Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 22 Aug 2006.

To cite this article: Frank Halley & Xavier Sava (1997) Synthesis of 5-Cyanoindazole and 1-Methyl and 1-Aryl-5-Cyanoindazoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:7, 1199-1207, DOI: 10.1080/00397919708003357

To link to this article: http://dx.doi.org/10.1080/00397919708003357

SYNTHETIC COMMUNICATIONS, 27(7), 1199–1207 (1997)

SYNTHESIS OF 5-CYANOINDAZOLE AND 1-METHYL AND 1-ARYL-5-CYANOINDAZOLES

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Abstract: 5-Cyanoindazoles are conveniently prepared in two to three steps from commercially available 5-bromo-2-fluorobenzaldehyde.

During the course of our work, we came across a series of 5-cyanoindazole derivatives. Although 5-cyanoindazole has previously been mentioned in a patent,[1] no experimental detail was given. The general synthesis of indazoles involving the cyclisation of arylhydrazones substituted with ortho bromo, chloro or nitro groups is known[2,3] but is limited mainly to hydrazones of aryl ketones. Only recently the cyclisation of the hydrazone of a benzaldehyde substituted with an ortho fluorine has been reported.[4] We therefore designed a two step synthesis from a commercially available

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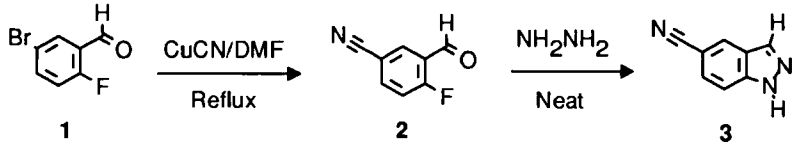
aldehyde which is depicted in Scheme 1. The 5-cyano-2-fluoro-benzaldehyde **2** was prepared *via* a Rosenmund-von Braun reaction, following a literature preparation of 3-cyanobenzaldehyde.[5] Compound **2** has also been prepared by lithiation and formylation of 4-fluorobenzonitrile.[6] The rational for the cyclisation step was that the para cyano group would facilitate the displacement of fluorine with hydrazine. Indeed, reacting the benzaldehyde **2** with hydrazine hydrate at room temperature gave after 18 h the compound **3** in good yield (see Table).

Scheme I : Preparation of 5-cyanoindazole



1 2 3

The reaction was then extended to commercially available substituted hydrazines. 5-Cyano-1-phenylindazole **5** was prepared by reacting 5-cyano-2-fluorobenzaldehyde **2** with one equivalent of phenylhydrazine in diethyl ether at room temperature to give the phenylhydrazone **4a** which was cyclised neat at 250°C for 2h (Scheme 2). The prepartion of 1-aryl-5-cyanoindazoles has already been reported in three patents: the synthesis involved an aromatic nucleophilic displacement with the preformed indazole (made by standard diazotisation-cyclisation of a substituted ortho-methyl aniline) on an activated fluoro[7] or chloro[8] aryl derivative.

A cyclisation of a perfluorobenzaldehyde phenylhydrazone, performed at 100°C in DMF, in presence of potassium carbonate has been reported.[4] The cyclisation of **4a** to **5** could be achieved at room temperature in DMF with potassium *tert*-butoxide, but the thermal cyclisation gave a cleaner product. The phenylhydrazone **4a** has been fully characterised, but in subsequent reactions, the intermediate hydrazones were isolated, identified by ^{1}H NMR and mass spectrometry and then cyclised (results are listed in the Table).

Scheme 2 : General preparation of 1-aryl- and 1-methyl-5-cyanoindazoles

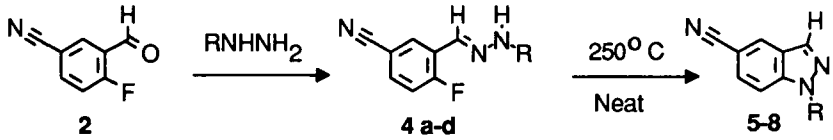


Table : Reaction Conditions and Yield of Hydrazones and Indazoles:

R	N°	Yield %	N°	Yield %	Time 250°C,h	*mp (°C)*
H	-	-	3	73	18h at rt	166-167
Ph	4a	96	5	90	2.5	157-158
Me	4b	91	6	75	2	132-134
2-Py	4c	68	7	65	0.5	179-181
3,4-Cl$_2$Ph	4d	59	8	32	2.5	184-186

In conclusion, we have found a new and simple synthesis of 5-cyanoindazole which can be extended to other 1-alkyl- and 1-aryl-5-cyanoindazoles.

Experimental

Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Proton NMR spectra were recorded using a Varian VXR 400 spectrometer; peak positions are reported in parts per million relative to internal tetramethylsilane on the δ scale. Mass spectra were recorded on a VG 7070E/250 spectrometer. Microanalyses were performed on a Carlo-Erba 1106 microanalyser. Compound **1** was obtained from LANCASTER. Yields are not optimised.

5-Cyano-2-fluorobenzaldehyde[6] **2.** This compound was prepared from 5-bromo-2-fluorobenzaldehyde **1**, following the cyanation procedure described for 3-bromobenzaldehyde.[5] The purification was achieved by column chromatography on silica gel (eluant dichloromethane). Compound **2** was obtained as a white solid (65% yield) mp = 70-72°C. ^{1}H NMR ($CDCl_3$) δ 7.39 (1H, t, J = 8 H_z , ArH), 7.84 (1H, m, ArH), 8.22 (1H, dd, J = 8, 2 H_z, ArH), 10.36 (1H, s, ArCHO). Anal. Calcd. for C_8H_4FNO: C, 64.43; H, 2.68; N, 9.40. Found: C, 64.43; H, 2.63; N, 9.66.

5-Cyanoindazole 3. Compound **2** (1.49g, 10mmol) was dissolved in hydrazine hydrate (25ml) at room temperature and the solution left to stand

for 18 h. The hydrazine was then distilled under reduced pressure (caution) and the residue purified by filtration through a pad of silica (eluant dichloromethane). Compound **3** (1.05g, 73%) was obtained as a white solid, mp = 166-167°C. ^{1}H NMR (DMSO-d_6) 7.66 (1H, dd, J = 8, 2 H_Z, ArH), 7.73 (1H, d, J = 8 H_Z, ArH), 8.27 (1H, s, ArH), 8.42 (1H, s, ArH), 13.60 (1H, br s, NH). MS (FAB) *m/z* 144 (MH^+). Anal. Calcd. for $C_8H_4N_2$: C, 67.13; H, 3.52; N, 29.35. Found: C, 67.35; H, 3.74; N, 28.27.

5-Cyano-2-fluorobenzaldehyde phenylhydrazone 4a. To a solution of **2** (1.49g, 10mmol) in diethyl ether (25ml) was added phenylhydrazine (0.98ml, 10mmol). The solution was stirred at room temperature for 0.5 h and the solvent distilled under reduced pressure. Purification of the residue by filtration through a pad of silica (eluant dichloromethane) afforded **4a** as a yellow solid (2.3g, 96%) having mp = 154-156°C. ^{1}H NMR ($CDCl_3$) 6.91 (1H, t, J = 8 H_Z, ArH), 7.10-7.18 (3H, m, ArH), 7.27-7.32 (2H, m, ArH), 7.50 (1H, m, ArH), 7.88 (1H, s, CH=N), 7.96 (1H,br s, NH), 8.32 (1H, dd, J = 8, 2H_Z, ArH). MS (FAB) *m/z* 240 (MH^+). Anal. Calcd. for $C_{14}H_{10}FN_3$: C, 70.29; H, 4.21; N, 17.56. Found: C, 69.85 H, 4.17; N, 17.68.

5-Cyano-1-phenylindazole 5. Compound **4a** (1.195g, 5mmol) was fused at 250°C for 2.5 h. The dark residue was dissolved into dichloromethane and

purified by filtration through silica gel (eluant dichloromethane) to give **5** (1g, 90%) as a white solid, having mp = 157-158°C. ^{1}H NMR ($CDCl_3$) 7.45 (1H, t, J = 8H_z, ArH), 7.53-7.72 (5H, m, ArH), 7.80 (1H, d, J = 8 H_z, ArH), 8.21 (1H, s ArH), 8.31 (1H, s, ArH). MS (FAB) *m/z* 220 (MH^+). Anal. Calcd. for $C_{14}H_9N_3 \bullet 0.1H_2O$: C, 76.08; H, 4.19; N, 19.08. Found: C, 76.02 H, 4.06; N, 19.08.

5-Cyano-1-methylindazole 6. To a solution of **2** (1.49g, 10mmol) in diethyl ether (25ml) was added methylhydrazine (0.52ml, 10mmol). The solution was stirred at room temperature for 1 h and the solvent distilled under reduced pressure. Purification of the residue by filtration through a pad of silica (eluant dichloromethane:methanol, 19:1) afforded the hydrazone as a white solid (1.61g, 91%). ^{1}H NMR (DMSO-d_6) 2.87 (3H, d, J = 4 H_z, CH_3), 7.32 (1H, s, CH=N), 7.42 (1H, dd, J = 10, 8 H_z, ArH), 7.70 (1H, m, ArH), 8.06 (1H, dd, J = 8, 2 H_z, ArH), 8.17 (1H, br q, J = 4 H_z, NH). MS (FAB) *m/z* 178 (MH^+). The hydrazone, (1.55g, 8.6mmol) was fused at 250°C for 2 h. The dark residue was dissolved into dichloromethane and purified by filtration through silica gel (eluant dichloromethane:methanol, 19:1) to give **6** (1g, 75%) as a white solid, having mp = 132-134°C. ^{1}H NMR (DMSO-d_6) 4.08 (3H, s, CH_3), 7.71 (1H, dd, , J = 8, 2 H_z , ArH), 7.84 (1H, d, J = 8 H_z, ArH), 8.22 (1H, s, ArH), 8.38 (1H, br s, ArH). MS (FAB) *m/z* 158 (MH^+).

Anal. Calcd. for $C_9H_7N_3 \bullet 0.15H_2O$: C, 67.61; H, 4.60; N, 26.28. Found: C, 67.95 H, 4.61; N, 25.99.

5-Cyano-1-(2-pyridyl)indazole 7. To a solution of **2** (1.49g, 10mmol) in diethyl ether (50ml) was added a solution of 2-pyridylhydrazine dissolved into diethyl ether (50ml). The clear solution was left to stand at room temperature for 18 h. A solid formed, which was filtered to give the hydrazone (1.65g, 68%). ^{1}H NMR (DMSO-d_6) 6.83 (1H, m, ArH), 7.43 (1H, d, J = 8 H_z , ArH), 7.51 (1H, dd, J = 10, 8 H_z, ArH), 7.67 (1H, m, ArH), 8.85 (1H, m, ArH), 8.12-8.17 (2H, m, ArH, CH=N),), 8.43 (1H, dd, J = 8, 2 H_z, ArH), 11.28 (1H, s, NH). MS (ESI) *m/z* 241 (MH^+). The hydrazone, (1.5g, 6.25mmol) was fused at 250°C for 0.5 h. The dark residue was dissolved into dichloromethane and purified by filtration through silica gel (eluant dichloromethane:methanol, 19:1) to give 7 (0.89g, 65%) as a white solid, having mp = 179-181°C. ^{1}H NMR ($CDCL_3$) 7.23 (1H, m, ArH), 7.71 (1H, dd, J = 8, 2 H_z, ArH), 7.87 (1H, m, ArH), 8.07 (1H, m, ArH), 8.15 (1H, s, ArH), 8.27 (1H, s, ArH), 8.55 (1H, m, ArH) 8.96 (1H, m, ArH). MS (APCI) *m/z* 221 (MH^+). Anal. Calcd. for $C_{13}H_8N_4$: C, 70.90; H, 3.66; N, 25.44. Found: C, 71.27 H, 3.40; N, 28.07.

5-Cyano-1-(3,4-dichlorophenyl)indazole 8. To a solution of **2** (1.49g, 10mmol) in dichloromethane (75ml) was added 3,4-dichlorophenylhydrazine

hydrochloride (2.37g, 10mmol) and triethylamine (1.4ml, 10mmol) the solution was stirred for 2 h and the precipitate filtered to give the hydrazone (1.8g, 59%). ^{1}H NMR (DMSO-d_6) 7.06 (1H, dd, J = 8, 2 H_z, ArH), 7.37 (1H, d, J = 2 H_z, ArH), 7.43 (1H, d, J = 8 H_z, ArH), 7.49 (1H, dd, J = 10, 8 H_z, ArH), 7.84 (1H, m, ArH), 7.98 (1H, s, CH=N), 8.47 (1H, dd, J = 8, 2 H_z, ArH), 11.04 (1H, s, NH). MS (FAB) *m/z* 308 (MH^+). The hydrazone (1g, 3.2mmol) was fused at 250°C for 2.5 h. The dark residue was dissolved into dichloromethane and purified by filtration through silica gel (eluant dichloromethane) to give **8** (0.3g, 32%) as a white solid, having mp = 184-186°C. ^{1}H NMR ($CDCl_3$) 7.58 (1H, dd, , J = 8, 2 H_z, ArH), 7.63-7.71 (2H, m, ArH), 7.79 (1H, d, J = 8H_z, ArH), 7.87 (1H, d, J = 2 H_z, ArH), 8.21 (1H, s, ArH), 8.32 (1H, s, ArH). MS (FAB) *m/z* 288. (MH^+). Anal. Calcd. for $C_{14}H_7Cl_2N_3 \bullet 0.2H_2O$: C, 57.60; H, 2.56; N, 14.39. Found: C, 57.73 H, 2.45; N, 13.66.

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(Received in the UK 14th August 1996)