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1,10-Phenanthroline-Catalyzed Tandem Reaction of 2-Iodoanilines with Isothiocyanates in Water

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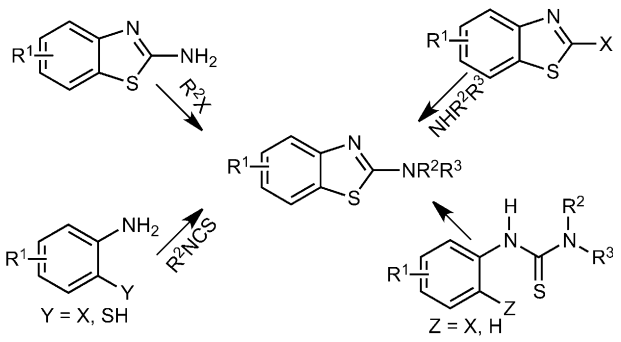
Abstract: The 1,10-phenanthroline-catalyzed tandem reaction of 2-iodoaniline with isothiocyanate in water is described, which provides an environmentally benign, efficient and simple route for the preparation of 2-aminobenzothiazoles. The present tandem process shows broad substrate scope in the absence of transition metals and phase-transfer catalysts.

Keywords: 2-aminobenzothiazoles; 2-iodoanilines; isothiocyanates; 1,10-phenanthroline; tandem reaction; water

Introduction

The 2-aminobenzothiazole is one of the most important structural motifs in pharmaceutically active compounds and natural products.[1] A great amount of compounds with the skeleton have been applied in drugs for the treatment of various diseases, such as tuberculosis,[2] tumors,[3] and cancer.[4] Therefore, the development of efficient methods for constructing 2-aminobenzothiazoles has received great interest from the perspective of medicinal chemistry and organic synthesis (Scheme 1). Among them, transition metal-catalyzed cross-coupling reactions of 2-halobenzothiazoles with amines[5] or 2-aminobenzothiazoles with aryl halides[6] and intramolecular cyclizations of 2-halobenzothioureas or benzothioureas represent the most powerful and reliable methodologies.[7] Recently, the direct oxidative coupling between benzothiazoles and amines,[8] as well as domino three-component reactions of carbon disulfides, amines and 2-haloanilines have attracted more attention from the viewpoints of atom economy and operational simplicity.[9] Also, tandem reactions for the efficient construction of heterocycles are important goals. Recently, several groups have reported independently on the construction of 2-aminobenzothiazole compounds from 2-haloanilines and isothiocyanates with the support of Cu(I) or Fe(III) catalysts (Scheme 2).[10] We found that one component played a crucial role in most of the synthetic processes: 1,10-phenanthroline (phen) *via* the analysis and comparison of the detailed reaction conditions. At the same time, we found that Shi and Shirakawa/Hayashi had already reported the direct C–H arylation of benzene with aryl halides in the presence of catalytic amounts of phen and its derivatives without the presence of a transition metal catalyst.[11]



Scheme 1. Efficient synthesis of 2-aminobenzothiazoles.

Arguably most reactions for the synthesis of *N*-substituted-2-aminobenzothiazoles were carried out in organic solvents such as DMSO, DME and toluene. From the viewpoints of economic and environmental aspects, it is desirable to avoid any use of hazardous, contaminated and expensive organic solvents. Water is considered to be the best solvent for it is cheap, non-toxic and nonpolluting. Recently, Fan et al. reported a significant rate acceleration of the tandem

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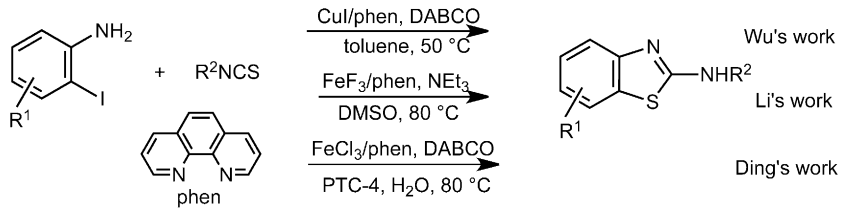


Scheme 2. Phen was used as ligand for the synthesis of 2-aminobenzothiazoles.

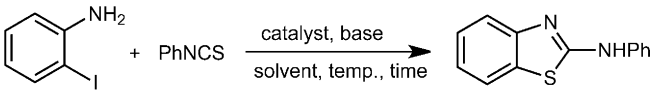
reaction of isothiocyanates with 2-aminothiophenols in water compared with commonly used organic solvents.[12]

Herein, we have developed a transition metal-free synthesis of 2-aminobenzothiazoles from 2-iodoanilines and isothiocyanates using phen as catalyst in water.

Results and Discussion

The reaction between 2-iodoaniline (**1a**) and phenyl isothiocyanate (**2a**) was greatly facilitated leading to the desired product in high yield. The effects of catalyst, base, solvent, temperature, and reaction time were investigated, and the results are summarized in Table 1. In the absence of either phen or base the reaction fails to generate the desired products and only intermediates 1-(2-iodophenyl)-3-phenylthiourea were obtained even after heating for 14 h (entries 1 and 2). In the presence of strong inorganic bases such as KOH and NaOH, only traces of the target product could be found (entries 3 and 4). To our surprise, the target product **3a** were obtained in 41% and 48% yield by using weak bases, such as K_2CO_3 or Na_2CO_3, respectively (entries 5 and 6). Further screening of bases revealed that $NaHCO_3$ was the most efficient base and the yield could be dramatically improved, giving an almost quantitative yield (entry 7). Organic bases such as NEt_3 and DABCO were evaluated, too. However, lower yields were obtained (entries 8 and 9). The catalytic activity of the different ligand-type organic compounds such as 2,2′-dipyridine, EDA, DMEDA, L-proline, and acetylacetone (H_2acac) were investigated (entries 10–14). Among these tested organocatalysts, 1,10-phenanthroline was found to be uniquely effective. Decreasing the catalyst amount from 10 to 5 mol% resulted in the decrease of the yield (entry 15). The effect of the solvent was also investigated, trace products were obtained in organic solvents such as DMSO, toluene, 1,4-dioxane, THF and DMF (entries 16–20). It may be due to the poor solubility of $NaHCO_3$ in organic solvents. When the reaction time was shortened to 1 h, the yield was only 35% (entry 21). The reaction could not be carried out at room temperature, and only trace products were generated even at 60 °C (entries 22 and 23).

Table 1. Optimization of the reaction conditions for the preparation of **3a**.[a]



1a **2a** **3a**

Entry	Catalyst	Base	Solvent	Yield [%][b]
1	–	$NaHCO_3$	H_2O	0[c]
2	phen	–	H_2O	0[c]
3	phen	KOH	H_2O	trace
4	phen	NaOH	H_2O	trace
5	phen	K_2CO_3	H_2O	41
6	phen	Na_2CO_3	H_2O	48
7	phen	$NaHCO_3$	H_2O	99
8	phen	NEt_3	H_2O	64
9	phen	DABCO	H_2O	trace
10	bipy	$NaHCO_3$	H_2O	32
11	EDA	$NaHCO_3$	H_2O	13
12	DMEDA	$NaHCO_3$	H_2O	0
13	L-Pro	$NaHCO_3$	H_2O	0
14	H_2acac	$NaHCO_3$	H_2O	0
15	phen	$NaHCO_3$	H_2O	33[d]
16	phen	$NaHCO_3$	DMSO	trace
17	phen	$NaHCO_3$	toluene	trace
18	phen	$NaHCO_3$	dioxane	trace
19	phen	$NaHCO_3$	THF	trace
20	phen	$NaHCO_3$	DMF	trace
21	phen	$NaHCO_3$	H_2O	35[e]
22	phen	$NaHCO_3$	H_2O	0[f]
23	phen	$NaHCO_3$	H_2O	trace[g]

[a] *Reaction conditions:* **1a** (0.25 mmol), **2a** (0.3 mmol), catalyst (10 mol%), base (2.0 equiv.), solvent (4 mL), stirred under air, 80 °C, 2 h.
[b] Isolated yield.
[c] 14 h.
[d] Phen (5 mol%).
[e] 1 h.
[f] Room temperature.
[g] 60 °C.

Thus, the optimal reaction conditions were set to be 10 mol% of phen in the presence of 2 equiv. of $NaHCO_3$ in water for 2 h at 80 °C. To our delight, this phen-catalyzed tandem reaction can be applied to gram-scale synthesis, a 96% yield was obtained when 5.48 g (25 mmol) of 2-iodoaniline were used under the optimized conditions.

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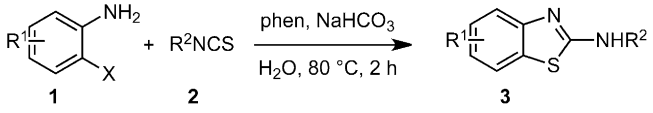
With the standard protocol in hand, we started to investigate the scope and functional group compatibility of the new organocatalytic tandem reaction. The reaction shows very high efficiency and tolerates many functional groups such as alkyl, chloro, cyano, trifluoromethyl, alkoxy and ester (Table 2). It was found that moderate to excellent yields were achieved for phenyl isothiocyanates with both electron-donating and electron-withdrawing substituents (Table 2, entries 1–9). In general, the presence of electron-donating groups and weak electron-withdrawing groups on phenyl isothiocyanates showed excellent efficiencies (entries 1, 5, 6, 13–15, 18). However, when phenyl isothiocyanates substituted by a strong electron-withdrawing group such as trifluoromethyl were used, only 55% yield was obtained (entry 8). Besides, isothiocyanate with a steric hindering substituent at the *ortho* position was tolerated in this reaction (entry 4).

Table 2. Tandem reaction between various substituted **1** and **2**.[a]



Entry	R^1/X	R^2	Product **3**	Yield [%][b]
1	H/I	4-MeC_6H_4	**3b**	98
2	H/I	2-MeC_6H_4	**3c**	91
3	H/I	2,6-$Me_2C_6H_3$	**3d**	89
4	H/I	2,6-(*i*-Pr)$_2C_6H_3$	**3e**	73
5	H/I	4-$EtOC_6H_4$	**3f**	97
6	H/I	4-ClC_6H_4	**3g**	95
7	H/I	4-CNC_6H_4	**3h**	81
8	H/I	4-$CF_3C_6H_4$	**3i**	55
9	H/I	$C_6H_5CH_2$	**3j**	85
10	H/I	cyclohexyl	**3k**	74
11	H/I	*n*-dodecyl	**3l**	78
12	4-Me/I	C_6H_5	**3m**	96
13	4-Me/I	4-MeC_6H_4	**3n**	98
14	4-Me/I	4-$EtOC_6H_4$	**3o**	99
15	4-Me/I	4-ClC_6H_4	**3p**	94
16	4-Me/I	4-CNC_6H_4	**3q**	83
17	4-Cl/I	C_6H_5	**3r**	93
18	4-Cl/I	4-$EtOC_6H_4$	**3s**	95
19	4-Cl/I	4-CNC_6H_4	**3t**	82
20	4-CF_3/I	C_6H_5	**3u**	72
21	4-CF_3/I	4-$EtOC_6H_4$	**3v**	83
22	4-CF_3/I	4-CNC_6H_4	**3w**	61
23	3-CO_2Me/I	C_6H_5	**3x**	87
24	4-NO_2/I	C_6H_5	**3y**	nr
25	H/Br	C_6H_5	**3a**	trace
26	H/Cl	C_6H_5	**3a**	nr

[a] *Reaction conditions:* **1** (0.25 mmol), **2** (0.30 mmol), phen (10 mol%), $NaHCO_3$ (0.5 mmol), H_2O (4 mL), stirred under air at 80 °C for 2 h.

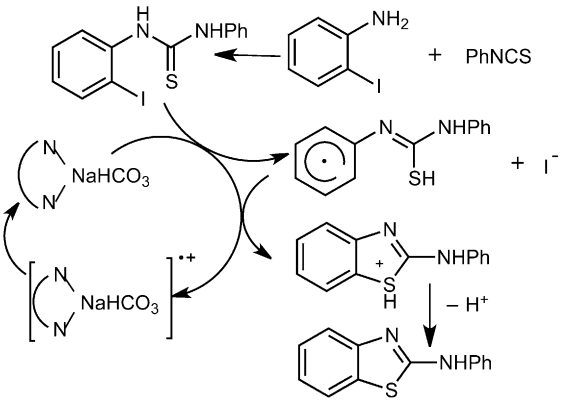
[b] Isolated yield; nr = no reaction.

Fortunately, several typical alkyl isothiocyanates were also suitable substrates under the standard condition, and provided good yields (entries 9–11).

Several representative 2-iodobenzenamine derivatives were examined. It could be seen that electronic effects played a significant role: 2-iodobenzenamines with electron-donating and weak electron-withdrawing groups such as methyl and chloro on the *para* position proceeded with good to excellent yields (entries 12–19). However, only moderate yields could be obtained when a strong electron-withdrawing group such as 4-trifluoromethyl was present (entries 20–22). Furthermore, the nitro group completely inhibited the reaction (entry 24).

The yields also depended on the nature of the halides. Unfortunately, a trace of the corresponding product was detected when the less active substrate 2-bromoaniline was investigated (entry 25); and even no target compound was obtained with 2-chloroaniline (entry 26).

A plausible mechanism, which accounts for the formation of the 2-aminobenzothiazoles by a tandem reaction, is shown in Scheme 3. First, the nucleophilic addition of 2-iodoanilines with NCS forms the intermediates 1-(2-iodophenyl)-3-phenylthiourea in the presence of base. This step was very easy without any additional external conditions in water. Second, the intermediates were converted to the final products through intramolecular cyclization with the aid of phen and $NaHCO_3$. Initially, we suspected that the reaction system could contain trace amounts of metal impurities that would induce this transformation. We repeated the reactions with new glassware and magneton; furthermore, we analyzed the reaction aqueous solution obtained after filtration using inductively coupled plasma-atomic emission spectroscopy (ICP-AES). The test results demonstrated the absence of Pd, Cu, Fe and other transition metals at the limits of detection. Therefore we perceive that the reaction mechanism was different from the previously reported



Scheme 3. Plausible mechanism.

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transition metal-catalyzed mechanism,[10b,d] and the second step might be a radical mechanism, in accordance with the mechanism of organocatalytic C–H arylation presented by Shi, Shirakawa/Hayashi and Studer.[11,13] To test this suggestion, a typical radical scavenger tetramethylpiperidine *N*-oxide (TEMPO) was added under the same conditions, and no trace of desired product could be obtained.

Conclusions

In summary, phen can effectively catalyze the tandem reaction of 2-iodoanilines and isothiocyanates to synthesize 2-aminobenzothiazole compounds in excellent yields. A more environmentally friendly and mild base was used. It is also noteworthy to point out that the reactions are carried out in water.

Experimental Section

Typical Experimental Procedure for 1,10-Phenanthroline-Catalyzed Tandem Reactions of 2-Iodobenzenamines with Isothiocyanates

A mixture of 2-iodoaniline **1** (0.25 mmol), isothiocyanate **2** (0.30 mmol, 1.2 equiv.), phen (0.025 mmol, 10 mol%), $NaHCO_3$ (0.5 mmol, 2 equiv.), and H_2O (4 mL) was stirred in air, heating from room temperature to 80 °C (about 0.5 h), then continued to stir at 80 °C for 2 h. Then the reaction was stopped and cooled down to room temperature, the mixture was extracted with ethyl acetate (3×10 mL), the combined organic layer was washed with water (2×10 mL), then dried over anhydrous $MgSO_4$ and evaporated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the corresponding product **3**.

***N*-Phenylbenzo[d]thiazol-2-amine (3a):**[14] White solid; mp 161–162 °C (lit. mp 157.2–159.4 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.3 Hz, 1H), 7.12–7.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 151.3, 140.0, 129.8, 129.6, 126.2, 124.5, 122.4, 120.9, 120.5, 119.3.

Acknowledgements

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