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SYNTHESIS OF 2-ARYLBENZOTHIAZOLES FROM 2-AMINOBENZENETHIOL AND ARYL ALDEHYDES CATALYZED BY SCANDIUM TRIFLATE [1]

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Abstract –2-Aminobenzenethiol and an aryl aldehyde reacted to give a benzothiazoline *via* an imine intermediate, and the benzothiazoline was aromatized by oxygen or hydrogen peroxide to give a high yield of 2-arylbenzothiazole in the presence of a catalytic amount of scandium triflate $Sc(OTf)_3$. The intermediary benzothiazoline was isolated and allowed to react with O_2 or H_2O_2 in the presence of $Sc(OTf)_3$, and the Lewis acid was found to also catalyze the oxidative process other than the ring closing step.

There are many studies[2] using lanthanide and related rare earth metal triflates as Lewis acid catalysts because they have unique features which other Lewis acids do not possess. The most remarkable character is that they are active even in the presence of water[3] and/or amino group.[4] In the field of syntheses of heterocycles, there are a lot of dehydration reactions between a carbonyl group and an amino group to form an imine derivative, followed by an intramolecular attack of a nucleophile with the assistance of an acid to bring about a ring closure. Therefore, these Lewis acids are thought to be appropriate catalysts for the synthesis of heterocyclic systems, and there are several works which carried out these processes.[5]

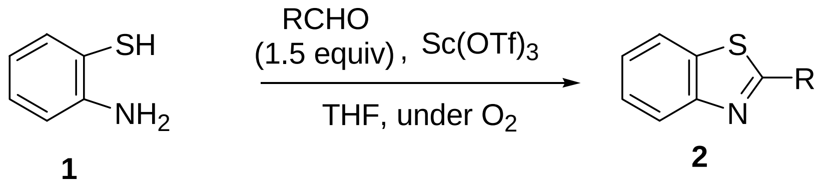
In addition, it was recently reported that scandium triflate activate hydrogen peroxide to accelerate the oxidation of thioethers to sulfoxides.[6] This result indicates that $Sc(OTf)_3$ can participate in the aromatization process of the synthesis of heteroaromatics.

In a previous paper,[7] we reported that 2-aminobenzenethiol reacted with formaldehyde in the presence of $Sc(OTf)_3$ to give benzothiazole in a good yield. Although the reaction completed slowly under O_2 atmosphere or quickly in the presence of dichlorodicyanoquinone (DDQ), it was not clarified whether $Sc(OTf)_3$ participated in the oxidation step.

In order to develop a new synthetic method for azaaromatics, and clarify the role of $Sc(OTf)_3$ on oxidation reaction, we have investigated the reaction of 2-aminobenzenethiol with aryl aldehydes in the presence of $Sc(OTf)_3$, and found that the corresponding 2-arylbenzothiazoles were obtained in good yields. Moreover, the reactivity of intermediary benzothiazoline was investigated, and it was revealed that the compound was oxidized by molecular oxygen or hydrogen peroxide only in the presence of Sc(OTf)$_3$. This paper describes these results.

Since 2-substituted benzothiazole derivatives are of industrial or biological interest,[8] methods for preparation of these compounds have been extensively studied.[9] Although the direct condensation of 2-aminobenzenethiol with an appropriate carboxylic acid provides the most direct route to the 2-substituted benzothiazoles, this process usually requires vigorous reaction conditions.[10] And, there is an only study that adopted 2-aminobenzenethiol and an aldehyde as starting material for 2-substituted benzothiazole in DMSO solvent.[11] Although DMSO must act as an oxidant in the reaction, the scope and the mechanism remain unclear.

In our reaction system, 2-aminobenzenethiol and an aldehyde were allowed to react at room temperature in the presence of a catalytic amount of Sc(OTf)$_3$ to give a corresponding benzothiazole in an excellent yield (Scheme 1 and Table 1).



Scheme 1

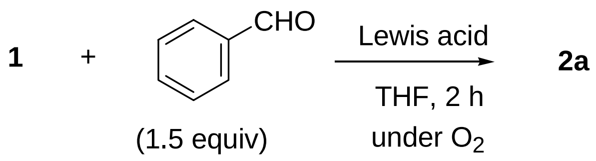
Table 1 The Reaction of 2-Aminobenzenethiol with Aryl Aldehyde in the Presence of Scandium Triflate

entry	R	product	Sc(OTf)$_3$ (mol%)	time (h)	yield of **2** (%)
1	Ph	**2a**	2	2	98
2	Ph	**2a**	0	2	9[a)]
3	*p*-Me-C_6H_4	**2b**	2	2	99
4	*p*-Cl-C_6H_4	**2c**	2	2	99
5	2-naphthyl	**2d**	2	3	97
6	*p*-MeO-C_6H_4	**2e**	2	2	97

a) By ^{1}H-NMR spectroscopy, formation of the corresponding imine was observed (y. 75%). The corresponding 2-arylbenzothiazoline was not identified in this reaction.

In the typical procedure, 2-aminobenzenethiol (0.2 mmol) was dissolved in THF (2 mL), and O_2 was introduced to the reaction vessel. Then benzaldehyde (0.3 mmol) and Sc(OTf)$_3$ (0.004 mmol) were added, and the mixture was allowed to react at room temperature for 2 h. Thereafter, ethyl acetate (12 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 2-phenylbenzothiazole. In the absence of Sc(OTf)$_3$, the reaction stopped at the step of the corresponding imine formation (Table 1, entry 2). Thus, it was suggested that Sc(OTf)$_3$ plays a catalytic role in the cyclization process which afford 2-arylbenzothiazoline.

Next, the reaction was carried out using other Lewis acids than $Sc(OTf)_3$, and the results are summarized in Scheme 2 and Table 2. Thus, it was found that $Sc(OTf)_3$ is a superior to the other metal triflate.

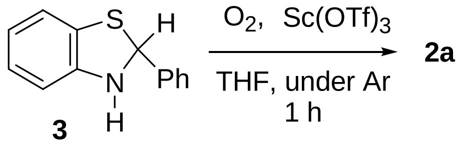


Scheme 2

Table 2 The Effect of Lewis Acid on the Reaction of **1** and Benzaldehyde

entry	catalyst	yield of **2a** (%)
1	$Sc(OTf)_3$	95
2	$Yb(OTf)_3$	89
3	$Sn(OTf)_2$	84
4	$Cu(OTf)_2$	13

In the reaction, the signals of a 2-arylbenzothiazoline as an intermediate was always observed by ^{1}H-NMR spectrum when shortening the reaction time. Thus, in order to clarify the step which $Sc(OTf)_3$ catalyzes, 2-phenylbenzothiazoline (**3**) was synthesized according to the reported method,[12] and used as a substrate. The isolated compound (**3**) was allowed to react with O_2 in the presence or absence of $Sc(OTf)_3$, and Table 3 presents the results (Scheme 3).

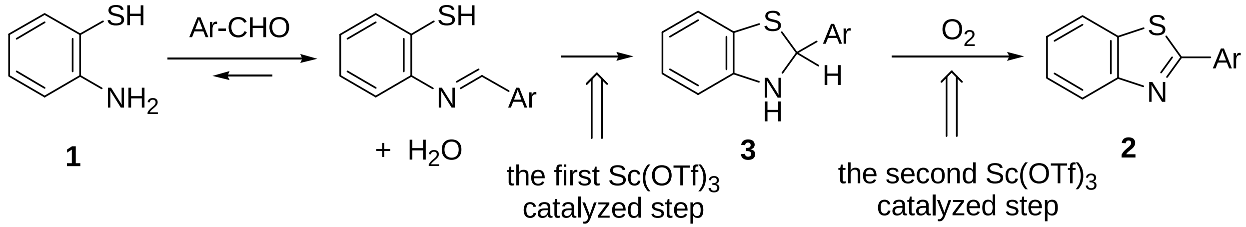


Scheme 3

Table 3 Oxidation of 2-Phenylbenzothiazoline with O_2 in the Presence of Scandium Triflate

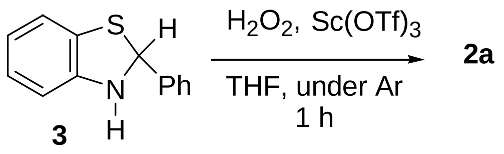
entry	$Sc(OTf)_3$ (mol %)	O_2 (equiv)	yield of **2a** (%)
1	0	excess	9
2	1	excess	48
3	2	excess	95
4	2	0	6
5	2	0.1	14

In the absence of $Sc(OTf)_3$ or oxygen, the reaction seldom proceeded (Table 3, entries 1 and 4). In addition, the limited amount of oxygen afforded only corresponding amount of **2a** (entry 5). These results shown in Table 1 and Table 3 suggest that $Sc(OTf)_3$ catalyzed both the cyclization step and the oxidation step which employs molecular oxygen as an oxidant (Scheme 4).



Scheme 4

To the best of our knowledge, there are no reports which claim that $Sc(OTf)_3$ catalyzes oxidation with molecular oxygen, and in the oxidation process of dihydroaromatics with O_2, hydrogen peroxide should be formed[13] accompanied with the reaction progress. Thus, the reaction using H_2O_2 was carried out under the same conditions as above (Scheme 5 and Table 4).



Scheme 5

Table 4 Oxidation of 2-Phenylbenzothiazoline with H_2O_2 in the Presence of Scandium Triflate

entry	$Sc(OTf)_3$ (mol %)	H_2O_2 (equiv)	yield of **2a** (%)
1	2	0	6
2	0	1.0	18
3	2	1.0	99
4	2	0.1	21

The oxidation of **3** seldom occurred when $Sc(OTf)_3$ was absent (entry 2), and quantitative formation of **2a** was observed by the use of equimolar H_2O_2 and a catalytic amount of $Sc(OTf)_3$ (entry 3). Thus, according to the data shown in Tables 3 and 4, we cannot definitely conclude which molecule (O_2 or H_2O_2) is activated by $Sc(OTf)_3$.[14]

In this communication, we described that the reaction of 2-aminobenzenethiol with an aryl aldehyde was accelerated by $Sc(OTf)_3$ to give a ring closing product, and succeeding aromatization was also carried out by participation of $Sc(OTf)_3$ as a catalyst to give **2** in a good yield. This type of ring closing-oxidation reaction is a ubiquitous process for the synthesis of heterocycles, and there are very few reports that used the rare earth metal triflates as a catalyst of oxidation reactions.[6,15] Thus the present reaction system is thought to be a new, general synthetic method for various heteroaromatics. The detailed reaction mechanism and application to synthesis of other heterocycles is now under investigation.

REFERENCES AND NOTES

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13. 2-Phenylbenzothiazoline is oxidized with O_2 slowly in the absence of the catalyst, and H_2O_2 must be formed in equimolar amount to that of benzothiazole.

14. We speculate that the activation of O_2 might occur because the reaction using O_2 was slightly faster than that of H_2O_2. According to the fact, it seems to be improbable that H_2O_2 is a true active species in the reaction of O_2.

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