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SYNTHESIS OF 2-ARYLBENZIMIDAZOLES IN WATER

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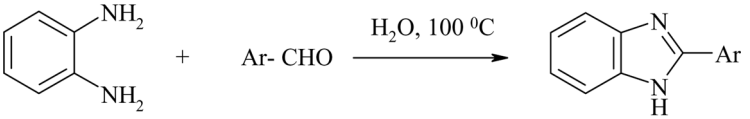
GRAPHICAL ABSTRACT



Ar = Aryl, heteroaryl

Abstract *A simple and efficient procedure for the synthesis of 2-arylbenzimidazoles through a one-pot condensation of* o*-phenylenediamines with aryl aldehydes in water is described. Short reaction time, large-scale synthesis, easy and quick isolation of the product, and excellent yield are the main advantages of this procedure.*

Keywords Benzimidazoles; excellent yields; green chemistry; *o*-phenylenediamine

INTRODUCTION

Benzimidazole is an important pharmacophore in modern drug discovery.[1] Benzimidazole derivatives exhibit significant activity against several viruses such as HIV,[2] herpes (HSV-1),[3] RNA,[4] influenza,[5] and human cytomegalovirus (HCMV).[2a] Bis-benzimidazoles are being developed as DNA minor-groove binding agents with antitumor activity[6] and can act as ligands to transition metals for modeling biological systems.[7] In addition, benzimidazoles are also important intermediates in organic synthesis, which is why benzimidazoles have gained considerable attention in recent years. Despite their importance, from pharmacological, industrial, and synthetic points of view, unfortunately very few methods have been reported for their preparation.

One such method involves coupling *o*-phenylenediamines and carboxylic acids or their derivatives (nitriles, imidates, or orthoesters) using strong acids such as polyphosphoric acid[8] or mineral acids[9] or high-temperature microwave irradiation.[10] Another method involves a two-step procedure involving oxidative cyclodehydrogenation of Schiff bases, which are often generated from the

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condensation of *o*-phenylenediamines and aldehydes. Various oxidative and catalytic reagents such as sulfamic acid,[11] I_2,[12] 2,3-dichloro-5,6-dicyanobenzoquinine (DDQ),[13] $In(OTf)_3$,[14] and $Sc(OTf)_3$[15] have been employed. Because of the availability of a vast number of aldehydes, condensation of *o*-phenylenediamines and aldehydes has been extensively used. Though these published methods are effective, they suffer from one or more disadvantages such as (a) poor yields, (b) use of expensive reagents, (c) multistage synthesis, (d) long reaction times, (e) tedious workup procedures, and (f) occurrence of several side reactions.

As a consequence, introduction of new methods and/or further work on technical improvements of procedures to overcome these limitations is still an important experimental challenge.

Legislation to maintain environmental friendliness requires us to prevent the generation of waste, avoid use of auxiliary substances (e.g., organic solvents, additional reagent), and minimize the energy requirement in the development of new procedures for the reaction.

Water is safe, nontoxic, environmentally friendly, and cheap. It has been employed as a solvent in the past for the formation of C–S,[16] C–N,[17] and C–C[18] bonds without using any catalyst. This inspired us to focus on the aspect of "on water" heterocycle synthesis. In this communication, we present a highly selective and efficient method for the synthesis of 2-arylbenzimidazole in water without using any catalyst.

RESULTS AND DISCUSSION

We report herein an efficient synthesis of 2-arylbenzimidazoles in water in the absence of any acid or base catalyst. The reaction of aryl aldehydes with *o*-phenylenediamine afforded benzimidazoles in excellent yields (Table 1).

The effect of solvent was studied by reacting *o*-pehenylenediamine and 4-methoxybenzaldehyde in an equimolar ratio in different solvents at different temperature as shown in Table 2. The yield of the product varied with the nature of the solvent. From the table, it is clear that water stands out as the solvent of choice, because it is nontoxic and results in good yield when the reaction is carried out for the same time. Comparable results were obtained when a similar reaction was carried out either in tap or distilled water, thereby saving the energy and effort required to make distilled water.

The plausible mechanism for the formation of benzimidazole in such a reaction is depicted in Schemes 1 and 2. Water plausibly exhibits ambiphilic dual activation catalysis[19] by cooperative formation of hydrogen bonds with the carbonyl oxygen and the hydrogen of the amine group of *o*-pehenylenediamine (TS-1), followed by cyclocondensation to form benzimidazoline (path a), which, on dehydrogenation, is converted into benzimidazole so that the heterocyclic moiety retains its aromatic character. The conjugation effect of the 2-aryl group with the imine bond may also play a significant role in the conversion of imidazoline to imidazole. The dissolved oxygen in water may act as a hydrogen acceptor to facilitate the dehydrogenation, corroborated by the faster rate of formation of imidazole by bubbling oxygen gas into the reaction mixture. The role of the oxygen was also confirmed by carrying out the reaction in degassed water.

Table 1. Condensation reaction of *o*-phenylenediamine (1.0 mmol) with different aldehydes (1.0 mmol) using water as a solvent

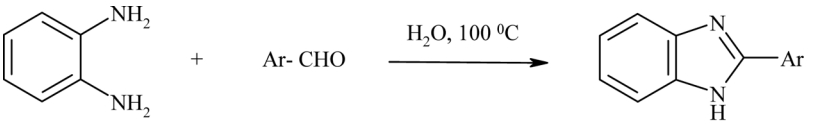
Compound **3**	Aldehyde	Time (h)	Yields[a] (%)	Melting points[b]
3a	C_6H_5CHO	2.0	85	295[14,20]
3b	4-F C_6H_4CHO	2.5	92	248[21]
3c	4-Cl C_6H_4CHO	2.0	90	302[14,18,20]
3d	4-Br C_6H_4CHO	2.0	94	300[21]
3e	4-NO_2 C_6H_4CHO	3.0	98	317[20]
3f	4-Me C_6H_4CHO	2.0	96	275[20,14]
3g	4-OH C_6H_4CHO	2.5	92	280[22]
3h	2-OH C_6H_4CHO	3.0	94	242[24]
3i	3,4-DiOH C_6H_3CHO	3.5	91	258[23]
3j	4-MeO C_6H_4CHO	2.0	95	228[14,20]
3k	3,4-DiMeO C_6H_3CHO	2.0	96	231[24]
3l	3,4,5-TriMeO C_6H_2CHO	2.5	98	259[24]
3m	3-MeO-4-OH C_6H_3CHO	3.0	94	220[24]
3n	4-MeO-3-OH C_6H_3CHO	3.0	96	224[24]
3o	Indole-3-carboxaldehyde	3.5	92	221[25]
3p	Thiophene-2-carboxaldehyde	4.5	88	330[14]
3q	Furan-2-carboxaldehyde	4.0	84	296[20]

[a]Isolated product.
[b]Resulting 2-arylbenzimidazole.

Table 2. Condensation reaction of *o*-phenylenediamine (1.0 mmol) with 4-methyl benzaldehyde (1.0 mmol) using different solvents

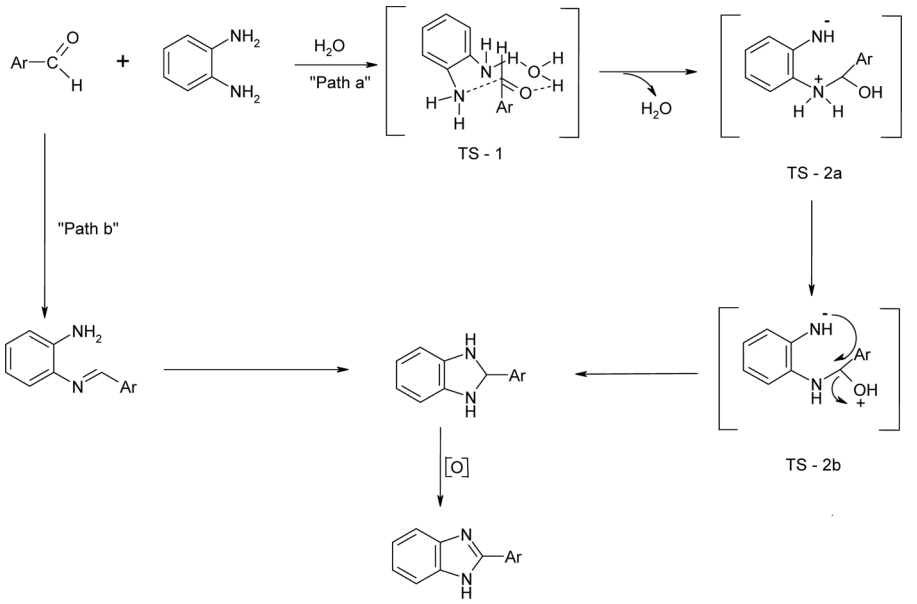
Entry	Solvent	Conditions[a]	Yield[b] (%)
1	CH_2Cl_2	reflux	19
2	THF	reflux	38
3	CH_3OH	reflux	40
4	C_2H_5OH	reflux	55
5	DMSO	100 °C	50
6	DMF	100 °C	48
7	H_2O	100 °C	96

[a]Reaction time 2 h.
[b]Isolated product.



1 **2** **3**

Scheme 1. Condensation reaction of *o*-phenylaminediamine with aryl aldehyde in water.



Scheme 2. Plausible mechanism for the formation of 2-arylbenzimidazole.

The faster rate of reaction in water as compared to the other solvents indicates that water plays a specific role (probably through the TS-1) in promoting the condensation of *o*-pehenylenediamine with the aldehyde. The alternate path (part b), involving formation of the imine followed by intramolecular nucleophilic attack by the NH_2 group and dehydrogenation of the resulting benzimidazoline, is also suggested.

To test the general scope and versatility of this procedure, we repeated the reaction with a number of different substituted arylaldehydes. We report here the formation of benzimidazole in each case in good yields. The results are summarized in Table 1. It clearly showed that aryl aldehydes bearing both electron-donating and electron-withdrawing substituents gave the desired benzimidazoles in good yields.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker Avance (400-MHz) spectrometer using tetramethylsilane (TMS) as an internal standard and dimethylsulfoxide (DMSO-d_6) as a solvent. Turnover frequency (TOF) mass spectra (m/z) were recorded on a Micromass Autospec LCTKC455. Fourier transform–infrared (FTIR) spectra were determined on a Perkin-Elmer 2000 spectrophotometer. Thin-layer chromatography (TLC) was done on GF_{254} plates using chloroform/methanol as the developing solvent. Aldehydes and *o*-phenylenediamine were all commercial products and procured from CDH, Spectrochem, Merck, and SRL and were used without further purification. Melting points were determined on an electronic apparatus and are uncorrected.

Typical Procedure for the Synthesis of 2-Arylbenzimidazole

The magnetically stirred mixture of *o*-phenylenediamine (1 mmol) and aldehyde (1 mmol) in water (10 ml) was heated at 100 °C in an oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were cooled to room temperature, the solvent was decanted, and the residue was extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the residue was purified by a silica-gel column. Elutions with hexane–EtOAc (90:10) gave the desired product.

All products were characterized by ^{1}H NMR, mass, and IR spectral data and also by comparing their melting points with those from the literature. Selected characterization data for some bezimidazoles prepared by this method are given.

Selected Data

2-(4-Fluorophenyl)-1H-1,3-benzimidazole (3b). White crystalline solid; mp 248 °C. IR (KBr) 3052, 1602, 1498, 1435, 1228, 837, 746 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 12.94 (s, 1H, D_2O exchangable), 8.23 (d, 2H, $J = 8.2$ Hz), 7.65 (m, 2H), 7.39 (d, 2H, $J = 8.2$ Hz), 7.19 (m, 2H). Mass m/z (TOF): 213 ($M^+ + 1$).

2-(4-Methylphenyl)-1H-1,3-benzimidazole (3f). Light yellow solid; mp 275 °C. IR (KBr) 3052, 1618, 1500, 1447, 1274, 821, 745 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 12.84 (s, 1H, D_2O exchangable), 8.07 (d, 2H, $J = 8.4$ Hz), 7.64 (m, 2H), 7.34 (d, 2H, $J = 8.4$ Hz), 7.18 (m, 2H). Mass m/z (TOF): 209 ($M^+ + 1$).

2-(3,4,5-Trimethoxyphenyl)-1H-1,3-benzimidazole (3l). White solid; mp 259 °C. IR (KBr) 3056, 1590, 1500, 1463, 1243, 1015, 747 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 12.86 (s, 1H, D_2O exchangable), 7.65 (m, 4H), 7.19 (s, 2H), 3.89 (s, 6H, $2 \times OCH_3$), 3.72 (s, 3H, OCH_3). Mass m/z (TOF): 285 ($M^+ + 1$).

CONCLUSION

A novel, simple, and efficient procedure for the synthesis of 2-arylsubstituted benzimidazoles has been explored. Short reaction time, large-scale synthesis, easy and quick isolation of the products, and excellent yields are the main advantages of this procedure, which make this method more attractive. It is certainly a useful contribution to the present methodologies.

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