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SYNTHESIS OF 3-SUBSTITUTED 6-AMINOURACILS

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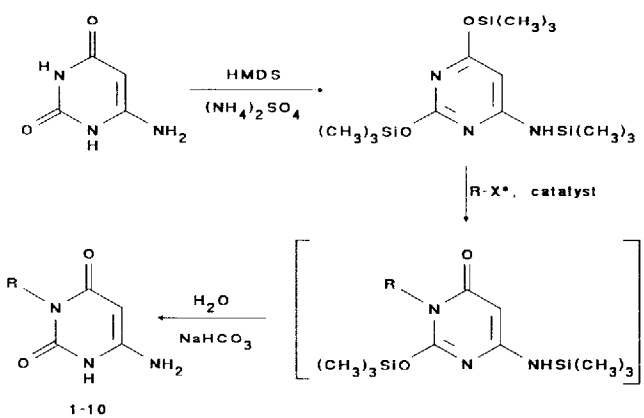
Abstract: *Tris(trimethylsilyl)6-aminouracil reacts with various alkyl- and arylalkyl halogenides and with tetraacetylribofuranose regiospecifically to the corresponding 3-substituted 6-aminouracil derivatives* **1–10**. *The reaction is catalyzed by $AlCl_3$ or, with the exception of the ribose derivative, more effectively by iodine. The described new synthesis offers the first general access to 3-substituted 6-aminouracils.*

6-Aminouracils are important intermediates for the synthesis of a variety of heterocyclic compounds including purines[1] and pteridines.[2] A wide range of xanthines can be synthesized from appropriately substituted 6-aminouracils. Our comprehensive structure activity analysis of xanthines as adenosine receptor antagonists[3] necessitated the synthesis of xanthines with a 1-substituent, but not a 3-substituent. The corresponding 3-monosubstituted 6-aminouracils were requisite precursors for such xanthines.

A general method to monosubstituted 6-aminouracils is the condensation of monosubstituted ureas with cyanoacetic acid. This reaction leads exclusively to the 1-substituted aminouracils.[4] Alkylation of uracil derivatives affords preferentially 1-mono- or 1,3-disubstituted products.[5] One method to prepare 3-substituted 6-aminouracils has been to protect the N-1-nitrogen, followed by alkylation at N-3 and subsequent deprotection.[6] Due to the low reactivity of the N-3 nitrogen of the N-1-protected aminouracils, this reaction appears to be limited to the preparation of 3-methyl-6-aminouracils.[7] Thus it was necessary to develop a novel general synthetic method for 3-substituted 6-aminouracils.

Our approach was to use the high reactivity of silylated uracil derivatives toward electrophilic compounds. In general, alkylation of silylated uracils takes place regioselectively at the N-1 position.[8] We found, in contrast to the observation with other uracils, that silylated 6-aminouracil reacts with alkyl halogenides specifically to the desired N-3-substituted 6-aminouracils.



Scheme. *For R,X see Table.

With the exception of methyl iodide, vigorous reaction conditions had to be applied.[9] Reactive alkyl bromides, such as propargyl and benzyl bromide, as well as tetraacetylribofuranose, reacted upon the addition of the Lewis acid $AlCl_3$ in equimolar amounts. Less reactive halogenides, however, such as n-propyl bromide, gave no reaction under these conditions. A recently described procedure applied iodine as a catalyst for the N-1-alkylation of silylated uracil.[10]

In our experiments, iodine proved to be a superior catalyst for the N-3-alkylation of silylated 6-aminouracil. A number of alkyl and arylalkyl bromides provided reasonable to excellent yields of 3-substituted 6-aminouracils. In some cases the formation of 1,3-disubstituted 6-aminouracils as by-products could be observed. In no case 1-substituted compounds were detected.

The identification of the 6-aminouracils as 3-substituted isomers is based on comparison of the spectra of some of the compounds with the corresponding 1-substituted 6-aminouracils. It was found that 1- and 3-regioisomers can easily be distinguished by the chemical shifts of the NH_2 protons in the ^{1}H-nmr spectra: 1-Substitution causes a large downfield shift compared to unsubstituted 6-aminouracil. Substituents in the 3-position have no or only a slight effect on the shift of the NH_2-protons (see table).

Table.

Compound	R	X	Catalyst	Yield [%]	m.p.[°C]	δ NH_2* [ppm]
1	Methyl	I	–	84	>300	6.14
2	n-Propyl	Br	I_2	81	275	6.14
3	n-Butyl	I	–	93	273	6.14
4	Cyclopentyl	Br	I_2	52	266	6.11
5	Allyl	Br	I_2	47	236	6.18
6	Propargyl	Br	$AlCl_3$	64	251	6.27
		Br	I_2	75		
7	2-Phenethyl	Br	I_2	89	243	6.16
8	Benzyl	Br	$AlCl_3$	53	252	6.23
		Br	I_2	83		
9	m-Chlorobenzyl	Br	I_2	86	222	6.22
10	AcRib**	Acetyl	$AlCl_3$	55	118	6.42

*In DMSO-d_6; unsubstituted 6-aminouracil: 6.15 ppm; 1-methyl-6-aminouracil: 6.73 ppm; 1-ethyl-6-aminouracil: 6.78 ppm; 1-n-propyl-6-aminouracil: 6.74 ppm. **Tri-O-acetyl-β-D-ribofuranosyl.

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9. General procedure: 6-Aminouracil is refluxed with excess hexamethydisilazane (HMDS) and a catalytic amount of $(NH_4)_2SO_4$ for 1–2 h until a clear solution is obtained. Excess HMDS is removed by distillation *in vacuo*. The catalyst ($AlCl_3$ or I_2) and the alkyl or aralkyl halogenide (1–2 eq) without solvent or the tetraacetylribofuranose dissolved in dichloroethane is added. After the initial exothermic reaction is completed the mixture is refluxed for 1–60 h. Then a saturated solution of $NaHCO_3$ is added in small portions with ice-cooling. The precipitate is collected and treated with hot water to remove unreacted 6-aminouracil. The products are further purified by recrystallisation, base-acid treatment, or column chromatography over silica gel with dichloromethane:methanol (9:1).
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