Halocyclization of Methyl 2-Alkynylbenzoates to Isocoumarins Using Cupric Halides

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Treatment of methyl 2-alkynylbenzoates with two to three equivalents of CuX_2 (X = Cl or Br) in refluxing acetonitrile gave isocoumarins **2** in good to excellent chemical yields.

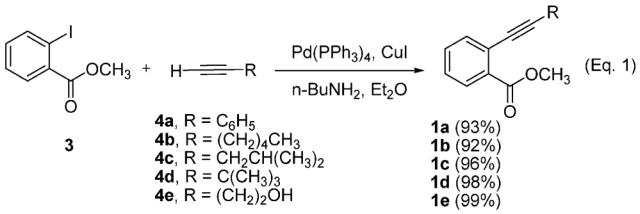
Keywords: Halocyclization; Isocoumarins.

INTRODUCTION

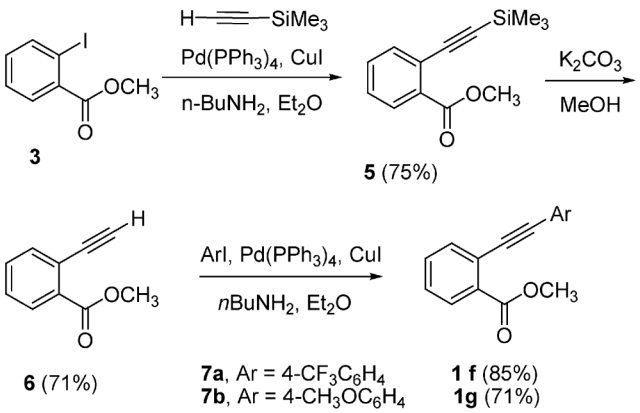
Numerous natural products that contain isocoumarin subunits exhibit a broad spectrum of biological activity, including as potent irreversible inhibitors of blood coagulation enzymes,[1] inhibitors of human leukocyte elastase,[2] as antifungal,[3] β-amyloid peptide production inhibitors[4] and as estrogen receptor beta selective ligands.[5] Although many synthetic methods to construct isocoumarins have been reported,[6] the electrophile induced cyclization of 2-alkynylbenzoates by Rossi[7] and Larock[8] proved to be a very efficient method to these molecules. However, the chlorocyclization reaction of this type of reaction has not been reported. We recently found that cupric halides, such as cupric chloride and cupric bromide, are powerful halocyclization agents of 2-alkynylthioanisoles to benzothiophenes.[9] We therefore anticipated that treatment of methyl 2-alkynylbenzoates under similar conditions would give isocoumarins. During our investigation of this cyclization reaction, a similar method for the synthesis of isocoumarins and α-Pyrone was reported.[10] In this paper, we disclose a general reaction of halocyclization of methyl 2-alkynylbenzoates using $CuCl_2$ and $CuBr_2$.

RESULTS AND DISCUSSION

The synthesis of methyl 2-alkynylbenzoates **1a-e** is outlined in Eq. 1. The palladium-catalyzed coupling reaction of methyl 2-iodobenzoate (**3**) with alkynes **4a-e** under Sonogashira reaction conditions gave the compounds **1a-e** in 92-99% yields. On the other hand, compounds **1f-g** were synthesized as shown in Scheme I. Treatment of methyl 2-iodobenzoate (**3**) with trimethylsilylacetylene using $Pd(PPh_3)_4$ as the catalyst under Sonogashira reaction conditions gave compound **5** in 75% yield. Desilylation of **5** was carried out by treatment of **5** with potassium carbonate in dry methanol to give **6** in 71% yield. Finally, compound **6** was coupled with aryl iodides **7a-b** using $Pd(PPh_3)_4$ as the catalyst to give the methyl 2-(arylethynyl)benzoates **1f** and **1g** in 85% and 71% yields, respectively. Compound **10** was prepared starting from compound **8**. (Eq. 2) Treatment of compound **8** with Tf_2O in the presence of Et_3N in CH_2Cl_2 gave vinyl triflate **9**. Vinyl triflate **9** was then converted to compound **10** in the yield of 86% under Sonogashira reaction conditions with **4b**.



Scheme I



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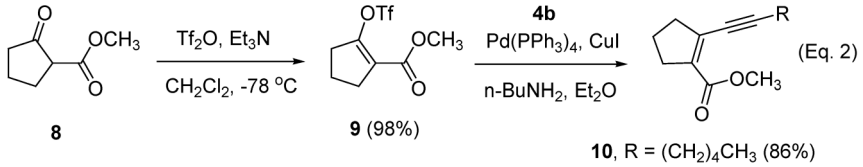


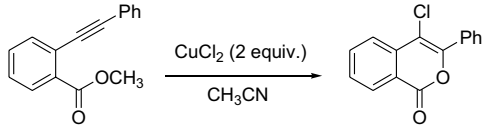
8 **9** (98%) **10**, R = $(CH_2)_4CH_3$ (86%)

The first attempt for the halocyclization of methyl 2-(2-phenylethynyl)benzoate (**1a**) was carried out by the treatment of **1a** with two equivalents of $CuCl_2$ in CH_3CN at room temperature. After stirring the reaction mixture for 24 h, the desired product **2a** was obtained in the yield of 62% and the starting material **1a** was recovered in 11% yield. We therefore increased the temperature by heating the reaction mixture to reflux. Under this temperature, this reaction went to completion after 2 h and the product **2a** was obtained in 98% yield. We also added 5 mol% of $PdCl_2$ into the reaction mixture of methyl 2-(2-phenylethynyl)benzoate (**1a**) with two equivalents of $CuCl_2$ in refluxing acetonitrile. Surprisingly, the yield of the product **2a** drops dramatically to 60%. It was also found that several uncharacterizable by-products were formed under these reaction conditions.

After finding the optimal reaction conditions for the chlorocyclization of **1a**, we then explored the generality of the cyclization reactions of compounds **1b-g**. The results are summarized in Table 2. The reactions proceeded very smoothly with different functional groups at the terminus of alkynes. Even a bulky substituent, such as a tertiary butyl group, (entry 3) gave the chlorocyclization product **2d** in 97% yield. The free hydroxyl group has a little influence in this reaction. Under the standard reaction conditions, cyclization of **1e** gave **2e** in 79% yield. The phenyl group bearing an electron-withdrawing group, such as trifluoromethyl, gave a little bit lower yield (entry 5). If only two equivalents of $CuCl_2$ were used for the cyclization of **1g**, the chlorocyclization product **2g** was obtained in 68% yield along with 24% yield of **11g**.[11] However, the side-product **11g** can be eliminated by treatment of **1g** with three equivalents of $CuCl_2$ (entry 7) and the desired product **2g** was obtained in 79% yield under these reaction conditions.

We have also found that treatment of $CuBr_2$ with **1a-g** under the described reaction conditions gave the bromocyclization adducts in good to excellent yields. The results are summarized in Table 3. Treatment of **1g** with two equiv-

Table 1. Cyclization of **1a** with cupric chloride

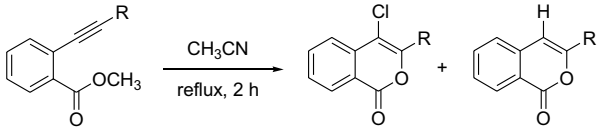


1a **2a**

Entry	Temp (°C)	Time (h)	Yields (%)
1	25	24	62(11)[a]
2	reflux	2	98
3[b]	reflux	2	60

[a] Recovered starting material.
[b] 5 mol % $PdCl_2$ was added.

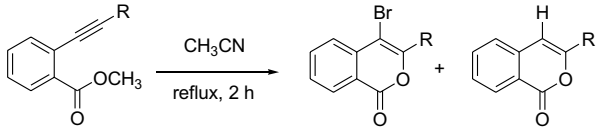
Table 2. Chlorocyclization of methyl 2-alkynylbenzoates **1b-g**



1 **2** **11**

Entry	$CuCl_2$ (eq)	R	Products, Yields (%)	
1	2	$(CH_2)_4CH_3$	**2b**, 85	
2	2	$CH_2CH(CH_3)_2$	**2c**, 97	
3	2	$C(CH_3)_3$	**2d**, 97	
4	2	$(CH_2)_2OH$	**2e**, 79	
5	2	4-$CF_3C_6H_4$	**2f**, 62	
6	2	4-$CH_3OC_6H_4$	**2g**, 68	**11g**, 24
7	3	4-$CH_3OC_6H_4$	**2g**, 79	

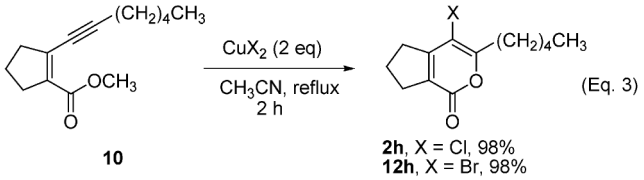
Table 3. Bromocyclization of methyl 2-alkynylbenzoates **1a-g**



1 **12** **11**

Entry	$CuBr_2$ (eq)	R	Products, Yields (%)	
1	2	Ph	**12a**, 99	
2	2	$(CH_2)_4CH_3$	**12b**, 71	
3	2	$CH_2CH(CH_3)_2$	**12c**, 98	
4	3	$C(CH_3)_3$	**12d**, 69	
5	2	$(CH_2)_2OH$	**12e**, 81	
6	2	4-$CF_3C_6H_4$	**12f**, 97	
7	2	4-$CH_3OC_6H_4$	**12g**, 70	**11g**, 23
8	3	4-$CH_3OC_6H_4$	**12g**, 89	

alents of $CuBr_2$ gave the desired bromocyclization product **12g** in 70% yield along with **11g** in 23% yield. Again, this side-product can be eliminated by using three equivalents of $CuBr_2$. A similar result was also observed for compound **1d**. (entry 4) Thus, treatment of **1d** with three equivalents of $CuBr_2$ gave **12d** in 69% yield. These cyclization reactions have also been extended to the cyclization of compound **10**. Thus, treatment of **10** with two equivalents of $CuCl_2$ under the described reaction conditions gave **2h** in 98% yield. A similar result was obtained by the reaction of compound **10** with $CuBr_2$ (Eq. 3).



A proposed mechanism for the formation of **2** and **12** is outlined in Scheme II. Cupric halide would first form a complex with alkyne such as the intermediate **13**. Intramolecular cyclization would then take place to give the oxonium ion **14**. Nucleophilic substitution replacement of the methyl group by the second equivalent of cupric halide would lead to the desired products **2** and **12**, respectively. It was reported that heating the cupric bromide to the refluxing acetonitrile temperature would generate bromine.[12] Therefore, the formation of **12** could also be promoted directly by bromine as in the report by Gandour.[13] The formation of **11g** is proposed by the acid-catalyzed cyclization reaction of **1g** as shown in Scheme II. The acids, HCl and HBr, could be generated by the halogenation of **1g** with CuX_2 on the anisole ring although we did not isolate any halogenated side-products.

CONCLUSION

In summary, we have developed an efficient method for the halocyclization reactions of methyl 2-alkynylbenzoates to give the isocoumarin adducts. This methodology should have its value for the application of the synthesis of medicinally or materially important compounds.

EXPERIMENTAL

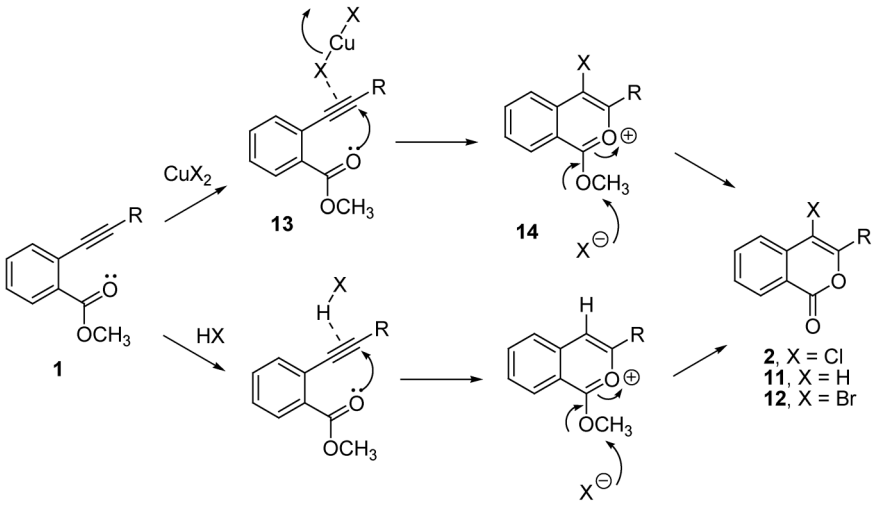
General procedure for cyclization compounds 2a-2h

To a stirred solution of **1a**-**1h** (10 mmol) in CH_3CN (10 mL) was added $CuCl_2$ (20 mmol). The resulting solution was heated to reflux and stirred at this temperature for 2 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration and removal of solvent *in vacuo*, the residue was purified by column chromatography on silica gel to yield the desired products.

4-Chloro-3-phenyl-1*H*-isochromen-1-one (2a)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 98% of a white solid, mp 142-143 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.95 (dt, *J* = 8.4, 0.8 Hz, 1H), 7.88-7.84 (m, 3H), 7.61 (td, *J* = 7.6, 0.8 Hz, 1H), 7.59-7.47

Scheme II A proposed mechanism of the formations of **2**, **11** and **12**



(m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.9, 150.4, 135.9, 135.3, 131.4, 130.2, 129.8, 129.3 (2C), 129.1, 128.2 (2C), 124.0, 120.5, 111.3; EA: calcd for C %: 70.19; H %: 3.53; found C %: 70.17, H %: 3.52.

4-Chloro-3-pentyl-1*H*-isochromen-1-one (2b)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 85% of a yellow liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.81-7.49 (m, 2H), 7.52 (td, *J* = 8.0, 2.0 Hz, 1H), 2.75 (t, *J* = 7.6 Hz, 2H), 1.73 (quin, *J* = 7.6 Hz, 2H), 1.38-1.33 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.3, 154.6, 135.5, 135.2, 129.7, 128.3, 123.1, 120.1, 110.7, 31.1 (2C), 26.4, 22.3, 13.9; HRMS (EI) calcd for $C_{14}H_{15}ClO_2$ 250.0761, found 250.0764.

4-Chloro-3-isobutyl-1*H*-isochromen-1-one (2c)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 97% of a brown solid, mp 56-57 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (dt, *J* = 8.4, 0.4 Hz, 1H), 7.82-7.77 (m, 2H), 7.53 (td, *J* = 8.0, 2.4 Hz, 1H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.25-2.18 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.2, 153.9, 135.5, 135.2, 129.7, 128.4, 123.2, 120.1, 111.7, 39.8, 27.3, 22.2 (2C); EA: calcd for C %: 65.98; H %: 5.50; found C %: 65.97, H %: 5.54.

4-Chloro-3-*tert*-butyl-1*H*-isochromen-1-one (2d)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 97% of a white solid, mp 129-130 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (ddd, *J* = 8.0, 1.2, 0.4 Hz, 1H), 7.89 (ddd, *J* = 8.0, 1.2, 0.4 Hz, 1H), 7.79 (td, *J* = 8.0, 1.6 Hz, 1H), 7.53 (td, *J* = 8.0, 1.2 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.0, 159.4, 136.7, 135.0, 129.4, 128.4, 123.2, 120.0, 110.8, 37.8, 28.3 (3C); EA: calcd for C %: 65.97; H %: 5.54; found C %: 65.96, H %: 5.56.

4-Chloro-3-(2-hydroxyethyl)-1*H*-isochromen-1-one (2e)

The compound was purified by column chromatography, eluting with hexane/EA (1:1) to give 79% of a yellow solid, mp 93-94 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.84-7.77 (m, 2H), 7.54 (td, *J* = 8.0, 2.0 Hz, 1H), 4.04 (t, *J* = 6.4 Hz, 2H), 3.07 (t, *J* = 6.4 Hz, 2H), 2.05 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.2, 151.4, 135.3, 135.2, 129.8, 128.8, 123.3, 120.2, 112.7, 59.5, 34.5; EA: calcd for C %: 58.81; H %: 4.04; found C %: 58.56, H %: 4.02.

4-Chloro-3-(4-(trifluoromethyl)phenyl)-1*H*-isochromen-1-one (2f)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 62% of a white solid, mp 141-142 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (dd, *J* = 8.0, 0.8 Hz, 1H), 8.01 (td, *J* = 8.0, 0.8 Hz, 3H), 7.91 (td, *J* = 7.2, 1.2 Hz, 1H), 7.75 (dd, *J* = 8.4, 0.4 Hz, 2H), 7.66 (td, *J* = 7.2, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.5, 148.8, 135.5, 134.8, 132.0, 131.7, 130.0, 129.8 (3C), 129.7, 125.3, 124.3 (2C), 120.7, 112.5; EA: calcd for C %: 59.19; H %: 2.48; found C %: 59.23, H %: 2.50.

4-Chloro-3-(4-methoxyphenyl)-1*H*-isochromen-1-one (2g)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 79% (three equivalents of $CuCl_2$ was used) of a yellow solid, mp 130-131 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (dd, *J* = 7.6, 0.4 Hz, 1H), 7.94 (dd, *J* = 7.6, 0.4 Hz, 1H), 7.86-7.83 (m, 3H), 7.58 (td, *J* = 8.0, 0.4 Hz, 1H), 7.01-6.97 (m, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.1, 160.8, 150.3, 136.2, 135.3, 130.9 (2C), 129.8, 128.7, 123.8, 123.7, 120.3, 113.6 (2C), 110.3, 55.4; EA: calcd for C %: 76.18; H %: 4.79; found C %: 75.89, H %: 4.79.

3-(4-Methoxyphenyl)-1*H*-isochromen-1-one (11g)

When two equivalents of $CuCl_2$ were used, **2g** was obtained in 68% yield along with **11g** in 24% yield. The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give a white solid, mp 142-143 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, *J* = 8.0 Hz, 1H), 7.82 (dd, *J* = 9.2, 2.0 Hz, 2H), 7.69 (td, *J* = 7.2, 1.2 Hz, 1H), 7.47-7.44 (m, 2H), 6.97 (dt, *J* = 9.2, 2.8 Hz, 2H), 6.83 (s, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.5, 161.1, 153.7, 137.9, 134.8, 129.6, 127.7, 126.8(2C), 125.7, 124.5, 120.1, 114.2 (2C), 100.2, 55.4; EA: calcd for C %: 76.18; H %: 4.79; found C %: 75.89, H %: 4.79.

4-Chloro-3-pentyl-6,7-dihydrocyclopenta[c]pyran-1-(5*H*)-one (2h)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 98% of a yellow liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.91-2.82 (m, 4H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.10 (quin, *J* = 7.6 Hz, 2H), 1.67 (quin, *J* = 7.6 Hz, 2H), 1.36-1.30 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.7, 160.4, 158.7, 125.2, 111.5, 34.0, 31.1, 30.7, 30.6, 26.5, 22.3 (2C), 13.9; HRMS (EI) calcd for $C_{13}H_{17}BrO_2$ 240.0917, found 240.0917.

General procedure for cyclization compound 12a-12h

To a stirred solution of **1a-1h** (10 mmol) in CH_3CN (10 mL) was added $CuBr_2$ (20 mmol) and the resulting solution was heated to reflux and stirred at this temperature

for 2 h. After cooling to room temperature, the reaction mixture was quenched with a saturated aqueous solution of NaCl. The aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration and removal of solvent *in vacuo*, the residue was purified by column chromatography on silica gel to yield the desired products.

4-Bromo-3-phenyl-1*H*-isochromen-1-one (12a)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 99% of a white solid, mp 126-127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.94 (dt, *J* = 8.0, 0.4 Hz, 1H), 7.85-7.78 (m, 3H), 7.58 (td, *J* = 8.0, 1.2 Hz, 1H), 7.49-7.45 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.0, 151.6, 136.5, 135.4, 132.6, 130.1, 129.7, 129.6 (2C), 129.1, 128.0 (2C), 126.6, 120.4, 101.4; EA: calcd for C %: 59.83; H %: 3.01; found C %: 59.87, H %: 3.02.

4-Bromo-3-pentyl-1*H*-isochromen-1-one (12b)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 71% of a yellow liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.80-7.78 (m, 2H), 7.53 (td, *J* = 8.0, 2.0 Hz, 1H), 2.81 (t, *J* = 7.6 Hz, 2H), 1.75 (quin, *J* = 7.6 Hz, 2H), 1.41-1.34 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.6, 155.8, 136.3, 135.3, 129.7, 128.4, 125.7, 120.2, 101.2, 33.4, 31.2, 26.6, 22.3, 13.9; HRMS (EI) calcd for $C_{14}H_{15}BrO_2$ 294.0255, found 294.0255.

4-Bromo-3-isobutyl-1*H*-isochromen-1-one (12c)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 98% of a yellow liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.77 (td, *J* = 7.6, 0.8 Hz, 2H), 7.53-7.49 (m, 1H), 2.70 (d, *J* = 7.2 Hz, 2H), 2.26-2.19 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.4, 155.0, 136.2, 135.3, 129.6, 128.5, 125.8, 120.1, 102.0, 41.9, 27.4, 22.2 (2C); HRMS (EI) calcd for $C_{13}H_{13}BrO_2$ 280.0099, found 280.0096.

4-Bromo-3-*tert*-butyl-1*H*-isochromen-1-one (12d)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 69% of a white solid, mp 123-124 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (ddd, *J* = 6.4, 1.2, 0.4 Hz, 1H), 7.96 (ddd, *J* = 7.2, 0.8, 0.4 Hz, 1H), 7.79 (td, *J* = 7.2, 1.6 Hz, 1H), 7.54 (td, *J* = 7.6, 1.2 Hz, 1H), 1.55 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.2, 160.2, 137.5, 135.2, 129.3, 128.5, 125.9, 120.1, 100.5, 38.5, 28.5 (3C); EA: calcd for C %: 55.54; H %: 4.66; found C %: 55.46, H %: 4.62.

4-Bromo-3-(2-hydroxyethyl)-1*H*-isochromen-1-one (12e)

The compound was purified by column chromatography, eluting with hexane/EA (1:1) to give 81% of a brown liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.77-7.75 (m, 2H), 7.50 (td, *J* = 8.4, 2.0 Hz, 1H), 4.02 (t, *J* = 6.4 Hz, 2H), 3.10 (t, *J* = 6.4 Hz, 2H), 2.02 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.4, 152.5, 135.4, 134.6, 129.6, 128.7, 125.8, 124.5, 120.2, 59.5, 36.7; HRMS (EI) calcd for $C_{14}H_{15}ClO_2$ 267.9735, found 267.9733.

4-Bromo-3-(4-(trifluoromethyl)phenyl)-1*H*-isochromen-1-one (12f)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 97% of a yellow solid, mp 136-137 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.00 (td, *J* = 7.6, 0.8 Hz, 3H), 7.92 (td, *J* = 6.8, 1.2 Hz, 1H), 7.75 (dd, *J* = 8.4, 0.4 Hz, 2H), 7.65 (td, *J* = 7.6, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.9, 154.4, 135.9, 135.1, 131.3, 130.7, 130.4, 129.9 (3C), 127.1, 125.7, 125.4 (2C), 120.9, 102.6; EA: calcd for C %: 52.06; H %: 2.18; found C %: 52.04, H %: 2.19.

4-Bromo-3-(4-methoxyphenyl)-1*H*-isochromen-1-one (12g)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 89% of a yellow solid, mp 150-151 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.95 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.84 (td, *J* = 8.0, 0.8 Hz, 1H), 7.79-7.72 (m, 2H), 7.57 (td, *J* = 7.2, 0.8 Hz, 1H), 6.99 (dd, *J* = 7.2, 2.4 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.3, 160.8, 151.7, 136.8, 135.4, 131.3 (2C), 129.7, 128.8, 126.5, 124.9, 120.4, 113.4 (2C), 100.6, 55.4; EA: calcd for C %: 58.03; H %: 3.35; found C %: 57.96, H %: 3.37.

4-Bromo-3-pentyl-6,7-dihydrocyclopenta[c]pyran-1-(5*H*)-one (12h)

The compound was purified by column chromatography, eluting with hexane/EA (40:1) to give 98% of a yellow liquid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.86-2.71 (m, 4H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.05 (quin, *J* = 8.0 Hz, 2H), 1.61 (quin, *J* = 7.2 Hz, 2H), 1.30-1.24 (m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.6, 160.2, 158.5, 125.0, 111.3, 33.9, 30.9, 30.6, 30.5, 26.3, 22.1 (2C), 13.7; HRMS (EI) calcd for $C_{13}H_{17}BrO_2$ 284.0412, found 284.0496.

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REFERENCES

1. Kam, C. M.; Kerrigan, J. E.; Plaskon, R. R.; Duffy, E. J.; Lollar, P.; Suddath, F. L.; Powers, J. C. *J. Med. Chem.* **1994**, *37*, 1298.
2. Kerrigan, J. E.; Oleksyszyn, J.; Kam, C. M.; Selzler, J.; Powers, J. C. *J. Med. Chem.* **1995**, *38*, 544.
3. Whyte, A. C.; James, B.; Gloer, J. B.; James, A.; Scott, J. A.; Malloch, D. *J. Nat. Prod.* **1996**, *59*, 765.
4. Bihel, F.; Quéléver, G.; Lelouard, H.; Petit, A.; Alvès da Costa, C.; Pourquié, O.; Checler, F.; Thellend, A.; Pierre, P.; Kraus, J. L. *Bioorg. Med. Chem.* **2003**, *11*, 3141.
5. Angelis, M. D.; Stossi, F.; Waibel, M.; Benita, S.; Katzenellenbogenb, B. S.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2005**, *13*, 6529.
6. (a) Nakamura, Y.; Ukita, T. *Org. Lett*. **2002**, *4*, 2317. (b) Garcia-Fortanet, J.; Debergh, J. R.; De Brabander, J. K. *Org. Lett*. **2002**, *7*, 685. (c) Subramanian, V.; Batchu, V. R.; Barange, D.; Pal, M. *J. Org. Chem*. **2005**, *70*, 4778. (d) Langer, J.; Gaertner, M.; Goerls, H.; Walther, D. *Synthesis* **2006**, *16*, 2697. (e) Chakravarty, M.; Kumara Swamy, K. C. *J. Org. Chem*. **2006**, *71*, 9128. (f) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem*. **2007**, *72*, 5362. (g) Oezcan, S.; Sahin, E.; Balci, M. *Tetrahedron Lett.* **2007**, *48*, 2151.
7. (a) Biagetti, M. A.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, *58*, 2023. (b) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067.
8. (a) Yao, T.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 7401. (b) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936.
9. Lu, W. D.; Wu, M. J. *Tetrahedron* **2007**, *63*, 356.
10. Liang, Y.; Xie, Y. X.; Li, J. H. *Synthesis*, **2007**, *15*, 400.
11. Liao, H. Y.; Cheng, C. H. *J. Org. Chem.* **1995**, *60*, 3711.
12. Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem*. **1965**, *30*, 587.
13. Oliver, M. A.; Gandour, R. D. *J. Org. Chem.* **1984**, *49*, 558.