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Efficient synthesis of new 3-heteroaryl-1-functionalized 1*H*-indazoles

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The efficient synthesis of novel 3-heteroaryl *N*-1-functionalized indazoles, via palladium cross-coupling reactions of ethyl (3-iodo-1*H*-indazol-1-yl)acetate with 2- and 3-pyrrolylboronic acids, 2-, 4- and 5-thiazolylstannanes, and other heteroarylmetallated derivatives are reported.

1. Introduction

(Hetero)aryl groups directly connected by single Csp^2–Csp^2 bonds to heteroaryl moieties are present as core structures in many biologically active compounds,[1] naturally-occurring substances[2] and materials in polymer science.[3] As a consequence, particular interest has been paid to devise highly efficient, regio- and chemoselective methods to form heteroaryl–heteroaryl C–C bonds. Since the late 1980s, the transition metal-catalyzed cross-coupling reactions between heteroaryl halides and heteroarylmetal derivatives, represented the most effective methodology for the synthesis of unsymmetrical biheteroaryl.[4–7] Although natural products containing indazole moieties are rare,[8] indazoles play an increasingly important role in drug discovery (they act as an efficient isostere for privileged structures, such as indoles and benzimidazoles) and many synthetic indazoles are known and recognized by their pharmaceutical activity.[8,9] A SciFinder search of the indazole core structure returned 77,974 individual hits. A text search of indazole returned 5944 references; of them 2091 were patents (847 dated from 2005 to nowadays). We were interested on indazoles substituted at C-3 with azolyl nuclei because they are found in various biologically active compounds.[6a,c–e,10] After revision of the reported methods for synthesizing them,[6–8,10c,11] we realize that the use of cross-coupling procedures for joining their heterocyclic moieties is rather limited, because only some examples of coupling of the indazol at C-3 with furan and thiophene rings and some occasional example concerning pyridine and indol rings have been reported.[6a–d,10d] In this paper we describe a systematic study of the Pd-catalyzed coupling of **1**[12] (containing an N(1)–CH_2–CO_2Et group, susceptible of being further functionalized) with pyrrol and thiazol moieties, through their different positions, as well as with isoxazol-4-yl and oxazol-2-yl.

2. Results and discussion

The method used for performing different cross-coupling reactions was based on the commercial availability or simplicity for synthesizing the starting compounds. Thus, for assembling indazol-3-yl with 2- and 3-pyrrolyl moieties, the Suzuki reaction appeared to be the best choice because the required pyrrolboronic acids are scarcely toxic, stable and commercially available reagents. The reaction of 3-iodoindazole **1** with 1.5 equiv of boronic acid **2**, under conditions reported for the reactions of 3-iodoindazoles with 2-furyl- and 2-thienylboronic acids,[6b] involving the use of Pd$(PPh_3)_4$ (5 mol%) as catalyst, under reflux in a 2:1 mixture of DME and water, containing an excess of aq sodium bicarbonate (4 equiv), afford after 1 h compound **3** in 34% isolated yield (Table 1 entry 1). A notable increase in the yield was observed by decreasing the proportion of water in the solvent (12.5:1 mixture DME/water, entries 2 and 3).[13] Under the conditions of entry 3, the cross-coupling compound **3** was isolated in 89% yield. This improvement can be explained by assuming that the main competing side reaction, the deboronation of **2** to give *N*-(Boc) pyrrole, is slower when the proportion of water in the solvent becomes lower.

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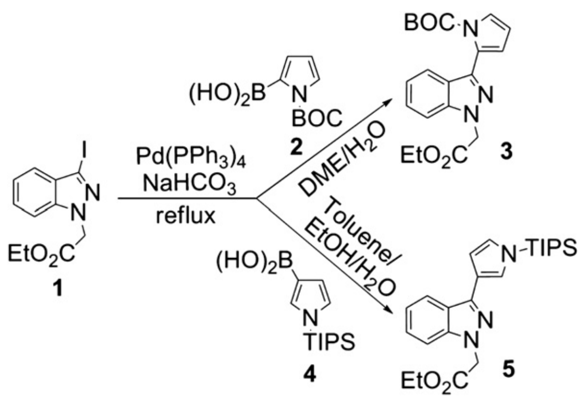
Table 1
Reactions of indazol **1** with pyrrolylboronic acids **2** or **4**



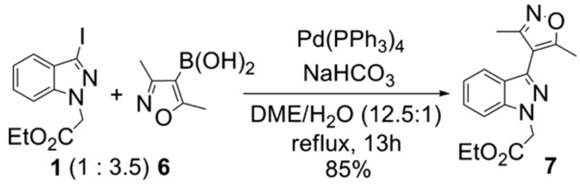
Entry	Boronic	DME/H_2O (toluene/EtOH/H_2O)	Time	Compound (% yield)[a]
1	**2**	2:1	1 h	**3** (34)
2	**2**	12.5:1	3 h[b]	**3** (65)
3	**2**	12.5:1	8.5 h	**3** (89)
4	**4**	12.5:1	13 h[b]	**5** (59)
5	**4**	12.5:1	16 h	**5** (56)
6	**4**	(19:1:1.6)	15 h	**5** (94)

[a] After column chromatography.
[b] Conversion (67%).

Reaction of indazol **1** with 2-pyrrolboronic acid **2** was also studied under $Pd(dba)_2/[(t\text{-}Bu)_3PH]BF_4$ catalysis under conditions reported by Fu for Suzuki cross coupling of aryl boronic acid and halides,[14] but it was not successful yielding a complex mixture.

Reactions of indazole **1** with 3-pyrrolboronic acid **4**, under conditions of the entry 3 in Table 1, also affords the expected cross-coupling biheterocyclic compound **5** in 59% yield after 13 h (Table 1, entry 4). The yield could not be improved by increasing the reaction time (entry 5). In this case, the best results were obtained by using a 19:1:1.6 mixture of toluene/EtOH/H_2O as solvent.[6b] In these conditions the degree of decomposition of **4** diminished, which determine a substantial improvement in the yield of **5** (94%, Table 1, entry 6). The use of these conditions in the reaction of **1** with **2** did not improve the results of the entry 3.

The cross-coupling reactions of **1** with the isoxazol-4-ylboronic acid **6** were studied under conditions of the entries 3 and 6 of Table 1. In this case, the use of a 19:1:1.6 mixture of toluene/EtOH/H_2O as solvent was completely unsuccessful, whereas under conditions of the entry 3 a 58:42 mixture of 3-isoxazolylindazol **7** and starting material was obtained after 21 h. The use of 3.5 equiv of the commercially available reagent **6** (instead of the 1.5 equiv) allowed to increases the yield of **7** up to 85% (after chromatographic purification, Scheme 1).

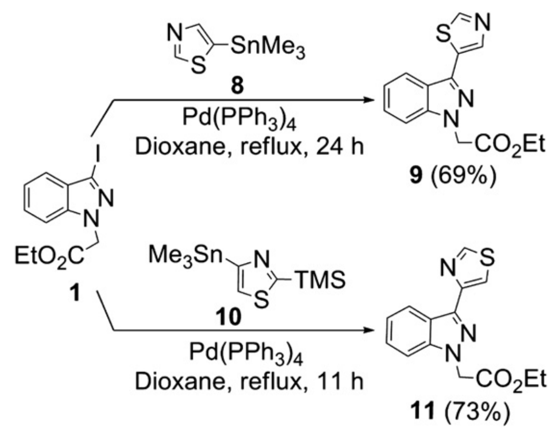


Scheme 1. Coupling of indazol **1** with isoxazol-4-ylboronic acid **6**.

These results evidence that the optimal experimental conditions for achieving the cross-coupling in each case depends on the nature of the heteroaryl partners.

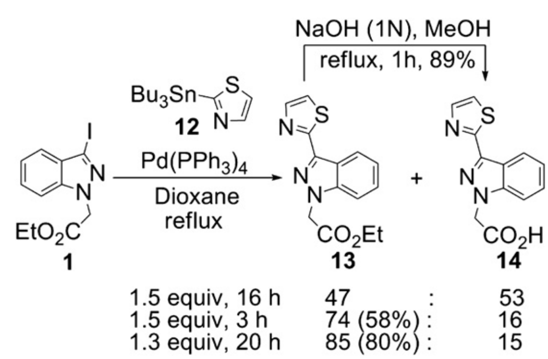
The use of the Suzuki's conditions for preparing the isomeric 3-(thiazolyl)indazoles had serious drawbacks. The first one was the high prize of the 2-, 4- and 5-thiazoleboronic acids, nowadays all of them commercially available.[15–17] Moreover, from a comparative study of Suzuki, Negishi, and Stille coupling, Stanetty[17] reported that the Stille coupling proved to be superior to the other methods with metal thiazoles. Since tin organyls are stable in the 2-, 4 or 5-position of thiazole and can easily be prepared[18] and stored for long periods of time, their Stille reactions with **1** were chosen for the preparation of the isomeric 3-(thiazolyl)indazoles.

Reactions of **1** with 1.5 equiv of 5-thiazolylstannane **8**[18,19] under $Pd(PPh_3)_4$ catalysis, in dry dioxane, afforded the ester **9** in 69% yield (after chromatographic purification) after 24 h (Scheme 2). Stannane **10**[18,20] is more reactive that **8**, and it evolves into the coupled product **11** (73% yield) in 11 h (Scheme 2). Longer reaction times reduce the yield, presumably due to the thermal unstability of **11**. Reactions conducted in toluene also gave worse results.



Scheme 2. Coupling of **1** with **8** and **10** under Stille conditions.

Reactions of 3-iodoindazole **1** with 1.5 equiv of stannane **12**, under similar conditions to those used in Scheme 2, ($Pd(PPh_3)_4$ as catalyst, reflux in dry dioxane) gave slightly different results (Scheme 3).



Scheme 3. Cross-coupling of indol **1** with 2-thiazolylstannane **12**.

After 16 h, we obtained a 47:53 mixture of **13** (the expected coupling product) and **14** (the acid resulting in the hydrolysis of **13**). This mixture could be completely transformed into **14** (89% yield after purification) by dissolving the crude reaction in a 1 N NaOH methanolic solution and heating it at 45–50 °C for 1 h (Scheme 3).[21]

The ratio **14**/**13** can be reduced by decreasing the reaction time (58% of the ester **13** could be obtained after 3 h) and even better by decreasing the excess of the starting stannane (80% of **13** can be