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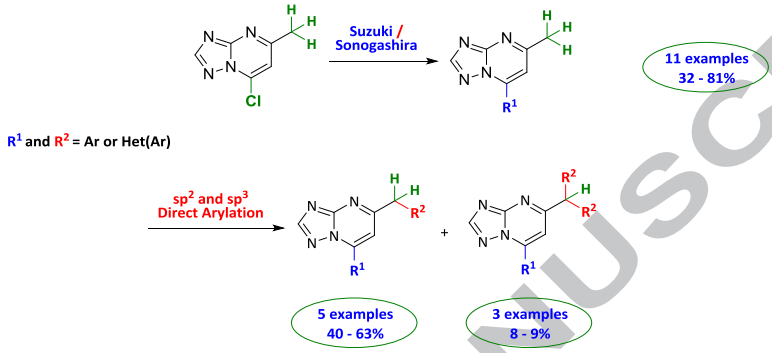

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Pd-catalyzed Suzuki/Sonogashira cross-coupling reaction and the direct sp^3 arylation of 7-chloro-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine

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ABSTRACT

A rapid and efficient method is reported for the synthesis of the [1,2,4]triazolo[1,5-*a*]pyrimidine motif. Palladium catalyzed Suzuki and Sonogashira cross coupling reactions on 7-chloro-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine were performed. The direct sp^3 arylation of compounds resulting from the Suzuki reaction was then carried out.

N-heterocycles or fused nitrogen heterocycles are interesting synthetic targets in the search for biologically active molecules. For this reason, nitrogen bridgehead heterocycles have received considerable attention in organic synthesis.[1]

In particular, the [1,2,4]triazolo[1,5-*a*]pyrimidine subunit has displayed a wide range of biological activities, for example as a PDE2a inhibitor for the treatment of memory disorders,[2] LSD1 inhibitor,[3] anti-Alzheimer's,[4] anticancer,[5] anti-malarial,[6] anti-tubercular,[7] anti-leishmanial,[8] anti-bacterial,[9] anti-viral,[10] and hypnotic agent,[11] and as a CB2 cannabinoid receptor inverse agonist.[12]

While condensation reactions are the most widely used method to prepare the [1,2,4]triazolo[1,5-*a*]pyrimidine scaffold,[13] relatively few publications have reported the functionalization of this scaffold using transition metals. Among the latter, the functionalization, or more precisely creation of a carbon-carbon bond, *via* a transition metal-catalyzed cross-coupling reaction is undoubtedly the most important and has been widely exploited in recent years. Palladium, the most commonly used metal, enables the synthesis of complex and functionalized organic molecules and its chemistry possesses interesting properties such as allowing heterogeneous and homogeneous catalysis under mild experimental conditions which are compatible with many functional groups. Several palladium-catalyzed cross-coupling reactions have been described such as the Suzuki[14] or Sonogashira reactions.[15] Recently, several heterocyclic systems have also been functionalized using direct C-H arylation.[16]

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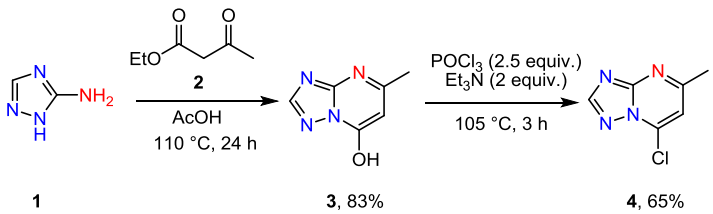
In continuation of our research program, we report herein a rapid and efficient pathway for the preparation of 7-(substituted)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine from [1,2,4]triazolo[1,5-*a*]pyrimidine by functionalization using Suzuki and Sonogashira palladium-catalyzed cross coupling reactions. The direct C-H arylation of 7-(substituted)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine at the sp^3 center is also described.

First, 7-chloro-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine **4** was synthesized in a two-step process (Scheme 1).

Scheme 1. Two-step preparation of the intermediate 7-chloro-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine **4**

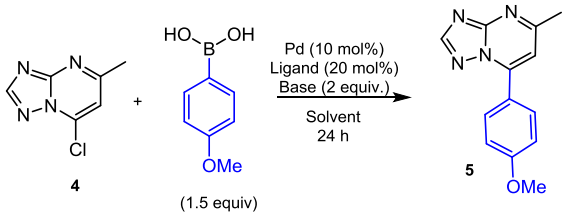


The condensation reaction between 2-aminotriazole **1** and ethyl acetoacetate resulted in the formation of 5-methyl[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol **3** in 83% yield. Next, chlorination of 5-methyl-[1,2,4]triazolo[1,5-*a*] pyrimidin-7-ol with $POCl_3$ gave 7-chloro-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine **4** in 65% yield.[17]

Optimization of the Suzuki cross coupling reaction with triazolo-pyrimidine skeleton **4** was performed using *p*-methoxyphenylboronic acid as a model substrate. The use of

different palladium sources (palladium(II) acetate or palladium(0) tetrakis triphenylphosphine) as catalysts, sodium bicarbonate or cesium carbonate as bases, and 1,4-dioxane or water as solvents were examined. The best conditions were determined as: boronic acid (1.5 equiv.), $Pd(PPh_3)_4$ (0.10 equiv.), Na_2CO_3 (2.0 equiv.) 1,4-dioxane/water (4/1), 105 °C, 24 h (Table 1, entry 3).

Table 1. Reaction conditions optimization for the Suzuki cross coupling reaction

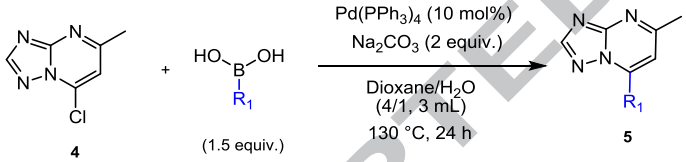


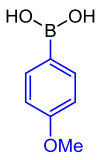
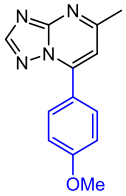
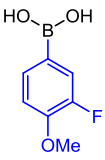
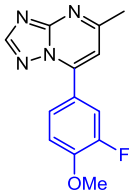
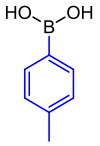
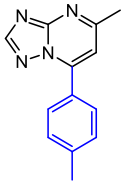
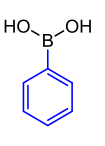
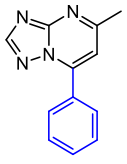
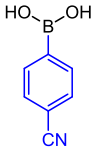
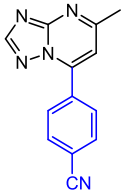
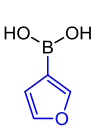
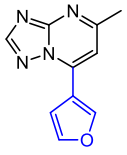
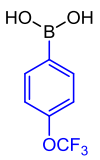
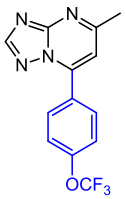
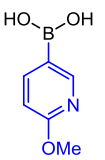
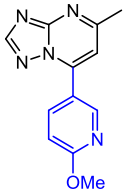
Entry	Pd	Base	Solvent (3 mL)	T (°C)	Yield 5 (%)[a]
1	$Pd(PPh_3)_4$	Na_2CO_3	water	105	49%
2	$Pd(OAc)_2$/ Xantphos	Cs_2CO_3	Dioxane	105	61%
3	**$Pd(PPh_3)_4$**	**Na_2CO_3**	**Dioxane/water (4/1)**	**105**	**81%**

[a] Isolated yield after column chromatography

Different boronic acids were then used to determine the reaction scope. Several 5-methyl-7-(aryl)-[1,2,4]triazolo[1,5-*a*]pyrimidines were obtained in good to excellent yields, showing that this strategy was compatible with both electron-rich (CH_3, OCH_3) and electron-poor (CN, OCF_3) boronic acids. The trifluoromethoxyphenyl boronic acid is an electron-poor boronic acid to an extent; however, its inductive electron-withdrawing ability is moderate compared to fluoride, and is actually a very weak resonance donor. This potentially explains the yield of **8** being closer to that of **6** than to that of **7**, the latter of which is derived from a more electron-deficient aryl boronic acid. The examples containing fluorine derivatives were chosen because of the well-known improvement of pharmacological properties often promoted with the introduction of fluorine. These conditions were also applied to introduce selected heteroarylboronic acids (Table 2).

Table 2. Scope of the Suzuki–Miyaura cross coupling of 7-chloro-5-methyl- [1,2,4]triazolo[1,5-*a*]pyrimidine **4**

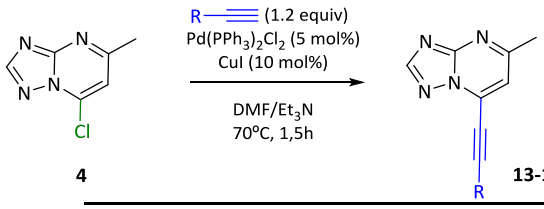


Entry	R-B(OH)$_2$	product		Yield (%)[a]	Entry	R-B(OH)$_2$	product		Yield (%)[a]
1			**5**	81%	5			**9**	51%
2			**6**	72%	6			**10**	65%
3			**7**	32%	7			**11**	63%
4			**8**	70%	8			**12**	46%

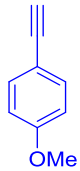
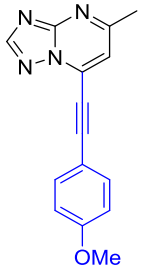
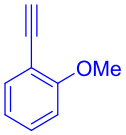
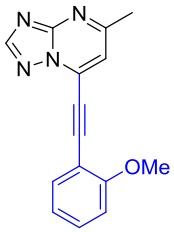
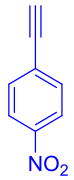
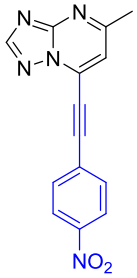
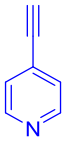
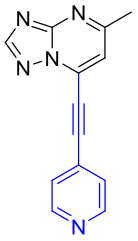
[a] Isolated yield after column chromatography

After having successfully achieved the Suzuki cross coupling reaction of 7-chloro-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine **4**, we then focused on introducing greater diversity by employing the Sonogashira coupling reaction. To achieve this goal, previously described[18] conditions were used (alkyne (1.2 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%), DMF/Et_3N (1/1), reflux, 1.5 h). Three alkynes were successfully introduced onto [1,2,4]triazolo[1,5-*a*]pyrimidine **4** with good yields (Table 3, entries 1, 3 and 4), except for the ethynyl benzene bearing a nitro group in the *para* position (Table 3, entry 2).

Table 3. Synthesis of 7-alkynyl-substituted-[1,2,4]triazolo[1,5-*a*]pyrimidines



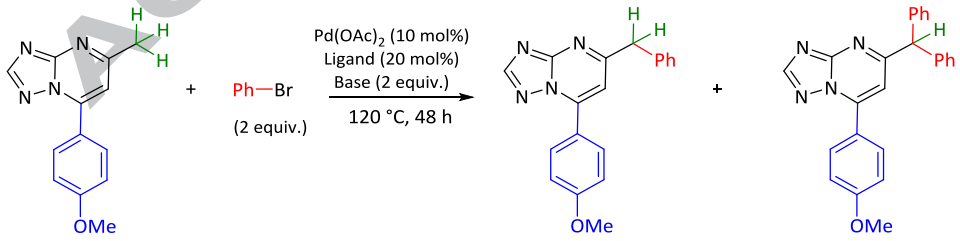
4 **13-15**

Entry	Alkyne	Product	Yield (%)[a]	Entry	Alkyne	Product	Yield (%)[a]
1			**13** 81%	3			**14** 65%
2			-	4			**15** 53%

[a] Isolated yield after column chromatography

The last stage was to study the direct C-H arylation. To optimize this reaction, 5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine containing a 4-methoxyphenyl group at the 7-position was used as the starting material, and bromobenzene as the coupling partner (Table 4). Various reaction conditions were investigated using different catalyst systems, bases, ligands, and solvents. Total conversion was obtained when TTBP•HBF_4/$Pd(OAc)_2$ was used as catalyst and K_2CO_3 as a base in toluene at 120 °C for 48 h, affording the desired products in 56% yield and an 85:15 ratio of mono vs disubstitution.

Table 4. Optimization of the direct C-H arylation of 7-(4-methoxyphenyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine **5**



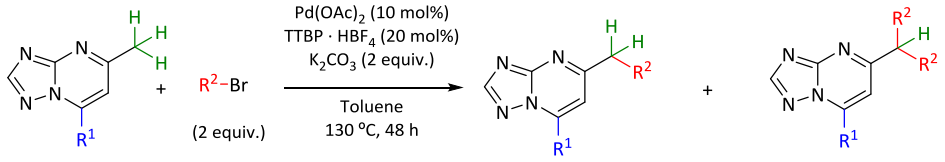
5 **16** **17**

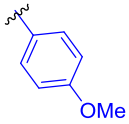
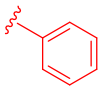
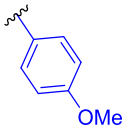
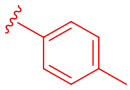
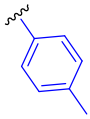
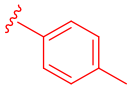
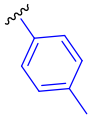
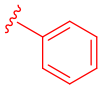
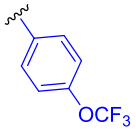
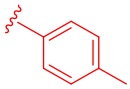
Entry	Ligand	Base	Solvent	Ratio [a] **16-17**		Yield (%)[b] **16-17**	
1	TTBP•**HBF_4**	**K_2CO_3**	**Toluene**	**85**	**15**	**56**	**9**
2	PPh_3	K_2CO_3	Toluene	62	38	36	12
3	TTBP•HBF_4	Cs_2CO_3	Toluene	75	25	27	7
4	-	K_2CO_3	Toluene	80	20	38	8[c]
5	-	K_2CO_3	Toluene	85	15	41	7
6	-	K_2CO_3	Dioxane	-	-	-[d]	-[d]
7	TTBP•HBF_4	K_2CO_3	Dioxane	-	-	-[d]	-[d]

[a] ^{1}H NMR ratio based on integration of the OCH_3 resonance; [b] Isolated yield after column chromatography; [c] reaction carried out with $Pd(PPh_3)_4$ (10 mol%); [d] degradation.

In order to examine the scope of the direct sp^3 arylation reaction, a series of 5-substituted-[1,2,4]triazolo[1,5-*a*]pyrimidines was prepared using the optimized reaction conditions. The desired compounds were isolated in acceptable yields. In entries 3 and 5 (Table 5) only the major products were recovered.

Table 5. Substrate scope for the direct C-H arylation



Entry	R^1	R^2	Yield (%)[a]	
1			**16**, 56%	**17**, 9%
2			**18**, 48%	**19**, 8%
3			**20**, 63%	**21**, 0%
4			**22**, 40%	**23**, 8%
5			**24**, 43%	**25**, 0%

[a] Isolated yield after column chromatography

In conclusion, originating from a rapid method to access the 7-(substituted)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine core, C-7 functionalization by Suzuki and Sonogashira cross-coupling reactions was successfully carried out. Further investigations were conducted involving a second functionalization by palladium-catalyzed direct sp^3 arylation.

A. Supplementary data

Supplementary data (experimental section and copies of spectra for all of compounds) associated with this article can be found, in the online version, at https://doi.org/

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HIGHLIGHTS

Heterocyclic nitrogen compounds
Triazolo[1,5-*a*]pyrimidine synthesis
Palladium cross-coupling
Direct sp^3 arylation