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Suzuki-Type Cross-Coupling Reaction of 3-Iodoindazoles with Aryl Boronic Acids: a General and Flexible Route to 3-Arylindazoles.

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Abstract: - This paper describes a Suzuki Type cross coupling reaction of 3-iodoindazoles with aryl and heteroaryl boronic acids as a general route to 3-arylindazoles. The coupling reaction is illustrated by the preparation of new aryl- or heteroarylindazoles **7**. Scope and limitation of the method are outlined. The coupling reaction works best on a 1-substituted indazole nucleus. The usefulness of the reaction is illustrated by a short practical synthesis of **YC-1**, a pharmacological agent potentialy useful for the treatment of cardiovascular diseases or erectile dysfunction.

The indazole nucleus[1] is a seldom used but effective pharmacophore in medicinal chemistry as illustrated by its application in pharmaceutical agents in fields as diverse as CNS disorders (granisetron), anti-inflammatory area[2] (e.g. Bendazac and Benzydamine) and HIV protease inhibition.[3] However, in comparison with indole or benzimidazole, indazole chemistry remains poorly studied due to the limited synthetic approaches to these compounds. Most syntheses of indazoles reported in literature proceed from benzene derivatives where the pyrazole moiety was generated by ring closure starting from isatines, *o*-substituted aniline or phenylhydrazines.[1] These traditional synthetic routes do not allow easy substitution of position 3 with aryl or heteroaryl nuclei. Nevertheless, a potent inhibitor of platelet aggregation, **YC-1** (Scheme 1), was disclosed.[4] This original 3-furylindazole is now considered as a lead to design new arylindazoles derivatives potentialy useful for treatment of various diseases linked to smooth muscle relaxation including cardiovascular insufficiency and erectile dysfunction. The common route to prepare this type of compound involves intramolecular cyclisation of hydrazones. **YC-1** was obtained according to this strategy with a very poor overall yield (4%).[4]

Recently 3-heteroarylindazoles **I** (Scheme 1), analogous to **YC-1**, were prepared using the palladium-catalysed Stille coupling starting from 1-benzyl-3-iodoindazole and appropriate stannanes.[5] During our work another method was described involving a new Stille coupling starting from the 1-benzylindazole-3-triflate which can be coupled with heteroaryl halides with Pd^0 and $(Me_3Sn)_2$ *in situ*.[6]

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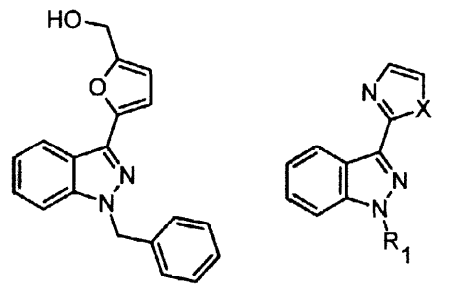


YC-1 I X=NH, O, or S

Scheme 1

In order to use less toxic reagents and avoid by-products, we investigated Suzuki-type coupling reactions. To our knowledge[7] no examples involving haloindazoles and aryl boronic acids were described to obtain a convergent synthesis of 3-arylindazoles.

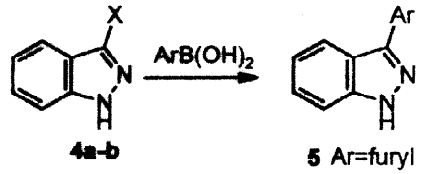
First we examined the coupling reaction between 3-bromoindazole[8] (prepared by treatment of indazole with bromine, 65%) and benzene boronic acid in the presence of catalytic amount of tetrakis(triphenylphosphine)palladium (0). No reaction occured after 18 h in refluxing DME. However we observed that the same reaction carried out with more reactive 2-furylboronic acid gave the expected coupling product **5** with a poor 10% yield. This first positive result prompted us to use 3-iodoindazole **4b** since in palladium-catalysed reactions Suzuki coupling of aryl halides the order of reactivity is usually reputed to be I>Br>>Cl. We obtained 3-iodoindazole with 90% yield from indazole by modifying the Bocchi method.[9]

This replacement enhanced the rate of Suzuki coupling beyond expectation giving, with 2-furyl boronic acid, **5** in 65% yield after 6 h in refluxing DME (Table 1). At this stage benzylation of **5** gave **7a** with 85% yield.

In order to optimize this sequence and considering that the presence of NH group of 3-iodoindazole **4b** could be the limiting factor, we decided to investigate the reactivity of 1-benzyl-3-iodoindazole **6**.

With this starting material, we observed that 2-furyl, 2-thienyl, benzene and substituted benzene boronic acids gave a quantitative coupling after short time of reaction (1-3h) and provided 68-80% yield of isolated product after column chromatography. Replacement of DME by toluene/ethanol (Method B) shortened the reaction time. This effect is particularly noticable with less reactive boronic acids such as benzene boronic acid (**7c**, Table 2).

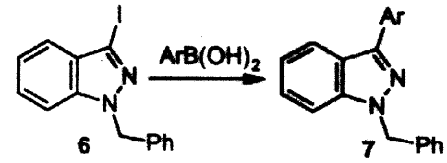
Finally, the synthesis of compound **7a** readily allowed a very efficient synthesis of **YC-1** on a multigram scale in 2 steps after the coupling reaction: formylation according to Vilsmeier-Haack reaction followed by reduction of the formyl group with sodium borohydride (Scheme 2).



X	Ar	Time (h)	Yield (%)
Br	phenyl	18	0
Br	2-furyl	18	10
I	2-furyl	6	65

Couplings were carried out at 80°C in DME in the presence of 5% $Pd(PPh_3)_4$ and 3.0 eq of $NaHCO_3$.

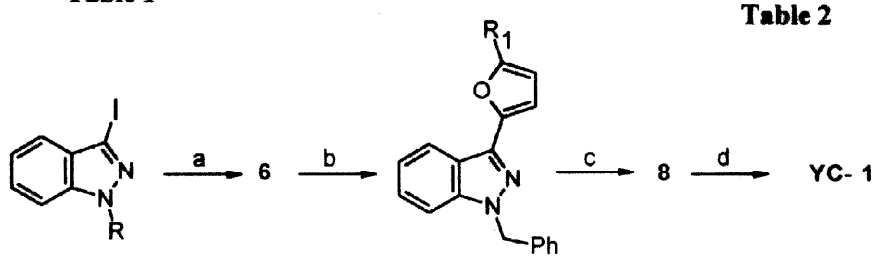
Table 1



	Ar	Method	Time (h)	Yield (%)
7a	2-furyl	A	3	79
7b	2-thienyl	A	3	76
7c	phenyl	A	7	69
7c	phenyl	B	1	72
7d	3,4di-OMe-phenyl	A	2	75
7e	4-Me-phenyl	A	2	71
7f	3,5-diCl-phenyl	A	2	68

Couplings were carried out in the presence of 5% $Pd(PPh_3)_4$ and 3.0 eq of $NaHCO_3$ in DME (Method A) or in toluene-EtOH 20/1 (Method B).

Table 2



4b: R=H
6: R=Bn

7a: R_1=H
8 : R_1=CHO

• Reagents and conditions: a: $PhCH_2Br$, *t*-BuOK, THF, 87%; b: $Pd(PPh_3)_4$, $NaHCO_3$, 2-furyl boronic acid, DME, reflux, 79%; c: $POCl_3$, DMF, 0°C then 80°C, 80%; d: $NaBH_4$, MeOH, rt., 90%.

Scheme 2

In conclusion, the Suzuki type cross-coupling procedure reported here represents a new regioselective general and convergent synthetic approach to various 3-aryl-indazoles. These intermediates are interesting pharmacophoric motifs allowing access to biologically active molecules.

EXPERIMENTAL SECTION

General. Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a

Genesis Series FTIR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (MS) were taken on a JEOL JMS GCMate spectrometer at a ionizing potential of 70 eV. Thin-layer chromatography (TLC) was performed on 0.2 mm precoated plates of silica gel 60F-264 (Merck). Visualization was made with ultraviolet light. Flash chromatography was carried out using silica gel 60 (0.063-0.2 mm) (Merck). Elemental analyses for new compounds were performed at the "Institut de Recherche en Chimie Organique Fine" (Rouen).

*3-iodoindazole (**4b**).* Iodine (16.0 g, 0.064 mol) and potassium hydroxide pellets (6.72 g, 0.12 mol) were successively added into a DMF solution (60 mL) of indazole (3.77 g, 0.032 mol) at room temperature under stirring. After 1 h, the reaction mixture was poured into 10% aqueous $NaHSO_3$ (200 mL) and extracted with Et_2O (2 x 150 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and the solvent evaporated to give a light yellow solid (6.90 g, 92%). **4b**: mp 141°C (lit.[10] mp 142°C); ^{1}H NMR ($CDCl_3$) δ 8.03 (b s, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.49 (d, J=8.0 Hz, 1H), 7.42 (t, J=7.3 Hz, 1H), 7.20 (t, J=7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 140.3, 127.1, 126.7, 121.1, 120.3, 110.4, 93.3.

*3-(2-Furyl)indazole (**5**).* To a mixture of 3-iodoindazole **4b** (244 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in DME (8 mL), 2-furyl boronic acid (125 mg, 1.1 mmol) was added followed by the addition of sodium hydrogen carbonate (252 mg, 3.0 mmol) in H_2O (4 mL). The reaction mixture was refluxed with vigorous stirring under nitrogen atmosphere for 6 h. The organic solvent was removed under reduced pressure, the crude product purified by chromatography (silica gel, EtOAc/hexane 1: 2) to give **5** as a light yellow solid (120 mg, 65%). **5**: mp 166°C (lit.[11] mp 165-166°C); ^{1}H NMR ($CDCl_3$) δ 10.70 (b s, 1H), 8.13 (d, J=4.0 Hz, 1H), 7.60-7.25 (m, 4H), 6.96 (d, J=4.0 Hz, 1H), 6.58 (d, J=4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 148.8, 142.3, 141.2, 137.8, 127.2, 121.6, 121.3, 120.1, 111.5, 110.1, 107.2.

*1-Benzyl-3-iodoindazole (**6**).* To a solution of **4b** (2.44 g, 0.01 mol) in THF (30 mL) cooled at 0°C was added potassium *tert*-butoxide (1.58 g, 0.014 mmol). After 1 h at 0°C, benzyl bromide (1.2 mL, 0.01 mmol) was added dropwise. The resulting mixture was stirred 4 h at rt then evaporated. The residue was dissolved with EtOAc (50 mL), washed with water and brine, dried ($MgSO_4$) and the solvent evaporated to give **6** as a light yellow oil (2.80 g, 87%). **6**: ^{1}H NMR ($CDCl_3$) δ 7.43-7.12 (m, 9H), 5.52 (s, 2H).

*1-Benzyl-3-aryl-indazoles (**7**). General procedure.* Method A: To a mixture of N-benzyl-3-iodoindazole **6** (322 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in DME (8 mL), the corresponding aryl boronic acid (1.1 mmol) was added followed by the addition of sodium hydrogen carbonate (252 mg, 3.0 mmol) in H_2O (4 mL). The reaction mixture was refluxed with vigorous stirring under nitrogen atmosphere and the rate of the reaction was followed by tlc. After the starting aryl halide was consumed, the organic solvent was removed under reduced pressure. The crude products were purified by column chromatography (ethyl acetate/hexane 1: 4); Method B: The reaction was carried out as described in the method A but the mixture of solvents was changed to toluene-EtOH (20 mL: 1 mL).

1-Benzyl-3-(2-furyl)indazole (7a). Method A (light yellow solid, 79%, mp 68°C). **7a**: ^{1}H NMR ($CDCl_3$) δ 8.08 (d, J=8.1 Hz, 1H), 7.58 (d, J=4.0 Hz, 1H), 7.34-7.19 (m, 8H), 6.93 (d, J=4.0 Hz, 1H), 6.56 (d, J=4.1 Hz, 1H), 5.64 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 148.8, 142.2, 140.5, 136.6, 136.4, 128.7, 127.7, 127.2, 127.1, 126.8, 121.6, 121.3, 111.4, 109.6, 106.9, 53.2; MS *m/z* 274. Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.67; H, 5.11; N, 10.18.

1-Benzyl-3-(2-thienyl)indazole (7b). Method A (white solid, 76%, mp 98°C). **7b**: ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J=8.1 Hz, 1H), 7.65 (d, J=3.2, 1H), 7.36-7.17 (m, 10H), 5.63 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 140.9, 139.2, 136.7, 136.0, 128.7, 127.7, 127.6, 127.1, 126.7, 124.9, 124.5, 121.7, 121.3, 121.2, 109.7, 53.1; MS *m/z* 290. Anal. Calcd for $C_{18}H_{14}N_2S$: C, 74.45; H, 4.86; N, 9.64. Found: C, 74.51; H, 4.81; N, 9.70.

1-Benzyl-3-phenylindazole (7c). Method B (light yellow oil, 72%). **7c**: ^{1}H NMR ($CDCl_3$) δ 8.03-7.98 (m, 3H), 7.54-7.06 (m, 11H), 5.63 (s, 2H); ^{13}C NMR δ ($CDCl_3$) 144.2, 141.0, 136.8, 133.6, 128.7, 128.6, 127.8, 127.6, 127.4, 127.1, 126.3, 122.0, 121.4, 121.1, 109.6, 53.0; MS *m/z* 284. Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.53; H, 5.62; N, 9.88.

1-Benzyl-3-(3,4-dimethoxyphenyl)indazole (7d). Method A (beige solid, 75%, mp 108°C). **7d**: ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J=8.2 Hz, 1H), 7.53-7.35 (m, 2H), 7.30-6.99 (m, 8H), 7.0 (d, J=8.2 Hz, 1H), 5.65 (s, 2H), 3.99 (s, 3H), 3.94 (s, 3H); ^{13}C NMR δ ($CDCl_3$) δ 149.3, 149.1, 144.1, 141.1, 136.9, 128.7, 127.7, 127.1, 126.4, 122.0, 121.4, 121.0, 120.1, 111.3, 110.6, 109.6, 56.0, 53.0; MS *m/z* 344. Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.71; H, 5;77; N, 8.17.

1-Benzyl-3-(4-methylphenyl)indazole (7e). Method A (white solid, 71%, mp 62°C). **7e**: ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J=8.0 Hz, 1H), 7.78 (d, J= 7.8 Hz, 2H), 7.22-7.01 (m, 10H), 2.29 (s, 3H); ^{13}C NMR δ ($CDCl_3$) δ 144.2, 140.9, 137.6, 136.9, 130.7, 129.4, 128.6, 127.6, 127.3, 127.0, 126.2, 122.0, 121.4, 120.9, 109.5, 52.9; MS *m/z* 298. Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.49; H, 6.03; N, 9.42.

1-Benzyl-3-(3,5-dichlorophenyl)indazole (7f). Method A (light yellow solid, 68%, mp 126°C). **7f**: ^{1}H NMR ($CDCl_3$) δ 7.98 (d, J=8.2 Hz, 1H), 7.89 (s, 2H), 7.38-7.15 (m, 9H), 5.65 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 141.3, 141.1, 136.6, 136.4, 135.3, 128.8, 127.9, 127.6, 127.1, 126.7, 125.5, 121.8, 121.7, 120.8, 109.9, 53.2; MS *m/z* 353. Anal. Calcd for $C_{20}H_{14}Cl_2N_2$: C, 68.00; H, 4.00; N, 7.93. Found: C, 68.07 H, 4.04; N, 7.91.

1-Benzyl-3-(5'-formyl-2-furyl)indazole (8). Phosphorus oxychloride (3.81 mL, 0.04 mol) was added dropwise at 0°C with constant stirring to DMF (3.14 mL, 0.04 mol). A solution of **7a** (2.8 g, 0.01 mol) in DMF (8 mL) was added with stirring over a period of 10 min. The ice bath was removed and the mixture heated at 50°C for 0.5 h. After cooling, H_2O (10 mL) was added. The aqueous layer basified with 6N aqueous NaOH was extracted with Et_2O (2 x 50 mL), dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/hexane 1: 2) to give **8** as a orange solid (2.46 g, 80%). **6**: mp 106°C; ^{1}H NMR ($CDCl_3$) δ 9.73 (s, 1H), 8.25 (d, J=8.0, 1H), 7.38-7.09 (m, 10H), 5.65 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 177.1, 154.9, 152.0, 140.5, 136.1, 134.9, 128.8, 127.9, 127.2, 127.1,

122.5, 121.9, 121.8, 109.7, 108.8, 53.5; IR (KBr) : 1672 (CO) cm^{-1}; MS *m/z* 302. Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.26. Found: C, 75.51; H, 4.69; N, 9.31.

1-Benzyl-3-(5'-hydroxymethyl-2-furyl)indazole (YC-1). To a solution of **8** (2.80 g, 9.29 mmol) dissolved in MeOH (35 mL) was added $NaBH_4$ (0.56 g, 10.44 mmol). After 1 h at rt, the resulting mixture was evaporated. The residue was dissolved with EtOAc (20 mL), washed with 2N HCl and water, dried ($MgSO_4$) and the solvent evaporated. Chromatography (silica gel, EtOAc/Hexane 1:2) followed by recrystallization from hexane gave **YC-1** as a white solid (2.53 g, 90%). **YC-1**: mp 112°C; ^1H NMR ($CDCl_3$) δ 7.35-7.21 (m, 8H), 6.87 (d, J=3.2 Hz, 1H), 6.47 (d, J=3.2 Hz, 1H), 5.65 (s, 2H), 4.74 (s, 2H), 1.86 (b s, 1H) ; ^{13}C NMR ($CDCl_3$) δ 153.9, 148.7, 140.5, 136.6, 136.2, 128.7, 127.8, 127.0, 126.9, 121.5, 121.4, 121.3, 109.7, 107.9, 107.8, 57.6, 53.2.; MS *m/z* 304. Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.89; H, 5.27; N, 9.24.

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