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A regioselective C7 bromination and C7 palladium-catalyzed Suzuki–Miyaura cross-coupling arylation of 4-substituted NH-free indazoles†

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A direct and efficient regioselective C7-bromination of 4-substituted 1*H*-indazole has been achieved. Subsequently, a successful palladium-mediated Suzuki–Miyaura reaction of C7-bromo-4-substituted-1*H*-indazoles with boronic acids has been performed under optimized reaction conditions. A series of new C7 arylated 4-substituted 1*H*-indazoles was obtained in moderate to good yields.

Introduction

The aryl-heteroaryl compounds are an important class of organic entities used as promising building blocks of many biologically active molecules and drugs^{1–6} and the ability to combine aryl and heteroaryl fragments by the formation of new C–C bonds^{7–11} is an important and challenging field in organic chemistry. The palladium-catalyzed Suzuki–Miyaura coupling process^{12–16} is probably one of the most efficient methods nowadays to create C(sp²)–C(sp²) bonds because of its mild reaction conditions, broad substrate scope, broad functional group tolerance, and the high air and water stability of the boronic acids.^{12,17–20}

Indazoles are often the key fragments in several important compounds, with a broad range of biological activities for anticancer,^{21–23} HIV-protease inhibition,²⁴ antimicrobial²⁵ and anti-inflammatory²⁶ purposes. For this reason, various procedures have been developed for their synthesis^{27–30} and functionalization.^{31–45}

In particular, indazoles and bioisosteres containing sulfonamide moieties on either the C7 or C4 position have shown interesting anticancer activities.^{46–48} For these reasons we decided to introduce sulfonamides at position C4 of the indazole ring prior to the functionalization at the C7 position in

order to give access to a diversity of new potentially bioactive compounds.

Recently, our group and others were actively involved in the functionalization of NH-free or protected 1*H* and 2*H*-indazoles. Despite the recent advances made in this field, namely the direct C3 and C7-arylations^{32,49–51} and the Suzuki–Miyaura coupling at C3, C4, C5 and C6 positions,^{31,52–54} to date, no example of selective arylation of NH-free or protected indazoles using Suzuki–Miyaura process, has been described at the C7 position. It is important to note that we previously reported only two examples of C7 direct arylation of indazoles containing a C4 nitro group in which C3 position was already substituted with a phenyl group. Moreover, during these investigations with nitro substrates, we were unable to introduce heteroaryl substituents.⁵⁵ At this point, it was clear to us that the higher reactivity of the C3 position over C7 unsubstituted indazole derivatives could be a limitation to efficiently prepare new C7 substituted and C3 free scaffolds.

To bypass this limitation, we examine herein the influence of the electronic properties of some C4 sulfonamido- or amido-substituents at the 1*H*-indazole nucleus, on the course of a regioselective C7-halogenation, followed by Suzuki–Miyaura coupling reactions, aiming at developing novel series of 7-aryl-4-sulfonamido or 7-aryl-4-amido-1*H*-indazole compounds.

Results and discussion

The first step in our investigation pathway was to prepare the 4-substituted 1*H*-indazoles **3a–c**, **4a–c**, used as starting materials in this study. They were synthesized following known procedures starting from 4-nitroindazole according to the Scheme 1.^{47,56} The sulfonylation of free 4-amino-indazole **2** with one equivalent of the selected sulfonyl chlorides gave the expected sulfonamides **3a–c** in 75–83% yields. The 4-amino acylation of indazole **2** with a carboxylic acid in the presence of coupling

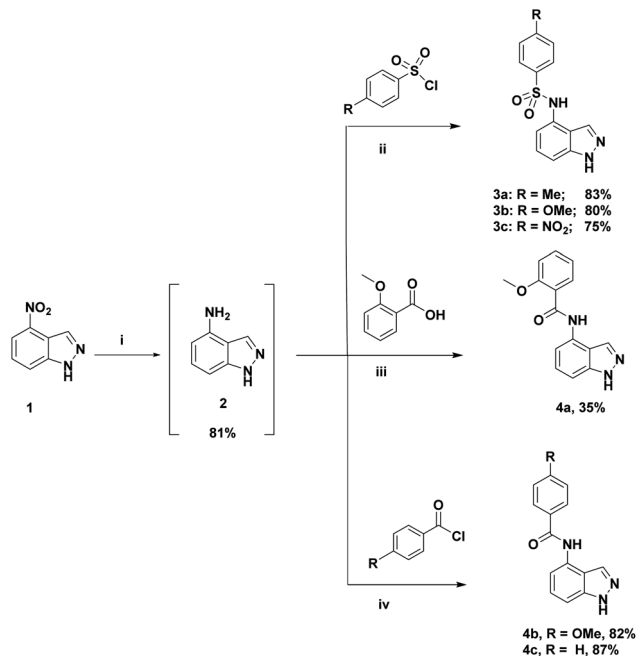
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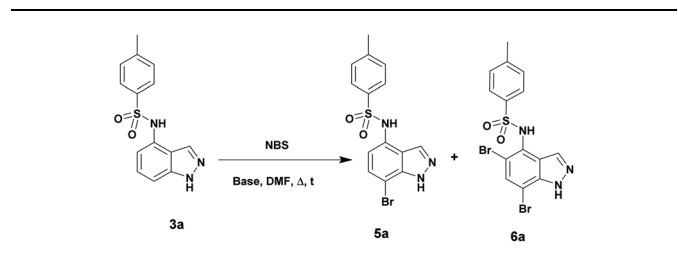




Scheme 1 Reagents and conditions for the synthesis of **3a–c** and **4a–c**. Reaction conditions. (i) Fe/NH₄Cl (6/10 equiv.), EtOH, rt for 3 h, 81%; (ii) ArSO₂Cl (1 equiv.), pyridine, 24 h, 75–83%; (iii) *o*-methoxy benzoic acid (1 equiv.), TBTU (1 equiv.), DIPEA (3 equiv.), DMF, rt for 16 h, 35%. (iv) *p*-methoxy benzoyl chloride (1.1 equiv.), DIPEA (2 equiv.), DCM, 0 °C–rt for 18 h, 82%.

reagents afforded amide **4a** with a low yield.⁵⁶ Satisfyingly, in dichloromethane as the solvent and with acyl chloride as the acylating agent, the yield could be optimized, due to the precipitation of the expected amide **4b** and **4c** during the reaction, probably avoiding the formation of *N*-1 acyl side-product.

Table 1 Bromination study of compound **3a** with NBS



Entry	<i>T</i> (°C)	NBS (equiv.)	<i>t</i> (h)	Base	Yields ^a 5a/6a
1	rt	1.1	18	None	26/4
2	80	1.1	18	None	84/10 ^b
3	120 ^c	1.1	0.5	None	Degradation
4	Reflux	2.0	18	None	tr ^e /88
5	80	1.1	18	NaOH ^d	45/28
6	80	1.1	18	KOH ^c	18/45

^a Yields after column chromatography purification. ^b Reaction conditions optimized for **5a**: **3a** (1 mmol), NBS (1.1 mmol), DMF (5 mL), 80 °C for 18 h. ^c MW = microwaves. ^d 2 equivalents of base. ^e tr = traces.

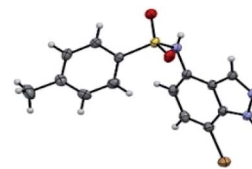
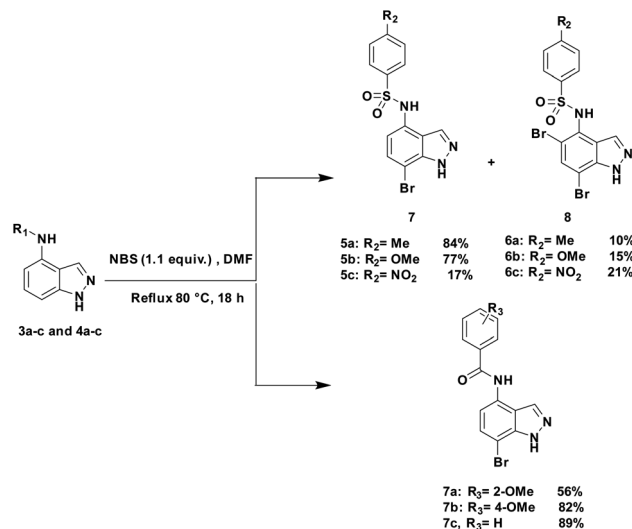


Fig. 1 Crystal structure of compound **5a**.



Scheme 2 Bromination of compounds **3a–c** and **4a–c** with NBS.

These compounds were isolated by simple filtration with high yields of 82% and 87%, respectively.

The regioselective C7 bromination of *N*-(1*H*-indazol-4-yl)-4-methylbenzenesulfonamide **3a**, used as model substrate, was attempted with *N*-bromosuccinimide (NBS)^{57,58} as depicted in Table 1. Compared to room temperature conditions (Table 1, entry 1), we were pleased to find that the treatment of *N*-(1*H*-

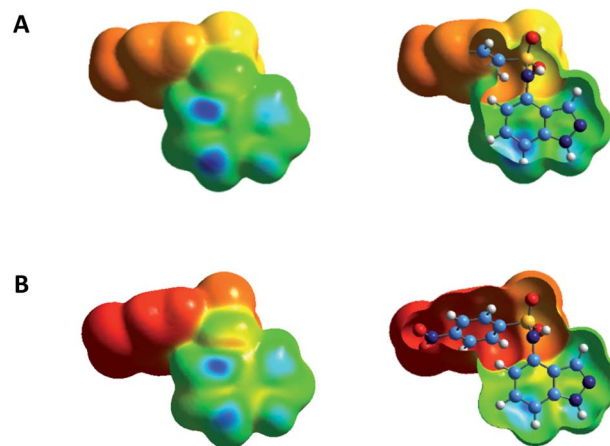


Fig. 2 Electrophilicity index f_k^+ Fukui function of compounds **3a** (A) and **3c** (B), shown on the electron density isosurfaces (0.001 e bohr⁻³) and calculated at the MN15/6-31++G(d, p) level of theory. The sites in blue are the most prone to a nucleophilic attack.



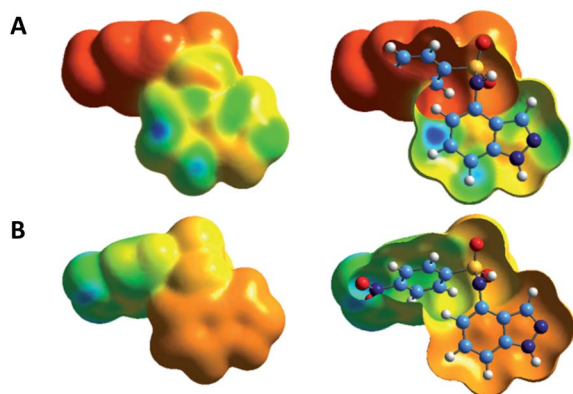


Fig. 3 Nucleophilicity index f_k^- Fukui function of compounds **3a** (A) and **3c** (B), shown on the electron density isosurfaces ($0.001 \text{ e bohr}^{-3}$) and calculated at the MN15/6-31+G(d, p) level of theory. The sites in blue are the most prone to an electrophilic attack.

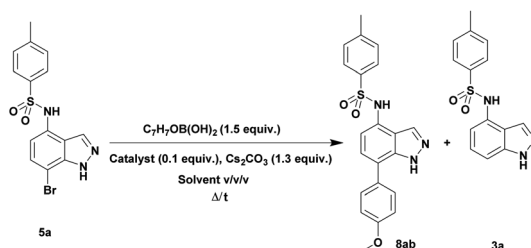
indazol-4-yl)-4-methylbenzenesulfonamide **3a** with 1.1 equivalents of NBS in DMF at 80°C provided the desired C7 halogenated product **5a** in 84% yield along with 10% of the 5,7-dibrominated compound **6a**, (Table 1, entry 2). Testing microwave activation conditions afforded degradation (Table 1, entry 3). Moreover, when 2 equivalents of NBS were used, the 5,7-dibrominated compound **6a** was obtained with 88% yield, without identification of any 3-brominated derivative (Table 1, entry 4). Based on previous results obtained for indazole halogenation in basic conditions,⁴⁶ we observed in this case a rapid formation of the dibrominated compound **6a**, in the presence of

2 equivalents of NaOH or KOH (Table 1, entries 5 and 6). The structure of the compound **5a** as its 7-bromo-1*H*-indazole form was proved by X-ray diffraction analysis (Fig. 1) (see the ESI†).

With this sequence in hand, we set out to extend the halogenation to the series of indazole derivatives containing sulfonamide or amide groups at C4 position (Scheme 2). These experiments highlighted the regioselectivity of the halogenation reaction with NBS but also the influence of the nature and the electronic effect of the C4 substituent group. Sulfonamides with electron-donating groups such as methyl or methoxy at *para*-position of the phenylsulfonyl group gave the desired C7 monohalogenated products **5** in high yields along with small amounts of 5,7-dihalogenated compounds **6** (**5a** : **6a**, 84%/10% and **5b** : **6b**, 77%/15%). Strong electron-withdrawing substituents such as NO_2 , also gave a mixture of both mono- and dihalogenated compounds but with a drastic decrease of the C7-mono brominated expected product **5c** (**5c**, 17%; **6c**, 21%) (Scheme 2). Satisfyingly, the bromination reaction with indazoles **4a-c** containing benzamide groups at C4 position and bearing electron-donating group at either the *ortho*- or *para*-position of the aryl ring, gave only the C7 halogenated products **7a-c**, and no traces of dihalogenated products were observed. In the case of the bromination reaction with **4a**, the reaction was not total and starting material **4a** was recovered.

DFT calculations have been performed to identify the main electrophilic, nucleophilic or radical reaction sites of compound **3a** and **3c**, with the aim to rationalize the preferred site of bromination experimentally observed. For compound **3a**, the projection of the f_k^+ Fukui function on the isodensity surface suggests that this compound will preferentially undergo

Table 2 Optimization of Suzuki–Miyaura reaction conditions^a



Entry	Catalyst 10 mol%	T ($^\circ\text{C}$)/ t (h)	Solvent (v/v)	Yields% 3a / 5a / 8ab
1 ^b	$\text{PdCl}_2(\text{PPh}_3)_2$	Reflux/48	DMF	0/100/0
2	$\text{PdCl}_2(\text{PPh}_3)_2$	Reflux/48	DMF	0/100/0
3 ^b	$\text{Pd}(\text{PPh}_3)_4$	Reflux/48	DMF	18/75/tr ^c
4	$\text{Pd}(\text{PPh}_3)_4$	Reflux/48	DMF	tr/80/tr
5	$\text{Pd}(\text{PPh}_3)_4$	140 MW/2	DMF	68/tr/11
6	$\text{Pd}(\text{PPh}_3)_4$	Reflux/2	Dioxane	0/100/0
7	$\text{Pd}(\text{PPh}_3)_4$	Reflux/48	Dioxane/EtOH 3/1	14/69/tr
8	$\text{Pd}(\text{PPh}_3)_4$	Reflux/48	Dioxane/EtOH/H ₂ O 3/1.5/0.5	14/32/46
9	$\text{Pd}(\text{PPh}_3)_4$	140 MW/2	Dioxane/EtOH/H ₂ O 3/1.5/0.5	tr/tr/70
10	$\text{Pd}(\text{PPh}_3)_4$	140 sealed tube/2	Dioxane/EtOH/H ₂ O 3/1.5/0.5	tr/tr/70

^a Optimized conditions: (**5a**) (1 mmol), $\text{Pd}(\text{PPh}_3)_4$ (10 mol%), Cs_2CO_3 (1.3 mmol), dioxane/EtOH/H₂O (3/1.5/0.5 mL), 140°C for 4 h. Yields of products after column chromatography purification. ^b K_2CO_3 was used as base. ^c tr = traces.



a nucleophilic attack from a Br^- anion on its C5 and C7 carbon atoms, as illustrated by the regions in blue in Fig. 2A. Likewise, compound **3c** is predicted to be the subject of a nucleophilic attack on the same sites (Fig. 2B). If experimentally, the C7 atom is the preferred site of bromination, it can be due to the greater steric hindrance at C5 on the second face of the aromatic moiety. Indeed, only one electrophilic site on C7 can be detected on the back side of the indazole moieties of **3a** and **3c**, as shown by the open surfaces in Fig. 2. Considering an electrophilic attack from a Br^+ cation, the representation of the fk^- Fukui function is less convincing, with a main site of interaction that would be between C5 and C6 for compound **3a**, and a secondary site on C7 (Fig. 3A). Furthermore, none of the indazole carbon atoms of **3c** seem to be prone to such an electrophilic attack (Fig. 3B). Similar trends are found with the assumption of a radical attack (Fig. S1, see ESI[†]), without any favorable carbon sites in **3c** and, for **3a**, two active sites on the C7 atom for the former and between the C5 and C6 atoms for the latter. The comparison of these different theoretical models mainly suggests that C3 bromination is never predicted, as experimentally observed. Additionally, following our bromination conditions at high temperature with NBS involving an electrophilic Br^+ , we could observe a higher reactivity of compound **3a** over compound **3c**.

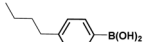
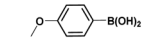
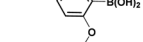
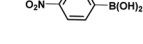


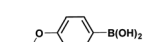
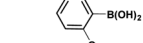
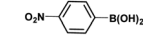
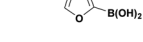
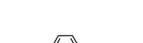

A direct and efficient regioselective C7-bromination of 4-substituted 1*H*-indazole has been achieved. Subsequently, a successful palladium-mediated Suzuki–Miyaura reaction of C7-bromo-4-substituted-1*H*-indazoles with boronic acids has been performed under optimized reaction conditions. A series of new C7 arylated 4-substituted 1*H*-indazoles was obtained in moderate to good yields.

Once the halogenation has been carried out on **3a**, the obtained *N*-(7-bromo-1*H*-indazol-4-yl)-4-methylbenzenesulfonamide **5a** was employed to optimize the Suzuki–Miyaura reaction with (4-methoxyphenyl)boronic acid as coupling partner under various reaction conditions exploring the effects of different bases, catalysts, solvents, and reaction times (Table 2). We began this study using 10 mol% of $\text{PdCl}_2(\text{PPh}_3)_2$ as catalyst and K_2CO_3 or Cs_2CO_3 as base in DMF at reflux for 48 h. These conditions failed to give the desired product **8ab** (entries 1 and 2). Using $\text{Pd}(\text{PPh}_3)_4$ as the catalyst instead of $\text{PdCl}_2(\text{PPh}_3)_2$, only traces of the desired product **8ab** were detected along with dehalogenated product **3a** (entries 3 and 4). Unfortunately, only a modest yield of 11% of coupled product **8ab** was obtained carrying out the reaction under microwaves irradiation for 2 h (entry 5). Then various parameters such as solvents (pure or as a mixture), temperature, pressure (sealed tube) or microwave activation conditions were changed (entries 6–10). We found that protocols realized in a mixture of dioxane/EtOH/ H_2O (3/1.5/0.5) as solvents in a sealed tube either under conventional heating or microwave irradiation provided the coupled product **8ab** in a good yield (70%) together with traces of both starting material **5a** and dehalogenated product **3a** (entries 9 and 10).

The optimized reaction conditions (1 equiv. of **5a–c**, 10 mol% of $\text{Pd}(\text{PPh}_3)_4$, 1.3 equiv. of Cs_2CO_3 , dioxane/EtOH/ H_2O (3/1.5/0.5 mL), 140 °C (2 h under MW or 4 h in a sealed tube))

were used to explore the substrate scope and limitations. A variety of aryl and heteroaryl boronic acids were successfully coupled with the 4-substituted-7-bromo-1*H*-indazoles **5a–c** (Table 3). The reactions of **5a** and **5b** bearing electron donating groups with phenylboronic acids bearing also electron donating groups resulted in the formation of the desired products **8aa–8ac** and **8ba–8bc** in good yields (Table 3, entries 1–3 and 7–9). The aryl boronic acid bearing electron-withdrawing group NO_2 at the C4 position, was also efficiently coupled with **7a** and **5b**, giving **8ad** and **8bd** in 78% and 75% yield, respectively (Table 3, entries 4 and 10). Additionally, the reaction of indazole **5c**

Table 3 Suzuki–Miyaura coupling of 7-bromo-4-sulfonamido-1*H*-indazoles **5a–c** to aryl boronic acids

Entry	$\text{ArB}(\text{OH})_2$	Product	Yield (%)
1		8aa	62
2		8ab	70
3		8ac	76 (70) ^a
4		8ad	78
5		8ae	75 (72) ^a
6		8af	80
7		8ba	57
8		8bb	81
9		8bc	75
10		8bd	75 (74) ^a
11		8be	72
12		8cb	71

^a Sealed tube, 2 h under MW.



Table 4 Suzuki–Miyaura coupling of 7-bromo-4-carboxamido-indazoles **7a–c** to aryl boronic acids

Entry	ArB(OH) ₂	Product	Yield (%)
1		9ab	78
2		9ba	70
3		9bb	82
4		9bd	76
5		9be	91
6		9bf	85
7		9ca	75
8		9cb	82

containing NO₂ on the sulfonamide moiety reacted with 4-methoxyphenyl boronic acid, to give the coupled product **8cb** in 71% yield (entry 12). These optimized conditions were also successfully applied to couple heteroaryl boronic acids such as thienyl and furyl-boronic acid. Thus, these derivatives were coupled with **5a** and **5b** to lead to **8ae** and **8be** in 75% and 72% yield, respectively (Table 3, entries 5 and 11). Comparatively, 2-thienyl boronic acid was coupled to **5a** to give **8af** with an excellent yield (80%, entry 6). It is noticed that except for the boronic acids bearing alkyl groups which gave the desired products **8aa** and **8ba** in moderate yields (entries 1 and 7, Table 3), the Suzuki–Miyaura cross-coupling reaction was not influenced by electronic or steric hindrance of the substituents on the boronic acid partners.

Finally, using the optimized conditions, the scope of this protocol was also extended to 4-amido-7-bromo-1*H*-indazole **7a–c**, in order to examine the effect of the nature of the functional group at C4 on the Suzuki–Miyaura reaction. With an amido substituent at C4 position, the starting material **7** efficiently reacted with various boronic acids to provide the corresponding C7 arylated products **9** in good yields either with aryl (Table 4, entries 1–3, 6–8) or heteroaryl reagents (Table 4,

entries 4 and 5). In this case, the reaction yields were not influenced by the electronic or steric hindrance of the substituents on the boronic acids. It is noticed so that in the case of unprotected 7-bromo-1*H*-indazoles bearing benzamide groups at C4 position, the heteroaryl boronic acids as coupling partners gave excellent yields.

Conclusions

We have prepared a novel series of C7 substituted unprotected NH indazoles in a two steps manner from 4-sulfonamido-1*H*-indazoles. A simple, fast and regioselective bromination reaction at the C7 position of the 4-sulfonamido-1*H*-indazoles was observed with *N*-bromosuccinimide and a computational study was performed to estimate the reactivity of the 4-sulfonamido NH-indazole ring. From the bromo NH-indazole precursors, a Suzuki–Miyaura cross-coupling reaction with a set of aryl boronic acids afforded the expected C7 (hetero)arylated NH-indazole derivatives, in moderate to excellent yields, regardless of any electronic influence or steric hindrance by the substituent on the boronic partner. Then, we have shown also that the bromination of unprotected NH indazoles bearing benzamide groups at C4 position took place in regioselective manner at C7 position. Again, the Suzuki–Miyaura cross-coupling reaction with various (hetero)aryl boronic acids led to the desired C7 (hetero)arylated NH-indazole derivatives in good yields.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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