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Copper-free Sonogashira reactions of 4-hydroxycoumarins with alkynes

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ABSTRACT

The palladium-catalyzed direct coupling reactions of 4-hydroxycoumarins with various alkynes under copper-free conditions are described. This transformation is highly effective under mild conditions and the desired products are obtained in good yields.

1. Introduction

Pd-catalyzed cross-coupling reactions can be considered nowadays to be the most reliable methodology for the formation of carbon–carbon bonds.[1] The types of reactions find increasing application in the synthesis of complex organic molecules.[2] It is well-known that in a cross-coupling reaction, an electrophile is combined with a nucleophile to provide the corresponding coupling product. Traditionally, the pre-activated substrates such as organic (pseudo)halides have to be utilized in these cross-coupling reactions. Recently, an example of palladium-catalyzed cross-coupling reactions with arylboronic acids via C–OH bond activation of tautomerizable heterocycles was reported.[3] In this reaction, the phosphonium salts were used as activation reagent, and the presence of phosphonium salt was proposed to enable an in situ activation of tautomerizable heterocycle, and then underwent the subsequent palladium-catalyzed cross-coupling reactions with arylboronic acids. Afterwhile, Ackermann reported that phenols could be used as proelectrophiles in ruthenium-catalyzed dehydrative direct arylations through functionalizations of C–H and C–OH bonds.[4] In this reaction process, *p*-toluenesulfonyl chloride acted as an activator. Meanwhile, we also realized the palladium-catalyzed cross-coupling reactions of 4-hydroxycoumarins with arylboronic acids using *p*-toluenesulfonyl chloride as an activation reagent.[5] Herein, we would like to disclose another example of palladium-catalyzed direct cross-coupling reactions of 4-hydroxycoumarins with alkynes. This transformation is highly effective under copper-free conditions.

Since a goal of chemical genetics is to find small molecules that modulate the individual functions of gene products with high potency and high specificity,[6] we have developed efficient methods to build up the libraries of natural product-like compounds.[7] Among the scaffold selected, we identified that coumarin was a universal skeleton for our chemical genetic approach. Although continuous efforts toward the coumarin synthesis have been reported due to the prominence of coumarin in natural products and biologically active molecules,[7j,8–10] developing a novel method for generation of coumarin compounds from commercially available 4-hydroxycoumarin would be of importance. On the other hand, the synthetic potential of alkynyl fragment in a conjugated enyne system has been demonstrated as precursor to construct even more complex molecules.[11] Since many alkynes are commercially available or synthetically accessible and the Sonogashira reaction[12] is a versatile method for carbon–carbon bond formation, we start to investigate the direct cross-coupling reactions of 4-hydroxycoumarins with alkynes.

2. Results and discussion

The reaction was initially studied with 4-hydroxycoumarin **1a** and phenyl acetylene **2a**, which were selected as suitable substrates for reaction development (Table 1). At the outset, various palladium catalysts were screened. To our delight, we observed the formation of the desired product **3a** when the reaction was carried out in the presence of $PdCl_2$ (5 mol%), CuI (10 mol%), *p*-toluenesulfonyl chloride (1.2 equiv), and $^{i}Pr_2NEt$ (3.0 equiv) in MeCN at 60 °C (35% yield, Table 1, entry 1). Similar results were obtained when

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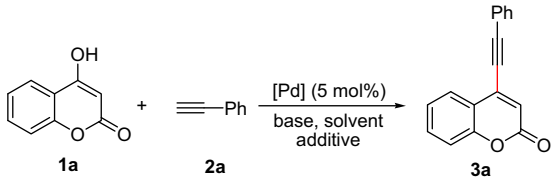
Table 1
Palladium-catalyzed direct cross-coupling reaction of 4-hydroxycoumarin **1a** with phenyl acetylene **2a**



Entry	[Pd] catalyst	Additive	Base	Solvent	Yield[a] (%)
1	$PdCl_2$	CuI (10 mol %)/TsCl (1.0 equiv)	$^iPr_2NEt$	MeCN	35
2	$Pd(OAc)_2$	CuI (10 mol %)/TsCl (1.0 equiv)	$^iPr_2NEt$	MeCN	36
3	$Pd(PPh_3)_4$	CuI (10 mol %)/TsCl (1.0 equiv)	$^iPr_2NEt$	MeCN	43
4	$Pd_2(dba)_3$	CuI (10 mol %)/TsCl (1.0 equiv)	$^iPr_2NEt$	MeCN	33
5	$PdCl_2(PPh_3)_2$	CuI (10 mol %)/TsCl (1.0 equiv)	$^iPr_2NEt$	MeCN	46 (80)[b]
6	$PdCl_2$(dppf)	CuI (10 mol %)/TsCl (1.0 equiv)	$^iPr_2NEt$	MeCN	15
7[b]	$PdCl_2(PPh_3)_2$	TsCl (1.0 equiv)	$^iPr_2NEt$	MeCN	81
8[b]	$PdCl_2(PPh_3)_2$	CuI (10 mol %)	$^iPr_2NEt$	MeCN	NR
9[b]	$PdCl_2(PPh_3)_2$	TsCl (1.0 equiv)	K_2CO_3	MeCN	Trace
10[b]	$PdCl_2(PPh_3)_2$	TsCl (1.0 equiv)	Na_2CO_3	MeCN	Trace
11[b]	$PdCl_2(PPh_3)_2$	TsCl (1.0 equiv)	K_3PO_4	MeCN	56
12[b]	$PdCl_2(PPh_3)_2$	MsCl (1.0 equiv)	$^iPr_2NEt$	MeCN	Trace
13[b]	$PdCl_2(PPh_3)_2$	TsCl (1.0 equiv)	$^iPr_2NEt$	THF	58

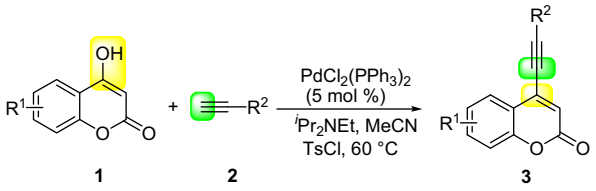
[a] Isolated yield based on 4-hydroxycoumarin.
[b] In the presence of 2.0 equiv of phenyl acetylene.

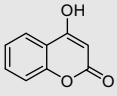
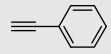
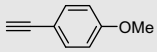
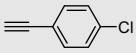
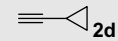
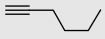
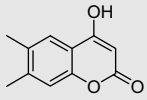
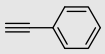
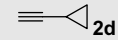
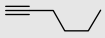
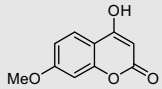
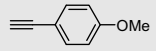
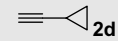
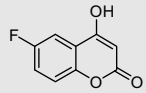
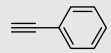
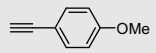
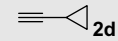
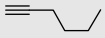
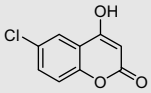
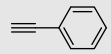
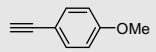
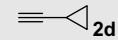
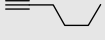
$Pd(OAc)_2$ was used as a replacement (36% yield, Table 1, entry 2). Further screening revealed that $PdCl_2(PPh_3)_2$ was the best choice for this transformation (51% yield, Table 1, entry 5). The yield of **3a** could be increased to 80% when the amount of phenyl acetylene was increased to 2.0 equiv. Interestingly, in the absence of copper iodide the reaction also proceeded smoothly to give the desired product **3a** in 81% yield (Table 1, entry 7). The copper-free Sonogashira reactions have been investigated in the last few years.[13] Addition of an activating agent was essential in the reaction. No reaction occurred without the addition of *p*-toluenesulfonyl chloride (Table 1, entry 8). Other bases were examined in the reaction. However, $^iPr_2NEt$ turned out to be the best one (Table 1, entries 9–11). Only trace amount of product was detected when methanesulfonyl chloride was used as an additive instead of *p*-toluenesulfonyl chloride (Table 1, entry 12). When the solvent was changed to THF, the yield was decreased to 58% (Table 1, entry 13).

With this result in hands and having defined an efficient catalytic system [$PdCl_2(PPh_3)_2$ (5 mol %), $^iPr_2NEt$, TsCl, MeCN], the scope of the palladium-catalyzed direct cross-coupling reactions of 4-hydroxycoumarins **1** with alkynes **2** was next explored. The results obtained are shown in Table 2. In all cases, 4-alkynylcoumarins **3** were obtained in moderate to good yields. For instance, reaction of 4-hydroxycoumarin **1a** with 4-methoxyphenyl acetylene **2b** gave rise to the desired product **3b** in 77% yield (Table 2, entry 2). 86% yield of compound **3d** was observed when ethynylcyclopropane **2d** was employed in the reaction (Table 2, entry 4). When 1-hexyne **2e** was utilized as a replacement in the reaction of 4-hydroxycoumarin **1a**, the transformation also proceeded well to furnish the corresponding products in good yields (71% yield, Table 2, entry 5). To assess the impact of the structural and functional motifs on the reaction we tested the linking units of 4-hydroxycoumarins meanwhile. We found that the conditions have proven to be useful for various 4-hydroxycoumarins. Both electron-rich and electron-poor 4-hydroxycoumarins were suitable partners in this process. However, better results were displayed when electron-donating groups attached on the aromatic ring of 4-hydroxycoumarins. For example, 6,7-dimethyl-4-hydroxycoumarin **1b** reacted with ethynylcyclopropane **2d** leading to the desired product **3g** in 91% yield (Table 2, entry 7).

In order to illustrate the reaction process, reaction of 4-tosyloxycoumarin with phenylacetylene **2a** under the copper-free conditions was performed [$PdCl_2(PPh_3)_2$ (5 mol %), $^iPr_2NEt$, MeCN]. As expected, the desired product **3a** was generated in 80% yield compared with our previous result.[9b] Since 4-tosyloxycoumarin could undergo the 1,4-addition and subsequent β-elimination in the presence of nucleophile, blank experiment without the

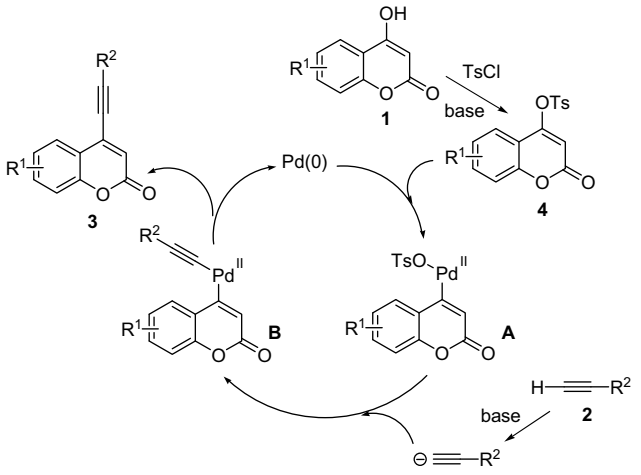
Table 2
Palladium-catalyzed direct coupling reaction of 4-hydroxycoumarin **1** with alkyne **2**



Entry	Coumarin **1**	Alkyne **2**	Product	Yield[a] (%)
1	 **1a**	 **2a**	**3a**	81
2	**1a**	 **2b**	**3b**	77
3	**1a**	 **2c**	**3c**	60
4	**1a**	 **2d**	**3d**	86
5	**1a**	 **2e**	**3e**	71
6	 **1b**	 **2a**	**3f**	78
7	**1b**	 **2d**	**3g**	91
8	**1b**	 **2e**	**3h**	81
9	 **1c**	 **2b**	**3i**	81
10	**1c**	 **2d**	**3j**	72
11	 **1d**	 **2a**	**3k**	48
12	**1d**	 **2b**	**3l**	60
13	**1d**	 **2d**	**3m**	53
14	**1d**	 **2e**	**3n**	54
15	 **1e**	 **2a**	**3o**	48
16	**1e**	 **2b**	**3p**	45
17	**1e**	 **2d**	**3q**	58
18	**1e**	 **2e**	**3r**	72

[a] Isolated yield based on 4-hydroxycoumarin **1**.

addition of palladium catalyst was then examined. However, no reaction was observed under the conditions. Thus, we proposed the possible mechanism for the palladium-catalyzed direct coupling reaction of 4-hydroxycoumarin **1** with alkyne **2** (Scheme 1). According to the previous reports,[13] we reasoned that the presence of *p*-toluenesulfonyl chloride would enable an in situ activation of 4-hydroxycoumarin. Therefore, oxidative addition of Pd(0) to 4-tosyloxycoumarin **4** would generated intermediate **A**, which then reacted with alkyne leading to intermediate **B**. The latter would undergo subsequent reductive elimination to afford the corresponding product **3**.



Scheme 1. Possible mechanism for the palladium-catalyzed direct coupling reaction of 4-hydroxycoumarin **1** with alkyne **2**.

3. Conclusions

In conclusion, we have described an efficient method for the palladium-catalyzed direct cross-coupling reactions of 4-hydroxycoumarins **1** with alkynes **2**. *p*-Toluenesulfonyl chloride was used as an activation reagent in the reaction process. In addition, this transformation was performed under copper-free conditions which generated the 4-alkynylcoumarins in good yields. Further investigation using phenols as substrates in cross-coupling reactions is ongoing, and the results will be reported in due course.

4. Experimental section

4.1. General method

All reactions were performed in reaction tubes under nitrogen atmosphere. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography was performed using glass plates precoated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C. Commercial reagents and solvents were used as received. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale.

4.2. General procedure for the palladium-catalyzed direct cross-coupling reactions of 4-hydroxycoumarins 1 with alkynes 2

A solution of 4-hydroxycoumarin **1** (0.2 mmol), *p*-toluenesulfonyl chloride (0.24 mmol, 1.2 equiv), $Pd(PPh_3)Cl_2$ (5 mol%) in CH_3CN (2.0 mL) was stirred at 60 °C. Subsequently, terminal acetylene **2** (0.4 mmol, 2.0 equiv), *N,N*-diisopropylethyl amine (0.6 mmol, 3.0 equiv) were added into the mixture. After completion of the reaction as indicated by TLC, the solvent was diluted with EtOAc (10 mL), washed with saturated brine (2×10 mL), and dried by anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding compound **3**.

*4.2.1. 4-(Phenylethynyl)-2H-chromen-2-one (**3a**)*[9b]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J=7.5 Hz, 1H), 7.66 (d, J=7.5 Hz, 2H), 7.59 (t, J=8.5, 7.0 Hz, 1H), 7.43–7.52 (m, 3H), 7.37 (t, J=8.0 Hz, 2H), 6.64 (s, 1H). ^{13}C NMR (125.7 MHz) δ 160.5, 153.8, 146.7, 137.5, 132.5, 132.4, 130.5, 129.0, 126.9, 124.7, 121.4, 118.6, 117.3, 102.4, 83.4.

*4.2.2. 4-((4-Methoxyphenyl)ethynyl)-2H-chromen-2-one (**3b**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J=7.8 Hz, 1H), 7.54–7.59 (m, 3H), 7.32–7.36 (m, 2H), 6.93–6.95 (d, J=8.7 Hz, 2H), 6.58 (s, 1H), 3.90 (s, 3H). ^{13}C NMR (100 MHz) δ 161.1, 160.4, 153.5, 137.6, 134.0, 132.1, 126.7, 124.3, 118.4, 117.5, 117.0, 114.4, 113.0, 102.9, 82.1, 55.4. HRMS (ESI) calcd for $C_{18}H_{12}O_3$ $[M+H]^+$ 277.0865, found 277.0858.

*4.2.3. 4-((4-Chlorophenyl)ethynyl)-2H-chromen-2-one (**3c**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.94 (m, 1H), 7.56–7.60 (m, 3H), 7.41–7.43 (m, 2H), 7.34–7.38 (m, 2H), 6.63 (s, 1H). ^{13}C NMR (100 MHz) δ 160.1, 153.5, 136.9, 136.5, 133.4, 132.4, 129.1, 126.5, 124.5, 119.6, 118.6, 118.2, 117.1, 100.7, 83.6. HRMS (ESI) calcd for $C_{17}H_9ClO_2$ $[M+H]^+$ 281.0369, found 281.0354.

*4.2.4. 4-(Cyclopropylethynyl)-2H-chromen-2-one (**3d**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J=7.8, 3.4 Hz, 1H), 7.51–7.53 (m, 1H), 7.27–7.30 (m, 2H), 6.43 (s, 1H), 1.59–1.62 (m, 1H), 0.98–1.06 (m, 4H). ^{13}C NMR (100 MHz) δ 160.4, 153.5, 138.0, 132.0, 126.7, 124.2, 118.8, 117.8, 116.8, 108.5, 70.1, 9.7, 0.6. HRMS (ESI) calcd for $C_{14}H_{10}O_2$ $[M+Na]^+$ 233.0579, found 233.0570.

*4.2.5. 4-(Hex-1-ynyl)-2H-chromen-2-one (**3e**)*[9b]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J=7.8, 1.4 Hz, 1H), 7.52–7.56 (m, 1H), 7.30–7.33 (m, 2H), 6.49 (s, 1H), 2.57 (t, J=6.9 Hz, 2H), 1.66–1.70 (m, 2H), 1.49–1.55 (m, 2H), 0.99 (t, J=7.4 Hz, 3H). ^{13}C NMR (100 MHz) δ 160.5, 153.5, 138.1, 132.1, 126.7, 124.3, 118.8, 118.2, 116.9, 105.1, 74.8, 30.2, 22.1, 19.5, 13.5.

*4.2.6. 6,7-Dimethyl-4-(phenylethynyl)-2H-chromen-2-one (**3f**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.66 (m, 3H), 7.43–7.46 (m, 3H), 7.11 (s, 1H), 6.54 (s, 1H), 2.35 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz) δ 160.7, 151.9, 142.4, 137.0, 133.2, 132.2, 130.0, 128.6, 126.5, 121.3, 117.5, 117.3, 116.0, 101.5, 83.0, 20.2, 19.3. HRMS (ESI) calcd for $C_{19}H_{14}O_2$ $[M+H]^+$ 275.1072, found 275.1059.

*4.2.7. 4-(Cyclopropylethynyl)-6,7-dimethyl-2H-chromen-2-one (**3g**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.06 (s, 1H), 6.35 (s, 1H), 2.31 (s, 3H), 2.34 (s, 3H), 1.60–1.63 (m, 1H), 1.04–1.06 (m, 2H), 0.97–0.99 (m, 2H). ^{13}C NMR (100 MHz) δ 160.9, 151.8, 142.1, 137.9, 133.0, 126.6, 117.4, 116.7, 116.5, 107.9, 70.3, 20.2, 19.3, 9.6, 0.6. HRMS (ESI) calcd for $C_{16}H_{14}O_2$ $[M+H]^+$ 239.1072, found 239.1060.

*4.2.8. 4-(Hex-1-ynyl)-6,7-dimethyl-2H-chromen-2-one (**3h**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.07 (s, 1H), 6.40 (s, 1H), 2.57 (t, J=7.3 Hz, 2H), 2.32 (s, 3H), 2.35 (s, 3H), 1.65–1.70 (m, 2H), 1.51–1.56 (m, 2H), 0.99 (t, J=7.3 Hz 3H). ^{13}C NMR (100 MHz) δ 160.9, 151.8, 142.1, 137.9, 133.0, 126.6, 117.3, 117.0, 116.5, 104.4, 75.0, 30.2, 22.0, 20.2, 19.5, 19.3, 13.5. HRMS (ESI) calcd for $C_{17}H_{18}O_2$ $[M+H]^+$ 255.1385, found 255.1380.

*4.2.9. 7-Methoxy-4-((4-methoxyphenyl)ethynyl)-2H-chromen-2-one (**3i**)*[9b]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J=8.7 Hz, 1H), 7.57 (d, J=9.2 Hz, 2H), 6.91–6.95 (m, 3H), 6.81 (d, J=2.3 Hz, 1H), 6.42 (s, 1H), 3.86 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (100 MHz) δ 163.0, 161.0, 160.8, 155.3, 137.5, 134.0, 127.6, 114.3, 114.2, 112.5, 113.2, 112.1, 102.3, 100.7, 82.3, 55.8, 55.4.

*4.2.10. 4-(Cyclopropylethynyl)-7-methoxy-2H-chromen-2-one (**3j**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J=8.7 Hz, 1H), 6.85 (d, J=8.7 Hz, 1H), 6.77 (d, J=2.8 Hz, 1H), 6.28 (s, 1H), 3.87 (s, 3H), 1.56–1.59 (m, 1H), 0.96–1.06 (m, 4H). ^{13}C NMR (100 MHz) δ 162.9, 160.9, 155.2, 138.0, 127.6, 114.5, 112.5, 112.4, 107.9, 100.6, 70.3, 55.8, 9.6, 0.6. HRMS (ESI) calcd for $C_{15}H_{12}O_3$ $[M+H]^+$ 241.0865, found 241.0860.

*4.2.11. 6-Fluoro-4-(phenylethynyl)-2H-chromen-2-one (**3k**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.66 (m, 3H), 7.45–7.47 (m, 3H), 7.26–7.36 (m, 2H), 6.68 (s, 1H). ^{13}C NMR (100 MHz) δ 160.0, 158.7 (d, J=222.1 Hz), 149.7, 136.4, 132.3, 130.4, 128.7, 120.8, 119.7 (d, J=24.8 Hz), 119.2, 118.6, 112.2, 102.7, 82.4. HRMS (ESI) calcd for $C_{17}H_9FO_2$ $[M+H]^+$ 265.0665, found 265.0660.

*4.2.12. 6-Fluoro-4-((4-methoxyphenyl)ethynyl)-2H-chromen-2-one (**3l**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.61 (m, 3H), 7.26–7.32 (m, 2H), 6.95–6.96 (m, 2H), 6.62 (s, 1H), 3.90 (s, 3H). ^{13}C NMR (100 MHz) δ 161.3, 158.8 (d, J=243.1 Hz), 149.7, 136.7, 134.1, 119.5 (d, J=24.8 Hz), 118.5, 118.3, 114.4, 112.7, 112.2 (d, J=24.8 Hz), 103.5, 81.7, 55.4. HRMS (ESI) calcd for $C_{18}H_{11}FO_3$ $[M+H]^+$ 295.0770, found 295.0762.

*4.2.13. 4-(Cyclopropylethynyl)-6-fluoro-2H-chromen-2-one (**3m**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, J=7.3, 2.3 Hz, 1H), 7.25–7.28 (m, 2H), 6.48 (s, 1H), 1.60 (m, 1H), 1.05–1.08 (m, 2H), 0.98–1.00 (m, 2H). ^{13}C NMR (100 MHz) δ 160.1, 158.8 (d, J=243.1 Hz), 149.6, 137.2, 119.7, 119.4 (d, J=24.8 Hz), 118.6, 118.4, 112.2 (d, J=24.8 Hz), 109.2, 69.7, 9.7, 0.6. HRMS (ESI) calcd for $C_{14}H_9FO_2$ $[M+H]^+$ 229.0665, found 229.0658.

*4.2.14. 6-Fluoro-4-(hex-1-ynyl)-2H-chromen-2-one (**3n**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J=7.3, 2.3 Hz, 1H), 7.25–7.29 (m, 2H), 6.53 (s, 1H), 2.57 (t, J=6.9 Hz, 2H), 1.67–1.71 (m, 2H), 1.50–1.55 (m, 2H), 0.99 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz) δ 160.1, 158.8 (d, J=243.1 Hz), 149.6, 137.2, 119.8, 119.4 (d, J=24.8 Hz), 119.0, 118.4, 112.3 (d, J=24.8 Hz), 105.7, 74.4, 30.2, 22.1, 19.5, 13.5. HRMS (ESI) calcd for $C_{15}H_{13}FO_2$ $[M+H]^+$ 245.0978, found 245.0982.

*4.2.15. 6-Chloro-4-(phenylethynyl)-2H-chromen-2-one (**3o**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J=2.3 Hz, 1H), 7.65–7.67 (m, 2H), 7.45–7.52 (m, 4H), 7.26–7.30 (1H), 6.66 (s, 1H). ^{13}C NMR (100 MHz) δ 159.6, 151.9, 136.2, 132.3, 132.2, 130.4, 129.9, 128.8, 126.1, 120.8, 119.5, 119.2, 118.5, 102.9, 82.2. HRMS (ESI) calcd for $C_{17}H_9ClO_2$ $[M+Na]^+$ 303.0191, found 303.0200.

*4.2.16. 6-Chloro-4-((4-methoxyphenyl)ethynyl)-2H-chromen-2-one (**3p**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J=2.3 Hz, 1H), 7.59 (d, J=9.2 Hz, 2H), 7.49–7.51 (m, 1H), 7.28 (d, J=9.2 Hz, 1H), 6.95–6.97 (m, 2H), 6.61 (s, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz) δ 161.3, 159.8, 151.9, 136.5, 134.1, 132.1, 129.8, 126.1, 119.6, 118.5, 118.3, 114.4, 112.7, 103.7, 81.6, 55.4. HRMS (ESI) calcd for $C_{18}H_{11}ClO_3$ $[M+H]^+$ 311.0475, found 311.0480.

*4.2.17. 6-Chloro-4-(cyclopropylethynyl)-2H-chromen-2-one (**3q**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J=2.3 Hz, 1H), 7.47 (dd, J=7.3, 2.7 Hz, 1H), 7.23–7.26 (m, 1H), 6.47 (s, 1H), 1.60–1.61 (m, 1H), 1.05–1.09 (m, 2H), 0.98–1.01 (m, 2H). ^{13}C NMR (100 MHz) δ 159.8, 151.9, 136.9, 131.9, 129.7, 126.1, 119.9, 118.6, 118.3, 109.4, 69.6, 9.8, 0.7. HRMS (ESI) calcd for $C_{14}H_9ClO_2$ $[M+H]^+$ 245.0369, found 245.0358.

*4.2.18. 6-Chloro-4-(hex-1-ynyl)-2H-chromen-2-one (**3r**)*[9b]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J=2.3 Hz, 1H), 7.48 (dd, J=9.2, 2.8 Hz, 1H), 7.24–7.26 (m, 1H), 6.51 (m, 1H), 2.58 (t, J=7.4 Hz, 3H), 1.67–1.71 (m, 2H), 1.51–1.55 (m, 2H), 0.99 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz) δ 159.8, 151.9, 137.0, 132.0, 129.7, 126.2, 119.9, 119.0, 118.3, 106.0, 74.3, 30.2, 22.1, 19.5, 13.5.

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