RSC Advances

PAPER

Cite this: *RSC Adv.*, 2023, **13**, 33495

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.

Received 4th October 2023
Accepted 7th November 2023

DOI: 10.1039/d3ra06747e

rsc.li/rsc-advances

Quinoline derivatives are very important structural skeletons that have long been known for their wide range of biological activities and chemotherapeutic activities.[1–5] 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.[6–9] Generally, brominated quinolines can be synthesized from benzene derivatives substituted with nitrogen functional groups by electrophilic cyclization using NBS or Br_2.[10–14] 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.[15,16] 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).[17] 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).[18] 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,[19–21] along with aerobic oxidation catalyzed by $Ru(phd)_3$,[22] Mn(Pc),[23] Co_3O_4-NGr/C,[24] and CuI/DEAD[25] *etc.* In addition, metal free catalytic systems,[26,27] photochemical methods,[28–30] and electrochemical methods[31] have also been reported. However, there are few reports on the simultaneous dehydrogenation and functionalization or halogenation of tetrahydroquinolines.

In 2008, Sahin[15] 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

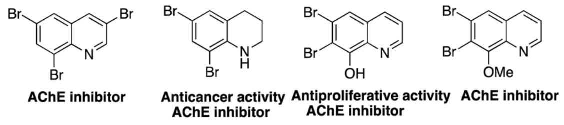

Fig. 1 Several bioactive multi-bromoquinolines.

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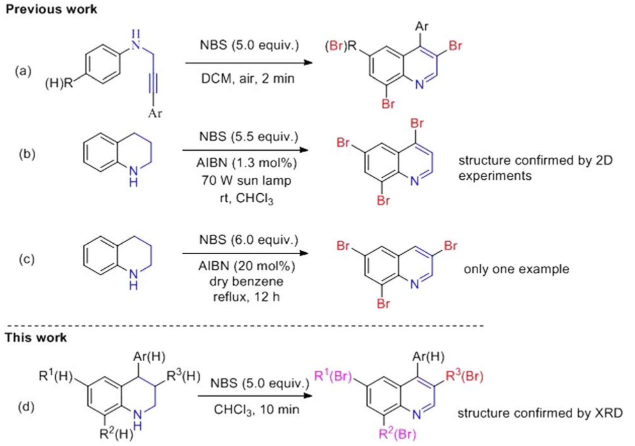
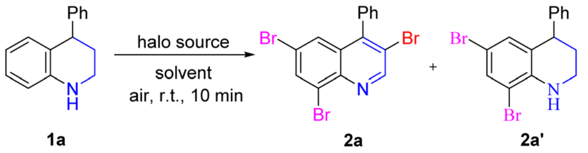
† Electronic supplementary information (ESI) available. CCDC 2295384. For ESI and crystallographic data in CIF or other electronic format see DOI: **https://doi.org/10.1039/d3ra06747e**



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

Table 1 Optimization of reaction conditions[a]



Entry	Halo source	Solvent	Yield[b] [%]
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.)	CH_3OH	Trace
5[c]	NBS (5.0 eq.)	THF	60
6	NBS (5.0 eq.)	1,4-Dioxane	65
7	NBS (5.0 eq.)	CH_3CN	50
8	NBS (5.0 eq.)	DMSO	Trace
9[b]	NBS (5.0 eq.)	$CHCl_3$	70
10[b]	NBS (5.0 eq.)	$CHCl_3$	80
11[b]	NBS (1.0 eq.)	$CHCl_3$	—
12[b, c]	NBS (2.0 eq.)	$CHCl_3$	—
13[b, c]	NBS (3.0 eq.)	$CHCl_3$	10
14[b, d]	NBS (4.0 eq.)	$CHCl_3$	68
15[b, e]	NBS (5.0 eq.)	$CHCl_3$	79
16[b, f]	NBS (5.0 eq.)	$CHCl_3$	78
17[b]	*N*-bromoacetamide (5.0 eq.)	$CHCl_3$	35
18[b]	Tribromoisocyanuric acid (5.0 eq.)	$CHCl_3$	20
19[b]	Dibromoisocyanuric acid (5.0 eq.)	$CHCl_3$	38
20[b, g]	Br_2 (5.0 eq.)	$CHCl_3$	—
21[b, h]	NCS (5.0 eq.)	$CHCl_3$	—
22[b, i]	NIS (5.0)	$CHCl_3$	—

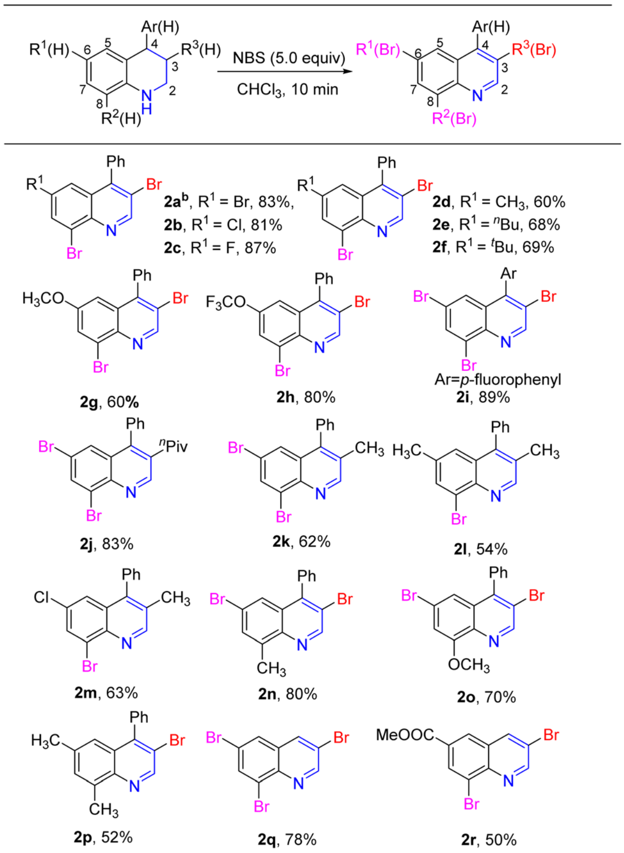
[a] Reaction conditions: 0.2 mmol **1a**, 5.0 equiv. NBS, 2.0 mL $CHCl_3$, r.t., air atmosphere. [b] Halo sources was added in batches. [c] **2a′** was isolated in 74% yield. [d] **2a′** was isolated in 15% yield. [e] Under argon atmosphere. [f] Under dark condition. [g] 65% product **2a** was isolated after quenching for 12 h. [h] 22% 6,8-Dichlorotetrahydronquinoline was isolated, some raw material decomposed. [i] Mixture, the raw material decomposed.

$CHCl_3$ 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).[16] 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,[32,33] 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 $CHCl_3$ 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 incompleted by increasing the amount of NBS to 3.0 equiv. or 4.0 equiv., and both **2a** and **2a′** were obtained 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 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 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 $CHCl_3$ 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

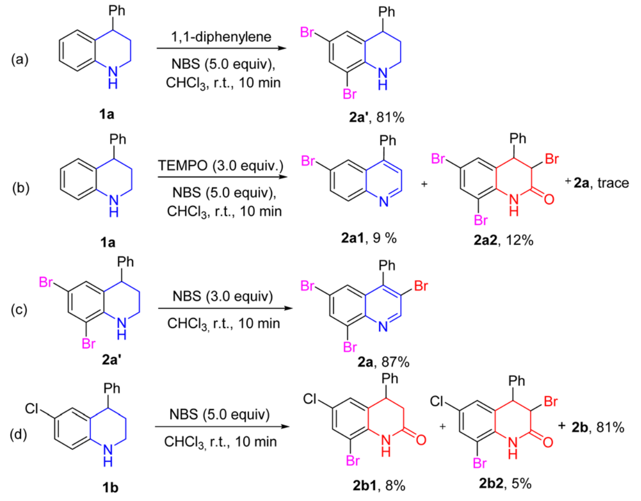


Scheme 2 Substrate scope studies. ^{a} Reaction conditions: 0.2 mmol **1a**–**1r**, 5.0 equiv. NBS (added one by one equivalent), in 2.0 mL $CHCl_3$ at room temperature under air. ^{b}6-bromo-4-phenyl-1,2,3,4-tetrahydroquinoline was used as the substrate.

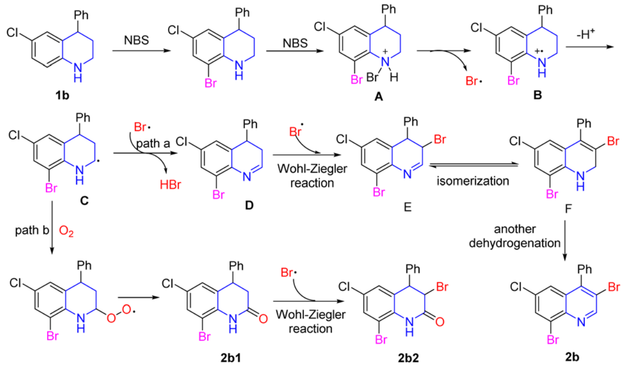
product quinolines **2a**–**2r** in moderate to good yields, as shown in Scheme 2. First, a series of 4-phenyl-tetrahydroquinolines were tested under the standard conditions. Substrates with weak electron-withdrawing groups in the C6-position of 4-phenyl-tetrahydroquinoline, such as Br, Cl or F, afforded the corresponding 3,8-dibromo-4-phenyl-quinolines **2a**–**2c** in good yields. When an alkyl group (^{t}Bu, ^{n}Bu or CH_3) or strong electron donating group (OCH_3) was in the C6 position, the corresponding 3,8-dibromo-4-phenyl-quinolines **2d**–**2g** were obtained in moderate yields. It was worth noting that substrate bearing trifluoromethoxy (OCF_3) in the C6-position gave a good yield. When substrate lacked a substituent in the C6-position, the corresponding tribromide quinoline **2i** was obtained in high yield. Next, the reaction was applied to the 4-phenyl tetrahydroquinoline with substituents at the C3 or C8 position. When an ^{n}Piv group was located in the C3 position, the resulting 6,8-dibromoquinoline derivative was obtained in 83% yield. The yield was relatively low when a methyl group was in the C3 position (**2k**–**2m**, 54–63%). When CH_3 or OCH_3 was at the C8 position of 4-phenyl-tetrahydroquinoline, the expected 3,6-dibromo-4-phenyl quinolines **2n**–**2p** were successfully be obtained in moderate yields. Furthermore, unsubstituted tetrahydroquinoline **1q** was also investigated under standard conditions, and the 3,6,8-tetrahydroquinoline **2q** was obtained in 78% yield. Finally, when an ester group was at the C6 position of tetrahydroquinoline, the target product **2r** was obtained in moderate yield.

To get insights into the mechanism of NBS-mediated bromination/dehydrogenation of tetrahydroquinolines, some control experiments were carried out (Scheme 3). First, substrate **1a** was reacted with 5.0 equiv. 1,1-diphenylene under the standard conditions, and the side-product **2a′** was isolated in 81% yield (Scheme 3a). The reaction was also performed in the presence of 2,2,6,6-tetramethylpiperidine oxide (TEMPO) as a radical scavenger under the standard conditions, and a trace amount of the target product was detected. Two side products **2a1** and **2a2** were isolated in 9% and 12%, respectively. This may be due to the oxidative property of TEMPO (Scheme 3b). Based on these results, it was believed that the bromination of benzene may have occurred *via* an ionic manner. Because of the activation of the amino group, electrophilic substitution of the aromatic rings could readily occur. However, the dehydrogenation and 3-bromination of tetrahydroquinoline may have occurred *via* a radical pathway. Moreover, the **2a′** could easily be transformed to **2a** in 87% yield in the presence of 3.0 equiv. NBS. This result indicated that compound **2a′** may be the intermediate in this reaction (Scheme 3c). Furthermore, when tetrahydroquinoline **1b** was used as the substrate, two other by-products (**2b1** and **2b2**) were obtained in addition to main product **2b** (Scheme 3d). These results all indicated that the dehydrogenation process of tetrahydroquinoline may have been *via* a radical pathway.

According to the above results and previous literature,[31,34–37] the possible reaction pathway from 4-phenyl-6-cholor-tetrahydroquinoline (**1b**) into 4-cholor-6,8-tribromo-quinolines (**2b**) was proposed as shown in Scheme 4. First, electrophilic bromination of the aryl ring occurred due to the activation of the amino group to give the 6-chloro-8-bromo-quinoline.[34] After that, the electron-rich amino group was further attacked by NBS to form quaternary ammonium salt intermediate **A**. The



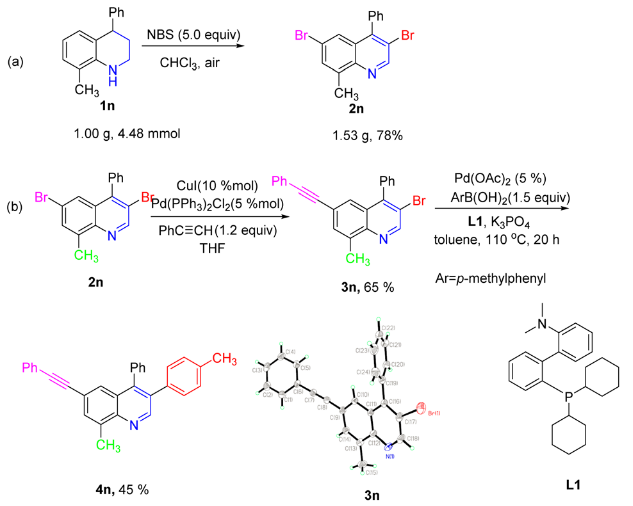
Scheme 3 (a) 1,1-Diphenylene suppression; (b) TEMPO suppression; (c) intermediate reaction; (d) byproducts.



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**.[35] The intermediate **C** could be captured by $Br^{\bullet}$, which was either followed by the removal of one 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).[35] 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**.[36] Then, 1,2-dihydroquinoline intermediate **F** was afforded through isomerization of intermediate **E**.[31] 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 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 Pd $(OAc)_2$/**L1** gave the target product **4n** in 45% yield.



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

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

We gratefully acknowledge the National Natural Science Foundation of China (NSFC, No. 22261019 and 22001101) Jiangxi Provincial Natural Science Foundation (20232BAB203006 and 20212BAB213014), the Education Department of Jiangxi Province (GJJ2201340) and Jiangxi Science and Technology Normal University (2020BSQD015) for financial support.

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