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Synthesis of phenanthridinones using Cu- or Pd-mediated C–N bond formation

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ABSTRACT

The chemoselective synthesis of phenanthridinones was studied using copper(I)- and palladium(II)-catalyzed C–N bond formation with various bases, ligands, and solvents. Phenanthridinones were obtained from 2-halobiarylcarboxylates and amines in a one-pot reaction. The phenanthridinones and heterocyclic-fused lactam derivatives were accomplished using developed methods.

1. Introduction

Phenanthridinone scaffold has been found widely in various biologically active compounds.[1–4] In 1893, phenanthridinone was first synthesized by Grabe and Wander using Hofmann reaction of 2,2'-amidobiphenylcarboxylic acid but the unsatisfied yield was obtained.[5] The Curtius degradation of diphenic monoazide in alcoholic solvent under the acid condition was then developed, leading to the phenanthridinone derivative but there remained limitations of variation of its analog.[6,7] The syntheses of phenanthridinones have been further studied for more effective routes.[8–12] Since the C–N bond formations have been conducted by Buchwald and Hartwig groups, palladium-catalyzed C–N bond formations using the necessary ligand and base were reported for more efficient conditions to construct the nitrogen containing compounds.[13–18]

Phenanthridinone is a common moiety found in bioactive alkaloids from many sources as shown in Fig. 1. Oxynitidine (**1**), a phenanthridinone derived from *Xanthoxylum*, is a potential antitumor and antiviral agent.[19] Pancratistatin (**2**), shows a high level of inhibition of *in vivo* cancer cell growth.[20] Indenoisoquinoline (**3**) acts as a non-camptothecin topoisomerase I inhibitor.[21] Azalamellarin D (**4**) is an extension of lamellarin D (**5**) investigated in our group.[22] The lactam within the B-ring of an azalamellarin replaces the lactone structure of lamellarin, improving the compound's stability.[22] Lamellarin D (**5**) has received attention from many research groups, including ours.[23] Biological and synthetic studies of lamellarin D in particular have been reported.[24]

Reported herein is a methodology for the one-pot synthesis of a small-molecule lactam model that is analogous to the core of many pharmacologically active compounds. Developing an efficient synthesis for this lactam will aid in optimizing reaction conditions for biologically active phenanthridinone derivatives, with a heterocyclic-fused lactam.

2. Results and discussion

2.1. Cu(I)-mediated lactone and lactam formation: completion of C–O and C–N bond formation

Methyl 2-bromocarboxylate (**6**) and homoveratylamine (**7**) were used to study the Cu(I)-catalyzed C–N bond formation of the

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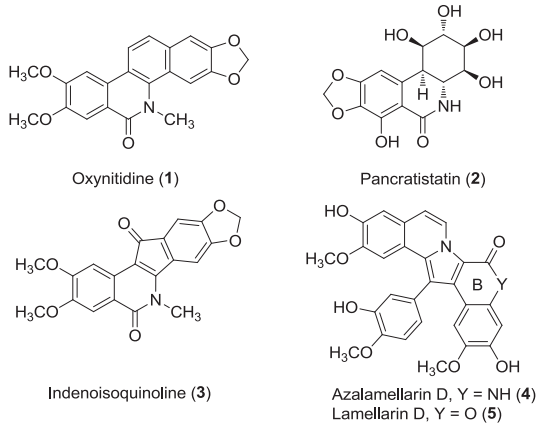


Fig. 1. Structures of oxynitidine (**1**), pancratistatin (**2**), indenoisoquinoline (**3**), azalamellarin D (**4**), and lamellarin D (**5**).

corresponding phenanthridinone **8**.[22,25] Various bases and bidentate ligands (**a** to **e** in Fig. 2) were screened with the subcritical water under the benign conditions to conform with the green chemistry aspect.[26] The competition of intermolecular C–N bond formation and intramolecular C–O bond formation was observed and afforded a mixture of the target compound **8** and benzopyranone **9** in moderate to good yields as summarized in the Table 1.

First, we examined the possibility of Cu(I)-catalyzed C–N bond formation of compounds **6** and **7** with subcritical water at 300 °C using copper thiophenecarboxylate (CuTC) as catalyst in the presence of Cs_2CO_3 as a base.[26] The C–N bond formation product, lactam **8** and C–O bond formation product, lactone **9** were obtained in 23% and 36% yields, respectively (Table 1, entry 1). The bidentate ligands **a-e** were screened and it was found that TMEDA (ligand **a**) gave the C–N bond formation product **8** in higher yield (Table 1, entry 2) compared with other bidentate ligands **b-e** which gave lactone **9** in higher yield (Table 1, entries 3 to 6). Some bases were then screened in the presence of TMEDA (ligand **a**), and gave lower yield of the corresponding lactam **8** (Table 1, entries 7 and 8). Interestingly, using phosphazine base *t*-Bu-P_4 as base in the absence of ligand, the highest overall yield was obtained in a 1:2 ratio of lactam **8**: lactone **9** (Table 1, entry 9). Adjusting the amounts of amine **7** (3–10 equivalents) under basic conditions and TMEDA as ligand, both lactam **8** and lactone **9** yields relatively increased (Table 1, entries 10 to 12). It was summarized that the intramolecular C–O bond formation occurred faster than the intermolecular C–N bond formation using subcritical water; this is in good accordance with our previous report.[26]

In an attempt to synthesize phenanthridione as the major product, the chemoselectivity of C–N bond formation was studied based on the result of entry 2 Table 1 that gave compound 8 as a major product using 0.5 equiv CuTC, in the presence of Cs_2CO_3 and TMEDA. We then optimized the conditions by screening other

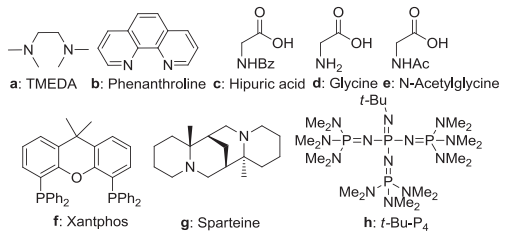
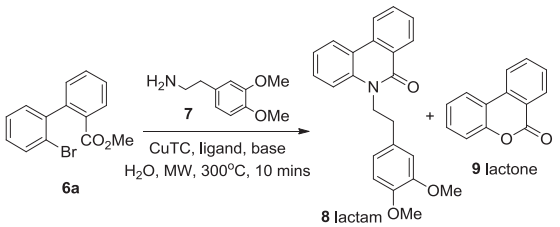


Fig. 2. Screened ligands **a-g** and phophazine base **h** in this study.

Table 1
Reaction of methyl-2-bromocarboxylate **6a** and homoveratylamine **7** mediated by CuTC in the subcritical water condition, use various bases and ligands.[a]

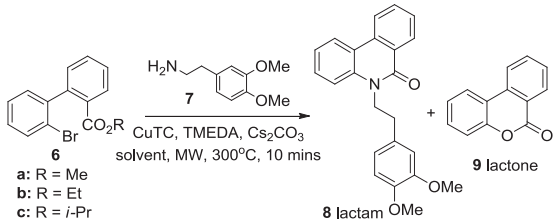


Entry	7 (equiv)	Base	Ligand	Yield 8 (%)[b]	Yield 9 (%)[b]
1	5	Cs_2CO_3	–	23	36
2	5	Cs_2CO_3	a	31	18
3	5	Cs_2CO_3	b	9	41
4	5	Cs_2CO_3	c	23	50
5	5	Cs_2CO_3	d	10	37
6	5	Cs_2CO_3	e	11	38
7	5	K_2CO_3	a	26	33
8	5	NaO*t*-Bu	a	16	34
9	5	*t*-Bu-P_4	–	31	60
10	3	Cs_2CO_3	a	20	36
11	7	Cs_2CO_3	a	34	36
12	10	Cs_2CO_3	a	34	49

[a] Unless otherwise noted, the reactions were performed in a 10 mL microwave vessel: 0.5 equiv of CuTC, 300 °C, 10 min. The 300 °C reactions should only be performed by a trained chemist using a dedicated, scientific reactor with adequate safety features.
[b] Isolated yields of pure product after PTLC on silica.

solvents with the different dielectric constant for microwave irradiation. To our delight, the ratio of compounds **8:9** increased to 1.7:1 ratio using dioxane as solvent (Table 2, entry 1). When the solvent was changed to DMF, the yield of mixture **8** and **9** increased, in a 1:1 ratio (Table 2, entry 2). A mixture of water and DMF or

Table 2
Screening of solvents and alkyl groups.[a]



Entry	Compound	Solvent	Yield 8 (%)[b]	Yield 9 (%)[b]
1	**6a**	Dioxane	17	10
2	**6a**	DMF	25	24
3	**6a**	H_2O:DMF 1:1	25	51
4	**6a**	H_2O:Toluene 1:1	18	31
5	**6a**	Toluene	trace	95
6	**6a**	DCM	NR[c]	NR[c]
7	**6a**	MeOH	NR[c]	NR[c]
8	**6a**	-[d]	NR[c]	NR[c]
9	**6b**	H_2O	23	39
10	**6c**	H_2O	19	18

[a] Unless otherwise noted, the reactions were performed in a 10 mL microwave vessel: 5 equiv of homoveratrylamine, 0.5 equiv of CuTC, 300 °C, 10 min. The 300 °C reactions should only be performed by a trained chemist using a dedicated, scientific reactor with adequate safety features.
[b] Isolated yields of pure product after PTLC on silica.
[c] NR: no reaction.
[d] Solvent-free reaction.