The Convenient Synthesis of Benzimidazole Derivatives Catalyzed by I_2 in Aqueous Media

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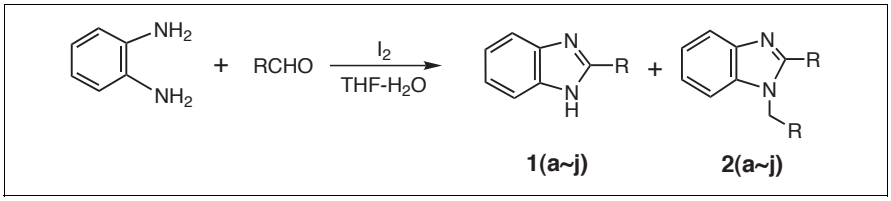

In the presence of catalytic amount of iodine, in THF–H_2O, the condensation of aldehydes with 1,2-phenylenediamine gave the benzimidazole derivatives under mild conditions in good yields. The method can be used for the synthesis of 2-substituted benzimidazoles or 1,2-disubstituted benzimidazoles.

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Benzimidazole Derivatives have received much interest in the field of medicinal chemistry [1]. For example, they have been shown to exhibit fungicide, antitumour, immunosuppressant and anti-convulsant properties [2]. Recently, they have also been used as ligands for asymmetric catalysis [3]. Many methods have been reported for the synthesis of these heterocycles. The condensation of 1,2-phenylenediamines with carboxylic acids or their derivatives is a common method, but it needs harsh conditions, for example, in the presence of polyphosphoric acid at 170–180°C [4]. Some methods using transition metal catalyzed coupling reactions to construct benzimidazole nucleus were also reported. Those involved palladium-catalyzed carbonylation reaction of an 1,2-phenylenediamine followed by cyclodehydration [5], palladium-catalyzed intramolecular *N*-arylation reaction of (*o*-bromophenyl)amidines [6], *et al*. In recent years, some solid-phase synthetic methods have been applied to the synthesis of benzimidazole derivatives [7]. Another alternative approache is the condensation of aldehyde with 1,2-phenylenediamine [8]. Recently, the condensations in the presence of triflate salts such as $Sc(OTf)_3$ or $Yb(OTf)_3$ were reported [9]. A method from activated alcohols and 1,2-phenylenediamine using TOP methodology was also described [10]. In these procedures, the oxidation using O_2 or MnO_2 as an oxidant was needed for the aromatization of the intermediate dihydrobenzimidazoles. The SET reaction of 2-nitroaniline with benzaldehyde in the presence of In/BNP, as well as the reductive cyclization of 2-nitroaniline with aldehydes in the presence of $Na_2S_2O_4$ were also used for the synthesis of benzimidazole derivatives [11]. However, many of these methods have several drawbacks. For example, expansive reagent was used, a special oxidation process and a long reaction time were required. In some case, 2-substituted and 1,2-disubstituted benzimidazoles were generated simultaneously with poor selectivity.

Our research interest focuses on the Lewis acids catalyzed organic reactions in recent years. As an inexpensive and easily available catalyst for various organic transformations, iodine has received considerable attention [12]. We found that in the presence of catalytic amount of iodine, the condensation of aldehydes with 1,2-phenylenediamine gave the benzimidazole derivatives under mild conditions.

The realization of simple and green synthetic procedures constitutes an important goal in organic synthesis. To make organic reactions in water or in aqueous media has gained in popularity in recent years. It was found that the I_2 catalyzed condensation of aldehydes with 1,2-phenylenediamine could take place in aqueous media in air to give 2-substituted benzimidazole (**1**) and *N*-alkylated 2-substituted benzimidazole (**2**). In pure water, as the poor solubility of the reactants and catalyst, the reaction proceeded slowly. But in THF-H_2O (1:1, v/v), it could complete within a short time at room

Scheme 1

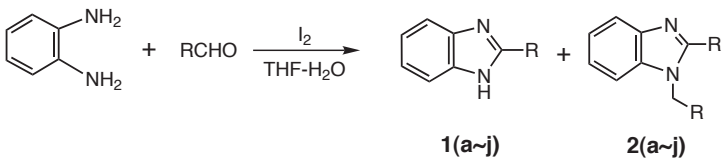

Table 1
The Formations of Benzimidazole Derivatives

Entry	Aldehyde	Time (h)	Yield of **1** (%) [a]	Yield of **2** (%) [a]
1	PhCHO	2.0	72 **1a** [13] [c]	20 / 88 [b] **2a** [13]
2	*p*-ClC_6H_4CHO	2.0	78 **1b** [13]	12 / 82 [b] **2b** [13]
3	*p*-BrC_6H_4CHO	2.5	75 **1c** [13]	10 / 85 [b] **2c** [13]
4	*p*-FC_6H_4CHO	1.5	70 **1d** [13]	25 / 90 [b] **2d** [13]
5	*o*-$NO_2C_6H_4CHO$	2.5	67 **1e** [14]	15 **2e** [15]
6	*o*-ClC_6H_4CHO	1.5	70 **1f** [11a]	22 **2f** [11a]
7	*p*-$CH_3OC_6H_4CHO$	3.0	56 **1g** [13]	25 **2g** [13]
8	Furfural	2.0	75 **1h** [11a]	16 / 86 [b] **2h** [11a]
9	CH_3CH_2CHO	2.5	Trace **1i** [16]	67 / 76 [b] **2i** [17]
10	$(CH_3)_2CHCHO$	2.5	58 **1j** [18]	Trace **2j**

[a] Isolated yields; [b] 2 Equivalent of aldehyde reacted with 1,2-phenylenediamine for 3 h; [c] Literature reference for the product. All products are known compounds. The structures of the products are confirmed by IR and ^{1}HNMR spectra.

temperature. It showed that I_2 exhibited a powerful catalytic activity in an amount as low as 2 mol%, which was enough to complete the reaction within less than 3 hours for all of the substrates we used. Without I_2, to the reaction of 1,2-phenylenediamine and benzaldehyde, only trace of the product was generated even refluxing for 24 hours. The reaction was found to be general and applicable to both aromatic and aliphatic aldehydes. The aromatic aldehydes bearing electron-donating and electron-withdrawing substituents gave the similar results. The results of the reaction are summarized in Table 1. When the mole ratio of 1,2-phenylenediamine to aldehyde was 1:1, both 2-substituted benzimidazole (**1**) and *N*-alkylated 2-substituted benzimidazole (**2**) were obtained, and 2-substituted benzimidazole (**1**) was the main product in the most case. It indicated that this iodine catalyzed reaction has a favorable selectivity for the synthesis of 2-substituted benzimidazoles. The latter compound (**2**) was thought to be produced when both of two amino groups of 1,2-phenylenediamine and aldehyde reacted before imidazoline ring was formed [9a]. But when 2 equivalent of aldehyde was used, almost only *N*-alkylated product **2** was obtained. The reaction gave the products (**1**) or (**2**) with moderate to good yields. Compared with the known methods for the synthesis of this type of compounds, it was a versatile and environmental friendly route.

In summary we have developed a new and efficient procedure for the condensation of aldehydes with 1,2-phenylenediamine catalyzed by I_2. The method offers several advantages like mild reaction conditions, short reaction time, high yields of products, and simple experimental operation, which leads to a useful and attractive process for the preparation of both 2-substituted benzimidazoles and *N*-alkylated 2-substituted benzimidazoles. The further application of this catalytic system in the synthesis of heterocyclic compounds is currently being explored in our laboratory.

EXPERIMENTAL

Melting points were determined on MP-3 digital melting point apparatus and were not corrected. ^{1}H NMR spectra were obtained on a Bruker-300 spectrometer using TMS as an internal reference. IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer. All reagents are commercially available and were used without further purification. All manipulations were conducted under air.

General Procedure for The Synthesis of Benzimidazole Derivatives.

Iodine (0.02 mmol) was dissolved in 4 mL THF–H_2O (1:1, v/v). To this solution was added 1,2-phenylenediamine (1.0 mmol) and *p*-florobenzaldehyde (1.0 mmol). The resulting mixture was stirred at room temperature for 1.5 h (monitored by TLC) then extracted with CH_2Cl_2 and purified by column chromatography on silica gel with hexane/ethyl acetate (5:1) as eluent to yield the products 2-(4-florophenyl)benzimidazole (**1d**) and 1-(4-florophenylmethyl)-2-(4-florophenyl)benzimidazole (**2d**). **1d**: white solid; mp 247–248℃; ^{1}H-nmr ($CDCl_3$): δ 8.10 (m, 2H), 7.65 (m, 2H), 7.30 (m, 1H), 7.10 (m, 3H); IR (KBr): 3445, 3067, 2846, 1435, 1266 cm^{-1}. **2d**: white solid; mp 88–90℃; ^{1}H-nmr ($CDCl_3$): δ 8.15 (m, 1H), 7.88 (d, *J*=7.4 Hz, 1H), 7.65 (m, 2H), 7.30 (m, 3H), 7.15 (m, 2H), 7.07 (m, 3H), 5.43 (s, 2H); IR (KBr): 3045, 3067, 2934, 2846, 1435, 1096 cm^{-1}.

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