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Microwave-Assisted Synthesis of 2′-*O*-Aryluridine Derivatives

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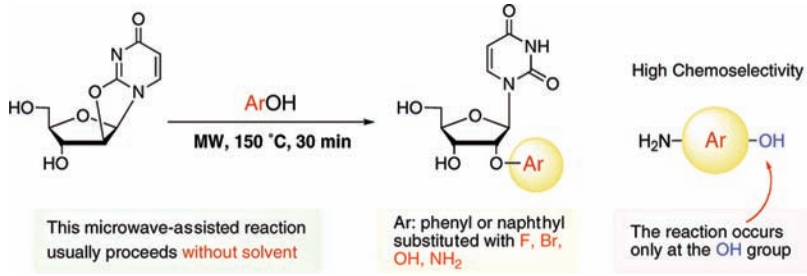
ABSTRACT



A new method for the synthesis of 2′-*O*-aryluridines was developed via the microwave-mediated reaction of 2,2′-anhydrouridine with aromatic alcohols. Aminophenol and aminonaphthol derivatives underwent selective 2′-O-arylation with 2,2′-anhydrouridine to produce 2′-*O*-(aminoaryl)uridine derivatives. These reactions proved to proceed without the need for any bases or solvents, but better results were obtained by use of *N*,*N*-dimethylacetamide (DMA) as the solvent in some cases.

In connection with recent developments in gene therapies based on antisense and RNAi strategies, a large number of 2′-O-modified RNA oligomers have been synthesized as promising nucleotide drugs.[1−5] However, most of these modified RNA oligomers are 2′-O-alkylated species. To the best of the authors' knowledge, only two examples have been reported as 2′-O-arylated RNA modifiers in the antisense and RNAi strategies.[6,7] One is the simplest derivative (i.e., oligodeoxynucleotides), incorporating 2′-*O*-phenyluridine, reported by Altmann in his review.[6] However, no details of the synthesis of the key starting material of 2′-*O*-phenyluridine were given in this review. The other example comprises oligoribonucleotides incorporating 2′-*O*-(2,4-dinitrophenyl)-

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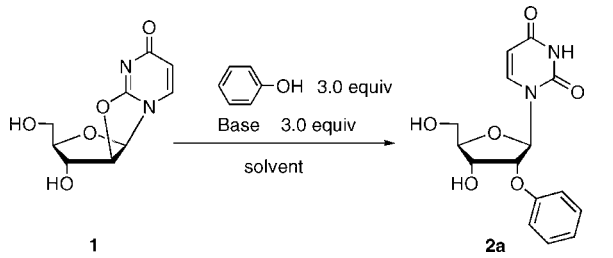
ribonucleosides, reported by Wang.[7] According to Wang's paper, these modified oligomers are directly obtained via the reaction of oligoribonucleotides with 2,4-dinitrophenyl fluoride. At the level of nucleosides, the synthesis of 2′-*O*-(2,4,6-trinitrophenyl)uridine via the reaction of uridine with 2,4,6-trinitrophenyl sulfonate was reported, but this compound was obtained as a Meisenheimer complex having a 2′,3′-cyclic spiro ring.[8] Thus far, little has been reported about the general and regioselective synthesis of 2′-*O*-arylribonucleosides.

To expand the limited use of 2′-O-alkylated ribonucleosides as components of modified RNA oligomers, it is desirable to find practical methods for the synthesis of 2′-*O*-arylribonucleosides as new RNA backbone structures. In addition, it is expected that two neighboring aryl groups could interact with each other when introduced into 2′-O-arylated oligoribonucleotides to stabilize RNA duplexes. Oligoribonucleotides incorporating 2′-*O*-arylribonucleosides would be of great interest as new siRNA molecules.

In this paper, we report a generally useful method for the synthesis of 2′-*O*-aryluridine derivatives using microwave-mediated ring-opening reactions of 2,2′-anhydrouridine with aryl alcohols.

Since no information concerning the synthesis of 2′-*O*-phenyluridine as the simplest 2′-*O*-aryluridine derivative is available, we decided to establish a practical method to synthesize this material. Since 2′-(*S*)-aryluridine derivatives were synthesized via the ring-opening reaction of 2,2′-anhydrouridine (**1**) with arylthiolates,[9] a similar reaction of **1** with 3 equiv of phenol was carried out in the presence of 3 equiv of triethylamine in *N*,*N*-dimethylacetamide (DMA) at 120 °C for 24 h. As a result, this reaction gave 2′-*O*-phenyluridine (**2a**) in 65% yield (Scheme 1). In order to shorten the reaction time, this

Scheme 1. Synthesis of 2′-*O*-Phenyluridine (**2a**)



reaction was applied to a microwave-mediated reaction. This microwave-assisted reaction of **1** with 3 equiv of phenol in DMA at 150 °C gave the desired product **2a** in 65% yield only after 30 min. The use of other bases such as Hünig's base or pyridine produced similar results. The reaction of **1** with 3 equiv of sodium phenoxide in DMA also gave the product **2a** in 60% yield using this microwave system (140 °C, 30 min). However, more interestingly, it was found that this reaction did not require any base or solvent. In conclusion, the neat reaction of **1** with 5 equiv of phenol gave the product **2a** in the highest yield of 82%, as shown in Table 1.

As far as the solvent is concerned, the use of DMA as the solvent gave better results when phenol derivatives have high melting temperatures (entries 8 and 9) or low ignition points (entry 7) and also tend to be easily air-oxidized (entries 16 and 17).

In the present microwave-assisted method, 1-naphthol and 2-naphthol underwent similar reactions with compound **1** to give the desired products **2b** and **2c** (entries 2 and 3 of Table 1). The use of halogenated phenols, such as 4-fluorophenol, 2-fluorophenol, 4-bromophenol, 2-bromophenol, and 2-bromonaphthol, gave the corresponding 2′-O-modified products **3a**, **3b**, **4a**, **4b**, and **4c** in 26−77% yields (entries 4−8). These products might be used for Buchwald−Hartwig reactions for further modification of the aromatic rings with various functional groups. However, the reaction of compound **1** with 1-bromo-2-naphthol failed. This result might be due to the steric hindrance of this phenol. In the case of 4-iodophenol and 2-iodophenol, the reactions gave complex mixtures, suggesting that the once-formed products **5a** and **5b** decomposed.

The reaction of compound **1** with 2-nitrophenol (pK_a 7.15) gave a 3:5 mixture of the product **6b** and its 3′-O-arylated regioisomer **6b′** in 23% yield. It is likely that the latter product was obtained by isomerization of the once-formed initial product **6a** under the MW conditions via an intermediate like a well-known Meisenheimer spiro complex.[10] On the other hand, the desired product **6a** could not be obtained by the reaction of compound **1** with more acidic 4-nitrophenol (pK_a 7.08). In contrast to these results, phenol derivatives substituted with a methoxy group as an elecron-donating group gave the 2′-*O*-aryluridine derivatives **7a** and **7b** in good yields (entries 14 and 15 of Table 1).

Bifunctional compounds containing two hydroxyl groups (i.e., 1,4-benzenediol and 1,5-naphthalenediol) gave the monosubstituted products **8a** and **8b** (entries 16 and 17). The remaining phenolic hydroxyl groups of these compounds could be used as reaction sites for further introduction of valuable functional groups into the uridine moiety.

When 4-aminophenol was used as a phenol derivative, the chemoselective reaction occurred exclusively to give the sole product **9a** without formation of the 2′-*N*-(4-hydroxyphenyl)-substituted product **10**, as shown in Scheme 2. Highly chemoselective reactions were also observed in the other aminophenol and aminonaphthol derivatives, which gave the products **9b**−**9f**, as shown in Table 2 (entries 2−6). When 1,5-naphthalenediamine was used as a nucleophile, no reaction was observed. On the basis of the above results, it was concluded that compound **1** showed no reactivity toward aromatic amines in the present microwave-assisted reaction. It is noteworthy that the amino group on the aromatic ring of products **9a**−**f** would also be better reaction sites for further modifications.

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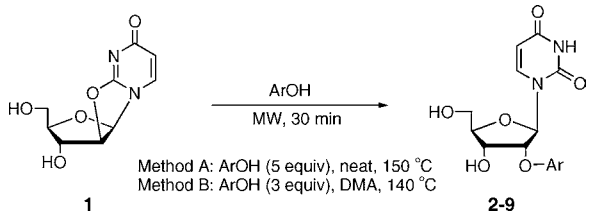
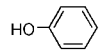
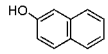
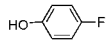
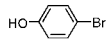
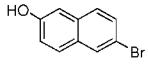
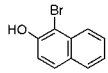
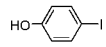
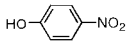
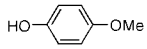
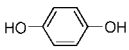
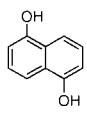
Table 1. Microwave-Assisted Synthesis of 2′-*O*-Aryluridines



entry	ArOH	conditions	product	yield (%)
1		Method A	**2a**	82
2		Method A	**2b**	68
3		Method A	**2c**	82
4		Method A	**3a**	75
5		Method A	**3b**	77
6		Method A	**4a**	50
7		Method B	**4b**	26
8		Method B	**4c**	64
9		Method B	**4d**	0
10		Method A	**5a**	0
11		Method A	**5b**	0
12		Method A	**6a**	0
13		Method A	**6b**+**6b′**[a]	23
14		Method A	**7a**	62
15		Method A	**7b**	75
16		Method B	**8a**	30
17		Method B	**8b**	66

[a] Compound **6b′** is 3′-*O*-(2-nitrophenyl)uridine.

To understand the inherent properties of this microwave-mediated reaction, several experiments were performed. When the reaction of **1** with 3 equiv of phenol using microwaves at 140 °C was carried out in the presence of amines, such as triethylamine and diisopropylethylamine, compound **2a** could not be formed. This is in sharp contrast to the results obtained via the reactions without the use of microwaves, as described earlier. The addition of BF_3 etherate to the original system gave no ring-opening product at all. The best results obtained in all cases were via the reactions with simple phenol derivatives without using any solvent, base, or catalyst. On the other hand, the reactions of **1** with aliphatic alcohols, such as propanol, allyl alcohol, and benzyl alcohol, failed. All attempts to use acetic acid, *p*-toluenesulfonic acid, or 10-camphorsulfonic acid as an acid catalyst also failed in the reaction of **1** with methanol. These results suggest that this reaction required protonation of the 4-oxygen or 3-nitrogen atom of **1** for activation through the

Scheme 2. Chemoselective Reaction of **1** with 4-Aminophenol

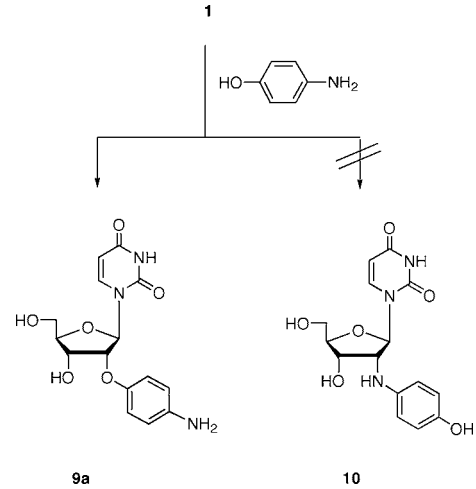
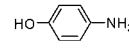
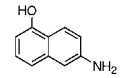
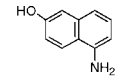
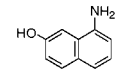
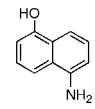


Table 2. 2′-O-Selective Arylation of 2,2′-Anhydrouridine with Aminophenol and Aminonaphthol Derivatives

Entry	Ar	Product	Yield (%)
1		**9a**	37
2		**9b**	70
3		**9c**	69
4		**9d**	62
5		**9e**	55
6		**9f**	56

use of more acidic phenols as reactants and the generation of phenoxide ions with sufficient nucleophilicity.

In particular, we showed that a variety of aromatic substituents could be introduced into the 2′-hydroxyl group of uridine. Therefore, there is increasing potential for these new 2′-O-arylated uridine derivatives as modification sites of RNA. 2′-*O*-Aryl-modified uridine derivatives containing halogenated aryl groups such as compounds **4a**−**d** could be used for the introduction of various functional groups by combination with the well-known Buchwald−Hartwig reaction,[11] which would enable the postmodification of RNA. The amino group on the aromatic rings of compounds **9a**−**9f** would also be useful for the introduction of fluorescent molecules using the amino group. Therefore, 2′-*O*-aryluridine derivatives are promising key intermediates for a wide variety of modifications. In our preliminary experiments, the introduction of several 2′-*O*-naphthyluridine moieties into oligoribonucleotides led to marked recovery of the hybridization ability of the mother RNA molecules, as long as the modified nucleosides were arranged in a consecutive manner. Particularly, the use of the 2-naphthyl group showed higher hybridization affinity than that of the phenyl and 1-naphthyl groups when 2′-O-methylated RNA oligomers were used as the complementary strands.

In this sense, we are now studying further applications using these new 2′-*O*-aryluridine derivatives. These results will be reported in the near future.

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Supporting Information Available: Material on the ^{1}H and ^{13}C data of all the new products reported here. This material is available free of charge via the Internet at http://pubs.acs.org.

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