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Annulation Reaction of 3-Acylmethylidene Oxindoles with Huisgen Zwitterions and Its Applications in the Syntheses of Pyrrolo[4,3,2-*de*]quinolinones and Marine Alkaloids Ammosamides

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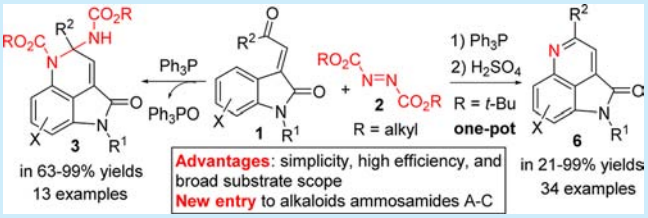
Supporting Information

ABSTRACT: A novel annulation reaction of 3-acylmethylidene oxindoles with Huisgen zwitterions is unveiled that leads to an unprecedented synthetic method for complex pyrrolo[4,3,2-*de*]quinolinones and marine alkaloids ammosamides A–C. This method features simplicity, high efficiency, and broad substrate scope and is accordingly anticipated to significantly facilitate the preparation and bioassay of the relevant pyrroloquinoline alkaloids and their analogues.



The pyrrolo[4,3,2-*de*]quinoline core represents a characteristic motif of many natural alkaloids that exhibit a wide range of biological activities, including potent cytotoxicity and pharmacological activity.[1] Shown in Figure 1 are some typical

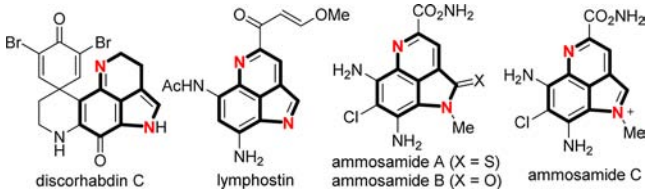
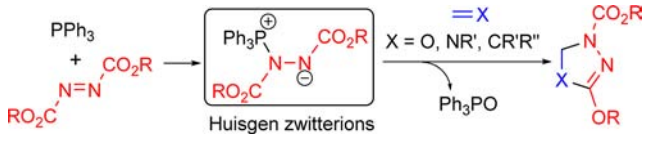


Figure 1. Representative natural pyrroloquinoline alkaloids.

examples of pyrroloquinoline alkaloids with attractive bioactivities.[2−5] Isolated early from marine sponges, discorhabdin C possesses potent cytotoxicities against several cancer cell lines such as murine leukemia cells P388 and L1210 and human colon cancer cells HCT-116.[2] Lymphostin as a natural immunosuppressant was first isolated from bacteria *Streptomyces* sp. KY11783 and exhibits potent inhibitory activities against lymphocyte kinase (IC_{50} 0.05 μM) and phosphatidylinositol 3-kinase (IC_{50} 0.001 μM).[3] Recently isolated from marine bacteria *Streptomyces* strain CNR-698, ammosamides A–C as new members of pyrroloquinoline alkaloids are able to influence tubulin and actin dynamics through myosin targeting.[4] Ammosamides A and B exhibit significant cytotoxicity against HCT-116.[4b] Ammosamide B and its methylated analogue have potent inhibitory activity against human quinone reductase II.[5] Owing to their promising biological properties and novel molecular structures, the pyrroloquinoline alkaloids have attracted a great deal of attention from the chemistry community in recent decades.[1] Many effective multistep synthetic strategies have already been developed in the total syntheses of some typical natural alkaloids.[1b,e,f,6] However, efficient and flexible synthesis of this family of alkaloids and their analogues remains a challenging goal.[7] A lack of simple and amendable synthetic methodology still hinders pyrroloquinoline alkaloids from the optimization of their biological activity and other relevant investigations. The development of general and efficient synthetic methods is therefore highly desirable.[8]

The Huisgen zwitterions, readily generated from Ph_3P and dialkyl azodicarboxylates, are well known as the key intermediate in the classical Mitsunobu reaction and early reported annulation reactions.[9] Recent renewed interest from Nair group and others has unveiled the attractive versatility of Huisgen zwitterions in the C–N bond-forming reactions.[10] In particular, in an array of annulation reactions with various electrophiles like carbonyls, imines, and electron-deficient alkenes, Huisgen zwitterions effect unique and efficient routes to aza-heterocycles (Scheme 1).[11,12]

Scheme 1. Annulation Modes of Huisgen Zwitterions



Intrigued by the unique annulation modes of Huisgen zwitterions and potential biological activity of oxindole derivatives, we very recently explored the possible annulation reaction between 3-acylmethylideneoxindoles **1** and in situ generated Huisgen zwitterions from azodicarboxylates **2** and Ph_3P (Table 1). To our surprise, an unexpected annulation reaction occurred, leading to dihydropyrrolo[4,3,2-*de*]-quinolinones **3**. This reaction does unveil a novel annulation

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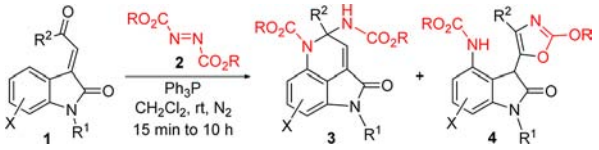
Table 1. Annulation Reaction between 3-Acylmethylidene Oxindoles 1 and Huisgen Zwitterions[a]



entry	X, R^1, R^2 in **1**	R in **2**	**3**[b] (%)	**4**[b] (%)
1	H, Bn, Ph (**1a**)	Et (**2a**)	**3a**, 84	**4a**, 13
2	H, Bn, 4-FC_6H_4 (**1b**)	**2a**	**3b**, 63	**4b**, 30
3	H, Bn, CO_2Et (**1c**)	**2a**	**3c**, 82	
4	**1c**	**2a**	**3c**, 99[c]	
5	H, Me, CO_2Et (**1d**)	**2a**	**3d**, 89[c]	
6	H, allyl, CO_2Et (**1e**)	**2a**	**3e**, 99[c]	
7	H, Boc, CO_2Et (**1f**)	**2a**	**3f**, 82[c]	
8	6-Br, Bn, CO_2Et (**1g**)	**2a**	**3g**, 85[c]	
9	H, Bn, Me (**1h**)	**2a**	complex	
10	**1a**	*i*-Pr (**2b**)	**3h**, 83	**4c**, 11
11	**1a**	*t*-Bu (**2c**)	**3i**, 96	trace
12	**1a**	Bn (**2d**)	**3j**, 94	trace
13	**1c**	**2b**	**3k**, 94[c]	
14	**1c**	**2c**	**3l**, 90[c]	
15	**1c**	**2d**	**3m**, 95[c]	

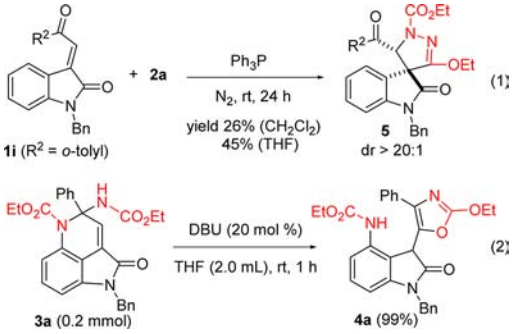
[a]Typical conditions: under a N_2 atmosphere, to a stirred mixture of **1** (0.5 mmol) and **2** (0.75 mmol) in CH_2Cl_2 (5.0 mL) was added Ph_3P (0.75 mmol), and the resulting mixture was stirred at rt for 15 min to 10 h until **1** was completely consumed. For details, see the Supporting Information. [b]Isolated yields. [c]THF was used instead of CH_2Cl_2.

mode of Huisgen zwitterions involving a rare N−N bond cleavage and also provides an unprecedented one-step strategy to construct a complex pyrrolo[4,3,2-*de*]quinoline skeleton. Further investigations have resulted in a simple and highly efficient synthetic methodology for a variety of pyrrolo[4,3,2-*de*]-quinolinones and natural alkaloid ammosamides A−C as well. Herein, we communicate the relevant results.

Initially, we surveyed the model reaction between 3-(benzoylmethylidene) oxindole **1a**, diethyl azodicarboxylate **2a**, and Ph_3P for optimal conditions by varying the ratio of reactants and the solvent (for details, see the Supporting Information). Under a nitrogen atmosphere, the reaction of **1a** (0.5 mmol), **2a** (0.75 mmol), and Ph_3P (0.75 mmol) in a solvent (5.0 mL) like CH_2Cl_2, $CHCl_3$, toluene, acetonitrile, 1,4-dioxane, and THF readily delivered the annulation product **3a** in fair to good yields after being stirred at rt for 15 min to 24 h. A concurrent minor product **4a** was also collected in less than 25% yields. The best yield (84%) of **3a** was obtained from the model reaction run in CH_2Cl_2 at rt for 15 min with the minor product **4a** in 13% yield (Table 1, entry 1).

The scope of the reaction was investigated under the preferred conditions (Table 1). With azodicarboxylate **2a** (R = Et) used as a representative reactant, a selection of 3-acylmethylidene oxindoles **1** were tested. The aryl-substituted oxindoles **1** like **1b** (R^2 = *p*-FC_6H_4) readily gave the annulation product **3b** in 63% yield and minor product **4b** in 30% yield (entry 2). Functional group ester-substituted oxindoles **1** (R^2 = CO_2Et) proved to be effective in the annulation reaction, giving the products **3** exclusively (Table 1, entries 3−8). Under the typical conditions, the reaction of **1c** and **2a** readily afforded **3c** as a sole product in 82% yield (entry 3). Running the reaction in THF even brought about a 99% yield (entry 4). Other typical ester-substituted oxindoles **1d−g** all exclusively delivered their annulation products **3** in good to excellent yields (entries 5−8). However, methyl-substituted oxindole **1h** (R^2 = Me) proved to be ineffective in the reaction with **2a** (entry 9). Choosing **1a** as one reactant, different azodicarboxylates **2** were also examined (entries 10−12). Diisopropyl azodicarboxylate (**2b**) readily gave the annulation product **3h** in 83% yield and minor product **4c** in 11% yield (entry 10). In contrast, azodicarboxylates **2c** (R = *t*-Bu) and **2d** (R = Bn) both delivered their annulation products **3** in excellent yields as the sole separable products (entries 11 and 12). In the annulation reactions with ester-substituted **1c**, azodicarboxylates **2b−d**, just like **2a**, all delivered their exclusive products **3** in high yields (entries 13−15).

As shown in Table 1, aryl-substituted oxindoles **1** are effective substrates, affording dihydropyrroloquinolinones **3** as the major product (Table 1, entries 1 and 2). However, an interesting exception was observed: under similar conditions, *o*-tolyl-substituted oxindole **1i** (R^2 = *o*-tolyl) failed to deliver the expected product but a spirooxindole−pyrazoline **5** in modest yields (eq 1). Presumably, the considerably increased steric effect

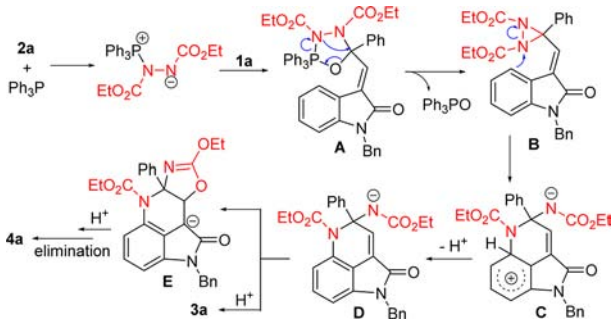


of *o*-tolyl group hindered its adjacent carbonyl from involvement in the expected annulation reaction, and consequently, the reaction was led to a distinct but known pathway.[13]

To discern clues about the formation of product **4**, we treated **3a** in THF with a catalytic amount of amine base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at rt for 1 h and found that **3a** was completely converted to **4a** in 99% yield (eq 2). This result shows the annulation product **3** is convertible to the concomitant product **4** under base catalysis.

Although a precise mechanism of this annulation reaction remains elusive, on the basis of our results and closely related reports,[14−16] a proposed reaction is exemplified in Scheme 2. The reaction sequence should be initiated with the in situ generation of Huisgen zwitterion.[17] As a nucleophile, Huisgen zwitterion engages in a nucleophilic addition to the ketone carbonyl of 3-acylmethylidene oxindole **1a** to form intermediate **A**, which then eliminates triphenylphosphine oxide to produce

Scheme 2. Proposed Mechanism of the Annulation



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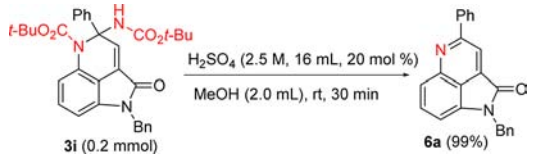
diaziridine **B**.[14] Under the intramolecular attack of the electron-rich benzene ring, highly strained diaziridine **B** undergoes a heterolytic fission of the N−N bond, generating tricyclic intermediate **C**.[15,16] Through a proton transfer, **C** readily furnishes the annulation product **3a** via a possible intermediate **D**. In another scenario, intermediate **D** undergoes an intramolecular oxo-Michael addition, followed by a proton transfer and a ring-opening elimination to generate the concomitant product **4a**.

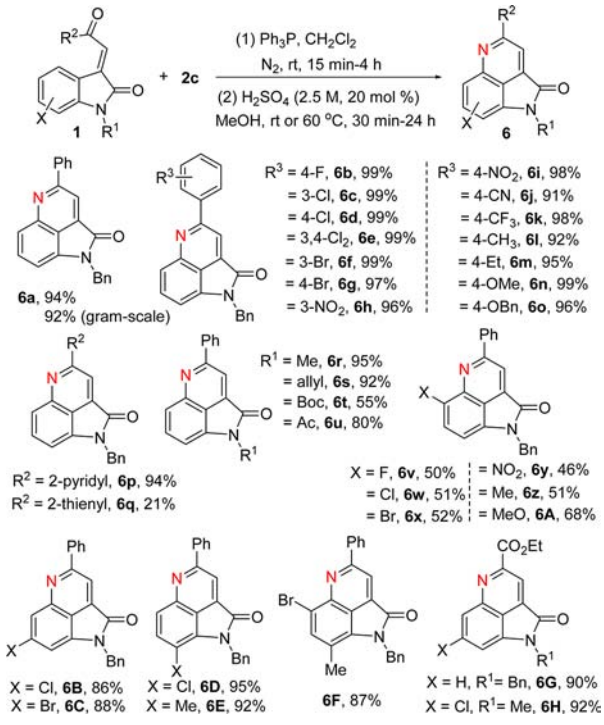
To expand its synthetic application of the annulation reaction to the challenging pyrrolo[4,3,2-*de*]quinolinone core, we further investigated the aromatization transformation of product **3**. Considering the susceptibility of Boc group to the acid-triggered decomposition, we chose the annulation product **3i** as a substrate and treated it with the catalytic amount of aq H_2SO_4 (2.5 M, 20 mol %) in methanol at rt for 30 min (Scheme 3). To our delight, the desired aromatization product **6a** was obtained in almost theoretical yield.

Scheme 3. Aromatization Transformation of 3i into 6a

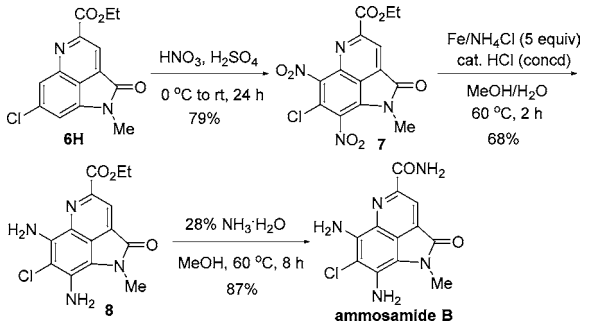


With this exciting result in hand, we devised a two-step, one-pot synthesis of pyrrolo[4,3,2-*de*]quinolinones **6** from 3-acylmethylidene oxindoles **1** and azodicarboxylate **2c** (Scheme 4). Under the typical conditions for the annulation reaction, **1** and **2c** reacted at rt until **1** was completely consumed. The reaction mixture was then treated with the catalytic amount of H_2SO_4, yielding the desired product **6** (for details, see the Supporting Information). The results listed in Scheme 4 reveal that this one-pot synthetic method of pyrrolo[4,3,2-*de*]-quinolinones **6** has a broad scope with respect to substrate **1**. Variation of substituents R^1, R^2, and X in **1** is flexible and compatible. When R^2 was aryl or heteroaryl, **1** readily afforded the corresponding products **6a−p** in excellent yields except **1j** (X = H, R^1 = Bn, R^2 = 2-thienyl) only delivered its product **6q** in a 21% yield. Other substrates **1** bearing representative substituents R^1 at the nitrogen atom or different substituents X on the indole framework all smoothly afforded their corresponding products **6r−z** and **6A−F** in moderate to excellent yields. Functional group ester substituted **1c** and **1k** (R^1 = Me, R^2 = CO_2Et, X = 6-Cl) were also effective, giving their corresponding products **6G** and **6H** in high yields. A gram-scale synthesis of **6a** was also illustrated in a 92% yield with **1a** (5.0 mmol) used (Scheme 4). Thus, this one-pot synthetic method constitutes a simple and efficient route to pyrrolo[4,3,2-*de*]quinolinones **6** with highly flexible substituents.

Scheme 4. One-Pot Synthesis of Pyrrolo[4,3,2-*de*]quinolinones



Scheme 5. Concise Total Synthesis of Ammosamide B



6H, ammosamide B can be readily obtained in three steps including nitration, reduction, and ammonolysis with an overall yield of 46.7%.[18] According to Fenical's reports,[4b,c] ammosamide B can be conveniently converted to ammosamides A and C through one or two more steps. Thus, this methodology provides simple and practical access to ammosamides A−C.

In summary, a novel annulation reaction between 3-acylmethylidene oxindoles and in situ generated Huisgen zwitterions is disclosed, which represents a new annulation mode of Huisgen zwitterions involving a rare N−N bond cleavage. More importantly, this reaction unveils an unprecedented one-step strategy to efficiently construct complex pyrrolo[4,3,2-*de*]quinoline skeleton from readily available materials. On the basis of this annulation reaction, a one-pot synthetic methodology has been successfully developed, providing simple and practical access to a wide variety of pyrrolo[4,3,2-*de*]quinolinones and natural alkaloid ammosamides A−C as well. This robust methodology is accordingly anticipated to significantly facilitate the structure−activity relationship studies of natural pyrroloquinoline alkaloids and their analogues. Relevant investigations are currently underway 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.6b00456.

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Experimental details, characterization data, X-ray crystal structures for **3a**,**c**, **4b**, **5**, **6a**, and **7**, and NMR spectra for new compounds (PDF)
Crystallographic file of product **3a**(CIF)
Crystallographic file of product **3c**(CIF)
Crystallographic file of product **4b**(CIF)
Crystallographic file of product **5**(CIF)
Crystallographic file of product **6a**(CIF)
Crystallographic file of product **7**(CIF)

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Notes

The authors declare no competing financial interest.

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(16) A similar electrophilic aromatic substitution with an in situ generated nitrenium ion is proposed in the synthesis of 2-oxindoles from *N*-chloro-*N*-methoxyamides. Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728.

(17) The in situ generation of Huisgen zwitterions is confirmed by the NMR monitoring experiments. For details, see the Supporting Information.

(18) Counting from the commercially available 6-chloroisatin, ammosamide B was synthesized in seven simple steps with an overall yield of 12.9%. A schematic synthetic route is available in the Supporting Information. This route currently represents the most efficient synthesis of ammosamide B. For the total synthesis of ammosamide B, see refs 4c, 6i,j,l, and 7e.

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