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Synthesis of Mono-substituted 5-Aminothiatriazoles and Their Conversion to Tetrazole-5-thiones

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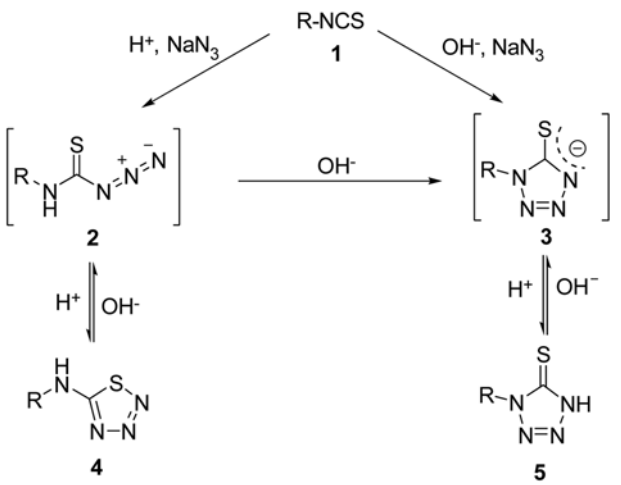
Azoles are biologically active compounds and synthetic intermediates, and therefore their medicinal and biological applications have been a focus of research.[1] In particular, aminothiatriazole derivatives play an important role in the intriguing chemistry of azoles.[2] For example, mono-substituted aminothiatriazoles (**4** in Scheme 1) exhibit a wide range of interesting biological properties, including antihypertensive,[3] antibacterial,[4] antitubercular,[5] antiviral,[6] fungicidal,[7] anticancer,[8] central nervous system stimulant, and muscle relaxant activities.[9]

Among currently available synthetic routes to mono-substituted aminothiatriazoles, the most widely used one is based upon the method outlined originally by Freund and his co-workers,[10] which involves the treatment of thiosemicarbazides with nitrous acid.[5,8,9,11] A related *aza*-transfer procedure with diazonium salts was also reported.[12] Mono-substituted aminothiatriazoles were synthesized as well by the reaction of hydrazoic acid,[11b,c,13] trimethyl azide,[14] or sodium azide[15] with organic isothiocyanates. Batey's group prepared aminotriazoles from thiocarbamoylimidazolium salts.[16] As discussed above, several methods to prepare mono-substituted aminothiatriazoles are known, but synthetic approaches for these compounds are needed.

We recently observed that the reactions of organic isothiocyanates (**1**) with sodium azide produced 1-substituted tetrazole-5-thiones (**5**) under basic conditions and aminothiatriazoles (**4**) under acidic conditions (Scheme 1).[17] Organic isothiocyanates are expected to afford 5-aminothiatetrazoles by the 1,5-dipolar cyclization of the intermediate (**2**) under acidic conditions. Inconsistent with this expectation, however, these compounds gave tetrazole-5-thiones *via* the anionic intermediate (**3**) under the basic conditions. Moreover, stirring a mixture of aminothiatriazoles (**4**) and bases for 12 h at room temperature gave the tetrazole-5-thiones (**5**). On the other hand, heating the same mixture produced by-products.

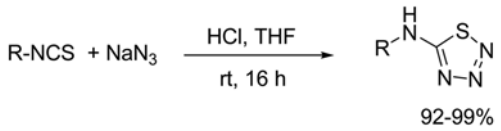


Scheme 1

Results and Discussion

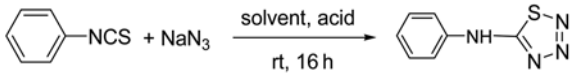
We found that the reaction of an organic isothiocyanate and sodium azide in THF was completed in 16 h at room temperature when HCl was added (Scheme 2).

To find out optimum conditions for the above preparations



Scheme 2

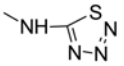
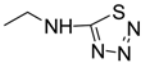
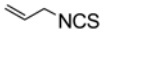
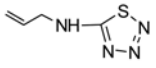
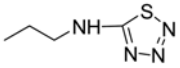
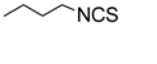
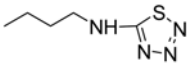
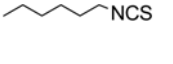
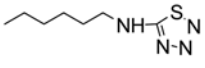
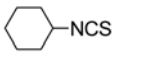
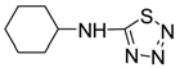
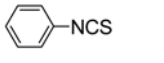
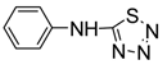
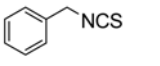
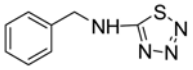
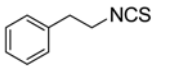
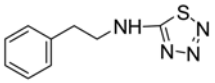
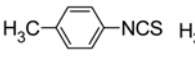
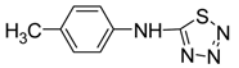
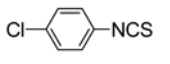
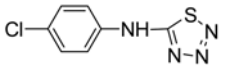
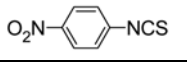
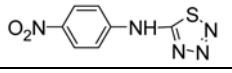
Table 1. Effects of solvents and acids in the reaction of phenyl isothiocyanate and sodium azide at rt[a]



Entry	Solvent	Acid	Yield (%)[c]
1	H_2O	H_2SO_4	11
2	CH_3CH_2OH	HNO_3	13
3	THF	HCl	99
4	THF	H_2SO_4	69
5	THF	HNO_3	47
6	H_2O/THF[b]	HCl	52
7	CH_3CH_2OH/THF[b]	H_2SO_4	19
8	CH_3CH_2OH/H_2O[b]	HNO_3	20

[a]Phenyl isothiocyanate (1 mmol) was reacted with sodium azide (1.2 mmol) and acid (3 mmol) in solvent (3 mL) for 16 h at rt. [b]Volume ratio, 1:1. [c]Isolated yields.

Table 2. Synthesis of mono-substituted thiatriazoles from organic isothiocyanates[a]

Entry	Isothiocyanate	Product	Yield (%)[b]	
1			**1a**	92
2			**1b**	94
3			**1c**	94
4			**1d**	97
5			**1e**	94
6			**1f**	99
7			**1g**	95
8			**lh**	99
9			**1i**	92
10			**1j**	99
11			**1k**	97
12			**ll**	96
13			**1m**	92

[a]Organic isothiocyanate (1 mmol) reacts with sodium azide (1.2 mmol) and conc. HCl (3 mmol) in THF (3 mL) at rt for 16 h. [b]Isolated yields.

of the aminothiatriazoles, we treated phenyl isothiocyanate as a representative substrate with various acids and solvents at room temperature (Table 1). As shown in Table 1, all the reactions were finished after 16 h, and the best experimental variables turned out to be THF as a solvent and HCl as an acid at room temperature.

While such experimental variables were fixed, various alkyl and aryl isothiocyanates were treated with sodium azide in the presence of 3 equiv of HCl in THF at room temperature (Table 2). All of the organic isothiocyanates smoothly underwent the reactions to give the corresponding aminothiatriazoles under mild conditions. The reactions were completed in high yields (92-99%). Isolated products were characterized by spectroscopy (IR and NMR) and elemental analysis. The NH hydrogen in alkyl-substituted aminothiatriazoles products appeared as a signal at 7.2-8.5 ppm in ^{1}H-NMR spectra. By contrast, the corresponding hydrogen peak in aryl-substituted ones appeared at 10.0-11.9 ppm. Such unusual down-field chemical shifts of NH hydrogens as compared with those in general amines are probably ascribed to hydrogen bonding (see below). The carbon in the thiatriazole ring of the aminothiatriazoles appeared at 172-179 ppm in ^{13}C NMR spectra. ORTEP drawing of **1j** (Figure 1) clearly confirms the formation of the aminothiatriazole compound. The crystal and refinements data for compound **1j** are presented in Table 5. Compound **1j** consists of two crystallographically independent molecules, which are chemically indistinguishable. As shown in Figure 1, these two molecules are connected by the hydrogen bonds of the N–H···N type. Atwood *et al.* also reported that the crystal structure of unsubstituted 5-amino-1,2,3,4-thiatriazole shows both intra- and intermolecular N–H···N hydrogen bonds.[18] The S–C (1.699(2) Å) and S–N (1.693(2) Å) in the 5-memebered thiatriazole ring indicate the single bonds. The phenyl and thiatriazole rings are essentially planar and twisted from each other with the dihedral angle of 73.60(8)°.

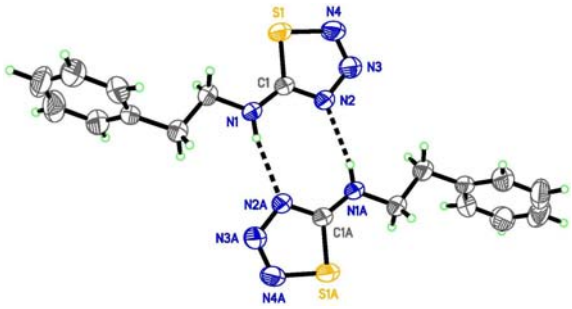
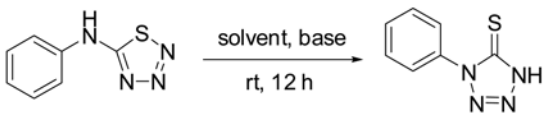


Figure 1. ORTEP drawing of *N*-Phenethyl-1,2,3,4-thiatriazol-5-amine (**1j**). Labeled and unlabeled atoms are related by the crystallographic center of symmetry. Selected bond lengths (Å) and bond angles (°): S1–N4 1.693(2), S1–C1 1.699(2), N4–N3 1.266(3), N3–N2 1.350(3), N2–C1 1.327(3), N1–C1 1.320(3), N1–C2 1.449(3), N1-HN1 0.82(2); N4–S1–C1 89.7(1), N3–N4–S1 111.2(2), N4–N3–N2 116.6(2), C1–N2–N3 110.8(2), C1–N1–C2 122.9(2), N1–C1–N2 123.4(2).

We examined the effects of solvents and bases in the room-temperature conversion of an aminothiatriazole to a tetrazole-thione under basic conditions (Scheme 3). THF, water, and their mixture were used as solvents. TEA, pyridine, and NaOH were used as bases for the reaction of *N*-phenyl-1,2,3,4-thiariazole-5-amine. As shown in Table 3, the conversion to 1-phenyl tetrazole-5-thione in a mixed solvent of THF and water in the presence of NaOH (a base) was accomplished in 67% yield.

We also investigated the reactivity of the aminothiatriazole toward organic aldehydes under basic conditions (Scheme 4). Various aldehydes were added to a mixture of an aminothiatriazole and Et_3N in THF at 70 °C. The reactions of *N*-



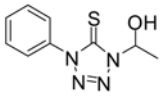
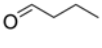
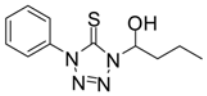
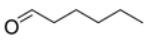
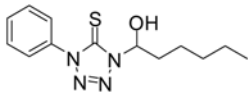
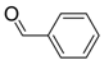
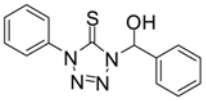
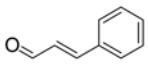
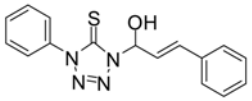
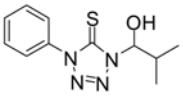
Scheme 3

Table 3. Effects of a solvent and a base in the conversion of thiatriazole-5-amine to tetrazole-5-thion at rt[a]

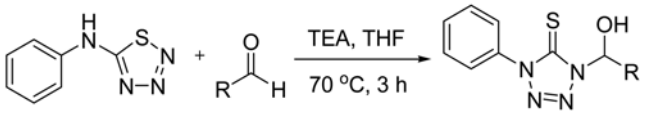
Entry	Solvent	Base	Yield (%)[c]
1	THF	TEA	10
2	H_2O	Py	14
3	THF	NaOH	21
4	THF/H_2O[b]	TEA	60
5	THF/H_2O[b]	NaOH	67

[a]*N*-Phenyl-1,2,3,4-thiatriazole-5-amine (1 mmol) reacted with a base (3 mmol) in solvent (3 mL) for 12 h at rt. [b]Volume ratio, 1:1. [c]Isolated Yields.

Table 4. Synthesis of 1-(1-hydroxy-alkyl(phenyl))-4-phenyl-1,4,-dihydro-tetrazole-5-thion from *N*-phenyl-1,2,3,4-thiatriazole-5-amine with various aldehydes[a]

Entry	Aldehyde	Product	Yield (%)[b]
1			**2a** 68
2			**2b** 72
3			**2c** 70
4			**2d** 82
5			**2e** 79
6			**2f** 67

[a]*N*-Phenyl-1,2,3,4-thiatriazole-5-amine (1 mmol) was reacted with aldehydes (1 equiv) and triethylamine (3 equiv) in THF (3 mL) at 70 °C for 3 h. [b]Isolated yields.



Scheme 4

phenyl-1,2,3,4-thiariazole-5-amine with diverse aldehydes give 1,4-disubstituted tetrazole-5-thiones in good yields (67-82%) within 3 h (Table 4).

In summary, mono-substituted 5-amino-1,2,3,4-thiatriazoles were prepared from organic isothiocyanates and sodium azide under basic conditions. We observed the room-temperature conversion of aminothiatriazoles to the corresponding tetrazole-thiones under basic conditions. Aminothiatriazoles reacted with organic aldehydes to produce 1,4-disubstituted tetrazole-5-thiones. In addition, one mono-substituted aminothiatriazole was structurally characterized by X-ray crystallography.

Table 5. X-ray data collection and structure refinement for compound **1j**

Empirical formula	$C_9H_{10}N_4S$
Formula weight	206.27
Temperature, K	296(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a, Å	5.4021(4)
b, Å	9.1859(5)
c, Å	20.8138(11)
β, (º)	96.878(4)°
V, Å^3	1025.41(11)
Z	4
d_{cal}, g cm^{-3}	1.336
μ, mm^{-1}	0.281
F(000)	432
T_{max}	0.9725
T_{min}	0.8911
θ range (º)	1.97-28.51
No. of reflns measured	16444
No. of reflns unique	2557
No. of reflns with $I > 2\sigma(I)$	1207
No. of params refined	167
Max., in $\Delta\rho$ (e Å^{-3})	0.218
Min., in $\Delta\rho$ (e Å^{-3})	0.159
GOF on F^2	0.991
R[a]	0.0528
wR2[b]	0.0916

[a]$R = \Sigma[|F_o| - |F_c|]/S|F_o|]$. [b]$wR2 = \Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]^{1/2}$

Experimental

General. All the solvents and reagents were purchased from Aldrich, Fluka, and Merck Chemical Companies. Melting points were measured with an Electrothermal melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol Lambda-300 MHz spectrometer or ECA 600 MHZ spectrometer. X-ray data were collected with Bruker Smart APEX2 diffractometer equipped with a Mo X-ray tube. Elemental analyses were performed with a CE instruments EA1110. Infrared spectra were recorded on a Perkin Elmer BX spectrophotometer in a KBr pellet. GC-Mass data were recorded on the Agilent 6890GC/5973i MSD.

General Procedure for the Synthesis of Mono-substituted Aminothiatriazoles. A representative procedure for Table 2: a mixture of phenyl isothiocyanate (135 mg, 1 mmol) and sodium azide (78 mg, 1.2 mmol) and conc. HCl (0.25 mL, 3 mmol) in THF (3 mL) was stirred for 16 h at room temperature. Water (3 mL) was added to the resulting mixture, and the aqueous layer was acidified with conc. HCl to pH 1. The acidified solution was extracted with ethyl acetate (3 mL × 3). The ethyl acetate extract was washed with water and dried over anhydrous $MgSO_4$, and the solvent was removed under vacuum to yield 176 mg (99%) of *N*-phenyl-1,2,3,4-thiatriazole-5-amine (**1h**) as an white crystal. This solid was recrystallized from ethyl acetate and *n*-hexane and charac-

terized by spectral and physical data.

General Procedure for the Synthesis of 1-(1-Hydroxyalkyl (phenyl))-4-phenyl-1,4-dihydro-tetrazole-5-thiones. A representative procedure for Table 3: a mixture of *N*-phenyl-1,2,3,4-thiatriazole-5-amine (178 mg, 1 mmol), sodium azide (78 mg, 1.2 mmol) and acetaldehyde (44 mg, 1 mmol) in THF (3 mL) was stirred at 70 °C. The reaction mixture stirred for 3 h, and then water (3 mL) was added. The resultant mixture was extracted with ethyl acetate (5 mL × 3). The combined organic layer was washed with water, dried over anhydrous $MgSO_4$, and the solvent was removed under vacuum to produce 211 mg (95% yield) of 1-(1-hydroxyethyl)-4-phenyl-1*H*-tetrazole-5(4*H*)-thione (**2a**) as a brown liquid.

X-ray Structure Determination. All X-ray data were collected with a Bruker Smart APEX2 diffractometer equipped with a Mo X-ray tube. Collected data were corrected for absorption with SADABS based upon the Laue symmetry by using equivalent reflections.[19] All calculations were carried out with the SHELXTL programs.[20] All structures were solved by direct methods. All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were generated in ideal positions and refined in a riding model.

CCDC 784736 contains the supplementary crystallographic data for this paper. Copies of this information may be obtained free of charge from: The director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336-033; email: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Supporting Information. IR, ^{1}H and ^{13}C NMR spectral data of all products are available through the internet http://jounal.kcsnet.or.kr.

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