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Copper(I)-Mediated and Microwave-Assisted $C_{aryl}-O_{carboxylic}$ Coupling: Synthesis of Benzopyranones and Isolamellarin Alkaloids

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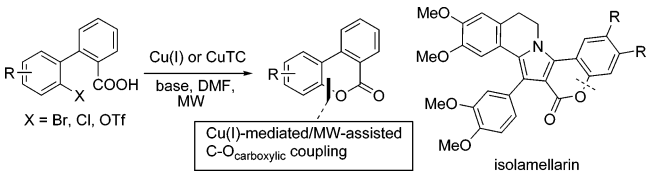

A simple and highly effective $C-O_{carboxylic}$ coupling reaction catalyzed by copper(I) salts has been developed to synthesize benzopyranones. The reaction of various 2-halobiarylcarboxylic acids was examined using microwave irradiation. A new class of pyrroloisoquinoline alkaloid, isolamellarin, was synthesized based on the annulation of dihydroisoquinoline with aryl pyruvates under basic condition and Cu-mediated/MW-assisted $C-O_{carboxylic}$ lactonization.

During the past 10 years, many research groups have developed Cu-mediated reactions to form C−O bonds using various copper salts in catalytic and/or stoichiometric amounts.[1] The classical Ullmann reaction[2] requires harsh conditions, high temperature, strong base, and long reaction times in high polar solvents with stoichiometric quantities of copper. Buchwald has reported $C_{aryl}-O$ bond formation using the modern Ullmann reaction.[3] Various copper(I) salts such as copper iodide (CuI), copper bromide (CuBr), and copper chloride (CuCl) as well as copper(I) thiophene carboxylate (CuTC) have been used for C−O bond formation. The latter has been developed and used in the Liebeskind group.[4] Recently, CuTC has been used in asymmetric synthesis and macrocyclic molecules.[5]

Since their isolation by Faulkner in 1985,[6] the lamellarin alkaloids have attracted much attention from various research groups[7] including our laboratory.[8] The lamellarins, in particular lamellarin D **4**, exhibit various biological activities and thus may be developed into potential drug candidates for treatment of some forms of cancer and AIDS.[9] In addition, the benzopyranone substructure is one of the most important heterocycles because it has been found in several natural compounds. Not only the lamellarins but also the benzopyranones represent components of pharmacologically active compounds including gilvocarcin V **1**,[10] alternariol **2**,[11] and coumestrol **3**[12] (Figure 1). Various synthetic methodologies have been devised for the synthesis of benzopyranone derivatives.[13]

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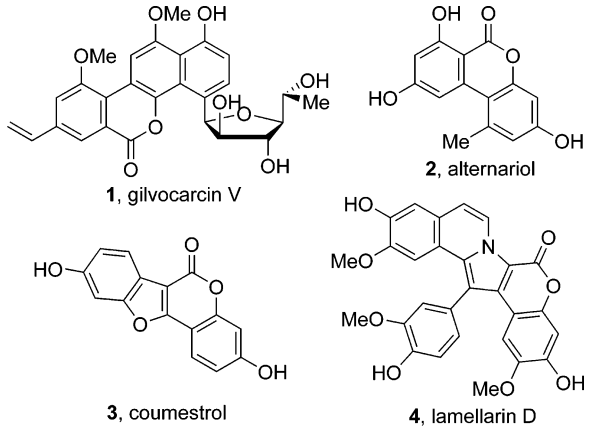

FIGURE 1. Biologically active compounds (**1**−**4**) containing aromatic lactone.

Herein, we report a new efficient synthesis of benzopyranones and isolamellarin alkaloids, isomeric with the marine lamellarin alkaloids. Our strategy is based on the Cu(I)-mediated and microwave-assisted[14] intramolecular $C_{aryl}-O_{carboxylate}$ lactone bond formation under ligand- and base-free conditions. A series of copper(I) salts including CuI, CuBr, CuCl, and CuTC as well as ligands and bases were examined for the model study. We note that the successful preparation of benzopyranones, to the best of our knowledge, is the first metal-catalyzed coupling of $C_{aryl}-O_{carboxylate}$ lactone bond formation using a combination of Cu(I)-mediated and microwave-assisted reactions. We have extended our work to synthesize various lactone systems.

In a preliminary investigation, the synthesis of dibenzo[*b*,*d*]-pyran-6-one **5a** was studied. Synthesis of the required 2-halobiarylcarboxylic acid **6** was prepared by the Suzuki cross-coupling reaction between the iodoaryl carboxylate esters and 2-haloarylboronic acids to form the C−C bond of the biaryl compounds **7**. The reaction involved the use of $Pd(PPh_3)_4$ as a catalyst and 10% Na_2CO_3 in solvent mixtures of toluene and EtOH.[15] To obtain the hydrolyzed products **6**, compounds **7** were saponified using potassium hydroxide as a base in methanol. The reaction was quenched with 2 N hydrochloric acid, and compounds **6** were obtained in good to excellent yields (89−96% yield).

Lactonization was carried out in DMF and/or solvent mixtures of DMF either with EtOH or water using a series of copper(I) salts under microwave irradiation. Among the various copper salts examined, CuTC provided the desired product **5a** in the best yields (Table 1, entries 7 and 8) using microwave irradiation with ligand- and base-free conditions. Our endeavor to use a single solvent, either EtOH or water, failed. However, the yields were moderate when mixtures of DMF/EtOH or DMF/water were used as solvents. This $C-O_{carboxylic}$ bond formation represents the first reported copper-mediated lactonization. However, using CuI gave the lowest yields as shown in Table 1, and stoichiometric amounts of copper salts (2 equiv) were necessary.

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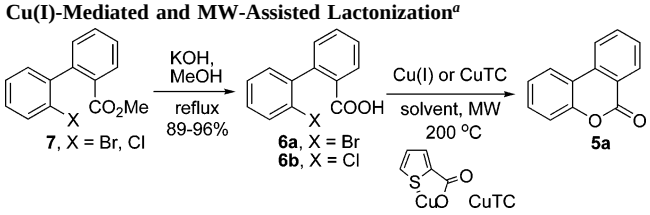
TABLE 1. Synthesis of Dibenzo[*b*,*d*]pyran-6-one 5a Using Cu(I)-Mediated and MW-Assisted Lactonization[a]



entry	acid	Cu(I)	solvent	yield (%)
1	**6a**	CuI	DMF	58
2	**6b**	CuI	DMF	53
3	**6a**	CuBr	DMF	88
4	**6b**	CuBr	DMF	84
5	**6a**	CuCl	DMF	65
6	**6b**	CuCl	DMF	81
7	**6a**	CuTC	DMF	94
8	**6b**	CuTC	DMF	97

[a] Unless otherwise noted, the reactions were performed in a 10 mL microwave vessel: compound **6** (0.2 mmol), Cu(I) salts (0.4 mmol) in DMF (3 mL), 200 °C, 20 min.

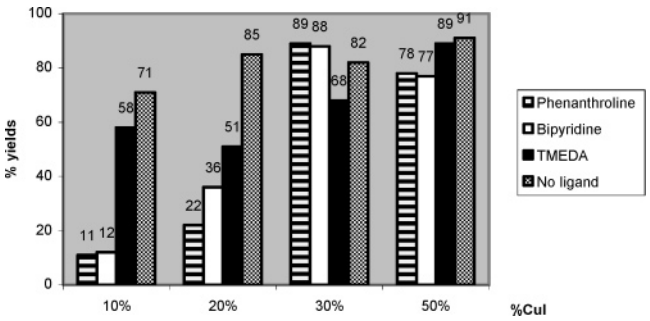


FIGURE 2. Ligands and differing amounts of CuI for the lactonization. MW heating conditions: 2-chlorobiphenylcarboxylic acid **6b** (0.2 mmol), Cs_2CO_3 (0.3 mmol), DMF, 200 °C, 20 min.

We next turned our attention to investigate the reaction conditions which may require only catalytic amount of Cu(I) salts for lactonization. CuI was used to study the Cu-catalyzed/microwave-assisted lactonization of biarylcarboxylic acid **6b** by varying the type and amount of ligands. A set of bidentate ligands including *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), bipyridine (Bip), and phenanthroline (Phen) was examined together with different substoichiometric amounts (10−50 mol %) of CuI as catalyst and Cs_2CO_3 as base in the three-component reaction in DMF using microwave irradiation. The effectiveness of several ligands was evaluated by comparing the ratio of CuI. However, no ligands were found to promote lactonization. The most effective condition was found to be 50 mol % of CuI without ligand (Figure 2, 91% yield).

Based on the above observations, we then examined the best conditions with various bases using 50 mol % of CuI under the optimized conditions. The most effective base for lactonization was found to be Na_2CO_3, which gave the best yield (Table 2, entry 2). The yield dramatically decreased without base under substoichiometric lactonization conditions.

To extend the scope of this methodology toward the synthesis of benzopyranone derivatives, the reaction of several biarylcarboxylic acids was studied under substoichiometric conditions using 50 mol % of CuI and Na_2CO_3 as base (method B). We also examined the lactonization using CuTC (method A) which gave the best result in stoichiometric amounts to compare Cu-mediated lactonization with Cu-catalyzed lactonization.

TABLE 2. Base Screening for the Lactonization[a]

entry	base	yield (%)
1	NaOAc	93
2	Na_2CO_3	99
3	K_2CO_3	92
4	Cs_2CO_3	91
5	no base	43

[a] MW heating conditions: 2-chlorobiphenylcarboxylic acid **6b** (0.2 mmol), 50 mol % of CuI, base (0.3 mmol), DMF, 200 °C, 20 min.

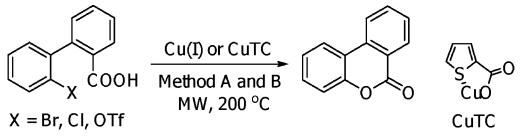
Benzopyranones **5a**−**d** were obtained in good to excellent yields from all biarylcarboxylic acids (Table 3, entries 1−6). Surprisingly, microwave irradiation provided powerful energy for the CuTC-mediated lactonization of 2-halophenylindole carboxylic acids to give indolactone **5e**,**f** in good to excellent yields. In contrast, using conventional heating under CuTC-mediated conditions[16] or CuI-mediated catalytic conditions using microwave irradiation (method B), the lactonization either proceeded in poor yield or resulted in no desired product (Table 3, entries 7−10). Under these basic and substoichiometric conditions, adducts from decarboxylation were obtained as major products. Coumestan **5g** was also obtained in good yield using CuTC-mediated lactonization from 2-(2-bromophenyl)benzofuran-3-carboxylic acid.[17] However, treatment of this acid under substoichiometric conditions afforded lactone **5g** in poor yield (Table 3, entry 11). The lactonization of 2-haloaryl aliphatic acids failed using either method, and oxidative decarboxylation adducts were observed (Table 3, entries 12−14).

Based on these results, the versatility of the procedure was illustrated, and it is shown that copper-mediated $C_{aryl}-O_{carboxylic}$ coupling lactonization reactions of dibenzopyranone derivatives work very well under both stoichiometric/base-free and substoichimetric/basic conditions from biarylcarboxylic acids. Indolecarboxylic acids and benzofurancarboxylic acids also gave lactones in good yields from stoichiometric/base-free conditions; however, the yield was decreased under substoichimetric/basic conditions. Both conditions failed to give the lactones from the 2-haloarylaliphatic acids.

Having successfully developed a route for the synthesis of benzopyranones, we then applied the above approach to the synthesis of isolamellarins **12**. In order to study the effect of substitution on the biological activity of the lamellarins and other closely related compounds, we have initiated synthetic studies for isolamellarin **12** where the α-carboxylic group and the *β*-aryl groups are transposed.

The synthesis of isolamellarin with a more complex oxygenation pattern in the lactone ring as normally found in natural lamellarin alkaloids was then studied as shown in Scheme 1. Toward this end, our first target was the isolamellarin **12a**, isomeric with lamellarin G trimethyl ether.[8e] The condensation of **8** with α-chloro-3-(4,5-dimethoxyphenyl) pyruvate[18] **9a** in the presence of K_2CO_3 in acetonitrile afforded pyrrolo[2,1-*a*]-isoquinoline carboxylate **10a** in moderate yield (49%). The reaction presumably involves the intramolecular reaction of the enamine derived from the isoquinolinium salt and the ketone as found in the Knorr pyrrole synthesis.[19] Ester compound **10a** was hydrolyzed with KOH in aqueous *i*-PrOH to give the pyrrolo[2,1-*a*]isoquinoline carboxylic acid **11a** in excellent yield

TABLE 3. Synthesis of Benzopyranone Derivatives 5 Using CuTC-Mediated (Method A) and CuI-Catalyzed (Method B) Lactonization[a]



entry	products	X	yield (%)A[b]	yield (%)B[c]
1		Br	94	99
2	**5a**	Cl	97	98
3		OTf	98	86
	5b			
	5c			
4		Br	85	62
5		Br	98	65
6	**5d**	Cl	95	63
7		Br	89	19
8	**5e**	Cl	99	5
9		Br	63	16
10	**5f**	Cl	81	9
11		Br[d]	79	31
	5g			
12		Br	N/A	N/A
13	**5h**	Cl	N/A	N/A
14		Br	N/A	N/A
	5i			

[a] Unless otherwise noted, the reactions were performed in a 10 mL microwave vessel: biarylcarboxylic acid (0.2 mmol) in DMF (3 mL). [b] Stoichiometric condition: CuTC (0.4 mmol), 200 °C, 20 min. [c] Substoichiometric conditions: 50 mol % of CuI, Na_2CO_3 (1.5 equiv), 200 °C, 20 min. [d] The reactions were performed in a 10 mL microwave vessel: 2-(2-bromophenyl)benzofuran-3-carboxylic acid (0.1 mmol) in DMF (2 mL).

(16) Lactone **5e** was obtained in only 3% yield from 3-(2-chlorophenyl)-indole-2-carboxylic acid under conventional heating, refluxing DMF overnight,and lactone **5f** was obtained in 7% yield from 2-(2-chlorophenyl)-indole-3-carboxylic acid. Reaction with (2-bromophenyl)indole carboxylic acid derivatives showed no lactone formation under the same conditions.

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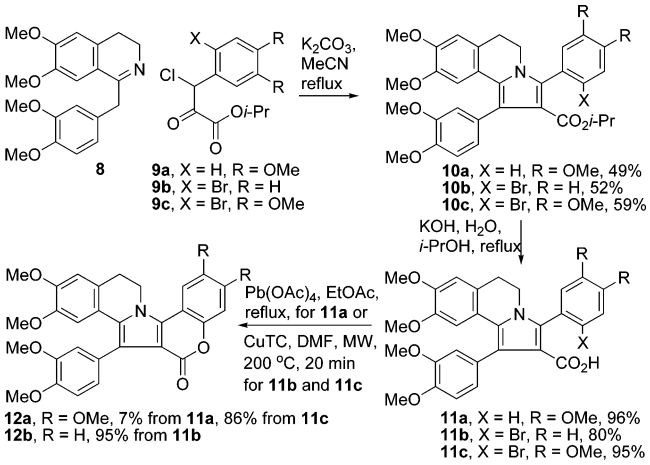
SCHEME 1. Synthesis of Isolamellarins 12



(96%). Steglich has successfully utilized lead(IV) acetate for lactone formation from the corresponding 2-pyrrolecarboxylic acid in an elegant synthesis of the lamellarin.[7e] However, treatment of **11a** in refluxing ethyl acetate with 1 equiv of lead(IV) acetate afforded lactone **12a** in a disappointing yield (7%). Presumably, for the reaction to proceed well, strict coplanarity of the aromatic ring and the carboxylic group is required.

An alternative method for the synthesis of the lactone was also investigated using our methodology. In an effort to form lactone ring in isolamellarin **12b** by the aromatic $C-O_{carboxylic}$ bond formation, we prepared the brominated analogue pyrrolo[2,1-*a*]isoquinoline **11b**. Successfully, the isolamellarin **12b** was prepared from the corresponding bromopyrrolecarboxylic acid **11b** in 95% yield using method A. Application of this protocol to the formation of lactone in the formation of isolamellarin **12a** furnished the desired product from the corresponding bromopyrrole carboxylic acid **11c** in 86% yield.

In conclusion, a simple and highly effective $C-O_{carboxylic}$ lactonization method catalyzed by copper(I) salts has been developed to synthesize benzopyranones. The reaction of various 2-halobiarylcarboxylic acids was examined using microwave irradiation. A new class of pyrroloisoquinoline alkaloids, isolamellarins, was synthesized on the basis of the ring annulation of dihydroisoquinoline with aryl pyruvates under basic conditions and Cu-mediated/MW-assisted $C-O_{carboxylic}$ lactonization. The method developed and reported here should be applicable to the synthesis of lactone system in natural products, biologically active compounds, and materials.

Experimental Section

General Procedure for Lactonization Reaction (Method A). Dibenzo[*b*,*d*]pyran-6-one (5a). In a 10 mL microwave vessel, 2′-halobiphenyl-2-carboxylic acid (e.g., **6a**; 55.4 mg, 0.2 mmol, 1.0 equiv) and CuTC (76.4 mg, 0.4 mmol, 2.0 equiv) were dissolved in DMF (3 mL) followed by sealing of the vessel and heating to 200 °C for 20 min in a microwave reactor. The reaction temperature increased from 25 to 200 °C in 120 s and was maintained at 200 °C for the duration. The yellow-brown precipitate was filtered through silica gel and washed with EtOAc (4 × 25 mL). The solvent was concentrated under reduced pressure to give a pale yellow solid which was then recrystallized with EtOAc/hexane to give benzopyran-6-one **5** (e.g., **5a**; 36.7 mg, 94% yield)[20] as a white solid.

General Procedure for Lactonization Reaction (Method B). Dibenzo[*b*,*d*]pyran-6-one (5a). In a 10 mL microwave vessel, 2′-halobiphenyl-2-carboxylic acid (e.g., **6b**; 46.5 mg, 0.2 mmol, 1.0 equiv), CuI (19.4 mg, 0.1 mmol, 0.5 equiv), and Na_2CO_3 (33 mg, 0.3 mmol, 1.5 equiv) were dissolved in DMF (3 mL) followed by sealing of the vessel and heating to 200 °C for 20 min in a microwave reactor. The reaction temperature increased from 25 to 200 °C in 120 s and was maintained at 200 °C for the duration. The yellow-brown precipitate was filtered through silica gel and washed with EtOAc (4 × 25 mL). The solvent was concentrated under reduced pressure to give a pale yellow solid which was then recrystallized with EtOAc/hexane to give benzopyran-6-one **5** (e.g., **5a**; 38.4 mg, 98% yield)[20] as a white solid.

General Procedure for Synthesis of Isolamellarin. 2,3,8,9-Tetramethoxy-13-(3,4-dimethoxyphenyl)-5*H*,6*H*-11-oxa-6a-azadibenzo[*a*,*g*]fluoren-12-one (12a). In a 10 mL microwave vessel, pyrrolo[2,1-*a*]isoquinolinecarboxylic acid (e.g., **11c**; 25 mg, 0.04 mmol, 1.0 equiv) and CuTC (18 mg, 0.08 mmol, 2.0 equiv) were dissolved in DMF (1 mL) followed by sealing of the vessel and heating to 200 °C for 20 min in a microwave reactor. The reaction temperature increased from 25 to 200 °C in 120 s and was maintained at 200 °C for the duration. The yellow-brown precipitate was filtered through silica gel and washed with EtOAc (4 × 25 mL). The solvent was concentrated under reduced pressure to give a pale yellow solid which was then recrystallized with EtOAc/hexane to give isolamellarin **12** (e.g., **12a**; 18.7 mg, 86% yield) as a gray solid: mp >235 °C (ethyl acetate−hexane); IR (KBr) ν_{max} 1713, 1515, 1465, 1267, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.08 (dd, J = 8.0, 1.0 Hz, 1H), 7.06 (d, J = 1.0 Hz, 1H), 7.01 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 6.67 (s, 1H), 4.62 (t, J = 6.4 Hz, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.39 (s, 3H), 3.18 (t, J = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 149.8, 148.7, 148.4, 148.1, 147.7, 147.5, 145.5, 133.9, 129.8, 126.3, 124.1, 123.2, 120.8, 119.7, 114.1, 111.0, 110.4, 108.6, 106.3, 104.4, 104.3, 101.6, 56.8, 56.1, 55.9 (3C), 55.3, 43.3, 29.0; HRMS (posFAB) calcd for $C_{31}H_{30}NO_8$ $(M + H)^+$ 544.1971, found 544.1973.

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Supporting Information Available: General methods, experimental procedures as well as spectroscopic data and copies of NMR spectra of all new compounds (**5b**−**g**, **10a**−**c**, **11a**−**c**, and **12a**,**b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For complete characterization of compound **5**, see the Supporting Information.