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Acid-Mediated Intermolecular [3 + 2] Cycloaddition toward Pyrrolo[2,1-*a*]isoquinolines: Total Synthesis of the Lamellarin Core and Lamellarin G Trimethyl Ether

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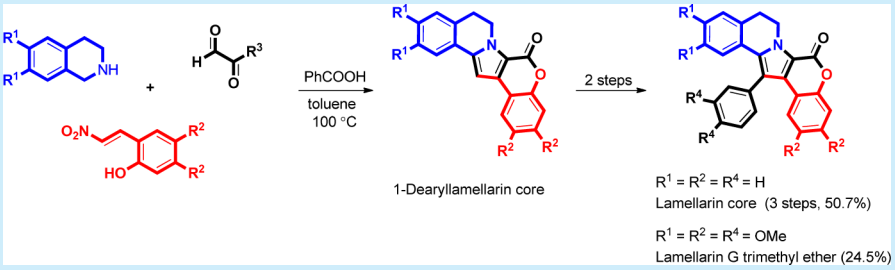
Supporting Information



ABSTRACT: A novel one-pot reaction has been developed for the efficient synthesis of pyrrolo[2,1-*a*]isoquinolines and 1-dearyllamellarin core from (*E*)-(2-nitrovinyl)benzenes and azomethine ylides generated *in situ*. This strategy provides a concise total synthesis of the lamellarin core and lamellarin G trimethyl ether using electrophilic substitution and palladium-catalyzed Suzuki−Miyaura cross-coupling reactions.

Pyrrolo[2,1-*a*]isoquinoline scaffolds form the core of the lamellarin alkaloids, which are natural products that were first isolated from the prosobranch mollusk *Lamellaria* sp. by Faulkner and co-workers in 1985.[1] Since then, more than 50 lamellarins have been isolated, mainly from marine organisms such as mollusks, ascidians, and sponges.[2] These alkaloids exhibit a wide spectrum of biological activities;[3] for example, lamellarin I reverses multidrug resistance by direct inhibition of P-glycoprotein-mediated drug efflux at noncytotoxic doses,[4] whereas lamellarin K and L have immunomodulatory effects in the micromolar range.[5] Furthermore, lamellarin D has been reported to be an inhibitor of human topoisomerase I,[4b,6] and lamellarin α-20-sulfate is a drug candidate for the inhibition of HIV integrase[7] (Figure 1).

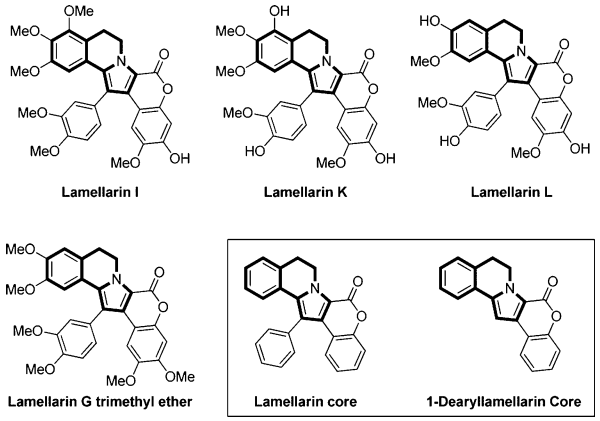


Figure 1. Molecular structures of lamellarin I, K, L, and G trimethyl ether.

The novel structures and intriguing biological properties of the lamellarin alkaloids have garnered considerable attention, and the diverse approaches to their synthesis and their biological activities have been reviewed.[2b,3,8] We anticipated that the lamellarin core could be synthesized from compound **6** by hydrolysis and subsequent oxidative ring closure with $Pb(OAc)_4$. Compound **6** was prepared by palladium-catalyzed cross-coupling of **5**, which was synthesized through electrophilic substitution of key intermediate pyrrolo[2,1-*a*]isoquinoline **4**. In fact, several important strategies, including transition metal-catalyzed, photocatalyzed, or other oxidation reaction have been reported for the construction of C1-substituted pyrrolo[2,1-*a*]isoquinolines[9] (Scheme 1). However, it is difficult to synthesize the lamellarins from those C1-substituted skeletons. Fortunately, we found that C1-unsubstituted pyrrolo[2,1-*a*]isoquinoline **4** could be obtained by intermolecular cycloaddition of **3** with azomethine ylide generated *in situ* from **1** and **2**. This novel reaction holds promise for the total synthesis of lamellarins, and our retrosynthetic strategy is depicted in Scheme 1.

We initially investigated the reaction conditions using 1,2,3,4-tetrahydroisoquinoline (THIQ) **1a**, phenylglyoxal monohydrate **2a**, and (*E*)-(2-nitrovinyl)benzene **3a** as model substrates.

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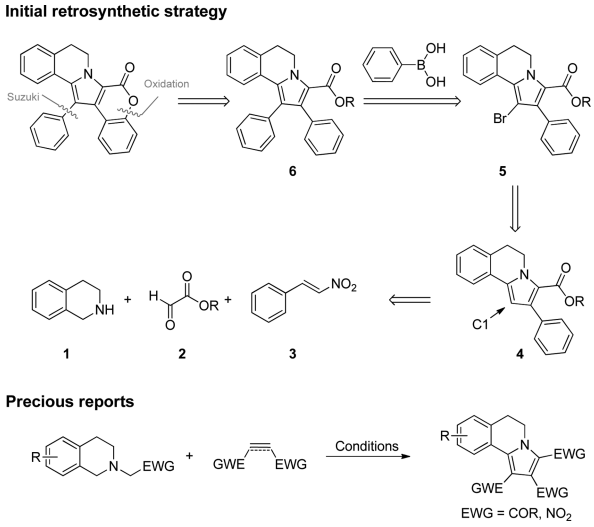
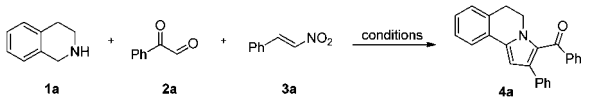
Scheme 1. Retrosynthetic Approach and Precious Reports



Compound **4a** was obtained in 34% yield when the reaction was performed in toluene at 80 °C for 2.5 h without any additives (entry 1). Encouraged by this result, various acids, solvents, and temperatures were screened for the reaction, and the results are summarized in Table 1. We were pleased to find that the addition of 2.0 equiv of $PhCO_2H$ remarkably improved the yield (entry 2). A variety of acids, including AcOH, TsOH, TfOH, and TFA, were screened to investigate their effect on the reaction, but there was no further improvement in the yield (entries 3−6). Solvent screening identified toluene as the optimum choice, and other solvents (DMSO, DMF, DCE, NMP, EG, EA, and 1,4-dioxane) gave lower yields (entries 7−13). The optimal reaction temperature for this protocol was determined to be 100 °C when we performed the reaction at temperatures between rt and 110 °C (entries 14−18). The optimized reaction conditions were thus identified as 1.0 equiv of **1a**, **2a**, and **3a** with 2.0 equiv of $PhCO_2H$ in toluene at 100 °C for 2.5 h.

Table 1. Optimization of the Reaction Conditions[a]

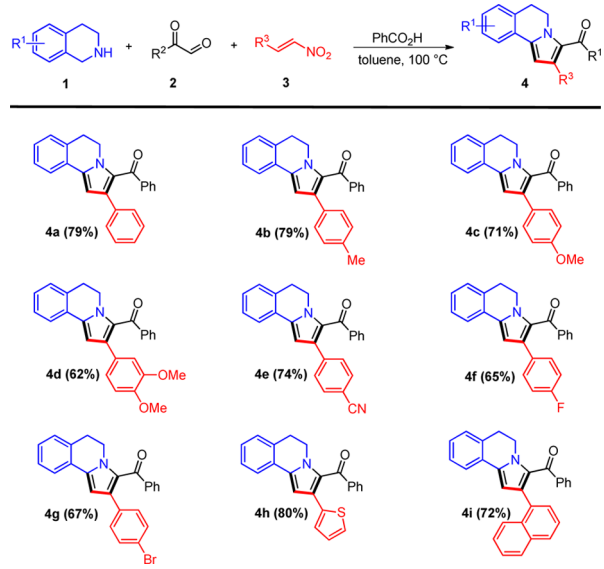


entry	solvent	acid	temp (°C)	yield[b] (%)
1	toluene		80	34
2	toluene	$PhCO_2H$	80	75
3	toluene	AcOH	80	72
4	toluene	TsOH	80	trace
5	toluene	TfOH	80	trace
6	toluene	TFA	80	69
7	DMSO	$PhCO_2H$	80	64
8	DMF	$PhCO_2H$	80	70
9	DCE	$PhCO_2H$	80	41
10	NMP	$PhCO_2H$	80	0
11	EG	$PhCO_2H$	80	60
12	EA	$PhCO_2H$	80	52
13	1,4-dioxane	$PhCO_2H$	80	50
14	toluene	$PhCO_2H$	rt	0
15	toluene	$PhCO_2H$	70	71
16	toluene	$PhCO_2H$	90	72
17	toluene	$PhCO_2H$	100	79
18	toluene	$PhCO_2H$	110	71

[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), **3a** (0.1 mmol, 1.0 equiv), acid (0.2 mmol, 2.0 equiv), and solvent (3 mL). The reaction was performed for 2.5 h. [b]Isolated yields.

With the optimized reaction conditions in hand, we proceeded to examine the scope of the reaction using a variety of substituted nitro olefins. As shown in Scheme 2, nitro olefins bearing

Scheme 2. Scope of Nitroolefin[a]



[a]Reaction conditions: **1a** (1 mmol, 1.0 equiv), **2a** (1 mmol, 1.0 equiv), **3** (1 mmol, 1.0 equiv), $PhCO_2H$ (2 mmol, 2.0 equiv), and solvent (5 mL). The reaction was performed for 2−8 h.

electron-neutral (H), electron-donating (4-Me, 4-OMe, 3,4-2OMe), or electron-withdrawing (4-CN) groups reacted smoothly to afford the corresponding products in excellent yields (62−79%; **4a**−**4e**). Halogen-substituted substrates (4-F, 4-Br) also reacted well to give the desired product **4f**−**4g** in 65% and 67% yields. (*E*)-2-(2-Nitrovinyl)thiophene and (*E*)-1-(2-nitrovinyl)naphthalene reacted as anticipated to give the corresponding products **4h**−**4i** in 80% and 72% yields, respectively. Aliphatic nitro alkenes were not compatible in this reaction (see the Supporting Information (SI)).

The scope of this reaction was subsequently expanded to arylglyoxal monohydrates, as shown in Scheme 3. The phenylglyoxal monohydrate bearing electron-donating (4-Me, 4-OMe) groups was smoothly transformed into corresponding products in good to excellent yields (72−82%; **4j**−**4k**). Satisfactory yields were also observed with halogen-substituted (4-Cl, 4-Br) groups attached to the benzene ring (68−70%; **4l**−**4m**). The desired products could be obtained in moderate yield from electron-withdrawing (4-NO_2) substrates (47%, **4n**). In addition, the heteroaromatic and sterically hindered substrate proceeded well to afford the expected product in good yield (69−73%; **4o**−**4p**). Additionally, the use of ethyl 2-oxoacetate **2i** as a substrate gave **4q** in 61% yield. We also reacted 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with **2i** and (*E*)-1,2-dimethoxy-4-(2-nitrovinyl)benzene, and corresponding product **4r** was obtained in 51% yield. The structure of **4q** was confirmed by X-ray crystallographic analysis (see the SI).

These results prompted us to attempt the synthesis of the lamellarin core, and the reaction scheme is shown in Scheme 4. Reaction of compound **4q** with NBS in DMF yielded C1-bromo-

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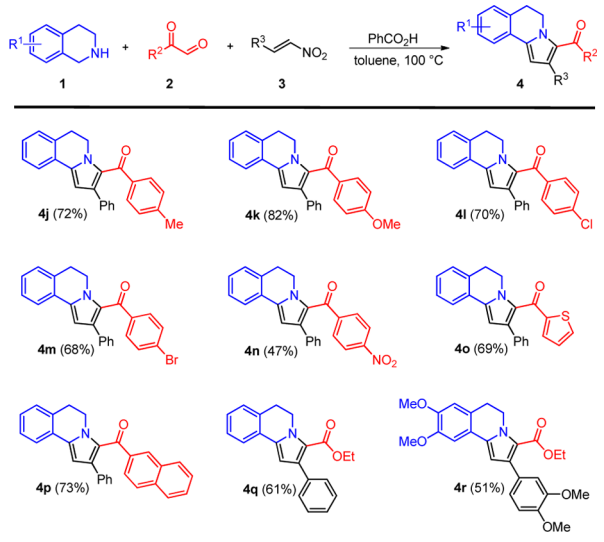
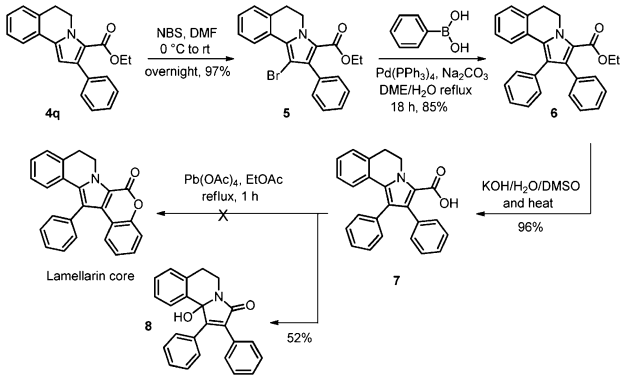
Scheme 3. Scope of Arylglyoxal Monohydrates[a]



[a]Reaction conditions: **1** (1 mmol, 1.0 equiv), **2** (1 mmol, 1.0 equiv), **3** (1 mmol, 1.0 equiv), $PhCO_2H$ (2 mmol, 2.0 equiv), and solvent (5 mL). The reaction was performed for 2−8 h.

Scheme 4. Suzuki Coupling and Attempted Oxidative Ring Closure

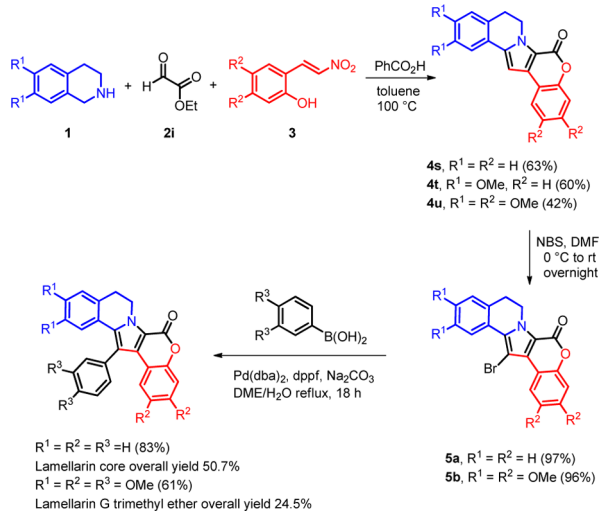


substituted compound **5** in 97% yield.[10] Then, palladium-catalyzed Suzuki−Miyaura coupling of **5** with phenylboronic acid under standard conditions [$Pd(dba)_2$ (10 mol %), Na_2CO_3, H_2O, DME, reflux, 18 h] afforded compound **6** in 85% yield.[11] Subsequent base-mediated hydrolysis of **6** provided compound **7** in 96% yield.[12] Unfortunately, reaction of **7** with $Pb(OAc)_4$ in refluxing EtOAc failed to furnish the lamellarin core but instead gave lactam **8**, which was confirmed by X-ray crystallographic analysis (see the SI). We reasoned that this behavior was caused by the larger electron density in the pyrrole ring.[13]

We next attempted to apply this reaction to **1a**, **2i**, and (*E*)-2-(2-nitrovinyl)phenol **3j**, hoping to synthesize ethyl 2-(2-hydroxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate because intermolecular lactonization would be easier than oxidative ring closure. Much to our delight, we obtained compound **4s** in 63% yield. The bromination proceeded cleanly to furnish compound **5a** in 97% yield. The final Suzuki−Miyaura coupling with phenylboronic acid under standard conditions proceeded as planned to afford the lamellarin core in an overall yield of 50.7%.

In addition, **3j** and (*E*)-4,5-dimethoxy-2-(2-nitrovinyl)phenol **3k** each reacted smoothly with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and **2i** to give the corresponding products in moderate yields (42%−60%; **4t**−**4u**), as shown in Scheme 5. This methodology was further utilized for the total synthesis of lamellarin G trimethyl ether with an overall yield of 24.5% in three steps.

Scheme 5. Synthetic Application



In conclusion, we have developed a novel and efficient intermolecular [3 + 2] cycloaddition for the directed synthesis of pyrrolo[2,1-*a*]isoquinolines and 1-dearyllamellarin core from available starting materials with simple reaction conditions. This methodology was extended to the three-step synthesis of the type Ia lamellarin core, which contains five fused rings, with an overall yield of 50.7%. In addition, we successfully achieved the total synthesis of lamellarin G trimethyl ether in three steps with an overall yield of 24.5%. To the best of our knowledge, this method represents the shortest access to the core of type Ia lamellarins with high yield.[7,8,9c,k,11,12,14] Further studies on lamellarin synthesis using this methodology are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00769.

Crystallographic data of **4q** (CIF)
Crystallographic data of **8** (CIF)
Experimental procedures, product characterizations, and copies of the ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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