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Synthesis of 5-aryltriazole ribonucleosides via Suzuki coupling and promoted by microwave irradiation

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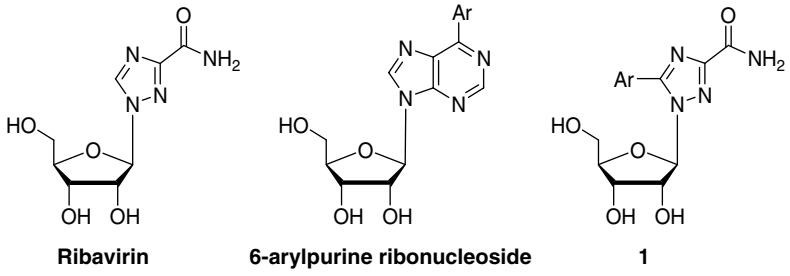
Abstract—Aryltriazole nucleosides with various aromatic groups in the 5-position on the triazole ring were synthesized and characterized with the aim to develop novel triazole nucleosides. The aromatic groups were introduced into the triazole ring via a Suzuki reaction starting with bromotriazole nucleoside. Microwave irradiation significantly promoted the Suzuki coupling, quickly giving clean products with good to excellent yields.

Synthetic nucleosides have attracted considerable attention because they hold great potential as surrogates for nucleic acid building units and as anti-metabolites endowed with antiviral, anticancer, and antimicrobial activities. Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, Scheme 1) was the first synthetic nucleoside showing a broad spectrum of antiviral activities against many RNA and DNA viruses.[1] In association with interferon-α, it is the only small molecule drug available to date for treating patients infected with hepatitis C virus.[2] Since its discovery over 30 years ago, ribavirin has been used for the treatment of a variety of viral infections.[3] Recently, 6-arylpurine ribonucleosides (Scheme 1) were found to show promising antiviral and cytostatic activities.[4] We are therefore interested in developing 5-aryltriazole ribonucleosides **1** (Scheme 1), which might be also interesting for screening of biological activity. Very few efforts have been made on 5-aryltriazole ribonucleosides, probably due to the lack of convenient and practical methods of synthesis. Here we report on an efficient and convenient method of synthesizing 5-aryltriazole ribonucleosides **1**, which consists in introducing the aromatic groups into the triazole ring via Suzuki coupling and then performing ammonolysis (Scheme 2).



Scheme 1. Ribavirin, 6-arylpurine ribonucleoside, and 5-aryltriazole ribonucleoside.

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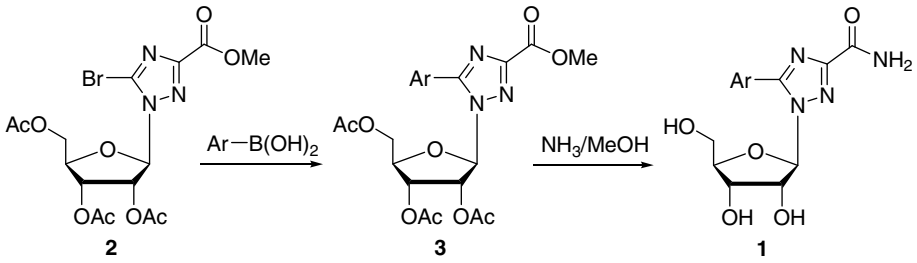
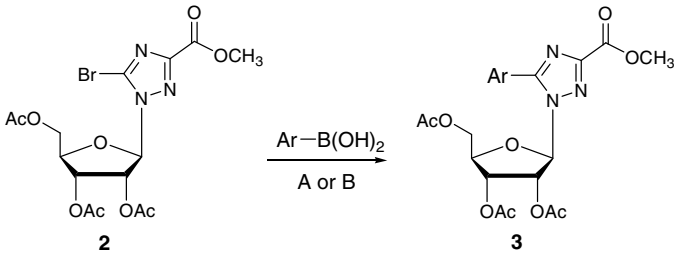
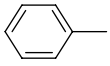
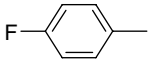
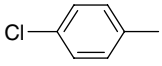
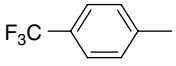
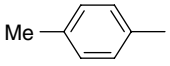
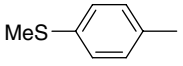
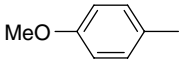
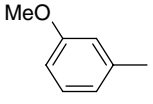
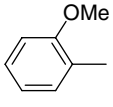


Scheme 2. Synthesis of 5-aryltriazole ribonucleosides.

Suzuki reaction[5] is a useful method of introducing various aryl functions into natural nucleobases such as purine and pyrimidine.[6] Our initial attempts to couple the bromotriazole nucleoside **2**[7] with various boronic

Table 1. Synthesis of **3** via Suzuki coupling of **2** with various boronic acids



Entry	Ar		Yields (%) of **3**	
			Conventional heating[a]	Microwave irradiation[b]
1		**3a**	53	91
2		**3b**	8	89
3		**3c**	11	74
4		**3d**	31	72
5		**3e**	51	76
6		**3f**	9	79
7		**3g**	56	80
8		**3h**	42	81
9		**3i**	39	70
10		**3j**	Undo	59[c]

[a] 0.05 equiv $Pd(PPh_3)_4$, 2 equiv K_2CO_3, toluene, 100 °C, 40 h.
[b] 0.05 equiv $Pd(PPh_3)_4$, 2 equiv K_2CO_3, toluene, microwave irradiation, 150 °C, 15 min.
[c] 0.05 equiv $Pd(PPh_3)_4$, 2 equiv K_2CO_3, 1,2-dimethoxyethane, microwave irradiation, 100 °C, 15 min.

acids to obtain **3** via a Suzuki reaction under conventional heating conditions were not satisfactory, since they gave only low to moderate yields and required long reaction times (Table 1).

Attempts to optimize the Suzuki coupling reaction by using several catalysts ($Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $PdCl_2$ or Pd/C) in the presence of various bases (K_2CO_3, Na_2CO_3, Cs_2CO_3, Et_3N) and solvents (toluene, 1,2-dimethoxyethane, CH_3CN) at different temperatures were not satisfactory (data not shown). The best yields obtained with a series of Suzuki reagents under conventional heating conditions amounted to around 50%: most of the reactions were not complete and gave yields of only around 10–30% (Table 2), with the starting material being recovered in yields ranging from 20% to 50% (data not shown).[8] One reason for the low yields might be that the ring carbon in **2** was highly electron-deficient, and therefore the bromotriazole did not lend itself to Suzuki coupling. Another reason might be that triazole ring formed a complex with Pd, resulting in low yield and uncompleted reaction.

Microwave irradiation has become an increasingly popular method in recent years for improving reaction yields and shortening reaction times.[9] It has been reported that microwave irradiation can significantly promote Suzuki reaction[10] We therefore performed the Suzuki reaction under microwave irradiation with a view to obtain **3** in good yields.

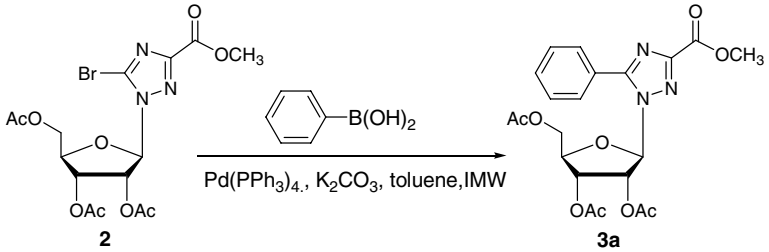
We first studied the microwave-promoted Suzuki coupling of phenylboronic acid with **2** to optimize the reaction conditions. The results of the optimization procedure are given in Table 2. The temperature is known to be a highly important factor in microwave-promoted reactions. Upon performing the reaction in a sealed tube, we observed that optimum yields were obtained at 150 °C. The reaction time was also finely tuned to 15 min in order to achieve maximum yields, since this enabled the complete reaction to occur, while preventing the decomposition of the products. It has been reported that polar solvents advantageously promote microwave assisted reactions, and 1,2-dimethoxyethane is frequently used to promote microwave assisted reactions. However, we did not obtain better results in 1,2-dimethoxyethane than in toluene, possibly because the reaction is strongly temperature-dependent and we cannot reach high temperatures with 1,2-dimethoxyethane due to its low boiling point.

Under the optimized conditions, the microwave assisted Suzuki reaction gave product **3** with good to excellent yields (Table 1) except for **3j**. The reason for the low yield of **3j** might be that the 2-furanylboronic acid was not stable and underwent rapid degradation in our experimental conditions. We therefore decreased the reaction temperature as well as using 1,2-dimethoxyethane as the solvent, which resulted in better yields (Table 1, entry 10). It is worth noting that starting material **2** was almost completely consumed in the reaction under microwave irradiation, which greatly simplified the product separation and purification steps.[8] In addition, the reactions were not significantly affected by the presence of the electron-donating or electron-withdrawing groups on the Suzuki reagent (Table 1, entries 1–7). Neither were any noteworthy steric effects observed (Table 1, entries 7–9). The microwave assisted Suzuki reaction method therefore turned out to provide an efficient shortcut for synthesizing **3**, probably due to the destabilization of the Pd–triazole complex through microwave irradiation.

Further treatment of **3** in NH_3/MeOH at room temperature resulted in deprotection of the sugar moiety and amination of the carboxylester group, yielding the corresponding 5-aryltriazole ribonucleosides **1** with good to excellent yields (Table 3).

We further obtained crystals of **1a** and determined its X-ray structure (Fig. 1).[11] The sugar moiety in **1a** exhibits its N-type conformation (C2′-*exo*-C3′-*endo*), similar as

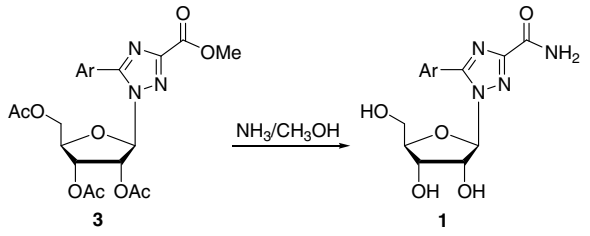
Table 2. Optimization of Suzuki coupling reaction under microwave irradiation



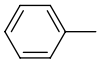
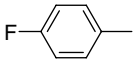
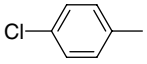
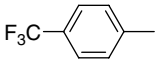
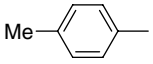
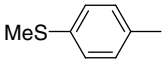
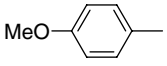
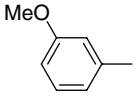
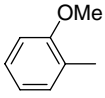
Entry	*T* (°C)	*t* (min)	Yield (%)
1	100	10	42
2	120	10	53
3	150	10	82
4	150	15	91
5	150	25	78
6[a]	120	15	46

[a] 1,2-Dimethoxyethane as solvent.

Table 3. Synthesis of **1** from **3**



3 **1**

Entry	Ar		Yields (%) of **1**
1		**1a**	86
2		**1b**	88
3		**1c**	91
4		**1d**	89
5		**1e**	93
6		**1f**	83
7		**1g**	89
8		**1h**	93
9		**1i**	81
10		**1j**	95

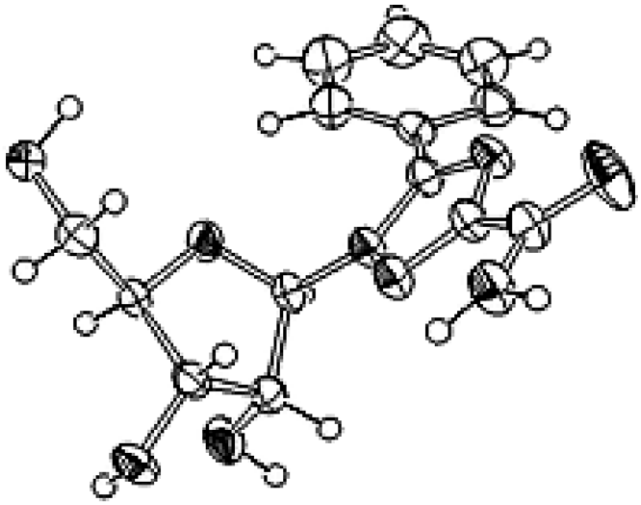


Figure 1. Crystal structure of **1a**.

in ribavirin.[12] However, the mutual orientation of ribose sugar and the triazole base in **1a** ($\chi = -86.1°$) was found to be far away from the usual *anti* conformation of natural nucleosides. This is because the aromatic substitution at position 5 in **1a** increases the steric bulk of the heterocyclic aglycon, which does not favor the usual *anti* conformation in order to prevent the occurrence of steric hindrance. The phenyl ring in **1a** is rotated out of the plane defined by the triazole ring ($\phi = 41.2°$) in order to release the steric hindrance occurring in the biaryl due to the two hydrogen atoms located in the *ortho*-positions on the phenyl ring.

In conclusion, triazole nucleosides with various aromatic groups in the 5-position on the triazole ring were synthesized and characterized. The aromatic group was introduced into the triazole ring via a Suzuki reaction using bromotriazole nucleoside **2** as the starting material. Under conventional heating conditions, the Suzuki reaction gave only moderate to low yields, whereas under microwave irradiation conditions, the Suzuki reaction was significantly improved, giving clean products with good to excellent yields within a much shorter reaction time. Further X-ray structural analysis of **1a** showed that ribose moiety is in the N-type conformation as in ribavirin, while the aryltriazole nucleoside is not in the usual *anti* conformation due to the steric hindrance. Studies on the biological and physico-chemical properties of these compounds are under way in our laboratories.

Acknowledgements

We are grateful to Dr. Michel Giorgi at the University of Aix-Marseilles III for performing X-ray structural analysis on the compound **1a**. Financial support from the Ministry of Science and Technology of China (No. 2003CB114400), Wuhan University and CNRS is gratefully acknowledged. W.J.Q. and Z.R.Z. contributed equally to this work.

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.2006.07.103.

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Votruba, I.; Dvořáková, H. *Collect. Czech. Chem. Commun.* **2001**, *66*, 483–499; (d) Hocek, M.; Nauš, P.; Pohl, R.; Votruba, I.; Furman, P. A.; Tharnish, P. M.; Otto, M. J. *J. Med. Chem.* **2005**, *48*, 5869–5873.
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8. It is very difficult to purify the products **3** when the starting material is not completely consumed because both **2** and **3** migrated very closely in TLC.
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11. Crystallographic data **1a**: colorless, orthorhombic space group $P2_12_12_1$, $Z = 4$, $a = 7.8520$ (2), $b = 12.1370$ (5), $c = 17.1450$ (8) Å, $\alpha = 90.00$, $\beta = 90.00$, $\gamma = 90.00$, $V = 1633.91$ (11) Å^3, R $(F^2 > 2\sigma F^2) = 0.0404$, and $wR = 0.1217$. The X-ray structure data has been deposited in the Cambridge Crystallographic Data Center with deposition No. CCDC 251213. Copy of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (e-mail: deposit@ccdc.cam.ac.uk).
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