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Ultrasound assisted one-pot synthesis of benzo-fused indole-4, 9-dinones from 1,4-naphthoquinone and α-aminoacetals

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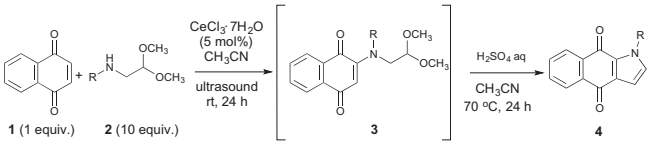
ABSTRACT

A one-pot synthesis of benzo[*f*]indole-4,9-diones from 1,4-naphthoquinone with α-aminoacetals has been developed. This method provides a straightforward synthesis of benzo[*f*]indole-4,9-diones via intramolecular nucleophilic attack of aminoquinones to aldehydes under mild reaction conditions. The detailed mechanism was also investigated.

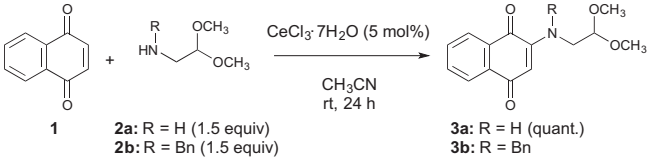
Introduction

p-Indolequinones are important heterocycles since they display interesting bioactivities such as anticancer activitiy[1–8] as well as the ability to trigger drug release.[9–13] Additionally, they are useful precursors for the syntheses of bioactive compounds.[14–18] Therefore, over decades, many methodologies have been investigated for the synthesis of *p*-indolequinones.[19] First, oxidation of indoles has been developed and used as a conventional method. However, the reactions can be problematic due to the less functional group tolerance. Thus, as alternate methodologies, the syntheses of *p*-indolequinones from *p*-quinones have been developed since the 1970s. In these quinone approaches, transition metals were mostly used to cyclize aminoquinones.[20–25] More recently, one-pot syntheses via Sonogashira coupling have been reported.[26–28] *p*-Quinones also successfully underwent reactions with enamines, in which aminoquinones were proposed to act as electrophiles.[29–32] In contrast to these works, there are three examples in which it seems that aminoquinones worked as nucleophiles. Although the mechanism was not mentioned, aminoquinones intramolecularly attack alcohol,[17] carboxylic,[33,34] or carbonyl carbons.[35] These reactions required multi-step procedures,[17] proceeded with only one specific substrate along with laborious syntheses of starting materials,[35] or resulted in low yields.[35,17] In addition, it was reported that the synthesis was irreproducible.[36] Thus, a general method was sought to develop a synthesis of *p*-indolequinones utilizing the nucleophilicity of aminoquinones. Herein, we report a new synthetic method of benzo[*f*]indole-4,9-diones from 1,4-naphthoquinone 1 and α-aminoacetals 2 in one-pot with a detailed mechanism (Eq. 1).



(1)

Our initial investigation was carried out in a two-step manner. The first step is the amination of 1,4-naphthoquinone **1**, catalyzed by $CeCl_3{\cdot}7H_2O$.[37] Using 1.5 equiv of a primary amine **2a** (R = H) in acetonitrile as a solvent, aminoquinone **3a** was obtained quantitatively (Eq. 2).



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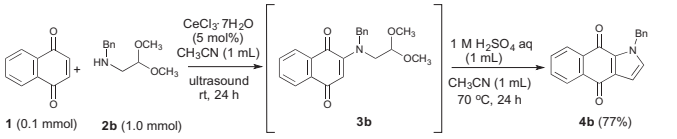
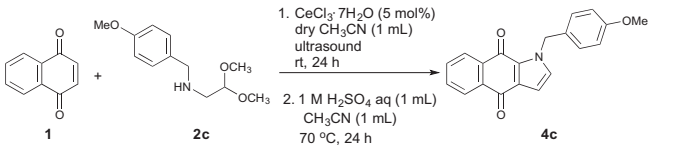
On the other hand, in the case of a secondary amine **2b** (R = Bn), the reaction did not complete, and 58% of **1** was recovered. 100% conversion of naphthoquinone was accomplished when the reaction was carried out in dry acetonitrile using 10 equiv of amine **2b** with the use of ultrasound. The formation of aminoquinone **3b** was confirmed by crude ^{1}H NMR. However, the product **3b** could not be isolated by column chromatography on silica gel or alumina since an N-debenzylation happened as reported.[38] The synthesis of indolequinones was further investigated in one-pot synthesis, as shown in Eq. 1. Ten equivalents of **2b** were added to a 1 mL of 1 M solution of **1** in dry acetonitrile in the presence of 5 mol % of $CeCl_3{\cdot}7H_2O$ at room temperature, and the mixture was placed in a sonicator for 24 h. The resulted solution was then diluted with additional 1 mL of acetonitrile and treated with 1 mL of 1 M H_2SO_4 aq and was kept at 70 °C for 24 h. The corresponding benzo-fused *p*-indolequinone **4b** was obtained in 77% yield (Eq. 3).



(3)

We examined the amount of amines under the same condition in Eq. 3, and it was determined that 10 equiv of the amines are required to achieve a good yield of indolequinone (Eq. 4, Table 1).



(4)

For an effective one-pot reaction, the amination step and deprotection–cyclization steps should work in the same solvent system. Since the deprotection of acetals requires water for the formation of aldehydes, water-miscible solvents were examined, which included acetonitrile, ethanol, THF, and nitromethane (Eq. 5, Table 2). The reaction in acetonitrile gave the highest yield, whereas THF and ethanol both resulted in a low yield of **4d**. We believe that the low yield in ethanol is due to the effect of the solvent on the equilibrium forming the aldehyde. In addition, the higher yield in acetonitrile compared to THF can be attributed to the miscibility with water. Furthermore, nitromethane was found to suppress the reaction process because of its amine sensitizing activity.[39]

The solvent miscibility with water has effects on the reaction, and the addition of more acetonitrile in the cyclization step was then investigated (Eq. 6, Table 3, entries 1–5). The addition of 1 mL of CH_3CN in the second step, which resulted in a total amount of 2 mL of CH_3CN, gave the highest yield (entry 3). Without the addition of CH_3CN, a significant drop in the yield was observed (entry 2). When the reaction was run under neat conditions, only trace amounts of the product formed (entry 1). The dilution of the reaction mixture with more than 1 mL of CH_3CN resulted in lower yields (entries 4, 5). In the cyclization step, acid is essential for the formation of an aldehyde as an electrophile. Therefore, the aqueous solutions of different acids were also examined. Ten equivalents of acids were used to assure the excess amount of amine was neutralized and was found not to hinder the cyclization. Sulfuric acid showed the better activity than TsOH or HCl (entries 2, 6, 7).

Table 1
Screening of amine equivalents

Equivalents of amine **2c**	Yield of **4c** (%)
2	19
5	43
10	87

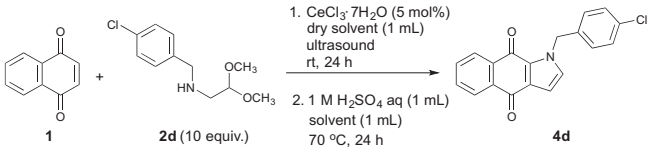
Table 2
The formation of **4d** in various solvents

Solvent	Yield of **4d** (%)
CH_3CN	81
THF	50
EtOH	47
CH_3NO_2	–

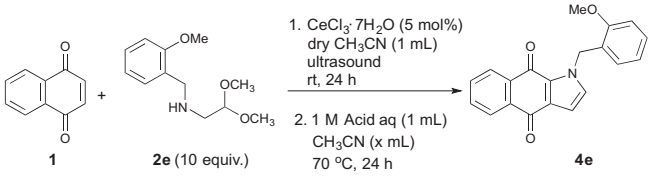
Table 3
Reaction concentration and acid scope

Entry	Addition of CH_3CN (x mL)	Acid	Yield (%)
1	0[a]	H_2SO_4	Trace
2	0	H_2SO_4	38
3	1	H_2SO_4	88
4	2	H_2SO_4	66
5	3	H_2SO_4	66
6	1	TsOH	63
7	1	HCl	16

[a] Reaction was run under neat conditions. No solvent was used in both steps.



(5)



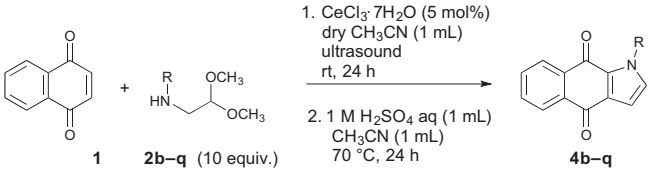
(6)

Table 4
Synthesis of benzo[*f*]indole-4,9-diones **4** from 1,4-naphthoquinone **1** and α-aminoacetals **2**[a]

Entry	Amines	R	Products	Yield (%)[b]
1	**2b**	$C_6H_5CH_2$	**4b**	77
2	**2c**	4-$CH_3OC_6H_4CH_2$	**4c**	87
3	**2d**	4-$ClC_6H_4CH_2$	**4d**	81 (61)
4	**2e**	3-$CH_3OC_6H_4CH_2$	**4e**	88
5	**2f**	4-$CH_3C_6H_4CH_2$	**4f**	80 (49)
6	**2g**	2-$CH_3C_6H_4CH_2$	**4g**	80
7	**2h**	2-$HOC_6H_4CH_2$	**4h**	83
8	**2i**	$C_6H_5C{\equiv}CCH_2$	**4i**	45
9	**2j**	1-Naph-CH_2	**4j**	70
10	**2k**	4-$BrC_6H_4CH_2$	**4k**	74 (67)
11	**2l**	4-$FC_6H_4CH_2$	**4l**	82
12	**2m**	$(CH_3)_2CH$	**4m**	–
13	**2n**	$CH_2{=}CHCH_2$	**4n**	25[c]
14	**2o**	4-$CH_3OC_6H_5$	**4o**	–
15	**2p**	4-$CH_3C_6H_5$	**4p**	–
16	**2q**	C_6H_5	**4q**	–

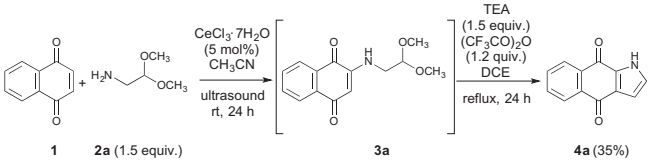
[a] All reactions were carried out with **1** (0.1 mmol), **2** (1 mmol), and $CeCl_3{\cdot}7H_2O$ (5 mol %) in CH_3CN (1 mL), then CH_3CN (1 mL) and 1 M H_2SO_4 aq (1 mL) were added.
[b] Yields without ultrasound in the amination step are given in parentheses.
[c] 42% of **1** was recovered.

More examples of benzo[*f*]indole-4,9-diones prepared using this optimized one-pot process are summarized in Table 4 (Eq. 7). Amines **2** were synthesized by reductive amination or substitution reaction of 2-chloroacetaldehyde dimethyl acetal. The presence of electron donating groups on the benzene ring resulted in better yields of the products **4** compared to other groups (entries 2, 4–7). Furthermore, halogen substituents had a positive effect the reaction yields (entries 3, 10, 11). In this one-pot condition, the use of ultrasound in the amination step was necessary to give higher yields (entries 3, 5, 10). The amine with an allyl substituent was found to be unstable under heating conditions. Consequently, the indolequinone **4n** was afforded in a low yield (entry 13). In the case of an alkyl amine, the amination step did not proceed well, and no cyclization product formed (entry 12). When aromatic amines were used, the amination was completed, but the cyclization step did not occur even in the presence of an electron-donating group on the benzene ring (entries 15–17). It is suggested that the nitrogen atom was deactivated due to the conjugation of the aromatic system.



(7)

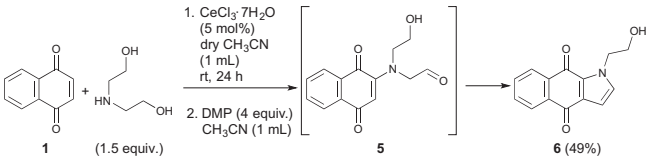
When the primary amine **2a** was used, product **4a** was not obtained under the optimized conditions. The result can be attributed to an acid–base reaction between the aminoquinone **3a** and sulfuric acid, which resulted in a salt. The salt made the substrate less reactive and led to the failure of the reaction. As a solution, when the cyclization step was performed under reflux conditions in dichloroethane in the presence of triethylamine and trifluoroacetic anhydride,[40] product 4a was obtained in 35% yield without isolation of **3a** (Eq. 8).



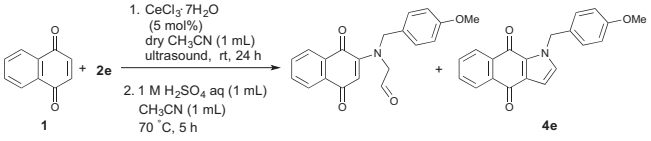
(8)

The proposed mechanism includes the formation of an aldehyde intermediate with a nucleophilic attack by the aminoquinone (Scheme 1). Subsequent dehydration furnishes *p*-indolequinones.

To confirm the aldehyde intermediate, an experiment using diethanolamine with Dess–Martin periodinane (DMP) was performed (Eq. 9). The amination followed by oxidation with DMP should generate the corresponding aldehyde and AcOH as a byproduct. The reaction resulted in 49% yield of product **6** without addition of aqueous acid. The result indicates that the aldehyde **5** is the intermediate, and AcOH provided the proton that is required in the deprotection process.

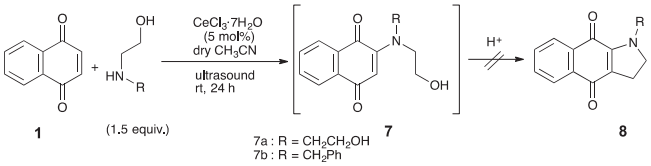


(9)



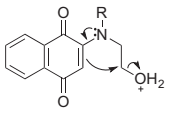
(10)

Furthermore, the reaction was stopped after 5 hours of addition of 1 M H_2SO_4 aq, and the reaction mixture was extracted using ice-cold deuterated chloroform (Eq. 10). ^{1}H NMR spectrum of the mixture showed a characteristic aldehyde signal at 9.97 ppm indicating the aldehyde was the intermediate.



(11)

In addition, the effect of alcohol group for the cyclization was investigated (Eq. 11). After protonation, intermediate **9** will be formed, and the cyclization may occur. When the diethanolamine and *N*-benzylethahanolamine were used, product **8** was not obtained using either sulfuric acid or TFA. There is one report of the use of β-hydroxylamine as a benzylalcohol in their course of the total synthesis.[17] In this case, the cyclization happens with TFA. Our results can be clarified that the oxonium ion does not make the α-carbon electrophilic enough for the cyclization. This result supports that our acetal strategy is a good solution for that remaining problem



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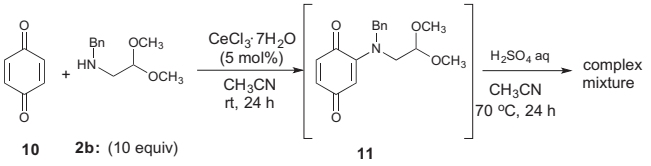
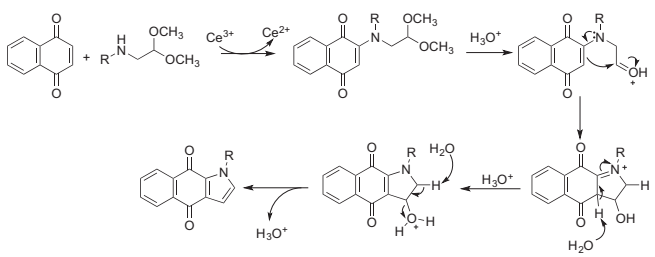


(12)

We also employed *p*-benzoquinone **10** as a starting material. It was confirmed by ^{1}H NMR that the amination step proceeded, but the cyclization did not occur under the optimized acidic condition and resulted in a complex mixture (Eq. 12). It is concluded that the aromatic ring of 1,4-naphthoquinone assists the nucleophilic attack of quinone on the aldehyde intermediate.



Scheme 1. Plausible mechanism.

Conclusions

A method was developed to synthesize benzo[*f*]indole-4,9-diones in one-pot from 1,4-naphthoquinone and α-aminoacetals. The use of easily synthesized α-aminoacetals eliminates undesirable laborious work for preparation of starting materials. The mechanism is unique to utilize the nucleophilicity of aminonaphothoquinones, and an aldehyde intermediate was confirmed. The present method provides an effective, inexpensive, and convenient way to synthesize *p*-indolequinones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.031.

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