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# Efficient and simple synthesis of 3-aryl-1*H*-pyrazoles

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**Abstract**—Efficient preparation of 3-aryl-1*H*-pyrazoles by reaction of 1-protected-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazoles with (het)aryl halides is described. The choice of THP protecting group is discussed.

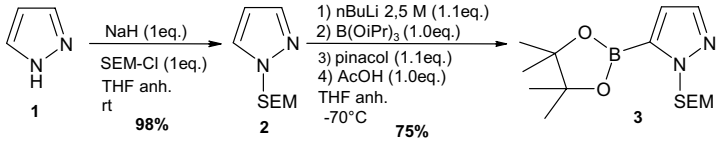

The synthesis of arylpyrazoles is of major interest. Indeed this class of heterocycles is usually used in pharmacochemistry and agrochemistry.[1,2] The main methods for preparing these heterocycles consist of reaction between hydrazines and β-difunctional compounds[3] or 1,3-dipolar cycloadditions of diazo compounds onto triple bonds.[4]

With the aim of constituting a library of pyrazoles linked to various scaffolds, we needed to develop efficient methodologies of cross-coupling reactions. These reactions were already achieved with halopyrazoles[5a] and more recently with pyrazole nonaflates[5b] and triflates[5c] but very few references described the cross-coupling reaction of pyrazolyl boronic derivatives. In our knowledge, only Young et al. described the synthesis of 1*H*-pyrazol-3-yl-boronic acid and performed a Suzuki coupling with this compound. Since 3-halo-1*H*-pyrazoles require harsh reaction conditions, we decided to study the synthesis of new stable pyrazolylboronic acid derivatives and their reactivity toward haloaromatics using Suzuki cross-coupling reaction techniques.

Herein we describe the very promising results concerning the synthesis of 3-aryl-1*H*-pyrazoles by the reaction of 1-protected-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole with (het)aryl halides.

To begin, we focused on the synthesis of 5-pyrazolyl boronic species. First the protection of pyrazole with an efficient and then labile protecting group is necessary. For this reason the use of [2-(trimethylsilyl)ethoxy]-methyl (SEM) function is recommended.[6] 1-SEM-1*H*-pyrazole **2** is obtained with a good yield by the reaction of sodium hydride and then [2-(trimethylsilyl)-ethoxy]methyl chloride in tetrahydrofuran according to the method of Fugina et al. (Scheme 1).[6a]

At the beginning of our work only some references and patents mentioned the use of 1-SEM-1*H*-pyrazol-5-yl-boronic acid[7] and only Han et al.[7a] described its synthesis. We first synthesized this compound but unfortunately in our hands the reaction was not complete and we obtained only an unseparable mixture of boronic acid and starting material. For this reason and because




**Scheme 1.**

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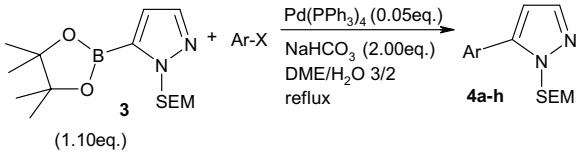
pinacyl esters are known to be more stable and often easier to isolate and to characterize, we decided to synthesize the 1-SEM-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole **3**. Concerning this product, no reference was found in the literature. Its synthesis requires the reaction of an organolithium compound with a trialkyl borate followed by a transesterification. In our case the azolyl lithium species is generated by direct metalation of 1-SEM-1*H*-pyrazole with *n*-BuLi at −70 °C in tetrahydrofuran, as described by Fugina.[6a] Then the lithio intermediate, stabilized by intramolecular coordination with the oxygen atom of the SEM group, is quenched by the addition of triisopropylborate.[8] The transesterification is then realized adapting

**Table 1.**



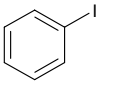
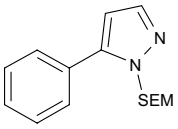
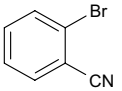
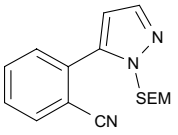
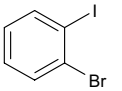
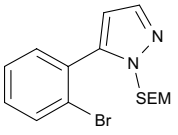
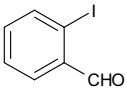
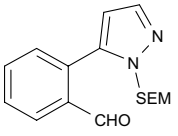
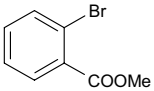
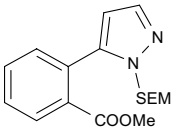
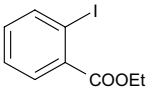
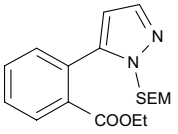
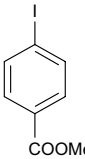
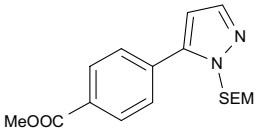
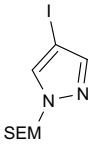
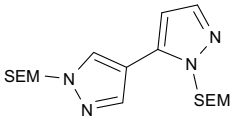
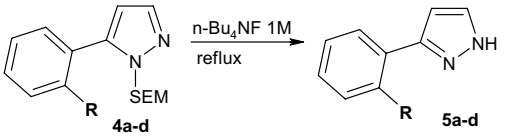

| Ar–X | Product | Time (h) | Yield (%) |
|---|---|---|---|
|  | **4a**  | 1 | 71 |
|  | **4b**  | 6 | 93 |
|  | **4c**  | 24 | 42 |
|  | **4d**  | 2 | 86 |
|  | **4e**  | 12 | 73 |
|  | **4f**  | 12 | 52 |
|  | **4g**  | 20 | 40 |
|  | **4h**  | 20 | 48 |

**Table 2.**



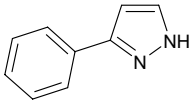
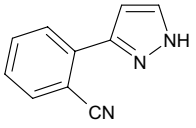
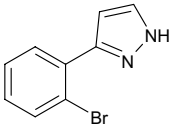
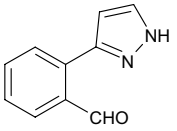
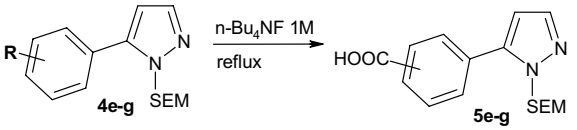
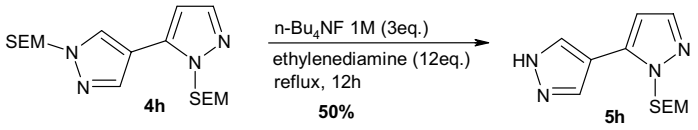

| Conditions | Product | | Yield (%) |
|---|---|---|---|
| *n*-$Bu_4NF$ 3 equiv, ethylenediamine 6 equiv, reflux, 20 h | **5a** |  | 95 |
| *n*-$Bu_4NF$ 3 equiv, reflux, 18 h | **5b** |  | 82 |
| *n*-$Bu_4NF$ 3 equiv, reflux, 18 h | **5c** |  | 65 |
| *n*-$Bu_4NF$ 3 equiv, reflux, 12 h | **5d** |  | 60 |

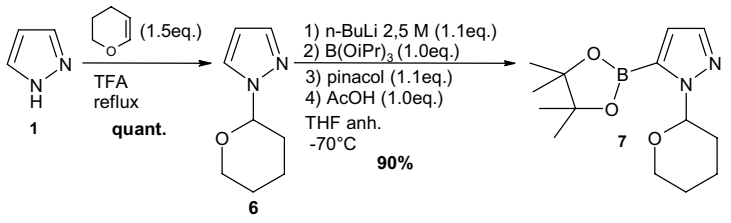
**Table 3.**




| R | Conditions | Product | Yield (%) |
|---|---|---|---|
| *o*-COOMe | (1) *n*-$Bu_4NF$ 3 equiv, reflux, 30 h | **5e** | (1) 17% |
| | (2) *n*-$Bu_4NF$ 6 equiv, reflux, 18 h | | (2) 10% |
| | (3) *n*-$Bu_4NF$ anhyd 10 equiv, reflux, 12 h | | (3) 32% |
| *o*-COOEt | *n*-$Bu_4NF$ 3 equiv, reflux, 30 h | **5f** | 22% |
| *p*-COOMe | *n*-$Bu_4NF$ 3 equiv, reflux, 30 h | **5g** | 12% |




**Scheme 2.**




**Scheme 3.**

the method of Coudret[9] with pinacol. The 1-SEM-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole **3** was obtained with 75% yield as a stable pale yellow oil.

This new boronic ester **3** was then coupled with a variety of different (het)aryl halides under standard Suzuki cross-coupling reaction type conditions.[10,18] The yields were good and the resulting 1-SEM-5-aryl-1*H*-pyrazoles **4a**–**h** were purified by column chromatography (Table 1).

During the following deprotecting step, we encountered some difficulties. In fact under mild conditions using tetra-*n*-butylammonium fluoride in tetrahydrofuran at room temperature, no deprotection occurred. This one needed more drastic conditions with excess of tetra-*n*-butylammonium fluoride in refluxing THF for a long period, more than 12 h. In these conditions deprotected 3-aryl-1*H*-pyrazoles **5a**–**d** were obtained with 60–95% yields (Table 2).[6a]

Without explanations being found and contrary to what was observed with the pyrrole series[11] it was impossible to produce the N-deprotection in the presence of carboxylate moiety and in all cases, carboxylates **4e**–**g** led, whatever the conditions, to the N-protected carboxylic acids **5e**–**g** and all the starting material was consumed (Table 3).

In a similar manner, only one SEM group of the disymmetric bipyrazole **4h** was removed to give the mono-protected **5h**. Oddly the SEM group of **5h** was unremovable under standard conditions (Scheme 2). The use of other reagents such as HF or HCl conducted to very poor results without isolated compound.

Vis-a-vis such problems and because SEM chemistry is very expensive, we search for an other protecting group possessing favorable requirements: the presence of an oxygen atom able to orient the lithiation on α of nitrogen atom, stability in basic conditions and lability under acid ones.

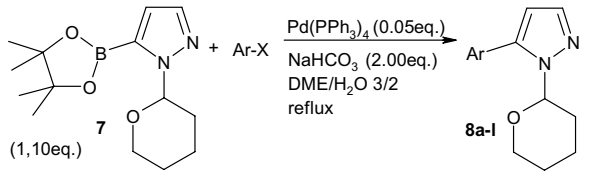
Although tetrahydropyran (THP) was not widely used for protection of NH groups, a survey of the literature showed us that it was nevertheless used with success in the pyrazole chemistry.[12] So the tetrahydropyranyl moiety was introduced by reacting pyrazole with dihydropyran as described by Young et al.[12a] We obtained the 1-THP-1*H*-pyrazole **6** in quantitative yield. This protecting pyrazole was then engaged in the lithiation reaction using slightly modified literature procedure.[12a] The lithio pyrazole was then reacted with triisopropylborate ($B(OiPr)_3$) and transesterification with pinacol finally gave the expected 1-THP-1*H*-pyrazolylboronic ester **7** with a very good yield (90%) as a stable white solid (Scheme 3).

At this stage a question still has to be raised to know whether this THP protecting group would be stable under the Suzuki cross-coupling reaction conditions ecause Young et al. prepared the N-deprotected boronic acid before the cross-coupling reaction[12a] and no example of such N-THP-boronic ester was described in the literature. Fortunately **7** behaved as a very efficient partner of cross-coupling reactions and gave, under the same conditions as the one described before with compound **3**, 1-THP-5-aryl-1*H*-pyrazole **8a**–**l** with satisfactory yields (Table 4).[18] However, in these conditions the cross-coupling reaction remained unsuccessful starting from 4-chloroanisole.

Finally taking as a starting point the works of Röder[13] and Beylin[12c] we found that treatment of these protected pyrazoles **8a**–**l** with ethanolic HCl at room temperature was able to cleave the THP after 1 h of reaction whatever the substituent of the (het)aryl moiety (Table 5).[12b,c,13,19] Thus we obtained 3-aryl-1*H*-pyrazoles **9a**–**l** with good yields, in mild conditions.

To conclude we have found that THP was an excellent N-protecting group for pyrazoles, able to orient the lithiation, to stabilize the boronic ester **7**, permitting a good reactivity in Suzuki cross-coupling reaction and having a great lability in acid conditions. This methodology is currently under application to produce

**Table 4.**



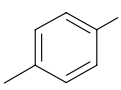
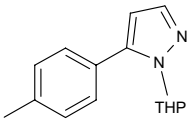
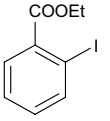
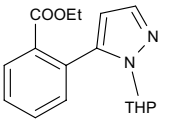
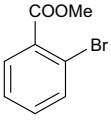
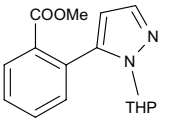
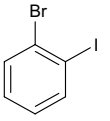
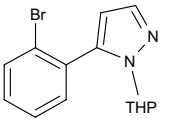
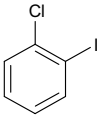
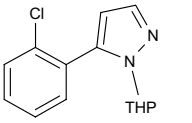
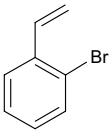
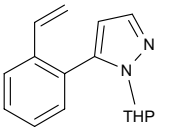
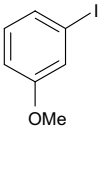
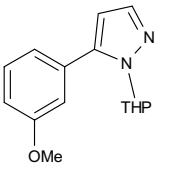
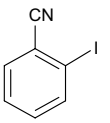
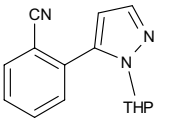
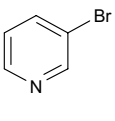
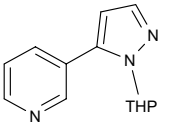

| Ar–X | | Product | Time (h) | Yield (%) |
|---|---|---|---|---|
|  | **8a** |  | 12 | 63 |
|  | **8b** |  | 18 | 30 |
|  | **8c** |  | 18 | 40 |
|  | **8d** |  | 24 | 46 |
|  | **8e** |  | 12 | 82 |
|  | **8f** |  | 12 | 53 |
|  | **8g** |  | 12 | 74 |
|  | **8h** |  | 20 | 45 |
|  | **8i** |  | 12 | 48 |

**Table 4** (*continued*)

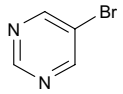
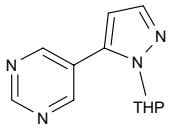
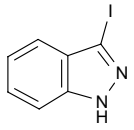
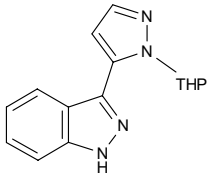
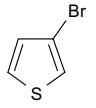
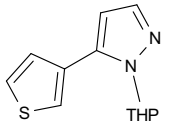
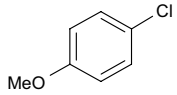
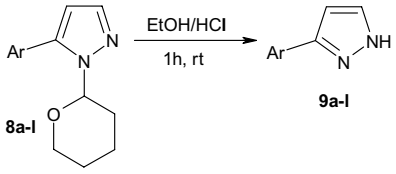
| Ar–X | Product | Time (h) | Yield (%) |
|---|---|---|---|
|  | **8j**  | 20 | 92 |
|  | **8k**  | 20 | 72 |
|  | **8l**  | 20 | 70 |
|  | | 20 | / |

**Table 5.**




| First material | Product | Yield (%) |
|---|---|---|
| **8a** | **9a**[14] | 85 |
| **8b** | **9b** | 40 |
| **8c** | **9c** | 15 |
| **8d** | **9d**[15] | 59 |
| **8e** | **9e**[15a] | 74 |
| **8f** | **9f** | 78 |
| **8g** | **9g**[16] | 76 |
| **8h** | **9h** | 90 |
| **8i** | **9i**[4b,17] | 77 |
| **8j** | **9j** | 77 |
| **8k** | **9k** | 77 |
| **8l** | **9l** | 93 |

new derivatives with potential interest in medicinal chemistry.

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18. *Typical procedure of the cross-coupling reaction*: To a solution mixture of halo-compound (6.53 mmol, 1 equiv) in DME (40 mL) under argon was added $Pd(PPh_3)_4$ (0.32 mmol, 0.05 equiv) followed by the addition of 1-THP-1*H*-pyrazolylboronic ester (7.19 mmol, 1.1 equiv) and sodium hydrogen carbonate (13 mmol, 2 equiv) in $H_2O$ (25 mL). The reaction mixture was refluxed and the rate of the reaction, followed by TLC. After the starting halo-compound was consumed, the organic solvent was removed under reduced pressure. The residue was extracted with AcOEt and the organic layer was dried ($MgSO_4$) and evaporated. The crude products were purified by column chromatography (AcOEt/cyclohexane).
19. *Typical procedure of deprotection*: A solution of **8** (2 mmol) in EtOH (5 mL) was treated with ethanolic HCl (10 mL) and stirred for 1 h at room temperature. After neutralization with aqueous sodium bicarbonate, the residue was extracted with AcOEt and the organic layer was dried ($MgSO_4$). The solvent was removed and the crude product was purified by column chromatography (AcOEt/cyclohexane).