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Synthesis of pyrrolo-[2,1-*j*]quinolone framework via intramolecular electrophilic *ipso*-cyclization

Lila Low-Beinart, Xiaohan Sun, Eli Sidman, Tanay Kesharwani *

Chemistry Program, Bard College, PO Box 5000, Annandale-on-Hudson, NY 12504, USA

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ABSTRACT

The challenging pyrrolo-[2,1-*j*]quinolone core structure has been synthesized from *N*-(alkynoyl)-6-methoxytetrahydroquinoline in good yields using electrophilic cyclization as the key step. These reactions require simple starting materials and mild reaction conditions. In addition, we have demonstrated that the iodine moiety, which could be easily introduced in the final step, is very useful for further functionalization by employing various palladium-catalyzed cross-coupling reactions.

1*H*-Pyrrolo-[2,1-*j*]quinolone is a commonly found core structure in the family of tricyclic marine alkaloids such as Lepadiformine[1] and Cylindricine (Fig. 1).[2] The complex three-ring core structure found in these molecules makes them intriguing synthetic targets. These alkaloids exhibit interesting biological activities such as cytotoxicity against cancer cells, antiarrhythmic properties, and other cardiovascular effects.[3] Ever since Cylindricines were isolated by Blackman et al.[2] many attempts have been made to synthesize them and the other marine alkaloids.[4] In these processes the synthesis of the core structure was lengthy, often requiring several steps, and resulted in low to moderate yields.

Over the last decade halogen mediated electrophilic cyclization reactions have emerged as a very useful method in organic synthesis.[5] Pioneering work in this area has been reported by Larock and co-workers as they have reported synthesis of several heterocycles and carbocycles including indole,[6] benzofuran,[7] benzo[*b*]thiophene,[8] benzo[*b*]selenophene,[9] furan,[10] quinoline,[11] isoquinoline,[12] and benzopyran.[13] Recently, synthesis of spiro[4.5]trienones was reported via *ipso*-iodocyclization of 4-(*p*-Methoxyaryl)-1-alkynes.[14] Several variations of these *ipso*-cyclization reactions have been reported since then.[15]

Herein we describe a novel approach for the synthesis of the 1*H*-pyrrolo-[2,1-*j*]quinolone core structure using the electrophilic *ipso*-cyclization of various *N*-(alkynoyl)-6-methoxytetrahydroquinolines (Scheme 1).[16] This method can be used to synthesize these highly functionalized heterocyclic compounds under mild

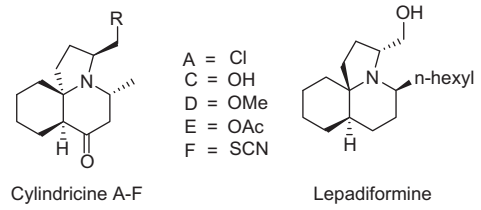
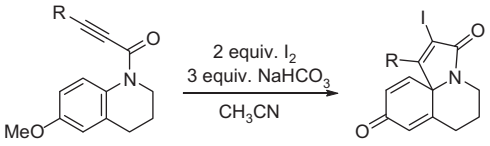


Figure 1. Core structures of naturally occurring Cylindricines and Lepadiformine.



Scheme 1. Synthesis of 1*H*-pyrrolo-[2,1-*j*]quinolone framework via *ipso*-iodocyclization.

reaction conditions starting from commercially available 6-methoxy-1,2,3,4-tetrahydroquinoline (**1**) in two or three steps.

To synthesize *N*-(alkynoyl)-6-methoxytetrahydroquinolines **2** and **3**, HATU coupling between tetrahydroquinoline **1**, and phenylpropiolic acid or octynoic acid was performed. These couplings were successful and produced propiolamides **2** and **3** in very high yields of 81% and 93%, respectively (Scheme 2). *N*-(alkynoyl)-6-methoxytetrahydro-quinolines **5**–**9** were synthesized by the reaction of carbomoyl chloride **4** with alkynyl lithiums in yields

* Corresponding author. Tel.: +1 845 752 2352.
E-mail address: tkesharw@bard.edu (T. Kesharwani).

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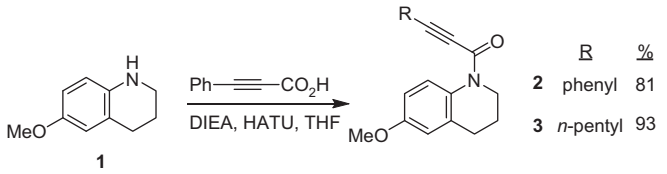
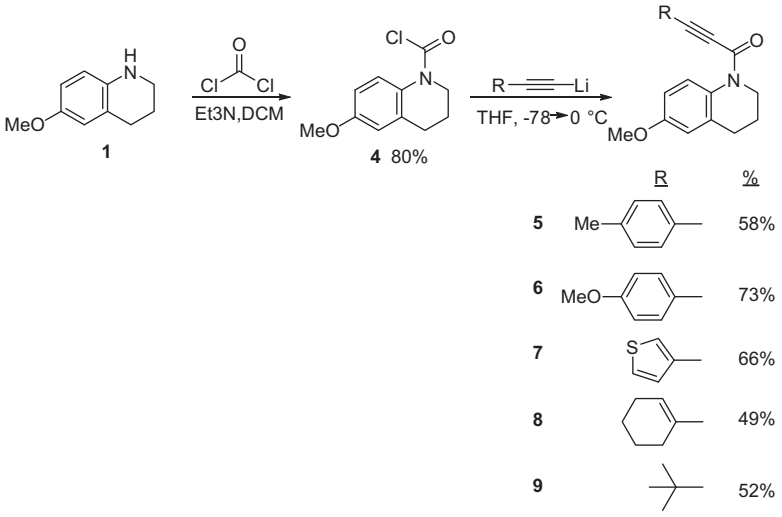


Scheme 2. Synthesis of *N*-(alkynoyl)-6-methoxytetrahydroquinolines via HATU coupling reaction.

ranging from 49% to 73% (Scheme 3). Carbomoyl chloride **4** was synthesized from the reaction of 6-methoxytetrahydro-quinoline with phosgene using Et_3N as a base. This reaction furnished **4** in high yield of 80% (Scheme 3).

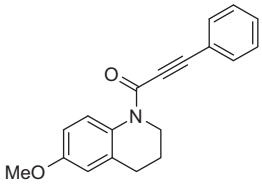
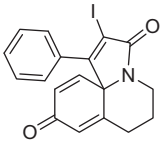
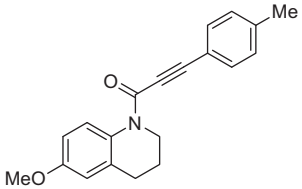
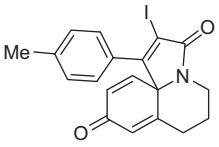
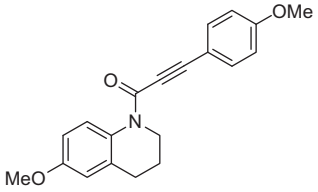
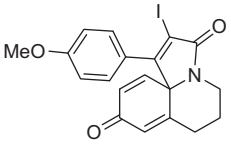
The reaction of propiolamide 2 with I_2 and $NaHCO_3$ using CH_3CN as solvent resulted in the formation of the desired pyrrolo-[2,1-*j*]quinolone **10** in an excellent yield of 91% (Table 1, entry 1). To study the scope of this reaction, various electrophiles such as Br_2, NBS, and NIS were employed. Cyclization attempts using Br_2 and NBS were unsuccessful whereas NIS in acetic acid resulted in the formation of **10** in a modest yield of 40% (entry 2). Since, NIS resulted in a lower yield of product we continued our study of electrophilic cyclization using I_2 as the electrophile.

To further study the scope of this reaction, substituted propiolamides were employed. Placing a tolyl functionality on the alkyne furnished **11** in slightly lower yield than **10** (entry 3). Using the stronger electron-rich group, *p*-methoxyphenyl, resulted in 83% yield of **12** (entry 4). The heteroaryl and vinyl groups were success-



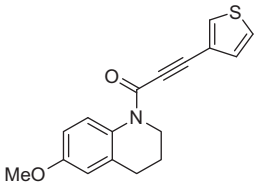
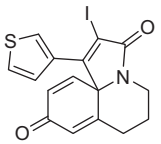
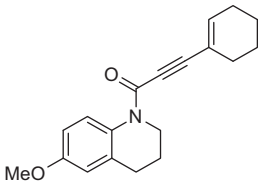
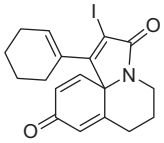
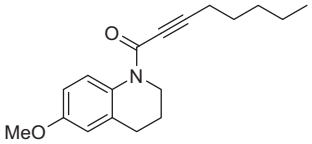
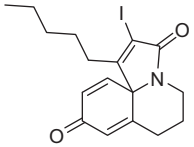
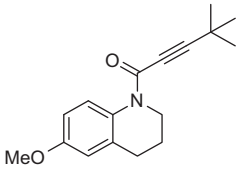
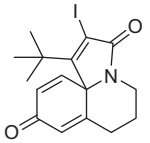
Scheme 3. Synthesis of *N*-(alkynoyl)-6-methoxytetrahydroquinolines from carbomoyl chloride **4** and alkynyl lithiums.

Table 1
Iodocyclization of *N*-(alkynoyl)-6-methoxytetrahydroquinolines[a]

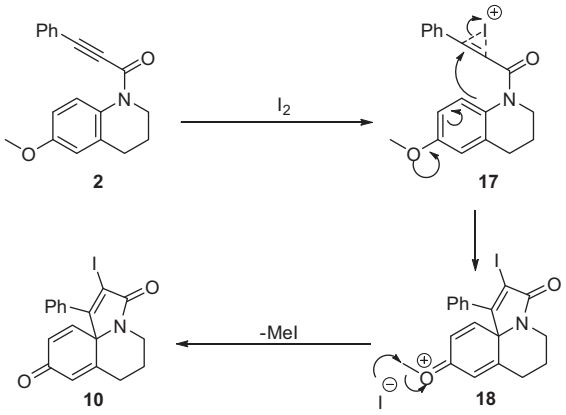
Entry	Alkyne		Reaction conditions[a]	Product		Yield[b] (%)
1		**2**	A		**10**	91
2		**2**	B		**10**	40[c,d]
3		**5**	A		**11**	89
4		**6**	A		**12**	83

(*continued on next page*)

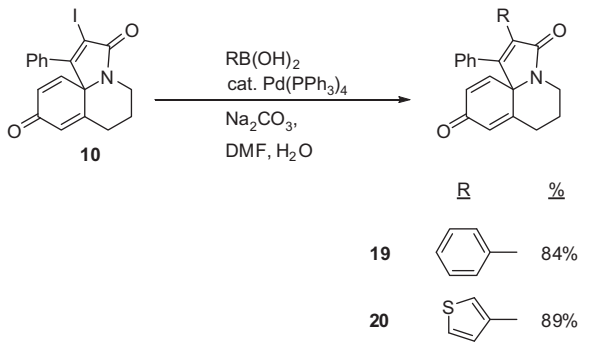
Table 1 (*continued*)

Entry	Alkyne		Reaction conditions[a]	Product		Yield[b] (%)
5		**7**	A		**13**	76
6		**8**	A		**14**	66
7		**3**	A		**15**	45
8		**9**	A		**16**	0

[a] All reactions were performed using 0.30 mmol of propiolamides, 2 equiv of I_2, and 3 equiv of $NaHCO_3$ in 6 mL of CH_3CN at room temperature for 24 h.
[b] Isolated yields.
[c] Reaction was performed using 0.25 mmol of propiolamides and 2 equiv of NIS in 2 mL of CH_3COOH at room temperature for 24 h.
[d] Yield was determined by NMR using 2-bromobenzaldehyde as an internal standard.



Scheme 4. Plausible mechanism for *ipso*-iodocyclization.



Scheme 5. Functionalization of **10** using Suzuki cross-coupling reactions.

fully employed, and the resulting products **13** and **14** were obtained in good yields of 76% and 66% respectively (entries 5 and 6). The cyclization of the *n*-pentyl group to form **15** resulted in the modest yield of 45% (entry 7) and the cyclization of the *tert*-butyl functionality did not lead to any cyclized product **16** (entry 8). The difference in yields of the two alkyl functionalities can be explained by their differing geometry. We believe that the *tert*-butyl group is unable to approach the quinoline's aromatic ring because of its bulky size resulting in no cyclization.

The proposed mechanism of electrophilic *ipso*-iodocyclization proceeds via initial co-ordination of electrophilic iodine with the alkyne to form intermediate **17**, followed by an *ipso*-attack from the electron-rich aromatic ring to generate cationic intermediate **18** (Scheme 4). The presence of the methoxy group increases the electron density on *ipso*-carbon, which in turn facilitates the necessary attack on alkyne by the aromatic ring. The methyl group in intermediate **18** is subsequently removed by the iodide nucleophile via S_N2 reaction.

In order to demonstrate the general utility of the *ipso*-iodocyclization products, attempts were made to further functionalize **10** using Suzuki coupling reactions (Scheme 5). The Suzuki coupling reaction using phenylboronic acid produced the desired product with a high yield of 84%. The electron rich 3-thienylboronic acid resulted in the formation of **20** in slightly higher yields of 89%.

In summary, the pyrrolo-[2,1-*j*]quinolonecore structure was successfully synthesized in high yields using electrophilic cyclization reaction. I_2 was successfully employed as electrophile in these cyclization reactions. Cyclization with NIS resulted in low yield of the product. Our efforts to synthesize bromine analogues of pyrrolo-[2,1-*j*]quinolone were unsuccessful as the cyclization reaction with Br_2 and NBS failed for reasons that we do not presently understand. Alkynes bearing aryl, heteroaryl, vinyl, and alkyl groups were successfully cyclized. The core structure was further functionalized using Suzuki cross-coupling reactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.014.

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16. *Method:* To a 6 dram vial containing alkyne (0.30 mmol), 4 mL of CH_3CN and $NaHCO_3$ (0.90 mmol, 76 mg) were added. To this solution I_2 (0.60 mmol, 152 mg) dissolved in 2 mL CH_3CN was added and the solution was allowed to stir for 24 h. Reaction was quenched with H_2O (10 mL) and $Na_2S_2O_7$ was added to remove excess I_2. This mixture was extracted with DCM (3×20 mL) and the resulting organic layer was dried over Na_2SO_4. After concentration under vacuum, the crude product was purified by column chromatography using hexanes/ethyl acetate (5:1) as the eluent. 2-iodo-1-phenyl-6,7-dihydro-3*H*-pyrrolo[2,1-*j*]quinoline-3,9(5*H*)-dione (**10**) was isolated as a light yellow solid (110 mg, 91%): mp 229–230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.32 (m, 3H), 7.07 (dd, J = 8.1, 1.6 Hz, 2H), 6.54 (d, J = 9.8 Hz, 1H), 6.36 (t, J = 1.7 Hz, 1H), 6.20 (dd, J = 9.8, 1.7 Hz, 1H), 4.24 (dd, J = 14.2, 8.0 Hz, 1H), 2.93–2.79 (m, 1H), 2.63–2.41 (m, 2H), 2.15–2.02 (m, 1H), 1.97–1.80 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.5, 171.5, 159.9, 157.4, 145.6, 132.1, 131.6, 130.1, 129.5, 128.64, 128.62, 128.1, 128.0, 98.3, 74.2, 37.69, 27.1, 26.2; HRMS (ESI+, m/z) calcd for $(C_{18}H_{15}INO_2)^+$ $(M+H)^+$ 404.0142, found 404.0126.