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Synthesis of Isocoumarins and α-Pyrones via Electrophilic Cyclization

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A variety of substituted isocoumarins and α-pyrones are readily prepared in excellent yields under very mild reaction conditions by the reaction of *o*-(1-alkynyl)benzoates and (*Z*)-2-alken-4-ynoates with ICl, I_2, PhSeCl, *p*-$O_2NC_6H_4SCl$, and HI. This methodology accommodates various alkynyl esters and has been successfully extended to the synthesis of polycyclic aromatic and biaryl compounds.

Introduction

Isocoumarins[1] and α-pyrones[2] represent two important classes of naturally occurring lactones, which are structural subunits in numerous natural products that exhibit a wide range of biological activities, such as antimicrobial,[3] androgen-like,[4] phytotoxic,[5] antifungal,[6] and pheromonal[7] effects. Recently, low molecular weight α-pyrones have been shown to be potent HIV-1 protease inhibitors.[8]

Considerable efforts have been directed toward the synthesis of isocoumarins[9] and α-pyrones[10] either by traditional approaches or by organometallic approaches. Isocoumarins have been prepared by the ortho-thallation of benzoic acids and subsequent palladium-catalyzed olefination by using simple olefins, as well as allylic and vinylic halides or esters.[9c] Unsubstituted or 3-substituted isocoumarins and pyrones have been prepared by the palladium-catalyzed coupling of 2-halobenzoate esters, 2-halobenzoic acids or 2-halobenzonitriles with alkenes,[11] vinylic stannanes[12] or terminal alkynes[13] and subsequent cyclization, or π-allylnickel cross-coupling and palladium-catalyzed cyclization.[9a] Isocoumarins and α-pyrones have also been prepared by the palladium-catalyzed annulation of internal alkynes.[14]

Previous workers have reported the synthesis of isocoumarins[15] and 5,6-disubstituted 2(2*H*)-pyranones[16] by the iodolactonization of 2-(1-alkynyl)benzoic acids and 5-substituted (*Z*)-2-alken-4-ynoic acids, respectively (eq

* Corresponding author.

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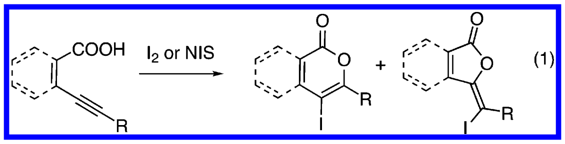
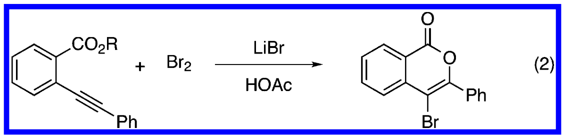
1). These acids have always produced a mixture of five- and six-membered-ring products.



Oliver and Gandour have reported the bromolactonization of alkyl 2-(2-phenylethynyl)benzoates (eq 2).[17] Unfortunately, only two examples were reported and the scope of this cyclization has not been examined.



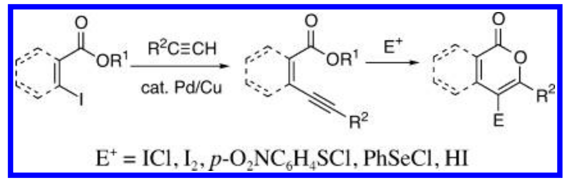
During the course of our investigation of the electrophilic cyclization of analogous esters,[18] Rossi et al. reported the synthesis of isocoumarins and α-pyrones by iodocyclization of the corresponding acetylenic esters.[19] They report that the reactions of four 2-alken-4-ynoate methyl esters with I_2 in CH_2Cl_2 generally afford mixtures of the corresponding iodo-pyrones and -furanones, but that the reaction with ICl in CH_2Cl_2 produces predominantly the six-membered-ring lactones, albeit in only 51–72% yields. Analogous reactions of four methyl 2-(arylethynyl)benzoates with I_2 in MeCN produce excellent yields of pure 4-iodoisocoumarins in two cases, but mixtures of five- and six-membered-ring lactones in 26% and 83% overall yields in the other two cases. The use of ICl in CH_2Cl_2 afforded an 81% yield of an essentially pure isocoumarin in one example, but only a 47% yield of a 55:45 mixture of six- and five-membered-ring products in another. Herein, we wish to report the successful electrophilic cyclization of analogous esters for the synthesis of isocoumarins and α-pyrones. This chemistry generally produces excellent yields of a single regioisomeric six-membered-ring lactone and can be extended to electrophiles other than I_2 and ICl. In a couple of cases, five-membered-ring lactones are cleanly produced.

Results and Discussion

A two-step approach to isocoumarins and α-pyrones has been examined involving (i) preparation of *o*-(1-alkynyl)benzoates and (*Z*)-2-alken-4-ynoates by a Sonagashira coupling reaction[20] and (ii) electrophilic cyclization (Scheme 1).

The *o*-(1-alkynyl)benzoates and (*Z*)-2-alken-4-ynoates required for our approach are readily prepared by Sonogashira coupling[20] of the corresponding iodo compounds with terminal alkynes, using 2% $PdCl_2(PPh_3)_2$ and 1%

SCHEME 1



CuI in Et_3N solvent at 55 °C. The yields of this process range from 80% to 100% and this procedure should readily accommodate considerable functionality.

To explore the scope of this electrophilic cyclization strategy, the reactions of alkynyl ester **1** with different electrophiles (ICl, I_2, *p*-$O_2NC_6H_4SCl$, PhSeCl, and HI) in CH_2Cl_2 at room temperature have been studied (Table 1, entries 1–5). Excellent ≥90% yields of a single regioisomeric isocoumarin have been obtained in all cases. Of all of the electrophilic reagents examined, ICl gave the fastest reaction, followed by I_2, *p*-$O_2NC_6H_4SCl$, and PhSeCl, while the reaction of HI took 96 h.

Both ICl and I_2 are efficient and quite general for the preparation of isocoumarins. Most of the functional groups that we have studied so far have tolerated the reaction conditions, and yields above 90% have been obtained in most cases (entries 1, 2, 6–8, 10, 13, and 14). Aryl-substituted (entries 1 and 2) and long-chain alkyl-substituted alkynes (entries 6 and 7) are readily accommodated, and the presence of an olefin (entry 8) or an alcohol group (entry 10) presents no difficulties. However, alkynes bearing a H or Si(*i*-Pr)$_3$ group (entries 11 and 12) have afforded exclusively the five-membered-ring products as determined by the carbonyl stretch in their IR spectra.[9i] Compound **14** has also been reported earlier by Rossi.[9b] This is apparently due to the limited stability of the resulting cationic intermediate[19b] (entry 11) and the steric bulk of the Si(*i*-Pr)$_3$ group (entry 12), respectively (see the later mechanistic discussion). Isocoumarins bearing electron-donating or electron-withdrawing substituents in the 4- and/or 5-positions of the aromatic ring have also been synthesized in excellent yields (entries 13 and 14). These cyclizations are not limited to simple methyl esters. The corresponding *tert*-butyl ester **22** has been cyclized by ICl in a quantitative yield (entry 16).

We next examined the possibility of preparing α-pyrones by this same methodology. (*Z*)-2-Alken-4-ynoates bearing both an aryl group (**23**) and an alkyl group (**27**) on the acetylene moiety have reacted with ICl, *p*-$O_2NC_6H_4SCl$, or PhSeCl to produce the corresponding α-pyrones **24**, **25**, **26**, and **28** in excellent yields (entries 17–20). Ethyl (*Z*)-2-methyl-5-phenyl-2-alken-4-ynoate (**29**) reacts with ICl to afford a 59% yield of the desired 5-iodo-α-pyrone **30**, along with an inseparable byproduct (entry 21). Fortunately, when using I_2, the iodocyclization product **30** is obtained as the only product in an 84% yield (entry 22). Ethyl (*Z*)-3,5-diphenyl-2-alken-4-ynoate (**31**) also gives a single pyrone product **32** in an 84% yield (entry 23). However, when 2,3-disubstituted (*Z*)-2-alken-4-ynoates are employed, mixtures of five- and six-membered-ring products are obtained no matter whether I_2, ICl, or PhSeCl is employed as the electrophile (entries 24–27). Thus, it appears that steric effects play an important role in the regioselectivity of cyclization. The more bulky the substituents are in positions 2 and 3 of

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(19) (a) Biagetti, M.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, *58*, 5023. (b) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067.
(20) For reviews, see: (a) Campbell, I. B. *The Sonogashira Cu–Pd–Catalyzed Alkyne Coupling Reaction. Organocopper Reagents*; Tayler, R. T. K., Ed.; IRL Press: Oxford, UK, 1994, pp 217–235. (b) Sonogashira, K.; Takahashi, S. *Yuki Gosei Kagaku Kyokaishi* **1993**, *51*, 1053. (c) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, UK, 1991; Vol. 3, pp 521–549.

TABLE 1. Synthesis of Substituted Isocoumarins and α-Pyrones (Scheme 1)[a]

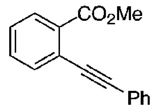
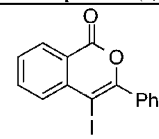
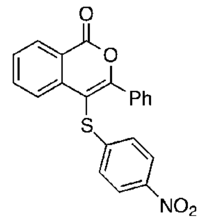
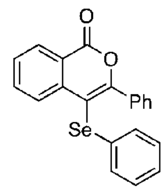
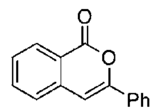
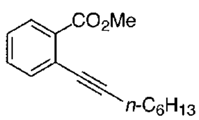
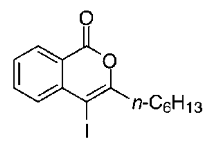
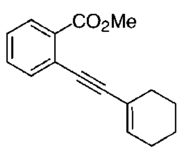
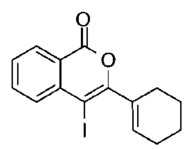
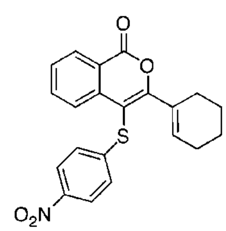
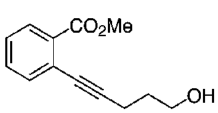
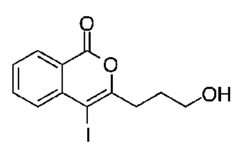
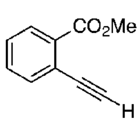
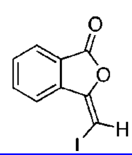
entry	alkynyl ester		electrophile	time (h)	product(s)		% isolated yield
1		**1**	ICl	0.5		**2**	90
2		**1**	I_2	1		**2**	93
3		**1**	*p*-$O_2NC_6H_4SCl$	1		**3**	90
4		**1**	PhSeCl	1		**4**	95
5		**1**	HI	96		**5**	92
6		**6**	ICl	0.5		**7**	85
7		**6**	I_2	1		**7**	90
8		**8**	ICl	0.5		**9**	98
9		**8**	*p*-$O_2NC_6H_4SCl$	1		**10**	70
10		**11**	ICl	0.5		**12**	51
11		**13**	ICl	0.5		**14**	63

Table 1 (Continued)

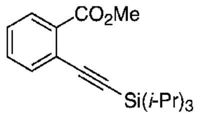
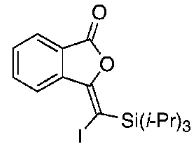
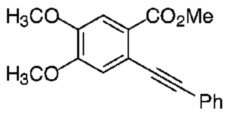
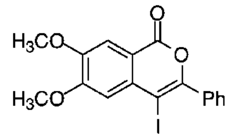
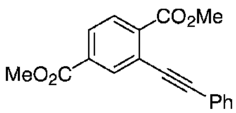
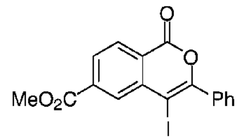
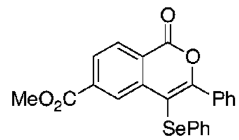
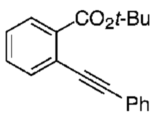
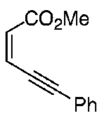
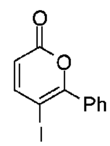
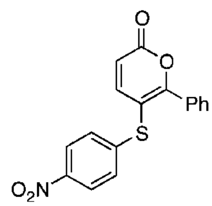
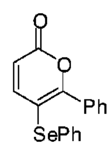
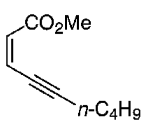
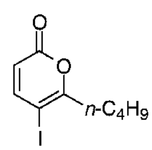
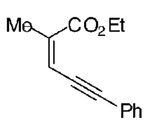
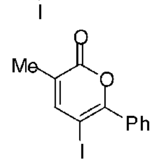
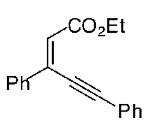
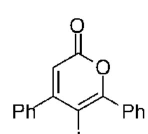
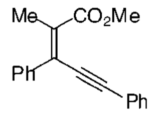
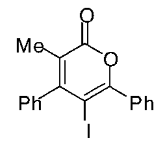
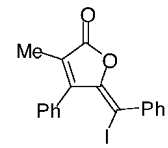
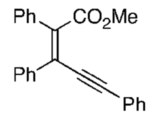
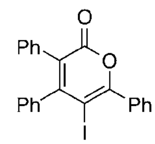
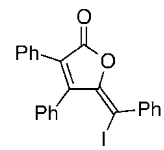
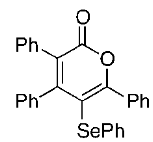
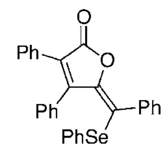
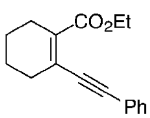
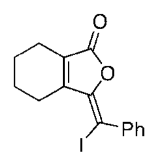
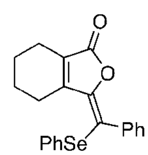
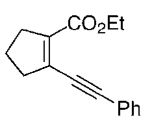
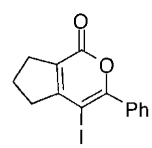
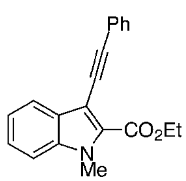
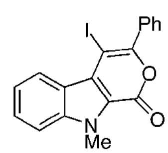
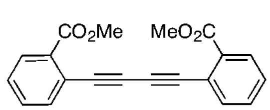
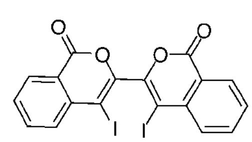
entry	alkynyl ester		electrophile	time (h)	product(s)		% isolated yield
12		**15**	ICl	0.5		**16**	96
13		**17**	ICl	0.5		**18**	100[b]
14		**19**	ICl	0.5		**20**	88
15		**19**	PhSeCl	1		**21**	73
16		**22**	ICl	0.5		**2**	100
17		**23**	ICl	0.5		**24**	94
18		**23**	p-$O_2NC_6H_4SCl$	1		**25**	80
19		**23**	PhSeCl	1		**26**	97
20		**27**	ICl	0.5		**28**	80
21		**29**	ICl	0.5		**30**	~59[c]
22		**29**	I_2	1		**30**	84
23		**31**	ICl	0.5		**32**	84

Table 1 (Continued)

entry	alkynyl ester		electrophile	time (h)	product(s)		% isolated yield
24		**33**	I_2	1	 **34** 	**35**	17 + 76
25		**36**	I_2	1	 **37** 	**38**	6 + 71
26		**36**	ICl	0.5	**37**	**38**	17 + 55
27		**36**	PhSeCl	1	 **39** 	**40**	30 + 41
28		**41**	ICl	0.5		**42**	55
29		**41**	PhSeCl	1		**43**	60
30		**44**	ICl	0.5		**45**	0
31		**44**	I_2	16		**45**	85
32		**46**	ICl	0.5		**47**	0
33		**46**	I_2	60		**47**	84
34		**48**	ICl	0.5		**49**	90[b]

[a] All reactions were run under the following conditions, unless otherwise specified: 0.30 mmol of the *o*-(1-alkynyl)benzoate or (*Z*)-2-alken-4-ynoate in 3 mL of CH_2Cl_2 was placed in a 4-dram vial under N_2 and 1.2 equiv of electrophile in 0.4 mL of CH_2Cl_2 was added at room temperature. [b] The reaction was run at −78 °C. [c] This product could not be obtained completely pure.

the (*Z*)-2-alken-4-ynoates, the lower the yield of the six-membered-ring product (compare entries 23 and 26, and 24 and 25). The bulkier substituents on the (*Z*)-2-alken-4-ynoates apparently force the oxygen of the carbonyl group closer to C-4 of the alkenynoate ester resulting in the five-membered-ring product (see the later mechanistic discussion). The nature of the electrophile plays an important role in these cyclization reactions. Compared with I_2, the stronger electrophilic reagent ICl affords a higher yield of the six-membered-ring product (compare entries 25 and 26), although the five-membered-ring lactone still predominates.

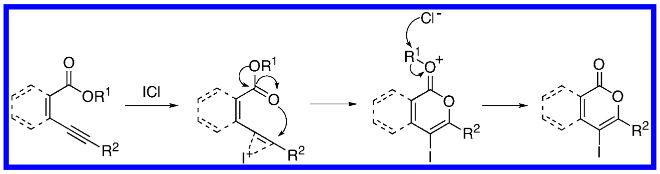
Ring-containing esters can also be used in this iodocyclization process (entries 28−33). The six-membered-ring ester **41** gives a 55% yield of the five-membered-ring product **42** with ICl (entry 28), and a 60% yield of the five-membered-ring product **43** with PhSeCl (entry 29). We believe that the six-membered cyclohexenyl ring in **41** forces the oxygen of the carbonyl group closer to C-4 of the alkenynoate ester resulting in five-membered ring formation (see the later mechanistic discussion). Interestingly, the five-membered-ring-containing esters **44** and **46** give only products of addition of ICl across the carbon−carbon triple bond. However, by using I_2 instead of ICl, both substrates **44** and **46** afford the desired bicyclic α-pyrones **45** and **47** respectively as the only products in excellent yields (entries 31 and 33). Note that these two iodocyclization reactions take a much longer time to reach completion. A reasonable explanation is that the reaction is slowed because the oxygen of the carbonyl group is oriented away from the carbon−carbon triple bond (see the later mechanistic discussion).

A biisocoumarin has also been prepared by this cyclization methodology as shown in entry 34. When ICl or I_2 is used at room temperature, a mixture of the desired biisocoumarin **49** and an inseparable byproduct were obtained. However, ICl at −78 °C afforded the biisocoumarin **49** as the only product in a 90% yield.

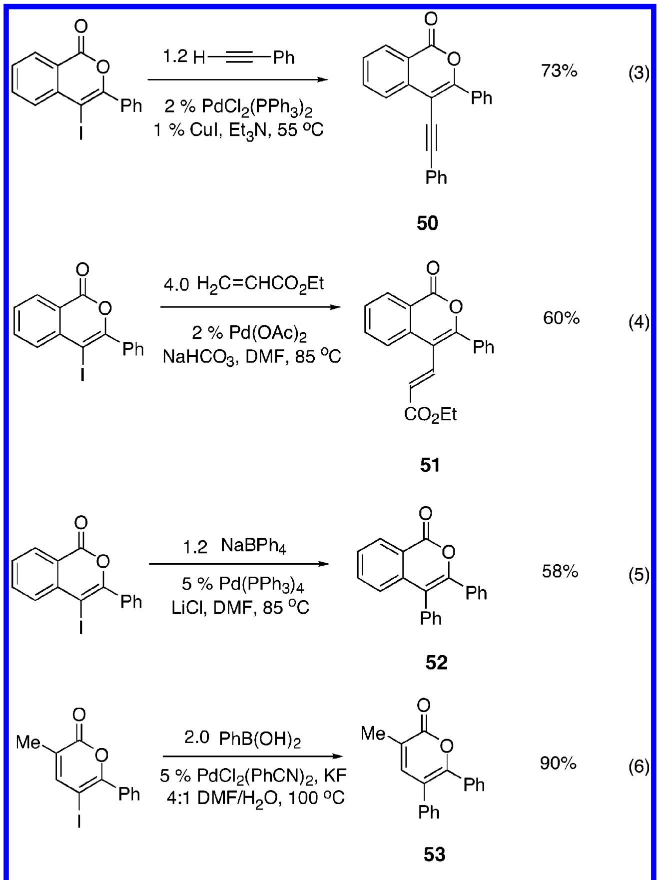
Our iodocyclization results are generally consistent with those reported by Rossi.[19] For instance, in our work, with ICl or I_2 as the electrophile and CH_2Cl_2 as the solvent, the reactions generally afford six-membered-ring lactones, except for alkynes **13**, **15**, and **41**, where five-membered-ring lactones are formed exclusively, and alkynes **33** and **36**, where mixtures of five- and six-membered-ring lactones are produced. Rossi has usually obtained a mixture of five- and six-membered-ring products from the cyclization of esters when using solvents other than CH_2Cl_2 and claimed that the solvent employed effects the regioselectivity of iodocyclization.[19a] With ICl and CH_2Cl_2, Rossi obtained almost exclusively the six-membered-ring lactone from the cyclization of ester **1**, and in some other cases, small amounts of five-membered-ring lactones were detected. Rossi obtained a mixture of (*E*)- and (*Z*)-five-membered-ring lactone **14** when using alkyne **13**.[19b] However, in our case, only (*E*)-**14** was obtained. We would like to point out that our reaction times (0.5−1 h) are much shorter than Rossi's (3−3.5 h), which might be the reason we get higher yields and better stereoselectivity.

Surprisingly, the nature of the R^1 group on the ester had very little effect on the reaction rate or the product yield. Even a *tert*-butyl ester **22** cyclized in approximately the same time and yield as the corresponding methyl ester **1** (compare entries 1 and 16). On the basis of this observation, we propose the following mechanism for this electrophilic cyclization (Scheme 2). Nucleophilic attack by the oxygen of the carbonyl group on the carbon−carbon triple bond activated by coordination to I^+ is followed by either S_N2 attack of the chloride on the R^1 group when R^1 = Me or perhaps S_N1 cleavage of the R^1 group in the case of the *tert*-butyl ester.

SCHEME 2



An interesting feature of this process is the fact that the iodoisocoumarins and iodo-2(2*H*)-pyrones generated can be further elaborated by using various palladium-catalyzed processes. For example, the Sonagashira (eq 3),[20] Heck (eq 4),[21] and Suzuki reactions (eqs 5 and 6)[22] afford the corresponding products **50**−**53**, respectively, in good yields.



Conclusions

Conclusions

Efficient syntheses of a wide variety of substituted isocoumarins and α-pyrones have been developed under very mild reaction conditions. This methodology accommodates a variety of alkynyl esters with various functional groups and affords the anticipated substituted isocoumarins and α-pyrones in excellent yields. In a few cases, five-membered-ring lactones or mixtures of five- and six-membered-ring lactones are formed. The resulting iodine-containing products are readily elaborated to

(21) For leading reviews of the Heck reaction, see: (a) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (b) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (d) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423

more complex products by using known organopalladium chemistry. Although Rossi et al.[19] have reported several reactions of alkynyl esters with ICl or I_2, we have extended the above chemistry to the synthesis of polycyclic aromatic and biisocoumarins and generally obtained cleaner reactions. We have also shown that electrophiles other than I_2 and ICl, namely HI, PhSeCl, and p-$O_2NC_6H_4SCl$, can be used in this chemistry.

Experimental Section

General Procedure for Preparation of the Ester Alkynes. To a solution of the corresponding organic iodide or triflate (1.0 mmol) and the terminal alkyne (1.2 mmol, 1.2 equiv) in Et_3N (4 mL) were added $PdCl_2(PPh_3)_2$ (1.4 mg, 2 mol %) and CuI (2.0 mg, 1 mol %). The resulting mixture was then heated under an N_2 atm at 55 °C. The reaction was monitored by TLC to establish completion. When the reaction was complete, the mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the corresponding ester alkyne.

Methyl 2-(Phenylethynyl)benzoate (1). Purification by flash chromatography (10:1 hexane/EtOAc) afforded 235 mg (99%) of the product as a yellow liquid with spectral properties identical with those previously reported.[23]

General Procedure for the Electrophilic Cyclization of Ester Alkynes by ICl. The ester alkyne (0.30 mmol) in 3 mL of CH_2Cl_2 was placed in a 4-dram vial and flushed with N_2. The ICl (1.2 equiv) in 0.5 mL of CH_2Cl_2 was added dropwise to the vial with a syringe. The reaction was stirred at room temperature for 30 min unless otherwise indicated. The reaction mixture was then diluted with 50 mL of ether, washed with 25 mL of satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

4-Iodo-3-phenylisocoumarin (2). Purification by flash chromatography (10:1 hexane/EtOAc) afforded 94.6 mg (90%) of the product as a white solid with spectral properties identical with those previously reported: mp 137−138 °C (lit.[19a] mp 136−138 °C).

General Procedure for the Electrophilic Cyclization of Ester Alkynes by I_2. The ester alkyne (0.30 mmol), I_2 (1.2 equiv), and 3 mL of CH_2Cl_2 were placed in a 4-dram vial and flushed with N_2. The reaction was stirred at room temperature for 60 min unless otherwise indicated. The reaction mixture was then diluted with 50 mL of ether, washed with 25 mL of satd aq $Na_2S_2O_3$, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

4-Iodo-3-phenyl-6,7-dihydrocyclopenta[*c*]pyran-1−5-(*H*)-one (45). Purification by flash chromatography (5:1 hexane/EtOAc) afforded 86 mg (85%) of the product as a white solid: mp 134−135 °C; ^{1}H NMR ($CDCl_3$) δ 2.07−2.18 (m, 2H), 2.92−3.05 (m, 4H), 7.42−7.47 (m, 3H), 7.68−7.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.7, 31.7, 40.7, 70.3, 125.6, 128.3, 129.8, 130.6, 134.0, 159.8, 160.6, 163.1; IR (neat, cm^{-1}) 1723; HRMS calcd for $C_{14}H_{11}O_2I$ 337.9804, found 337.9808. Anal. Calcd for $C_{14}H_{11}O_2I$: C, 49.73; H, 3.28. Found: C, 49.62; H, 2.81.

General Procedure for the Electrophilic Cyclization of Ester Alkynes by PhSeCl or p-$O_2NC_6H_4SCl$. The ester alkyne (0.30 mmol), PhSeCl or p-$O_2NC_6H_4SCl$ (1.5 equiv), and CH_2Cl_2 (3 mL) were placed in a 4-dram vial and flushed with N_2. The reaction mixture was stirred at room temperature for 1 h unless otherwise indicated. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

3-Phenyl-4-(phenylselenyl)isocoumarin (4). Purification by flash chromatography (7:1 hexane/EtOAc) afforded 124 mg (95%) of the product as a white solid: mp 137−139 °C; ^{1}H NMR ($CDCl_3$) δ 7.12−7.22 (m, 5H), 7.38−7.48 (m, 3H), 7.54 (t, J = 7.5 Hz, 1H), 7.65−7.74 (m, 3H), 8.05 (d, J = 8.1 Hz, 1H), 8.37 (dd, J = 8.1, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 105.0, 121.1, 126.7, 128.1, 128.5, 129.0, 129.1, 129.7, 129.9, 130.0, 130.4, 132.1, 134.3, 135.6, 138.7, 159.8, 162.0; IR (neat, cm^{-1}) 1739; HRMS calcd for $C_{21}H_{14}O_2Se$ 378.0160, found 378.0167.

General Procedure for the Electrophilic Cyclization of Ester Alkyne 1 by HI. The ester alkyne **1** (0.30 mmol), 40% HI (2.0 equiv), and CH_2Cl_2 (3 mL) were placed in a 4-dram vial and flushed with N_2. The reaction mixture was stirred at room temperature for 96 h. The reaction mixture was then diluted with 50 mL of ether, washed with 25 mL of satd aq $NaHCO_3$ and 25 mL of H_2O, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

3-Phenylisocoumarin (5). Purification by flash chromatography (20:1 hexane/EtOAc) afforded 63 mg (92%) of the product as a white solid with spectral properties identical with those previously reported: mp 87−89 °C (lit.[24] mp 90−91 °C).

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for partial support of this research, and Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for donations of palladium catalysts.

Supporting Information Available: Characterization data for the compounds listed in Table 1 and experimental procedures and characterization data for the reactions summarized in eqs 3−6. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034308V

(22) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 2.
(23) Shi, C.; Zhang, Q.; Wang, K. K. *J. Org. Chem.* **1999**, *64*, 925.
(24) Gray, T. I.; Pelter, A.; Ward, R. S. *Tetrahedron* **1979**, *35*, 2539.