

SCANDIUM TRIFLATE CATALYZED FORMATION OF BENZOTHAZOLE FROM 2-AMINOENZENETHIOL AND FORMALDEHYDE IN THE PRESENCE OF WATER ¹

Takashi Itoh, Kazuhiro Nagata, Michiko Miyazaki, and Akio Ohsawa*

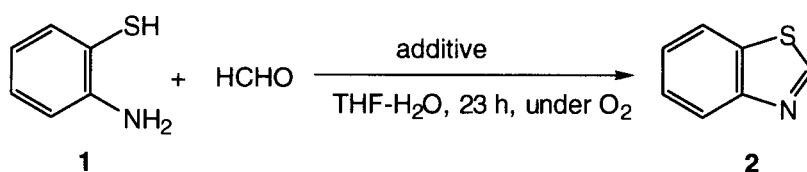
School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

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 H₂O.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.



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/H₂O under O₂,

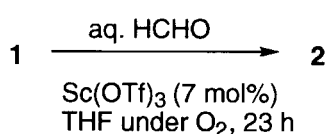
benzothiazole (**2**) was obtained only in 12% yield (Scheme 1 and Table 1, Entry 1).⁷ The addition of 7 mol% of scandium triflate, however, brought about a sharp increase of the yield of **2** (Entry 2).

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 ·H ₂ O	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. K₂CO₃ (2 mL), and brine (2 mL), dried over MgSO₄, and evaporated off. The residue was chromatographed on silica gel (CH₂Cl₂) 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.



Scheme 2

Table 2

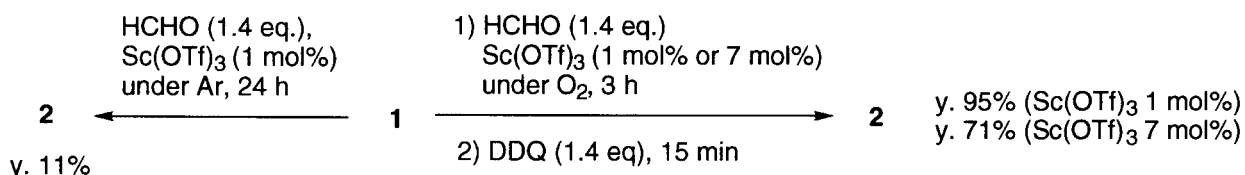
HCHO (eq.)	Yield (%) of 2
0.7	37
1.0	63
1.4	84
2.0	74
2.7	70

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

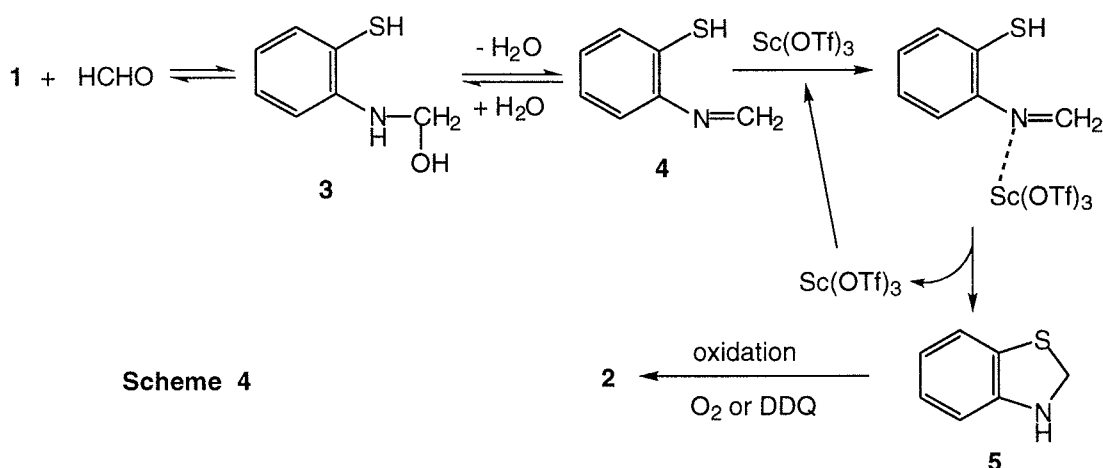
Entry	mol% of Sc(OTf) ₃	Reaction Time (h)	Yield (%) of 2
1	14	23	71
2	7	23	84
3	2.5	23	86
4	1.5	23	89
5	1	23	83
6	0.7	23	77
7	0.14	42	86
8	0.07	42	92

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 formaldehyde¹³ 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.



Scheme 4

REFERENCES AND NOTES

- 1 This paper is dedicated to the Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.
- 2 "Lanthanides: Chemistry and Use in Organic Synthesis," ed. by S. Kobayashi, Springer, Berlin, 1999.
- 3 S. Kobayashi, "Organic Synthesis in Water," ed. by P. A. Grieco, Blackie Academic & Professional, London, 1998, pp 262-305.
- 4 a) J. H. Forsberg, V. T. Spaziano, T. M. Balasubramanian, G. K. Liu, S. A. Kinsley, C. A. Duckworth, J. J. Poteruca, P. S. Brown, and J. L. Millwe, *J. Org. Chem.*, **1987**, *52*, 1017. b) S. Matsubara, M. Yoshioka, and K. Utimoto, *Chem. Lett.*, **1994**, 827. c) M. Meguro, N. Asao, and Y. Yamamoto, *Tetrahedron Lett.*, **1994**, *35*, 7395.
- 5 Any current textbooks of heterocycles include the synthesis *via* this process; see, a) T. L. Gilchrist, "Heterocyclic Chemistry," 3rd ed. Longman, Harlow, 1997. b) J. A. Joule, K. Mills, and G. F. Smith, "Heterocyclic Chemistry," 3rd ed. Chapman & Hall, London, 1995.
- 6 Pioneering works of this field were presented recently in a review; see, S. Kobayashi and H. Ishitani, *Chem. Rev.*, **1999**, *99*, 1069.
- 7 There are few reports concerning the synthesis of parent benzothiazole from 2-aminobenzenethiol and formaldehyde (or its derivative). A paper showed that 2-aminobenzenethiol, ethyl orthoformate, and sulfuric acid were reacted without a solvent at 170-180°C to give **2** in 75-85%; G. L. Jenkins, A. M. Knevel, and C. S. Davis, *J. Org. Chem.*, **1961**, *26*, 274.
- 8 Even when 4 mmol of the substrate was used under the same conditions, the reaction proceeded smoothly. Thus, we think that the procedure is of practical use.
- 9 When 1 mol% of HCl was added to the mixture instead of Sc(OTf)₃, the yield of **2** was remained at 10% (in the absence of an acid: 12% (Table 1, Entry 1).
- 10 In this case, a spot other than **2** was observed on TLC, and the addition of DDQ changed the spot to that of **2**. Thus, it was suggested that benzothiazoline was remained unoxidized under Ar.
- 11 Though the formation of the imine (**4**) was confirmed by ¹H-NMR, signals derived from the addition product (**3**) were not observed.
- 12 In a previous paper, it was claimed that aromatization of benzothiazoline needs an oxidant such as ferric chloride; see, J. Metzger and H. Plank, *Chimie et Industrie*, **1956**, *75*, 929. In our reaction system, molecular oxygen is a sufficient oxidant for aromatization. Therefore, it cannot be denied completely that Sc(OTf)₃ participate in the process to accelerate the oxidation.
- 13 The use of benzaldehyde instead of HCHO under the same conditions afforded 2-phenylbenzothiazole in 99% yield. The application to other aldehyde will be presented in the near future.

Received, 30th July, 1999