

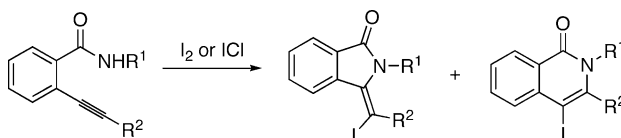
Regio- and Stereoselective Synthesis of Isoindolin-1-ones via Electrophilic Cyclization

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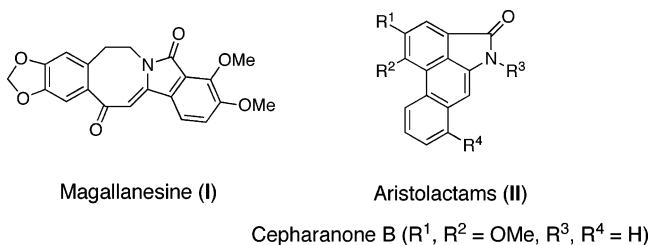
A variety of substituted isoindolin-1-ones are readily prepared in good to excellent yields under very mild reaction conditions by the reaction of *o*-(1-alkynyl)benzamides with ICl, I₂, and NBS. In a few cases, substituted isoquinolin-1-ones were obtained as the major product instead. This methodology accommodates various alkynyl amides and functional groups and has been successfully extended to heterocyclic starting materials. This chemistry has been successfully applied to the synthesis of a biologically interesting alkaloid, cepharanone B.

Introduction

The isoindolin-1-one ring system represents a key structural subunit in numerous natural and synthetic products that exhibit a wide range of biological activities, including antihypertensive,¹ antiinflammatory,² antiulcer,³ and antileukemic⁴ properties. For example, magallanesine (**I**), an isoindolobenzazocine, has been isolated from various *Berberis* species (Scheme 1).⁵ Aristolactams (**II**) are found exclusively among the plants of the family Aristolochiaceae.⁶ The current interest elicited by these fused phenanthrene lactams arises from their varied pharmaceutical and biological activities reported in folk medicine⁷ and as immunostimulant and anticancer agents.⁶

Considerable efforts have been directed toward the synthesis of isoindolinones (phthalimidines). Isoindoli-

SCHEME 1



nones have been prepared via Grignard⁸ or lithiation⁹ procedures, as well as by Wittig,¹⁰ Diels–Alder,^{4,11} rearrangement,¹² and photochemical reactions.¹³ The reduction of *N*-substituted phthalimides¹⁴ and the condensa-

(1) Ferland, J.-M.; Demerson, C. A.; Humber, L. G. *Can. J. Chem.* **1985**, *63*, 361.

(2) Li, S.; Wang, X.; Guo, H.; Chen, L. *Yiyao Gongye* **1985**, *16*, 543; *Chem. Abstr.* **1985**, *105*, 3788.

(3) Lippmann, W. U.S. Patent 4 267 189, 1981; *Chem. Abstr.* **1981**, *95*, 61988m.

(4) Taylor, E. C.; Zhou, P.; Jennings, L. D.; Mao, Z.; Hu, B.; Jun, J.-G. *Tetrahedron Lett.* **1997**, *38*, 521.

(5) Valencia, E.; Fajardo, V.; Freyer, A. J.; Shamma, M. *Tetrahedron Lett.* **1985**, *26*, 993.

(6) (a) Chang, Z.-L.; Zhu, D.-Y. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31, p 29. (b) Han, D. S.; Cheng, B. S.; Chi, H. J.; Lee, H. S. *Korean J. Pharmacogn.* **1989**, *20*, 1. (c) Lee, H. S.; Han, D. S.; Won, D. K. *Korean J. Pharmacogn.* **1990**, *21*, 52.

(7) Kijjoo, A.; Pinto, M. M. M.; Tantisewie, B.; Herz, W. *Planta Med.* **1989**, *55*, 193.

(8) (a) Heidenbluth, V. K.; Tonjes, H.; Scheffier, R. *J. Prakt. Chem.* **1965**, *30*, 204. (b) Ang, W. S.; Halton, B. B. *Aust. J. Chem.* **1971**, *24*, 851.

(9) (a) Watanabe, H.; Mao, C.-L.; Barnish, I. T.; Hauser, C. R. *J. Org. Chem.* **1969**, *34*, 919. (b) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1188. (c) Couture, A.; Deniau, E.; Grandclaude, P. *Tetrahedron* **1997**, *53*, 10313. (d) Couture, A.; Deniau, E.; Ionescu, D.; Grandclaude, P. *Tetrahedron Lett.* **1998**, *39*, 2319.

(10) (a) Flitsch, W.; Peters, H. *Tetrahedron Lett.* **1969**, 1161. (b) Mali, R. S.; Yeola, S. *Synthesis* **1986**, 755. (c) Epszajn, J.; Grzelak, R.; Jozwiak, A. *Synthesis* **1996**, 1212.

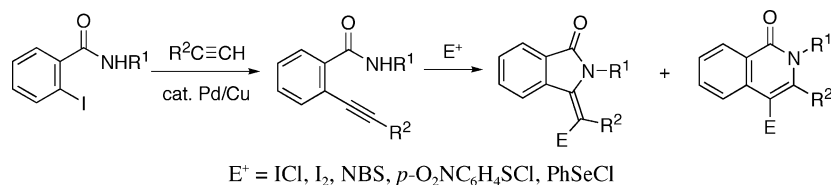
(11) Gutierrez, A. J.; Shea, K. J.; Svoboda, J. J. *J. Org. Chem.* **1989**, *54*, 4335.

(12) Guillaumel, J.; Boccara, N.; Demerseman, P.; Royer, R. *J. Chem. Soc., Chem. Commun.* **1988**, 1604.

(13) (a) Freccero, M.; Fasani, E.; Albini, A. *J. Org. Chem.* **1993**, *58*, 1740. (b) Weidner-Wells, M. A.; Oda, K.; Mazzocchi, P. H. *Tetrahedron* **1997**, *53*, 3475.

(14) (a) Brewster, J. H.; Fusco, A. M.; Carosino, L. E.; Corman, B. G. *J. Org. Chem.* **1963**, *28*, 498. (b) Milewska, M. J.; Bytner, T.; Polonski, T. *Synthesis* **1996**, 1485.

SCHEME 2



tion of phthalaldehyde¹⁵ also afford isoindolinones. Besides the classical methods, metal-catalyzed syntheses of isoindolinones have also been reported. Cobalt and rhodium carbonyl complexes can be used as the catalysts to synthesis isoindolinones.¹⁶ Several examples of palladium catalysis have appeared.¹⁷ Recently, the intramolecular cyclization of alkynamides has been reported to produce isoindolinones.¹⁸

We and others have developed methods for the synthesis of benzo[*b*]thiophenes,¹⁹ isoquinolines and naphthyridines,²⁰ isocoumarins and α -pyrones,²¹ benzofurans,²² furans,²³ indoles,²⁴ furopyridines,²⁵ cyclic carbonates,²⁶ 2,3-dihydropyrroles and pyrroles,²⁷ pyrilium salts,²⁸ and bicyclic β -lactams²⁹ via electrophilic cyclization of functionally substituted alkynes. In a continuation of our studies, we have investigated the possibility of using electrophilic cyclization for the synthesis of isoindolinones and isoquinolinones. Herein, we report the successful electrophilic cyclization of *o*-(1-alkynyl)benzamides for

TABLE 1. Iodocyclization of *o*-(1-alkynyl)benzamide **1** (eq 1)^a

entry	electrophile	base	solvent	time (h)	% yield of 2	% yield of 3
1 ^b	ICl		CH ₂ Cl ₂	0.5	54	40
2	I ₂		CH ₂ Cl ₂	1	60	20
3	I ₂		CH ₃ CN	1	75	14
4	I ₂	NaHCO ₃	CH ₃ CN	1	86	10
5	I ₂	NaHCO ₃	MeOH	1	85	8

^a All reactions were run under the following conditions, unless otherwise indicated: 0.30 mmol of **1**, 0.90 mmol of electrophile, and 0.90 mmol of base in 3 mL of solvent were stirred at room temperature under Ar for the specified period of time. ^b 0.36 mmol of electrophile was employed.

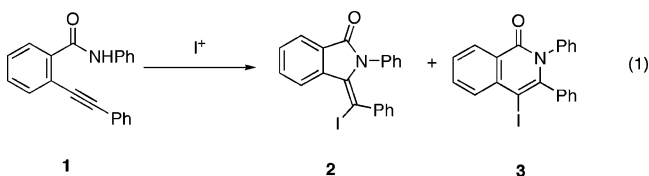
the synthesis of isoindolinones. This chemistry generally produces good to excellent yields of the five-membered ring lactams with good regioselectivity.

Results and Discussion

A two-step approach to isoindolinones has been examined involving (i) preparation of *o*-(1-alkynyl)benzamides by a Sonogashira coupling reaction,³⁰ and (ii) electrophilic cyclization (Scheme 2).

The *o*-(1-alkynyl)benzamides required for our approach are readily prepared by Sonogashira coupling³⁰ of the corresponding iodobenzamides with terminal alkynes using 2% PdCl₂(PPh₃)₂ and 1% CuI in Et₃N solvent at 55 °C. The yields of this process range from 74 to 99%, and this procedure should readily accommodate considerable functionality.

The reaction of *o*-(1-alkynyl)benzamide **1** with electrophiles was chosen as a model system for optimization of this electrophilic cyclization process (eq 1). The results are summarized in Table 1.



Benzamide **1** reacts at room temperature in CH₂Cl₂ to afforded a mixture of lactams **2** and **3** (Table 1, entry 1). Compared with the stronger electrophile ICl, the weaker electrophile I₂ shows better regioselectivity (compare entries 1 and 2). The regioselectivity of this process also depends on the solvent employed in the reaction. Using CH₃CN as the solvent afforded better regioselectivity and

(30) For reviews, see: (a) Campbell, I. B. *The Sonogashira Cu–Pd-Catalyzed Alkyne Coupling Reaction*. *Organocopper Reagents*; Taylor, R. J. K., Ed.; IRL Press: Oxford, UK, 1994; pp 217–235. (b) Sonogashira, K.; Takahashi, S. *Yuki Gosei Kagaku Kyokaiishi* **1993**, 51, 1053. (c) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 3, pp 521–549.

- (15) (a) Yamamoto, I.; Tabo, Y.; Gotoh, H. *Tetrahedron Lett.* **1971**, 2295. (b) Dominh, T.; Johnson, A. L.; Jones, J. E.; Senise, P. P., Jr. *J. Org. Chem.* **1977**, 42, 4217. (c) Grigg, R.; Gunaratne, H. Q. N.; Sridharan, V. *J. Chem. Soc., Chem. Commun.* **1985**, 1183. (d) Takahashi, I.; Kawakami, T.; Hirano, E.; Yokota, H.; Kitajima, H. *Synlett* **1996**, 353. (e) Takahashi, I.; Hatanaka, M. *Heterocycles* **1997**, 45, 2475.
- (16) Wilkinson, G.; Stone, F. G. A.; Abel, E. W. *Comprehensive Organometallic Chemistry*, 1st ed.; Pergamon: Oxford, 1982; Vol. 1.
- (17) (a) Mori, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, 43, 1684. (b) Larock, R. C.; Liu, C.-L.; Lau, H. H.; Varaprath, S. *Tetrahedron Lett.* **1984**, 25, 4459. (c) Burns, B.; Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron* **1992**, 48, 7297. (d) Cho, C. S.; Jiang, L. H.; Shim, S. C. *Synth. Commun.* **1998**, 28, 849. (e) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, 56, 4777. (f) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, 50, 11803.
- (18) (a) Koseki, Y.; Kusano, S.; Sakata, H.; Nagasaka, T. *Tetrahedron Lett.* **1999**, 40, 2169. (b) Kundu, N. G.; Khan, M. W.; Mukhopadhyay, R. *Tetrahedron* **1999**, 55, 12361.
- (19) (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.
- (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) (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.
- (22) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432.
- (23) (a) Bew, S. P.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1996**, 1007. (b) Djuardi, E.; McNelis, E. *Tetrahedron Lett.* **1999**, 40, 7193.
- (24) Barluenga, J.; Trincado, M.; Rublio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, 42, 2406.
- (25) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, 4, 2409.
- (26) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, 64, 3798.
- (27) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Chem. Commun.* **1998**, 2207.
- (28) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, 125, 9028.
- (29) Ren, X.-F.; Konaklieva, M. I.; Shi, H.; Dickey, S.; Lim, D. V.; Gonzalez, J.; Turos, E. *J. Org. Chem.* **1998**, 63, 8898.

a higher yield than CH_2Cl_2 (compare entries 2 and 3). The yield and selectivity can be further improved by adding NaHCO_3 to neutralize the acid generated in the reaction (compare entries 3 and 4). A similar yield and regioselectivity were also obtained when using MeOH as the solvent (entry 5). Thus, we have chosen the following reaction conditions A for the synthesis of isoindolin-1-ones: 0.30 mmol of the *o*-(1-alkynyl)benzamide, 3 equiv of I_2 , and 3 equiv of NaHCO_3 in 3 mL of CH_3CN stirred at room temperature for 1 h. We have also employed reaction conditions B on occasion: 0.30 mmol of the *o*-(1-alkynyl)benzamide and 1.2 equiv of ICl in 3 mL of CH_2Cl_2 stirred at room temperature for 0.5 h. The reaction of amide **1** with bis(collidine)iodonium hexafluorophosphate in CH_2Cl_2 afforded only very slow reactions and a mixture of five- and six-membered ring lactams with the former predominating.

To explore the scope of this electrophilic cyclization strategy, the reactions of alkynyl amide **1** with different electrophiles (ICl , I_2 , NBS, $p\text{-O}_2\text{NC}_6\text{H}_4\text{SCl}$, and PhSeCl) at room temperature have been studied (Table 2, entries 1–5). When using ICl , I_2 , and NBS as the electrophilic reagents, a mixture of five- and six-membered ring products has been obtained. In all cases, the five-membered ring product predominates. However, ICl generally affords larger amounts of the six-membered ring lactam. When using $p\text{-O}_2\text{NC}_6\text{H}_4\text{SCl}$ and PhSeCl , the reaction proceeds smoothly. Unfortunately, the five-membered ring products could not be isolated because they appear to decompose easily. Only small amounts of the six-membered ring products could be isolated.

The effect of ICl and I_2 on the regiochemistry of ring closure of several different amide moieties has been examined (compare entries 1 and 2, 7 and 8, and 9 and 10). Although the results vary somewhat with the nature of the substituent on the nitrogen, I_2 exhibits much better regioselectivity than ICl in all cases examined. A small amount of the six-membered ring product is always observed. However, when using I_2 and nonsubstituted or disubstituted amides, none of the desired cyclization products could be obtained (entries 11 and 12).

A wide variety of alkynylarene-carboxamides have been examined in this cyclization process. First of all, using *N*-phenylcarboxamides, we have examined the effect of various substituents on the remote end of the alkyne moiety (entries 13–16). Aryl- (entries 1 and 2) and a long-chain alkyl-substituted alkyne **22** (entry 13) afford similar results. Even the TMS-substituted alkyne **25** underwent smooth iodocyclization with I_2 (entry 14). The isoindolinone **26** was obtained in 77% yield, along with a small amount of the corresponding diiodoisoquinolinone **27**. Obviously, the silyl group in the isoquinolinone has undergone iododesilylation either prior to or soon after cyclization. Surprisingly, the presence of an olefin (entries 15 and 16) affords the six-membered ring isoquinolinone **30** as the major product, no matter whether ICl or I_2 is used. The six-membered ring lactam is formed fairly cleanly when using ICl (entry 16).

The effect of substitution on the aromatic ring has also been examined. Isoindolinone **32** bearing two electron-donating methoxy substituents on the aromatic ring and a silyl moiety has been obtained in a good yield (entry 17). However, the corresponding alkyne in which the silyl

group has been replaced by a hydrogen failed to give any recognizable products (entry 18).

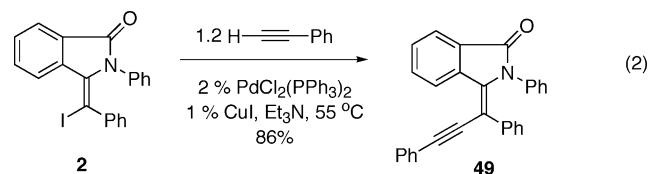
This electrophilic cyclization is not limited to simple benzene-containing aromatics. The pyridine-containing substrates **37**, **40**, and **43** have also been observed to give good yields of cyclization products (entries 19–25). A comparison of entry 19 with entry 20 indicates that a higher yield of the five-membered ring product **38** can actually be obtained using a shorter reaction time. It appears that this isoindolinone is somewhat unstable under the reaction conditions. Interestingly, using ICl produces the six-membered ring product **39** as the major product, while I_2 affords the five-membered ring product as the major isomer (compare entries 20 and 21). The alkyl-substituted alkyne **40** reacts in a similar fashion affording the five-membered ring lactam **41** as the major product when using I_2 and generating the six-membered ring product **42** as the major product when ICl is used as the electrophile (entries 22 and 23). Introduction of a vinylic moiety directly on the alkyne leads to exclusive six-membered ring formation no matter whether I_2 or ICl is employed (entries 24 and 25).

We have also briefly examined the cyclization of a ring-containing alkenynamide **46**. The five-membered ring substrate **46** reacts with I_2 to afford a mixture of lactams **47** and **48** in which the six-membered ring product **48** predominates presumably due to ring strain (entry 26).

The isoindolinones have been distinguished from the isoquinolinones on the basis of their IR spectra. The five-membered ring products generally exhibit a carbonyl absorption band at $1710\text{--}1680\text{ cm}^{-1}$, while in the six-membered ring products the carbonyl absorption is observed at $1640\text{--}1650\text{ cm}^{-1}$. The (*E*)-stereochemistry of isoindolinone **32** has been assigned using a NOESY experiment. This compound exhibits a cross-peak between the CH_2 of the benzyl group and the CH_3 of the TMS group. The stereochemistry of the other isoindolinones is assigned by analogy to lactam **32**.

We propose the following mechanism for this electrophilic cyclization (Scheme 3). Nucleophilic attack by the nitrogen of the amide group on the carbon–carbon triple bond activated by coordination to I^+ is followed by deprotonation to afford the cyclized products.

An interesting feature of this process is the fact that the isoindolinones and isoquinolinones produced by iodocyclization can be further elaborated using various palladium-catalyzed processes. For example, the Sonagashira reaction³⁰ of lactam **2** affords the coupling product **49** in an excellent yield (eq 2).



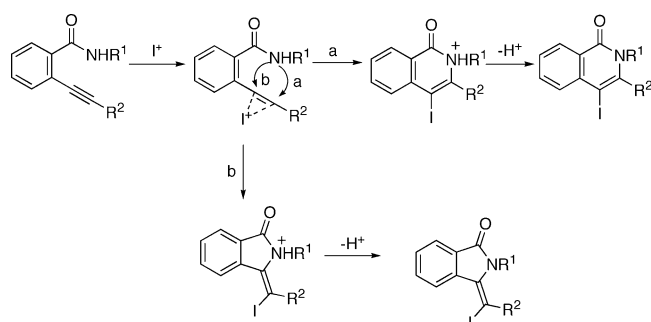
To further demonstrate the versatility of this electrophilic cyclization chemistry, we have applied this methodology to the synthesis of the biologically interesting alkaloid cepharanone B. Cepharanone B displays many pharmacological activities, including fertility-regulat-

TABLE 2. Electrophilic Cyclization of Alkynyl Carboxamides^a

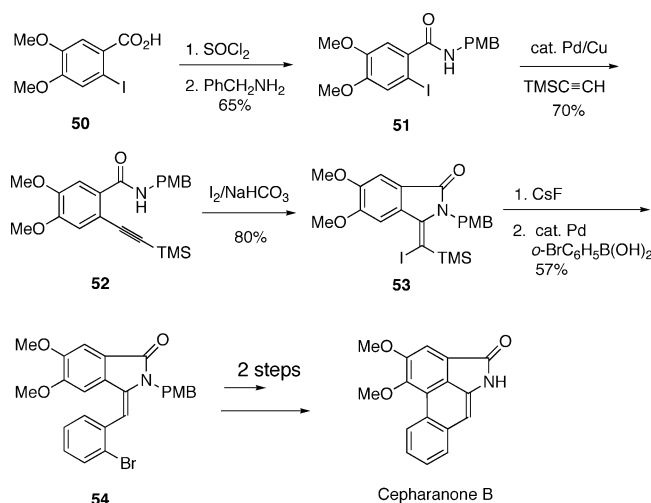
entry	substrate	electrophile	time (h)	products				% isolated yield	
1		1	ICl ^b	0.5		2		E	54 + 40
2		I ₂	1		2		3	I	86 + 10
3		NBS ^b	1		4		5	Br	82 + 17
4		PhSeCl ^b	0.5		6		7	PhSeCl	0 + 12
5		<i>p</i> -O ₂ NC ₆ H ₄ SeCl ^b			8		9	<i>p</i> -O ₂ NC ₆ H ₄ SeCl	0 + 7
7		ICl ^b	0.5		11		12		57 + 17
8		I ₂	1		11		12		80 + 6
9		ICl ^b	0.5		14		15		60 + 30
10		I ₂	1		14		15		85 + 8
11		I ₂	1		17		18		0 + 0
12		I ₂	1		20		21		0 + 0
13		I ₂	1		23		24		90 + 9
14		I ₂	1		26		27		77 + 7
15		I ₂	1		29		30		31 + 68
16		ICl ^b	0.5		29		30		8 + 74
17		I ₂	1		32		33		80 + 6
18		I ₂	1		35		36		0 + 0
19		I ₂	12		38		39		41 + 16
20		I ₂	3		38		39		63 + 15
21		ICl ^b	0.5		41		42		16 + 53
22		I ₂	1		41		42		55 + 17
23		ICl ^b	0.5		41		42		22 + 40
24		I ₂	1		44		45		0 + 61
25		ICl ^b	0.5		44		45		0 + 60
26		I ₂	1		47		48		~15 + 58

^a All reactions were run under the following conditions, unless otherwise specified: 0.3 mmol of the alkynyl amide, 3 equiv of the electrophile, and 3 equiv of NaHCO₃ in 3 mL of CH₃CN at room temperature for 1 h. ^b 0.3 mmol of the alkynyl amide and 1.2 equiv of the electrophile in 3 mL of CH₂Cl₂ at room temperature for 0.5 h.

SCHEME 3



SCHEME 4



ing,³¹ cyclooxygenase inhibitory,³² and cytotoxic activity.³³ Although the synthesis of cepharanone B has been achieved previously,³⁴ our approach may provide a useful alternative to existing methodology.

The construction of the isoindolinone unit of lactam **53** has been accomplished by using our iodocyclization chemistry (Scheme 4). The requisite starting alkyne **52** is easily prepared using straightforward methodology and the Sonogashira reaction of aryl iodide **51** and trimethylsilyl acetylene. The iodocyclization of amide **52** afforded an 80% yield of vinylic iodide **53**. Desilylation and Suzuki cross-coupling with 2-bromophenylboronic acid afforded the (*Z*)-arylmethylene-1*H*-isoindolin-1-one **54** in good yield. Initially we tried to obtain the fused aristolactam directly via organopalladium chemistry. Unfortunately, none of the desired aristolactam could be obtained. However, this constitutes a convenient synthesis of the intermediate **54**, which should prove useful for the synthesis of the desired cepharanone B using previous reported methodology.³⁴

Conclusions

An efficient, regio- and stereoselective synthesis of indolinones from *o*-(1-alkynyl)benzamides under very

mild reaction conditions has been developed. A wide variety of alkynyl amides bearing various functional groups readily undergo cyclization using I_2 and ICl . The resulting iodine-containing products are readily elaborated to more complex products using known organopalladium chemistry. This methodology should prove quite useful for the synthesis of biologically interesting isoindolin-1-ones such as the aristolactams.

Experimental Section

General Procedure for Preparation of the Alkynylamides. To a solution of the corresponding organic iodide (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 alkynylamide.

***N*-Phenyl 2-(phenylethynyl)benzamide (1).** Purification by flash chromatography (5:1 hexane/ $EtOAc$) afforded 218.2 mg (74%) of the product as a white solid with spectral properties identical to those previously reported: mp 150–152 °C (lit.^{15f} mp 151–153 °C).

General Procedure for Electrophilic Cyclization of the Alkynylamides by ICl . The alkynylamide (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 by 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.

(3*E*)-3-[Iodo(phenyl)methylene]-2-phenylisoindolin-1-one (2). Purification by flash chromatography (10:1 hexane/ $EtOAc$) afforded 68.8 mg (54%) of the product as a yellow solid: mp 97–99 °C; 1H NMR ($CDCl_3$) δ 7.09 (t, J = 6.6 Hz, 1H), 7.22–7.36 (m, 7H), 7.59–7.73 (m, 4H), 8.05 (d, J = 7.5 Hz, 1H), 8.86 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 124.1, 125.07, 125.1, 125.4, 128.1, 128.7, 130.5, 130.9, 132.0, 132.8, 135.8, 140.6, 145.0, 147.8, 152.0 (one carbon missing due to overlap); IR (neat, cm^{-1}) 1684; HRMS calcd for $C_{21}H_{14}INO$ 423.0120, found 423.0129.

4-Iodo-2,3-diphenylisoquinolin-1(2*H*)-one (3). Purification by flash chromatography (10:1 hexane/ $EtOAc$) afforded 50.5 mg (40%) of the product as a light yellow solid: mp 131–132 °C; 1H NMR ($CDCl_3$) δ 7.06 (t, J = 7.3 Hz, 1H), 7.20–7.33 (m, 4H), 7.39–7.41 (m, 3H), 7.49 (t, J = 7.5 Hz, 1H), 7.59–7.67 (m, 3H), 7.76 (d, J = 7.5 Hz, 1H), 8.40 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 123.1, 124.0, 124.1, 127.7, 128.2, 128.9, 129.4, 130.1, 130.2, 131.5, 133.2, 135.0, 135.6, 146.1, 148.7, 153.4; IR (neat, cm^{-1}) 1645; HRMS calcd for $C_{21}H_{14}INO$ 423.0120, found 423.0129.

General Procedure for Electrophilic Cyclization of the Alkynylamides by I_2 . The alkynylamide (0.30 mmol), I_2 (3.0 equiv), $NaHCO_3$ (3.0 equiv), and 3 mL of CH_3CN 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.

(3*E*)-3-[Iodo(phenyl)methylene]-2-methylisoindolin-1-one (11). Purification by flash chromatography (7:1 hexane/ $EtOAc$) afforded 86.2 mg (80%) of the product as a yellow

(31) Che, C. T.; Ahmed, M. S.; Kang, S. S.; Waller, D. P.; Bingel, A. S.; Martin, A.; Rajamahendran, P.; Bunyaphatsara, N.; Lamkin, D. C. *J. Nat. Prod.* **1984**, *47*, 331.

(32) Proebstle, A.; Bauer, R. *Planta Med.* **1992**, *58*, 568.

(33) Sun, N. J.; Antoun, M.; Chang C. J. *J. Nat. Prod.* **1987**, *50*, 843.

(34) (a) Couture, A.; Deniau, E.; Grandclaudeon, P.; Lebrun, S. *Synlett* **1997**, 1475. (b) Couture, A.; Deniau, E.; Grandclaudeon, P.; Hoarau, C. *J. Org. Chem.* **1998**, *63*, 3128.

solid: mp 122–125 °C; ^1H NMR (CDCl_3) δ 3.16 (s, 3H), 7.28 (t, $J = 7.2$ Hz, 1H), 7.39 (t, $J = 7.5$ Hz, 2H), 7.52–7.67 (m, 4H), 7.85 (d, $J = 7.5$ Hz, 1H), 8.83 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 35.2, 73.5, 123.2, 125.2, 128.2, 128.5, 130.4, 130.8, 131.4, 132.0, 136.2, 140.9, 147.5, 154.9; IR (neat, cm^{-1}) 1714; HRMS calcd for $\text{C}_{16}\text{H}_{12}\text{INO}$ 360.9964, found 360.9968.

General Procedure for Electrophilic Cyclization of the Alkynylamides by NBS. The alkynylamide (0.30 mmol), NBS (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*E*)-3-[Bromo(phenyl)methylene]-2-phenylisoindolin-1-one (4). Purification by flash chromatography (5:1 hexane/EtOAc) afforded 93.2 mg (82%) of the product as a white solid: mp 90–92 °C; ^1H NMR (CDCl_3) δ 7.13 (t, $J = 7.2$ Hz, 1H), 7.26–7.41 (m, 7H), 7.60–7.75 (m, 4H), 8.06 (d, $J = 6.6$

Hz, 1H), 8.64 (d, $J = 8.1$ Hz, 1H); IR (neat, cm^{-1}) 1690; HRMS calcd for $\text{C}_{16}\text{H}_{12}\text{BrNO}$ 375.0259, found 375.0266.

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Supporting Information Available: Characterization data for the compounds listed in Table 2 and experimental procedures and characterization data for the reactions summarized in eq 2 and Scheme 4. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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