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Note

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Regio- and Stereoselective Synthesis of Cyclic Imidates via Electrophilic Cyclization of 2-(1-Alkynyl)benzamides. A Correction

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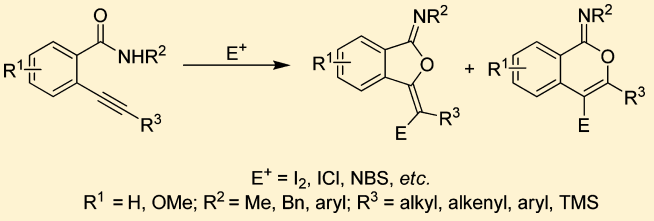
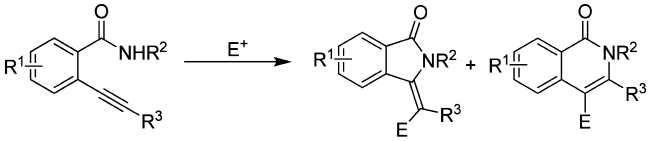
Supporting Information

ABSTRACT: The electrophilic cyclization of 2-(1-alkynyl)-benzamides affords high yields of cyclic imidates, instead of the previously reported isoindolin-1-ones, where cyclization proceeds on the oxygen of the carbonyl group rather than the nitrogen of the amide functionality. X-ray crystallography and spectroscopic techniques have been used to characterize the products. A correction is hereby provided in order to rectify the previous misassignment of structure.

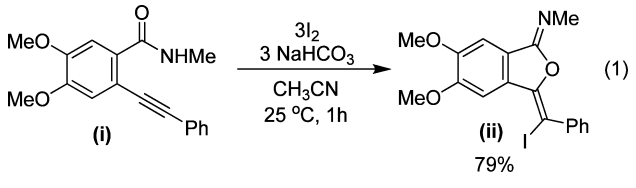


The iodocyclization of functionalized alkynes has been a powerful tool for the synthesis of a wide variety of heterocyclic and carbocyclic compounds.[1] Using this methodology, we and others have reported the synthesis of several important scaffolds, e.g., benzofurans,[2] furans,[3] benzothiophenes,[4] indoles,[5] carbazoles,[6] quinolines,[7] isoxazoles,[8] pyrroles,[9] etc.[10] As a continuation of our studies, we investigated the electrophilic cyclization of 2-(1-alkynyl)benzamides and published a synthesis of what we believed to be isoindolinones and isoquinolinones (Scheme 1).[11] We hereby reassign the structure of those products as cyclic imidates.

Scheme 1. Previously Reported Synthesis of Isoindolinones and Isoquinolinones by the Electrophilic Cyclization of 2-(1-Alkynyl)benzamides[11]



A few years later, in an effort to generate a modest sized library of isoindolin-1-ones for biological evaluation, we explored the scope of that earlier methodology and discovered that we had misassigned their structures. Thus, a new substrate **i**, bearing more polar functionality, has been cyclized (eq 1)



using our previously optimized reaction conditions, and the structure of the product **ii** has been established with the help of single-crystal X-ray and NMR spectroscopic data (Figure 1).[12]

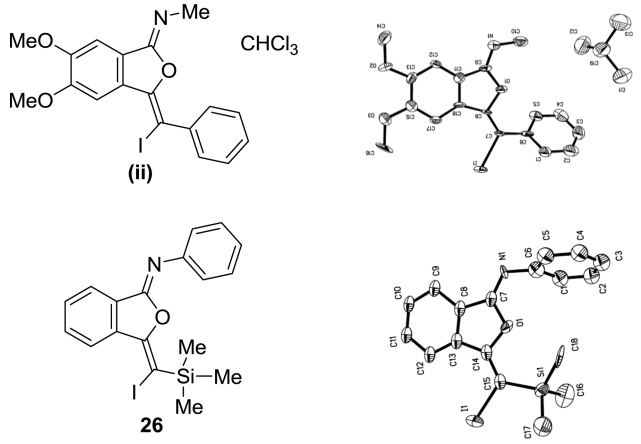


Figure 1. X-ray evidence.[13]

To our surprise, the data indicated that the cyclization had actually occurred on the oxygen of the carbonyl group rather than the nitrogen of the amide functionality, leading to the corresponding cyclic imidates or iminolactones instead of isoindolin-1-ones. To recheck our earlier results, we synthesized one of the compounds (**26**)[12] that we reported in our original publication using our standard experimental procedure, and it was characterized with the help of single-crystal X-ray spectroscopic data (Figure 1). It again confirmed the formation of a cyclic imidate and not an isoindolin-1-one. In addition to the X-ray spectroscopic data, we have also re-examined the ^{13}C

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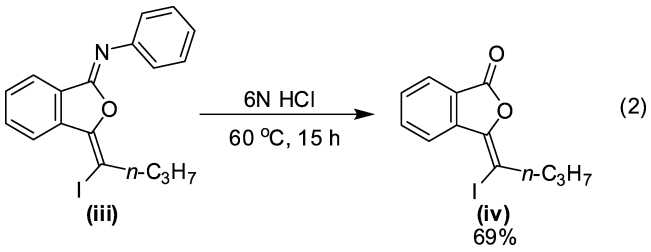
NMR spectra of the cyclized products. The absence of any diagnostic signals for the C=O bonds in a lactam at δ >160 ppm in the ^{13}C NMR spectra of all of the 5- and 6-membered ring-containing products further ruled out *N*-cyclization.[14]

Furthermore, we examined the hydrolysis of the cyclized products. The 5-membered cyclic imidate **iii** was synthesized from the corresponding alkyne using our standard iodocyclization procedure. It was then subjected to acid hydrolysis, yielding the corresponding lactone **iv** in a moderate yield (eq 2). This result confirms the formation of cyclic imidates upon



(2)

cyclization of the 2-(1-alkynyl)benzamides. All of this evidence supports the formation of cyclic imidates instead of isoindolin-1-ones.

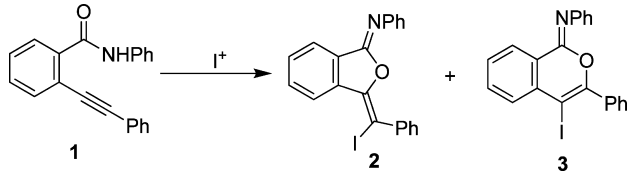
Recently, Chen et al. have reported their results for the I_2-mediated cyclization of nitrone−alkynes, and they too seem to have mischaracterized the products as isoindolin-1-ones instead of cyclic imidates.[15] In light of the evidence given above, we are hereby correcting all of the schemes and tables reported previously by us for the electrophilic cyclization of 2-(1-alkynyl)benzamides to indicate that cyclic imidates are actually formed.

Scheme 2 shows the two-step approach we have used to prepare the cyclic imidates, which involves (1) the preparation of 2-(1-alkynyl)benzamides by a Sonogashira reaction[16] and (2) electrophilic cyclization. The synthesis of previously prepared starting amides can be found in our original publication,[11] while the synthesis of two new amides is reported in the Supporting Information.[17]

The 2-(1-alkynyl)benzamide **1** was chosen as the substrate for optimization of this electrophilic cyclization process, and the best conditions are shown in Table 1.[11]

Using these optimized conditions, a wide variety of 2-(1-alkynyl)arenecarboxamides with substitution on the amide nitrogen atom, the aromatic ring, and the remote end of the alkyne moiety have been examined in this cyclization process. The cyclized products have been characterized by spectral and analytical data, and the results (with corrected structures of the products) are presented in Table 2.[18] The relative stereochemistry (*Z*/*E*) of the other cyclic imidates is assigned by analogy to the compounds **ii** and **26**. Furthermore, as described in the original paper, the 5-membered-ring-containing cyclic imidates have been distinguished from their 6-membered

Table 1. Iodocyclization of 2-(1-Alkynyl)benzamide 1: Summary of Optimization Studies



entry	electrophile	base	solvent	time (h)	% yield of **2**	% yield of **3**
1[a]	I_2	$NaHCO_3$	CH_3CN	1	86	10
2[b]	ICl		CH_2Cl_2	0.5	54	40

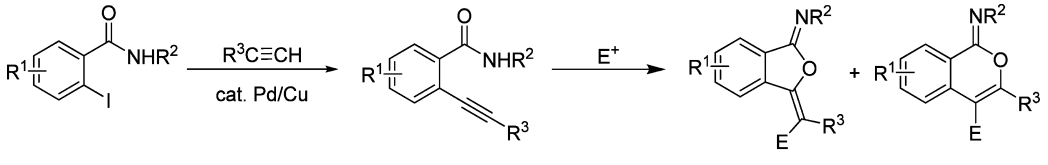
[a]0.30 mmol of the 2-(1-alkynyl)benzamide, 3 equiv of I_2, and 3 equiv of $NaHCO_3$ in 3 mL of CH_3CN were stirred at room temperature for 1 h under Ar. [b]0.30 mmol of the 2-(1-alkynyl)benzamide and 1.2 equiv of ICl in 3 mL of CH_2Cl_2 were stirred at room temperature for 0.5 h under Ar.

counterparts on the basis of their IR spectra. The 5-membered ring products generally exhibit a C=NR band at 1680−1710 cm^{-1}, while in the 6-membered ring products the corresponding absorption is observed at 1640−1650 cm^{-1}.

Our proposed mechanism for this electrophilic cyclization is shown in Scheme 3. There are several reports in the literature that indicate the ambident nature of the amide group as a nucleophile and also the fact that different products can be obtained from amides under different reaction conditions using various reagents.[19] It appears that under our reaction conditions, the oxygen atom is more nucleophilic than the nitrogen atom presumably due to the delocalization of the lone-pair of electrons and/or due to the steric hindrance on the nitrogen atom of the amide group. Moreover, the *O*-selective cyclization in the iodocyclization reactions in olefinic amide substrates has been explained on the basis of the HSAB theory; that is, an oxygen atom, being more electronegative than the nitrogen atom, preferentially attacks the iodine−olefin π-complex that has been characterized as a hard electrophile.[20] Thus, the nucleophilic attack by the oxygen atom of the amide group on the carbon−carbon triple bond activated by coordination to I^+ is followed by deprotonation to afford the corresponding cyclic imidates.

Based upon our studies, we believe that in general various factors determine the regiochemical outcome of the reaction, including the stability of the presumed intermediate carbocation, the relative rates of the competing reactions, the nature of the electrophile, and the relative stabilities of the possible products. As far as the electrophile is concerned, better regioselectivity has been observed when I_2 was used as compared to the more reactive electrophile ICl that generally affords larger amounts of the six-membered cyclic imidate (compare entries 1 and 2, 6 and 7, and 8 and 9 in Table 2). In most cases, the 5-membered cyclic imidate has been isolated as

Scheme 2. Two-Step Approach to Cyclic Imidates



$E^+ = I_2$, ICl, NBS, *etc.*
R^1 = H, OMe; R^2 = Me, Bn, aryl; R^3 = alkyl, alkenyl, aryl, TMS

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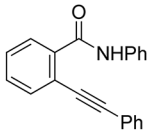
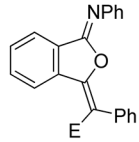
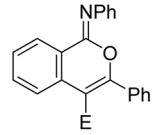
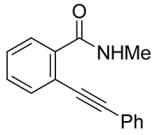
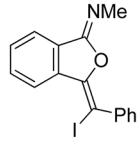
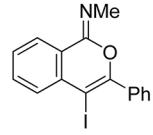
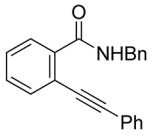
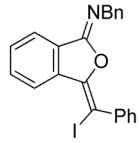
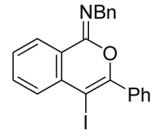
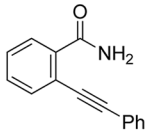
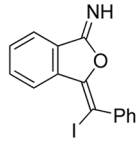
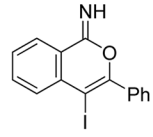
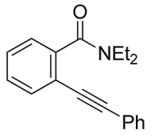
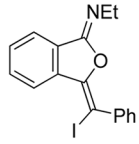
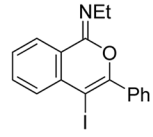
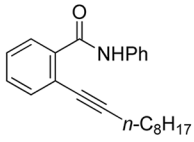
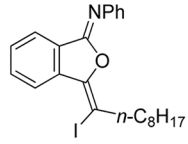
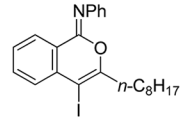
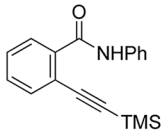
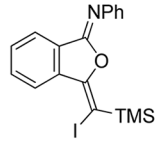
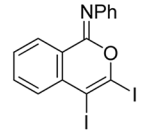
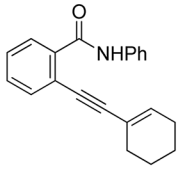
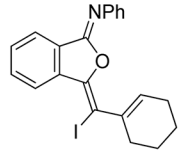
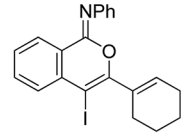
Table 2. Electrophilic Cyclization of 2-(1-Alkynyl)arenecarboxamides[a]

entry	Substrate		electrophile	time (h)	product(s)				% isolated yield
								E	
1		**1**	ICl[b]	0.5		**2**		**3**	I	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**	PhSe	0 + 12
5			p-$O_2NC_6H_4SCl$[b]			**8**		**9**	p-$O_2NC_6H_4S$	0 + 7
6		**10**	ICl[b]	0.5		**11**		**12**		57 + 17
7			I_2	1						80 +6
8		**13**	ICl[b]	0.5		**14**		**15**		60 + 30
9			I_2	1						85 + 8
10		**16**	I_2	1		**17**		**18**		0 + 0
11		**19**	I_2	1		**20**		**21**		0 + 0
12		**22**	I_2	1		**23**		**24**		90 + 9
13		**25**	I_2	1		**26**		**27**		77 + 7
14		**28**	I_2	1		**29**		**30**		31 + 68
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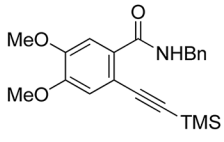
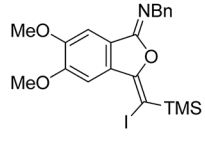
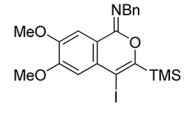
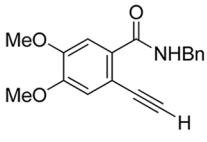
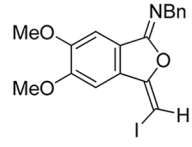
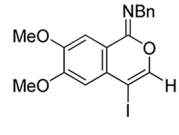
16		**31**	I_2	1		**32**		**33**		80 + 6
17		**34**	I_2	1		**35**		**36**		0 + 0

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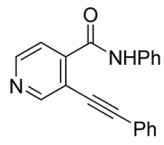
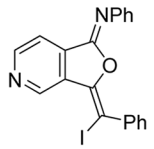
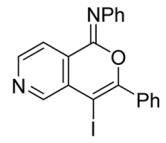
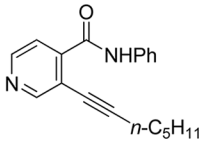
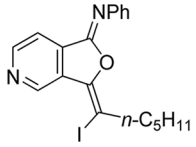
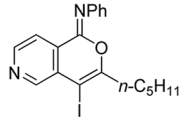
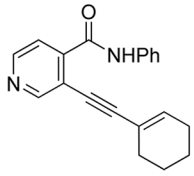
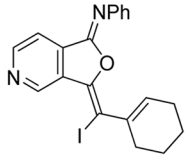
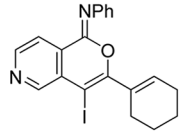
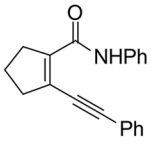
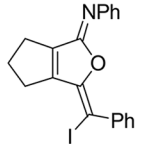
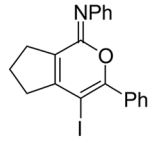
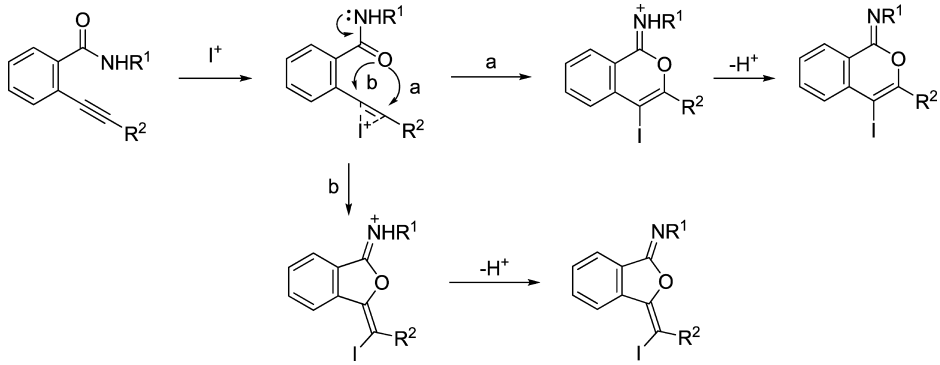
Table 2. continued

entry	Substrate		electrophile	time (h)	product(s)		% isolated yield
18		**37**	I_2	12		**38**  **39**	41 + 16
19			I_2	3			63 + 15
20			ICl[b]	0.5			16 + 53
21		**40**	I_2	1		**41**  **42**	55 + 17
22			ICl[b]	0.5			22 + 40
23		**43**	I_2	1		**44**  **45**	0 + 61
24			ICl[b]	0.5			0 + 60
25		**46**	I_2	1		**47**  **48**	~15 + 58

[a]All reactions were run under the following conditions, unless otherwise specified: 0.3 mmol of alkynamide, 3 equiv of electrophile and 3.0 equiv of $NaHCO_3$ in 3 mL of CH_3CN at room temperature for 1 h. [b]0.3 mmol of alkynamide and 1.2 equiv of electrophile in 3 mL of CH_2Cl_2 at room temperature for 0.5 h.

Scheme 3. Proposed Mechanism for the Iodocyclization of 2-(1-Alkynyl)arenecarboxamides



the major product, although there are a few exceptions to this. For example, using a cyclohexenyl group at the distal end of the alkyne, the 6-membered cyclic imidate was isolated as the major (entries 14 and 15) or the only product (entries 23 and 24), no matter whether ICl or I_2 is used. In general, the formation of a 5-membered ring seems to be faster than the corresponding 6-membered ring, except for the reactions of substrates with a cyclohexenyl group at the distal end of the alkyne, where other factors, e.g. the thermodynamic stability of the products seems to take precedent over kinetic factors.

Even the TMS group containing alkyne substrate **25** underwent smooth iodocyclization with I_2 (entry 13). The 5-membered cyclic imidate **26** was obtained in 77% yield, along with a small amount of a diiodo derivative corresponding to the 6-membered cyclic imidate **27**. Obviously, the silyl group in the 6-membered cyclic imidate has undergone iododesilylation either prior to or soon after cyclization. Similarly, cyclic imidate **32** bearing two electron-donating methoxy substituents on the aromatic ring and a silyl moiety has been obtained in a good yield (entry 16).

The reaction of the alkene-containing amide **46** with I_2 affords a mixture of cyclic imidates **47** and **48** in which the six-membered ring product **48** predominates, presumably due to ring strain (entry 25).

In a few cases (entries 10, 11, and 17), recognizable products could not be isolated, presumably due to the poor stability of the initial cyclic intermediates and/or the final products. In the case of a primary amide (entry 10), the desired cyclic imidate could not be isolated presumably because of the absence of any group helping to stabilize the positive charge on the N atom (Figure 2a). The reaction also fails to yield the desired product in the case of a tertiary amide (entry 11). The possible reason in this case might be that under the reaction conditions the ethyl group on the nitrogen atom is not as good a leaving group as a proton (Figure 2b). Also, the reaction fails in the case of a terminal alkyne (entry 17), presumably due to the absence of

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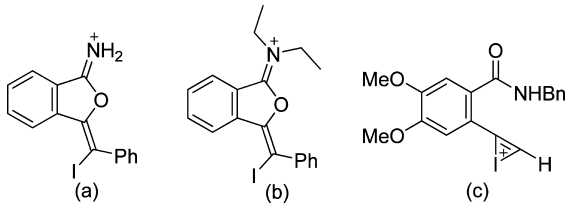
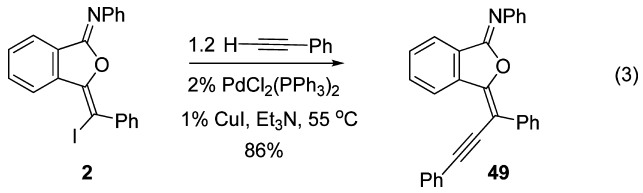


Figure 2. Possible unstable intermediates involved in the failed reactions.

any group to stabilize the positive charge on the alkyne (Figure 2c).

The cyclic imidates produced by iodocyclization can be further elaborated using various palladium-catalyzed processes. For example, the Sonogashira reaction of cyclic imidate **2** yields the coupling product **49** in very good yield (eq 3). In fact, in a



(3)

continuation of our research group's efforts to synthesize new heterocycles with novel biological activities, we have synthesized a midsized library of these cyclic imidates, the results of which will be published elsewhere.

It is important to mention that in our original paper, our iodocyclization chemistry was applied to the synthesis of the biologically interesting isoindolinone alkaloid cepharanone B (Scheme 4). In fact, the cyclic imidate **53** was prepared in an 80% yield, and subsequent desilylation and Suzuki coupling with 2-bromophenylboronic acid afforded the corresponding imidate **54** in a good yield. Our subsequent attempts to synthesize cepharanone B failed for obvious reasons.

As far as the synthesis and applications of these cyclic imidates are concerned, there have been some studies on this heterocyclic scaffold. Over the years, several groups have reported various synthetic routes to cyclic imidates/iminolactones containing 5- and 6-membered rings.[21] Since there is generally a remarkable similarity in the reactivity and bioactivities of the oxygen species and their nitrogen counterparts, one would anticipate that these cyclic imidates might have potential bioactivities similar to those of their structurally similar isocoumarin and isoindolin-1-one counterparts. In fact, the biological potential of this heterocyclic scaffold has been investigated in a few cases and important biological activities have been observed. For example, gossylic iminolactone (GIL, **I**) derived from the natural product gossypol (**II**) has been found to exhibit anti-HIV activity (Figure 3).[22] Furthermore,

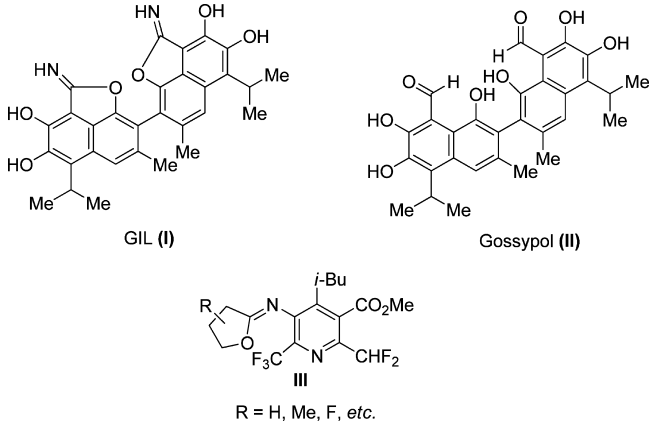
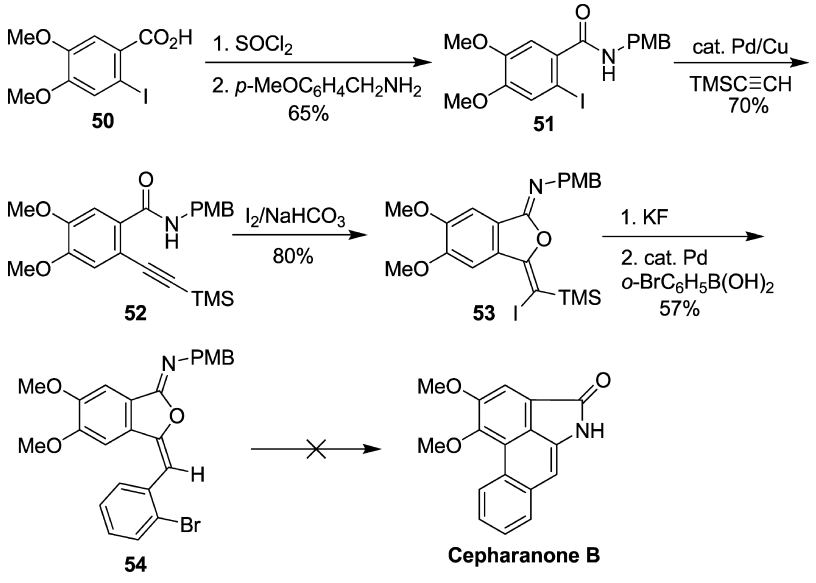


Figure 3. Biologically active cyclic imidates and related compounds.

Hegde et al. reported several cyclic imidate derivatives **III** of 5-amino-2,6-bis(polyfluoroalkyl)pyridine-3-carboxylates having interesting herbicidal activities.[23] This has generated further interest in the synthesis and study of this relatively unexplored scaffold.

In conclusion, under the mild electrophilic cyclization conditions reported here, 2-(1-alkynyl)arenecarboxamides undergo *O*-cyclization leading to cyclic imidates, with reasonable regio- and stereoselectivity. The resulting iodine-containing products can be elaborated to more complex

Scheme 4. Failed Attempt To Synthesize Cepharanone B



dx.doi.org/10.1021/jo301958q | J. Org. Chem. 2012, 77, 10938–10944

products using known organopalladium chemistry. Finally, the methodology can be further extended to the regioselective synthesis of 5-membered ring lactones by hydrolysis of the cyclic imidates.

EXPERIMENTAL SECTION

General Procedure for Preparation of the Amides. 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 2-(1-alkynyl)benzamide.

***N*-Methyl-4,5-dimethoxy-2-(phenylethynyl)benzamide (i).** Purification by flash chromatography (hexane/EtOAc) afforded the product in 87% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.07 (d, J = 4.8 Hz, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 7.01 (s, 1H), 7.39−7.41 (m, 3H), 7.51−7.53 (m, 2H), 7.65 (br s, 1H), 7.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 56.2, 56.3, 88.1, 94.5, 112.1, 112.7, 115.1, 122.4, 128.8, 129.05, 129.13, 131.5, 149.6, 150.5, 166.6; HRMS calcd for $C_{18}H_{17}NO_3$ 295.12084, found 295.12139.

General Procedure for Electrophilic Cyclization of the 2-(1-Alkynyl)arenecarboxamides by I_2. The 2-(1-alkynyl)-arenecarboxamide (0.30 mmol), I_2 (3.0 equiv), $NaHCO_3$ (3.0 equiv), and CH_3CN (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 reaction mixture was then diluted with ether (50 mL), washed with satd aq $Na_2S_2O_3$ (25 mL), dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography on a silica gel column.

***N*-[(*E*)-3-(Iodo(phenyl)methylene)-5,6-dimethoxyisobenzofuran-1(3*H*)-ylidene]methanamine (ii).** Purification by flash chromatography (hexane/EtOAc) afforded the product in 79% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (s, 3H), 3.97 (s, 3H), 4.03 (s, 3H), 7.25−7.29 (m, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.63 (d, J = 7.6 Hz, 2H), 8.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1, 56.46, 56.53, 71.6, 103.9, 106.9, 125.3, 128.0, 128.2, 129.5, 130.4, 140.7, 147.3, 151.8, 154.8 (one signal missing due to overlap); HRMS calcd for $C_{18}H_{16}INO_3$ 421.01749, found 421.01870.

***N*-[(*E*)-3-(1-Iodobutylidene)isobenzofuran-1(3*H*)-ylidene]-aniline (iii).** Purification by flash chromatography (hexane/EtOAc) afforded the product as yellow oil in 92% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.6 Hz, 3H), 1.56−1.62 (m, 2H), 2.81 (t, J = 7.6 Hz, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.42−7.51 (m, 4H), 7.94 (d, J = 7.2 Hz, 1H), 8.56 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 22.5, 41.6, 82.2, 123.7, 123.9, 124.2, 124.8, 128.7, 129.9, 131.6, 132.2, 135.3, 145.5, 147.3, 152.1; HRMS calcd for $C_{18}H_{16}INO$ 389.02766, found 389.02853.

***N*-[(*E*)-3-(Iodo(phenyl)methylene)isobenzofuran-1(3*H*)-ylidene]aniline (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; ^{1}H 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.

***N*-(4-Iodo-3-phenyl-1*H*-isochromen-1-ylidene)aniline (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; ^{1}H 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.

Hydrolysis of the Cyclic Imidate iii. A 150 mg (0.39 mmol) portion of the cyclic imidate **iii** was mixed with 2.4 mL of 6 N HCl, and the reaction mixture was heated at 100 °C for 15 min and at 60 °C for 15 h. The reaction mixture was then extracted with EtOAc, dried ($MgSO_4$), and purified by column chromatography using EtOAc−hexane as the eluent.

(*E*)-3-(1-Iodobutylidene)isobenzofuran-1(3*H*)-one (iv). Purification by flash chromatography (hexane/EtOAc) afforded the lactone **iv** as yellow oil in 69% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.6 Hz, 3H), 1.62−1.72 (m, 2H), 2.99 (t, J = 7.6 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 8.77 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 22.8, 41.9, 88.1, 124.3, 125.8, 126.5, 130.4, 134.3, 138.4, 144.4, 165.8; HRMS calcd for $C_{12}H_{11}IO_2$ 313.98038, found 313.98122.

ASSOCIATED CONTENT

Supporting Information

General experimental methods, reaction procedures, corrected names and characterization data, copies of ^{1}H and ^{13}C NMR spectra for previously unreported compounds, and X-ray crystallographic data for compounds **ii** and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) The detailed data as well as the CIFs can be found in the Supporting Information.
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■ NOTE ADDED IN PROOF

During the review of our paper, Opatz et al. reported a similar *O*-cyclization in the iodocyclization of 2-(1-alkynyl)-benzamides. See: Schlemmer, C.; Andernach, L.; Schollmeyer, D.; Straub, B. F.; Opatz, T. *J. Org. Chem.* **2012**, *77*, 10118−10124.