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RESEARCH ARTICLE

Facile One-Pot Multicomponent Synthesis of Biaryl Tetrazoles through *In Situ* Formed Secondary Amides

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Abstract: A series of novel tetrazoles was synthesized through the multicomponent reactions of piperonal, aryl diamines and aroyl chlorides in a one-pot fashion. All the synthesized products were characterized by elemental analyses, FT-IR, ^{1}H NMR ^{13}C NMR and LC-Mass spectral data.

Keywords: Tetrazole, Piperonal, Aryldiamines

Introduction

Tetrazoles are synthetic compounds with the highest nitrogen contents among the stable heterocycles[1]. They have long been recognized as carboxylic acid isosteres[2,3] and are important heterocycles in medicinal chemistry, owing to their increased stability towards metabolic degradation pathways[4]. The acidity of the tetrazole NH group corresponds roughly to that of the carboxylic acid[5]. Interest in tetrazole chemistry over the past few years has been increasing rapidly, mainly as a result of the role played by this heterocyclic functionality in medicinal chemistry as a metabolically stable surrogate for carboxylic acid functionalities[6-8]. Tetrazoles are well known compounds with a number of biological activities[9-12] such as antibacterial, antifungal and analgesic. Piperonal is a molecule widely used as basis for the heliotrope-type perfumes and for cosmetic preparations, being also applied as an intermediate for agrochemical and pharmaceutical products. It has been moreover demonstrated that piperonal has powerful aroma therapeutic qualities able to elevate mood and to impart a general well-being[13-17].

In addition, synthetic compounds containing piperonyl ring possess enormous biological activity such as anti-cancer[18,19], anti-convulsant[20,21], anti-amoebic[22], antiproliferative[23], antiviral[24], anti-tumor[25], anti-plasmodial[26], COX-2 inhibitor[27]. Considering the importance of tetrazole and piperonyl molecules in pharmaceutical filed, we have developed a series of piperonyl-tetrazolo compounds.

Experimental

All the reagents were purchased from Sigma-Aldrich. Solvents were purchased from Finar chemicals and purified prior to use. The reactions were monitored by analytical TLC on silica gel G/GF 254 plates and column chromatography was performed with 60-120 mesh silica gel. Melting points were determined on a veego (India) capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer by using KBr. ^{1}H and ^{13}C NMR spectra were recorded in Bruker 300 and 75 MHz spectrometer.

*General procedure for the synthesis of compounds (**4a-4o**)*

To a stirred solution of benzo[1,3]dioxole-5-carbaldehyde **1a** (0.005 mol), phenyldiamine **2a-2c** (0.005 mol) and benzoyl chlorides **3a-3e** (0.005 mol) were added and refluxed for 4 h at 70 °C. To this reaction mixture KOH (1 mmol), PCl_5 (0.001 mol) and NaN_3 (0.005 mol) were added and stirred for 6 h at 80 °C. The reaction progress was monitored by TLC by using ethyl acetate-hexane (80:20%). After the completion of the reaction, the solvent was evaporated *in vacuo* and the residue was diluted with CH_2Cl_2 (50 mL) and washed with saturated NH_4Cl (20 mL) and water (20 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane/ethyl acetate as eluent.

*4(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-2-(5-phenyl-1H-tetrazol-1-yl)aniline (**4a**)*

Anal. Calcd. (%) for $C_{21}H_{15}N_5O_2$: C, 68.28; H, 4.09 ; N, 18.96. Found (%): C, 68.26 ; H, 4.08 ; N, 18.94; Pale yellow solid; m. p. 166-168°C; R_f = 0.41; FT-IR (KBr, cm^{-1}): 1609, 1586; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 9.22 (s, 1H), 7.77-6.35 (m, 12H), 6.02 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm):165.49, 158.01, 150.66, 147.28, 145.48, 138.50, 134.11, 132.59, 130.26, 129.05, 128.51, 128.12, 126.51, 120.28, 108.17, 106.56, 101.73; LC-MS (*m/z*): 369.1249.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-2-(5-(4-chlorophenyl)-1H-tetrazol-1-yl)aniline (**4b**)*

Anal. Calcd. (%) for $C_{21}H_{14}ClN_5O_2$: C, 62.46; H, 3.49 ; N, 17.34. Found (%): C, 68.44; H, 3.46; N, 17.31. Yellow solid; m. p.180-182 °C; R_f = 0.47. FT-IR (KBr, cm^{-1}): 1652, 1596; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 9.76 (s, 1H), 7.97-6.50 (m, 11H), 5.98 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6,δ/ppm):165.13, 156.58, 150.81, 147.58, 145.05, 137.52, 134.90, 131.52, 130.73, 128.51, 127.82, 125.43, 121.55, 120.86, 108.25, 106.19, 101.58; LC-MS (*m/z*): 403.1114.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-2-(5-(4-fluorophenyl)-1H-tetrazol-1-yl)aniline (**4c**)*

Anal. Calcd. (%) for$C_{21}H_{14}FN_5O_2$: C, 65.11; H, 3.64; N, 18.08. Found (%): C, 65.07; H, 3.62; N, 18.04; Yellow solid; m. p.145-147 °C; R_f = 0.49; FT-IR (KBr, cm^{-1}):1603, 1594 ; ^{1}H NMR (300 MHz, $CDCl_3$,δ/ppm): 7.92 (s, 1H), 7.82-6.50 (m, 11H), 6.01 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6,δ/ppm):165.05, 152.83, 151.51, 148.99, 147.67, 146.55, 136.89, 135.44, 131.61, 129.20, 128.74, 128.07, 126.65, 121.73, 120.83, 109.90, 106.52, 102.07; LC-MS (*m/z*) 387.1209.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-2-(5-(4-methoxyphenyl)-1H-tetrazol-1-yl)aniline (**4d**)*

Anal. Calcd. (%) for$C_{22}H_{17}N_5O_3$: C, 66.16; H, 4.29; N, 17.53. Found (%):C, 66.14 ; H, 4.25; N, 17.50; Brown solid; m. p.112-14 °C; R_f = 0.39; FT-IR (KBr, cm^{-1}): 1607, 1581; ^{1}H NMR (300 MHz, $CDCl_3$,δ/ppm): 9.43 (s, 1H), 7.98-6.52 (m, 11H), 5.98 (s, 2H), 3.85 (s, 3H); ^{13}C NMR(75 MHz, DMSO-d_6,δ/ppm):165.34, 155.83, 149.03, 147.91, 146.11, 137.29, 135.08,

131.66, 130.87, 128.61, 127.52, 125.68, 121.48, 120.66, 109.11, 106.57, 101.99, 54.36; LC-MS(*m/z*): 399.1201.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-2-(5-(p-tolyl)-1H-tetrazol-1-yl)aniline (**4e**)*

Anal. Calcd. (%) for$C_{22}H_{17}N_5O_2$: C, 68.92; H, 4.47; N, 18.27; Found (%): C, 68.88; H, 4.43; N, 18.25; Yellow solid; m. p. 137-139 °C; R_f = 0.40; FT-IR (KBr, cm^{-1}): 1609, 1573; ^{1}H NMR (300 MHz, $CDCl_3$,δ/ppm): 9.23 (s, 1H), 7.80-6.55 (m, 11H), 6.02 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6,δ/ppm):165.28, 158.50, 150.01, 147.96, 146.72, 137.20, 134.91, 131.50, 130.97, 128.34, 127.55, 125.52, 121.29, 120.61, 108.37, 106.10, 101.64, 20.96; LC-MS (*m/z*) 383.3875.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-4-(5-phenyl-1H-tetrazol-1-yl)aniline (**4f**)*

Anal. Calcd. (%) for$C_{21}H_{15}N_5O_2$: C, 68.28; H, 4.09; N, 18.96. Found (%): C, 68.27; H, 4.07; N, 18.95; Colorless solid; m. p.155-157 °C; R_f = 0.43; FT-IR (KBr, cm^{-1}): 1604, 1578; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.37 (s, 1H), 7.71-6.52 (m, 12H), 6.04 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6,δ/ppm):165.41, 158.33, 151.11, 148.19, 147.02, 137.38, 134.27, 130.89, 129.92, 128.51, 128.01, 126.49, 121.77, 120.61, 107.84, 106.33, 101.71; LC-MS (*m/z*): 369.1236.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-4-(5-(4-chlorophenyl)-1H-tetrazol-1-yl)aniline (**4g**)*

Anal. Calcd.(%) for$C_{21}H_{14}ClN_5O_2$: C, 62.46; H, 3.49; N, 17.34. Found (%): C, 62.43; H, 3.47 ; N, 17.32; Brown solid; m. p.144-146 °C; R_f = 0.44; FT-IR (KBr, cm^{-1}): 1622, 1595; ^{1}H NMR (300 MHz, $CDCl_3$,δ/ppm):8.38 (s, 1H), 7.84-6.48 (m, 11H), 6.04 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6,δ/ppm):164.26, 158.96, 150.11, 149.01, 147.96, 146.87, 136.97, 134.83, 133.58, 130.95, 129.56, 128.40, 125.67, 121.89, 120.67, 108.37, 106.16, 101.67; LC-MS (*m/z*): 403.3265.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-4-(5-(4-fluorophenyl)-1H-tetrazol-1-yl)aniline (**4h**)*

Anal. Calcd. (%) for$C_{21}H_{14}FN_5O_2$: C, 65.11; H, 3.64; N, 18.08. Found (%): C, 65.09; H, 3.63 ; N, 18.06; Colorless solid; m. p.137-139 °C; R_f = 0.51; FT-IR (KBr, cm^{-1}): 1605, 1593; ^{1}H NMR (300 MHz, $CDCl_3$,δ/ppm):8.36 (s, 1H), 7.83-6.57 (m, 11H), 6.05 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6,δ/ppm):165.22, 164.26, 162.74, 158.54, 150.02, 147.96, 146.79, 137.08, 134.86, 131.34, 130.96, 125.53, 121.89, 120.99, 115.38, 108.36, 106.09, 101.65; LC-MS(*m/z*): 387.3789.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-4-(5-(4-methoxyphenyl)-1H-tetrazol-1-yl)aniline (4i)

Anal. Calcd. (%) for $C_{22}H_{17}N_5O_3$: C, 66.16; H, 4.29; N, 17.53. Found (%): C, 66.14; H, 4.27; N, 17.51;Yellow solid; m. p.150-152 °C; R_f = 0.42; FT-IR (KBr, cm^{-1}): 1609, 1594; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm):8.38 (s, 1H), 7.86-6.89 (m, 11H), 6.04 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm):165.31, 148.33, 141.52, 139.36, 132.03, 131.46, 129.29, 128.85, 127.70, 126.87, 115.97, 112.98, 108.55, 106.26, 102.29, 101.56, 55.38; LC-MS (*m/z*): 399.4026.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-4-(5-(p-tolyl)-1H-tetrazol-1-yl)aniline (**4j**)*

Anal. Calcd. (%) for$C_{22}H_{17}N_5O_2$: C, 68.92; H, 4.47; N, 18.27. Found (%): C, 68.90; H, 4.45; N, 18.26; Pale yellow solid;m. p. 159-161 °C; R_f = 0.46; FT-IR (KBr, cm^{-1}): 1605, 1590; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.37 (s, 1H), 7.86-6.89 (m, 11H), 6.03 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 165.19, 158.94, 150.11, 149.01, 147.96, 146.60, 141.50, 137.30, 134.89, 132.04, 128.86, 127.62, 125.68, 121.89, 120.92, 108.36, 106.16, 101.67; LC-MS(*m/z*): 383.4089.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-3-(5-phenyl-1H-tetrazol-1-yl)aniline (**4k**)*

Anal. Calcd. (%) for$C_{21}H_{15}N_5O_2$: C, 68.28; H, 4.09; N, 18.96. Found (%): C, 68.27 ; H, 4.08; N, 18.95;Colorless solid;m. p.190-192 °C; R_f = 0.46; FT-IR (KBr, cm^{-1}): 1601, 1582; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm):9.81 (s, 1H), 7.79- 6.67 (m, 12H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm):165.54, 139.32, 134.93, 131.52, 129.08, 128.73, 128.54, 128.33, 127.67, 116.07, 112.95, 108.55, 106.26, 102.30, 100.83; LC-MS (*m/z*): 369.1311.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-3-(5-(4-chlorophenyl)-1H-tetrazol-1-yl)aniline (**4l**)*

Anal. Calcd. (%) for$C_{21}H_{14}ClN_5O_2$: C, 62.46; H, 3.49; N, 17.34. Found (%): C, 62.44; H, 3.47 ; N, 17.32;Pale yellow solid; m. p.187-189 °C; R_f = 0.52; FT-IR (KBr, cm^{-1}): 1623, 1594; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 9.82 (s, 1H), 7.72- 6.45 (m, 11H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm):164.48, 139.17, 136.41, 136.15, 133.61, 130.99, 129.66, 129.56, 128.95, 128.56, 128.44, 116.23, 112.95, 108.58, 108.44, 106.29, 102.32, 101.75; LC-MS (*m/z*): 403.0340.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-3-(5-(4-fluorophenyl)-1H-tetrazol-1-yl)aniline (**4m**)*

Anal. Calcd. (%) for$C_{21}H_{14}FN_5O_2$: C, 65.11; H, 3.64; N, 18.08. Found (%): C, 65.09 ; H, 3.62; N, 18.06; Colorless solid; m. p.197-198 °C; R_f = 0.53; FT-IR (KBr, cm^{-1}): 1604, 1589; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 9.84 (s, 1H), 7.86- 6.54 (m, 11H), 5.98 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm):165.28, 164.41, 162.80, 139.23, 131.46, 131.34, 131.31, 130.45, 130.36, 128.57, 116.09, 115.37, 115.15, 112.89, 108.55, 106.26, 102.29; LC-MS (*m/z*):387.3741.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-3-(5-(4-methoxyphenyl)-1H-tetrazol-1-yl)aniline (**4n**)*

Anal. Calcd. (%) for$C_{22}H_{17}N_5O_3$: C, 66.16; H, 4.29; N, 17.53. Found (%):C, 66.14; H, 4.27; N, 17.51;Colorless solid; m. p.182-183 °C; R_f = 0.58; FT-IR (KBr, cm^{-1}): 1605, 1557; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 9.80 (s, 1H), 7.99- 6.07 (m, 11H), 5.96 (s, 2H), 3.87(s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm):165.89, 164.84, 163.10, 161.86, 139.43, 131.19, 129.60, 126.93, 121.80, 115.85, 114.00, 113.54, 112.95, 51.77; LC-MS (*m/z*): 399.4012.

*(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-3-(5-(p-tolyl)-1H-tetrazol-1-yl)aniline (**4o**)*

Anal. Calcd. (%) for $C_{22}H_{17}N_5O_2$: C, 68.92; H, 4.47; N, 18.27. Found (%): C, 68.90; H, 4.45; N, 18.24; Colorless solid; m. p. 175-176 °C; R_f = 0.59; FT-IR (KBr, cm^{-1}): 1607, 1591; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 9.79 (s, 1H), 7.57- 6.26 (m, 11H), 5.97 (s, 2H), 2.58 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm):165.42, 148.51, 142.56, 139.74, 132.51, 131.23, 129.62, 128.99, 128.05, 126.63, 116.09, 112.74, 108.38, 106.85, 102.59, 101.35, 21.55; LC-MS(*m/z*): 383.4019.

Results and Discussion

We started our investigation by employing piperonal, *o*-phenyl diamine with benzoyl chloride in the presence of PCl_5 and NaN_3 as model substrates. As we expected the reaction was successful and gave the desired biaryl tetrazole. However, the yield of expected tetrazole is very low. Hence, the reaction was optimized to increase the yield and find out the most suitable conditions for the synthesis of biaryl tetrazole. We studied the various parameters such as solvents, base and temperature to achieve suitable conditions and the results are summarized in Table 1-3.

It was observed that, among all solvents, the best result (80%) was obtained in ethanol (Table 1). Further, the increasing volume of solvent did not affect the yield of tetrazole. Next, variety of organic and inorganic bases were utilized this reaction. Inorganic bases such as KOH, NaOH, K_2CO_3, Na_2CO_3, were effectively increases the target product and found KOH is the best one. In spite of, organic bases such as pyridine, piperidine and triethylamine were did not increase the yield of expected product (Table 2). The expected product was not obtained when the reaction was carried out in the absence of PCl_5. Thus prove the crucial role of PCl_5 in the conversion of secondary amide to tetrazole *in situ*.

Table 1. Effect of solvents

Entry	Solvent	Yield, %
1	Ethanol	78
2	Methanol	72
3	*n*-Propanol	68
4	Toluene	61
5	DMF	57
6	DMAc	59
7	DMSO	52

Table 2. Effect of bases

Entry	Base	Yield, %
1	No base	35
2	KOH	78
3	K_2CO_3	71
4	NaOH	74
5	Na_2CO_3	65
6	Pyridine	40
7	Piperidine	35
8	Triethylamine	49

Table 3. Effect of temperature

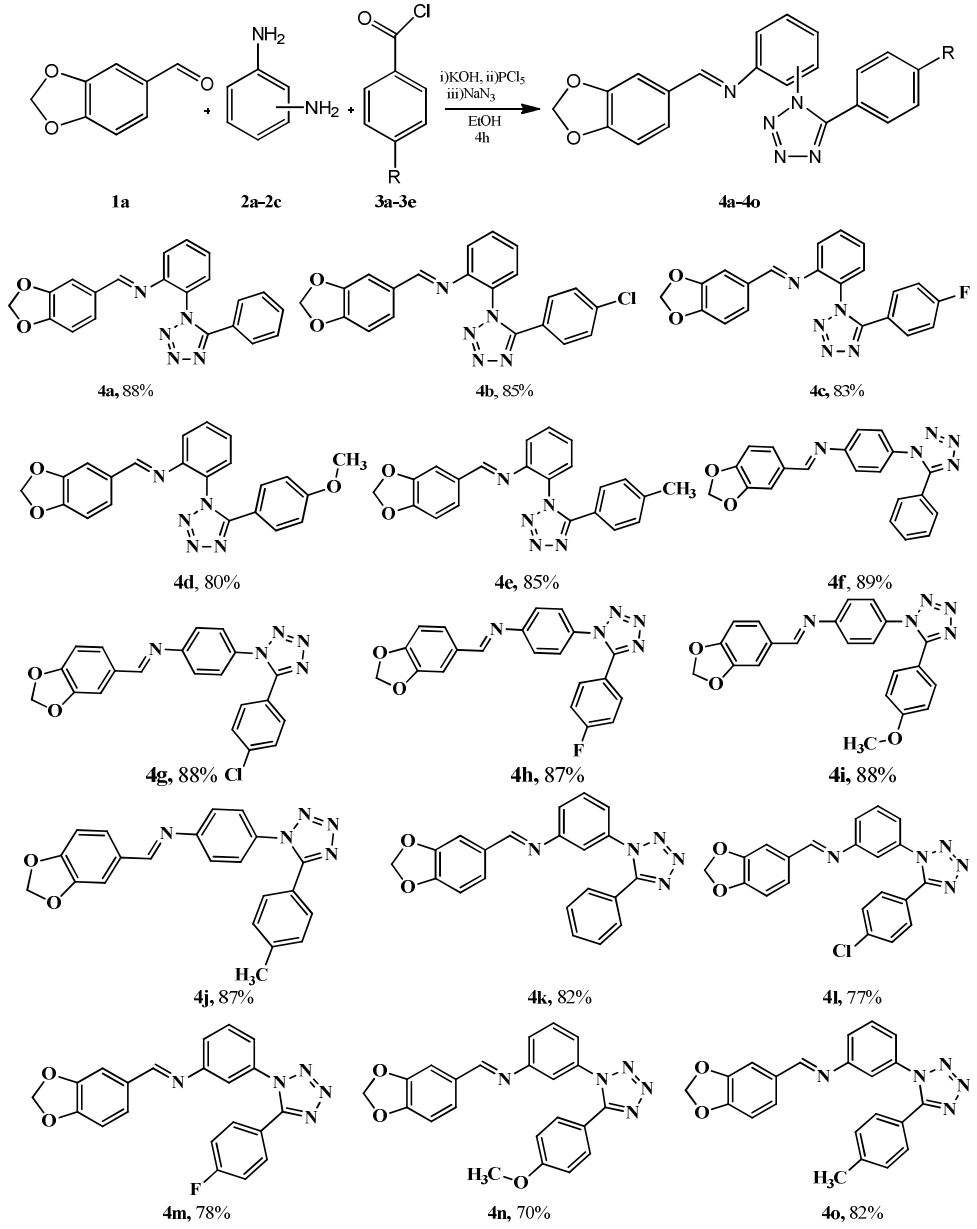
Entry	Temperature, °C	Yield, %
1	RT	No reaction
2	40	55
3	50	68
4	60	79
5	70	88
6	80	87
7	90	71

We further examined the effect of temperature on the tetrazole synthesis. At the beginning, the reaction was carried out in room-temperature. No progress was observed and hence the same reaction was studied by increasing the temperature from 50-90 °C. Higher yield was obtained at 70 °C. No significant increase in the yield of product was observed as the reaction temperature was raised from 70 °C to 110 °C. Therefore, 70 °C was chosen for this reaction. With this optimized reaction conditions in hand we next explore the reaction scope. A variety of aryl diamine and benzoylchlorides possessing either electron-donating or –withdrawing groups.

Generally, all the aryl diamines **(2a-2c)** and benzoyl chlorides **(3a-3e)** underwent above resulting protocol smoothly and afforded expected products in good yields. In all the cases, the reactions proceeded in an excellent regioselective manner and provided only a particular regioisomer as sole product. At the outset, sterically hindered *ortho*-phenydiamine was allow to react with piperonal and substituted benzoyl chlorides **(3a-3e)** underwent this reaction successfully and provided **4a-4e** in 80-88% of isolated yields. Among those, unsubstituted benzoyl chloride gave 88% of the desired product (Scheme 1).

Next, the reaction of **1a** with *para*-phenyl diamine **(2b)** and benzoyl chlorides **(3a-3e)** gave **4f-4j** in an excellent yield (87-89%). 89% of the tiled product was obtained by using unsubstituted benzoyl chloride. In the same way, the reaction of meta-phenyl diamine **(2c)** with **1a** and **3a-3e** smoothly participated and provided biaryl tetrazoles **(4k-4o)** in good quantities. The current investigation has merits over the existing methods in metal catalysts

were employed. Facile manner of synthesis, use of simple reagents, ease of isolation of products and milder reaction conditions are the unique features of this method.

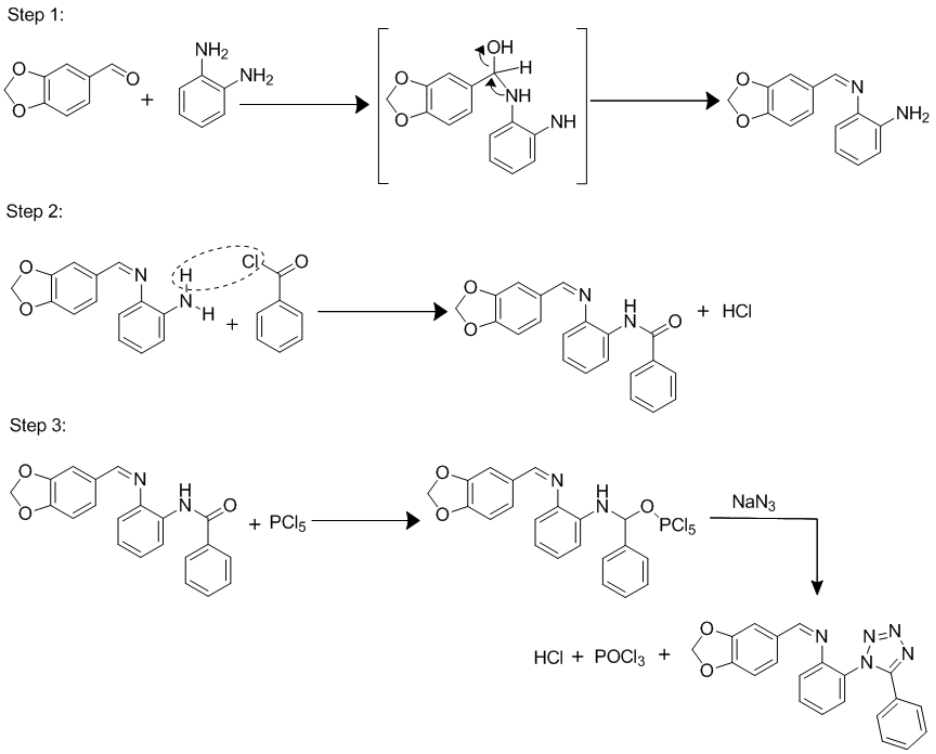


Scheme 1. Syntheses of tetrazole derivatives

Reaction mechanism

The reaction mechanism (Scheme 2) involves three steps. The step 1 involved the condensation reaction of piperanol with *ortho*-phenylene diamine to form Schiff base. First, the amine nitrogen acts as a nucleophile, attacking the carbonyl carbon. This is closely analogous to

hemiacetal and hemiketal formation. In the next step, Schotten-Baumann reaction of Schiff base derived from step 1 with benzoyl chloride provided secondary amide. In the final step, secondary amide initially reacts with PCl_5 and gives an intermediate. This intermediate further reacted with NaN_3 to yield expected tetrazole through cyclization process.



Scheme 2. Proposed reaction mechanism of the synthesis of tetrazoles from secondary amide *in situ*

Conclusion

We have developed an extremely efficient and metal free protocol for the synthesis of biologically active tetrazole derivatives. All the synthesized products were confirmed through IR, ^{1}H, ^{13}C NMR and LC-MS. This is the first report of the synthesis of tetrazoles *via* multicomponent reaction of piperonal, various aryldiamines, substituted benzoylchlorides, in the presence of PCl_5 and NaN_3 an inexpensive azide source. The advantages of this new method are operational simplicity; high to excellent yields of products in short reaction times and easy workup procedures.

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