ChemPubSoc Europe

DOI: 10.1002/ejoc.201900100

EurJOC European Journal of Organic Chemistry

Full Paper

Thiazole Synthesis

2-Amino-4-arylthiazoles through One-Pot Transformation of Alkylarenes with NBS and Thioureas

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Abstract: Treatment of alkylarenes with *N*-bromosuccinimide in a mixture of ethyl acetate and water at 60 °C, a mixture of acetonitrile and water at 80 °C, or a mixture of diethyl carbonate and water under irradiation with a tungsten lamp, followed by a reaction with thioureas or arenethioamides provided the corresponding 2-amino- 4-arylthiazoles or 2,4-diarylthiazoles in good to moderate yields, respectively, in one pot. The present reaction is an efficient one-pot transformation method of alkylarenes into 2-amino-4-arylthiazoles and 2,4-diarylthiazoles directly under mild and transition-metal-free conditions.

Introduction

Thiazole is one of the most important heteroaromatic units, as there are many pharmaceuticals and natural products bearing a thiazole unit.[1] For example, Fanetizole (an anti-inflammatory agent), Abafungin (an antifungal agent), Famotidine (a histamine H_2 receptor antagonist), and Fentiazac (an anti-inflammatory agent) are typical pharmaceuticals bearing a thiazole unit, as shown in Figure 1.[1f] Vitamin B_1 (thiamine) contains a thiazolium unit as an important reaction site.

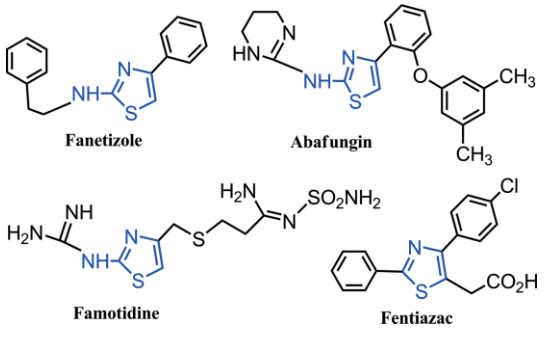

Figure 1. Examples of pharmaceuticals bearing the thiazole unit.

Therefore, the still extensive synthetic study of thiazoles has been carried out. Examples of recent synthetic study of thiazoles without transition metals are as follows:[2] thiazoles from the reaction of acetophenone derivatives and thiourea in the presence of molecular iodine under microwave irradiation;[2a] the reaction of α-bromoketones, amines, and trimethylsilyl isothiocyanate;[2b] the reaction of α-boryl-α-bromoaldehydes and thioamides;[2c] the reaction of ketones and thiourea in the presence of O_2/KI/NH_4NO_3;[2d] the reaction of thioamides and ethyl glyoxalate in the presence of acetyl chloride and NaCN;[2e] the reaction of α-bromoketones, thioacid potassium salts, and $AcONH_4$ under toluene refluxing conditions;[2f] the reaction of α-nitroepoxides and *S*-alkyl dithiocarbamates;[2g] the reaction of α-nitroepoxides and ammonium thiocyanate;[2h] the reaction of styrenes, thioureas, and 1,3-dibromo-5,5-dimethylhydantoin (DBH);[2i] and the reaction of aromatic aldehydes and cysteine esters with iodine and *tert*-butyl hydroperoxide (TBHP).[2j] We also enumerate recent synthetic studies of thiazoles with transition metals, as follows:[3] the reaction of terminal alkynes and MsOH in the presence of Au catalyst, followed by the reaction with thioamides;[3a] the reaction of terminal alkynes, sulfonyl azides, and thionoesters in the presence of Cu and Rh catalysts;[3b] the reaction of vinyl azides and KSCN in the presence of Pd or Fe catalyst;[3c] the reaction of oximes, carboxylic anhydrides, and KSCN in the presence of CuI catalyst;[3d] the reaction of aliphatic primary amines, aliphatic aldehydes, and elemental sulfur in the presence of 1,10-phenanthroline and $CuBr_2$;[3e] and the reaction of enamines and elemental sulfur in the presence of $FeCl_3$.[3f] Among these reactions, the most useful and practical one is the Hantzsch thiazole synthesis using α-haloketones and thiourea or thioamides.[4] Previously, we reported a one-pot preparation of aromatic nitriles from methylarenes[5a] and primary aromatic amides from ethylarenes,[5b] respectively, by using *N*-bromosuccinimide (NBS), molecular iodine, and aq. ammonia. Here, as part of our continuing synthetic studies of nitrogen-containing heterocycles,[6] we would like to report a novel one-pot transformation of alkylarenes into 2-amino-4-arylthiazoles and 2,4-diarylthiazoles by the treatment with NBS, followed by the reaction with thioureas or thioamides under mild and transition-metal-free conditions.

Results and Discussion

Based on our previous study,[5b] the transformation of ethylarenes **1** (1.0 mmol), such as ethylbenzene (**1a**), *n*-propyl-

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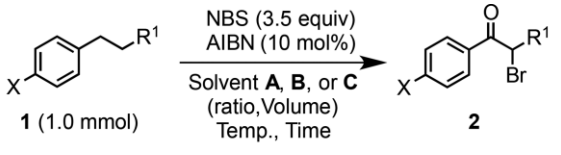
benzene (**1j**), *n*-butylbenzene (**1k**), *n*-hexylbenzene (**1l**), phenethylbenzene (**1m**), *p*-(methoxycarbonyl)ethylbenzene (**1b**), *p*-(methoxycarbonyl)-*n*-propylbenzene (**1r**), *p*-(methoxy)ethylbenzene (**1c**), and *p*-(methoxy)-*n*-propylbenzene (**1w**) into aryl α-bromoalkyl ketones **2** with NBS (3.5 equiv.) and AIBN (10 mol-%) in a mixture of ethyl acetate and water (**A**) at 60 °C, a mixture of acetonitrile and water (**B**) at 80 °C, and a mixture of diethyl carbonate and water (**C**) under irradiation with a tungsten lamp at 35 °C–40 °C was carried out under the optimized reaction conditions, as shown in Table 1. Here, the organic solvent was changed from ethyl acetate to acetonitrile and to diethyl carbonate, respectively, depending on the electron density of the aromatic ring in alkylarenes **1**. Treatment of alkylbenzenes (**1a**, **1j**–**1m**) in a mixture of ethyl acetate and water at 60 °C gave α-bromoalkyl phenyl ketones (**2a**, **2j**–**2m**) in good yields, respectively (entries 1–5). For *p*-(methoxycarbonyl)ethylbenzene (**1b**) and *p*-(methoxycarbonyl)-*n*-propylbenzene (**1r**) bearing an electron-withdrawing group, treatment of them in a mixture of acetonitrile and water at 80 °C gave α-bromomethyl *p*-(methoxycarbonyl)phenyl ketone (**2b**) and α-bromoethyl *p*-(methoxycarbonyl)phenyl ketone (**2r**) in good yields, respectively (entries 6, 7). On the other hand, treatment of *p*-(methoxy)ethylbenzene (**1c**) and *p*-(methoxy)-*n*-propylbenzene (**1w**) with NBS (5.0 equiv.) in a mixture of diethyl carbonate and water under irradiation with a tungsten lamp at 35 °C–40 °C gave α-bromomethyl 3-bromo-4-methoxyphenyl ketone (**2c**) and α-bromoethyl 3-bromo-4-methoxyphenyl ketone (**2w**) in good yields, respectively (entries 8, 9). Here, the electron-rich *p*-methoxyphenyl group in *p*-(methoxy)ethylbenzene (**1c**) and *p*-(methoxy)-*n*-propylbenzene (**1w**) is smoothly brominated prior to the Wohl-Ziegler reaction. The key points in using solvents **A**, **B**, and **C** are the hydrolysis of α,α-(dibromo)alkylarenes that are formed through the dual Wohl-Ziegler reaction of alkylarenes **1** and the α-bromination of alkyl aryl ketones formed by the hydrolysis of α,α-(dibromo)alkylarenes.

Based on the optimized reaction conditions for transformation of alkylarenes **1** into aryl α-bromoalkyl ketones, the successive treatment of ethylarenes **1**, such as ethylbenzene (**1a**), *p*-(methoxycarbonyl)ethylbenzene (**1b**), and *p*-(methoxy)-ethylbenzene (**1c**), with NBS (3.5 equiv. for **1a** and **1b**, 5.0 equiv. for **1c**) and AIBN (10 mol-%) in solvents **A**, **B**, and **C** (1st step), followed by the reaction with thiourea (**I**, 1.1 equiv.) at room temperature for 1 h (2nd step) was carried out to generate 2-amino-4-phenylthiazole (**3a-I**) in 84 % yield (entry 1), 2-amino-4-(4′-methoxycarbonylphenyl)thiazole (**3b-I**) in 53 % yield (entry 4), and 2-amino-4-(3′-bromo-4′-methoxyphenyl)thiazole (**3c-I**) in 73 % yield (entry 7), respectively, as shown in Table 2. As a gram-scale experiment, when ethylbenzene (**1a**, 10 mmol) was used under the same procedure and conditions, 2-amino-5-phenylthiazole **3a-I** was obtained in 82 % yield, as shown in Scheme 1. On the other hand, the same successive treatment of the above three ethylarenes (**1a**–**1c**) with *N*-chlorosuccinimide (NCS) or *N*-iodosuccinimide (NIS) in solvents **A**, **B**, and **C**, respectively, followed by the reaction with thiourea (**I**) was carried out. However, the corresponding 2-amino-5-arylthiazoles were not obtained at all (entries 2, 3, 5, 6, 8, and 9), and mainly starting ethylarenes were recovered. An exception was the formation of 4-ethyl-2-iodoanisole from *p*-(methoxy)ethylbenzene (**1c**) with NIS (entry 9), as shown in Table 2. Thus, NBS plays an important role in the formation of aryl α-bromomethyl ketones from ethylarenes **1a**–**1c** via the Wohl-Ziegler reaction.

Table 1. Transformation of alkylarenes **1** to aryl α-bromoalkyl ketones **2** with optimum reaction conditions.

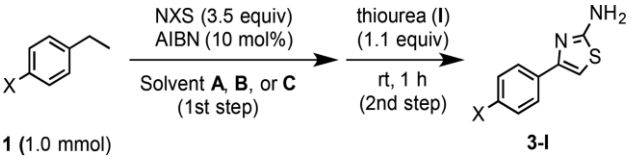


Solvent, Temp.= **A**: AcOEt : H_2O, 60 °C,
B: MeCN : H_2O, 80 °C,
C: $(EtO)_2CO$: H_2O, 35-40 °C

Entry	X	R^1	Solvent (ratio)	Volume (mL)	Time (h)	Yield (%)
1	H	H (**1a**)	**A** (7:1)	6.0	4	88 (**2a**)
2	H	Me (**1j**)	**A** (9:1)	6.0	6	93 (**2j**)
3	H	Et (**1k**)	**A** (9:1)	6.0	6	94 (**2k**)
4	H	*n*-Bu (**1l**)	**A** (9:1)	6.0	6	87 (**2l**)
5	H	Ph (**1m**)	**A** (7:1)	6.0	12	74 (**2m**)
6	CO_2Me	H (**1b**)	**B** (3:1)	10.0	6	67 (**2b**)
7	CO_2Me	Me (**1r**)	**B** (7:1)	6.0	6	84 (**2r**)
8	OMe	H (**1c**)	**C** (4:1)	3.0	10[a]	62 (**2c**)[b]
9	OMe	Me (**1w**)	**C** (9:1)	3.0	10[a]	82 (**2w**)[c]

[a] NBS (5.0 equiv) was used, and the reaction was carried out under irradiation with a tungsten lamp (300 W) without AIBN.
[b] Yield of 3-bromo-4-methoxyphenyl α-bromomethyl ketone (**2c**).
[c] Yield of 3-bromo-4-methoxyphenyl α-bromoethyl ketone (**2w**).

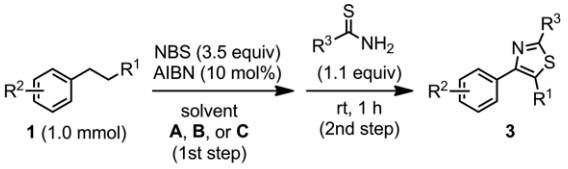
Table 2. Transformation of ethylarenes **1** to 2-amino-4-arylthiazoles **3-I**.



Solvent (ratio, volume)= **A**: AcOEt : H_2O (7:1, 6 mL),
B: MeCN : H_2O (3:1, 10 mL),
C: $(EtO)_2CO$: H_2O (4:1, 3 mL)

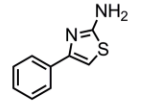
Entry	X	NXS	Solvent	Temp.	Time (h)	Yield (%)
1	H (**1a**)	NBS	**A**	60 °C	4	84 (**3a-I**)
2	H (**1a**)	NCS	**A**	60 °C	4	0
3	H (**1a**)	NIS	**A**	60 °C	4	0
4	CO_2Me (**1b**)	NBS	**B**	80 °C	12	53 (**3b-I**)
5	CO_2Me (**1b**)	NCS	**B**	80 °C	12	0
6	CO_2Me (**1b**)	NIS	**B**	80 °C	12	0
7	OMe (**1c**)	NBS	**C**	35-40 °C[a]	10	73 (**3c-I**)
8	OMe (**1c**)	NCS	**C**	35-40 °C[a]	10	0
9	OMe (**1c**)	NIS	**C**	35-40 °C[a]	10	0[b]

[a] NBS, NCS, or NIS (5.0 equiv) was used, and the reaction was carried out under irradiation with a tungsten lamp (300 W) without AIBN.
[b] 4-Ethyl-2-iodoanisole was obtained in 41% yield.

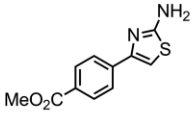


R^3 = NH_2 (**I**), NHMe (**II**), $NHCH_2CH_2Ph$ (**III**), Me (**IV**), Ph (**V**), C_6H_4Me-4 (**VI**), C_6H_4OMe-4 (**VII**), C_6H_4Cl-4 (**VIII**)

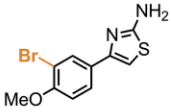
Solvent **A** (AcOEt :H_2O ratio, 6.0 mL), 60 °C
Product, Yield, (ratio, time)



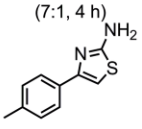
3a-I 84% (82%)[a] (84%)[h] (7:1, 4 h)



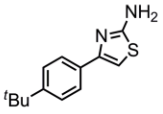
3b-I 6%[d2] (9:1, 6 h)



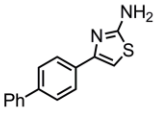
3c-I 3%[d2] (9:1, 6 h)



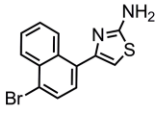
3d-I 73%[b1,c] (7:1, 4 h)



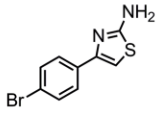
3e-I 77%[b2,c] (7:1, 4 h)



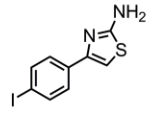
3f-I 84% (7:1, 4 h)



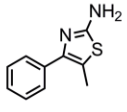
3g-I 61%[b2,i] (9:1, 6 h)



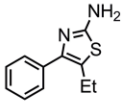
3h-I 79% (7:1, 4 h)



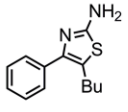
3i-I 75%[h] (7:1, 4 h)



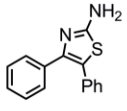
3j-I 75%[d1] (9:1, 6 h)



3k-I 70%[d1,e] (9:1, 6 h)

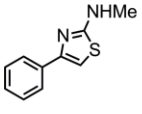


3l-I 57%[d1,e] (9:1, 6 h)

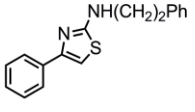


3m-I 61%[b2,d1,e,h] (9:1, 12 h)

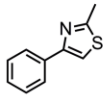
Solvent **A** (AcOEt : H_2O, 7:1, 6.0 mL), 60 °C, 4 h
Product, Yield



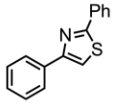
3a-II 83%



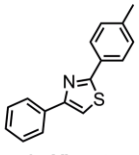
3a-III 85%



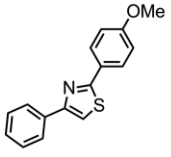
3a-IV 86%[m]



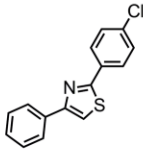
3a-V 85%



3a-VI 90%

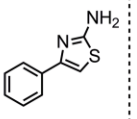


3a-VII 93%

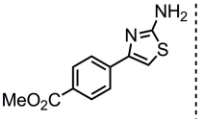


3a-VIII 81%

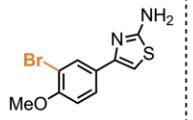
Solvent **B** (MeCN : H_2O ratio, volume), 80 °C, 12 h



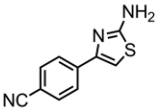
3a-I 72%[d1] (3:1, 10 mL)



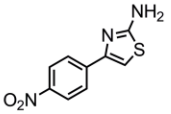
3b-I 53% (63%)[j] (3:1, 10 mL)



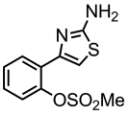
3c-I 25%[d1] (3:1, 10 mL)



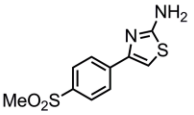
3n-I 64%[k] (7:1, 6 mL)



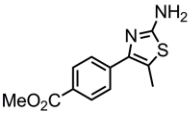
3o-I 66%[k] (7:1, 6 mL)



3p-I 72%[d1] (7:1, 6 mL)

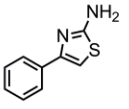


3q-I 68% (3:1, 10 mL)

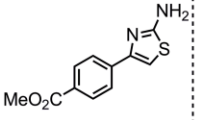


3r-I 69%[d1] (7:1, 6 mL)

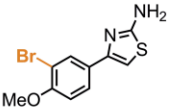
Solvent **C** ($(EtO)_2CO$: H_2O ratio, volume), 35-40 °C, 10 h[f]
Product, Yield



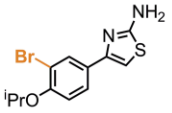
3a-I 62%[d2] (4:1, 3.0 mL)



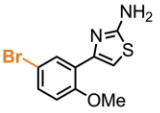
3b-I 23%[d2] (4:1, 3.0 mL)



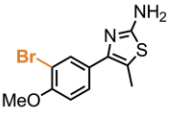
3c-I 73%[d1,g] (4:1, 3.0 mL)



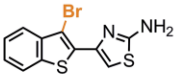
3s-I 53%[d2,e,g] (4:1, 3.0 mL)



3t-I 74%[d2,e,g] (4:1, 3.0 mL)



3u-I 72%[d2,e] (9:1, 3.0 mL)



3v-I 51%[h,l] (4:1, 3.0 mL)

[a] Reaction was carried out with substrate **1a** (10 mmol).
[b] Volume of the solvent was [1] 7.0 mL or [2] 8.0 mL.
[c] Reaction time for 1st step was 6 h.
[d] 2nd step was conducted at 60 °C for [1] 6 h or [2] 14 h.
[e] Thiourea (2.2 equiv) was used.
[f] NBS (5.0 equiv) was used, and the reaction was carried out under irradiation with a tungsten lamp without AIBN.
[g] Heated at 80 °C for 1 h after 1st step.
[h] K_2CO_3 (1.5 equiv) was added at 2nd step.
[i] NBS (4.5 equiv) was used.
[j] After 1st step, TMSCl (1.0 mL) and MeOH (5.0 mL) were added, and the mixture was stirred for 3 h at 70 °C.
[k] After 1st step, NBS (1.1 equiv) and HBr (1.0 mL) were addded, and the mixture was stirred for 40 min at 80 °C.
K_2CO_3 (8.5 equiv) was added at 2nd step.
[l] 2nd step was conducted at 100 °C for 14 h.
[m] Reaction time for 2nd step was 2 h.

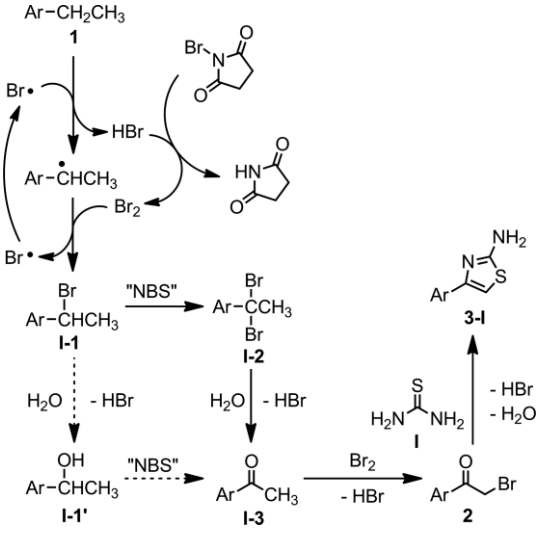
Scheme 1. Transformation of alkylarenes **1** to 2-amino-4-arylthiazoles **3**.

Based on those results, treatment of alkylarenes **1**, such as *p*-(methyl)ethylbenzene (**1d**), *p*-(*tert*-butyl)ethylbenzene (**1e**), *p*-(phenyl)ethylbenzene (**1f**), 4-bromo-1-ethylnaphthalene (**1g**), *p*-(bromo)ethylbenzene (**1h**), *p*-(iodo)ethylbenzene (**1i**), *n*-propylbenzene (**1j**), *n*-butylbenzene (**1k**), *n*-hexylbenzene (**1l**), and phenethylbenzene (**1m**), with NBS (3.5 equiv.) and AIBN (10 mol-%) in solvent **A** at 60 °C (1st step), followed by the reaction with thiourea (**I**, 1.1 equiv.) at room temperature for 1 h (2nd step) provided 2-amino-4-arylthiazoles **3d-I**–**3m-I** in good yields, respectively, as shown in Scheme 1. In contrast, when *p*-(methoxycarbonyl)ethylbenzene (**1b**) and *p*-(methoxy)ethylbenzene (**1c**) were treated in solvent **A** under the same procedure and conditions, 2-amino-4-(4′-methoxycarbonyl)phenylthiazole **3b-I** and 2-amino-4-(3′-bromo-4′-methoxyphenyl)thiazole **3c-I** were obtained in very low yields, respectively. For the reactions with other thioureas and thioamides instead of thiourea (**I**), treatment of ethylbenzene (**1a**) with NBS (3.5 equiv.) and AIBN (10 mol-%) in solvent **A** at 60 °C (1st step), followed by the reactions with thioureas or thioamides, such as *N*-methylthiourea (**II**), *N*-phenethylthiourea (**III**), thioacetamide (**IV**), thiobenzamide (**V**), *p*-methylthiobenzamide (**VI**), *p*-methoxythiobenzamide (**VII**), and *p*-chlorothiobenzamide (**VIII**), at room temperature for 1 h (2nd step) gave 2-(*N*-methyl)amino-4-phenylthiazole (**3a-II**), 2-(*N*-phenethyl)amino-4-phenylthiaozle (**3a-III**), 2-methyl-4-phenylthiazole (**3a-IV**), 2,4-diphenylthiazole (**3a-V**), 2-(4′-methylphenyl)-4-phenylthiazole (**3a-VI**), 2-(4′-methoxyphenyl)-4-phenylthiazole (**3a-VII**), and 2-(4′-chlorophenyl)-4-phenylthiazole (**3a-VIII**) in good yields, respectively, as shown in Scheme 1. Here, 2-(*N*-phenethylamino)-4-phenylthiaozle **3a-III**, i.e., Fanetizole in Figure 1, was obtained from ethylbenzene in 85 % yield.

Then, treatment of *p*-(*p*-methoxycarbonylphenyl)ethylbenzene (**1b**), *p*-(cyano)ethylbenzene (**1n**), *p*-(nitro)ethylbenzene (**1o**), *o*-(methanesulfonyloxy)ethylbenzene (**1p**), *p*-(methanesulfonyl)ethylbenzene (**1q**), and *p*-(methoxycarbonyl)-*n*-propylbenzene (**1r**) bearing electron-withdrawing groups, with NBS (3.5 equiv.) and AIBN (10 mol-%) in solvent **B** at 80 °C (1st step), followed by the reaction with thiourea (**I**, 1.1 equiv.) at room temperature for 1 h (2nd step), gave 2-amino-4-arylthiazoles (**3b-I**, **3n-I**, **3o-I**, **3p-I**, **3q-I**, and **3r-I**) in good to moderate yields, respectively, as shown in Scheme 1. The yield of **3b-I** was slightly improved to 63 % by treatment of the reaction mixture with TMSCl (1 mL) and MeOH (5 mL) at 70 °C for 3 h after the 1st reaction step, which converted partly hydrolyzed carboxylic acid into the methyl ester. For the formation of **3n-I** and **3o-I**, NBS (1.1 equiv.) and aq. HBr (50 %, 1 mL) were added to the reaction mixture to promote the formation of aryl α-bromomethyl ketones from the formed aryl methyl ketones after the 1st reaction step. When ethylbenzene (**1a**) and *p*-(methoxy)ethylbenzene (**1c**) were treated in solvent **B** at 60 °C under the same procedure and conditions, 2-amino-4-phenylthiazole **3a-I** and 2-amino-4-(3′-bromo-4′-methoxyphenyl)thiazole **3c-I** were obtained in 72 % and 25 % yields, which were lower than those obtained in solvent **A** and solvent **C**, respectively.

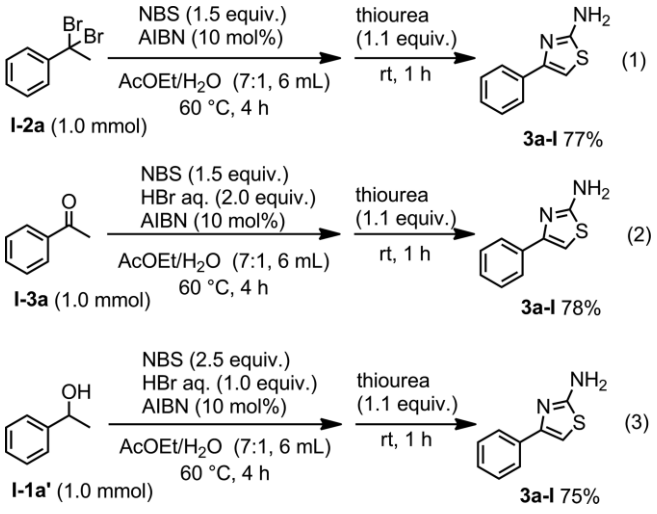
Finally, the reactions of *p*-(isopropoxy)ethylbenzene (**1s**), *o*-(methoxy)ethylbenzene (**1t**), *p*-(methoxy)-*n*-propylbenzene (**1u**), and 2-ethylbenzothiophene (**1v**) bearing electron-rich aryl groups, with NBS (5.0 equiv.) in solvent **C** under irradiation with a tungsten lamp (300 W) at 35 °C–40 °C (1st step) for 10 h, followed by the reaction with thiourea (**I**, 1.1 equiv.) at room temperature for 1 h (2nd step), gave 2-amino-4-(3′-bromo-4′-isopropoxyphenyl)thiazole **3s-I**, 2-amino-4-(5′-bromo-2′-methoxyphenyl)thiazole **3t-I**, 2-amino-4-(3′-bromo-4′-methoxyphenyl)-5-methylthiazole **3u-I**, and 2-amino-4-(3′-bromobenzothiophen-2′-yl)thiazole **3v-I** in good to moderate yields, respectively, as shown in Scheme 1. Under the present irradiation conditions at 35 °C–40 °C, the aromatic rings of those alkylarenes (**1s**–**1v**) were smoothly brominated by NBS via an ionic pathway at the 1st reaction step.

Possible reaction pathway for the transformation of alkylarenes **1** into 2-amino-4-arylthiazoles **3-I** is shown in Scheme 2. Ethylarene **1** reacts with bromine atom to form α-bromoethylarene **I-1** through the Wohl-Ziegler reaction. α-Bromoethylarene **I-1** reacts again with bromine atom to form α,α-dibromoethylarene **I-2** which undergoes further hydrolysis to generate aryl methyl ketone **I-3** and HBr. Aryl methyl ketone **I-3** reacts with NBS in acidic conditions smoothly to form aryl α-bromomethyl ketone **2**. Once aryl α-bromomethyl ketone **2** is formed, it smoothly reacts with thiourea **I** to form 2-amino-4-arylthiazole **3-I**. Practically, treatment of α,α-dibromoethylarene **I-2a** with NBS (1.5 equiv.) and AIBN (10 mol-%), and of aryl methyl ketone **I-3a** with NBS (1.5 equiv.), AIBN (10 mol-%), and aq. HBr (50 %, 2.0 equiv.) in a mixture of ethyl acetate and water (7:1, solvent **A**) for 4 h at 60 °C, followed by the reaction with thiourea (**I**, 1.1 equiv.) at room temperature for 1 h gave 2-amino-4-phenylthiazole **3a-I** in 77 % and 78 % yields, respectively, as shown in Scheme 3 (Equation 1 and Equation 2). Treatment of α-phenylethanol **I-1a′** with NBS (2.5 equiv.) and AIBN (10 mol-%) in the presence of aq. HBr (50 %, 1.0 equiv.) in a mixture of ethyl acetate and water (7:1, solvent **A**) for 4 h at 60 °C, followed by the reaction with thiourea (**I**, 1.1 equiv.) at room temperature for 1 h also gave 2-amino-4-phenylthiazole **3a-I** in 75 % yield (Equation 3). Therefore, the formation of α-arylethanol **I-1′** by the hydrolysis of α-bromoethylarene **I-1** and its oxidation to



Scheme 2. Possible reaction pathway.

aryl methyl ketone **I-3** by bromine atom may also partly participate.



Scheme 3. Control experiments.

Conclusions

A one-pot transformation of alkylarenes with NBS in a mixture of ethyl acetate, acetonitrile, or diethyl carbonate with water, depending on the substituent of the aromatic ring, followed by the reaction with thioureas and arenethioamides proceeded with ease to give 2-amino-4-arylthiazoles and 2,4-diarylthiazoles in good to moderate yields, respectively. The present method would be useful for the preparation of 2-substituted 4-arylthiazoles from alkylarenes as the reactions could be carried out with easily available substrates and reagents under transition-metal-free conditions.

Experimental Section

General: ^{1}H NMR spectra were measured on 400 MHz spectrometers. Chemical shifts were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; *t* = triplet; q = quartet; sext = sextet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on 100 MHz spectrometers. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm, or $[D_6]$DMSO at 39.5 ppm). Characteristic peaks in the infrared (IR) spectra were recorded in wave number, cm^{-1}. High-resolution mass spectra (HRMS) were recorded by Thermo Fisher Scientific Exactive Orbitrap mass spectrometers. Melting points were uncorrected. Thin-layer chromatography (TLC) was performed using 0.25 mm silica gel plates (60F254). The products were purified by column chromatography on neutral silica gel 60N (63–200 mesh).

Typical Procedures for Direct Transformation of Alkylarenes 1 into 2-Amino-4-arylthiazoles 3

Procedure A: To a solution of ethylbenzene **1a** (1.0 mmol, 106.2 mg) in AcOEt/water (7:1, 6.0 mL) were added NBS (3.5 mmol, 635.6 mg) and AIBN (0.1 mmol, 16.8 mg) at room temperature, and the mixture was stirred for 4 h at 60 °C. After cooling to room temperature, thiourea (1.1 mmol, 85.4 mg) was added to the reaction mixture, and the obtained mixture was stirred for 1 h at room temperature. The mixture was quenched by adding sat. aq. $NaHCO_3$ (10 mL), and extracted with AcOEt (20 mL × 3). Then, the organic layer was dried with Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by short column chromatography on silica gel (hexane/AcOEt = 2:1) to afford 2-amino-4-phenylthiazole **3a-l** in 84 % yield (148.0 mg).

Procedure B: To a solution of *p*-(methoxycarbonyl)ethylbenzene **1b** (1.0 mmol, 167.6 mg) in CH_3CN/water (3:1, 10.0 mL) were added NBS (3.5 mmol, 635.6 mg) and AIBN (0.1 mmol, 16.8 mg) at room temperature, and the mixture was stirred for 12 h at 80 °C. After cooling to room temperature, thiourea (1.1 mmol, 85.4 mg) was added to the reaction mixture, and the obtained mixture was stirred for 1 h at room temperature. The mixture was quenched by adding sat. aq. $NaHCO_3$ (10 mL), and extracted with $CHCl_3$ (20 mL × 3). Then, the organic layer was dried with Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by short column chromatography on silica gel (hexane/AcOEt = 2:1) to afford 2-amino-4-(4′-methoxycarbonylphenyl)thiazole **3b-l** in 53 % yield (124.2 mg).

Procedure C: To a solution of *p*-(methoxy)ethylbenzene **1c** (1.0 mmol, 139.7 mg) in diethyl carbonate/water (4:1, 3.0 mL) was added NBS (5.0 mmol, 908.0 mg) at room temperature, and the mixture was stirred under irradiation with a tungsten lamp for 10 h at room temperature. Thiourea (1.1 mmol, 85.4 mg) was added to the reaction mixture, and the obtained mixture was stirred for 1 h at room temperature. The mixture was quenched by adding sat. aq. $NaHCO_3$ (10 mL), and extracted with $CHCl_3$ (20 mL × 3). Then, the organic layer was dried with Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by short column chromatography on silica gel (hexane/AcOEt = 2:1) to afford 2-amino-4-(3′-bromo-4′-methoxyphenyl)thiazole **3c-l** in 73 % yield (208.2 mg).

2-Amino-4-phenylthiazole (**3a-l**): Yield: 148.0 mg (84 %); white solid; mp: 147–148 °C; IR(neat): 3436, 3254, 3114, 1598, 1518 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.17 (br, 2H), 6.72 (s, 1H), 7.29 (t, 1H, *J* = 7.5 Hz), 7.38 (t, 2H, *J* = 7.3 Hz), 7.77 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 102.8, 126.0, 127.7, 128.6, 134.6, 151.3, 167.5; HRMS (APCI): Calcd for $C_9H_9N_2S$ $[M + H]^+$ = 177.0481, Found = 177.0480.

2-Amino-4-(4′-methoxycarbonylphenyl)thiazole (**3b-l**): Yield: 124.2 mg (53 %); white solid; mp: 196–197 °C; IR(neat): 3407, 3314, 3153, 1695, 1606, 1546, 1281, 1110 cm^{-1}; ^{1}H-NMR (400 MHz, $[D_6]$DMSO): δ = 3.84 (s, 3H), 7.16 (br, 2H), 7.24 (s, 1H), 7.91 (d, 2H, *J* = 8.8 Hz), 7.94 (d, 2H, *J* = 8.8 Hz); ^{13}C-NMR (100 MHz, $[D_6]$DMSO): δ = 52.1, 104.5, 125.6, 127.9, 129.6, 139.1, 148.7, 166.1, 168.4; HRMS (APCI): Calcd for $C_{11}H_{11}O_2N_2S$ $[M + H]^+$ = 235.0536, Found = 235.0531.

2-Amino-4-(3′-bromo-4′-methoxyphenyl)thiazole (**3c-l**): Yield: 208.2 mg (73 %); pale orange solid; mp: 181–182 °C; IR(neat): 3422, 3230, 3112, 2858, 1639, 1478 cm^{-1}; ^{1}H-NMR (400 MHz, $[D_6]$DMSO): δ = 3.84 (s, 3H), 6.96 (s, 1H), 7.06 (br, 2H), 7.09 (d, 1H, *J* = 8.8 Hz), 7.75 (dd, 1H, *J* = 8.6, 2.0 Hz), 7.99 (d, 1H, *J* = 2.0 Hz); ^{13}C-NMR (100 MHz, $[D_6]$DMSO): δ = 56.2, 100.7, 110.7, 112.6, 126.0, 129.2, 130.0, 148.1, 154.5, 168.3; HRMS (APCI): Calcd for $C_{10}H_{10}ON_2BrS$ $[M + H]^+$ = 284.9692, Found = 284.9691.

2-Amino-4-(4′-methylphenyl)thiazole (**3d-l**): Yield: 138.9 mg (73 %); white solid; mp: 130–131 °C; IR(neat): 3454, 3219, 3117, 1636, 1522 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 5.02 (br, 2H), 6.67 (s, 1H), 7.18 (d, 2H, *J* = 7.9 Hz), 7.66 (d, 2H, *J* = 8.1 Hz);

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.2, 101.9, 125.8, 129.2, 131.9, 137.5, 151.2, 167.5; HRMS (ESI): Calcd for $C_{10}H_{11}N_2S$ $[M + H]^+$ = 191.0637, Found = 191.0636.

2-Amino-4-(4′-*tert*-butylphenyl)thiazole (**3e-I**): Yield: 178.9 mg (77 %); pale yellow solid; mp: 134–135 °C; IR(neat):3442, 3274, 3114, 1604, 1519, 1268 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9H), 5.03 (br, 2H), 6.68 (s, 1H), 7.40 (d, 2H, *J* = 8.6 Hz), 7.70 (d, 2H, *J* = 8.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 31.2, 34.5, 101.9, 125.5, 125.7, 131.9, 150.7, 151.2, 167.6; HRMS (ESI): Calcd for $C_{13}H_{17}N_2S$ $[M + H]^+$ = 233.1107, Found = 233.1105.

2-Amino-4-(biphenyl-4′-yl)thiazole (3f-I): Yield: 211.9 mg (84 %); white solid; mp: 200–201 °C; IR(neat): 3437, 3287, 3106, 1629, 1523 cm^{-1}; ^{1}H-NMR (400 MHz, $[D_6]$DMSO): δ = 7.06 (s, 1H), 7.08 (br, 2H), 7.35 (t, 1H, *J* = 7.3 Hz), 7.45 (t, 2H, *J* = 7.3 Hz), 7.65–7.70 (m, 4H), 7.87 (d, 2H, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz, $[D_6]$DMSO): δ = 101.8, 126.1, 126.4, 126.7, 127.4, 129.0, 134.0, 138.7, 139.7, 149.5, 168.3; HRMS (ESI): Calcd for $C_{15}H_{13}N_2S$ $[M + H]^+$ = 253.0794, Found = 253.0791.

2-Amino-4-(4′-bromonaphthalen-1′-yl)thiazole (3g-I): Yield: 185.7 mg (61 %); gray solid; mp: 182–183 °C; IR(neat): 3460, 3275, 3065, 1636, 1500 cm^{-1}; ^{1}H-NMR (400 MHz, $[D_6]$DMSO): δ = 6.82 (s, 1H), 7.16 (br, 2H), 7.53 (d, 1H, *J* = 7.9 Hz), 7.61 (t, 1H, *J* = 7.0 Hz), 7.69 (t, 1H, *J* = 6.8 Hz), 7.88 (d, 1H, *J* = 7.7 Hz), 8.18 (d, 1H, *J* = 8.4 Hz), 8.50 (d, 1H, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz, $[D_6]$DMSO): δ = 105.8, 121.6, 126.6, 126.9, 127.1, 127.2, 127.7, 129.7, 131.3, 132.0, 133.9, 149.1, 168.3; HRMS (APCI): Calcd for $C_{13}H_{10}N_2BrS$ $[M + H]^+$ = 304.9743, Found = 304.9741.

2-Amino-4-(4′-bromophenyl)thiazole (**3h-I**): Yield: 201.6 mg (79 %); white solid; mp: 178–179 °C; IR(neat): 3439, 3274, 3111, 1633, 1533 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.98 (br, 2H), 6.74 (s, 1H), 7.50 (d, 2H, *J* = 8.6 Hz), 7.65 (d, 2H, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz, $[D_6]$DMSO): δ = 102.4, 120.1, 127.6, 131.4, 134.1, 148.6, 168.4; HRMS (APCI): Calcd for $C_9H_8N_2BrS$ $[M + H]^+$ = 254.9586, Found = 254.9585.

2-Amino-4-(4′-iodophenyl)thiazole (**3i-I**): Yield: 226.5 mg (75 %); white solid; mp: 176–177 °C; IR(neat): 3422, 3275, 3109, 1631, 1532 cm^{-1}; ^{1}H-NMR (400 MHz, $[D_6]$DMSO): δ = 7.07 (s, 1H), 7.08 (br, 2H), 7.58 (d, 2H, *J* = 8.5 Hz), 7.70 (d, 2H, *J* = 8.5 Hz); ^{13}C-NMR (100 MHz, $[D_6]$DMSO): δ = 93.0, 102.4, 127.7, 134.4, 137.2, 148.8, 168.3; HRMS (APCI): Calcd for $C_9H_8N_2IS$ $[M + H]^+$ = 302.9447, Found = 302.9445.

2-Amino-5-methyl-4-phenylthiazole (**3j-I**): Yield: 142.7 mg (75 %); pale yellow solid; mp: 112–113 °C; IR(neat): 3418, 3276, 3063, 2923, 1633, 1530 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 4.91 (br, 2H), 7.30 (t, 1H, *J* = 7.3 Hz), 7.40 (t, 2H, *J* = 7.3 Hz), 7.56 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.3, 117.3, 127.1, 128.2, 128.3, 135.1, 146.0, 164.1; HRMS (ESI): Calcd for $C_{10}H_{11}N_2S$ $[M + H]^+$ = 191.0637, Found = 191.0637.

2-Amino-5-ethyl-4-phenylthiazole (**3k-I**): Yield: 143.1 mg (70 %); pale yellow solid; mp: 68–69 °C; IR(neat): 3446, 3279, 3116, 2965, 1602, 1528 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, 3H, *J* = 7.5 Hz), 2.81 (q, 2H, *J* = 7.5 Hz), 4.88 (br, 2H), 7.30 (t, 1H, *J* = 7.3 Hz), 7.39 (t, 2H, *J* = 7.3 Hz), 7.52 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.7, 20.5, 125.5, 127.1, 128.1, 128.3, 135.3, 145.1, 164.6; HRMS (ESI): Calcd for $C_{11}H_{13}N_2S$ $[M + H]^+$ = 205.0794, Found = 205.0791.

2-Amino-5-butyl-4-phenylthiazole (**3l-I**): Yield: 132.3 mg (57 %); pale orange solid; mp: 61–62 °C; IR(neat): 3418, 3255, 3080, 2930, 1627, 1540 cm^{-1}; ^{1}H-NMR (400 MHz, $[D_6]$DMSO): δ = 0.83 (t, 3H, *J* = 7.5 Hz), 1.30 (sext, 2H, *J* = 7.3 Hz), 1.51 (quin, 2H, *J* = 7.9 Hz), 2.69 (t, 2H, *J* = 7.3 Hz), 6.78 (br, 2H), 7.27 (t, 1H, *J* = 7.3 Hz), 7.37 (t, 2H, *J* = 7.5 Hz), 7.47 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR (100 MHz, $[D_6]$DMSO): δ = 13.6, 21.8, 26.2, 33.8, 121.2, 126.9, 128.1 (2C), 135.7, 144.9, 164.8; HRMS (APCI): Calcd for $C_{13}H_{17}N_2S$ $[M + H]^+$ = 233.1107, Found = 233.1102.

2-Amino-4,5-diphenylthiazole (**3m-I**): Yield: 154.3 mg (61 %); white solid; mp: 181–182 °C; IR(neat): 3423, 3276, 3051, 1631, 1527 cm^{-1}; ^{1}H-NMR (400 MHz, $[D_6]$DMSO): δ = 7.14 (br, 2H), 7.18–7.30 (m, 8H), 7.35–7.37 (m, 2H); ^{13}C-NMR (100 MHz, $[D_6]$DMSO): δ = 119.1, 127.1, 127.3, 128.1, 128.5, 128.7, 129.0, 132.8, 135.4, 144.9, 166.2; HRMS (APCI): Calcd for $C_{15}H_{13}N_2S$ $[M + H]^+$ = 253.0794, Found = 253.0791.

2-(*N*-Methylamino)-4-phenylthiazole (**3a-II**): Yield: 98.6 mg (83 %); pale yellow solid; mp: 134–135 °C; IR (neat): ṽ = 3106, 3057, 1498, 1170 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.92 (d, 3H, *J* = 3.9 Hz), 6.43 (br, 1H), 6.69 (s, 1H), 7.28 (t, 1H, *J* = 7.3 Hz), 7.38 (t, 2H, *J* = 7.3 Hz), 7.79 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 32.2, 100.6, 126.1, 127.6, 128.5, 135.1, 151.7, 171.3; HRMS (ESI): Calcd for $C_{10}H_{11}N_2S$ $[M + H]^+$ = 191.0637, Found = 191.0636.

2-(*N*-Phenethylamino)-4-phenylthiazole (**3a-III**): Yield: 238.3 mg (85 %); white solid; mp: 111–112 °C; IR (neat): ṽ = 3192, 3061, 2925, 1584, 1482 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.91 (t, 2H, *J* = 7.0 Hz), 3.51 (q, 2H, *J* = 6.8 Hz), 5.76 (br, 1H), 6.68 (s, 1H), 7.16–7.39 (m, 8H), 7.79 (d, 2H, *J* = 7.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 35.4, 47.2, 100.7, 126.0, 126.6, 127.6, 128.5, 128.6, 128.7, 135.0, 138.4, 151.5, 169.5; HRMS (ESI): Calcd for $C_{17}H_{17}N_2S$ $[M + H]^+$ = 281.1107, Found = 281.1103.

2-Methyl-4-phenylthiazole (**3a-IV**): Yield: 150.7 mg (86 %); white solid; mp: 68–69 °C; IR (neat): ṽ = 3106, 2924, 1497, 1440, 1169, 740 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.75 (s, 3H), 7.28 (s, 1H), 7.31 (t, 1H, *J* = 7.3 Hz), 7.40 (t, 2H, *J* = 7.3 Hz), 7.87 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 19.3, 112.2, 126.2, 127.9, 128.6, 134.5, 155.1, 165.8; HRMS (ESI): Calcd for $C_{10}H_{10}NS$ $[M + H]^+$ = 176.0528, Found = 176.0528.

2,4-Diphenylthiazole (**3a-V**): Yield: 201.7 mg (85 %); pale orange solid; mp: 70–71 °C; IR (neat): ṽ = 3061, 1598, 1476, 759 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 –7.41 (m, 7H), 7.94–8.01 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 112.5, 126.3, 126.4, 128.0, 128.6, 128.7, 129.9, 133.6, 134.3, 156.1, 167.6; HRMS (ESI): Calcd for $C_{15}H_{12}NS$ $[M + H]^+$ = 238.0685, Found = 238.0684.

4-Phenyl-2-(4′-methylphenyl)thiazole (**3a-VI**): Yield: 226.2 mg (90 %); white solid; mp: 121–122 °C; IR (neat): ṽ = 3116, 1612, 1477, 739 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 7.27 (d, 2H, *J* = 6.6 Hz), 7.35 (t, 1H, *J* = 7.3 Hz), 7.43 (s, 1H), 7.45 (d, 2H, *J* = 8.4 Hz), 7.94 (d, 2H, *J* = 8.2 Hz), 8.00 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.4, 112.1, 126.4, 126.5, 128.1, 128.7, 129.6, 131.1, 134.6, 140.2, 156.1, 168.0; HRMS (ESI): Calcd for $C_{16}H_{14}NS$ $[M + H]^+$ = 252.0841, Found = 252.0840.

2-(4′-Methoxyphenyl)-4-phenylthiazole (**3a-VII**): Yield: 248.6 mg (93 %); white solid; mp: 97–98 °C; IR (neat): ṽ = 3109, 3057, 2838, 1605, 1519, 1172 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3H), 6.98 (d, 2H, *J* = 9.0 Hz), 7.35 (t, 1H, *J* = 7.4 Hz), 7.41 (s, 1H), 7.45 (t, 2H, *J* = 7.2 Hz), 7.97–8.00 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 55.4, 111.7, 114.2, 126.4, 126.7, 128.1 (2C), 128.7, 134.6, 156.0, 161.1, 167.7; HRMS (ESI): Calcd for $C_{16}H_{14}ONS$ $[M + H]^+$ = 268.0791, Found = 268.0787.

2-(4′-Chlorophenyl)-4-phenylthiazole (**3a-VIII**): Yield: 220.1 mg (81 %); white solid; mp: 101–102 °C; IR (neat): ṽ = 3117, 3066, 1593, 1501, 739 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36 (t, 1H, *J* = 7.4 Hz), 7.42–7.47 (m, 4H), 7.49 (s, 1H), 7.99 (d, 4H, *J* = 8.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 112.8, 126.4, 127.8, 128.3, 128.8, 129.1,

132.2, 134.3, 135.9, 156.5, 166.5; HRMS (ESI): Calcd for $C_{15}H_{11}NCIS$ $[M + H]^+$ = 272.0295, Found = 272.0294.

2-Amino-4-(4′-cyanophenyl)thiazole (**3n-I**): Yield: 127.8 mg (64 %); pale orange solid; mp: 154–155 °C; IR(neat): 3379, 3299, 3126, 2228, 1645, 1540 cm^{-1}; ^{1}H-NMR (400 MHz, [D_6]DMSO): δ = 7.18 (br, 2H), 7.32 (s, 1H), 7.81 (d, 2H, *J* = 8.6 Hz), 7.96 (d, 2H, *J* = 8.6 Hz); ^{13}C-NMR (100 MHz, [D_6]DMSO): δ = 105.5, 109.2, 119.1, 126.1, 132.6, 138.9, 148.0, 168.6; HRMS (ESI): Calcd for $C_{10}H_8N_3S$ $[M + H]^+$ = 202.0433, Found = 202.0432.

2-Amino-4-(4′-nitrophenyl)thiazole (**3o-I**): Yield: 145.2 mg (66 %); white solid; mp: 127–128 °C; IR(neat): 3151, 3116, 1541, 1507, 1372 cm^{-1}; ^{1}H-NMR (400 MHz, [D_6]DMSO): δ = 7.23 (br, 2H), 7.41 (s, 1H), 8.03 (d, 2H, *J* = 9.1 Hz), 8.22 (d, 2H, *J* = 8.8 Hz); ^{13}C-NMR (100 MHz, [D_6]DMSO): δ = 106.7, 124.0, 126.3, 140.9, 145.9, 147.9, 168.7; HRMS (ESI): Calcd for $C_9H_8O_2N_3S$ $[M + H]^+$ = 222.0332, Found = 222.0331.

2-Amino-4-[2′-(methanesulfonyloxy)phenyl]thiazole (**3p-I**): Yield: 195.7 mg (72 %); white solid; mp: 109–110 °C; IR(neat): 3401, 3276, 3124, 1631, 1523, 1356, 1155 cm^{-1}; ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 2.91 (s, 3H), 5.16 (br, 2H), 7.05 (s, 1H), 7.35–7.39 (m, 2H), 7.47–7.49 (m, 1H), 7.92–7.95 (m, 1H); ^{13}C-NMR (100 MHz, [D_6]DMSO): δ = 38.6, 106.5, 122.8, 127.3, 128.3, 128.5, 130.5, 144.5, 145.9, 167.5; HRMS (APCI): Calcd for $C_{10}H_{11}O_3N_2S_2$ $[M + H]^+$ = 271.0206, Found = 271.0204.

2-Amino-4-(4′-methanesulfonylphenyl)thiazole (**3q-I**): Yield: 172.9 mg (68 %); white solid; mp: 246–247 °C; IR(neat): 3420, 3235, 3130, 1592, 1540, 1293, 1145 cm^{-1}; ^{1}H-NMR (400 MHz, [D_6]DMSO): δ = 3.21 (s, 3H), 7.19 (br, 2H), 7.30 (s, 1H), 7.89 (d, 2H, *J* = 8.5 Hz), 8.03 (d, 2H, *J* = 8.5 Hz); ^{13}C-NMR (100 MHz, [D_6]DMSO): δ = 43.6, 105.2, 126.1, 127.4, 138.8, 139.4, 148.2, 168.6; HRMS (APCI): Calcd for $C_{10}H_{11}O_2N_2S_2$ $[M + H]^+$ = 255.0256, Found = 255.0251.

2-Amino-4-(4′-methoxycarbonylphenyl)-5-methylthiazole (**3r-I**): Yield: 171.3 mg (69 %); pale yellow solid; mp: 175–176 °C; IR(neat): 3412, 3292, 3131, 1604, 1537, 1281, 1101 cm^{-1}; ^{1}H-NMR (400 MHz, [D_6]DMSO): δ = 2.36 (s, 3H), 3.84 (s, 3H), 6.87 (br, 2H), 7.71 (d, 2H, *J* = 8.5 Hz), 7.96 (d, 2H, *J* = 8.7 Hz); ^{13}C-NMR (100 MHz, [D_6]DMSO): δ = 12.3, 52.1, 117.4, 127.4, 127.9, 129.2, 140.0, 143.8, 164.5, 166.1; HRMS (APCI): Calcd for $C_{12}H_{13}O_2N_2S$ $[M + H]^+$ = 249.0692, Found = 249.0688.

2-Amino-4-(3′-bromo-4′-isopropoxyphenyl)thiazole (**3s-I**): Yield: 166.0 mg (53 %); white solid; mp: 163–164 °C; IR(neat): 3417, 3307, 3163, 2924, 1636, 1535 1272 cm^{-1}; ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 1.39 (d, 6H, *J* = 6.1 Hz), 4.58 (sep, 1H, *J* = 6.1 Hz), 4.96 (br, 2H), 6.61 (s, 1H), 6.91 (d, 1H, *J* = 8.8 Hz), 7.65 (dd, 1H, *J* = 8.5, 2.2 Hz), 7.97 (d, 1H, *J* = 2.2 Hz); ^{13}C-NMR (100 MHz, [D_6]DMSO): δ = 21.8, 71.3, 100.6, 112.4, 115.4, 125.9, 129.2, 130.1, 148.1, 152.9, 168.2; HRMS (APCI): Calcd for $C_{12}H_{14}ON_2BrS$ $[M + H]^+$ = 313.0005, Found = 313.0004.

2-Amino-4-(5′-bromo-2′-methoxyphenyl)thiazole (**3t-I**): Yield: 211.6 mg (74 %); white solid; mp: 146–147 °C; IR(neat): 3328, 3162, 2925, 2844, 1633, 1525, 1241 cm^{-1}; ^{1}H-NMR (400 MHz,$CDCl_3$): δ = 3.91 (s, 3H), 4.95 (s, 2H), 6.83 (d, 1H, *J* = 8.8 Hz), 7.24 (s, 1H), 7.33 (dd, 1H, *J* = 8.8, 2.7 Hz), 8.22 (sd, 1H, *J* = 2.7 Hz); ^{13}C-NMR (100 MHz, [D_6]DMSO): δ = 55.8, 107.2, 111.9, 113.8, 125.0, 130.1, 131.3, 144.1, 155.7, 166.5; HRMS (APCI): Calcd for $C_{10}H_{10}ON_2BrS$ $[M + H]^+$ = 284.9692, Found = 284.9691.

2-Amino-4-(3′-bromo-4′-methoxyphenyl)-5-methylthiazole (**3u-I**): Yield: 165.0 mg (72 %); white solid; mp: 204–205 °C; IR(neat): 3396, 3289, 3100, 1638, 1530, 1261 cm^{-1}; ^{1}H-NMR (400 MHz, [D_6]DMSO): δ = 2.30 (s, 3H), 3.85 (s, 3H), 6.78 (br, 2H), 7.11 (d, 1H, *J* = 8.8 Hz), 7.52 (dd, 1H, *J* = 8.6, 2.0 Hz), 7.75 (sd, 1H, *J* = 2.0 Hz); ^{13}C-NMR (100 MHz, [D_6]DMSO): δ = 12.1, 56.1, 110.3, 112.2, 114.2, 128.1, 129.5, 132.2, 143.0, 154.1, 164.3; HRMS (ESI): Calcd for $C_{11}H_{12}ON_2BrS$ $[M + H]^+$ = 298.9848, Found = 298.9848.

2-Amino-4-(3′-bromobenzo[b]thien-2′-yl)thiazole (**3v-I**): Yield: 159.7 mg (51 %); pale yellow solid; mp: 223–224 °C; IR(neat): 3452, 3290, 3158, 3125, 1626, 1516, 1318, 1013, 752 cm^{-1}; ^{1}H-NMR (400 MHz, [D_6]DMSO): δ = 7.33 (br, 2H), 7.43 (t, 1H, *J* = 7.0 Hz), 7.49 (t, 1H, *J* = 7.0 Hz), 7.54 (s, 1H), 7.74 (d, 1H, *J* = 7.5 Hz), 7.96 (d, 1H, *J* = 7.7 Hz); ^{13}C-NMR (100 MHz, [D_6]DMSO): δ = 102.0, 105.7, 122.5, 122.7, 125.5, 125.7, 134.1, 136.5, 138.7, 142.0, 167.6; HRMS (ESI): Calcd for $C_{11}H_8N_2BrS_2$ $[M + H]^+$ = 310.9307, Found = 310.9305.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra of all thiazoles **3a-I**–**3v-I** and **3a-II**–3**a-VIII**.

Acknowledgments

Financial support from the Ministry of Education, Culture, Sports, Science, and Technology in Japan in the form of a Grant-in-Aid for Scientific Research (No. 15K05418) is acknowledged.

Keywords: Heterocycles · Thiazoles · Cyclization · One-pot reactions · Synthetic methods

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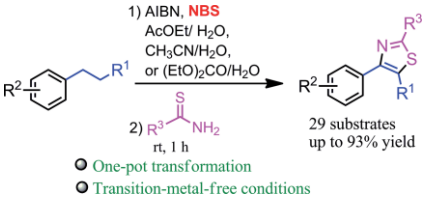
Received: January 21, 2019

Thiazole Synthesis



Various alkylarenes were successfully transformed into the corresponding 2-amino-4-arylthiazoles and 2,4-diarylthiazoles in good to moderate yields by the treatment with NBS, followed by the reaction with thioureas or arenethioamides.

DOI: 10.1002/ejoc.201900100