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Synthesis of 3*H*-Pyrrolo[2,3-*c*]quinoline by Sequential I_2-Promoted Cyclization/Staudinger/Aza-Wittig/Dehydroaromatization Reaction

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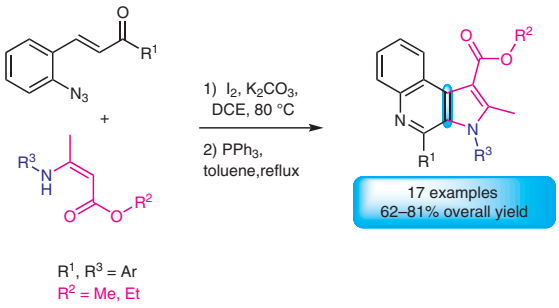

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Abstract A facile synthetic approach to access of 3*H*-pyrrolo[2,3-*c*]quinoline derivatives has been achieved by a sequential I_2-promoted cyclization/Staudinger/aza-Wittig/dehydroaromatization reaction. The targeted products were received in moderate to good yields (62–81%). The broad substrate scope and easy availability of the starting materials make this method a valuable tool for generating 3*H*-pyrrolo[2,3-*c*]quinoline products.

Key words 3*H*-pyrrolo[2,3-*c*]quinolines, I_2-promoted cyclization, aza-Wittig reaction, azides, dehydroaromatization

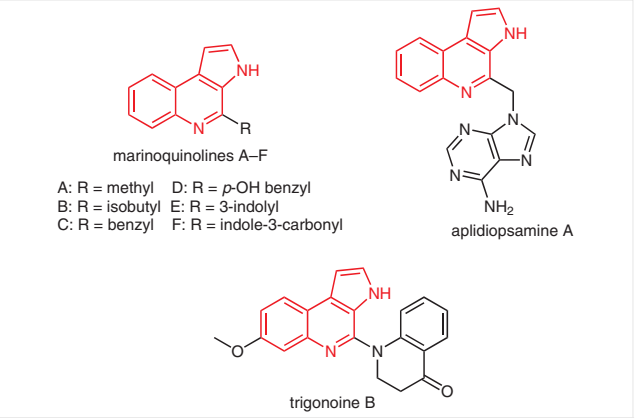


Figure 1 Representative bioactive compounds containing 3*H*-pyrrolo[2,3-*c*]quinoline skeletons

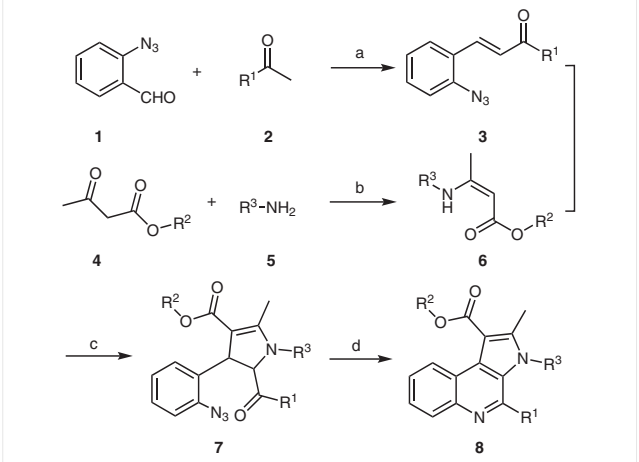
The rapid construction of N-heterocyclic scaffolds is an attractive and lively research area in organic synthesis because of their promising biochemical and materials properties.[2] Among them, the pyrrolo[2,3-*c*]quinoline system is one of the privileged structural motifs, and its derivatives can be found in numerous natural products and biologically active molecules such as marinoquinolines **A–F**,[3] aplidiopsamine **A**,[4] and trigonoine **B**[5] (Figure 1). These compounds and their various analogues exhibit important biological activities, such as antimicrobial,[6] antimalarial,[7] acetylcholinesterase-inhibiting activity,[8] antitubercular,[9] and antitumor[10] along with metal- and anion-sensing capabilities.[11] Hence, the study on pyrrolo[2,3-*c*]quinolines continues to be an active research area.

So far, tremendous efforts have been devoted to the exploration of efficient methodologies for the synthesis of the pyrrolo[2,3-*c*]quinoline molecules.[12] In 2015, Takasu et al. constructed the 3*H*-pyrrolo[2,3-*c*]quinoline frameworks favorably through a brønsted acid-promoted arene-ynamide cyclization.[4b] In 2017, Xu et al. described a straightforward and facile access to highly functionalized 3*H*-pyrrolo[2,3-*c*]quinolines through bicyclization of azomethine ylide.[12a] Very recently, Bhattacharya et al. utilized a microwave-assisted approach for the synthesis of 4-substituted pyrrolo[2,3-*c*]quinolines starting from easily available quinoline.[12b] However, some of the synthetic methods suffer from multistep processes, difficult-to-synthesize starting materials, and poor precursor scopes with low substituent diversities. Thus, the development of new and straightforward

synthetic pathways for the construction of diversified pyrrolo[2,3-*c*]quinolines is still highly desirable.

Over the past decades, great efforts have been made by chemists to construct C–N bonds, and lots of methods have constantly been reported.[13] Among them, the traditional aza-Wittig reaction has received considerable attention for the synthesis of heterocyclic compounds and natural products because of its mild reaction conditions.[14] In previous work, Gao and co-workers had reported the iodine-promoted construction of multisubstituted 2,3-dihydropyrrole derivatives.[15] Inspired by this, we embarked on a project to explore the synthesis of pyrrolo[2,3-*c*]quinoline derivatives (Scheme 1) initiated from 2-azidobenzaldehyde **1** and acetophenones **2** (2-azido chalcones **3**[16] were prepared), with acetoacetates **4** and aromatic amines **5** (β-enamine esters **6**[17] were presynthesized). As part of our ongoing investigation into the synthesis of nitrogen-containing heterocycles, herein, we wish to disclose a new and concise synthesis of polysubstituted pyrrolo[2,3-*c*]quinoline derivatives by means of sequential I_2-promoted cyclization/Staudinger/aza-Wittig/dehydroaromatization procedures.

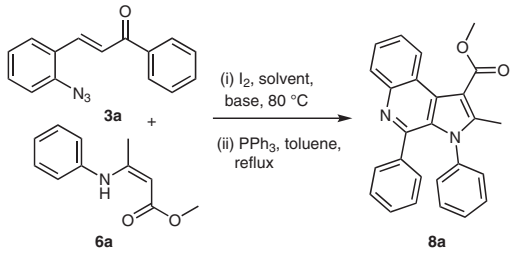
Our initial investigations were focused on optimizing the reaction conditions of chalcone **3a** and β-enamine ester **6a** in different ratios, in the presence of bases and solvents. A model reaction (**3a**/**6a** = 1:1) was performed in the presence of 1.0 equivalent of iodine in 1,2-dichloroethane (DCE) as the solvent without any base at 80 °C for 10 h. Gratifyingly, without the isolation of 2,3-dihydropyrrole **7a**, product **8a** could obtained by Staudinger/aza-Wittig reaction in a yield of 53% (Table 1, entry 1).



Scheme 1 Proposed pathway for the synthesis of compounds **8**. Reagents and conditions: (a) NaOH, EtOH,0 °C, 2 h; (b) CF_3SO_3Zn (20%), 15 min, rt; (c) I_2, K_2CO_3, dry DCE, 80 °C; (d) PPh_3, toluene, reflux

Subsequently, a substrates ratio screening showed that **3a**/**6a** (1:1.5) was optimal and the yield was promoted to 62% (Table 1, entries 2–3). Encouraged by this result, the conversion with a series of bases such as NEt_3, DABCO, $NaHCO_3$, Na_2CO_3, K_2CO_3, DMAP, DBU was studied (Table 1, entries 4–10), and K_2CO_3 was the most effective base for this reaction to give the desired product **8a** in 75% yield. Moreover, further investigation on switching the solvents from DCE to EtOH, CH_3CN, toluene, or DMF did not give a better result (Table 1, entries 11–14).

Table 1 Optimization of the Reaction Conditions[a]



Entry	Ratio (**3a**/**6a**)	Base	Solvent	Yield (%)[b]
1	1:1	–	DCE	53
2	1.5:1	–	DCE	47
3	1:1.5	–	DCE	62
4	1:1.5	NEt_3	DCE	52
5	1:1.5	DABCO	DCE	55
6	1:1.5	$NaHCO_3$	DCE	64
7	1:1.5	Na_2CO_3	DCE	69
8	1:1.5	K_2CO_3	DCE	75
9	1:1.5	DMAP	DCE	60
10	1:1.5	DBU	DCE	51
11	1:1.5	K_2CO_3	EtOH	22
12	1:1.5	K_2CO_3	CH_3CN	trace
13	1:1.5	K_2CO_3	toluene	65
14	1:1.5	K_2CO_3	DMF	trace

[a] Reaction conditions: (i) chalcone **3a** (1.0 equiv), β-enamine ester **6a**, base (1.0 equiv), and I_2 (1.0 equiv) in solvent (5 mL) at 80 °C for 10 h; (ii) PPh_3 (1.0 equiv), toluene, reflux, 12 h.
[b] Isolated yields based on substrate **3a**.

The structure of 3*H*-pyrrolo[2,3-*c*]quinoline **8c** was confirmed by its spectral data. Furthermore, a single crystal of **8c** was grown from the ethyl acetate/petroleum ether solution, and its structure was verified by single-crystal X-ray analysis (Figure 2).[18]

Having the optimized conditions in hands, we employed a variety of chalcones **3** and β-enamine esters **6** in the reaction. As shown in Table 2, chalcones **3** bearing various electron-withdrawing and electron-donating substituents (R^1 = Ph, 2,4-Cl_2Ph, 4-ClPh, 2-ClPh, 4-BrPh, 4-CH_3Ph, 4-OCH_3Ph) on the aryl rings were smoothly converted to the corresponding products in moderate to good yields (Table 2, 8a–e, 8i–l, 8m–q). As a whole, the reactions gave slightly better yields in the presence of electron-withdrawing substituents. For some substituted β-enamine esters (R^3 = Ph, 3-

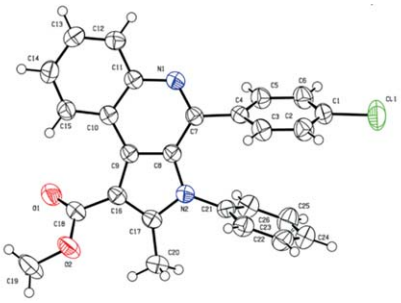
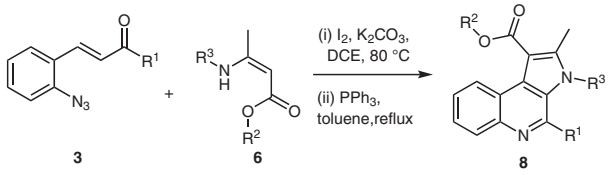


Figure 2 X-Ray crystal structure of compound **8c**

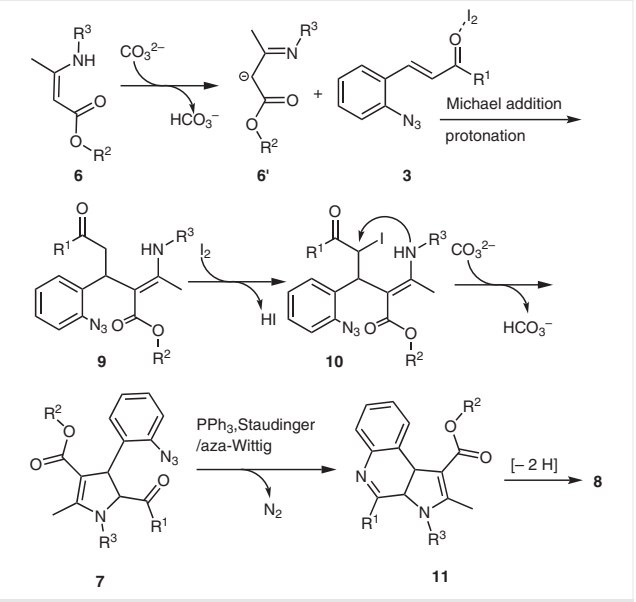
Table 2 Synthesis of 3*H*-Pyrrolo[2,3-*c*]quinolines **8**[a]



Comp.	R^1	R^2	R^3	Yield (%)
8a	Ph	Me	Ph	75
8b	4- CH_3Ph	Me	Ph	70
8c	4-ClPh	Me	Ph	79
8d	4-OCH_3Ph	Me	Ph	67
8e	2,4-Cl_2Ph	Me	Ph	81
8f	Ph	Me	3-ClPh	72
8g	Ph	Me	4-OCH_3Ph	77
8h	Ph	Me	4-CH_3Ph	73
8i	Ph	Me	2-CH_3Ph	68
8j	2-ClPh	Me	2-CH_3Ph	70
8k	4-OCH_3Ph	Me	2-CH_3Ph	62
8l	4-CH_3Ph	Me	2-CH_3Ph	72
8m	4-BrPh	Et	2-CH_3Ph	79
8n	Ph	Et	2-CH_3Ph	77
8o	4-CH_3Ph	Et	2-CH_3Ph	74
8p	Ph	Et	3-ClPh	71
8q	4-ClPh	Et	3-ClPh	75

[a] Isolated yields based on substrates **3**

ClPh, 2-CH_3Ph, 4-CH_3Ph, 4-OCH_3Ph), the reactions proceeded well and provided the desired products (Table 2, 8f–i, 8n, 8p). Further reactions successfully afforded the expected products when R^2 groups were replaced by methyl or ethyl. In addition, the steric effects of the substituents on the benzene ring (R^1 or R^3) were examined, and the results indicate that steric hindrance does not significantly affect the reactions (Table 2, 8c, 8e, 8j, 8q).



Scheme 2 A possible mechanism for the synthesis of **8**

On the basis of the previous reports[19,12a] and abovementioned results, a plausible reaction mechanism for the formation of **8** is depicted in Scheme 2. It presumably involves in the following steps: (i) transformation of β-enamine esters **6** into the carbanions **6'** in the presence of solid K_2CO_3; (ii) a Michael addition reaction between chalcones **3** and carbanions **6'** gives intermediates **9** followed by an electrophilic substitution with iodine to generate intermediates **10**; (iii) intramolecular nucleophilic substitution to give the key dihydropyrrole intermediates **7** in the presence of base K_2CO_3; (iv) tandem Staudinger/aza-Wittig reaction of **7** to produce **11**, which undergoes a dehydroaromatization reaction to afford the target 3*H*-pyrrolo[2,3-*c*]quinoline derivatives **8**.

In summary, we have illustrated a convenient synthesis of highly substituted 3*H*-pyrrolo[2,3-*c*]quinoline derivatives by a sequential I_2-promoted cyclization/Staudinger/aza-Wittig/ dehydroaromatization reaction in moderate to good yields.[20] Additionally, the easily accessible starting materials and broad substrate scope make this method a valuable tool for generating diverse 3*H*-pyrrolo[2,3-*c*]quinoline derivatives, which are of considerable interest in synthetic and medicinal chemistry.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610688.

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(1) These authors contributed equally.
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(18) Crystallographic data of compound **8c** in this manuscript have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1870525. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [deposit@ccdc.cam.ac.uk].
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(20) **General Experimental Procedure for the Synthesis of 3*H*-Pyrrolo[2,3-c]quinolines**
To a solution of chalcone **3** (1 mmol), β-enamine ester (**6**, 1.5 mmol), K_2CO_3 (0.138 g, 1 mmol) in anhydrous DCE (5 mL) was added iodine (0.254 g, 1 mmol). The reaction was stirred at 80 °C for 10 h, and the reaction progress was monitored by TLC. Then, the mixture was washed with aqueous $Na_2S_2O_3$, dried with dry sodium sulfate, and the solvent was evaporated under reduced pressure to give the crude product dihydropyrrole intermediate **7**. Afterwards, toluene (5 mL) and PPh_3 (0.262 g, 1 mmol) were added to the reaction system, and the mixture was heated to 110 °C for 12 h. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (ethyl acetate/petroleum ether = 1:8) to afford 3*H*-pyrrolo[2,3-*c*]quinolines **8a–q** in 62–81% yield.
Analytical Data for Compound 8a:
White solid (yield 0.294 g, 75%), mp 212–214 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.08 (d, *J* = 8.0 Hz, 1 H), 8.21 (d, *J* = 8.0 Hz, 1 H), 7.67–6.88 (m, 12 H), 4.07 (s, 3 H), 2.43 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 147.8, 145.3, 143.5, 138.6, 137.1, 129.8, 128.7, 128.4, 127.8, 127.4, 127.3, 126.9, 125.8, 125.3, 122.1, 108.6, 51.7, 13.8. LC-MS: *m*/*z* = 392. Anal. Calcd for $C_{26}H_{20}N_2O_2$ (392.46): C, 79.57; H, 5.14; N, 7.14. Found: C, 79.54; H, 5.23; N, 7.09.