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A FACILE SYNTHESIS OF DIVERSE LIBRARIES OF BENZIMIDAZOLE, BENZOXAZOLE, BENZOTHIAZOLE AND QUINAZOLIN-4(3H)-ONE VIA PPDS-$CUSO_4$ MEDIATED REACTIONS OF ALDEHYDES IN AQUEOUS MICELLES

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Abstract: Libraries of 2-substituted-benzimidazoles, benzoxazoles, benzothiazoles as well as quinazolin-4(3H)-ones were synthesized via PPDS-$CuSO_4$ mediated oxidative coupling of aldehydes with o-phenylenediamines, o-aminophenols, o-aminothiophenols and anthranilamide respectively in aqueous micelles. The strategy opens the way for rapid generation of libraries of small heterocycles for biological screening. The reagent is commercially available, cheap and highly chemoselective. The yields were superior in aqueous micelles to those in organic solvents. Short reaction times, large-scale synthesis, excellent chemoselectivity, excellent yields as well as environmental friendliness are the main advantages of this diversity oriented synthesis.

Keywords: Diversity oriented synthesis; Benzimidazoles; Benzoxazoles; Benzothiazoles; Quinazolin-4(3H)-ones; PPDS-$CuSO_4$; Oxidative coupling reactions; Aqueous micelles

Introduction

Low molecular weight heterocycles are securing their place among the most highly recognized pharmacophores [I-III]. Among them, 2-substituted benzimidazoles, benzoxazoles, are of particular interest, since they are well known to exhibit a broad range of biological activities [IV-X].

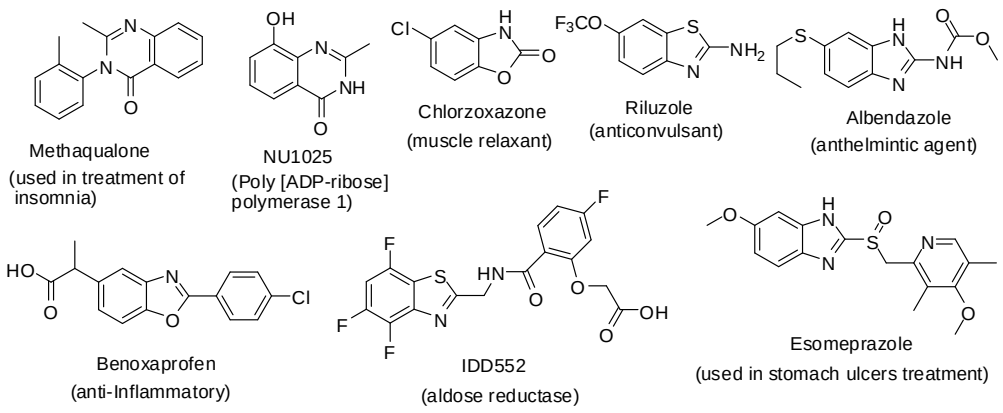


Figure 1. Benzimidazole, benzoxazole, benzothiazoles and quinazolin drugs

Depending upon the substitutions in benzimidazoles, they have shown numerous biological activities like antiprotozoal [XI], antitumour [XII], H1-anti- histaminic [XIII] and antiviral activity [XIV]. Benzoxazoles and benzothiazoles have shown anticonvulsant [XV], antitumour [XVI], and anticancer activities [XVII]. Quinazolinone derivatives have drawn much attention due to their broad range of pharmacological activities [XVIII-XIX] for example anticancer [XX], anti-inflammatory [XXI] and anticonvulsant [XXII] activities. Consequently, these heterocycles are prized as potential drug candidate and biological probes (Figure 1).

All these biologically important heterocycles can be represented by a general formula **I**. The retro synthesis of scaffold **I** show that it could be synthesized by oxidative coupling of **II** with **III**. Thus the synthesis of the libraries of 2-substituted-benzimidazole, benzoxazole, benzothiazole and quinazolin-4(3H)-one could be carried out by coupling aldehydes with o-arylenediamines, o-aminophenols, o-aminothiophenols and anthranilamide respectively with a suitable oxidant (Figure 2).

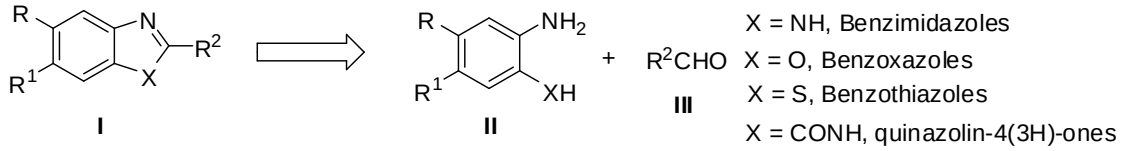


Figure 2. Retrosynthetic approach for 2-substituted-benzimidazoles, benzoxazoles, benzothiazoles and quinazolin-4(3H)-ones

Potassium peroxydisulphate (PPDS) is largely used for bleaching, textile desizing, as an oxidizing agent, antiseptic, in purification of ammonium sulfate, in the manufacture of soap and pharmaceuticals. The peroxydisulphate ion is a versatile oxidizing agent in aqueous solution. The standard oxidation–reduction potential of PPDS in oxidation reactions is estimated to be -2.01 V [XXIII]. Bhatt and Perumal have explored PPDS for the conversion of electron rich benzylic hydrocarbons to carbonyls. PPDS has been used in polymerization of acrylamide in polar media (water, DMF) [XXIV], regio- and stereoselective oxygenation of flavanol and biflavanoid-derivatives [XXV]. Due to its strong redox potential, PPDS has also been used in Elbs and Baeyer–Villiger oxidations [XXVI-XXVII]. Reactions involving peroxydisulphate ions are generally slow at room temperature. The rate of peroxydisulphate decomposition increases with temperatures [XVIII]. Transition metal salts like cobalt, copper, iron, etc. also increases the decomposition of perosydisulphate ions. Many oxidations with PPDS in the presence of these transition metal salts have been reported [XXIX].

Due to the increasing environmental concerns, chemical industries have been prompted to minimize the use of toxic and hazardous solvents in chemical manufacture. It is strongly recommended to replace technologies that pollute the environment by benign alternatives. Thus, organic chemists are turning their attention to develop clean, economical and environmental safer methodologies. Water as reaction medium is generally considered as cheap, safe and environmentally benign alternative to unnatural solvents [XXX]. However, water has not yet become a widely accepted solvent for synthetic transformations. This may be due to concerns about the poor solubility of organic compounds in water. In most of the cases the poor solubility of organic compounds in water has been overcome by addition of a suitable surfactant in water [XXXI].

Application of PPDS-copper sulphate for direct α-thiocyanation of carbonyl and β-dicarbonyl compounds is also reported in litrature [XXXII]. Our previous work in field of synthesis of small organic molecules motivated us to plan a diversity oriented synthesis of the libraries of benzimidazoles as well as benzoxazoles via PPDS-CuSO4 mediated oxidative

coupling reactions of aldehydes with o-arylenediamines, o-aminophenols, o-aminothiophenols and anthranilamide respectively in aqueous micelles.

Materials and general information

Unless otherwise specified all the reagents were purchased from Sigma-Aldrich and were used without further any purification. The common organic solvents were purchased from Ranchem. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using flash chromatography on 230-400 mesh silica gel. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel plates visualized under UV light, iodine or $KMnO_4$ staining. ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX -300 Spectrometer. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. Mass spectra (ESI MS) were obtained by Micromass Quattro II instrument. Melting points were obtained on a COMPLAB melting point apparatus and are uncorrected.

Typical experimental procedure for synthesis of 2-substituted benzimidazoles, benzoxazoles, benzothiazoles and quinazolin-4(3H)-ones

Aldehyde (2 mmol), o-arylenediamine/2-aminophenol/2-aminothiophenol/anthranilamide (2 mmol), PPDS (2 mmol) and $CuSO_4$ (0.02 mmol) were taken in 5-10 ml of aqueous micelles (0.05 g/ml SDS). It was stirred for 25-60 min at 60 ^{0}C. The reaction was followed by TLC monitoring. After completion of the reaction (TLC), the reaction mixture was diluted with brine and the precipitate was filtered off. The pure product was obtained by crystallyzation of the crude from ethanol. When the product was oily it was extracted by ethyl acetate and purified by silica gel column chromatography.

Spectral and analytical data of 2-aryl benzimidazoles (3a-j):

2-Phenylbenzimidazole (3a): mp > 250 ^{0}C. ESI MS (*m/z*) = 195 [M+1]. ^1H NMR (300 MHz, DMSO-d_6) δ = 7.19-7.27 (m, 2H), 7.43-7.65 (m, 5H), 8.23-8.27 (m, 2H), 13.00 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 110.9, 118.3, 121.6, 125.9, 126.4, 128.4, 129.2, 129.7, 134.4, 143.2, 150.7. Analysis Calculated for $C_{13}H_{10}N_2$; C 80.39, H 5.19, N 14.42; found C 80.30, H 5.12, N 14.30.

2-(1H-indol-3-yl)-1H-benzo[d]imidazole (3b): mp >225^{0}C. ESI Mass (*m/z*) = 234 M+1). ^1H NMR (Acetone-d_6, 300 MHz) δ = 7.21-7.29 (m, 4H), 7.35 (s, 1H), 7.46-7.51 (m, 1H), 7.59-7.64(m, 2H), 7.93(s, 1H), 8.22-8.27 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 100.9, 105.7, 108.7, 112.8, 121.1, 121.9, 123.2, 124.0, 129.1, 130.3, 137.0, 140.7, 141.7, 147.2, 158.0.

2-(Pyridin-3-yl)-1H-benzimidazole (3c): mp 241-243 ^{0}C. ESI MS (*m/z*) = 196 [M+1]. ^1H NMR (300 MHz, DMSO-d_6) δ = 7.21-7.28 (m, 2H), 7.54-7.64 (m, 3H), 8.50 (dt, *J* = 8.2, 2.0 Hz, 1H), 8.68 (dd, *J* = 4.8, 1.6 Hz, 1H), 9.37 (d, *J* = 2.0 Hz, 1H), 13.09 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 112.0, 118.9, 121.2, 122.6, 122.7, 124.2, 126.9, 135.4, 143.9, 147.8, 149.1, 150.7. Analysis Calculated for $C_{12}H_9N_3$: C 73.83, H 4.65, N 21.52; found C 73.70, H 4.58, N 21.40.

5-Methyl-2-phenyl-1H-benzimidazole (3d): mp > 250 ^{0}C. ESI MS (*m/z*) = 209 [M+1]. ^1H NMR (300 MHz, DMSO-d_6) δ = 2.42 (s, 3H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.37-7.56 (m, 5H), 8.13-8.18 (m, 2H), 12.81 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 21.6, 111.4, 118.7, 123.6, 126.5, 129.2, 130.0, 130.5, 130.9, 132.3, 135.5, 151.1. Analysis Calculated for $C_{14}H_{12}N_2$; C 80.74, H 5.81, N 13.45; found C 80.62, H 5.72, N 13.33.

5-Fluoro-2-phenyl-1H-benzimidazole (3e): mp > 225 ^{0}C ESI MS (*m/z*) = 213 [M+1]. ^1H NMR (300 MHz, DMSO-d_6) δ = 7.05-7.12 (m, 1H), 7.41-7.54 (m, 5H), 8.27-8.31 (m, 2H), 13.18 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 110.3, 110.7, 126.9, 129.2, 130.2, 130.4,

153.1, 157.6, 160.7. Analysis Calculated for $C_{13}H_9FN_2$: C 73.57, H 4.27, N 13.20; found C 73.65, H 4.18, N 13.08.

5-Methyl-2-(pyridin-3-yl)-1H-benzimidazole (3f): mp 220-221 ^{0}C. ESI MS (*m*/*z*) = 210 [M+1]. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.41 (s, 3H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.41-7.56 (m, 3H), 8.49 (dt, *J* = 8.3, 1.8 Hz, 1H), 8.65 (dd, *J* = 4.8, 1.6 Hz, 1H), 9.38 (dd, *J* = 2.2, 0.7 Hz, 1H), 12.98 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 21.5, 111.4, 118.8, 123.8, 124.1, 126.6, 132.6, 133.8, 135.5, 142.2, 147.7, 148.7, 150.5; Analysis Calculated for $C_{13}H_{11}N_3$: C 74.62, H 5.30, N 20.08; found C 74.70, H 5.20, N 19.92.

5-Fluoro-2-(pyridin-3-yl)-1H-benzimidazole (3g): mp > 225 ^{0}C ESI MS (*m*/*z*) = 214 [M+1]. ^{1}H NMR (300 MHz, DMSO-*d*6) = 7.05-7.12 (m, 1H), 7.43 (d, *J* = 8.0, 1H), 7.54-7.65 (m, 2H), 8.47 (dt, *J* = 8.2, 1.8 Hz, 1H), 8.67 (dd, *J* = 4.8, 1.6 Hz, 1H), 9.34 (d, *J* = 1.6 Hz, 1H), 13.23 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) = 110.7, 111.0, 124.2, 126.1, 134.0, 147.7, 150.5, 150.8, 157.4, 157.5, 160.5, 160.6. Analysis Calculated for $C_{12}H_8FN_3$: C 67.60, H 3.78, N 19.71; found C 67.55, H 3.69, N 19.58.

2-Pentyl-1H-benzimidazole (3h): mp 154-157 ^{0}C. ESI MS (*m*/*z*) = 189 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.80-0.87 (m, 3H), 1.25-1.34 (m, 4H), 1.77-1.89 (m, 2H), 2.93 (t, *J* = 7.4 Hz, 2H), 6.40 (bs, 1H), 7.18-7.26 (m, 2H), 7.52-7.58 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.8, 21.8, 27.3, 28.5, 30.8, 110.6, 118.0, 120.9, 134.3, 143.4, 155.1. Analysis Calculated for $C_{12}H_{16}N_2$; C 76.55, H 8.57, N 14.88; found C 76.51, H 8.48, N 14.70.

2-Cyclohexyl-1H-benzimidazole (3i): mp > 225 ^{0}C. ESI MS (*m*/*z*) = 201 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.24-1.50 (m, 3H), 1.56-1.89 (m, 5H), 2.13-2.18 (m, 2H), 2.86-2.97 (m, 1H), 4.35 (bs, 1H), 7.18-7.27 (m, 2H), 7.52-7.59 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 25.7, 25.8, 31.7, 38.1, 111.2, 118.6, 121.2, 121.8, 134.6, 143.5, 159.3. Analysis Calculated for $C_{13}H_{16}N_2$; C 77.96, H 8.05, N 13.99; found C 77.88, H 7.95, N 13.82.

5-Methyl-2-pentyl-1H-benzimidazole (3j): ESI MS (*m*/*z*) = 203 [M+1]. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 0.84 (t, *J* = 6.7 Hz, 3H), 1.22-1.33 (m, 4H), 1.69-1.79 (m, 2H), 2.37 (s, 3H), 2.77 (t, *J* = 7.5 Hz, 2H), 6.91 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.24-7.32 (m, 2H), 12.10 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 14.0, 21.4, 22.1, 27.6, 28.7, 31.1, 110.7, 117.8, 122.5, 130.4, 134.7, 141.7, 155.0. Analysis Calculated for $C_{13}H_{18}N_2$: C 77.18, H 8.97, N 13.85; found C 77.08, H 8.90, N 13.70.

Spectral and analytical data of 2-aryl benzoxazoles/benzothiazoles:

2-Phenylbenzoxazole (6a): mp 100-101 ^{0}C. ESI MS (*m*/*z*): 196 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.28-7.37 (m, 2H), 7.47-7.58 (m, 4H), 7.74-7.79 (m, 1H), 8.22-8.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 110.4, 119.8, 124.3, 124.9, 127.0, 127.4, 128.7, 131.3, 141.9, 150.5, 162.8. Analysis Calculated for $C_{13}H_9NO$; C 79.98, H 4.65, N 7.17; found C 79.85, H 4.54, N 7.00.

4-Methyl-2-phenylbenzoxazole (6b): mp 82-85 °C. ESI MS (*m*/*z*) = 210 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.67 (s, 3H), 7.13 (d, *J* = 6.6 Hz, 1H), 7.20-7.25 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.49-7.53 (m, 3H), 8.23-9.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 16.5, 107.8 124.7, 125.0, 127.4, 128.8, 130.6, 131.2, 141.4, 150.5, 162.2. Analysis Calculated for $C_{14}H_{11}NO$; C 80.36, H 5.30, N 6.69; found C 80.20, H 5.35, N 6.54.

6-Methyl-2-phenylbenzoxazole (6c): mp 92-93 ^{0}C. ESI MS (*m*/*z*) = 210 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.50 (s, 3H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.38 (s, 1H), 7.48-7.66 (m, 3H), 7.64 (d, *J* = 8.2 Hz, 1H), 8.19- 8.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.5, 110.5, 119.1, 125.6, 127.2, 128.6, 131.0, 135.3, 139.7, 150.8, 162.3. Analysis Calculated for $C_{14}H_{11}NO$: C 80.36, H 5.30, N 6.69; found C 80.25, H 5.32, N 6.80.

5-Chloro-2-phenylbenzoxazole (6d): mp 94-96 ^{0}C. ESI MS (*m*/*z*) = 230 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.26-7.31 (m, 1H), 7.44-7.52 (m, 4H), 7.27 (s, 1H), 8.20-8.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 111.2, 119.9, 125.3, 126.6, 127.7, 128.9, 130.0, 131.8, 143.2, 149.3, 164.3. Analysis Calculated for $C_{13}H_8ClNO$: C 67.99, H 3.51, N 6.10; found C 67.90, H 3.42, N 6.00.

2-(Pyridin-3-yl)benzoxazole (6e): mp 113-114 ^{0}C ESI MS (*m*/*z*) = 197 [M+1].. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.37- 7.50 (m, 3H), 7.59-7.64 (m, 1H), 7.78-7.82 (m, 1H), 8.52 (dt, *J* = 8.2, 2.0, 1H), 8.77 (dd, *J* = 4.8, 2.0 Hz, 1H), 9.47-9.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 110.4, 119.9, 123.2, 123.4, 124.6, 125.4, 134.3, 141.4, 148.4, 150.4, 151.6, 160.2. Analysis Calculated for $C_{12}H_8N_2O$: C 73.46, H 4.11, N 14.28; found C 73.39, H 4.03, N 14.16.

4-Methyl-2-(pyridin-3-yl)benzoxazole (6f): ESI MS (*m*/*z*) = 211 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.66 (s, 3H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.38-7.44 (m, 2H), 8.49 (tt, *J* = 8.0, 1.7 Hz, 1H), 8.73 (dd, *J* = 4.9, 1.7 Hz, 1H), 9.45 (dd, *J* = 2.1, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 16.4, 107.9, 123.5, 123.6, 125.2, 125.2, 130.8, 134.5, 141.0, 148.6, 150.4, 151.7, 159.7. Analysis Calculated for $C_{13}H_{10}N_2O$: C 74.27, H 4.79, N 13.33; found C 74.38, H 4.84, N 13.25.

2-Pentylbenzoxazole (6g): ESI MS (*m*/*z*) = 190 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$): 0.88-0.95 (m, 3H), 1.37-1.44 (m, 4H), 1.81-1.93 (m, 2H), 2.92 (t, *J* = 7.8 Hz, 2H), 7.26-7.31 (m, 2H), 7.45-7.49 (m, 1H), 7.64-7.69 (m, 1H); ^{13}C NMR (75 MHz, CDCl3) δ = 13.8, 22.2, 26.4, 28.5, 31.2, 110.1, 119.4, 123.9, 124.3, 141.3, 150.7, 167.3; Analysis Calculated for $C_{12}H_{15}NO$: C 76.16, H 7.99, N 7.40; found C 76.08, H 8.15, N 7.28.

4-Methyl-2-pentylbenzoxazole (6h): ESI MS (*m*/*z*) = 204 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.90-0.96 (m, 3H), 1.35-1.43 (m, 4H), 1.82-1.97 (m, 2H), 2.62 (s, 3H), 2.95 (t, *J* = 7.2 Hz, 1H), 7.08-7.12 (m, 1H), 7.15-7.23 (m, 1H), 7.28-7.34 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.9, 16.5, 22.3, 26.8, 28.8, 31.3, 107.5, 124.0, 129.8, 140.5, 150.5, 166.6; Analysis Calculated for $C_{13}H_{17}NO$: C 76.81, H 8.43, N 6.89; found C 76.69, H 8.45, N 6.78.

2-Cyclohexylbenzoxazole (6i): ESI MS (*m*/*z*) = 202 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.23-1.51 (m, 3H), 1.60-1.90 (m, 5H), 2.12-2.19 (m, 2H), 2.86-3.01 (m, 1H), 7.21-7.31 (m, 2H), 7.41-7.48 (m, 1H), 7.62-7.69 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.6, 25.7, 30.4, 37.9, 110.2, 119.6, 123.9, 124.3, 141.2, 150.6, 170.4; Analysis Calculated for $C_{13}H_{15}NO$: C 77.58, H 7.51, N 6.96; found C 77.50, H 7.44, N 6.85.

2-(2-chlorophenyl)-1, 3-benzoxazole (6j). mp 63-64 ^{0}C; ESI MS (m/z) = 230 [M+1]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.36-7.46 (m, 4H), 7.56-7.57 (m, 1H), 7.61-7.62 (m, 1H), 7.84-7.86 (m, 1H), 8.13-8.15 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 110.9, 120.6, 124.8, 125.7, 126.2, 127.1, 131.5, 131.9, 132.0, 133.6, 141.8, 150.6, 161.1. Analysis Calculated for $C_{13}H_8ClNO$: C 67.99, H 3.51, N 6.10; found C 68.79, H 3.40, N 5.95.

5-chloro-2-(3-nitrophenyl)-1, 3-benzoxazole (6k). mp 184-186 ^{0}C; ESI MS (m/z) = 275 [M + 1]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.38 (q, 1H, *J* = 8.4 Hz), 7.54 (d, 1H, *J* = 9.1 Hz), 7.72 (d, 1H, *J* = 8.4 Hz), 7.78, (s, 1H), 8.39 (d, 1H, *J* = 8.8 Hz), 8.55 (d, 1H, *J* = 7.6 Hz), 9.07 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 111.8, 120.5, 122.7, 126.3, 126.5, 130.4, 130.7, 133.3, 142.9, 149.5, 157.5, 161.9. Analysis Calculated for $C_{13}H_7ClN_2O_3$: C 56.85, H 2.57, N 10.20; found C 56.75, H 2.49, N 10.10.

2-(2-chlorophenyl)-5-methyl-1, 3-benzoxazole (6l). mp 74-76 ^{0}C; ESI MS (m/z) = 244 [M+1]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.49 (s, 3H), 7.18 (d, 1H, *J* = 8.4 Hz), 7.38 (m, 2H), 7.47 (d, 1H, *J* = 8.4 Hz), 7.54 (d, 1H, *J* = 9.2 Hz), 7.62 (s, 1H), 8.11 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 21.6, 110.2, 120.4, 123.5, 126.5, 126.8, 126.9, 131.4, 131.9, 133.5, 134.6, 141.9, 148.9, 161.1. Analysis Calculated for $C_{14}H_{10}ClNO$: C 69.00, H 4.14, N 5.75; found C 69.22, H 4.25, N 5.88.

5-methyl-2-(4-nitrophenyl)-1,3-benzoxazole (6m). mp 218-250 ^{0}C; ESI MS (m/z) = 255 [M+1]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.50 (s, 3H), 7.22 (d, 1H, *J* = 8.4 Hz), 7.48 (d, 1H, *J* = 8.4, Hz), 7.59 (s, 1H), 8.35-8.41 (m, 4H). ^{13}C NMR ($CDCl_3$, 75MHz) δ = 21.6, 110.4, 120.5, 124.3, 127.6, 128.4, 133.0, 135.3, 142.2, 149.4, 160.8, 162.7. Analysis Calculated for $C_{14}H_{10}N_2O_3$: C 66.14, H 3.96, N 11.02; found C 66.32, H 4.10, N 10.92**.**

6-Flouro-2-phenyl benzoxazole (6n). mp 108-110 ^{0}C; ESI MS (m/z) = 214 [M+1]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.13-7.16 (m, 1H), 7.33-7.35 (dd, 1H, *J* = 2.4 Hz, 5.6 Hz), 7.55-7.58 (m, 3H), 7.70-7.74 (m, 1H), 8.23-8.26 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 98.5, 98.8, 112.4, 112.6, 120.2, 120.3, 126.8, 127.4, 128.9, 131.5. Analysis Calculated for $C_{13}H_8FNO$: C 73.23, H 3.78, N 6.57; found C 73.29, H 3.68, N 6.40.

5-Methoxy-2-phenylbenzoxazole (6o). mp 82–84 ^{0}C; ESI MS (m/z) = 226 [M+1]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 3.85 (s, 3H), 6.94 (dd, 1H, *J* = 8.8 and 3.1 Hz), 7.41 (d, 1H, *J* = 3.0 Hz), 7.48-7.56 (m, 4H), 8.21-8.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 55.9, 102.9, 110.7, 113.7, 127.3, 127.5, 128.9, 131.4, 142.9, 145.4, 157.4, 163.8. Analysis Calculated for $C_{14}H_{11}NO_2$: C 74.65, H 4.92, N 6.22; found C 74.54, H 4.82, N 6.16.

5, 6-Dimethoxy-2-phenylbenzoxazole (6p). mp 114–115 ^{0}C; ESI MS (m/z) = 256 [M+1]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 7.14 (s, 1H, ArH), 7.26 (s, 1H, ArH), 7.48-7.51 (m, 3H, ArH), 8.19-8.23 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 56.4, 56.5, 94.3, 101.8, 127.0, 127.5, 128.9, 130.9, 134.9, 145.1, 147.8, 148.4, 162.3. Analysis Calculated for $C_{15}H_{13}NO_3$: C 70.58, H 5.13, N 5.49; found C 70.42, H 5.22, N 5.58.

2-Phenylbenzothiazole (6q): mp 107-110°C; ESI MS (*m*/*z*) = 212 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.21 (t, *J* = 7.6 Hz, 1H), 7.34-7.40 (m, 4H), 7.71 (d, *J* = 7.9 Hz, 1H), 8.00-8.06 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 121.3, 122.9, 124.8, 126.0, 127.2, 128.6, 130.6, 133.2, 134.7, 153.8, 167.6. Analysis Calculated for $C_{13}H_9NS$; C 73.90, H 4.29, N 6.63; found C 73.80, H 4.36, N 6.54.

5-Chloro-2-phenylbenzothiazole (6r): mp 138-139°C; ESI MS (*m*/*z*) = 246 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.46-7.51 (m, 3H), 7.77 (d, *J* = 8.6 Hz, 1H), 8.03-8.07 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 122.3, 123.0, 125.6, 127.5, 129.0, 131.3, 132.3, 133.1, 133.2, 154.9, 169.9. Analysis Calculated for $C_{13}H_8ClNS$; C 63.54, H 3.28, N 5.70; found C 63.40, H 3.35, N 6.58.

2-(2-chlorophenyl)-1, 3-benzothiazole (6s). mp 71-73 ^{0}C; ESI MS (m/z) = 246 [M+1]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.38-7.44 (m, 3H), 7.51-7.54 (m, 2H), 7.93 (d, 1H, *J* = 7.6 Hz), 8.13 (d, 1H, *J* = 8.4 Hz), 8.20-8.21 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 121.5, 123.6, 125.6, 126.4, 127.2, 130.9, 131.3, 131.9, 132.4, 132.8, 136.2, 152.6, 164.3. Analysis Calculated for $C_{13}H_8ClNS$: C 63.54, H 3.28, N 5.70; found C 63.44, H 3.33, N 5.67.

2-(3-nitrophenyl)-1, 3-benzothiazole (6t). mp 181-183 ^{0}C; ESI MS (m/z) = 257 [M+1]. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.42 (t, 1H, *J* = 7.6 Hz), 7.51 (t, 1H, *J* = 7.6 Hz), 7.65 (t, 1H, *J* = 7.6 Hz), 7.92 (d, 1H, *J* = 7.6Hz), 8.09 (d, 1H, *J* = 7.6 Hz), 8.30 (dd, 1H, *J* = 6.9 Hz, *J* = 9.2 Hz), 8.38 (d, 1H, *J* = 7.6 Hz), 8.90 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 121.9, 122.4, 123.8, 125.2, 126.1, 126.9, 130.2, 133.1, 135.3, 135.4, 148.8, 154.0, 164.9. Analysis Calculated for $C_{13}H_8N_2SO_2$: C 60.93, H 3.15, N 10.93; found C 60.75, H 3.22, N 10.89.

5-Methoxy-2-phenylbenzothiazole (6u). mp 75–77 ^{0}C; ESI MS (m/z) = 242 [M+1]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 3.87 (s, 3H), 7.04 (dd, 1H, *J* = 3.0 & 9.0 Hz), 7.45 (m, 3H), 7.55 (d, 1H, *J* = 2.0 Hz), 7.68 (d, 1H, *J* = 9.0 Hz), 8.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 75MHz) δ = 56.0, 106.1, 115.9, 122.2, 127.4, 127.8, 129.4, 131.2, 134.2, 155.9, 159.6, 169.6. Analysis Calculated for $C_{14}H_{11}NOS$: C 69.68, H 4.59, N 5.80; found C 69.52, H 4.48, N 5.70.

5,6-Dimethoxy-2-phenylbenzothiazole (6v). mp 145–146 ^{0}C; ESI MS (m/z) = 272 [M+1]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 3.91 (s, 3H), 3.93 (s, 3H), 7.58-7.62 (m, 3H), 7.66 (s, 1H), 7.73 (s, 1H), 8.07-8.12 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 56.1, 56.3, 103.7, 105.8, 126.7, 126.9, 129.7, 131.0, 133.6, 148.2, 148.9, 165.2. Analysis Calculated for $C_{15}H_{13}NO_2S$: C 66.40, H 4.83, N 5.16; found C 66.32, H 4.88, N 5.04.

Spectral and analytical data of 2-substituted* quinazolin-4(3H)-one*:

2-phenylquinazolin-4(3H)-one (8a): mp > 225 ^{0}C; ESI MS (m/z) = 223 [M+1]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 7.52-7.81 (m, 6H), 7.92 (d, *J* = 7.3 Hz, 2H), 8.10 (d, *J* = 7.8 Hz, 1H), 11.30 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 120.1, 121.1, 125.9, 126.4, 127.2, 128.2, 130.2, 132.0, 133.6, 148.5, 149.8, 161.1. Analysis Calculated for $C_{14}H_{10}N_2O$: C 75.66, H 4.54, N 12.60; found C 75.78, H 4.56, N 12.75.

2-(2,4-dichlorophenyl)quinazolin-4(3H)-one (8b): mp 225 ^{0}C; ESI MS (m/z) = 268 [M+1]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 7.59 (t, *J* = 7.2 Hz, 1H), 7.64-7.68 (m, 2H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.79 (s, 1H), 7.87 (t, *J* = 7.7 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 11.00 (s, 1H); ^{13}C NMR (DMSO-d_6, 75MHz) δ = 121.3, 125.8, 127.2, 127.5, 130.4, 130.6, 131.3, 131.4, 131.7, 134.6, 135.3, 148.4, 150.9, 161.3. Analysis Calculated for $C_{14}H_8Cl_2N_2O$: C 57.76 H 2.77, N 9.62; found C 57.84, H 2.63, N 9.50.

2-(4-bromophenyl)quinazolin-4(3H)-one (8c): mp >225 ^{0}C; ESI MS (m/z) = 300 [M+1]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 7.54 (t, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.85 (t, *J* = 7.4 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 2H), 8.16 (d, *J* = 8.0 Hz, 1H), 11.10 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 121.0, 125.2, 125.8, 126.7, 127.5, 129.8, 131.6, 131.9, 134.6, 148.5, 151.4, 162.1. Analysis Calculated for $C_{14}H_9BrN_2O$: C 55.84, H 3.01, N 9.30; found C 55.80, H 2.92, N 9.18.

4-(4-oxo-3,4-dihydroquinazolin-2-yl)benzonitrile (8d): mp >225 ^{0}C; ESI MS (m/z) = 248 [M+1]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 7.58 (t, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.88 (t, *J* = 7.6 Hz, 2H), 8.05 (d, *J* = 8.2 Hz, 2H), 8.16-8.20 (m, 1H), 8.34 (d, *J* = 8.2 Hz, 2H), 11.10 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 113.5, 118.3, 121.1, 125.8, 127.2, 127.7, 128.6, 132.5, 134.7, 136.8, 148.3, 150.9, 162.0. Analysis Calculated for $C_{15}H_9N_3O$: C 72.87, H 3.67, N 16.99; found C 72.78, H 3.60, N 17.09

2-(4-nitrophenyl)quinazolin-4(3H)-one (8e): mp >225 ^{0}C; ESI MS (m/z) = 268 [M+1]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 7.59 (t, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.89-7.95 (m, 2H), 8.19 (d, *J* = 8.1 Hz, 2H), 8.38 (d, *J* = 8.1 Hz, 2H), 11.15 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 121.2, 123.6, 125.9, 127.3, 127.8, 129.3, 134.8, 138.6, 148.3, 149.0, 150.8, 162.1. Analysis Calculated for $C_{14}H_9N_3O_3$: C 62.92, H 3.39, N 15.72; found C 62.81, H 3.44, N 15.82.

2-(2-nitrophenyl)quinazolin-4(3H)-one (8f): mp 225 ^{0}C; ESI MS (m/z) = 268 [M+1]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 7.59 (t, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.81-7.96 (m, 4H), 8.21-8.30 (m, 2H), 11.20 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 121.2, 124.5, 125.9, 127.1, 127.4, 129.2, 131.4, 131.5, 133.9, 134.7, 147.5, 148.5, 151.6, 165.5. Analysis Calculated for $C_{14}H_9N_3O_3$: C 62.92, H 3.39, N 15.72; found C 62.90, H 3.47, N 15.86.

2-(4-hydroxyphenyl)quinazolin-4(3H)-one (8g): mp >225 ^{0}C; ESI MS (m/z) = 239 [M+1]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 6.91 (d, *J* = 8.7 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 2H), 8.13 (d, *J* = 8.0 Hz, 1H), 9.40 (s, 1H), 11.22 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 115.4, 120.6, 123.2, 125.8, 125.9, 127.2, 129.6, 134.5, 149.1, 152.1, 160.6, 162.3. Analysis Calculated for $C_{14}H_{10}N_2O_2$: C 70.58, H 4.23, N 11.76; found C 70.50, H 4.30, N 11.91.

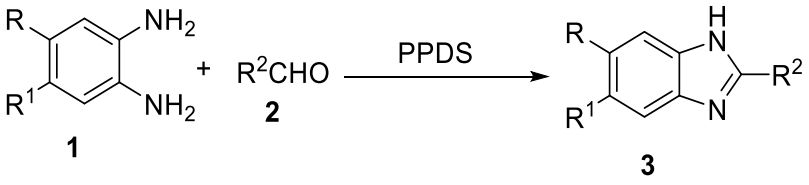
2-(4-(dimethylamino)phenyl)quinazolin-4(3H)-one (8h): mp >225 ^{0}C; ESI MS (m/z) = 266 [M+1]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 3.04 (s, 6H), 6.82 (d, *J* = 9.0 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.81 (t, *J* = 7.6 Hz, 1H), 8.10 (t, *J* = 9.0 Hz, 2H), 8.13 (d, *J* = 8.0 Hz, 1H); 10.90 (s, 1H) ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 39.6, 111.3, 118.7, 120.3, 125.6, 125.8, 127.0, 128.9, 134.6, 145.3, 149.3, 152.3, 162.4. Analysis Calculated for $C_{16}H_{15}N_3O$: C 72.43, H 5.70, N 15.84; found C 72.49, H 5.60, N 15.94.

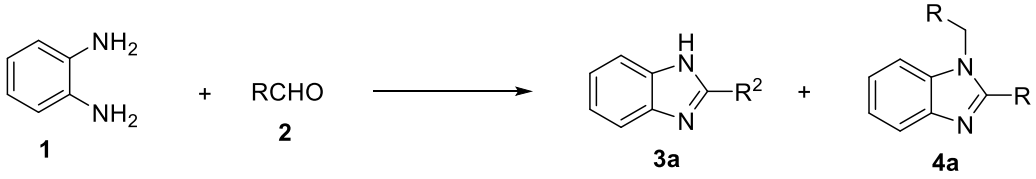
2-(4-hydroxy-3-methoxyphenyl)quinazolin-4(3H)-one (8i): mp >225 ^{0}C; ESI MS (m/z) = 269 [M+1]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 3.90 (s, 3H), 6.93 (d, *J* = 8.3 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 8.3 Hz, 1H), 7.82 (s, 1H), 7.85 (t, *J* = 7.2 Hz, 2H), 8.13 (d, *J* = 7.8 Hz, 1H), 9.82 (s, 1H), 11.30 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 55.8, 111.3, 115.4, 120.6, 121.5, 123.4, 125.8, 125.9, 127.2, 134.5, 147.5, 149.0, 149.9, 162.3. Analysis Calculated for $C_{15}H_{12}N_2O_3$: C 67.16, H 4.51, N 10.44; found C 67.08, H 4.57, N 10.30.

2-(furan-2-yl)quinazolin-4(3H)-one (8j): mp 220 ^{0}C; ESI MS (m/z) = 213 [M+1]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 6.73 (dd, *J* = 1.3 & 3.4 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 3.4Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 1.3 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 11.20 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 112.5, 114.5, 121.1, 125.9, 126.4, 127.2, 134.6, 144.0, 146.1, 146.5, 148.6, 161.5. Analysis Calculated for $C_{12}H_8N_2O_2$: C 67.92, H 3.80, N 13.20; found C 67.99, H 3.74, N 13.09.

Results and discussion

We studied in detail the effects of solvents, oxidants, additive/catalyst and temperature on oxidative coupling reaction of aldehydes with o-arylenediamines resulting to the formation of a library of 2-substituted benzimidazoles (Scheme 1).





Stirring a mixture of o- phenylenediamine (1 mmol) and benzaldehyde (1 mmol) in aqueous micelles (SDS-water) at 60 ^{0}C for 12 hours yielded a crude product, from which the two products **3a** (36 %) and **4a** (32 %) were isolated by column chromatography (Scheme 2).

When the same reaction was carried out with 1 mmol of PPDS, the reaction was complete in 5 hours and after workup **3a** (68 %) was obtained and **4a** was not isolated. When the reaction was carried out with 1 mmol of PPDS and 0.01 mmol of $CuSO_4$ at 60 ^{0}C, it was complete within 50 min and **3a** was isolated in 90 % yield. Thus, it was observed that introduction of just catalytic amount of copper sulphate not only reduces the reaction time but also increases the product yields. We studied the catalytic effect of various additives. It was observed that

the catalytic effect of copper (II) sulphate was superior to other transition metal salts like cupric chloride, cobalt (III) nitrate, ferric chloride and nickel sulphate (Table 1).

Table 1. Effects of PPDS-additives (transition metal salts) over oxidative coupling of benzaldehyde and o- phenylenediamine [a]

Entry	Oxidant/additive	Oxidant/additive (mol%)	Time (h)	% Yield of **3a**[b]	% Yield of **4a**[b]
1	None	-	12	36	32
2	$CuSO_4$	100	12	48	24
3	PPDS	100	5	68	NF[c]
4	PPDS-$CuSO_4$	100:1	<1	90	NF
5	PPDS-$CuCl_2$	100:1	<1	82	NF
6	PPDS-$Co(NO_3)_3$	100:1	<1	80	NF
7	PPDS-$FeCl_3$	100:1	<1	81	NF
8	PPDS-$NiSO_4$	100:1	<1	80	NF

[a] Reaction conditions: o- phenylenediamine (1 mmol), benzaldehyde (1 mmol), SDS-H_2O (3 ml, 0.05g/ml), 60 ^{0}C. [b] Isolated yield. [c] NF = not formed

Stirring a mixture of o-phenylenediamine and an aldehyde (1:1) with PPDS-$CuSO_4$ in aqueous micelles at 60 ^{0}C, the reaction was complete within 50 min and the product was isolated in 90 % yield. At room temperature took longer time to complete (3h) but the yield was same (90%). Upon refluxing the reaction mixture the reaction time was decreased (30 min) but the yield was also decreased to some extent (85%). Thus, stirring the reaction mixture at 60 ^{0}C in the presence of PPDS-$CuSO_4$ was optimal for the synthesis of 2-substituted benzimidazoles.

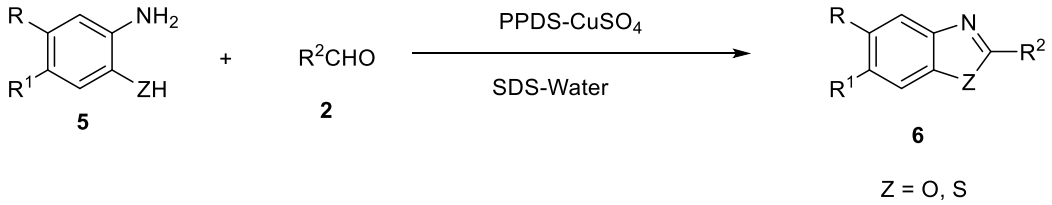
In order to study the effect of solvent over the oxidative coupling of benzaldehyde with 1, 2-phenylenediamines, we carried out the reaction in different solvents. Less polar solvents like dichloromethane and tetrahydrofuran were not suitable for the reaction. Although in more polar organic solvents like ethanol, methanol and acetonitrile yields were not satisfactory, their combination with water resulted satisfactory yields of products. The results clearly indicate that water must be present in PPDS mediated oxidations. Indeed, the reaction in neat water gave poor yields. This was attributed to the poor solubility of reactants in water. To increase the solubility of reactants in water, we carried out the reaction in aqueous solution of sodium dodecyl sulphate (SDS). The reaction in aqueous micelles resulted excellent yield of products. The results are summarized in Table 2.

Table 2. Synthesis of 2-phenyl benzimidazoles using PPDS-$CuSO_4$[a]

Entry	Medium	Reaction time (h)	Yield (%)[b]
1	CH_2Cl_2	6	24
2	THF	4	35
3	CH_3CN	4	37
4	C_2H_5OH	4	48
5	CH_3OH	2	44
6	H_2O	2	31
7	CH_3CN– H_2O (7:3)	1	74
8	CH_3OH – H_2O (7:3)	1	72
9	C_2H_5OH- H_2O (7:3)	1	78
10	H_2O-SDS[c]	<1	90

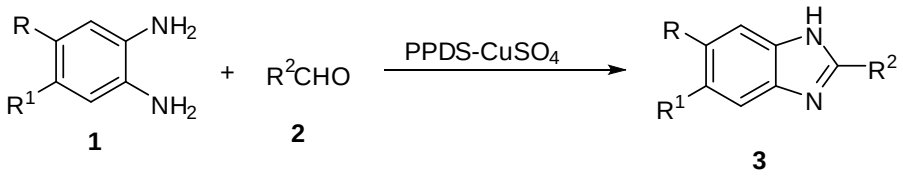
[a] *Reaction conditions: o- Phenylenediamine (1 mmol), benzaldehyde (1 mmol), PPDS (1 mmol), $CuSO_4$ (0.01 mmol), solvent (3 ml) .* [b] *Isolated yield.* [c] *Surfactant 0.05 g/ml.*

In order to study the generality of this oxidative coupling reaction of aldehydes with o-arylenediamines, a library of benzimidazoles was synthesized using optimized reaction conditions. The reaction was not much affected by the nature of aldehydes. Electron rich as well as electron deficient aldehydes gave the oxidative coupling reaction with o-arylenediamines in high yields. The reaction works equally well with aliphatic aldehydes leading to the high yields of products. The results of this study are shown in Table **3**.
Next we examined the oxidative coupling reactions of aldehydes with o-aminophenol and o-aminothiophenol (Scheme 3).



Scheme 3: Oxidative coupling reactions of aldehydes and o-aminophenol.

Table 3. Synthesis of benzimidazole libraries via PPDS-$CuSO_4$ mediated oxidative coupling of aldehydes with o-arylenediamines.[a]

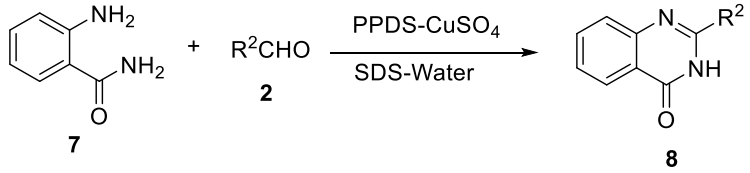


Entry	R	R^1	R^2	Product	Time (min)	Yield (%)[b]
1	H	H	C_6H_5	**3a**	50	90
2	H	H	Indol-3-yl	**3b**	50	88
3	H	H	Pyridin-3-yl	**3c**	45	85
4	CH_3	H	C_6H_5	**3d**	45	81
5	F	H	C_6H_5	**3e**	45	91
6	CH_3	H	Pyridin-3-yl	**3f**	45	82
7	F	H	Pyridin-3-yl	**3g**	40	83
8	H	H	*n*-Pentyl	**3h**	50	86
9	H	H	Cyclohexyl	**3i**	50	85
10	CH_3	H	*n*-Pentyl	**3j**	50	83

[a]*Reaction conditions: aldehyde (1 mmol), o-arylenediamine (1 mmol), PPDS (1 mmol), $CuSO_4$ (0.01 mmol), SDS-water (3 ml, c = 0.05 g/ml), 60 ^{0}C, stirr.* [b]*Isolated yield.*

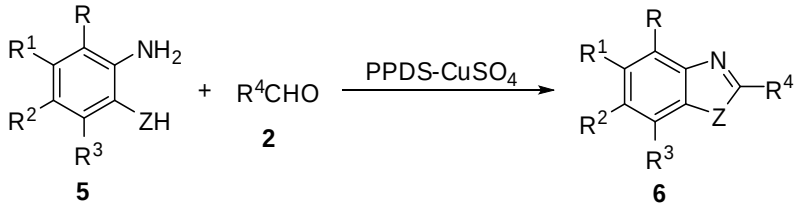
In an optimized reaction conditions, o-aminophenol/thiophenol (1 mmol), aldehyde (1 mmol), PPDS (1 mmol), $CuSO_4$ (0.01 mmol) were taken in aqueous micelles (aqueous SDS 0.05 g/ml) and the reaction mixture was stirred at 60 ^{0}C. The reaction was complete in 40-60 min and products were obtained in high yield. The yield was not much affected with substitution in aldehydes and high yields of products were obtained with both the aliphatic as well as aromatic aldehyde. Using the optimized reaction conditions, we synthesized the libraries of 2-substituted benzoxazoles and benzthiazoles (Table 4).

We then investigated the PPDS-$CuSO_4$ mediated oxidative coupling of aldehydes to form six membered heterocycles. For this, anthranilamide was coupled with aldehydes in the presence of PPDS-$CuSO_4$ resulting to the formation quinazolin-4(3H)-ones (Scheme 4).



Scheme 4: Synthesis of quinazolin-4(3H)-ones.

Table 4. Synthesis of benzoxazole and benzothiazole libraries via PPDS-$CuSO_4$ mediated oxidative coupling of aldehydes with 2-aminophenols and 2-aminothiophenols respectively.[a]



Entry	R	R^1	R^2	R^3	R^4	Z	Product	Time (min)	Yield (%)[b]
1	H	H	H	H	C_6H_5	O	**6a**	50	90
2	CH_3	H	H	H	C_6H_5	O	**6b**	50	88
3	H	H	CH_3	H	C_6H_5	O	**6c**	45	85
4	H	Cl	H	H	C_6H_5	O	**6d**	40	81
5	H	H	H	H	Pyridin-3-yl	O	**6e**	40	91
6	CH_3	H	H	H	Pyridin-3-yl	O	**6f**	40	82
7	H	H	H	H	*n*-Pentyl	O	**6g**	60	83
8	CH_3	H	H	H	*n*-Pentyl	O	**6h**	50	86
9	H	H	H	H	Cyclohexyl	O	**6i**	50	85
10	H	H	H	H	2-ClC_6H_4	O	**6j**	45	83
11	H	Cl	H	H	3-$NO_2C_6H_4$	O	**6k**	40	90
12	H	CH_3	H	H	2-ClC_6H_4	O	**6l**	40	85
13	H	CH_3	H	H	4-$NO_2C_6H_4$	O	**6m**	40	86
14	H	H	F	H	C_6H_5	O	**6n**	60	80
15	H	OCH_3	H	H	C_6H_5	O	**6o**	40	82
16	H	OCH_3	OCH_3	H	C_6H_5	O	**6p**	50	83
17	H	H	H	H	C_6H_5	S	**6q**	40	90
18	H	Cl	H	H	C_6H_5	S	**6r**	60	85
19	H	H	H	H	2-ClC_6H_4	S	**6s**	40	86
20	H	H	H	H	3-$NO_2C_6H_4$	S	**6t**	50	80
21	H	OCH_3	H	H	C_6H_5	S	**6u**	60	82
22	H	OCH_3	OCH_3	H	C_6H_5	S	**6v**	45	88

[a]*Reaction conditions: aldehyde (1 mmol), o-aminophenol/o-aminothiophenol (1 mmol), PPDS (1 mmol), $CuSO_4$ (0.01 mmol), SDS-water (3 ml, c = 0.05 g/ml), 60 ^{0}C, stirr.* [b]*Isolated yield.*

The reaction was carried out with a number of aromatic and aliphatic aldehydes. Generally, the reaction was fast and completed in 25-40 min at 60^{0}C and 2-substituted quinazolin-4(3H)-ones were obtained in high yields. The reaction was carried out in aqueous micelles of SDS. Yields of 2-substituted quinazolin-4(3H)-ones were better in aqueous micelles to those in organic solvents. We synthesized a library of 2-substituted quinazolin-4(3H)-ones by PPDS-$CuSO_4$ mediated oxidative coupling of anthranilamide with aldehydes. The results of this study are shown in table 5.

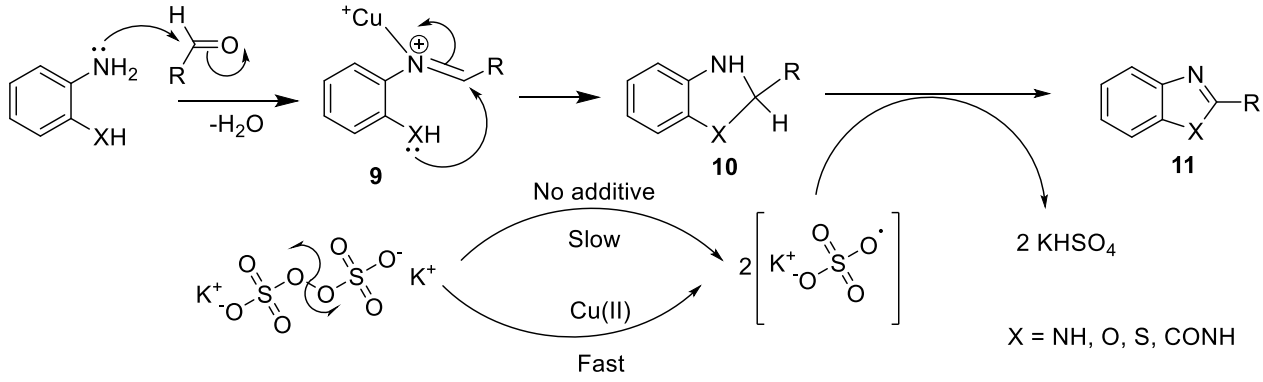
We propose a mechanism for PPDS-$CuSO_4$ mediated oxidative coupling reactions of aldehydes with o-phenylenediamines/o-aminphenols/o-aminothiophenol/anthranilamide (Scheme 5). The reaction of amine with aldehyde forms an imine **9.** Imine **9** is activated by Cu (II) ion and then is attacked by the neighboring nucleophilic group (XH) to form an intermediate **10**. In the presence of transition metal salts (e.g. $CuSO_4$) fast decomposition of PPDS takes place and the intermediate **10** is rapidly oxidized by the radicals anions generated by the PPDS to form 2-substituted benzimidazole/benzoxazoles/benzothiazoles/ quinazolin-4(3H)-ones **11**.

Table 5. Synthesis of a library of quinazolin-4(3H)-ones using PPDS-$CuSO_4$[a]

Entry	R^2	Product	Reaction time (min)	Yield (%)[b]
1	C_6H_5	**8a**	35	94
2	2,4-$Cl_2C_6H_3$	**8b**	35	95
3	4-BrC_6H_4	**8c**	30	92

4	4-CNC_6H_4	**8d**	30	97
5	4-$NO_2C_6H_4$	**8e**	30	94
6	2-$NO_2C_6H_4$	**8f**	25	95
7	4-HOC_6H_4	**8g**	40	90
8	4-$(CH_3)_2NC_6H_4$	**8h**	30	92
9	4-HO-3-$CH_3OC_6H_3$	**8i**	40	90
10	2-Furyl	**8j**	30	92

[a] Reaction conditions: anthranilamide (1 mmol), aldehyde (1 mmol), PPDS (1 mmol), $CuSO_4$ (0.01 mmol), SDS-water (3 ml, c = 0.05 g/ml), 60 ^{0}C, stirr. [b] Isolated yield.



Scheme 5. Proposed mechanism for PPDS-Cu(II)SO4 mediated oxidative coupling reactions of aldehydes with o-phenylenediamines/o-aminphenols/o-aminothiophenol/anthranilamide

Conclusion

In conclusion, we have developed a diversity oriented synthesis of the libraries of the biologically important heterocycles like benzimidazole, benzoxazole, benzothiazole as well as quinazolin-4(3H)-one via PPDS-$CuSO_4$ mediated via oxidative coupling of aldehydes with o-phenylenediamines, o-aminphenols, o-aminothiophenol and anthranilamide respectively in aqueous micelles. The process is a simple and high yielding. In addition, low-cost, environmental friendliness, easy availability, short reaction times as well as excellent chemoselectivity make this methodology a valid contribution to the existing processes in the field of benzimidazoles, benzoxazoles, benzothiazoles and quinazolin-4(3H)-ones.

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