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Diphosphorus Tetraiodide (P_2I_4): An Efficient Catalyst for Synthesis of 2-Aryl-1,3-benzazoles *via* Cyclocondensation of *o*-Amino/Mercaptan/Hydroxy Anilines with Aryl Acids

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An efficient and versatile approach for the synthesis of 2-substituted 1,3-benzazoles has been developed *via* diphosphorus tetraiodide (P_2I_4) catalyzed condensation reaction of *ortho*-substituted anilines (–NH_2, –SH and –OH) with various aromatic acids to give benzimidazoles, benzothiazoles and benzoxazoles in excellent yields. Additionally, the synthetic approach reported herein has advantages such as mild reaction conditions, broad substrate scopes as well as simple one-pot operation, common for all the three 1,3-benzazoles, which makes this strategy highly attractive.

Keywords: Aryl/heteroaryl acids, Heterocycles, Benzimidazole, Benzothiazole, Benzoxazole, Diphosphorus tetraiodide.

INTRODUCTION

1,3-Benzazoles, which include three scaffolds *i.e.*, benzimidazole, benzothiazole and benzoxazole, are an important class of compounds that provide a common scaffold to various derivatives exhibiting exciting and diverse biological and pharmaceutical properties and are therefore considered privileged structures in the design and discovery of new drugs. The 2-substituted benzofused azoles have gained importance in medicinal chemistry owing to their use as anti-inflammatory, antimicrobial, antidiabetic, antiulcer, antihelmentic, antihypertensive, antiviral and anticancer agents [1-8].

There are several classical methods in the literature to obtain 1,3-benzazoles which involves the condensation reactions of either *o*-phenylenediamine, *o*-aminobenzenethiol, or *o*-aminophenol with substituted carboxylic acids, aldehydes, acyl chlorides, or nitriles [9-15]. Alternatively, benzimidazoles have also been synthesized using transition-metal catalyzed amination followed by condensation [16] and cyclization of *o*-nitroaniline derivatives with aryl isothiocyanates [17]. Recently, substituted alcohols have been used for the synthesis of benzimidazoles and benzothiazoles, however, the use of oxidative steps in case of aldehydes or alcohols affect the overall economy of the reaction [18]. Also, benzoxazoles have been obtained by reacting *o*-hydroxyphenyl ketoximes with PCl_5 or P_2O_5 and reaction of 2-aminophenols with allenic and acetylenic nitriles [19,20]. However, the above mentioned methods suffer from several disadvantages like harsh reaction conditions (strong acid, high temperature), high catalyst cost, occurrence of side reactions (which leads to poor yield and difficulty in isolation), low reaction rate, additional oxidation step, tedious work-up procedure and lack of selectivity.

In the course of our research on the development of efficient methods to access these bioactive 1,3-benzazoles, we decided to explore a single versatile synthetic protocol by condensing carboxylic acids with *o*-phenylenediamines, *o*-aminobenzenethiol and *o*-aminophenols respectively, utilizing an iodine reagent under mild reaction conditions. The ready availability of diverse set of carboxylic acids and their higher stability compared to aldehydes and alcohols, prompted us to focus on carboxylic acids as reagents for this isohypsic heterocyclization. However, these types of organic transformations, involving loss of water, require the use of strong dehydrating agents. The ideal features in a dehydrating agent include easy preparation, selectivity for oxygen, minimum unwanted by-product formation, enough reactivity for rapid reaction at moderate temperatures, utility in a range of common solvents. This encouraged us to explore various iodine reagents including diphosphorus tetraiodide (P_2I_4) as a suitable dehydrating reagent for such conversion.

EXPERIMENTAL

Chemicals and solvents used were of LR grade and purchased from SD fine, Avra Synthesis or Spectrochem and used without purification. The purity determination of the starting materials and reaction monitoring was accomplished by thin-layer chromatography (TLC) on Merck silica gel G F_{254} plates.

Silica gel 60-120 mess was used for column chromatography. Melting points of all the compounds were recorded on Thermomik Campbell melting point apparatus having an oil bath system and are uncorrected. The FTIR spectra (KBr) were recorded on Shimadzu FTIR Affinity-1 Fourier transform infrared spectrophotometer. ^{1}H NMR spectra were recorded on MR400 Agilent Technology NMR spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO-d_6/$CDCl_3$ as a solvent. All the products are known compounds and were identified by ^{1}H NMR spectroscopy.

General procedure for synthesis of 2-aryl-benzimidazoles/2-aryl-benzoxazoles/2-aryl-benzothiazoles: To a mixture of *ortho*-substituted (–NH_2 or –SH or –OH) anilines (1 mmol) and aryl acids (1 mmol) in acetonitrile (2 mL) in a sealed tube (10 mL) was added diphosphorus tetraiodide (0.2 mmol) under nitrogen atmosphere. Then, the tube was capped and the mixture heated in an oil bath at 80 °C with stirring until the reaction was complete as monitored by TLC. After being cooled to room temperature, the reaction was quenched with aqueous $NaHCO_3$ solution and extracted with ethyl acetate three times. The combined organic layer was washed with water and brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate, to afford the corresponding product. The products obtained were known compounds and were identified by melting point and ^{1}H NMR spectroscopy. The spectral data were compared with the literature values.

2-Phenyl-1*H*-benzimidazole (Table-2, entry 1): m.p.: 290-293 °C (Lit. [21] 292-294 °C); IR (KBr, ν_{max}, cm^{-1}): 3450, 3045, 1620, 1580, 1458; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.08–7.14 (m, 2H), 7.31–7.5 (m, 5H), 7.96 (d, 2H), 12.80 (s, 1H); ^{13}C NMR (DMSO-d_6, TMS): δ 116.5, 123.1, 127.4, 128.6, 129.5, 130.7, 139.0, 152.7; MS (ESI) *m/z*: $[M+H]^+$ 195.1.

2-(4-Chlorophenyl)-1*H*-benzimidazole (Table-2, entry 2): m.p.: 290–292 °C (Lit. [21] 289–291 °C); IR (KBr, ν_{max}, cm^{-1}): 3448, 3050, 1640, 1580, 1480, 745; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.22 (d, 2H), 7.46–7.62 (m, 4H), 8.25 (d, 2H), 12.91 (s, 1H); ^{13}C NMR (DMSO-d_6, TMS): δ 150.5, 143.8, 135.1, 134.7, 129.2, 129.0, 127.5, 122.4, 121.8, 117.5, 111.4; MS (ESI) *m/z*: $[M+H]^+$ 229.01.

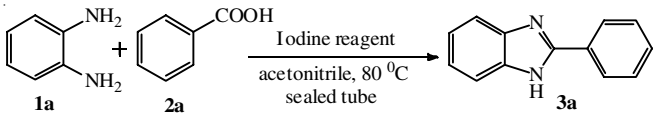
2-(2-Thiophen)-1*H*-benzimidazole (Table-2, entry 6): m.p.: 341-343 °C (Lit. [21] 342–343 °C). IR (KBr, ν_{max}, cm^{-1}): 3380, 3040, 1635, 1569, 1451, 1420, 1310, 1255. ^{1}H NMR (400 MHz, DMSO-d_6): 7.1 (m, 1H), 7.25–7.52 (m, 3H), 7.75–7.90 (m, 2H), 8.2–8.22 (m, 1H), 12.49 (bs, 1H), ^{13}C NMR (DMSO-d_6, TMS): δ 111.1, 118.4, 121.6, 122.5, 126.6, 128.0, 128.6, 133.6, 134.5, 143.6, 146.4. MS (ESI) *m/z*: $[M+H]^+$ 201.05.

2-Phenylbenzoxazole (Table-3, entry 1): m.p.: 99–101 °C (Lit. [22] 101–102 °C); IR (KBr, ν_{max}, cm^{-1}): 3458, 3060, 2951, 1640, 1460,1340, 1240, 1050, 1022; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.16 (m, 2H), 7.26-7.41 (m, 3H), 7.58 (m, 2H), 8.01 (m, 2H); ^{13}C NMR (DMSO-d_6, TMS): δ 121.5, 122.4, 123.5, 124.7, 125.6, 129.6, 132.2, 138.7, 150.5, 154.2, 162.3; MS (ESI) *m/z*: $[M+H]^+$ 196.1.

2-Phenylbenzothiazole (Table-3, entry 6): m.p.: 111–114 °C (Lit. [23] 110–112 °C); IR (KBr, ν_{max}, cm^{-1}): 3430, 1660, 1445; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19 (m, 1H), 7.27-7.31 (m, 4H), 7.73 (d, 1H), 7.93 (m, 3H); ^{13}C NMR (DMSO-d_6, TMS): δ 121.5, 122.1, 123.6, 125.5, 126.7, 129.1, 132.4, 135.3, 151.2, 154.3, 166.4; MS (ESI) *m/z*: $[M+H]^+$ 212.05.

RESULTS AND DISCUSSION

In an initial attempt, we selected *o*-phenylenediamine (**1a**) and benzoic acid (**2a**) as the model substrates to probe the optimal reaction conditions (**Scheme-I**).



Scheme-I: Reaction between *o*-phenylenediamine and benzoic acid in presence of iodine reagents

The desired product 2-phenyl-1*H*-benzimidazole (**3a**) was not obtained in absence of the catalyst upon reacting **1a** and **2a** in stoichiometric amounts using acetonitrile as a solvent in a sealed tube [15] at 80 °C (Table-1, entry 1); Next, various iodine reagents like iodine, sodium iodide/*o*-phosphoric acid, aqueous hydroiodic acid (56 %), red phosphorus/aq. hydroiodic acid/iodine were used as a catalyst in the reaction, however, either the reaction did not afford the desired product or the yield was very low (Table-1, entry 2-5). We next attempted the reaction using 1 equivalent P_2I_4 in a sealed tube at 80 °C, the desired product **3a** was obtained in 92 % yield after 3 h (Table-1, entry 6). Further, reducing the amount of P_2I_4 to 0.7, 0.5 and 0.2 equivalents had no significant impact on the yield of the product **3a** (Table-1, entry 7-9). However, a further decrease in the amount of P_2I_4 to 0.1 equivalents affected the yield adversely (Table-1, entry 10).

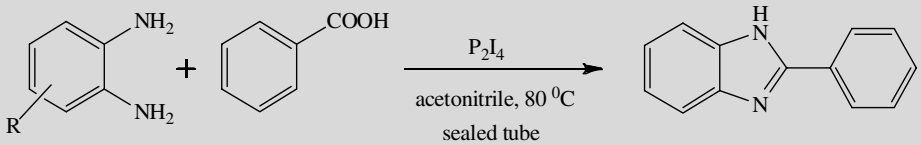
TABLE-1
SCREENING OF IODINE REAGENTS IN THE SYNTHESIS OF BENZIMIDAZOLES[a]

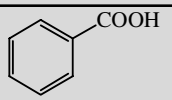
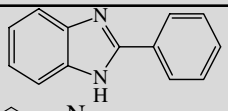
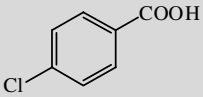
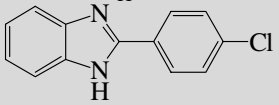
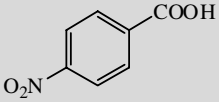
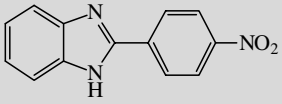
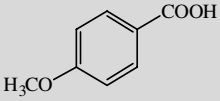
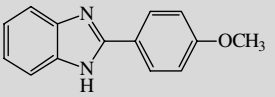
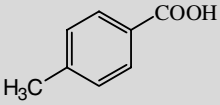
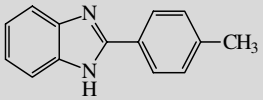
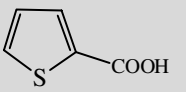
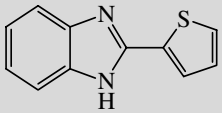
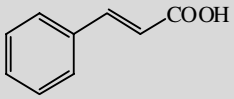
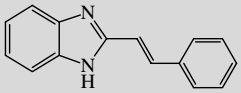
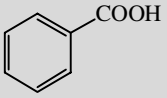
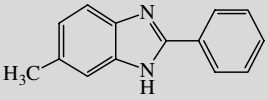
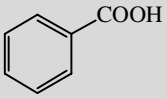
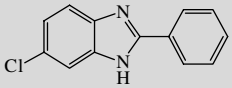
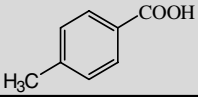
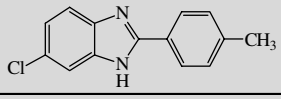
Entry	Catalyst	Equivalents	Time (h)	Yield[c] (%)
1	–	–	24	NR
2	I_2	1.0	24	NR
3	NaI/H_3PO_4	0.3/1.1	24	NR
4	Aq. HI	1.0	24	5-10
5	Red P/aq. HI/I_2	5/1/2	24	30
6	P_2I_4	1.0	3	92
7	P_2I_4	0.7	3	91
8	P_2I_4	0.5	3	94
9	P_2I_4	0.2	3	95
10	P_2I_4	0.1	6	60
11[b]	P_2I_4	0.2	24	30
12[b]	P_2I_4	1.0	24	35

[a]Reaction conditions: *o*-phenylenediamine (**1a**, 1 mmol), benzoic acid (**2a**, 1 mmol) and catalyst were reacted in acetonitrile in a sealed tube at 80 °C. [b]Reaction carried out in acetonitrile at 80 °C under reflux. [c]Isolated yield.

We also carried out the reaction using P_2I_4 under reflux condition using acetonitrile as a solvent, however, the desired product **3a** was obtained in a very low yield even with up to 1 equivalents of P_2I_4 (Table-1, entry 11-12). Reaction at a temperature lower than 80 °C resulted in poor conversion, while no obvious improvement was achieved when the temperature was

TABLE-2
SYNTHESIS OF VARIOUS SUBSTITUTED 2-ARYL-BENZIMIDAZOLES[a]



Entry	Amine (R)	Acid	Product	Yield[b] (%)
1	H			95
2	H			93
3	H			92
4	H			94
5	H			91
6	H			88
7	H			91
8	4-CH_3			94
9	4-Cl			93
10	4-Cl			94

[a]Reaction conditions: substituted 1,2-diamines (1 mmol), aryl acid (1 mmol) and P_2I_4 (0.2 equivalent) in acetonitrile were reacted in a sealed tube at 80 °C for 3-5 h. [b]Isolated yields after column chromatography and structures were confirmed by comparison of IR, ^{1}H NMR and melting point with literature reports.

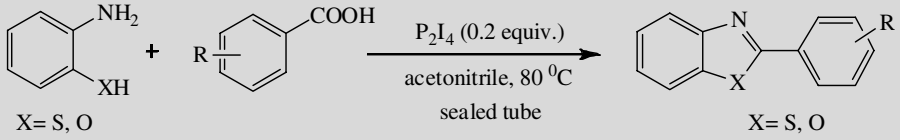
increased to 120 °C. The use of other solvents such as ethanol, 1,4-dioxane, tetrahydrofuran, DMSO and toluene were also examined, although most of the solvents promoted the reaction, acetonitrile was found the most suitable media for this cyclization reaction.

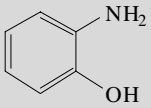
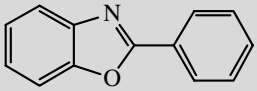
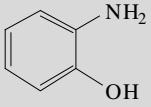
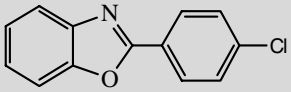
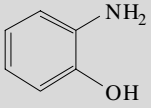
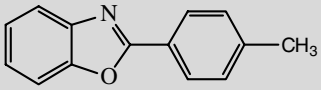
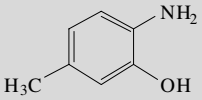
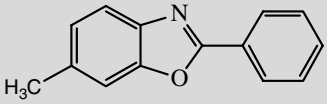
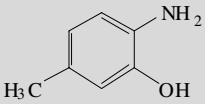
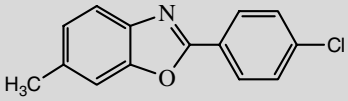
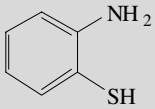
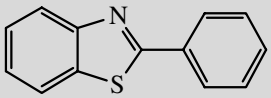
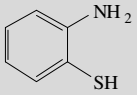
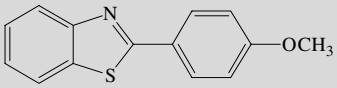
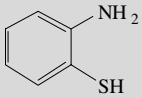
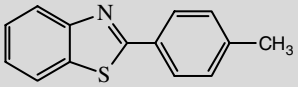
With the optimized conditions in hand (Table-1, entry 9), to study the generality and scope of this cyclization protocol, a variety of aryl/heteroaryl acids were reacted with *o*-phenylenediamine and its derivatives (Table-2). The reaction proceeded well in all the cases to give the corresponding benzimidazoles in excellent yields. Aromatic acids containing various substituents, such as electron-withdrawing (Table-2, entries 2-3) and electron-donating (Table-2, entries 4-5), were well tolerated and did not affect the product yields. This methodology also worked well with heteroaromatic acid (Table-2, entry 6) as well as α,β-unsaturated carboxylic acids like cinnamic acid (Table-2, entry 7). Significantly, good yields of the corresponding benzimidazoles were obtained upon reaction of various *o*-phenylenediamine derivatives with different aromatic acids (Table-2, entries 8-10).

Gratifyingly, when the similar reaction conditions were expanded to the synthesis of benzoxazoles and benzothiazoles from *o*-aminophenol and *o*-aminobenzenethiol respectively, using various aromatic acids, all the reactions proceeded efficiently and the products were obtained in good to excellent yields (Table-3, entries 1-8).

The present method is a convenient alternative to the most widely used polyphosphoric acid catalyzed synthesis of 1,3-benzazoles, overcoming the major drawbacks of polyphosphoric acid like its physical attributes including hygroscopic nature and extremely high viscosity which makes it virtually impossible to stir effectively or manipulate conveniently at

TABLE-3
SYNTHESIS OF VARIOUS SUBSTITUTED 2-ARYL-BENZOXAZOLES AND 2-ARYL-BENZOTHIAZOLES[a]



Entry	Amine	Acid (R)	Product	Yield[b] (%)
1		H		90
2		4-Cl		88
3		4-CH_3		89
4		H		89
5		4-Cl		87
6		H		90
7		4-OCH_3		88
8		4-CH_3		87

[a]Reaction conditions: *o*-substituted aniline derivative (1 mmol), aryl acid (1 mmol) and P_2I_4 (0.2 equivalent) in acetonitrile were reacted in a sealed tube at 80 °C for 3-4 h. [b]Isolated yields after column chromatography and structures were confirmed by comparison of IR, ^{1}H NMR and melting point with literature reports.

temperatures below 60-90 °C. It is difficult to handle on a large scale, even at elevated temperature, over 200 °C, which is required for this condensation reaction. Some organics are only sparingly soluble in polyphosphoric acid and, in any case, rates of dissolution are low. The hydrolysis of polyphosphoric acid in work-up procedures is always tedious.

Conclusion

In conclusion, an effective and quick method, providing a single protocol for the synthesis of all the three 1,3-benzazoles, by condensation between *o*-phenylenediamines, *o*-amino-benzenethiol and *o*-aminophenols, with various aryl acids using diphosphorus tetraiodide (P_2I_4) as a catalyst has been reported. The use of commercially available starting materials, low catalyst loading, no isolation of intermediates, short reaction times, easy work-up procedure and purification by simple column chromatography, excellent yields of product, safe and mild reaction conditions and applicability with a broad range of substrate are noteworthy advantages of this method over the existing process. Overall, the present methodology is especially suitable in medicinal chemistry and drug discovery for a rapid access to the library of novel small molecules based on diverse 1,3-benzazole framework for biological evaluation.

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