Cu(II) catalyzed oxidation-[3 + 2] cycloaddition-aromatization cascade: Efficient synthesis of pyrrolo [2, 1-*a*] isoquinolines†

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A novel and synthetically efficient Cu(II) catalyzed oxidation-dipolar cycloaddition-aromatization cascade reaction has been developed for a "one-pot" synthesis of biologically important pyrrolo [2, 1-*a*] isoquinolines.

Pyrrolo [2, 1-*a*] isoquinolines constitute the core structure of the novel marine natural products lamellarin alkaloids with more than 30 family members.[1] They display a broad spectrum of promising biological properties. For example, lamellarin D is a potent inhibitor of topoisomerase I,[2] while related lamellarin α-20-sulfonate serves as a selective HIV integrase inhibitor (Fig. 1).[3] Lamellarin I is an MDR inhibitor[4] and its analogue lamellarin K exhibits antitumor activity.[5] Their intriguing biological activities have provoked significant recent interest in the target-[6] and diversity-[7] oriented synthesis. Despite the fact that several strategies involving dipolar[8] and azadiene Diels–Alder cycloadditions,[6c] oxidative dimerization[6b] and double-barreled Heck cyclization[9] have been reported in the preparation of the pyrrolo [2, 1-*a*] isoquinoline core structures, the general observation is that they require multiple synthetic steps and/or highly functionalized substrates. For example, dipolar [3 + 2] cycloadditions between azomethines and activated double bonds are an efficient approach to hexahydropyrrolo [2, 1-*a*] isoquinolines.[8,10,11] Nevertheless, an extra oxidation step is required to convert the pyrrolidines to the pyrroles. In addition, the method has a limited scope, restricted to the substrates bearing electron-donating substituents.

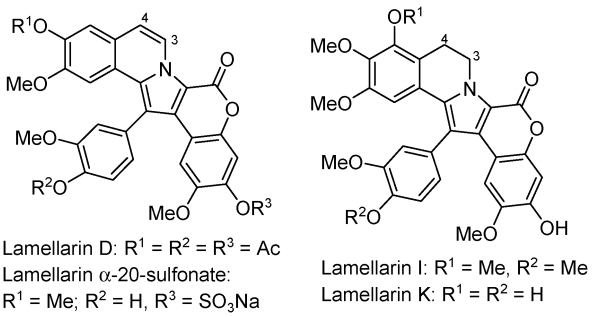

Fig. 1 Biologically important pyrrolo [2, 1-*a*] isoquinoline lamellarin alkaloids.

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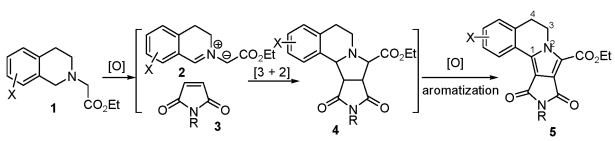
These studies highlight the challenges and potentials of the dipolar cycloaddition reactions in construction of the important molecular architecture. More synthetically efficient strategies will allow for the target- and diversity-oriented synthesis of the biologically significant lamellarin alkaloids and the exploration of their biomedical applications.

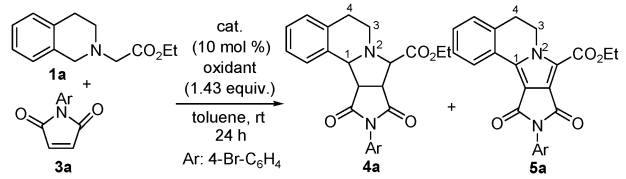
As a result of high reactivity of the essential azomethines in dipolar cycloaddition reactions,[8,12] in general, they are formed *in situ* from corresponding labile imines, whose preparations are nontrivial. The use of readily prepared and stable tetrahydroisoquinolines **1** could offer significant synthetic and economic benefits (Scheme 1). We envisioned that oxidation of tetrahydroisoquinolines **1** would lead to formation of azomethines **2**, which were trapped by a dipolarophile such as maleimides **3** for a subsequent [3 + 2] cycloaddition to give adducts **4**. Under the same reaction conditions, the resulting hexahydropyrrolo [2, 1-*a*] isoquinolines **4** would be oxidized subsequently to afford the target pyrrolo [2, 1-*a*] isoquinolines **5**.[13] The proposal looks simple on paper. However, we faced two challenging issues. First, a direct oxidation of isoquinolines **1** to unstable azomethines **2** has not been reported previously. Moreover, it is unclear if we could find a suitable oxidation system for forming the azomethines **2**, while compatible with subsequent dipolar cycloaddition and aromatization processes. In this communication, we wish to disclose the results by the discovery of a new "one pot" approach to the pyrrolo [2, 1-*a*] isoquinolines from simple starting materials. A novel Cu(II) catalyzed oxidation-[3 + 2] cycloaddition-aromatization cascade process is developed. Notably, the reaction displays a broad substrate scope that a variety of dipolarophiles including maleimides, maleic anhydride, quinones, and alkynes can effectively engage in the process, thus generating the products with significant structural diversity.

To validate the hypothesis, the reaction of tetrahydroisoquinoline ester **1a** with *N*-*p*-bromophenylmaleimide **3a** in the presence of oxidant TBHP (*t*-butyl hydroperoxide) and a Lewis acid in toluene at room temperature was performed initially (Table 1).[14] It was shown that the catalyst was critical for the process (entries 1–3). Only copper salts delivered the desired product **5a** albeit a low yield (25%). The low yield largely attributed to the incomplete conversion of the 1, 3-dipolar adduct **4a** (38% yield) to **5a**. It was noted that under the oxidative reaction conditions, the C_3–C_4 bond was not oxidized and thus 3,4-dihydroquinoline



Scheme 1 A proposed catalytic oxidation-[3 + 2] cycloaddition-aromatization cascade.

Table 1 Optimization of reaction conditions[a]



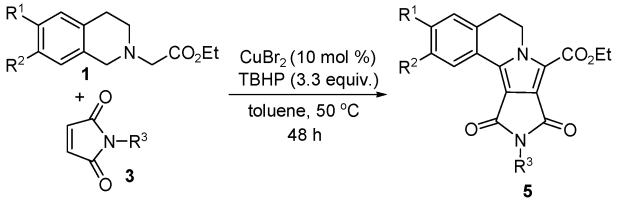
Entry	Cat.	Oxidant	Solvent	% Yield **4a**/**5a**[b]
1	CuBr	TBHP	Toluene	38/25
2	$FeCl_3$	TBHP	Toluene	<5/<5
3	$Pd(OAc)_2$	TBHP	Toluene	0/0
4	$CuBr_2$	TBHP	Toluene	29/30
5	CuCl	TBHP	Toluene	36/11
6	$CuCl_2$	TBHP	Toluene	40/12
7	CuOTf·1/2Tol	TBHP	Toluene	33/4
8	$Cu(OTf)_2$	TBHP	Toluene	36/7
9	CuBr	TBHP	CH_2Cl_2	27/16
10	CuBr	TBHP	DME	16/9
11	CuBr	TBHP	MeOH	0/0
12	CuBr	TBHP	EtOAc	32/21
13	CuBr	TBHP	Toluene/H_2O (v/v: 9/1)	30/14
14	CuBr	TBHP	Toluene	0/0
15	CuBr	(*t*-BuO)$_2$	Toluene	24/26
16	CuBr	$(PhCO_2)_2O$	Toluene	33/29
17	CuBr	$PhCO_3t$-Bu	Toluene	15/5
18	CuBr	TBHP[c]	Toluene	13/42
19	$CuBr_2$	TBHP[c]	Toluene	0/55
20	$CuBr_2$	TBHP[d]	Toluene	0/52
21	**$CuBr_2$**	**TBHP**[e]	**Toluene**	**0/76**

[a] Reaction conditions: unless specified, to a solution of an ethyl 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (0.1 mmol) and 60 μL of TBHP (3.3 equiv.) in the presence of 10 mol% catalyst $CuBr_2$ in toluene (1.0 mL) was added a *N*-substituted maleimide (or other dipolarophiles) (0.1 mmol) and the resulting solution was stirred for 48 h at 50 °C. [b] Isolated yields. [c] 3.3 equiv. of TBHP used. [d] 6.6 equiv. of TBHP used. [e] At 50 °C.

was obtained. Therefore the method is complementary to that was developed by Porco and co-workers, where the quinolines were produced.[11] Furthermore, the 3,4-dihydroquinolines can be conveniently converted to the quinolines by DDQ oxidation.[15] We decided to employ Cu salts as catalysts for the optimization of reaction conditions (entries 4–8). It was found that CuBr gave the best total yield (63%, entry 1), while $CuBr_2$ afforded the better yield of product **5a** (30%, entry 4). Survey of solvent effect using CuBr as a catalyst concluded that toluene was the preferred medium for the reaction. TBHP proved to be the most effective among the oxidants including (*t*BuO)$_2$, benzoyl peroxide and $PhCO_2Ot$Bu probed (entries 1 and 14–17). Increasing the loading of TBHP (3.3 equiv.) resulted in the improvement of the yield of **5a** (42%), but still a pronounced amount of **4a** remained (entry 18). A cleaner reaction with exclusive formation of **5a** was obtained with $CuBr_2$ and the yield was also improved (55%, entry 19). Further increasing the loading of the oxidant (6.6 equiv.) was not beneficial (entry 20). Nevertheless, elevating the reaction temperature to 50 °C enhanced the yield (76%) dramatically (entry 21).

With the optimized condition in hand, we then explored the scope and limitations of the reaction using various maleimides **3** and tetrahydroisoquinolines **1**. As shown in Table 2, the reaction proceeded smoothly with *N*-substituted maleimides, which have significant structural variations bearing electron-neutral (entry 1), donating (entries 2–5) and withdrawing (entries 6–9)

Table 2 Reaction scope with maleimides and tetrahydroisoquinolines[a]



Entry	R^1, R^2, R^3, **5**	% Yield[b]
1	H, H, Ph, **5b**	57
2	H, H, 2-MeC_6H_4, **5c**	60
3	H, H, 3-MeC_6H_4, **5d**	77
4	H, H, 2,6-$Me_2C_6H_3$, **5e**	50
5	H, H, 4-MeOC_6H_4, **5f**	64
6	H, H, 2-FC_6H_4, **5g**	61
7	H, H, 4-BrC_6H_4, **5a**	76
8	H, H, 3,5-$(CF_3)_2C_6H_3$, **5h**	80
9	H, H, 3-MeO-4-BrC_6H_3, **5i**	70
10	H, H, $C_6H_4CH_2$, **5j**	66
11	H, Br, 4-BrC_6H_4, **5k**	81
12[c]	MeO, MeO, 4-BrC_6H_4, **5l**	72

[a] Reaction conditions: unless specified, see footnote a in Table 1 and ESI.† [b] Isolated yields. [c] 1.5 equiv. of **1a** and 5 equiv. of TBHP used.

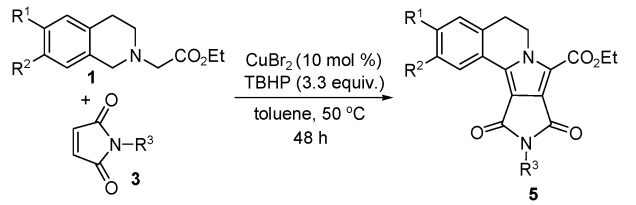
substituents in aryl groups and aliphatic moiety (entry 10). It appeared that the steric hindrance of the substituents had some degree of influence on the process and relatively lower reaction yields were obtained (entries 2, 4 and 6). Probing the electronic impact of substituents on tetrahydroisoquinolines **1** indicated that such effect was limited (entries 11 and 12). It is noteworthy that the structure of the product **5l** bearing two MeO groups is related to the lamellrin alkaloids.

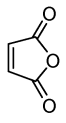
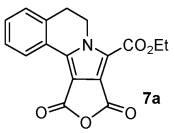
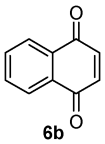
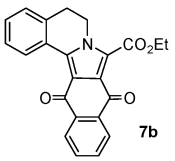
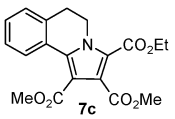
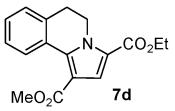
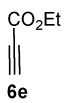
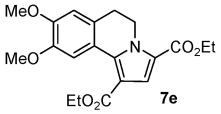
To demonstrate the powerful Cu(II) promoted oxidation-[3 + 2] cycloaddition-aromatization cascade with the broader synthetic utility, we also examined other dipolarophiles and gave good yields (Table 3). Maleic anhydride (entry 1), 1, 4-naphthoquinone (entry 2), activated alkynes (entries 3–5) were found to be effective dipolarophiles engaged in the reaction in good yields. It is noted that high regioselectivity of the reaction was observed and only one regioisomer was formed (entries 4 and 5). Compound **7e** is a known compound, which allows us to establish the structure of the regioisomer.[16] The high regioselectivity may attribute to the steric and electronic effects.[17]

A controlled experiment using compound **4a** as an example showed that the end products pyrrolo [2, 1-*a*] isoquinolines **5** indeed were transformed from [3 + 2] cyclcoaddition adducts **4** (Scheme 2). This indicates that the formed final products go through an oxidation-[3 + 2] cycloaddtion-aromatization sequence in a cascade manner.

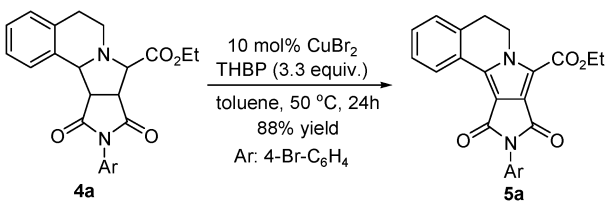
In conclusion, we have developed a synthetically efficient strategy, relying on a novel Cu(II) catalyzed oxidation-dipolar cycloaddition-aromatization cascade for the "one-pot" synthesis of highly valuable pyrrolo [2, 1-*a*] isoquinolines. A wide range of substrates can effectively participate in the reactions under mild reaction conditions to create structurally diverse products. Notably, the cascade processes involve an unprecedented dipolar cycloaddition reaction with *in situ* formation of azomethine ylides from simple and stable amines. Further investigations of the powerful strategy in the development of new reactions are under way in our laboratory.

Table 3 Extending scopes using different dipolarophiles[a]



Entry	Dipolarophile **6**	Product **7**	% Yield[b]
1	 **6a**	 **7a**	72
2	 **6b**	 **7b**	87
3	 **6c**	 **7c**	68
4[c]	 **6d**	 **7d**	70
5[d]	 **6e**	 **7e**	57

[a] Unless specified, see footnote a in Table 1 and supporting information. [b] Isolated yield. [c] 2 equiv. **6d** used. [d] Reaction time: 2 h.



Scheme 2 Oxidation of hexahydropyrrolo [2, 1-*a*] isoquinoline **4a** to pyrrolo [2, 1-*a*] isoquinoline **5a**.

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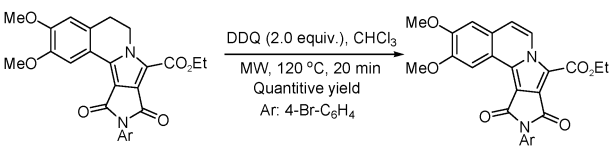

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