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Regioselective Copper-Mediated Synthesis of Thieno[2,3-*c*]pyrane-7-one, Indolo[2,3-*c*]pyrane-1-one, and Indolo[3,2-*c*]pyrane-1-one

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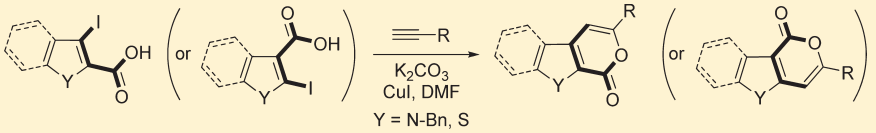
Supporting Information

ABSTRACT:



In the presence of copper(I) iodide, heteroaromatic β-iodo-α,β-unsaturated carboxylic acid systems opposed to terminal alkyne afford selectively 6-*endo-dig* cyclization products via a tandem coupling oxacyclization reaction.

INTRODUCTION

Pyranones are an important class of molecules, and indeed these lactones are structural subunits in a wide variety of naturally occurring substances that have an extensive range of biological and pharmacological uses as, for example, antibiotic,[1a,b] phytotoxic,[1c] or antifungal agents.[1d−f] This may also be said of indole and thiophene moieties. Combining a pyranone structure with the latter may lead to potentially bioactive molecules (Figure 1). Indeed thieno[2,3-*c*]pyrane derivatives are considered to be tumor cell growth inhibitors,[2] while indolo[2,3-*c*]pyrane derivatives are known to inhibit the hepatitis C virus NS5B polymerase.[3]

In this study, we focused on the synthesis of thieno[2,3-*c*]-pyran-7-one (**1**), indolo[2,3-*c*]pyrane-1-one (**3**), and indolo-[3,2-*c*]pyrane-1-one (**4**) from easily available β-iodo-α,β-unsaturated carboxylic acid systems (Figure 1). It is interesting to note that **3** and **4** may constitute interesting precursors to β- and γ-carbolinone alkaloids, respectively. β-Carbolinones act on the central nervous system[4] and are recognized as HeLa and HLE cell inhibitors,[5] while some γ-carbolinones are serotonin 5-HT_3 receptor antagonists.[4d] A certain number of methods to access these molecules have been reported in the literature. To the best of our knowledge, compounds **3** and **4** can be accessed from γ-cetoester cyclization,[6] anhydride rearrangement,[4a,b,7] metal-catalyzed enyne cyclization,[8] or metal-catalyzed coupling,[9] while compounds **1** can be obtained via enyne cyclization,[10] Sonogashira-like cross-coupling,[2,11] or metal-catalyzed oxidative condensation.[9b]

We have recently published an easy and mild palladium-free process for rapid access to isocoumarines from a β-iodo-α, β-unsaturated carboxylic acid system (Scheme 1).[12] Indeed, *o*-iodo-substituted benzoic acid is able to undergo a tandem coupling−heterocyclization sequence in the presence of copper(I) iodide and an alkaline carbonate.

Although the transformation suffered from a lack of selectivity, we obtained phthalide and isocoumarin mixtures with the balance in favor of the 6-*endo-dig* cyclization. We report here a valuable synthetic extension of this method onto heterocyclic substrates such as indole and thiophene bearing a β-iodo-α,β-unsaturated carboxylic acid system.

RESULTS AND DISCUSSION

Synthesis of Thieno[2,3-c]pyran-7-one. The previously published process involved was 20 mol % of CuI with 2 equiv of alkyne and the same amount of potassium carbonate for 1 equiv of 2-iodo benzoic acid in DMF at 55−60 °C.[12] While the use of the same process with 2-iodobenzoic acid led to a mixture of phthalides and isocoumarines, the effect on commercially available 3-iodo-thiophene-2-carboxylic acid opposed to phenylacetylene as a reference system resulted in a single product. In fact, we only obtained 6-*endo-dig* cyclization, whatever the alkyne used. A study similar to that already reported[13] performed on our reference system brought us to the same conclusions. We found that the best base was K_2CO_3 instead of Cs_2CO_3, NaOH, or K_3PO_4, while the best copper salt was still CuI instead of CuCN, CuBr, Cu_2O, or $CuBr_2$. The solvent of choice was still the DMF or DMSO. On the other hand, the yield was satisfactory only when we used at least 0.4 equiv of CuI instead of 0.2 equiv. Four hours was required to achieve the reaction from 4 mmol of the acid. Increasing the temperature to 100 °C did not improve yield nor change the regiochemistry. Decreasing the temperature to room temperature lowered the yields to traces. We were able to react alkynes bearing electron-withdrawing groups (aryl, acetal) or an electron-donating group (alkyl) with average isolated yields without losing regioselectivity. Functional groups like malonyl (Table 1, entry 3) or acetal (Table 1, entry 4) were well tolerated. The results obtained are set out in Table 1.

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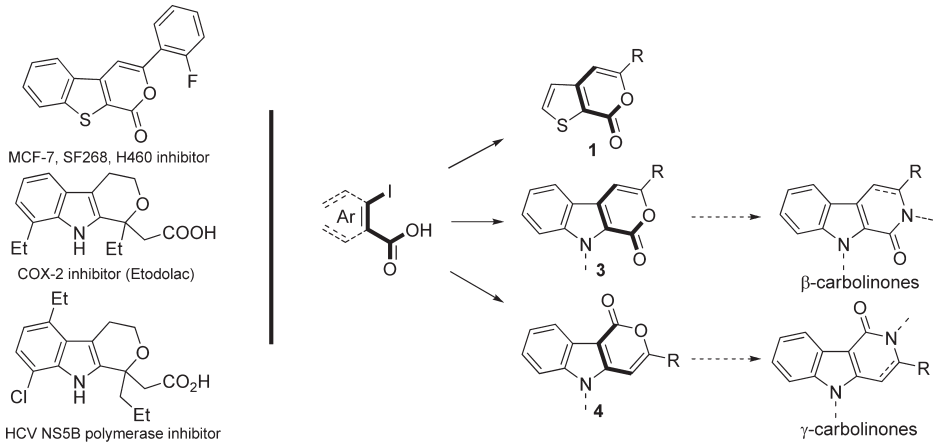
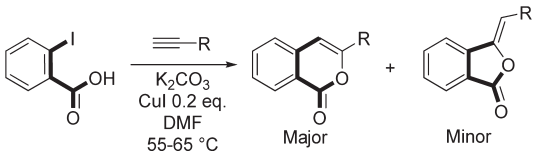


Figure 1. Pyranone and indole or thiophene fused cycles of interest.

Scheme 1. Copper-Catalyzed Preparation of Isocoumarins



Synthesis of Indolo[2,3-c]pyrane-1-one and Indolo[3,2-c]-pyrane-1-one. To achieve our aims, **2a** and **2b** were synthesized in good yields from the corresponding commercial indoles (Scheme 2). Indole **2a** was obtained in four steps from (1*H*)-indole-2-carboxylic acid. After esterification of the starting indole and halogenation of the ester with *N*-chlorosuccinimide/sodium iodide (NCS/NaI) in DMF, the resulting indole was reacted with benzylbromide and saponified into **2a** in good yields. It was impossible to obtain indole **2b** in the same way. Methylindole-3-carboxylate was benzylated prior to halogenation and saponification. The NCS/NaI system in DMF was unable to halogenate position 2 of the indole. Treatment with *t*-BuLi and molecular iodine permitted us to achieve our goals in good yields, while *n*-BuLi and *s*-BuLi led to moderate or poor yields.

The conditions used with 3-iodothiophene carboxylic or 2-iodobenzoic acid[12] could not be applied to indole derivatives. With **2a** and phenylacetylene as reference system, only traces of cyclization product were detected with 0.2−0.4 equiv of CuI at 60 °C (Table 2, entries 3 and 4). Increasing the temperature to 100 °C with the same amount of copper iodide afforded only 5% yield (Table 2, entry 5). The best result was obtained when using 1 equiv of CuI at 120 °C for about 12−14 h for 2 mmol of acid (Table 2, entries 6 and 7). As with thiophene acid, we obtained only 6-*endo-dig* cyclization. Assays using indole **2b** provided the same type of transformation. Various alkynes were used to investigate the scope of these reaction conditions. The results obtained from **2a** and **2b** are summarized in Table 3. In addition, a study similar to that performed for the thiophene moiety about the copper source, the base, and the solvent gave the same conclusions.

Various alkynes bearing electron-withdrawing groups (aryl, pyridinyl, thiophenyl) or an electron-donating group (alkyl) were reacted with good yields on average. In contrast to non-aromatic starting materials,[12] the presence of an electron-donating group on the terminal alkyne did not affect the regioselectivity of the coupling−oxacyclization process at all (Table 3, entries 7, 12, and 13). Various other functional groups were well tolerated whether directly connected to the triple bond or not (such as alkenyl, dienyl, alkynyl, methoxyl, hydroxyl, malonyl, and even ferrocenyl), providing average to good yields of only the corresponding pyranones. Although the use in the case on indole and thiophene of a diyne derived from diethylmalonate provided a moderate yield (Table 1, entry 3 and Table 3, entry 11), only one alkynyl function was used. Only traces of the double coupling of the alkyne were detected in the case of indole. This alkyne provided original indole which may afford a pentacyclic molecule with expedient conditions. Inversion of the iodine and carboxylic acid function positions had no effect on the selectivity or yields, as can be seen in the case of the indole moiety.

The stereochemistry observed with aromatic and heteroaromatic substrates could be explained by the preferential formation of the thermodynamic product in our conditions due to the temperature and the structure of our starting materials. It is accepted that Baldwin's rules[13] predict that 5-*exo-dig* and 6-*endo-dig* cyclization are almost equally favorable, making selective synthesis difficult in practice. In the case of 2-iodobenzoic acid,[12] we obtained a mixture of isocoumarin and phthalides at an average ratio of 70/30 in favor of 6-*endo-dig* cyclization, while with the five-membered heterocyclic starting material the cyclization was totally regioselective. Experiments performed at room temperature in the case of 2-iodobenzoic acid and 3-iodothiophen-2-carboxylic acid showed the preferential formation of products from the 5-*exo-dig* cyclization with 2-iodobenzoic acid, while only traces were detected after 72 h with 2-iodothiophene carboxylic acid. On the other hand, reactions performed at 110 °C with the same material afforded the 6-*endo-dig* cyclization product and up to 10% of the regioisomer in the case of 2-iodobenzoic acid and only the thienopyranone in the case of 2-iodothiophene carboxylic acid. This indicates that the 5-*exo-dig* product is actually the kinetic product but is not favorable in the case of 2-iodothiophene carboxylic acid, probably due to the structure of the latter substrate. Indeed, it appears that building a five-membered cycle over another five-membered cycle is more unfavorable than building the same cycle over a six-membered cycle. Moreover, the pH of the medium has no effect on the regiochemistry of the cyclization. According to Rao and Sakamoto et al.,[14] if we consider an enyne intermediate, the regiochemistry of the cyclization may be influenced by the pH of the medium. A basic medium may lead to the 5-*exo-dig* product,

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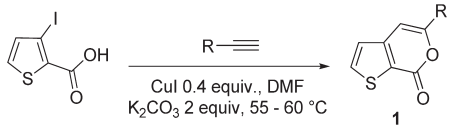
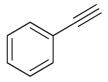
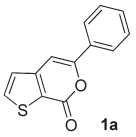
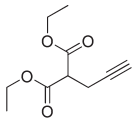
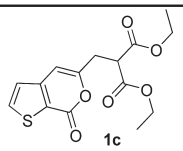
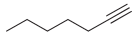
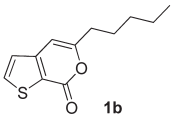
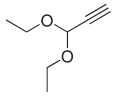
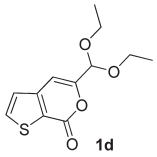
Table 1. Scope of Copper-Catalyzed Preparation of Thieno[2,3-*c*]pyran-7-one



Entry	Alkyne	Product	Yield (%)	Entry	Alkyne	Product	Yield (%)
1		 1a	65	3		 1c	68
2		 1b	49	4		 1d	59

Scheme 2. Preparation of Iodo-indole Carboxylic Acids 2a and 2b

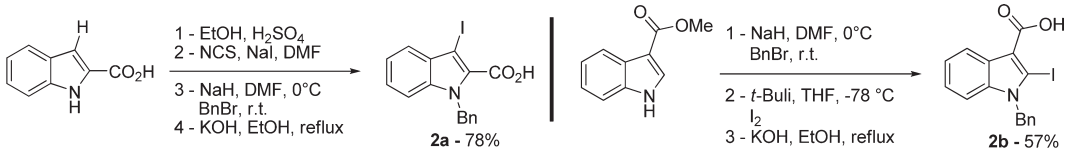
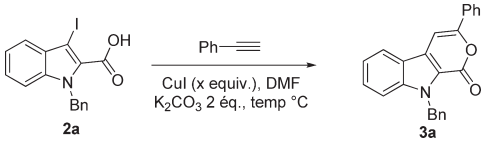


Table 2. Optimization of Indolo[2,3-*c*]pyrane-1-one Preparation



entry	CuI (equiv)	*T* (°C)	yield %
1	0.2	20	0
2	0.4	20	0
3	0.2	60	traces
4	0.4	60	traces
5	0.4	100	5
6	1	100	30
7	**1**	**120**	**40**

while an acidic medium should yield 6-*endo-dig*. In our study, we worked under basic conditions but obtained only 6-*endo-dig* cyclization. This evidence points to the crucial role of the thermodynamic control on the regiochemistry of the cyclization, instead of pH or the nature of the alkyne substituent. As previously reported,[12] the presence of the copper salt and the base are also very critical; indeed, starting materials were fully recovered after assays performed between 3-iodothiophene-2-carboxylic acid and phenylacetylene without copper or potassium carbonate.

In the case of indoles, difficulties revealed in the transformation regarding the amount of catalyst may have resulted from trapping of the copper by the nitrogen, making the metal unavailable for the transformation and thus slowing the reaction. This reactivity was greatly decreased when indole was reacted unprotected. Assays with indole **2c** (Scheme 3), obtained following the method used by Merour et al.,[15] led to full recovery of the starting material. Similar results were obtained while unsuccessfully trying to couple alkynes bearing primary, secondary, and tertiary amine function on nonaromatic and aromatic substrates.

On the other hand, Gaussian[16] was employed to optimize and visualize the 3D conformation of selected molecules presented herein. For each studied compound, a DFT calculation was performed using the B3LYP-DZVP basic set to compare *xyz* coordinates for each atom in generated compounds. From this work, we observed that the oxygens of the carboxylate group on **2a** were oriented away from the halogen (or the triple bond) with the comparisons of dihedral angles (Table 4). We consider this was also a cause of the lengthening of the reaction time and increase in temperature when compared with 2-iodobenzoic or 3-iodothiophene-2-carboxylic acid starting materials where the carboxylate function is in the same plane as iodine (or triple bond).

Although the mechanism of this reaction has not yet been fully elucidated, we propose it could take place through the formation of copper carboxylate **1** (Figure 2) followed by the oxidative insertion of the copper in the carbon iodide bond, creating a copper(III) intermediate **2**. This intermediate, which reminds of the CuTC structure used in Ullmann biaryl coupling,[17] would then allow the insertion of the alkyne followed by 6-*endo-dig*

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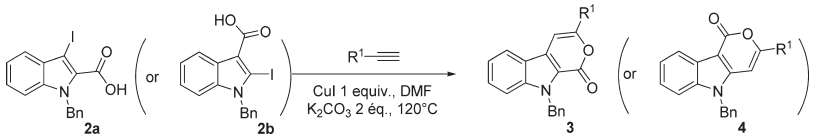
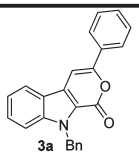
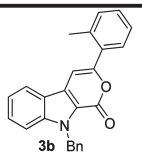
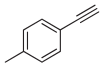
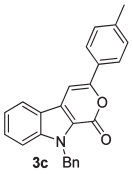
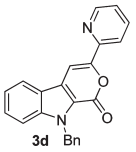
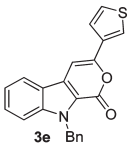
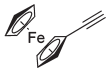
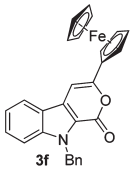
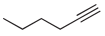
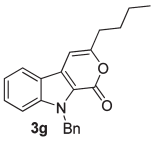
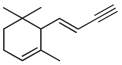
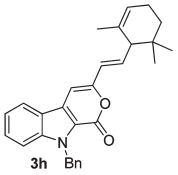
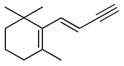
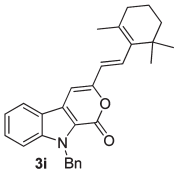
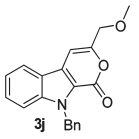
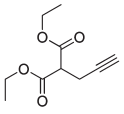
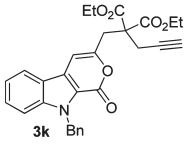
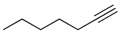
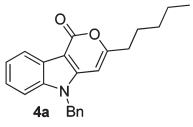
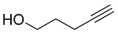
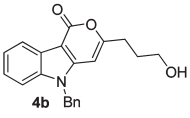
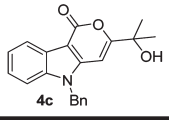
Table 3. Scope of Copper-Mediated Preparation of Indolo[2,3-*c*]pyrane-1-one and Indolo[3,2-*c*]pyrane-1-one



2a 2b 3 4

Entry	Alkyne	Product	Yield(%)	Entry	Alkyne	Product	Yield(%)
1		 **3a**	40	2		 **3b**	40
3		 **3c**	60	4		 **3d**	75
5		 **3e**	69	6		 **3f**	70
7		 **3g**	79	8		 **3h**	70
9		 **3i**	72	10		 **3j**	77
11		 **3k**	30	12		 **4a**	76
13		 **4b**	63	14		 **4c**	58

cyclization and reductive elimination. Copper(I) would be regenerated after hydrolysis of the C−Cu bond of intermediate **5** by water released after the formation of the carboxylate with potassium carbonate.

CONCLUSION

In summary, we describe a copper-mediated regioselective route to original thieno[2,3-*c*]pyrane-7-one, indolo[2,3-*c*]pyrane-1-ones, and indolo[3,2-*c*]pyrane-1-ones. The reactions were very versatile and constitute an effective methodology for the preparation of these structures from aromatic and heteroaromatic substrates containing a β-iodo-α,β-unsaturated acid moiety. We were able to prepare several variously substituted thiophene and indole derivatives in average to good yields. The reactions were mild in the case of 2-iodo-thiophenecarboxylic acid and needed high temperatures and stoichiometric amounts of copper(I) in the case of an indole starting material. This approach constitutes a cheap alternative to the expensive palladium cross-coupling generally used to access this kind of molecule and to be sure to obtain β- and γ-carbolinones at the same time.

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EXPERIMENTAL SECTION

General Procedure for the Preparation of Thieno[2,3-*c*]-pyrane-7-ones. A dry Schlenk tube equipped with a Teflon-coated magnetic stirrer was charged with 1.4 g of K_2CO_3 (10 mmol, 2 equiv) and 1.2 g of 3-iodothiophene carboxylic acid (5 mmol, 1 equiv). Anhydrous DMF (20 mL) was added, and the suspension was stirred for 15 min. The mixture was evacuated cold for 10 min and backfilled with Argon. After reaching room temperature, alkyne (10.0 mmol, 2 equiv) was added, and finally 0.384 g of CuI (2.0 mmol, 0.2 equiv) was added. The Schlenk tube was placed in an oil bath preheated at 65 °C for 4 h stirring. The temperature inside the Schlenk tube should be between 55 and 60 °C. The reaction mixture was then allowed to reach room temperature and was hydrolyzed at 0 °C with a saturated NH_4Cl aqueous solution (15 mL). Et_2O (50 mL) was added in the Schlenk tube, and the mixture was filtered over a Celite pad. The pad was washed with additional Et_2O (50 mL). The aqueous phase was removed, and the organic layer was washed several times with water (6 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The raw material obtained was purified by flash chromatography on silica gel to give the desired thieno[2,3-*c*]pyrane-7-one.

5-Phenylthieno[2,3-*c*]pyran-7(7*H*)-one (1a). Yield: 65%; gray solid. Mp: 121−123 °C. IR (KBr): 3120, 2923, 2846, 1848, 1728, 1710, 1607. ^{1}H NMR (300 MHz, $CDCl_3$): 7.12 (s, 1H), 7.24 (d, 1H, J = 5.1), 7.35−7.55 (m, 3H), 7.78−7.95 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 99.2, 123.1, 124.8, 125.5, 129.0, 130.3, 132.0, 136.9, 147.6, 156.6, 158.5. MS (70 eV, EI) m/z (%) = 228 (M^+, 100), 201 (10), 200 (100), 172 (15), 171 (100), 151 (10), 95 (30), 77 (35). HRMS (ESI): Anal. calcd for $C_{13}H_8O_2S$ (M+H) 229.0318, found 228.0317.

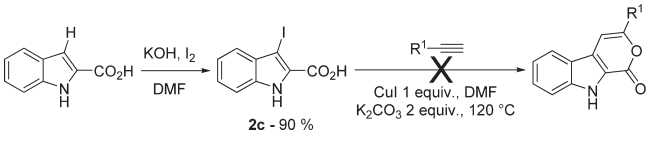
5-Pentylthieno[2,3-*c*]pyran-7(7*H*)-one (1b). Yield: 49%; light yellow gum. IR (NaCl): 3084, 2955, 2928, 2859, 1720, 1626. ^{1}H NMR (300 MHz, $CDCl_3$): 0.87 (t, 3H, J = 7.4), 1.27−1.35 (m, 4H), 1.60−1.76 (m, 2H), 2.52 (t, 2H, J = 7.4), 6.42 (s, 1H), 7.08 (d, 1H, J = 5.1), 7.76 (d, 1H, J = 5.1). ^{13}C NMR (75 MHz, $CDCl_3$): 13.9, 22.4, 26.9, 31.6, 33.5, 100.5, 122.0, 124.2, 136.7, 147.7, 159.4, 161.1. LRMS (ESI) 223 (M+H). HRMS (ESI): Anal. calcd for $C_{12}H_{14}O_2S$ (M+H) 223.0787, found 223.0789.

Diethyl 2-((7-oxothieno[2,3-*c*]pyran-5(7*H*)-yl)methyl)-malonate (1c). Yield: 68%; orange gum. IR (NaCl): 3285, 2984, 2939, 1736. ^{1}H NMR (300 MHz, $CDCl_3$): 1.18 (t, 6H, J = 7.0), 3.10 (d, 2H, J = 7.5), 3.84 (t, 1H, J = 7.5), 4.00−4.20 (m, 4H), 6.51 (s, 1H), 7.07 (d, 1H, J = 5.1), 7.77 (d, 1H, J = 5.1). ^{13}C NMR (75 MHz, $CDCl_3$): 13.9, 32.6, 49.6, 61.9, 102.4, 122.6, 124.4, 136.9, 147.0, 156.0, 158.5, 168.1. LRMS (ESI) 325 (M+H). HRMS (ESI): Anal. calcd for $C_{15}H_{16}O_6S$ (M+H) 325.0740, found 325.0753.

5-(Diethoxymethyl)thieno[2,3-*c*]pyran-7(7*H*)-one (1d). Yield: 59%; light yellow solid. Mp: 56−58 °C. IR (KBr): 3085, 2978, 2929, 2895, 1763, 1714, 1633. ^{1}H NMR (300 MHz, $CDCl_3$): 1.23 (t, 6H, J = 7.0), 3.62 (q, 2H, J = 7.5), 3.68 (q, 2H, J = 7.5), 5.24 (s, 1H), 6.90 (s, 1H), 7.17 (d, 1H, J = 5.5), 7.81 (d, 1H, J = 5.5). ^{13}C NMR (75 MHz, $CDCl_3$): 15.2, 62.5, 97.7, 101.1, 123.8, 124.9, 136.8, 146.4, 155.7, 158.1. LRMS (ESI) 255 (M+H), 277 (M+Na). HRMS (ESI): Anal. calcd for $C_{12}H_{14}O_4S$ (M+H) 255.0613, found 255.0615.

Synthesis of 1-Benzyl-3-iodo-indole-2(1*H*)-carboxylic Acid (2a). **2a** was synthesized in four steps from indole-2-carboxylate. In a round-bottomed flask fitted with a condenser and containing 20 g of indole-2(1*H*)-carboxylic acid (124 mmol, 1 equiv) are added 200 mL of absolute ethanol and a few drops of concentrated sulfuric acid. The mixture is refluxed for 24 h. The ethanol is removed under vacuum, and the residue is dissolved in 200 mL of Et_2O. The mixture is washed successively with $NaHCO_3$ (3 × 40 mL), brine (40 mL), and water (2 × 40 mL). After treatment with $MgSO_4$, the solvent was removed under vacuum. The desired ester obtained in 89% yield was pure enough for

Scheme 3. Assay of Copper-Mediated Reaction with Unprotected Indole



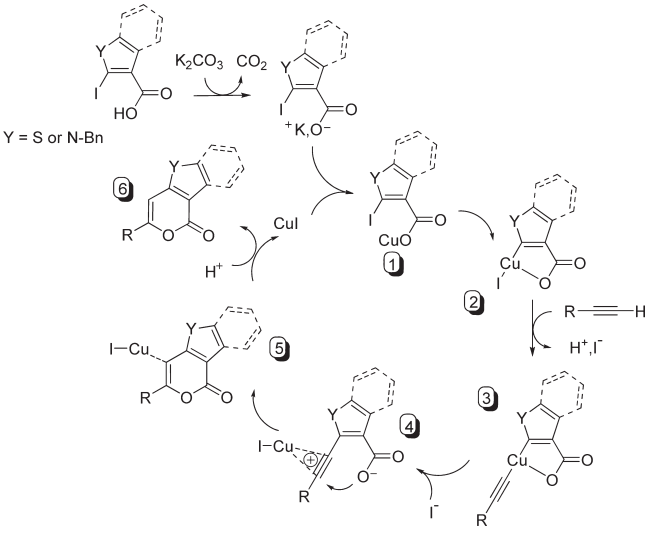
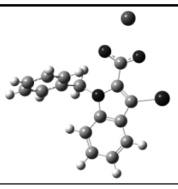
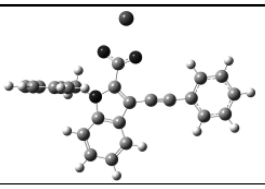
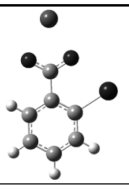
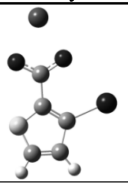


Figure 2. Proposed mechanism for the tandem coupling oxacyclization reaction.

Table 4. Comparison of Dihedral Angles of Different *β*-Iodo-*α*,*β*-unsaturated Carboxylic Acid Bearing Systems

	2a K salt	**2a** enyne K salt	K-2-iodobenzoate	K-3-iodothiophene carboxylate
				
	Dihedral angles (°)			
RCCC	-0.3464	-1.1177	0.0028	0.0000
O^1CCC	22.3455	12.0404	0.0094	-0.0068
O^2CCC	-156.4457	-167.3222	179.9921	179.9907

R: Iodine or triple bond. O^1: Oxygen near to R O^2: Oxygen far from R.

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further reaction. The ^{1}H NMR characteristics matched with those found in the literature.[18]

In a three-necked round-bottomed flask, containing 16.74 g of *N*-chlorosuccinimide (74 mmol, 1.2 equiv) and 100 mL of DMF is added 11.15 g of NaI (74 mmol, 1.2 equiv) in small portions. The mixture is stirred for 30 min at room temperature. An amount of 11.75 g of previously prepared ethyl indole-2-carboxylate (62 mmol, 1 equiv) is then added drop by drop at 0 °C, and the mixture is stirred for 1 h at room temperature. The medium is hydrolyzed by sodium thiosulfate (10% aq Sol., 60 mL). An amount of 40 mL of water is then added, and the mixture is stirred for 30 min. The precipitate formed is filtered and washed with petroleum spirit and dried under vacuum. The ethyl 3-iodoindole-2(1*H*)-carboxylate obtained in 95% yield was pure enough for further use. The analytical characteristics matched with those in the literature.[19]

In a three-necked round-bottomed flask containing 19.55 g of ethyl 3-iodoindole-2(1*H*)-carboxylate (62 mmol, 1 equiv) in 80 mL of DMF is gently added 2.73 g of sodium hydride (60% in oil, 68.2 mmol, 1.1 equiv) at 0 °C. After the end of evolution of hydrogen, 9.39 mL of benzylbromide (80.6 mmol, 1.3 equiv) is added drop by drop at 0 °C, and the mixture is left for stirring for 2 h at room temperature. The medium is hydrolyzed with 100 mL of water and extracted with ethyl acetate (2 × 30 mL). After treatment of the organic phase with $MgSO_4$, the solvent is evaporated under vacuum. Ethyl 1-benzyl-3-iodo-indole-2(1*H*)-carboxylate was obtained sufficiently pure for further reaction.

Ethyl-1-benzyl-3-iodo-indole-2(1*H*)-carboxylate. Yield: 97%; light yellow solid. Mp: 139−139 °C. IR (KBr): 3062, 2980, 1701, 1610. ^{1}H NMR (300 MHz, $CDCl_3$): 1.43 (t, 3H, *J* = 7.1), 4.46 (q, 2H, *J* = 7.1), 5.86 (s, 2H), 7.20−7.50 (m, 8H), 7.64 (d, 1H, *J* = 7.9). MS (70 eV, EI) *m*/*z* (%) = 405 ($M^{\bullet+}$, 65), 360 (10), 269 (15), 248 (5), 232 (20), 205 (20), 204 (40), 91 (100). HRMS (ESI): Anal. calcd for $C_{18}H_{16}INO_2$ (M+H) 405.0226, found 405.0228.

In a round-bottomed flask is placed 25.11 g of ethyl 1-benzyl-3-iodo-indole-2(1*H*)-carboxylate (1 equiv, 62 mmol), 80 mL of ethanol, and 76.5 mL of KOH (12% aq. sol., 3 equiv). The mixture is refluxed for 24 h. Ethanol is removed, and the residue is acidified with HCl 1 M to pH 2. The aqueous phase is extracted with Et_2O (2 × 30 mL). The organic phase is washed with brine (20 mL) and water (20 mL), treated with $MgSO_4$, and evaporated under vacuum. The 1-benzyl-3-iodo-indole-2(1*H*)-carboxylic acid (**2a**) is obtained pure after recrystallization in methylene chloride.

1-Benzyl-3-iodo-indole-2(1*H*)-carboxylic acid (2a). Yield: 96%; light yellow solid. Mp: 202−203 °C. IR (KBr): 3200−2500, 3028, 1672, 1608, 1276, 742, 724. ^{1}H NMR(300 MHz, $CDCl_3$): 5.72 (s, 2H), 6.90 (dd, 2H, *J* = 1.2), 7.00−7.12 (m, 4H), 7.13−7.22 (m, 2H), 7.44 (d, 1H, *J* = 8.1). ^{13}C NMR (75 MHz, $CDCl_3$): 48.9, 67.6, 111.0, 121.5, 123.8, 126.0, 126.2, 127.1, 128.4, 129.2, 130.4, 138.0, 138.7, 162.7. MS (70 eV, EI) *m*/*z* (%) = 377 ($M^{\bullet+}$, 29), 127 (10), 91 (100), 77 (5). HRMS (ESI): Anal. calcd for $C_{16}H_{12}INO_2$ (M+H) 377.9986, found 377.9990.

Synthesis of 1-Benzyl-3-iodo-indole-2(1*H*)-carboxylic acid (2b). **2b** was synthesized in three steps from methyl indole-3(1*H*)-carboxylate. In a three-necked round-bottomed flask containing 19.53 g of methyl indole-3(1*H*)-carboxylate (111.5 mmol, 1 equiv) in 80 mL of DMF is gently added 4.90 g of sodium hydride (60% in oil, 122.65 mmol, 1.1 equiv) at 0 °C. After the end of evolution of hydrogen, 17.24 mL of benzylbromide (144.95 mmol, 1.3 equiv) is added drop by drop at 0 °C, and the mixture is left for stirring for 2 h at room temperature. The medium is hydrolyzed with 100 mL of water and extracted with ethyl acetate (2 × 75 mL). After treatment of the organic phase with $MgSO_4$, the solvent is evaporated under vacuum. Ethyl 1-benzyl-2-iodo-indole-3(1*H*)-carboxylate obtained in 64% was sufficiently pure for further reaction. The analytical characteristics matched with those found in the literature.[20]

In a two-necked round-bottomed flask is placed 16.44 g of methyl indole-3-carboxylate (1.0 equiv, 62 mmol) dissolved in 50 mL of THF. The solution is brought to −78 °C before the addition drop by drop of 47 mL of *t*BuLi (1.2 equiv, 1.6 M in hexanes). The temperature is then set to −50 °C, and 17.32 g of iodine is rapidly added. The mixture is allowed to reach room temperature and stirred for 2 h. The medium is then hydrolyzed with a 10% aqueous solution of sodium thiosulfate until discoloration. The organic phase is isolated and washed with water (40 mL). After treatment with $MgSO_4$, the organic phase is evaporated. The methyl 2-iodo-indole-3(1*H*)-carboxylate is obtained pure after recrystallization in methylene chloride.

Methyl-2-iodo-indole-3(1*H*)-carboxylate. Yield: 96%; light yellow solid. Mp: 96−98 °C. IR (KBr): 3030, 2950, 1697, 1492, 1451, 1173. ^{1}H NMR (300 MHz, $CDCl_3$): 4.00 (s, 3H), 5.55 (s, 2H), 7.00−7.08 (m, 2H), 7.12−7.34 (m, 6H), 8.13−8.22 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 51.4, 60.5, 95.3, 110.7, 112.1, 121.8, 122.3, 123.4, 126.4, 127.2, 127.7, 127.9, 129.0, 136.0, 138.5. LRMS (ESI) 392 (M+H). HRMS (ESI): Anal. calcd for $C_{10}H_8INO_2$ (M+H) 392.0069, found 392.0069.

In a round-bottomed flask is placed 20.0 g of methyl 1-benzyl-2-iodo-indole-3(1*H*)-carboxylate (1 equiv, 51.1 mmol), 80 mL of ethanol, and 63.1 mL of KOH (12% aq. sol., 3 equiv). The mixture is refluxed for 24 h. Ethanol is removed, and the residue is acidified with HCl 1 M to pH 2. The aqueous phase is extracted with Et_2O (2 × 30 mL). The organic phase is washed with brine (20 mL) and water (20 mL), treated with $MgSO_4$, and evaporated under vacuum. 1-Benzyl-3-iodo-indole-2(1*H*)-carboxylic acid (**2a**) is obtained pure after recrystallization in methylene chloride.

1-Benzyl-2-iodoindole-3(1*H*)-carboxylic Acid (2b). Yield: 93%; Light yellow solid. Mp: 226−228 °C. IR (KBr): 3200−2300, 1662, 1495, 1451, 1282, 1186. ^{1}H NMR (300 MHz, $CDCl_3$): 5.37 (s, 2H), 6.84−7.15 (m, 8H), 8.03−8.10 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 50.8, 94.9, 110.2, 112.1, 121.5, 121.6, 122.7, 126.0, 127.3, 127.6, 128.4, 135.7, 138.0, 165.7. MS (70 eV, EI) *m*/*z* (%) = 378 ($M^{\bullet+}$, 29), 360 (15), 204 (10), 127 (10), 91 (100), 77 (5). HRMS (ESI): Anal. calcd for $C_{16}H_{12}INO_2$ (M+H) 377.9986, found 377.9995.

General Procedure for the Preparation of Indolo Pyrane-1-one. A dry Schlenk tube equipped with a Teflon-coated magnetic stirrer was charged with 552 mg of K_2CO_3 (4 mmol, 2 equiv) and 750 mg of iodoindole carboxylic acid (2 mmol, 1 equiv). Anhydrous DMF (15 mL) was added, and the suspension was stirred for 15 min. The mixture was evacuated cold for 10 min and backfilled with Argon. After reaching room temperature, alkyne (4.0 mmol, 2 equiv) was added and finally 381 mg of CuI (2.0 mmol, 1 equiv). The Schlenk tube was placed in an oil bath preheated at 126 °C for 48 h stirring. The temperature inside the tube should be between 120 and 123 °C. The reaction mixture was then allowed to reach room temperature and was hydrolyzed at 0 °C with a saturated NH_4Cl aquaeous solution (15 mL). Et_2O (50 mL) was added in the Schlenk tube, and the mixture was filtered over a Celite pad. The pad was washed with additional Et_2O (50 mL). The aqueous layer was removed, and the organic layer was washed several times with water (6 × 15 mL). The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The raw material obtained was purified by flash chromatography on silica gel to give the desired indolopyranones. In the case of product **3j**, 5 equiv of methoxypropargylic alkyne was used. In the case of products **3g** and **4a**, 10 equiv of hexyne and heptyne was used.

9-Benzyl-3-phenylindolo[2,3-*c*]pyrane-1(9*H*)-one (3a). Yield: 40%; yellow solid. Mp: 160−161 °C. IR (KBr): 3025, 2939, 1716, 1616, 1605, 1526. ^{1}H NMR (300 MHz, $CDCl_3$): 5.97 (s, 2H), 7.20−7.53 (m, 12H), 7.92−8.00 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 48.2, 97.3, 100.1, 111.6, 121.0, 121.4, 121.8, 125.1, 126.5, 127.2, 127.7, 128.3, 128.8, 129.0, 129.3, 132.7, 137.5, 141.2, 153.0, 156.8. MS (70 eV, EI) *m*/*z* (%) = 351 ($M^{\bullet+}$, 100), 260 (59), 232 (23), 204 (18), 105 (12), 91, 45, 77 (14). HRMS (ESI): Anal. calcd for $C_{24}H_{17}NO_2$ (M+H) 352.1332, found 352.1322.

9-Benzyl-3-*o*-tolylindolo[2,3-*c*]pyrane-1(9*H*)-one (3b). Yield: 40%; brown gum. IR (NaCl): 3063, 3031, 1714, 1544. ^{1}H NMR (300 MHz, $CDCl_3$): 2.61 (s, 3H), 5.33 (s, 2H), 7.13−7.37 (m, 11H), 7.42 (s, 1H), 7.52−7.57 (m, 1H), 7.82−7.91 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 21.1, 50.5, 87.1, 90.3, 98.2, 110.2, 120.4, 120.7, 123.0, 124.1, 125.7, 127.1, 127.6, 128.0, 129.0, 129.5, 131.5, 136.0, 136.7, 139.6. LRMS (ESI) 366 (M+H). HRMS (ESI): Anal. calcd for $C_{25}H_{19}NO_2$ (M+H) 365.1416, found 365.1419.

9-Benzyl-3-*p*-tolylindolo[2,3-*c*]pyrane-1(9*H*)-one (3c). Yield: 60%; yellow solid. Mp: 184−185 °C. IR (KBr): 3087, 3061, 3032, 1696, 1615, 1515. ^{1}H NMR (300 MHz, $CDCl_3$): 2.43 (s, 3H), 5.97 (s, 2H), 7.22−7.33 (m, 8H), 7.38 (s, 1H), 7.46−7.54 (m, 2H), 7.83 (d, 2H, J = 8.2), 7.98 (d, 1H, J = 8.0). ^{13}C NMR (75 MHz, $CDCl_3$): 21.5, 48.2, 96.6, 111.6, 120.8, 121.2, 121.8, 125.0, 126.7, 127.2, 127.6, 128.2, 128.8, 129.6, 129.9, 137.5, 139.5, 141.1, 153.2, 156.9. MS (70 eV, EI) m/z (%) = 365 ($M^{\bullet+}$, 100), 274 (63), 246 (21), 218 (27), 119 (12), 91 (44), 65 (12). HRMS (ESI): Anal. Calcd for $C_{25}H_{19}NO_2$ (M+H) 366.1489, found 366.1485.

9-Benzyl-3-(pyridin-2-yl)indolo[2,3-*c*]pyrane-1(9*H*)-one (3d). Yield: 75%; yellow solid. Mp: 183−184 °C. IR (KBr): 3033, 1717, 1616, 1582, 1526. ^{1}H NMR (300 MHz, $CDCl_3$): 5.98 (s, 2H), 7.23−7.35 (m, 7H), 7.48−7.51 (m, 2H), 7.83 (td, 1H, J = 7.7,1.7), 9.90−8.10 (m, 2H), 8.16 (s, 1H), 8.68 (dq, 1H, J = 4.7,0.8). ^{13}C NMR (75 MHz, $CDCl_3$): 48.2, 99.7, 111.6, 119.8, 121.7, 121.8, 122.1, 123.6, 126.3, 127.2, 127.7, 128.4, 128.8, 137.4, 141.2, 149.5, 150.0, 151.3, 156.4. MS (70 eV, EI) m/z (%) = 352 ($M^{\bullet+}$, 100), 261 (51), 233 (26), 204 (10), 106 (10), 91 (54), 78 (19). HRMS (ESI): Anal. calcd for $C_{23}H_{16}N_2O_2$ (M+H) 353.1285, found 353.1273.

9-Benzyl-3-(thiophen-3-yl)indolo[2,3-*c*]pyrane-1(9*H*)-one (3e). Yield: 69%; yellow solid. Mp: 177−179 °C. IR (KBr): 3102, 3032, 2932, 1693, 1612. ^{1}H NMR (300 MHz, $CDCl_3$): 5.91 (s, 2H), 7.19 (s, 1H), 7.24−7.32 (m, 6H), 7.39 (dd, 1H, J = 5.1, 3.0), 7.45−7.50 (m, 3H), 7.82 (dd, 1H, J = 3.0, 1.1), 7.92 (d, 1H, J = 8.0). ^{13}C NMR (75 MHz, $CDCl_3$): 48.1, 96.9, 111.5, 120.5, 121.2, 121.6, 121.7, 122.7, 124.3, 126.4, 126.8, 127.2, 127.6, 128.2, 128.7, 134.8, 137.5, 141.0, 149.8, 156.5. MS (70 eV, EI) m/z (%) = 357 ($M^{\bullet+}$, 92), 267 (18), 266 (100), 238 (34), 210 (11), 111 (24), 91 (50), 65 (12). HRMS (ESI): Anal. calcd for $C_{22}H_{15}NO_2S$ (M+H) 358.0896, found 358.0887.

9-Benzyl-3-(ferrocenyl)indolo[2,3-*c*]pyrane-1(9*H*)-one (3f). Yield: 70%; orange solid. Mp: 230−232 °C. IR (KBr): 3084, 3031, 1700, 1617, 1606. ^{1}H NMR (300 MHz, $CDCl_3$): 4.12 (s, 5H), 4.34 (s, 2H), 4.77 (s, 2H), 5.86 (s, 2H), 6.93 (s, 1H), 7.21 (s, 6H), 7.39 (s, 2H), 7.86 (d, 1H, J = 8.0). ^{13}C NMR (75 MHz, $CDCl_3$): 47.9, 65.9, 69.7, 77.82, 95.1, 111.3, 119.8, 120.9, 121.1, 121.7, 126.9, 127.1, 127.4, 128.1, 128.6, 137.5, 141.0, 155.0, 157.0. MS (70 eV, EI) m/z (%) = 459 ($M^{\bullet+}$, 100), 368 (30), 340 (14), 274 (24), 91 (14). HRMS (ESI): Anal. calcd for $C_{28}H_{21}FeNO_2$ (M+H) 460.0995, found 460.0900.

9-Benzyl-3-butylindolo[2,3-*c*]pyrane-1(9*H*)-one (3g). Yield: 79%; orange solid. Mp: 90−91 °C. IR (KBr): 3079, 3025, 1700, 1624, 1532. ^{1}H NMR (300 MHz, $CDCl_3$): 0.98 (t, 3H, J = 7.3), 1.44 (sext, 2H, J = 7.4), 1.76 (q, 2H, J = 7.8), 2.65 (t, 2H, J = 7.5), 5.93 (s, 2H), 6.72 (s, 1H), 7.10−7.31 (m, 6H), 7.41−7.48 (m, 2H), 7.88 (d, 1H, J = 8.0). ^{13}C NMR (75 MHz, $CDCl_3$): 13.9, 22.3, 29.6, 33.4, 48.0, 98.2, 111.4, 120.2, 120.9, 121.3, 121.7, 126.5, 127.2, 127.6, 128.0, 128.7, 137.7, 141.0, 157.5, 157.8. LRMS (ESI) 332 (M+H), 370 (M+Na). HRMS (ESI): Anal. calcd for $C_{22}H_{21}NO_2$ (M+H) 332.1645, found 332.1650.

(*E*)-9-Benzyl-3-[2-(2,6,6-trimethylcyclohex-2-enyl)vinyl]-indolo[2,3-*c*]pyrane-1(9*H*)-one (3h). Yield: 70%; orange solid. Mp: 86−88 °C. IR (KBr): 3060, 3031, 1710, 1640, 1593. ^{1}H NMR (300 MHz, $CDCl_3$): 0.92 (s, 3H), 0.97 (s, 3H), 1.20−1.28 (m, 1H), 1.49−1.60 (m, 1H), 1.65 (d, 3H, J = 1.3), 2.02−2.12 (m, 2H), 2.30 (d, J = 9.5, 1H), 5.50 (bs, 1H), 5.92 (s, 2H), 6.12 (d, 1H, J = 15.4), 6.46 (dd, 1H, J = 15.4/9.5), 6.76 (s, 1H), 7.24−7.30 (m, 6H), 7.45−7.53 (m, 2H), 7.87 (d, 1H, J = 8.0). ^{13}C NMR (75 MHz, $CDCl_3$): 23.2, 23.2, 27.1, 28.1, 31.4, 32.8, 48.1, 54.8, 99.3, 111.5, 120.8, 121.2, 121.6, 121.8, 121.9, 123.3, 126.6, 127.2, 127.6, 128.1, 128.8, 133.3, 135.8, 137.6, 141.0, 152.0, 156.9. MS (70 eV, EI) m/z (%) = 423 ($M^{\bullet+}$, 41), 368 (12), 367 (40), 331 (24), 301 (20), 289 (10), 288 (39), 91 (100). HRMS (ESI): Anal. calcd for $C_{29}H_{29}NO_2$ (M+H) 424.2271, found 424.2279.

(*E*)-9-Benzyl-3-[2-(2,6,6-trimethylcyclohex-1-enyl)vinyl]-indolo[2,3-*c*]pyrane-1(9*H*)-one (3i). Yield: 72%; dark brown solid. Mp: 153−155 °C. IR (KBr): 3057, 3015, 1700, 1565. ^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (s, 6H), 1.48−1.53 (m, 2H), 1.62−1.68 (m, 2H), 1.81 (s, 3H), 2.07 (t, 2H, J = 5.8), 5.92 (s, 2H), 6.13 (d, 1H, J = 15.9), 6,77 (s, 1H), 7.02 (d, 1H, J = 15.9), 7.25 (s, 6H), 7.42−7.50 (m, 2H), 7.87 (d, 1H, J = 7.9). ^{13}C NMR (75 MHz, $CDCl_3$): 19.3, 21.9, 29.1, 33.3, 34.4, 39.8, 48.1, 99.6, 111.5, 120.7, 121.2, 121.6, 121.8, 124.2, 126.7, 127.2, 127.6, 128.1, 128.7, 131.0, 131.5, 137.3, 137.6, 141.0, 152.4, 156.8. LRMS (ESI) 424 (M+H), 446 (M+Na). HRMS (ESI): Anal. calcd for $C_{29}H_{29}NO_2$ (M+H) 424.2271, found 424.2275.

9-Benzyl-3-methoxyindolo[2,3-*c*]pyrane-1(9*H*)-one (3j). Yield: 77%; colorless solid. Mp: 121−122 °C. IR (KBr): 3069, 1698, 1626, 1615, 1212, 1084. ^{1}H NMR (300 MHz, $CDCl_3$): 3.50 (s, 3H), 4.36 (d, 2H, J = 0.7), 5.90 (s, 2H), 7.00 (s, 1H), 7.20−7.32 (m, 6H), 7.45−7.50 (m, 2H), 7.90 (d, 1H, J = 8.0). ^{13}C NMR (75 MHz, $CDCl_3$): 48.0, 58.9, 71.0, 99.9, 111.5, 120.7, 121.3, 121.4, 121.7, 125.4, 127.1, 127.6, 128.1, 128.7, 137.4, 140.8, 152.3, 156.9. MS (70 eV, EI) m/z (%) = 319 ($M^{\bullet+}$, 68), 288 (27), 260 (8), 168 (11), 91 (100). HRMS (ESI): Anal. calcd for $C_{20}H_{17}NO_3$ (M+H) 320.1281, found 320.1276.

Diethyl-2-[(9-benzyl-1,9-dihydroindolo[2,3-*c*]pyrane-3-yl)-methyl]-2-(prop-2-ynyl)malonate (3k). Yield: 30%; white solid. Mp: 165−166 °C. IR (KBr): 3256, 1735, 1709, 1628. ^{1}H NMR (300 MHz, $CDCl_3$): 1.31 (t, 6H, J = 7.1), 2.15 (t, 1H, J = 2.5), 2.87 (d, 2H, J = 2.5), 3.44 (s, 2H), 4.25−4.37 (m, 4H), 5.89 (s, 2H), 6.90 (s, 1H), 7.01−7.34 (m, 6H), 7.40−7.50 (m, 2H), 7.89 (d, 1H, J = 8.0). ^{13}C NMR (75 MHz, $CDCl_3$): 14.1, 22.9, 36.3, 48.1, 56.3, 62.3, 72.2, 79.0, 102.0, 111.5, 121.2, 121.3, 121.8, 125.6, 126.4, 127.1, 127.6, 128.1, 128.8, 137.5, 140.9, 151.2, 156.7, 169.3. MS (70 eV, EI) m/z (%) = 485 ($M^{\bullet+}$, 19), 441 (40), 368 (17), 367 (33), 294 (11), 288 (17), 91 (100). HRMS (ESI): Anal. calcd for $C_{29}H_{27}NO_6$ (M+H) 486.1911, found 486.1914.

5-Benzyl-3-pentylindolo[3,2-*c*]pyrane-1(5*H*)-one (4a). Yield: 76%; colorless solid. Mp: 123−125 °C. IR (KBr): 3155, 3034−2872, 1793, 1713, 1626, 1608. ^{1}H NMR (300 MHz, $CDCl_3$): 0.88 (t, 3H, J = 6.4), 1.27−1.35 (m, 4H), 1.65−1.80 (m, 2H), 2.57 (t, 2H, J = 7.9), 5.38 (s, 2H), 6.29 (s, 1H), 7.03−7.12 (m, 3H), 7.27−7.35 (m, 6H), 7.97−8.03 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.1, 22.5, 27.1, 31.3, 34.6, 47.7, 92.7, 99.6, 109.9, 121.4, 122.8, 124.5, 126.3, 128.2, 129.2, 135.7, 138.4, 146.7, 160.2, 164.5. LRMS (ESI) 346 (M+H). HRMS (ESI): Anal. calcd for $C_{23}H_{23}NO_2$ (M+H) 346.1729, found 346.1736.

5-Benzyl-3-(3-hydroxypropyl)indolo[3,2-*c*]pyrane-1(5H)-one (4b). Yield: 63%; orange solid. Mp: 149−151 °C. IR (KBr): 3413, 2930−2860, 1694, 1559. ^{1}H NMR (300 MHz, $CDCl_3$): 1.71 (bs, 1H), 1.92−2.05 (m, 2H), 2.73 (t, 2H, J = 7.3), 3.71 (t, 2H, J = 6.1), 5.38 (s, 2H), 6.36 (s, 1H), 7.03−7.10 (m, 2H), 7.23−7.39 (m, 6H), 8.18−8.26 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 30.3, 31.0, 47.3, 61.7, 93.2, 99.7, 110.0, 121.4, 122.9, 124.5, 124.7, 126.4, 128.2, 129.2, 135.7, 138.5, 146.6, 160.2, 163.6. LRMS (ESI) 333 (M+H), 356 (M+Na), 372 (M+K). HRMS (ESI): Anal. calcd for $C_{21}H_{19}NO_3$ (M+H) 333.1365, found 333.1367.

5-Benzyl-3-(2-hydroxypropan-2-yl)indolo[3,2-*c*]pyrane-1(5*H*)-one (4c). Yield: 58%; colorless solid. Mp: 156−158 °C. IR (KBr): 3590, 3449, 3110−2920, 1698, 1682. ^{1}H NMR (300 MHz, $CDCl_3$): 1.63 (s, 6H), 3.07 (bs, 1H), 5.29 (s, 2H), 6.80 (s, 1H), 7.01−7.07 (m, 2H), 7.25−7.37 (m, 6H), 8.19−8.25 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 28.7, 47.1, 71.8, 89.7, 99.4, 110.0, 121.3, 122.8, 124.2, 124.7, 126.3, 128.1, 129.1, 135.5, 138.4, 146.5, 159.6, 168.4. LRMS (ESI) 333 (M+H). HRMS (ESI): Anal. calcd for $C_{21}H_{19}NO_3$ (M+H) 333.1365, found 333.1361.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H NMR and ^{13}C NMR of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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