Asian Journal of Chemistry; Vol. 27, No. 10 (2015), 3633-3638

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.18894

Synthesis of Novel Pyridazinonylbenzotriazoles

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Received: 2 December 2014; *Accepted*: 6 January 2015; *Published online*: 22 June 2015; AJC-17316

4-Chlorobenzaldehyde **(1)** was reacted with crotononitrile **(2)** in the presence of sodium cyanide yielding 4-(4-chlorophenyl)-3-methyl-4-oxobutyronitrile **(3)** which on refluxing with concentrated HCl gave 4-(4-chlorophenyl)-3-methyl-4-oxobutyric acid **(4)**. The latter, on treatment with fuming nitric acid, yielded 4-(4-chloro-3-nitrophenyl)-3-methyl-4-oxobutyric acid **(5)**, which on treatment with hydrazine hydrate gave 6-(4-chloro-3-nitrophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazine-3-one **(6)**. Azidation and reduction of **6** with sodium azide gave the amino derivative **7** which on reductive alkylation gave **10(a-i)** followed by reduction with commercially available sodium hydrogen sulphide solution gave the substituted diamine derivative **11(a-i)**. The compound **7** directly undergoes reduction with sodium hydrogen sulphide yielding **(8).** Finally, **8** and **11(a-i)** was converted into the target compounds by diazotized-cyclization with sodium nitrite giving pyridazinonylbenzotriazoles **9** and **12(a-i)**.

Keywords: Pyridazinone, Benzotriazole, Michael addition, Hydrazinolysis, Diazotized-cyclization, Pyridazinonyl derivatives.

INTRODUCTION

The syntheses of novel pyridazinonyl derivatives have gained much importance in recent years. Pyridazinonyl derivatives have been shown to exhibit a variety of pharmacological activities mostly related to cardiovascular effects[1-5]. Literature survey revealed that substituted pyridazinones have been reported to possess antidepressant[6,7], antihypertensive[8-10], antithrombotic[11], antifungal[12,13], antibacterial[14,15], antimicrobial[16], anti-inflammatory[17-19], anticancer[20] activity.

A large number of compounds containing benzotriazole system have been investigated because of their broad spectrum of biological activities which include analgesic, antibacterial, antifungal, antiparasitic, antiviral, anti-inflammatory, anticonvulsant, DNA cleavage, herbicidal, antitubercular[21], antiemetic, respiratory syndrome protease inactivation activities and also as an active ester in the peptide synthesis[22] and as agonists of peroxisome proliferator activated receptors[23]. In addition to these considerable biological applications, benzotriazoles are important intermediates, protecting groups and final products in organic chemistry[24].

In the past, quite a few new drugs belonging to 5-methyl-6-substituted phenyl pyridazinones were designed[25-28]. One prominent fact is the increase in potency exerted by the introduction of a substituent into the pyridazinonyl ring in the 5th position and thus introducing chirality into the molecule. It has been shown that the optimum was reached with a methyl group[29].

This paper relates to the synthesis of novel 5-methyl-6-(1-substituted 1*H*-benzotriazol-5-yl)-4,5-dihydropyridazin-3(2*H*)-one derivaties (**10a-j**). Different strategies for the preparation of 5-alkylpyridazinones have been reported in the literature[30,31]. A modified version of Stetter and Schreckenberg's procedure[32], in its considerably simplified form, has been adopted for the current preparation.

EXPERIMENTAL

Unless stated otherwise, all reactions were performed under nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel 100-200 and 230-400 mesh using hexane, ethyl acetate, dichloro methane. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$, DMSO-d_6 and CD_3OD solution by using Bruker AC-300 and 400 MHz spectrometers. Proton chemical shifts (δ) are relative to tetra methyl silane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Infrared spectra were recorded on a Perkin-Elmer1720 FT-IR spectrometer (KBr Pellets). Melting points were determined in a Polmon melting point apparatus and are uncorrected. Mass spectra were recorded on Agilent 6120 LCMS instrument giving M^+ values either on $M^+ + 1$ or $M^+ - 1$ modes.

Preparation of 4-(4-chlorophenyl)-3-methyl-4-oxobutyronitrile (3): Sodium cyanide (3.5 g, 71.42 mmol) was added to DMF (350 mL) at 35 °C and stirred for 25 min to get clear solution. A solution of 4-chlorobenzaldehyde **(1)** (100 g, 714.2 mmol) in DMF (200 mL) was added to the cyanide solution over a period of 1.5 h. The mixture was stirred for 0.5 h at 35-38 °C and then crotononitrile **(2)** (47.8 g, 714.2 mmol) in DMF (200 mL) was added in a drop-wise fashion to the above reaction mixture in about 45 min. The stirring was continued for 2-3 h, with the temperature below 40 °C. The reaction was continuously monitored by TLC. After the completion of the reaction, the mixture was poured into crushed-ice (4 L) with stirring. The separated solid was filtered, washed with water (2 × 1 L) and dried. Yield = 121.3 g, (88 %), m.p.: 49-51 °C. (lit[33] m.p.: 52-53 °C).

Preparation of 4-(4-chlorophenyl)-3-methyl-4-oxobutyric acid (4): A mixture of **3** (100 g, 518.1 mmol) in conc. HCl (550 mL) and water (550 mL) was stirred at refluxing temperature for 5 h, while the reaction was monitored by TLC. After the completion of reaction, the mixture was cooled to room temperature and extracted with dichloromethane (300 mL × 3). The total organic layer was washed with water (500 mL) and concentrated under reduced pressure. The resulting crude residue was dissolved in methyl *t*-butylether (500 mL) and then extracted into saturated $NaHCO_3$ solution (200 mL × 3). The combined aq. layer was cooled to 10 °C, the pH adjusted to 2-2.5 using conc. HCl and the mixture extracted with dichloromethane (200 mL × 3). The dichloromethane layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a residue that was crystallized from hexane to get an off-white solid. Yield = 79 g, (72 %), m.p.: 78-80 °C. (lit[33] m.p. = 80-82 °C).

Preparation of 4-(4-chloro-3-nitrophenyl)-3-methyl-4-oxobutyric acid (5): Compound **4** (75 g, 353.7 mmol) was added portion-wise to fuming nitric acid (356.6 g, 5660.9 mmol) at (-) 15 °C, while maintaining the temperature at (-) 10 to (-) 15 °C. Afterwards the mixture was stirred for an additional 30 min at same temperature, while monitoring the reaction by TLC. The whole mixture was then poured into crushed ice (2.5 L) with stirring. The insoluble solid was filtered off, washed with water (200 mL × 3) and dried. Yield: 82 g, (90 %), m.p.: 110-114 °C. (lit[33] m.p.= 114-116 °C).

Preparation of 6-(4-chloro-3-nitrophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (6): To a solution of **5** (80 g, 311.2 mmol) in acetic acid (500 mL), hydrazine hydrate (16.3 g, 326.7 mmol) was added in a drop-wise manner at 30 °C. Then, the temperature of mixture was slowly raised to 100 °C. The mixture was stirred for 4.5 h at this temperature, while the reaction was monitored by TLC. At the end of the reaction, the mixture was cooled to room temperature and poured into ice-water (3 L) with stirring. The insoluble product was filtered, washed with water (200 mL × 4) and dried. Yield: 79 g, (95 %), m.p.: 192-195 °C. (lit[33] m.p.= 188-190 °C).

Preparation of 6-(4-amino-3-nitrophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (7): To a solution of **6** (25 g, 93.6 mmol) in DMSO:H_2O (80 mL: 10 mL) were added L-proline (2.15 g, 18.7 mmol), Na_2CO_3 (1.98 g, 18.7 mmol), NaN_3 (7.3 g, 112.2 mmol), sodium ascorbate (2.77 g, 14.0 mmol) and cupric sulphate pentahydrate (3.45 g, 18.7 mmol). The reaction temperature was slowly raised to 70 °C and maintained at this temperature for 24 h. At the end of this period, the mixture was cooled to room temperature and poured into water (1 L). The precipitated yellow solid was filtered, washed with water (300 mL) and dried. The solid was recrystallized from tetrahydrofuran to get a yellow coloured solid Yield: 22 g, (95 %), m.p.: 244-246 °C, IR (KBr, ν_{max}, cm^{-1}): 3445-3297 (-NH_2, str), 3164 (N-H, str), 1632 (NH-C=O, str), 1343 (C-N, str) 2060; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.85 (1H, s, NH), 8.25 (1H, d), 7.85 (1H, dd), 7.75 (2H, bs), 7.1(1H, dd), 3.3 (1H, m), 2.4-2.65 (1H, m) 2.2 (1H, dd), 1.05 (3H, d); LC-MS: *m/z* = 249 [M^++1].

Preparation of 6-(3,4-diaminophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (8): A suspension of **7** (10 g, 40.3 mmol) in methanol (100 mL) was slowly raised to 65 °C, then the commercially available sodium hydrogen sulphide (30 % in H_2O, w/w) (4.9 g, 40.38.17 mmol) was added drop-wise to the above reaction mixture at the same temperature. At this stage, the mixture was stirred for 6 h, while the reaction was monitored by TLC. At the end of the reaction, methanol was distilled out under reduced pressure and the residue cooled to 15 °C. To the latter was added 3N HCl (150 mL) and the mixture stirred at room temperature for 30 min. The separated solid was filtered, washed with water (100 mL × 2) and dried to get brown solid. Yield: 6.3 g, (75 %), m.p.: 178-181 °C. (lit[33] m.p.: 183-185 °C). IR (KBr, ν_{max}, cm^{-1}): 3397-3263 cm^{-1} (-NH_2 broad peak), 1625 cm^{-1} (amide, C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.7 (1H, bs), 7.1 (1H, s), 6.9 (1H, d), 6.5 (1H, d), 4.6-4.8 (4H, bs, $2NH_2$) 3.2 (1H, m), 2.6 (1H, dd), 2.1 (1H,d), 1.05 (3H, d). LC-MS: *m/z* = 218 [M^++1].

Preparation of 5-methyl-6-(1*H*-benzotriazol-5-yl)-4,5-dihydropyridazin-3(2*H*)-one (9). To a suspension of **8** (19.23 mmol, 1eq) in acetic acid (50 mL) was added a solution of $NaNO_2$ (23.07 mmol, 1.2 eq) in 7 mL of water in a drop-wise fashion at 20-25 °C for 20 min. The mixture was stirred for 4-5 h at 25 °C, while monitoring it by TLC. At the end of this period, the mixture was poured into ice-water (400 mL) and stirred for 2 h at room temperature. The separated product was filtered, washed with water (100 mL × 2) and dried to get an off-white solid. Pale brown solid Yield: 3.2 g, (75 %), m.p.: 246-250 °C (dec), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.2 (1H, s, NH), 8.3 (1H, s), 7.9 (2H, dd), 3.5 (2H, m), 2.6-2.8 (1H, m) 2.3 (1H, dd), 1.2 (3H, d); LC-MS: *m/z* = 230 [M^++1]. Anal. (%) for $C_{11}H_{11}N_5O$, calc. C, 57.63; H, 4.84; N, 30.55; Founds: C, 67.51; H, 4.85; N, 30.53.

General preparation method of 6-(4-substituted amino-3-nitrophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (10a-i): To a solution of **7** (40.3 mmol) in acetic acid (150 mL), was added the corresponding aldehydes or the ketones (formaldehyde, acetaldehyde, acetone, isobutyraldehyde, furfuraldehyde, benzaldehyde, *p*-chloro benzaldehyde, *p*-bromo benzaldehyde, *p*-flouro benzaldehyde) (44.33 mmol) and the mixture stirred for 15 min, then cooled to 10 °C and sodium triacetoxyborohydride (88.66 mmol) was added portion-wise in about 0.5 h. After the addition, mixture was stirred for 15 h at room temperature and also monitored the reaction by TLC. At the end of this period, the mixture was poured into saturated

$NaHCO_3$ solution (1 L) and then extracted with ethyl acetate (200 mL × 2). The combined organic layer was washed with water (200 mL × 2), dried over anh. Na_2SO_4 and concentrated under reduced pressure. The crude residue was stirred with methyl *tert*-butylether (30 mL) and filtered. The insoluble product was dried to obtain **10(a-i)**.

Compound 10a: Orange solid; 6.33 g, (60 %), m.p.: 192-194 °C, IR (KBr, ν_{max}, cm^{-1}): 3224 (N-H, str), 1627 (NH-C=O, str), 1346 (C-N, str); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 8.4 (1H, d), 8.1 (1H, dd), 8 (1H, dd), 7.2(1H, dd), 4.0 (1H, s), 3.4 (1H, m), 2.6-2.7 (1H, m) 2.25 (1H, dd), 1.1 (3H, d); LC-MS: *m/z* = 263 [M^++1].

Compound 10b: Orange solid; 6.89 g (62 %), m.p.: 185-188 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 8.4 (1H, d), 8.1 (1H, dd), 8 (1H, dd), 7.2(1H, dd), 4.0 (1H, quartet), 3.4 (1H, m), 2.6-2.7 (1H, m) 2.25 (1H, dd), 1.4 (3H, t), 1.1 (3H, d); LC-MS: *m/z* = 276 [M^++1].

Compound 10c: Orange solid; 8.18 g, (70 %), m.p.: 171-173 °C, IR (KBr, ν_{max}, cm^{-1}): 3224 (N-H, str), 1627 (NH-C=O, str), 1346 (C-N, str); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 8.4 (1H, d), 8.1 (1H, dd), 8 (1H, dd), 7.2(1H, dd), 4.0 (1H, m), 3.4 (1H, m), 2.6-2.7 (1H, m) 2.25 (1H, dd), 1.3 (6H, d), 1.1 (3H, d); LC-MS: *m/z* = 291 [M^++1].

Compound 10d: Orange solid; 9.1 g, (71 %), m.p.: 158-162 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 8.4 (1H, d), 8.1 (1H, dd), 8 (1H, dd), 7.2(1H, dd), 3.5 (2H, t), 3.4 (1H, m), 2.6-2.7 (1H, m) 2.25 (1H, dd), 2 (1H, m), 0.9 (6H, d), 1.1 (3H, d); LC-MS: *m/z* = 305 [M^++1].

Compound 10e: Orange solid; 7.93 g, (60 %), m.p.:195-196 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 9 (1H, t), 8.6 (1H, s), 8 (1H, dd), 7.3 (1H,dd), 7.0, (1H, dd), 6.3 (1H, m), 6.0 (1H, dd), 4.25 (2H, d), 3.4 (1H, m), 2.6-2.7 (1H, m) 2.25 (1H, dd), 1.2 (3H, d); LC-MS: *m/z* = 329 [M^++1].

Compound 10f: Orange solid; 10.22 g, (75 %), m.p.: 202-204 °C, IR (KBr, ν_{max}, cm^{-1}): 3217 (N-H, str), 1629 (NH-C=O, str), 1343 (C-N, str); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 8.9 (1H, t), 8.4 (1H, s), 7.9 (1H, dd), 7.4-7.5(4H, m), 7.3 (1H, m), 7.0 (1H, dd), 4.7 (2H, d), 3.3 (1H,m), 2.4-2.6 (1H, m) 2.2 (1H, dd), 1.01(3H, d); LC-MS: *m/z* = 339 [M^++1].

Compound 10g: Orange solid; 10.5 g, (70 %), m.p.; 211-212 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 8.9 (1H, t), 8.4 (1H, s), 7.9 (1H, dd), 7.5(2H, dd), 7.4 (2H, dd), 7.2 (1H, dd), 4.85 (2H, d), 3.3 (1H,m), 2.4-2.6 (1H, m) 2.2 (1H, dd), 1.01(3H, d); LC-MS: *m/z* = 373 [M^++1].

Compound 10h: Orange solid; 12.58 g, (75 %), m.p.: 222-224 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 8.9 (1H, t), 8.4 (1H, s), 7.9 (1H, dd), 7.65(2H, dd), 7.25 (2H, dd), 7.0 (1H, dd), 4.8 (2H, d), 3.3 (1H,m), 2.4-2.6 (1H, m) 2.2 (1H, dd), 1.01(3H, d); LC-MS: *m/z* = 417 [M^++1].

Compound 10i: Orange solid; 10.33 g, (72 %), m.p.: 206-208 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 8.9 (1H, t), 8.4 (1H, s), 7.9 (1H, dd), 7.2 (2H, dd), 7.0 (1H, dd), 6.9 (2H, dd), 4.7 (2H, d), 3.3 (1H,m), 2.4-2.6 (1H, m) 2.2 (1H, dd), 1.01(3H, d); LC-MS: *m/z* = 357 [M^++1].

General procedure for preparation of 6-(3-amino-4-substituted aminophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (11a-i): A suspension of **10 (a-i)** (5 g, 14.79 mmol, 1eq) in methanol (75 mL) was slowly raised to a temperature of 65 °C and sodium hydrogen sulphide (commercially available) (30 % in H_2O, w/w) (32.54 mmol, 2.2 eq) was added drop-wise to the above reaction mixture at the same temperature. The reaction mixture was then stirred for 6 h at the same temperature. At the end of this period, methanol was distilled out under reduced pressure and the residue cooled to 15 °C. To the mixture, was added 3N HCl (35 mL) and the resulting mixture was stirred for 30 min. The separated product was filtered and washed with water (10 mL × 2) and dried.

Compound 11a: Off white solid; 2.87 g, (65 %), m.p.: 171-172 °C, IR (KBr, ν_{max}, cm^{-1}): 3357 (-NH_2, str), 3224 (N-H, str), 1627 (NH-C=O, str), 1346 (C-N, str); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.75 (1H, S, NH), 8.7 (2H, bs), 7.4 (1H, d), 7.2 (2H, dd), 6.5 (1H, dd), 3.7 (1H, s), 3.3 (1H, m), 2.6-2.7 (1H, m) 2.25 (1H, dd), 0.9 (3H, d); LC-MS: *m/z* = 233 [M^++1].

Compound 11b: Off white solid; 3.11 g, (70 %), m.p.: 161-163 °C, IR (KBr, ν_{max}, cm^{-1}): 3357 (-NH_2, str), 3224 (N-H, str), 1627 (NH-C=O, str), 1346 (C-N, str); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.7 (1H, S, NH), 8.8 (2H, bs), 7.5 (1H, dd), 7.2 (2H, m), 6.6(1H, dd), 3.8 (1H, quartet), 3.2 (1H, m), 2.6-2.7 (1H, m) 2.25 (1H, dd), 1.2 (3H, t), 0.9 (3H, d); LC-MS: *m/z* = 247 [M^++1].

Compound 11c: Off white solid; 2.6 g, (60 %), m.p.: 153-156 °C, IR (KBr, ν_{max}, cm^{-1}): 3357 (-NH_2, str), 3224 (N-H, str), 1627 (NH-C=O, str), 1346 (C-N, str); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.7 (1H, S, NH), 8.8 (2H, bs), 7.6 (1H, dd), 7.3 (2H, m), 6.7 (1H, dd), 3.8 (1H, m), 3.25 (1H, m), 2.6-2.7 (1H, m) 2.25 (1H, dd), 1.3 (6H, d), 0.9 (3H, d); LC-MS: *m/z* = 261 [M^++1].

Compound 11d: Pale brown solid; 2.75 g, (62 %), m.p.: 135-137 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.75 (1H, S, NH), 8.9 (2H, bs), 7.7 (1H, dd), 7.4 (2H, m), 6.6 (1H, dd), 3.4 (2H, t), 3.2 (1H, m), 2.6-2.7 (1H, m), 2.25 (1H, dd), 1.8 (1H, m), 0.9 (3H, d), 0.75 (6H, d); LC-MS: *m/z* = 275 [M^++1].

Compound 11e: Pale brown solid; 3.2 g, (72 %), m.p.: 161-162 °C (dec), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.8 (1H, S, NH), 9 (2H, bs), 7.9 (1H, s), 7.7 (2H, m), 7.0 (1H,dd), 6.5, (1H, dd), 6.0 (2H, m), 4.0 (2H, d), 3.3 (1H, m), 2.6-2.7 (1H, m) 2.25 (1H, dd), 1.0 (3H, d); LC-MS: *m/z* = 299 [M^++1].

Compound 11f: Off white solid; 3.46 g, (78 %), m.p.: 170-174 °C (dec), IR (KBr, ν_{max}, cm^{-1}): 3344 (-NH_2, str), 3027 (N-H, str), 1630 (NH-C=O, str), 1341 (C-N, str), 1292, 1025; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.8 (1H, s), 8.5-9 (2H, bs, NH_2), 7.6 (1H, S), 7.2-7.5 (7H, m), 6.6 (1H, d), 4.4 (2H, d), 3.2 (1H, m), 2.6 (1H, m) 2.2 (1H, dd), 1.0 (3H, d); LC-MS: *m/z* = 309 [M^++1].

Compound 11g: Off white solid; 3.2 g, (70 %), m.p.; 180-182 °C (dec), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.85 (1H, S, NH), 8 - 8.5 (2H, bs), 7.4 (1H, s), 7.2 (2H, m), 7.0 (2H, dd), 6.5 (3H, m), 4.3 (2H, d), 3.2 (1H,m), 2.6 (1H, m) 2.2 (1H, dd), 1.0 (3H, d); LC-MS: *m/z* = 343 [M^++1].

Compound 11h: Off white solid; 2.98 g, (65 %), m.p.: 193-195 °C (dec), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.7 (1H, S, NH), 8 - 8.5 (2H, bs), 7.2 (1H, s), 7.0 (2H, m), 6.7 (2H, dd), 6.3 (3H, m), 4.2 (2H, d), 3.2 (1H,m), 2.5 (1H, m) 2.2 (1H, dd), 1.0 (3H, d); LC-MS: *m/z* = 387 [M^++1].

Compound 11i: Off white solid; 2.89 g, (63 %), m.p.: 175-177 °C (dec), IR (KBr, ν_{max}, cm^{-1}): 3335 (-NH_2, str), 3020

(N-H, str), 1629 (NH-C=O, str), 1335 (C-N, str), 1285, 1025; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.5 (1H, s, NH), 8.5 (2H, bs), 7.0 (1H, s), 6.5 (3H, m), 7.0 (1H, dd), 6.1 (3H, m), 4.0 (2H, d), 3.15 (1H,m), 2.4 (1H, m), 2.2 (1H, dd), 1.0 (3H, d); LC-MS: *m/z* = 327 [M$^+$+1].

General procedure for preparation of 5-methyl-6-(1-substituted 1*H*-benzotriazol-5-yl)-4,5-dihydropyridazin-3(2*H*)-one derivatives (12a-i): To a suspension of **11a-i** (3.88 mmol, 1eq) in acetic acid (100 mL) was added a solution of $NaNO_2$ (4.66 mmol, 1.2 eq) in 15 mL of water in a drop-wise fashion at 20-25 °C for 20 min. The mixture was stirred for 4-5 h at 25 °C, while monitoring it by TLC. At the end of this period, the mixture was poured into ice-water (400 mL) and stirred for 2 h at room temperature. The separated product was filtered, washed with water (100 mL × 2) and dried to get an off-white solid.

Compound 12a: Off-white solid; 0.75 g, (80 %), m.p.: 212-214 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.1(1H, s, NH), 8.4 (1H, s), 8.1 (1H, dd), 7.9 (1H, dd), 5.1 (3H, s), 3.6 (1H, m), 2.8 (1H, m) 2.3 (1H, dd), 1.2 (3H, d); LC-MS: *m/z* = 244 [M$^+$+1]. Anal. (%) for $C_{12}H_{13}N_5O$, calc. C, 59.25; H, 5.39; N, 28.79; Founds: C, 59.24; H, 5.41; N, 28.77.

Compound 12b: Off-white solid; 0.84 g, (85 %), m.p.: 197-199 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.1 (1H, s, NH), 8.5 (1H, s), 8.2 (1H, dd), 7.8 (1H, dd), 5.15 (2H, quartet), 3.5 (1H, m), 2.6-2.7 (1H, m), 2.25 (1H, dd), 1.7 (3H, t), 1.2 (3H, d); LC-MS: *m/z* = 258 [M$^+$+1]. Anal. (%) for $C_{13}H_{15}N_5O$, calc. C, 60.69; H, 5.88; N, 27.22; Founds: C, 60.68; H, 5.85; N, 27.24.

Compound 12c: Off-white solid; 0.95 g, (90 %), m.p.: 185-188 °C, IR (KBr, ν_{max}, cm^{-1}) : 3227 (N-H, str), 1676 (NH-C=O, str), 1342 (C-N, str), ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.1 (1H, s, NH), 8.4 (1H, s), 8.1 (1H, dd), 7.9 (1H, dd), 5.3 (1H, septet), 3.6 (1H, m), 2.8 (1H, m), 2.3 (1H, dd), 1.6 (6H, d), 1.1 (3H, d); LC-MS: *m/z* = 272 [M$^+$+1]. Anal. (%) for $C_{14}H_{17}N_5O$ calc. C, 61.98; H, 6.32; N, 25.81 Founds: C, 61.95; H, 6.33; N, 25.78.

Compound 12d: Off-white solid; 0.9 g, (82 %) m.p.: 166-168 °C, IR (KBr, ν_{max}, cm^{-1}) ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 8.4 (1H, d), 8.1 (1H, dd), 8 (1H, dd), 7.2(1H, dd), 5.2 (2H, d), 3.5 (1H, m), 2.7 (1H, m), 2.3 (1H, dd), 2.1 (1H, m), 1.3 (6H, d), 1.1 (3H, d); LC-MS: *m/z* = 286 [M$^+$+1]. Anal. (%) for $C_{16}H_{21}N_5O$. calc. C, 64.19; H, 7.07; N, 23.39; Founds: C, 64.21; H, 7.02; N, 23.41.

Compound 12e: Off-white solid; 0.95 g, (80 %), m.p.: 193-195 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11 (1H, s, NH), 8.45 (1H, s), 81 (1H, dd), 7.9 (1H,dd), 7.2 (1H, dd), 6.7 (1H, m), 6.4 (1H, dd), 6.2 (2H, s), 3.65 (1H, m), 2.6-2.8 (1H, m) 2.3 (1H, dd), 1.2 (3H, d); LC-MS: *m/z* = 310 [M$^+$+1]. Anal. (%) for $C_{16}H_{15}N_5O_2$. calc. C, 62.13; H, 4.89; N, 22.64; Found. C, 62.11; H, 4.86; N, 22.67;

Compound 12f: Off-white solid; 1.07 g, (87 %), m.p.: 186-189 °C, IR (KBr, ν_{max}, cm^{-1}): 3215 (N-H, str), 1675 (NH-C=O, str), 1347 (C-N, str); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11 (1H, s, NH), 8.35 (1H, s), 8.15 (1H, dd), 7.8 (1H, dd), 7.3-7.45 (5H, m), 7.3 (1H, m), 6.0 (2H, s), 3.6 (1H,m), 2.7-2.8 (1H, m) 2.3 (1H, dd), 1.1 (3H, d); LC-MS: *m/z* = 320 [M$^+$+1]. Anal. (%) for $C_{18}H_{17}N_5O$ calc. C, 67.72; H, 5.35; N, 21.92; Found. C, 67.70; H, 5.37; N, 21.93;

Compound 12g: Off-white solid; 1.16 g, (85 %), m.p.; 197-200 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 8.9 (1H, t), 8.4 (1H, s), 7.9 (1H, dd), 7.5(2H, dd), 7.4 (2H, dd), 7.2 (1H, dd), 4.85 (2H, d), 3.3 (1H,m), 2.4-2.6 (1H, m) 2.2 (1H, dd), 1.01(3H, d); LC-MS: *m/z* = 354 [M$^+$+1]. Anal. (%) for $C_{18}H_{16}N_5OCl$ calc. C, 61.10; H, 4.56; N, 19.79. Found. C, 61.07; H, 4.54; N, 19.76.

Compound 12h: Off-white solid; 1.35 g, (88 %), m.p.: 218-220 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 8.9 (1H, t), 8.4 (1H, s), 7.9 (1H, dd), 7.65(2H, dd), 7.25 (2H, dd), 7.0 (1H, dd), 4.8 (2H, d), 3.3 (1H,m), 2.4-2.6 (1H, m) 2.2 (1H, dd), 1.01(3H, d); LC-MS: *m/z* =398 [M$^+$+1]. Anal. (%) for $C_{18}H_{16}N_5OBr$ calc. C, 54.28; H, 4.05; N, 17.59; Found. C, 54.30; H, 4.00; N, 17.57.

Compound 12i: Off-white solid; 1.07 g, (82 %), m.p.: 201-204 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.95 (1H, S, NH), 8.9 (1H, t), 8.4 (1H, s), 7.9 (1H, dd), 7.2 (2H, dd), 7.0 (1H, dd), 6.9 (2H, dd), 4.7 (2H, d), 3.3 (1H,m), 2.4-2.6 (1H, m) 2.2 (1H, dd), 1.01(3H, d); LC-MS: *m/z* = 338 [M$^+$+1]. Anal. (%) for $C_{18}H_{16}N_5OF$ calc. C, 64.09; H, 4.78; N, 20.76; Found. C, 64.12; H, 4.76; N, 20.79.

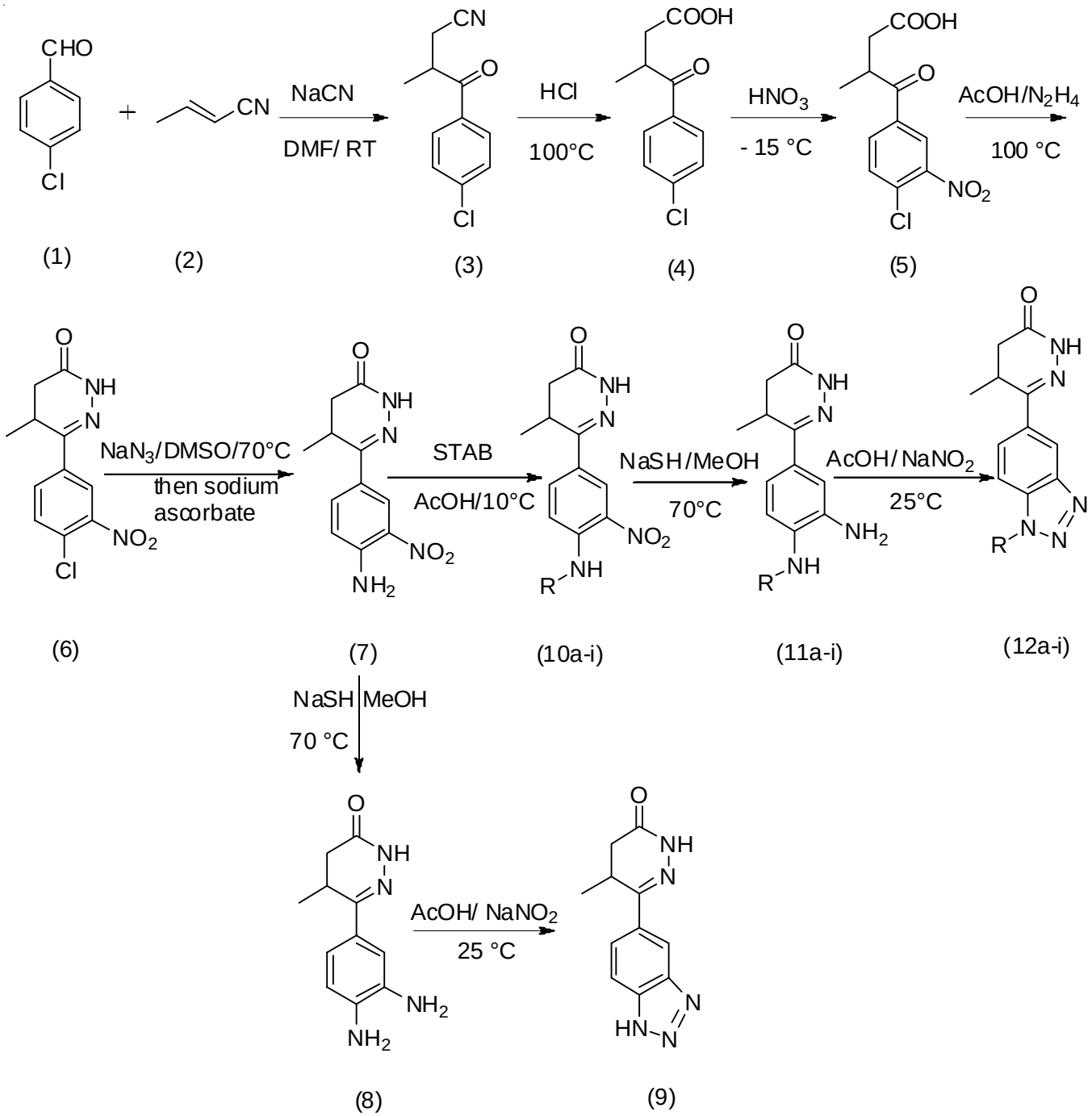
RESULTS AND DISCUSSION

The reaction sequence leading to the formation of title compounds is outlined in **Scheme-I**.

4-Chlorobenzaldehyde underwent Michael addition with the commercially available crotononirile in the presence of sodium cyanide in DMF at room temperature giving the previously reported[33] 4-(4-chlorophenyl)-3-methyl-4-oxobutyronitrile (**3**). The hydrolysis of the Michael adduct **3** with hydrochloric acid at refluxing temperature led to the formation of β-benzoylpropionic acid derivative *i.e.* 4-(4-chlorophenyl)-3-methyl-4-oxobutryric acid (**4**). The latter, on nitration, with fuming nitric acid at low temperature, gave 4-chloro-3-nitro acid derivative (**5**), which on hydrazinolysis with hydrazine hydrate gave the known[33] 6-(4-chloro-3-nitro-phenyl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one (**6**).

Compound **6** was converted to 6-(4-amino-3-nitrophenyl)-5-methyl-2,3,4,5-tetrahydro-pyridazin-3-one (**7**) by a one pot azidation-reduction reaction, adopting the reported procedure[34] using sodium azide, sodium carbonate, sodium ascorbate, catalytic amount of L-proline and cupper sulphate penthydrate in acq. DMSO at 70 °C. Compound **7** has been characterized on the basis of its spectral data. Thus, its IR spectrum (KBr) showed a characteristic –NH_2 group at ν_{max} of 3445-3184 cm^{-1} (broad peak) and a sharp, strong peak at 1632 cm^{-1} due to amide carbonyl group. ^{1}H NMR (DMSO-d_6/TMS) spectrum showed signals at δ: 10.9 (dihydropyridazinone NH-C=O), 8.35 (d, 1H), 7.85 (dd, 1H), 7.7 (bs, 2H, NH_2), 7.1(d, 1H), 3.4 (m, 1H), 2.6 (m, 1H), 2.2 (d, 1H), 1.05 (d, 3H, -CH_3). Its LC-MS showed the molecular ion peak (M$^+$+1) at *m/z*: 249 corres-ponding to a molecular mass of 248, when recorded in the Q+1 mode.

The amino nitro compound **7** on condensation with various aldehydes and ketones gave the corresponding Schiff's bases which on reduction with sodium triacetoxyborohydride (STAB) in acetic acid at room temperature afforded reductively alkylated derivatives **10(a-i)**, which have been characterized on the basis of their spectral and analytical data.



R = a) Methyl, b) Ethyl, c) Isopropyl, d) Isobutyl, e) furfuryl, f) Ph-CH_2-, g) p-Cl-Ph-CH_2- h) p-Br-Ph-CH_2-, i) p-F-Ph-CH_2- .

Scheme-I

Compound **10(a-i)** on reduction with 30 % aq. sodium hydrogen sulphide (NaSH) in methanol at refluxing temperature for 6 h gave the corresponding diamine derivatives *i.e.*, 6-(3-amino-4-(substituted amino)phenyl)-5-methyl-2,3,4,5-tetrahydro-pyridazin-3-one **11(a-i)** which have been characterized on the basis of their spectral and analytical data.

Direct reduction of compound **7** with NaSH gave the 6-(3,4-diaminophenyl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one (**8**), which has been characterized on the basis of its spectral data. Thus, its IR spectrum (KBr) showed a characteristic peaks at ν_{max} of 3397-3263 cm^{-1} (-NH_2 broad peak) and a sharp, strong peak at 1625 cm^{-1} due to amide carbonyl group ^{1}H NMR (DMSO-d_6/TMS) spectrum showed signals at δ: 10.7 (dihydropyridazinone NH-C=O), 7.1 (s, 1H), 6.9 (d, 1H), 6.5 (d, 1H), 4.6-4.8 (bs, 4H, $2NH_2$) 3.2 (m, 1H,CH), 2.6 (dd,1H), 2.1 (d,1H), 1.05 (d, 3H, CH_3).

In another sequence of reaction, **8** and **11(a-i)** were treated with aq. $NaNO_2$ in acetic acid at room temperature giving 5-methyl-6-(1-substituted 1*H*-benzotriazol-5-yl)-4,5-dihydropyridazin-3(2*H*)-one derivatives **9** and **12(a-i)** respectively. The

latter have been characterized on the basis of their IR, ^{1}H NMR spectra and LC-MS data.

ACKNOWLEDGEMENTS

The authors are thankful to the authorities of Civenti Chem (India) Pvt. Ltd., IDA, Jeedimetla, Hyderabad, India, for providing laboratory facilities. The authors are also grateful to the authorities of J.N.T. University, Hyderabad, India for encouragement.

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