Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6163–6167

Synthesis of 4-substituted and 3,4-disubstituted indazole derivatives by palladium-mediated cross-coupling reactions

Saïd El Kazzouli,[a,b] Latifa Bouissane,[a,b] Mostafa Khouili[b] and Gérald Guillaumet[a,*]

[a]*Institut de Chimie Organique et Analytique, UMR CNRS 6005, Université d'Orléans, BP 6759, 45067 Orléans Cedex 2, France*
[b]*Faculté des Sciences et Techniques de Beni-Mellal, Université Cadi-Ayyad, BP 523, 23000 Beni-Mellal, Marocco*

Received 11 April 2005; revised 9 June 2005; accepted 15 June 2005

Abstract—The synthesis of 4-substituted indazole derivatives by palladium-mediated cross-coupling reactions was described. Suzuki, Heck, Sonogashira and Stille cross-coupling reactions were used to introduce aryl, vinyl and alkynyl substituents in 4-position of indazole derivatives. The selectivity of bis-Suzuki reactions of 3,4-diiodo- and 3-bromo-4-iodoindazoles was investigated.

1. Introduction

The indazole ring system is a common structural motif found in numerous biologically active molecules. For instance, it is found in inhibitors of platelet aggregation,[1] and of HIV protease[2] and in antagonists of integrin a_vb_3.[3] If several procedures have been developed for the functionalisation of indazoles at the 3-position using palladium catalysts,[4] however, no examples involving the arylation, alkynylation of indazoles at the 4-position by palladium-mediated cross-coupling reactions have been described in the literature.

2. Results and discussion

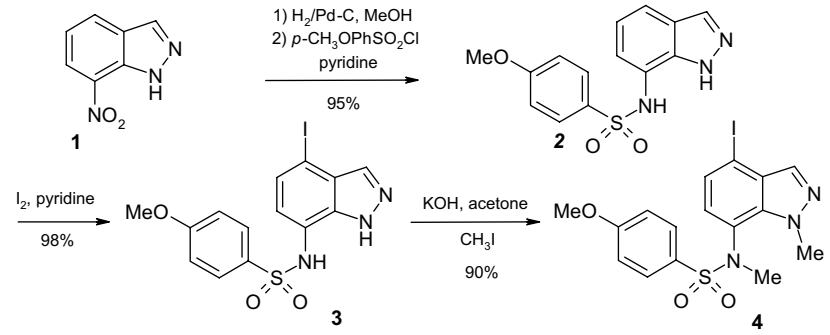
In our ongoing research programme for new polyfunctionalised indazoles,[5] we report herein the facile functionalisation at the 4- and 3,4-positions of *N*-(7-indazolyl)-arylsulfonamide based on a palladium-mediated cross-coupling reaction. Compound **4**, which serves as the central intermediate for a variety of coupling products, was prepared from 7-nitroindazole **1**[6] in three steps. Thus, compound **1** was hydrogenated in the presence of 10% palladium on carbon in methanol and then immediately treated with 4-methoxybenzenesulfonyl chloride in pyridine to give the desired product **2** in 95% yield. The reaction of sulfonamide **2** with iodine in pyridine afforded regioselectively the 4-iodoindazole **3**[7] in excellent yield, this is due to the presence of an electron-donating *N*-sulfonamide at 7-position. The structure of **3** was established by 2D NMR experiments (HMBC, HMQC). We observed, in particular, the coupling between the H_6 and the NH sulfonamide and the disappearance of the coupling between H_3 and H_4. We applied the known Pd(0) mediated trans-metalation steps (Stille, Sonogashira, Suzuki) and alkene insertion (Heck) for the synthesis of 4-alkynyl, aryl and vinyl derivatives. Compound **3** was first converted to the desired *N*-alkylated product **4** using methyl iodide in the presence of potassium hydroxide (Scheme 1) in order to avoid any Pd(0)-catalysed dehalogenation.

A Suzuki reaction[8] on **4** with $Pd(PPh_3)_4$ in the presence of 4-methoxyphenyl- or 3-thiopheneboronic acid in refluxing dimethoxyethane afforded then the coupling products **5a**,**b**[9] with 80% and 85%, respectively, the reaction of the iodide **4** with methyl acrylate under typical Heck conditions[10] afforded the compound **5c**[11] in high yield. In addition, application of the Stille[12] reaction of the heteroaryl iodide with 2-(tributylstannyl)furan in the presence of $Pd_2(dba)_3$ and Ph_3As gave the coupling product **5d**[13] in 82% yield. Finally, we explored the Sonogashira reaction with the 4-iodoindazole **4** and phenylacetylene, this reaction provided **5e**[14] in good yield (Scheme 2 and Table 1).

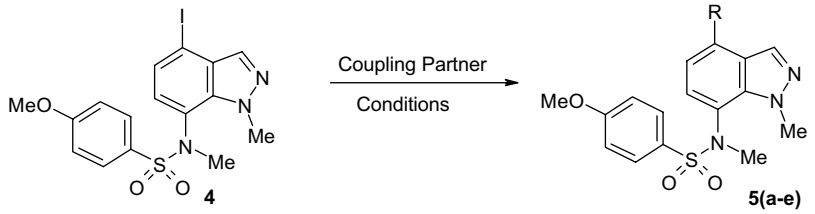
In a further investigation, we developed a bis-Suzuki cross-coupling reaction of 3,4-dihalogenoindazoles with

Keywords: Indazoles; Palladium; 3-Bromo-4-iodoindazole.
* Corresponding author. Tel.: +33 2 38 41 70 73; fax: +33 2 38 41 70 78; e-mail: gerald.guillaumet@univ-orleans.fr

0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.06.080

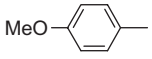
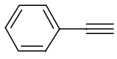


Scheme 1.



Scheme 2.

Table 1. Results of palladium cross-coupling reactions of 4-iodoindazole

R	Conditions	Product	Yield (%)
	$Pd(PPh_3)_4$, DME, Na_2CO_3, reflux	**5a**	85
		**5b**	80
$-CH_2=CH-CO_2CH_3$	$PdCl_2(dppf)$, TBAI, Et_3N, DMF, 50 °C	**5c**	79
	$Pd_2(dba)_3$, Ph_3As, dioxane, 50 °C	**5d**	82
	Pd $Cl_2(PPh_3)_2$, CuI, Et_3N, DMF, rt	**5e**	71

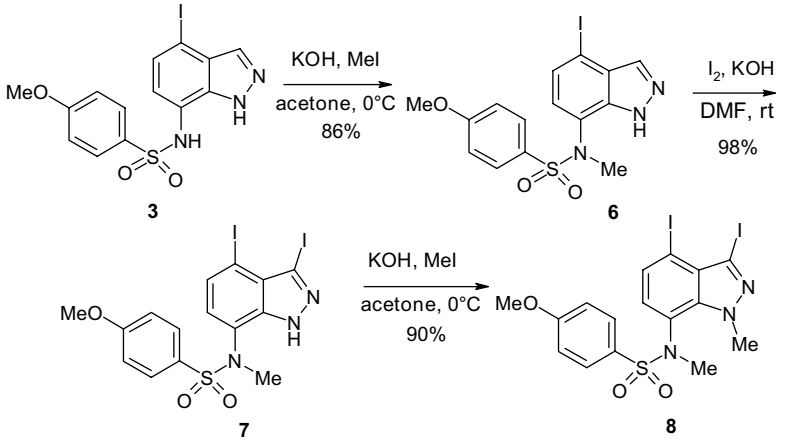
arylboronic acid as general route to 3,4-diarylindazole derivatives. Scheme 3 outlined the synthesis of the 4-methoxy-*N*-methyl-*N*-(3,4-diiodo-1-methyl-7-indazolyl)-benzenesulfonamide **8**.

Mono-*N*-alkylation at the nitrogen in 7-position of **3** with 1 equiv of methyl iodide was necessary for the regioselective introduction of the iodine atom at the 3-position of the indazole derivative **6**. The bis-iodinated compound **7** was converted to **8** in 90% yield by a simple alkylation with methyl iodide.

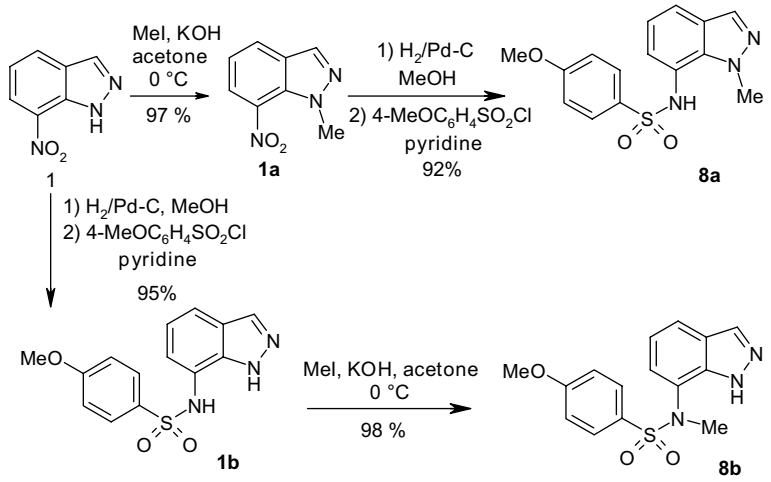
The selectivity of the monoalkylation of the NH group at 7-position of indazole **6** was established based on the ^1H NMR data of the synthesised 4-methoxy-*N*-(-1-methyl-7-indazolyl)-benzenesulfonamide **8a** and 4-methoxy-*N*-methyl-*N*-(7-indazolyl)-benzenesulfonamide **8b** from 7-nitroindazole (Scheme 4). The ^1H NMR spectra of **6**, **8a** and **8b**, recorded in DMSO-d_6, showed the singlet at δ 3.22 ppm (NCH_3) for **6**, δ NCH_3 signal at 3.48 for **8a** and δ NCH_3 signal at 3.21 for **8b**. These results served to confirm the structure of **6**.

The reaction of **8** with 1 equiv of 4-methoxyphenylboronic acid under Suzuki conditions afforded a mixture of **9** (42% yield) with the unsubstituted sulfonamide **10** (26% yield). In order to improve the formation of **9**, 2 equiv of boronic acid were used and the bis-arylindazole **9** was isolated in 82% yield (Scheme 5).

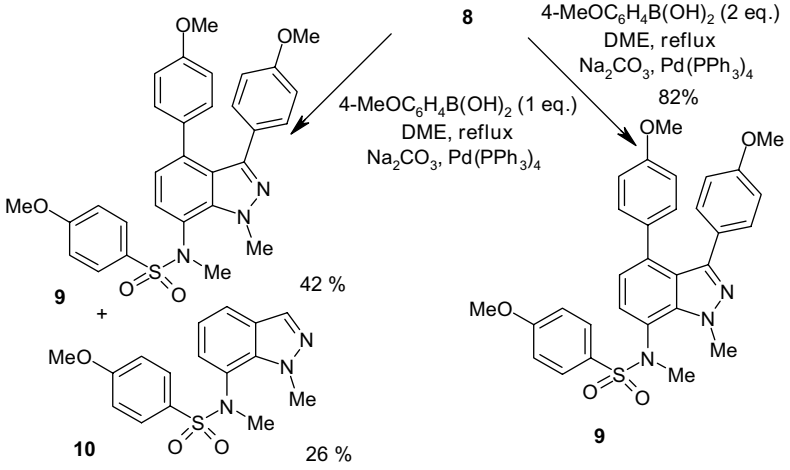
We thus demonstrated that the Suzuki cross-coupling reaction of **8** is not regioselective. Consequently, we decided to apply this sequence to the *N*-(3-bromo-4-iodo-7-indazolyl)arylsulfonamide **12**, obtained from **6**. Compound **6** was treated with *N*-bromosuccinimide in refluxing acetonitrile to afford **11** in 80% yield. It is noteworthy that no reaction was observed when compound **11** was reacted with 4-methoxyboronic acid under Suzuki coupling conditions. We thus protected the *N*-1 position using methyl iodide. The reaction gave *N*-(3-bromo-4-iodo-7-indazolyl)arylsulfonamide **12** with 89% yield. Contrary to the results obtained for the derivative 3,4-diiodoindazole **8**, reaction of **12** with 1 equiv of 4-methoxyphenylboronic acid gave only the 4-monosubstituted product **13**[15] in good yield. Thus, a tandem sequence



Scheme 3.



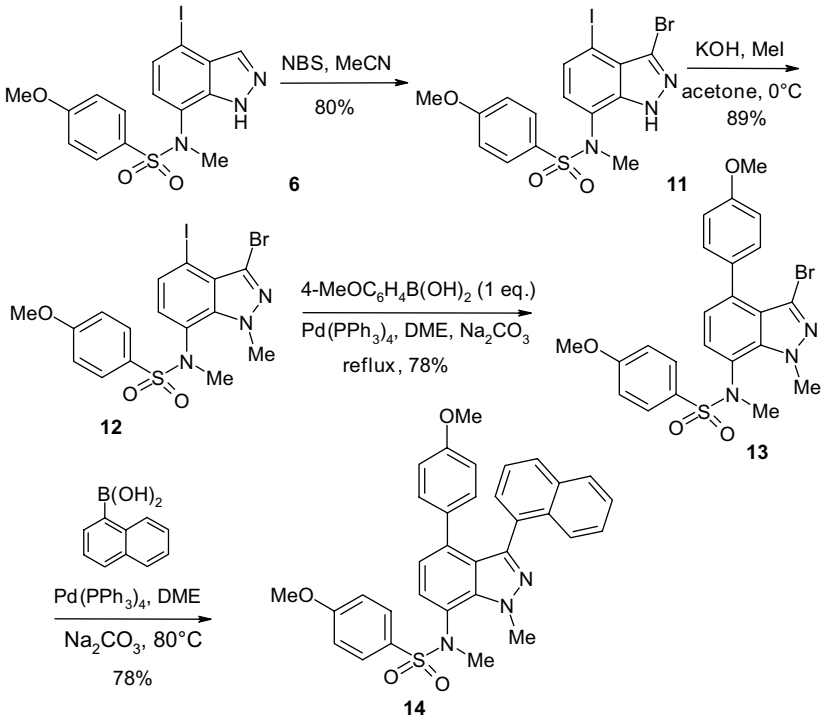
Scheme 4.



Scheme 5.

giving unsymmetrical 3,4-diarylindazoles seemed feasible.[16] So, reaction of **13** with 1-naphthaleneboronic acid under the same Suzuki conditions gave the desired compound **14**[17] in 78% yield (Scheme 6).

In summary, palladium cross-coupling reactions constitute a new means to functionalise 4- and 3,4-positions of indazole. This method is especially useful for the preparation of various 4-aryl, vinyl and ethynylindazoles. The



Scheme 6.

selectivity of sequential Suzuki–Suzuki reaction with a 3-bromo-4-iodoindazole derivative allowed us to prepare 3,4-disubstituted indazole. This methodology is a valuable and general method for the preparation of new functionalised indazoles.

References and notes

1. Collot, V.; Dallemagne, P.; Bovy, P. R.; Rault, S. *Tetrahedron* **1999**, *55*, 6917.
2. Sun, J.-H.; Teleha, C. A.; Yan, J.-S.; Rodgers, J. D.; Nugiel, D. A. *J. Org. Chem.* **1997**, *62*, 5627.
3. Batt, D. G.; Petraitis, J. J.; Houghton, G. C.; Modi, D. P.; Cain, G. A.; Corjay, M. H.; Mousa, S. A.; Bouchard, P. J.; Forsythe, M. S.; Harlow, P. P.; Barbera, F. A.; Spitz, S. M.; Wexler, R. R.; Jadhav, P. K. *J. Med. Chem.* **2000**, *43*, 41.
4. (a) Amautu, A.; Collot, V.; Ros, J. C.; Alayrac, C.; Witulski, B.; Rault, S. *Tetrahedron Lett.* **2002**, *43*, 2695; (b) Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron Lett.* **2000**, *41*, 9053; (c) Collot, V.; Varlet, D.; Rault, S. *Tetrahedron Lett.* **2000**, *41*, 4363; (d) Gordon, D. W. *Synlett* **1998**, 1065; (e) Welch, W. M.; Hanau, C. E.; Whalen, W. M. *Synthesis* **1992**, 937.
5. (a) Bouissane, L.; El Kazzouli, S.; Leger, J.-M.; Jarry, C.; Rakib, E. M.; Khouili, M.; Guillaumet, G. *Tetrahedron* **2005**, *61*, 8218; (b) Bouissane, L.; El Kazzouli, S.; Léonce, S.; Pfeiffer, B.; Rakib, E. M.; Khouili, M.; Guillaumet, G. *Bioorg. Med. Chem.*, submitted for publication.
6. Noelting, E. *Berichte* **1904**, *37*, 2556.
7. Procedure for the synthesis of 4-methoxy-*N*-(4-Iodo-7-indazolyl)-benzenesulfonamide **3**: To a solution of 4-methoxy-*N*-(7-indazolyl)-benzenesulfonamide **2** (100 mg, 0.33 mmol) in pyridine (10 mL), iodine (90 mg, 0.33 mmol) was added. The reaction mixture was stirred at room temperature for 3 h and then poured into 10% aqueous $NaHSO_3$ (5 mL) and extracted with Et_2O (3×5 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$ and the solvent was evaporated to give a colorless solid **3** (139 mg, 98%). Mp 172–173 °C. ^{1}H NMR (DMSO-d_6, 250 MHz) δ 3.77 (s, 3H, OCH_3), 6.73 (d, 1H, $J = 7.5$ Hz), 7.03 (d, 2H, $J = 8.7$ Hz), 7.36 (d, 1H, $J = 7.5$ Hz), 7.69 (d, 2H, $J = 8.7$ Hz), 7.85 (s, 1H), 10.05 (s, 1H, NH), 13.07 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 62.89 MHz) δ 55.6, 95.7, 114.3, 119.5, 121.7, 128.2, 128.4, 129.1, 129.8, 130.4, 136.9, 142.6. MS (+ESI): $m/z = 430$ [MH^+].
8. Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763.
9. General procedure for Suzuki-type cross coupling reaction: Under argon atmosphere, to a mixture of 4-iodoindazole derivatives (0.43 mmol) and boronic acid (0.48 mmol) in DME (8 mL), sodium carbonate (1.29 mmol) in H_2O (4 mL) and $Pd(PPh_3)_4$ (0.043 mmol) was added. The reaction mixture was refluxed with vigorous stirring for 2 h and then the solvent was evaporated. Ethyl acetate (5 mL) was added and the organic phase was washed with a saturated solution of sodium chloride (10 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by column chromatography over silica gel (eluted with a EtOAc/EP).
   4-Methoxy-*N*-methyl-*N*-[4-(4-methoxyphenyl)- 1-methyl-7-indazolyl]-benzenesulfonamide (**5a**): Colorless solid **5a** (162 mg, 85%). Mp 109–110 °C. ^{1}H NMR (acetone-d_6, 250 MHz) δ 3.26 (s, 3H, NCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.45 (s, 3H, NCH_3), 6.51 (d, 1H, $J = 7.5$ Hz), 6.92 (d, 1H, $J = 7.5$ Hz), 6.98 (d, 2H, $J = 8.7$ Hz), 7.01 (d, 2H, $J = 8.1$ Hz), 7.57 (d, 2H, $J = 8.7$ Hz), 7.64 (d, 2H, $J = 8.1$ Hz), 8.09 (s, 1H). ^{13}C NMR (acetone-d_6, 62.89 MHz) δ 38.8, 40.0, 55.3, 55.6, 97.3, 114.1, 114.3, 119.2, 124.6, 124.7, 125.1, 128.0, −129.6, 130.5, 132.4, 131.4, 135.7, 137.4, 159.6. MS (+ESI): $m/z = 438$ [MH^+].
10. Ruhland, B.; Bombrun, A.; Gallop, M. A. *J. Org. Chem.* **1997**, *62*, 7820.

11. Procedure for the synthesis of (*E*)-(7-[(4-methoxybenzenesulfonyl)-methyl-)-methylamino]-1*H*-4-indazolyl]-acrylic acid methyl ester (**5c**): To a mixture of compound **4** (200 mg, 0.43 mmol), methyl acrylate (50 μL, 0.86 mmol) and tetrabutylammonium iodide (324 mg, 0.86 mmol) in a mixture of DMF/TEA (8 mL, 5/5, v/v) under argon was added $PdCl_2$(dppf) (30 mg, 0.043 mmol). The reaction mixture was stirred overnight at 45 °C and then the solution was evaporated. Ethyl acetate (5 mL) was added and the organic phase, washed with water and brine, was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel (eluted with a EtOAc/EP) to give **5c** (143 mg, 79%). Mp 155–156 °C. ^{1}H NMR (acetone-d_6, 250 MHz) δ 3.23 (s, 3H, NCH_3), 3.76 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.32 (s, 3H, NCH_3), 6.59 (d, 1H, J = 7.8 Hz), 6.80 (d, 1H, J = 16.0 Hz), 7.18 (d, 2H, J = 9.1 Hz), 7.44 (d, 1H, J = 7.8 Hz), 7.59 (d, 2H, J = 9.1 Hz), 7.96 (d, 1H, J = 16.0 Hz), 8.50 (s, 1H). ^{13}C NMR (acetone-d_6, 62.89 MHz) δ 38.4, 39.4, 51.6, 55.7, 96.7, 114.5, 120.5, 121.5, 124.4, 125.4, 127.2, 127.6, 130.2, 131.2, 140.7, 136.8, 143.1, 166.4. MS (+ESI): m/z = 416 [MH^+].
12. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.
13. Procedure for the synthesis of 4-methoxy-*N*-methyl-*N*-[4-(furan-2-yl)-1-methyl-7-indazolyl]-benzenesulfonamide (**5d**): To a solution of **4** (100 mg, 0.21 mmol), 2-(tributylstannyl)furan (77 mg, 0.25 mmol) and triphenylarsin (153 mg, 0.5 mmol) in 1,4-dioxan (5 mL) under argon was added $Pd_2(dba)_3$-$CHCl_3$ (21 mg, 0.021 mmol). The reaction mixture was heated at 80 °C overnight and then the solvent was evaporated. Ethyl acetate (5 mL) was added and the organic phase, washed with water and brine, was dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel (eluted with a EtOAc/EP) to give **5d** (70 mg, 82%). Mp 126–127 °C. ^{1}H NMR (acetone-d_6, 250 MHz) δ 3.32 (s, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 4.40 (s, 3H, NCH_3), 6.61 (d, 1H, J = 7.8 Hz), 6.66 (dd, 1H, J = 1.5, 3.4 Hz), 7.11 (d, 1H, J = 3.4 Hz), 7.18 (d, 2H, J = 9.1 Hz), 7.33 (d, 1H, J = 7.8 Hz), 7.65 (d, 2H, J = 9.1 Hz), 7.78 (d, 1H, J = 1.5 Hz), 8.44 (s, 1H). ^{13}C NMR (acetone-d_6, 62.89 MHz) δ 39.0, 40.2, 56.2, 109.2, 112.0, 115.1, 116.9, 122.8, 124.6, 125.5, 126.4, 129.1, 131.4, 133.0, 144.2, 138.6, 143.3, 153.3. MS (+ESI): m/z = 397 [MH^+].
14. Procedure for the synthesis of 4-methoxy-*N*-methyl-*N*-(4-phenylethynyl-1-methyl-7-indazolyl)-benzenesulfonamide (**5e**). To a solution of **4** (200 mg, 0.43 mmol), phenylacetylene (70 μL, 0.63 mmol) and CuI (17 mg, 0.09 mmol) in a mixture of DMF/TEA (8 mL, 5/5, v/v) under argon was added $Pd(PPh_3)_2Cl_2$ (30 mg, 0.043 mmol). The reaction mixture was stirred at room temperature overnight and then the solvent was evaporated. Ethyl acetate (5 mL) was added and the organic phase, washed with water and brine, was dried over $MgSO_4$. The solvent removed in vacuo and the residue was purified by column chromatography over silica gel (eluted with a EtOAc/EP) to give **5e** (132 mg, 71%). Mp 84–85 °C. ^{1}H NMR (acetone-d_6, 250 MHz) δ 3.32 (s, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 4.39 (s, 3H, NCH_3), 6.61 (d, 1H, J = 7.5 Hz), 7.15–7.19 (m, 3H), 7.44–7.47 (m, 3H), 7.62–7.67 (m, 4H), 8.09 (s, 1H). ^{13}C NMR (acetone-d_6, 62.89 MHz) δ 39.0, 40.1, 56.2, 94.4, 86.9, 115.1, 116.5, 124.9, 125.3, 128.0, 128.3, 128.7, 129.5, 129.8, 131.4, 132.5, 132.6, 137.9, 142.5. MS (+ESI): m/z = 432 [MH^+].
15. 4-Methoxy-*N*-methyl-*N*-(3-bromo-4-(4-methoxyphenyl)-1-methyl-7-indazolyl)-benzenesulfonamide (**13**): Colorless solid, yield 78%. Mp 178–179 °C. ^{1}H NMR (acetone-d_6, 250 MHz) δ 3.33 (s, 3H, NCH_3), 3.87 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.39 (s, 3H, NCH_3), 6.69 (d, 1H, J = 7.5 Hz), 6.86 (d, 1H, J = 7.5 Hz), 7.02 (d, 2H, J = 8.7 Hz), 7.17 (d, 2H, J = 8.9 Hz), 7.36 (d, 2H, J = 8.7 Hz), 7.67 (d, 2H, J = 8.9 Hz). ^{13}C NMR (acetone-d_6, 62.89 MHz) δ 39.4, 40.2, 55.6, 56.2, 113.9, 115.1, 117.4, 118.9, 123.6, 126.3, 126.4, 128.9, 129.1, 130.3, 131.4, 132.2, 137.3, 140.7, 164.5. MS (+ESI): m/z = 517.5 [MH^+].
16. During the submission of this article, similar results were published. Witulski, B.; Azcon, J. R.; Alayrac, C.; Arnautu, A.; Collot, V.; Rault, S. *Synthesis* **2005**, 771.
17. 4-Methoxy-*N*-[4-(4-methoxyphenyl)-1-methyl-3-naphtalenyl-7-indazolyl]-*N*-methylbenzenesulfonamide (**14**): Yellow solid, yield 78%. Mp 109–110 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.35 (s, 3H, NCH_3), 3.55 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.58 (s, 3H, NCH_3), 6.14 (d, 2H, J = 7.8 Hz), 6.57 (d, 1H, J = 7.5 Hz), 6.71 (d, 2H, J = 8.8 Hz), 6.82 (d, 1H, J = 7.5 Hz), 7.02 (d, 1H, J = 8.8 Hz), 7.22–7.32 (m, 4H), 7.67–7.75 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.89 MHz) δ 39.1, 40.3, 55.2, 55.8, 112.2, 114.2, 121.1, 124.3, 124.7, 125.4, 125.8, 126.1, 127.6, 128.4, 128.7, 129.8, 130.5, 131.5, 132.7, 133.3, 137.8, 138.4, 143.5, 158.5, 163.5. MS (+ESI): m/z = 564.0 [MH^+].