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REDUCTION OF NITROINDAZOLES: PREPARATION OF NEW AMINO AND CHLOROAMINO DERIVATIVES

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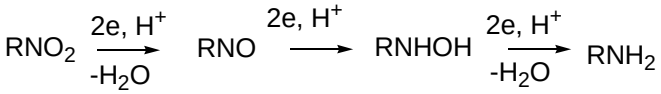
Abstract – The synthesis of chloroaminoindazoles by the reduction of the nitro group of indazoles using stannous chloride in alcoholic acid solution is reported. Using catalytic hydrogenation with palladium the expected reduction to amino-indazoles occur.

INTRODUCTION

The reduction of nitro derivatives is one of the most studied reactions in organic chemistry. Various reductive agents have been employed, among them those containing metals like Zn, Sn or Pd, being amongst the most frequently used.

The conversion of a nitro derivative into amine went through various steps as represented Scheme 1.

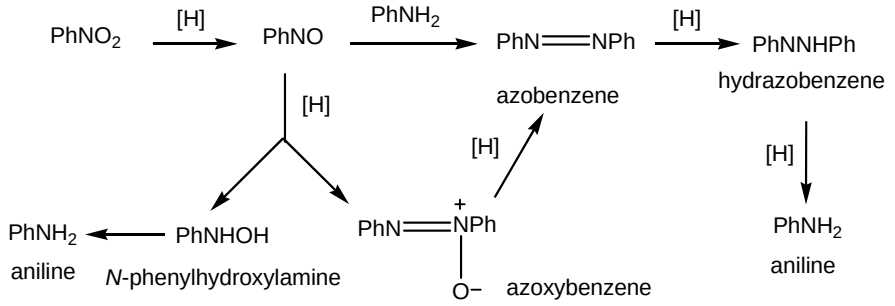


Scheme 1 Nitro reduction

Many synthetic pathways have been developed to obtain the reduced product at the desired step,[1] the most important being the total reduction into aromatic amines due to the importance of these compounds as key intermediates for biological compounds. Indeed, amino aromatics are interesting for the development of numerous compounds used as pharmaceuticals, agronomics, colorants and antioxidants.

In the case of catalytic hydrogenation, the reduction can lead to various intermediaries as shown in the

nitrobenzene reduction reported example Scheme 2.[2]



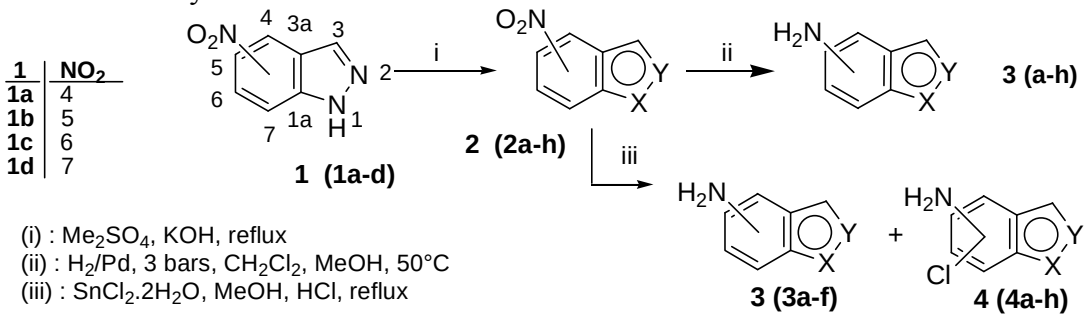
Scheme 2 Nitrobenzene reduction

More effective methods of reduction of aromatic nitro compounds into amines have been developed, for instance, in the presence of a basic nickel complex[1,3] with aluminium amalgam,[4] with ferric chloride,[5] selenium,[6] 1,1-dialkyl-4,4'-bipyridinium,[7] baker yeast,[8] sodium hydride/bismuth trichloride,[9] indium,[10] hydroiodic acid,[11] hydrazine/palladium,[12] Raney nickel,[13] DBU/DMF,[14] H_2/palladium on carbon,[15] $SnCl_2$/MeOH/HCl,[16] and iron powder/AcOH.[17]

As part of our program on the synthesis of functionalized ring systems like tetracyclic phenothiazines as candidates for pharmacological evaluation,[18] we were interested in the preparation of primary amino benzazoles, like indazole, useful for *N*-arylation cross-coupling reactions with organobismuth or organoboron complexes.[19] Our starting materials were different commercially available nitroindazoles (nitro on position 4, 5, 6 and 7), which were methylated and reduced into amino methylindazole isomers using alternatively two different methods: palladium catalyzed hydrogenation[20] or stannous chloride reduction.[21]

RESULTS AND DISCUSSION

First, 4-, 5-, 6- and 7-nitroindazoles (**1a-d**) were treated with dimethyl sulfate according to Jaffari and Nunn with dimethyl sulfate in potassium hydroxide solution.[22] In each case, the reaction led to a mixture of two methyl isomers which were separated by silicagel column chromatography to afford methyl-1 (**2a**, **2c**, **2e**, **2g**) and methyl-2 (**2b**, **2d**, **2f**, **2h**) indazoles respectively. Non commercial 4-nitroindazole (**1a**) was prepared by addition of aqueous sodium nitrite solution on 2-methyl-3-nitroaniline in acetic acid, and was obtained with 65% yield.[23]



Scheme 3 Preparation of indazoles (**3a-h**) and (**4a-h**)

The results reported in table 1 showed that the yields were low to medium after separation and purification (27-44%).

Table 1 Preparation of methylnitroindazoles **(2a-h)**

2	**NO_2**	**X**	**Y**	Yield %
a	4	NMe	N	34
b	4	N	NMe	35
c	5	NMe	N	42
d	5	N	NMe	44
e	6	NMe	N	42
f	6	N	NMe	43
g	7	NMe	N	41
h	7	N	NMe	27

The nitro derivatives (**2a-h**) were reduced quantitatively into amines with palladium under hydrogen atmosphere (3 bars), in a CH_2Cl_2/MeOH solution (1/1), to yield the corresponding amino indazoles (**3a-i**), (see Table 2). The yields were good, except for compounds (**3g**) and (**3i**).

Table 2 Yields of amino- (**3a-i**) and chloroaminoindazoles (**4a-h**) prepared alternatively by hydrogenation with palladium or catalyst stannous chloride reduction

Position NH_2	**3**	**Yield % [a]**	**Yield % [b]**	**4**	**Position Cl**	**Yield % [b]**
4	**a**	93	59	**a**	7	24
4	**b**	85	37	**b**	7	12
5	**c**	60	11	**c**	4	27
5	**d**	98	20	**d**	4	20
6	**e**	97	54	**e**	7	34
6	**f**	38	42	**f**	7	11
7	**g**	18	-	**g**	4	77
7	**h**	58	-	**h**	4	55
4	**i**	27	-	-	-	-

[a]Reduction with H_2/Pd. [b]Reduction with $SnCl_2$/HCl.

This reduction was also performed with stannous chloride in acidic methanol[22] but a mixture of

derivatives (**3a-f**) and (**4a-h**) was obtained. After separation and purification, amino compounds (**3a-f**) were recovered but with lower yields (11-59 %), while an unexpected aromatic chlorination on the benzene moiety led to compounds (**4a-f**). Indeed, chlorination turned out to be regioselective and led to single C-4 or C-7 chloro isomers (**4a-h**) depending on the nitro aromatic position: 4- and 6-nitroindazoles conduced to 7-chloro derivatives, while 5- and 7-nitro compounds led to 4-chloro isomers. No other side products of reaction was obtained. For example reduction with $SnCl_2$ of 1-methyl-4-nitroindazole (**2a**) conduced to a mixture of 4-amino-1-methylindazole (**3a**) and 4-amino-7-chloro-1-methylindazole (**4a**) which were separated by column chromatography to yield the chloro derivative (**4a**) (24 %) which was obtained first followed by (**3a**) (59 %), (see Table 2). Under the same conditions of reaction the reduction of 7-nitroindazoles (**2g-h**) led only to the chloro amino compounds (**4g**) and (**4h**).

The assignment of the structure of the chloro compounds was unambiguously supported by the ^1H and ^{13}C NMR spectra, in particular by the evaluation of the multiplet pattern of the C-ring proton signals: two doublets would be expected for 5-H and 6-H with substituted 4-C or 7-C indazoles; indeed this former pattern was effectively observed. These interesting results prompted us to react directly aminoindazole; *e.g.* 6-aminoindazole, with $SnCl_2$ but no chlorinated product was isolated. To our knowledge no chlorination on the benzene moiety of indazoles has been reported until yet in the literature using a $SnCl_2$/HCl mixture on nitro indazoles; therefore the mechanism could be described as an electrophilic chlorination as reported by Lee and Beak, favoring a dissociative mechanism or an intermediate that has an oblique angle between the entering and leaving groups.[24]

In conclusion we reported a synthesis of chloroaminoindazoles using stannous chloride reduction. These chloro indazoles will be used for subsequent *N*-substitution and preparation of a new class of potent nonsteroidal estrogen receptor ligands, useful in the treatment of rheumatoid arthritis.[25]

EXPERIMENTAL

Solvents or reagents were grade quality and were used without further purification, except methanol. Melting points were measured on an Electrothermal IA 9300 apparatus and were uncorrected. Column chromatography was performed on silica gel (Merck Kieselgel, 230-240 mesh). ^1H NMR and ^{13}C NMR spectra were recorded on BRUKER AM 300 and AMX 400 spectrometers. Spectra were referenced to the residual solvent peak. Elemental analysis for carbon, hydrogen and nitrogen were performed on a Thermo-Finnigan AE1112 elemental analyzer.

4-Nitroindazole (1a): In a 1L round bottomed flask were introduced 10 g (66 mmol) of 2-methyl-3-nitroaniline and 500 mL of AcOH. The solution was warmed under stirring until completed dissolution. Addition drop by drop of a solution of 4.6 g (75.41 mmol) of $NaNO_2$ in 10 mL of water led to diazonium salt precipitation. The solution was stirred until this precipitate redisolved and the mixture was

concentrated to the third of its initial volume. Then hot water (600 mL) was added to yield an orange-yellow product. The mixture was warmed and filtered hot. After cooling the obtained precipitate was filtered, washed with cold water and dried to yield **1a**; 7 g, 65%; mp 201-202 °C**.** ^{1}H-NMR (DMSO-d_6) δ: 13.91 (1H, s, NH), 8.51 (1H, s, H-3); 8.12 (1H, d, J = 6.0, H-5), 8.07 (1H, d, J = 1.3, H-7), 7.57 (1H, t, J = 6.0, H-6). ^{13}C-NMR (DMSO-d_6) δ: 141.68 (C-1a), 133.33 (C-3), 125.72 (C-6), 125.72 (C-3a), 118.31 (C-5), 115.27 (C-7), 144.68 (C-4). CAS: 2942-40-7.

General procedure for preparation of methylnitroindazoles (2a-h):

In a 250 mL flask were introduced 5 g (30.7 mmol) of the corresponding nitroindazole (**1a-d)**, 15 g (300 mmol) of KOH and 15 mL of water. The solution was warmed to 45°C until complete dissolution. After the addition drop by drop of 13 mL (17.5 g, 138 mmol, d = 1.33) of Me_2SO_4, the mixture was heated with 75°C during half an hour. After cooling, the solution was filtrated, the residue was washed with water and dried at a temperature of 50°C. The residue was chromatographed on silica gel with diethyl Et_2O/pentane (1/1) as the eluent. The 2-methyl derivatives (**2b**, **2d**, **2f**) were eluted first, followed by the 1-methyl derivatives (**2a**, **2c**, **2e**).

1-Methyl-4-nitroindazole (**2a**): 1.85 g, 34%, mp 108-110°C**.** ^{1}H-NMR (DMSO-d_6) δ: 8.40 (1H, s, H-3); 8.17 (1H, d, J = 8.9, H-5); 8.09 (1H, d, J = 8.9, H-7); 7.59 (1H, t, J = 8.9, H-6); 4.14 (3H, s, Me). ^{13}C-NMR (DMSO-d6) δ: 141.35 (C-4), 139.70 (C-1a), 131.37 (C-3), 125.72 (C-6), 118.48 (C-5), 118.17 (C-7), 115.93 (C-3a), 36.21 (Me). CAS: 26120-43-4.

2-Methyl-4-nitroindazole (**2b**): 1.89 g, 35%, mp 105°C**.** ^{1}H-NMR (DMSO-d_6) δ: 8.69 (s, 1H, H-3); 8.04 (2H, d, J = 8.0, H-5 and H-7); 7.37 (1H, t, J = 8.1, H-6); 4.23 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 149.36 (C-1a), 140.02 (C-4), 126.09 (C-7), 125.60 (C-6), 124.43 (C-3), 120.37 (C-5), 114.19 (C-3a), 40.63 (Me). CAS: 26120-44-5.

1-Methyl-5-nitroindazole (**2c**): 2.28 g, 42%, mp 162°C**.** ^{1}H-NMR (DMSO-d_6) δ: 8.78 (1H, d, J = 0.9, H-4); 8.36 (1H, s, H-3); 8.20 (1H, dd, J = 1.0, 8.5, H-6); 7.82 (1H, d, J = 8.5, H-7); 4.11 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 141.70 (C-5), 141.32 (C-1a), 135.73 (C-3), 122.61 (C-3a), 120.64 (C-6), 118.68 (C-4), 110.29 (C-7), 35.85 (Me). CAS: 5228-49-9.

2-Methyl-5-nitroindazole (**2d**): 2.39 g, 44%, mp 132°C**.** ^{1}H-NMR (DMSO-d_6) δ: 8.78 (1H, d, J = 1.0, H-4); 8.76 (1H, s, H-3); 7.98 (1H, dd, J = 1.0, 8.5, H-6); 7.75 (1H, d, J = 8.5, H-7); 4.25 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 149.12 (C-1a), 141.78 (C-5), 128.67 (C-3), 120.01 (C-6), 120.03 (C-3a), 119.32 (C-4), 117.56 (C-7), 40.61 (Me). CAS: 5228-48-8.

1-Methyl-6-nitroindazole (**2e**): 2.28 g, 42%, mp 125°C**.** ^{1}H-NMR (DMSO-d_6) δ: 8.72 (1H, d, J = 1.0, H-7), 8.28 (1H, s, H-3), 8.00 (1H, dd, J = 0.8, 8.8, H-4), 7.93 (1H, dd, J = 1.8, 8.8, H-5), 4.19 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 145.45 (C-6), 137.92 (C-1a), 132.71 (C-3), 126.20 (C-3a), 121.62 (C-4), 114.30 (C-5), 106.43 (C-7), 35.75 (Me). CAS: 6850-23-3.

2-Methyl-6-nitroindazole (**2f**): 2.34 g, 43%, mp 160°C**.** ^{1}H-NMR (DMSO-d_6) δ: 8.60 (1H, s, H-3); 8.59 (1H, d, J = 0.4, H-7); 7.97 (1H, dd, J = 0.4, 9.0, H-4); 7.80 (1H, dd, J = 1.7, 9.0, H-5); 4.28 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 147.82 (C-1a), 146.04 (C-6), 126.12 (C-3), 124.07 (C-3a), 122.20 (C-4), 114.55 (C-7), 114.53 (C-5), 40.84 (Me). CAS: 6850-22-2.

Preparation of 1-methyl and 2-methyl-7-nitroindazoles: we used the following: 1 g (6.2 mmol) of 7-nitroindazole, 3 g (60 mmol) of KOH, 3 mL of water and 2.60 mL (3.5 g, 27.6 mmol) of Me_2SO_4. **2h** was eluted first, followed by **2g**.

1-Methyl-7-nitroindazole (**2g**): 0.45 g, 41%, mp 98 °C**.** ^{1}H-NMR (DMSO-d_6) δ: 8.38 (1H, s, H-3); 8.24* (1H, d, J = 8.5, H-5); 8.18* (1H, d, J = 8.5, H-4); 7.33 (1H, t, J = 8.5, H-6); 4.14 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 128.39 (C-1a), 130.41 (C-7), 128.58 (C-4), 134.31 (C-3), 125.44 (C-3a), 124.50 (C-5), 120.13 (C-6), 40.27 (Me). CAS: 58706-36-8.

2-Methyl-7-nitroindazole (**2h**): 0.30 g, 27%, mp 143°C**.** ^{1}H-NMR (DMSO-d_6) δ: 8.75 (s, 1H, H-3); 8.30* (d, J = 8.5, 1H, H-5); 8.27* (d, J = 8.5, 1H, H-4); 7.24 (t, J = 8.5, 1H, H-6); 4.27 (s, 3H, Me). ^{13}C-NMR (DMSO-d_6) δ: 139.62 (C-1a), 136.30 (C-7), 129.81 (C-4), 127.73 (C-3), 125.32 (C-3a), 124.50 (C-5), 119.54 (C-6), 40.60 (Me). CAS: 13436-58-3.

Typical procedure for preparation of aminoindazoles 3a-i: reduction with palladium catalyst.

In a 250 mL flask were introduced 8 g (50 mmol) of 4-nitroindazole (**1a**), a solution of MeOH/CH_2Cl_2 (160 mL, 1/1) and 8 mg of palladium on carbon (10%). The mixture was warmed under hydrogen pressure (3 bars) to 50°C during 3 hours. After cooling, the solution was filtered and concentrated. The obtained residue was purified by silica gel chromatography with diethyl Et_2O/toluene (1/1) as solvent to yield 4-aminoindazole (**3i**), 4.0 g, 27%, mp 120°C. ^{1}H-NMR (DMSO-d_6) δ: 12.61 (1H, s, NH), 8.08 (1H, sbr, H-3), 6.98 (1H, t, J = 7.6, H-6), 6.64 (1H, t, J = 8.1, H-7), 6.12 (1H, t, J = 7.4, H-5), 5.62 (2H, s, NH_2). ^{13}C-NMR (DMSO-d_6) δ: 142.25 (C-4), 141.76 (C-1a), 132.67 (C-3), 127.66 (C-6), 113.71 (C-3a), 101.32 (C-5), 97.00 (C-7). CAS: 41748-71-4.

4-Amino-1-methylindazole (3a): As reported for 4-aminoindazole but with 0.80 g, (4.52 mmol) of 1-methyl-4-nitroindazole (**2a**), 20 mL of MeOH/CH_2Cl_2 (1/1) and 2 mg of palladium on carbon (10%); 0.62 g; 93 %; mp 165°C. ^{1}H-NMR (DMSO-d_6) δ: 8.07 (1H, s, H-3), 7.04 (1H, t, J = 8.0, H-6), 6.64 (1H, d, J = 8.0, H-7), 6.17 (1H, d, J = 8.0, H-5), 3.91 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 142.44 (C-4), 141.38 (C-1a), 130.99 (C-3), 127.81 (C-6), 114.07 (C-3a), 101.56 (C-5), 96.29 (C-7), 35.37 (Me). CAS: 77894-69-0.

4-Amino-2-methylindazole (3b): As reported for 4-aminoindazole but with 0.27 g, (1.52 mmol) of 2-methyl-4-nitroindazole (**2b**), 10 mL of MeOH/CH_2Cl_2 (1/1) and 2 mg of palladium on carbon (10%); 0.19g; 85%; mp 105-107°C. ^{1}H-NMR ($CDCl_3$) δ: 7.66 (1H, s, H-3), 6.19 (1H, d, J = 8.3, H-5), 7.06 (1H, t, J = 8.3, H-6), 7.08 (1H, d, J = 8.3, H-7), 4.05 (3H, s, Me). ^{13}C-NMR ($CDCl_3$) δ: 150.18 (C-1a), 139.03

(C-4), 121.16 (C-3), 127.11 (C-6), 115.05 (C-3a), 106.97 (C-7), 102.65 (C-5), 39.97 (Me). CAS: 82013-51-2

5-Amino-1-methylindazole (3c): As reported for 4-aminoindazole but with 3.36 g, (19 mmol) of 1-methyl-5-nitroindazole (**2c**), 60 mL of MeOH/CH_2Cl_2 (1/1) and 3.5 mg of palladium on carbon (10%); 2.73 g; 60%; mp 153°C. ^{1}H-NMR (DMSO-d_6) δ: 7.66 (1H, s, H-3), 7.30 (1H, d, J = 8.5, H-7), 6.81 (1H, dd, J = 8.5, 1.9, H-6), 6.73 (1H, d, J = 1.9, H-4), 3.90 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 142.61 (C-5), 134.63 (C-1a), 130.19 (C-3), 124.80 (C-3a), 118.19 (C-6), 109.91 (C-7), 100.72 (C-4), 35.42 (Me). CAS: 50593-24-3.

5-Amino-2-methylindazole (3d): As reported for 4-aminoindazole but with 2 g, (11 mmol) of 2-methyl-5-nitroindazole (**2b**), 40 mL of MeOH/CH_2Cl_2 (1/1) and 2 mg of palladium on carbon (10%); 1.57 g; 98%; mp 122°C. ^{1}H-NMR (DMSO-d_6) δ: 7.83 (1H, s, H-3), 6.55 (1H, d, J = 1.9, H-4), 6.71 (1H, dd, J = 8.5, 1.9, H-6), 7.29 (1H, d, J = 8.5, H-7), 4.02 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 144.38 (C-1a), 142.36 (C-5), 123.06 (C-3a), 121.25 (C-3), 120.41 (C-6), 117.48 (C-7), 97.63 (C-4), 39.70 (Me). CAS: 60518-59-4.

6-Aminomethylindazoles (3e-f): As reported for 4-aminoindazole but with 4 g, (22.60 mmol) of a mixture of 1- and 2-methyl-6-nitroindazole (**2e**) and (**2f**), 80 mL of MeOH/CH_2Cl_2 (1/1) and 4 mg of palladium on carbon (10%); **3f** was obtained first, followed by **3e**.

6-Amino-1-methylindazole (3e): 1.25 g; 97%; mp 130°C. ^{1}H-NMR (DMSO-d_6) δ: 7.67 (1H, s, H-3), 7.35 (1H, d, J = 8.5, H-4), 6.48 (1H, brd, J = 8.5, H-5), 6.44 (1H, brs, H-7), 3.80 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 148.06 (C-6), 141.85 (C-1a), 132.21 (C-3), 121.12 (C-4), 116.20 (C-3a), 112.47 (C-5), 89.66 (C-7), 34.98 (Me). CAS: 74728-65-7.

6-Amino-2-methylindazole (3f): 0.60 g; 38%; mp 165°C. ^{1}H-NMR (DMSO-d_6) δ: 7.48 (1H, s, H-3), 7.28 (1H, d, J = 8.5, H-4), 6.43 (1H, dd, J = 8.5, 1.9 Hz, H-5), 6.67 (1H, brs, H-7), 3.90 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 150.08 (C-1a), 144.58 (C-6), 123.43 (C-3), 120.39 (C-4), 116.47 (C-3a), 115.67 (C-5), 96.13 (C-7), 39.34 (Me). CAS: 50593-30-1.

7-Aminomethylindazoles (3g-h): As reported for 4-aminoindazole but with 3.60 g, (20.33 mmol) of a mixture of 1-methyl and 2- methyl-7-nitroindazole (**2g**) and (**2h**), 80 mL of MeOH/CH_2Cl_2 (1/1) and 4 mg of palladium on carbon (10%); **3h** was obtained first, followed by **3g**.

7-Amino-1-methylindazole (**3g)**: 1.72 g; 18%; mp 135°C. ^{1}H-NMR (DMSO-d_6) δ: 8.16 (1H, s, H-3), 6.75 (1H, dd, J = 8.2, 7.7, H-5), 7.42 (1H, d, J = 8.0, H-4), 6.42 (1H, d, J = 8.2, H-6), 4.27 (3H, s, Me). ^{13}C-NMR ($CDCl_3$) δ: 131.35 (C-3), 119.94 (C-5), 110.33 (C-4), 109.60 (C-6), 134.18 (C-7), 129.89 (C-1a), 124.03 (C-3a), 37.78 (Me). CAS: 41926-06-1.

7-Amino-2-methylindazole (**3h**): 0.80 g; 58%; mp 73°C. ^{1}H-NMR (DMSO-d_6) δ: 8.07 (1H, s, H-3), 6.86 (1H, d, J = 8.3, H-4), 6.79 (1H, dd, J = 8.3, 7.7, H-5), 6.32 (1H, d, J = 7.7, H-6), 4.12 (3H, s, Me).

^{13}C-NMR (DMSO-d_6) δ: 141.33 (C-1a), 137.79 (C-7), 123.88 (C-3), 122.54 (C-5), 122.26 (C-3a), 107.90 (C-4), 103.32 (C-6), 39.69 (Me). CAS: 90223-02-2.

Typical procedure for preparation of methylaminoindazoles (3a-h) and (4a-h): **reduction with $SnCl_2$.**

4-Amino-1-methylindazole (3a) and 4-amino-7-chloro-1-methylindazole (4a): In a 250 mL bicol were introduced 2.59 g (14.64 mmol, 1 equiv.) of 1-methyl-4-nitroindazole (**2a**), a solution of MeOH/conc. HCl (50 mL, 1/1). The solution was heated to 100°C until complete dissolution of the substrate. Then, 15.28 g (80.54 mol, 5.5 equiv.) of $SnCl_2$ was introduced. The mixture was carried to the backward flow during 1 hour and under stirring. After evaporation of solvent, the white crude was dissolved in hot water. The mixture was basified with a solution of KOH (3N). The aqueous solution was extracted 3 times with diethyl oxyde. The organic phases were recovered, dried with $MgSO_4$ and evaporated. The precipitate were purified with silicagel chromatography, with CH_2Cl_2/ethyl acetate (1/1) as the eluant. The chloro derivative (**4a**) was obtained first, followed by **3a** (1.28 g, 59%).

4-Amino-7-chloro-1-methylindazole (4a): 0.65 g; 24%; mp 115-116°C. ^{1}H-NMR (DMSO-d_6) δ: 8.14 (1H, s, H-3), 7.02 (1H, d, J = 8.0, H-6), 6.12 (1H, d, J = 8.0, H-5), 4.20 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 142.01 (C-4), 136.50 (C-1a), 131.63 (C-3), 128.68 (C-6), 116.44 (C-3a), 102.59 (C-5), 99.93 (C-7), 38.41 (Me). *Anal.* Calcd for $C_8H_8N_3Cl$: C, 52.90; H, 4.44; N, 23.14. Found: C, 52.79; H, 4.49; N, 23.32.

4-Amino-2-methylindazole (3b) and **4-amino-7-chloro-2-methylindazole (4b)**: As reported for compounds (**3a**) and (**4a**), but with 1.7 g, (9.60 mmol) of 2-methyl-4-nitroindazole (**2b**), 35 mL of MeOH/conc. HCl (1/1) and 10 g (74.80 mmol.) of $SnCl_2.H_2O$. **4b** was obtained first, followed by **3b** (0.52 g, 37%).

4-Amino-7-chloro-2-methylindazole (4b): 0.21 g; 12%; mp 124°C. ^{1}H-NMR ($CDCl_3$) δ: 7.64 (1H, s, H-3), 6.96 (1H, d, J = 8.7, H-6), 6.03 (1H, d, J = 8.7, H-5), 3.95 (3H, s, Me). ^{13}C-NMR ($CDCl_3$) δ: 146.80 (C-1a), 138.23 (C-4), 126.09 (C-6), 122.74 (C-3), 115.83 (C-3a), 110.44 (C-7), 103.03 (C-5), 40.25 (Me). *Anal.* Calcd for $C_8H_8N_3Cl$: C, 52.90; H, 4.44; N, 23.14. Found: C, 52.64; H, 4.49; N, 23.28.

5-Amino-1-methylindazole (3c) and 5-amino-4-chloro-1-methylindazole (4c): As reported for compounds (**3a**) and (**4a**), but with 4.9 g, 27.68 mmol of 1-methyl-5-nitroindazole (**2c**)**,** 100 mL of MeOH/conc. HCl (1/1) and 28.88 g (209.44 mmol.) of $SnCl_2.H_2O$. **4c** was obtained first, followed by **3c** (0.45g, 11%).

5-Amino-4-chloro-1-methylindazole (4c): 1.37 g; 27%; mp 98°C. ^{1}H-NMR (DMSO-d_6) δ: 7.73 (1H, s, H-3), 7.37 (1H, d, J = 8.5, H-7), 6.98 (1H, d, J = 8.5, H-6), 3.95 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 138.57 (C-5), 135.01 (C-1a), 128.51 (C-3), 123.39 (C-3a), 118.70 (C-6), 109.50 (C-7), 103.89 (C-4), 35.77 (Me). *Anal.* Calcd for $C_8H_8N_3Cl$: C, 52.90; H, 4.44; N, 23.14. Found: C, 52.99; H, 4.67; N, 23.40.

5-Amino-2-methylindazole (3d) and 5-amino-4-chloro-2-methylindazole (4d): As reported for compounds (**3a**) and (**4a**), but with 2 g, 13.60 mmol of 2-methyl-5-nitroindazole (**2d**), 40 mL of MeOH/coc. HCl (1/1) and 10 g (74.80 mmol.) of $SnCl_2.H_2O$. **4d** was obtained first, followed by **3d** (0.40 g, 20%).

5-Amino-4-chloro-2-methylindazole (4d): 0.50 g; 20%; mp 97°C. ^{1}H-NMR (DMSO-d_6) δ: 7.96 (1H, s, H-3), 7.35 (1H, d, *J* = 8.5, H-7), 6.92 (1H, d, *J* = 8.5, H-6), 4.06 (3H, s, Me). ^{13}C-NMR (DMSO-d_6) δ: 143.73 (C-1a), 137.99 (C-5), 122.24 (C-3a), 120.53 (C-6), 120.03 (C-3), 116.52 (C-7), 100.31 (C-4), 39.43 (Me). *Anal.* Calcd for $C_8H_8N_3Cl$: C, 52.90; H, 4.44; N, 23.14. Found: C, 52.99; H, 4.16; N, 23.45.

6-Amino-1-methylindazole (3e) and 6-amino-7-chloro-1-methylindazole (4e): As reported for compounds (**3a**) and (**4a**), but with 1 g, 3.40 mmol of 1-methyl-6-nitroindazole (**2e**)**,** 20 mL of MeOH/conc. HCl (1/1) and 5g (37.40 mmol.) of $SnCl_2.H_2O$. **4e** was obtained first, followed by **3e** (0.27 g, 54%).

6-Amino-7-chloro-1-methylindazole (4e): 0.21 g; 34%; mp 172°C. ^{1}H-NMR (DMSO-d_6) δ: 7.77 (1H, s, H-3), 7.35 (1H, d, *J* = 8.5, H-4), 6.67 (1H, brd, *J* = 8.5, H-5), 4.18 (3H, s, Me). ^{13}C-NMR ($CDCl_3$) δ: 142.25 (C-6), 137.20 (C-1a), 132.71 (C-3), 119.82 (C-4), 119.64 (C-3a), 112.57 (C-5), 97.99 (C-7), 35.83 (Me). *Anal.* Calcd for $C_8H_8N_3Cl$: C, 52.90; H, 4.44; N, 23.14. Found: C, 52.67; H, 4.23; N, 23.01.

6-Amino-2-methylindazole (3f) and 6-amino-7-chloro-2-methylindazole (4f): As reported for compounds (**3a**) and (**4a**), but with 0.7 g, 3.95 mmol of 2-methyl-6-nitroindazole (**2f**), 15 mL of MeOH/conc. HCl (1/1) and 5 g (37.40 mmol.) of $SnCl_2.H_2O$. **4f** was obtained first, followed by **3f** (0.24 g, 42%).

6-Amino-7-chloro-2-methylindazole (4f): 0.08 g; 11%; mp 70°C. ^{1}H-NMR ($CDCl_3$) δ: 7.68 (1H, s, H-3), 7.28 (1H, d, *J* = 9.1, H-4), 6.57 (1H, d, *J* = 9.1, H-5), 4.07 (3H, s, Me). ^{13}C-NMR ($CDCl_3$) δ: 147.39 (C-1a), 140.40 (C-6), 124.87 (C-3), 119.02 (C-4), 117.32 (C-3a), 115.54 (C-5), 101.01 (C-7), 39.99 (Me). *Anal.* Calcd for $C_8H_8N_3Cl$: C, 52.90; H, 4.44; N, 23.14. Found: C, 52.74; H, 4.56; N, 23.37.

7-Amino-4-chloro-1-methylindazole (4g): As reported for compounds (**3a**) and (**4a**), but with 0.45 g, 2.54 mmol of 1-methyl-7-nitroindazole (**1g**), 10 mL of MeOH/conc. HCl (1/1) and 10 g (74.80 mmol.) of $SnCl_2.H_2O$; only one chlorinated indazole (**4g**) was obtained, 0.35 g; 77%; mp 80°C**.** ^{1}H-NMR ($CDCl_3$) δ: 7.85 (1H, s, H-3), 6.78 (1H, d, *J* = 8.0, H-5), 6.38 (1H, d, *J* = 8.0, H-6), 4.24 (3H, s, Me). ^{13}C-NMR ($CDCl_3$) δ: 130.65 (C-3), 130.65 (C-7), 130.45 (C-1a), 124.30 (C-3a), 120.41 (C-5), 115.38 (C-4), 111.84 (C-6), 38.26 (Me). *Anal.* Calcd for $C_8H_8N_3Cl$: C, 52.90; H, 4.44; N, 23.14. Found: C, 52.72; H, 4.30; N, 23.42.

7-Amino-4-chloro-2-methylindazole (4h): As reported for compounds (**3a**) and (**4a**), but with 0.29 g, 1.64 mmol of 2-methyl-7-nitroindazole (**2h**), 6 mL of MeOH/HCl (1/1) and 1.72 g (12.86 mmol.) of $SnCl_2.H_2O$; only one chlorinated indazole (**4h**) was obtained, 0.16 g; 55%; mp 120°C. ^{1}H-NMR ($CDCl_3$)

δ: 7.76 (1H, s, H-3), 6.82 (1H, d, *J* = 8.1, H-5), 6.28 (1H, d, *J* = 8.0, H-6), 4.09 (3H, s, Me). RMN ^{13}C-NMR ($CDCl_3$) δ: 130.70 (C-3), 130.65 (C-7), 130.45 (C-1a), 124.30 (C-3a), 120.41 (C-5), 115.38 (C-4), 111.84 (C-6), 38.26 (Me). *Anal.* Calcd for $C_8H_8N_3Cl$: C, 52.90; H, 4.44; N, 23.14. Found: C, 53.12; H, 4.68; N, 23.40.

REFERENCES

1. R. G. Coombes, 'Comprehensive Organic Chemistry', ed. by D. H. R. Barton and W. D. Ollis, Pergamon Press, Oxford, 1979, Vol. 2, pp. 343-344.
2. B. Loubinoux, J. J. Chanot, and P. Caubere, *J. Organomet. Chem.*, 1975, **88**, C4; A. M. Tafesch and J. Weiguny, *Chem. Rev*., 1996, **96**, 2035; R. S. Downing, P. J. Kunkeler, and H. Van Bekkum, *Catalysis Today*, 1997, **37**, 2, 121.
3. J. G. Lee, K. I. Choi, H. Y. Koh, Y. Kim, and Y. S. Cho, *Synthesis*, 2001, 81; H. S. Wilkinson, G. J. Taoury, S. A. Wald, and C. H. Senanayake, *Tetrahedron Lett*., 2001, **42**, 176; C. Yu, B. Liu, and L. Hu, *J. Org. Chem.*, 2001, **66**, 919; M. R. Pitts, J. R. Harrison, and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 2001, 955; N. Radhan and T. Pal, *Langmuir*, 2001, **17**, 1800; B. L. Miller, *Tetrahedron Lett.*, 1999, **40**, 245; R. A. Schenerman and D. Tumelty, *Tetrahedron Lett*., 2000, **40**, 6531; C. Baix and M. Poliakoff, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1487; T. Sukinoki and H. Tsusuki, *Green Chem*., 2001, **3**, 37.
4. J. H. Boyer and H. Alul, *J. Org. Chem.*, 1958, **81**, 2136.
5. A. Vass, J. Dudas, J. Toth, and R. S. Varma, *Tetrahedron Lett*., 2001, **42**, 5347.
6. K. Yanada, H. Yamaguchi, H. Meguri, and S. Uchida, *J. Chem. Soc., Chem. Comm*., 1986, **22**, 1655.
7. K. K. Park, C. H. Oh, and W.-J. Sim, *J. Org. Chem.*, 1995, **60**, 6202.
8. W. Baik, J. L. Han, N. H. Lee, B. H. Kim, and J. T. Hahn, *Tetrahedron Lett.*, 1994, **23**, 3965.
9. H. N. Borah, D. Prajapati, and J. S. Sandhu, *J. Chem. Res.*, (*S*), 1994, **6**, 228.
10. A. Kamal, G. S. K. Reddy, and K. L. Reddy, *Tetrahedron Lett.*, 2001, **42**, 6969.
11. J. S. D. Kumar, M. M. Ho, and T. Toyokuni, *Tetrahedron Lett*., 2001, **42**, 5601.
12. M. Rodel, F. Thieme, H. Buchholz, and B. Konig, *Synth. Commun.*, 2002, **32**, 1181.
13. J. Thesing, G. Semler, and G. Mohr, *Chem. Ber*., 1962, **95**, 2205.
14. Z. Wrobel, *Tetrahedron*, 2003, **59**, 101.
15. M. Kamel, M. A. Allam, F. I. Abdel Hay, and M. A. Osman, *J. prakt. Chem.,* 1966, **31**, 100.
16. S. Morel, G. Boyer, F. Coulet, and J.-P. Galy, *Synth. Commun.*, 1996, **26**, 2443.
17. P. T. Gallagher, B. Iddon, and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2358.
18. S. Morel, F. Chatel, G. Boyer, and J.-P. Galy, *J. Chem. Res.,* 1998 (S) 4-5; (M), 115; F. Chatel, S. Morel, G. Boyer, and J.-P. Galy, *Heterocycles*, 2000, **53**, 11, 2535; F. Chatel, G. Boyer, and J.-P. Galy,

Synth. Commun., 2002, **32**, 18, 2893.

19. A. Miloudi, D. El-Abed, G. Boyer, J.-P. Finet, J.-P. Galy, and D. Siri, *Eur. J. Org. Chem.*, 2004, **7**, 1509; K. Shimi, G. Boyer, J.-P. Finet, and J.-P. Galy, *Lett. Org. Chem.*, 2005, **2**, 5, 136-138.
20. P. Bouchet, C. Coquelet, G. Joncheray, and J. Elguero, *Synth. Commun.*, 1974, **4**, 57.
21. A. Albert and B. Ritchie, *J. Soc. Chem. Ind.*, 1941, **60**, 120.
22. G. A. Jaffari and A. J. Nunn, *J. Chem. Soc., Perkin Trans. 2*, 1973, **20**, 2371.
23. E. Noelting, *Ber.*, 1904, **37**, 2556.
24. S. J. Lee, M. S. Terrazas, D. J. Pippel, and P. Beak, *J. Am. Chem. Soc.*, 2003, **125**, 7307.
25. R. J. Steffan, E. Matelan, M. A. Ashwell, W. J. Moore, W. R. Solvibile, E. Trybulski, C. C. Chadwick, S. Chippari, T. Kenney, A. Eckert, L. Borges-Marcucci, J. C. Keith, Z. Xu, L. Mosyak, and D. C. Harnish, *J. Med. Chem.*, 2004, **47**, 26, 6435.