Research Article

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An Efficient and Regioselective Synthesis of Tetrazoles under Transition - Metal-Free Conditions

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ABSTRACT

A novel protocol for the synthesis of series of tetrazoles is demonstrated via in-situ formed secondary amides under transition-metal free conditions. The reaction well tolerates a wide variety of functional groups to afford structurally diverse tetrazoles in good to excellent yields at 70°C. All the synthesized compounds were characterized by FT- IR, ^{1}H /^{13}C NMR, LC-Mass spectral data, and elemental analyses.

Keywords: Diamine; Piperonal; Tetrazole.

1. INTRODUCTION

Tetrazole and its derivatives were found to possess several biological activities, including antiallergic (Ikeda *et al.* 1992; Imai *et al.* 2016), antimicrobial activity (Varadharaji *et al.* 2010; Dai *et al.* 2015; Feinn *et al.* 2017), antihypertensive activity, antiinflammatory activity (Mohite *et al.* 2010), central nervous system stimulant activity (Shin-ichi *et al.* 1997), antitubercular activity (Ademac *et al.* 2005), etc. The numerous biological activities of tetrazoles are considered due to their distinctive characteristic properties, *viz.*, (i) a close similarity is observed between the acidity of the tetrazole group and the carboxylic acid group (Meanwell, 2011; Allen *et al.* 2012; Pagacz-Kostrzewa *et al.* 2012) and (ii) the tetrazole function is metabolically stable than that acid function. This aspect has been considered a primary driving force for continual research in the area of tetrazole chemistry.

2. RESULTS & DISCUSSIONS

To test our hypothesis, we treated piperonal hydrazine hydrate with benzoyl chloride in the presence of PCl_5 and NaN_3 as model substrates under metal-free conditions. Pleasingly, the reaction was successful and afforded the desired tetrazoles. Nevertheless, the yield of expected tetrazole is very low. Hence, the reaction conditions were optimized to achieve the yield and find out the most suitable conditions for the synthesis of aryl tetrazole. We investigate the various reaction parameters such as solvents, base, and temperature to achieve suitable conditions, and the results are summarized in Table 1-Table 3. The screening of a series of solvents indicated that polar solvents such as DMSO and DMF disfavored the desired transformation and that ethanol was the best reaction media (Table 1). Subsequently, the increasing volume of solvent did not affect the yield of tetrazole. Next, a variety of organic and inorganic bases have utilized this reaction. The selected reaction also proceeded in the absence of a base. In such a case, we obtained a lower quantity of the product. Incorporating various inorganic bases such as KOH, NaOH, K_2CO_3, Na_2CO_3, were effective increases the titled product and found KOH is the best one. However, organic bases such as pyridine, piperidine, and triethylamine were done not increase the yield of the target product (table 2). The expected product was not obtained when the reaction was carried out in the absence of PCl_5. Thus prove the vital role of PCl_5 in the conversion of *in-situ* formed secondary amide to tetrazole.

Table 1. Effect of solvents.

Entry	Solvent	Yield (%)
1	Ethanol	75
2	Methanol	68
3	n-Propanol	62
4	Toluene	63
5	DMF	55
6	DMAc	57
7	DMSO	56

Table 2. Effect of bases.

Entry	Base	Yield (%)
1	No base	12
2	KOH	75
3	K_2CO_3	66
4	NaOH	70
5	Na_2CO_3	63
6	Pyridine	52
7	Piperidine	29
8	Triethylamine	41

Table 3. Effect of temperature.

Entry	Temperature(°C)	Yield (%)
1	RT	No reaction
2	40	50
3	50	59
4	60	61
5	70	77
6	80	73
7	90	68

The effect of temperature on the synthesis of tetrazole was undertaken. Initially, the chosen reaction was performed at room temperature, wherein no reaction occurred, and hence the same reaction was studied by increasing the temperature from 50-90 °C. A higher yield was obtained at 70 °C. A dramatic decrease in yield was observed when the reaction temperature was raised from 90 °C to 110 °C. Therefore, 70 °C was chosen for this reaction.

With these optimized reaction conditions in hand, we then examined the scope of aroyl chlorides and diamine. A variety of diamine and aroyl chlorides possessing either electron-donating or-withdrawing groups. The optimized reaction conditions were found to be applicable to a broad range of substrates (Fig 1).

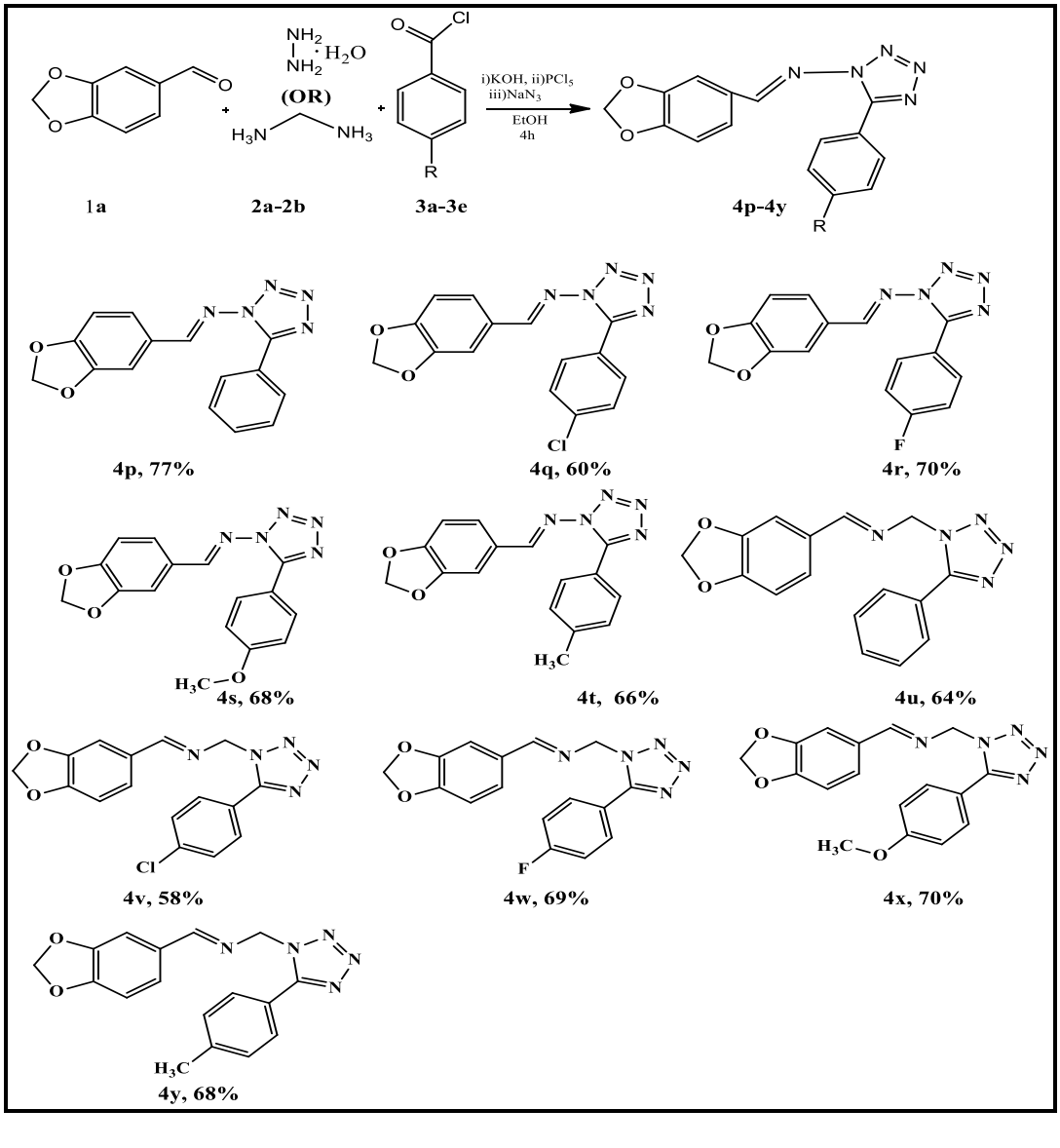


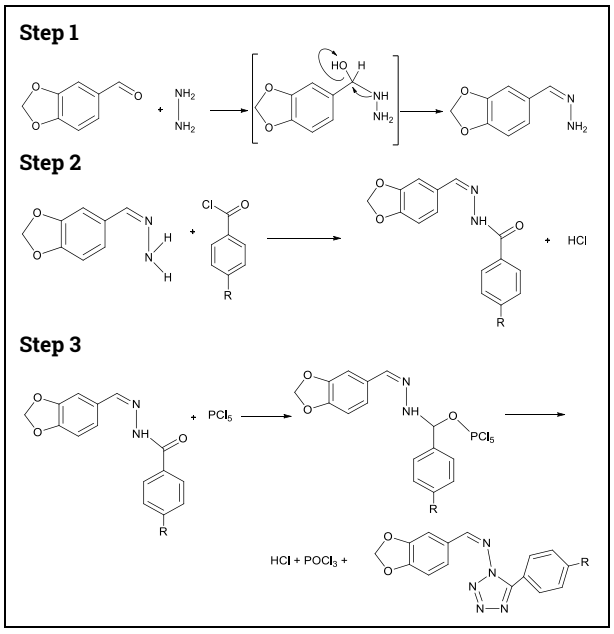
Fig 1: Synthesis of tetrazole derivatives.

Generally, all the diamines (2a-2b) and aroyl chlorides (3a-3e) underwent the above-resulting protocol smoothly and afforded expected tetrazoles in good yields. In all the cases, the reactions proceeded in an excellent regioselective manner and provided only a particular regioisomer as a single product. At the outset, hydrazine hydrate(2a)was allowed to react with piperonal, and substituted benzoyl chlorides (3a-3e) underwent this reaction successfully and provided 4p-4t in 77-60% of isolated yields. Among those, unsubstituted benzoyl chloride gave 77% of tetrazole.

After that, the reaction of 1a with methylene diamine (2b) and aroyl chlorides (3a - 3e) gave 4u -4y in an excellent yield (58 -70%). 70% of the tiled product was obtained by using 4-methoxybenzoyl chloride. The present exploration has virtues over the existing protocols in metal catalysts were employed. Simplistic manner of synthesis, use of simple and commercially available reagents, ease of isolation of products and milder reaction conditions are the unique features of this method.

3. REACTION MECHANISM

The proposed reaction mechanism involves three steps. The first step involved the condensation reaction of piperanol with a diamine to form a Schiff base. Initially, 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 the cyclization process.



4. EXPERIMENTAL

4.1 General Information

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. ^1H and ^{13}C NMR spectra were recorded in Bruker 300 and 75 MHz spectrometers.

4.2 General Procedure for the Synthesis of Compounds 4p-4y

To a stirred solution of benzo[1,3]dioxole-5-carbaldehyde 1a (0.005 mol), diamines 2a-2b (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.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-5-phenyl-1H-tetrazol-1-amine (4p)

Anal. Calcd. (%) for$C_{15}H_{11}N_5O_2$: C, 61.43 ; H, 3.78 ; N, 23.88. Found (%):C, 61.41 ; H, 3.75 ; N, 23.86; Yellow Solid; m.p. 89-91°C; R_f = 0.53; FT-IR (KBr, cm^{-1}): 1603, 1571; ^1H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.52 (s, 1H), 7.60-6.58 (m, 8H) 6.04 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 164.26, 160.22, 147.47, 129.72, 129.59, 127.81, 124.63, 115.20, 115.12, 114.91, 108.09, 105.49, 101.22; LC-MS (m/z): 293. 3567.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-5-(4-chlorophenyl)-1H-tetrazol-1-amine(4q)

Anal. Calcd. (%) for $C_{15}H_{10}ClN_5O_2$: C, 54.97 ; H, 3.08 ; N, 21.37. Found (%):C, 54.95 ; H, 3.06 ; N, 21.35; Yellow solid;m. p. 96-97°C; R_f= 0.48; ; FT-IR (KBr, cm^{-1}): 1601, 1585; ^1H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.53 (s, 1H), 7.44-7.11 (m, 7H) 7.17 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.02 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 163.96, 160.24, 147.49, 146.04, 129.74, 129.61, 127.83, 124.65, 115.22, 114.93, 108.11, 105.51, 101.24; LC-MS (m/z): 327.6845.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-5-(4-fluorophenyl)-1H-tetrazol-1-amine (4r)

Anal. Calcd. (%) for $C_{15}H_{10}FN_5O_2$: C, 57.88 ; H, 3.24 ; N, 22.50; Found (%):C, 57.87 ; H, 3.22 ; N, 22.49; Yellow solid; m. p. 92-93°C; R_f = 0.54; FT-IR (KBr, cm^{-1}): 1603, 1582; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.54 (s, 1H), 7.45-6.85 (m, 7H), 6.02 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 164.30, 160.26, 149.58, 147.51, 129.76, 129.63, 128.71, 127.85,124.67, 115.24, 115.16, 114.95, 108.13, 105.53, 101.26; LC-MS (m/z): 311.3412.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-5-(4-methoxyphenyl)-1H-tetrazol-1-amine (4s)

Anal. Calcd. (%) for $C_{16}H_{13}N_5O_3$: C, 59.44 ; H, 4.05 ; N, 21.66; Found (%):C, 59.42 ; H, 4.03 ; N, 21.64; Yellow solid; m. p. 98-99°C; R_f = 0.42; FT-IR (KBr, cm^{-1}): 1602, 1574; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.53 (s, 1H), 7.44-7.25 (m, 5H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.02 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 164.10, 159.28, 147.14, 128.78, 128.65, 126.87, 123.69, 114.26, 113.97, 107.15, 104.55, 100.28, 53.88; LC-MS (m/z): 323.1851.

(E)-N-(benzo[d][1,3]dioxol-5-ylmethylene)-5-(p-tolyl)-1H-tetrazol-1-amine (4t)

Anal. Calcd. (%) for $C_{16}H_{13}N_5O_2$: C, 62.53 ; H, 4.26 ; N, 22.79; Found (%):C, 62.51 ; H, 4.25 ; N, 22.77; Yellow solid;m. p. 87-88°C; R_f = 0.57; FT-IR (KBr, cm^{-1}): 1602, 1575 ; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.53 (s, 1H), 7.38-7.10 (m, 5H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.05 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 163.90, 160.18, 148.04, 129.68, 129.55, 127.77, 124.59, 115.16, 114.87, 108.05, 105.45, 101.18, 21.85; LC-MS (m/z): 307.9128.

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

Anal. Calcd. (%) for $C_{16}H_{13}N_5O_2$: C, 62.53; H, 4.26; N, 22.79; Found (%):C, 62.51 ; H, 4.25 ; N, 22.80; White solid; m. p.112-114°C; R_f = 0.38; FT-IR (KBr, cm^{-1}): 1604, 1587 ; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.14 (s, 1H), 7.52-6.78 (m, 8H), 5.98 (s, 2H), 3.89 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): δ161.66, 149.73, 148.15, 130.97, 124.29, 107.96, 106.50, 101.35, 61.39; LC-MS (m/z): 307.5497.

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

Anal. Calcd. (%) for $C_{16}H_{12}ClN_5O_2$: C, 56.23; H, 3.54; N, 20.49; Found (%):C, 56.22 ; H, 3.51 ; N, 20.50; White solid; m. p.119-121°C; R_f = 0.53; FT-IR (KBr, cm^{-1}): 1623, 1571;^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.23 (s, 1H), 7.60-6.87 (m, 7H), 5.99 (s, 2H), 3.92 (s, 2H);^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 161.75, 149.82, 148.24, 131.06, 128.59, 126.91, 124.38, 122.04, 108.05, 106.59, 101.44, 61.48; LC-MS (m/z): 341.1987.

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

Anal. Calcd. (%) for$C_{16}H_{12}FN_5O_2$: C, 59.08; H, 3.72; N, 21.53; Found: C, 59.11 ; H, 3.69 ; N, 21.50; White solid; m. p. 124-125°C; R_f = 0.58; FT-IR (KBr, cm^{-1}): 1610, 1582 ; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.13 (s, 1H), 7.79-6.83 (m, 7H), 5.97 (s, 2H), 3.88 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 161.86, 154.09, 152.58, 149.93, 148.35, 131.17, 130.54, 129.95, 124.49, 122.15, 108.16, 106.70, 101.55, 61.59; LC-MS (m/z): 325. 6385

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

Anal. Calcd. (%) for $C_{17}H_{15}N_5O_3$: C, 60.53; H, 4.48; N, 20.76; Found: C, 60.52 ; H, 4.46 ; N, 20.75; White solid;m. p.129-130°C; R_f = 0.56; FT-IR (KBr, cm^{-1}): 1608, 1589; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.11 (s, 1H), 7.41-6.29 (m, 7H), 5.99 (s, 2H), 3.88 (s, 3H), 3.87 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 161.87, 153.90, 149.74, 148.16, 130.98, 130.35, 129.76, 124.30, 121.96, 107.97, 106.51, 101.36, 61.40, 55.14; LC-MS (m/z): 337.0789

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

Anal. Calcd. (%) for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79; Found (%):C, 63.51 ; H, 4.70 ; N, 21.78; White solid;m. p. 132-133°C; R_f = 0.59; FT-IR (KBr, cm^{-1}): 1611, 1598; ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.10 (s, 1H), 7.84-6.55 (m, 7H), 5.98 (s, 2H), 3.88 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, δ/ppm): 161.69, 153.89, 149.73, 148.18, 130.98, 130.36, 129.75, 124.30, 121.95, 107.93, 106.50, 101.35, 76.58, 61.39, 20.44; LC-MS (m/z): 321.1036.

5. CONCLUSION

In summary, we have demonstrated a metal-free protocol for the synthesis of tetrazole derivatives from the reactions of piperonal, diamine, and aroyl chlorides in a one-pot fashion. FT- IR, ^{1}H/ ^{13}C NMR, and LC-MS studies were utilized for the structural conformation of all the synthesized products. The present strategy features high chemo- and regioselectivity and excellent tolerance for a wide range of functional groups. Moreover, the combinational use of PCl_5 and NaN_3 has been demonstrated to be robust to activate the C=O bond of secondary amide and enable the assembly of tetrazoles, which also opens a new entry to amides based tetrazole synthesis based on metal-free protocol. Other fascinating merits of this new protocol are operational simplicity, excellent yields of products in short reaction times, and easy workup procedures.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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