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Synthesis of Novel N-Aryl-1*H*-indazolamines from Amino-1*H*-indazoles and Arylboronic Acids

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An efficient and high-yielding synthesis of N-aryl-1*H*-indazolamines from amino-1*H*-indazole and arylboronic acids are described. In this study a series of novel N-aryl-1*H*-indazolamines (**1a-i**) were synthesized using arylboronic acids and amino-1*H*-indazoles (**3a-c**).

Keywords: Amino-1*H*-indazole, Arylboronic acid.

INTRODUCTION

Indazoles constitute an important class of heterocycles that display interesting biological properties[1,2] such as anti-depressant[3], antiinflammatory[4,5], analgesic and antipyretic[6], dopamine antagonist[7], antitumor[8], antiemetic[9], and anti-HIV activities[10]. The indazole ring system is also present in many other compounds such as herbicides, dyes or sweeteners like guanidine-1*H*-indazole[1,2,11]. Indazole derivatives have been tested in various biological test systems and some of them have shown to have important pharmacological activities. Aromatic amines are important compounds found throughout the pharmaceutical[12] and agro chemical[13] industries. Uses for aromatic amines can range from conducting polymers[14] in material science to ligands for asymmetric homogeneous chemistry[15].

The formation of carbon-hetero atom bonds using metal catalysis is emerging as one of the most significant classes of cross-coupling reactions. Copper-mediated C-N bond formation *via* cross coupling of arylboronic acids and nitrogen-based nucleophiles have become an important synthetic strategy since the initial reports by Chan *et al.* and Lam *et al.*[16]. Under the conditions, reported *N*-arylation[17] of nitrogen-based nucleophiles by arylboronic acids occurs using a stoichiometric amount of Cu salt and several equivalents of an external base/ligand. A variety of amines, anilines and nitrogen heterocycles have been *N*-arylated, both in the liquid phase and on solid support[18]. As discussed above, indazole moiety shows activities in multiple therapeutic areas, hence an attempt was made at first for the synthesis of novel *N*-aryl-1*H*-indazolamines.

EXPERIMENTAL

Melting points of newly synthesized compounds were determined in an open glass capillary tubes using buchi/polman melting point apparatus and are uncorrected. Infrared spectra were recorded as potassium bromide pellets with a Perkin IR spectrometer. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUCKER 300 and 75 MHz, respectively. Chemical shifts were quoted relative to residual solvent [7.26 ppm (1H) and 77.0 ppm (13 C) for $CHCl_3$, 2.54 ppm (1 H) and 39.5 ppm (13 C) for DMSO, 3.31 ppm (1 H) and 49 ppm (13 C) for MeOH] and coupling constants (J) were given in Hz to the nearest 0.5 Hz. Chemical shifts were expressed in δ (ppm) values with tetramethylsilane as an internal standard. Mass spectra was recorded on Agilent-LC-MS instrument giving only $M^{+\bullet}$ values using ($M^{\bullet+}$ + 1) mode. Analytical TLC was performed with Silica gel GF-254 from Merck & Co., (Germany). Spots were detected under UV-light or in iodine. All reactions were carried out with continuous stirring under an atmosphere of dry nitrogen. Column chromatography was carried out using commercial silica gel (100-200 mesh). The following general experimental procedures were followed for the synthesis of all compounds.

Typical experimental procedure for arylboronic acid coupling 2a-i: A suitable arylboronic acid (0.20 mol) and *N*-BOC-amino-1*H*-indazole **3a-c** (0.10 mol) were dissolved in *N*,*N*-dimethylformamide subsequently added *N*,*N*-diisopropylethylamine (0.40 mol) and stirred the reaction for 10 to 12 h at room temperature. After completion of the reaction, reaction mixture was filtered and to the filtrate added water. Product was extracted with ethyl acetate and solvent dried over

anhydrous sodium sulfate. Solvent was evaporated under reduced pressure the crude product was further chromatographed on a silica gel column eluted with a mixture of ethyl acetate: hexane (0 to 20 %) afforded desired compound **2a-i**.

***tert*-Butyl-4-anilino-1*H*-1-indazole carboxylate (2a):** Yield: 68 %; Brown colour syrupy mass; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H, Ar-H), 7.70 (d, 1H, *J* = 8.34 Hz, Ar-H), 7.26-7.40 (m, 3H, Ar-H), 7.16 (t, 2H, *J* = 7.53 Hz, Ar-H), 7.01 (dd, 2H, *J* = 7.35, 7.08 Hz, Ar-H), 6.14 (s, 1H, -NH-), 1.71 (s, 9H, -CH_3); ESI-MS: *m/z* 310 $[M + H]^+$.

***tert*-Butyl-4-(4-toluidino)-1*H*-1-indazole carboxylate (2b):** Yield: 72 %; Brown colour syrupy mass; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (s, 1H, Ar-H), 7.65 (d, 1H, *J* = 8.31 Hz, Ar-H), 7.36 (t, 1H, *J* = 8.04 Hz, Ar-H), 7.13 (dd, 4H, *J* = 8.40, 9.81 Hz, Ar-H), 6.89 (d, 1H, *J* = 7.71 Hz, Ar-H), 6 (bs, 1H, -NH-), 2.21 (s, 3H, -CH_3), 1.72 (s, 9H, -CH_3); ESI-MS: *m/z* 324 $[M + H]^+$.

***tert*-Butyl-4-(4-methoxyanilino)-1*H*-1-indazole-carboxylate (2c):** Yield: 76 %; Light brown colour powder; m.p.: 176-181°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (s, 1H, Ar-H), 7.60 (d, 1H, *J* = 8.31 Hz, Ar-H), 7.33 (t, 1H, *J* = 7.95 Hz, Ar-H), 7.16 (dd, 2H, *J* = 2.16, 4.62 Hz, Ar-H), 6.91 (dd, 2H, *J* = 2.34, 4.41 Hz, Ar-H), 6.73 (d, 1H, *J* = 7.80 Hz, Ar-H), 5.90 (bs, 1H, -NH-), 3.82 (s, 3H, -CH_3), 1.71 (s, 9H, -CH_3); ESI-MS: *m/z* 340 $[M + H]^+$.

***tert*-Butyl-5-anilino-1*H*-1-indazole carboxylate (2d):** Yield: 75 %; Brown colour syrupy mass; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (t, 1H, *J* = 9 Hz, Ar-H), 7.39 (d, 1H, *J* = 1.8 Hz, Ar-H), 7.30-7.25 (m, 4H, Ar-H), 7.06 (dd, 2H, *J* = 1.11, 7.59 Hz, Ar-H), 6.93 (s, 1H, Ar-H), 5.77 (bs, 1H, -NH-), 1.72 (s, 9H, CH_3); ESI-MS: *m/z* 310 $[M + H]^+$.

***tert*-Butyl-5-(4-toluidino)-1*H*-1-indazole carboxylate (2e):** Yield: 68 %; Brown colour syrupy mass; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.35-7.25 (m, 4H, Ar-H), 7.09 (dd, 2H, *J* = 1.11, 7.59 Hz, Ar-H), 6.96 (s, 1H, -NH-), 2.24 (s, 3H, -CH_3), 1.74 (s, 9H, -CH_3); ESI-MS: *m/z* 324 $[M + H]^+$.

***tert*-Butyl-5-(4-methoxyanilino)-1*H*-1-indazole carboxylate (2f):** Yield: 73 %; Brown colour syrupy mass; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, 2H, *J* = 10.12 Hz, Ar-H), 7.25-7.05 (m, 4H, Ar-H), 6.88 (d, 2H, *J* = 8.91 Hz, Ar-H), 3.80 (s, 3H, CH_3), 1.71 (2, 9H, -CH_3); ESI-MS: *m/z* 340 $[M + H]^+$.

***tert*-Butyl-6-anilino-1*H*-1-indazolecarboxylate (2g):** Yield: 65 %; Brown colour solid; m.p.: 156-159 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.54 (d, 1H, *J* = 8.55 Hz, Ar-H), 7.35-7.30 (m, 2H, Ar-H), 7.21 (dd, 2H, *J* = 1.14, 7.50 Hz, Ar-H), 7.05-6.95 (m, 2H, Ar-H), 6.01 (bs, 1H, -NH-), 1.66 (s, 9H, -CH_3); ESI-MS: *m/z* 310 $[M + H]^+$.

***tert*-Butyl-6-(4-toluidino)-1*H*-1-indazolecarboxylate (2h):** Yield: 69 %; Light brown colour solid; m.p.: 136-139 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8 (s, 1H, Ar-H), 7.71 (s, 1H, Ar-H), 7.51 (d, 1H, *J* = 8.61 Hz, Ar-H), 7.11 (dd, 4H, *J* = 2.55, 6.18 Hz, Ar-H), 6.92 (dd, 1H, *J* = 1.98, 6.63 Hz, Ar-H), 5.92 (bs, 1H, -NH-), 2.33 (s, 3H, -CH_3), 1.65 (s, 9H, -CH_3); ESI-MS: *m/z* 324 $[M + H]^+$.

***tert*-Butyl-6-(4-methoxyanilino)-1*H*-1-indazolecarboxylate (2i):** Yield: 71 %; Light brown solid; m.p.: 155-161 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 1H, Ar-H), 7.56 (s, 1H, Ar-H), 7.49, (d, 1H, *J* = 8.61 Hz, Ar-H), 7.18 (dd, 2H, *J* = 2.19, 4.41 Hz, Ar-H), 6.92 (dd, 2H, *J* = 1.95, 4.44 Hz, Ar-H), 6.84 (dd, 1H, *J* = 2.01, 6.60 Hz, Ar-H), 5.80 (bs, 1H, -NH-), 3.82 (s, 3H, -CH_3), 1.68 (s, 9H, -CH3); ESI-MS: *m/z* 340 $[M + H]^+$.

***tert*-Butyl-5-[4-(ethoxycarbonyl)aniline]-1*H*-1-indazole carboxylate (6):** Yield: 76 %; Light brown colour solid; m.p.: 162-168 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.88 (s, 1H, -NH-), 8.30 (s, 1H, Ar-H), 8.02 (d, 1H, *J* = 8.91 Hz, Ar-H), 7.80 (d, 2H, *J* = 8.37 Hz, Ar-H), 7.62 (s, 1H, Ar-H), 7.40 (d, 1H, *J* = 8.94 Hz, Ar-H), 7.03 (d, 2H, *J* = 8.43 Hz, Ar-H), 4.23 (q, 2H, *J* = 6.99, 14.07 Hz, -CH_2-), 1.62 (s, 9H, -CH_3), 1.26 (t, 3H, *J* = 6.99, 14.07 Hz, -CH_3); ESI-MS: *m/z* 326 [M-*t*-butyl]$^+$.

Typical experimental procedure for de-protection of BOC group: The compound **2a-i** (10 mmol) was dissolved in methanol (30 mL) at room temperature followed by addition of methanolic. HCl (10 mL). The mixture was stirred around 1 to 2 h at room temperature. After completion of the reaction, solvent was evoparated under reduced pressure to get residue. Residue was further diluted with 5 % sodium bicarbonate to afford the solid, which filtered and washed with water. Dried the product under reduce pressure at 50 °C to gave desired compound.

***N*-4-Phenyl-1*H*-4-indazolamine (1a):** Yield: 92 %; Light brown colour solid; m.p.: 205-209 °C; IR (KBr, ν_{max}, cm^{-1}): 3397, 3290, 2813, 1595, 1164, 768; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.17 (s, 1H, Ar-H), 7.28-7.11 (m, 5H, Ar-H), 6.93-6.86 (m, 2H, Ar-H), 6.76 (d, 1H, *J* = 7.38 Hz, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 177.18, 172.26, 168.32, 151.16, 148.62, 145.70, 139.41, 133.01 126.47, 125.88, 125.49, 122.66, 118.88, 117.60; ESI-MS: *m/z* 210 $[M + H]^+$.

***N*-4-(4-Methylphenyl)-1*H*-4-indazolamine (1b):** Yield: 86 %; Light brown colour solid; m.p.: > 225 °C; IR (KBr, ν_{max}, cm^{-1}): 3393, 3290, 2678, 1602, 1527, 1099; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.13 (s, 1H, Ar-H), 7.08 (dd, 5H, *J* = 8.46, 0.93 Hz, Ar-H), 6.86 (d, 1H, *J* = 8.16 Hz, Ar-H), 6.64 (d, 1H, *J* = 7.56 Hz, Ar-H), 2.23 (s, 3H, -CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 141.81, 140.04, 138.38, 131.75, 130.57, 130.21, 129.88, 128.76, 123.10, 120.08, 114.82, 102.26, 100.73, 20.73; ESI-MS: *m/z* 224 $[M + H]^+$.

***N*-4-(4-Methoxyphenyl)-1*H*-4-indazolamine (1c):** Yield: 88 %; Brown colour solid; m.p.: 160-165 °C; IR (KBr, ν_{max}, cm^{-1}): 3387, 3291, 2827, 2730, 1603, 1508, 1108; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.12 (s, 1H, Ar-H), 7.15 (dd, 2H, *J* = 2.16, 4.53 Hz, Ar-H), 7.06 (t, 1H, *J* = 7.8 Hz, Ar-H), 6.89 (dd, 2H, *J* = 2.19, 4.59 Hz, Ar-H), 6.80 (d, 1H, *J* = 8.22 Hz, Ar-H), 6.48 (d, 1H, *J* = 7.47 Hz, Ar-H), 3.75 (s, 3H, -NH-); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.09, 141.79, 139.50, 135.35, 131.67, 128.80, 125.56, 122.92, 155.05, 144.81, 144.33, 101.06, 99.98, 55.60; ESI-MS: *m/z* 240 $[M + H]^+$.

***N*-5-Phenyl-1*H*-5-indazolamine (1d):** Yield: 90 %; Light brown colour solid; m.p.: >225 °C; IR (KBr, ν_{max}, cm^{-1}): 3414, 2669, 1639, 1598, 1082; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.91 (s, 1H, Ar-H), 7.41 (dd, 2H, *J* = 12.30, 1.47 Hz, Ar-H), 7.18-7.12 (m, 3H, Ar-H), 6.96 (d, 2H, *J* = 7.62 Hz, Ar-H), 6.72 (t, 1H, *J* = 7.26 Hz, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 144.77, 137.03, 136.62, 131.91, 129.52, 123.21, 123.10, 119.82, 116.43, 111.69, 107.24; ESI-MS: *m/z* 210 $[M + H]^+$.

***N*-5-(4-Methylphenyl)-1*H*-5-indazolamine (1e):** Yield: 94 %; Light brown color solid; m.p.: 188-193 °C; IR (KBr, ν_{max}, cm^{-1}): 3329, 2992, 2643, 1644, 1512, 1081; ^1H NMR (300 MHz, DMSO-d_6): δ 7.94 (s, 1H, Ar-H), 7.44 (d, 1H, *J* = 8.85 Hz, Ar-H), 7.35 (d, 1H, *J* = 1.50 Hz, Ar-H), 7.15 (dd, 1H, *J* = 2.01, 6.84 Hz, Ar-H), 7 (dd, 4H, *J* = 8.37, 13.62 Hz, Ar-H), 2.18 (s, 3H, -CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 141.70, 137.26, 136.64, 132.07, 130.00, 129.50, 123.28, 122.45, 117.58, 111.64, 106.68, 20.63; ESI-MS: *m/z* 224 $[M + H]^+$.

***N*-5-(4-Methoxyphenyl)-1*H*-5-indazolamine (1f):** Yield: 84 %; Light brown colour solid; m.p.: 142-149 °C; IR (KBr, ν_{max}, cm^{-1}): 3394, 2634, 1605, 1509, 1026; ^1H NMR (300 MHz, DMSO-d_6): δ 7.95 (s, 1H, Ar-H), 7.44 (d, 1H, *J* = 8.82 Hz, Ar-H), 7.32 (s, 1H, Ar-H), 7.15-7.05 (m, 3H, Ar-H), 6.85 (d, 2H, *J* = 8.85 Hz, Ar-H), 3.68 (s, 3H, -CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.97, 137.15, 136.71, 135.28, 132.24, 122.96, 122.30, 121.77, 115.15, 112.01, 107.75, 55.73; ESI-MS: *m/z* 240 $[M + H]^+$.

***N*-6-Phenyl-1*H*-6-indazolamine (1g):** Yield: 95 %; Brown colour solid; m.p.: 175-181 °C; IR (KBr, ν_{max}, cm^{-1}): 3270, 2782, 1643, 1598, 1026; ^1H NMR (300 MHz, DMSO-d_6): δ 8.15 (s, 1H, Ar-H), 7.63 (d, 1H, *J* = 8.79 Hz, Ar-H), 7.28 (t, 2H, *J* = 8.37 Hz, Ar-H), 7.16 (t, 2H, *J* = 7.50 Hz, Ar-H), 7.06 (d, 1H, *J* = 0.39 Hz, Ar-H), 6.96-6.89 (m, 2H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 143.09, 142.34, 141.77, 131.07, 129.63, 122.80, 121.90, 119.38, 117.06, 115.64, 91.22; ESI-MS: *m/z* 210 $[M + H]^+$.

***N*-6-(4-Methylphenyl)-1*H*-6-indazolamine (1h):** Yield: 89 %; White color solid; m.p.: 217-221 °C; IR (KBr, ν_{max}, cm^{-1}): 3292, 2911, 2693, 1640, 805; ^1H NMR (300 MHz, $CDCl_3$): δ 8.22 (dd, 1H, *J* = 8.7, 1.83 Hz, Ar-H), 7.90 (s, 1H, Ar-H), 7.55 (d, 1H, *J* = 8.76 Hz, Ar-H), 7.02-7.09 (m, 4H, Ar-H), 6.97 (d, 1H, *J* = 0.75 Hz, Ar-H), 2.22 (s, 3H, -CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 145.40, 141.89, 140.12, 132.12, 130.60, 130.06, 122.18, 119.57, 116.25, 115.68, 91.32, 20.72; ESI-MS: *m/z* 224 $[M + H]^+$.

***N*-6-(4-Methoxyphenyl)-1*H*-6-indazolamine (1i):** Yield: 91 %; brown colour solid; m.p.: > 225 °C; IR (KBr, ν_{max}, cm^{-1}): 3274, 3121, 1641, 1592, 1023; ^1H NMR (300 MHz, DMSO-d_6): δ 8.04 (s, 1H, Ar-H), 7.55 (d, 1H, *J* = 9.54 Hz, Ar-H), 7.12 (dd, 2H, *J* = 2.22, 4.47 Hz, Ar-H), 6.91 (dd, 2H, *J* = 2.22, 4.53 Hz, Ar-H), 6.80 (t, 2H, *J* = 7.92 Hz, Ar-H), 3.71 (s, 3H, -CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.57, 148.25, 142.03, 134.57, 130.68, 123.17, 122.96, 116.92, 115.02, 88.86, 55.62; ESI-MS: *m/z* 240 $[M + H]^+$.

Ethyl-4-(1*H*-5-indazolylamino)benzoate (7): Yield: 90 %; Light brown colour solid; 111-115 °C; IR (KBr, ν_{max}, cm^{-1}): 3349, 3070, 2926, 2559, 1678, 1596, 1284, 773; ^1H NMR (300 MHz, DMSO-d_6): δ 7.97 (d, 1H, *J* = 0.93 Hz), 7.73 (dd, 2H, *J* = 1.89, 5.07 Hz), 7.49-7.52 (m, 2H), 7.17 (dd, 1H, *J* = 1.86, 7.02 Hz), 6.93 (dd, 2H, *J* = 1.89, 5.04 Hz), 4.21 (q, 2H, *J* = 7.08 Hz), 1.25 (t, 3H, *J* = 7.11 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.69, 60.10, 111.39, 111.49, 113.24, 118.71, 123.29, 123.58, 131.38, 133.06, 134.40, 137.46, 150.51, 165.99; ESI-MS: *m/z* 282 $[M + H]^+$.

Typical procedure for ester hydrolysis (8): The compound **7** (2.6 mmol) and lithium hydroxide monohydrate (3.9 mmol) in THF (10 mL) and water (0.5 mL) was refluxed for 2 h. After completion of the reaction, as indicated by TLC, the reaction mixture was concentrated *in vacuo* to get residue. The residue was dissolved in water and acidified with conc. HCl and product was filtered and washed with water followed by methanol to give desired compound **8**. Yield: 91 %; Light yellow colour solid; m.p.: > 225 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 1H, -NH-), 7.97 (s, 1H, Ar-H), 7.73 (d, 2H, *J* = 8.70 Hz, Ar-H), 7.50 (dd, 2H, *J* = 3.60, 1.80 Hz, Ar-H), 7.17 (dd, 1H, *J* = 1.80, 7.20 Hz, Ar-H), 6.89 (d, 2H, *J* = 8.70 Hz, Ar-H); ESI-MS: *m/z* 254 $[M + H]^+$.

Typical procedure for amide formation 9a-c: The compound **8** (10 mmol) and amine **(11)** (20 mmol) were dissolved in dimethyl sulfoxide at room temperature and followed by the addition of *N*,*N*-diisopropylethylamine (40 mmol) and TBTU (13.5 mmol) under stirring and reaction mixture was kept as such for 3 to 6 h at room temperature. After completion of the reaction as indicated by TLC, water was added. Product was extracted into ethyl acetate and organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Organic layer was concentrated *in vacuo* to get residue. The residue was chromatographed on a silica gel column and eluted with a mixture of ethyl acetate: hexane (1:9) to afford desired compound **9a-c**.

***N*-1-Benzyl-4-(1*H*-5-indazolylamino)benzamide (9a):** Yield: 76 %; Cream colour solid; m.p.: 160-165 °C; IR (KBr, ν_{max}, cm^{-1}): 3295, 3063, 2631, 1606, 1557, 1525, 1365, 798; ^1H NMR (300 MHz, $CDCl_3$): δ 8.69 (t, 1H, *J* = 5, 40 Hz, Ar-H), 7.95 (d, 1H, *J* = 0.90 Hz, Ar-H), 7.43 (d, 2H, *J* = 8.70 Hz, Ar-H), 7.48 (t, 2H, *J* = 8.70 Hz, Ar-H), 7.15-7.29 (m, 5H, Ar-H), 6.91 (d, 2H, *J* = 9 Hz, Ar-H), 4.43 (d, 2H, *J* = 6 Hz, -CH_2-); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.30, 148.54, 140.54, 137.08, 135.53, 132.53, 129.23, 128.53, 127.51, 126.91, 123.91, 123.38, 113.63, 111.61, 109.74, 42.79; ESI-MS: *m/z* 343 $[M + H]^+$.

***N*-1-(4-Methoxybenzyl)-4-(1*H*-5-indazolylamino)-benzamide (9b):** Yield: 84 %; Brown colour solid; m.p.: 148-153 °C; IR (KBr, ν_{max}, cm^{-1}): 3287, 3094, 2925, 1604, 1508, 764; ^1H NMR (300 MHz, $CDCl_3$): δ 12.94 (s, 1H, -NH-), 8.61 (t, 1H, *J* = 5.70 Hz, 6 Hz, Ar-H), 8.39 (s, 1H, Ar-H), 7.95 (s, 1H, Ar-H), 7.70 (d, 2H, *J* = 8.70 Hz, Ar-H), 7.47 (d, 2H, *J* = 8.70 Hz, Ar-H), 7.15-7.21 (m, 3H, Ar-H), 6.82-6.93 (m, 3H, Ar-H), 4.35 (d, 3.69 (s, 3H, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.42, 158.43, 148.74, 134.98, 132.92, 132.28, 129.02, 128.75, 123.77, 123.64, 122.68, 113.72, 113.31, 111.02, 110.44, 55.19, 42.38; IR ESI-MS: *m/z* 373 [M + H]+.

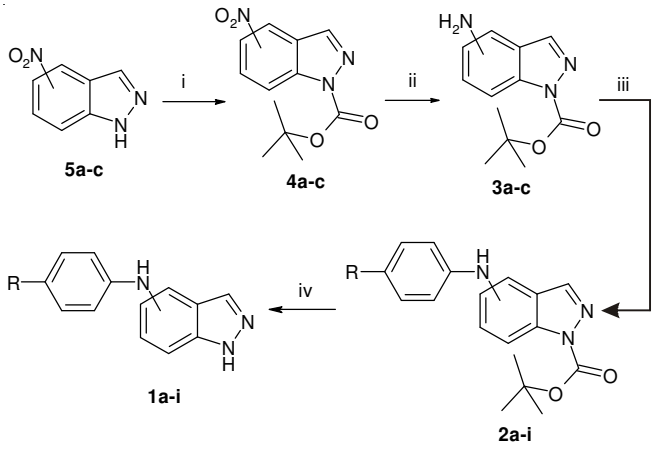
***N*-1-(4-Fluorobenzyl)-4-(1*H*-5-indazolylamino)-benzamide (9c):** Yield: 68 %; White powder; m.p.: 208-215 °C; IR (KBr, ν_{max}, cm^{-1}): 3297, 3064, 2633, 1607, 1528, 1366, 799; ^1H NMR (300 MHz, $CDCl_3$): δ 8.77 (br, 3H, -NH-), 8 (d, 1H, *J* = 0.60 Hz, Ar-H), 7.75 (d, 2H, *J* = 8.70 Hz, Ar-H), 7.49 (dd, 2H, *J* = 8.70, 0.60 Hz, Ar-H), 7.29-7.33 (m, 2H, Ar-H), 7.20 (dd, 1H, *J* = 2.10, 6.90 Hz, Ar-H), 7.07-7.13 (m, 2H, Ar-H), 6.95 (d, 2H, *J* = 8.70 Hz, Ar-H), 4.39 (d, 2H, *J* = 4,20 Hz, -CH_2-); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.31, 163, 159.80, 148.29, 136.91, 136.72, 136.68, 135.93, 132.01, 129.54, 129.43, 129.25, 123.98, 123.13, 115.34, 115.06, 113.84, 111.81, 109.31, 42.13; ESI-MS: *m/z* 361 $[M + H]^+$.

RESULTS AND DISCUSSION

Here in we report the synthesis, starting from 1*H*-indazole of several indazole derivatives substituted at the 4th, 5th and 6th positions with substituted phenyl groups. Nitroindazole

derivatives were prepared according to the literature reports[19]. We now wish to report a new set of reaction conditions, optimized for the cross-coupling of BOC protected 4, 5 and 6-amino-1*H*-indazoles, with aryl boronic acids in the presence of $Cu(OAc)_2$ and either with diisopropylethylamine/triethylamine or pyridine as a base.

Reaction of nitroindazoles **5a-c** treated with BOC anhydride in presence of potassium carbonate in acetone at room temperature for 12 h, gave known BOC protected nitroindazole **4a-c**. The latter compound was reduced with Pd/C in the presence of hydrogen gas in ethanol resulted BOC amino indazole **3a-c**, which was purified by column chromatography. Further, it was coupled with phenylboronic acid in the presence of $Cu(OAc)_2$ and TEA as base at room temperature, followed by processing gave a coupled product BOC-*N*-aryl-1*H*-indazole **2a-i**. Further deprotection BOC in methanolic HCl gave *N*-aryl-1*H*-indazole **1a-i**. Similar results were obtained when DIPEA or pyridine used in the presence of 4 Å molecular sieves instead of TEA. The above reaction proceeded very smoothly and it has been extended to other aryl boronic acid such as 4-methylphenyl boronic acid and 4-methoxyphenyl boronic acid (**Scheme-I**, Table-1).



Conditions: (i) BOC anhydride, K_2CO_3, acetone; (ii) 10 % Pd/C (50 % wet), H_2 gas, ethanol, 35 to 45 ºC; (iii) Ar-$B(OH)_2$ (Ar=Ph, 4-MePh, 4-MeOPh), $Cu(OAc)_2$, TEA (16-24 h) or pyridine, MS A° (14-20 h); (iv) MeOH. HCl, RT/2 h

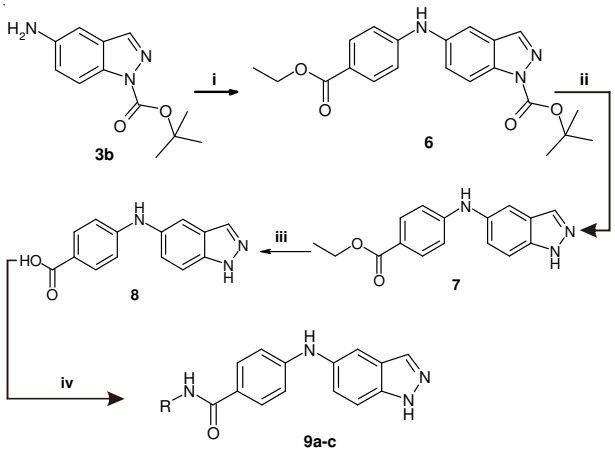
Scheme-I

TABLE-1

Entry	Substrate	R	Time (h)	Yield (%)*
1	**3a**	H	18	68
2	**3a**	4-MeO	20	72
3	**3a**	4-MeO	20	76
4	**3b**	H	16	75
5	**3b**	4-MeO	18	68
6	**3b**	4-MeO	18	73
7	**3c**	H	20	65
8	**3c**	4-MeO	22	69
9	**3c**	4-MeO	19	71

*Isolated yield

In similar manner, 4, 5 and 6-amino indazoles (**3a-c**) were coupled with 4-ethoxycarbonyl phenyl boronic acid (**10**) using $Cu(OAc)_2$ in the presence of TEA or pyridine/MS resulted in the formation of *tert*-butyl-5-[4-(ethoxycarbonyl)aniline]-1*H*-indazolecarboxylate 6, followed by BOC group deprotection in presence of acid medium *i.e.*, MeOH. HCl in methanol to gave compound **7**. Upon ester hydrolysis in presence of LiOH. H_2O to give acid compound **8**. The acid compound 8 was coupled with various amines in presence of coupling reagents like HATU/TBTU/HBTU/Py-BOP to give amide product **9a-c** (**Scheme-II**, Tables 2 and 3).



Conditions: (i) 4-Ethoxycarbonylphenyl boronic acid 10, $Cu(OAc)_2$, TEA (16-24 h) or pyridine, MS A° (14-20 h); (ii) MeOH·HCl/MeOH/RT/6-12 h; (iii) LiOH. H_2O, THF, H_2O, reflux, 6 h; (iv) RNH_2 (**11a**) R = Bn, (**11b**) 4-MeOBn, (**11c**) 4-FBn), HATU, DMSO, DIPEA, rt, 6 h

Scheme-II

TABLE-2
COUPLING WITH 4-ETHOXYCARBONYLPHENYLBORONIC ACID (**10**)

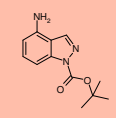
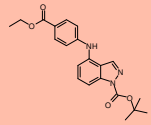
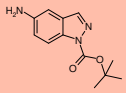
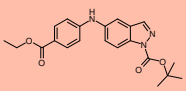
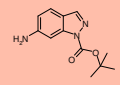
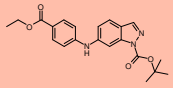
Entry	Substrate	Product	Time	Yield (%)
1			24 h	No reaction
2			16 h	76
3			24 h	No reaction

TABLE-3
COUPLING WITH ARYL AMINES

Entry	Substrate	Product	Time	Yield (%)
1	8	9a	4 h	76
2	8	9b	6 h	84
3	8	9c	5 h	68

Conclusion

The work presented here demonstrates a method which is operationally straight forward, mild and selective, utilizing the commercial reagents and also demonstrated an efficient preparation of novel *N*-aryl indazole amines *via* Chan-Lam mediated coupling conditions. We have also successfully demonstrated the synthesis of the positional isomers of amino-1*H*-indazoles (4-6 positions) in good yields. The high pharmacological importance of indazole amines prompted us to synthesize these derivatives.

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