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Palladium-Catalyzed Arylation and Heteroarylation of Azolopyrimidines

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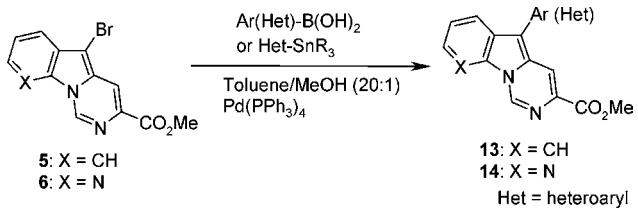

A comparative study of the palladium-catalyzed arylation and heteroarylation of 5-bromoazolopyrimidines shows that aryl and electron-rich heteroaryl boronic acids gave higher yields than those obtained using the corresponding aryl and heteroaryl tributyl stannanes. In contrast, the reaction with electron-poor heteroaryl tributyl stannanes gave better results than the corresponding boronic acids.

Indolizines (**1**) are compounds that are generally associated with pharmaceutical activities such as antiinflammatory (oxygenase inhibitors), antitumor (alkylating), or even CNS activity.[1] A number of aza-indolizines (pyrrolodiazines) (for example, 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine derivatives **2**) exhibit antihypertensive, ischemic, anxiolytic, and equistomicidal activities,[2] and the pyrrolo[1,2-*c*]pyrimidine system (6-azaindolizine) is present in the marine alkaloid hinckdentine, some analogues of which have cataleptogenic activity,[3] and in the variolins, a family of alkaloids isolated from the Antarctic sponge *Kirkpatrickia varialosa*, which have antitumor and antiviral activity[4,5] (Figure 1).

Studies carried out in our laboratory on pyrrolodiazine chemistry led to the synthesis of pyrrolo[1,2-*c*]pyrimidine and some simple derivatives by a route with significantly fewer steps than previous approaches. The method is based on the reaction between pyrrolecarboxaldehydes and TosMIC and constitutes the best procedure reported to date for the synthesis of pyrrolo-[1,2-*c*]pyrimidines.[6,7]

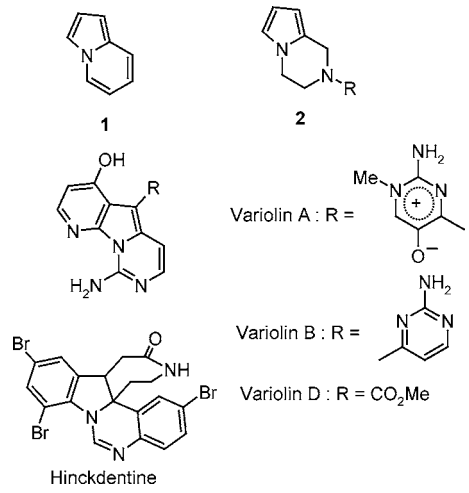

FIGURE 1. Indolizines and natural alkaloids with the pyrrolopyrimidine heterocyclic system.

Recently, we also reported a novel heterocyclization procedure for the synthesis of a new series of substituted azolopyrimidines **3** and **4** by reaction of TosMIC[8,9] and TosMIC[10] derivatives with bromomethylazoles (Scheme 1).

Tricyclic compounds **3** and **4**, specifically methoxycarbonyl derivatives of the pyrimido[1,6-*a*]indole nucleus present in the hinckdentine alkaloid and derivatives of the pyrido[3′,2′:4,5]-pyrrolo[1,2-*c*]pyrimidine system, which is the heterocyclic core of the variolin alkaloids, exhibited interesting vanilloid activity.[11]

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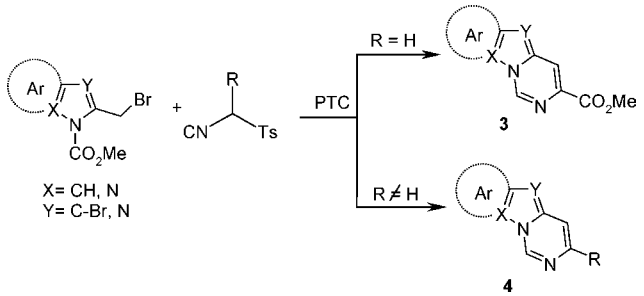
SCHEME 1



In an effort to obtain an improvement in the activity, we initiated a search for new derivatives of these tricyclic azolopyrimidines. We report here a comparative study involving the preparation of derivatives from 5-bromo-3-methoxycarbonylpyrimido[1,6-*a*]indole (**5**) and 5-bromo-7-methoxycarbonylpyrimido[3′,2′:4,5]-pyrrolo[1,2-*c*]pyrimidine (**6**) through palladium-catalyzed reactions (Stille and Suzuki) to introduce aryl and heteroaryl substituents in the C5 position of both azolopyrimidine systems.

Palladium-promoted cross-coupling reactions have been successfully employed in the functionalization of some halopyrroles and indoles[12] and therefore we decided to explore palladium-catalyzed C−C bond formation methods to achieve an efficient preparation of target compounds **13** and **14**. With this aim in mind, compounds **5** and **6** were prepared according to the previously reported procedure.[8,9] Our initial strategy was to convert both tricyclic compounds into the heteroaryltin **9** and heteroaryl boronic acid **10** derivatives to test the well-known Stille[13,14] and Suzuki[15,16] reactions with a variety of commercially available aryl and heteroaryl halides. The preparation of stannane **9** initially seemed a straightforward goal since 2- and 3-(trimethylstannyl)-7-azaindole have previously been prepared by reaction of the corresponding lithiated indoles with trimethyltin chloride.[17] However, all our attempts to prepare **9** by this methodology were unsuccessful. Attempts to synthesize heteroaryl boronic acid **10** using either trimethoxyborane or the more selective triisopropoxylborane as reagents with the (presumably) lithiated heterocycles **7** and **8** (generated by treatment of **5** and **6** with *n*BuLi at −78 °C in THF) were also unsuccessful. Further studies demonstrated the instability of both of these bromoheterocycles to different metalation conditions, with extensive decomposition of the heterocycles observed in the attempted quenching of the lithiated intermediates with deuterated water.

The one-step procedure reported by Miyaura and co-workers for the preparation of aryl boronic esters was also tested.[18] This procedure is based on a palladium-catalyzed coupling reaction of the pinacol ester of diboron and **5** and **6**, but this approach also failed and decomposition of the haloheterocycles was observed. Finally, we studied the formation of **9** using the coupling reaction between **5** and hexamethyldistannane in the presence of a palladium catalyst.[19] Under the conditions shown in Scheme 2, compound **5** did not react to any significant extent and decomposition products, the starting material, traces of **9**, and the homocoupling compound **11** (<5%) were identified in the reaction mixture after 48 h at room temperature. The addition of a fluoride source and/or a change in the palladium catalyst did not significantly improve the formation of stannane **9** and, in these cases, **11** was the main reaction product, albeit in a very low yield (5%).

The strategy attempted here is based on the synthesis of the azolopyrimidine stannane **9** or boronic acid **10** as partners in the Stille and Suzuki reactions to introduce diversity in the C-5 position of **5** and **6**. However, the failure of this approach led us to explore the use of these bromo derivatives as electrophilic reagents with aryl- and heteroaryl boronic acids and stannanes. A comparative study of both haloheterocycles was carried out with tributylphenyl stannane and phenyl boronic acid. The results showed that coupled compounds were formed in these reactions, although yields were clearly higher on using Suzuki conditions when compared with those obtained under the Stille reaction. A summary of the reaction conditions and yields is given in Table 1 for substrate **5**.

It can be seen that the best yield of the desired coupled compound **13a** was obtained with phenyl boronic acid in a mixture of toluene/MeOH (20:1) as solvent and using palladium tetrakistriphenylphosphine as the catalyst (Table 1, entry 2). Although the reaction proceeded much more slowly in the absence of water, the use of an anhydrous base (K_2CO_3) suspended in toluene clearly afforded a better yield, probably due to the stability of **5** to ester hydrolysis under nonaqueous conditions (Table 1, entry 1).

The reaction of **5** with tributylphenyl tin was first attempted using typical conditions (Table 1, entry 3). The reaction did not take place at room temperature, and heating the mixture to 80 °C resulted in extensive hydrolysis of the ester group, with the corresponding acid formed in more than 50% yield. The use of toluene as a solvent to avoid ester saponification resulted in the formation of **13a** in 58% yield (Table 1, entry 4), but complete reaction required heating and a longer reaction time. A slight increase in the solvent polarity (20:1 mixture of toluene/MeOH) was found to be moderately beneficial for the yield of the reaction, which increased to 63% (Table 1, entry 5). A change in the palladium catalyst and the phosphine did not improve the yield (Table 1, entries 6 and 7). Finally, when the reaction was conducted in dimethylacetamide (DMA) in the presence of $Pd_2(dba)_3$/P(*o*-tol)$_3$, **13a** was obtained in only 24% yield (Table 1, entry 8) with the corresponding dehalogenated compound also formed in 20% yield.

Comparison of the results obtained in the reaction of **6** and phenyl boronic acid or tributylphenyl tin shows that they are very similar to those shown in Table 1 for **5**. Therefore, the

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SCHEME 2

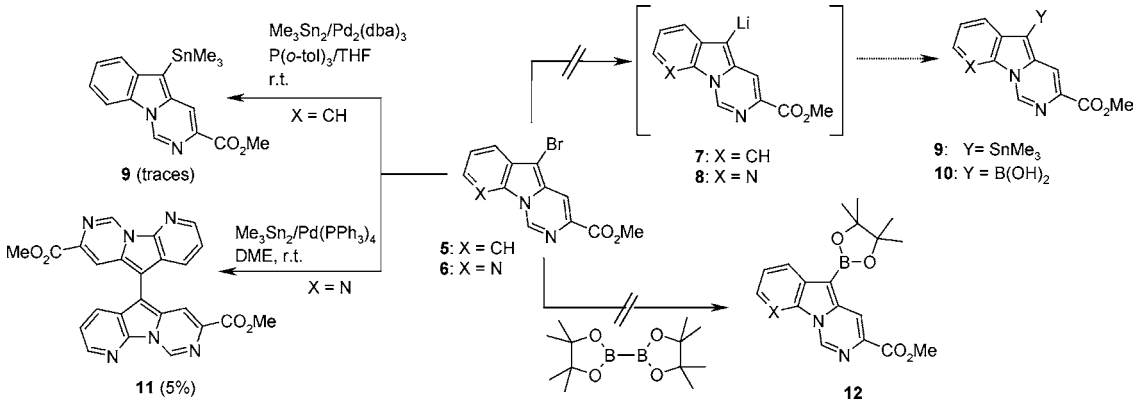
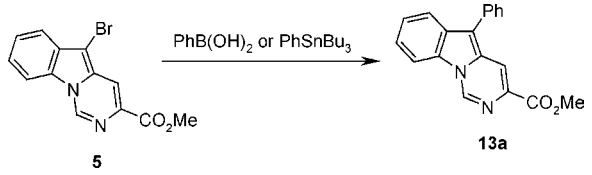


TABLE 1. Optimized Suzuki and Stille Reactions on 5



entry	stannane/ boronic acid	conditions	isolated yield (%)
1	$PhB(OH)_2$	toluene/MeOH/H_2O/K_2CO_3 $Pd(PPh_3)_4$, reflux	63
2	$PhB(OH)_2$	toluene/MeOH/K_2CO_3 $Pd(PPh_3)_4$, reflux	85
3	Bu_3SnPh	DMF/$Pd(PPh_3)_4$/LiCl, 80 °C	–
4	Bu_3SnPh	toluene/$Pd(PPh_3)_4$, reflux	58
5	Bu_3SnPh	toluene/MeOH/$Pd(PPh_3)_4$, reflux	63
6	Bu_3SnPh	toluene/MeOH/$Pd_2(dba)_3$/P(*o*-tol)$_3$, reflux	23
7	Bu_3SnPh	toluene/MeOH/$Pd(AcO)_2$/PPh_3, reflux	19
8	Bu_3SnPh	DMA/$Pd_2(dba)_3$/P(*o*-tol)$_3$, r.t.	24

Suzuki reaction was chosen as the most suitable method for the efficient aryl functionalization of the C-5 position in both **5** and **6**. A variety of commercially available aryl and heteroaryl boronic esters were reacted with **5** and **6** under the optimal conditions shown in Table 1 (entry 2) for the synthesis of **13a**. The results of these reactions are shown in Table 2.

It can be seen from Table 2 that the palladium-catalyzed C-5 arylation of compound **5** is not particularly sensitive to electronic effects and aryl boronic acids bearing electron-withdrawing or electron-donating groups produced similar isolated yields of the coupled products. The difference in yields seems to be associated with the solubility of the aryl derivative **13** in the reaction medium, with less soluble compounds isolated in higher yields. Compound **6** exhibits a similar reactivity to **5** in reactions with aryl boronic acids, although isolated yields are comparatively lower in some cases (**13a** versus **14a**, Table 2, entries 1 and 2, and **13f** versus **14f**, Table 2, entries 8 and 9).

The most significant difference in reactivity between **5** and **6** was observed in the reactions with heteroaryl boronic acids. The reactions of **5** with 3-thienyl boronic acid and 2-benzothienyl boronic acid proceeded in excellent yields (87% and 97%, respectively, entries 12 and 14 in Table 2). Furthermore, 2-benzofuranyl boronic acid afforded the coupled compound **13j** in 67% yield in the reaction with **5**, whereas the reaction of **6** with 3-thienyl boronic acid afforded only a modest yield (40%) of **14h** (Table 2, entry 13). Curiously, both benzoazolyl boronic acids failed to react with **6** under the optimized reaction conditions used for the other aryl boronic acids. Although a clear correlation between electronic effects and chemical yields cannot be deduced from the above results, the results of the reactions with benzoazolyl boronic acids seem to suggest that electronic effects have a greater impact on the yield for substrate **6** than for **5**.

To further explore the electronic effects in the coupling reactions with **5** and **6** and, at the same time, to achieve diversity in terms of substitution, electron-poor heteroaryl boronic acids were also subjected to the reaction conditions. In sharp contrast to results obtained with electron-rich heteroaryl boronic acids, **5** did not react to any appreciable extent with 3- and 4-pyridyl boronic acids. This unexpected failure led us to retry the Stille reaction with heteroaryl stannanes as coupling partners for **5** and **6** (Scheme 3). Our previous studies aimed at optimizing the conditions for **13a** showed that the highest yield was obtained using $Pd(PPh_3)_4$ as a catalyst in toluene/MeOH (Table 1, entry 5), and these conditions were therefore used in the attempted coupling reactions between some azinyl stannanes and **5** and **6**.

These conditions were appropriate to obtain the coupling product between **6** and 2-pyridyl stannane or 2-methylthio 4-pyrimidyl stananne[20] in moderate yields (Table 3, entries 2 and 5). These conditions also proved successful for the synthesis of the phenylethynyl derivative **16d**, albeit in lower yield (36%) (Table 3, entry 7), but failed to give the coupling product with 3-pyridyl stannane (Table 3, entry 4). The coupling reactions between these stannanes and **5** are more problematic, and only modest yields of the coupling product were obtained (Table 3, entries 1 and 6). The 3-pyridyl stannane also failed to react with **5**. In a final attempt to improve these yields, we explored the use of other catalysts [$Pd_2(dba)_3$ and $Pd(OAc)_2$] and ligands [P(*o*-tol)$_3$ and PPh_3], but results showed a very limited influence of the catalytic system on the reaction yield, which did not vary appreciably.

In conclusion, palladium-catalyzed arylation and heteroarylation of 5-bromo-3-methoxycarbonylpyrimido[1,6-*a*]indole and 5-bromo-7-methoxycarbonylpyrido[3′,2′:4,5]pyrrolo[1,2-*c*]-pyrimidine using aryl- and heteroaryl boronic acids and stannanes have proven to be a practical means to introduce aromatic

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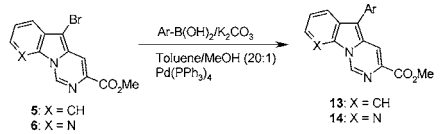
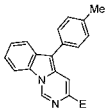
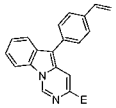
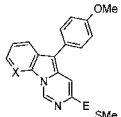
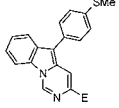
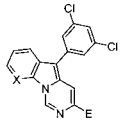
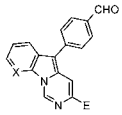
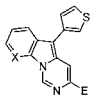
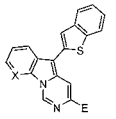
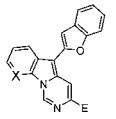
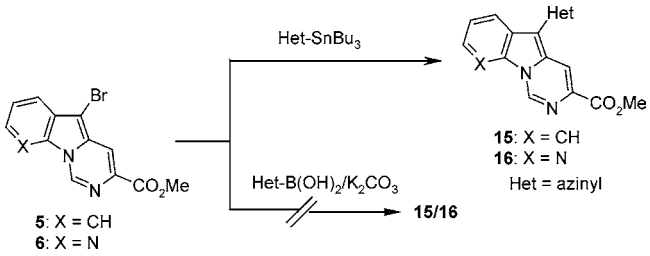
TABLE 2. Suzuki Coupling of 5 and 6 with Aryl and Heteroaryl Boronic Acids



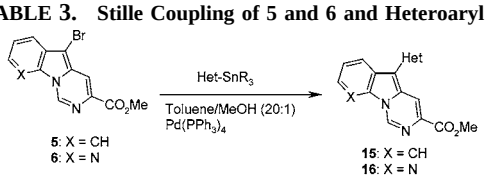
entry	boronic acid	bromo azolopyrimidine	coupled compound	yield (%)[a]
1		**5**	 **13a** (X = CH)	85
2		**6**	**14a** (X = N)	66
3		**5**	 **13b**	68
4		**5**	 **13c**	56
5		**5**	 **13d** (X = CH)	49
6		**6**	**14d** (X = N)	52
7		**5**	 **13e**	71
8		**5**	 **13f** (X = CH)	87
9		**6**	**14f** (X = N)	60
10		**5**	 **13g** (X = CH)	72
11		**6**	**14g** (X = N)	65
12		**5**	 **13h** (X = CH)	89
13		**6**	**14h** (X = N)	40
14		**5**	 **13i** (X = CH)	97
15		**6**	**14i** (X = N)	--
16		**5**	 **13j** (X = CH)	67
			14j (X = N)	--

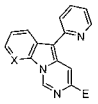
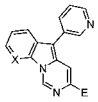
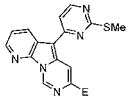
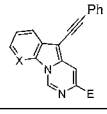
SCHEME 3



and heteroaromatic diversity on the pyrrole ring of these tricyclic azolopyrimidines. The Suzuki reaction is particularly useful with aryl and electron-rich heteroaryl boronic acids when compared with the Stille reaction. However, the latter approach is the method of choice to produce substitution with electron-poor heterocycles because of the failure of the Suzuki reaction with electron-poor boronic acids. These reactions give the coupled products in moderate yields.

TABLE 3. Stille Coupling of 5 and 6 and Heteroaryl Stannanes



entry	stannane	bromo azolopyrimidine	coupled compound	yield (%)[a]
1		**5**	 **15a** (X = CH)	23
2		**6**	**16a** (X = N)	42
3		**5**	 **15b** (X = CH)	--
4		**6**	**16b** (X = N)	--
5		**6**	 **16c**	63
6		**5**	 **15d** (X = CH)	26
7		**6**	**16d** (X = N)	36

Experimental Section

General. General experimental details can be found in the Supporting Information.

Synthesis of Derivatives 13 and 14. General Procedure. To a mixture of **5** (or **6**) (1.0 mmol), the aryl or heteroaryl boronic acid (1.0 mmol), and K_2CO_3 (192 mg, 1.4 mmol) in toluene/MeOH (20:1) (25 mL) was added $Pd(PPh_3)_4$ (57 mg, 0.049 mmol) under argon, and the mixture was heated under reflux. The workup of the reaction mixture is detailed for each compound in the Supporting Information.

Synthesis of Derivatives 15 and 16. General Procedure. To a suspension of **5** (or **6**) (1.0 mmol) in toluene/MeOH (20:1) (5 mL) was added the corresponding heteroaryl stannane (1.0 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) under argon. The mixture was heated under reflux for 14 h. The workup of the reaction mixture is detailed for each compound in the Supporting Information.

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Supporting Information Available: Complete experimental procedures for the synthesis and analytical and characterization data (^{1}H NMR/^{13}C NMR, IR, MS) for compounds **11**, **13**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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