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# NBS-mediated bromination and dehydrogenation of tetrahydro-quinoline in one pot: scope and mechanistic study†

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A facile and general approach was developed for the efficient construction of functionalized bromoquinolines by the dehydrogenation of tetrahydroquinolines using NBS as the electrophile and as oxidant. The cascade transformation proceeded with good functional group tolerance under metal-free conditions with a short reaction duration. Various tetrahydroquinolines bearing either electron-rich or electron-deficient groups at different positions were successfully converted into the corresponding target products in moderate to high yields under mild conditions. It is worth noting that the obtained polybromoquinolines could further undergo classic metal-catalyzed cross-coupling reactions with good regioselectivity. The Sonagashira coupling reaction occurred regioselectively in the C-6 position of the obtained products followed by a Suzuki coupling reaction to give multifunctionalized quinolines. The mechanism indicated that electrophilic bromination/radical dehydrogenation sequences occurred in one pot.

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Quinoline derivatives are very important structural skeletons that have long been known for their wide range of biological activities and chemotherapeutic activities.<sup>1–5</sup> Of these compounds, bromo-quinolines are of interest to chemists as precursors for heterocyclic compounds with multi functionality, providing synthetic access to a wide variety of compounds.<sup>6–9</sup> Generally, brominated quinolines can be synthesized from benzene derivatives substituted with nitrogen functional groups by electrophilic cyclization using NBS or Br<sub>2</sub>.<sup>10–14</sup> However, these methods are mainly used to construct monobromo-quinolines; the synthesis of polybromoquinolines is rarely reported.

Polybromoquinolines are very important synthetic intermediates in organic synthesis because the aromatic ring contains several bromine atoms with different reactivities, which can provide a potential opportunity for the construction of other functionalized quinolines.<sup>15,16</sup> In addition, multi-bromoquinolines also played an important role in pharmacological chemistry with effective antibacterial, anticancer activities and some metabolic enzyme inhibition activities (Fig. 1).<sup>17</sup> Recently, our group reported the NBS-promoted cascade electrophilic cyclization of *N*-(3-phenylprop-2-ynyl) anilines for the construction of di-/tribromoquinolines (Scheme 1a).<sup>18</sup> However,

the regioselectivity was poor when the substituent was located in the *meta*-position of the propargyl amino group. Additionally, when there was a substituent in the *ortho*-position, the reaction could not occur due to steric hindrance. Therefore, it is necessary to develop a new strategy to solve the problem of regioselectivity for the synthesis of multi-brominated quinolines with diverse functional groups.

The dehydrogenation of tetrahydroquinolines, as an efficient and atom-economical approach towards quinolines, has been investigated extensively in recent years. Numerous examples include metal-complex catalysed acceptor less dehydrogenation,<sup>19–21</sup> along with aerobic oxidation catalyzed by Ru(phd)<sub>3</sub>,<sup>22</sup> Mn(Pc),<sup>23</sup> Co<sub>3</sub>O<sub>4</sub>-NGr/C,<sup>24</sup> and CuI/DEAD<sup>25</sup> *etc.* In addition, metal free catalytic systems,<sup>26,27</sup> photochemical methods,<sup>28–30</sup> and electrochemical methods<sup>31</sup> have also been reported. However, there are few reports on the simultaneous dehydrogenation and functionalization or halogenation of tetrahydroquinolines.

In 2008, Sahin<sup>15</sup> reported an NBS-mediated bromination/dehydrogenation of 1,2,3,4-tetrahydroquinoline for the synthesis of 4,6,8-tribromoquinoline in the presence of AIBN in

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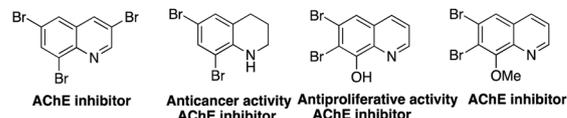
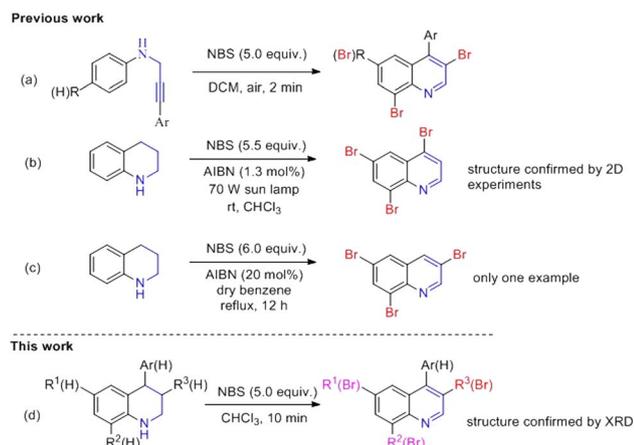


Fig. 1 Several bioactive multi-bromoquinolines.





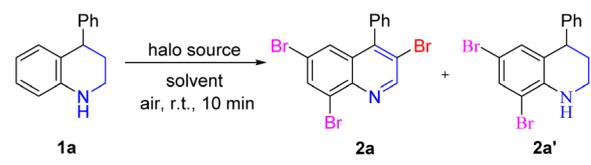
**Scheme 1** Synthesis of multi-bromo quinolines: (a) our group's previous work; (b) Sahin's work; (c) Langer's work; (d) this work.

$\text{CHCl}_3$  under sun lamp irradiation at 70 W (Scheme 1b). The product 4,6,8-tri-bromoquinoline was obtained in 75% yield with the structure confirmed by 2D experiments. Moreover, a very similar work was also reported by Langer *et al.* in which 1,2,3,4-tetrahydroquinoline reacts with 6.0 equivalents of NBS in the presence of AIBN in benzene at reflux (Scheme 1c).<sup>16</sup> However, these reactions only occurred in the presence of radical initiator AIBN, and the substrate scope was not investigated in these two studies.

On basis of our continuing studies in the synthesis of quinolines,<sup>32,33</sup> we herein reported an oxidative bromination/dehydrogenation of tetrahydroquinolines in the presence of NBS without a radical initiator under mild conditions. The mechanism indicated that NBS not only functioned as an electrophilic reagent to undergo electrophilic bromination, but also as an oxidant to achieve the oxidative dehydrogenation of tetrahydroquinoline *via* a radical pathway. Notably, the obtained multi-bromoquinolines could readily undergo the Sonagashira reaction and Suzuki coupling to afford the different substituted quinolines, which provide a method for constructing the library of quinolines (Scheme 1d).

Initially, 4-phenyltetrahydroquinoline **1a** was chosen as the model substrate with 5.0 equiv. NBS and DCM as the solvent (Table 1). Fortunately, the multi-bromination and dehydrogenation reactions occurred successfully, affording the desired product 3,6,8-tribromoquinoline (**2a**) in 50% yield. Next, some representative solvents were screened, and  $\text{CHCl}_3$  was selected as the best solvent for this transformation (entries 2–9). Notably, a great deal of heat was released from the reaction system when NBS was added at once, so NBS was added in batches, which was greatly increased the yield (entry 10). Next, the equivalent of NBS was also screened (entries 11–14). When the amount of NBS was 1.0 equiv. or 2.0 equiv., the desired product **2a** was not observed. However, the side product **2a'**, resulting from the 6,8-dibromination of tetrahydroquinoline, was isolated in 85% yield when 2.0 equiv. NBS was added. The reaction was incompletely by increasing the amount of NBS to 3.0 equiv. or 4.0 equiv., and both **2a** and **2a'** were obtained

**Table 1** Optimization of reaction conditions<sup>a</sup>



Entry	Halo source	Solvent	Yield <sup>b</sup> [%]
1	NBS (5.0 eq.)	DCM	50
2	NBS (5.0 eq.)	Toluene	67
3	NBS (5.0 eq.)	EA	45
4	NBS (5.0 eq.)	$\text{CH}_3\text{OH}$	Trace
5 <sup>c</sup>	NBS (5.0 eq.)	THF	60
6	NBS (5.0 eq.)	1,4-Dioxane	65
7	NBS (5.0 eq.)	$\text{CH}_3\text{CN}$	50
8	NBS (5.0 eq.)	DMSO	Trace
9 <sup>b</sup>	NBS (5.0 eq.)	$\text{CHCl}_3$	70
10 <sup>b</sup>	NBS (5.0 eq.)	$\text{CHCl}_3$	80
11 <sup>b</sup>	NBS (1.0 eq.)	$\text{CHCl}_3$	—
12 <sup>b, c</sup>	NBS (2.0 eq.)	$\text{CHCl}_3$	—
13 <sup>b, c</sup>	NBS (3.0 eq.)	$\text{CHCl}_3$	10
14 <sup>b, d</sup>	NBS (4.0 eq.)	$\text{CHCl}_3$	68
15 <sup>b, e</sup>	NBS (5.0 eq.)	$\text{CHCl}_3$	79
16 <sup>b, f</sup>	NBS (5.0 eq.)	$\text{CHCl}_3$	78
17 <sup>b</sup>	<i>N</i> -bromoacetamide (5.0 eq.)	$\text{CHCl}_3$	35
18 <sup>b</sup>	Tribromoisocyanuric acid (5.0 eq.)	$\text{CHCl}_3$	20
19 <sup>b</sup>	Dibromoisocyanuric acid (5.0 eq.)	$\text{CHCl}_3$	38
20 <sup>b, g</sup>	$\text{Br}_2$ (5.0 eq.)	$\text{CHCl}_3$	—
21 <sup>b, h</sup>	NCS (5.0 eq.)	$\text{CHCl}_3$	—
22 <sup>b, i</sup>	NIS (5.0)	$\text{CHCl}_3$	—

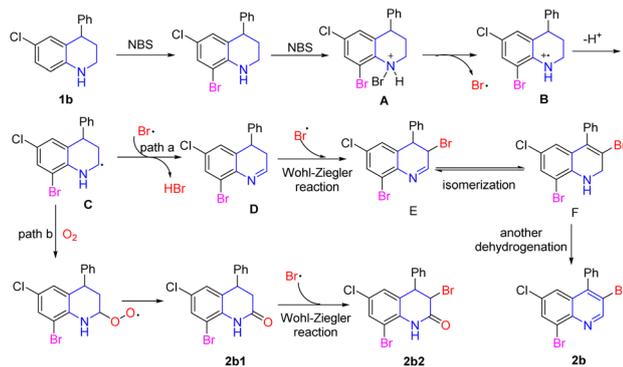
<sup>a</sup> Reaction conditions: 0.2 mmol **1a**, 5.0 equiv. NBS, 2.0 mL  $\text{CHCl}_3$ , r.t., air atmosphere. <sup>b</sup> Halo sources was added in batches. <sup>c</sup> **2a'** was isolated in 74% yield. <sup>d</sup> **2a'** was isolated in 15% yield. <sup>e</sup> Under argon atmosphere. <sup>f</sup> Under dark condition. <sup>g</sup> 65% product **2a** was isolated after quenching for 12 h. <sup>h</sup> 22% 6,8-Dichlorotetrahydroquinoline was isolated, some raw material decomposed. <sup>i</sup> Mixture, the raw material decomposed.

simultaneously. Subsequently, when the reaction was carried out under an argon atmosphere or dark conditions, the reaction efficiency was slightly reduced (entries 15–16). Other halo sources *N*-bromoacetamide, tribromoisocyanuric acid, dibromoisocyanuric acid and  $\text{Br}_2$  were also conducted in this reaction and no better yield was obtained than NBS (entries 17–20). Interestingly, no product was observed when  $\text{Br}_2$  was used. However, product **2a** was isolated in 65% yield after quenching for 12 h. When NBS was replaced by NCS or NIS, no corresponding product was not observed. When NCS was added, some raw materials decomposed, and only 22% of 6,8-dichlorotetrahydroquinoline was isolated. When NIS was used, most of the raw material decomposed quickly (entries 21–22). Therefore, the optimal reaction conditions were obtained, that is, 5.0 equiv. NBS, was added in batches, with  $\text{CHCl}_3$  as solvent under an air atmosphere.

Based on these results, a one-pot construction of the multi-bromoquinolines from tetrahydroquinolines **1** was carried out. Various substitutions of tetrahydroquinolines **1**, bearing electron-donating and electron-withdrawing groups, were investigated under the standard conditions, giving the target



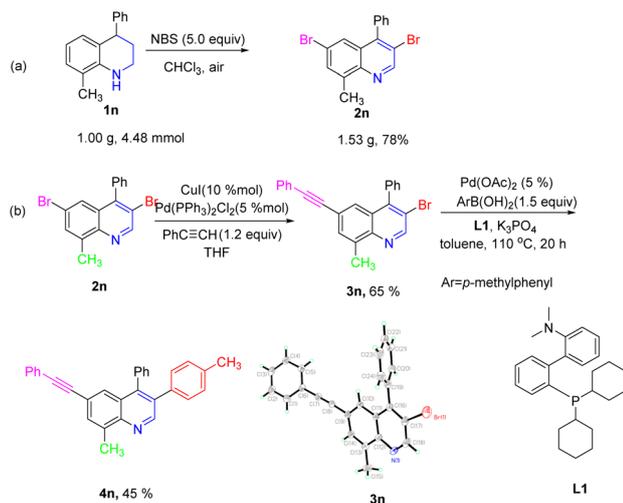




Scheme 4 The proposed mechanism.

nitrogen cation radical intermediate **B** was obtained by dehydrogenation under the action of the succinimide anion. Then, the key carbon radical intermediate **C** was generated after the rearrangement of the intermediate **B**.<sup>35</sup> The intermediate **C** could be captured by  $\text{Br}^\bullet$ , which was either followed by the removal of one  $\text{HBr}$  molecule to form 3,4-dihydroquinoline **D** (path a), or it could be captured by oxygen to form a by-product **2b1** (path b).<sup>35</sup> In path a, the Wohl-Ziegler reaction was occurred in the *ortho*-position of 3,4-dihydroquinoline **D** leading to the formation of intermediate **E**.<sup>36</sup> Then, 1,2-dihydroquinoline intermediate **F** was afforded through isomerization of intermediate **E**.<sup>31</sup> The desired multi-bromination product **2b** was formed through another dehydrogenation. In path b, the Wohl-Ziegler reaction occurred in the *ortho*-position of the carbonyl group to furnish the by-product **2b2**.

It was worth noting that the reaction could be effectively scaled up with good efficiency. As shown in Scheme 5a, the desired product **2n** was isolated in 78% yield by gram-scale reaction. Moreover, the obtained product **2n** could be transformed into various quinoline derivatives *via* classic metal-catalyzed cross-coupling reactions (Scheme 5b). For example, the regioselective Sonogashira coupling reaction between the



Scheme 5 (a) Gram-scale reaction; (b) synthetic applications.

obtained product **2n** and phenylacetylene occurred at the C6-position and the corresponding target product **3n** was isolated in 65% yield. Notably, the structure of the product **3n** was unambiguously verified by X-ray crystallography. Subsequently, the Suzuki-Miyaura coupling reaction of **3n** with 4-methylphenylboronic acid in the presence of  $\text{Pd}(\text{OAc})_2/\text{L1}$  gave the target product **4n** in 45% yield.

## Conclusions

In conclusion, an NBS-mediated bromination/dehydrogenation of tetrahydroquinolines under mild conditions was developed. Various quinolines bearing different functional groups were obtained in good yields. Furthermore, the Sonogashira reaction occurred regioselectively at the C6-position of dibromoquinoline. The mechanistic study revealed that the reaction may have been *via* electrophilic bromination and radical dehydrogenation to give the multibromoquinolines.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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