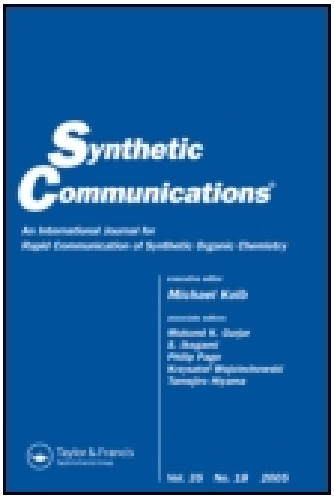


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Studies on the Reduction of the Nitro Group in 4-Nitroindazoles by Anhydrous $SnCl_2$ in Different Alcohols

N. Abbassi [a], E. M. Rakib [a], L. Bouissane [a], A. Hannioui [a], M. Khouili [a], A. El Malki [a], M. Benchidmi [b] & E. M. Essassi [b]

[a] Laboratory of Organic and Analytical Chemistry, Faculty of Sciences and Technology, Béni-Mellal, Morocco

[b] Laboratory of Heterocyclic Chemistry, Faculty of Sciences, Rabat, Morocco

Published online: 03 Mar 2011.

To cite this article: N. Abbassi, E. M. Rakib, L. Bouissane, A. Hannioui, M. Khouili, A. El Malki, M. Benchidmi & E. M. Essassi (2011) Studies on the Reduction of the Nitro Group in 4-Nitroindazoles by Anhydrous $SnCl_2$ in Different Alcohols, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:7, 999-1005, DOI: 10.1080/00397911003707212

To link to this article: http://dx.doi.org/10.1080/00397911003707212

Synthetic Communications®, 41: 999–1005, 2011

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911003707212

Taylor & Francis
Taylor & Francis Group

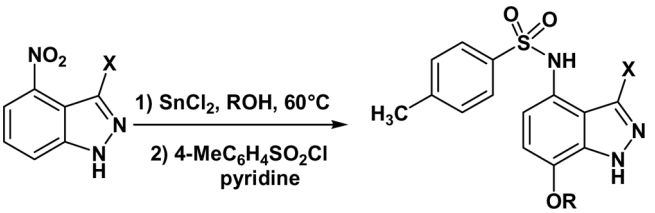
STUDIES ON THE REDUCTION OF THE NITRO GROUP IN 4-NITROINDAZOLES BY ANHYDROUS $SnCl_2$ IN DIFFERENT ALCOHOLS

N. Abbassi,[1] E. M. Rakib,[1] L. Bouissane,[1] A. Hannioui,[1] M. Khouili,[1] A. El Malki,[1] M. Benchidmi,[2] and E. M. Essassi[2]

[1]*Laboratory of Organic and Analytical Chemistry, Faculty of Sciences and Technology, Béni-Mellal, Morocco*

[2]*Laboratory of Heterocyclic Chemistry, Faculty of Sciences, Rabat, Morocco*

GRAPHICAL ABSTRACT



Abstract *The synthesis of new 7-alkoxy-4-amino-protected indazole and 4-amino-protected indazole derivatives by the reduction of the nitro group of 4-nitroindazoles using anhydrous stannous chloride in different alcohols is described.*

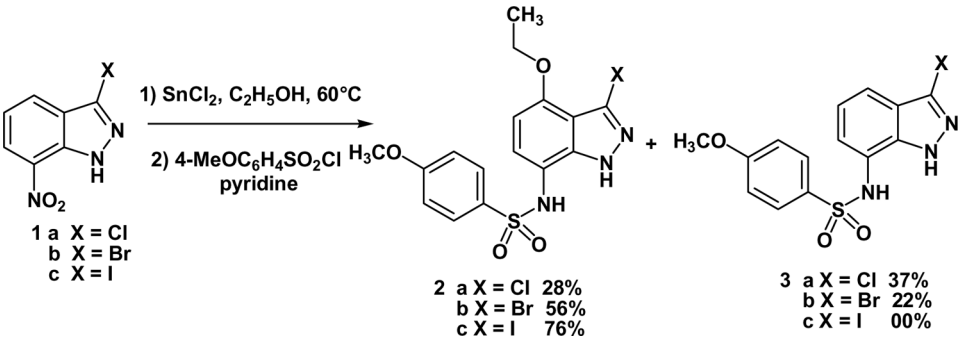
Keywords 7-Alkoxy-4-aminoindazoles; 4-nitroindazoles; $SnCl_2$/alcohol

INTRODUCTION

Reduction of aromatic nitro compounds to the corresponding amines is an important chemical transformation in synthetic organic chemistry. This is because the nitro group is often used to activate the aromatic nucleus for nucleophilic substitution reactions, but the amino group often serves as a site for further derivatization to final products. A variety of methods for the direct reduction of aromatic nitro compounds to the corresponding amines has been well documented.[1–3] Common methods for the reduction of nitro groups to amines include Zn,[4] Sn,[5] and Fe[6] in the presence of acid, $TiCl_3$,[7] Raney Ni–hydrazine,[8] and catalytic hydrogenation.[9] Reduction of aromatic nitro compounds with anhydrous $SnCl_2$ in alcohol was reported recently by our research group.[10] However, reduction of 7-nitroindazoles with $SnCl_2$ in ethanol produced a mixture of two products: the desired amine

Received January 26, 2010.

Address correspondence to E. M. Rakib, Laboratory of Organic and Analytical Chemistry, Faculty of Sciences and Technology, B.P. 523, Béni-Mellal, Morocco. E-mail: elmostapha1@ymail.com



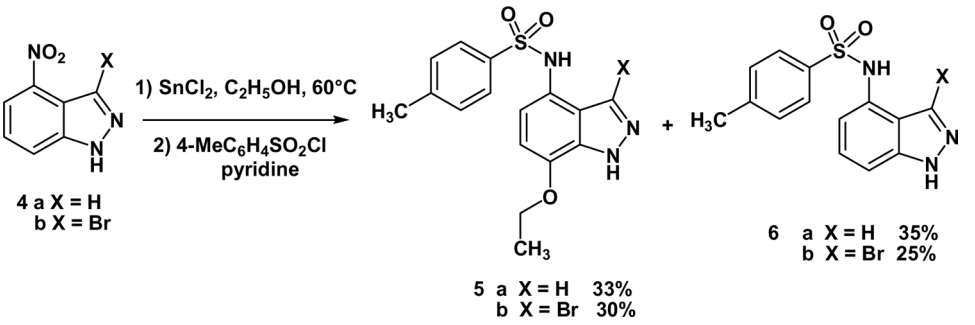
Scheme 1. Reduction of 3-halogeno-7-nitroindazoles with $SnCl_2$ in ethanol.

and the amine substituted with ethoxy group in the 4-position of indazole. We observed a new kind of transformation of 7-nitroindazoles under the action of stannous chloride in ethanol leading to 4-ethoxy-7-aminoindazoles accompanied by the desired amine (Scheme 1). It is noteworthy that significant degradation of aromatic primary amine was observed. Consequently, we immediately protected the amine by using 4-methoxylbenzenesulfonyl chloride in pyridine. We selected arylsulfonyl chloride as a protective agent of aminoindazole because in our previous study, we found that N-(7-indazolyl)arylsulfonamides[11] showed an important antiproliferative activity against human (colon and prostate) and murine (leukemia) cell lines.

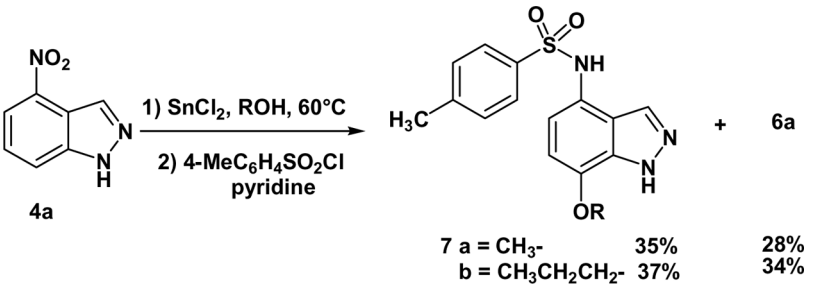
As an extension of these preliminary results, in the present work, we continue our studies on reactions of the reduction of aromatic nitro compounds with anhydrous $SnCl_2$ in alcohol. Here, we report the results of our more detailed study on the reduction of the nitro group in 4-nitroindazoles by anhydrous $SnCl_2$ in different alcohols.

RESULTS AND DISCUSSION

Treatment of 4-nitroindazoles **4a** and **4b** with anhydrous $SnCl_2$ in ethanol provided a mixture of two products, 4-aminoindazoles and 7-ethoxy-4-aminoindazoles, which were immediately coupled by 4-methybenzenesulfonamide chloride in pyridine (Scheme 2). 4-Nitroindazole **4a** was prepared by addition of aqueous sodium nitrite



Scheme 2. Reduction of 3-halogeno-4-nitroindazoles with $SnCl_2$ in ethanol.



Scheme 3. Reduction of 4-nitroindazole with $SnCl_2$ in alcohol.

solution on 2-methyl-3-nitroaniline in acetic acid and was obtained with 85% yield.[12] Compound **4b** was obtained by brominating 4-nitroindazole **4b** with N-bromosuccinimide in refluxing acetonitrile.

The yields of isolated products **5a, 5b, 6a**, and **6b** were determined after flash chromatography. The assignment of the structure of 7-ethoxy-N-(4-indazolyl)-4-methylbenzenesulfonamides **5a** and **5b** 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 were observed at δ 6.24–6.64 ppm and 6.38–6.78 ppm due to 6-H and 5-H protons of indazole.

We further studied the reduction of the 4-nitroindazole **4a** with $SnCl_2$ in different alcohols to introduce an alkoxy group in the 7-position of indazole. The 7-alkoxy-N-(4-indazolyl)-4-methylbenzenesulfonamides **7a** and **7b** were formed in 35% and 37% yields, respectively, after separation by flash chromatography (Scheme 3).

These results could be related to the important role played by nitro groups of 4-nitro-indazole with regards to the introduction of the substituent alkoxy in 7-position. Because of its electron-withdrawing effect, the nitro group in nitroarene activates in *ortho* and *para* for addition of nucleophilic agents.[13–15] Thus, the formation of the compound substituted by an alkoxy group in the 7-position could be explained by the presence of the RO^- anion in the reaction mixture, followed by the SN_H on 4-nitroindazole.

In conclusion, we reported a new synthesis of N-(4-indazolyl)-4-methylbenzenesulfonamides and 7-alkoxy-N-(4-indazolyl)-4-methylbenzenesulfonamides using anhydrous stannous chloride in different alcohols as a method of reduction. This methodology is a valuable and general method for the preparation of new functionalized indazoles such as 7-alkoxy-4-aminoprotectedindazoles.

EXPERIMENTAL

Melting points were determined using a Büchi-Tottoli apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 577 spectrometer using KBr disks; only noteworthy IR absorptions are listed (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded in dimethylsulfoxide (DMSO-d_6) and solution (unless otherwise specified) with textramethylsilane (TMS) as an internal reference

using a Bruker AC 300 (^{1}H) or 75 MHz (^{13}C) instruments. Chemical shifts are given in δ parts per million (ppm) downfield from tetramethylsilance (TMS). Multiplicities of ^{13}C NMR resources were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Low-resolution mass spectra (MS) were recorded on a Perkin-Elmer Sciex API 3000 spectrometer. Column chromatography was carried out on SiO_2 (silica gel 60 Merck 0.063–0.200 mm). Thin-layer chromatography (TLC) was carried out on SiO_2 (silica gel 60, F 254 Merck 0.063–0.200 mm), and the spots were located with ultraviolet light. Commercial reagents were used without further purification unless stated.

4-Nitroindazole 4a

In a 500-mL, round-bottomed flask were introduced 2-methyl-3-nitroaniline (5 g, 33 mmol) and 200 mL of AcOH. The solution was warmed under stirring until completed dissolution. Addition drop by drop of a solution of $NaNO_2$ (2.3 g, 37.70 mmol) in 5 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 (250 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 **4a**: 85%; mp 198–200 °C; ^{1}H NMR (DMSO-d_6): δ 7.54 (t, 1H, $J = 7.9$ Hz), 7.87 (d, 1H, $J = 7.5$ Hz), 7.94 (d, 1H, $J = 7.9$ Hz), 8.46 (s, 1H), 13.98 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 118.1, 119.3; 125.9, 127.1 (4CH), 110.6, 141.4, 143.4 (3C).

3-Bromo-4-nitro-1H-indazole 4b

N-Bromosuccinimide 1.2 g, in acetonitrile was added to a solution of 4-nitroindazole (1 g, 6.13 mmol) and heated at reflux for 1 h 30 min. The solvent was removed in vacuo, and the residue was taken up in 50 mL of ethyl acetate, and washed with 2×100 ml of water, 100 mL of 10% sodium thiosulfate, and brine and then dried. The solvent was removed in vacuo, and the residue was recrystallized from methanol.

Yield: 84%; mp: 200–202 °C; IR (KBr, cm^{-1}): 3130 (NH), 1630 (CN), 1520, 1330 (NO_2); ^{1}H NMR (DMSO-d_6): δ 7.57 (t, 1H, $J = 7.7$ Hz), 7.88 (d, 1H, $J = 7.5$ Hz), 7.98 (d, 1H, $J = 7.7$ Hz), 14.23 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 117.7, 119.0, 127.1 (3CH), 112.7, 117.7, 141.7, 143.2 (4C). MS $m/z = 242$ (^{79}Br) $[M + 1]^+$, 244 (^{81}Br) $[M + 3]^+$.

General Method for the Synthesis of 7-Ethoxy-N-(4-indazolyl)-4-methylbenzene Sulfonamides and N-(4-Indazolyl)-4-methylbenzenesulfonamides

A mixture of 3-halogeno-4-nitroindazole **4a** and **4b** (1.22 mmol) and anhydrous $SnCl_2$ (1.1 g, 6.1 mmol) in 25 mL of absolute ethanol was heated at 60 °C. After reduction, the starting material disappeared, and the solution was allowed to cool down. The pH was made slightly basic (pH 7–8) by addition of 5% aqueous potassium bicarbonate before extraction with ethyl acetate. The organic phase was washed with brine and dried over magnesium sulfate. The solvent was removed to afford the

amine, which was immediately dissolved in pyridine (5 mL) and then reacted with 4-methylbenzenesulfonyl chloride (0.26 g, 1.25 mmol) at room temperature for 24 h. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by flash chromatography (eluted with EtOAc/hexane 1/9).

***N*-(7-Ethoxy-1H-4-indazolyl)-4-methyl-benzenesulfonamide 5a.** Yield: 33%, mp: 210–212 °C; IR (KBr, cm^{-1}): 3340, 3220 (NH), 1585 (CN), 1338, 1165 (SO_2); ^1H NMR (DMSO-d_6): δ 1.37 (t, 3H, CH_3, $J = 6.9$ Hz), 2.28 (s, 3H, CH_3), 4.12 (q, 2H, OCH_2, $J = 6.9$ Hz), 6.64 (d, 1H, $J = 8.1$ Hz), 6.72 (d, 1H, $J = 8.1$ Hz), 7.25 (d, 2H, $J = 8.1$ Hz), 7.58 (d, 2H, $J = 8.1$ Hz), 7.97 (s, 1H), 10.06 (s, 1H, NH), 13.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): (15.1 (CH_3), 21.3 (CH_3), 64.2 (CH_2O), 106.1, 114.9, 127.2, 129.9, 132.7 (5 CH), 120.6, 122.3, 132.9, 137.4, 142.4, 143.4 (6 C); MS $m/z = 332$ $[M + 1]^+$.

***N*-(1H-4-Indazolyl)-4-methyl-benzenesulfonamide 6a.** Yield: 35%; mp: 170–172 °C; IR (KBr, cm^{-1}): 3340, 3235 (NH), 1595 (CN), 1335, 1160 (SO_2); ^1H NMR (DMSO-d_6): δ 2.27 (s, 3H, CH_3), 6.92 (dd, 1H, $J = 2.1$ Hz and 6.1 Hz), 7.16 (d, 2H, $J = 6.2$ Hz), 7.28 (d, 2H, $J = 8.3$ Hz), 7.68 (d, 2H, $J = 8.3$ Hz), 8.22 (s, 1H), 10.51 (s, 1H, NH), 13.05 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): (21.3 (CH_3), 106.7, 111.0, 126.9, 127.2, 130.1, 132.4 (6 CH), 117.3, 130.5, 137.3, 141.4, 143.7 (5C); MS $m/z = 288$ $[M + 1]^+$.

***N*-(3-Bromo-7-ethoxy-1H-4-indazolyl)-4-methyl-benzenesulfonamide 5b.** Yield: 30%; mp: 118–120 °C; IR (KBr, cm^{-1}): 3345, 3231 (NH), 1600 (CN), 1338, 1162 (SO_2); ^1H NMR (DMSO-d_6): δ 1.39 (t, 3H, CH_3, $J = 7.0$ Hz), 2.36 (s, 3H, CH_3), 4.15 (q, 2H, OCH_2, $J = 7.0$ Hz), 6.24 (d, 1H, $J = 8.1$ Hz), 6.38 (d, 1H, $J = 8.1$ Hz), 7.35 (d, 2H, $J = 8.0$ Hz), 7.57 (d, 2H, $J = 8.0$ Hz), 9.49 (s, 1H, NH), 13.69 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ (15.0 (CH_3), 21.4 (CH_3), 64.5 (CH_2O), 106.6, 121.0, 127.4, 130.0 (4 CH), 118.0, 119.2, 120.8, 134.4, 138.4, 142.1, 143.5 (7 C); MS $m/z = 410$ (^{79}Br) $[M + 1]^+$, 412 (^{81}Br) $[M + 3]^+$.

***N*-(3-Bromo-1H-4-indazolyl)-4-methyl-benzenesulfonamide 6b.** Yield: 25%; mp: 150–152 °C; IR (KBr, cm^{-1}): 3335, 3225 (NH), 1595 (CN), 1340, 1156 (SO_2); ^1H NMR (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 6.57 (d, 1H, $J = 7.4$ Hz), 7.25 (t, 1H, $J = 7.4$ Hz), 7.35 (d, 2H, $J = 8.1$ Hz), 7.41 (d, 1H, $J = 7.3$ Hz), 7.63 (d, 2H, $J = 8.1$ Hz), 9.69 (s, 1H, NH), 13.50 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 21.4 (CH_3), 109.8, 118.3, 127.4, 127.9, 130.0 (5 CH), 117.9, 118.7, 129.3, 138.1, 142.8, 143.5 (6C); MS $m/z = 366$ (^{79}Br) $[M + 1]^+$, 368 (^{81}Br) $[M + 3]^+$.

Synthesis of Compounds 7a and 7b

These compounds were synthesized as described for **4a** and **4b** by using the appropriate alcohol (methanol or propanol).

***N*-(7-Methoxy-1H-4-indazolyl)-4-methyl-benzenesulfonamide 7a.** Yield: 35%; mp: 230–232 °C; IR (KBr, cm^{-1}): 3320, 3200 (NH), 1590 (CN), 1340, 1158 (SO_2); ^1H NMR (DMSO-d_6): δ 2.27 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.68 (d, 1H, $J = 6.9$ Hz), 6.87 (d, 1H, $J = 6.9$ Hz), 7.24 (d, 2H, $J = 7.9$ Hz), 7.55 (d, 2H, $J = 7.9$ Hz), 7.94 (s, 1H), 10.05 (s, 1H, NH), 13.24 (s, 1H, NH); ^{13}C NMR

(DMSO-d_6): δ 21.4 (CH_3), 55.9 (CH_3O), 105.3, 114.8, 127.2, 129.9, 132.4 (5 CH), 120.5, 122.4, 132.7, 137.3, 141.4, 143.4 (6 C); MS $m/z = 318$ $[M + 1]^+$.

***N*-(7-Propoxy-1H-4-indazolyl)-4-methyl-benzenesulfonamide 7b.** Yield: 37%; mp: 135–137 °C; IR (KBr, cm^{-1}): 3350, 3260 (NH), 1585 (CN), 1328, 1155 (SO_2); ^{1}H NMR (DMSO-d_6): δ 1.00 (t, 3H, CH_3, $J = 7.4$ Hz,), 1.74 (m, 2H, CH_2), 2.26 (s, 3H, CH_3), 3.99 (t, 2H, OCH_2, $J = 6.8$ Hz), 6.63 (d, 1H, $J = 8.0$ Hz), 6.69 (d, 1H, $J = 8.0$ Hz), 7.24 (d, 2H, $J = 8.1$ Hz), 7.53 (d, 2H, $J = 8.1$ Hz), 7.93 (s, 1H), 10.02 (s, 1H, NH), 13.20 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 11.0 (CH_3), 21.4 (CH_3), 22.5 (CH_2), 69.9 (CH_2O), 105.9, 114.9, 127.2, 129.9, 132.7 (5 CH), 120.6, 122.2, 132.9, 137.4, 142.7, 143.4 (6 C). MS $m/z = 346$ $[M + 1]^+$.

REFERENCES

1. Stéphane, U.; Falguières, A.; Guy, A.; Ferroud, C. Ultrasonically activated reduction of substituted nitrobenzenes to corresponding *N*-arylhydroxylamines. *Tetrahedron Lett.* **2005**, *46*, 5913–5917.
2. Kabalka, G. W.; Verma, R. S. Reduction of nitro and nitroso compounds; In *Comprehensive Organic Synthesis*; B. M. Trost and E. Fleming (Eds.); Pergamon Press: Oxford, 1991; Vol. 8, pp. 363–379.
3. Moglie, Y.; Vitale, C.; Radivoy, G. Synthesis of azo compounds by nanosized iron-promoted reductive coupling of aromatic nitro compounds. *Tetrahedron Lett.* **2008**, *49*, 1828–1831.
4. (a) Martin, E. L. *o*-Phenylenediamine. *Org. Synth. Coll.* **1943**, *2*, 501; (b) Shundberg, R.; Pitts, W. Synthesis of cycloprop[c]indol-5-ones from 4-diazo-3-[n-(2-propenyl)amido]-cyclohexadien-1-ones: Exploration of copper(I) and copper(II) complexes as catalysts. *J. Org. Chem.* **1991**, *56*, 3048–3054.
5. (a) Hartman, W. W.; Dickey, J. B.; Stampfli, J. G. 2,6-Dibromoquinone-4-chloroimide. *Org. Synth. Coll.* **1943**, *2*, 175; (b) Clarke, H. T.; Hartman, W. W. Phloroglucinol. *Org. Synth. Coll.* **1941**, *1*, 455.
6. Ponticello, G. S.; Baldwin, J. J. Useful synthesis of 4-substituted indoles. *J. Org. Chem.* **1979**, *44*, 4003–4005.
7. Somei, M.; Inoue, S.; Tokutake, S.; Yamada, F.; Kaneko, C. The chemistry of indoles, XIII: Syntheses of substituted indoles carrying an amino, nitro, methoxycarbonyl, or benzyloxy group at the 4-position and their 1-hydroxy derivatives. *Chem. Pharm. Bull.* **1981**, *29*, 726–738.
8. Batcho, A. D.; Leimgruber, W. Indoles from 2-methylnitrobenzenes by condensation with formamide acetals followed by reduction: 4-Benzyloxyindole. *Org. Synth. Coll.* **1990**, *7*, 34.
9. (a) Rylander, P. N. *Catalytic Hydrogenation Over Platinum Metals*; Academic Press; New York, 1967; pp. 168–202; (b) Siegel, S.; In *Comprehensive Organic Synthesis*; B. M. Trost, and I. Flemming (Eds.); Pergamon Press: Oxford, 1991; vol. 8, pp. 418–442; (c) Hudlicky, M. *Reductions in Organic Chemistry*; Ellis Horwood Ltd: Chichester, 1984; pp. 1–13; (d) Smith, G. V.; Nothesiz, F. *Heterogeneous Catalysis in Organic Chemistry*; Academic Press: New York, 1999; pp. 71–79.
10. Bouissane, L.; El Kazzouli, S.; Leger, J. M.; Jarry, C.; Rakib, E. M.; Khouili, M.; Guillaumet, G. New and efficient synthesis of bi- and trisubstituted indazoles. *Tetrahedron* **2005**, *61*, 8218–8225.
11. Bouissane, L.; El Kazzouli, S.; Léonce, S.; Pfeiffer, P.; Rakib, E. M; Khouili, M. Guillaumet, G. Synthesis and biological evaluation of N-(7-indazolyl)benzenesulfonamide derivatives as potent cell cycle inhibitors. *Bioorg. Med. Chem.* **2006**, *14*, 1078–1088.

12. Noelting, E. Ueber bildung von indazolen aus nitrirten orthomethyllirten aminen. *Ber.* **1904**, *37*, 2556–2597.
13. Terrier, F. *Nucleophilic Aromatic Displacement: The Influence of the Nitro Group*; VCH: New York, 1991.
14. (a) Makosza, M.; Wojciechowski, K. Nucleophilic aromatic substitution of hydrogen as a tool for the synthesis of indole and quinoline derivatives. *Heterocycles* **2001**, *54*, 445–474; (b) Makosza, M.; Stalewski, J. The vicarious nucleophilic substitution of hydrogen and related reactions in nitrobenzoxazoles. *Tetrahedron* **1995**, *51*, 7277–7286; (c) Makosza, M.; Sienkiewiez, K. Hydroxylation of nitroarenes with alkyl hydroperoxide anions via vicarious nucleophilic substitution of hydrogen. *J. Org. Chem.* **1998**, *63*, 4199–4209.
15. Chupakhin, O. N.; Charushin, V. N.; van der Plas, H. C. *Nucleophilic Aromatic Substitution of Hydrogen*; Academic Press: San Diego, 1994.