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Diversity-Oriented Synthesis of 3-Iodochromones and Heteroatom Analogues via ICl-Induced Cyclization

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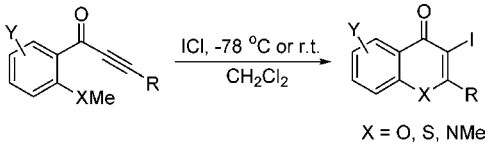

The ICl-induced cyclization of heteroatom-substituted alkynones provides a simple, highly efficient approach to various 3-iodochromones and analogues. This process is run under mild conditions, tolerates various functional groups, and generally provides chromones in good to excellent yields. Subsequent palladium-catalyzed transformations afford a rapid increase in molecular complexity and a convenient preparation of a wide range of functionally substituted chromones, furans, and polycyclic compounds. Iodothiochromenones and iodoquinolinones are also prepared by similar ICl-induced cyclizations.

Introduction

Diversity-oriented synthesis (DOS) is an emerging field involving the synthesis of combinatorial libraries of diverse small molecules for biological screening, which has served as a new driving force for advancing synthetic organic chemistry.[1] As a privileged structure in drug discovery,[2] chromones are abundant in numerous naturally occurring products[3] and possess a wide range of biological activities. Known as nature's tender drugs, they have been shown to be effective tyrosine and protein kinase C inhibitors, as well as antifungal, antiviral, antitubulin, antihypertensive, antioxidant, antiinflammatory, immunomodulatory, antithrombotic, and anticancer agents.[4] Traditionally, chromones have been prepared by the Baker−Venkataraman reaction[5] or the oxidative cyclization of chalcones.[6,7] However, these approaches normally involve harsh reaction conditions, such as the use of strong acids or bases, high temperature, etc. A limited number of chromone deviratives have also been efficiently synthesized by microwave heating[8] and by the Pd-catalyzed carbonylative Sonogashira reaction.[9] Due to the importance of chromones as pharmacologically active molecules, a general and diversity-oriented approach toward these compounds is highly desirable.

(1) For diversity-oriented synthesis, see: Tan, D. S. *Nature Chem. Biol.* **2005**, *1*, 74. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (c) Schreiber, S. L. *Science* **2000**, *287*, 1964.

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

(3) For reviews, see: (a) Saengchantara, S. T.; Wallace, T. W. *Nat. Prod. Rep.* **1986**, 465. (b) Houghton, P. J. *Alkaloids* **1987**, *31*, 67. (c) Houghton, P. J. *Stud. Nat. Prod. Chem.* **2000**, *21*, 123.

(4) For representative reviews, see: (a) Havsteen, B. *Biochem. Pharmacol.* **1983**, *32*, 1141. (b) Edwards, A. M.; Howell, J. B. L. *Clin. Exp. Allergy* **2000**, *30*, 756. (c) Birt, D. F.; Hendrich, S.; Wang W. *Pharmacol. Ther.* **2001**, *90*, 157. (d) Kim, H. P.; Son, K. H.; Chang, H. W.; Kang, S. S. *J. Pharmacol. Sci.* **2004**, *96*, 229. (e) Kosmider, B.; Osiecka, R. *Drug Dev. Res.* **2004**, *63*, 200.

(5) For representative Baker-Venkataraman examples, see: (a) Lee, K. S.; Seo, S. H.; Lee, Y. H.; Kim, H. D.; Son, M. H.; Chung, B. Y.; Lee, J. Y.; Jin, C.; Lee, Y. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2857. (b) Zembower, D. E.; Zhang H. *J. Org. Chem.* **1998**, *63*, 9300. (c) Krohn, K.; Vitz, J. *Eur. J. Org. Chem.* **2004**, *1*, 209. (d) Baker, W. *J. Chem. Soc.* **1933**, 1381.

(6) For representative syntheses by the chalcone route, see: (a) Joo, Y. H.; Kim, J. K.; Kang, S. H.; Noh, M. S.; Ha, J. Y.; Choi, J. K.; Lim, K. M.; Lee, C. H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 413. (b) Zhang, F.-J.; Lin, G.-Q.; Huang, Q.-C. *J. Org. Chem.* **1995**, *60*, 6427. (c) Chen, F. C.; Chang, C. T.; Chen, C. Y.; Hung, M.; Lin, Y. C. *J. Org. Chem.* **1962**, *27*, 310.

(7) For more representative syntheses of chromones, see: (a) Lin, C.-F.; Duh, T.-H.; Lu, W.-D.; Lee, J.-L.; Lee, C.-Y.; Chen, C.-C.; Wu, M.-J. *J. Chin. Chem. Soc.* **2004**, *51*, 183. (b) Bhat, A. S.; Whetstone, J. L.; Brueggemeier, R. W. *Tetrahedron Lett.* **1999**, *40*, 2469. (c) Nakatani, K.; Okamoto, A.; Saito, I. *Tetrahedron* **1996**, *52*, 9427. (d) McGarry, L. W.; Detty, M. R. *J. Org. Chem.* **1990**, *55*, 4349. (e) Pflieger, D.; Muckensturm, B. *Tetrahedron Lett.* **1990**, *31*, 2299. (f) Alvaro, M.; Garcia, H.; Iborra, S.; Miranda, M. A.; Primo, J. *Tetrahedron* **1987**, *43*, 143. (g) Garcia, H.; Iborra, S.; Primo, J.; Miranda, M. A *J. Org. Chem.* **1986**, *51*, 4432. (h) Luxen, A. J.; Christiaens, L. E.; Renson, M. J. *J. Organomet. Chem.* **1985**, *287*, 81. (i) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218.

(8) (a) Seijas, J. A.; Vázquez-Tato, M. P.; Carballido-Reboredo, R. *J. Org. Chem.* **2005**, *70*, 2855. (b) Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.* **2005**, *46*, 6315. (c) Varma, R. S. *J. Heterocycl. Chem.* **1999**, *36*, 1565.

(9) (a) Liang, B.; Huang, M.; You, Z.; Xiong, Z.; Lu, K.; Fathi, R.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 6097. (b) Miao, H.; Yang. Z. *Org. Lett.* **2000**, *2*, 1765.

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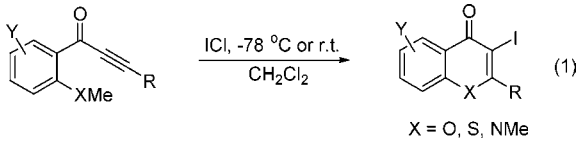
Recent work by our group and others has shown the electrophilic cyclization of functionally substituted alkynes to be an efficient way of generating benzo[*b*]thiophenes,[10] benzofurans,[11] bicyclic β-lactams,[12] cyclic carbonates,[13] 2,3-dihydropyrroles and pyrroles,[14] furans,[15] furopyridines,[16] indoles,[17] isochromenes,[18] isocoumarins and α-pyrones,[19] isoquinolines and naphthyridines,[20] isoxazoles,[21] naphthalenes,[22] polycyclic aromatics,[23] and quinolines.[24] Herein, we report an efficient approach to various 3-iodochromones via ICl-induced cyclization (eq 1). These reactions are run under very mild neutral reaction conditions, tolerate various functional groups, and generally provide the iodochromone products in good to excellent yields. Iodothiochromenones and iodoquinolinones are also prepared by analogous ICl-induced cyclization. The iodide products can be further elaborated to a wide range of functionally substituted chromones, furans, and polycyclic compounds using subsequent palladium-catalyzed processes.

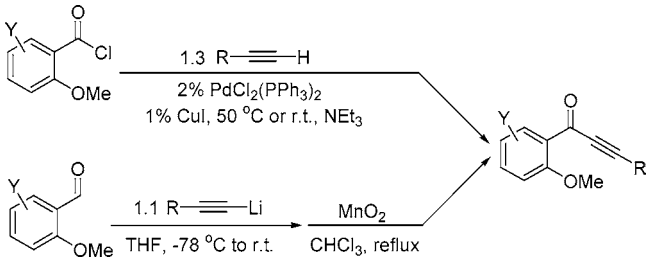


(1)

Results and Discussion

The 2-methoxyaryl-containing alkynones required for our approach can be readily prepared in one or two steps by two complementary methods: (1) the palladium/copper-catalyzed Sonogashira coupling of an acid chloride with a terminal acetylene at room temperature or 50 °C[25] or (2) the addition of a lithium acetylide to an aldehyde, followed by oxidation of the resulted secondary alcohol by activated MnO_2[26] (Scheme 1). Generally, the requisite alkynones are obtained in 66−98% yields by these straightforward approaches (see the Supporting Information for details).

SCHEME 1. Synthesis of Alkynones



To examine the feasibility of the iodocyclization of such alkynones, we initially studied the reaction of 1-(2-methoxyphenyl)-3-phenylpropynone (**1**) and ICl. To our delight, the 3-iodochromone **2** was obtained in a 96% isolated yield after stirring alkynone **1** (0.25 mmol) and 1.5 equiv of ICl in 3 mL of CH_2Cl_2 at room temperature for only 10 min (Table 1, entry 1). It is noteworthy that no chromone **2** was obtained when the weaker electrophile I_2 was employed instead of ICl using CH_2Cl_2 as the solvent at room temperature for 6 h. The reaction is still very efficient and provides the iodochromone **2** in a 99% yield when run at −78 °C for 2 h (entry 2). It is noteworthy that the reaction can be easily run on a multigram scale and the iodochromone **2** is obtained in excellent yield without the use of any column chromatography (see the Experimental Section for details).

The scope of this reaction is quite general. Excellent yields have been obtained when substituting the phenyl moiety of the alkynone **1** by various electron-rich and ortho-substituted arenes (entries 3−6). Also noteworthy is the fact that this chemistry tolerates acetoxy (entry 7) and thiophene (entry 8) groups, and the corresponding chromones are obtained in excellent yields. However, none of the desired product was obtained when an electron-poor 3-pyridyl group was introduced (entry 9).[27] A 45% isolated yield of chromone was obtained when a 3,5-bis(trifluoromethyl)phenyl group was employed (entry 10). This reaction needed to be run at room temperature for a longer time. A 3:1 ratio of regioisomeric side products arising from ICl addition to the triple bond was also obtained from this reaction in a 46% yield. It is likely that the introduction of more electron-deficient aromatic rings on the distal end of the triple bond destabilizes the expected carbocation-like iodonium intermediate, disfavoring cyclization and resulting in direct addition of ICl across the triple bond (see the later mechanistic discussion). A 96% isolated yield of iodochromone was obtained when a 1-cyclohexenyl group was introduced into the alkynone (entry 11). Alkyl-substituted alkynones are less reactive (entries 12−14). Nonetheless, the desired products can be obtained in good yields when the reactions are run under more dilute conditions for a longer reaction time (entries 12 and 13). Unfortunately, none of the desired product was obtained when the methoxymethyl-substituted alkynone **25** was employed, consistent with destabilization of a polarized cationic intermediate (entry 14). The TMS-substituted alkynone **27** afforded none of the desired

(10) (a) Larock, R. C.; Yue, D. *Tetrahedron Lett*. **2001**, *42*, 6011. (b) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905. (c) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett*. **2001**, *3*, 651.

(11) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432.

(12) Ren, X.-F.; Konaklieva, M. I.; Shi, H.; Dickey, S.; Lim, D. V.; Gonzalez, J.; Turos, E. *J. Org. Chem.* **1998**, *63*, 8898.

(13) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798.

(14) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Chem. Commun.* **1998**, 2207.

(15) (a) Bew, S. P.; Knight, D. W. *J. Chem. Soc., Chem. Commun*. **1996**, 1007. (b) Djuardi, E.; McNelis, E. *Tetrahedron Lett.* **1999**, *40*, 7193. (c) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769. (d) Yao, T.; Zhang X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679. (e) Liu, Y.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609.

(16) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409.

(17) (a) Barluenga, J.; Trincado, M.; Rublio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406. (b) Muhammad, A.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539. (c) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037.

(18) (a) Barluenga, J.; Vazque-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc*. **2003**, *125*, 9028. (b) Yue, D.; Della Ca, N.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581.

(19) (a) Yao, T.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 7401. (b) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936. (c) Oliver, M. A.; Gandour, R. D. *J. Org. Chem.* **1984**, *49*, 558. (d) Biagetti, M.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, *58*, 5023. (e) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067.

(20) (a) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett*. **2001**, *3*, 2973. (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437.

(21) Waldo, J. P.; Larock, R. C.*Org. Lett*. **2005**, *7*, 5203.

(22) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *Org. Lett.* **2003**, *5*, 4121.

(23) (a) Yao, T.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6*, 2677. (b) Yao, T.; Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3511.

(24) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett*. **2005**, *7*, 763.

(25) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777.

(26) Lin, C.-F.; Lu, W.-D.; Wang, I.-W.; Wu, M.-J. *Synlett* **2003**, 2057.

(27) The starting material is fully recovered after the reaction. It is possible that the ICl coordinates to the nitrogen moiety of the pyridine to form a pyridinium salt first, which makes the pyridine ring even more electron-deficient and unreactive.

TABLE 1. Synthesis of Iodochromones and Heteroatom Analogues by ICl-Induced Cyclization (eq 1)[a]

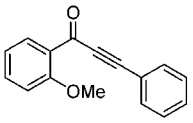
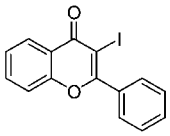
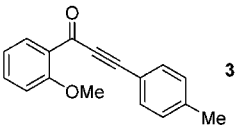
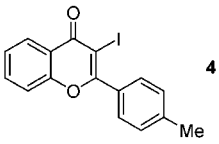
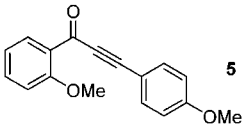
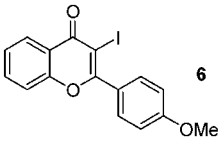
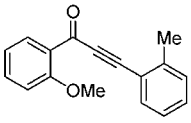
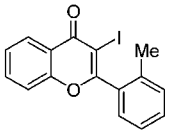
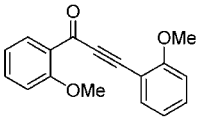
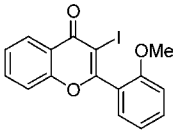
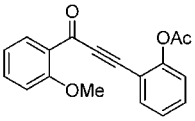
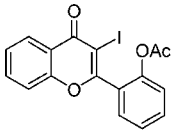
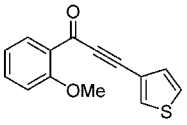
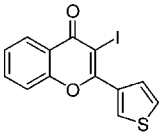
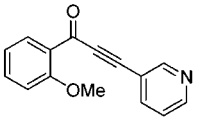
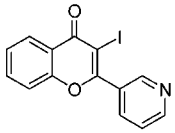
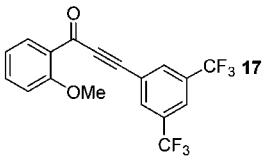
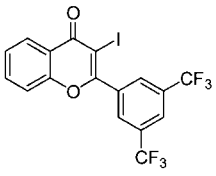
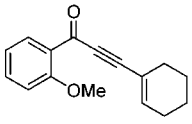
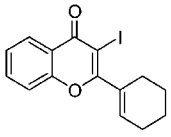
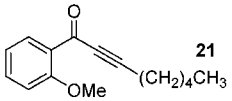
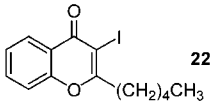
entry	alkynone	temp (°C)	time	product(s)	% yield[b]
1	 **1**	r.t.	10 min	 **2**	96
2		-78	2 h		99
3	 **3**	-78	2 h	 **4**	95
4	 **5**	-78	2 h	 **6**	98
5	 **7**	-78	2 h	 **8**	92
6	 **9**	-78	2 h	 **10**	97
7	 **11**	-78	2 h	 **12**	98
8	 **13**	-78	2 h	 **14**	95
9	 **15**	-78 to r.t.	6 h	 **16**	0[c]
10[d]	 **17**	-78 to r.t.	6 h	 **18**	45[e]
11	 **19**	-78	2 h	 **20**	96
12[d]	 **21**	-78 to r.t.	6 h	 **22**	85

Table 1. (Continued)

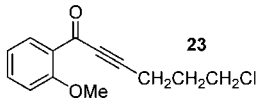
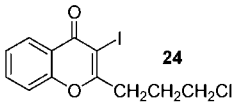
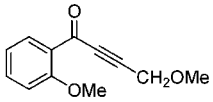
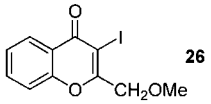
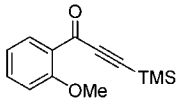
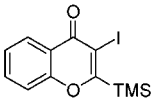
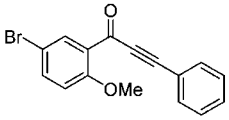
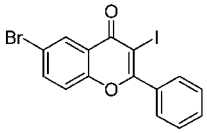
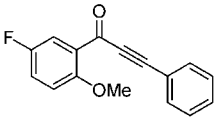
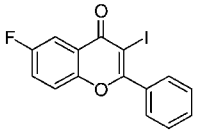
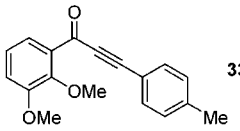
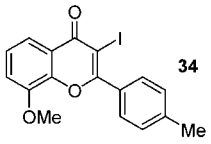
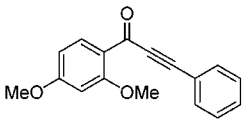
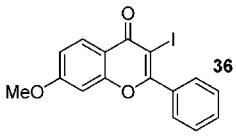
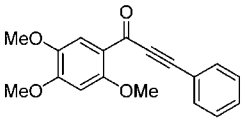
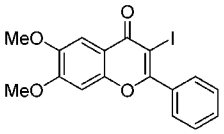
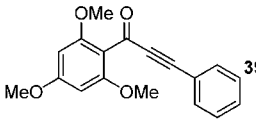
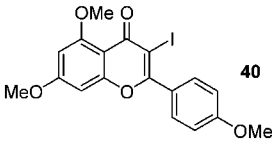
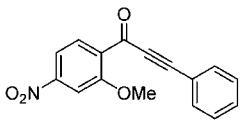
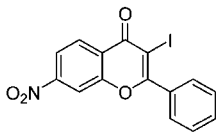
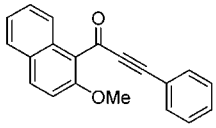
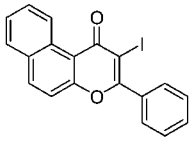
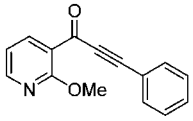
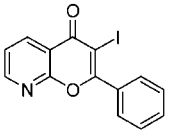
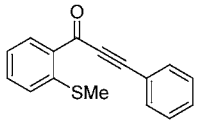
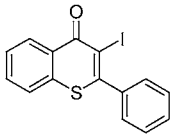
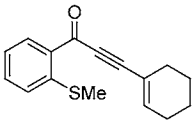
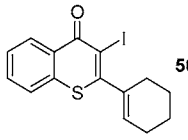
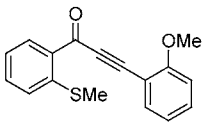
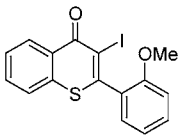
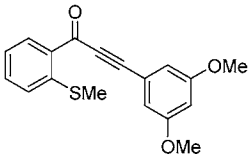
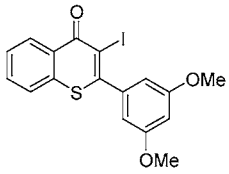
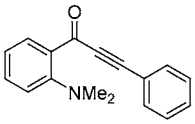
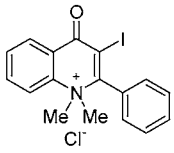
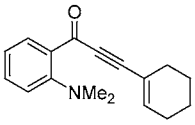
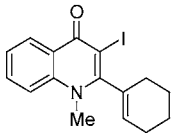
entry	alkynone	temp (°C)	time	product(s)	% yield[b]
13[d]	 **23**	-78 to r.t.	6 h	 **24**	76
14[d]	 **25**	-78 to r.t.	6 h	 **26**	0[f]
15[d]	 **27**	-78 to r.t.	6 h	 **28**	0[g]
16	 **29**	-78	2 h	 **30**	92
17	 **31**	-78	2 h	 **32**	90
18	 **33**	-78	2 h	 **34**	93
19	 **35**	-78	2 h	 **36**	88
20	 **37**	-78	2 h	 **38**	92
21	 **39**	-78 to r.t.	6 h	 **40**	0[g]
22	 **41**	-78 to r.t.	6 h	 **42**	91
23	 **43**	-78 to r.t.	6 h	 **44**	92
24	 **45**	-78 to r.t.	6 h	 **46**	93

Table 1. (Continued)

entry	alkynone		temp (°C)	time	product(s)		% yield[b]
25		**47**	-78	2 h		**48**	88
26		**49**	-78	2 h		**50**	90
27		**51**	-78	2 h		**52**	92
28		**53**	-78	2 h		**54**	70
29		**55**	-78	2 h		**56**	78[h]
30		**57**	-78	2 h		**58**	93

[a] All reactions were carried out using 0.25 mmol of the alkynone and 0.375 mmol of ICl in 3 mL of CH_2Cl_2 at the indicated temperature and time unless otherwise specified. [b] The yields are based on products isolated by column chromatography. [c] The starting material was recovered. [d] The reactions were run in 10 mL of CH_2Cl_2. [e] The products from ICl addition to the alkyne have been isolated in a 46% yield. [f] The product from ICl addition to the alkyne has been obtained in a 90% yield. [g] A complex mixture was obtained. [h] Attempts to efficiently transform this salt to the iodoquinolinone have so far failed.

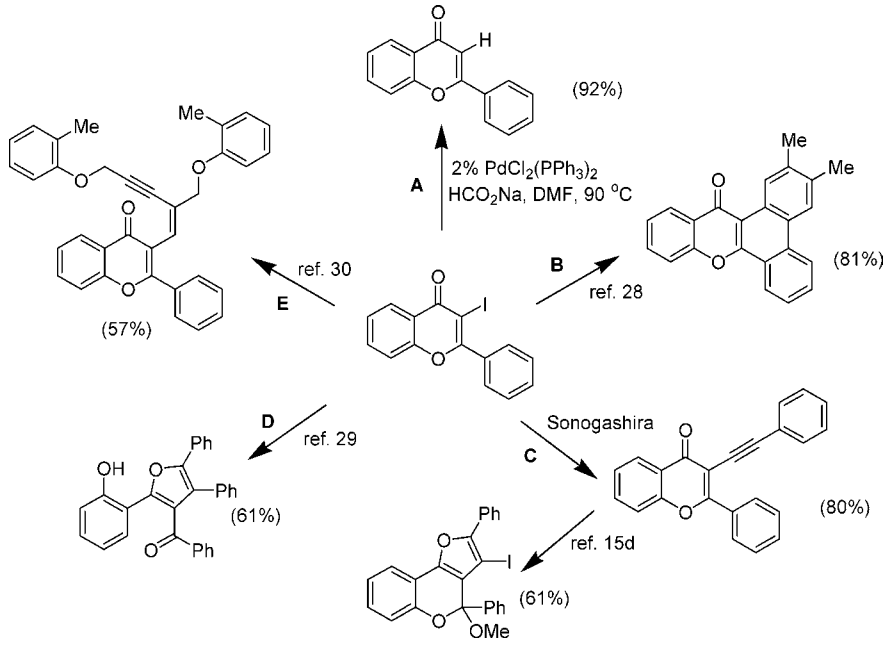
chromone (entry 15), possibly due to steric hindrance to cyclization by the highly hindered TMS group that blocks the incoming oxygen nucleophile (see the later mechanistic discussion). Generally substituents on the 2-methoxyaryl moiety of the alkynone have little effect on the efficiency of the iodocyclization process. Various halogen and methoxy-containing chromones can be obtained in excellent yields (entries 16−20). None of the desired product was obtained when the 2,4,6-trimethoxyphenyl alkynone **39** was employed, despite the fact that the analogous 2,4-dimethoxyphenyl and 2,4,5-trimethoxyphenyl alkynones provide excellent yields of the desired products (compare entry 21 with entries 19 and 20). It seems likely that the methoxy substituents in the 2- and 6-positions force the alkynone unit out of planarity with the methoxy-substituted arene, thus preventing cyclization. 2-Methoxy-4-nitrophenyl-, 2-methoxynaphthyl-, and a pyridyl-containing alkynone have all provided the desired chromones in excellent yields (entries 22−24).

This chemistry is not limited to the synthesis of iodochromones; analogous iodothiochromenones and iodoquinolinones can also be obtained in good to excellent yields (entries 25−30). For reasons we do not presently understand, the alkynone **55** bearing a phenyl group gave the corresponding methyl salt **56** in good yield, while the cyclohexenyl-substituted substrate **57** afforded the quinolinone **58** in high yield. Thus, a wide variety of diversely substituted chromones, thiochromenones, and quinolinones can be synthesized in high yields by this simple, highly efficient ICl-induced cyclization.

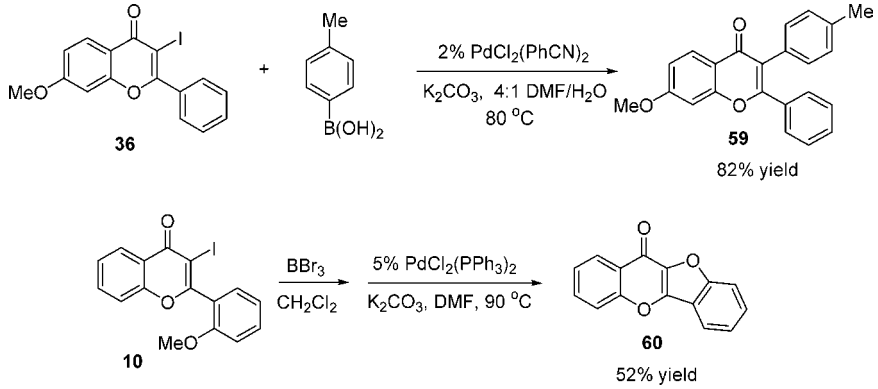
We believe that this approach to 3-iodochromones should prove very useful for the synthesis of additional more highly substituted chromones and other heterocycles, via elaboration of the resulting iodide functionality into other substituents (Scheme 2). For example, a flavone can be obtained in 92% yield by Pd-catalyzed reduction of the 3-iodochromone by sodium formate (path A). The 3-iodochromones can also be transformed to polycyclic aromatic products by the Pd-catalyzed annulation of arynes (path B).[28] The Sonogashira reaction has proven to be quite successful on these 3-iodochromones, and the resulting alkynyl chromones can be readily cyclized to highly functionalized furans by iodocyclization (path C).[15d] These 3-iodochromones can also provide phenol-containing furans by

(28) Liu, Z.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc*. **2005**, *127*, 15716.

SCHEME 2. Pd-Catalyzed Diversification of 3-Iodochromones



SCHEME 3. Pd-Catalyzed Diversification of 3-Iodochromone Derivatives

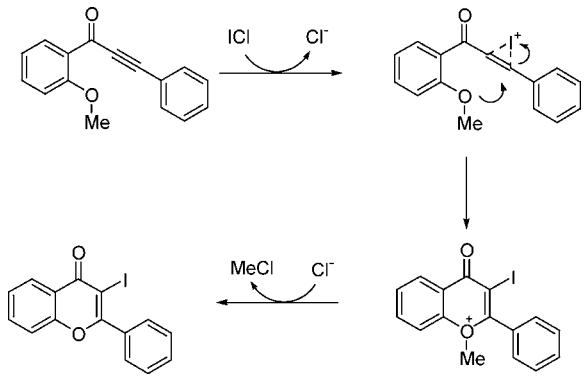


the Pd-catalyzed coupling with internal alkynes (path D).[29] Enyne-substituted chromones can also be obtained by a modified Sonogashira reaction (path E).[30]

2,3-Diarylchromones are known to be antihypertensive and antiinflammatory agents, as well as COX-2 inhibitors.[6a,31] Such chromones are easily generated by Suzuki cross-coupling of the 3-iodochromones. For example, 3-(4′-methylphenyl)-2-phenylchromone (**59**) can be obtained in an 82% yield by reaction of the 3-iodochromone **36** and *p*-tolylboronic acid (Scheme 3). These 3-iodochromones are also easily transformed into tetracyclic furan-containing products, such as **60**, by demethylation of methoxy-substituted chromones such as **10** and subsequent Pd-catalyzed intramolecular C−O bond formation (Scheme 3).

Mechanistically, we believe that these iodocyclizations proceed by the following key steps: (1) coordination of the carbon−carbon triple bond to the ICl or attack of the iodine cation on the triple bond to generate an iodonium intermediate, (2) nucleophilic attack of the oxygen of the *o*-methoxy group on the activated iodonium intermediate to produce a chromonium salt, and (3) facile removal of the methyl group via S_N2 displacement by the chloride anion present in the reaction mixture to generate the 3-iodochromone product and one molecule of MeCl (Scheme 4). Only chromones have been obtained from this process. No benzofuranone product has ever

SCHEME 4. Proposed Mechanism



(29) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.

(30) Pal, M.; Dakarapu, R.; Parasuraman, K.; Subramanian, V.; Yeleswarapu, K. R. *J. Org. Chem.* **2005**, *70*, 7179.

(31) (a) Wu, E. S. C.; Cole, T. E.; Davidson, T. A.; Blosmr, J. C.;Borrelli, A. R.; Kinsolving, C. R.; Parker, R. B. *J. Med. Chem.* **1987**, *30*, 788. (b) Wu, E. S. C.; Cole, T. E.; Davidson, T. A.; Dailey, M. A.; Doring, K. G.; Fedorchuk, M.; Loch, J. T., III; Thomas, T. L.; Blosser, J. C.; Borrelli, A. R.; Kinsolving, C. R.; Parker, R. B. *J. Med. Chem.* **1989**, *32*, 183. (c) Wu, E. S. C.; Loch, J. T., III; Toder, B. H.; Borrelli, A. R.; Gawlak, D.; Radov, L. A.; Gensmante, N. P. *J. Med. Chem.* **1992**, *35*, 3519.

been observed to arise by this process. Obviously, 6-*endo* cyclization is more facile than 5-*exo* cyclization, presumably because the more stable cationic intermediate is expected to form on the β-carbon of the alkynone system.

Conclusions

In summary, we have developed a simple, highly efficient approach to various functionalized 3-iodochromones via ICl-induced cyclization. These reactions are run under mild conditions, tolerate various functional groups, and generally provide the chromone products in good to excellent yields. A successful multigram scale synthesis of an iodochromone without the use of column chromatography is demonstrated. Iodocyclization of readily available alkynones, followed by various palladium-catalyzed transformations, affords a rapid increase in molecular complexity and provides a powerful tool for the preparation of a wide range of functionally substituted chromones, furans, and polycyclic aromatic compounds. Thiochromenones and quinolinones can also be readily prepared by similar ICl-induced cyclizations.

Experimental Section

General Procedure for the Synthesis of 3-Iodochromones (Table 1). The alkynone (0.25 mmol) and ICl (0.375 mmol) were each dissolved in 1.5 mL of dry CH_2Cl_2 in separate vials and cooled to −78 °C. The ICl solution was added dropwise to the alkynone solution over approximately 1 min, and the reaction was stirred at the indicated temperature for the indicated time. To the reaction mixture was then added 2 mL of satd aq $Na_2S_2O_3$ solution and then 20 mL of satd NaCl solution. The resulting mixture was extracted three times with ethyl ether (30 mL each time). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue provided NMR pure (>95% purity) product in most cases, but sometimes the product was isolated by chromatography on a silica gel column.

Preparation of Iodochromone 2 on a Multigram Scale without the Use of Column Chromatography. 2-Methoxybenzaldehyde (2.72 g, 20 mmol) was added to a 500 mL round-bottom flask and dissolved in 250 mL of dry, oxygen-free THF. The flask was flushed with N_2 and allowed to cool to −78 °C. Lithium phenylacetylide (20 mL of a 1.0 M solution in THF) was then added dropwise under N_2. The resulting mixture was stirred at −78 °C for 30 min and allowed to gradually warm to room temperature. The reaction mixture was quenched by satd aq NH_4Cl (200 mL) and extracted with ethyl ether 3 times (100 mL each time). The organic layers were combined, dried, and concentrated under reduced pressure. The residue was then dissolved in $CHCl_3$ (250 mL), and activated MnO_2 (3.6 g, 40 mmol) was added. The suspension was refluxed for 2 h, the solution was cooled and filtered through a pad of Celite, and the filtrate was concentrated to afford the desired alkynone **1**. The alkynone **1** was then dissolved in 50 mL of dry CH_2Cl_2 and cooled to −78 °C. ICl (4.06 g, 25 mmol) was dissolved in 200 mL of dry CH_2Cl_2 and cooled to −78 °C. The ICl solution was slowly added to the alkyne dropwise over a period of 15 min. The reaction was then allowed to slowly warm to room temperature. To the reaction mixture was added 50 mL of satd aq $Na_2S_2O_3$ solution and then 100 mL of satd aq NaCl solution. The resulting mixture was extracted 3 times with ethyl ether (100 mL each time). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue (6.8 g, 98% yield) proved to be chromone **2** (>95% purity by ^1H and ^{13}C NMR analysis).

Acknowledgment. We gratefully acknowledge the National Institute of General Medical Sciences (GM 070620) and the National Institutes of Health Kansas University Chemical Methodologies and Library Development Center of Excellence (P50 GM069663) for support of this research and Kawaken Fine Chemicals Co., Ltd., and Johnson Matthey, Inc., for donating the palladium salt. The boronic acid was contributed by Frontier Scientific, Inc.

Supporting Information Available: Experimental details and product characterization data and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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