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Syntheses of Isochromenes and Naphthalenes by Electrophilic Cyclization of Acetylenic Arenecarboxaldehydes

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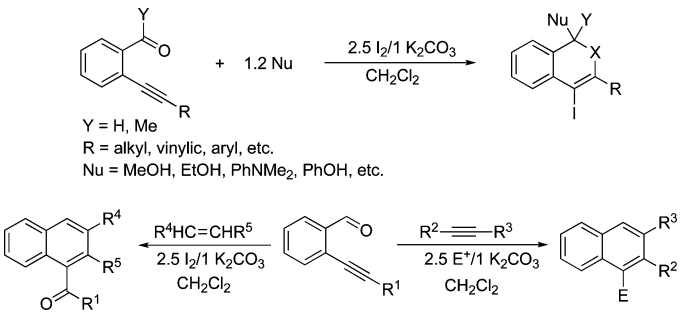
Received November 29, 2005



Highly substituted 1*H*-isochromenes, isobenzofurans, and pyranopyridines can be prepared by allowing *o*-(1-alkynyl)arenecarboxaldehydes and ketones to react with I_2, ICl, NIS, Br_2, NBS, *p*-$O_2NC_6H_4SCl$, or PhSeBr and various alcohols or carbon-based nucleophiles at room temperature. Naphthyl ketones and iodides are also readily prepared by the reaction of 2-(1-alkynyl)arenecarboxaldehydes with I_2 and simple olefins or alkynes.

Introduction

The electrophilic cyclization of functionally substituted alkenes has provided an extremely useful route to a wide variety of heterocyclic and carbocyclic compounds, which have proven useful as intermediates in the synthesis of natural products and pharmaceuticals.[1] Analogous chemistry of alkynes has been far less studied, although it would appear to be a very promising route to an extraordinary range of useful, functionally substituted heterocycles and carbocycles.[2] Our recent work and that of others have indicated that benzofurans,[3] benzothiophenes,[4] isoquinolines,[5] indoles,[3c,6] isocoumarins,[7] isoindolinones,[8] polycyclic aromatics,[9] and a number of other heterocycles[10] can be easily synthesized by the electrophilic cyclization of appropriate functionally substituted alkynes using iodine-, bromine-, sulfur-, and selenium-containing electrophiles under exceptionally mild reaction conditions (Scheme 1).

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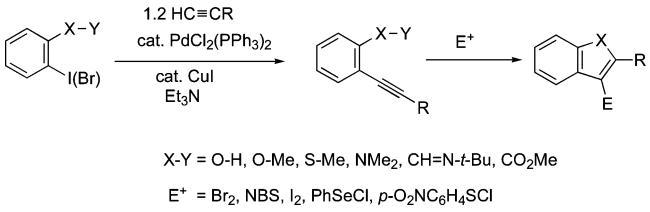
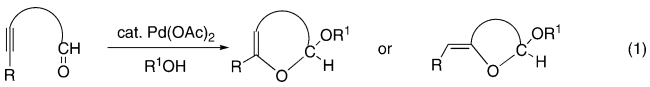
10.1021/jo0524573 CCC: $33.50 © 2006 American Chemical Society
Published on Web 04/06/2006

SCHEME 1

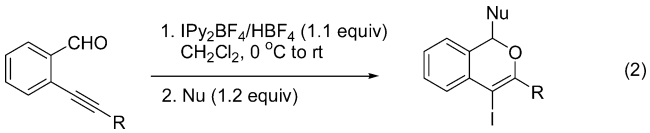


Not long ago, Yamamoto reported an interesting cyclization of acetylenic aldehydes to 1-alkoxy-1*H*-isochromenes catalyzed by $Pd(OAc)_2$ (eq 1).[11] The Pd(II) salt employed was claimed to



(1)

exhibit a dual role as both a Lewis acid and a transition-metal catalyst. Recently, a similar preparation of 4-iodo-1*H*-isochromenes has been achieved upon reaction of bis(pyridine)-iodonium tetrafluoroborate (IPy_2BF_4) and HBF_4 with the same acetylenic carbonyl precursors in the presence of various nucleophiles (eq 2).[12] The use of expensive IPy_2BF_4 together



(2)

with $B(OMe)_3$ or toxic, strongly acidic HBF_4, and the relatively complicated stepwise procedure employed have certain drawbacks synthetically. Furthermore, the full scope of this cyclization has yet to be reported.

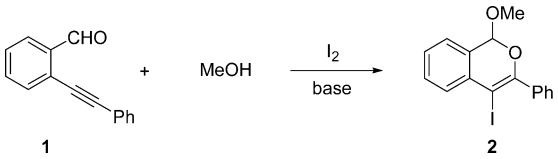
We simultaneously found that this three-component reaction[13] proceeds smoothly by using the simple electrophiles ICl, NIS, Br_2, NBS, *p*-$O_2NC_6H_4SCl$, and PhSeBr to generate the corresponding iodine-, bromine-, sulfur-, and selenium-substituted heterocycles in high yields under very mild reaction conditions.[14] Herein, we wish to report further details on this efficient approach to heterocycles and carbocycles involving electrophilic cyclization using a range of electrophiles and nucleophiles.

Results and Discussion

Our initial studies were aimed at finding optimal reaction conditions for the electrophilic cyclization of the *o*-(1-alkynyl)-benzaldehydes. Our investigation began with the reaction of *o*-(phenylethynyl)benzaldehyde (**1**), methanol, and I_2 (eq 3, Table 1).

The reaction was first attempted using 0.25 mmol of *o*-(phenylethynyl)benzaldehyde (**1**), 1.2 equiv of methanol, 1.0 equiv of K_2CO_3, and 1.2 equiv of I_2 in CH_2Cl_2 at room temperature. Iodocyclization proceeded smoothly and provided an 88% yield of the desired product **2**. Other solvents, such as CH_3CN and DMF, were also investigated and proved to be far less effective. $KHCO_3$ and NEt_3 were also investigated as bases.

TABLE 1. Iodocyclization of 2-(Phenylethynyl)benzaldehyde



(3)

1 **2**

solvent	MeOH (equiv)	I_2 (equiv)	base (equiv)	yield (%)
CH_2Cl_2	1.2	1.2	K_2CO_3(1.0)	88
CH	1.2	1.2	K_2CO_3(1.0)	40
DMF	1.2	1.2	K_2CO_3(1.0)	trace
CH	1.2	1.2	$KHCO_3$ (1.0)	70
CH	1.2	1.2	Et_3N	
CH	2.0	2.5	K_2CO_3(1.0)	80
CH	2.0	2.5	K_2CO_3(2.0)	78
MeOH	-	2.5	K_2CO_3(2.0)	68

While $KHCO_3$ provided a slightly lower yield of the desired product than K_2CO_3, NEt_3 proved to be totally ineffective and none of the desired product was detected. Although CH_2Cl_2 is not a good solvent for K_2CO_3, the presence of K_2CO_3 was crucial for a clean, high-yielding reaction. K_2CO_3 is presumed to neutralize the byproduct HI of the electrophilic cyclization, which can also react with the acetylenic aldehyde and generate the corresponding pyrilium salt.[15] Increasing the amount of methanol from 1.2 equiv to using MeOH as the solvent actually resulted in a lower yield. Using 1.2 equiv of I_2 has proven to be enough to achieve a high yield. Further increasing the amount of I_2 did not give any better yield. Based on the above optimization efforts, the combination of 1.2 equiv of nucleophile, 1.0 equiv of K_2CO_3, and 1.2 equiv of I_2 and using CH_2Cl_2 as the solvent at room temperature gave the best results. This procedure has been used as our standard reaction conditions for subsequent electrophilic cyclizations.

To explore the scope of this cyclization, other commercially available iodine, bromine, phosphorus, sulfur, and selenium electrophiles have also been used in this process under similar reaction conditions. The results are summarized in Table 2. It has been found that I_2, NIS, ICl, NBS, PhSeBr, and *p*-$O_2NC_6H_4SCl$ are all good electrophiles for the reaction of 2-(phenylethynyl)benzaldehyde (**1**) and MeOH, providing decent yields of the desired cyclization products (entries 1−7). The strong electrophile Br_2 also readily reacted with aldehyde **1** to generate the desired cyclization product (entry 5). However, the reaction is not clean and only 21% of the desired product was obtained. Electrophiles, such as *tert*-butylsulfinyl chloride and diphenylphosphinous chloride (Ph_2PCl), did not react with aldehyde **1**, and none of the desired product was observed (entries 8 and 9).

To further explore the scope of this chemistry, various nucleophiles have been tested in this process using 2-(phenylethynyl)benzaldehyde (**1**) and I_2. Alcohols, such as MeOH, *n*-BuOH, *t*-BuOH and 2-iodobenzyl alcohol, all react well and provide good to excellent yields of the desired iodocyclization products (entries 1 and 10−12). The reaction with *t*-BuOH provided only a modest yield due apparently to the steric hindrance of the *tert*-butyl group or perhaps dehydration of this alcohol (entry 11).

Nucleophiles other than alcohols have also been examined under our standard cyclization conditions. While the reaction using *N*,*N*-dimethylaniline as the nucleophile provided an

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TABLE 2. Electrophilic Cyclization of Acetylenic Aldehydes, Ketones, and Imines[a]

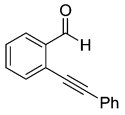
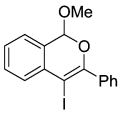
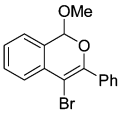
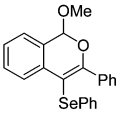
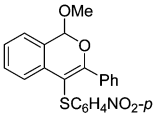
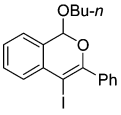
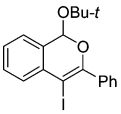
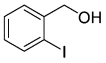
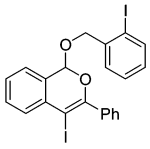
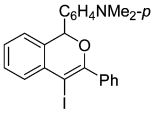
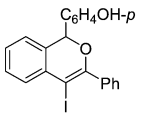
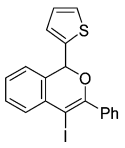
entry	alkyne		nucleophile	electrophile	product		isolated yield (%)
1		**1**	MeOH	I_2		**2**	93[b]
2			MeOH	NIS		**2**	60
3			MeOH	ICl		**2**	74
4			MeOH	NBS		**3**	51
5			MeOH	Br_2		**3**	21
6			MeOH	PhSeBr		**4**	65
7			MeOH	*p*-$O_2NC_6H_4SCl$		**5**	74
8			MeOH		-		-
9			MeOH		-		-
10			*n*-BuOH	I_2		**6**	81
11			*t*-BuOH	I_2		**7**	49
12				I_2		**8**	87
13				I_2		**9**	88
14				I_2		**10**	35[c]
15				I_2		**11**	43

Table 2 (Continued)

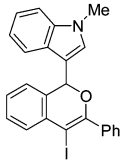
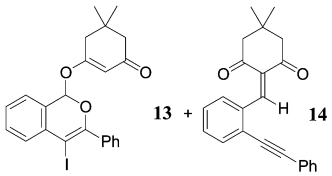
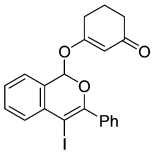
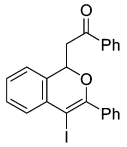
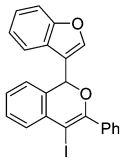
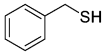
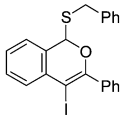
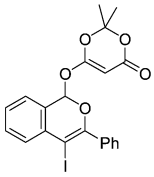
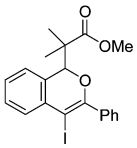
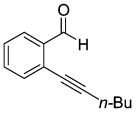
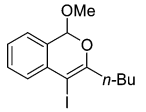
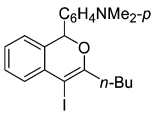
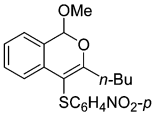
entry	alkyne		nucleophile	electrophile	product		isolated yield (%)
16				I_2		**12**	30[d]
17				I_2		**13** + **14**	53:35
18				I_2		**15**	54[d]
19				I_2		**16**	63[e]
20				I_2			-
21				I_2			-
22				I_2			-
23				I_2			-
24		**17**	MeOH	I_2		**18**	84
25				I_2		**19**	70
26			MeOH	*p*-$O_2NC_6H_4SCl$		**20**	73

Table 2 (Continued)

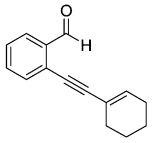
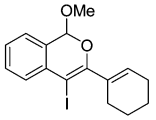
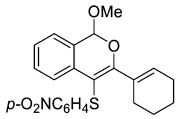
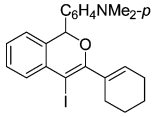
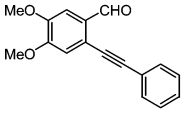
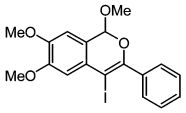
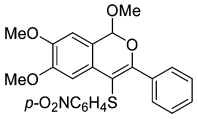
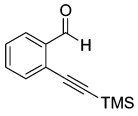
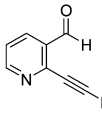
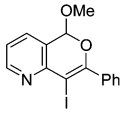
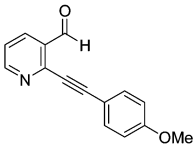
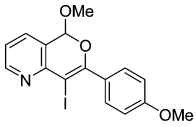
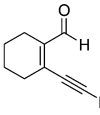
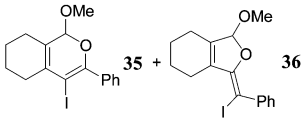
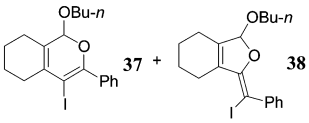
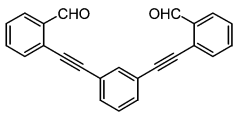
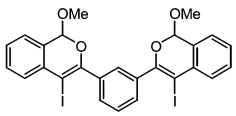
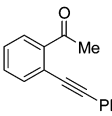
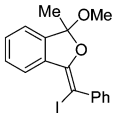
entry	alkyne		nucleophile	electrophile	product		isolated yield (%)
27		**21**	MeOH	I_2		**22**	81
28			MeOH	ICl		**22**	53
29			MeOH	*p*-$O_2NC_6H_4SCl$		**23**	60
30				I_2		**24**	83
31		**25**	MeOH	I_2		**26**	100
32		**25**	MeOH	*p*-$O_2NC_6H_4SCl$		**27**	51[f]
33		**28**	MeOH	I_2	-		-
34		**29**	MeOH	I_2	-		-
35		**30**	MeOH	I_2		**31**	70
36			MeOH	ICl		**31**	64
37		**32**	MeOH	I_2		**33**	96
38		**34**	MeOH	I_2	 **35** + **36**		60[d] (1:1)
39			*n*-BuOH	NIS	 **37** + **38**		39[d] (1:7)
40		**39**	MeOH	I_2		**40**	75
41		**41**	MeOH	I_2		**42**	90

Table 2 (Continued)

[a] The reactions were run under the following conditions, unless otherwise specified. While stirring a solution of 2.5 mL of CH_2Cl_2 containing 0.25 mmol of the alkyne, 0.30 mmol of the nucleophile, and 0.25 mmol of K_2CO_3, 0.30 mmol of electrophile was added, and the resulting mixture was further stirred at room temperature until the total disappearance of the starting material upon TLC analysis. [b] The reaction was run on a 1.0 mmol scale; the 0.25 mmol scale reaction provides an 88% yield of compound **2**. [c] A 25% yield of O-trapping product was also observed. [d] This yield was determined by ^{1}H NMR spectroscopic analysis due to the apparent instability of the product. [e] 1 equiv of KF was added. [f] A 45% yield of adduct formed by direct addition of *p*-$O_2NC_6H_4SCl$ to the triple bond.

excellent yield of the cyclization product (entry 13), those using phenol, thiophene, *N*-methylindole, 5,5-dimethyl-1,3-cyclohexanedione, and 1,3-cyclohexanedione only afforded modest yields of the desired cyclization products (entries 14−18). The reaction with phenol provided both carbon- and oxygen-trapping products (entry 14). The reactions which have produced carbon coupling products were highly regioselective. The 1,3-diketone reactions gave enol trapping products, plus some aldol product in the case of 5,5-dimethyl-1,3-cyclohexanedione (entries 17 and 18). The reaction with the trimethylsilyl enol ether of acetophenone did not afford the desired cyclization product under our standard reaction conditions; only the aldol condensation product was observed. However, adding 1 equiv of KF as a promoter greatly affected the reaction pathway, affording a 63% yield of the desired cyclization product (entry 19). Other nucleophiles, such as benzofuran, benzylthiol, Meldrum's acid, and 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene failed to react under our standard reaction conditions, and none of the desired products were observed (entries 20−23). Thiols did not prove to be useful nucleophiles, perhaps due to oxidation to disulfides by iodine. Primary and secondary amines have also been used as nucleophiles, but none of the expected products were formed.

To further examine the generality of this chemistry, acetylenic aldehydes bearing different substituents on the carbon−carbon triple bond were synthesized in high yields by palladium/copper-catalyzed coupling of the appropriate *o*-bromoarenecarboxaldehydes and the corresponding terminal alkynes.[16] The resulting acetylenic aldehydes were then allowed to react under our standard electrophilic cyclization conditions to afford the corresponding 1*H*-isochromene products. Alkynes bearing an alkyl and a vinylic substituent on the triple bond also react well and provide the desired electrophilic cyclization products in good yields, when methanol and *N*,*N*-dimethylaniline are used as the nucleophiles (entries 24, 25, 27, 28, and 30). 4,5-Dimethoxy-2-(phenylethynyl)benzaldehyde (**25**) also underwent smooth iodocyclization, providing a quantitative yield of the MeOH-trapped product (entry 31).

Besides the successful use of PhSeBr as an electrophile (entry 6, Table 2), we have also been able to extend this cyclization chemistry to sulfur electrophiles. Thus, aryl-, alkyl-, and vinylic-substituted acetylenes undergo cyclization and provide sulfur-substituted isochromenes in 60−74% yields, respectively (entries 7, 26, and 29). The reaction of aldehyde **25** and *p*-$O_2NC_6H_4$-SCl afforded only a 51% yield of the desired cyclization product, alongside a 45% yield of the product of simple addition of the electrophile to the carbon−carbon triple bond (entry 32).

Rather unstable 2-ethynylbenzaldehyde (**28**) and 2-(trimethylsilylethynyl)benzaldehyde (**29**) have also been employed as aldehydes, but they did not undergo cyclization when MeOH and I_2 were used (entries 33 and 34). The reactions were messy, and unidentifiable mixtures were observed instead.

Pyridinecarboxaldehyde derivatives **30** and **32** have also been allowed to react under our standard cyclization conditions using MeOH as a nucleophile and I_2 or ICl as electrophiles. The electron-deficient aromatic ring of these aldehydes did not affect cyclization. We still obtained the desired iodocyclization products using aldehyde **30** and either I_2 or ICl in 70% and 64% yields, respectively (entries 35 and 36). The presence of an electron-donating group on the aromatic ring on the distal end of the carbon−carbon triple bond greatly enhanced the cyclization, and a 96% yield of the desired cyclization product was obtained when pyridinecarboxaldehyde **32** was employed (entry 37).

Besides aromatic carboxaldehydes, vinylic carboxaldehyde **34** has also been examined under our standard iodocyclization conditions. Using I_2 and methanol, a 1:1 mixture of 5- and 6-membered ring products was observed by ^{1}H NMR spectroscopic analysis (entry 38). Using NIS and *n*-BuOH, a mixture was again obtained, but this time the 5-membered ring product was favored by a 7:1 ratio (entry 39). The ratio of 5- to 6-membered ring products thus varies depending on the nucleophile and electrophile used in the reaction.

We have also investigated the possibility of carrying out a double iodocyclization, which might be quite useful for the quick assembly of systems with extended conjugation. Compound **39** underwent smooth iodocyclization to afford the double cyclization product in a 75% yield (entry 40). In all cases where we have compared results, these reactions with readily available, inexpensive iodine have given higher yields than the corresponding process using the expensive iodonium salt and HBF_4 reported by Barluenga.[12]

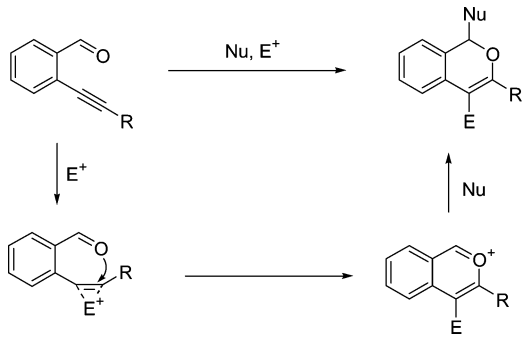
We have also examined the cyclization of a ketone-containing alkyne. Ketone **41** has been allowed to react with I_2 and methanol under our standard reaction conditions (entry 41). This reaction proceeded smoothly to provide a 90% yield of a 5-*exo*-*dig* cyclization product, rather than the 6-membered ring ether formed by the electrophilic cyclization of analogous benzaldehyde derivatives. The use of K_2CO_3 in our standard procedure provides very mild basic conditions and avoids the acid-initiated, partial decomposition of this cyclization product described by Barluenga.[12]

Interestingly, we were unable to get high yields of the desired iodocyclization products when we employed our reagents in a stepwise manner analogous to that described by Barluenga.[12] Instead, an unreactive solid, presumed to be the pyrilium salt,[15] was generated. Based on this observation, a possible mechanism for our process is proposed in Scheme 2. We believe that these cyclizations proceed by *anti* attack of the electrophile and the carbonyl to produce a pyrilium intermediate. Before it forms an insoluble precipitate,[15] the pyrilium intermediate is immediately trapped by the nucleophile present in the reaction mixture.

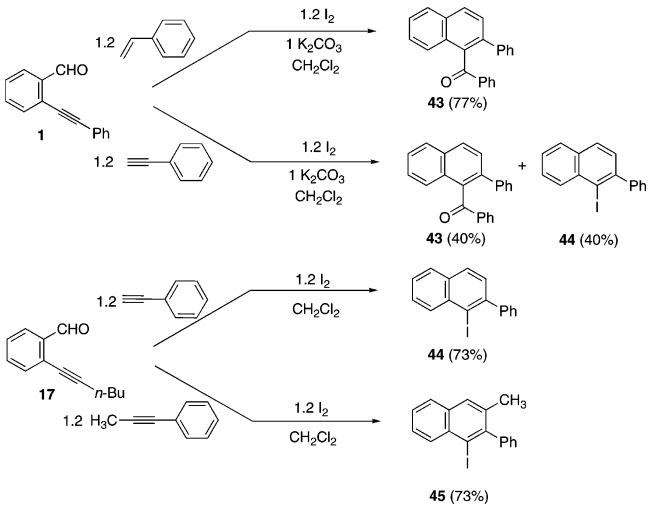
Recently, a number of new naphthalene synthesis have been reported, which involve alkyne cyclizations.[17] For example, Barluenga et al. have reported that IPy_2BF_4, *o*-alkynyl-substituted carbonyl compounds, and alkynes react to give

(16) (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 5, pp 203−229. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

SCHEME 2



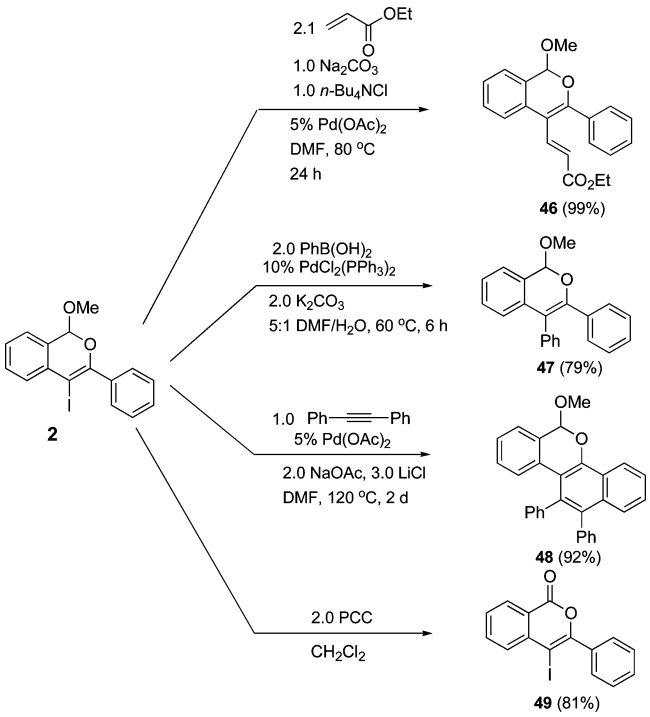
SCHEME 3



1-iodonaphthalene derivatives and the reaction with alkenes instead of acetylenes afforded related naphthyl ketone derivatives.[17d] Our studies have shown that the same substituted naphthalenes can be synthesized in high yields comparable to those obtained by Barluenga employing our I_2 procedure and alkenes or alkynes as the trapping reagent (Scheme 3). The use of the more sophisticated iodonium reagent IPy_2BF_4 employed by Barluenga[17d] for this same process is not necessary. These reactions are believed to proceed through a similar pyrilium intermediate, which is trapped by the alkene or alkyne. Once again, the use of readily available, easily handled I_2 greatly simplifies the procedure developed by Barluenga.[17d]

We believe that this approach to heterocycles should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting halogen, sulfur and selenium functionalities into other substituents. For instance, the resulting heterocyclic iodides should be particularly useful intermediates in many palladium-catalyzed processes, such as Sonogashira,[16] Suzuki,[18] Stille,[19] and Heck[20] cross-couplings. For instance, compound **2** has been treated under standard Heck and Suzuki conditions, providing the corresponding coupling products **46** and **47** in 99% and 79% yields respectively (Scheme 4). Using the palladium-catalyzed annulation of an internal alkyne developed in our group,[21] we have been able to convert compound **2** to **48** in a 92% yield. Compound **2** is also readily oxidized to 4-iodoisocoumarin **49** in an 81% yield by using PCC (Scheme 4).

SCHEME 4



Conclusions

Efficient syntheses of a variety of substituted oxygen-containing heterocycles and carbocycles have been developed using the electrophilic cyclization of acetylene-containing aldehydes and ketones, and the generality of this process has been explored. This method accommodates various functional groups and affords substituted heterocycles in good to excellent yields. The resulting iodoheterocycles are readily elaborated to more complex compounds by using known organopalladium chemistry. Although Barluenga[12,17d] reported similar reactions using *o*-(1-alkynyl)benzaldehydes and IPy_2BF_4 plus HBF_4, we have been able to extend the above chemistry to polycyclic compounds and bisisochromenes using readily available, inexpensive, easily handled I_2 as the iodine source, and we have generally obtained cleaner and higher yielding reactions. We have also shown that electrophiles, such as ICl, NIS, NBS, Br_2, *p*-$O_2NC_6H_4SCl$,and PhSeBr, can be used in this chemistry.

(17) For metal-catalyzed synthesis of naphthalenes, see: (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921. (c) Asao, N.; Kasahara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3504. For the iodonium ion-prompted synthesis of naphthalenes, see: (d) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; González, J. M. *Org. Lett.* **2003**, *5*, 4121. (e) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Adv. Synth. Catal.* **2005**, *347*, 526.

(18) (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145. (c) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 49−97. (d) Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457.

(19) (a) Negishi, E.; Dumond, Y. *Handb. Organopalladium Chem. Org. Synth.* **2002**, *1*, 767. (b) Kosugi, M.; Fugami, K. *Handb. Organopalladium Chem. Org. Synth.* **2002**, *1*, 263. (c) Kosugi, M.; Fugami, K. *J. Organomet. Chem.* **2002**, *653*, 50.

(20) (a) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (b) Brase, S.; De Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 99−166. (c) *Palladium Reagents in Organic Synthesis*; Heck, R. F., Ed.; Academic Press: San Diego, 1985; pp 276−287.

(21) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm) or a basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. Low-resolution mass spectra were recorded on a triple quadrupole mass spectrometer. High-resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institute of General Medical Sciences (GM070620), and the National Institutes of Health (KU Chemical Methodologies and Library Development Center of Excellence, P50 GM069663) for financial support of this research. We also thank Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Ltd., for donations of palladium salts. We thank Dr. Xiaoxia Zhang for help in the preparation of this manuscript.

Supporting Information Available: General experimental procedures and spectral data for all previously unreported starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0524573