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A MICROWAVE-ASSISTED, TWO-STEP SYNTHESIS OF INDOLO[3,2-*c*]QUINOLINES VIA FISCHER INDOLIZATION AND OXIDATIVE AROMATIZATION

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Abstract – Herein, we describe a practical two-step synthesis of an indolo[3,2-*c*]quinoline scaffold from substituted 4-methoxyquinolines using Fischer indole method and oxidative aromatization in one-pot under microwave radiation. With this protocol, a biologically active natural product, isocryptolepine, and its analogues can be readily and efficiently accessed. Also, this method has been efficiently utilized to generate a series of novel pyrrole-containing derivatives of this heterocyclic system.

INTRODUCTION

Indoloquinoline skeletons, hosting fused an indole and a quinoline rings, are widely present in various natural and unnatural products endowed with diverse biological and pharmacological activities.[1] They have played significant role in the design and development of new drugs, as they are intercalating into DNA molecules, resulting in alteration of physiological functions of the DNA, and eventually led to inhibit its biosynthesis.[2] Therefore, indoloquinoline hosting structures are reported to have broad spectrum of biological activities including antiproliferative, antiparasitic, antifungal, antibacterial, cytotoxic, anti-inflammatory and antihyperglycaemic. This heterocyclic system is abundant in alkaloids isolated from *Cryptolepis sanguinolenta* plants, as depicted in Figure 1.[3] Among them, isocryptolepine (**1**) exhibits antimalarial activity, which has been remarkably improved by various substituents on the phenyl rings as demonstrated by the synthetic analogue **2** (Figure 1).[4]

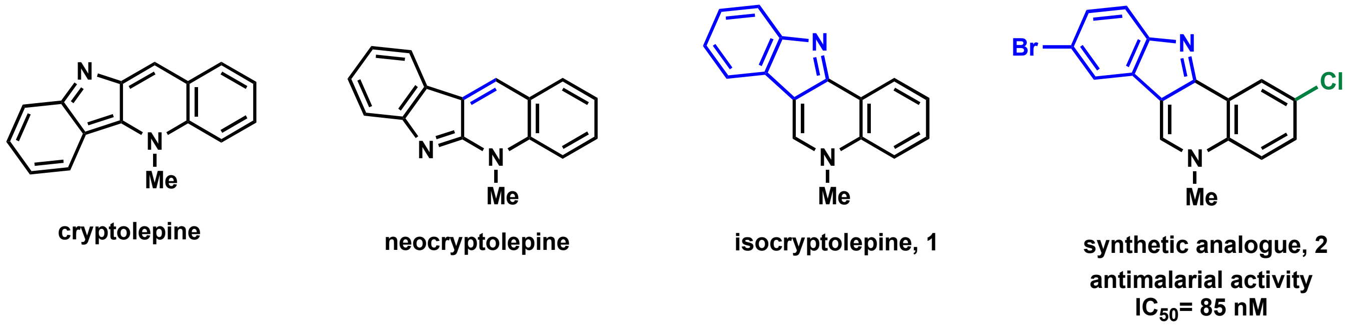


Figure 1. Indoloquinoline-containing alkaloids and a synthetic derivative

There are many synthetic approaches available to access an indolo[3,2-*c*]quinoline skeleton, especially for the synthesis of isocryptolepine and its derivatives.[5] Highly efficient, economical and environmentally benign synthesis are still desirable not only to access this privileged heterocyclic skeleton but also synthetic derivatives for drug discovery. Among these strategies, Fischer indole synthesis has been utilized by four different groups using 4-quinolinones indicated in Figure 2.[6] Due to limited availability and versatility of these starting materials, we focused on developing cheaper, faster and more efficient synthetic approach involving to generate structurally diverse indolo[3,2-*c*]quinoline framework.

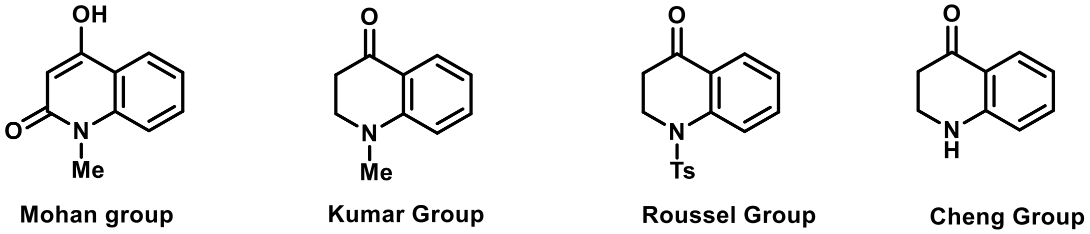
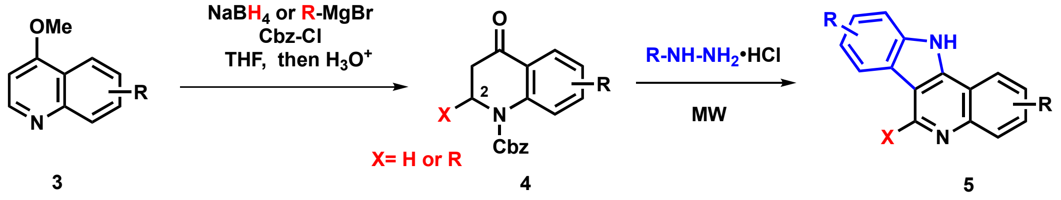


Figure 2. 4-Quinolinones used for Fischer indole formation

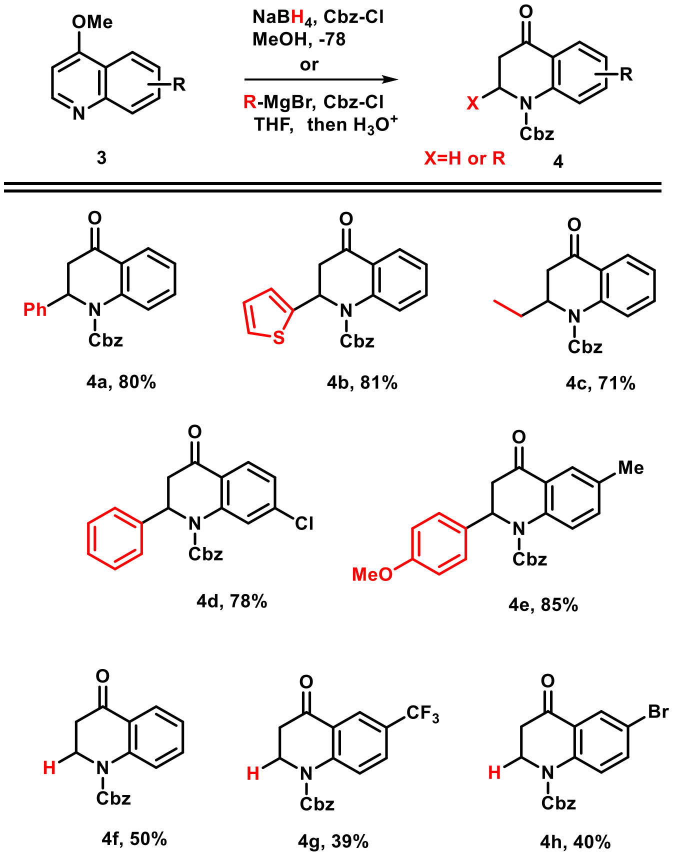
As part of our research program to develop novel methods for the synthesis of substituted and fused pyridines by oxidative aromatization,[7] we have become interested in developing a facile and general route to access indolo[3,2-*c*]quinoline skeleton. In this route, this heterocyclic framework will be accessed in two steps from commercially available substituted 4-methoxyquinolines (**3**), which is summarized in Scheme 1. In the first step, 2,3-dihydro-4-quinolinones (**4**) can be generated by the addition of a hydride or carbon nucleophile to the activated 4-methoxyquinolonium salts. In the second key step, three type of transformation can be realized in one pot under acidic condition: Fischer indole formation, protecting group cleavage and then oxidative aromatization. Expectedly, the formation of **5** will be promoted by microwave irradiation in terms of efficiency, which has been routinely applied for synthesis.[8]



Scheme 1. Strategy to access indolo[3,2-*c*]quinoline in two steps

RESULTS AND DISCUSSION

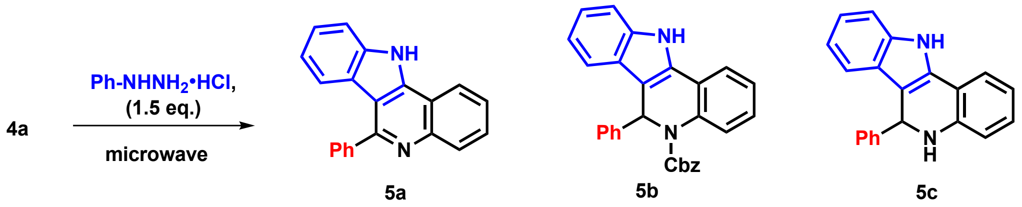
In situ formed *N*-acyl-4-methoxyquinolinium salts, interestingly, have not been studied in detail for a nucleophilic addition,[9] unlike *N*-acyl-4-methoxypyridinium salts, which have been used to obtain 2,3-dihydropyridones by the addition of hydride or organometallic reagents followed by acidic work-up.[10] In a similar way, 4-methoxyquinolines (**3**) could afford substituted (X=R in **4** at C-2) or unsubstituted (X=H in **4**) 2,3-dihydroquinolinones (**4**) in one-pot after activation with an acyl group, nucleophilic addition and then acidic hydrolysis. To our surprise, hydride addition to this type of quinolinium salts have not been studied and only some examples of Grignard addition has been reported in the literature.[11] Therefore, we initially focused on the addition various type of Grignard reagents with modified procedure as depicted in Scheme 2.



Scheme 2. Generation of 2,3-dihydroquinolinones

As seen from the results, aryl, heteroaryl, alkyl Grignard reagents can be smoothly added to the salts carrying various substituents on the phenyl. As for hydride addition, $NaBH_4$ was applied among others, which afforded superior results in case of *N*-Cbz protected 4-methoxypyridinium salts.[12] As indicated in Scheme 2, 2,3-dihydroquinolinones were generated in moderate yields.

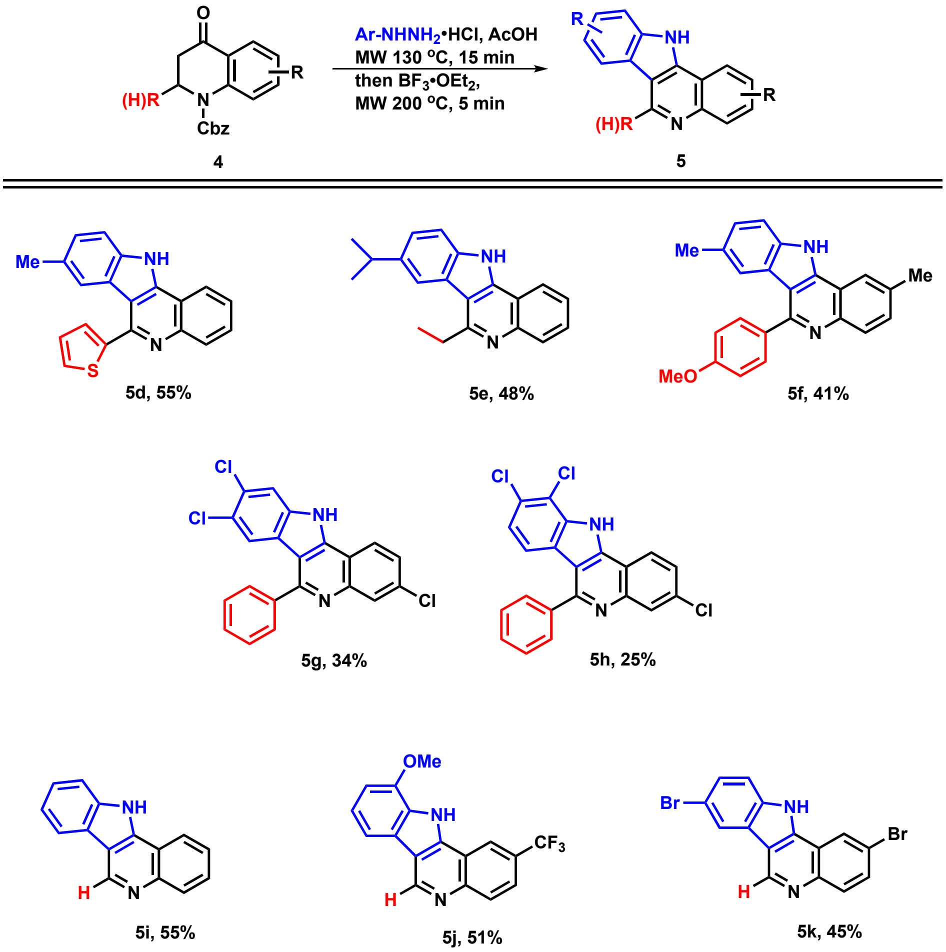
Table 1. Studies for Fischer indolization and oxidative aromatization[a]



Entry[a]	MW Condition (Temp., and Time)	Solvent	Additive (Eq.)	Yield for **5a** (%)	Yield for **5b** (%)
1	120 °C, 5 min	AcOH	-	0	85
2	220 °C, 5 min	AcOH	-	72	0
3	120 °C, 5 min then 200 °C, 5 min	AcOH	-	0	94
4	120 °C, 5 min then 220 °C, 5 min	AcOH	-	67	0
5	120 °C, 5 min then 220 °C, 5 min	AcOH	TsOH (1.0)	66	0
6	220 °C, 5 min	AcOH	$Cu(OTf)_2$ (1.0)	58	0
7	220 °C, 5 min	AcOH	$Pd(OAc)_2$ (0.2)	61	0
8	120 °C, 5 min	toluene	$AlCl_3$	47	0
9	220 °C, 5 min	EtOH	HCl (1.0)	72	5
10	130 °C, 15 min then BF_3•OEt_2, 200 °C, 5 min	AcOH	BF_3•OEt_2 (10)	78	0

[a] Yields were determined after purification on silica gel chromatography

After obtaining the starting materials, the second step, which involves microwave-enhanced three transformations in one-pot, was investigated using **4a** and phenylhydrazine hydrochloride as model substrates. This step potentially could lead to the formation of the desired product **5a**, the Cbz-protected indole product **5b** and the unoxidized indole product **5c**. As shown in Table 1, **5a** was not observed in refluxing acetic acid, while **5b** was the major product (entry 1). When the temperature was raised to 220 °C, **5a** was generated in 72% yield (entry 2), and no **5b** was observed, which indicated the Cbz cleavage could be realized at high temperatures.[13] Interestingly, **5c**, which could be easily oxidized to **5a**, was not observed under these conditions.[14] In entry 3, we applied a gradual temperature rise (120 °C for 5 min then 200 °C for 5 min) to first ensure **5b** formation, which improved the yield for **5b** (94%), but no **5a** is observed. This indicates that higher temperature (more than 200 °C) is required to cleave the Cbz group under this condition. Therefore, the temperature was raised to 220 °C after the indole formation, which expectedly generated **5a** in 67% yield (entry 4). Various additives, solvents, and temperatures (entries 5-9) were applied, but the yields for **5a** were in moderate range. When the reaction was radiated to 130 °C for 15 min and then Lewis acid BF_3•OEt_2 addition followed by heating to 200 °C for 5 min, the superior yield 78% was obtained for the formation of **5a** (entry 10).[15]

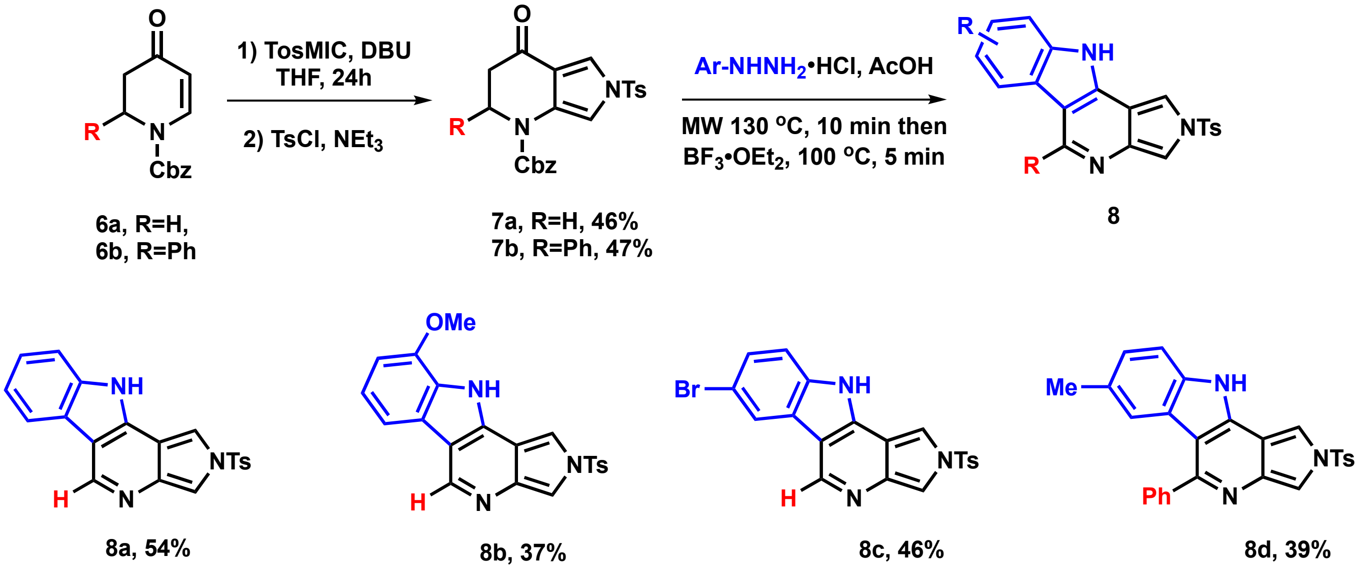


Scheme 3. Synthesis of indoloquinolines from 2,3-dihydroquinolinones

With the optimal reaction protocol for microwave irradiation established, the scope of the reaction was investigated using substituted and unsubstituted 2,3-dihydroquinolinones (**4**) and arylhydrazines.

As seen from the results in Scheme 3, **4** with various groups such as aryl (**4a**, **4d**, **4e**), heteroaryl (**4b**), alkyl (**4c**) afforded the desired indole products **5d**, **5e** and **5f** in moderate yields (41% to 59%). Additionally, when arylhydrazines with electron donating (alkyl and alkoxy) and withdrawing groups (halides) were employed, no significant change was observed in yields. In case of 3,4-dichlorophenylhydrazine hydrochloride, the formation of two regioisomers **5g** and **5h** is observed in almost 3:2 ratio. Similarly, unsubstituted **4** (i.e., R=H) gave the indole products **5i**, **5j** and **5k** in moderate yields (45% to 55%).

Our group also focused on generation of novel pyrroles from electron-poor alkenes using TosMIC reagent and their further modifications.[7b] Therefore, we decided to use the pyrrole structures **7a** and **7b**, in which the benzene in **4** was replaced by a pyrrole ring, for the one-pot synthesis of the unique pyrrole-containing indoloquinoline **8**. Firstly, **7a** (R=H) and **7b** (R=Ph) were easily accessed from **6a** and **6b** using the well-developed protocol, which afforded them in 46% and 47% yield over two steps, respectively. In a similar way, **7a** and **7b** are exposed to our optimal condition to generate **8**, however; in this case, lower temperature (100 °C) is employed for the Cbz group cleavage and oxidation, as pyrroles decomposed at higher temperature. Pleasingly, with this modified condition, **7a** and **7b** afforded the pyrrole derivatives indoloquinolines **8a-8d** in moderate yields by using arylhydrazines with various substituted groups. As pyrroles are electron rich heteroaromatics, which can possibly facilitate the oxidation process under these conditions, could rationalize using lower temperatures.



Scheme 4. Synthesis of pyrrole containing indoloquinolines

We have developed a protocol for the rapid and efficient synthesis of indoloquinolines from easily available 2,3-dihydroquinolinones and arylhydrazines under microwave irradiation. This approach is used to access pyrrole derivatives of this unique heterocyclic system. This two-step transformation, which takes place with high efficiency and shows a wide range of functional group tolerance, can be employed to generate novel isocryptolepine derivatives. Further studies for the potential utility of this method are under investigation in our laboratory.

EXPERIMENTAL

All chemicals were obtained from commercial sources and used directly without further purification. Solvents used in the experiment have been purified over molecular sieve. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light. Flash chromatography was performed using SiO_2 to purify the crude reaction mixtures. ^{1}H and ^{13}C NMR were recorded in 400 MHz apparatus using $CDCl_3$ and acetonitrile-d_3 as solvent. The frequency used for measuring ^{1}H NMR was 400 MHz and 100 MHz for ^{13}C NMR, respectively. Chemical shifts were recorded in ppm by employing TMS as internal standard. HRMS data were obtained under ESI model. Discover 2.0 Microwave from CEM corporation was used.

General Procedure for Grignard Addition to Quinolinium Salts

To a stirred solution of substituted 4-methoxyquinolines (1.0 eq) in THF (0.2 M) at -15 ^oC was slowly added Grignard reagent (2.0 eq). After stirring for 30 min at the indicated temperature, it was treated slowly with a solution of Cbz-Cl (2.0 equiv.) in toluene (3 M). The resulting mixture was allowed to warm up to room temperature and stirred another 3 h. The reaction mixture was quenched with 2N HCl and stirred for 30 min, after which was extracted with EtOAc (3x). The combined extracts were dried over Na_2SO_4 and the solvent was removed under vacuum. The residue was purified with flash chromatography on silica gel using a mixture of hexane and EtOAc as an eluent to give corresponding products.

General Procedure for Hydride Addition to Quinolinium Salts

To a stirred solution of substituted 4-methoxyquinolines (1.0 eq) in MeOH (0.2 M) at -78 ^oC was added $NaBH_4$ (2.0 eq). After stirring for 15 min at the indicated temperature, it was treated slowly with a solution of Cbz-Cl (2.0 eq) in toluene (3 M). The resulting mixture was allowed to warm up to room temperature and stirred another 3 h. The reaction mixture was quenched with 2N HCl at -15 ^oC and stirred for 1 h, after which was extracted with EtOAc (3x). The combined extracts were dried over Na_2SO_4 and the solvent was removed under vacuum. The residue was purified with flash chromatography on silica gel using a mixture of hexane and EtOAc as an eluent to give corresponding products.

General Procedure for the Formation of Indoloquinolines

Substituted or unsubstituted 2,3-dihydroquinolinones (1.0 eq) dissolved in acetic acid was treated with arylhydrazines (1.5 eq) and then irradiated with MW at 130 °C for 15 min. The reaction mixture was then treated with BF_3•OEt_2 (10 equiv.) and irradiated again with MW at 200 °C for 10 min. The mixture was quenched with saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3x). The combined extracts were dried over Na_2SO_4 and the solvent was removed under vacuum. The residue was purified with flash chromatography on silica gel using a mixture of hexane and EtOAc as an eluent to give indoloquinoline products.

Procedure for the Synthesis of 7b

To a stirred solution of pyrrole **6b** (3 g, 11.10 mmol) in 100 mL of MeCN (0.1 M) was added triethylamine (1.70 mL, 12.21 mmol) and tosyl chloride (2.24 g, 11.65 mmol) at room temperature. The reaction mixture was stirred overnight (24 h) then quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc (3x) and the combined organic extracts were dried over Na_2SO_4. After evaporation of solvent, the crude product was purified by silica gel chromatography (Hexane/EtOAc, 4:1 to 2:1 as eluent) to afford the corresponding product **7b** (3.9 g, 83% yield).

SUPPORTING INFORMATION

Supplementary (synthesis of the starting azides, HPLC chromatograms, IR, ^{1}H and ^{13}C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27717/104/10.

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