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Unified Approach to (Thio)chromenones via One-Pot Friedel–Crafts Acylation/Cyclization: Distinctive Mechanistic Pathways of β-Chlorovinyl Ketones

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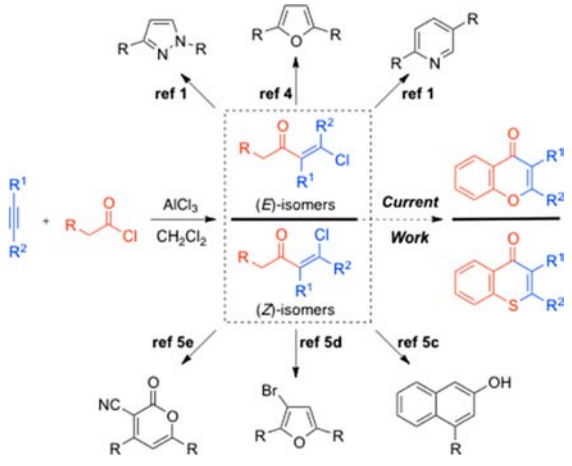
Supporting Information

ABSTRACT: A facile synthetic method to chromenones and thiochromenones has been developed using a one-pot Friedel–Crafts acylation of alkynes with suitably substituted benzoyl chlorides. This unified approach to (thio)-chromenones is readily applicable to aryl- and alkylalkynes where the stereochemically well-defined β-chlorovinyl ketone intermediates undergo distinctively different cyclization pathways. The ready availability of both starting materials, alkynes and benzoyl chlorides, coupled with the experimental simplicity makes the current synthetic method to (thio)-chromenones fast, efficient, and practical.

β-Chlorovinyl ketones serve as fertile ground for the development of heterocycle synthesis.[1] While the addition of acid chloride to alkyne generally provides β-chlorovinyl ketones,[2] the stereoselective formation of (*E*)-β-chlorovinyl ketones still relies on the Friedel–Crafts acylation of alkynes under the catalysis of $AlCl_3$ (Scheme 1).[3]

Scheme 1. Synthetic Utility of β-Chlorovinyl Ketones



In particular, we have recently shown that (*E*)-β-chlorovinyl ketones undergo soft α-vinyl enolization more than 10–50 times faster than (*Z*)-β-chlorovinyl ketones in the presence of Et_3N.[4] Such discrepancy in the rate of enolization could be useful in differentiating the mechanistic pathways of stereoisomeric β-chlorovinyl ketones. With the aim of expanding the synthetic versatility of β-chlorovinyl ketones,[5] we devised a new synthetic strategy to chromenone derivatives including flavones and thiochromenones.

Chromenones are the key constituent of numerous natural products with various biological activities.[6] The traditional synthetic approaches include the intramolecular condensation of *o*-hydroxy 1,3-diones[7] and the intramolecular conjugate addition of *o*-hydroxy chalcones under oxidation conditions.[8] While there have been intensive synthetic efforts to develop the efficient synthesis of chromenone derivatives, most of the methods typically involves multistep synthesis of the precursors to chromenones.[9] For example, the intramolecular iodocyclization of alkynones,[10] the intermolecular benzyne addition to allenoic acids,[11] and the Wittig reactions require the synthesis of elaborated starting materials.[12] The recent development of C–H activation of chromenone also provides a ready access to chromone derivatives; however, the methodology is limited to the introduction of flavones (R^2 = Ar).[13] Currently, the Pd-catalyzed cyclocarbonylation of *o*-iodophenols with terminal alkynes stands out among the synthetic approaches to chromenones in terms of ready access to starting materials and operational simplicity.[14] As a congener of chromenones, thiochromenones also display interesting biological activities.[15] Although a few direct synthetic methods to thiochromenones exist using the Sonogashira coupling of *o*-haloaroyl chloride with alkynes,[16] the Ni-catalyzed reactions of thioisatins (or thiophthalic anhydrides) and alkynes,[17] and the Pd-catalyzed carbonylative cycloaddition of 1-fluoro-2-iodobenzene with alkynes,[18] the introduction of alkyl substituents at the 2-

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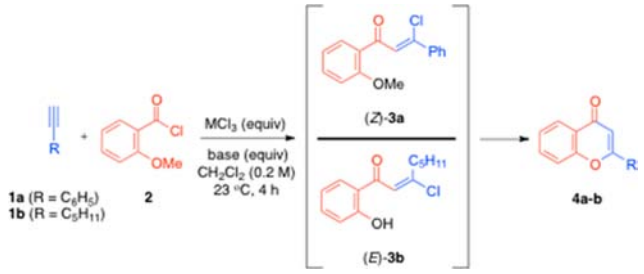
position remains a challenging class of thiochromenone derivatives.

Because of the lack of direct and unified synthetic approaches to both chromenone and thiochromenone derivatives with a diverse substitution pattern at 2-position, we envisioned the use of β-chlorovinyl ketones as a versatile precursor to (thio)-chromenones. Herein, we report a one-pot synthetic approach to (thio)chromenones using the stereospecific Friedel–Crafts acylation of alkynes followed by an intramolecular cyclization of in situ generated β-chlorovinyl ketones. The current approach to (thio)chromenones signifies the conformational preferences of stereoisomeric β-chlorovinyl ketones, the key reaction factor for the efficient intramolecular cyclization to (thio)chromenone derivatives.

To investigate the synthetic route to chromenones via β-chlorovinyl ketones, we first examined the stereochemical outcome of Friedel–Crafts acylation of alkynes with 2-methoxybenzoyl chloride (Table 1). When phenylacetylene

Table 1. Optimization of the One-Pot Synthesis of Chromenones[a]



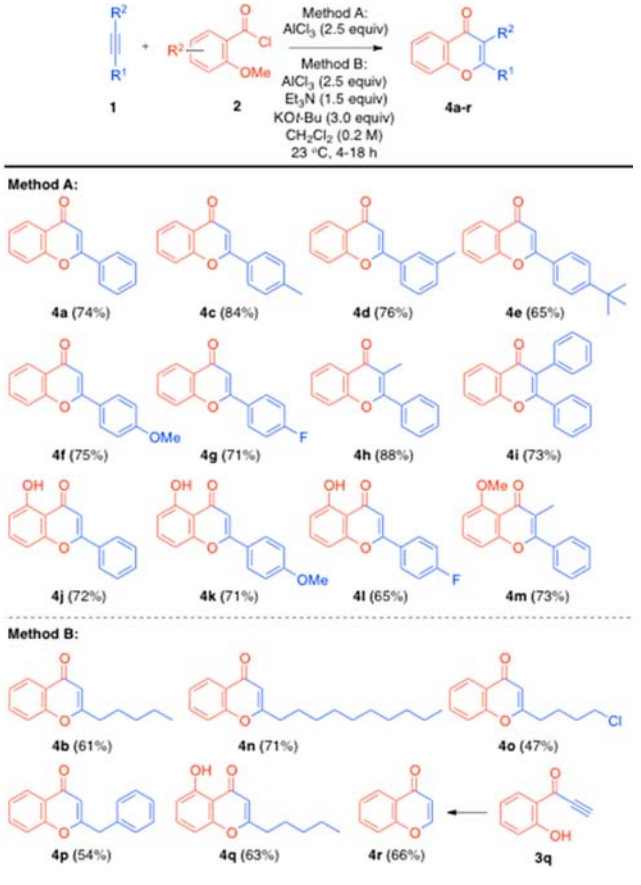
entry	1	MCl_3 (equiv)	base (equiv)	conv[b] (%)
1	**1a**	$AlCl_3$ (1.1)		48[c]
2	**1a**	$AlCl_3$ (1.5)		50[d]
3	**1a**	$AlCl_3$ (2.0)		72[e]
4	**1a**	$AlCl_3$ (2.0)		78[f]
5	**1a**	$AlCl_3$ (2.5)		100 (74)
6	**1a**	$AlCl_3$ (3.0)		100 (52)
7	**1a**	$FeCl_3$ (3.0)		0[g]
8	**1b**	$AlCl_3$ (2.5)		0[h]
9	**1b**	$AlCl_3$ (4.0)		0[h]
10	**1b**	$AlCl_3$ (2.5)	K_2CO_3 (2.0)	17
11	**1b**	$AlCl_3$ (2.5)	NaOH (2.0)	20
12	**1b**	$AlCl_3$ (2.5)	KOH (2.0)	27
13	**1b**	$AlCl_3$ (2.5)	KO-*t*-Bu (2.0)	35
14	**1b**	$AlCl_3$ (2.5)	KO-*t*-Bu (10)	46
15	**1b**	$AlCl_3$ (2.5)	Et_3N (1.5)	10[i]
16[j]	**1b**	$AlCl_3$ (2.5)	(1.5) + (2.0)	78
17[j]	**1b**	$AlCl_3$ (2.5)	(1.5) + (3.0)	100 (61)

[a]Reaction conditions: **1** (0.5 mmol) and **2** (0.5 mmol) in CH_2Cl_2 (2.5 mL) under argon atmosphere. [b]Conversion by ^1H NMR and, in parentheses, isolated yield of chromenones **4** after column chromatography. [c]**3a** (52%). [d]**3a** (50%). [e]**3a** (28%). [f]Reaction for 7 h; **3a** (22%). [g]**1a** (100%). [h]**3b** (100%). [i]**3b** (90%). [j]Use of Et_3N and KO-*t*-Bu.

1a in the presence of 1.1 equiv of $AlCl_3$ was used, the formation of chromenone **4a** was observed in 48% yield (entry 1). The isolation of (*Z*)-**3a** indicated the intermediacy of (*Z*)-**3a** to chromenone **4a** by a concomitant demethylation of the methoxy group in (*Z*)-**3a** by $AlCl_3$. Our subsequent control reaction using (*Z*)-**3a** as the starting material to chromenone **4a** confirmed the role of $AlCl_3$ in the demethylation followed by an intramolecular conjugate addition/elimination sequence. Next, we sought the optimal amount of $AlCl_3$ (entries 2–6) and found that the use of 2.5 equiv of $AlCl_3$ cleanly led to the formation of chromenone **4a** in an isolated yield of 74%. Although we also screened other Lewis acids instead of $AlCl_3$ (entry 7), no reaction was observed. The stereochemical outcome of the Friedel–Crafts acylation of 1-heptyne **1b** was opposite to that of phenylacetylene **1a**. Thus, upon using **1b** under otherwise identical reaction conditions the stereoselective formation of demethylated (*E*)-**3b** was observed (entry 8). Further addition of $AlCl_3$ did not alter the outcome of the reaction, and (*E*)-**3b** was reisolated as a sole product (entry 9). Next, we studied the role of bases upon quenching the reaction (entries 10–14). While the formation of the desired chromenone **4b** was observed upon using an excess amount of bases, especially KO-*t*-Bu, the reactions were accompanied by multiple side products,[19] making them synthetically unviable (entry 14). Gratifyingly, we found that the use of 1.5 equiv of Et_3N could initiate the soft α-vinyl enolization of (*E*)-**3b**, leading to the rapid formation of chromenone **4b** (entry 15).[20] Finally, the combination of 1.5 equiv of Et_3N and 3.0 equiv of KO-*t*-Bu smoothly transformed (*E*)-**3b** to chromenone **4b** in one pot with an isolated yield of 61%.

The optimized reaction conditions for aryl- and alkylalkynes were further evaluated using various alkynes and benzoyl chlorides (Scheme 2). As for the arylalkynes using 2.5 equiv of $AlCl_3$ (method A), the normal H_2O-quenching procedure for the Freidel–Crafts acylation reaction provided chromenones **4c–g** in 65–88% yields. The reaction could be extended to

Scheme 2. Scope of One-Pot Synthesis of Chromenones



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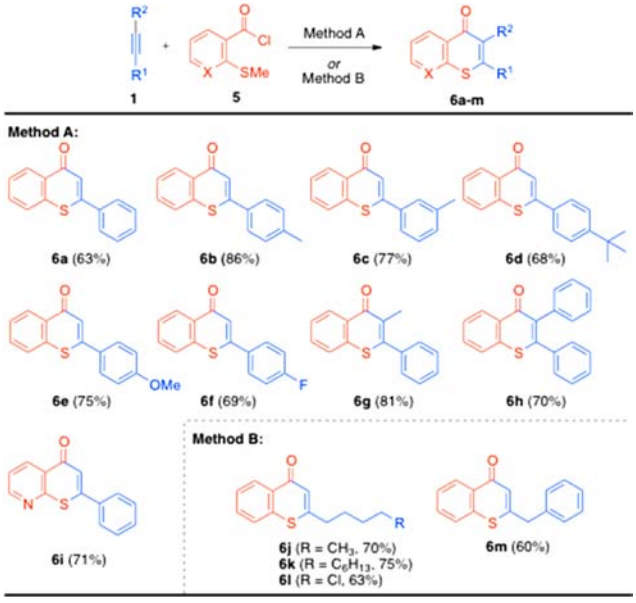
disubstituted alkynes as well as substituted benzoyl chlorides to give diversely substituted chromenones **4h**–**l**. Interestingly, the use of dimethoxy-substituted benzoyl chloride retained one methoxy group upon use of disubstituted alkyne to give chromenones **4m**. The use of alkylalkynes again required quenching treatment with 1.5 equiv of Et_3N and 3.0 equiv of KO-*t*-Bu (method B) and provided the desired chromenones **4n**–**q** in 47–71% yields. The Friedel–Crafts acylation of (trimethylsilyl)acetylene led to the formation of alkynone **3q** after a concomitant demethylation and desilylation by $AlCl_3$. The alkynone **3q** only underwent cyclization upon treatment under basic conditions, including method B.[21]

Motivated by the facile synthetic routes to chromenones from stereodefined *β*-chlorovinyl ketones, we employed 2-(methylthio)benzoyl chloride **5** for the one-pot synthesis of thiochromenones (Scheme 3). The reactions were readily

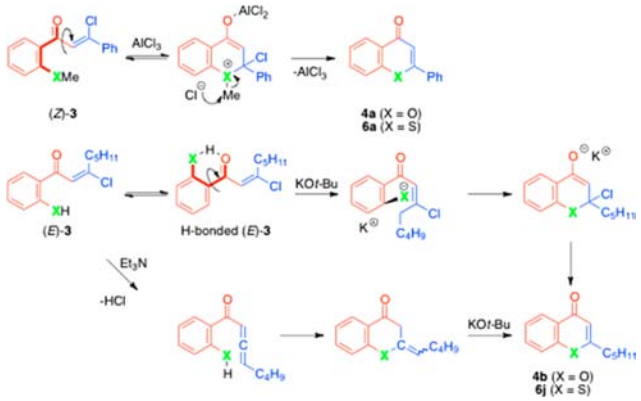
Scheme 3. Application to One-Pot Synthesis of Thiochromenones



applicable to aryl- and alkylalkynes, providing substituted thiochromenones **6a**–**m** in 63–86% yields. Notably, the syntheses of 4*H*-thiopyrano[2,3-*b*]pyridin-4-one **6i** as well as a chloride-containing thiochromenone **6l** were achieved in good yields.

The stereochemical outcomes of the Friedel–Crafts acylation of aryl- and alkylalkynes provide mechanistic insight into the subsequent cyclization to (thio)chromenones. Thus, the formation of (*Z*)-**3** with an intact (thio)methoxy group from arylalkynes implies that the most probable conformation of (*Z*)-**3a** would place the carbonyl group far away from the (thio)methoxy group (Scheme 4). The role of $AlCl_3$ would then be the Lewis acid to activate the carbonyl group, so the (thio)methoxy group could initiate a conjugate addition reaction. Once the demethylation of the oxonium (or thionium) ion occurs, after the elimination of chloride, the (thio)chromenones are obtained. In contrast, the formation of (*E*)-**3** with a hydroxyl (or thiol) group from alkyl alkynes suggests that the most probable conformation of (*E*)-**3** would be the intramolecularly H-bonded conformation. The fact that the H-bonded conformation of (*E*)-**3** did undergo cyclization to (thio)chromenones under the influence of bases illustrates

Scheme 4. Stereochemical and Conformational Consideration on the Cyclization of *β*-Chlorovinyl Ketones to (Thio)chromenones



the validity of the non-H-bonded conformation of (*E*)-**3** to (thio)chromenones. However, the use of strong bases brings about the functional group compatibility issues under strong basic conditions, leading to (thio)chromenones in low yields. The use of mild base, Et_3N, prompts a mild *α*-vinyl enolization of (*E*)-**3** to allenes that in turn undergo a rapid cyclization to (thio)chromenones. It is likely that the conformation of hydroxy (or thiol)-substituted allenes effectively competes with the H-bonded conformations;[22] thus, the allene intermediates undergo either conjugate addition followed by alkene isomerization or hydration/hydrothiolation to give the (thio)chromenones.

In summary, we have developed a facile and unified one-pot synthesis to (thio)chromenones from readily available alkynes and suitably substituted benzoyl chlorides. The divergent reaction pathway of stereoisomeric *β*-chlorovinyl ketones is a good reminder of the stereochemical as well as conformational significance of *β*-chlorovinyl ketones in the subsequent reaction pathways to important heterocycles. Our current research efforts are directed to detailed mechanistic studies and expanding the chemistry to other heterocyclic compounds, and our results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03348.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For reviews, see: (a) Pohland, A. E.; Benson, W. R. *Chem. Rev.* **1966**, *66*, 161−197. (b) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9592−9594.

(2) For recent examples, see: (a) Gandeepan, P.; Parthasarathy, K.; Su, T.-H.; Cheng, C.-H. *Adv. Synth. Catal.* **2012**, *354*, 457−468. (b) Cano, R.; Yus, M.; Ramón, D. J. *Tetrahedron* **2013**, *69*, 7056−7065. (c) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2012**, *134*, 1268−1274. (d) Kashiwabara, T.; Tanaka, M. *Adv. Synth. Catal.* **2011**, *353*, 1485−1490. (e) Wang, B.; Wang, S.; Li, P.; Wang, L. *Chem. Commun.* **2010**, *46*, 5891−5893. (f) See ref 1a.

(3) (a) Benson, W. R.; Pohland, A. E. *J. Org. Chem.* **1964**, *29*, 385−391. (b) Oh, K.; Kim, H.; Cardelli, F.; Bwititi, T.; Martynow, A. M. *J. Org. Chem.* **2008**, *73*, 2432−2434.

(4) Kim, H. Y.; Li, J.-Y.; Oh, K. *J. Org. Chem.* **2012**, *77*, 11132−11145.

(5) For the previous contributions from our group, see: (a) Kim, H. Y.; Li, J.-Y.; Oh, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 3736−3740. (b) Kim, H. Y.; Rooney, E. O.; Meury, R. P.; Oh, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 8026−8030. (c) Kim, H. Y.; Oh, K. *Org. Lett.* **2014**, *16*, 5934−5936. (d) Kim, H. Y.; Lee, S.; Kim, S.; Oh, K. *Org. Lett.* **2015**, *17*, 450−453. (e) Kim, H. Y.; Oh, K. *Org. Lett.* **2015**, *17*, 6254−6257.

(6) For selected reviews, see: (a) Kosmider, B.; Osiecka, R. *Drug Dev. Res.* **2004**, *63*, 200−211. (b) Teillet, F.; Boumendjel, A.; Boutonnat, J.; Ronot, X. *Med. Res. Rev.* **2008**, *28*, 715−745. (c) Talhi, O.; Silva, A. M. S. *Curr. Org. Chem.* **2012**, *16*, 859−896. (d) Kumazawa, Y.; Takimoto, H.; Matsumoto, T.; Kawaguchi, K. *Curr. Pharm. Des.* **2014**, *20*, 857−863.

(7) For selected examples, see: (a) Okombi, S.; Schmidt, J.; Mariotte, A.; Perrier, E.; Boumendjel, A. *Chem. Pharm. Bull.* **2005**, *53*, 1460−1462. (b) Chee, C. F.; Buckle, M. J. C.; Rahman, N. A. *Tetrahedron Lett.* **2011**, *52*, 3120−3123. (c) Zhao, J.; Zhao, Y.; Fu, H. *Org. Lett.* **2012**, *14*, 2710−2713.

(8) For selected examples, see: (a) Lorenz, M.; Kabir, M. S.; Cook, J. M. *Tetrahedron Lett.* **2010**, *51*, 1095−1098. (b) Du, Z.; Ng, H.; Zhang, K.; Zeng, H.; Wang, J. *Org. Biomol. Chem.* **2011**, *9*, 6930−6933. (c) Sashidhara, K. V.; Kumar, M.; Kumar, A. *Tetrahedron Lett.* **2012**, *53*, 2355−2359.

(9) For recent reviews, see: (a) Gaspar, A.; Matos, M. J.; Garrido, J.; Uriarte, E.; Borges, F. *Chem. Rev.* **2014**, *114*, 4960−4992. (b) Tome, S. M.; Silva, A. M. S.; Santos, C. M. M. *Curr. Org. Synth.* **2014**, *11*, 317−341.

(10) For selected examples, see: (a) Zhou, C.; Dubrovsky, A. V.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 1626−1632. Using TfOH, see: (b) Yoshida, M.; Fujino, Y.; Doi, T. *Org. Lett.* **2011**, *13*, 4526−4529.

(11) Chai, G.; Qiu, Y.; Fu, C.; Ma, S. *Org. Lett.* **2011**, *13*, 5196−5199.

(12) For selected examples, see: (a) Kumar, P.; Bodas, M. S. *Org. Lett.* **2000**, *2*, 3821−3823. (b) Das, J.; Ghosh, S. *Tetrahedron Lett.* **2011**, *52*, 7189−7194.

(13) For selected examples, see: (a) Kim, K.; Choe, H.; Jeong, Y.; Lee, J. H.; Hong, S. *Org. Lett.* **2015**, *17*, 2550−2553. (b) Lee, J.; Yu, J.; Son, S. H.; Heo, J.; Kim, T.; An, J.-Y.; Inn, K.-S.; Kim, N.-J. *Org. Biomol. Chem.* **2016**, *14*, 777−784.

(14) For selected examples, see: (a) Liang, B.; Huang, M.; You, Z.; Xiong, Z.; Lu, K.; Fathi, R.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 6097−6100. (b) Awuah, E.; Capretta, A. *Org. Lett.* **2009**, *11*, 3210−3213. (c) Yang, Q.; Alper, H. *J. Org. Chem.* **2010**, *75*, 948−950.

(15) For examples, see: (a) Wang, H.-K.; Bastow, K. F.; Cosentino, L. M.; Lee, K.-H. *J. Med. Chem.* **1996**, *39*, 1975−1980. (b) Dekermendjian, K.; Kahnberg, P.; Witt, M.-R.; Sterner, O.; Nielsen, M.; Liljefors, T. *J. Med. Chem.* **1999**, *42*, 4343−4350. (c) Kataoka, T.; Watanabe, S.; Mori, E.; Kadomoto, R.; Tanimura, S.; Kohno, M. *Bioorg. Med. Chem.* **2004**, *12*, 2397−2407.

(16) Fuchs, F. C.; Eller, G. A.; Holzer, W. *Molecules* **2009**, *14*, 3814−3832.

(17) (a) Inami, T.; Baba, Y.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2011**, *13*, 1912−1915. (b) Inami, T.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2014**, *16*, 5660−5662.

(18) Shen, C.; Spannenberg, A.; Wu, X.-F. *Angew. Chem., Int. Ed.* **2016**, *55*, 5067−5070.

(19) Among other unidentifiable products, the formation of hydrated products was observed.

(20) The formation of allenyl ketone intermediates was not observed upon treating the purified (*E*)-**3b** with Et_3N. Instead, the formation of chromenone **4b** was observed from (*E*)-**3b** in 85% yield.

(21) The use of $AlCl_3$ did not effect the cyclization of alkynone **3q** under the method A conditions.

(22) The fact that the soft α-vinyl enolization of (*E*)-**3b** prompts the direct formation of chromenone **4b** suggests that the intermediate, hydroxyallenyl ketone, might readily undergo the cyclization to chromenone under slightly basic/neutral conditions. The β-chlorovinyl ketones derived from 1,2-dialkylalkynes failed to provide (thio)chromenones, possibly due to the lack of α-hydrogen for the soft vinyl enolization to give allenyl ketone intermediates.

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