

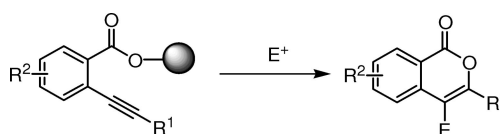
## Solid-Phase Synthesis of Isocoumarins: A Traceless Halocyclization Approach

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A straightforward and traceless solid-phase methodology was developed for the synthesis of isocoumarins. This two-step process involves a Sonogashira cross-coupling reaction between polymer-bound 2-bromobenzoates and terminal alkynes, followed by an electrophile-induced halocyclization of the resulting 2-(alk-1-ynyl)benzoates through activation of the triple bond with the subsequent release of the 3-substituted 4-haloisocoumarins. This polymer-bound parallel synthetic approach allowed us to achieve large diversity in good to excellent yields and purities.

### Introduction

Isocoumarins<sup>1</sup> (1*H*-2-benzopyran-1-one) are an important class of naturally occurring lactones that exhibit a wide range of biological activities such as antimicrobial,<sup>2</sup> antifungal,<sup>3</sup> antiangiogenic<sup>4</sup> properties, and enzyme inhibition.<sup>5</sup> In addition, the isocoumarin ring system is a useful synthetic intermediate for the synthesis of hetero- and carbocyclic compounds including

isocarbostyrls, isochromenes, or isoquinolines.<sup>6</sup> Accordingly, numerous synthetic routes to this scaffold have been reported in the literature.<sup>7</sup> Unsubstituted and 3-substituted isocoumarins were prepared by either (i) ortho-thallation/Pd-catalyzed olefination of benzoic acids<sup>8</sup> or (ii) Pd-catalyzed coupling of 2-halobenzoic acids/esters with alkenes, vinylic stannanes, or terminal alkynes and subsequent acid- or metal-catalyzed cyclization.<sup>9</sup> Efficient procedures to produce 3,4-disubstituted isocoumarins were also developed by direct Rh/Cu-catalyzed oxidative coupling of benzoic acid<sup>10</sup> or by Pd-catalyzed annu-

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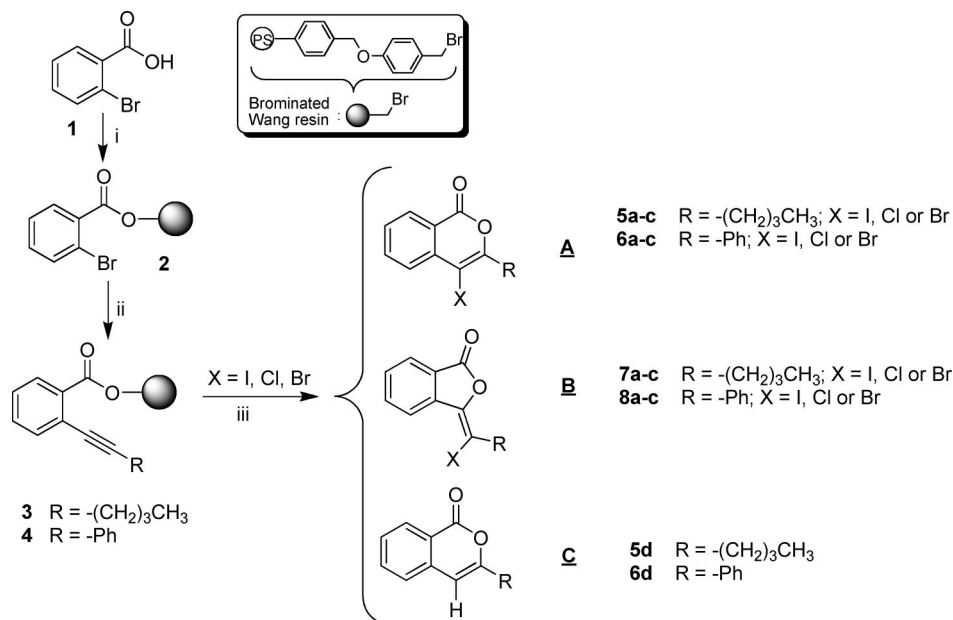
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SCHEME 1. General Solid-Phase Synthetic Pathway to Isocoumarins (A) and Possible Byproducts (B, C)<sup>a</sup>

<sup>a</sup> Reagents and conditions: (i) (a)  $Cs_2CO_3$  (0.5 equiv), EtOH, rt, 3 h, (b) bromo-Wang resin, DMF, rt, 12 h; (ii) alkyne (hex-1-yne or phenylacetylene, 10 equiv),  $PdCl_2(PPh_3)_2$  (0.2 equiv), CuI (0.1 equiv),  $Et_3N/CH_2Cl_2$  (5:1), 65°C, 12 h; (iii) see conditions in Table 1.

lation of internal alkynes with 2-halobenzoate esters.<sup>11</sup> In this vein, the main access to 4-haloisocoumarins consists of a 6-*endo*-dig electrophile-induced halocyclization first described from 2-(alk-1-ynyl)benzoic acids as starting material and *N*-halosuccinimide (NXS) or  $X_2$  (X = I, Br) as electrophiles.<sup>12</sup> A drawback of these reactions is their unsatisfactory selectivity due to the formation of the five-membered ring byproduct via a 5-*exo*-dig cyclization. In the past decade, studies were particularly focused on the iodolactonization process from 2-(alk-1-ynyl)benzoate esters to afford 4-iodoisocoumarins by a selective 6-*endo*-dig cyclization using ICl as electrophilic reagent.<sup>12c,13</sup> While the stability of the halonium intermediates decreases in the order  $I > Br > Cl$ , electrophilic bromo- and chlorocyclizations were also reported.<sup>12a,14</sup> As an example, Li and co-workers<sup>15</sup> have recently described the selective synthesis of 4-bromo- and 4-chloroisocoumarins using  $CuX_2$  (X = Br, Cl) as the electrophilic reagent with the corresponding HX salt of dicyclohexylamine to prevent the formation of the nonhalogenated byproduct.

As part of our ongoing medicinal projects, the 3-substituted 4-haloisocoumarin scaffold has retained our attention. In this drug discovery context, the synthesis of combinatorial focused libraries is crucial to explore structure–activity relationships, and the main key for the success of such an approach is to develop a parallel solid-phase synthesis. Since isocoumarins are versatile intermediates in medicinal and organic chemistry, to the best of our knowledge, no parallel SPOS has been described

yet for the production of highly diverse 3-substituted 4-haloisocoumarin libraries. Our aim was to develop such a synthetic approach to gain both efficiency and diversity around the isocoumarin scaffold. In this study, we report a new efficient parallel solid-phase synthesis of 3-substituted 4-haloisocoumarins based on an electrophile-promoted traceless halocyclization of supported 2-(alk-1-ynyl)benzoates to simultaneously form and release the target compounds.<sup>16</sup> This route was optimized to limit the formation of the five-membered ring and the nonhalogenated byproduct, allowing its application in the preparation of a highly structurally diverse library.

## Results and Discussion

Among previously reported syntheses of 4-haloisocoumarins in solution, we decided to investigate and adapt a two-step strategy involving (i) a Sonogashira cross-coupling reaction between polymer-bound 2-bromobenzoates and terminal alkynes, followed by (ii) an electrophile-induced halocyclization of the resulting 2-(alk-1-ynyl)benzoates through activation of the triple bond with the subsequent release of the isocoumarins (Scheme 1). In addition to the well-known advantages of the solid support, including the temporary protection of one functional group (i.e., the carboxylic group), the traceless cleavage would ensure that only the desired cyclized product is released from the polymer with no cleavage of side products arising from an incomplete Sonogashira reaction. This guarantees a significant enhancement of the final purity. To validate this strategy, we first focused on the synthesis of 3-substituted 4-iodo-, 4-bromo-, 4-chloro-, and 4-*H*-isocoumarins **5a–d** and **6a–d** as model compounds. The main challenge was to find conditions for the electrocyclization of the supported 2-(alk-1-ynyl)benzoates that give the desired

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TABLE 1. Optimization of electrocyclization conditions

Entry	X	Conditions and reagents	R = $-(\text{CH}_2)_3\text{CH}_3$			R = Ph		
			Yield <sup>a</sup> (%)	Purity <sup>b</sup> (%)	Ratios <sup>b</sup> A/B/C	Yield <sup>a</sup> (%)	Purity <sup>b</sup> (%)	Ratios <sup>b</sup> A/B/C
1	I	ICl, $\text{CH}_2\text{Cl}_2$ , rt	quant.	99	96:4:0	96	97	100:0:0
2	I	$\text{I}_2$ , $\text{CH}_2\text{Cl}_2$ , rt	65	99	99:1:0	93	98	100:0:0
3	Cl	$\text{CuCl}_2$ , $\text{Cy}_2\text{NH}\cdot\text{HCl}$ , $(\text{CH}_2\text{Cl})_2$ , 80 °C	n.d.	n.d.	n.d.	23	48	48:0:52
4	Cl	$\text{CuCl}_2$ , $\text{Cy}_2\text{NH}\cdot\text{HCl}$ , $(\text{CH}_2\text{Cl})_2$ , 65 °C	62	>99	100:0:0	41	67	67:0:33
5	Cl	$\text{CuCl}_2$ , $\text{Cy}_2\text{NH}\cdot\text{HCl}$ , $(\text{CH}_2\text{Cl})_2$ , rt	n.d.	n.d.	n.d.	19	28	28:0:72
6	Cl	$\text{CuCl}_2$ , $\text{Et}_3\text{N}\cdot\text{HCl}$ , $(\text{CH}_2\text{Cl})_2$ , 65 °C	n.d.	n.d.	n.d.	45	40	40:0:60
7	Br	$\text{CuBr}_2$ , $\text{Cy}_2\text{NH}\cdot\text{HBr}$ , $(\text{CH}_2\text{Cl})_2$ , 65 °C	60	93	96:0:4	60	59	70:0:30
8	Br	$\text{CuBr}_2$ , $\text{Cy}_2\text{NH}\cdot\text{HBr}$ , $(\text{CH}_2\text{Cl})_2$ , rt	n.d.	n.d.	n.d.	47	95	96:0:4
9	H	TFA/ $\text{CH}_2\text{Cl}_2$ (1:1 v/v), rt	71	89	100:0 <sup>c</sup>	73	98	100:0 <sup>c</sup>
10	H	$\text{ZnCl}_2$ , $\text{Cy}_2\text{NH}\cdot\text{HCl}$ , $(\text{CH}_2\text{Cl})_2$ , 65 °C	41	80	100:0 <sup>c</sup>	45	>99	73:27 <sup>c</sup>
11	H	PTSA, $(\text{CH}_2\text{Cl})_2$ , 65 °C	n.d.	n.d.	n.d.	55	98	97:3 <sup>c</sup>

<sup>a</sup> Based on ascertained loading of resin **2** and determined by NMR analyses using HMDSO as an internal standard (total amount of **A**, **B**, and **C** was considered), yields are indicated for the combination of Sonogashira reaction plus cyclization. <sup>b</sup> As determined by reverse-phase HPLC with monitoring at 214 nm and confirmed by NMR. Purity is based on added amounts of **A**, **B**, and **C**. <sup>c</sup> For X = H, compounds **A** and **C** are identical.

6-endo-dig products with good yield and high purity. To this aim, we first explored the electrocyclization conditions of two model compounds **3** and **4** (Scheme 1 and Table 1).

In a first synthetic step, 2-bromobenzoic acid cesium salt was loaded onto the commercially available, widely used, and acid-cleavable bromo-Wang resin (4-(bromomethyl)phenoxybenzylpolystyrene, 1% divinylbenzene, 1.6 mmol·g<sup>-1</sup>) in DMF at room temperature for 12 h (Scheme 1).<sup>17</sup> The loading of the resin was ascertained by treating a measured amount of the resin-bound 2-bromobenzoate with 50% TFA in DCM and evaluating the recovery of the starting material (for resin **2**, the experimental loading was measured to be 1.15 mmol·g<sup>-1</sup>). Overall yields<sup>18</sup> are given depending on this experimental loading of resin **2**. In a second synthetic step, the Sonogashira cross-coupling<sup>19</sup> between the polymer-bound arylbromide **2** and 1-hexyne (R = *n*-butyl) or phenylacetylene (R = phenyl) was performed using PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.2 equiv) and CuI (0.1 equiv) in Et<sub>3</sub>N/CH<sub>2</sub>Cl<sub>2</sub> (5:1 v/v) at 65 °C to readily afford the alkynes **3** and **4**. To explore the scope of the lactonization, different electrophiles (ICl, I<sub>2</sub>, CuCl<sub>2</sub>, CuBr<sub>2</sub>, ZnCl<sub>2</sub>, PTSA, TFA) in DCM or DCE have been studied. At this stage, the relative abundance of the six- (**A**) and five-membered ring (**B**) compounds as well as the nonhalogenated (**C**) isocoumarin was evaluated by HPLC and NMR analyses. Results are summarized in Table 1.

Iodolactonization was performed using ICl (1.2 equiv) or I<sub>2</sub> (3 equiv) in CH<sub>2</sub>Cl<sub>2</sub> at rt for 5 h (Table 1, entries 1 and 2). At the end of the reaction, 4-iodoisocoumarins **5a** and **6a** as a mixture with the excess of the electrophilic reagent were recovered by filtering the resin. Since the methodology has to be useful for parallel synthesis, treatment of the reaction mixture has to be straightforward for a combinatorial approach. Therefore, we developed an original purification process that directly allowed elimination of salts and excess reagents. It consists of

the quenching of the excess of iodine reagent with an aqueous sodium thiosulfate solution (0.4 g·mL<sup>-1</sup>, 2 mL), followed by a subsequent filtration of the mixture on a disposable cartridge packed with diatomaceous earth. Finally, the resulting organic solutions were evaporated under reduced pressure (see Experimental Section). Whatever the substituent in position 3 (R = *n*-butyl or phenyl), the corresponding 4-iodoisocoumarins **5a** and **6a** were obtained in good yields (ICl being somewhat more efficient than I<sub>2</sub>), high purities (97–99%), and excellent selectivity (96–100%) with no nonhalogenated byproduct **C** (**5d** or **6d**). When R was an alkyl group, the five-membered ring isomer (**B**) was detected at a low level and a slightly higher A/B ratio was observed when I<sub>2</sub> (vs ICl) was used (A/B ratio was 96/4 and 99/1 with ICl and I<sub>2</sub> respectively, Table 1, entries 1 and 2). This was confirmed on a large variety of supported 2-(alk-1-ynyl)benzoates (see Tables 2 and 3, compounds **9a**, **10a**, **12a**, **20a**, **22a**, **24a**, **34a**, **36a**). When R was an aryl group, a total selectivity was observed due to its α-cation-stabilizing property. Therefore, the results observed on the solid support are similar to those previously described in solution.<sup>13c</sup> Since ICl generally afforded the desired product with better yields, it appeared as the reagent of choice. However, when a significant amount of the five-membered cycle is formed, I<sub>2</sub> might be a useful alternative.

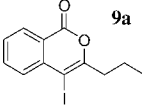
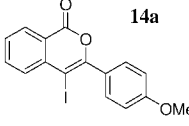
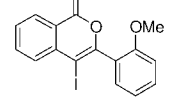
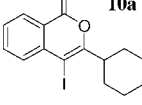
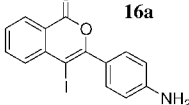
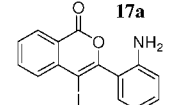
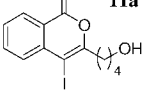
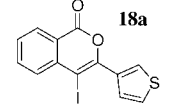
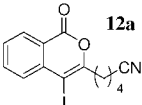
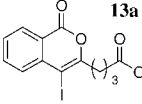
While electrocyclization leading to the 4-chloro- or 4-bromoisocoumarins is less documented, a recent study<sup>15</sup> has reported a useful system CuX<sub>2</sub>/Cy<sub>2</sub>NH·HX (X = Cl, Br) for the selective synthesis of 4-haloisocoumarins. These conditions were applied to polymer-bound models **3** and **4**. At the end of the reaction, 4-chloro- and 4-bromoisocoumarins along with the excess of the electrophilic reagent were recovered by draining the resin. In this case, an efficient treatment consisting of filtration of the reaction mixture through a pad of silica gel was applied to remove the excess of reagents and salts followed by concentration of the solvent. Results were greatly dependent on the R alkyne substituent. When R = *n*-butyl, the use of CuX<sub>2</sub> (4 equiv) and Cy<sub>2</sub>NH·HX (0.1 equiv) in DCE at 65 °C gave 4-chloro- and 4-bromoisocoumarins **5b,c** with satisfactory yield (>60%) and purity (>93%) as well as 6-endo-dig cyclization selectivity (>96%) (Table 1, entries 4 and 7). However, in the same conditions, for R = phenyl, the 4-haloisocoumarins **6b,c** were obtained in a mixture along with around 30% of the 4-*H*-isocoumarin **6d** (Table 1, entries 4 and 7). Concerning the bromolactonization, a temperature decrease from 65 °C to rt led to the desired 4-bromoisocoumarin in 47% yield with less

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(18) Yields were determined by NMR titration according to Yan, B. *Analysis and Purification Methods in Combinatorial Chemistry*; John Wiley & Sons: New York, 2004. The crude isocoumarin was dissolved in 0.5 mL of CDCl<sub>3</sub> containing hexamethyldisiloxane (2.5 μmol/mL) as internal standard. Yield was determined by quantitative <sup>1</sup>H NMR titration of the isocoumarin relative to the standard. The accuracy of the method was estimated to 5% as confirmed by calibration with weighted quantities (18, 29, 53 mg) of 4-methoxybenzylalcohol and is consistent with the literature data.

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TABLE 2. Substrate Scope (Variable R Group) for Sonogashira and Electrocyclization Steps

Compounds	E <sup>+</sup>	Yield <sup>a</sup> (%) (Purity <sup>b</sup> )	Ratios <sup>b</sup> A/B/C	Compounds	E <sup>+</sup>	Yield <sup>a</sup> (%) (Purity <sup>b</sup> )	Ratios <sup>b</sup> A/B/C
	ICl	78 (98)	93:7:0		ICl	81 (>99)	100:0:0
	I <sub>2</sub>	58 (99)	96:4:0		ICl	90 (93)	100:0:0
	ICl	48 (100)	81:19:0		ICl	20 (39)	100:0:0
	I <sub>2</sub>	48 (51)	92:8:0		ICl	28 (70)	100:0:0
	ICl	89 (98)	96:4:0		ICl	77 (89)	100:0:0
	I <sub>2</sub>	45 (86)	96:4:0				
	ICl	91 (100)	73:27:0				
	I <sub>2</sub>	72 (96)	89:11:0				
	ICl	49 (86)	86:14:0				

<sup>a</sup> Based on ascertained loading of resin **2** and determined by NMR analyses using HMDSO as an internal standard (total amount of **A**, **B**, and **C** was considered), yields are indicated for the combination of Sonogashira reaction plus cyclization. <sup>b</sup> As determined by reverse-phase HPLC with monitoring at 214 nm and confirmed by NMR. Purity is based on added amounts of **A**, **B**, and **C**.

than 5% of **6d** (A/C ratio 96:4) and an excellent purity (95%) (Table 1, entry 8). On the other hand, whatever the conditions (temperature or catalyst) used for chlorolactonization of the supported 2-(2-phenylethynylbenzoate) **4** (Table 1, entries 3–6), the selectivity of the reaction was not improved.

We also explored the formation of 4-*H*-isocoumarins by acid-promoted cyclization of supported 2-(alk-1-ynyl)benzoates **3** and **4**. Three main protocols, which have been recently reported in the literature for the synthesis of such compounds in solution, were evaluated. First, the Lewis acid, ZnCl<sub>2</sub>, which has been reported as a heteroannulation inducing reagent in a two-step one-pot synthesis of isocoumarin,<sup>9g</sup> was tested on polymer-bound derivatives **3** and **4**. Only moderate yields (about 40% for R = *n*-Bu and Ph) and incomplete selectivity (for R = Ph) were achieved (Table 1, entry 10). In a second protocol described by Le Bras and co-workers,<sup>9n</sup> *p*-toluenesulfonic acid (Table 1, entry 11) was used to produce the isocoumarin **6d** through a PTSA-catalyzed annulation of the supported diaryl-alkyne **4** with an excellent 6-*endo*-dig cyclization selectivity. Third, we tested the use of TFA<sup>9o</sup> (Table 1, entry 9). Satisfying to very good yields and purity and complete selectivity were obtained, making this protocol the most efficient for the synthesis of both 3-alkyl- and 3-phenylisocoumarins **5d** and **6d**.

In parallel to these studies, other solid supports were evaluated. In particular, the Merrifield resin also gave good results with slightly lower efficiency in terms of selectivity (results not shown).

Thus, we developed an efficient traceless route to prepare 4-*X* isocoumarins (X = H, I, Cl, Br) in three steps, without purification, with moderate to good yields (41–99%) and

purities (up to 99%). Considering the results described above, the reagent elected for iodolactonization was ICl (when 5-*exo*-dig cyclization is detected, I<sub>2</sub> is preferred). For bromo- and chlorolactonization, we recommend the use of the CuX<sub>2</sub>/Cy<sub>2</sub>NH·HX system. In the case of 4-*H*-isocoumarin, TFA appeared to be the best reagent.

With these optimized conditions in hand (Table 1, entries 1, 2, 4, 7, and 9), the scope of this route was then investigated toward (i) various substituted terminal alkynes and (ii) a selection of substituted (het)aryl bromides as substrates. All the compounds of this library were synthesized on a parallel synthesizer apparatus (Tables 2 and 3).

With respect to the alkyne partner (Table 2, X = I, compounds **9a**–**18a**), most of the functional groups studied so far are compatible with iodolactonization conditions, and good to excellent yields, purities (above 80%), and A/B ratios were generally observed. Alkyl groups (**9a**–**13a**) and substituted (het)aryl (**14a**, **15a**, and **18a**) were readily accommodated. A particular case was the anilines **16a** and **17a**, which were obtained in low yields. This was due to the formation of extra-iodinated byproduct, as identified by LC-MS, highlighting the significant reactivity of the aniline aromatic ring. The presence of a nitrile, an alcohol, or even a carboxylic acid (**11a**–**13a**) group did not cause any difficulty. Finally, as established during the study on models **3** and **4** (Table 1, entries 1 and 2), low selectivity obtained with ICl could be improved using I<sub>2</sub> but this resulted in lower yields.

In a second set of experiments, keeping R = *n*-butyl or phenyl, the scope of the process was investigated with respect to the benzene ring, which was substituted with electron-rich



TABLE 3. Substrate Scope (Variation on Aromatic Ring) for Sonogashira and Electrocyclization Steps

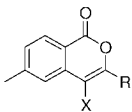
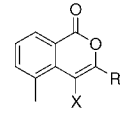
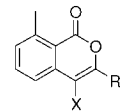
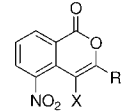
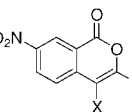
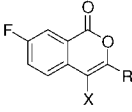
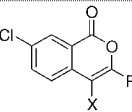
Entry	Compounds	R	X	E <sup>+</sup>	Yield <sup>a</sup> (%)	Purity <sup>b</sup> (%)	Ratios <sup>b</sup> A/B/C	
1		<b>19a</b>	Ph	I	ICl	quant.	96	100:0:0
2		<b>20a</b>	Bu	I	ICl	88	97	96:4:0
3		<b>20a</b>	Bu	I	I <sub>2</sub>	71	96	98:2:0
4		<b>20b</b>	Bu	Cl	CuCl <sub>2</sub>	72	99	99:0:1
5		<b>20c</b>	Bu	Br	CuBr <sub>2</sub>	69	95	96:0:4
6		<b>20d</b>	Bu	H	TFA	71	82	100:0 <sup>c</sup>
7		<b>21a</b>	Ph	I	ICl	56	70	100:0:0
8 <sup>d</sup>		<b>21a</b>	Ph	I	ICl	69	93	100:0:0
9		<b>22a</b>	Bu	I	ICl	25	69	54:46:0
10 <sup>d</sup>		<b>22a</b>	Bu	I	ICl	24	73	48:52:0
11 <sup>d</sup>		<b>22a</b>	Bu	I	I <sub>2</sub>	28	59	100:0:0
12 <sup>d</sup>		<b>22b</b>	Bu	Cl	CuCl <sub>2</sub>	n.d.	25	25:0:75
13 <sup>d</sup>		<b>22c</b>	Bu	Br	CuBr <sub>2</sub>	42	88	90:0:10
14 <sup>d</sup>		<b>22d</b>	Bu	H	TFA	68	97	100:0 <sup>c</sup>
15		<b>23a</b>	Ph	I	ICl	60	65	100:0:0
16		<b>24a</b>	Bu	I	ICl	53	68	88:12:0
17		<b>24a</b>	Bu	I	I <sub>2</sub>	44	58	98:2:0
18		<b>25a</b>	Ph	I	ICl	25	63	100:0:0
19		<b>26a</b>	Bu	I	ICl	30	56	91:9:0
20		<b>26a</b>	Bu	I	I <sub>2</sub>	n.d.	12	83:17:0
21		<b>27a</b>	Ph	I	ICl	49	79	100:0:0
22		<b>28a</b>	Bu	I	ICl	86	99	100:0:0
23		<b>28b</b>	Bu	Cl	CuCl <sub>2</sub>	40	64	64:0:36
24 <sup>e</sup>		<b>28b</b>	Bu	Cl	CuCl <sub>2</sub>	72	81	92:0:8
25		<b>28c</b>	Bu	Br	CuBr <sub>2</sub>	42	97	98:0:2
26		<b>28d</b>	Bu	H	TFA	42	90	100:0 <sup>c</sup>
27		<b>29a</b>	Ph	I	ICl	92	92	100:0:0
28		<b>30a</b>	Bu	I	ICl	87	>99	98:2:0
29		<b>30a</b>	Bu	I	I <sub>2</sub>	87	97	99:1:0
30		<b>30b</b>	Bu	Cl	CuCl <sub>2</sub>	74	95	96:0:4
31		<b>30c</b>	Bu	Br	CuBr <sub>2</sub>	90	90	91:0:9
32		<b>30d</b>	Bu	H	TFA	86	87	100:0 <sup>c</sup>
33		<b>31a</b>	Ph	I	ICl	84	94	100:0:0
34		<b>32a</b>	Bu	I	ICl	91	99	100:0:0

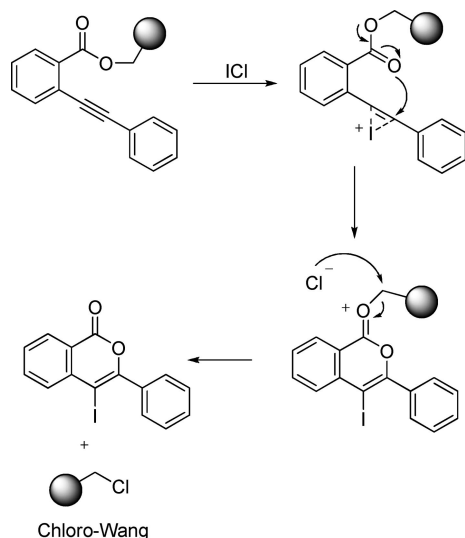
TABLE 3. Continued

Entry	Compounds	R	X	E <sup>+</sup>	Yield <sup>a</sup> (%)	Purity <sup>b</sup> (%)	Ratios <sup>b</sup> A/B/C	
35		<b>33a</b>	Ph	I	ICl	31	80	100:0:0
36		<b>34a</b>	Bu	I	ICl	53	87	97:3:0
37		<b>34a</b>	Bu	I	I <sub>2</sub>	74	86	100:0:0
38		<b>34b</b>	Bu	Cl	CuCl <sub>2</sub>	62	98	100:0:0
39	<b>34c</b>	Bu	Br	CuBr <sub>2</sub>	60	97	100:0:0	
40		<b>35a</b>	Ph	I	ICl	62	80	100:0:0
41		<b>36a</b>	Bu	I	ICl	63	73	97:3:0
42		<b>36a</b>	Bu	I	I <sub>2</sub>	60	84	100:0:0
43		<b>37a</b>	Ph	I	ICl	n.d.	62	100:0:0
44		<b>38a</b>	Bu	I	ICl	28	62	68:32:0
45		<b>38a</b>	Bu	I	I <sub>2</sub>	26	37	n.d.
46		<b>39a</b>	Ph	I	ICl	71	96	100:0:0
47		<b>40a</b>	Bu	I	ICl	59	98	100:0:0
48		<b>41a</b>	Ph	I	ICl	quant.	97	100:0:0
49		<b>42a</b>	Bu	I	ICl	99	>99	100:0:0
50		<b>42b</b>	Bu	Cl	CuCl <sub>2</sub>	80	98	100:0:0
51		<b>42c</b>	Bu	Br	CuBr <sub>2</sub>	84	93	99:0:1
52		<b>42d</b>	Bu	H	TFA	55	94	100:0 <sup>c</sup>

<sup>a</sup> Based on ascertained loading of resin **2** and determined by NMR analyses using HMDSO as an internal standard (total amount of **A**, **B**, and **C** was considered), yields are indicated for the combination of Sonogashira reaction plus cyclization. <sup>b</sup> As determined by reverse-phase HPLC with monitoring at 214 nm and confirmed by NMR. Purity is based on added amounts of **A**, **B**, and **C**. <sup>c</sup> For X = H, compounds **A** and **C** are identical. <sup>d</sup> Experiments on resin loaded at 0.42 instead of 0.98 mmol·g<sup>-1</sup>. <sup>e</sup> Et<sub>3</sub>N·HCl was used as the catalyst (instead of Cy<sub>2</sub>NH·HCl).

or -poor substituent or replaced by various aromatic moieties (Table 3). All of the expected 4-X isocoumarins (X = I, Cl, Br, H) were generated using our experimental conditions. Generally, good to excellent selectivity was obtained with a percentage of the desired isocoumarin often close to 100. Isocoumarins bearing an electron-donating or electron-withdrawing substituent at the position 6 or 7 (compounds **19**, **20**, **27**–**34**) and isosteric pyridine- and thiophene-containing analogues (compounds **39**–**42**) were synthesized in good yields (Table 3, entries 1–6, 21–39, and 46–52 except for entries 25, 26, and 35). However, when substituents were located at position 5 or 8 of the scaffold (Table 3, entries 7–20 and 43–45), lower yields were obtained. These results very likely originated from the bulkiness sensitivity of the Sonogashira reaction. In order to promote completion of this reaction, the palladium-catalyzed cross-coupling of 1-hexyne with the resin-bound 2-bromobenzoate **2** and 2-bromo-3-methylbenzoate analogue was performed under microwave irradiation (150 °C, 2 h). While the reaction time was significantly shortened in the case of the unhindered 2-bromobenzoate (2 h vs 16 h under classical heating), the conversion rate of 2-bromo-3-methylbenzoate was not improved, even when adding KI to enhance reactivity via

Br/I exchange. To circumvent this issue, we decided to diminish the resin loading. Going from 0.98 to 0.42 mmol·g<sup>-1</sup> gave a complete Sonogashira reaction between hex-1-yne or phenylacetylene with the resin-bound 2-bromo-3-methylbenzoate, leading to 4-*H*- and 4-haloisocoumarins with good purities and high yields (Table 3, entries 8, 13, and 14). This result indicated that the proximity between adjacent sites imposed by the cross-linked polymer had its own influence on the Sonogashira reaction: too high loadings, meaning high proximity, might hinder complete accessibility of the reactive sites. Moreover, a substituent in position 3 onto the polymer-bound 2-(alk-1-ynyl)benzoates seemed to disrupt the halonium's addition on the triple bond because low selectivity remained in particular when R = *n*-Bu (Table 3, entry 10). Other unexpected different behaviors have been observed during the electrocyclization reaction in solution and on solid phase. For instance, the synthesis of 4-chloro-7-nitroisocoumarins in solution was already reported (with R = C<sub>8</sub>H<sub>17</sub>).<sup>15</sup> The authors described that, when using CuCl<sub>2</sub>/Cy<sub>2</sub>NH·HCl as electrocyclization reagents, the 4-chloro-7-nitro-3-octylisocoumarin was obtained in 87% yield as the sole product, while when using CuBr<sub>2</sub>/Cy<sub>2</sub>NH·HBr, the 4-bromo analogue was isolated in 68% yield in combination

**SCHEME 2. Proposed Mechanism of Polymer-Bound Iodolactonization with ICl for Compound 6a**


with 29% of the 4-*H* analogue. However, during the electrophile-induced annulation on the solid support, we observed opposite results, with  $\text{CuBr}_2/\text{Cy}_2\text{NH}\cdot\text{HBr}$  giving the 6-*endo*-dig compound with very high selectivity (with  $\text{R} = \text{C}_6\text{H}_9$ , entries 23–25). This was not the case for the chlorolactonization (64: 36, Table 3, entry 23). Nevertheless, in the latter, higher selectivity could be achieved by changing the catalyst from  $\text{Cy}_2\text{NH}\cdot\text{HCl}$  to  $\text{Et}_3\text{N}\cdot\text{HCl}$  (Table 3, entry 24). Although no explanation could be drawn for this behavior, these results showed again unexpected interference of the solid support, which could be relieved by limited condition changes.

To conclude this study, we exploited the previously described<sup>13c</sup> mechanism of the electrophile-induced cyclization with ICl to recycle the resin (Scheme 2). According to Scheme 2, nucleophilic attack by the oxygen of the carbonyl group on the triple bond activated by iodonium coordination would be followed by the nucleophilic substitution of the chloride anion on the polymer's vicinal methylene group. Therefore, a chloro-Wang resin should be generated and could enter a new synthetic cycle (Table 4). To test this hypothesis, the resin **4** was reacted with ICl (1.2 equiv) in  $\text{CH}_2\text{Cl}_2$  at rt to afford the 4-iodoisocoumarin **6a**. The recovered resin was washed and dried under reduced pressure before being loaded again with the 2-bromobenzoic acid cesium salt. Because the chlorinated solid support was less reactive than the bromo-Wang resin, the loading needed to be performed at higher temperature (i.e., 65 °C). This recycled resin was resubmitted to the Sonogashira reaction with phenylacetylene and electrocyclization, with ICl leading to a second batch of compound **6a** with high purity (97%, as obtained for the first batch). The yield was slightly lower (93%)

**TABLE 4. Resin Recycling Results When Using ICl and  $\text{CuBr}_2$  as Electrophile Reagents**

Cycle	X <sup>a</sup>	Electrophile	Yield <sup>b</sup> (%)	Purity (%)	Ratios A/B/C
1st	I	ICl	96	97	100:0:0
2nd	I	ICl	93	97	100:0:0
3rd	I	ICl	79	92	100:0:0
1st	Br	$\text{CuBr}_2$	47	95	96:0:4
2nd	Br	$\text{CuBr}_2$	31	71	98:0:2
3rd	Br	$\text{CuBr}_2$	11	39	98:0:2

<sup>a</sup> Compounds **6a** ( $\text{X} = \text{I}$ ) and **6c** ( $\text{X} = \text{Br}$ ) were chosen as model experiments. <sup>b</sup> Based on ascertained loading of resin **2** ( $1.15 \text{ mmol}\cdot\text{g}^{-1}$ ).

compared to that obtained after the first cycle. In the third cycle, a more significant difference appeared since the isocoumarin **6a** was obtained with 79% yield and 92% purity (Table 4). The other electrocyclization conditions were also evaluated. The  $\text{I}_2$ -cleaved resin cannot be loaded again. By using  $\text{CuCl}_2$ , reloading of the 2-bromobenzoic cesium salt was much less efficient: after a second cycle, the 4-chloroisocoumarin **6b** was obtained in low yield and low purity. In the case of  $\text{CuBr}_2$ , 2-bromobenzoic cesium salt was loaded at rt for a second cycle, indicating that bromo-Wang was effectively regenerated. However, yield and purity were not as satisfactory as for ICl, and a large drop in efficiency was obtained during the third cycle (Table 4). Although the results obtained with copper halides were less satisfying, halo-Wang resins seemed to be at least partially generated. This is not in agreement with the mechanism proposed in solution for such copper reagents that should result only in the formation of the alcohol-Wang resin.<sup>15</sup> Thus, we established that only resins used for the preparation of iodinated isocoumarins with ICl could be recycled at least once.

## Conclusions

In conclusion, we have developed a straightforward and traceless electrophile-promoted halocyclization solid-phase methodology that provides access to the isocoumarin scaffold. This first polymer-bound parallel synthetic approach allowed large variations at positions 3 and 4 of the isocoumarin scaffold and on the aromatic moiety. Moreover, further derivatization of the synthesized 4-haloisocoumarins ( $\text{X} = \text{I}, \text{Cl}, \text{Br}$ ) should enlarge the library. Yields for the key reactions (Sonogashira cross-coupling and electrocyclization) were moderate to excellent (30% to quantitative). Because we also optimized the purification process, allowing direct elimination of salts and excess reagents to obtain desired compounds with high purities (82% of compounds with purity above 80%), this methodology represents a valuable improvement for the parallel synthesis of isocoumarins and analogues. Moreover, we demonstrated that the use of ICl as electrophile allowed recycling of the resin. In a fundamental point of view based on results obtained during resin recycling experiments, we assume that the proposed mechanism of the electrophile-induced annulation with  $\text{CuX}_2/\text{Cy}_2\text{NH}\cdot\text{HX}$  has to be re-examined. Further studies to understand this mechanism will be described in due course.

## Experimental Section

### General SPS Procedure for the Synthesis of Isocoumarins.

To a solution of 2-bromobenzoic acid derivative (4 equiv) in EtOH (10 mL/mmol) was added portionwise  $\text{Cs}_2\text{CO}_3$  (2 equiv). After stirring for 2 h at rt, the reaction mixture was concentrated and dried under vacuum. The cesium salt was dissolved in DMF then added to the preswollen (DMF) bromo-Wang resin (1.6 mmol). The suspension was stirred for 16 h at rt. After filtration, the resulting resin **2** was washed with DMF ( $3 \times 3 \text{ mL}$ ),  $\text{H}_2\text{O}$  ( $2 \times 2 \text{ mL}$ ), DMF ( $1 \times 3 \text{ mL}$ ),  $\text{CH}_2\text{Cl}_2$  ( $2 \times 3 \text{ mL}$ ), MeOH ( $2 \times 3 \text{ mL}$ ), and  $\text{CH}_2\text{Cl}_2$  ( $2 \times 3 \text{ mL}$ ) and dried under vacuum. Experimental loading of resin was determined by cleavage of 100 mg of the resin with TFA/ $\text{CH}_2\text{Cl}_2$  (1:1, 1 mL) for 1 h at rt. The solution was collected by filtration, the resin was washed with  $\text{CH}_2\text{Cl}_2$  (1 mL), and the filtrates were mixed and evaporated under reduced pressure. The loading was determined from the weight of recovered product (data concerning the loading are available in the Supporting Information). Resin (200 mg) was loaded into a polypropylene tube equipped with a polyethylene frit and swelled in  $\text{CH}_2\text{Cl}_2$  for 1 h. The resin was filtered and suspended in a mixture of anhydrous

CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and Et<sub>3</sub>N (5 mL). CuI (0.1 equiv), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.2 equiv), and alkyne (10 equiv) were added. The reaction mixture was heated for 16 h at 65 °C. The resin was drained and washed successively with CH<sub>2</sub>Cl<sub>2</sub> (2 × 5 mL), H<sub>2</sub>O/DMF (1:1, 2 × 5 mL), 5% DIEA/DMF (2 × 5 mL), MeOH (1 × 5 mL), DMF (1 × 5 mL), MeOH (2 × 5 mL), and CH<sub>2</sub>Cl<sub>2</sub> (2 × 5 mL). Eventually, a second cycle of reaction was performed depending on the conversion rate determined by HPLC analysis after cleavage of a sample of resin by TFA/CH<sub>2</sub>Cl<sub>2</sub> (1:1).

**A: Typical Procedure for Iodolactonization: Synthesis of 3-Substituted 4-Iodo-1*H*-isochromen-1-ones.** Polymer-bound 2-(alk-1-ynyl)benzoate (150 mg) was loaded into a polypropylene tube equipped with a polyethylene frit and swelled in CH<sub>2</sub>Cl<sub>2</sub> for 1 h. The resin was filtered and suspended in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3 mL). A solution of ICl (1.0 M, 1.2 equiv) in CH<sub>2</sub>Cl<sub>2</sub> or I<sub>2</sub> (3 equiv) was added. The suspension was stirred at rt for 4 h, then the resin was drained and washed with CH<sub>2</sub>Cl<sub>2</sub> (3 × 3 mL). The filtrates were mixed and treated with 1 mL of aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (4.0 g in 10 mL of water). To remove the aqueous phase, the biphasic mixture was filtered over a cartridge (5 mL) packed with diatomaceous earth. The recovered organic phase was evaporated under reduced pressure, yielding the desired 3-substituted 4-iodo-1*H*-isochromen-1-ones.

**3-Butyl-4-iodo-1*H*-isochromen-1-one, 5a:** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.34–1.48 (m, 2H), 1.62–1.76 (m, 2H), 2.88 (t, *J* = 7.9 Hz, 2H), 7.45 (ddd, *J* = 8.1, 6.7, 1.8 Hz, 1H), 7.66–7.76 (m, 2H), 8.41 (dd, *J* = 8.1, 0.7 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 14.1 (CH<sub>3</sub>), 22.0 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 37.4 (CH<sub>2</sub>), 76.4 (C), 120.3 (C), 128.8 (CH), 129.9 (CH), 130.7 (CH), 134.4 (C), 135.9 (CH), 158.5 (C), 162.2 (C); IR  $\nu_{\max}$  (neat) 1731, 1609, 1473, 1177, 1100, 1053, 1029, 982, 759, 687 cm<sup>-1</sup>; HPLC *t*<sub>R</sub> 3.31 min; LC-MS (ESI+) *m/z* (%) 329 [M + H]<sup>+</sup> (100); HRMS (ESI+) *m/z* calcd for C<sub>13</sub>H<sub>14</sub>O<sub>2</sub>I 329.0039, found 329.0019.

**4-Iodo-3-phenyl-1*H*-isochromen-1-one, 6a<sup>12c</sup>:** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.40–7.45 (m, 3H), 7.52 (ddd, *J* = 7.9, 7.2, 1.3 Hz, 1H), 7.62–7.66 (m, 2H), 7.76 (ddd, *J* = 7.9, 7.2, 1.4 Hz, 1H), 7.81–7.86 (m, 1H), 8.25 (dd, *J* = 7.9, 0.9 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 76.8 (C), 120.6 (C), 128.4 (2 × CH), 129.5 (CH), 130.0 (CH), 130.3 (2 × CH), 130.5 (CH), 131.8 (CH), 135.0 (C), 136.0 (CH), 138.5 (C), 155.1 (C), 161.9 (C); IR  $\nu_{\max}$  (neat) 1725, 1599, 1471, 1231, 1075, 1029, 946, 758, 687 cm<sup>-1</sup>; HPLC *t*<sub>R</sub> 3.06 min; LC-MS (ESI+) *m/z* (%) 349 [M + H]<sup>+</sup> (100); HRMS (ESI+) *m/z* calcd for C<sub>15</sub>H<sub>10</sub>O<sub>2</sub>I 348.9726, found 348.9724.

**B: Typical Procedure for Bromo- or Chlorolactonization: Synthesis of 3-Substituted 4-Bromo- or 4-Chloro-1*H*-isochromen-1-ones.** The polymer-bound 2-(alk-1-ynyl)benzoate (150 mg) was swelled in anhydrous CICH<sub>2</sub>CH<sub>2</sub>Cl for 1 h, filtered, and suspended in anhydrous CICH<sub>2</sub>CH<sub>2</sub>Cl (3 mL). CuX<sub>2</sub> (X = Cl or Br) (4 equiv) and Cy<sub>2</sub>NH·HX or Et<sub>3</sub>N·HX (0.1 equiv) were added. The suspension was stirred at 65 °C for 16 h, then the resin was drained and washed with CH<sub>2</sub>Cl<sub>2</sub> (3 × 3 mL). The filtrates were mixed and passed through a cake of silica gel. The recovered organic phase was evaporated under reduced pressure, yielding the desired 3-substituted 4-bromo- or 4-chloro-1*H*-isochromen-1-one.

**3-Butyl-4-chloro-1*H*-isochromen-1-one, 5b:** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.32–1.46 (m, 2H), 1.62–1.75 (m, 2H), 2.74 (t, *J* = 7.4 Hz, 2H), 7.45–7.54 (m, 1H), 7.72–7.80 (m, 2H), 8.25 (dd, *J* = 7.9, 0.8 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 14.0 (CH<sub>3</sub>), 22.5 (CH<sub>2</sub>), 29.1 (CH<sub>2</sub>), 31.3 (CH<sub>2</sub>), 111.2 (C), 120.6 (C), 123.5 (CH), 128.7 (CH), 130.1 (CH), 135.5 (CH), 135.9 (C), 155.0 (C), 162.2 (C); IR  $\nu_{\max}$  (neat) 1740, 1631, 1478, 1271, 1051, 1027, 761, 688 cm<sup>-1</sup>; HPLC *t*<sub>R</sub> 3.22 min; LC-MS (ESI+) *m/z* (%) 280 (3), 278 [M + CH<sub>3</sub>CN + H]<sup>+</sup> (11), 239 (32), 237 [M + H]<sup>+</sup> (100); HRMS (ESI+) *m/z* calcd for C<sub>13</sub>H<sub>14</sub>O<sub>2</sub>Cl 237.0682, found 237.0691.

**4-Bromo-3-butyl-1*H*-isochromen-1-one, 5c:** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.32–1.45 (m, 2H), 1.63–1.74 (m, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 7.44–7.51 (m, 1H), 7.71–7.79 (m, 2H), 8.22 (d, *J* = 7.8 Hz, 1H); <sup>13</sup>C NMR (75 MHz,

CDCl<sub>3</sub>) δ 14.0 (CH<sub>3</sub>), 22.5 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 33.4 (CH<sub>2</sub>), 101.4 (C), 120.5 (C), 125.9 (CH), 128.7 (CH), 130.0 (CH), 135.6 (CH), 136.6 (C), 156.0 (C), 161.7 (C); IR  $\nu_{\max}$  (neat) 1735, 1624, 1475, 1285, 1102, 1051, 1027, 999, 759, 687 cm<sup>-1</sup>; HPLC *t*<sub>R</sub> 3.24 min; LC-MS (ESI+) *m/z* (%) 324 (12), 322 [M + CH<sub>3</sub>CN + H]<sup>+</sup> (12), 283 (88), 281 [M + H]<sup>+</sup> (100); HRMS (ESI+) *m/z* calcd for C<sub>13</sub>H<sub>14</sub>O<sub>2</sub>Br 281.0177, found 281.0175.

**4-Chloro-3-phenyl-1*H*-isochromen-1-one, 6b:** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.43–7.51 (m, 3H), 7.56–7.62 (m, 1H), 7.81–7.89 (m, 3H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.33 (dd, *J* = 7.9, 1.2 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 111.5 (C), 120.7 (C), 124.2 (CH), 128.4 (2 × CH), 129.3 (CH), 129.5 (2 × CH), 130.0 (CH), 130.4 (CH), 131.6 (C), 135.5 (CH), 136.1 (C), 150.6 (C), 161.0 (C); IR  $\nu_{\max}$  (neat) 1723, 1558, 1489, 1055, 981, 710, 694 cm<sup>-1</sup>; HPLC *t*<sub>R</sub> 3.02 min; LC-MS (ESI+) *m/z* (%) 300 (3), 298 [M + CH<sub>3</sub>CN + H]<sup>+</sup> (10), 259 (32), 257 [M + H]<sup>+</sup> (100); HRMS (ESI+) *m/z* calcd for C<sub>15</sub>H<sub>10</sub>O<sub>2</sub>Cl 257.0369, found 257.0392.

**4-Bromo-3-phenyl-1*H*-isochromen-1-one, 6c<sup>12a</sup>:** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.40–7.45 (m, 3H), 7.52 (ddd, *J* = 7.9, 7.2, 1.3 Hz, 1H), 7.62–7.66 (m, 2H), 7.76 (ddd, *J* = 7.9, 7.2, 1.4 Hz, 1H), 7.81–7.86 (m, 1H), 8.25 (dd, *J* = 7.9, 0.9 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 76.8 (C), 120.6 (C), 128.4 (2 × CH), 129.5 (CH), 130.0 (CH), 130.3 (2 × CH), 130.5 (CH), 131.8 (CH), 135.0 (C), 136.0 (CH), 138.5 (C), 155.1 (C), 161.9 (C); IR  $\nu_{\max}$  (neat) 1737, 1619, 1474, 1231, 1086, 1054, 1020, 960, 758, 688 cm<sup>-1</sup>; HPLC *t*<sub>R</sub> 3.01 min; LC-MS (ESI+) *m/z* (%) 344 (10), 342 [M + CH<sub>3</sub>CN + H]<sup>+</sup> (10), 303 (99), 301 [M + H]<sup>+</sup> (100); HRMS (ESI+) *m/z* calcd for C<sub>15</sub>H<sub>10</sub>O<sub>2</sub>Br 300.9864, found 300.9850.

**C: Typical Procedure for Electrocyclization with TFA: Synthesis of 3-Substituted 4-*H*-Isochromen-1-ones.** The polymer-bound 2-(alk-1-ynyl)benzoate (150 mg) was swelled in CH<sub>2</sub>Cl<sub>2</sub> for 1 h, filtered, and suspended in a mixture of CH<sub>2</sub>Cl<sub>2</sub>/TFA (v/v 1:1, 4 mL). The suspension was stirred at rt for 2 h, then the resin was drained and washed with CH<sub>2</sub>Cl<sub>2</sub> (3 × 3 mL). The filtrates were mixed and evaporated under reduced pressure, yielding the desired 3-substituted 4-*H*-isochromen-1-one.

**3-Butyl-1*H*-isochromen-1-one, 5d<sup>9b</sup>:** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.31–1.46 (m, 2H), 1.58–1.75 (m, 2H), 2.48 (t, *J* = 7.4 Hz, 2H), 6.20 (s, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.39 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.62 (dd, *J* = 7.8, 7.4 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 14.0 (CH<sub>3</sub>), 22.3 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 33.4 (CH<sub>2</sub>), 103.1 (CH), 120.4 (C), 125.2 (CH), 127.7 (CH), 129.7 (CH), 134.9 (CH), 137.9 (C), 158.6 (C), 163.3 (C); IR  $\nu_{\max}$  (neat) 1723, 1655, 1483, 1160, 1045, 1022, 755, 690 cm<sup>-1</sup>; HPLC *t*<sub>R</sub> 2.78 min; LC-MS (ESI+) *m/z* (%) 244 [M + CH<sub>3</sub>CN + H]<sup>+</sup> (23), 203 [M + H]<sup>+</sup> (100); HRMS (ESI+) *m/z* calcd for C<sub>13</sub>H<sub>15</sub>O<sub>2</sub> 203.1072, found 203.1052.

**3-Phenyl-1*H*-isochromen-1-one, 6d<sup>9k</sup>:** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.86 (s, 1H), 7.27–7.52 (m, 5H), 7.64 (m, 1H), 7.80 (m, 2H), 8.16–8.30 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 102.1 (CH), 120.7 (C), 125.4 (2 × CH), 126.3 (CH), 128.4 (CH), 129.1 (2 × CH), 129.8 (CH), 130.2 (CH), 132.1 (C), 135.2 (CH), 137.8 (C), 153.8 (C), 162.6 (C); IR  $\nu_{\max}$  (neat) 1717, 1638, 1482, 1238, 1070, 1028, 749, 681 cm<sup>-1</sup>; HPLC *t*<sub>R</sub> 2.74 min; LC-MS (ESI+) *m/z* (%) 264 [M + CH<sub>3</sub>CN + H]<sup>+</sup> (7), 223 [M + H]<sup>+</sup> (100); HRMS (ESI+) *m/z* calcd for C<sub>15</sub>H<sub>11</sub>O<sub>2</sub> 223.0759, found 223.0775.

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**Supporting Information Available:** Experimental details and <sup>1</sup>H and <sup>13</sup>C NMR spectral data for described compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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