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Synthesis of *N*-Substituted-2-Aminothiazolo[4,5-*b*]pyrazines by Tandem Reaction of *o*-Aminohalopyrazines with Isothiocyanates

Se Hun Kwak, Gee-Hyung Lee, and Young-Dae Gong*

*Department of Chemistry, Dongguk-University-Seoul, Seoul 100-715, Korea. *E-mail: ydgong@dongguk.edu*
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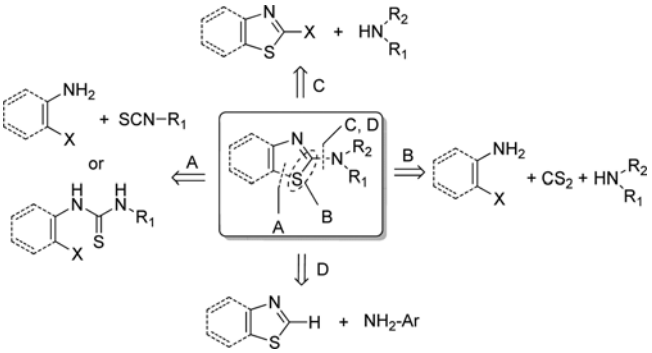
Bicyclic aromatic rings containing aminothiazoles have a wide spectrum of biological and pharmaceutical activities. Among them, 2-aminobenzothiazoles[1] and 2-aminothiazolopyridines[2] have been most frequently researched. In addition, 2-aminothiazolopyrimidines were explored for identification as the vanilloid receptor 1 (TRPV1) antagonists,[3a] epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors,[3b] others[3c-d] and for their synthesis.[4] In contrast, 2-aminothiazolopyrazines have attracted little research attention.[5]

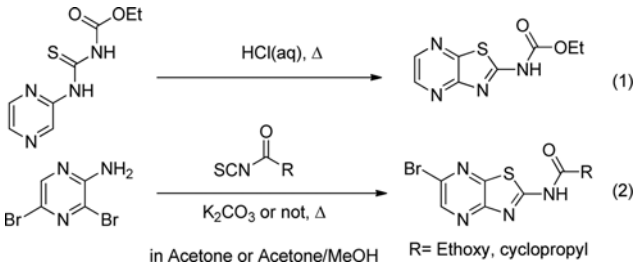
Recently developed methods to construct 2-aminobenzothiazoles comprise of transition metal-catalyzed cyclization and metal-free cyclization of 2-haloaminobenzothioureas (A in Scheme 1),[6] tandem reaction of 2-haloanilines with isothiocyanates (A)[7] and a cascade three-component reaction using CS_2, 2-haloanilines and secondary amines (B).[8] Substitution reactions of 2-halobenzothiazoles with N nucleophilies (C)[9] and copper-catalyzed oxidative intermolecular amination of benzothiazoles (D)[10] are attractive, but the preparation of the substrates is not generally convenient.[8]

In case of 2-aminothiazolopyrazines, oxidative cyclization of pyrazinethiourea (Eq. (1) in Scheme 2),[5a] prepared from aminopyrazine with ethoxycarbonyl isothiocyanate, and tandem or stepwise reaction of 2-amino-3,5-dibromopyrazine (Eq. (2)) with isothiocyantes were reported.[5b-c]

In generally, it could be considered that pyridines and pyrimindines, which have a leaving group to the alpha position of electronegative nitrogen, can be easily fused with isothiocyanates. But, without optimization of conditions, acceptable high yield could not be achieved as seen in the literature.[4a,7a] And we suffered difficulties to obtain the 2-aminothiazolopyrazines from known conditions.[5b-c] This led us to report the synthesis of the compounds. In this letter, we report the synthesis of *N*-substituted-2-aminothiazolo[4,5-*b*]pyrazine by tandem reaction of *o*-aminohalopyrazines

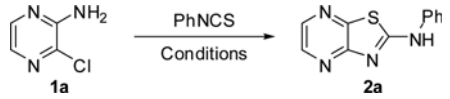


Scheme 1. Retrosynthetic analysis of the synthesis of 2-aminobenzothiazoles.



Scheme 2. Synthetic routes to 2-aminothiazolopyrazines.

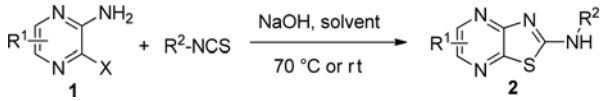
Table 1. Optimization of Reaction Conditions for the One-Pot Preparation of **2a**[a]

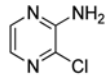
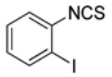
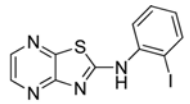
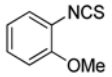
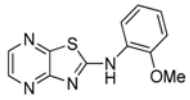
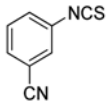
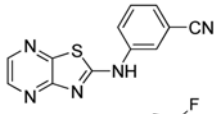
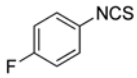
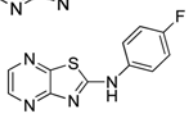
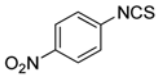
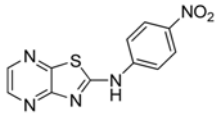
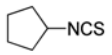
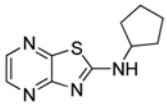
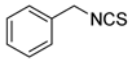
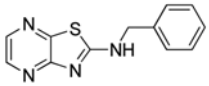
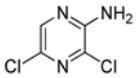
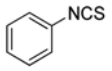
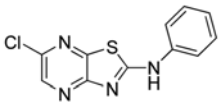
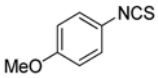
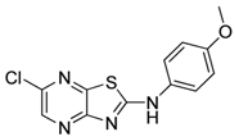
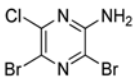
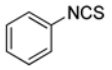
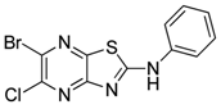


Entry	Base (equiv)	Solvent	Temp. (°C)	Time[b] (h)	Yield[c] (%)
1	K_2CO_3 (2.5)	Acetone	80	3	trace
2	K_2CO_3 (2.5)	DMSO	100	3	trace
3	NaOH (2.5)	Acetone	80	3	53
4	KOH (2.5)	Acetone	80	1.5	45
5	LiOH (2.5)	Acetone	80	5	trace
6[d]	NaOH (2.5)	Acetone	80	3	36
7	NaOH (2.5)	THF	80	15	30
8	NaOH (2.5)	DMF	80	2	55
9	NaOH (2.5)	NMP	80	2	69
10	NaOH (2.5)	DMSO	70	2	72
11	NaOH (3.5)	DMSO	70	1	70
12	NaOH (3.5)	DMSO	100	1	62
13[e]	NaOH (3.5)	DMSO	70	0.5	77
14[e,f]	NaOH (3.5)	DMSO	70	0.5	75

[a]Reaction conditions: 3-chloro-2-aminopyrazine **1a** (0.8 mmol), PhNCS (1.3 equiv), base, solvent (6 mL). [b]Time was checked after addition of PhNCS. [c]Isolated yield based on 3-chloro-2-aminopyrazine **1a**. [d]In the presence of CuI (3 mol %). [e]Reaction mixture (**1a**, solvent, base) was heated at 50 °C for 20 minutes before addition of the PhNCS **2b**. [f]PhNCS (1.15 equiv) was used.

Table 2. Synthesis of *N*-Substituted-2-aminothiazolo[4,5-*b*]pyrazines[a]



Entry		Pyrazines	Isothiocyantes		Product	T' °C/T" °C	Time (h)[b]	Yield (%)[c]
1	**1a**			**2b**		50/70	0.5	60
2	**1a**			**2c**		50/70	1	64
3	**1a**			**2d**		rt/rt	1	81
4	**1a**			**2e**		50/70	1	72
5	**1a**			**2f**		rt/rt	0.6	70
6	**1a**			**2g**		50/70	1	71
7	**1a**			**2h**		50/70	0.5	83
8	**1b**			**2i**		50/70	0.5	54
9[d]	**1b**			**2i**		50/70	1	65
10[d]	**1b**			**2j**		50/70	2	81
11	**1c**			**2k**		rt/70	1	27
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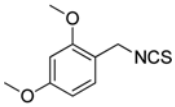
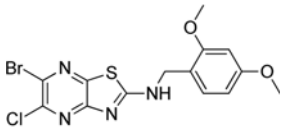
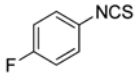
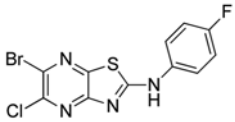
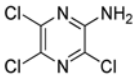
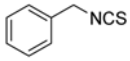
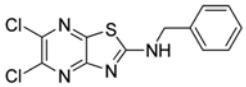
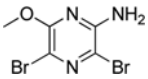
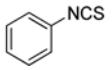
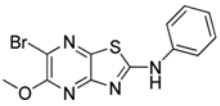
13[d]	**1c**			**2l**		rt/70	1	92
14[d]	**1c**			**2m**		rt/70	1	92
15[d]	**1d**			**2n**		rt/70	1	83
16	**1e**			**2o**		rt/70	1	70

[a]Reaction conditions: pyrazines **1** (0.8 mmol), isothiocyanates (1.15 equiv), NaOH (3.5 equiv) and DMSO (6 mL). [b]The reaction time was not optimized. [c]Isolated yield. [d]Acetone was used instead DMSO.

with isothiocyanates. We initiated our investigations by examining 2-amino-3-chloropyrazine **1a** and phenylisothiocyanate as model substrates (Table 1).

The reaction was initially carried out in acetone with K_2CO_3 since similar reactions were described in patents (Table 1, entry 1).[5b-c] After 3 h, the pyrazine **1a** remained unreacted. When changing the solvent to DMSO, we obtained the intermediate thiourea compound instead of the desired product **2a** (Table 1, entry 2). Interstingly, replacing K_2CO_3 with a stronger base such as NaOH, KOH and LiOH, afforded **2a** in moderate yield, except with LiOH (Table 1, entries 3-5). The addition of CuI was deteriorative (Table 1, entry 6). Different solvents were screened in order to increase the yield (Table 1, entries 7-10). The best result was obtained when DMSO was used as a solvent (Table 1, entry 10). The reaction time was reduced by using more base equivalent with a similar yield (Table 1, entry 11). The yield was diminished at 100 °C (Table 1, entry 12). When NaOH, DMSO and **1a** were stirred at 50 °C before the addition of PhNCS, the yield was slightly enhanced, and the reaction time was reduced (Table 1, entry 13). Finally, we changed the amount of PhNCS, which was little difference in the yield (Table 1, entry 14).

The established optimized reaction conditions were then examined through variable isothiocyantes. The corresponding results are listed in Table 2. We initially conducted the reaction of 3-chloro-2-aminopyrazine **1a** with aryl isothiocyanates bearing either electron-donating group or electron-withdrawing groups, affording the desired products in moderate yield (Table 2, entries 1-5). In the case of aryl isothiocyanates with electron-withdrawing group (-CN, $-NO_2$) the reaction were proceeded well to give the corresponding products at room temperature (Table 2, entries 3 and 5). Cyclopentyl isothiocyante and benzyl isothiocyante also reacted well with **1a** (Table 2, entries 6 and 7). Subsequently, other pyrazines **1b-e** synthesized from commercially available 2-aminopyrazine and 2-amino-6-chloropyrazine (see the supporting information) were examined. Unlike **1a**, better result was observed when acetone was used instead of DMSO (Table 2, entries 8 and 9). According to the result, acetone was employed as the solvent in the reaction of **1b** with 4-methoxyphenyl isothiocyanate, giving a reasonable yield (Table 2, entry 10). When 2-amino-3,5-dibromo-6-chloropyrazine **1c** was used, acetone was also a better solvent than DMSO (Table 2, entries 11 and 12). The low yield of entry 11 was found to be the low stability of the product **2k** in DMSO containing NaOH. Finally, the other tetra-substituted pyrazine **1e** (Table 2, entry 16) was tested and found to form in good yield.

In conclusion, a convenient and mild method for the synthesis of *N*-substituted-2-aminothiazolo[4,5-*b*]pyrazines, which might either exhibit potential pharmacological activities or be used as building blocks, via tandem reactions of various pyrazines and isothiocyanates has been developed. All substrates were well converted to the desired products. The generality of this reaction could enable its application to other substrates.

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Supporting Information. Experimental details, general information and characterization data for all compounds.

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