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Direct synthesis of 5-aryltriazole acyclonucleosides via Suzuki coupling in aqueous solution

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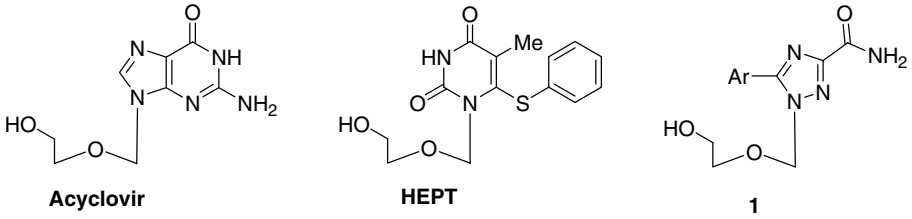
Abstract—5-Aryltriazole acyclonucleosides with various aromatic groups on the triazole ring were synthesized via the Suzuki coupling reaction in aqueous solution and promoted by microwave irradiation. Careful optimization of the reaction conditions led in good to excellent yields to the Suzuki products, while the cyclization side-reaction could be completely suppressed.

Nucleoside derivatives occupy a pivotal position in the arsenal of drug candidates for combating various viruses.[1,2] Acyclic nucleosides belong to an important class of biologically active nucleosides. Acyclovir (Scheme 1) was the first acyclic nucleoside to be successfully tested and developed.[3] It has become the gold standard for the treatment of herpes simplex viral infections.[3] Since then, various acyclonucleosides, such as ganciclovir, tenofovir, and cidofovir, have been developed for use as antiviral agents.[4] Acyclic nucleoside derivative HEPT, of which the pyrimidine nucleobase bears a phenylthio group at the 6-position, was recently reported to show anti-HIV activity and to be less toxic than the clinical drug AZT.[5] Meanwhile, 6-arylpurine ribonucleosides have also been found to show promising antiviral and cytostatic characteristics.[6] The large aromatic systems, present in the scaffold of such compounds, may recognize their biological targets more selectively and specifically because of the stronger and more efficient interactions occurring between their respective aromatic units. The biaryl motif is known to be a widely occurring structural feature in biologically active compounds.[7] However, relatively few attempts have been made so far to develop biaryl nucleoside derivatives.[8]

In our ongoing project, which focuses on novel triazole compounds of medicinal and agrochemical potentials,[9] we are interested in developing aryl-triazole nucleoside derivatives. We recently synthesized 5-aryltriazole ribonucleosides[9b] by employing a synthetic sequence involving a Suzuki coupling reaction.[10,11] Here, we report on the synthesis of novel acyclic aryltriazole nucleoside analogues **1** (Scheme 1), using a simple and efficient one-step procedure involving the direct Suzuki coupling of the unprotected 5-bromotriazole acyclonucleoside **5** with Suzuki reagents in aqueous solution under microwave irradiation. Good to excellent yields were obtained without requiring any yield-limiting and time-consuming protection/deprotection steps.



Scheme 1. Acyclovir, HEPT, 5-aryltriazole acyclonucleoside **1**.

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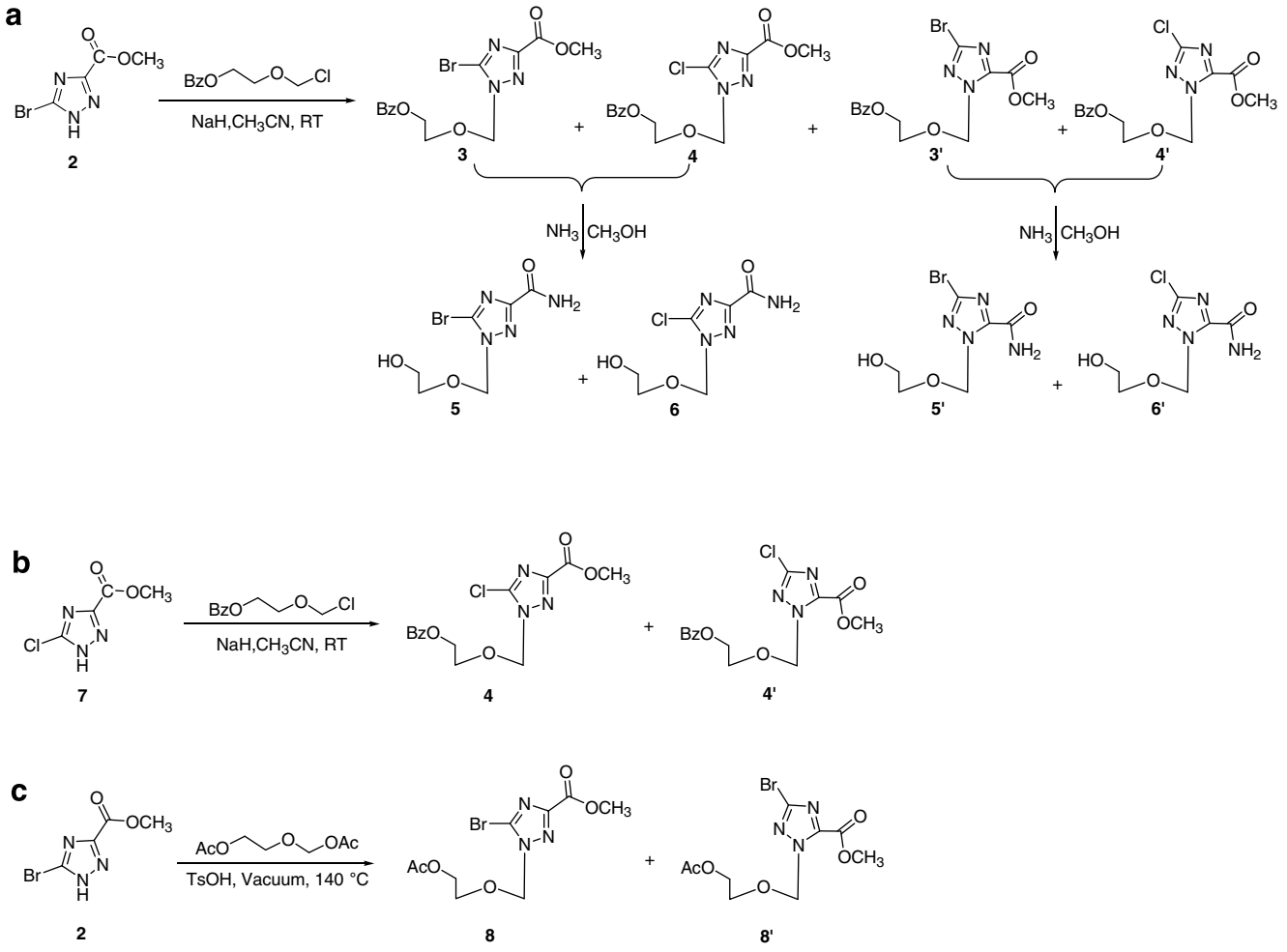
In order to prepare the bromotriazole acyclonucleosides for use as starting material for the Suzuki coupling reaction, we first attempted to synthesize bromotriazole acyclonucleoside **3** via alkylation[12] of bromotriazole **2** with 2-(chloromethoxy)ethyl benzoate (Scheme 2a).[13] However, the reaction yielded the expected 5-bromotriazole derivative **3** and its 3-bromo isomer **3′**, as well as two unexpected chlorotriazole derivatives **4** and **4′**. We were only able, by performing flash chromatography, to separate the mixture of 5-halogeno isomers (**3** and **4**) from the mixture of 3-halogeno ones (**3′** and **4′**), while the bromo isomers **3** and **3′** were resolutely inseparable from their corresponding chloro analogues **4** or **4′**, due to their very similar silica gel column behavior. Evidence of the presence of 5-chloro derivative **4** as an impurity in 5-bromotriazole **3** was provided by ^{13}C NMR analysis and further confirmed by mass spectral analysis due to the noticeable differences observed for the chemical shift of the anomeric carbons and the molecular mass between **3** and **4**. Further ammonolysis of the mixture of **3** and **4** led to the mixture of the corresponding products **5** and **6**, from which **6** could be isolated by careful crystallization in CH_3OH/CH_2Cl_2. X-ray structural analysis of both **5** and **6** (Fig. S1 in Supplementary data)[14] confirmed the unexpected finding that the chlorotriazole derivative **4** was formed in the preparation of **3** during the alkylation step.

In order to prepare pure halogenated triazole derivatives to further confirm the obtained reaction mixtures as well as to serve as starting material for the subsequent Suzuki coupling reaction, we performed the alkylation reaction of 2-(chloromethoxy)ethyl benzoate, by replacing bromotriazole **2** with the corresponding chlorotriazole **7** (Scheme 2b).[15] The corresponding pure chlorotriazole products **4** and **4′** could be obtained after column separation. Bromotriazole acyclonucleosides **8** and **8′** were further synthesized using the fusion method[16] by coupling bromotriazole **3** with 2-(acetoxymethoxy)ethyl acetate (Scheme 2c).[17] Further ammonolysis of **8**, **8′**, **4**, **4′** gave the corresponding products **5**, **5′**, **6** and **6′**, respectively, in good to excellent yields.

We attempted to perform the Suzuki coupling reactions with the 5-bromo derivative **8** under similar experimental conditions to those previously used for the synthesis of 5-aryltriazole ribonucleosides.[9b] However, the results were not satisfactory because the reaction was not complete and the yields were very low (data not shown). The low reactivity of **8** toward the Suzuki reaction might be



Scheme 2. Synthesis of triazole acyclonucleoside starting materials for Suzuki coupling.

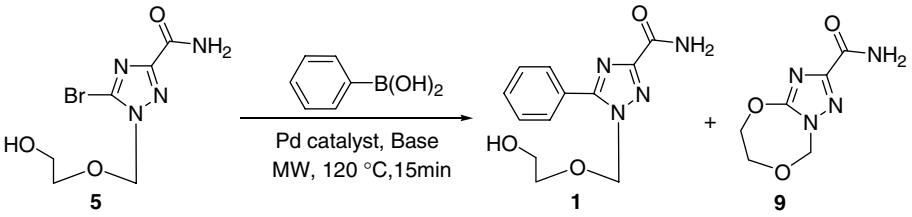
due to the formation of a stable Pd-complex with the oxygen atoms in both the ether and acyl functions in the side chain of **8**. The flexible feature of the side chain of **8** may greatly favor the formation of such complex.

It has been reported that in some cases, aqueous solvents can significantly promote Suzuki coupling reactions.[18] Besides, the use of water as a solvent for transition-metal-catalyzed reactions is of particular interest in organic chemistry for economical, environmental, and safety reasons. We therefore performed the Suzuki reaction in aqueous solution, using the water soluble substrate **5**. Good to excellent results were obtained with **5** when the Suzuki reaction was performed in aqueous solution under microwave irradiation (Tables 1 and 2).

During our efforts to optimize the experimental conditions of the Suzuki coupling reaction (Table 1) a side product **9** was isolated, the structure of which was confirmed by X-ray analysis (Fig. S2 in Supplementary data).[19] Compound **9** resulted from the intra-molecular nucleophilic substitution of **5**, mainly due to the particularly favorable structure and reactivity of **5** for such cyclization. This was supported by further experimental results: in the presence of a weak base such as K_2CO_3, the 5-bromo derivative **5** underwent cyclization and gave product **9** in excellent yields (87%). Under the same conditions, 3-bromo isomer **5′** did not undergo any such intra-molecular cyclization, probably due to its unfavorable molecular geometry and low chemical reactivity.

Since the undesired cyclization of **5** competes with the Suzuki coupling reaction, we decided to optimize the reaction conditions by promoting the Suzuki coupling while suppressing the cyclization reaction. Various parameters were studied and judiciously adjusted in order to obtain the optimized reaction conditions. First, the choice of solvent was crucial. The use of dioxane/H_2O system significantly improved the reaction yields, while either pure water or pure organic solvents gave the desired product in very low amounts (Table 1, entries 1–4). The beneficial effects of this solvent system may have resulted from the fact that substrate **5** is water soluble, while the Pd catalytic systems usually prefer organic solvents. Polar solvents favor nucleophilic substitution, and thus promote the intramolecular cyclization of **5** into **9**, while the less polar solvent system dioxane/H_2O (3:1) gave better Suzuki product yields (Table 1, entries 5–6). Second, the nature of the Pd catalyst also played an important role. Three common Pd catalysts, $Pd(PPh_3)_4$, $Pd_2(dba)_3$ and $Pd(OAc)_2$/TBAB, were used. Among them, $Pd(PPh_3)_4$ was the only catalyst that was able to efficiently catalyze the Suzuki coupling, while both $Pd_2(dba)_3$ and $Pd(OAc)_2$/TBAB showed no catalytic activity under our experimental conditions (Table 1, entries 6–8). Higher loading of $Pd(PPh_3)_4$ did not significantly improve the yields of **1**, nor could the cyclization reaction be further suppressed (data not shown). Finally, the influence of a suitable base was of greatest importance. Stronger bases, such as NaOH, accelerated the cyclization reaction and therefore gave **9** as the main product. Weaker organic bases, such as triethylamine, efficiently suppressed the cyclization, but it was not in favor of the Suzuki coupling. Better results were obtained using K_2CO_3, with which products **1a**–**m** were obtained in yields ranging from good to excellent (Table 1, entry 6, and Table 2). Further spectacular results were obtained using Li_2CO_3: **1a**–**m** were obtained in nearly quantitative yields in most cases, while the cyclization side reaction was completely suppressed (Table 1, entry 11, and Table 2). These results may be attributable to the formation of a Li^+-complex with the

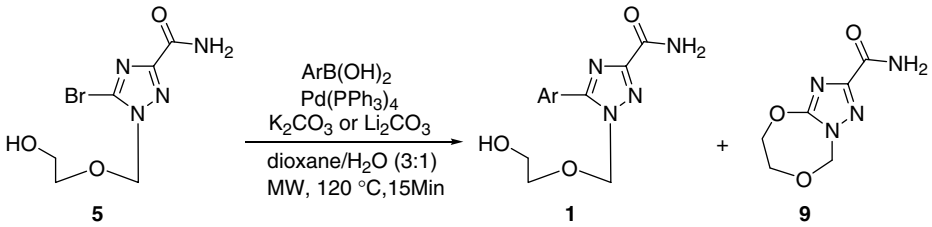
Table 1. Optimizing the Suzuki coupling reaction

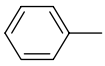
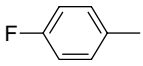
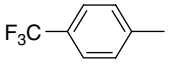
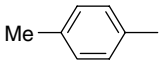
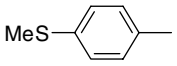
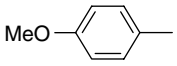
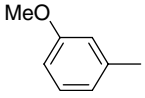
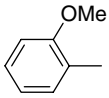
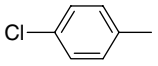
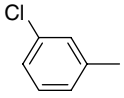
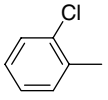


Entry[a]	Solvent	Base	Pd catalyst	**1** (%)	**9** (%)
1	H_2O	K_2CO_3[b]	$Pd(PPh_3)_4$	21	21
2	CH_3OH	K_2CO_3[b]	$Pd(PPh_3)_4$	13	5
3	CH_3CN	K_2CO_3[b]	$Pd(PPh_3)_4$	0	0
4	Dioxane	K_2CO_3[b]	$Pd(PPh_3)_4$	6	11
5	Dioxane/H_2O (1:1)	K_2CO_3[b]	$Pd(PPh_3)_4$	42	25
6	Dioxane/H_2O (3:1)	K_2CO_3[b]	$Pd(PPh_3)_4$	79	20
7	Dioxane/H_2O (3:1)	K_2CO_3[b]	$Pd_2(dba)_3$	0	41
8	Dioxane/H_2O (3:1)	K_2CO_3[b]	$Pd(OAc)_2$, TBAB	0	41
9	Dioxane/H_2O (3:1)	NaOH[c]	$Pd(PPh_3)_4$	9	55
10	Dioxane/H_2O (3:1)	NEt_3[d]	$Pd(PPh_3)_4$	47	5
11	Dioxane/H_2O (3:1)	Li_2CO_3[e]	$Pd(PPh_3)_4$	97	0

[a] 1.1 equiv $PhB(OH)_2$, 0.05 equiv Pd catalyst.
[b] 1.2 equiv K_2CO_3.
[c] 2.0 equiv NaOH.
[d] 2.0 equiv NEt_3.
[e] 2.0 equiv Li_2CO_3.

Table 2. Synthesis of **1** via the Suzuki coupling between **5** and various boronic acids

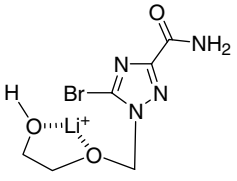


Entry	Ar	Product	**1/9**[a] (%)	**1**[b] (%)
1		**1a**	79/20	97
2		**1b**	81/13	98
3		**1c**	58/18	92
4		**1d**	88/0.4	98
5		**1e**	77/9	92
6		**1f**	92/0.3	97
7		**1g**	95/5	99
8		**1h**	89/10	97
9		**1i**	72/4	83
10		**1j**	78/5	86
11		**1k**	72/7	98
12		**1l**	49/14	66
13		**1m**	50/9	97

[a] 1.1 equiv $ArB(OH)_2$, 0.05 equiv $Pd(PPh_3)_4$, 1.2 equiv K_2CO_3.
[b] 1.1 equiv $ArB(OH)_2$, 0.05 equiv $Pd(PPh_3)_4$, 2.0 equiv Li_2CO_3.

side chain of **5** (Scheme 3), which may have prevented the cyclization of **5** and promoted the Suzuki coupling reaction by blocking the formation of the undesirable Pd–O complex during the oxidative insertion process.

Under our optimized conditions, that is, with $Pd(PPh_3)_4$ and Li_2CO_3, using dioxane/H_2O (3:1, v/v) as solvent (Table 2), starting material **5** was completely consumed during the Suzuki coupling reaction, which greatly sim-



Scheme 3. Proposed Li^+-complex of **5**.

plified the purification procedure.[20] The Suzuki coupling reaction was not affected by the presence of either electron-donating or electron-withdrawing substituents on the aromatic ring of the boronic acids used as Suzuki reagents (Table 2, entries 1–6), nor were any noteworthy steric effects observed (Table 2, entries 6–11). To our great surprise, 2-thienyl product **1m** was obtained in a quantitative yield, while only moderate yields were obtained with the 2-furanylboronic acid (Table 2, entries 12–13). The slightly lower yields obtained for **1i** and **1j** might be due to their further coupling with the corresponding Suzuki reagent.[21]

In conclusion, 5-aryltriazole acyclonucleosides **1a**–**m** bearing various aromatic groups on the triazole ring were synthesized. The aromatic group was introduced onto the triazole ring via a Suzuki coupling reaction using bromotriazole acyclonucleoside **5**. The coupling reaction was significantly promoted in aqueous solution under microwave irradiation, giving the corresponding compounds in good to excellent yields. The method used here to directly synthesize the aryltriazole acyclonucleosides **1a**–**m** in aqueous solvent involved no protection and deprotection steps, and thus provides an efficient and convenient one-step procedure for synthesizing various novel triazole acyclonucleosides **1**. Studies on the biological and physico-chemical properties of these novel triazole compounds are now under way at our laboratories.

Acknowledgements

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Supplementary data

Experimental procedures, analytical data and NMR spectra of all new compounds are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.154.

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19. The X-ray structure data of **9** have been deposited in the Cambridge Crystallographic Data Center with deposition No. CCDC 630923.
20. It was very difficult to separate **1** and **5** since both compounds migrated very closely on TLC.
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