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Metal-Free, Brønsted Acid-Mediated Synthesis of Coumarin Derivatives from Phenols and Propiolic Acids

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ABSTRACT

A novel synthesis of coumarin derivatives by Brønsted acid-mediated condensation and intramolecular cyclization of phenols and propiolic acids was reported. This transformation requires the use of TfOH in place of a conventional metal mediator, and it occurs under mild conditions and provides rapid access to coumarin derivatives in good yields.

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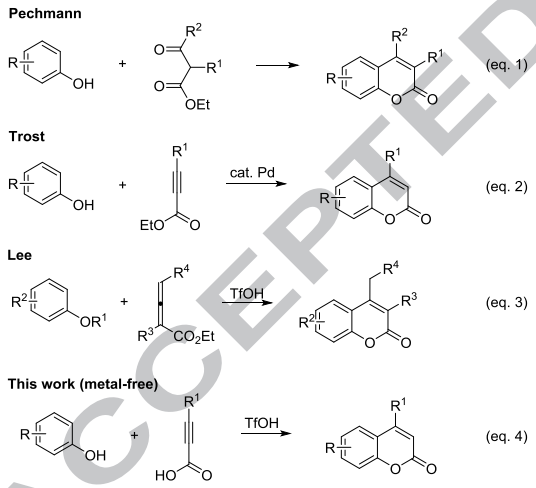
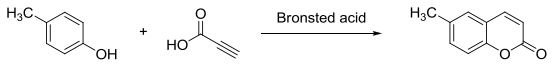
Heterocyclic compounds are extremely significant in numerous natural products and biological active pharmaceuticals.[1] Accordingly, much effort has been devoted to construct skeletons of heterocyclic molecules.[2] In particular, coumarins are the basic structural units present in various natural products with a wide range of biological activities.[3] Recently, they have been used as effective organic electroluminescent materials.[4] Because of their many applications, numerous synthetic methods such as Perkin, Pechmann, Knoevenagel, Reformatsky, and Wittig reactions have been developed for obtaining different coumarin derivatives.[5] Among these, the most commonly used reaction is the Pechmann reaction, which involves condensation of phenols and β-ketoesters (Scheme 1, eq. 1).[6] However, Pechmann reaction has certain drawbacks as well; e.g., requirement of the excessive amount of acid and, in certain instances, generation of by-products such as chromone. Therefore, more efficient transition-metal-mediated methods for the preparation of coumarins were developed.[7] However, most of these reactions require an iodoarene precursor such as iodophenol; they also generate halide waste because of the activation of the C–X bond by the transition metal. Trost et al. developed an atom-economic synthesis of coumarins *via* palladium-catalyzed C–H bond functionalization of phenols with propiolic acid, leading to C–C bond formation (eq. 2).[8] In another report, coumarins were prepared by metal-promoted alkyne activation.[9] Recently, Lee and co-workers reported a metal-free method of coumarins *via* Brønsted acid-mediated condensation of allenes (eq. 3).[10] In this work, we describe metal-free synthesis of coumarin derivatives by Brønsted acid-mediated condensation of phenols with propiolic acids (eq. 5).



Scheme 1.

In order to determine the optimal conditions, the reaction wasperformed in chlorobenzene at 80 °C in the presence of a Brønsted acid. The use of 2 equiv of HCl, acetic acid, or TFA was not effective (Table 1, entries 1-3), whereas addition of TsOH or MsOH produced small amounts of the desired product (Table 1, entries 4 and 5). Conducting the reaction at 80 °C for 3 h in the presence of 2 equiv of TfOH afforded product **3a** in 75% ^{1}H NMR yield (Table 1, entry 6). On increasing the reaction temperature to 100 °C, the desired product was generated in 84% ^{1}H NMR yield and 76% isolated yield (Table 1, entry 7). When the amount of TfOH was reduced to 1 equiv, the reaction yield decreased dramatically (Table 1, entry 8). When different solvents were screened, keeping TfOH as the activating agent, chlorobenzene was found to be optimal (Table 1, entries 10-12).



1a **2a** **3a**

Table 1. Optimization of reaction conditionsa

Entry	Acid(equiv.)	Solvent	Temp. (°C)	Time (h)	Yield [b] (%)
1	HCl (2.0)	Chlorobenzene	80	6	0
2	CH_3CO_2H (2.0)	Chlorobenzene	80	6	0
3	CF_3CO_2H (2.0)	Chlorobenzene	80	6	0
4	TsOH (2.0)	Chlorobenzene	80	6	4
5	MsOH (2.0)	Chlorobenzene	80	6	13
6	TfOH (2.0)	Chlorobenzene	80	3	75
7	**TfOH (2.0)**	**Chlorobenzene**	**100**	**1**	**84(76)[c]**
8	TfOH (1.0)	Chlorobenzene	80	3	11
9	TfOH (2.0)	DCE	80	3	37
10	TfOH (2.0)	CH_3CN	80	3	0
11	TfOH (2.0)	Toluene	80	3	38
12	TfOH (2.0)	THF	80	3	0

[a] Reaction Conditions: *p*-cresol (**1a**, 1.0 mmol), propiolic acid (**2a**, 0.5 mmol), solvent (3.0 mL), under a nitrogen atmosphere.

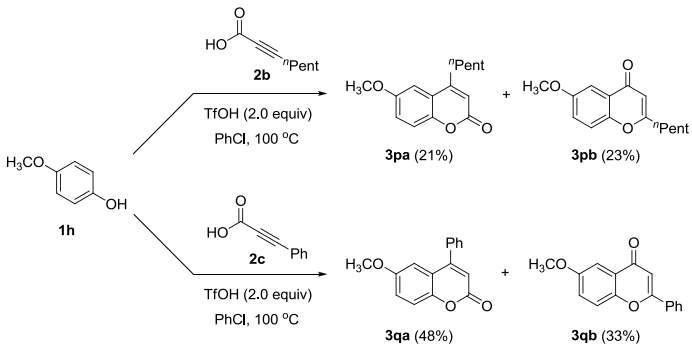
[b] Yields are based on **2a**, determined by crude ^{1}H NMR using dibromomethane as the internal standard.

[c] Isolated yield.

In order to evaluate the applicability of this transformation, we investigated the reaction of propiolic acid **2a** with phenols bearing various functional groups. Unsubstituted phenol **1a** afforded coumarin derivative **3a** in 76% yield after 2 h (Table 2, entry 1). Introduction of a methyl substituent at the ortho position resulted in 74% yield of the corresponding derivative **3b** (entry 2). When the methyl substituent was introduced at the meta position, 7-methylcoumarin **3ca** and 5-methylcoumarin **3cb** were produced in 90% and 10% ^{1}H NMR yields, respectively, and **3ca** was isolated in 75% yield (entry 3). The reaction of *p*-methylphenol **1d** and 3,5-dimethylphenol **1e** also proceeded in good to excellent yields to form the corresponding derivatives (entries 4 and 5). Introduction of a phenyl group at the para position produced derivative **3f** in 54% yield (entry 6). When the substituent is a methoxy group, the yields diminished, and 7-methoxycoumarin **3ga** was found to be the major product in the reaction of *m*-methoxyphenol (entries 7 and 8). Introduction of an electron-withdrawing group such as chloride at the ortho or para position resulted in low yields (13% and 14%, respectively; entries 9 and 11). However, when the chloride was introduced in the *meta*-position, the reactivity increased, and, regioselectively, 7-chlorocoumarin (**3j**) was formed (entry 10). When resorcinol (**1l**) was used, 7-hydroxycoumarin (**3la**) and 5-hydroxycoumarin (**3lb**) were obtained in 81% and 5% isolated yields, respectively (entry 12). The reactions of 1-naphthol (**1m**) and 2-naphthol (**1n**) afforded 2*H*-benzo[*h*]chromen-2-one (**3m**) and 3*H*-benzo[*f*]chromen-3-one (**3n**), respectively, in good yields (entries 14 and 15). Moreover, the reaction of 5,6,7,8-tetrahydronaphthalen-1-ol (**1o**) afforded coumarin derivative **3o** in good yield.

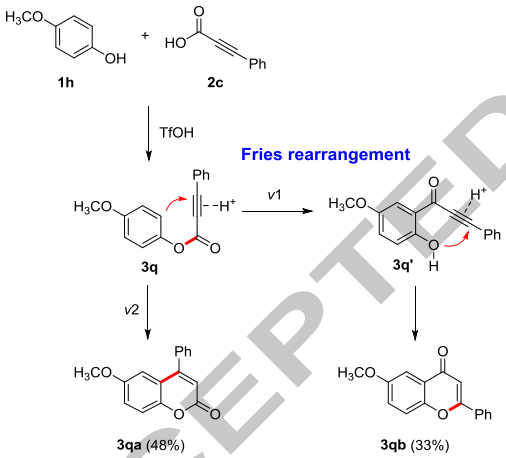
Next, the reactivity of various propiolic acids was investigated by testing compounds carrying an *n*-pentyl or a phenyl substituent at the terminal alkyne carbon. When the *n*-pentyl substituent was introduced, the expected coumarin (**3pa**) and

chromone (**3pb**) produced by Fries rearrangement were obtained in 21% and 23% isolated yields, respectively. The reaction of 3-phenylpropiolic acid (**2c**) with 4-methoxyphenol (**1h**) afforded coumarin **3qa** and chromone **3qb** in 48% and 33% yields, respectively (Scheme 2).



Scheme 2.

In our proposed mechanism, TfOH-mediated condensation of the two substrates yields intermediate ester **3q** that can undergo an acid-activated intramolecular hydroarylation of the alkyne moiety generating coumarin **3qa**. Chromone **3qb** is obtained by the intramolecular cyclization of ketone intermediate **3q'** produced from the acid-induced Fries rearrangement of intermediate ester **3q** (Scheme 3).



Scheme 3.

In conclusion, this study presents the development of a novel synthetic method for coumarin derivatives by metal-free, Brønsted acid (TfOH)-mediated condensation of phenols with propiolic acids, followed by intramolecular hydroarylation. This method represents an efficient, rapid, and mild protocol for the preparation of various coumarin derivatives, which are important precursors in the synthesis of bioactive compounds.

Acknowledgments

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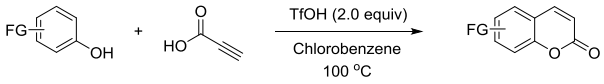
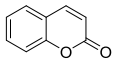
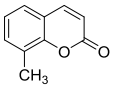
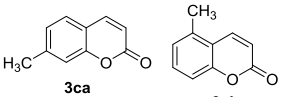
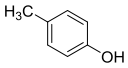
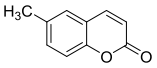
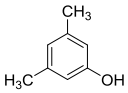
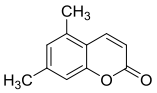
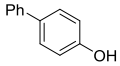
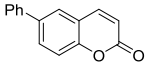
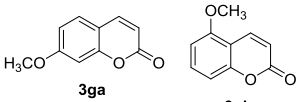
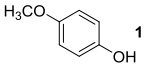
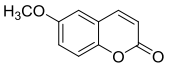
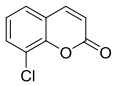
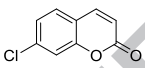
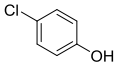
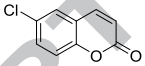
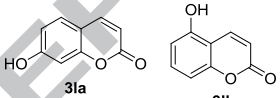
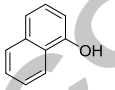
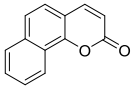
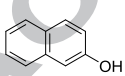
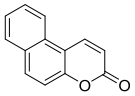
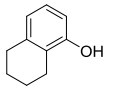
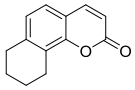
Table 2. TfOH-Mediated Synthesis of Coumarin Derivatives[a]



1 **2a** **3**

Entry	Substrate	Product	Time (h)	Yields[b] (%)
1	 **1a**	 **3a**	1	76
2	 **1b**	 **3b**	1	74
3	 **1c**	 **3ca** **3cb**	1	(90 : 10)[c] 75[d]
4	 **1d**	 **3d**	1	76
5	 **1e**	 **3e**	2	95
6	 **1f**	 **3f**	3	54
7	 **1g**	 **3ga** **3gb**	1	(57 : 11)[c] 47[d]
8	 **1h**	 **3h**	6	36
9	 **1i**	 **3i**	1	13
10	 **1j**	 **3j**	1	69
11	 **1k**	 **3k**	1	14
12	 **1l**	 **3la** **3lb**	6	(90 : 8)[c] 81 : 5
13	 **1m**	 **3m**	1	81
14	 **1n**	 **3n**	1	80
15	 **1o**	 **3o**	2	85

[a] Reaction Conditions: phenol (1.0 mmol), propiolic acid (**2a**, 0.5 mmol), solvent (3.0 mL), under a nitrogen atmosphere.

[b] Isolated yield.

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Graphical Abstract

Metal-Free, Brønsted Acid-Mediated Synthesis of Coumarin Derivatives from Phenols and Propiolic acids

Hyuck Choi, Jaehyun Kim, and Kooyeon Lee

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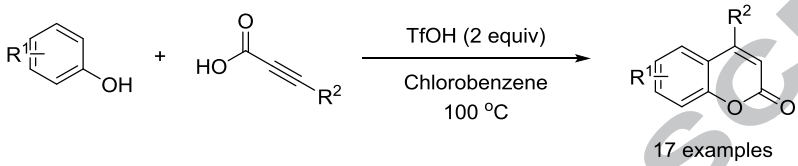

Research highlights

- ►A novel synthesis of coumarins was developed which exploits metal-free condition.
- ►The method was used to produce a range of coumarins in excellent yields.
- ►This transformation requires the use of TfOH in place of a conventional metal mediator.
- ►The mechanism explains Brønsted acid-mediated condensation and intramolecular cyclization.