SCANDIUM TRIFLATE CATALYZED FORMATION OF BENZOTHIAZOLE FROM 2-AMINOBENZENETHIOL AND FORMALDEHYDE IN THE PRESENCE OF WATER [1]

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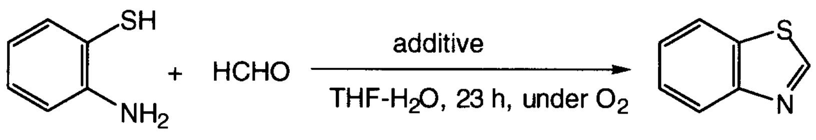
Abstract – In the presence of a catalytic amount of scandium triflate, 2-aminobenzenethiol and formaldehyde in water reacted to give an imine, followed by ring closure to afford a thiazoline, which was aromatized by oxygen or DDQ to give a high yield of benzothiazole.

Since lanthanides and related rare earth metals have been widely known to have Lewis acidic character even in aqueous solutions,[2] syntheses using these reagents have attracted much attention for C-C bond forming reaction in the presence of H_2O.[3] These Lewis acids also act properly even in the presence of amino groups, thus application of them to the synthesis of aza compounds is one of the major topics in this field.[4]

In the course of the synthesis of heteroaromatics, there are a lot of dehydration reactions between a carbonyl group and an amino group to form an imine derivative, followed by attack of an intramolecular nucleophile to bring about a ring closure.[5] Thus application of lanthanide Lewis acid to this type of reactions is considered to be rational approach, though the examples are rare.[6]

To substantiate the above supposition, we first investigated the reaction of 2-aminobenzenethiol with formaldehyde, and found that the ring closing reaction occurred smoothly in the presence of a catalytic amount of scandium triflate, accompanied by aromatization of thiazoline ring to give benzothiazole. This paper describes these results.



1 2

Scheme 1

Formaldehyde is an inexpensive reagent, and is generally available as a solution in water. When 37% aqueous solution of HCHO was allowed to react with 2-aminobenzenethiol (**1**) in THF/H_2O under O_2, benzothiazole (**2**) was obtained only in 12% yield (Scheme 1 and Table 1, Entry 1).[7] The addition of 7 mol% of scandium triflate, however, brought about a sharp increase of the yield of **2** (Entry 2).

Table 1 The Yield of Benzothiazole by the Reaction of 2-Aminobenzenethiol with Formaldehyde in the Presence of an Additive

Entry	1	2	3	4	5
Additive (7 mol%)	-	$Sc(OTf)_3$	$Sn(OTf)_2$	$Yb(OTf)_3 \cdot H_2O$	$Cu(OTf)_2$
Yield (%) of **2**	12	84	58	64	14

In the typical procedure, 2-aminobenzenethiol (0.37 mmol)[8] and HCHO (0.5 mmol, 37% aqueous solution) were dissolved in THF (1.5 mL). Scandium triflate (0.025 mmol, 7 mol%) was added under oxygen atmosphere, and the mixture was allowed to stir for 23 h at room temperature. Then ethyl acetate (10 mL) was added, and the organic layer was washed with 5% aq. K_2CO_3 (2 mL), and brine (2 mL), dried over $MgSO_4$, and evaporated off. The residue was chromatographed on silica gel (CH_2Cl_2) to give the product. Several other Lewis acids were applied to the reaction whose results are shown in Entries 3-5. Although ytterbium and tin (II) triflate gave moderate yields, the catalytic activities did not surpass those of $Sc(OTf)_3$.

Next, the reaction was carried out using various amounts of HCHO. The results are summarized in Scheme 2 and Table 2, which suggested that 1.4 eq. of HCHO gave the best result, and that excess use slightly decreased the yields.

$$\mathbf{1} \xrightarrow[\substack{\text{Sc(OTf)}_3\text{ (7 mol\%)} \\ \text{THF under O}_2\text{, 23 h}}]{\text{aq. HCHO}} \mathbf{2}$$

Scheme 2

Table 2

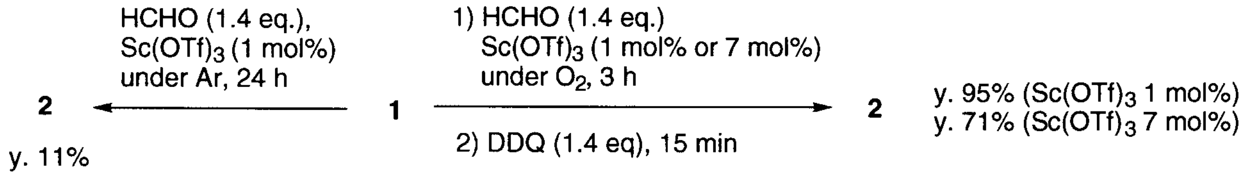
HCHO (eq.)	Yield (%) of **2**
0.7	37
1.0	63
1.4	84
2.0	74
2.7	70

The amount of $Sc(OTf)_3$ was varied to study the efficiency as a catalyst, and the results are shown in Table 3. Even the amount less than 0.001 eq. was efficient for the completion of the reaction (Table 3, Entry 8). The data in Table 3 show that the variation of the catalyst amount only slightly affected the reaction yield. The phenomenon is rationally explained by the fact that there exists a slow oxidation step after the $Sc(OTf)_3$ catalyzed step.

Table 3 The Yield of **2** Using Various Amounts of $Sc(OTf)_3$ in the Presence of 1.4 eq. of aq. HCHO

Entry	mol% of $Sc(OTf)_3$	Reaction Time (h)	Yield (%) of **2**
1	14	23	71
2	7	23	84
3	2.5	23	86
4	1.5	23	89
5	1	23	83
6	0.7	23	77
7	0.14	42	86
8	0.07	42	92

When 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was added after the reaction of **1** with HCHO in the presence of 1 mol% of $Sc(OTf)_3$ for 3 h, the reaction completed within 15 min to give **2** in 95% yield. When the amount of the catalyst was increased to 7 mol%, the yield was slightly decreased. Thus the catalytic process was revealed to function efficiently by the use of 0.01 eq. of $Sc(OTf)_3$, and the increase of the catalyst might cause side reactions to decline the yield.[9] A significant decrease in the yield was observed when the reaction was carried out under Ar atmosphere (Scheme 3).[10] Thus, the oxidation seems to be a rate-limiting step for the reaction.



Scheme 3

Consequently, the reaction mechanism is summarized as shown in Scheme 4. The reaction is supposed to commence with the condensation of **1** with formaldehyde to form the imine(**4**). The formation of **4** was observed even in the absence of $Sc(OTf)_3$, thus the process is non-catalytic step.[11] In the presence of $Sc(OTf)_3$, the imine(**4**)is activated by the Lewis acid, and an intramolecular nucleophilic attack occurs to afford benzothiazoline (**5**). The final step is the oxidation of **5** to aromatized **2** by oxygen or DDQ. $Sc(OTf)_3$ is supposed not to participate in the step.[12]

In this communication, we described that the reaction of 2-aminobenzenethiol with formaldehyde[13] was accelerated by $Sc(OTf)_3$ to give ring closing product in the presence of water, and the succeeding aromatization was carried out by the mild air oxidation or DDQ to give **2** in a good yield. This kind of ring closing reaction is a ubiquitous process for the synthesis of heterocycles, and application to synthesis of other heterocycles is now under investigation.

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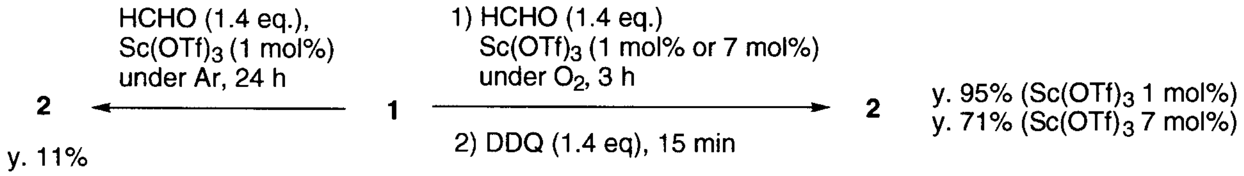

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