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Selective carboxylate directed ortho functionalization in copper catalyzed reaction of polyiodo aromatics: A straightforward preparation of 5,7-diiodo-1*H*-isochromen-1-ones

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Dedication ((optional))

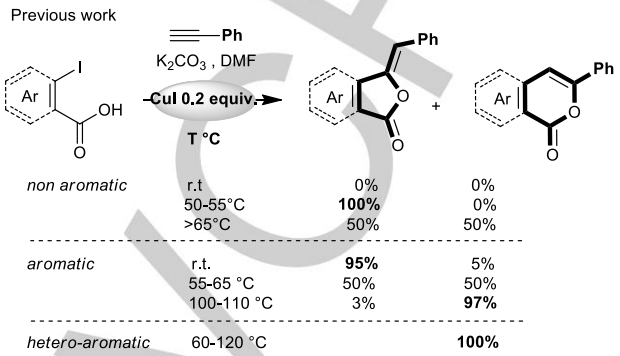
Abstract: A facile, and totally regioselective one pot approach to synthesize 5,7-diiodo-3-substituted-isocoumarins is described. This reaction was realized using copper iodide as the catalyst under mild reaction conditions. The methodology was used to design a wide variety of compounds and was tolerant to a large number of functions. Interestingly, among the three possible carbon-iodine bonds, only one was found to be reactive leaving intact the two others for further functionalization.

Introduction

Isocoumarins, also known as isochromenones, are an important class of lactones because of their significant presence in various natural molecules exhibiting extensive ranges of biological and pharmacological purposes.[1] Actually, several members derived from this family of compounds are of great interest in medicinal chemistry as antibiotic,[1a-c] phytotoxic[1d] or antifungal agents.[1e,f] In a recent patent, the potential of this type of structures was highlighted by their use for the treatment of muscular atrophy.[2]

Their synthesis is described in the literature via numerous pathways,[3] mainly including the transition metal-catalyzed cyclization of alkynes possessing a nucleophile in close proximity to the triple bond.[4] A great number of catalysts have been used such as the copper, palladium, silver, ruthenium, rhodium or iridium salts/complexes to elaborate these isocoumarin ring based compounds.[5, 6] Indeed, these heterocycle have been prepared by the palladium-catalyzed coupling of 2-halobenzoate esters or 2-halobenzonitriles with alkenes,[7] vinylic stannanes,[8] or terminal alkynes,[9] with subsequent cyclization or π-allylnickel cross-coupling and palladium-catalyzed cyclization,[10] itself by coupling of 2-(2,2-dibromovinyl)benzoates and organostannes,[11] by palladium-catalyzed annulation of terminal alkynes and 2-iodophenols,[12] or via C-H olefination and oxidative coupling of benzoic acid and vinylarenes.[13] Most often, these methods involve multistep sequences, harsh conditions, or expensive catalysts and ligands. Also in some of these syntheses, mixtures of isocoumarin and 3-benzylidenephthalide are obtained.[14,15]

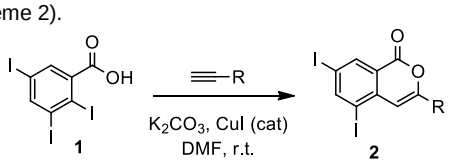
Within the past decade, our group already described a new versatile route to lactones through the reaction of terminal alkynes and β-halo-α,β-unsaturated carboxylic acids in the presence of a catalytic amount of copper (I) salts.[16] This regio- and stereoselective reaction led to either γ-alkylidene butenolides with a non-aromatic β-halo-α,β-unsaturated carboxylic acids as starting material,[17] or exclusively to δ-alkylidene phthalides in the case of heteroaromatic substrates (Scheme 1).[18] In the case of aromatic substrates like 2-iodobenzoic acid, we were pleased to demonstrate that the simple change of the temperature of the reaction could totally inverse the selectivity of the transformation giving rise to the five membered ring at room temperature or to the six membered ring under heating. These results have been also confirmed few years later by an article published by Kumar *et al.*[19]



Scheme 1: General behavior of β-halocarboxylic derivatives in reaction with phenylacetylene in the presence of copper iodide.

The preparation of halogenated phthalides and isocoumarins is rare in the literature and described, in most cases, under harsch conditions. For instance, perfluoro indanes, benzocyclobutenones or benzocyclohexanones treated with SbF_5 and (or) SiO_2 may yield diversely fluorinated 4-carboxy-3-trifluoromethyl isocoumarins in mixture with other compounds.[20] These reactions were generally realized at high temperature and unfortunately limited to a trifluoromethyl group as the substitution at the position 3 of the starting cycles. Yao *et al*[21] reported a simple copper catalyzed route to isocoumarins and halo isocoumarins using 2-halo benzamide derivatives and 2,4-diketones. The synthesis was conducted in polar aprotic solvents in the presence of cesium carbonate, but needed high temperature (up to 100 °C) to produce the compounds. Liu *et al.*[22] reported the possibility to obtain diversely substituted isocoumarins using an interesting C-H activation procedure catalyzed by rhodium complexes at 60°C. More recently, Shang *et al* reported the rhodium(III)-catalyzed C-H activation/esterification reaction for the synthesis of isocoumarins containing a bromine or chlorine atom on the aromatic ring.[23] Finally, Panda *et al* described the silver-mediated cyclization of 2-iodo enol esters affording the 7-halo 3,4-disubstituted isocoumarins with moderate to good yields.[24]

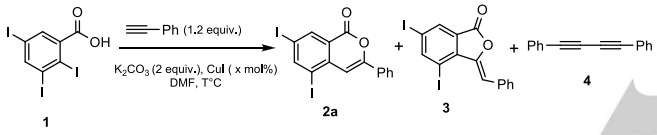
On the basis of our previously established methodology[17,18] and in order to prepare a unified way to extend the functionalities of this interesting heterocycle, we report in this paper a very mild and convenient copper catalyzed route to synthesize exclusively 5,7-diiodo-3-substituted isocoumarins, starting from 2,3,5-triiodobenzoic acid (Scheme 2).



Scheme 2: Cooper-catalyzed synthesis of 5,7-diiodo-3-substituted isocoumarins **2**.

Results and Discussion

The commercially available 2,3,5-triiodobenzoic acid **1** was chosen as the substrate for our study in order to obtain diiodo lactones. Based on our previous results, we started to apply to this compound our classical conditions, 20 mol % of copper iodide (CuI) with 1.2 equiv. of phenylacetylene at room temperature.[18] Surprisingly, no trace of the expected 3-benzylidene phthalide [(*Z*)-3-benzylidene-4,6-diiodoisobenzofuran-1(3*H*)-one] **3** was detected. The 3-phenyl-5,7-diiodoisocoumarin **2a** was exclusively isolated with an excellent yield of 89% (Table 1, entry 2). No significant difference in the yield was observed using a stoichiometric amount of CuI (Table 1, entry 3). Lowering the amount of catalyst to 10 mol% provided only 51% yield of **2a** (Table 1, entry 1). This selectivity, six versus five membered ring, was completely opposite to that of our published previous studies. The alkylidene phthalides were indeed obtained at room temperature probably as the kinetic major product, while the isocoumarin derivatives prevailed when the working temperatures were higher than 65°C (Scheme 1). We consequently increased the reaction temperatures to try to inverse the regioselectivity. Unfortunately, the only effect was the rise of the formation of dimer **4** sometimes accompanied with some side products (Table 1, entry 5).[25] Working at around 50°C, leads to product **2a** but with a yield of 68% (Table 1, entry 4). Interestingly, the nature of the catalyst was found to be crucial. So, using Sonogashira conditions,[26] the diyne **4** resulting from dimerization was isolated as major product accompanied by a minor amount of coupling products of the different iodine atoms (Table 1, entry 6).

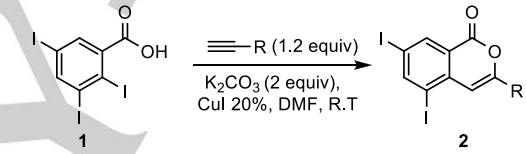


Entry	Cat (x mol%)	T°C	2a (%)	3 (%)	4 (%)
1	CuI (10)	25	51	0	0
2	CuI (20)	25	89	0	4
3	CuI (100)	25	91	0	5
4	CuI (20)	50	68	0	19
5	CuI (20)	100	4	0	>90
6	$PdCl_2(PPh_3)_2$, CuI	25	0	0	>88

Table 1: Influence of reaction conditions for synthesis of isocoumarin **2**

This unexpected but very interesting selectivity led us to investigate the scope of the reaction with various substituted terminal alkynes. Alkyl substituted alkynes showed a tendency to give moderate yields [**2b** (60%), **2c** (53%) and **2d** (30%)], while conjugated alkynes were particularly suitable to the applied conditions, providing the expected products **2e** (66%) and **2f** (90%). Alkynes possessing a protected alcohol and ether functions were very well tolerated producing the corresponding isocoumarins **2g** and **2h** in good yields. Free propargylic and homopropargylic alcohols were also engaged in reaction with success, providing the desired products **2i**, **2j** and **2k** with 59%, 81% and 68%, respectively. Propargylic diethyl acetal and homopropargylic diethyl acetal reacted at room temperature but led only to 32% and 31% yields of **2l** and **2m**, respectively.

With but-3-ynoic acid, no reaction occurred at room temperature. As a possible explanation, we hypothesize a strong competitive chelation of carboxylate onto the copper salt leading ineffective the oxidative addition step in the carbon-iodine bond. Assuming that the carboxylate of the alkyne is a stronger ligand of the copper (I) that the aromatic carboxylate and also a possible ligand metathesis promoted by temperature, the reaction was conducted at higher temperature. Satisfyingly, changing the temperature to 80°C, the heterocycle formation occurred along with a decarboxylation reaction providing isocoumarin **2n** in fair yield. This non-expected product globally results from the reaction of 2,3,5-triiodo benzoic acid with propyne, which is gaseous at ambient temperature. Finally, we planned to examine the possible double reactivity starting from a terminal diyne. Interestingly, using diyne **1o**, the coupling-cyclization sequence led to only isocoumarin **2o** in fair yield. While this selectivity was not expected, no rational hypothesis supports this result. According to our knowledge, internal alkynes were ineffective with our conditions. Actually, no transformation occurred while using 1,2-diphenylacetylene, nor 1-phenyl-1-propyne.
As shown in Table 2, this reaction was doubly selective: no trace of the five-membered ring lactones was observed, and no Sonogashira type reaction was observed with the other atoms of iodine of the aromatic ring.



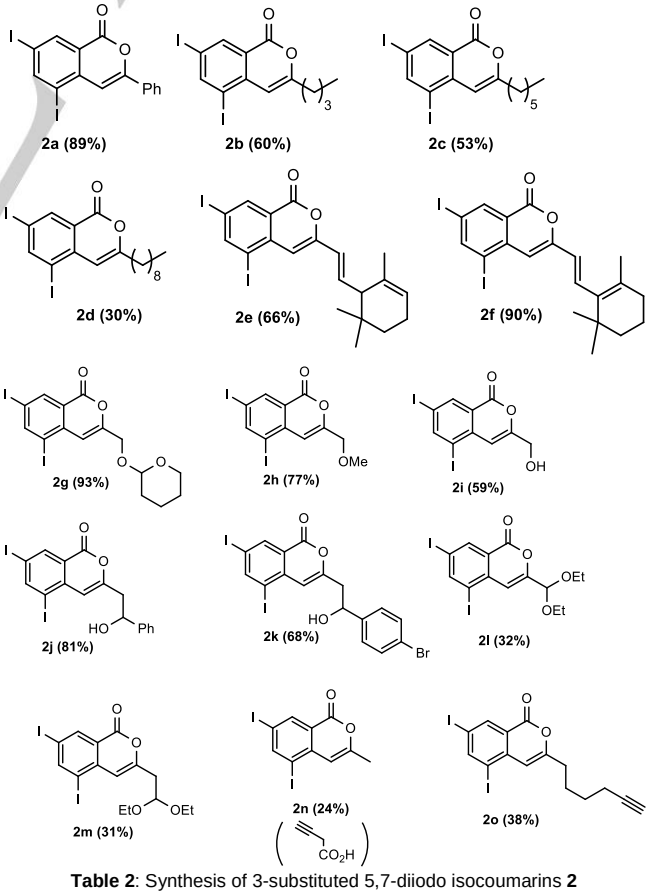


Table 2: Synthesis of 3-substituted 5,7-diiodo isocoumarins **2**

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Each product was fully characterized and the structures of the 3-substituted-5,7-diiodoisocoumarins were confirmed by spectroscopic (MS, IR, ^{1}H and ^{13}C NMR) data. The isocoumarins **2a-o** could be unambiguously differentiated from the corresponding 3-ylidene phthalides on the basis of several spectroscopic data, especially IR and ^{1}H NMR spectra. Indeed, no ^{1}H NMR triplet ($^{3}J_{H-H}$) corresponding to the methylene near the double bond exocyclic was observed in the case of alkynes substituted with alkyl groups, indicating the non-formation of alkylidene phthalides. Furthermore, on the basis of the reported comparison between the five- and six-membered lactone rings of substituted isocoumarins [$\nu_{max\ C=O}$ 1720-1740 cm^{-1}] and 3-ylidene phthalides [$\nu_{max\ C=O}$ 1765-1800 cm^{-1}], we noticed a great agreement between our IR spectroscopic data with those reported for isocoumarins.[4a, 27] In addition, the structure of isocoumarin **2a** was unambiguously attributed thanks to single-crystal X-ray crystallography (Figure 1).[28]

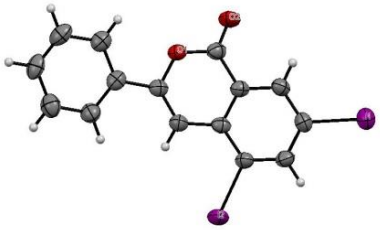
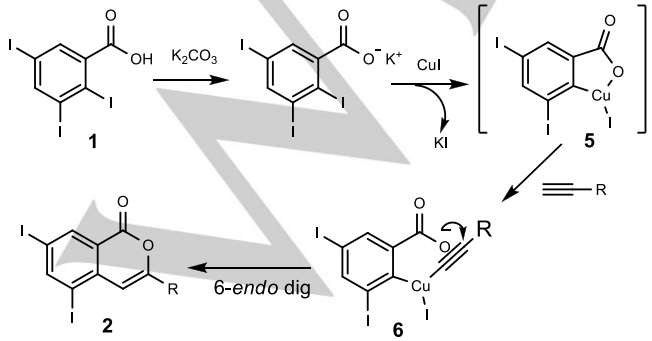


Figure 1. X-ray single-crystal structure of isocoumarin **2a**

The reactivity of the iodine in position 2 of the benzene ring is certain, in comparison with the others. In a previous paper,[8] we have already shown that the coupling/oxacyclization is very sensitive to the position of the halogen towards the carboxyl group. We reported the lack of reactivity when using (*E*)-3-iodoacrylic acid compared to the very good reactivity of (*Z*)-3-iodoacrylic acid.

Furthermore, we did not find any evidence of the formation of the corresponding enynoic acids, which means no coupling occurs if the carboxyl group and the halogen are not close enough and in the same 3D space area. Considering this observation, we, then, expected that the iodine atoms in position 3 and 5 to be safe especially under selected reaction conditions. As expected, we confirmed also a similar behavior when 3-iodobenzoic acid is used as a substrate, as no reaction occurred and the starting materials were then fully recovered.

Based on these results and on our previous works,[9] we propose a reaction pathway involving the formation of a copper (III) intermediate **5** to explain this selectivity as shown in Scheme 3. Driven by the formation of a copper (I) carboxylate, the oxidative addition reaction is hypothesized to occur only at the carbon-iodine bond in ortho position. In fact, this may explain that only the iodine ortho to the carboxylic function is displaced. Next step could involve the Sonogashira-type coupling reaction followed by a cyclization reaction with only a 6-*endo* dig cyclization to give the isocoumarin **2**. Unfortunately, we were not able to isolate the intermediate **6** to prove this path. However, this is in accordance with the mechanism described by Kumar.[10] This mechanism is currently being studied in our laboratory to elucidate the effect of other two iodine atoms on this regioselectivity.



Scheme 3: The proposed reaction pathway leading to **2**

Conclusions

In summary, we have developed a straightforward synthesis of 3-substituted 5,7-diiodo isocoumarins under very mild reaction conditions. Compared to 2-iodo benzoic acid, our copper-catalyzed tandem coupling heterocyclization conditions applied to 2,3,5-triiodo benzoic acid led only to the formation of the six-membered lactones even at room temperature, without any trace of the corresponding 5-membered ring lactones. This ligand free copper catalyzed reaction proceeded in good yields. Currently, work is being carried out in our laboratory to elucidate the parameters which govern this regioselectivity. Furthermore, the residual unaffected carbon-iodine bonds constitute a diversity point that we are currently studying the reactivity.

Experimental Section

General Methods. All reactions were carried out under argon atmosphere. TLC spots were examined under UV light. NMR spectra were obtained at 200 MHz for ^{1}H, and 50 MHz for ^{13}C with a Brucker Avance FT-NMR spectrometer. Chemical shifts are given in parts per million (δ) relative to the residual chloroform peak (7.26 ppm). Electrospray ionization high-resolution mass spectrometry experiments (HRMS) were performed on a hybrid tandem quadrupole/time-of flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manchester, U.K.) operated in positive mode.

General Procedure for synthesis of 3-alkyl (aryl)-5,7-diiodo 1*H*-Isochromen-1-ones 2.
Under an argon atmosphere, 2,3,5-triidobenzoic acid (500 mg, 1 mmol), K_2CO_3 (276 mg, 2 mmol) and DMF (10 mL) were placed in a Schlenk tube. The reaction mixture was stirred at room temperature during 10 minutes followed by the addition of CuI (38 mg, 0.2 mmol) and the alkyne (1.2 mmol). After being stirred for 16h, the crude mixture was extracted with ethyl ether. The organic layers were then washed with satured NH_4Cl, with water and dried over anhydrous magnesium sulfate. The solvents were removed by vacuum, and the crude residue was purified using silica gel column chromatography, preparative TLC or by recrystallization.

3-Phenyl-5,7-diiodoisocoumarin **2a**
The reaction with phenylacetylene provided a yellow solid (89%) after purification by recrystallization from diethyl ether. Mp = 204 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.11 (s, 1H), 7.46-7.50 (m, 3H), 7.87-7.91 (m, 2H), 8.47 (d, *J* = 2.0 Hz, 1H), 8.59 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 92.5, 96.9, 105.1, 122.5, 125.7, 129.1, 130.8, 131.5, 138.8, 139.2, 152.6, 155.2, 160.3. IR (ATR, cm^{-1}): 1623, 1715, 1729. HRMS Calcd. for $C_{15}H_9I_2O_2$: 474.86864. Found: 474.86790 $[M+H]^+$ (δ = -1.5).

3-Butyl-5,7-diiodoisocoumarin **2b**
The reaction with hexyne provided a pale beige solid (60%) without any purification. Mp = 116 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.2 Hz, 3H), 1.43 (sext, *J* = 7.4 Hz, 2H), 1.70 (quint, *J* = 7.0 Hz, 2H), 2.54 (t, *J* = 7.0 Hz, 2H), 6.43 (s, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 8.55 (d, *J* = 2.0 Hz, 1H) .^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8, 22.3, 29.0, 33.8, 91.8, 95.8, 106.3, 122.2, 138.7, 139.3, 152.4, 160.5, 160.9. IR (ATR, cm^{-1}): 1642, 1723, 1737. HRMS Calcd. for $C_{13}H_{13}I_2O_2$: 454.89994. Found: 454.89929 $[M+H]^+$ (δ = -1.44).

3-(Hexyl)-5,7-diiodoisocoumarin **2c**
The reaction with octyne provided a pale beige solid (53%) after purification by recrystallization from diethyl ether. Mp = 94°C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3H), 1.28-1.35 (m, 6H), 1.68-1.71 (m, 2H), 2.54 (t, *J* = 7.0 Hz, 2H), 6.43 (s, 1H), 8.45 (s, 1H), 8.56 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 14.1, 22.6, 26.9, 28.8, 31.6, 34.1, 91.8, 95.8, 106.2, 122.2, 138.6, 139.3, 152.4, 160.5, 160.9. IR (ATR, cm^{-1}): 1627, 1736, 1721. HRMS Calcd. for $C_{15}H_{17}I_2O_2$: 482.93124. Found: 482.92908 $[M+H]^+$ (δ = -4.4).

3-(Nonyl)-5,7-diiodoisocoumarin **2d**
The reaction with undecyne provided a pale beige solid (30%) after purification by recrystallization from diethyl ether. Mp = 91 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.0 Hz, 3H), 1.27-1.32 (m, 12H), 1.67-1.74 (m, 2H), 2.53 (t, J = 8.0 Hz, 2H), 6.42 (s, 1H), 8.43 (d, *J* = 2.0 Hz, 1H), 8.54 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 14.2, 22.8, 26.9, 29.1, 29.4, 29.4, 29.5, 31.9, 34.1, 91.8, 95.8, 106.2, 122.2, 138.6, 139.3, 152.4, 160.5, 160.9.

IR (ATR, cm^{-1}): 1650, 1731. HRMS Calcd. for $C_{18}H_{23}I_2O_2$: 524.97819. Found: 524.97646 $[M+H]^+$ (δ = -3.3).

3-[(E) 2-(2,6,6-Trimethylcyclohex-2-enyl)vinyl]-5,7-diiodoisocoumarin **2e**
The reaction with (*E*)-2-(but-1-en-3-ynyl)-1,3,3-trimethylcyclohex-1-ene provided a yellow solid (90%) after purification by recrystallization from diethyl ether. Mp = 141 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.08 (s, 6H), 1.45-1.69 (m, 4H), 1.79 (s, 3H), 2.06 (t, *J* = 6.0 Hz, 2H), 6.08 (d, *J* = 16.0 Hz, 1H), 6.45 (s, 1H), 7.12 (d, *J* = 16.0 Hz, 1H), 8.41 (d, *J* = 2.0 Hz, 1H), 8.56 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.1, 22.0, 29.0 (2C), 33.5, 34.4, 39.8, 91.7, 96.2, 107.3, 122.4, 123.5, 133.5, 134.7, 136.9, 138.7, 139.6, 152.4, 154.4, 160.2. IR (ATR, cm^{-1}): 1604, 1631, 1736. HRMS Calcd. for $C_{20}H_{21}I_2O_2$: 546.96254. Found: 546.96019 $[M+H]^+$ (δ = -4.3).

3-[(E)-2-(2,6,6-Trimethylcyclohex-1-enyl)vinyl]-5,7-diiodoisocoumarin **2f**
The reaction with (*E*)-6-(but-1-en-3-ynyl)-1,5,5-trimethylcyclohex-1-ene provided an orange solid (66%) after purification by column chromatography on silica gel (Et_2O/petroleum ether: 1/9). Mp = 135 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (s, 3H), 0.94 (s, 3H), 1.17-1.25 (m, 1H), 1.46-1.56 (m, 1H), 1.60 (s, 3H), 2.04-2.06 (m, 2H), 2.30 (d, *J* = 6.0 Hz, 1H), 5.49-5.51 (m, 1H), 6.06 (d, *J* = 14.0 Hz, 1H), 6.45 (s, 1H), 6.56 (dd, *J* = 14.0 Hz, *J* = 8.0 Hz, 1H), 8.42 (d, *J* = 2.0 Hz, 1H), 8.55 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.1, 23.2, 27.0, 28.0, 31.3, 32.9, 54.9, 91.9, 96.3, 107.1, 122.4, 122.6, 122.9, 132.4, 138.8, 139.6, 140.0, 152.5, 153.9, 160.3. IR (ATR, cm^{-1}): 1605, 1642, 1741. HRMS Calcd. for $C_{20}H_{21}I_2O_2$: 546.96254. Found: 546.95990 $[M+H]^+$ (δ = -4.8).

3-[(Tetrahydro-2H-pyran-2-yloxy)methyl]-5,7-diiodoisocoumarin **2g**
The reaction with 2-(prop-2-ynyloxy)-tetrahydro-2*H*-pyran provided a white solid (93%) after purification by recrystallization from diethyl ether. Mp = 131 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.57-1.91 (m, 6H), 3.56-3.62 (m, 1H), 3.87-3.95 (m, 1H), 4.34 (d, *J* = 14.0 Hz, 1H), 4.54 (d, *J* = 14.0 Hz, 1H), 4.80 (t, *J* = 3.0 Hz, 1H), 6.76 (bs, 1H), 8.48 (d, *J* = 2.0 Hz, 1H), 8.58 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.1, 25.4, 30.4, 63.3, 65.1, 92.9, 96.5, 98.6, 107.3, 122.8, 138.8, 152.6, 155.9, 160.3. IR (ATR, cm^{-1}): 1627, 1735, 1723. HRMS Calcd. for $C_{15}H_{15}I_2O_4$: 512.90542. Found: 512.90292 $[M+H]^+$ (δ = -4.8).

3-Methoxymethyl-5,7-diiodoisocoumarin **2h**
The reaction with 3-methoxyprop-1-yne provided a yellow solid (77%) after purification by recrystallization from diethyl ether. Mp = 170 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.51 (s, 3H), 4.27 (s, 2H), 6.72 (s, 1H), 8.49 (d, *J* = 2.0 Hz, 1H), 8.57 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 59.3, 70.6, 92.9, 96.4, 107.0, 122.8, 138.7, 138.8, 152.7, 155.7, 160.1. IR (ATR, cm^{-1}): 1652, 1728, 1738. HRMS Calcd. for $C_{11}H_9I_2O_3$: 442.86356. Found : 442.86134 $[M+H]^+$ (δ = -4.9).

3-(Hydroxymethyl)-5,7-diiodoisocoumarin **2i**
The reaction with propargyl alcohol provided the title compound as a beige solid (59%) without any purification. Mp = 201 °C (uncorrected). ^{1}H NMR (200 MHz, DMSO *d*^{6}): δ = 4.51 (d, *J* = 6.0 Hz, 2H), 5.78 (t, *J* = 6.0 Hz, 1H), 6.70 (s, 1H), 8.34 (s, 1H), 8.61 (s, 1H). ^{13}C NMR (50 MHz, DMSO *d*^{6}): δ = 59.5, 93.9, 98.1, 104.3, 121.7, 137.1, 138.3, 151.7, 159.6 (2C). IR (ATR, cm^{-1}): 1647, 1694, 3454. HRMS Calcd. for $C_{10}H_7I_2O_3$: 428.84791. Found: 428.84653 $[M+H]^+$ (δ = -3.2).

3-(2-Hydroxy-2-phenylethyl)-5,7-diiodoisocoumarin **2j**
The reaction with 1-phenyl but-3-yn-1-ol provided the title compound as pale beige solid (81%) after purification by recrystallization from diethyl ether. Mp = 149 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.12 (bs, 1H), 2.87-2.95 (m, 2H), 5.21 (dd, *J* = 8.0 Hz, *J* = 5.0 Hz, 1H), 6.53 (s, 1H), 7.31-7.41 (m, 5H), 8.44 (d, *J* = 2.0 Hz, 1H), 8.55 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.9, 71.4, 92.3, 96.0, 108.7, 122.3, 125.7, 125.8, 128.3, 128.6, 128.9, 138.6, 139.0, 143.1, 152.6, 156.4, 160.7. IR (ATR, cm^{-1}): 1647, 1702, 1737, 3436. HRMS Calcd. for $C_{17}H_{13}I_2O_3$: 518.89486. Found: 518.89321 $[M+H]^+$ (δ = -3.1).

3-[2-(4-Bromophenyl)-2-hydroxyethyl]-5,7-diiodoisocoumarin **2k**
The reaction with 1-(4-bromophenyl)but-3-yn-1-ol provided a brown solid (68%) after purification by recrystallization from diethyl ether. Mp = 183 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.65 (bs, 1H), 2.88-2.91 (m, 2H), 5.19 (dd, *J* = 8.0 Hz, *J* = 5.0 Hz, 1H), 6.52 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 8.46 (d, *J* = 2.0 Hz, 1H), 8.54 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.9, 70.8, 92.5, 96.1, 108.9, 122.0, 122.3, 127.5, 132.0, 138.7, 138.9, 142.1, 152.7, 155.9, 160.6. IR (ATR, cm^{-1}): 1629, 1729, 1736, 3455. HRMS Calcd. for $C_{17}H_{12}BrI_2O_3$: 596.80537. Found: 596.80276 $[M+H]^+$ (δ = -4.3).

3-Diethoxymethyl-5,7-diiodoisocoumarin **2l**
The reaction with 3,3-diethoxyprop-1-yne provided an orange solid (32%) after purification by recrystallization from diethyl ether. Mp = 125 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.0 Hz, 6H), 3.71 (q, *J* = 7.0 Hz, 4H), 5.20 (s, 1H), 6.93 (s, 1H), 8.48 (d, *J* = 2.0 Hz, 1H), 8.57 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 15.2 , 62.9 , 93.3, 97.0, 97.8, 107.1, 123.1, 138.5, 138.8, 152.7, 154.8, 160.0. (ATR, cm^{-1}): 1653, 1725, 1737. HRMS Calcd. for $C_{14}H_{15}I_2O_4$: 500.90542. Found: 500.90373 $[M+H]^+$ (δ = -3.3).

3-(2,2-Diethoxyethyl)-5,7-diiodoisocoumarin **2m**
The reaction with 4,4-diethoxybut-1-yne provided a beige solid (31%) after purification by column chromatography on silica gel (petroleum ether/CH_2Cl_2: 8/2). Mp = 116 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.0 Hz, 6H), 2.86 (d, *J* = 6.0 Hz, 2H), 3.52-3.60 (m, 2H), 3.67-3.75 (m, 2H), 4.91 (t, *J* = 6.0 Hz, 1H), 6.57 (bs, 1H), 8.45 (d, *J* = 2.0 Hz, 1H), 8.55 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.3, 39.1, 62.3, 92.2, 96.0, 100.0, 108.4 , 122.3, 138.6, 139.2, 152.5, 155.7, 160.6. IR (ATR, cm^{-1}): 1652, 1721. HRMS Calcd. for $C_{15}H_{17}I_2O_4$: 514.92107. Found: 514.91862 $[M+H]^+$ (δ = -4.7).

3-(Methyl)-5,7-diiodoisocoumarin **2n**
The reaction with but-3-ynoic acid required heating of the reaction mixture at 80°C during 12 hours and provided a beige solid (24%) after purification by column chromatography on silica gel (CH_2Cl_2/Et_2O: 90/10). Mp = 202 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.31 (s, 3H), 6.45 (s, 1H), 8.43 (d, *J* = 2.0 Hz, 1H), 8.54 (d, J = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 20.2, 91.8, 95.5, 106.9, 122.1, 138.7, 139.3, 152.5, 156.7, 160.8. IR (ATR, cm^{-1}): 1720, 1734. HRMS Calcd. for $C_{10}H_7I_2O_2$: 412.85299 Found:412.85297 $[M+H]^+$ (δ = -0.06).

3-(Hex-5-ynyl)-5,7-diiodoisocoumarin **2o**
The reaction with 1,7-octadiyne provided a pale yellow solid (38%) after purification by recrystallization from diethyl ether. Mp = 95 °C (uncorrected). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.59-1.69 (m, 2H), 1.78-1.90 (m, 2H), 1.99 (t, *J* = 2.0 Hz, 1H), 2.27 (td, *J* = 7.0 Hz ; *J* = 2.0 Hz, 2H), 2.60 (t, *J* = 7.0 Hz, 2H), 6.44 (s, 1H), 8.43 (d, *J* = 2.0 Hz, 1H), 8.53 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.1, 26.0, 27.8, 33.5, 69.0, 83.9, 91.9, 95.8, 106.5, 122.2, 138.6, 139.2, 152.4, 159.8, 160.8. IR (ATR, cm^{-1}): 1645, 1719, 1734, 2115. HRMS calcd. for $C_{15}H_{13}I_2O_2$: 478.89994. Found: 478.89772 $[M+H]^+$ (δ = -4.6).

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Keywords: 2,3,5-triiodo benzoic acid • cooper-catalyzed reaction • heterocyclization • regioselective synthesis • 3-substituted 5,7-diiodo isocoumarins.

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[28] CCDC 1486755 [for isocoumarin **2a**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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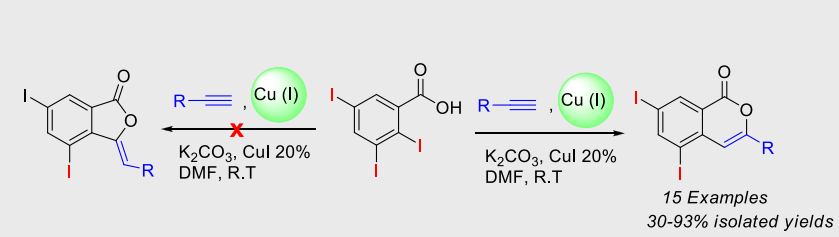

5,7-diiodo 3-substituted isocoumarins

*Elsa Anselmi,[f] Zineb Bahlaouan, Samuel Inack Ngi, Jean Luc Parrain, Emmanuel Magnier, Mohamed Abarbri**

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Title **Selective Carboxylate Directed ortho functionalization in copper catalyzed reaction of polyiodo aromatics: a Straightforward preparation of 5,7-diiodo-1*H*-isochromen-1-one**

A straightforward copper catalyzed synthesis of 5,7-diiodo-1*H*-isochromen-1-ones was developed starting from 2,3,5-triiodo benzoic acid and terminal alkynes