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An efficient one-step cyclization of thiobenzanilides to benzothiazoles: using *N*-bromosuccinimide under mild conditions

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Benzothiazoles were readily prepared in one step from thiobenzanilides using *N*-bromosuccinimide in CH_2Cl_2–CCl_4 (1:1 V/V) at room temperature, with good yields under mild reaction conditions.

Keywords: benzothiazoles; *N*-bromosuccinimide; thiobenzanilide; thioamide; 2-arylbenzothiazoles

1. Introduction

Benzothiazoles are an important class of benzo-fused azoles, and they are remarkable heterocyclic scaffold in biologically active and medicinally significant compounds (*1*, *2*). Therefore, regarding their potent antitumor activity (*3*, *4*) and other industrial utilities (*5*), synthesis of these compounds is of considerable interest.

Numerous synthetic methods are available for the synthesis of 2-arylbenzothiazoles (*6–10*), and among existing methods, there are two major routes to benzothiazoles: (1) radical cyclization of phenylthioformamides promoted by potassium ferricyanide or bromine; (2) Pd-catalyzed cyclization of 2-bromophenylthioformamides (Scheme 1) (*11*).

Although these reactions usually proceed efficiently, these methodologies usually suffer from one or more disadvantages including: the lack of ease of availability, use of costly toxic substances such as 2-aminophenols, and harsh reaction conditions. Thus, these disadvantages necessitate the development of an alternate synthetic route to benzothiazole ring formation. Several useful methods toward the synthesis of benzothiazoles have been reported (*12–21*).

In this letter, we report an ultimately simple and efficient one-step synthesis of 2-arylbenzothiazoles by the reaction of thiobenzanilides in the presence of *N*-bromosuccinimide (NBS) in a mixture of dichloromethane/carbon tetrachloride (1:1 V/V) at room temperature.

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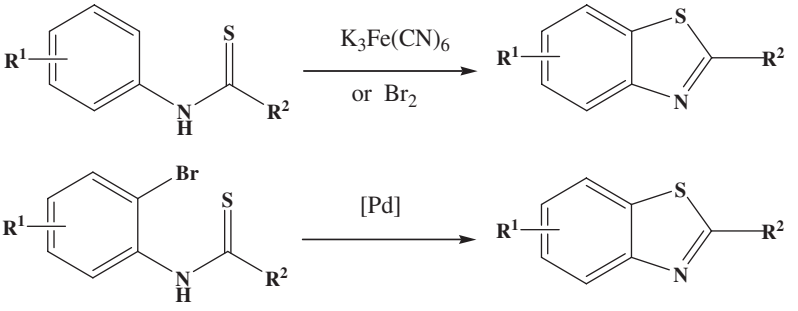
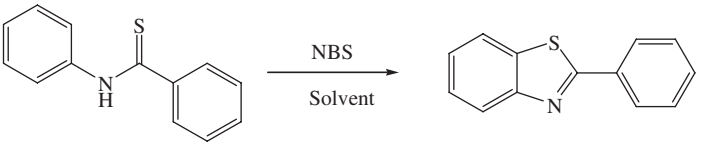


Scheme 1. Two major routes to benzothiazoles.

Table 1. Variation of solvent in cyclyzation of thiobenzanilide with 1.2 (mol equiv.) NBS.



1 **2**

Entry	Reaction conditions	Solvent	Yield (%)
1	r.t/2.5 h	MeOH	<5
2	r.t/2.5 h	AcOH	<10
3	r.t/2.5 h	DMF	<10
4	r.t/2.5 h	1,4-Dioxane	<12
5	r.t/30 min	CH_2Cl_2	43
6	r.t/30 min	CH_2Cl_2–CCl_4	68

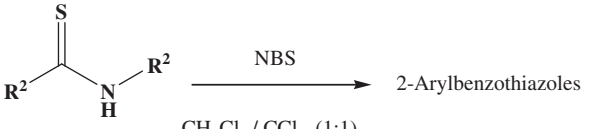
2. Results and discussion

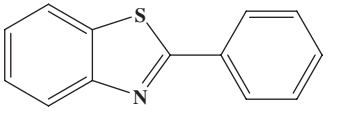
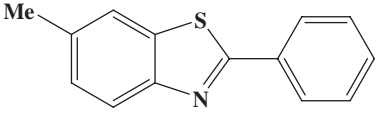
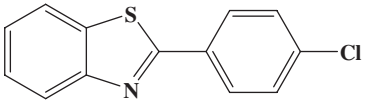
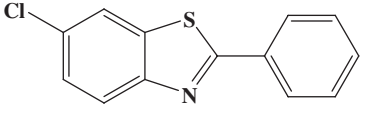
At the outset of our study in order to determine the optimized reaction conditions, the model compound **1** was allowed to react with NBS in different solvents to obtain the corresponding 2-arylbenzothiazole **2**, and the results are shown in Table 1.

Dichloromethane was an inferior solvent compared with the mixture of dichloromethane and carbon tetrachloride. Next, the effect of the amount of the NBS was examined, and the suitable molar ratio of (NBS/**1)** was (1.2/1 mol equiv.) in CH_2Cl_2–CCl_4 (1:1 V/V) and at room temperature. The yield could not be improved even if an excess amount of NBS is used or the reaction time is prolonged. In continuation of our study, the reaction of other thiobenzanilides and NBS in CH_2Cl_2–CCl_4 (1:1 V/V) were performed at room temperature to afford the corresponding 2-arylbenzothiazoles (Entry 1–8, Table 2).

A rational mechanism is proposed for cyclization of thiobenzanilide reactions (Scheme 2). Reaction of thiobenzanilide **1** with NBS gives the sulfonium cation **3.** Electrophilic substitution of aromatic ring **3** followed by aromatization of cation **4** delivers the target product **2**.

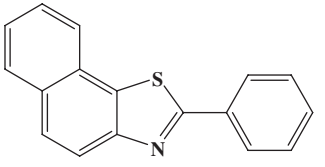
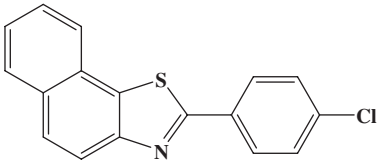
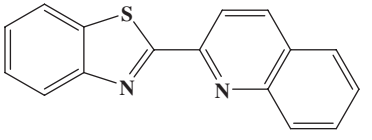
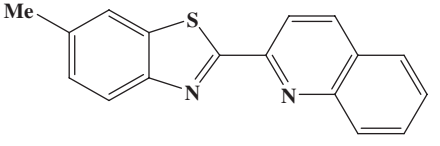
Table 2. Cyclization of thiobenzanilides to 2-arylbenzothiazoles.



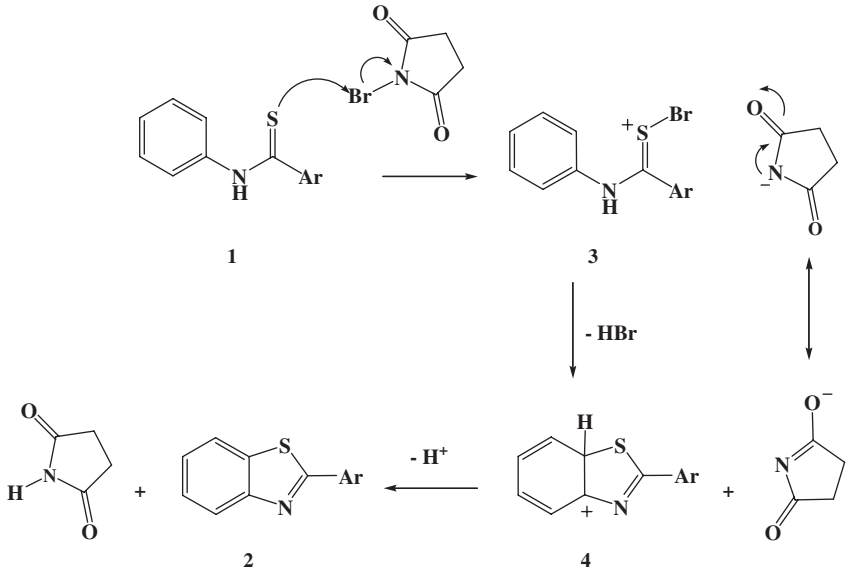
Entry	R^1	R^2	Product	Time (min)	Mp (°C)	Mp^{lit} (°C)	Yield (%)*
1	Ph	Ph		30	112–114	113–114[22a]	68
2	Ph	*p*-MePh		30	130–132	131–134[12]	72
3	*p*-ClPh	Ph		40	116–118	117–118[22a]	66
4	Ph	*p*-ClPh		45	138–140	140–141[22a]	50

(*Continued*)

Table 2. Continued.

Entry	R^1	R^2	Product	Time (min)	Mp (°C)	Mp^{lit} (°C)	Yield (%)*
5	Ph	2-Naphthyl		40	108–110	109–110[22b]	68
6	*p*-ClPh	2-Naphthyl		45	147–150	–	60
7	2-Quinolyl	Ph		35	198–200	198–200[22c]	62
8	2-Quinolyl	*p*-MePh		40	217–220	220–221[22c]	65

Note: *Yields are referred to isolated products and all the products exhibited the expected spectral data.



Scheme 2. The proposed mechanism for benzothiazole ring formation in the presence of NBS.

3. Conclusion

In conclusion, we have presented a simple and efficient methodology for one-step formation of 2-arylbenzothiazoles in good yields, avoiding harsh reaction conditions. On the other hand, we have succeeded in converting thiobenzanilide substrates in to benzothiazole moieties; therefore, this method would overcome the requirement for using 2-aminothiophenols as precursors. As a consequence, the methodology could be applicable to a wide variety of thiobenzanilides with different functional group on aromatic rings in both sides as substrate.

4. Experimental

The compounds gave all satisfactory spectroscopic data. A Bruker (DRX-500 Avanes) NMR was used to record the ^{1}H-NMR spectra. All NMR spectra were determined in $CDCl_3$ at ambient temperature. Melting points were determined on a Buchi B540 apparatus.

4.1. *General procedure for preparation of thiobenzanilide*

The thiobenzanilide derivatives used in this study were prepared by reacting the appropriate benzanilides with P_2S_5 in THF at room temperature. Also some of the thiobenzanilides having a nitrogen heterocycle were prepared by the Willgerodt–Kindler reaction of quinaldine with aromatic amines under microwave irradiation (*21*).

4.2. *General procedure for preparation of 2-arylbenzothiazole*

To a stirred solution of thiobenzanilide (1 mmol) in CH_2Cl_2–CCl_4 (50:50, 8 mL), NBS (1.2 mmol) was added in several portions. The reaction mixture was stirred for 30 min at room temperature;

after removing the solvent under reduced pressure, the residue was subjected to column chromatography (EtOAc – Hexane, 1:6, Silica gel) to obtain pure product.

4.3. *Spectroscopic data for selected compounds*

4.3.1. *6-Methyl-2-phenyl-1,3-benzothiazole (Entry 2, Table 2)*

^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 8.28$ (d, $J = 7.3$ Hz, 2 H), 8.16 (d, $J = 8.2$ Hz, 1 H), 7.31 (s, 1 H), 7.15–7.22 (m, 3 H), 7.09 (d, $J = 8.2$ Hz, 1 H), 2.22 (s, 3H).

4.3.2. *2-Phenynaphtho[2,1-d]-1,3-thiazole (Entry 5, Table 2)*

^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 8.96$ (d, $J = 7.8$ Hz, 1 H), 8.17 (d, $J = 7.0$ Hz, 2 H), 7.83 (d, $J = 7.8$ Hz, 1 H), 7.75 (d, $J = 8.6$ Hz, 1 H), 7.66 (d, $J = 8.3$ Hz, 1 H), 7.60 (t, $J = 7.2$ Hz, 1 H), 7.48 (t, $J = 7.5$|,Hz, 1 H), 7.36–7.41 (m, 3 H).

4.3.3. *4-Chloro-2-phenylnaphtho[2,1-d]-1,3-thiazole (Entry 6, Table 2)*

^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 8.92$ (d, $J = 10$ Hz, 1H), 8.18 (d, $J = 10$ Hz, 2H), 7.95(m, 2H), 7.84 (d, $J = 10$ Hz, 1H), 7.72(t, $J = 7.5$ Hz, 1H), 7.62, (t, $J = 7.5$ Hz, 1H), 7.53 (d, $J = 10$ Hz, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): $\delta = 166.0$ (C), 150.8 (C), 137.0 (C), 132.9 (C), 132.5 (C), 132.1 (C), 129.6 (CH), 129.1 (C), 128.5 (CH), 127.4 (CH), 126.7 (CH), 126.6 (CH), 124.4 (CH), 119.3 (CH). MS (EI) m/z: 297 (M+2, 40), 295 (M+, 100), 158 (28), 114 (19).

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