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Study on the synthesis of 6-alkylaminouridines via the nucleophilic aromatic substitution reaction of 6-cyanouridine derivatives

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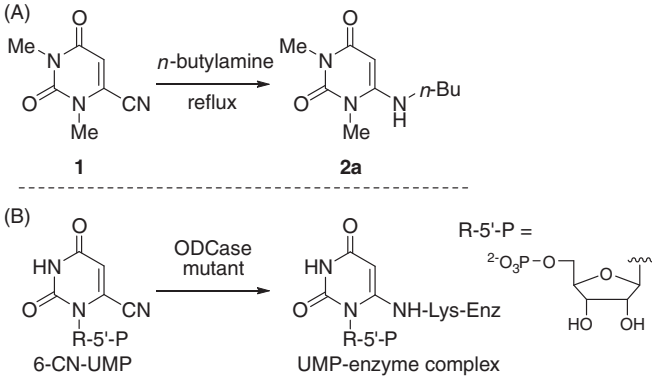
ABSTRACT

6-Cyanouracil derivatives underwent direct substitution reactions with selective primary amines in the presence of *N*,*N*-dimethylaminopyridine as a catalyst to give the corresponding 6-alkylaminouracils. This reaction provides a facile access to versatile 6-alkylaminouridine derivatives.

6-Aminouridine derivatives have received considerable attention because of their interesting chemical and biological properties. They could serve as precursors for the synthesis of uridine-fused bicyclic nucleosides.[1–8] Besides, some of the derivatives have been shown to exhibit a variety of biological activities.[9–13] The most intriguing is their potent inhibitory effects against orotidine 5′-monophosphate decarboxylase (ODCase) which has been correlated with antiparasitic and anticancer activities.[9–11]

A perusal of the literature revealed that there are only few synthetic routes available for the preparation of the 6-aminouridine derivatives.[4,5,8–11,13–16] The most straightforward approach has used the direct substitution of 6-iodouridine derivatives with various amines.[9–11,13,14] However, the synthesis of 6-iodouridines by lithiation–iodination of sugar-protected uridines suffered lower yields and limited scales,[17,18] which has restricted the synthesis of 6-aminouridines.

The reactions of 6-cyanouracil derivatives reported by Senda et al. in 1970s have received our attention. When 6-cyano-1,3-dimethyluracil (6-CN-1,3-DMU, **1**) was reacted with *n*-butylamine, the 6-cyano group was substituted by the incoming nucleophile to give 6-*n*-butylamino-1,3-dimethyluracil (6-*n*-BuNH-1,3-DMU, **2a**) in a good yield (Scheme 1A).[19–21] Furthermore, an enzymatic conversion of 6-cyanouridine 5′-monophosphate (6-CN-UMP) to a covalent Lys–UMP complex was observed by which the cyano group of 6-CN-UMP was replaced by the Lys residue in the active site of an ODCase mutant (Scheme 1B).[22–24] Both the chemical and enzymatic reactions suggested that the unique nucleophilic substitution of 6-cyanouracils could be amenable for the synthesis of the 6-aminouridine derivatives. Meanwhile, understanding the chemical reactions of 6-cyanouracil derivatives could open up an opportunity to gain a mechanistic insight of ODCase.[25] Herein, we report our studies on the synthesis of 6-alkyluridines via the nucleophilic aromatic substitution reaction of 6-cyanouridine derivatives.



Scheme 1.

The reaction with a non-nucleoside model was first investigated in order to establish the reaction condition. 6-CN-1,3-DMU (**1**), prepared from 5-bromouracil by the literature procedures,[19–21] was heated solely with *n*-butylamine as the solvent to give

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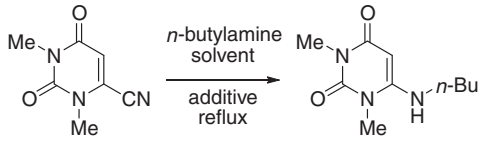
Table 1
Reaction of 6-CN-1,3-DMU (**1**) with *n*-butylamine

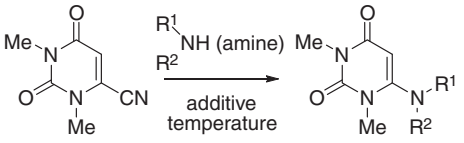


1 **2a**

Entry	Solvent	Additive	Time[a] (h)	Yield[b]
1	—	—	3	84%
2	DMF[c]	—	>12	N.D.[d]
3	Dioxane[c]	—	>12	N.R.[e]
4	CH_3CN[c]	—	18	22%
5	CH_3CN[c]	DMAP (0.1 equiv)	23	68%
6	EtOH[c]	DMAP (0.1 equiv)	24	58%[f]

[a] Until 6-CN-1,3-DMU (**1**) was completely consumed.
[b] Isolated yield.
[c] *n*-$BuNH_2$/solvent = 1:1 (v/v).
[d] N.D. = no desired product.
[e] N.R. = no reaction.
[f] Also obtained 1,3-dimethyl-6-ethoxyuracil (17%).

Table 2
Reaction of 6-CN-1,3-DMU (**1**) with various amines



2b R^1, R^2 = -$(CH_2)_4$-
2c R^1 = H, R^2 = allyl
2d R^1 = H, R^2 = Me

1 **2b-d**

Entry	Amine	Additive (0.1 equiv)	Time[a] (h)	Product (yield)[b]
1	Diethylamine	DMAP	>12	N.R.[c]
2	Pyrrolidine	—	3	**2b** (81%)
3	Piperidine	DMAP	>12	N.R.[c]
4	Morpholine	DMAP	>12	N.R.[c]
5	Isopropylamine	DMAP	>12	N.R.[c]
6	Cyclopentylamine	DMAP	>12	N.D.[d]
7	Cyclohexylamine	DMAP	>12	N.D.[d]
8[e]	Aniline	DMAP	>12	N.R.[c]
9	Allylamine	DMAP	6	**2c** (45%)
10	Methylamine[f]	—	1.5	**2d** (30%)
11	Ammonia[g]	DMAP	>12	N.D.[d,h]

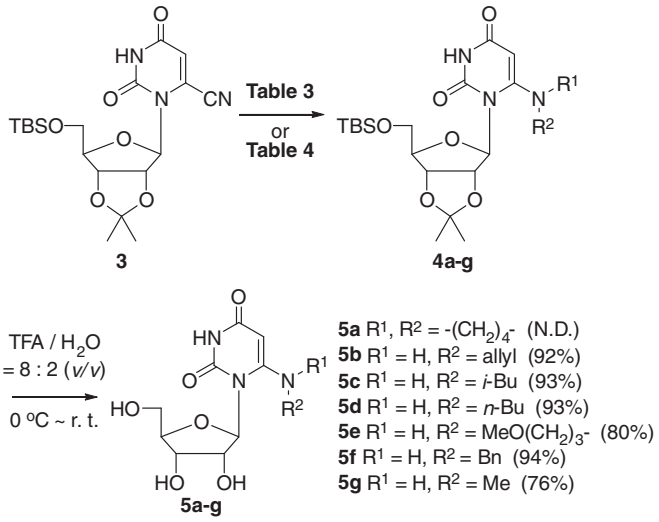
[a] Until 6-CN-1,3-DMU (**1**) was completely consumed.
[b] Isolated yield.
[c] N.R. = no reaction.
[d] N.D. = no desired product.
[e] Reaction temperature = 150 °C.
[f] 40% aqueous solution.
[g] 28% aqueous solution.
[h] Hydrolyzed product, recovered only 1,3-dimethyluracil-6-carboxamide.

6-Bu-NH-1,3-DMU (**2a**) in 84% yield, which is in agreement with Senda's observation.[25] (entry 1 in Table 1) The reaction of 6-CN-1,3-DMU (**1**) with *n*-butylamine in various solvents was also tested. The results showed that the use of solvents decreased the yields. In addition, the substitution reaction could be improved by the addition of a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP). On the basis of the preliminary results, we chose to use the alkylamines as solvents and reactants for subsequent studies.

To explore the scope and generality, the reactions of 6-CN-1,3-DMU (**1**) with a variety of alkylamines were performed and the results were summarized in Table 2. In the reactions with secondary amines (entries 1–4), pyrrolidine was found to give the substitution product (**2b**) in a very good yield but surprisingly none of the other secondary amines could react with 6-CN-1,3-DMU (**1**). Primary amines with branched α-carbons, including aliphatic and aromatic primary amines, were examined and none of them could give the desired products (entries 5–8). Only the treatment of 6-CN-1,3-DMU (**1**) with allylamine or aqueous methylamine gave the desired substituted products (**2c–d**) (Table 2). The survey of the reaction indicated that 6-CN-1,3-DMU (**1**) could only react with pyrrolidine and primary amines with unbranched α-carbons.

Subsequently, the reaction was applied to the 6-cyanouridine derivatives. 5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-cyanouridine (**3**), readily prepared from 5-bromouridine,[26] was heated with a variety of amines as solvents and reactants in the presence of a catalytic amount of DMAP. As expected in accordance with the model reactions, the sugar-protected 6-cyanouridine **3** could react with pyrrolidine (entry 2) and a variety of primary amines with unbranched α-carbons (entries 5–9) to afford the corresponding sugar-protected 6-alkylaminouridines (**4a–f**) in good yields (Scheme 2 and Table 3).

Although the reaction is effective, the major drawback is the use of a large excess of alkylamines as solvents for the reaction.



3 **4a-g** **5a-g**

Scheme 2.

Table 3
Reaction of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-cyanouridine (**3**) with various amines

Entry[a]	Amine	Temperature	Time[b] (h)	Product (yield)[c]
1	Diethylamine	Reflux	>12	N.R.[d]
2	Pyrrolidine	Reflux	6	**4a** (45%)
3	Piperidine	Reflux	>12	N.R.[d]
4	Aniline	120 °C	>12	N.D.[e]
5	Allylamine	Reflux	8	**4b** (53%)
6	Isobutylamine	Reflux	7	**4c** (60%)
7	*n*-Butylamine	Reflux	6	**4d** (53%)
8	3-Methoxypropylamine	Reflux	4	**4e** (56%)
9	Benzylamine	100 °C	6	**4f** (64%)
10	Methylamine[f]	Reflux	>12	N.D.[e]

[a] Additive = DMAP (0.1 equiv).
[b] Until 6-CN-1,3-DMU (**1**) was completely consumed.
[c] Isolated yield.
[d] N.R. = no reaction.
[e] N.D. = no desired product.
[f] 40% aqueous solution.

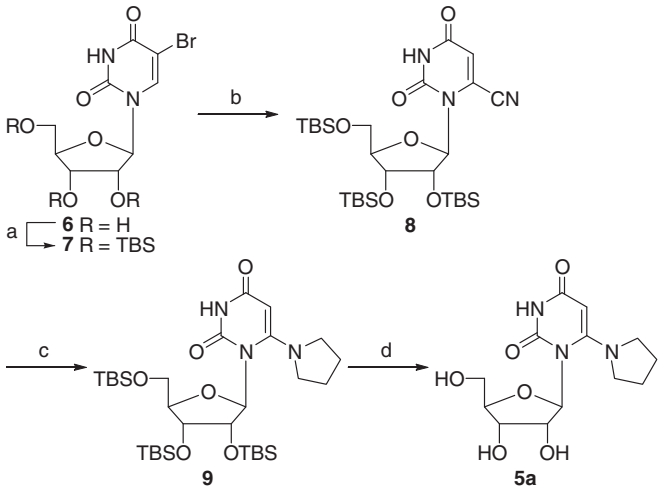
Table 4
Reaction of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-cyanouridine (**3**) with various amines with absolute ethanol as the solvent in a stainless steel vessel

Entry[a]	Amine	Solvent	Temperature	Time[b](h)	Product (yield)[c]
1	*n*-Butylamine	EtOH[d,e]	100 °C	3	**4d** (54%)
2	Benzylamine	EtOH[d,f]	120 °C	4	**4f** (57%)
3	Methylamine[g]	EtOH[g]	80 °C	3	**4g** (55%)
4	Cyclopentylamine	EtOH[d,f]	Reflux	>12	N.D.[h]

[a] Additive = DMAP (0.1 equiv).
[b] Until 6-CN-1,3-DMU (**1**) was completely consumed.
[c] Isolated yield.
[d] Absolute ethanol.
[e] *n*-$BuNH_2$/EtOH = 1:2 (v/v).
[f] $BnNH_2$/EtOH = 1:4 (v/v), $BnNH_2$ = approximately 10 equiv.
[g] 33 wt % solution in absolute ethanol.
[h] N.D. = no desired product.

Therefore, the reaction requires an appropriate solvent in order to reduce the amine components to a stoichiometric magnitude. Our investigation has shown that the reaction could be carried out with ethanol as the solvent by heating above its boiling point in a sealed stainless steel reactor. For instance, the sugar-protected 6-cyanouridine **3** with methylamine, *n*-butylamine or benzylamine in ethanol was heated in the sealed reactor to give the products (**4d**, **4f** and **4g**) in good yields (Table 4). It is noteworthy that the volatile methylamine is also applicable to the reaction. The sealed reaction condition enhanced the reactivity of the alkylamines and allowed the amount of alkylamines to be reduced to 10 equiv to maintain comparable yields. Nevertheless, the reaction scope is still limited to the primary amines with unbranched α-carbons and pyrrolidine as an exception.

The acid-labile isopropylidene and *t*-butyldimethylsilyl (TBS) groups of **4b–g** were deblocked with aqueous trifluoroacetic acid (TFA) to give the desired 6-alkylaminouridines **5b–g** in good yields. However, deprotection of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-(pyrrolidin-1-yl)uridine (**4a**) under various acidic media only resulted in the deglycosylation, which suggested that the target compound **5a** is unstable toward acidic conditions (Scheme 2). In order to obtain the deprotected product **5a**, our initial attempt was to apply the substitution reaction to the unprotected 6-cyanouridine[26] (**12**), but the reaction gave a complicated result in which 6-(pyrrolidin-1-yl)uridine (**5a**) was not obtained. This unforeseen difficulty prompted us to replace the isopropylidene with two TBS groups to avoid the acidic deprotection step in the synthesis. Hence, 2′,3′,5′-tri-*O*-*t*-butyldimethylsilyl-6-cyanouridine (**8**) was prepared from 5-bromouridine (**6**) and was subjected to the reaction with pyrrolidine to give the sugar-protected 6-(pyrrolidin-1-yl)uridine (**9**). Subsequent deprotection with tetra-*n*-butylammonium fluoride (TBAF) afforded the desired 6-(pyrrolidin-1-yl)uridine (**5a**) (Scheme 3).

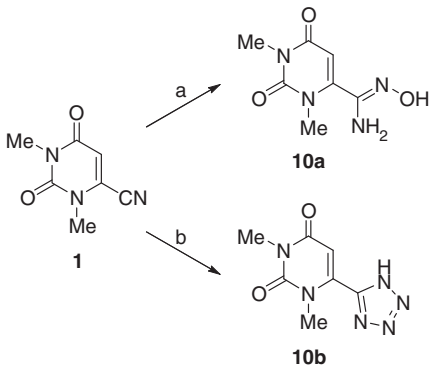


Scheme 3. Reagents and conditions: (a) TBSCl (3.3 equiv), imidazole (6.6 equiv), DMAP (0.1 equiv), DMF, 0 °C to rt, 8 h, 85%; (b) NaCN (1.5 equiv), DMF, rt, 46 h, 88%; (c) DMAP (0.1 equiv), pyrrolidine, reflux, 6 h, 30%; (d) 1 M TBAF in THF with 5% H_2O, 0 °C to rt, 7.5 h, 92%.

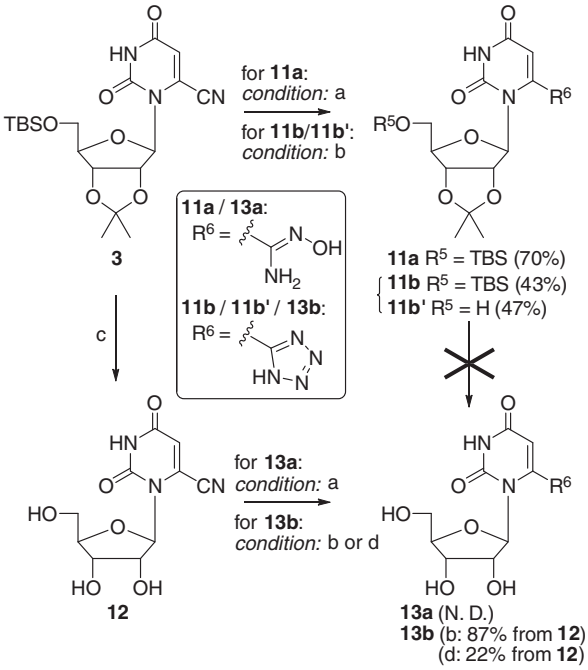
The limited scope of the alkylamine reactants for the substitution has led us to examine the reaction of 6-cyanouracil derivatives with other strong and less hindered nitrogen nucleophiles, including hydroxylamine and azide. The reaction of 6-CN-1,3-DMU (**1**) with hydroxylamine in EtOH under reflux provided 1,3-dimethyluracil-6-carboxamidoxime (**10a**) as the only product. Meanwhile, 6-CN-1,3-DMU (**1**) was heated with sodium azide and ammonium chloride in DMF and only 1,3-dimethyl-6-(tetrazol-5-yl)uracil (**10b**) was obtained from the reaction (Scheme 4). The results indicated that the addition of hydroxylamine or azide to the nitrile took place instead of the direct displacement of the cyano group of 6-cyanouracil derivatives.

In a similar fashion, the sugar-protected 6-cyanouridine **3** was reacted with hydroxylamine and sodium azide, respectively, to give the corresponding carboxamidoxime (**11a**) and tetrazole (**11b** and **11b′**) adducts in good yields. It is noteworthy that the TBS group was partially deprotected in the reaction with sodium azide and ammonium chloride. Nonetheless, several attempts to remove the acid-labile isopropylidene and TBS groups from **11a** and **11b**/**11b′** were unsuccessful. Alternatively, both reactions were carried out with the sugar-unprotected 6-cyanouridine **12**.[26] While the reaction of 6-cyanouridine **12** with hydroxylamine gave a complicated result and did not afford the desired uridine-6-carboxamidoxime (**13a**), 6-(tetrazol-5-yl)uridine (**13b**) was formed in a good yield from the reaction of 6-cyanouridine **12** with sodium azide (Scheme 5).

In summary, our investigation has demonstrated the versatile reactivities of 6-cyanouracil derivatives toward different nitrogen



Scheme 4. Reagents and conditions: (a) 50 wt % NH_2OH in H_2O (2 equiv), EtOH, reflux, 2 h, 80%; (b) NaN_3 (1.2 equiv), NH_4Cl (1.2 equiv), DMF, 100 °C, 19 h, 64%.



Scheme 5. Reagents and conditions: (a) 50 wt % NH_2OH in H_2O, EtOH, reflux; (b) NaN_3 (1.2 equiv), NH_4Cl (1.2 equiv), DMF, 95 °C; (c) TFA/H_2O = 9:1 (v/v), 0 °C, 15 min, 74%; (d) NaN_3 (1.2 equiv), DMF, 100 °C, 4 h (N.D. = no desired product).

nucleophiles. The reaction of 6-cyanouracil derivatives with hydroxylamine or azide involved addition of the nitrogen nucleophiles at the nitrile carbons. However, the nucleophilic substitution reaction took place when 6-cyanouracil derivatives were reacted with pyrrolidine or primary amines with unbranched α-carbons. This novel reaction has provided an alternative approach toward versatile 6-alkylaminouridine derivatives.

Acknowledgments

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Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra for representative compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.033.

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