Highly Efficient Access to 4-Chloro-2*H*-chromenes and 1,2-Dihydroquinolines under Mild Conditions: TMSCl-Mediated Cyclization of 2-Propynolphenols/Anilines

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Highly Efficient Access to 4-Chloro-2*H*-chromenes and 1,2-Dihydroquinolines under Mild Conditions: TMSCl-Mediated Cyclization of 2-Propynolphenols/Anilines

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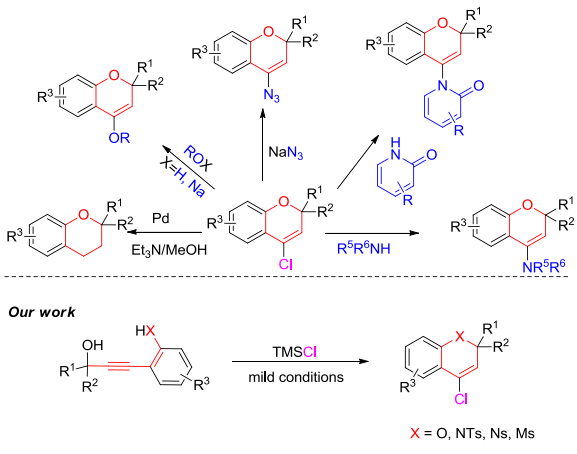
ABSTRACT

A novel and efficient TMSCl-mediated cyclization reaction of easily prepared 2-propynolphenols/anilines is developed to give 4-chloro-2*H*-chromenes and 1,2-Dihydroquinolines in good to efficient yields. It is noted that TMSCl acts not only as a promoter in this reaction, and also as the chloro source. Both tertiary and secondary propargylic alcohols with diverse functional groups were tolerated under the mild conditions. Moreover, this method can be enlarged to gram scale (yield up to 90%).

Introduction

2*H*-chromene is a considerably significant flavonoid skeletal structure, which widely distributes in a variety of natural products and pharmaceutically active molecules.[1-3] Meanwhile, in view of the potential bioactivity and pharmaceutical activities of such compounds, as well as the crucial position in organic synthetic chemistry, the development of atom- and step-economical approaches for the synthesis of benzopyran structures has attracted considerable attentions. The general approaches for the synthesis of functionalized 2*H*-chromenes include the modification of pre-constructed of chromonone nucleus,[4] and the cyclization of substituted phenolic propargyl ether compounds.[5] Not long ago, Kumar and Su group reported a mild synthesis of 4-chloro-2*H*-chromenes from the Vilsmeier-type reaction of 2'-hydroxychalcones.[6] Despite these pioneering methodologies for the synthesis of 2*H*-chromenes, some of them suffered one or more shortcomings, such as tedious procedures, harsh conditions, limited substrates, and the unsatisfactory yields. So, it is still desirable to develop an efficient and straightforward method for the synthesis of functionalized 2*H*-chromenes in mild conditions with broad substrates scope.

Owing to the potential intrinsic reactivity of alkynols, the tandem reaction of alkynols has recently received considerable attention and has become powerful tool for the construction of various carbo- and heterocyclic compounds.[7] Recently, our group developed a tandem process to synthesize heterocyclic building blocks by using 2-propynolphenols as the starting materials.[8] To the best of our knowledge, the direct transformation of 2-propynolphenols to 4-chloro-2*H*-chromenes has been not disclosed yet. As shown in scheme 1, 4-chloro- 2*H*-chromenes have been extensively used as valuable intermediates for the construction of various *O*-heterocyclic compounds with potential bioactivity. [9-12] Herein, we describe an efficient and novel approach to access 4-chloro-2*H*-chromenes or 1,2-dihydroquinolines under mild reaction conditions (Scheme 1). Compared to the traditional strategies, our developed methods could be conveniently operated, which may open up a new potential application for these systems in industrial production. It is noted that TMSCl acts not only as a promoter in this reaction, and also as the chloro source.

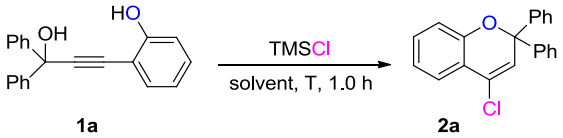


Scheme 1 Various applications of 4-chloro-2*H*-chromenes and our work

Results and Discussion

The initial exploration for the construction of 4-chloro-2*H*-chromenes began by employing 2-propynolphenols **1a** (0.2 mmol) as the model substrate with TMSCl (1.5 equiv) in CH_3NO_2 at 50 °C for 1.0 h (Table 1, entry 1). To our delight, the desired product, 4-chloro-2,2-diphenyl-2*H*-chromene (**2a**), was isolated in 87%. Subsequently, various representative solvents were screened. And MeCN proved to be the most efficient one, which increased the yield of **2a** to 95% (Table 1, entries 2–7). When the temperature was increased to 80 °C, **2a** was obtained in a lower yield (Table 1, entry 8). We considered that a higher temperature was advantageous to the side reaction. 79% yield of **2a** was obtained at room temperature for 4.0 h due to the relatively lower reactivity, as expected (Table 1, entry 9). Furthermore, other adjustments indicated that the most appropriate amount of TMSCl was 1.5 equiv (Table 1, entries 10–11). In addition, no better yields were obtained, when *conc.*HCl (12 mol/L) was applied instead of TMSCl in this reaction (Table 1, entry 12). Ultimately, the optimal reaction conditions for generating **2a** were determined to be the use of TMSCl (1.5 equiv) in MeCN (2.0 mL) at 50 °C for 1.0 h.

Table 1 Optimization of the reaction conditions[a]



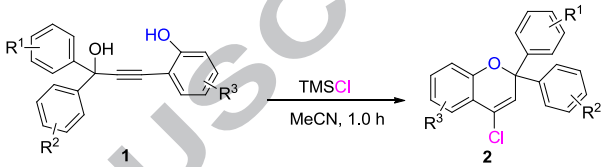
1a **2a**

Entry	Solvent	TMSCl (equiv)	*T*[°C]	Yield
1	$MeNO_2$	1.5	50	87
2	DCE	1.5	50	91
3	MeCN	1.5	50	95
4	CH_2Cl_2	1.5	50	88
5	THF	1.5	50	89
6	HOAc	1.5	50	91
7	1,4-dioxane	1.5	50	90
8	MeCN	1.5	80	90
9[b]	MeCN	1.5	rt	79
10	MeCN	2.0	50	96
11	MeCN	1.2	50	90
12[c]	MeCN	1.5	50	86

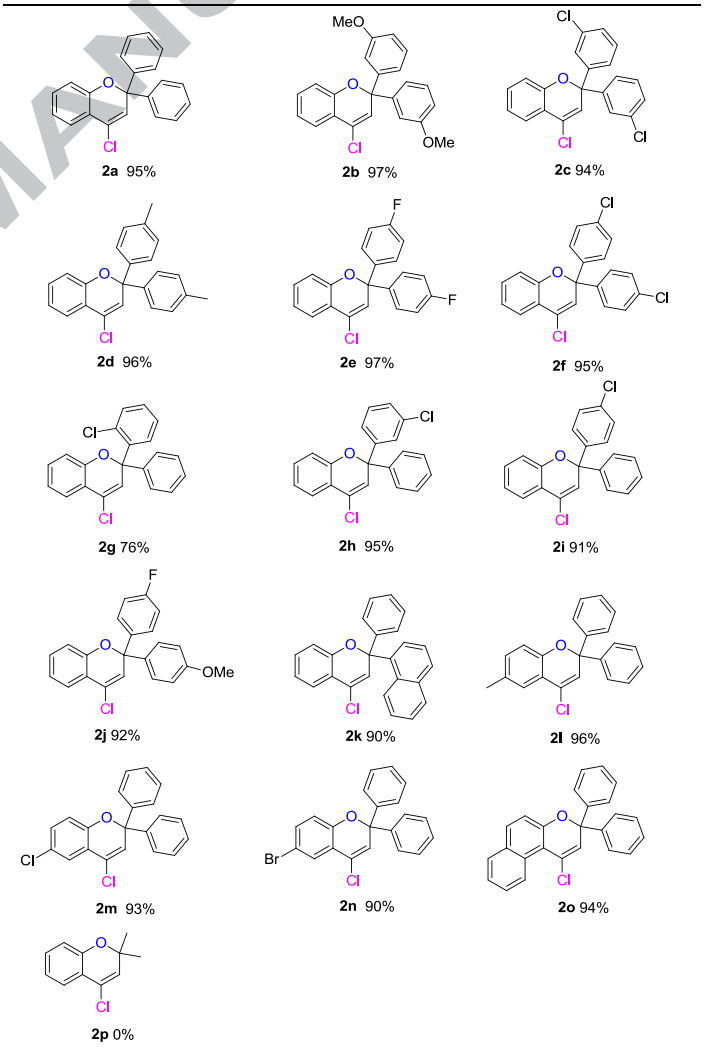
[a]Unless otherwise noted, all reactions were performed with 0.2 mmol of **1a** with TMSCl, in solvent (2.0 mL) at 50 °C. [b] 4.0 h. [c] HCl was used instead of TMSCl.

With the optimized reaction conditions in hand, a variety of substituted 2-propynolphenols were prepared to investigate the scope of this tandem reaction. The corresponding 4-chloro-2*H*-chromene products (**2a**–**2o**) were obtained in good to excellent yields (up to 97%) under the optimal reaction conditions (Table 2). The structure of **2n** was also confirmed by an X-ray diffraction (see the Supporting Information). Firstly, various substituted tertiary propargylic alcohols **1** were treated with TMSCl to explore the substituents effects. In general, both electron-donating (Me, OMe) and -withdrawing (F, Cl) substituents on either of the two aryl groups could be tolerated and afforded the desired products in good to excellent yields (**2a**–**2j**). Moreover, the steric effect of substituents exerted a clear influence on this transformation; the substituents on the *ortho*-position of aryl groups gave slightly lower yields (**2g**). When the substrates with two different aryl groups ($R^1 \neq R^2$) were employed under optimal reaction conditions, the corresponding products were obtained in good to excellent yields (**2g**–**2j**). Furthermore, substrates with diverse substituents (Me, Cl and Br) as the R^3 group could also readily participate in this tandem reaction to generate the desired products in excellent yields (**2l**–**2n**). Especially, the reaction proceeded smoothly for the substrates with a multiple-ring group (naphthyl group, **1k** and **1o**). Unfortunately, no desired product was obtained when alkyl-

Table 2 Transformation of tertiary propargylic alcohols to 4-chloro-2*H*-chromenes[a]



1 **2**

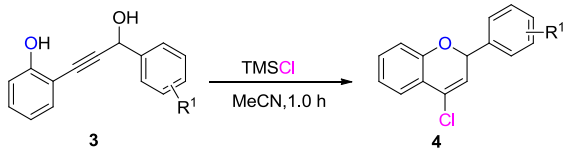


[a]Unless otherwise noted, all reactions were performed with 0.2 mmol of **1**, 1.5 equiv of TMSCl in CH_3CN (2.0 mL) at 50 °C.

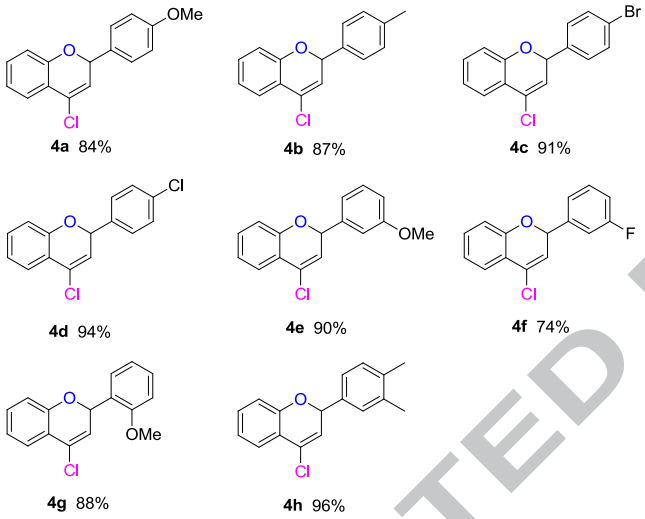
substituted propargylic alcohol 1**p** was employed in this reaction.

Encouraged by the above results, the reactions of secondary propynols were also examined under the optimized reaction conditions (Table 3). Some representative substrates **3a**–**3h** smoothly transformed into the corresponding mono-phenyl substituted 4-chloro-2*H*-chromenes in good to excellent yields (**4a**–**4h**). And the electronic properties of the substituent (R^1) exerted a clear influence on this transformation. Substrates with electron-rich moieties on R^1 showed better results than those with electron-withdrawing ones in this transformation (**3e** vs **3f**).

Table 3 Transformation of secondary propargylic alcohols into 4-chloro-2H-chromenes[a]



3 **4**



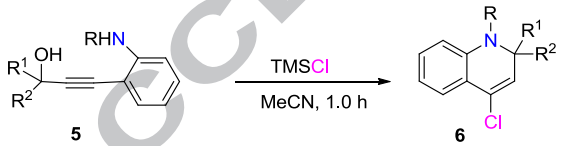
4a 84% **4b** 87% **4c** 91%

4d 94% **4e** 90% **4f** 74%

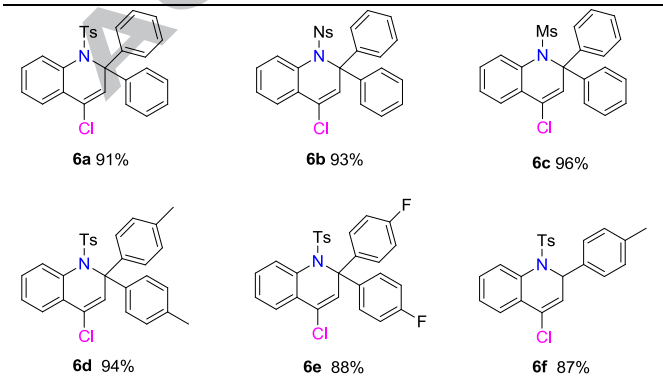
4g 88% **4h** 96%

[a]Unless otherwise noted, all reactions were performed with 0.2 mmol of **3**, 1.5 equiv of TMSCl in CH_3CN (2.0 mL) at 50 °C.

Table 4 Transformation of 2-propynolanilines into 4-chloro-2*H*- quinolines [a]



5 **6**



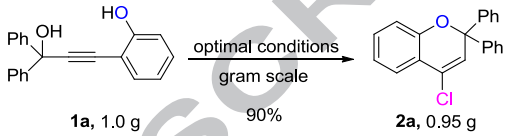
6a 91% **6b** 93% **6c** 96%

6d 94% **6e** 88% **6f** 87%

[a]Unless otherwise noted, all reactions were performed with 0.2 mmol of **5**, 1.5 equiv of TMSCl in CH_3CN (2.0 mL) at 50 °C. Ns = *p*-Nitrobenzenesulfonyl. Ms = Methanesulfonyl.

In addition, some representative 2-propynolanilines **5a**-**5f** were also investigated under the optimal conditions, and the corresponding products 4-chloro-2*H*-quinolines were obtained in good to excellent yields (Table 4). 1,2-Dihydroquinolines are important organic synthetic intermediates for pharmaceuticals, antimicrobials, and biologically active compounds.[13]

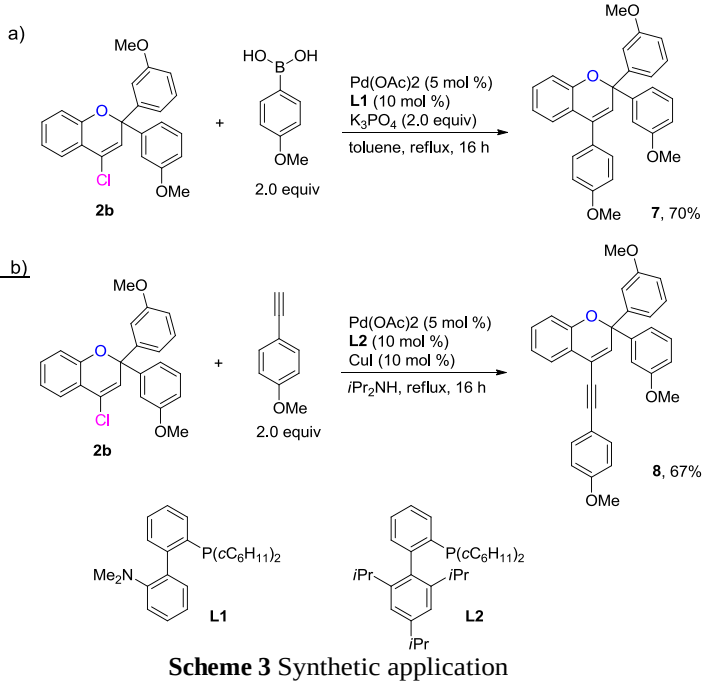
Noticeably, an obvious advantage of our developed reaction system is that this reaction could be scaled-up to gram quantities. When substrate 2-propynolphenol **1a** (1.0 g) was performed under the optimal reaction conditions, the corresponding product **2a** was obtained in a high yield to 90%, which might provide a potential application in organic synthesis industrial production (Scheme 2).



1a, 1.0 g **2a**, 0.95 g

Scheme 2 Scale-up experiment

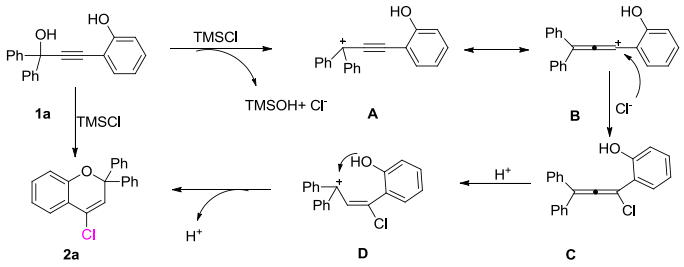
Moreover, the synthetic application of the 4-chloro-2*H*-chromene products was demonstrated by an array of palladium-catalyzed cross-coupling reactions (Scheme 3).[14] Suzuki-Miyaura coupling of **2b** with arylboronic acid proceeded by using **L1** as the ligand to yield **7** in good yields (Scheme 3a). The products **2b** also underwent Sonogashira coupling with 4-methoxyphenylacetylene by using **L2** as the ligand to provide **8** in moderate yields (Scheme 3b).



Scheme 3 Synthetic application

On the basis of the above detailed investigation and previous reports,[15] a plausible mechanism of this transformation is shown in Scheme 4. Firstly, propargylic alcohol **1** is converted to the propargylic cation **A** in the presence of TMSCl, which would then undergo a mesomerism to produce the allenic cation **B**. Then the allenic substitution occurs by the attack of the chloro anion, resulting in intermediate **C**. Intermediate **C** could then be protonated to give intermediate **D**, which is attacked by the

phenolic hydroxy group to produce product 4-chloro-2*H*-chromene **2**.



Scheme 4 Proposed mechanism.

In conclusion, we have developed a novel and highly efficient method for the construction of 4-chloro-2*H*-chromenes and -1,2-Dihydroquinolines via a TMSCl-mediated cyclization reaction of propargyl alcohols. This reaction performed smoothly with a C−Cl bond and a C−O/N bond constructed concurrently under mild conditions in very high yields (up to 97%). It is noted that TMSCl acted as not only a promoter, and also the chloro source in this reaction. In addition, this reaction system could be enlarged to gram scale in an excellent yield to 90% under very mild conditions, which might provide a potential application in the organic synthesis for industrial production.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at XX.

Graphical Abstract

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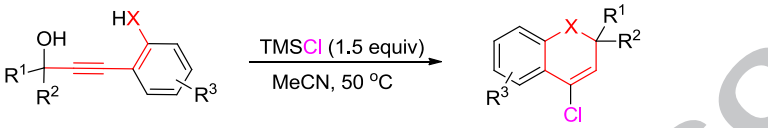

29 examples yield up to 97%
R^1, R^2 = H, aryl ;R^3 = Br, Cl, Me
X= O, NTs, Ns, Ms

or altere

Highlights

- TMSCl-mediated synthesis of 4-chloro-2H-chromenes and 1,2-Dihydroquinolines.
- Both tertiary and secondary propargylic alcohols with diverse functional groups were tolerated.
- TMSCl acts not only as a promoter in this reaction, and also as the chloro source.
- This method can be enlarged to gram scale (yield up to 90%).