# Application of *N*,*N*′-Diiodo-*N*,*N*′-1,2-ethandiylbis(*p*-toluene sulfonamide) as a New Reagent for Synthesis of 2-Arylbenzimidazoles and 2-Arylbenzothiazoles under Solvent-free Conditions

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*N*,*N*′-Diiodo-*N*,*N*′-1,2-ethandiylbis(*p*-toluene sulfonamide) (NIBTS) is a good and new reagent for synthesis of 2-arylbenzimidazoles and 2-arylbenzothiazoles at room temperature under solvent-free condition with good to high yield. Absence of solvent, short reaction times, non-corrosive, operational simplicity and environmentally friendliness are the main advantages of this procedure.

**Keywords** 2-arylbenzimidazoles, 2-arylbenzothiazoles, NIBTS, solvent-free

## Introduction

Benzimidazoles and benzothiazoles are very useful building blocks for the development of molecules that are important in medicinal chemistry.[1] Consequently, the synthesis of the heterocyclic nucleus contained in such compounds has gained importance. Substituted benzimidazole and benzothiazoles derivatives have been found to be used as diverse therapeutic agents, including antiulcers, antihypertensives, antivirals, antifungals, anticancers and antihistaminics.[5-7] These bicyclic compounds consist of the fusion of benzene and imidazole. The most prominent benzimidazole compound in nature is *N*-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin $B_{12}$.[2]

Benzimidazoles, in an extension of the well-elaborated imidazole system, have been used as carbon skeletons for *N*-heterocyclic carbenes. The *N*-heterocyclic carbenes are usually used as ligands for transition metal complexes. They are often prepared by deprotonating an *N*,*N*′-disubstituted benzimidazolium salt at the 2-position with a base.[3,4] Because of their importance, the synthesis of substituted benzimidazoles has gotten a focus of synthetic organic chemistry. Various oxidative reagents such as DDQ,[8] $MnO_2$,[9] $Pb(OAc)_4$,[10] Oxone,[11] IBD,[12] $Yb(OTf)_3$,[13] $H_2O_2$/HCl,[14] silica sulfuric acid[15] and oxalic acid[16] have been use to effect this transformation.

However, a number of these methods have some drawbacks such as low yields, the use of expensive reagents and/or chlorinated organic solvents and harsh reaction conditions.

## Experimental

### Materials

All commercially available chemicals were obtained from Merck and Fluka companies, and used without further purifications unless otherwise stated. Nuclear magnetic resonance (NMR) spectra were recorded on a Jeol 90 MHz FT NMR spectrometer. Infrared (IR) was conducted on a Perkin Elmer GX FT-IR spectrometer. All yields refer to isolated products.

### General procedure for the synthesis of 2-arylbenzimidazoles with NIBTS

A mixture of *o*-phenylenediamine (1 mmol) and aryl aldehyde (1.1 mmol) was well stirred with *N*,*N*′-diiodo-*N*,*N*′-1,2-ethandiylbis(*p*-toluene sulfonamide) (0.5 mmol) at room temperature for a period time specified in Table 1. The reaction was monitored by TLC [3∶1 *V*(*n*-hexane)/*V*(acetone)]. After completion of the reaction, $CH_2Cl_2$ (5 mL) was added, and the sulphonamide was removed by filtration. Evaporation of the solvent under reduced pressure gives the product. Further purification was achieved by preparative thin-layer chromatography using *n*-hexane/acetone (*V*∶*V*=7∶3) as the eluent system to afford the benzimidazoles.

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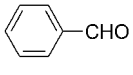
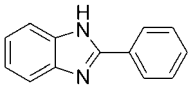
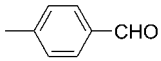
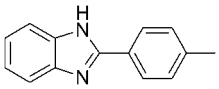
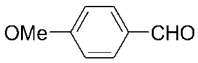
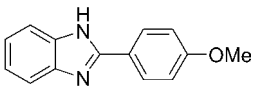
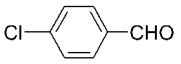
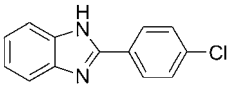
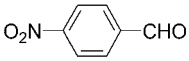
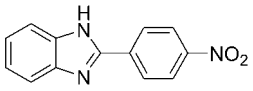
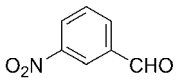
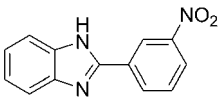
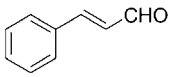
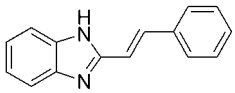
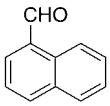
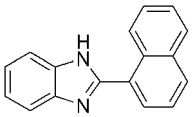
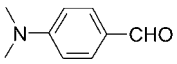
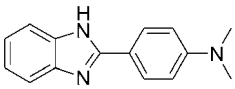
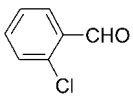
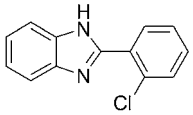
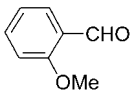
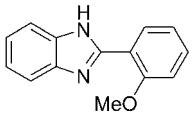
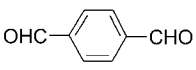
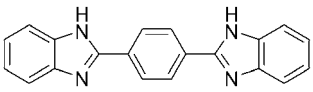
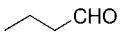
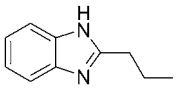
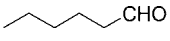
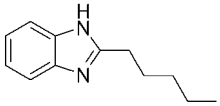
**Table 1** Reaction of aryl aldehydes with *o*-phenylenediamine

| Entry | Substrate | Product[a] | Time/min | Yield[b]/% |
|---|---|---|---|---|
| 1 |  |  | 20 | 96 |
| 2 |  |  | 25 | 90 |
| 3 |  |  | 20 | 92 |
| 4 |  |  | 30 | 90 |
| 5 |  |  | 80 | 82 |
| 6 |  |  | 65 | 85 |
| 7 |  |  | 45 | 75 |
| 8 |  |  | 35 | 90 |
| 9 |  |  | 60 | 85 |
| 10 |  |  | 25 | 92 |
| 11 |  |  | 20 | 96 |
| 12 |  |  | 45 | 90 |
| 13 |  |  | 120 | 70 |
| 14 |  |  | 145 | 75 |

[a] The products were characterized by comparison of their spectroscopic and physical data with those of samples synthesized by reported procedures. [b] Yield refer to pure isolated products.

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### General procedure for the synthesis of 2-arylbenzothiazoles with NIBTS

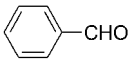
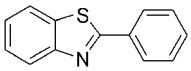
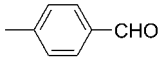
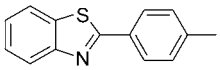
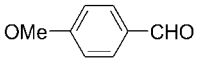
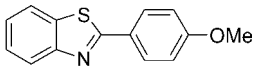
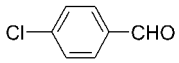
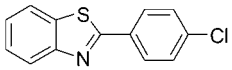
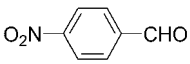
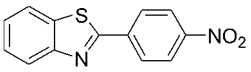
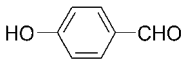
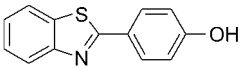
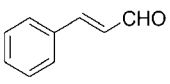
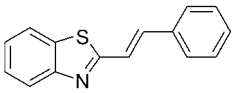
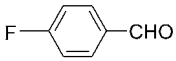
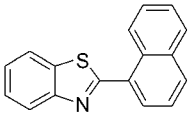
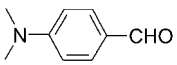
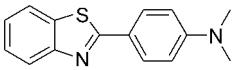
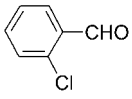
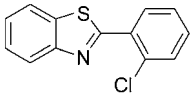
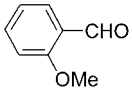
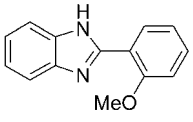
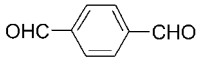
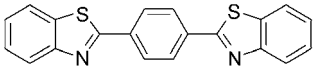
A mixture of 2-aminothiophenol (1.1 mmol) and aryl aldehyde (1 mmol) was well stirred with *N*,*N*′-diiodo-*N*,*N*′-1,2-ethandiylbis(*p*-toluene sulfonamide) (0.5 mmol) at 40 ℃ for a period time specified in Table 2. The reaction was monitored by TLC [3∶1 *V*(*n*-hexane)/*V*(acetone)]. After completion of the reaction, $CH_2Cl_2$ (5 mL) was added, and the sulphonamides was removed by filtration. Evaporation of the solvent under reduced pressure gives the product. Further purification was achieved by preparative thin-layer chromatography using *n*-hexane/acetone (*V*∶*V*=7∶3) as the eluent system to afford the benzothiazoles.

### Spectra data for selected products

**2-(2-Chlorophenyl)-1*H*-benzimidazole (Table 1, Entry 10)** m.p. 232—233 ℃; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$: 7.26—7.32 (m, 2H), 7.56—7.73 (m, 5H), 7.93—7.96 (m, 1H), 12.78 (br, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$: 112.1, 119.4, 122.1, 123.1, 127.8, 130.3, 130.7, 131.6, 132.4, 149.4; IR (KBr) $\nu$: 3442, 1620 cm$^{-1}$; MS (eV) *m*/*z*: 228 [M$^+$]. Anal. calcd for $C_{13}H_9ClN_2$: C 68.28, H 3.97, N 12.25; found C 67.95, H 3.80, N 12.13.

**2-(4-Methoxyphenyl)-1*H*-benzimidazole (Table 1, Entry 3)** m.p. 225—227 ℃; $^1$H NMR (DMSO-$d_6$, 90 MHz) $\delta$: 12.72 (s, 1H), 7.14—8.11 (m, 8H), 3.75 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$: 56.3, 115.6, 119.1,

**Table 2** Reaction of aryl aldehydes with 2-aminothiophenol

| Entry | Substrate | Product[a] | Time/h | Yield[b]/% |
|---|---|---|---|---|
| 1 |  |  | 1.5 | 90 |
| 2 |  |  | 2 | 90 |
| 3 |  |  | 1 | 96 |
| 4 |  |  | 1 | 98 |
| 5 |  |  | 3 | 80 |
| 6 |  |  | 2 | 85 |
| 7 |  |  | 1.7 | 82 |
| 8 |  |  | 1.2 | 92 |
| 9 |  |  | 3.5 | 70 |
| 10 |  |  | 1.1 | 96 |
| 11 |  |  | 1 | 95 |
| 12 |  |  | 1 | 92 |

[a] The products were characterized by comparison of their spectroscopic and physical data with those of samples synthesized by reported procedures. [b] Yield refer to pure isolated products.

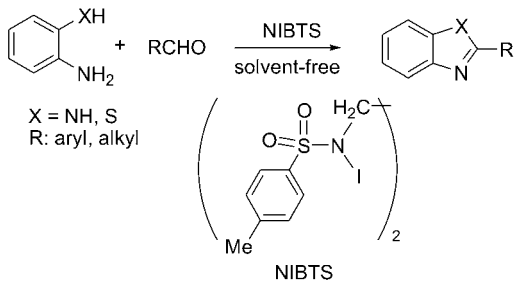
121.9, 122.6, 126.7, 127.8, 129.8, 135.3, 139.9, 144.1, 151.7; IR (KBr) $\nu$: 3447, 1624 $cm^{-1}$; MS (eV) *m*/*z*: 193 [$M^+$]. Anal. calcd for $C_{13}H_9N_2$: C 80.81, H 4.69, N 14.59; found C 80.64, H 4.42, N 14.25.

**2-(4-Methylphenyl)benzothiazole (Table 2, Entry 2)** m.p. 86—88 ℃; $^1$H NMR (DMSO-$d_6$, 90 MHz) $\delta$: 7.25—8.09 (m, 8H), 2.56 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz) $\delta$: 22.2, 123.0, 124.5, 125.5, 127.4, 128.4, 130.8, 132.1, 135.9, 150.2, 1555.2, 169.2; IR (KBr) $\nu$: 3050, 1635 $cm^{-1}$; MS (eV) *m*/*z*: 225 [$M^+$]. Anal. calcd for $C_{14}H_{11}NS$: C 74.63, H 4.92, N 6.22; found C 74.24, H 5.06, N 5.95.

## Results and discussion

In continuation of our interest in the application of *N*,*N*′-diiodo-*N*,*N*′-1,2-ethandiylbis(*p*-toluene sulfonamide) (NIBTS)[17] in organic synthesis,[17-19] we report a new and efficient method for the one step synthesis of 2-substituted benzimidazoles by the condensation of *o*-phenylenediamine with arylaldehydes using NIBTS as an efficient reagent and oxidant at room temperature (Scheme 1).

**Scheme 1**




The reaction was carried out in neat at room temperature for 20 min, using aldehyde (1.1 mmol) and *o*-phenylenediamine (1mmol) in the presence of NIBTS (0.5 mmol) in 96% yield (Table 1, Entry 1). In the same manner, a variety of aldehydes were coupled with *o*-phenylenediamine in the presence of *N*,*N*′-diiodo-*N*,*N*′-1,2-ethandiylbis(*p*-toluene sulfonamide) (NIBTS) as an efficient reagent and oxidant at room temperature to give the corresponding 2-substituted benzimidazoles in good to excellent yields (Table 1). We also observed that the reaction in DCM, methanol, ethanol, acetonitrile, or THF takes longer times than in the neat conditions. This acceleration is probably attributable to the concentration effect.

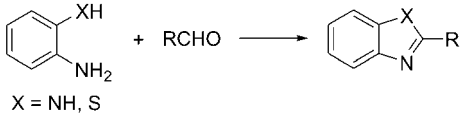
As shown in Table 1, both electron-rich and electron-deficient aldehydes react without any significant difference to give the corresponding benzimidazoles in good yield (Table 1, Entries 1—12).

We have also developed this synthetic method for the preparation of 2-arylbenzothiazoles derivatives in a 1.1∶1∶0.5 molar ratio of 2-aminothiophenol to aldehyde and NIBTS at 40 ℃ for appropriate times under solvent-free conditions (Scheme 1).

After optimizing the conditions, the generality of this procedure was examined by the reaction of several substituted aryl aldehydes with 2-aminothiophenol. As shown in Table 2, a variety of substituted aromatic aldehydes, bearing either electron-donating or electron-withdrawing substituents, afforded the corresponding 2-arylbenzothiazoles in excellent yields. It was pleasing to observe the remarkable stability of a variety of functional groups such as ether, nitro, hydroxyl, halides and conjugated carbon-carbon double bond under the reaction conditions.

Nevertheless, this protocol has its limitations. Octanal, an aliphatic aldehyde, only provided 30% yield of the desired product.

**Table 3** Comparison of methods for the synthesis of 2-arylbenzimidazoles and 2-arylbenzothiazoles




| Entry | Ar | XH | Condition | Time | Yield/% |
|---|---|---|---|---|---|
| 1 | Ph | $NH_2$ | NIBTS, solvent-free, r.t. | 20 min | 96 |
| | | | DDQ, MeCN, r.t.[23] | 6 h | 90 |
| | | | $Me_2S^+Br^+Br^-$, MeCN, r.t.[24] | 5h | 85 |
| | | | PS-$PPh_3$, $CCl_3CN$, MeCN MW, 150 ℃[25] | 15 min | 79 |
| 2 | 4-$MeC_6H_4$ | $NH_2$ | NIBTS, solvent-free, r.t. | 25 min | 90 |
| | | | Pyridine, $SOCl_2$, $CH_2Cl_2$, 0—20 ℃[26] | 18 h | 80 |
| | | | $I_2$, KI, $K_2CO_3$, $H_2O$, $PhNO_2$, $SiO_2$, 90 ℃[27] | 45 min | 75 |
| | | | MW, 110 ℃[28] | 10 min | 84 |
| 3 | Ph | SH | NIBTS, solvent-free, r.t. | 1.5 h | 90 |
| | | | $H_3PO_4$, solvent-free, 250 ℃[30] | 4 h | 90 |
| | 4-$MeOC_6H_4$ | SH | NIBTS, solvent-free, r.t. | 1 h | 96 |
| | | | $PhNO_2$, $SiO_2$, MW[31] | 8 min | 61 |
| | | | $MnO_2$, $SiO_2$, MW, 110 ℃[29] | 4 min | 91 |

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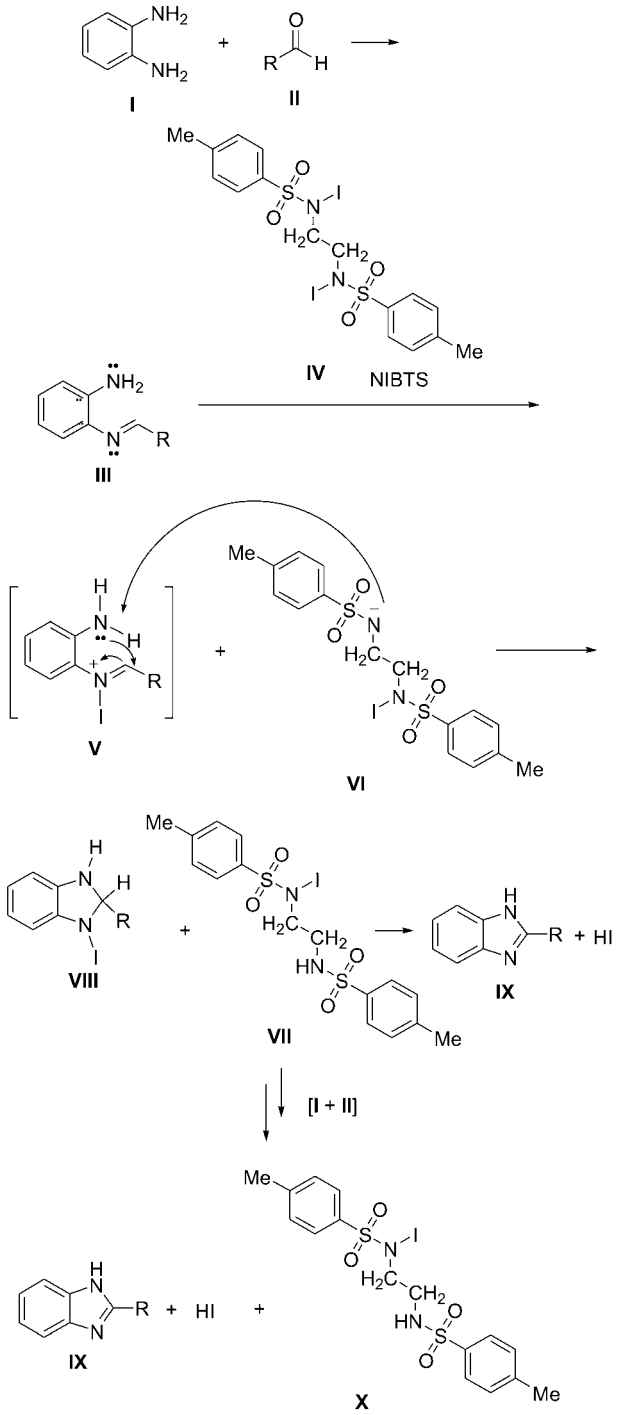
A comparison of the efficiency of this method with selected previous methods is collected in Table 3. The results show that this method is superior to some previously reported methods in terms of yields and reaction times.

Since NIBTS contain iodine atoms which are attached to nitrogen atoms, it is very possible that they release $I^+$ *in situ* which can act as catalyst and oxidant in the reaction medium. Therefore, the mechanism shown in Scheme 2 can be suggested for the formation of benzimidazoles.[12,14]

**Scheme 2**




After the reaction of NIBTS with [**I**+**II**], the sulphonamide is recovered and can be reused many times without decreasing yield.

In conclusion, NIBTS was found to be mild and effective new reagent for the convenient synthesis of 2-arylbenzimidazoles and 2-arylbenzothiazoles in excellent yields from 1,2-phenylenediamine and 2-aminothiophenol and a wide variety of aryl aldehydes under solvent-free conditions. Moreover, the method has advantages in terms of product yields, absence of solvent, short reaction times, non-corrosive, operational simplicity, operational simplicity (easy work up of reactions).

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