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SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLES BY REACTION OF *o*-PHENYLENEDIAMINE WITH ALDEHYDES IN THE PRESENCE OF $Sc(OTf)_3$[1]

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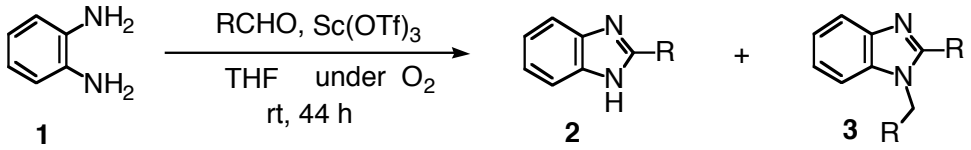
Abstract – 2-Substituted benzimidazoles were synthesised under mild conditions by reaction of *o*-phenylenediamine with aldehydes in the presence of $Sc(OTf)_3$ as a Lewis acid catalyst.

Benzimidazole nucleus has recently received interest in the field of medicinal chemistry,[2]and some solid-phase syntheses have been applied to their synthesis.[3] A conventional method for the synthesis of benzimidazoles is the reaction of *o*-phenylenediamine with carboxylic acids or their derivatives under harsh conditions.[4] In recent literatures, some methods using transition metal catalyzed coupling reactions to construct benzimidazole nucleus were reported. Those involved palladium-catalyzed carbonylation reaction of an *o*-phenylenediamine followed by cyclodehydration,[5] palladium-catalyzed intramolecular *N*-arylation reaction of (*o*-bromophenyl)amidines,[6] and rhodium-catalyzed hydroformylation of *N*-alkenyl-*o*- phenylenediamines.[7] In the course of our studies on the synthesis of heteroaromatics using $Sc(OTf)_3$, which acts as a Lewis acid catalyst even in the presence of water, we found that the reaction of 2-aminobenzenethiol with aqueous HCHO gives benzothiazole in a high yield.[8] In the reaction, initial formation of an imine followed by intramolecular nucleophilic attack of the sulfanyl group afforded benzothiazoline which was then oxidized to give benzothiazole. Thus, we applied this type of reaction to the synthesis of benzimidazoles by use of *o*-phenylenediamine instead of 2-aminobenzenethiol, and found a new method for the synthesis of 2-substituted benzimidazoles. We describe these results in this paper.

When *o*-phenylenediamine was allowed to react with 37% aqueous solution of HCHO in the presence of $Sc(OTf)_3$ (1 mol%), benzimidazole was obtained in 24% yield and 1-methylbenzimidazole was also produced in 27% yield. The latter compound was produced when both of two amino groups of *o*-phenylenediamine and HCHO reacted before imidazoline ring was formed. The reaction using benzaldehyde, however, exclusively gave 2-phenylbenzimidazole in 97% yield. Therefore, we investigated the scope of the synthesis of 2-substituted benzimidazloes from *o*-phenylenediamine and



1 2 3

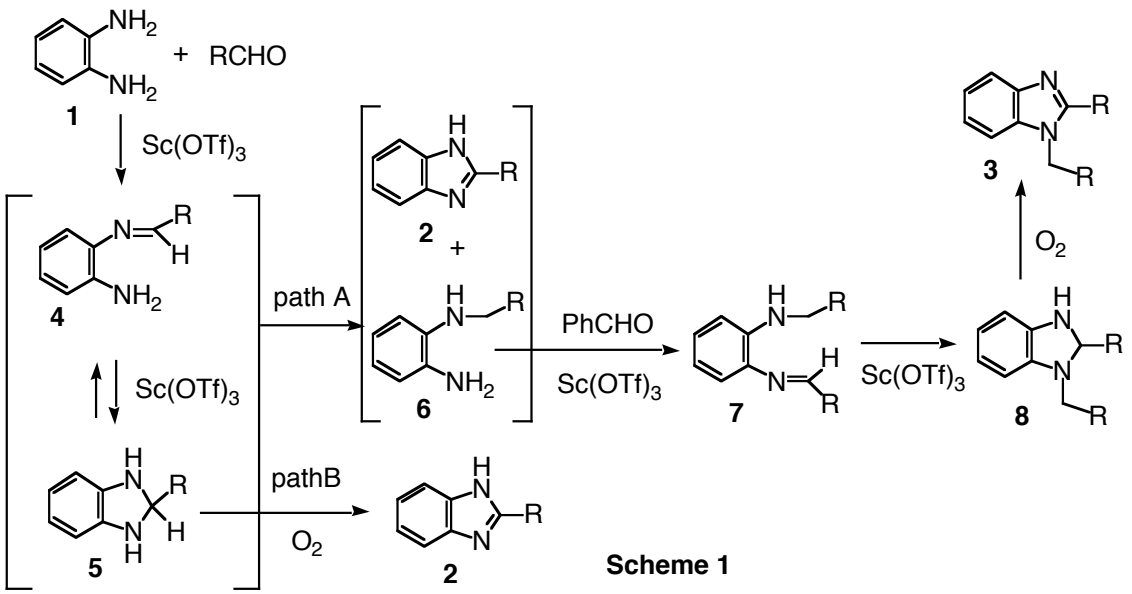
Table 1 Reaction of *o*-Phenylenediamine with Aldehydes in the Presence $Sc(OTf)_3$ under Oxygen Atmosphere

entry	R	concentration of **1** (M)	$Sc(OTf)_3$ (mol%.)	aldehyde (equiv)	yield of **2** (%)	yield of **3** (%)
1	Ph	0.35	1.0	1.0	97	1
2	*p*-ClPh	0.35	1.0	1.0	37	6
3	1-naphthyl	0.35	1.0	1.0	43	9
4	*p*-MePh	0.35	1.0	1.0	37	19
5	*p*-ClPh	0.01	10	1.5	63	35
6	1-naphthyl	0.01	10	1.5	53	31
7	*p*-MePh	0.01	10	1.5	55	35
8	*p*-ClPh	0.002	10	1.5	95	3
9	1-naphthy	0.002	10	1.5	82	12
10	*p*-MePh	0.002	10	1.5	72	23
11[a)]	Me	0.002	10	1.5	52	42
12[b)]	Me_3C	0.002	10	1.5	98	0

a) The reaction was completed over 3 h. b) The reaction was completed over 20 h.

some aldehydes, and the results are shown in Table 1. In the procedure of entry 1, *o*-phenylenediamine (0.52 mmol) was dissolved in THF (1.5 mL), and $Sc(OTf)_3$ (3 mg, 1 mol%) was added under O_2 atmosphere. After benzaldehyde (0.54 mmol) was added dropwise, the reaction mixture was allowed to stir for 44 h at room temperature. When other aromatic aldehydes were employed under the same conditions as those of entry 1, yields of corresponding 2-arylbenzimidazoles(**2**) were low due to the formation of *N*-arylmethyl-*o*-phenylenediamine(**6**) which is a precurser of *N*-alkylated 2-arylbenzimidazole(**3**). After several examinations of conditions, it was revealed that the use of 1.5 equivalent of aldehyde increased the total yield and that the reaction under low concentration resulted in the dominant formation of **2** over **3**. Thus, 2-arylbenzimidazoles were obtained in good yields by carrying out the reaction in dilute solution (entries 8-10). In the reaction with aliphatic aldehydes, bulky pivalaldehyde afforded corresponding benzimidazole in a high yield. It was found, however, that acetaldehyde afforded considerable amount of *N*-ethyl-2-methylbenzimidazole other than 2-methylbenzimidazole.

A plausible reaction mechanism is shown in Scheme 1. The reaction of *o*-phenylenediamine with aldehyde initially affords the imine (**4**). The imine is considered to disproportionate to give benzimidazole (**2**) and *N*-alkyl-*o*-phenylenediamine (**6**), because **2** and **6** co-existed when



Scheme 1

o-phenylenediamine and benzaldehyde were mixed in THF. In that disproportioation reaction, imidazoline (**5**) which is formed by cyclization of **4** acts as a reducing agent to afford **6** from **4**. Therefore, when the reaction is run under O_2 atmosphere, another route to **2** should be appeared parallel to path A, that is, the one that includes an oxidation step of the imidazoline (**5**) by oxygen (path B in Scheme 1). And *N*-alkylated benzimidazole (**3**) seems to be produced through the reaction of **6** with an aldehyde followed by ring closing reaction and oxidation. The disproportionation reaction in path A would be retarded when the reaction is run in a dilute solution, and oxidation reaction of imidazoline (**5**) by oxygen would occur preferentially to give 2-substituted benzimidazole (**2**) in a good yield. When *o*-phenylenediamine and benzaldehyde were reacted under O_2 atmosphere in the absence of $Sc(OTf)_3$ for 44 h, imine (**4**) and 2-phenylbenzimidazole were obtained in 52% and 12% yields, respectively. Thus, it was revealed that $Sc(OTf)_3$ accelerates both the ring closing step from **4** and oxidation step of imidazoline (**5**) by oxygen. Though it has not been reported that $Sc(OTf)_3$ catalyzes the oxidation reaction by molecular oxygen, $Sc(OTf)_3$ is likely to catalyze the oxidation by O_2 to give desired product dominantly in the present reaction. It has been reported that *o*-phenylenediamine and benzaldehyde react to give *N*-benzal-*o*-phenylenediamine which affords **8** (R=Ph) and **3** (R=Ph) other than 2-phenylbenzimidazole through the path A after several days.[9] Thus, we succeeded to obtain 2-substituted benzimidazoles in good yields by changing the reaction path by use of $Sc(OTf)_3$ as a cayalyst.

In this communication we described a new method for the synthesis of 2-substituted benzimidazoles(**2**) by the reaction of *o*-phenylenediamine with aldehydes in the presence of $Sc(OTf)_3$. The reaction is simple and can be carried out under mild conditions compared with the methods that has been reported so far. Application of this type of reaction to the synthesis of other azoles is now in progress.

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