SYNTHESIS OF NEW BIS(INDAZOL-1-YL)PHENYLMETHANES

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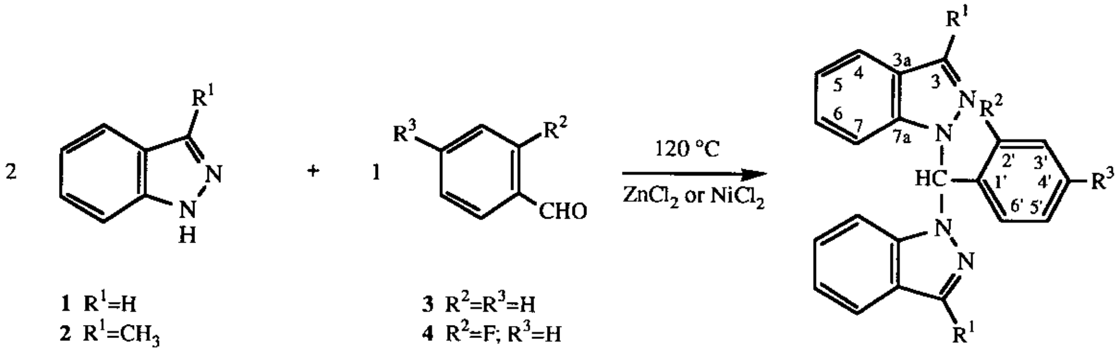
Abstract -Synthesis and spectroscopic characterization of new bis(indazol-1-yl)fluoro- or nitrophenylmethanes are reported. They have been prepared by reaction of indazole and 3-methylindazole with *ortho*-fluoro-, *para*-fluoro- and *para*-nitrobenzaldehydes in the presence of $ZnCl_2$ and $NiCl_2$.

Bis(indazol-1-yl)phenylmethanes behave as nitrogen-donor neutral ligands[1-2] with capability to chelate heavy metals such as rhodium and iridium. The complexes are able to present similar properties to those reported for bis(pyrazol-1-yl)phenylmetanes, bis(pyrazol-1-yl)methanes and tris(pirazol-1-yl)methanes complexes.[3-5] Recently we have described a pentacoordinate rhodium (I) complex derived from bis(indazol-1-yl)pyridin-2′-ylmethane.[6] Some bis(indazol-1-yl)arylmethanes have been easily prepared by thermal reaction of indazole with the corresponding aromatic or heteroaromatic aldehyde in the presence of $ZnCl_2$.[6,7] In this work we extend the procedure to fluoro- and nitrobenzaldehydes using as well $NiCl_2$ as an alternative Lewis acid catalyst.

Synthesis of bis(indazol-1-yl)phenylmethanes (**7**-**13**) has been performed by condensation at 120 °C of indazole with the corresponding benzaldehyde in the presence of $ZnCl_2$ or $NiCl_2$ (Scheme I). The reaction proceeds regioselectively to give the thermodinamically more stable 1,1-isomer as we demonstrated previously.[8] According to the yields shown in Table I, the use of $NiCl_2$ seems to be more adequate for the reaction of indazole and *ortho*-fluorobenzaldehyde, but no significant improvement with the other aldehydes was obtained.



1 R^1=H
2 R^1=CH_3

3 R^2=R^3=H
4 R^2=F; R^3=H
5 R^2=H; R^3=F
6 R^2=H; R^3=NO_2

7 R^1=R^2=R^3=H
8 R^1=H; R^2=F; R^3=H
9 R^1=H; R^2=H; R^3=F
10 R^1=CH_3; R^2=F; R^3=H
11 R^1=CH_3; R^2=H; R^3=F
12 R^1=R^2=H; R^3=NO_2
13 R^1=CH_3; R^2=H; R^3=NO_2

Scheme I

New compounds (**8-13**) were fully characterized by ^{1}H and ^{13}C nmr spectroscopy (Tables II and III). Assignments of all protons and carbons were made on the basis of previous data[7,8] and with the help of 2D homonuclear and heteronuclear correlations. The bis(indazol-1-yl) isomer was easily recognized by the characteristic chemical shift (see table III) of the carbon atom at the position 3 (ca. 135 ppm for indazole nucleus and ca. 143 for 3-methylindazole nucleus) and at the position 7 (ca. 110 ppm for both nucleus). The chemical shift values of these carbon atoms in compounds (**8-13**) were in agreement with those found in other 1-substituted indazoles.[9] Another significant feature was that proton H-7 of the indazole ring resonates in all compounds at higher field than proton H-4. This behaviour is also found in unsubstituted indazole. However, in aliphatic series such as bis(indazol-1-yl)alkanes, proton H-7 always resonates at lower field than proton H-4.[8]

EXPERIMENTAL

Melting points were obtained on a Gallenkamp MFB-595 and are uncorrected. Elemental analyses were performed with a Perkin Elmer 240 apparatus. Mass spectra were determined on a VG-12-250

Table I. Isolated yields, melting points and elemental analyses of compounds (**8-13**).

Compound	Lewis acid	Yields %	mp °C	Formula	Elemental Analyses					
					Calculated			Found		
					C	H	N	C	H	N
7	$ZnCl_2$	64[a]	136-138 (Ethanol)							
	$NiCl_2$	26								
8	$ZnCl_2$	30	138-140 (Ethanol)	$C_{21}H_{15}N_4F$	73.65	4.42	16.37	73.38	4.75	16.60
	$NiCl_2$	51								
9	$ZnCl_2$	59	119-121 (Ethanol)	$C_{21}H_{15}N_4F$	73.65	4.42	16.37	73.90	4.32	16.45
	$NiCl_2$	52								
10	$ZnCl_2$	73	155-157 (Hexane-Ethanol)	$C_{23}H_{19}N_4F$	74.57	5.17	15.12	74.48	5.14	14.92
11	$ZnCl_2$	42	168-169 (Ethanol)	$C_{23}H_{19}N_4F$	74.57	5.17	15.12	74.20	5.25	15.17
12	$ZnCl_2$	58	154-156 (Ethanol)	$C_{21}H_{15}N_5O_2$	68.28	4.10	18.66	68.01	4.27	18.75
13	$ZnCl_2$	62	187-189 (Ethanol)	$C_{23}H_{19}N_5O_2$	69.51	4.82	17.62	69.21	4.76	17.65

a: From reference 7.

Table II. ^{1}H Nmr chemical shifts (δ) and coupling constants (Hz) of compounds (**8-13**) in $CDCl_3$ at 200.13 MHz.

Compound	H_3	H_4	H_5	H_6	H_7	CH(sp^3)	$H_{2'}$	$H_{3'}$	$H_{4'}$	$H_{5'}$	$H_{6'}$	CH_3
8	8.09(d)	7.70(ddd)	7.17-7.09(m)	7.17-7.09(m)	7.37(dddd)	8.55(s)		7.33-7.09(m)	7.33-7.09(m)	7.33-7.09(m)	7.33-7.09(m)	
	J_{37}=0.9; J_{45}=8.0; J_{46}=1.2; J_{47}=0.9; J_{67}=8.2											
9	8.07(d)	7.70(ddd)	7.16(ddd)	7.33(ddd)	7.51(dddd)	8.44(s)	7.15-6.99(m)	7.15-6.99(m)		7.15-6.99(m)	7.15-6.99(m)	
	J_{37}=0.9; J_{45}=8.0; J_{46}=1.2; J_{47}=0.9; J_{56}=7.0; J_{57}=1.5; J_{67}=8.5											
10		7.61(ddd)	7.36-7.20(m)	7.36-7.20(m)	7.36-7.20(m)	8.40(s)		7.15-7.02(m)	7.15-7.02(m)	7.15-7.02(m)	7.15-7.02(m)	2.55(s)
	J_{45}=8.0; J_{46}=0.9; J_{47}=0.9											
11		7.60(ddd)	7.11(ddd)	7.29(ddd)	7.49(ddd)	8.29(s)	7.05-6.95(m)	7.05-6.95(m)		7.05-6.95(m)	7.05-6.95(m)	2.53(s)
	J_{45}=8.0; J_{46}=1.1; J_{47}=0.9; J_{56}=7.0; J_{57}=0.9; J_{67}=8.4											
12	8.10(d)	7.73(ddd)	7.18(ddd)	7.34(ddd)	7.54(dddd)	8.51(s)	7.30(d)	8.21(d)		8.21(d)	7.30(d)	
	J_{37}=0.9; J_{45}=8.0; J_{46}=1.1; J_{47}=1.0; J_{56}=6.9; J_{57}=1.5; J_{67}=8.4; $J_{2'3'}$=$J_{5'6'}$=9.0											
13		7.63(ddd)	7.14(ddd)	7.32(ddd)	7.52(ddd)	8.34(s)	7.27(d)	8.18(d)		8.18(d)	7.27(d)	2.55(s)
	$J_{4,5}$=8.0; J_{46}=1.1; J_{47}=0.9; J_{56}=6.9; J_{57}=1.0; J_{67}=8.4; $J_{2'3'}$=$J_{5'6'}$=8.9											

s, singlet; d, doublet; t, triplet; m, multiplet.

Table III. ^{13}C Chemical shifts (δ) of compounds (**8-13**) in $CDCl_3$ at 50.33 MHz.

Compound	C_3	C_{3a}	C_4	C_5	C_6	C_7	C_{7a}	CH(sp^3)	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	$C_{6'}$	CH_3
8	134.7	124.8	121.2	121.6	127.1	109.8	139.6	70.0	123.1	160.0	115.7	128.9	124.2	131.1	
	$J_{C1'F}$=12.7; $J_{C2'F}$=249.6; $J_{C3'F}$=21.0; $J_{C4'F}$=2.6; $J_{C5'F}$=3.7; $J_{C6'F}$=8.4														
9	134.8	124.7	121.0	121.5	126.8	110.6	139.6	74.0	130.8	129.3	115.5	162.7	115.5	129.3	
	$J_{C1'F}$=3.3; $J_{C2'F}$=8.4; $J_{C3'F}$=21.8; $J_{C4'F}$=248.3														
10	142.9	124.3	120.3	120.6	126.8	109.9	140.4	69.9	123.7	160.1	115.5	128.9	124.0	130.6	12.0
	$J_{C1'F}$=12.8; $J_{C2'F}$=249.5; $J_{C3'F}$=21.1; $J_{C4'F}$=2.6; $J_{C5'F}$=3.6; $J_{C6'F}$=8.3														
11	143.0	124.3	120.1	120.5	126.5	110.8	140.5	73.5	131.5	129.3	115.3	162.6	115.3	129.3	11.9
	$J_{C1'F}$=3.1; $J_{C2'F}$=8.2; $J_{C3'F}$=21.8; $J_{C4'F}$=247.8														
12	135.2	124.8	121.2	121.8	127.2	110.3	139.5	73.7	142.0	128.6	123.6	147.9	123.6	128.6	
13	143.6	124.4	120.3	120.9	126.9	110.5	140.5	73.3	142.9	128.7	123.5	147.8	123.5	128.7	12.0

spectrometer at 70 eV. Nmr spectra were recorded with a Bruker AC-200 (200.13 MHz for ^1H, and 50.33 MHz for ^{13}C). ^1H and ^{13}C chemical shifts (δ) are given from internal tetramethylsilane with an accuracy of ±0.01 and ±0.1 ppm respectively. Coupling constants (J) are accurate to ±0.2 Hz for ^1H nmr spectra and ±0.6 Hz for ^{13}C nmr spectra. Homonuclear ^1H-^1H COSY-90 and heteronuclear ^1H-^{13}C correlations were performed in the usual manner.[10,11] Tlc chromatography was performed on DC-Alufolien/Kieselgel 60 F_{254} (Merck, 0.2 mm) and column chromatography through silica gel Merck 60 (70-230 mesh). Products were purchased from commercial sources. $ZnCl_2$ and $NiCl_2$ were stored in a vacuum desicator prior to use. 3-Methylindazole was prepared by a described procedure.[12] Isolated yields, melting points and elemental analyses of the new bis(indazol-1-yl)phenylmethanes (**8-13**) are given in Table I.

Reaction of Indazoles (**1-2**) *with Benzaldehydes* (**3-6**). *General method.* A one-necked round-bottomed flask was fitted with a reflux condenser attached to drying tube ($CaCl_2$) and with a magnetic stirrer. The flask was charged with the indazole (10 mmol), the corresponding aldehyde (5 mmol) and $ZnCl_2$ or $NiCl_2$ (0.25 mmol) (2:1: 1/20 molar ratio). The mixture was heated with stirring in an oil bath at 120-125 °C for 16 to 20 h. After cooling to room temperature the reaction mixture was purified by silica gel column chromatography using methylene chloride as eluent.

Bis(indazol-1-yl)-ortho-fluorophenylmethane (**8**) Rf = 0.32. Ir (KBr) 3120, 3080, 1615, 1490, 1450, 1415, 1370, 1330, 1310, 1285, 1225, 1185, 1160, 1095, 900, 850, 790, 740 cm^{-1}. Ms m/z (%) 342 (M^+, 27), 328 (9), 327 (3), 226 (26), 225 (100), 224 (3), 205 (3), 196 (5), 170 (4).

Bis(indazol-1-yl)-para-fluorophenylmethane (**9**) Rf = 0.38. Ir (KBr) 3200, 2930, 2840, 1620, 1500, 1470, 1415, 1370, 1320, 1225, 1160, 1120, 1025, 900, 800, 760 cm^{-1}. Ms m/z (%) 342 (M^+, 9), 226 (16), 225 (100), 224 (2), 196 (4), 170 (3).

Bis(3-methyl-indazol-1-yl)-ortho-fluorophenylmethane (**10**) Rf = 0.22. Ir (KBr) 3060, 2920, 1600, 1505, 1480, 1440, 1395, 1350, 1290, 1230, 1200, 1165, 1070, 1030, 1015, 880, 805, 770, 735 cm^{-1}. Ms m/z (%) 370 (M^+, 3), 240 (19), 239 (100), 219 (5), 170 (2), 102 (2).

Bis(3-methyl-indazol-1-yl)-para-fluorophenylmethane (**11**) Rf = 0.26. Ir (KBr) 3070, 2925, 1610, 1505, 1430, 1330, 1280, 1260, 1170, 1150, 1130, 1075, 1035, 1020, 850, 825, 800, 760, 740 cm^{-1}. Ms m/z (%) 370 (M^+, 2), 240 (20), 239 (100), 238 (1), 237 (2), 223 (1), 170 (2).

Bis(indazol-1-yl)-para-nitrophenylmethane **(12)** Rf = 0.32. Ir (KBr) 3100, 3075, 2970, 1600, 1510, 1330, 1300, 1275, 1250, 1190, 1160, 1140, 1100, 1025, 910, 860, 840, 825, 760, 740 cm^{-1}. Ms m/z (%) 370 (12), 369 (M$^+$, 12), 253 (16), 252 (100), 225 (3), 206 (15), 205 (12), 178 (3).

Bis(3-methyl-indazol-1-yl)-para-nitrophenylmethane **(13)** Rf = 0.24. Ir (KBr) 3080, 3050, 2920, 1605, 1595, 1505, 1440, 1390, 1290, 1200, 1175, 1080, 1010, 830, 800, 750, 740, 725 cm^{-1}. Ms m/z (%) 397 (M$^+$, 2), 267 (20), 266 (100), 220 (16), 219 (14), 144 (6), 77 (10).

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REFERENCES

1. M. A. Garralda and L. A. Oro, *Trans. Met. Chem.*, 1980, **5**, 65.
2. P. J. Steel, *Coord. Chem. Rev.*, 1990, **106**, 227; S. Trofimeko, *Prog. Inorg. Chem.*, 1986, **34**, 115.
3. P. Y Leung and I. K. Peterson, *J. Organomet. Chem.*, 1981, **219**, 409.
4. L. A. Oro, M. Esteban, R. M. Claramunt, J. Elguero, C. Foces-Foces, and F. H. Cano, *J. Organomet. Chem.*, 1984, **276**, 79.
5. M. A. Misubi and F. O. Anumba, *Trans. Met. Chem.*, 1985, **10**, 5.
6. M. C. López, P. Ballesteros, R. M. Claramunt, M. Cano, J. V. Heras, E. Pinilla, and A. Monge, *J. Organomet. Chem.*, 1993, **450**, 237.
7. P. Ballesteros, J. Elguero, and R. M. Claramunt, *Tetrahedron*, 1985, **41**, 5955; P. Ballesteros, R. M. Claramunt, M. C. López, J. Elguero, and G. Gómez-Alarcón, *Chem. Pharm. Bull.*, 1988, **36**, 2036.
8. M. C. López, R. M. Claramunt, and P. Ballesteros, *J. Org. Chem.*, 1992, **57**, 5240.
9. M. Begtrup, R. M. Claramunt, and J. Elguero, *J. Chem. Soc.*, *Perkin Trans. II*, 1978, 99.
10. K. Nagayama, A. Kumar, K. Wüthrich, and R. R. Ernst, *J. Magn. Reson.*, 1980, **40**, 321.
11. A. Bax and G. Morris, *J. Magn. Reson.*, 1981, **42**, 501.
12. R. Sureau and R. Pernot, *Bull. Soc. Chim. Fr.*, 1958, 156.

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