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Synthesis of various substituted 5-methyluridines (xm^5U) and 2-thiouridines (xm^5s^2U) via nucleophilic substitution of 5-pivaloyloxymethyluridine/2-thiouridine

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Pivaloyloxyl group

ABSTRACT

5-Pivaloyloxymethyluridine and its 2-thio analogue have been utilized as convenient substrates for the synthesis of various 5-methyluridines (xm^5U) and 5-methyl-2-thiouridines (xm^5s^2U). The pivaloyloxy group (OPiv) located at the pseudobenzylic position was effectively substituted with a series of nucleophiles: ammonia, primary and secondary amines including secondary cyclic amines, tetrabutylammonium salts of amino acids, an alkoxide and a thiolate.

5-Methyluridines (xm^5U) and their 2-thio analogues (xm^5s^2U) are a biologically important class of modified nucleosides.[1] In particular, 5-aminomethyluridine/2-thiouridine derivatives, for example, 5-methylaminomethyl- (mnm^5U and mnm^5s^2U), 5-carboxymethylaminomethyl- ($cmnm^5U$ and $cmnm^5s^2U$) and 5-taurinomethyl-modified uridines (τm^5U and τm^5s^2U), are present at the first position of the anticodon (the wobble position) in several cytosolic and/or mitochondrial tRNAs that are responsible for precise recognition of the purine-ending codons.[2,3] In some cases, the lack of xm^5s^2U wobble units totally inhibits the protein biosynthesis.[4,5] For example, the absence of $\tau m^5s^2U_{34}$ in the sequence of human mitochondrial (mt) $tRNA^{Lys}$ gives a defect of UUA and UUG-rich genes translation that results in mitochondrial encephalomyopathic disease MERRF.[4] In DNA sequences, the presence of xm^5-modified 2′-deoxyuridines (xm^5dU) is limited to 5-hydroxymethyldU that is a well-characterized product of thymine oxidation and was recently shown to be an epigenetic base in mouse embryonic stem cells DNA.[6]

Site-specific incorporation of the native 5-methyluridines/2-thiouridines into oligoribonucleotide sequences offers a reliable tool for model studies on the structural requirements of tRNA interactions with partners in complex bioprocesses.[3,7] Efficient and simple approaches to the synthesis of 5-methyluridine and 2-thiouridine derivatives are an important element of those studies. Moreover, native 5-methyluridines xm^5U/xm^5s^2U are frequently used as authentic standards to identify individual ribonucleosides in RNA hydrolyzates using liquid chromatography–mass spectrometry analysis.[8] Some of them are important synthons for the preparation of more complex nucleosides, for example, mnm^5s^2U or $cmnm^5s^2U$ can be considered as substrates for the synthesis of recently discovered 5-substituted *S*-geranylated 2-thiouridines.[9]

Unnatural C5-modified pyrimidine nucleosides have been screened for antiviral and antibacterial activities.[10] Various 5-amine or 5-thiol containing pyrimidine nucleosides have found application as useful units for duplex structure stabilization as well as for the introduction of additional RNA functionality such as aptamers, biosensors or catalysts.[11] The protected forms of 5-hydroxymethyldU were applied in the transient chemical protection of DNA against cleavage by restriction endonucleases.[12]

The most frequently used method for the synthesis of the title compounds involves nucleophilic substitution of 5-chloromethyl-2′,3′-*O*-isopropylideneuridine/2-thiouridine (**1a**/**1b**, Fig. 1).[13–17] The reactions of **1a**/**1b** with nucleophiles proceed under mild anhydrous conditions affording xm^5U/xm^5s^2U products (x = –CN, $–N_3$, $–NHCH_3$, $–NHCH_2COOH(R)$, $–NHCH_2CH_2SO_3H(R)$) in moderate yields.[13–17] However, a significant decrease in yield has been observed in the synthesis of 2-thiouridine analogues.[14–16] Additionally, the susceptibility of the chloromethyl group of **1a**/**1b** to hydrolysis renders some nucleophilic substitution

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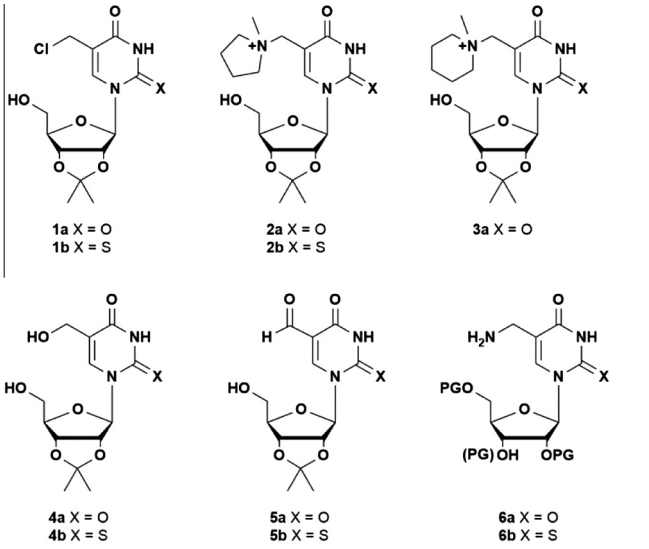


Figure 1. Substrates utilized for the synthesis of 5-methyluridines xm^{5}U and 2-thiouridines xm^{5}s^{2}U reported in the literature.

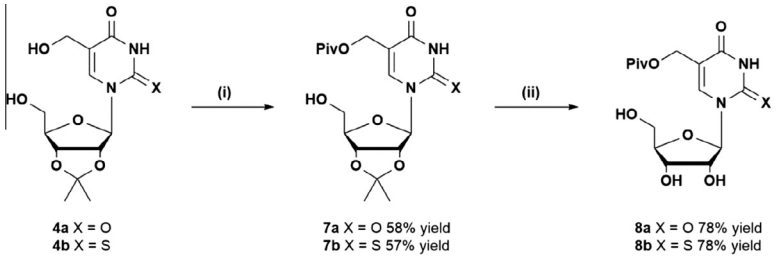
reactions unsuccessful, for example, amination of **1a**/**1b** with aqueous NH_3.[17] Alternative methods involve using *N*-methyl quaternary ammonium salts **2a**/**2b**, **3a** (Fig. 1),[17–19] 5-hydroxymethyluridine/2-thiouridine **4a**/**4b**,[20] 5-formyluridine/2-thiouridine **5a**/**5b**[15] or 5-aminomethyluridine/2-thiouridine **6a**/**6b**[21] derivatives as substrates. The reactions involving compounds **2a**/**2b**–**6a**/**6b** proceed with moderate to low yields and have been demonstrated only on a single target molecule. Notably, the treatment of 2-thiouridines **2b** or **4b** with a nucleophile resulted in partial desulfurization ($s^2 \rightarrow o^2$).[16,20]

In this work, we present an effective and convenient approach to the synthesis of various 5-methyluridines (xm^{5}U) and 2-thiouridines (xm^{5}s^{2}U) utilizing the reaction of 5-pivaloyloxymethyluridine **8a** and its 2-thio analogue **8b** and a set of different nucleophiles: ammonia, primary and secondary amines, amino acid salts, an alkoxide and a thiolate. Previous studies reported partial nucleophilic substitution of 5-acetoxymethyl-2′-deoxyuridine/cytidine-modified DNAs with ammonia that involved a substitution of the acetoxy group (OAc) located at the pseudobenzylic position.[22] However, ammonolysis of the acetate ester was predominant and regeneration of the parent pseudobenzyl alcohol was observed.[22] Contrary to other ester based alcohol protecting groups, pivalate shows relative stability in the presence of base; thus we assumed that its ammonolysis would be significantly reduced or even eliminated under basic conditions. Additionally, the formation of a pivalate ester at the pseudobenzylic position could effectively promote an S_N reaction, with nucleophilic attack occurring at the pseudobenzylic carbon with OPiv acting as a leaving group.

To prepare 5-pivaloyloxymethyluridine (**8a**) and its 2-thio analogue **8b**, 5-hydroxymethyl-2′,3′-*O*-isopropylideneuridine/2-thiouridine[23] (**4a**/**4b**) was converted into **8a**/**8b** by selective pivaloylation of the 5-hydroxymethyl group followed by removal of the 2′,3′-isopropylidene protecting group (Scheme 1). Different reactivities of the 5′-hydroxyl and 5-hydroxymethyl groups under acidic conditions were previously reported by Sowers and Beardsley for selective acetylation of 5-hydroxymethyl-2′-deoxyuridine.[24] Using a similar procedure, compound **4a** was treated with pivalic acid (PivOH) in the presence of trifluoroacetic acid at 120 °C for 10 h. Although the desired regioisomer **7a** was formed, the following isolation and purification proved difficult for separation of the pure product from the pivalic acid side-products. Multiple attempts to purify **7a** resulted in a significant decrease in yield (<30%). A more effective method of 5-hydroxymethyl acylation involved a strategy previously reported for the regioselective pivaloylation of carbohydrates.[25] Compounds **4a**/**4b** were treated with 1.1 equiv of pivaloyl chloride (PivCl) in pyridine (Scheme 1) under mild conditions (0 °C, 7 h). Although the low temperature significantly increased the selectivity of pivaloylation, a mixture of unreacted substrate **4a**/**4b**, 5-pivalate-**7a**/**7b** and 5,5′-bispivalate esters in a 1:2:1 ratio was obtained. To achieve the complete conversion of substrates **4a**/**4b**, an additional 0.9 equiv of PivCl was added and the reaction continued for 10 h. Mono 5-pivalate component **7a**/**7b** was separated by column chromatography and treated with 50% aq acetic acid for effective removal of the 2′,3′-acetonide. After purification, 5-pivaloyloxymethyluridine (**8a**, Pivom^{5}U) and its 2-thio analogue (**8b**, Pivom^{5}s^{2}U) were obtained in ca. 50% total yield in each case.

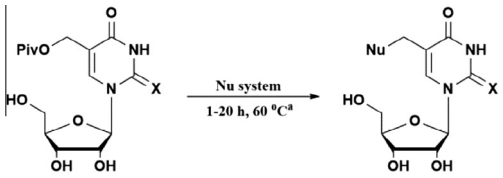
Nucleosides **8a**/**8b** were then reacted with a wide range of structurally diverse nucleophilic reagents: ammonia, primary and secondary amines including cyclic amines (piperidine, morpholine), tetrabutylammonium salts of amino acids (glycine and taurine), an alkoxide and a thiolate (ESI, pg. S6–S14). The reaction conditions were optimized in terms of solvent (EtOH/MeOH, water, DMF and neat conditions), reaction time and the excess of nucleophilic reagent (Table 1). The products of nucleophilic substitution **9a**–**17a**/**9b**–**17b** were purified by preparative RP HPLC and their structures unambiguously confirmed by ^{1}H and ^{13}C NMR as well as mass spectrometry (ESI, pg. S32–S49).

In general, these reactions were carried out at elevated temperature (50–60 °C) except for the nucleophilic substitution with methylamine (entry 4) which proceeded at room temperature. Esters **8a**/**8b** rapidly reacted with ammonia and methylamine (1–4 h) under anhydrous conditions using 8 M NH_3/EtOH (entry 1) and 8 M $MeNH_2$/EtOH (entries 3 and 4) to give products **9a**/**9b** and **10a**/**10b**, respectively, in good yields of 86–90%. Interestingly, changing from anhydrous conditions to an aqueous solution of ammonia or methylamine (entries 2 and 5) resulted in only a slight decrease in yield which was attributed to aminolysis of the pivalate ester and regeneration of 5-hydroxymethyluridine/2-thiouridine (hm^{5}U/hm^{5}s^{2}U). On the other hand, effective nucleophilic



Scheme 1. Synthetic route to 5-pivaloyloxymethyluridine/2-thiouridine (**8a**/**8b**). Reagents and conditions: (i) PivCl (1.1 → 2 equiv), py, 17 h, 0 °C; (ii) 50% aq AcOH, 1.5 h, 85 °C.

Table 1
Nucleophilic substitution of 5-pivaloyloxymethyluridine (**8a**) and 5-pivaloyloxymethyl-2-thiouridine (**8b**)

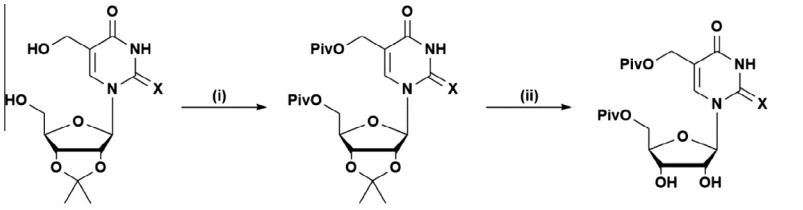


8a X = O
8b X = S

9a - 17a X = O
9b - 17b X = S

Entry	–Nu	Nu system	Time (h)	Product	Yield[b] (%)	Product	Yield[b] (%)
1	$-NH_2$	8 M NH_3/EtOH	4	**9a**	87	**9b**	86
2	$-NH_2$	30% aq NH_3	2	**9a**	80	**9b**	80
3	–NHMe	8 M $MeNH_2$/EtOH	1	**10a**	90	**10b**	90
4	–NHMe	8 M $MeNH_2$/EtOH	2	**10a**	89	**10b**	87
5	–NHMe	40% aq $MeNH_2$	1	**10a**	85	**10b**	84
6	$-NEt_2$	Et_2NH/H_2O 4/1 v/v	20	**11a**	70	**11b**	70
7	$-NC_4H_8O$	Morpholine/H_2O 4/1 v/v	20	**12a**	84	**12b**	80
8	$-NC_5H_{10}$	Piperidine/EtOH 1/1 v/v	20	**13a**	85	**13b**	80
9	$-NC_5H_{10}$	Piperidine/H_2O 4/1 v/v	20	**13a**	80	**13b**	75
10	$-NHCH_2COOH$	0.8 M $NH_2CH_2COO^-NBu_4^+$/EtOH	20	**14a**	77	**14b**	75
11	$-NH(CH_2)_2SO_3H$	0.8 M $NH_2(CH_2)_2SO_3^-NBu_4^+$/EtOH	20	**15a**	75	**15b**	75
12	–OMe	0.1 M K_2CO_3/MeOH	1	**16a**	72	**16b**	70
13	–SEt	0.5 M EtSNa/EtOH	1	**17a**	70	**17b**	70

[a] rt for synthesis of **10a**, **10b** (entry 4), 50 °C for synthesis of **11a**, **11b** (entry 6).
[b] Isolated yields.



4a X = O
4b X = S

18a X = O
18b X = S

19a X = O 70% yield (2 steps)
19b X = S 70% yield (2 steps)

Scheme 2. Synthetic route to 5′-*O*-pivaloyl-5-pivaloyloxymethyluridine/2-thiouridine (**19a**/**19b**). Reagents and conditions: (i) PivCl (3 equiv), py, 2 h, rt; (ii) 50% aq AcOH, 2 h, 85 °C.

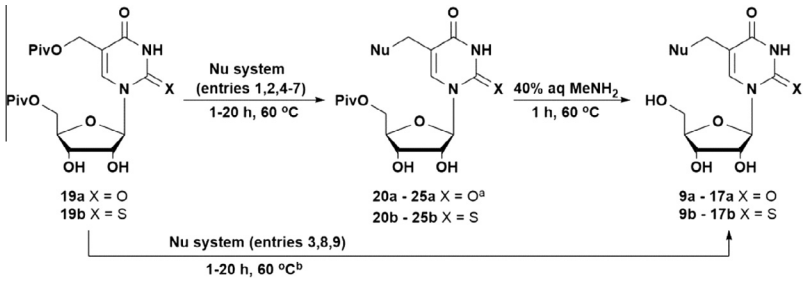
substitution of **8a**/**8b** with a secondary aliphatic amine and morpholine (entries 6 and 7) required aqueous conditions for complete substrate conversion. For piperidine, both anhydrous and aqueous solutions provided products **13a**/**13b** in good yield (entries 8 and 9). Contrary to ammonia and methylamine, the reactions of **8a**/**8b** with secondary amines required prolonged reaction times. Due to the use of aqueous conditions, the formation of minor amounts of hm^5U/hm^5s^2U (1–5%) was also observed. Attempts to substitute the 5-OPiv group of **8a**/**8b** with amino acids were performed with glycine and taurine which are the fragments of native, wobble 5-substituted uridines and 2-thiouridines. Prior to the reaction, both amino acids were converted into their corresponding tetrabutylammonium salts, providing good solubility in EtOH as well as enhanced nucleophilicity compared to their zwitterionic forms. The reactions of **8a**/**8b** with 0.8 M solutions of the tetrabutylammonium salts of glycine or taurine in anhydrous EtOH (entries 10 and 11) proceeded at 60 °C for 20 h to give 5-carboxymethylaminomethyluridine/2-thiouridine **14a**/**14b** and 5-taurinomethyluridine/2-thiouridine **15a**/**15b**, all in ca. 75% yields.

In addition to nitrogen nucleophiles, alkoxide and thiolate nucleophilic reagents were utilized for 5-OPiv substitution. The reactions of **8a**/**8b** with 0.1 M K_2CO_3/MeOH (entry 12) and 0.5 M EtSNa/EtOH (entry 13) proceeded rapidly under anhydrous conditions yielding 5-methoxymethyluridine/2-thiouridine (**16a**/**16b**) and 5-ethylthiomethyluridine/2-thiouridine (**17a**/**17b**), respectively, along with small amounts of hm^5U/hm^5s^2U (<5%). For the preparation of **16a**/**16b**, 10% DBU/MeOH and 0.5 M MeONa/MeOH were also tested, however methanolysis of the pivalate ester was predominant.

To investigate the potential of the new method, we carried out the nucleophilic substitution of the 5-OPiv group in a moiety containing an additional pivalate ester at the aliphatic 5′-hydroxyl position. The conditions previously screened for 5-OPiv substitution (Table 1) were used to investigate the reactivity of the 5′-pivaloyl group. For the synthesis of bispivalate esters **19a**/**19b** 5-hydroxymethyl-2′,3′-*O*-isopropylideneuridine/2-thiouridine (**4a**/**4b**) were reacted with 3 equiv of PivCl (rt, 2 h) and the cis diol functional group was selectively deprotected by treatment with 50% aq acetic acid to give **19a**/**19b** in 70% overall yield (Scheme 2) (ESI).

Compounds **19a**/**19b** were reacted with the same series of nucleophiles (Table 2). In general, the 5′-*O*-pivaloyl group proved to be stable under the employed conditions, affording compounds **20a**–**25a**/**20b**–**25b**. Exceptions included Et_2NH/H_2O (4/1 v/v), 0.1 M K_2CO_3/MeOH and 0.5 M EtSNa/EtOH solutions (entries 3, 8 and 9), in which nucleophilic substitution at the pseudobenzylic carbon was accompanied by deprotection of the 5′-hydroxyl functional group of the sugar moiety. Products **11a**/**11b**, **16a**/**16b** and **17a**/**17b** were afforded in 60–70% yields. In these cases, detectable

Table 2
Nucleophilic substitution of 5′-*O*-pivaloyl-5-pivaloyloxymethyluridine (**19a**) and 5′-*O*-pivaloyl-5-pivaloyloxymethyl-2-thiouridine (**19b**)



Entry	–Nu	Nu system	Time (h)	Product	Yield[c] (%)	Product	Yield[c] (%)
1	$-NH_2$	8 M NH_3/EtOH	4	**9a**	80[d]	**9b**	77[d]
2	–NHMe	8 M $MeNH_2$/EtOH	1	**10a**	90[d]	**10b**	88[d]
3	$-NEt_2$	Et_2NH/H_2O 4/1 v/v	20	**11a**	67	**11b**	65
4	$-NC_4H_8O$	Morpholine/H_2O 4/1 v/v	20	**12a**	85[d]	**12b**	80[d]
5	$-NC_5H_{10}$	Piperidine/EtOH 1/1 v/v	20	**13a**	70[d]	**13b**	70[d]
6	$-NHCH_2COOH$	0.8 M $NH_2CH_2COO^-NBu_4^+$/EtOH	20	**14a**	75[d]	**14b**	72[d]
7	$-NH(CH_2)_2SO_3H$	0.8 M $NH_2(CH_2)_2SO_3^-NBu_4^+$/EtOH	20	**15a**	85[d]	**15b**	75[d]
8	–OMe	0.1 M K_2CO_3/MeOH	1	**16a**	70	**16b**	60
9	–SEt	0.5 M EtSNa/EtOH	1	**17a**	70	**17b**	70

[a] The numbering of the intermediate compounds has been assigned as follows: **20a**/**20b** ($-NH_2$), **21a**/**21b** (–NHMe), **22a**/**22b** ($-NC_4H_8O$), **23a**/**23b** ($-NC_5H_{10}$), **24a**/**24b** ($-NHCH_2COOH$), **25a**/**25b** ($-NHCH_2CH_2SO_3H$).
[b] 50 °C for the synthesis of **11a**, **11b** (entry 3).
[c] Isolated yields.
[d] Yield over 2 steps.

amounts of hm^5U/ hm^5s^2U (<5%) were also formed. The crude compounds **20a**–**25a**/**20b**–**25b** were then deprotected using 40% aq $MeNH_2$ (60 °C, 1 h) to give the products of 5′-pivalate ester aminolysis. Compounds **9a**–**17a**/**9b**–**17b** were isolated and purified by preparative RP HPLC with overall yields of 60–90% (ESI). The yields obtained were comparable with those for substitution of $Pivom^5U$/ $Pivom^5s^2U$ **8a**/**8b** (Table 1) and both methods can be used interchangeably.

In conclusion, the nucleophilic substitution of 5-pivaloyloxymethyluridine/2-thiouridine (**8a**/**8b**) was found to be a simple and efficient approach for the preparation of various 5-methyluridines and 5-methyl-2-thiouridines (xm^5U and xm^5s^2U), including natural tRNA components (mnm^5U, mnm^5s^2U $cmnm^5U$, $cmnm^5s^2U$, τm^5U, τm^5s^2U). The remarkable stability of **8a**/**8b** under acidic and mild basic conditions indicates the possibility for their transformation into suitable phosphoramidites and incorporation into RNA sequences. $Pivom^5U$/$Pivom^5s^2U$-containing oligoribonucleotides can serve as a valuable tool for the synthesis of variously xm^5U/xm^5s^2U-modified oligomers by post-synthetic nucleophilic substitution of the pivaloyloxy group. The chemical synthesis of RNA oligomers containing $Pivom^5U$/$Pivom^5s^2U$ is currently underway.

Acknowledgments

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Supplementary data

Supplementary data (general information, detailed synthesis and characterization of the reported compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.023.

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