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Oxidative Carbon−Carbon Bond Formation in the Synthesis of Bioactive Spiro β-Lactams

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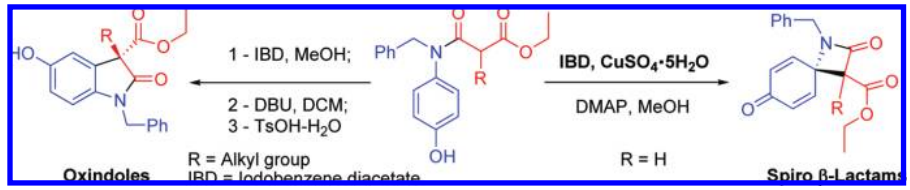
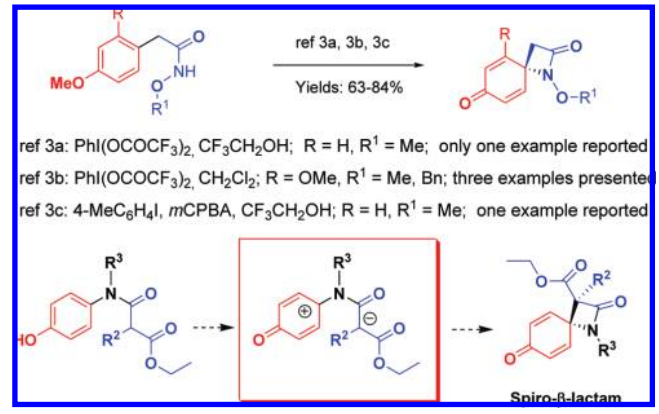
ABSTRACT



New oxidative dearomatization procedures leading to spiro β-lactams and oxindoles were developed. By a variation of the oxidative reaction conditions, the usefulness of phenolic amides, derived from 4-aminophenol, in the synthesis of structurally different types of molecules was demonstrated.

In the past few years, there is growing interest in the synthesis of azetidinones. Numerous synthetic methods exist that lead to azetidinones,[1] so why bother choosing β-lactam? The reason was quite simple: the β-lactam substructure is not only present in biologically active natural products but is also incorporated into numerous pharmaceutical ingredients such as penicillins and carbapenems.[2] It is well-known that bacterial resistance to existing antibiotics is increasing and therefore there is great demand for the creation of a new type of compound bearing a β-lactam motif. Of the methods leading to azetidinones, we were especially interested in the oxidative dearomatization strategies developed by the groups of Kikugawa,[3a] Wardrop[3b] and Kita.[3c] In their methods, a carbon−nitrogen bond was formed in the oxidation steps as indicated in Scheme 1. Inspired by these elegant oxidative dearomatization procedures, we began to ponder whether a new synthetic methodology that leads to β-lactam building blocks could be developed by an oxidative carbon−carbon bond formation of phenolic amide derivatives (Scheme 1).

Scheme 1. Synthesis of Spiro-β-lactams by Oxidative C−N Coupling and Our Speculation Towards the Synthesis of Highly Functional Azetidinones



(1) For reviews on synthesis and application of β-lactams, see: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437. (b) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 594. (c) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631.

(2) Butler, M. S. *Nat. Prod. Rep.* **2005**, *22*, 162.

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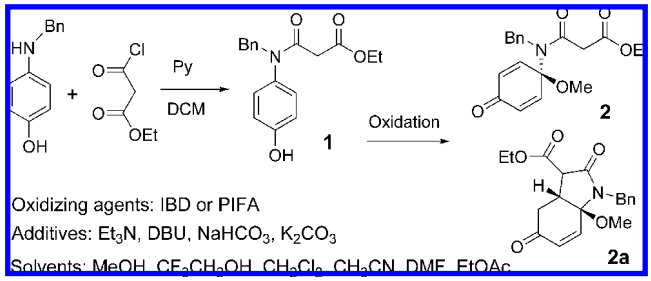
If an oxidative dearomatization followed by a concomitant carbon−carbon formation occurs, β-lactams with a rich functionality could be readily provided and thus diverse manipulation is possible. The success of such a procedure may rely on the oxidative dearomatization of phenol derivatives with proper oxidants. After an intensive survey of the literature,[4] we decided to use the readily available hypervalent iodine reagents,[5] namely, iodobenzene diacetate (IBD). A program with the aim of synthesizing highly functional spiro β-lactams, as shown in Scheme 1, was then initiated.

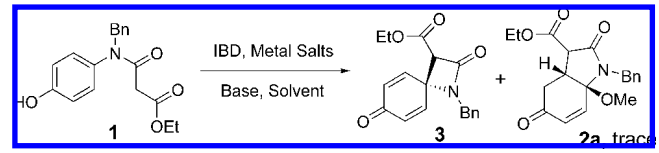
Scheme 2. Initial Attempts Towards Oxidative Coupling



The first amide (compound **1** in Scheme 2) was obtained by the direct reaction of 4-(benzylamino)phenol with ethyl 3-chloro-3-oxopropanate in 92% yield. Although oxidation of phenols with polyvalent iodine reagents to enone derivatives has been well documented in the literature,[8] no oxidative reaction has ever been conducted using amide **1**. The initial oxidative coupling of amide **1** was then attempted with IBD in methanol at room temperature. To our disappointment, only cyclohexadienone **2** and **2a** were detected and no desired coupling reaction occurred. Using PIFA ($PhI(OCOCF_3)_2$) as an oxidizing agent as well as using a base (Et_3N, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), $NaHCO_3$ and K_2CO_3) as an additive to the reaction system did not alter the reaction pathway, with compound **2** and compound **2a** being the isolated products. Varying the solvents in the reaction system (dichloromethane, trifluoroethanol, acetonitrile, ethyl acetate, DMF) was also fruitless.

Having failed to effect the desired transformation, an alternative way was thus sought. Because copper salts have been widely employed in coupling reactions,[6] we decided to examine the combination of copper salts and IBD first. A number of copper salts were tested, and the results are summarized in Table 1. To our surprise, the addition of

Table 1. Attempts Towards the Synthesis of Spiro-β-lactams[a]



entry	copper salts	ligand (base)	solvent	yield[b]
1	CuI	–	MeOH	20%
2	$CuCl_2$	–	MeOH	25%
3	$Cu(acac)_2$	–	MeOH	12%
4	$Cu(OAc)_2$	–	MeOH	24%
5	$CuSO_4{\cdot}5H_2O$	–	MeOH	35%
6	$CuSO_4{\cdot}5H_2O$	PPh_3	MeOH	<5%
7	$CuSO_4{\cdot}5H_2O$	Proline	MeOH	<5%
8	$CuSO_4{\cdot}5H_2O$	TMEDA	MeOH	<5%
9	$CuSO_4{\cdot}5H_2O$	Pyridine	MeOH	51%
10	$CuSO_4{\cdot}5H_2O$	DMAP	MeOH	85%
11	$CuSO_4{\cdot}5H_2O$	DMAP	MeOH	57%[c]
12	$CuSO_4{\cdot}5H_2O$	DMAP	CH_3CN	30%
13	$CuSO_4{\cdot}5H_2O$	DMAP	MeOH	0%[d]

[a] Reactions, except entry 11 and 13, were carried out at 0 °C with amide **1** (0.5 mmol) and IBD (0.6 mmol, 1.2 equiv) in a solvent (10 mL) for 1−2 h in the presence of a copper salt (0.5 mmol, 1.0 equiv). Entries 6−12 were carried out with a ligand (0.5−0.6 mmol). [b] Yields represent isolated yields of **3**. [c] Reaction was conducted at 0 °C with amide **1** (0.5 mmol), IBD (0.6 mmol, 1.2 equiv), catalytic amount of $CuSO_4{\cdot}5H_2O$ (0.1 mmol) and DMAP (0.12 mmol) for 2 h. [d] Reaction was conducted at 0 °C with amide **1** (0.5 mmol), $CuSO_4{\cdot}5H_2O$ (1.2 mmol, 2.4 equiv) and DMAP (1.2 mmol) for 2 h in methanol (10 mL) in the absence of IBD.

copper salts resulted in the desired azetidinone **3**. Characteristic NMR peaks that were observed for compound **3** are a singlet signal at 4.14 ppm in the ^1H NMR spectrum and a quaternary carbon resonance at 57.7 ppm in the ^{13}C NMR spectrum. The best result (Table 1, entry 10) was obtained upon the addition of copper(II) sulfate pentahydrate and 4-dimethylaminopyridine (DMAP) in methanol. The desired azetidinone (**3**) was obtained in 85% yield together with a trace amount of byproduct **2a**. In the absence of IBD, however, copper(II) sulfate pentahydrate did not promote the formation of the spiro-β-lactam (Table 1, entry 13).

To get further insights toward the generality of this process, a number of phenol derived amides (**1**−**1i**) were prepared and evaluated under optimized conditions. Good yields were obtained, and the results are summarized in Table 2. After careful recrystallization, an X-ray crystal structure for compound **3i** was obtained and the spiro β-lactam structure was confirmed. All azetidinone compounds listed in Table 2 are bioactive against a number of tumor cell lines with IC_{50} potencies ranging from 17 to 0.3 μM.[7]

The reaction pathway might consist of a radical coupling reactions between the *para*-position of a phenol unit and the

(3) (a) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *Heterocycles* **2003**, *53*, 149. (b) Wardrop, D. J.; Burge, M. S. *J. Org. Chem.* **2005**, *70*, 10271. (c) Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 1224.

(4) For recent reviews on oxidative coupling, see: (a) Quideau, S.; Pouysegu, L.; Deffieux, D. *Synlett* **2008**, 467. (b) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, 3759. (c) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383. (d) Rodrígues, S.; Wipf, P. *Synthesis* **2004**, 2767. (e) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.

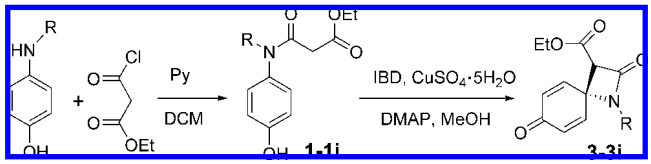
(5) For reviews on polyvalent iodine chemistry, see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (b) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402. (c) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (d) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523, and references cited therein.

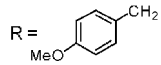
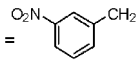
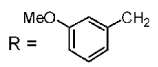
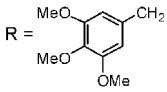
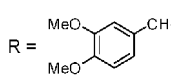
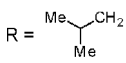
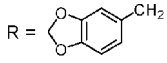
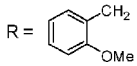
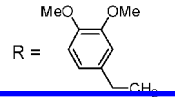
(6) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

(7) The bioassay was carried out with the MTT method. In vitro studies demonstrated that the azetidinones listed in Table 2are active against A431, HepG-2 and Skov-3 tumor cells.

(8) (a) Peng, H. M.; Wester, R. D. *J. Org. Chem.* **2008**, *73*, 2169. (b) Eickhoff, H.; Jung, G.; Rieker, A. *Tetrahedron* **2001**, *57*, 353, references cited therein.

Table 2. β-Lactams Prepared under Optimized Conditions[a]



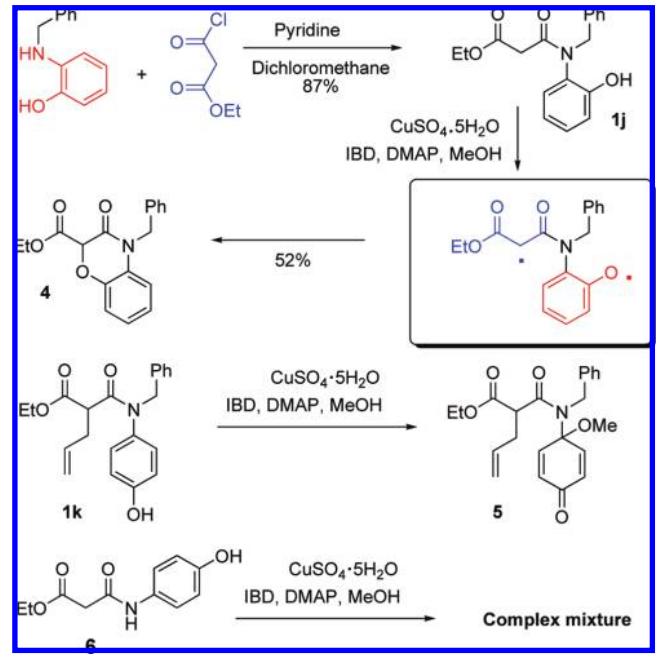
amides,	lactams	yield	amides,	lactams	yield
1	R = 	92%	**1e**	R = 	83%
3		85%	**3e**		77%
1a	R = 	78%	**1f**	R = 	83%
3a		87%	**3f**		85%
1b	R = 	77%	**1g**	R = 	81%
3b		83%	**3g**		85%
1c	R = 	86%	**1h**	R = 	84%
3c		87%	**3h**		76%
1d	R = 	87%	**1i**	R = 	79%
3d		84%	**3i**		84%

[a] For reaction conditions, see the Supporting Information. [b] Yields represent isolated yields (average of two runs).

α-position of the two carbonyl groups and both radical species might be generated through oxidation reactions of IBD in the presence of copper(II) sulfate pentahydrate (Table 1, entry 10). To better understand the mechanism of this coupling process, amide **1j** was prepared from 2-(benzylamino)phenol and subjected to the oxidative coupling (Scheme 3). In this reaction, a new carbon−oxygen bond rather than a carbon−carbon bond formed by a direct coupling of the *ortho*-phenolic oxygen with the methylene carbon adjacent to the two carbonyl groups. Although we are unable to exclude the possibility of an ionic pathway[8] (as shown in Scheme 1) between the phenoxonium cation generated by the oxidation of phenol and the enolate produced by the copper salt in the presence of a base (DMAP), more evidence needed, we favor a radical mechanism.[8b] The outcome of the oxidative coupling of amide **1j** could be better explained by a radical pathway. The role of the copper salts in this typical coupling reaction has not been determined and it was speculated that it might act as a co-oxidizing agent and electron acceptors.[9] With a substituent (allyl group, amide **1k**) present at the α-position of the two carbonyl groups, no azetidinone was observed, with compound **5** being isolated in 91% yield. This was possibly due to the steric hindrance imposed by the substitutent which sheltered the α-position adjacent to the two carbonyl groups against further carbon−carbon bond coupling under our oxidizing condition as indicated in Scheme 3. A complex mixture was produced in the absence of a substituent (**6**, Scheme 3) in the nitrogen atom of amide **6**.

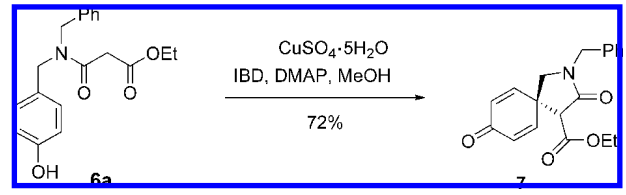
(9) Baran, P. S.; DeMartino, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7083.

Scheme 3. Further Attempts Towards Oxidative Coupling under Optimized Conditions



To extend the utility of our oxidative conditions (IBD coupled with $CuSO_4{\cdot}5H_2O$), we then synthesized an benzyl amide derivative **6a** and attempted an oxidative coupling under optimized reaction conditions. To our delight, a spiro pyrrolidone, compound **7**, was obtained in 72% yield. By the way, spiro pyrrolidone **7**, which bears a full carbon quarternary carbon center as shown in Scheme 4, could not be prepared by C−N coupling methods reported in the literature (ref 3).

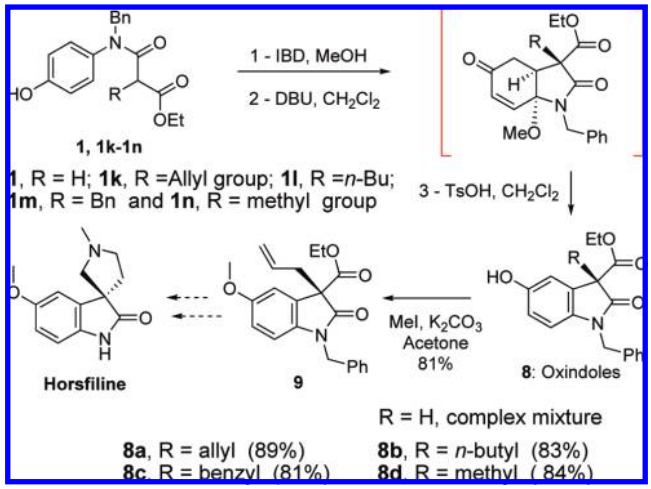
Scheme 4. Attempts Towards the Synthesis of Spiro Pyrrolidone



Inspired by the results presented in Scheme 3 (**1k** to **5**), we next set our goal toward the synthesis of oxindole units using phenolic amides derived from 4-aminophenol. Oxindole substructures are also widely found in bioactive natural products as well as in pharmaceuticals.[10] We considered that the oxindole structure might also be synthesized from the same phenolic amides through an oxidative dearomatization followed by an intramolecular Michael addition and an acid

catalyzed rearomatization. A number of amides (**1**, **1k**−**1n**) were then examined for the synthesis of oxindoles (Scheme 5). In the absence of copper salts, oxidation with IBD in methanol resulted in 4-methoxyl cyclohexadienenones in nearly quantitative yields. After removal of the solvent, Michael additions were achieved by the addition of DBU in dichloromethane. After treatment of the crude products with TsOH, oxindoles were obtained in 81−89% yields. Although oxindole and dihydroindoles have been realized by using oxidative dearomatization as the key step,[10g,h,11] our oxindole procedure produced a full carbon quarternary carbon center adjacent to the aromatic ring, therefore afforded useful building blocks for the synthesis of natural alkaloids such as Horsfiline. It is noteworthy that amide **1** (R = H), after oxidation with IBD and subsequent Michael addition in the presence of DBU, did not give an oxindole after treatment of **2a** with *p*-toluenesulfonic acid (Scheme 5). Treatment of compound **8a** with methyl iodide in the presence of potassium carbonate and in acetone provided an advanced intermediate for the total synthesis of Horsfiline.[12]

Scheme 5. Synthesis of Oxindoles by Oxidative Dearomatization



In summary, we have introduced an alternative reaction for the synthesis of highly functional spiro-β-lactams, a supplement to the Staudinger reaction. To the best of our knowledge, this is the first oxidative carbon−carbon bond forming procedure that has led to spiro-β-lactams and spiropyrrolidone.[3,13] We have also developed a useful synthetic procedure that leads to oxindoles. An especially attractive feature of this research is that both methods are based on an oxidative dearomatization from similar phenolic amide derivatives. By varying the oxidative reaction conditions, we demonstrate the usefulness of phenolic amides, derived from 4-aminophenol, in the synthesis of structurally different molecules. Syntheses of β-lactams and oxindoles are efficient, have high yield and are easily handled. Further biological studies of β-lactams as well as the total synthesis of oxoindole related natural products are currently underway in our laboratories and will be reported in due course.

Acknowledgment. This work was supported by grants from the Chinese Ministry of Education for fostering important scientific research program (706052), the Yunnan Provincial Science & Technology Department (2007B0006Z) and the National Natural Science Foudation of China (20832005).

Supporting Information Available: ^{1}H NMR, ^{13}C NMR spectra of all key intermediates and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901005X

(10) For recent synthesis of oxindoles, see: (a) Felpin, F.-X.; Ibarguren, O.; Nassar-Hardy, L.; Fouquet, E. *J. Org. Chem.* **2009**, *74*, 1349. (b) Luan, X.; Mariz, R.; Robert, C.; Gatti, M.; Blumentritt, S.; Linden, A.; Dorta, R. *Org. Lett.* **2008**, *10*, 5569. (c) Shanmugam, P.; Vaithiyanathan, V. *Tetrahedron* **2008**, *64*, 3322. (d) Hillgren, J. M.; Marsden, S. P. *J. Org. Chem.* **2008**, *73*, 6459. (e) Kündig, E. P.; Seidel, T. M.; Jia, Y.-X.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8484. (f) Teichert, A.; Jantos, K.; Harms, K.; Studer, A. *Org. Lett.* **2004**, *6*, 3477, and references cited thereinFor recent synthesis of oxindoles with an oxidative dearomatization strategy, see: (g) Pouységu, L.; Avellan, A.-V.; Quideau, S. *J. Org. Chem.* **2002**, *67*, 3425. (h) Quideau, S.; Pouységu, L.; Avellan, A.-V.; Whelligan, D. K.; Looney, M. A. *Tetrahedron Lett.* **2001**, *42*, 7393.

(11) In the literature, Quideau and Clive had elegantly demonstrated the synthesis of 2,3-dihydroindoles with an oxidative dearomatization strategy, see: (a) Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M. A. *Tetrahedron* **2001**, *57*, 319. (b) Fletcher, S. P.; Clive, D. L. J.; Peng, J.; Wingert, D. A. *Org. Lett.* **2005**, *7*, 23.

(12) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027.

(13) Formation of spirolactams by oxidative carbon-nitrogen bond coupling had been elegantly demonstrated by ref 3 and: (a) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534, and references cites therein. (b) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765, and references cites therein.