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Iodine-Promoted Synthesis of Dipyrazolo/Diuracil-Fused Pyridines and *o*-Amino Diheteroaryl ketones via Oxidative Domino Annulation of 2/4-Methylazaarenes

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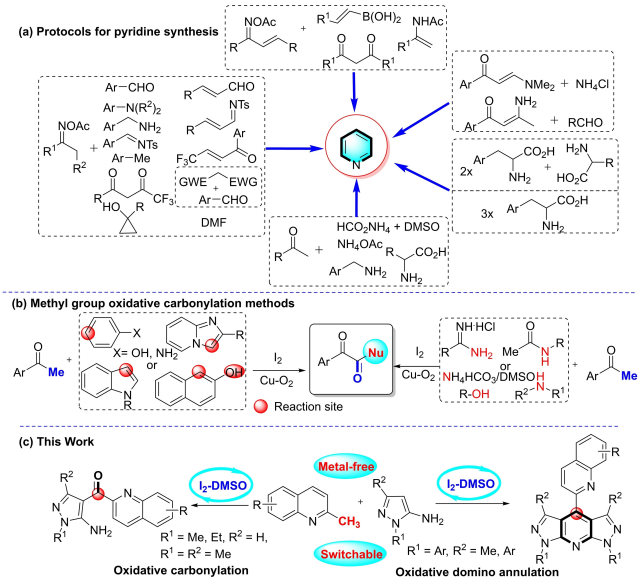
Abstract: The iodine-promoted oxidative domino annulation and carbonylation process has been developed for the synthesis of biologically important azaarene-substituted bis-pyrazolo[3,4-*b*:4′,3′-*e*] pyridines (BPPs), diuracilpyridines and *o*-amino diheteroaryl ketones. The domino procedure proceeded with easily available methyl azaarenes, 5-aminouracils and substituted 5-aminopyrazoles. This protocol is a simple and metal-free approach which exhibits high functional group compatibility and broad substrates scope. Moreover, this transformation can be applied for the preparation of dipyrazolo/diuracil-fused pyridines on a gram scale.

Keywords: Dipyrazolo/diuracil-fused pyridines; Methyl-azaarenes; Oxidative domino cyclization; Oxidative carbonylation; Iodine

Introduction

As privileged scaffolds, pyridines is prevalent in natural products, top-selling drugs, and ligands for catalytic reactions.[1] In addition, pyridine-fused bicyclic and tricyclic skeletons, such as pyrazolopyridine, carboline, and dipyrazolo/diuracil-fused pyridines, are also widely applied as pharmaceutical intermediates, agricultural chemicals, and functional materials.[2] Due to their excellent biological and pharmacological activities, they also have been utilized as versatile building blocks for the synthesis of useful molecules.[3]

Given their important activities and fascinating research prospects, the construction of pyridine and its derivatives has attracted considerable attention in recent times. Several efficient methods for their synthesis have been reported.[4] Among all methods, the direct functionalization of C–H bond from simple and easily available feedstocks represents the most straightforward approach to construct a pyridine motif (Scheme 1a). For instance, oxime acetates have emerged as meritorious starting materials for the synthesis of substituted pyridines. They can react with various coupling partners, such as aldehydes, *N*,*N*-dialkylanilines, *N*,*N*-dimethylformamide, acroleins, enals, α,β-unsaturated imines, β-CF_3 enones, isatin, activated methylenes with aldehydes, cyclopropanols, toluene, benzylamine, and *p*-toluenesulfonylhydrazone derivatives to afford the corresponding functionalized pyridine derivatives. Generally, these strategies can proceed with metal catalysis, in metal-free conditions or via oxidation-reduction (redox) processes.[5] Besides, the coupling of α,β-unsaturated ketoximes with 1,3-dicarbonyl compounds or *N*-acetyl enamides is also an efficient method for the synthesis of pyridines.[6] Another efficient approach is the coupling of simple methyl ketones with different nitrogen sources, such as aromatic methylamines, ammonium formate, and natural amino acids.[7] Wu et al. developed an elegant approach which involved the oxidative trimerization of amino acids for the synthesis of diverse multi-substituted pyridines from very simple



Scheme 1. The methods for pyridines synthesis and methyl group oxidative carbonylation.

starting materials.[8] Moreover, Wan et al. discovered some domino reactions involving enaminones with aldehydes and ammonium chloride for the synthesis of substituted pyridines.[9]

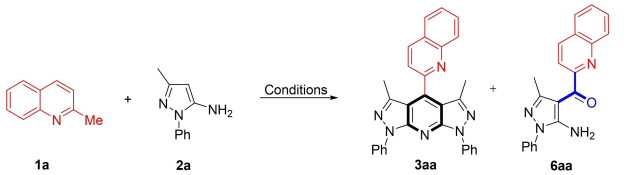
Methyl azaarenes are important bioactive structural motifs and versatile building blocks for organic synthesis.[10] In recent years, many effective methods have been established for the synthesis of heterocycles via a direct functionalization of the sp^3 C–H bond of methyl azaarenes.[11] However, as far as we know, no method has been reported for the synthesis of azaarenes-substituted dipyrazolo/diuracil-fused pyridines via a direct functionalization of the sp^3 C–H bond of methyl azaarenes by a metal-free approach. Meanwhile, it is very difficult to synthesize dipyrazolo/diuracil-fused pyridines containing heterocyclic fragments, such as quinoline, quinoxaline, benzo[*f*]quinoline, benzothiazole, benzoxazole, and pyridine. The existing methods have only been successful in introducing aryl and alkyl groups to dipyrazolo/dipyrimidine-fused pyridines. Moreover, it is very challenging to achieve the oxidative methyl azaarenes to form *o*-amino diheteroaryl ketones. Presently, the oxidative carbonylation of methyl groups is limited to aryl methyl ketones (Scheme 1b). For example, studies exist on the oxidative carbonylation of aryl methyl ketones with aryl amines, aryl phenol, indoles, imidazo[1,2-*a*]pyridines, benzo[*d*]imidazo[2,1-*b*]thiazole and 2-naphthol.[12] Also, the oxidative carbonylation of methyl aryl ketones with acetamides, formamidine, secondary amines, and alcohols was investigated for the synthesis of α-carbonylamides and α-ketoesters.[13]

As part of our ongoing interest in the synthesis of heterocycles from methyl azaarenes,[14] we herein reported a switchable approach for the synthesis of azaarene-substituted dipyrazolo/diuracil-fused pyridines and *o*-amino diheteroaryl ketones from methyl azaarenes. This method allows a switchable oxidative functionalization and carbonylation of methyl azaarenes to afford different products via a metal-free manner (Scheme 1c).

Results and Discussion

Initially, we chose 2-methyl quinoline (**1a**, 0.3 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2a**, 2.0 equiv., 0.6 mmol) as the model substrates to optimize the reaction parameters (see Table 1). With 1.0 equivalent of I_2 the reaction in DMSO at 110 °C produced the expected product **3aa** in 56% yield and trace mount of *o*-amino diheteroaryl ketone product **6aa** (entry 1). Subsequently, the effect of the varying amounts of I_2 was investigated, and the optimum result was obtained with 1.5 equivalent of I_2. The yield of **3aa** was increased to 70% at the same time (Table 1, entries 2–4). Next, an evaluation of various solvents, such as DMF, 1,4-dioxane and DMAc, revealed that the reaction can be carried out in different solvents, but

Table 1. Optimization of the reaction conditions[a]



Entry	I_2 (equiv.)	Solvent	Temp (°C)	**3aa** yield[b] (%)
1	1.0	DMSO	110	56 (trace)[d]
2	0.5	DMSO	110	48 (trace) [d]
3	1.5	DMSO	110	70 (15) [d]
4	2.0	DMSO	110	58 (11) [d]
5	1.5	DMF	110	51 (trace) [d]
6	1.5	1,4-dioxane	110	54 (10) [d]
7	1.5	DMAc	110	59 (trace) [d]
8	1.5	DMSO	100	63 (16) [d]
9	1.5	DMSO	120	77 (13) [d]
10	1.5	DMSO	130	74 (10) [d]
11 [c]	1.5	DMSO	120	83 (11) [d]
12 [e]	1.5	DMSO	120	78 (11) [d]
13 [f]	1.5	DMSO	120	52 (18) [d]
14 [g]	1.5	DMSO	120	71 (14) [d]

[a] Reaction conditions: 2-methyl quinoline **1a** (0.3 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2a** (0.6 mmol) and I_2 in solvent (3.0 mL) at different temperatures for 6 hours.
[b] Isolated yields of **3aa** based on **1a**.
[c] 2.2 equivalent of **2a** was added.
[d] The yield of compound **6aa**.
[e] 2.5 equivalent of **2a** was added.
[f] Reaction time for 3 h.
[g] Reaction time for 9 h.

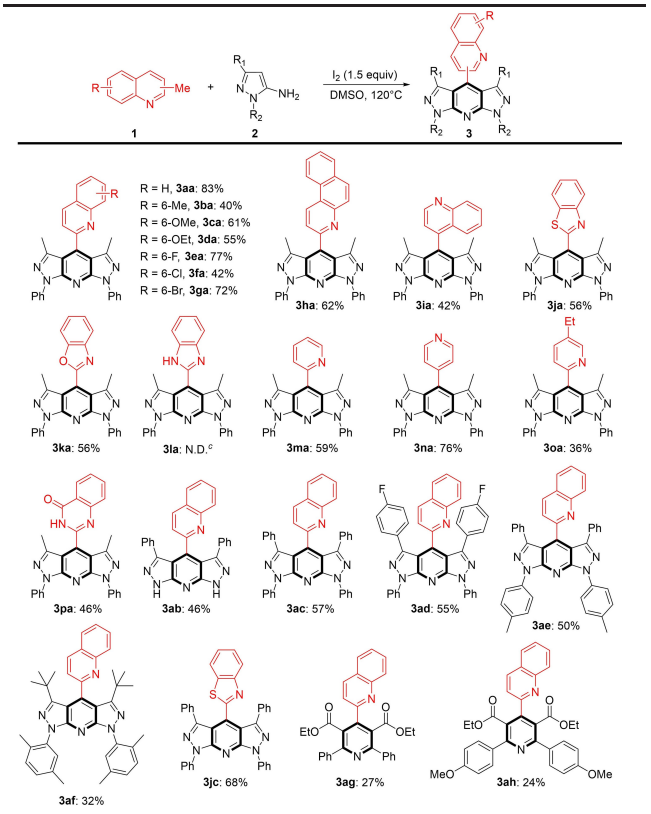
DMSO proved to be the most efficient solvent for the reaction as it afforded the best yield of the desired product (Table 1, entries 5–7). The reaction was further tested under different temperature, ranging from 100 to 130 °C, and the results showed that the optimum reaction temperature was 120 °C (Table 1, entries 8–10). Additionally, the effect of varying substrates ratio was evaluated to determine the best ratio for the reaction, and the highest yield was recorded for 2-methyl quinoline (**1 a**) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2 a**) ratio of 1:2.2 (Table 1, entries 11–12). Furthermore, the influence of time on the reaction was investigated, and the results revealed that the maximum yield was obtained after 6 hours reaction time. Consequently, lower yields were recorded below and above this optimum reaction time (Table 1, entries 13–14).

With the optimal reaction conditions in hand, we next explored the generality of this domio annulation reaction for substituted methyl azaarenes and various aminopyrazoles (Table 2). The protocol showed an excellent tolerance for the substituted methyl quinolines bearing electron-donating (eg. 6-Me, 6-OMe, and 6-OEt), and electron-withdrawing (eg. 6-F, 6-Cl, and 6-Br) groups. All the substrates proceeded smoothly to afford the desired products in moderate to good yields (**3 ba**–**3 ga**, 40–77%). Furthermore, various methyl *N*-heterocycles, such as 2-methyl-1,8-naphthyridine (**1 h**) and 4-methyl quinoline (**1 i**) participated satisfactorily in the reaction, affording the desired products, **3 ha** and **3 ia**, in 62% and 42% yields, respectively. Further investigations were carried out on several methyl azaarenes, such as 2-methylbenzothiazole (**1 j**) and 2-methylbenzoxazole (**1 k**), and they produced the desired products, **3 ja** and **3 ka**, in moderate yields. However, 2-methylbenzimidazole (**1 l**) proved unsuitable for the reaction. Interestingly, some methyl pyridines, namely 2-methylpyridine (**1 m**), 4-methylpyridine (**1 n**) and 4-ethyl-2-methylpyridine (**1 o**), proved feasible for the reaction by affording the corresponding products, **3 ma**–**3 oa**, in 36–76% yields. 2-Methylquinazolin-4(3*H*)-one (**1 p**) also proved suitable for the reaction as it afforded the desired product, **3 pa**, in a moderate yield.

A variety of substituted amino pyrazoles were subsequently investigated. Herein, 4-phenyl-1*H*-pyrrol-2-amine (**2 b**) reacted with 2-methyl quinoline (**1 a**) to give 46% yield of the desired product, **3 ab**. Amino pyrazoles containing substituted groups, such as phenyl, 6-F-phenyl and tert-butyl, were also suitable for the reaction, producing moderate yields of the desired products, **3 ac**, **3 ad**, and **3 af**. In addition, 3-amino-3-phenyl-2-propenoic acid ethyl ester (**2 g**) and 3-amino-3-(3-methoxyphenyl)-2-propenoic acid ethyl ester (**2 h**) reacted with 2-methyl quinoline to afford 27% and 24% yields of **3 ag** and **3 ah**, respectively. However, when the substrate was converted to either 1-methyl-1*H*-pyrazol-5-amine (**2 i**), 1,3-dimethyl-1*H*-pyrazol-5-amine (**2 j**) or 1-ethyl-1*H*-pyrazol-5-amine (**2 k**), the main product changed to *o*-aminoaromatic ketones (see Table 4).

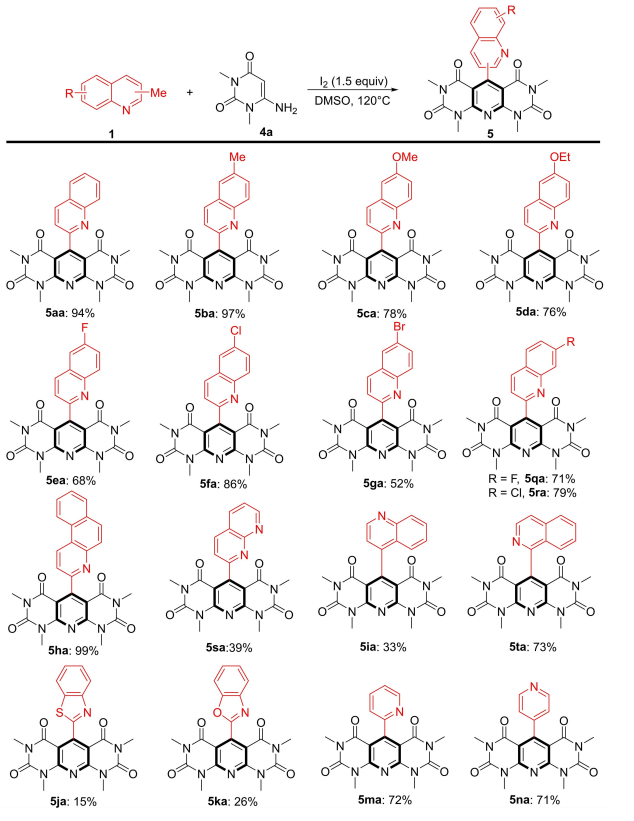
After the synthesis of a series of azaarene substituted dipyrazolo-fused pyridines, we next explored the scope of substituted quinolines and 6-amino-1,3-dimethylpyrimidine-2,4-dione (**4 a**) under the standard conditions (see Table 3). Generally, most of the 2-methyl quinolines containing different substituents were employed in this protocol. For instance, several 2-methyl quinolines bearing electron-rich substituents (e. g. 6-Me, 6-OMe, and 6-OEt) were investigated, and their corresponding products, **5 ba**–**5 da**, were obtained in 97%, 78% and 76% yields, respectively. Moreover, the reactions afforded the corresponding products in moderate to good yields when halogen atoms were attached to the aryl rings (e. g. 6-F, 6-Cl, 6-Br 7-F, 7-Cl). Besides, 99% yield of **5 ha** was obtained for the test with methylbenzo[*f*]quinoline (**1 h**). 2-Methyl-1,8-naphthyridine (**1 s**), 4-methylquinoline (**1 i**), and 1-methyl isoquinoline (**1 t**) were also suitable for the reaction, and their corresponding

Table 2. Scope of bis-pyrazolopyridines.[a,b]



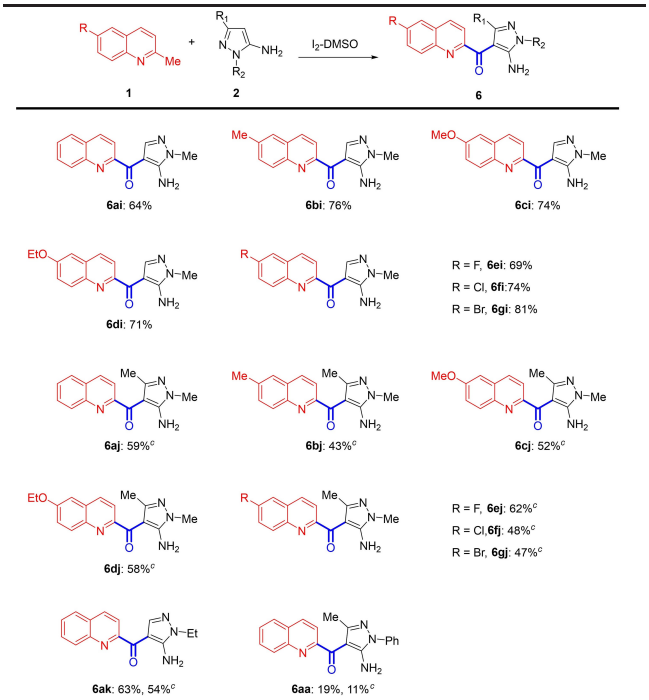
[a] Reaction conditions: **1** (0.30 mmol), **2** (0.66 mmol), I_2 (0.45 mmol) in DMSO (3 mL) at 120 °C for 6 h.
[b] Isolated yields.
[c] N.D. = Not detected.

Table 3. Scope of dipyrimidine-2,4(1*H*,3*H*)-dione pyridines.[a,b]



[a] Reaction conditions: **1** (0.30 mmol), **2** (0.66 mmol), I_2 (0.45 mmol) in DMSO (3 mL) at 120 °C for 6 h.
[b] Isolated yields.

Table 4. Scope of *o*-amino diheteroaryl ketones.[a,b]



[a] Reaction conditions: **1** (0.30 mmol, 1.0 equiv.), **2** (0.54 mmol, 1.8 equiv.), I_2 (0.54 mmol, 1.8 equiv.) in DMSO (3 mL) at 130 °C for 6 h.
[b] Isolated yields.
[c] Reaction conditions: **1** (0.30 mmol, 1.0 equiv.), **2** (0.66 mmol, 2.2 equiv.), I_2 (0.45 mmol, 1.5 equiv.) in DMSO (3 mL) at 120 °C for 6 h.

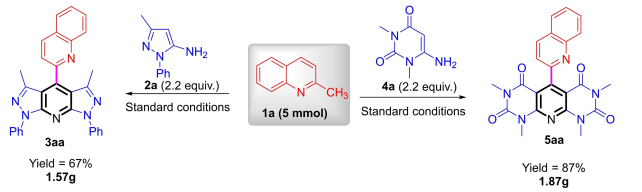
products were obtained in moderate yields. Furthermore, 2-methylbenzothiazole (**1 j**) and 2-methylbenzoxazole (**1 k**) reacted with 6-amino-1,3-dimethylpyrimidine-2,4-dione (**4 a**) under the optimal conditions to afford their corresponding products, **5 ja** and **5 ka**, in 15% and 26% yields, respectively. Meanwhile, methyl pyridines, such as 2-methyl pyridine (**1 m**) and 4-methyl pyridine (**1 n**) showed excellent reactivities as substrates, affording the desired products, **5 ma** and **5 na**, in good yields.

Several *o*-amino diheteroaryl ketones were obtained under the I_2/DMSO system (see Table 4). At the outset, 2,6-dimethylquinoline and 1-methyl-1*H*-pyrazol-5-amine were chosen as the model substrates and investigated under the optimal conditions. (*see SI optimization of the reaction conditions 2.*) With 1-methyl-1*H*-pyrazol-5-amine (**2 i**), the reaction showed broad substrate tolerance for the substituted 2-methylquinolines (e. g. 6-Me, 6-OMe, 6-OEt, 6-F, 6-Cl, 6-Br). These reactions proceeded successfully to produce the corresponding products, **6 bi-6 gi**, in good yields. Similarly, when the substrate was changed to 1,3-dimethyl-1*H*-pyrazol-5-amine (**2 j**), moderate to good yields of the products, **6 aj–6 gj**, were obtained, although not specific (*see SI details in* Table 4). Furthermore, 1-ethyl-1*H*-pyrazol-5-amine (**2 k**) was also tested in this reaction. Unfortunately, when 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2 a**) was applied as a substrate, the reaction mainly transformed towards the structure of bis-pyrazolopyridines instead of *o*-amino diheteroaryl ketones. The distinctively different behaviour of the above-mentioned substrates may have resulted from the low electron density on the aminopyrazole ring when the 1-position was substituted by an alkyl group, which reduced the ability of the second molecule of the aminopyrazole substrate to attack the intermediate B (*see* Scheme 3).

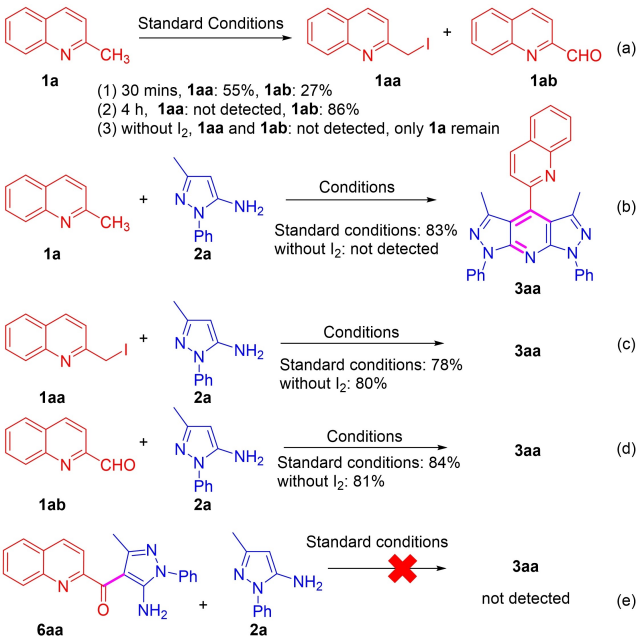
To show the potential application of this synthetic route, gram-scale reactions were conducted on the starting material **1 a** (5 mmol), with **2 a** and **4 a** under the standard conditions (see Table 5). To our delight, the desired products, **3 aa** and **4 aa**, were obtained in 67% (1.57 g) and 87% (1.87 g) yields, respectively (Table 4). These promising results present the possibility for large-scale applications.

In order to obtain further insights into the reaction mechanism, a series of control experiments were conducted (Scheme 2). The conversion process of 2-

Table 5. Scale-up of the reaction.[a,b]



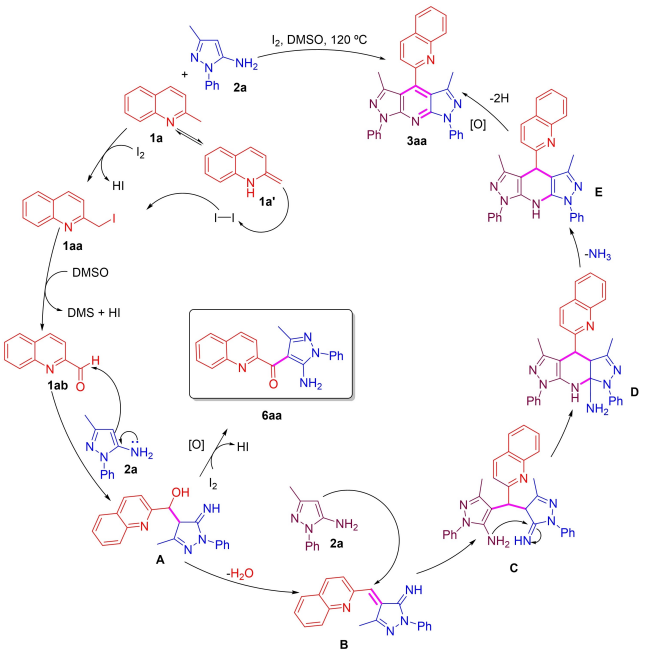
[a] Reaction conditions: **1a** (5 mmol, 1.0 equiv.), **2a** or **4a** (11 mmol, 2.2 equiv.), I_2 (7.5 mmol, 1.5 equiv.) in DMSO (30 mL) at 130 °C for 6 h.
[b] Isolated yields.



Scheme 2. Control experiments.

methylquinoline (**1a**) was initially explored under the standard conditions. 2-(Iodomethyl)quinoline (**1aa**) was obtained in 55% yield after the reaction proceeded for 30 minutes, while quinolin-2-carboxaldehyde (**1ab**) was obtained in 27% yield. With prolonged time (after 4 hours), 2-(iodomethyl)quinoline (**1aa**) was gradually converted to quinolin-2-carboxaldehyde (**1ab**). Nevertheless, 2-(iodomethyl)quinoline (**1aa**) and quinolin-2-carboxaldehyde (**1ab**) were not realized in the absence of iodine (Scheme 2a). The reaction of 2-methylquinoline (**1a**) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2a**) did not proceed without molecular iodine (Scheme 2b). Without and with iodine, 2-(iodomethyl)quinoline (**1aa**) and quinolin-2-carboxaldehyde (**1ab**) each reacted with 5-aminopyrazole (**2a**) to afford good yields of the desired product, **3aa** (Scheme 2c and 2d). Moreover, the product **6aa** could not react with 5-aminopyrazole (**2a**) to give the desired product **3aa** under the standard conditions (Scheme 2e). These results indicate that compounds **1aa** and **1ab** were the potential intermediates, while compound **6aa** was an independent product in the oxidation reaction.

Based on the aforementioned results, a plausible mechanism for the oxidative domino cyclization was proposed, as shown in Scheme 3. Initially, 2-methyl quinoline (**1a**) was converted into the intermediate 2-(iodomethyl)quinoline (**1aa**) with I_2 via an iodination reaction. Kornblum oxidation occurred subsequently in the presence of DMSO to generate quinoline-2-carbaldehyde (**1ab**), then the activated aldehyde group of the quinoline-2-carbaldehyde (**1ab**) was attacked by the C-nucleophilic center of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2a**) to produce intermediate **A**. Since intermediate **B** has a more stable conjugated structure than intermediate **A**, the intermediate **A** would convert to intermediate **B** after the loss of water. Furthermore, intermediate **A** can also be oxidized by iodine or DMSO to afford product **6aa**. Intermediate **B** reacted with another molecule of **2a** to form intermediate **C** via a Michael addition. Finally, intermediate **C** went through a series of reactions, such as intramolecular cyclization, deamination, and oxidative aromatization, to afford the target product **3aa**. Analogously, the reaction between 2-methylquinoline (**1a**) and 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**4a**) can be explained with a similar mechanism (*see SI*).



Scheme 3. The plausible mechanism.

Conclusion

In summary, an iodine-promoted domino annulation and oxidative carbonylation method was developed for the synthesis of azaarene substituted dipyrazolo/diuracil-fused pyridines and *o*-amino diheteroaryl ketones from easily available methyl azaarenes, 5-aminopyrazoles and 6-amino-pyrimidine-2,4-diones. This protocol is a simple and metal-free approach, that tolerates high functional group and broad substrates scope, such as methyl quinolines, methyl pyridines, 2-methyl quinoxaline, 2-methyl benzothiazole, 2-methyl benzoxazole and 2-methyl-4(3*H*)-quinazolinone. Moreover, this transformation can be applied for the preparation of dipyrazolo/diuracil-fused pyridines on a gram scale.

Experimental Section

General Procedure for the Synthesis of Bis-Pyrazolopyridines (3 aa as an Example)

A 25 mL pressure vial was charged with 2-methylquinoline (**1 a**) (43.0 mg, 0.30 mmol, 1.0 equiv.), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2 a**) (114.3 mg, 0.66 mmol, 2.2 equiv.), I_2 (114.2 mg, 0.45 mmol, 1.5 equiv.) and DMSO (3.0 mL). The vial was sealed and the resulting mixture was stirred at 120 °C for 6 h under an air atmosphere. After the reaction was completed (monitored by TLC), and added 50 mL water to the mixture, then extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 10% $Na_2S_2O_3$ solution (w/w), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to yield the corresponding product **3 aa** as a green solid (83% yield).

General Procedure for the Synthesis of Diuracilpyridines (5 aa as an Example)

A 25 mL pressure vial was charged with 2-methylquinoline (**1 a**) (43.0 mg, 0.30 mmol, 1.0 equiv.), 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**4 a**) (102.4 mg, 0.66 mmol, 2.2 equiv.), I_2 (114.2 mg, 0.45 mmol, 1.5 equiv.) and DMSO (3.0 mL). The vial was sealed and the resulting mixture was stirred at 120 °C for 6 h under an air atmosphere. After the reaction was completed (monitored by TLC), and added 50 mL water to the mixture, then extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 10% $Na_2S_2O_3$ solution (w/w), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to yield the corresponding product **5 aa** as a white solid (94% yield).

General Procedure for the Synthesis of *o*-Aminoaromatic Ketones (6 ai as an Example)

A 25 mL pressure vial was charged with 2-methylquinoline (**1 a**) (43.0 mg, 0.30 mmol, 1.0 equiv.), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2 i**) (52.4 mg, 0.54 mmol, 1.8 equiv.), I_2 (137 mg, 0.54 mmol, 1.8 equiv.) and DMSO (3.0 mL). The vial was sealed and the resulting mixture was stirred at 130 °C for 6 h under an air atmosphere. After the reaction was completed (monitored by TLC), and added 50 mL water to the mixture, then extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 10% $Na_2S_2O_3$ solution (w/w), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to yield the corresponding product **6 ai** as a yellow solid (64% yield).

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UPDATES

Iodine-Promoted Synthesis of Dipyrazolo/Diuracil-Fused Pyridines and *o*-Amino Diheteroaryl ketones via Oxidative Domino Annulation of 2/4-Methylazaarenes

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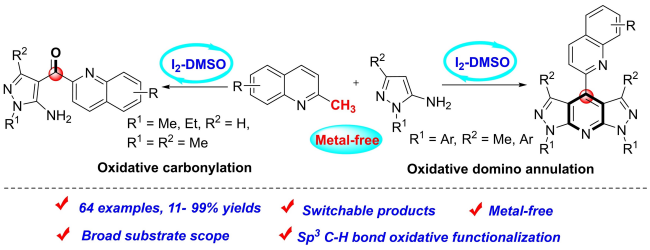

- 64 examples, 11- 99% yields
- Switchable products
- Metal-free
- Broad substrate scope
- Sp^3 C-H bond oxidative functionalization