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ARTICLE TYPE

Quaternary Ammonium Salt as Alkylation Agent in the Three-Component Reactions for the Synthesis of Benzothiazoles in Water

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Substituted benzothiazoles are synthesized by metal-catalyst free three-component reactions of o-iodoaniline, quaternary ammonium salt, and sulfur powder in water with moderate to excellent yields up to 95%.

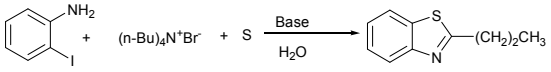
Multicomponent reactions (MCRs) have gained considerable and steadily increasing interests recently due to their convenience and atomic economy,[1] and they have served as a powerful tool in synthetic chemistry.[2]

Substituted benzothiazoles cores are important biologically active motifs, which can be usually found in many natural products, [3] drug molecules, [4] and novel materials for sensor and indicator et.al.[5] There have been reported several synthetic approaches to obtain them. For example, one of the most general and flexible methods is the condensation reaction of 2-aminothiophenols with carboxylic acids or aldehydes, which might be limited by the difficulties to obtain unstable 2-aminothiophenol substrate.[6] Other methods containing metal-catalyzed coupling reactions such as copper- or palladium-catalyzed intramolecular reactions starting from amine have then been developed.[7] Recently, Itoh and Ma and coworkers reported a novel and practical synthetic method by using copper- or palladium-catalyzed cross-coupling reactions between 2-haloanilides and metal sulfides[8] or 2-ethylhexyl-3-mercaptopropionate.[9] Sun and coworkers also reported an efficient and convenient method for the formation of 2-substituted benzothiazoles via a copper-catalyzed condensation of 2-aminobenzenethiols with nitriles.[10] In general, in most of these cases, metal catalysts were used and organic solvents were applied as reaction media.[11]

Recently, we reported Cu-catalyzed three-component reactions involving 2-iodoaniline, aldehydes, and sulfur powder for the synthesis of substituted benzothiazoles in water.[12] To our surprise, during this work we found that substituted benzothiazoles could even be obtained in high yields without transition-metal catalyst when the quaternary ammonium salts were used instead of aldehydes. This reaction has the following advantages compared with the reported literatures: (i) easy availability of substrates such as quaternary ammonium salt, o-iodoaniline, and sulfur powder; (ii) metal-catalyst free in the reaction avoid the introduction of heavy metal into product as well as convenient work-up step; (iii) water was used as sole solvent instead of normally used organic media; (iv) the reactions can be carried out in the air without inert atmosphere; (v) quaternary ammonium salts act as chemoselective alkylation agents as well as phase transfer reagents during reaction.[13]

Initially, 2-iodoaniline, tetrabutylammonium bromide (TBAB) and elemental sulfur were tried as model substrates to optimize the reaction conditions. As shown in Table 1, bases seemed to be essential to the reactions, and control experiments confirmed that no product was detected without addition of bases (Table 1, entry 1). Screening of different bases indicated KOH to be the proper one to give 93% yield, while the employment of organic bases and other inorganic bases such as triethylamine, pyridine, carbonate salts or NH3•H2O resulted in lower yields (Table 1, entries 2-8). Reaction temperature was another important factor to affect the results, lower temperature than 140 ºC decelerated the reaction rate (Table 1, entries 9-11). In addition, shorter reaction time had negative effects on the results, and 14 hours was chosen for the further studies (Table 1, entries 12-14). The loading of tetrabutylammonium bromide and base was then investigated, and it was observed that decreasing the amount of the tetrabutylammonium bromide or base resulted in lower yields. Meanwhile, the amount of sulfur could be reduced to be around 1.2 mmol with similar results (Table 1, entries 15-18). In summary, the optimal conditions for the synthesis of benzothiazoles in water consist of 2-iodoaniline (1.0 mmol), tetrabutylammonium bromide (1.0 mmol), sulfur powder (1.2 mmol) and KOH (2.0 mmol) at 140 °C for 14 h.

Table 1. Screening of reaction conditions for the three-component reactions.[a]



Entry	Base	Temp/°C	Time/h	Yield [%][b]
1	-	140	14	0
2	K_2CO_3	140	14	86
3	Cs_2CO_3	140	14	82
4	KOH	140	14	93
5	NaOH	140	14	90
6	$NH_3•H_2O$	140	14	5
7	Pyridne	140	14	8
8	Et_3N	140	14	7
9	KOH	80	14	15
10	KOH	100	14	27
11	KOH	120	14	58
12	KOH	140	6	62
13	KOH	140	10	79

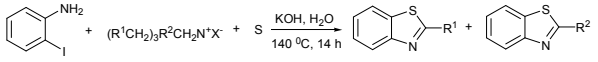
14	KOH	140	20	94
15	KOH	140	14	40 [c]
16	KOH	140	14	92 [d]
17	KOH	140	14	32 [e]
18	KOH	140	14	83 [f]

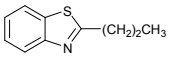
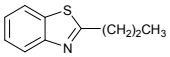
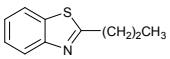
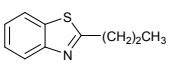
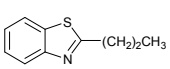
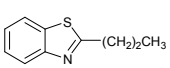
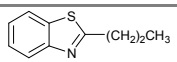
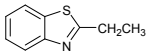
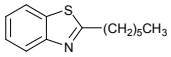
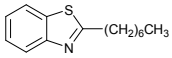
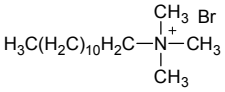
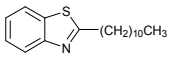
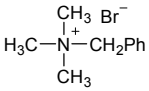
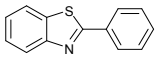
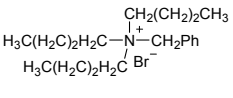
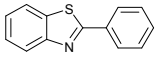
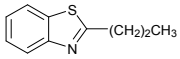
[a] Unless otherwise noted, the reactions were carried out with 2-iodoaniline (1.0 mmol), $(n\text{-}Bu)_4NBr$ (1.0 mmol), sulfur powder (3.0 mmol), base (2.0 mmol) in water (10 mL) at 140 °C. [b] Isolated yields. [c] $(n\text{-}Bu)_4NBr$ (0.5 mmol) was used. [d] Sulfur powder (1.2 mmol) was added. [e] KOH (1.0 mmol) was added. [f] Sulfur powder (1.0 mmol) was added.

Then, several commercially available quaternary ammonium salts were explored under the optimized reaction conditions. As shown in Table 2, most of the substrates provided moderate to excellent yields ranging from 74% to 93%. Anions of the quaternary ammonium salts showed few effects on the reaction. For example, when the cations are the same as tetrabutylammonium, different anions including I-, Br-, Cl-, F-, HSO4-, OH- and CH3COO- gave similar results around 90% yields (Table 2, entries 1-7). On the contrary, different cations exhibited significant effects on the results. Long chain alkyl group seemed to be beneficial to the reaction. Thus, tetrapropylammonium bromide, tetraheptylammonium bromide and tetraoctylammonium bromide gave 85%, 95% and 95% yields respectively (Table 2, entries 8-10).

More importantly, these reactions seemed to be highly chemoselective when the quaternary ammonium salts consisted of different alkyl groups. For example, when dodecyltrimethylammonium bromide, benzyltrimethylammonium bromide or benzyltributylammonium bromide were reacted with 2-iodoaniline, the corresponding major products were 2-undecylbenzenethiazole, 2-phenylbenzothiazole respectively (Table 2, entries 11-13), which indicated quaternary ammonium salts would act as potential alkylation reagents, and long chain or benzyl alkyl groups seemed to be beneficial to the reactions.

Table 2. Synthesis of substituted benzothiazoles by using different quaternary ammonium salts. [a]

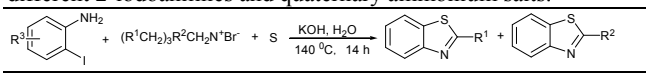


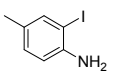
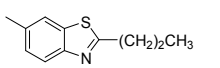
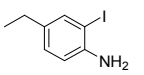
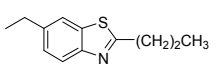
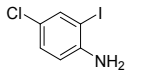
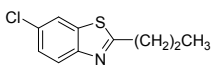
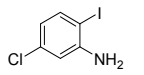
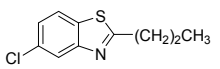
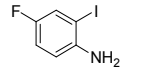
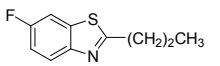
Entry	PTC	Products	Yield [%] [b]
1	$(CH_3CH_2CH_2CH_2)_4NI$		89
2	$(CH_3CH_2CH_2CH_2)_4NBr$		93
3	$(CH_3CH_2CH_2CH_2)_4NCl$		92
4	$(CH_3CH_2CH_2CH_2)_4NF$		91
5	$(CH_3CH_2CH_2CH_2)_4NHSO_4$		90
6	$(CH_3CH_2CH_2CH_2)_4N(OCOCH_3)$		80
7	$(CH_3CH_2CH_2CH_2)_4NOH$		87
8	$(CH_3CH_2CH_2)_4NBr$		85
9	$[CH_3(CH_2)_6]_4NBr$		95
10	$[CH_3(CH_2)_7]_4NBr$		95
11		 	74 18
12		 	80 -
13		 	78 17

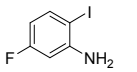
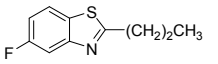
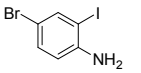
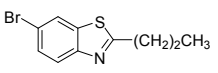
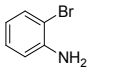
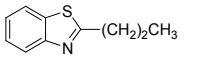
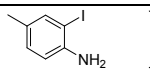
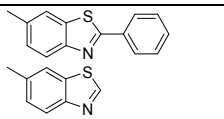
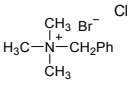
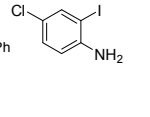
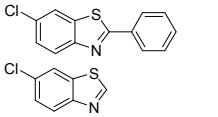
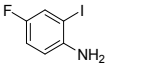
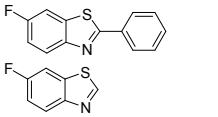
[a] Reaction conditions: 2-iodoaniline (1.0 mmol), quaternary ammonium salt (1.0 mmol), sulfur powder (1.2 mmol), KOH (2.0 mmol), H_2O (10 mL), 140 °C, 14 h. [b] Isolated yields.

In an endeavor to expand the scope of this methodology, a series of substituted 2-halogenated anilines were also examined in the presence of straight-chain quaternary ammonium salts (TBAB) and benzyltrimethylammonium bromide. As shown in Table 3, most of 2-iodoaniline especially those bearing electron-donating substituents provided good to excellent yields. The highest yield 94% was obtained in the case of 2-iodo-4-methylbenzenamine, while 81% yield was obtained in the case of 5-fluro-2-iodoaniline when TBAB was used (entries 1 and 6). As expected, in the case that benzyltrimethylammonium bromide was used as PTC as well as alkylation reagent, lower yields were obtained due to the competition reaction between different alkyl groups (entries 9-11). Furthermore, 2-bromoaniline gave lower yield of product as 65% compared with iodo analogs (entry 8).

Table 3. Synthesis of substituted benzothiazoles by using different 2-iodoanilines and quaternary ammonium salts.[a]

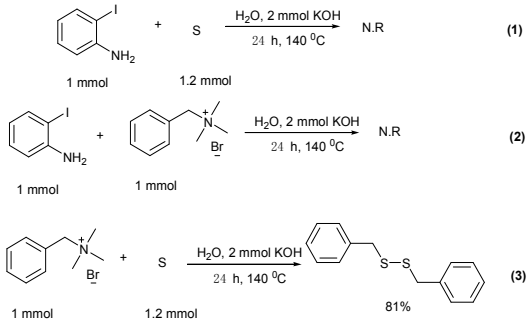


Entry	PTC	Iodoaniline	Products	Yield [%] [b]
1				94
2				92
3	$[CH_3(CH_2)_3]_4NBr$			82
4				86
5				83

6			81	
7			82	
8			65	
9			84	trace
10				70
11			62	trace

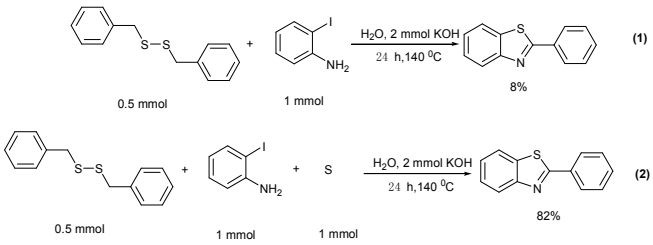
[a] Reaction conditions: o-iodoaniline (1.0 mmol), PTC (1.0 mmol), sulfur powder (1.2 mmol), KOH(2.0 mmol), H_2O (10 mL), 140 °C, 14 h. [b] Isolated yields.

Next, the reaction pathway was studied in the synthesis of benzothiazoles from 2-iodoaniline, quaternary ammonium salt, and sulfur powder. According to Scheme 1, disulfide ether could be obtained in high yield from quaternary ammonium salt and sulfur powder. Meanwhile, no reaction was observed in the case of iodoaniline with sulfur or PTC, indicating the difference between this reaction and our former work, in which disulfide ether was obtained from iodoaniline with sulfur in the presence of copper catalyst.[12]



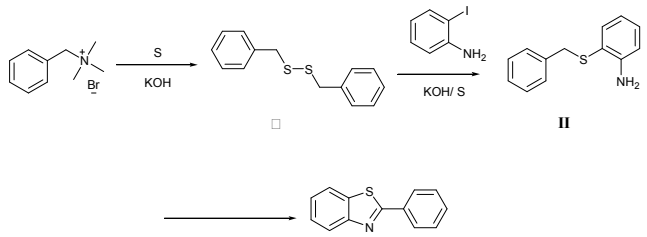
Scheme 1. Investigation of the reaction pathway

Then, disulfide ether was isolated and reacted with iodoaniline as shown in Scheme 2. Similar with our former work, product could be obtained in high yield in the presence of elemental sulfur, which indicated the excess amount of sulfur was necessary in the reaction. Furthermore, 2-(benzylthio)benzenamine was detected during reaction, which would be possible intermediate. Actually, the isolated 2-(benzylthio)benzenamine could be smoothly transformed to be final product under the reaction conditions.



Scheme 2. Control experiments

Based on our work as well as literatures, a plausible reaction pathway was proposed as shown in Scheme 3. Benzyltrimethyl ammonium bromide was firstly reacted with sulfur powder to generate dibenzyl disulfide **I**, which would be reacted with iodoaniline to give 2-(benzylthio)benzenamine II. Then, the target product was obtained after the intramolecular cyclization reaction of **II**.[14]



Scheme 3. Possible reaction pathway for the three-component synthesis of substituted benzothiazoles

In summary, we have developed an efficient and environmentally friendly method for the preparation of substituted benzothiazoles by three-component reactions of *o*-iodoaniline, quaternary ammonium salt, and sulfur powder in a simple one-pot procedure in water. This method avoids the use of transition-metal catalyst, and water was used as solvent. Quaternary ammonium salt acts as phase transfer reagent as well as alkylation reagent. The application of this method is still in progress in this lab.

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Notes and references

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‡ 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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