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Iodine-Catalyzed Construction of Dihydrooxepines via 3-Methyl-5-Pyrazolones C–H Oxidation/Functionalization of Quinolines Cascade

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An efficient iodine-catalyzed [3 + 3 + 1] annulation for the construction of dihydrooxepine scaffolds with quinoline units was developed. This strategy involves a seven-membered dihydrooxepine with a broad substrate scope through a formal three-component tandem reaction. Further derivation of the target product produced a trioxabicycle scaffold, which formed the basic core of natural products and pharmaceutical molecules.

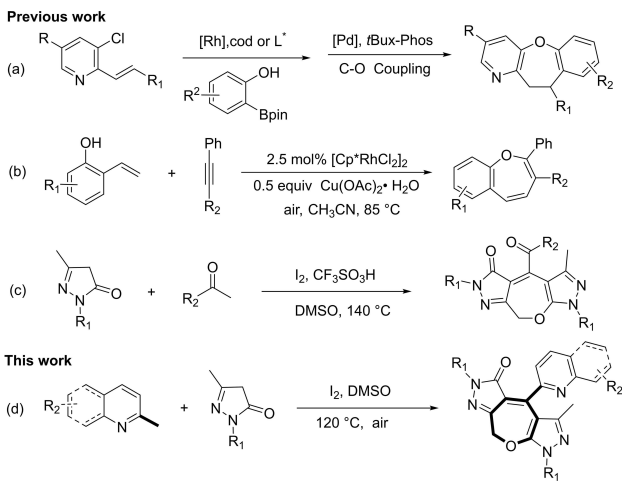
Introduction

Quinoline and its derivatives are important building blocks of heterocyclic species. They are widely present in bioactive reagents and seen in the material sciences.[1] Because they have so many applications, chemists continue to pay a great deal of attention to the highly functionalized quinolines to develop novel means of synthesizing them.[2] As a Lewis base, quinoline inactivates Lewis acids and consequently suppresses Friedel-Crafts reactions.[3] This creates a challenge for the functionalization of quinoline. Significant advance in C–H functionalization has revealed one method of producing directly functionalized quinolones.[4] Even though there are several elegant means of synthesizing functionalized quinolines, the use of harsh reaction conditions and some limits based on the nature of the involved reagents make the development of more efficient methods of synthesis a significant problem in organic chemistry.[5] Thus, the exploitation of metal-free catalysis and avoidance of oxidants strategies are a desirable part of the method for the functionalization of quinoline.

Medium-sized heterocycles are one of the most significant classes of cyclic compounds due to their importance in organic chemistry.[6] With respect to the seven-membered heterocycles, the oxepine and hydrooxepine frameworks form the basic core of natural products and pharmaceutical molecules,[7] such as artemisinin, dihydroartemisinin, acetylapoaranotin, and (+)-MPC 1001. Therefore, assembling them from readily available precursors can be of great value. In recent years, several important approaches have been realized, including [4 + 3] and [5 + 2] metal-catalyzed cyclization, to construct oxepine and hydrooxepine derivatives.[8] In 2013, Lautens and co-workers used a Rh/Pd catalytic system to develop a domino cyclization leading to a series of aza-dihydrodibenzoxepines with excellent chemoselectivity (Scheme 1a).[9] Soon after, Mascareñas and Gulías' group used a Rh-catalyzed cycloaddition strategy involving a C–H activation process to realize an efficient construction of benzoxepines (Scheme 1b).[10] In 2017, Wu's group developed I_2-catalyzed with an organic strong acid to construct Dihydrooxepines (Scheme 1c).[11] The use of precious metals and additive is necessary in the previous works, but reported herein is the use of iodine catalysis without additive to describe a successful design process involving the functionalization of quinolines and three-component cyclization of 3-methyl-5-pyrazolones.

Results and Discussion

The initial discovery and optimization began via use of the commercially available 2-methylquinoline (**1a**) and easily prepared 3-methyl-1-phenyl-5-pyrazolones (**2a**) as the standard partners. Encouragingly, our anticipated product **3a** was



Scheme 1. Strategies for the construction of oxepine and hydrooxepine Derivatives.

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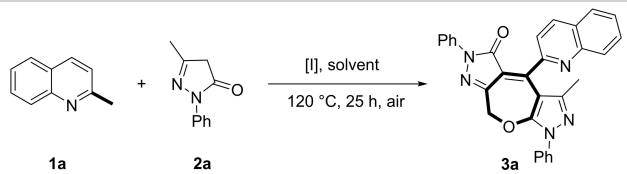
produced using I_2 and DMSO at 120 °C for 25 h (Table 1, entry 1). Subsequently, various iodine sources were screened in the reaction, but an inferior performance was observed in comparison with I_2 (entries 2–3). Much to our delight, when the amount of I_2 decrease to 20 mol%, thus producing 44% yield of the product (entry 4–5). No better results were obtained after investigating the effect of the solvents (entries 6–7). The subsequent adjustment of the loading of **2a** had excellent yield (entries 8–9). Further screening of the reaction temperature and time produced lower yields for the formation of **3a** (entries 10–11). No product formed in the absence of I_2 (entry 12). The optimized reaction conditions were characterized as follows: 0.2 mmol **1a**, 0.8 mmol **2a**, and 0.2 equiv. I_2 in DMSO at 120 °C for 25 h.

Table 1. Optimization of reaction conditions.[a]



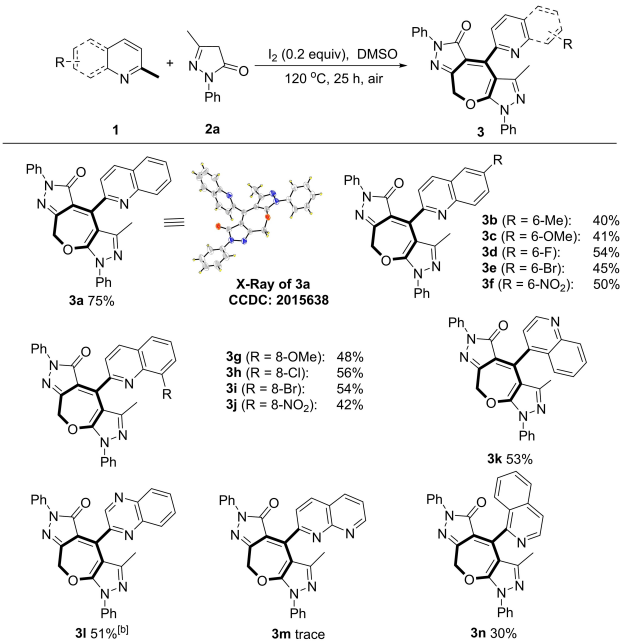
1a **2a** **3a**

Entry[a]	**2a** [mmol]	[I] [equiv]	Solvent	Yield[b] [%]
1	0.4	I_2 (1.0)	DMSO	36
2	0.4	NIS (1.0)	DMSO	28
3	0.4	TBAI (1.0)	DMSO	trace
4	0.4	I_2 (0.2)	DMSO	44
5	0.4	I_2 (0.1)	DMSO	36
6	0.4	I_2 (0.2)	Sulfolane	trace
7	0.4	I_2 (0.2)	CH_3CN	0
8	0.6	I_2 (0.2)	DMSO	58
9	**0.8**	**I_2 (0.2)**	**DMSO**	**75**
10[c]	0.8	I_2 (0.2)	DMSO	0
11[d]	0.8	I_2 (0.2)	DMSO	56
12	0.8	-	DMSO	-

[a] Reaction conditions: **1a** (0.2 mmol), **2a**, [I], solvent (1.0 mL), 25 h under air at 120 °C. [b] Isolated yields. [c] At 100 °C. [d] Reaction time = 20 h.

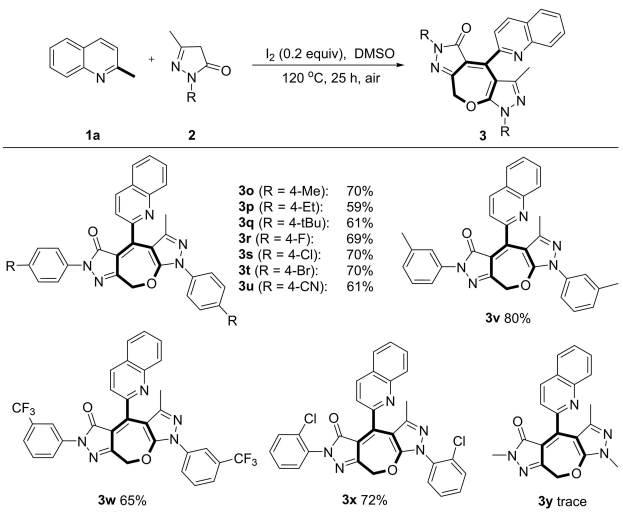
With the optimized reaction conditions in hand, a series of 2-methylquinolines were converted into the corresponding products in generally satisfactory yields (Scheme 2). The presence of the electron-donating groups at the 2-methylquinoline, such as 6-methyl and 6-methoxy, performed with moderate yields (**3b** and **3c**). The electron-withdrawing groups were tolerated better than the electron-donating groups, forming (**3d–3f**) in 45%-54% yields. Furthermore, the substituent groups of 8-methoxy, 8-chloro, 8-bromo, and 8-nitro were also compatible with the reaction (**3g–3j**). We tested 4-methylquinoline instead of 2-methylquinoline, producing the corresponding product **3k** in 53% yield. 2-Methylquinoxaline was also found to participate in the reaction (**3l**). Unfortunately, 2-methyl-1,8-naphthyridine failed to react under the optimized conditions (**3m**). We used 1-methylisoquinoline for the desired cyclization to produce the product **3n** at a 30% yield.

To further ascertain the scope of the chosen reaction conditions, study of the electronic effect of substituted 3-methyl-5-pyrazolones. was necessary (Scheme 3). The aryl group on the 3-methyl-5-pyrazolones. was explored first, thus affording the corresponding products in moderate to good yields (**3o–3x**). The electron-donating groups, including 4-methyl, 4-ethyl, and 4-*tert*-butyl, were tolerated and produced satisfactory yields (**3o–3q**). Moreover, electron-withdrawing groups at the *para*-position were also found to undergo the [3+3+1] cyclization with good results (**3r–3u**). Regardless of substituents at the *ortho*- or *meta*-position, they all reacted smoothly to produce compounds **3v–3x** with 65%–80% yields. Unfortunately, substrate **2y** failed to produce the corresponding product **3y**.



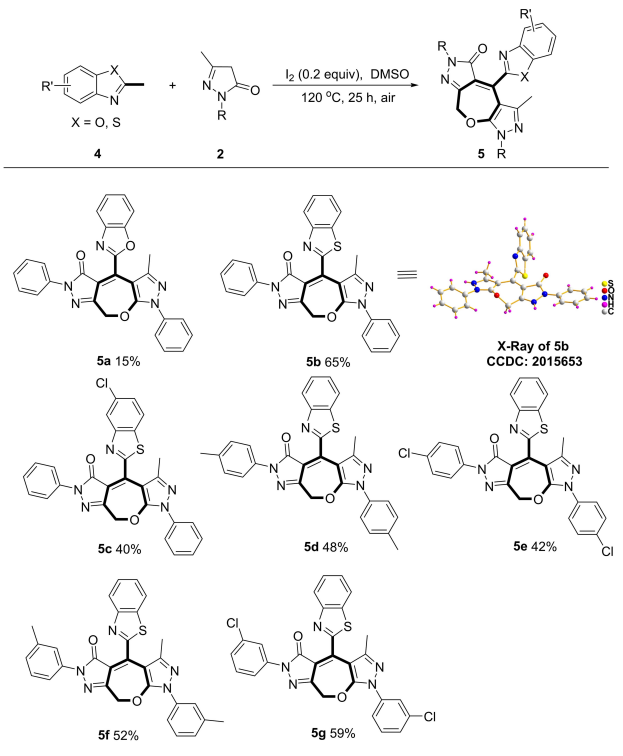
[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.8 mmol), I_2 (0.2 equiv), DMSO (1.0 mL), under air at 120 °C, 25 h. Isolated yields are shown. [b] At 130 °C.

Scheme 2. Substrate scope with respect to the 2-methylquinolines.[a]



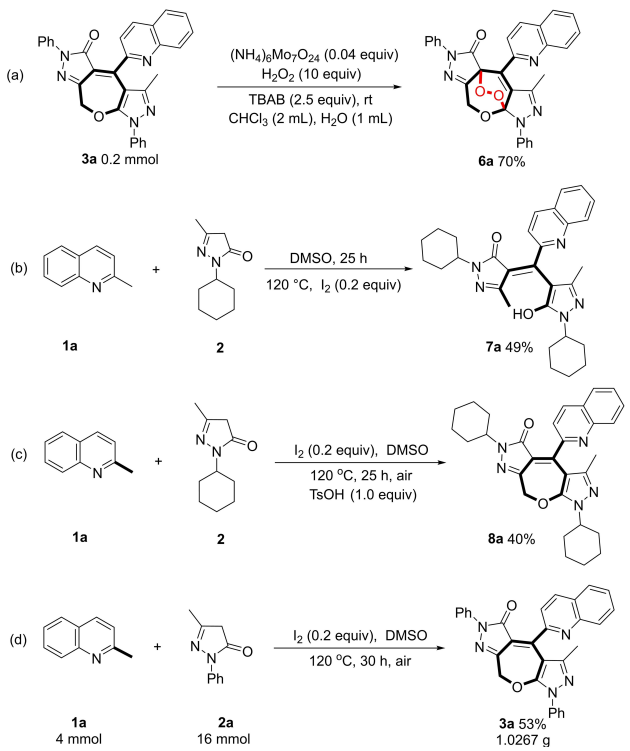
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.8 mmol), I_2 (0.2 equiv), DMSO (1 mL), under air at 120 °C, 25 h. Isolated yields are shown.

Scheme 3. Substrate scope with respect to the 3-methyl-5-pyrazolones.[a]



[a] Reaction conditions: **4** (0.2 mmol), **2** (0.8 mmol), I_2 (0.2 equiv), DMSO (1.0 mL), 25 h, under air at 120 °C. Isolated yields are shown.

Scheme 4. Substrate Scope with Respect to the other *N*-heteroarylmethanes.[a]

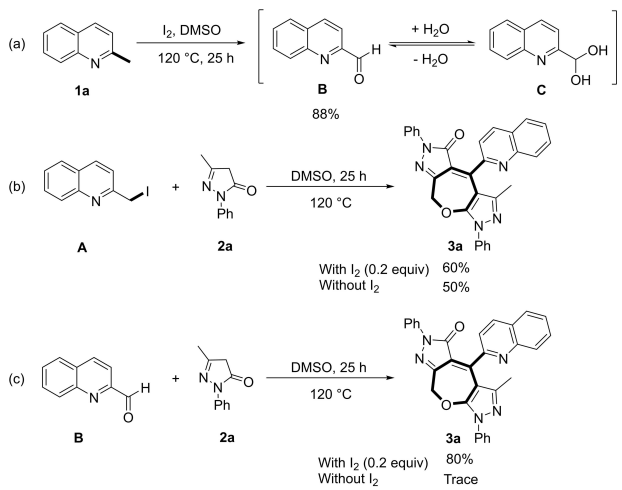


Scheme 5. Diversification of this protocol.

Substrates other than quinolines are desired for the reaction scope. After screening a variety of *N*-heteroarylmethanes, we found that benzoxazole and benzothiazole could also be used in the current catalytic system. The results are summarized in Scheme 4. Although the 2-methylbenzoxazole was reacted and produced **5a** only 15% yield, 2-methylbenzothiazole was tolerated smoothly and showed good yield (**5b**). The chloro group on the benzothiazole was also evaluated, and this produced product **5c**. The process also worked for substituted 3-methyl-5-pyrazolones, thus affording corresponding products (**5d–5g**) in moderate yields.

To establish the diversity of this reaction, a trioxabicycle scaffold containing quinoline was prepared with good yield (Scheme 5a), **6a**). Notably, the core structure of artemisinin also involves a trioxabicycle scaffold. By tuning the group of 3-methyl-5-pyrazolones, the uncyclized product was used to produce 49% yield (Scheme 5b), **7a**). When the TsOH was used as additive, cyclized product was obtained with 40% yield (Scheme 5c), **8a**), Another eminent advantage of this protocol is that the reaction could be scaled up to gram quantities (Scheme 5d).

For the sake of further investigating the reaction mechanism, a suite of controlled experiments was carried out. 2-methylquinoline **1a** (0.2 mmol) was heated with I_2 (0.04 mmol) in DMSO at 120 °C to gain quinoline-2-carbaldehyde **B** and the corresponding hydrated species **C** (Scheme 6a). As previously reported,[12] 2-methylquinoline could be iodinated employing iodine to generate **A**, the α-iodoquinoline **A** with 3-methyl-1-phenyl-5-pyrazolones **2a** was found successful, and the product **3a** was obtained in moderate yields both with and without I_2 (Scheme 6b). Quinoline-2-carbaldehyde **B** was also subjected to the optimized reaction conditions and produced **3a** with 80% yield, whereas no product was obtained in the absence of iodine, demonstrating that iodine played an important role in the oxidation process (Scheme 6c). These results suggested that α-iodoquinoline **A** and quinoline-2-carbaldehyde **B** were key intermediates in this transformation.



Scheme 6. Control experiments.

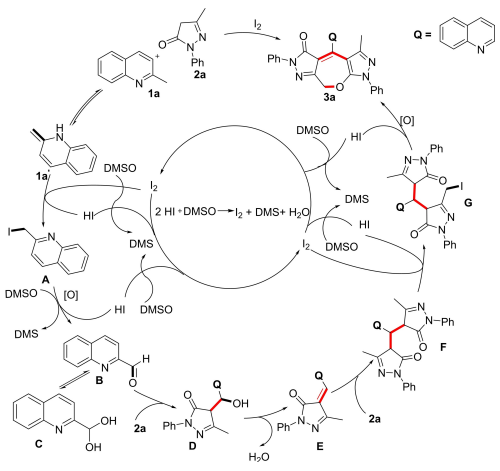
On the basis of the results of control experiments, and results of previously published works,[11]–[13] a plausible mechanism was proposed (Scheme 7). First, *N*-heteroaromatic methanes underwent an enamine tautomerization under specific conditions,[14] and 2-methylquinoline was iodinated with iodine by DMSO to generate α-iodoquinoline **A**. The α-iodoquinoline **A** was oxidized by DMSO to form quinoline-2-carbaldehyde **B** via Kornblum oxidation with the removal of HI and DMS. Then intermediate **B** trapped by the enol form of 3-methyl-1-phenyl-5-pyrazolones **2a** to gain intermediate **D**, which came through further dehydration to yield intermediate **E**. Next, intermediate **E** reacted with another equivalent of **2a** to provide intermediate **F** via Michael addition. Intermediate **F** would be iodinated to produce intermediate **G**. Afterward, intermediate **G** underwent an in-situ iodine-based oxidative coupling to generate the desired product **3a**. Finally, HI was oxidized to I_2 to fulfill the catalytic cycle.

Conclusion

In conclusion, we reported an efficient functionalization of quinolines under an iodine-catalyzed system, thus affording seven-membered dihydrooxepine scaffolds. Notably, the diverse *N*-heteroarylmethanes could also be executed to improve the efficiency of the reactions. More importantly, in the derivatization of this protocol, the synthesis of trioxabicycle scaffold reveals a potential biological activity.

Experimental Section

General procedure for the synthesis of 3a: A dried 25 ml glass tube containing a stir bar was charged with 3-methyl-1-phenyl-5-pyrazolones (**2a**, 0.8 mmol, 139.4 mg) and iodine (0.04 mmol, 10.2 mg). After addition of 2-methylquinoline (**1a**, 0.2 mmol, 27 μL) and 1 mL DMSO under air atmosphere, the mixture was stirred at 120 °C for 25 h. till almost completed conversion of the substrates by TLC analysis, the mixture was quenched with saturation $Na_2S_2O_3$ solution (60 mL), extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc = 10/1) to afford the product **3a.**



Scheme 7. Proposed mechanism

Crystallographic data: Deposition Numbers 2015638 (for **3a**) and 2015653 (for **5b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Dihydrooxepines · Iodine · Quinoline · Three-component tandem reaction · Trioxabicycle

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