstituted-2*H*-chromenes in high yields (64–90%) by cyclocondensation of a phenol and a 1,1-disubstituted propargyl alcohol at room temperature using an inexpensive Lewis acid $BF_3{\cdot}Et_2O$ as the catalyst as shown in Scheme 1.

**Table 2**
Synthesis of 2,2-dimethyl-2*H*-chromenes by condensation of a phenol and 2-methylbut-3-yn-2-ol under $BF_3{\cdot}Et_2O$ catalysis



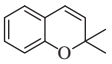
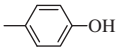
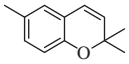
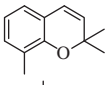
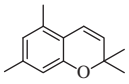
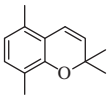
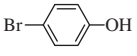
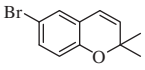
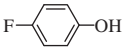
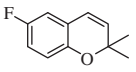
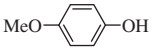
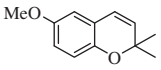
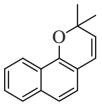
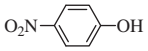
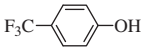
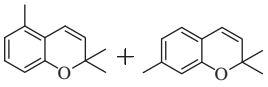
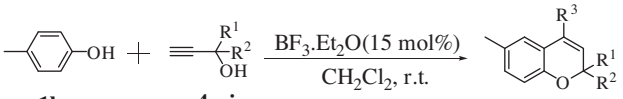

| Entry | Phenol **1** | 2*H*-Chromene **3** | Reaction time (h) | Yield[a] (%) |
|---|---|---|---|---|
| a |  |  | 6.0 | 82 |
| b |  |  | 6.5 | 84 |
| c |  |  | 7.5 | 75 |
| d |  |  | 6.5 | 90 |
| e |  |  | 7.0 | 88 |
| f |  |  | 6.5 | 84 |
| g |  |  | 7.0 | 72 |
| h |  |  | 6.0 | 86 |

**Table 2** (*continued*)

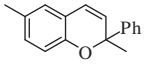
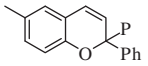
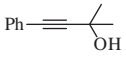
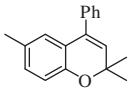
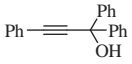
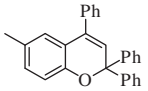
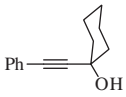
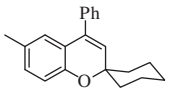
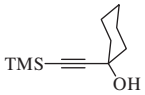
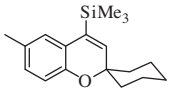
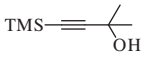
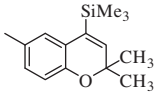
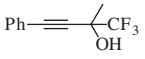
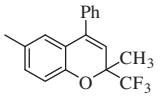
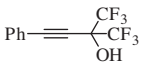
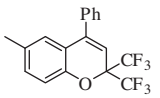
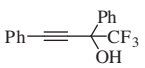
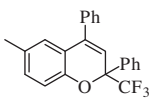
| Entry | Phenol **1** | 2*H*-Chromene **3** | Reaction time (h) | Yield[a] (%) |
|---|---|---|---|---|
| i |  |  | 5.0 | 82 |
| j |  | N.R. | – | – |
| k |  | N.R. | – | – |
| l |  |  1:1 | 6.5 | 80[b] |

[a] Isolated yields. All products gave satisfactory $^1$H, $^{13}$C NMR, IR and Mass spectral data.
[b] Corresponds to the mixture of isomers.

**Table 3**
Synthesis of 2,2-disubstituted-2*H*-chromenes by condensation of *p*-cresol and a 1,1-disubstituted propargyl alcohol under $BF_3{\cdot}Et_2O$ catalysis




**1b** **4a-j** **5a-j**

| Entry | Propargyl alcohol **4** | 2*H*-Chromene **5** | Reaction time (h) | Yield[a] (%) |
|---|---|---|---|---|
| a |  |  | 6.0 | 82 |
| b |  |  | 6.5 | 78 |
| c |  |  | 7.5 | 80 |
| d |  |  | 6.5 | 75 |
| e |  |  | 6.5 | 75 |
| f |  |  | 7.0 | 68 |
| g |  |  | 8.0 | 76 |
| h |  |  | 36.0 | 65 |
| i |  |  | 48.0 | 76 |
| j |  |  | 24.0 | 64 |
| k |  | N.R. | 24.0 | – |
| l |  | N.R. | 24.0 | – |

[a] Isolated yields. All products gave satisfactory $^1$H, $^{13}$C NMR, IR, and Mass spectral data.

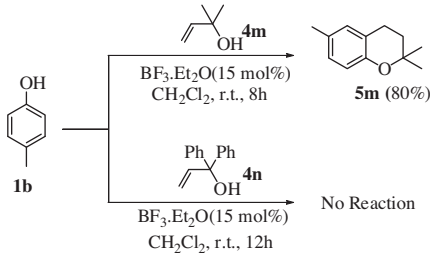
Initially, we investigated the condensation reaction of phenol **1a** and 1,1-dimethyl propargyl alcohol(2-methyl-3-butyn-2-ol) **2** using a variety of Lewis and Bronsted acid catalysts such as $BF_3{\cdot}Et_2O$, $AlCl_3$, $FeCl_3$, $ZnCl_2$, $SbCl_3$, $InCl_3$, $Yb(OTf)_3$, $Eu(OTf)_3$, sulfuric acid, and trifluoroacetic acid at room temperature using dichloromethane as solvent to obtain 2,2-dimethyl-2*H*-chromene **3a** and the results are shown in Table 1. In this study, we observed best results with $BF_3{\cdot}Et_2O$, which gave 2,2-dimethyl-2*H*-chromene **3a** in 82% yield in 6 h in dichloromethane. When this reaction was carried out using other solvents such as 1,2-dichloroethane, *n*-hexane, acetonitrile, toluene under similar conditions, **3a** was obtained in 65%, 60%, 15%, and 10% yields, respectively in 24 h and no reaction was observed in methanol.

We also studied the present reaction with a variety of phenols **1a–i**, which were reacted with 1,1-dimethyl propargyl alcohol **2** using $BF_3{\cdot}Et_2O$ as the catalyst in dichloromethane at room temperature to obtain corresponding 2,2-dimethyl-2*H*-chromenes **3a–i** in 72–90% yields as shown in Table 2.[16] In this study, however, phenols having electron withdrawing groups such as *p*-nitrophenol **1j** and *p*-trifluoromethylphenol **1k** were found to be unreactive even under reflux for 24 h in 1,2-dichloroethane. When an unsymmetrical phenol *m*-cresol **1l** was reacted with 1,1-dimethyl propargyl alcohol **2** at room temperature in dichloromethane using $BF_3{\cdot}Et_2O$ as the catalyst, we did not observe any selectivity and obtained an inseparable 1:1 mixture of two regioisomeric chromenes (**3l**, Table 2).

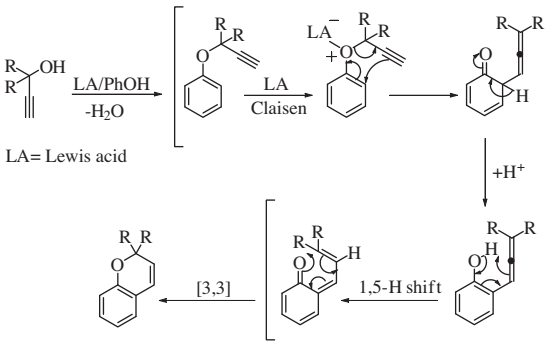
Next, we studied the present reaction using a variety of 1,1-disubstituted propargyl alcohols **4a–j,** which were reacted with *p*-cresol **1b** under $BF_3{\cdot}Et_2O$ catalysis in dichloromethane at room temperature to obtain corresponding 2,2-disubstituted-2*H*-chromenes **5a–j** in 64–82% yields as shown in Table 3. In this study, however, unsubstituted propargyl alcohol **4k** and monosubstituted propargyl alcohol **4l** did not participate in the condensation reaction with *p*-cresol under similar conditions. Primary and secondary propargyl alcohols **4k** and **4l** were unreactive possibly because the formation of carbocations from these substrates could be energetically not favorable under the reaction conditions when compared to tertiary propargyl alcohols **4a–j**.

We observed that the present condensation reaction to proceed well also with an allylic alcohol substituted with an electron rich group such as 1,1-dimethyl allylic alcohol **4m**, which was reacted with *p*-cresol **1b** at room temperature in dichloromethane under $BF_3{\cdot}Et_2O$ catalysis to obtain 2,2-dimethyl chroman **5m** in 80% yield. However, 1,1-diphenyl allyl alcohol **4n** did not react with *p*-cresol **1b** under similar conditions as shown in Scheme 2.

In the present study, we prepared, for the first time, 4-silyl functionalized 2*H*-chromenes **5f** and **5g** in 68 and 76% yields, respectively, which were obtained by the reaction of *p*-cresol **1b** with 1-((trimethylsilyl)ethynyl)cyclohexanol **4f** and 2-methyl-4-(trimethylsilyl)but-3-yn-2-ol **4g** respectively at room temperature using $BF_3{\cdot}Et_2O$ as the catalyst in dichloromethane (Table 3). In this reaction, trimethylsilyl group was found to exhibit good tolerance to the reaction conditions.




**Scheme 2.** A study of the reactivity of 1,1-disubstituted allylic alcohol with *p*-cresol under $BF_3{\cdot}Et_2O$ catalysis.




**Scheme 3.** Plausible mechanism for formation of 2,2-disubstituted-2*H*-chromenes under Lewis acid catalysis.

The functional groups $CH_3$ and $CF_3$ are known as bioisosteres[17] in medicinal chemistry. In several existing studies, bioefficacy was found to improve dramatically when the $CH_3$ group present in a bioactive molecule was replaced with a $CF_3$ group, which improves the lipophilicity, bioavailability, and metabolic stability of the molecule.[18] In literature, synthesis and study of trifluoromethyl functionalized 2*H*-chromenes are so far not known and in present study, we prepared trifluoromethyl functionalized 2*H*-chromenes **5h–j** (Table 3) by condensation of *p*-cresol **1b** and propargyl alcohols[19] **4h–j** using $BF_3{\cdot}Et_2O$ as the catalyst under reflux in 1,2-dichloroethane. In this study, trifluoromethyl functionalized propargyl alcohols were found to be relatively sluggish when compared to methyl functionalized propargyl alcohols**,** as they required high temperature (reflux condition in 1,2-dichloroethane) and longer reaction times (>24 h) to undergo the condensation reaction.

Thermal Claisen rearrangement of aryl propargyl ethers and their subsequent transformation into 2*H*-chromenes are extensively studied subjects in literature.[20] Sames et al.,[21] carried out this transformation at room temperature using a Lewis acid catalyst $PtCl_4$. In the present study also, we believe that the initial step of the reaction involves formation of aryl propargyl ether as a transient intermediate from the reaction of a phenol and a propargyl alcohols under Lewis acid catalysis. In the subsequent step, the resulting aryl propargyl ether possibly undergoes rapid Claisen rearrangement under Lewis acid catalysis and converts into 2*H*-chromene as shown in Scheme 3.

In conclusion, we have developed an efficient, simple, and mild general method for the preparation of 2,2-disubstituted-2*H*-chromenes by condensation of a propargyl alcohol and a phenol using $BF_3{\cdot}Et_2O$ as the catalyst. In this study, we report the first synthesis of 2-trifluoromethyl functionalized 2*H*-chromenes and 4-silyl functionalized 2*H*-chromenes.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version(experimental procedures, characterization data and $^1H$ & $^{13}C$ NMR spectra of the compounds), at http://dx.doi.org/10.1016/j.tetlet.2012.07.077.

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16. *Typical experimental procedure for preparation of 2,2,6-trimethyl-2H-chromene* (**3b**): *p*-Cresol **1b** (1.0 g, 9.21 mmol), 2-methyl-3-butyn-2-ol **2** (0.77 g, 9.21 mmol, 0.8 mL) and dichloromethane (10 mL) were taken into a 50 mL round-bottomed flask fitted with a condenser and calcium chloride guard tube. To this, $BF_3{\cdot}Et_2O$ (0.26 g, 1.8 mmol, 0.2 mL) was added and the mixture was stirred at room temperature for 6 h. After completion of the reaction (TLC), solvent was removed from the mixture under reduced pressure and the crude product was purified by column chromatography (silica gel 60-120 mesh, *n*-hexane) to obtain 6-methyl-2,2-dimethyl-2*H*-chromene **3b** (1.34 g, 84%) as a colorless oil, which gave the following spectral data: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 6.83 (dd, *J* = 7.5, 2.6 Hz, 1H), 6.72 (d, *J* = 2.6 Hz, 1H), 6.59 (d, *J* = 7.5 Hz, 1H), 6.22 (d, *J* = 9.8 Hz, 1H), 5.52 (d, *J* = 9.8 Hz, 1H), 2.21 (s, 3H), 1.39 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 151.4, 130.6, 129.5, 122.7, 120.5, 116.1, 112.6, 75.6, 29.4, 28.0; IR (neat): $\upsilon$ 2998, 2853, 1606, 1510, 1316, 1249, 1037, 907, 826, 755 cm$^{-1}$; ESI-HRMS observed for $C_{12}H_{15}O(+H)$ : 175.1118 (calculated: 175.1123).
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19. *Typical experimental procedure for preparation of 1,1,1-Trifluoro-2,4-diphenylbut-3-yn-2-ol* (**4j**): Phenylacetylene (1 mL, 0.9 mmol) and THF (10 mL) were taken into a two necked r.b. flask fitted with a condenser, nitrogen balloon, and a rubber septum. To this, *n*-BuLi in hexane (4.2 mL, 2.5 M, 0.9 mmol) was added drop-wise with a syringe at 0 °C and after addition was complete, the mixture was allowed to stir for 30 min. Next, the mixture was cooled to −78 °C and then, 2,2,2-trifluoroacetophenone (1.3 mL, 0.9 mmol) was added slowly with a syringe. After 15 min, the mixture was warmed to 0 °C and stirred for an additional 30 min. Then, water (10 mL) was added slowly to the mixture, extracted with diethyl ether (2 × 15 mL) and the combined organic layer was dried over anhy. $Na_2SO_4$. After removal of the solvent from the mixture under reduced pressure and purification of the crude product by column chromatography (silica gel 60–120 mesh, *n*-hexane) gave 1,1,1-trifluoro-2,4-diphenyl-3-yn-2-ol **4j** (1.49 g, 94%) as an yellow oil. which gave the following spectral data: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.83–7.81 (m, 2H), 7.53–7.34 (m, 8H), 3.72 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 135.4, 131.9, 129.4, 128.3, 128.1, 127.1, 120.9, 87.9, 84.4, 73.2; IR (neat): $\upsilon$ 3449, 3065, 2959, 2233, 1491, 1450, 1247, 1183, 1066, 694 cm$^{-1}$; ESI-HRMS: Exact mass observed for $C_{11}H_7F_6O$ : 277.0758 (calculated: 277.0762).
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