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FACILE AND EFFICIENT *N*-BOC DEPROTECTION OF AMIDE AND SULFONAMIDE UNDER MICROWAVE IRRADIATION IN WATER

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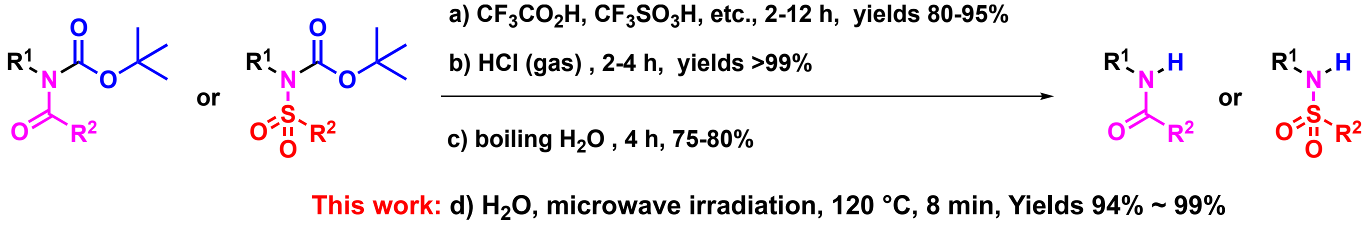
Abstract – A facile and efficient microwave-assisted *N*-Boc deprotection of amide and sulfonamide in water was developed. With environmentally friendly, operational-simplicity, good substrate scope and excellent product yields, this methodology is superior to the existing approach. Significantly, the target compound was obtained after filtration and dry.

The *tert*-butyloxycarbonyl (Boc) group is one of the most important protection group in the core fragment amide and sulfonamide.[1-5] Also, the application of *N*-Boc protection in the organic synthesis was widely due to the mild reaction conditions and high yields.[6-8] Herein, the removal of the Boc group remains of vital importance. While, the most general approach to the *N*-Boc deprotection of amide and sulfonamide was under the acid conditions (**Scheme 1**, **method a**).[9-11] Recently, the alternative deprotection has been developed such as HCl gas and high-temperature water (**Method b**, **c**).[13-17] However, the **methods a** and **b** could produce the waste acid (The HCl gas was released from the reaction of H_2SO_4 and NaCl). Additionally, the **method c** offers moderate yields in 4 hours. Furthermore, the organic solvent was inevitably used in the chemical synthesis such as the post-manipulations, purification steps.[18-20] Thus, the facile, eco-friendly strategy with excellent yields was strongly desired. In our previous works, the

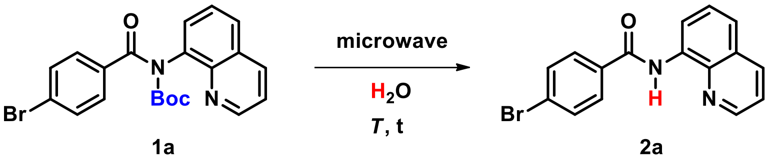


Scheme 1. Selected *N*-Boc deprotection of amide and sulfonamide

microwave irradiation could accelerate the reaction and enhance the yields.[21-23] Herein, the green solvent water was used to decompose the *N*-Boc in amide and sulfonamide under microwave irradiation with operational-simplicity, environmentally friendly, excellent yields and good substrate scope (**Method d**). Significantly, the target compound was obtained after filtration and dry.

Although the deprotection of *N*-Boc is known, it is still great challenge to find the optimum condition to perform microwave-assisted approach in water. The reaction of **1a** and water was chosen as a benchmark reaction (**Table 1**). Unfortunately, the *N*-Boc deprotection was not performed at 60 °C and 80 °C (**Table 1**, **entries 1-2**). Then, 52% of **2a** was obtained with a temperature of 100 °C in 10 minutes (**Entry 3**). Therefore, the reaction temperature was enhanced to improve the yields. Thus, the yield of **2a** was increased with an increase of temperature (**Entries 4-6**). Then, the reaction yields of 8 minutes were higher than that of 6 minutes (**Entries 7**, **8**). Additionally, the conversion of **1a** was completely at 130 °C in 6 minutes (**Entry 9**). Compared with conventional heating method (**Entry 10**), microwave irradiation could significantly accelerate the reaction and notably improve the yield. As a result, the combination of 0.5 mmol **1a** and 3.0 mL water with a temperature of 120 °C in 8 minutes was fixed (**Entry 7**), as optimal conditions.

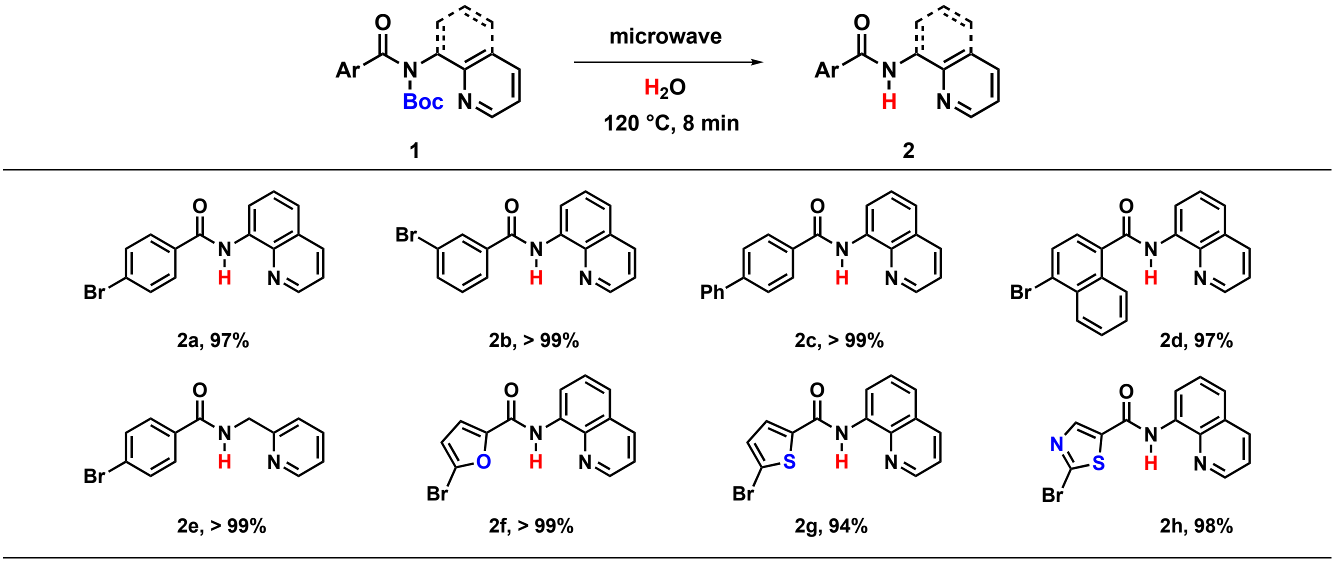
Table 1. The optimization microwave-assisted approach in water[a]



Entry	*T* / (°C)	t / (min)	Yield (**2a**) / %[b]
1	60	10	0
2	80	10	0
3	100	10	52
4	110	10	85
5	120	10	97
6	130	10	97
7	**120**	**8**	**97**
8	120	6	93
9	130	6	97
10[c]	100	180	79

[a] Reactions conditions : **1a** 0.5 mmol, **water** 3.0 mL, microwave irradiation; [b] Isolated yield; [c] Conventional heating.

Table 2. Microwave-assisted *N*-Boc deprotection of amide (**1**)[a]



2a, 97%

2b, > 99%

2c, > 99%

2d, 97%

2e, > 99%

2f, > 99%

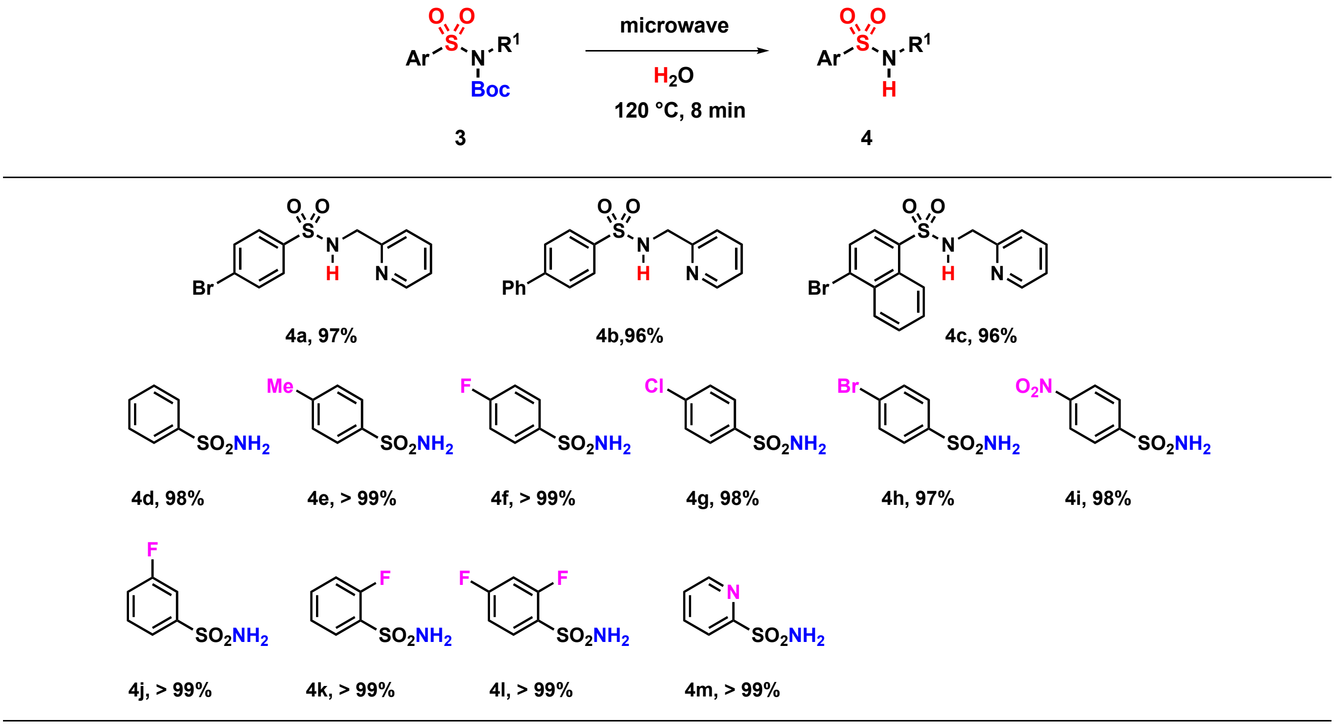
2g, 94%

2h, 98%

[a] Reactions conditions : **1** 0.5 mmol, **water** 3.0 mL, microwave irradiation; [b] Isolated yield.

Once the optimized reaction conditions were identified, the limitation and scope of the microwave-assisted approach were examined. Various *N*-Boc aromatic amides were explored, the result was shown in **Table 2**. The deprotection of *N*-Boc benzamide (**2a**, **2b**, **2e**), biphenylamide (**2c**) and naphthylamide (**2d**) always went smoothly and the yields were excellent. In addition, the five-membered heteroaryl carboxamide were also afforded (**2f-2h**) in excellent yields.

Table 3. Microwave-assisted *N*-Boc deprotection of sulfonamide (**3**)[a]



4a, 97%

4b,96%

4c, 96%

4d, 98%

4e, > 99%

4f, > 99%

4g, 98%

4h, 97%

4i, 98%

4j, > 99%

4k, > 99%

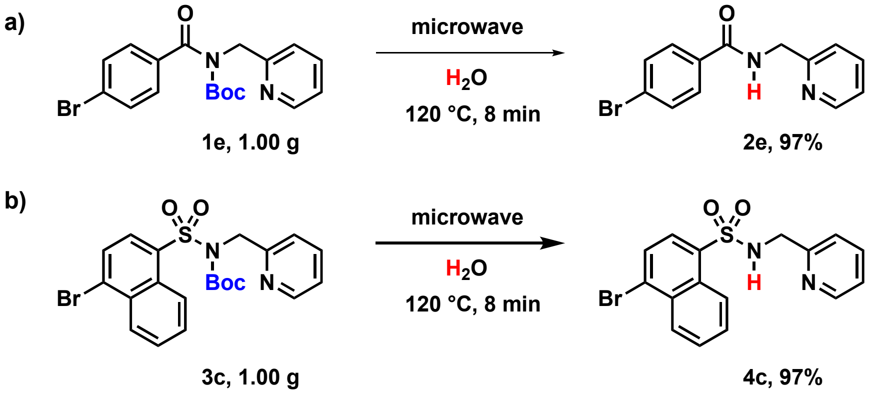
4l, > 99%

4m, > 99%

[a] Reactions conditions : **3** 0.5 mmol, **water** 3.0 mL, microwave irradiation; [b] Isolated yield.

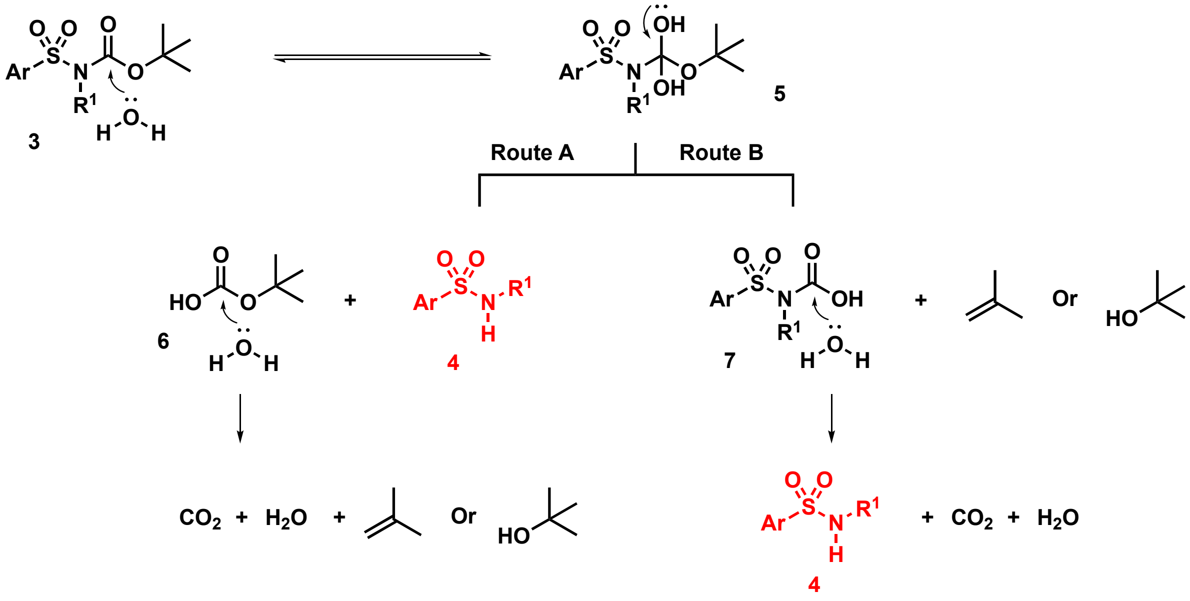
To increase the scope of microwave-assisted method, the *N*-Boc aromatic sulfonamide (**3**) was tested (**Table 3**). The deprotection of **3a-3c** (R^1 was pyridin-2-ylmethyl) in water gave excellent yields. Furthermore, it was obvious that the deprotection of **3d-3m** (R^1 was hydrogen) took place extremely smoothly. Both electron-donating and electron-withdrawing groups, such as 4-methyl (**4e**) and 4-nitro (**4i**), 4-halogen (**4f-4h**) afforded the desired products in excellent yields. More importantly, the group in different substituted position had no effect on the reaction, such as 3-fluoro (**4j**) and 2-fluoro (**4k**). In addition, the *N*-Boc-2,4-difluorobenzenesulfonamide (**3l**) was also investigated and afforded the corresponding product (**4l**). Finally, the deprotection of **3m** could offer the desired compound **4m** in excellent yields.

To fully demonstrate the applicability of this methodology, a scale-up reaction for **1e** and **3c** was carried out with three times. The yields were excellent (**Scheme 2**).



Scheme 2. Gram-scale synthesis

More importantly, the deprotection mechanism was shown in **Scheme 3**. Firstly, the water attacked the amid carbonyl group in high temperature under microwave irradiation.[14,15] Then, **5** could be decomposed into target molecule (**4**) and **6** (**Route A**). Subsequently, **6** was attacked by water and CO_2, H_2O and tertiary butanol or 2-methylpropene was released. Additionally, **5** could also be decomposed into **7** and tertiary butanol or 2-methylpropene (**Route B**). Subsequently, the water attacked the carboxy group of **7**. Finally, the target molecule **4** was obtained.



Scheme 3. Proposed reaction mechanism

In summary, we have reported a facile and efficient microwave-assisted *N*-Boc deprotection of amide and sulfonamide in water. With environmentally friendly, operational-simplicity, good substrate scope, excellent product yields, and gram-scale synthesis, this methodology is superior to the existing approach. Significantly, the target compound was obtained after filtration and dry.

SUPPORTING INFORMATION

Supplementary (synthesis of the target molecule, ^{1}H spectra, ^{13}C spectra, etc.) data associated with this article can be found, in the online version, at URL: hhttps://www.heterocycles.jp/newlibrary/downloads/PDFsi/27691/104/9.

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