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ARTICLE TYPE

Metal-Free Oxidative Olefination of Primary Amines with Benzylic C-H Bonds through Direct Deamination and C-H Bond Activation

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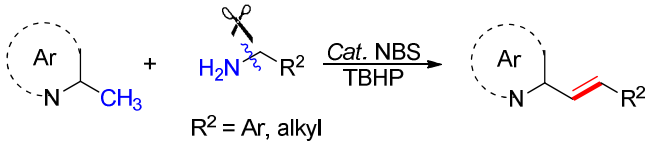
An oxidative olefination reaction between aliphatic primary amines and benzylic sp3 C-H bonds has been achieved with NBS as the catalyst and TBHP as the friendly oxidant. This olefination reaction proceeds under mild, metal-free conditions through the direct deamination and benzylic C-H bond activation, and provides an easy access to biologically active 2-styrylquinolines with (*E*)- configuration.

The deamination of aliphatic primary amines to achieve α-carbon functionalization is an important transformation in organic synthesis. Traditionally, the deamination is mainly approached through an oxidative reaction of aliphatic amines with oxidants. Many strong and unfriendly oxidants such as nitrous acids, [1] permanganates, [2] dichromates,[3] quinonoid species[4] and other oxidants[5] are frequently used in these classical methods, which are still suffering from low selectivity and overoxidation. Deamination reaction of primary amine under mild conditions is still a challenge in organic chemistry.

Very recently, a novel class of iodide-catalyzed oxidative cross-dehydrogenative coupling (CDC) reactions has received considerable attention due to using mild, metal-free conditions and environmentally friendly oxidants, such as H_2O_2, O_2 and TBHP. [6] In contrast, the catalytic utilization of bromine, which is also an important halogen in organic synthesis and lies in the same column with iodine at periodic table, has been ignored in these oxidative coupling reactions. Several recent studies revealed that the replacement of iodides with bromides could promote catalytic efficiencies obviously, and even lead to some unexpected transformations.[7] Thus, the exploration of corresponding bromide-catalyzed oxiditive coupling reactions would be highly desirable.

2-Styrylquinolines have been recognized as potent HIV-1 integrase inhibitors that block HIV-1 replication in cell based assays.[8] The SAR results clearly indicated that the (*E*)-configuration in these structures is required for the biological activity.[8b, 9] The conventional approach to the preparation of 2-styrylquinolines is the aldol-type condensation of 2-methylquinolines with aldehydes at high temperatures by using acetic anhydride.[8a, 10] Recent advances include the use of some variants of aldehydes, such as *N*-aryl imines,[11] *N*-sulfonyl imines[12] and *in situ* generated *N*-aryl imines,[13] which enable successful olefination with 2-methylquinolines. To our knowledge, the olefination reaction of aliphatic primary amines with sp3 C-H bonds through direct deamination and C-H activation is unknown (Scheme 1). As our continuous efforts toward the development of halide-mediated cross-dehydrogenative coupling (HCDC) reactions,[14] we report herein a *N*-bromosuccinimide (NBS)-catalyzed method for the construction of olefins *via* direct deamination of aliphatic primary amines and benzylic C-H bond activation of 2-methylquinolines. This protocol uses TBHP as a green oxidant and enables the direct deamination and benzylic C-H bond olefination to occur under mild and metal-free conditions, furnishing the alkenes with (*E*)-configuration.

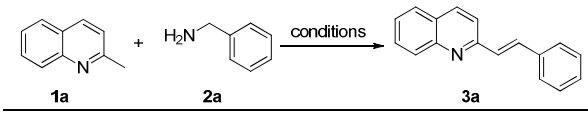


Scheme 1. The olefination reaction of primary amine.

We initiated our investigation with 2-methylquinoline **1a** and benzylamine **2a** as model substrates to identify optimum reaction conditions (Table 1). The iodine-based catalysts were firstly investigated in the olefination reactions. When 2-methylquinoline **1a** was treated with benzylamine **2a** (2 equiv) in the presence of Bu_4NI (40 mol%) and TBHP (2 equiv) at 80 °C for 24 h, only a trace amount of the desired product **3a** was observed (Table 1, Entry 1). Further research exhibited that I_2 was ineffective for this transformation (Table 1, Entry 2) and KI gave a low yield of 34% (Table 1, Entry 3). We next investigated the bromine-based catalysts, including Bu_4NBr, PhBr and NBS. With the addition of 40 mol% of Bu_4NBr or PhBr, it was found that the reaction provided the olefination product **3a** in 37% and 25% yields, respectively (Table 1, Entry 4, 5). Inspiringly, when NBS was used as the catalyst, a 66% yield of **3a** was obtained (Table 1, Entry 6). There was no decrease on the yield when reducing the

amounts of the benzylamine **2a**, NBS and TBHP at the same time (Table 1, Entry 7). Then we continued optimizing the reaction conditions based on Entry 7. Among the oxidants tested, such as 70% TBHP in water, TBPB (*tert*-butyl peroxybenzoate), 30% H_2O_2 in water, $K_2S_2O_8$ (Table 1, Entries 7-10,) aqueous TBHP provided the best result, producing **3a** in 67% yield (Table 1, Entry 7). The olefination products were isolated in lower yields in the presence of TBPB and H_2O_2 (Table 1, Entries 8, 9) while the use of $K_2S_2O_8$ led to no olefination product (Table 1, Entry 10). The yield of **3a** was decreased evidently when the reaction proceeded under N_2 atmosphere (Table 1, Entry 11). Among the reaction temperatures examined, it turned out that the reaction at 100 °C offered **3a** in 70% yield (Table 1, Entry 12). Gratifyingly, the highest yield of the desired product **3a** was obtained when conducting this reaction in the dark for a prolonged reaction time (Table 1, Entry 13). Thus, the combination of 20 mol% of NBS as the catalyst and 2 equiv of aqueous TBHP as the oxidant at 100 °C for 48 h in the dark was found to be the optimal conditions for this transformation.

Table 1. Optimization of the reaction conditions. [a]



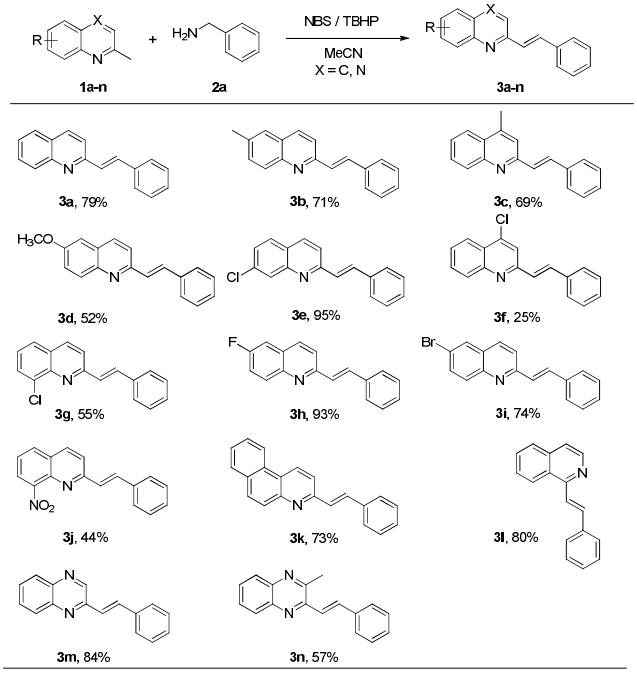
1a **2a** **3a**

Entry	**2a** (mmol)	Catalyst (mol%)	Oxidant (mmol)	Yield (%)
1	1.0	Bu_4NI (40)	TBHP (2.0)	trace
2	1.0	I_2 (40)	TBHP (2.0)	0
3	1.0	KI (40)	TBHP (2.0)	34
4	1.0	Bu_4NBr (40)	TBHP (2.0)	37
5	1.0	PhBr (40)	TBHP (2.0)	25
6	1.0	NBS (40)	TBHP (2.0)	66
7	0.6	NBS (20)	TBHP (1.0)	67
8	0.6	NBS (20)	TBPB (1.0)	37
9	0.6	NBS (20)	H_2O_2 (1.0)	48
10	0.6	NBS (20)	$K_2S_2O_8$ (1.0)	0
11 [b]	0.6	NBS (20)	TBHP (1.0)	28
12 [c]	0.6	NBS (20)	TBHP (1.0)	70
13 [d]	0.6	NBS (20)	TBHP (1.0)	79

[a] Reaction Conditions: **1a** (0.5 mmol) and **2a** in 1 mL of CH_3CN under air, 80 °C, 24 h, isolated yield. [b] under nitrogen. [c] 100 °C. [d] in the dark, 100 °C, 48 h.

With the optimized reaction conditions in hand, the scope of the reaction substrates was investigated (Table 2). 2-Methylquinolines with functional groups, such as fluoro, chloro, bromo, methoxy, methyl and nitro group were compatible with the reaction conditions and gave the corresponding products in moderate to good yields (Table 2, **3a**-**3n**). 2, 6-Dimethyl and 2, 4-dimethyl substituted quinolines could provided the desired products in 71% and 69% yield, respectively (Table 2, **3b**, **3c**). Interestingly, the active C-4 methyl group of 2, 4-dimethyl quinoline remained unaffected under these reaction conditions. The reactions of various chloro-quinolines afforded the corresponding products in yields ranging from 25% to 95% (Table 2, **3e**-**3g**). The olefination of 7-chloro-2-methylquinoline successfully produced 7-chloro-2-styrylquinoline in 95% yield (Table 2, **3e**) while 4-chloro-2-methylquinoline only gave the desired product **3f** in 25% yield (Table 2, **3f**). When 8-chloro-2-methylquinoline was used, a moderate yield of **3g** was isolated. 2-Methylquinolines containing other electron-withdrawing groups (fluoro, bromo, nitro) were olefinated in moderate to good yields (Table 2, **3h**-**3j**). 3-Methylbenzo[*f*]quinoline **1k** with big aromatic ring also exhibited excellent reactivity (Table 2, **3k**). The olefination of 1-methylisoquinoline with benzylamine gave a good yield of the product **3l**. We also tested 2-methylquinoxaline and 2, 3-dimethyl quinoxaline, which could undergo the olefination reaction in moderate and high yields (Table 2, **3m**, **3n**). Moreover, 2, 3-dimethyl quinoxaline reacted with benzylamine **2a** to afford the olefination product **3n** on the 2-methyl position selectively without any 3-methyl olefination product. The structure of compound **3a** was further confirmed by single crystal X-ray crystallographic analysis (Fig. 1).[15] The X-ray crystallography and ^1H NMR spectrum firmly established the absolute (*E*)-configuration of the olefination product.

Table 2. Substrate scope of various quinolines. [a]



[a] Reactions were carried out in the dark with quinolines (0.5 mmol), benzylamine (0.6 mmol), NBS (0.1 mmol) and TBHP (1.0 mmol) in MeCN (1 mL) at 100 °C for 48 h, isolated yield.

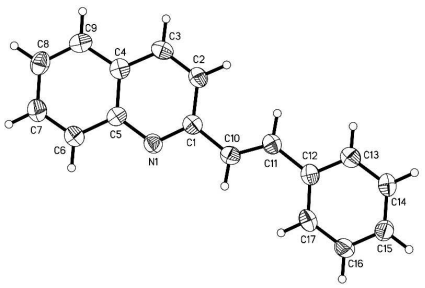
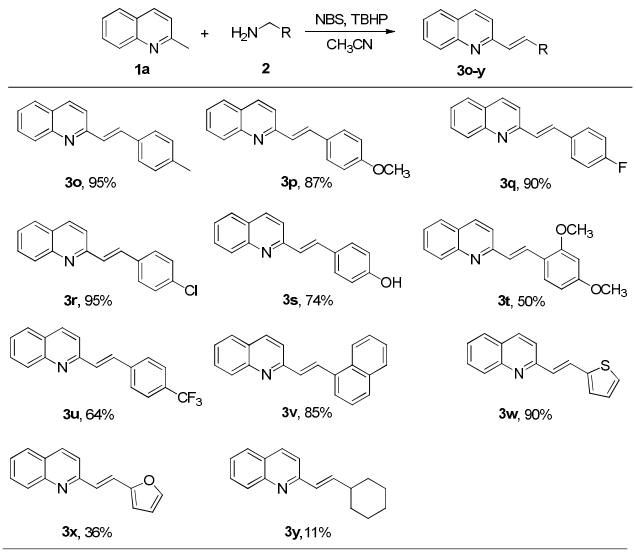


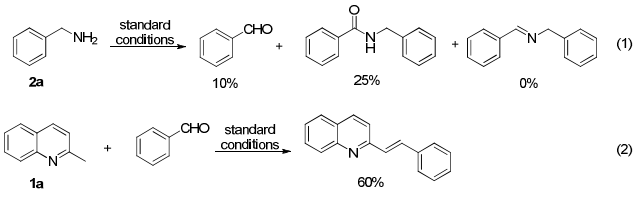
Figure 1. The crystal structure of compound **3a**.

The present olefination was successfully extended to various amines (Table 3). Benzylamines bearing electron-donating (Table 3, **3o**, **3p**, **3s**, **3t** and **3v**) or electron-withdrawing (Table 3, **3q**, **3r** and **3u**) groups reacted with 2-methylqinonline smoothly, affording the corresponding products in 50-95% yields. It was found that heterocyclic methanamines, such as 2-thiophen-methanamine and 2-furan-methanamine, can be transformed into their corresponding olefination products in good yields (Table 3, **3w**, **3x**). The deamination of aliphatic amine also proceed to give desirable product **3y**, albeit in a low yield.

Table 3. Substrate scope of various amines. [a]

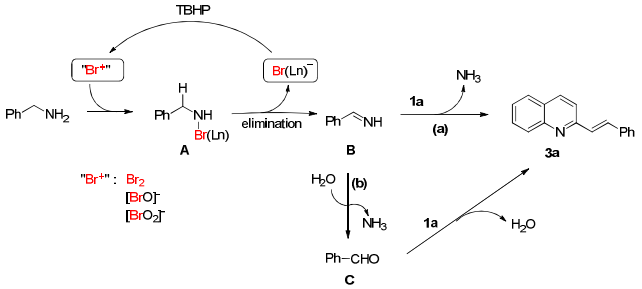


[a] Reactions were carried out in the dark with 2-methylquinoline (0.5 mmol), amines (0.6 mmol), NBS (0.1 mmol) and TBHP (1.0 mmol) in MeCN (1 mL) at 100 °C for 48 h, isolated yield.



Scheme 2. Control experiments for mechanism.

To get insight into the mechanism of this olefination, several control experiments were carried out. When benzylamine **2a** alone was subjected to the standard conditions, benzaldehyde and N-benzylbenzamide were isolated in 10% and 25% yield, respectively. The self-condensation product, benzylimine was not detected under the oxidative conditions. (Scheme 2, eq. 1) 2-Methylquinoline **1a** was then treated with benzaldehyde under standard conditions, providing **3a** in 60% yield. (Scheme 2, eq. 2) The results indicate that benzaldehyde may be involved in the olefination as a key intermediate. On the basis of earlier studies[6b, 13b, 16] and results obtained above, we propose a plausible reaction mechanism shown in Scheme 3 using for simplicity 2-methylquinoline and benzylamine as the substrates. First, the oxidation of bromine source with TBHP produces high active electrophilic bromine species (Br_2, $[BrO]^-$, $[BrO_2]^-$), which then adds to benzylamine to give N-bromoamine **A**, followed by an elimination to generate imine **B**. Two pathways of imine **B** were proposed to provide the target compound. In pathway (a), the imine **B** which bears an electrophilic carbon atom was attacked directly by 2-methylquinoline and lost a molecule of ammonia to generate product **3a**. In another pathway (b), the imine **B** is partly hydrolyzed to benzaldehyde **C** in the presence of water, which further reacted with 2-methylquinoline *via* adol-type condensations to give the olefination product **3a**.



Scheme 3. Possible mechanism of the olefination reaction.

Conclusions

In summary, we have developed a mild and metal-free olefination reaction between primary amines and benzylic C-H bonds. Through the direct deamination and benzylic C-H bond activation, this oxidative olefination provides biologically active 2-styrylquinolines with (*E*)-configuration. Further work on the synthetic application of the catalysts is ongoing in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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15 The information of crystal structure of **3a** (CCDC 942456) can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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