Synthesis of Isocoumarins from *o*-Iodobenzoic Acid and Terminal Acetylenes Mediated by Palladium Complexes and Zinc Chloride

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o-Iodobenzoic acid (**1**) reacts with various terminal acetylenes (HC≡CR) in the presence of $Pd(PPh_3)_4$, Et_3N, and $ZnCl_2$ in DMF to give the corresponding 3-substituted isocoumarins ($C_6H_4COOC(R)CH$: R = *n*-C_4H_9 (**2a**); *n*-C_3H_7 (**3a**); CH_2OCH_3 (**4a**); $C(CH_3)_2OH$ (**5a**); CH_2OH (**6a**); C_6H_5 (**7a**); *p*-$CH_3C_6H_4$ (**8a**); 1-cyclohexenyl (**9a**); *o*-$NH_2C_6H_4$ (**10a**)) in fair to excellent yields. In some of these catalytic reactions, substituted isocoumarin **b** ($C_6H_4COOC(R)C(C{\equiv}CR)$) and alkylidenephthalide **c** were isolated in a few percent yields. Under similar conditions, treatment of **1** with a trimethylsilyl 1,3-diyne **12** led to the formation of products 3-(2-indolyl)isocoumarin (**13**) and an indolylphthalide **14** in a 95:5 ratio. The reaction of *o*-1-pentynylbenzoic acid with $ZnCl_2$ and Et_3N gave **3a** as the sole product indicating that $ZnCl_2$ is likely responsible for the selective formation of the six-membered isocoumarin ring. Based on this observation and the known palladium chemistry, a mechanism involving the participation of palladium complexes in the alkynylation of **1** and zinc chloride in the heteroannulation of the reaction intermediate *o*-1-alkynylbenzoate is proposed for the present catalytic reactions.

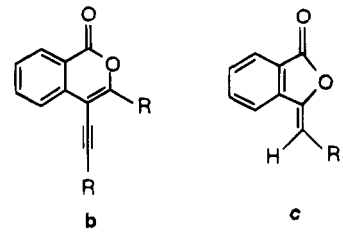
Introduction

Isocoumarins are a class of naturally occurring lactones that display a wide range of biological activity.[1] Several methods using organometallic reagents to synthesize isocoumarins have been developed.[2-8] Hegedus *et al.* reported a method involving a π-allylnickel halide as an intermediate and a facile palladium-assisted cyclization of 2-allylbenzoic acids.[2] Izumi showed that treatment of 2-alkenylbenzoic acids with palladium chloride produced isocoumarins.[3] Larock and his co-workers successfully synthesized isocoumarins via thallation and olefination of benzoic acid.[4] In all these methods, either stoichiometric reactions were involved or several steps were required for the preparation of isocoumarins.

The reaction of *o*-iodobenzoic acid (**1**) with terminal acetylenes or acetylides to yield isocoumarins has been investigated.[5,6] In the earliest report by Castro and coworkers, the interaction of *o*-iodobenzoic acid with cuprous phenylacetylide was claimed to give 3-phenylisocoumarin,[5a,b] but in a later paper by the same authors the structure of this product was reassigned as 3-benzylidenephthalide.[5c] The reactions of *o*-iodobenzoic acid with cuprous acetylides gave generally the corresponding phthalides; only in the reaction with cuprous *n*-propylacetylide was a mixture of phthalide and isocoumarin observed. On the basis of these results, Stevenson *et al.* developed a method for the synthesis of 3-*n*-propylisocoumarin and 3-*n*-butylisocoumarin.[6] Recently, Kundu and Pal reported the use of *o*-iodobenzoic acid and terminal acetylenes in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and Et_3N for the preparation of phthalides.[9] The corresponding isocoumarins were observed as minor products from these reactions. In this paper, we describe a simple and efficient method for the synthesis of isocoumarins from the reaction of *o*-iodobenzoic acid and terminal acetylenes in the presence of $Pd(PPh_3)_4$, $ZnCl_2$, and Et_3N (Scheme 1). In contrast to the results reported previously, this palladium–zinc chloride system exhibits greater selectivity for isocoumarins than for phthalides for most terminal acetylenes.

Results and Discussion

Treatment of *o*-iodobenzoic acid (**1**) with 1-hexyne in the presence of $Pd(PPh_3)_4$, Et_3N, and $ZnCl_2$ in DMF at 100°C gave isocoumarin **2a** (R = *n*-Bu) in 84% yield. A side product **2b** (R = *n*-Bu), which involves the reaction of two 1-hexyne molecules for each **2b**, was also isolated in 5% from the catalytic reaction. There was no five-membered-ring phthalide (**c**) detected from the solution. Control reactions (Table 1) indicate that in the absence of Pd species, no desired product was observed, while the omission of triethylamine afforded only a trace of the expected product. In addition to Pd species and triethylamine, $ZnCl_2$ was a necessary component for the catalysis. The yield of **2a** increased with increasing amount of $ZnCl_2$ used until the molar ratio of $ZnCl_2$ to **1** reached 1:1. Further increase of $ZnCl_2$ did not lead to noticeable change of the product yield (Table 1).



In addition to 1-hexyne, terminal alkynes with various substituents react with **1** to give the corresponding

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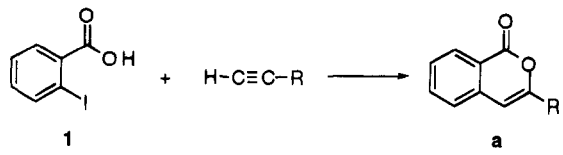
Scheme 1



1 a

Table 1. Dependence of the Yield of Isocoumarin 2a on the Amount of $ZnCl_2$ and Pd Complexes[a]

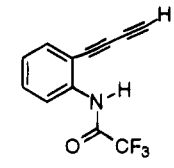
entry	catalyst	$ZnCl_2$ (mmol)	Et_3N (mmol)	yield (%)
1	$Pd(PPh_3)_4$	1.00	5.0	84
2	$Pd(PPh_3)_4$	0.50	5.0	63
3	$Pd(PPh_3)_4$	0.10	5.0	17
4	$Pd(PPh_3)_4$	1.00	0	<10
5	$Pd(PPh_3)_4$	0	5.0	trace
6	$Pd(PPh_3)_2Cl_2$	2.00	5.0	75
7	–	1.00	5.0	0

[a] Reaction conditions: *o*-iodobenzoic acid (1.00 mmol), 1-hexyne (3.00 mmol), palladium complex (0.0500 mmol for each run except run 7), $ZnCl_2$, and Et_3N in DMF (1.0 mL); the mixture was heated at 100 °C for 24 h.

substituted isocoumarins **2a–10a** in fair to excellent yields (Table 2). The reactions provide a convenient method for the synthesis of various isocoumarins. Of the several examples shown in Table 2, **3a** is a naturally occurring isocoumarin, whereas **4a** is a precursor for a natural product, artemidin.[6] In some of these catalytic reactions, side products **b** and **c** in a few percent yields were isolated. The selectivity for six-membered-ring isocoumarins is excellent for most terminal alkynes tested. There was no five-membered-ring product **c** observed when 1-hexyne, 1-pentyne, propargyl alcohol, and 2,2-dimethylpropargyl alcohol were used as the substrates. For methyl propargyl ether and phenyl acetylene, the corresponding phthalides **c** were found in 10 and 5% yields, respectively. Of the terminal alkynes tested, all but acetylene reacted with **1** to give the corresponding isocoumarin as the major products. The reaction of acetylene with **1** afforded only phthalide **11c** (entry 13). No isocoumarin was formed in this catalytic reaction.

The key information to distinguish products **a** and **c** that have the same chemical formula are provided by IR and NMR spectra of these compounds.[6,9] The carbonyl stretching frequencies of isocoumarins appear at 1705–1740 cm^{-1}, but the corresponding frequencies of the five-membered-ring alkylidene phthalides are at 1760–1790 cm^{-1}. In ^1H NMR spectra, the olefinic proton signal on the lactone ring of an isocoumarin generally appears in the range 6.2–6.9 ppm, whereas the corresponding signal for an alkylidene phthalide exhibits at δ 5.2–5.8. The former is *ca.* 0.8 ppm more downfield than that of the latter. In addition, for most terminal acetylenes in Table 2, the olefin proton of **c** couples with the neighboring methylene protons, whereas such coupling is absent for the corresponding isocoumarin **a**. The alkylidene phthalides **4c** and **7c** from the present reactions are assigned as *Z*-isomers based on comparison of the ^1H NMR spectrum of **7c** with that reported in literature.[10] Isocoumarin **b** is characterized by the carbonyl stretching frequency at 1734–1740 cm^{-1} similar to that of the corresponding isocoumarin **a** in the IR spectrum and by the alkynyl resonances in the ^1H and ^{13}C NMR spectra.

The results of the reaction of *o*-iodobenzoic acid (**1**) with a trimethylsilyl 1,3-diyne **12** prepared according to known methods further demonstrate the synthetic utility of the present catalytic reactions (Scheme 2). In the presence of $Pd(PPh_3)_4$, Et_3N, and $ZnCl_2$, in DMF at 100 °C, the reaction led to the formation of products 3-(2-indolyl)-isocoumarin (**13**) and an indolylphthalide **14** in a 95:5 ratio. Again, the six-membered-ring product **13** was favored in this double heteroannulation reaction. Both products **13** and **14** consist of an indolyl functionality in addition to the isocoumarin or phthalide ring, respectively. The formation of indole derivatives from N-(*o*-iodophenyl) trifluoroacetamide and alkynes in the presence of Cu(I) or palladium[11] complexes was reported previously. Under the catalytic conditions, the trimethylsilyl 1,3-diyne **12** is gradually converted to diyne **15** via desilylation. Although **15** may be isolated from desilylation of **12**, it decomposes gradually in the solid state to unknown product. On the basis of the results shown in Table 2, we expect that **15** reacts with **1** to give the observed products **13** and **14**.



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In contrast to the $Pd(PPh_3)_4$–$ZnCl_2$–Et_3N system, $Pd(PPh_3)_2Cl_2$–CuI–Et_3N catalyzed the reaction of terminal acetylenes with **1** to give 3-alkylidene phthalides as the major products and the corresponding isocoumarins as minor products.[9] The observed product variation between the $Pd(PPh_3)_2Cl_2$–CuI–Et_3N and $Pd(PPh_3)_4$–$ZnCl_2$–Et_3N catalyzed reactions led us to investigate further the role of $ZnCl_2$ and CuI. For this purpose, *o*-1-pentynylbenzoic acid, believed to be an intermediate in the palladium–zinc or palladium–copper-catalyzed reaction of 1-pentyne with **1**, was synthesized by the following steps (Scheme 3). Treatment of *o*-1-pentynylbenzoic acid with $ZnCl_2$ (0.2 equiv) and NEt_3 (2 equiv) in d_6-DMSO at 25 °C for 6 days led to heteroannulation of the acetylenoic acid to give **3a** as the sole product. In the absence of $ZnCl_2$ and NEt_3, no cyclization took place. In the same solvent and in the presence of CuI (0.2 equiv) and NEt_3 (2 equiv), *o*-1-pentynylbenzoic acid was converted in 1 h to a mixture of **3a** and **3c** in a 70:30 ratio. The product ratio did not change with reaction duration. The results indicate that both $ZnCl_2$ and CuI catalyze the heteroannulation of *o*-1-pentynylbenzoic acid, but with different product selectivity and catalytic activity. Moreover, these observations suggest that in the catalysis of reaction 1, $ZnCl_2$ is likely responsible for the heteroannulation and for the selective formation of isocoumarin. Several transition metals, Ag,[12] Hg,[8,13–15] Pd,[16] and Rh,[17] are known to catalyze the cyclization of acetylenoic acids.

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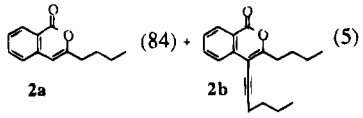
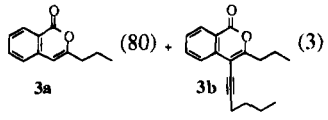
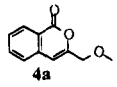
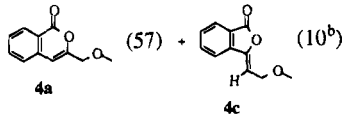
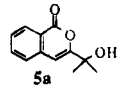
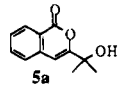
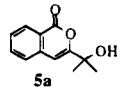
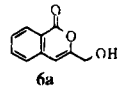
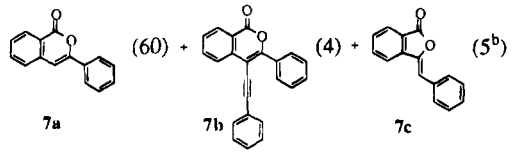
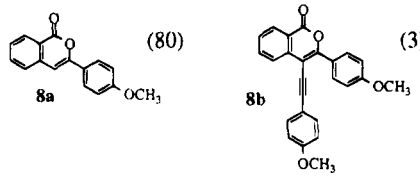
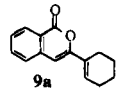
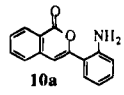
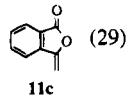
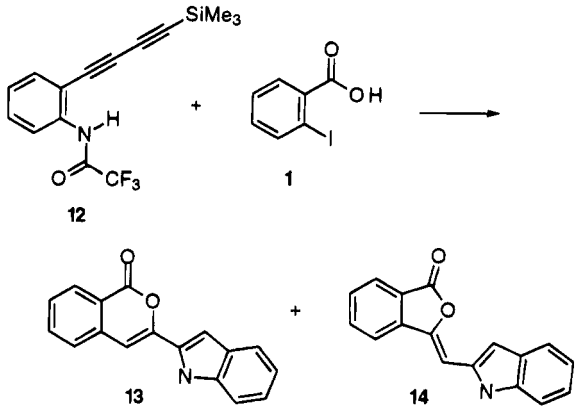
Table 2. Results of the Reactions of Terminal Acetylenes with *o*-Iodobenzoic Acid in the Presence of Palladium Complex, $ZnCl_2$, and NEt_3[a]

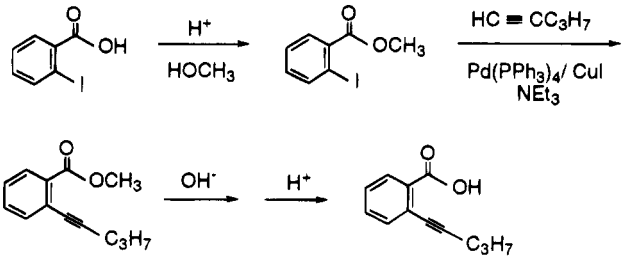
entry	$HC{\equiv}CR$ / R	temp/°C	product (yield/%)	total yield(%)
1	*n*-C_4H_9	100	 **2a** (84) + **2b** (5)	89
2	*n*-C_3H_7	100	 **3a** (80) + **3b** (3)	83
3	CH_2OCH_3	100	 **4a** (67)	67
4	CH_2OCH_3	60	 **4a** (57) + **4c** (10[b])	67
5	$C(CH_3)_2OH$	100	 **5a** (82)	82
6	$C(CH_3)_2OH$	60	 **5a** (96)	96
7[c]	$C(CH_3)_2OH$	60	 **5a** (88)	88
8	CH_2OH	60	 **6a** (45)	45
9	C_6H_5	100	 **7a** (60) + **7b** (4) + **7c** (5[b])	69
10[d]	*p*-$CH_3OC_6H_4$	100	 **8a** (80) **8b** (3)	83
11	1-*cyclo*-C_6H_9	100	 **9a** (77)	77
12	*o*-$H_2NC_6H_4$	100	 **10a** (69)	69
13	H	60	 **11c** (29)	29

[a] Except otherwise mentioned, the reaction conditions for each run were similar to those described in the experimental section for the preparation of **2a** and **2b**. [b] The ratio of isocoumarin **a** to alkylidenephthalide **c** was determined by ^1H NMR spectroscopy. [c] $Pd(PPh_3)_2Cl_2$ was used instead of $Pd(PPh_3)_4$. [d] $ZnCl_2$: 2 mmol; NEt_3: 1 mmol.

Scheme 2



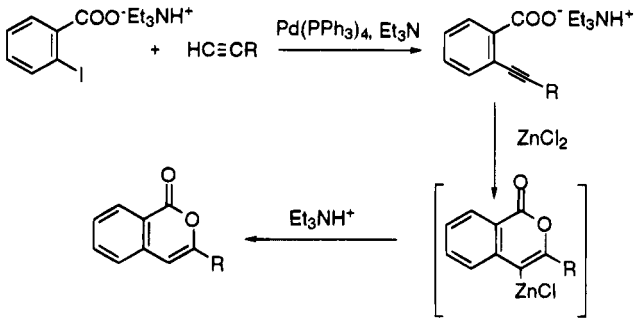
Scheme 3



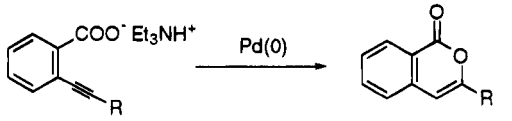
In most metal-catalyzed ring formations, five-membered ring products are strongly favored. The present Pd-$(PPh_3)_4$–$ZnCl_2$–Et_3N-catalyzed reactions appears to be the only few known examples favoring six-membered ring products. It appears that the selectivity of five- and six-membered ring products depends both on the type of acetylenoic acid and the nature of the catalyst.

Based on the above observations and the known palladium chemistry, a mechanism may be proposed to account for the catalysis of reaction 1. It is expected that **1** is rapidly neutralized by Et_3N to give the corresponding ammonium salt under the catalytic conditions. Oxidative addition of this ammonium salt to $Pd(PPh_3)_4$ yields an palladium(II)–aryl species. Addition of an acetylide to the palladium(II) complex followed by reductive elimination gives an organic intermediate 2-alkynylbenzoate. Cyclization of 2-alkynylbenzoate with $ZnCl_2$ affords the final product isocoumarin (Scheme 4). An alternative pathway for the catalysis involves cyclization of 2-alkynylbenzoate by palladium(0) to give the final product (Scheme 5). We believe this pathway is less likely because it involves a negative palladium(0) species **16**

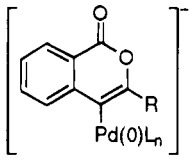
Scheme 4



Scheme 5



which is energetically unfavorable. In addition, it is difficult to explain the difference in product distribution of the reactions of terminal acetylenes with **1** catalyzed by $PdCl_2(PPh_3)_2$, CuI, and NEt_3 and by $Pd(PPh_3)_4$, $ZnCl_2$, and Et_3N, if the same organic intermediate 2-alkynylbenzoate and the same palladium(0) were involved in the cyclizations in these two catalytic reactions. It would be



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more feasible if cyclization of 2-alkynylbenzoate to give isocoumarin or phthalide were catalyzed by a Pd(II) complex.[16] However, under the catalytic conditions for reaction 1, there appears no suitable Pd(II) species to cyclize 2-alkynylbenzoate. We prefer $ZnCl_2$ over Pd species for the cyclization of 2-alkynylbenzoate (Scheme 1) in view of the resemblance of the observed product for heteroannulation of *o*-1-pentynylbenzoic acid catalyzed by $ZnCl_2$ and for reactions of terminal acetylenes with **1** catalyzed by the $Pd(PPh_3)_4$, $ZnCl_2$, and Et_3N. The mechanism for the formation of phthalides from **1** and terminal alkynes catalyzed by the $PdCl_2(PPh_3)_2$–CuI–NEt_3 system was not clearly proposed by Kundu *et al.*, but the pathway involving cyclization of 2-alkynylbenzoate by a palladium species was implicated. In view of the facile cyclization of *o*-1-pentynylbenzoic acid to give **3a** and **3c** in the presence of CuI and NEt_3, the step of cyclization of 2-alkynylbenzoate is likely catalyzed by CuI instead of a Pd species during the catalytic formation of phthalides.

In conclusion, we have demonstrated a convenient one-pot synthesis of isocoumarins from terminal acetylenes and *o*-iodobenzoic acid catalyzed by a $Pd(PPh_3)_4$–$ZnCl_2$–Et_3N system. The present results contrast those obtained from the reactions of terminal acetylenes and *o*-iodobenzoic acid catalyzed by $Pd(PPh_3)_4$, CuI, and Et_3N system which gave phthalides as the major products. It is evident that the product difference between these two systems is due to the involvement of $ZnCl_2$ and CuI in cyclization of an organic intermediate 2-alkynylbenzoate.

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Experimental Section

All reactions were performed under dry nitrogen, and all solvents were dried according to standard methods. ^1H and ^{13}C NMR experiments were performed at 300 or 400 MHz. Melting points are uncorrected.

o-Iodobenzoic acid, 1-hexyne, 1-pentyne, methyl propargyl ether, propargyl alcohol, 1,1-dimethylpropargyl alcohol, 1-cyclohexenylacetylene, phenylacetylene, (trimethylsilyl)acetylene, 1,4-bis(trimethylsilyl)-1,3-butadiyne (Aldrich), *o*-iodoaniline (TCI), DMF, NEt_3 (Merck), methyl lithium/ lithium bromide complex (6% solution in diethyl ether) (Janssen), and $ZnCl_2$ (Fluka) were used as purchased. (*p*-Methoxyphenyl)-acetylene and (*o*-aminophenyl)acetylene were prepared according to reported methods.[18]

Reaction of *o*-Iodobenzoic Acid (1) with 1-Hexyne in the Presence of $Pd(PPh_3)_4$, Et_3N, and $ZnCl_2$. To a solution consisting of *o*-iodobenzoic acid (**1**) (1.00 mmol), 1-hexyne (3.00 mmol), and Et_3N (5.0 mmol) in DMF (1.0 mL) under nitrogen were added $Pd(PPh_3)_4$ (0.050 mmol) and zinc chloride (1.0 mmol). The mixture was heated at 100 °C for 24 h and then separated on a silica gel column with ethyl acetate/*n*-hexane as eluent to give the corresponding isocoumarin **2a** in 84% yield. A side product **2b** was also isolated in 5% yield from the catalytic reaction. Spectral data of 3-*n*-butylisocoumarin (**2a**): ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (q, J = 7.2 Hz, 3H), 1.39 (m, 2H), 1.68 (m, 2H), 2.51 (t, J = 7.6 Hz, 2H), 6.24 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 8.23 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.75 (q), 22.09 (t), 28.94 (t), 33.19 (t), 102.88 (d), 120.09 (s), 125.01 (d), 127.53 (d), 129.47 (d), 134.69 (d), 137.63 (s), 158.29 (s), 163.12 (s); IR (neat) 2921, 1732, 1656, 1568, 1483, 1312, 1160, 757, 691 cm^{-1}; MS m/z (rel intensity) 202 (M^+, 53), 160 (24), 131 (26), 118 (100), 89 (42); HRMS calcd for $C_{13}H_{14}O_2$ 202.0994 , found 202.0990.

Similar reaction conditions were employed for the preparation of compounds **3a**–**10a**, **2b**, **3b**, **7b**, **8b**, **4c** and **11c**. The reaction conditions and the yields of products for each reaction are listed in Table 2. Important spectral data of these compounds are listed below. Part of the spectral data of compounds **2a**, **3a**, **7a**, and **11c** were reported previously.

3-*n*-Propylisocoumarin (3a): ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (q, J = 7.2 Hz, 3H), 1.67 (m, 2H), 2.43 (t, J = 7.4 Hz, 2H), 6.19 (s, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.29 (q), 20.02 (t), 35.19 (t), 102.84 (t), 119.88 (s), 124.91 (d), 127.35 (d), 129.18 (d), 134.52 (d), 137.40 (s), 157.79 (S), 162.85 (s); IR (neat) 2931, 1731, 1656, 1568, 1473, 1329, 1154, 758, 691 cm^{-1}; MS m/z (rel intensity) 188 (M^+, 100), 159 (20), 131 (48), 118 (79), 89 (44); HRMS calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0831.

3-(Methoxymethyl)isocoumarin (4a): ^1H NMR (400 MHz, $CDCl_3$) δ 3.41 (s, 3H), 4.19 (s, 2H), 6.46 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 58.88 (q), 70.38 (t), 103.76 (d), 120.55 (S), 125.55 (d), 128.22 (d), 129.50 (d), 134.78 (d), 136.66 (s), 153.44 (s), 162.15 (s); mp 48–49 °C; IR (neat) 2889, 1735, 1663, 1606, 1470, 1360, 1106, 760, 690 cm^{-1}; MS m/z (rel intensity) 190 (M^+, 100), 161 (36), 145 (48), 131 (33), 89 (92); HRMS calcd for $C_{11}H_{10}O_3$ 190.0630, found 190.0631.

3-(1-Hydroxy-1-methylethyl)isocoumarin (5a): ^1H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 6H), 2.35 (br s, O*H* , 1H), 6.64 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 28.11 (q), 70.93 (s), 99.85 (d), 120.06 (s), 125.86 (d), 128.01 (d), 129.44 (d), 134.84 (d), 137.15 (s), 161.76 (s), 162.48 (s); mp 64–65 °C; IR (KBr) 2955, 1721, 1652, 1605, 1483, 1320, 1139, 758, 692 cm^{-1}; MS m/z (rel intensity) 204 (M^+, 14), 190 (51), 161 (20), 145 (44), 131 (20), 89 (100); HRMS calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0778.

3-(Hydroxymethyl)isocoumarin (6a): ^1H NMR (400 MHz, $CDCl_3$) δ 2.75 (br s 1H), 4.47 (s, 2H), 6.53 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 61.37 (t), 103.05 (d), 120.48 (s), 125.69 (d), 128.32 (d), 129.62 (d), 134.97 (d), 136.85 (s), 155.58 (s), 162.47 (s); mp 97–98 °C; IR (neat) 3427, 1705, 1658, 1483, 1330, 1162, 1088, 830, 758, 689 cm^{-1}; MS m/z (rel intensity) 176 (M^+, 77), 147 (70), 145 (61), 117 (28), 89 (100); HRMS calcd for $C_{10}H_8O_3$ 176.0473, found 176.0471. Anal. Calcd for $C_{10}H_8O_3$: C, 68.20; H: 4.50. Found: C, 67.83; H, 6.66.

3-Phenylisocoumarin (7a): ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 7.41–7.51 (m, 5H), 7.71 (t, J = 7.2 Hz, 1H), 7.87 (m, 2H), 8.30 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.77 (d), 120.48 (s), 125.20 (d), 125.93 (d), 128.11 (d), 128.78 (d), 129.60 (d), 129.93 (d), 131.91 (s), 134.84 (d), 137.47 (s), 153.57 (s), 162.28 (s); IR (KBr) 3060, 1732, 1637, 1606, 1487, 1234, 1068, 765, 690 cm^{-1}; MS m/z (rel intensity) 222 (M^+, 100), 194 (63), 165 (41), 105 (12), 89 (15); HRMS calcd for $C_{15}H_{10}O_2$ 222.0681, found 222.0678.

3-(4-Methoxyphenyl)isocoumarin (8a): ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.71 (s, 1H), 6.87 (d, J = 7.2 Hz, 2H), 7.36 (m, 2H), 7.60 (m, 1H), 7.71 (d, J = 7.2 Hz, 2H), 8.18 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.21(q), 100.03 (d), 114.05 (d), 119.88 (s), 124.28 (s), 125.58 (d), 126.59 (d), 127.44 (d), 129.32 (d), 134.63 (d), 137.69 (s), 153.44 (s), 160.88 (s), 162.27 (s); mp 148–149 °C; IR (KBr) 3037, 2966, 2929, 2836, 1730, 1633, 1603, 1512, 1291, 1180, 1064, 1030, 826, 754, 687 cm^{-1}; MS m/z (rel intensity) 252 (M^+, 100), 224 (50), 209 (14), 181 (25), 152 (14); HRMS calcd for $C_{16}H_{12}O_3$ 252.0783, found 252.0789. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.20 H: 4.76. Found: C, 75.95; H, 4.82.

3-(1-Cyclohexenyl)isocoumarin (9a): ^1H NMR (400 MHz, $CDCl_3$) δ 1.58–1.62 (m, 2H), 1.69–1.72 (m, 2H), 2.19–2.24 (m, 4H), 6.28 (s, 1H), 6.74 (t, J = 4 Hz, 1H), 7.30–7.36 (m, 2H), 7.58 (t, J = 7.2 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.67 (t), 22.15 (t), 23.95 (t), 25.50 (t), 99.96 (d), 120.41 (s), 125.68 (d), 127.38 (d), 128.14 (s), 129.30 (s), 129.88 (s), 134.47 (d), 137.69 (s), 154.15 (s), 162.16 (s); mp 81–82 °C; IR (KBr) 2930, 1729, 1639, 1620, 1563, 1482, 1220, 1074, 818, 756, 688 cm^{-1}; MS m/z (rel intensity) 226 (M^+, 100), 189 (34), 145 (13), 89 (25); HRMS calcd for $C_{15}H_{14}O_2$ 226.0994, found 226.0989. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.65; H: 6.19. Found C, 78.93; H, 6.74.

3-(2-Aminophenyl)isocoumarin (10a): ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (br s 1H), 6.75 (s, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.82 (t, J =7.6 Hz, 1H), 7.20(t, J = 8.0 Hz, 1H), 7.42–7.48 (m, 3H), 7.68 (t, J = 8.0 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 104.29 (d), 116.93 (d), 117.24 (s), 118.14 (d), 119.65 (s), 125.65 (d), 127.79 (d), 128.96 (d), 129.22 (d), 130.85 (d), 134.70 (d), 137.54 (s), 144.95 (s), 154.66 (s), 162.13 (s); mp 98–99 °C; IR 3469, 3400, 1731, 1642, 1619 cm^{-1}; GC/MS m/z (rel intensity) 237 (M^+, 100), 209 (28), 208 (27), 180 (33); HRMS calcd for $C_{15}H_{11}NO_2$ 237.0790, found 237.0790.

3-*n*-Butyl-4-hexynylisocoumarin (2b): ^1H NMR (400 MHz, $CDCl_3$) δ 0.92–0.98 (m, 6H), 1.41 (m, 2H), 1.52 (m, 2H), 1.61 (m, 2H), 1.72 (m, 2H), 2.50 (t, J = 6.8 Hz, 2H), 2.79 (t, J = 7.6 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.55 (q), 13.70 (q), 19.25 (t), 21.98 (t), 22.16 (t), 29.26 (t), 30.81 (t), 32.24 (t), 72.27 (s), 97.94 (s), 100.52 (s), 119.36 (s), 124.55 (d), 127.77 (d), 129.29 (d), 134.84 (d), 137.08 (s), 161.72 (s), 162.00 (s); IR (KBr) 2944, 1740, 1623, 1566, 1485, 1317, 1021, 769, 696 cm^{-1}; MS m/z (rel intensity) 282 (M^+, 72), 239 (100), 253 (30); HRMS calcd for $C_{19}H_{22}O_2$ 282.1614, found 282.1616.

3-*n*-Propyl-4-(1-pentynyl)isocoumarin (3b): ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.6 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H), 1.69 (m, 2H), 1.78 (m, 2H), 2.50 (t, J = 7.4 Hz, 2H), 2.79 (t, J = 7.8 Hz, 2H), 7.50 (t, J = 8.0 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.56 (2 x q), 20.64 (t), 21.54 (t), 22.21 (t), 34.40 (t), 72.42 (s), 97.79 (s), 100.67 (s), 119.35 (s), 124.58 (d), 127.80 (d), 129.26 (d), 134.83 (d), 137.04 (s), 161.68 (s), 161.72 (s); IR (KBr) 2963, 1739, 1623, 1566, 1485, 1458, 1318, 1019, 769, 695 cm^{-1}; MS m/z (rel intensity) 254 (M^+,

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51), 239 (14), 225 (100); HRMS calcd for $C_{17}H_{18}O_2$ 254.1302, found 254.1300.

3-Phenyl-4-(phenylacetylenyl)isocoumarin (7b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 3H), 7.46–7.52 (m, 5H), 7.58 (t, J = 8.2 Hz, 1H), 7.84 (t, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 2H), 8.34 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 82.64 (s), 97.48 (s) 99.67 9 (s), 119.61 (s), 122.70 (s), 125.34 (d), 128.13 (d), 128.50 (d), 128.62 (d), 128.71 (d), 129.44 (d), 130.38 (d), 131.29 (d), 132.26 (s), 135.11 (d), 136.96 (s), 156.63 (s), 160.91 (s); mp 144–145 °C; IR (KBr) 3054, 1740, 1605, 1482, 1320, 1224, 1096, 1020, 758, 690 m^{-1}; MS m/z (rel intensity) 322 (M^+, 100), 265 (36), 189 (12); HRMS calcd for $C_{23}H_{14}O_2$ 322.0990, found 322.0978. Anal. Calcd for $C_{23}H_{14}O_2$: C, 85.71; H: 4.35. Found: C, 85.36; H, 4.34.

3-(4-Methoxyphenyl)-4-[(4-methoxyphenyl)acetylenyl]-isocoumarin (8b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.85 (s, 3H), 6.88 (d, J = 7.6 Hz, 2H), 6.98 (d, J = 7.2 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 7.2 Hz, 1H), 7.78 (t, J = 7.2 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 7.2 Hz, 2H), 8.27 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 55.30 (q), 55.34 (q), 81.63 (s), 97.47 (s), 98.43 (s), 113.47 (d), 114.14 (d), 114.95 (s), 119.34 (s), 124.82 (s), 125.16 (d), 128.14 (d), 129.30 (d), 126.72 (s), 130.17 (d), 132.73 (d), 134.96 (d), 137.42 (s), 156.01 (s), 159.88 (s), 161.08 (s); mp 119–120 °C; IR (KBr) 2944, 1734, 1602, 1510, 1481, 1253, 1025, 831, 767, 691 cm^{-1}; MS m/z (rel intensity) 382 (M^+, 100), 367 (20), 339 (13), 268 (13), 252 (55), 239 (25), 224 (37), 181 (24), 135 (29); HRMS calcd for $C_{25}H_{18}O_4$ 382.1200, found 382.1213.

3-(Z-Methoxyvinylidene)phthalide (4c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 4.37 (d, J = 6.8 Hz, 2H), 5.72 (t, J = 6.8 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.68 (m, 2H), 7.90 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 58.40 (q), 66.17 (t), 104.55 (d), 120.27 (d), 124.70 (s), 125.46 (d), 130.32 (d), 134.57 (d), 139.00 (s), 146.98 (s), 166.55 (s); IR (neat) 2916, 1784, 1690, 1471, 1270, 1051, 981, 762, 690 cm^{-1}; MS m/z (rel intensity) 190 (M^+, 22), 160 (26), 149 (100), 76 (58).

3-Methylenephthalide (11c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (dd, J = 2.8, 4.4 Hz, 2H), 7.57 (m, 1H), 7.71 (m, 2H), 7.90 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 91.27 (t), 120.57 (d), 125.07 (s), 125.26 (d), 130.44 (d), 134.45 (d), 138.96 (s), 151.79 (s), 166.85 (s); IR (KBr) 3060, 1780, 1662, 1473, 1270, 1004, 770, 690 cm^{-1}.

Synthesis of (o-Aminophenyl)(trimethylsilyl)-1,3-butadiyne. To bis(trimethylsilyl)-1,3-butadiyne (1.35 g, 7.0 mmol) in THF (5 mL) at 0 °C was added slowly a ether solution of methyl lithium/lithium bromide complex (4 mL, 2 M, 8 mmol). The solution was left at the same temperature for 20 min and was then warmed to room temperature.[19] The solvent was removed in vacuo and to the same system were added $Pd(PPh_3)_4$ (0.19 g. 0.170 mmol), *o*-iodoaniline (0.75 g, 3.4 mmol), CuI (0.093 g, 0.490 mmol), $HNEt_3Cl$ (0.40 g, 2.88 mmol), and Et_3N (8.0 mL). The system was heated with stirring at 60 °C for 24 h. On addition of a mixture of ethyl acetate and *n*-hexane (150 mL,1:20, v/v), the system was washed with water (50 mL) three times. The organic layer was dried over anhydrous $MgSO_4$, concentrated and separated on a silica gel column with a mixture of ethyl acetate and *n*-hexane (1:20, v/v) as eluent to afford the desired product (0.57 g, 2.69 mmol) in 79% yield. Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.23 (s, 9H), 4.18 (br s, 2H), 6.32 (m, 2H), 7.12 (t, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.40 (q), 73.94 (s), 79.33 (s), 87.87 (s), 91.67 (s), 105.55 (s), 114.34 (d), 117.86 (d), 130.71 (d), 133.24 (d), 149.84 (s); IR: 3479, 3383, 2960, 2196, 2097, 1615, 1490, 1251, 848, 751 cm^{-1}; GC/MS m/z (rel intensity) 213 (M^+, 100), 198 (67), 154 (11), 73 (12).

Synthesis of 1-[o-(Trifluoroacetamido)phenyl]-4-(trimethylsilyl)-1,3-butadiyne (12). To (*o*-aminophenyl)(trimethylsilyl)-1,3-butadiyne (1.00 mmol) in THF (2 mL) was slowly added trifluoroacetic anhydride (1.2 mmol) over 10 min at room temperature to generate 1-[*o*-(trifluoroacetamido)-phenyl]-4-(trimethylsilyl)-1,3-butadiyne (**12**). After evaporation of the solvent, the remaining material was purified by crystallization from n-hexane. Spectral data of **12**: ^{1}H NMR-(400 MHz, $CDCl_3$) δ 0.24 (s, 9H), 7.16 (t, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.56 (br, 1H); IR 3354, 2968, 2206, 2102, 1715, 1542, 1196, 842 cm^{-1}; mp 108–109 °C; GC/MS m/z (rel intensity) 309 (M^+, 48), 266 (51), 240 (100), 216 (36); HRMS calcd for $C_{15}H_{14}F_3NOSi$ 309.0791, found 309.0794. Anal. Calcd for $C_{15}H_{14}F_3NOSi$: C, 58.55; H, 4.53; N, 4.53. Found: C, 58.14; H, 4.48; N, 4.52.

Reaction of o-Iodobenzoic Acid (1) with 1-[o-(Trifluoroacetamido)phenyl]-4-(trimethylsilyl)-1,3-butadiyne (12) in the Presence of $Pd(PPh_3)_4$, Et_3N, and $ZnCl_2$. 1-[*o*-(Trifluoroacetamido)phenyl]-4-(trimethylsilyl)-1,3-butadiyne (1.00 mmol) was added to a side-arm flask containing *o*-iodobenzoic acid (0.82 mmol), $Pd(PPh_3)_4$ (0.050 mmol), $ZnCl_2$ (3.3 mmol), NEt_3 (1.2 mL), and DMF (2.5 mL). The mixture was heated at 100 °C for 66 h and then separated on a silica gel column using ethyl acetate/*n*-hexane (1/5, v/v) as eluent to give 3-(2-indolyl)isocoumarin and 3-[(2-indolyl)methylidene]-phthalide in a 95:5 ratio and a total yield of 68% (0.146 g).

3-(2-Indolyl)isocoumarin (13): ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.14 (d, J = 1.6 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.45 (s, 1H), .5.57 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.93 (t, J = 8.0 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 11.92 (br, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) 100.85 (d), 101.96 (d), 111.75 (d), 119.60 (s), 119.91 (d), 120.87 (d), 123.20 (d), 126.16 (d), 127.71 (s), 128.17 (d), 129.02 (d), 130.15(s), 135.37 (d), 137.17 (s), 137.48 (s), 147.52 (s), 160.95 (s); mp 258–259 °C; IR 3288, 1686, 1629, 1326, 1081, 787, 735, 679 cm^{-1}; GC/MS m/z (rel intensity) 261 (M^+, 100), 232 (14), 204 (49); HRMS calcd for $C_{17}H_{11}NO_2$ 261.0787, found 261.0792; Anal. Calcd for $C_{17}H_{11}NO_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.18; H, 6.71; N, 10.35.

Desilylation of 1-[o-(Trifluoroacetamido)phenyl]-4-(trimethylsilyl)-1,3-butadiyne (12). 1-[*o*-(Trifluoroacetamido)phenyl]-4-(trimethylsilyl)-1,3-butadiyne (**12**) (0.112 g) was dissolved in a DMF (0.5 mL) solution containing Et_3N (0.50 mL). After stirring at 50 °C for 1 h, EA was added and the mixture washed with aqueous NaCl solution, dried, concentrated in vacuo, and chromatographed using 20:1 hexane/ethyl acetate to afford the product. Spectral data for 1-[*o*-(trifluoroacetamido)phenyl]-1,3-butadiyne (**15**):^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.43 (t, J = 7.2 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.56 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 66.68 (d), 68.97 (s), 74.48 (s), 81.37 (s), 111.47 (s), 115.52 (q, $^1J_{C-F}$ =287 Hz), 120.104, (d) 125.64 (d), 131.04 (d), 133.27 (d), 137.80 (s), 154.70 (q, $^2J_{C-F}$= 38 Hz); IR 3298, 1707, 1543, 1174, 758, 632 cm^{-1}; GC/MS m/z (rel intensity) 237 (M^+, 100), 140 (37), 113 (38).

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