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REGIOSELECTIVE ONE-POT SYNTHESIS OF 2-ARYL-6-BROMO-BENZOTHIAZOLE FROM ARYLALDEHYDE AND 2-AMINOTHIO-PHENOL WITH PHENYLTRIMETHYLAMMONIUM TRIBROMIDE IN THE PRESENCE OF A CATALYTIC AMOUNT OF ANTIMONY(III) BROMIDE

Shinsei Sayama*

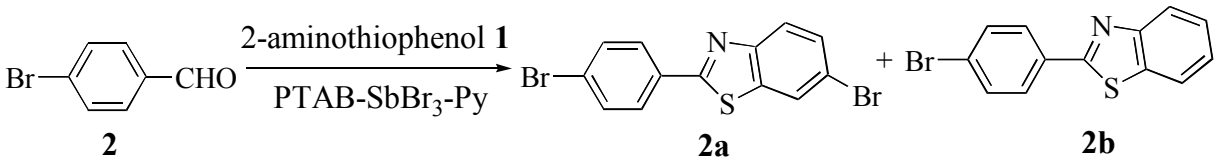
Department of Chemistry, Fukushima Medical University, Hikariga-oka, Fukushima 960-1295, Japan. ssayama@fmu.ac.jp

Abstract – Various 2-aryl-6-bromo-1,3-benzothiazoles were regioselectively afforded in good yields by the reaction of arylaldehydes and 2-aminothiophenol with phenyltrimethylammonium tribromide in the presence of a catalytic amount of $SbBr_3$ in CH_2Cl_2 at room temperature.

2- or 6-Substituted 1,3-benzothiazoles are important class of biologically active compounds in medicinal chemistry.[1,2] Therefore, there have been many reports for the synthetic procedures of 2- and 6-substituted 1,3-benzothiazoles.[2,3] The synthesis of 6-halogenated benzothiazoles such as 2-aryl-6-chloro-1,3-benzothiazoles employing Suzuki-Miyaura coupling reaction was especially well studied by Heo and co-workers.[3d] As 6-halogenated 1,3-benzothiazoles are useful as key intermadiates for the syntheses of other intricate structure of 6-substitutd 1,3-benzothiazoles,[1a] there has been considerable interest in continuing investigating regioselective synthesis of 6-halogenated 1,3-benzothiazoles.

On the other hand, phenyltrimethylammonium tribromide (PTAB) and pyridinium hydrobromide perbromide (PHPB) were reported to be useful for the esterification of aldehyde and for the syntheses of 2-substituted imidazolines and oxazolines from aldehyde in water.[4a,4b] PTAB and PHPB were also useful for the chemoselective conversion of 3-alkoxyfurans to 2-alkoxy-3(2*H*)-furanones.[4c,4d] Further, the PTAB-$SbBr_3$–pyridine (Py) system was also reported to be convenient and chemoselective for the oxidation of secondary alcohols[5a] and for the oxidative conversion of aromatic epoxide and 1,2-diol to 1,3-dioxane derivatives.[5b] Therefore, there has been much interest in further applications for the alternative one-pot synthesis of 6-bromo-1,3-benzothiazoles with PTAB in the presence of $SbBr_3$.[6-8] We would like to report the results of our studies concerning the regioselective one-pot synthesis of 2-aryl-6-bromo-1,3-benzothiazoles from arylaldehydes and 2-aminothiophenol with PTAB-$SbBr_3$-Py in CH_2Cl_2.

Table 1. Reaction of 2-aminothiophenol **1** and *p*-bromobenzaldehyde **2** with PTAB-$SbBr_3$[a]



2 **2a** **2b**

Run	Molar ratio / **2**			Solvent[b]	Time (h)	Products, Yield (%)		
	PTAB	$SbBr_3$	Py			**2a**	**2b**	Recovered **2**
1	4.0	0.2	4.0	A	24	89	2	--
2	3.0	0.2	4.0	A	20	23	51	2
3	2.0	0.2	4.0	A	22	5	31	24
4	--	0.2	4.0	A	71	--	63	--
5	--	0.2	--	A	22	--	74	--
6	4.0	0.2	--	A	20	43	43	--
7	4.0	--	4.0	A	46	53	19	--
8	4.0	--	--	A	46	35	40	--
9	4.0	0.2	4.0	B	23	5	21	64
10	4.0	0.2	4.0	C	92	21	40	--
11	4.0	0.2	4.0	D	20	58	5	15
12	4.0	0.2	4.0	E	23	88	7	--

[a] 2-aminothiophenol (**1**): 0.3 mmol; *p*-bromobenzaldehyde (**2**): 0.25 mmol; Solvent: 6 mL; Temp: room temperature.
[b] A=CH_2Cl_2, B=C_6H_{14}, C=MeOH, D=DMSO, E=MeCN

At first, the reaction of 2-aminothiophenol (**1**) and *p*-bromobenzaldehyde (**2**), chosen as a representative aldehyde for this study, was carried out with various molar ratios of PTAB, $SbBr_3$ and Py over **2** for

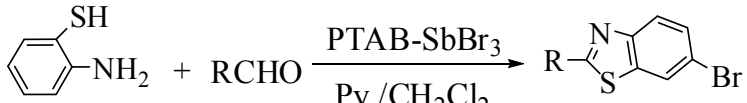
obtaining bromobenzothiazole. The results are summarized in Table 1. At 4.0 molar ratio of PTAB and Py over **2** in the presence of 0.2 molar equivalent of $SbBr_3$, 6-bromo-1,3-benzothiazole (**2a**) was predominantly afforded (run 1). The reaction of **2** at 2.0 or 3.0 molar equivalents of PTAB over **2**, was not brought about the desired yields of **2a**, accompanied by benzothiazole (**2b**) and recovered **2** (runs 2, 3). In the present experiments, there is need to use 4.0 molar equivalent of PTAB over **2** for obtaining 6-bromo-2-(4-bromophenyl)-1,3-benzothiazole **2a** in good yield.

To examine the solvent effect of CH_2Cl_2 in this method, the reaction of **1** and **2** was carried out in various solvents under the same reaction conditions. In hexane the reaction of **1** and **2** did not give **2a** in high yield, accompanied by a mixture of benzothiazole **2b** and **2** (run 9). Accordingly it was suggested that polar solvents such as MeOH, acetonitrile, DMSO promoted bromination of benzothiaoles. In MeOH or DMSO, bromobenzothiazole **2a** was afforded, but with less satisfactory yields of **2a** (runs 10, 11). The reaction of **1** and **2** in acetonitrile, took place to give **2a** in good yield (run 12). CH_2Cl_2 and MeCN were found to be more effective for the one-pot conversion of *p*-bromobenzaldehyde **2** to 6-bromo-2-(4-bromophenyl)-1,3-benzothiazole **2a** with PTAB-$SbBr_3$-Py than that of other solvents.

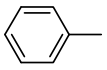
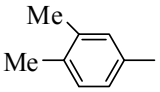
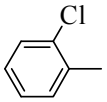
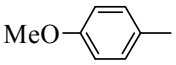
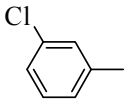
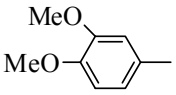
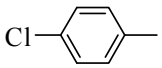
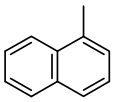
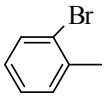
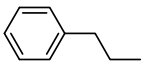
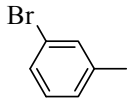
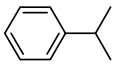
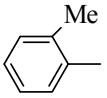
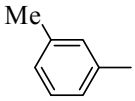
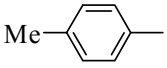
To clarify the effects of PTAB, $SbBr_3$ and Py in this system, the reaction of aminothiophenol **1** and *p*-bromobenzaldehyde **2** without using PTAB, $SbBr_3$, or Py was carried out respectively. Obviously bromobenzothiazole **2a** was not afforded without PTAB (run 4). Similarly the yields of **2a** were not fully satisfactory without Py (runs, 6, 8). Further, the satisfactory yields of **2a** without $SbBr_3$ were not observed accompanied by benzothiazole **2b** (runs 7, 8). This one-pot synthesis of 6-bromobenzothiazole was suggested to rest on the complemental function of PTAB, $SbBr_3$, and Py.

To clarify the limitations for this conversion of aldehyde to 6-bromo-1,3-benzothiazole, the reaction of various aldehydes and aminothiophenol **1** with PTAB-$SbBr_3$-Py was examined under the same reaction conditions. The results are summarized in Table 2. Benzaldehyde (**3**) was converted to 6-bromobenzothiazole (**3a**) in good yield (run 1). The reaction of *o*-, *m*-, *p*-chlorobenzaldehydes (**4**), (**5**), and (**6**) took place to give the corresponding bromobenzothiazoles (**4a**), (**5a**), and (**6a**) (runs 2, 3, 4). *o*-, *m*-Bromobenzaldehydes (**7**) and (**8**) were also converted to corresponding 6-bromobenzothiazoles (**7a**) and (**8a**) (runs 5, 6), as expected. 6-Bromobenzothiazoles (**9a**), (**10a**), (**11a**) were easily afforded from *o*-, *m*-, *p*-tolualdehydes (**9**), (**10**), and (**11**) respectively (runs 7, 8, 9). 3,4-Dimethylbenzaldehyde (**12**) was similarly converted to bromobenzothiazole (**12a**) in good yield (run 10). Bromobenzothiazoles (**13a**) and (**14a**) were easily obtained from 4-methoxybenzaldehyde (**13**) and 3,4-dimethoxybenzaldehyde (**14**) (runs 11, 12). The reaction of naphthaldehyde (**15**) also afforded bromobenzothiazole (**15a**) (run 13). Thus, various arylaldehydes were found to be regioselectively converted to corresponding 6-bromobenzothiazoles in good yields.

Table 2. Reaction of various aldehyde and 2-aminothiophenol **1** with PTAB-$SbBr_3$ in CH_2Cl_2[a]



1 **S** **a**

Run	Substrate (**S**) R		Time (h)	Products(**a**) Yield (%)		Run	Substrate(**S**) R		Time (h)	Products(**a**) Yield (%)	
1		**3**	41	**3a**	90	10		**12**	18	**12a**	89
2		**4**	14	**4a**	81	11		**13**	20	**13a**	88
3		**5**	16	**5a**	82	12		**14**	18	**14a**	77
4		**6**	20	**6a**	82	13		**15**	20	**15a**	68
5		**7**	44	**7a**	67	14		**16**	23	**16a**	43
6		**8**	44	**8a**	82	15		**17**	23	**17a**	44
7		**9**	47	**9a**	79	16	C_8H_{18}—	**18**	37	**18a**	49
8		**10**	47	**10a**	84	17	Me—	**19**	48	**19a**	54
9		**11**	41	**11a**	65						

[a] Substrate (**S**): 0.25 mmol; 2-aminothiophenol (**1**): 0.30 mmol; PTAB: 1.00 mmol; $SbBr_3$: 0.05 mmol; Py: 1.00 mmol; CH_2Cl_2: 6 mL; Temp: room temperature.

In contrast, alkylaldehydes (**16**), (**17**), (**18**), and (**19**) were also converted to corresponding 6-bromobenzothiazoles (**16a**), (**17a**), (**18a**), and (**19a**), but less satisfactory yields of 6-bromobenzothiazoles (runs 14-17).[9]

Further, to examine the superiority of $SbBr_3$ in this method, the reaction of **1** and *p*-chlorobenzaldehyde **6** was carried out with other metal halides such as $SbCl_3$, $CuBr_2$, $NiBr_2$, $ZnBr_2$ under the same reaction

conditions. The yield of 6-bromobenzothiazole **6a** with $SbCl_3$ was satisfactory as expected (79%). On the contrary, the yields of **6a** with other metal halides such as $CuBr_2$, $NiBr_2$, $ZnBr_2$ were less than 60% under the same reaction conditions. Accordingly, antimony halides $SbBr_3$ and $SbCl_3$ were ascertained to be essential and effective for regioselective synthesis of 6-bromobenzothiazoles from arylaldehydes in CH_2Cl_2 at room temperature. Consequently, the system PTAB-$SbBr_3$-Py was confirmed to be a regioselective one-pot procedure for synthesis of 2-aryl-6-bromo-1,3-benzothiazoles from various arylaldehydes without overbromination of benzothiazole ring.[10]

The combination of PTAB and $SbBr_3$ appeared to generate Br^+ and $SbBr_4^-$ via $SbBr_5$.[11] This selective bromination at 6-position of 1,3-benzothiazole ring was accounted for by a Br^+ substitution of aromatic ring on benzothiazoline intermediate or 2-aminothiophenol as follows. The reaction of 2-methyl-1,3-benzothiazole **21** with PTAB-$SbBr_3$-Py recovered **21** unchanged.[12] In contrast, the reaction of 2-aminothiophenol **1** under the same reaction conditions took place to give a complex mixture of bromo derivatives and related compounds. Therefore, it can be assumed that an electrophilic attack of aromatic ring on benzothiazoline intermediate or 2-aminothiophenol by Br^+ possibly causes selective bromination at 6-position of 1,3-benzothiazole ring in this method, and successively produces a π complex, a σ cmplex, and bromo derivative after loss of proton by $SbBr_4^-$. Loss of proton from the intermediate bromine-containing cation results in an additional formation of HBr and $SbBr_3$ as a catalyst.

In addition 6-bromo-1,3-benzothiazole nucleus is of particular interest in organic synthesis and medicinal chemistry for applications in drug discovery.[1,3d,3l] Since 6-halogenated 1,3-benzothiazoles as intermediates are seemed to be useful for the syntheses of those biologically active 6-substituted 1,3-benzothiazoles via Suzuki-Miyaura coupling reaction or aromatic substitution reactions, the system PTAB-$SbBr_3$-Py provides an alternative significant method for the key intermediates syntheses of various biologically active 1,3-benzothiazoles.

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9. The structure of 6-bromo-1,3-benzothiazole was determined on the basis of ^{1}H and ^{13}C NMR spectral data. For example, the structure of 6-bromo-2-methyl-1,3-benzothiazole (**19a**) was confirmed by spectral data in comparison with that of authentic 5-bromo-2-methyl-1,3-benzothiazole (**20**) as follows; **19a**: IR (neat, cm^{-1}) 3046, 2918, 1542, 1518, 1434, 1587, 1400, 1373, 1303, 1269, 1234, 1173, 1078, 1048, 994, 848, 810, 744. ^{1}H NMR ($CDCl_3$) δ 2.82 (3H, s), 7.54 (1H, dd, *J* = 8.1, 2.7 Hz), 7.80 (1H, d, *J* = 8.1), 7.95 (1H, d, *J* = 2.7). ^{13}C NMR ($CDCl_3$) δ 20.07, 118.21, 123.47, 129.32, 129.36, 137.30, 152.24, 167.50. *Anal*. Calcd for C_8H_6NSBr: C, 42.12; H, 2.65; N, 6.14. Found: C, 42.16; H, 2.69; N, 6.00. **20**: ^{1}H NMR ($CDCl_3$) δ 2.83 (3H, s), 7.45 (1H, dd, *J* = 8.1, 2.7 Hz), 7.67 (1H, d, *J* = 8.1), 8.09 (1H, d, *J* = 2.7). ^{13}C NMR ($CDCl_3$) δ 20.15, 119.47, 122.37, 125.30, 127.77, 134.41, 154.53, 168.71.
10. Typical procedure: To a solution of PTAB (376 mg, 1.0 mmol), $SbBr_3$ (18 mg, 0.05 mmol), and Py (80 μL, 1.0 mmol) in CH_2Cl_2 (6 mL) were added 3-chlorobenzaldehyde (**5**, 35 mg, 0.25 mmol) and 2-aminothiophenol [**1**, 41 mg (35 μL), 0.3 mmol]. After stirring for 16 h at rt, the reaction mixture was treated with 0.5 M aq $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with 0.5 M aq $Na_2S_2O_3$ and successively washed with sat. aq. NaCl, and dried over $MgSO_4$. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel (Wakogel C-200) with CCl_4. 6-bromo-2-(3-chlorophenyl)-1,3-benzothiazole (**5a**) (67 mg, 0.206 mmol) was obtained in 82% yield. **5a**: IR (KBr, cm^{-1}) 3054, 1584, 1568, 1541, 1508, 1458, 1438, 1424, 1398, 1305, 1238, 1227, 1090, 1078, 997, 895, 853, 819, 779, 732. ^{1}H NMR ($CDCl_3$) δ 7.40-7.49 (2H, m), 7.60 (1H, dd, *J* = 8.1, 2.7 Hz), 7.90-7.93 (2H, m), 8.04-8.10 (2H, m). ^{13}C NMR ($CDCl_3$) δ 119.19, 124.23, 124.50, 125.68, 127.40, 130.08, 130.32, 131.16, 134.81, 135.36, 136.66, 152.82, 166.85. *Anal*. Calcd for $C_{13}H_7NSBrCl$: C, 48.09; H, 2.17; N, 4.31. Found: C, 48.17; H, 2.25; N, 4.25.
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12. A reaction of 2-methyl-1,3-benzothiazole (**21**) with pyridinium hydrobromide perbromide in H_2O afforded a mixture of 6-, 5-, and 4-bromo-2-methyl-1,3-benzothiazoles; S. Sayama, presented at 40th Congress of Heterocyclic Chemistry, Sendai, Japan, 2010, Abstr., p. 133.