Protected Indazole Boronic Acid Pinacolyl Esters: Facile Syntheses and Studies of Reactivities in Suzuki–Miyaura Cross-Coupling and Hydroxydeboronation Reactions

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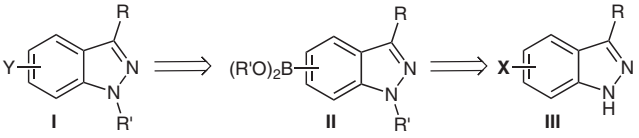
Abstract: The paper describes a rapid and efficient synthesis for the isolation of protected indazolylboronic esters. These compounds were synthesized by reaction between prepared protected haloindazoles and bis(pinacolato)diboron. The effects of solvent, temperature, reaction time, and the nature of halogen atom as well as protecting group were investigated. Additionaly, these compounds reacted either with aryl halides in a Suzuki–Miyaura cross-coupling reaction or with hydrogen peroxide in a hydroxydeboronation reaction showing the potential access to new aryl and hydroxyindazole libraries.

Key words: indazole boronic acid pinacolyl esters, Suzuki–Miyaura cross-coupling reaction, palladium-mediated reaction, protected halo-1*H*-indazoles, hydroxydeboronation

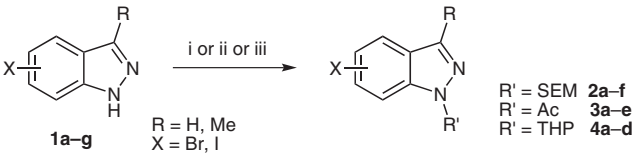
Our group has long been interested in the design and synthesis of new polyfunctionalized indazole libraries,[1] particularly those derived from the 2-aza bioisosteres of tryptamine, serotonin, melatonin, or tryptophan.[2]

In the present work we extend the studies on our ongoing research program to the development of a rapid methodology for the synthesis of indazolylboronic esters for the purpose to prepare new valuable building blocks in medicinal chemistry. Boronic acids and esters have emerged as two of the most useful classes of organoboron compounds in organic synthesis, particularly for the formation of carbon–heteroatom bonds[3] and in Pd-catalyzed cross-coupling reactions with organic halides and triflates (the Suzuki–Miyaura reaction).[4] Moreover, these synthetic intermediates provide a versatile and efficient access to hydroxy,[5] halo,[6] nitro,[7] and keto[8] compounds as well as amino acids.[9] Furthermore, over the past few years there has been an increased availability of heteroaromatic boronic acids and esters.[10,11] In contrast, indazolylboronic acids or esters have been surprisingly poorly investigated, and an exhaustive survey of literature revealed only few articles and patents wherein procedures were not always clearly explained.[12–15]

With this in mind, we first evaluated the feasibility of the transformation of various haloindazoles **III** into the corresponding boronates **II**. Several reaction parameters were varied, including the nature of protecting group and halogen atom as well as the effects of solvent, temperature, and reaction time. This was followed by a Pd-catalyzed coupling reaction of several freshly prepared boronates showing the reactivity of these functionalized building blocks and a potential access to a promise heterocyclic library **I**. In addition, we now provide as well an alternative for the synthesis of hydroxyindazoles by hydroxydeboronation (Scheme 1).



Scheme 1



Scheme 2 *Reagents and conditions*: i) SEMCl (1.1 equiv), TBABr (0.01 equiv), CH_2Cl_2/KOH aq 50%, 0 °C for 1 h then at r.t. for 2 h, 52–99%; ii) Ac_2O, reflux conditions, 2 h, 80–100%; iii) DHP (2.5 equiv), TFA (cat), EtOAc, reflux conditions, 6 h, 70–100%.

First, indazoles **1a–g** bearing bromo or iodo halogen atoms in position 4, 5, 6, and 7 were prepared from the corresponding 2-alkylanilines according to a previously successful method developed in our laboratory.[16] Then, it was required to protect the nitrogen atom of the indazole nucleus at this stage for potential subsequent reactions as well as avoiding possible side reactions during the borylation. Accordingly, the following groups have been used for the protection step: 2-(trimethylsilanyl)ethoxymethyl (SEM), acetyl (Ac) and tetrahydropyran-2-yl (THP). Next, a procedure recently published by Kania and coworkers,[17] protection in a biphasic mixture CH_2Cl_2/KOH (50% solution in H_2O) in the presence of SEMCl (1.1 equiv) and a catalytic amount of TBABr, provided 1-SEM-1*H*-haloindazoles **2a–f**. Protected indazoles **3a–e** were obtained by reaction with acetic anhydride for two hours under reflux conditions with excellent yields. Moreover,

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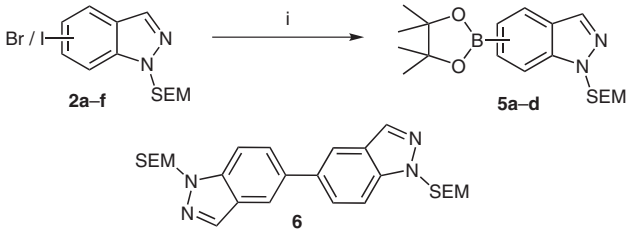
Table 1 Synthesis of Protected Halo-1*H*-indazoles **2a–f**, **3a–e**, and **4a–d** from the Corresponding Halo-1*H*-indazoles **1a–g**

Indazoles	X	R	Yield (%) of **2**		Yield (%) of **3**		Yield (%) of **4**	
1a	4-Br	H	**2a**	96	**3a**	100	**4a**	82
1b	4-I	H	**2b**	52	–	–	–	–
1c	5-Br	H	**2c**	81	**3b**	92	**4b**	70[a]
1d	5-Br	Me	–	–	**3c**	83	–	–
1e	5-I	H	**2d**	99	–	–	–	–
1f	6-Br	H	**2e**	92	**3d**	86	**4c**	100[a]
1g	7-Br	H	**2f**	97	**3e**	80	**4d** = **4da/4db** (3:1)	76

[a] The reaction was performed in $CHCl_3$.

taking into account the previously described works in pyrazole[18] and imidazole series,[19] in which THP was an excellent N-protecting group to prepare boronic acid derivatives, haloindazoles **1a**,**c**,**f**,**g** reacted with dihydropyran following a standard procedure described by Young and co-workers.[20] These conditions provided THP-protected indazoles **4a–d** in very good yields. For the compounds **4b**,**c**, chloroform was used as solvent instead of ethyl acetate with increasing yields. Concerning the protected indazole **4d**, it has been determinated by ^{1}H NMR that this product was a mixture of (N-1 and N-2)-THP-indazole with a **4da/4db** ratio of 3:1 (Scheme 2 and Table 1).

In order to establish conditions that enable an efficient and convenient protocol for the formation of indazolylboronic esters and acids in general, our initial focus was on optimizing the synthesis of 5-indazolyl boronic species. During the last decades, alkyl and aryl boronate esters and acids were occasionally prepared by reacting an organometallic intermediate generated from an arene or an aryl halide and stoichiometric quantities of a metalating agent with a boron electrophile.[21] Thus, taking into account our know-how in the laboratory about the halogen–metal exchange for the synthesis of various boronic species,[22] bromine–lithium exchange and iodine–lithium exchange were carried out (starting from *N*-SEM indazoles **2c** and **2d**) in dry THF at –78 °C with *n*-BuLi or *t*-BuLi followed by a subsequent quench with triisopropylborate [B(O*i*-Pr)$_3$] as electrophile. Unfortunately, only the deshalo products were recovered. In front of our unsuccessful preliminary attempts, we decided to modify our strategy to obtain indazolylboronic esters. In 1995, Miyaura and co-workers reported the synthesis of arylboronates by the palladium-mediated cross-coupling reaction of tetraalkoxydiboron reagents with haloarenes.[23] They used bis(pinacolato)diboron as an easily handled source of nucleophilic organoboron reagent, 1,1-bis(diphenylphosphino)ferrocenedichloropalladium–CH_2Cl_2 [$PdCl_2$(dppf)] as a source of palladium and potassium acetate (KOAc) as base which is recognized to be a suitable weak base for a wide variety of aromatic substrates and enables to achieve high yields and purities, in a polar solvent. Furthermore, the resultant pinacolyl boronate esters have the advantage of being stable compounds which can be purified by chromatography. With this in mind and starting from 5-iodoindazole **2d**, bis(pinacolato)diboron, $PdCl_2$(dppf), and KOAc, the procedure recently described by Reich and co-workers was applied using DMSO as solvent at 80 °C for two hours (Scheme 3).[24] But in our hands, only the byproduct **6** (called dimer)[2a] resulting of the homo-coupling reaction was isolated in a 85% yield (Table 2, entry 1).

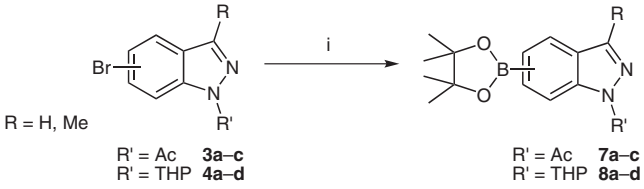


Scheme 3 *Reagents and conditions*: i) KOAc (4.6 equiv), $PdCl_2$(dppf)–CH_2Cl_2 (0.08 equiv), bis(pinacolato)diboron (1.15 equiv), argon, 79–98%.

Table 2 Study of the Formation of Protected Indazolylboronic Esters **5a–d**

Entry	Indazoles **2**	Solvent	Time (min)	Yield (%) of **5** or **6**	
1	**2d**	DMSO[a]	120	**6**	85
2	**2d**	DMSO	15	**5b**	85
3	**2c**	DMSO	15	**6**	87
4	**2c**	1,4-dioxane[b]	30	**5b**	67
5	**2a**	1,4-dioxane	45	**5a**	98
6	**2e**	1,4-dioxane	15	**5c**	98
7	**2f**	1,4-dioxane	240	**5d**	79

[a] With DMSO as solvent the reactions were performed at 80 °C.
[b] With 1,4-dioxane as solvent the reactions were performed under reflux conditions.



Scheme 4 *Reagents and conditions*: i) KOAc (4.6 equiv), $PdCl_2(dppf)$–CH_2Cl_2 (0.08 equiv), bis(pinacolato)diboron (1.15 equiv), argon, 1,4-dioxane, reflux, time, 18–98%.

Table 3 Synthesis of Protected Indazolylboronic Esters **7a–c** and **8a–d**

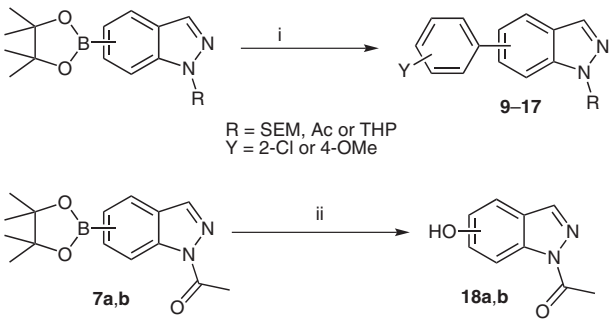
Indazoles	Time (h)	Yield (%) of **7** or **8**	
3a	0.25	**7a**	98
3b	4	**7b**	97
3c	24	**7c**	90[a]
4a	3	**8a**	87
4b	3	**8b**	89
4c	4	**8c**	77
4d	4	**8d**	18

[a] The reaction was performed at 80 °C with DMSO as solvent.

Next, reducing the reaction time to 15 minutes (reaction was monitored by TLC) resulted in the formation of desired boronate **5b** with a very good yield of 85% without formation of the dimer (Table 2, entry 2). Surprisingly, the same conditions applied to the protected 5-bromoindazole **2c** provided exclusively the dimer **6** with 87% yield (Table 2, entry 3). To avoid the formation of this byproduct, the effect of the solvent was examined. Gratifyingly, a high conversion of **2c** into the desired boronate **5b** (Table 2, entry 4) was obtained when 1,4-dioxane was used as solvent. Furthermore, running the reaction in 1,4-dioxane eliminated the formation of the dimer side product **6** and gave the indazolylboronic esters **5a** and **5c**,**d** in excellent yields when the corresponding bromoindazoles **2a** and **2e**,**f** were used (Table 2, entries 5–7).

Finally, the conditions selected for additional studies in position 4, 5, 6, and 7 of the indazole ring with acetyl and THP protecting groups encompassed the use of 1,4-dioxane as solvent under reflux conditions and starting from the bromo derivatives with a control of the reaction times (Scheme 4).[25] Similarly, the acetyl-protected indazoles **3a–c** were converted into the corresponding boronic esters **7a–c** with excellent yields (90–98%). Unfortunately, indazoles **3d**,**e** gave the corresponding unprotected haloindazoles under the same conditions. Next, indazolylboronic esters **8a–c** were obtained from the related 1-THP-1*H*-haloindazoles **4a–c** with very good yields (77–89%). However, a moderate yield was obtained for the 7-indazolylboronic ester **8d** probably due to the hindrance generated by the group THP on the C-7 position of the indazole nucleus (Table 3).

Subsequently, with the aim to investigate the reactivity of prepared protected indazole boronic acid pinacolyl esters, two examples of their potential applications are depicted in Scheme 5. Boronates were coupled with 4-iodoanisole or 1-chloro-2-iodobenzene in a standard Suzuki–Miyaura cross-coupling reaction, furnishing a range of arylindazoles **9–17** (Table 4). Our first attempts at 60 °C in DMF with K_3PO_4 (1 equiv) as base and aryl halide (1.2 equiv) provided the desired compounds in moderate to good yields (25–65%).[26] In order to compare other reaction conditions, Cs_2CO_3 (2 equiv) as base in a mixture 1,4-dioxane–water (2:1) under reflux conditions with $Pd(Ph_3P)_4$ (5 mol%) and aryl halide (1.5 equiv) gave similar or better yields (37–73%).[27,28] Moreover, the synthesis of hydroxyindazoles from the corresponding boronic esters has been examined. Action of hydrogen peroxide for one hour at room temperature on compounds **5a–d** bearing a SEM group did not afford the expected products. But the same conditions applied to the acylated 4- and 5-indazolylboronic esters **7a** and **7b** provided the corresponding hydroxy compounds **18a** and **18b** with 98% and 36% yields, respectively, providing an interesting alternative for the synthesis of hydroxyindazoles.[29,30] These results



Scheme 5 *Reagents and conditions*: i) Method I: 4-iodoanisole or 1-chloro-2-iodobenzene (1.2 equiv), K_3PO_4 (1 equiv), $Pd(Ph_3P)_4$ (0.08 equiv), argon, DMF, 60 °C, 3 h, 25–65%; Method II: 4-iodoanisole (1.5 equiv), Cs_2CO_3 (2 equiv), $Pd(Ph_3P)_4$ (0.05 equiv), argon, 1,4-dioxane–water (2:1), reflux, 12 h, 37–73%; ii) H_2O_2 aq, EtOAc, r.t., 1 h, 36–98%.

Table 4 Synthesis of Protected Arylindazoles **9–17**

Boronates	Method	Y	Yield (%) of indazole	
5a	I	2-Cl	**9**	42
5b	I	4-MeO	**10**	65
5c	I	4-MeO	**11**	25
5d	II	4-MeO	**12**	37
7a	I	4-MeO	**13**	40
8a	II	4-MeO	**14**	50
8b	I	4-MeO	**15**	34
8c	II	4-MeO	**16**	64
8d	II	4-MeO	**17**	73

demonstrate that construction of new arylindazole as well as hydroxyindazole libraries are feasible.

In summary, an efficient and rapid protocol for synthesis of various N-protected indazole boronic acid pinacolyl esters in good to high yields has been developed, providing a promising access to new aryl and hydroxyindazole libraries after subsequent Suzuki–Miyaura cross-coupling or hydroxydeboronation reactions. Considering the important properties of indazole derivatives, this methodology allowing the facile introduction of indazole moiety on various scaffolds could be a great interest for organic chemists to achieve new valuable building blocks for the use in medicinal chemistry as well as diversity-oriented synthesis. Further studies concerning construction of new substituted derivatives are currently in progress.

Acknowledgment

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(25) **Typical Experimental Procedure for the Synthesis of Indazolylboronic Esters**
To a solution of 1-(4-bromoindazol-1-yl)ethanone (**3a**, 1.5 g, 6.3 mmol) in 1,4-dioxane (25 mL) were added successively bis(pinacolato)diboron (1.8 g, 7.2 mmol, 1.15 equiv) and KOAc (2.8 g, 23.8 mmol, 4.6 equiv) at r.t. The reaction mixture was degassed under vacuum with argon replacement three times, then $PdCl_2$(dppf)–CH_2Cl_2 (0.3 g, 0.5 mmol, 0.08 equiv) was added, and the degassing procedure was repeated twice. The reaction was heated under reflux conditions for 15 min then concentrated in vacuo. After the addition of EtOAc, the organic layer was washed successively with H_2O and brine, dried over $MgSO_4$, and the solvent evaporated in vacuo. The crude material was purified by flash column chromatography on SiO_2 (EtOAc–cyclohexane, 1:3) to give 1-[4-(4,4,5,5-tetramethyl[1,3,2]-dioxaborolan-2-yl)indazol-1-yl)ethanone (**7a**); yield 1.8 g (98%); pink solid; mp 128 °C. TLC: R_f = 0.6 (EtOAc–cyclohexane, 1:4). IR (KBr): 2976, 1713, 1601, 1415, 1349, 1325, 1174, 1151, 932, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 12 H), 2.80 (s, 3 H), 7.55 (t, *J* = 8.3 Hz, 1 H), 7.82 (d, *J* = 7.1 Hz, 1), 8.54 (d, *J* = 7.1 Hz, 1 H), 8.55 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1, 25.0, 84.2, 118.3, 128.6, 130.6, 132.0, 138.3, 141.7, 171.1. MS (EI): *m/z* (%) = 286 (53) [M^+], 244 (100), 243 (39), 229 (14), 158 (70), 145 (34), 144 (68), 134 (67). Anal. Calcd for $C_{15}H_{19}BN_2O_3$: C, 62.96; H, 6.69; N, 9.79. Found: C, 62.39; H, 6.48; N, 9.23.

(26) For Suzuki–Miyaura cross-coupling reactions using K_3PO_4 as base in DMF, see: (a) Cailly, T.; Fabis, F.; Rault, S. *Tetrahedron* **2006**, *62*, 5862. (b) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.

(27) For Suzuki–Miyaura cross-coupling reactions using Na_2CO_3 or Cs_2CO_3 as base in dioxane, see: (a) Song, Y. S.; Lee, Y.-J.; Kim, B. T.; Heo, J.-N. *Tetrahedron Lett.* **2006**, *47*, 7427. (b) Heo, Y.; Song, Y. S.; Kim, B. T.; Heo, J.-N. *Tetrahedron Lett.* **2006**, *47*, 3091. (c) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1999**, *37*, 3387.

(28) **7-(4-Methoxyphenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (17)**
Yield 0.3 g (73%); white solid. TLC: R_f = 0.1 (EtOAc–cyclohexane, 1:10). IR (KBr): 3428, 2932, 1611, 1497, 1245, 1078, 1032, 824 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.37–1.42 (m, 2 H), 1.76–1.78 (m, 1 H), 1.90–1.95 (m, 1 H), 2.56–2.58 (m, 1 H), 2.91–2.96 (m, 1 H), 3.74–3.80 (m, 1 H), 3.91 (s, 3 H), 4.04–4.07 (m, 1 H), 5.00 (dd, *J* = 12.7, 2.2 Hz, 1 H), 7.02 (dd, *J* = 7.3, 1.4 Hz, 2 H), 7.18–7.19 (m, 2 H), 7.23–7.26 (m, 2 H), 7.64–7.70 (m, 1 H), 8.12 (s, 1 H). MS (EI): *m/z* (%) = 308 (22) [M^+], 224 (100), 209 (26), 192 (2), 182 (8), 154 (7), 85 (8). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.30; H, 6.74; N, 9.28.

(29) Schumann, P.; Collot, V.; Hommet, Y.; Gsell, W.; Dauphin, F.; Sopkova, J.; McKenzie, E. T.; Duval, D.; Boulouard, M.; Rault, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1153.

(30) The use of Oxone® ($2KHSO_5$–$KHSO_4$–K_2SO_4) as oxidative reagent in the presence of Na_2CO_3 in a mixture of H_2O–acetone (1:1) at 0 °C led to the desired compounds but in lower yields.