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Efficient Assembly of Chromone Skeleton from 2,3-Allenoic Acids and Benzynes

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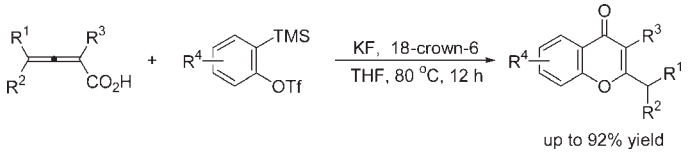
ABSTRACT



Chromone derivatives were synthesized from 2,3-allenoic acids and benzynes in moderate to excellent yields under mild conditions. Instead of the cyclic conjugate addition of the intermediate A formed by the nucleophilic addition of allenoic acid with benzyne, this intermediate undergoes 1,2-addition with the carbonyl group, which was followed by the ring opening, conjugate addition, and protonolysis to afford chromone derivatives. This protocol allows the diversity due to the substituent-loading capability of 2,3-allenoic acids as well as benzynes.

Chromones and their derivatives are a class of compounds existing widely in nature, and much attention has been paid to this class of compounds due to their biological and pharmacological activities.[1] They could serve as antibacterial, antifungal, anticancer, antioxidant, and anti-HIV agents[2] and have been considered as privileged structures in drug development.[3] Although synthetic approaches to this family of compounds have been extensively investigated in the past decades,[4] general protocols for the synthesis of polysubstituted chromones with diversified functionality under mild conditions are still highly desirable for further study in this area. Herein we wish to report an efficient assembly of a chromone sekleton from 2, 3-allenoic acids and benzynes under mild conditions in moderate to excellent yields.

In our recent reports, the nucleophilic addition reactions of organometallic reagents with 2,3-allenoates afforded diversified compounds such as β,γ-unsaturated alkenoates,[5a−c] 5-benzylidenecyclohex-2-enones,[5d] allenols,[5e] naphthols,[5f] and cyclobutenones[5g] depending on the nature of substrates, nucleophiles, and conditions applied, showing the diversified reactivities of 2,3-allenoates toward nucleophiles. On the other hand, benzynes have been proven to be very useful in the construction of benzo-fused rings since the formal insertion of benzynes into carbon−carbon, carbon−heteroatom, and heteroatom−hydrogen bonds by accepting a nucleophilic attack has been extensively studied in recent years.[6] These results encouraged us to investigate the reaction of allenoic acids with benzynes, since the intramolecular Michael addition of allenoate-type intermediate **A** generated from 2,3-allenoic acids with benzynes would be a convenient way to synthesize diversified coumarin products due to the substituent-loading capability of 2, 3-allenoic acids as well as benzynes (Scheme 1). On the

(1) (a) Ellis, G. P., Ed. *Chromenes, chromanones, and chromones*; Wiley: New York, 1977. (b) Saengchantara, S. T.; Wallace, T. W. *Nat. Prod. Rep.* **1986**, 465. (c) Houghton, P. J. *Stud. Nat. Prod. Chem.* **2000**, *21*, 123.

(2) For reviews, see: (a) Edwards, A. M.; Howell, J. B. L. *Clin. Exp. Allergy* **2000**, *30*, 756. (b) Havsteen, B. H. *Pharmacol. Ther.* **2002**, *96*, 67. (c) Kim, H. P.; Son, K. H.; Chang, H. W.; Kang, S. S. *J. Pharmacol. Sci.* **2004**, *96*, 229. (d) Kosmider, B.; Osiecka, R. *Drug Dev. Res.* **2004**, *63*, 200. (e) Grazul, M.; Budzisz, E. *Coord. Chem. Rev.* **2009**, *253*, 2588.

(3) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(4) Li, N.-G.; Shi, Z.-H.; Tang, Y.-P.; Ma, H.-Y.; Yang, J.-P.; Li, B.-Q.; Wang, Z.-J.; Song, S.-L.; Duan, J.-A. *J. Heterocycl. Chem.* **2010**, *47*, 785.

(5) (a) Lu, Z.; Chai, G.; Ma, S. *J. Am. Chem. Soc.* **2007**, *129*, 14546. (b) Lu, Z.; Chai, G.; Zhang, X.; Ma, S. *Org. Lett.* **2008**, *10*, 3517. (c) Chai, G.; Lu, Z.; Fu, C.; Ma, S. *Adv. Synth. Catal.* **2009**, *351*, 1946. (d) Lu, Z.; Chai, G.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6045. (e) Chen, B.; Lu, Z.; Chai, G.; Fu, C.; Ma, S. *J. Org. Chem.* **2008**, *73*, 9486. (f) Chai, G.; Lu, Z.; Fu, C.; Ma, S. *Chem.—Eur. J.* **2009**, *15*, 11083. (g) Chai, G.; Wu, S.; Fu, C.; Ma, S. *J. Am. Chem. Soc.* **2011**, *133*, 3740.

(6) For reviews, see: (a) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215. (b) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579. (c) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502.

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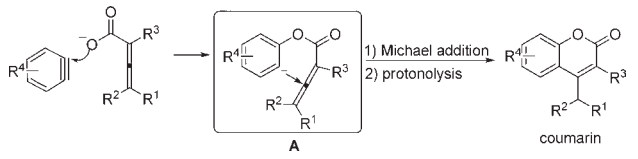
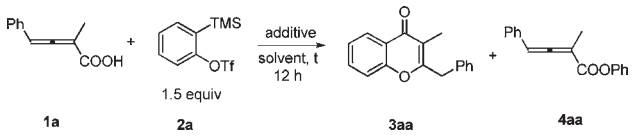
Scheme 1



other hand, it should be noted that Larock et al. reported the reaction of alkynoic (or alkenoic) acids with arynes.[7]

Table 1. Optimization of the Reaction Conditions[a]



				yield[b] (%)		
entry	solvent	additive (equiv)	temp (°C)	**3aa**	**4aa**	**1a**
1	CH_3CN	CsF (4)	rt	17	33	0
2	THF	KF/18-crown-6 (2)	rt	82	9	0
3	THF	KF/18-crown-6 (2)	40	84	5	0
4	THF	KF/18-crown-6 (2)	60	88	0	0
5	THF	KF/18-crown-6 (2)	80	95	0	0
6[c]	THF	KF (2)	80	0	0	51
7[c]	THF	KF/18-crown-6 (1.5)	80	88	0	0
8[d,e]	THF	KF/18-crown-6 (2)	80	88	0	0
9	dioxane	KF/18-crown-6 (2)	80	37	10	0
10	CH_3CN	KF/18-crown-6 (2)	80	15	0	0
11	toluene	KF/18-crown-6 (2)	80	76	0	0
12	[f]	KF/18-crown-6 (2)	80	76	0	0
13	THF	CsF (2)	80	49	11	14
14	THF	TBAT (2)	80	51	0	0
15	THF	TBAF (2)	80	5	0	7

[a] The reaction was conducted with 0.2 mmol of 2,3-allenoic acid, 1.5 equiv of benzyne precusor, and additives in 2 mL of solvent. [b] Determined by ^1H NMR of crude product using dibromomethane as internal standard. [c] The reaction time was 18 h. [d] The reaction time was 17 h. [e] 1.2 equiv of precursor **2a** were used. [f] 2-Methyltetrahydrofuran was used as solvent.

Our initial effort focused on the use of 2-(trimethylsilyl)-phenyl triflate **2a** as a benzyne precusor and 2-methyl-4-phenyl-2,3-butadienoic acid **1a** as a reaction partner in CH_3CN in the presence of CsF. However, instead of the expected coumarin product, the 2,3-allenoic acid phenyl ester **4aa** was formed as the major product in 33% yield along with an unexpected new product **3aa** in 17% yield (entry 1, Table 1), which was confirmed to have a chromone skeleton instead of coumarin through careful NMR spectroscopy, MS, and X-ray diffraction analysis (Figure 1).[8]

(7) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117.

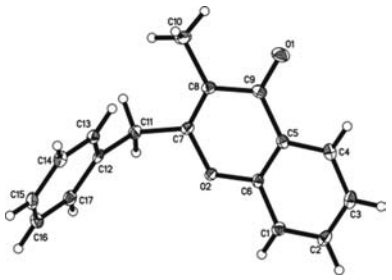
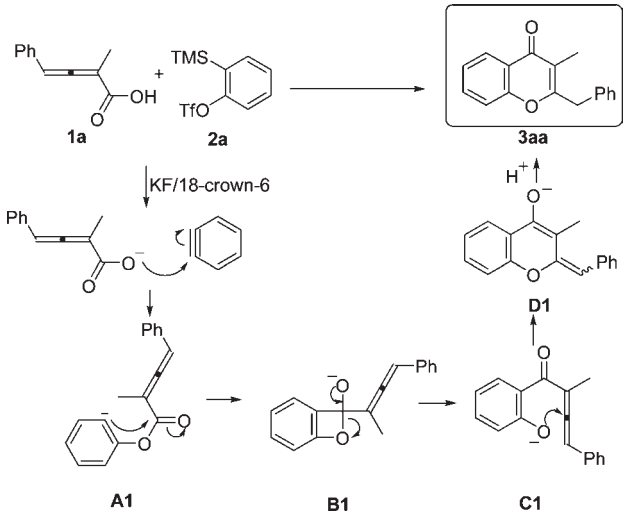


Figure 1. ORTEP representation of **3aa**.

The formation of **3aa** could be explained as follows (Scheme 2): nucleophilic addition of allenoic acid **1a** to the benzyne would form aryl anion intermediate **A1**. Instead of the intramolecular Michael addition to form coumarin shown in Scheme 1, intermediate **A1** undergoes rearrangement to form *o*-(1-oxo-2,3-allenyl)phenoxide **C1** via cyclic 1,2-addition with the carbonyl group forming **B1** and the subsequent four-membered ring-opening process.[6,7] Intramolecular oxa-Michael addition of intermediate **C1** affords bicyclic intermediate **D1**, which upon subsequent hydrolysis would afford chromone **3aa** as the final product.

Scheme 2



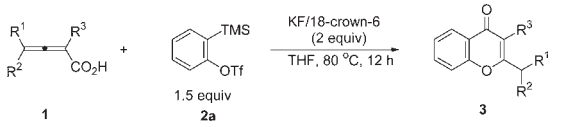
After some trials and errors, we were pleased to find that, in the presence of KF and 18-crown-6,[9] the reaction of **1a** with **2a** in THF at room temperature could afford **3aa** in

(8) Crystal data for compound **3aa**: $C_{17}H_{14}O_2$, MW = 250.28, Monoclinic, space group *C*2/*c*, Final *R* indices [$I > 2\sigma(I)$], *R*1 = 0.0372, *wR*2 = 0.0906, *R* indices (all data) *R*1 = 0.0462, *wR*2 = 0.0961, *a* = 15.3311(5) Å, *b* = 8.9614(2) Å, *c* = 18.9054(6) Å, α = 90°, *β* = 103.569(4)°, *γ* = 90°, *V* = 2524.88(14) Å^3, *T* = 293(2) K, *Z* = 8, reflections collected/unique: 5765/2315 (R_{int} = 0.0181), number of observations [$> 2\sigma(I)$] 1925, parameters: 173. CCDC 833186.

(9) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

82% yield (entry 2, Table 1). Further screening of the temperature effect revealed that the formation of byproduct **4a** could be suppressed at higher temperature and the yield of **3aa** could be further improved to 95% when the reaction was conducted at 80 °C in a closed vial (entries 3–5, Table 1). In the absence of 18-crown-6, the starting material **1a** was recovered (entry 6, Table 1). Reducing the amounts of either KF/18-crown-6 or benzyne precursor **2a** led to lower yields (entries 7 and 8). We tried to use other solvents with higher boiling points such as 1,4-dioxane, CH_3CN, toluene, and 2-methyltetrahydrofuran to avoid the use of a pressure vessel; however, lower yields were observed (entries 9–12, Table 1). The use of another F^- source in THF also failed to give better results (entries 13–15, Table 1). Therefore, we defined the reaction of 2,3-allenoic acid with 1.5 equiv of benzyne precursor in the presence of 2 equiv of KF/18-crown-6 in THF at 80 °C as the standard reaction conditions (entry 5, Table 1).

Table 2. Reaction of Different Allenoic Acids with Benzyne Precursor **2a**[a]

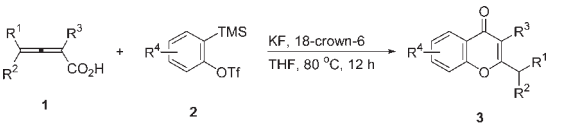


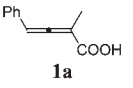
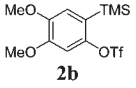
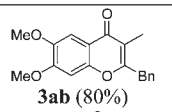
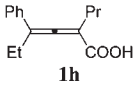
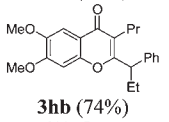
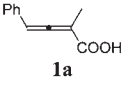
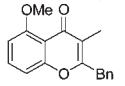
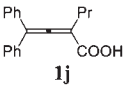
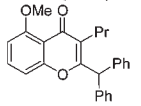
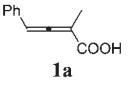
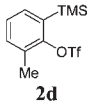
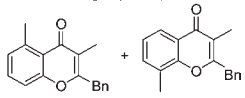
	1			
entry	R^1	R^2	R^3	yield of **3** (%)[b]
1	Ph	H	Me (**1a**)	**3aa** (88)
2	*p*-MeC_6H_4	H	Me (**1b**)	**3ba** (90)
3	*p*-BrC_6H_4	H	Me (**1c**)	**3ca** (76)
4	*p*-ClC_6H_4	H	Me (**1d**)	**3da** (78)
5	Ph	H	Pr (**1e**)	**3ea** (92)
6	*n*-C_7H_{15}	H	Pr (**1f**)	**3fa** (75)
7	Ph	Et	Me (**1g**)	**3ga** (89)
8	Ph	Et	Pr (**1h**)	**3ha** (89)
9	Ph	Ph	Me (**1i**)	**3ia** (90)
10	Ph	Ph	Pr (**1j**)	**3ja** (92)
11	Et	Et	Ph (**1k**)	**3ka** (70)
12	Me	Me	Me (**1l**)	**3la** (75)
13	*n*-C_8H_{17}	H	H (**1m**)	**3ma** (60)
14	H	H	Bn (**1n**)	**3na** (80)
15[c]	Ph	H	Me (**1a**)	**3aa** (91)

[a] The reaction conditions: a mixture of 0.4 mmol of allenoic acid, 1.5 equiv of benzyne precursor, and 2.0 equiv of KF/18-crown-6 in 4 mL of THF was heated in a sealed pressure vessel at 80 °C for 12 h. [b] Isolated yield. [c] The reaction was conducted with a 6 mmol (1.0480 g) scale of **1a**.

With the optimal conditions in hand, we proceeded to examine the scope of this transformation (Tables 2 and 3). Overall, the method works smoothly and a variety of mono-, di-, and fully substituted 2,3-allenoic acids with benzyne precursor **2a** afforded the corresponding chromones **3aa**–**3na** in moderate to excellent yields (entries 1–15, Table 2). The substituent on the allenoic acids could be aryl, alkyl, and H. It should be noted that C–Br or C–Cl bonds were well tolerated with **3ca** and **3da** being formed in

Table 3. Reaction of Substituted Benzyne Precursors[a]



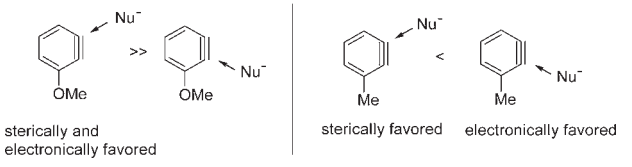
entry	allenoic acid **1**	benzyne precursor **2**	chromone **3**[b]
1	 **1a**	 **2b**	 **3ab** (80%)
2[c]	 **1h**	**2b**	 **3hb** (74%)
3	 **1a**	 **2c**	 **3ac** (85%)
4	 **1j**	**2c**	 **3jc** (90%)
5	 **1a**	 **2d**	 **3ad** (31%) + **3ad'** (52%) 1·1.7

[a] The reaction conditions: 0.4 mmol of allenoic acid, 1.5 equiv of benzyne precursor, and 2.0 equiv of KF/18-crown-6 in 4 mL of THF were heated in a sealed pressure vessel at 80 °C for 12 h. [b] Isolated yield. [c] 2,3-Allenoic acid aryl ester **4hb** was also isolated in a yield of 9%.

76% and 78% yields, respectively (entries 3 and 4, Table 2). The reaction can be easily conducted on a scale of 6 mmol of **1a** (1.0480 g) in a slightly higher yield (entry 15, Table 2).

In addition to simple benzyne precursor **2a**, disubstituted benzyne precursor **2b** may also be used to afford chromones **3ab** and **3hb** in good yields (entries 1 and 2, Table 3). It should be noted that when 3-MeO-substituted benzyne precursor **2c** was utilized, single regioisomers of corresponding chromones **3ac** and **3jc** were formed exclusively in excellent yields (entries 3 and 4, Table 3). The regioselectivity observed here can be rationalized in terms of steric and electronic effects, both of which favor nucleophilic attack at the *meta* position of the methoxy group (Scheme 3).[6,7] However, the use of 2-Me-substituted

Scheme 3



benzyne precursor **2d** led to two separable regioisomers in a ratio of 1:1.7 (entry 5, Table 3), in which nucleophilic attack at the *ortho* position of the methyl group dominates, showing that the reaction is controlled electronically rather than sterically (Scheme 3).

In summary, we have developed an efficient and general method to synthesize polysubstituted chromones with moderate to excellent yields. Because of the mild conditions utilized and the broad scope, this protocol will be of high interest in organic synthesis and medicinal chemistry. Further studies in this area are being conducted in our laboratory.

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Supporting Information Available. General procedure and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.