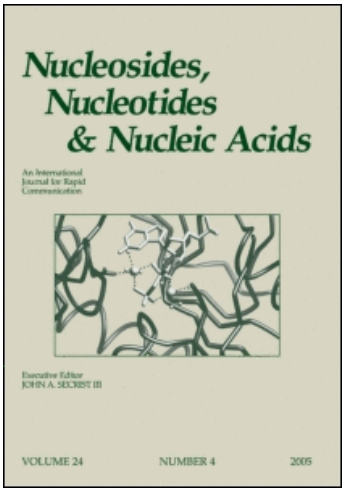


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Mechanisms of Formation of Cyclic Urea Nucleosides. 2. Direct N-Glycosylation Versus O- to N-Transglycosylation

Victor E. Marquez[a]
[a] Drug Design and Chemistry Section Laboratory of Medicinal Chemistry and Biology Developmental Therapeutics Program Division of Cancer Treatment, National Cancer Institute National Institutes of Health, Bethesda, Maryland

To cite this Article Marquez, Victor E.(1983) 'Mechanisms of Formation of Cyclic Urea Nucleosides. 2. Direct N-Glycosylation Versus O- to N-Transglycosylation', Nucleosides, Nucleotides and Nucleic Acids, 2: 1, 81 — 90
To link to this Article: DOI: 10.1080/07328318308078851
URL: http://dx.doi.org/10.1080/07328318308078851

NUCLEOSIDES & NUCLEOTIDES, 2(1), 81-90 (1983)

MECHANISMS OF FORMATION OF CYCLIC UREA NUCLEOSIDES. 2. DIRECT N-GLYCOSYLATION VERSUS O- TO N-TRANSGLYCOSYLATION.

Victor E. Marquez

Drug Design and Chemistry Section
Laboratory of Medicinal Chemistry and Biology
Developmental Therapeutics Program
Division of Cancer Treatment
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

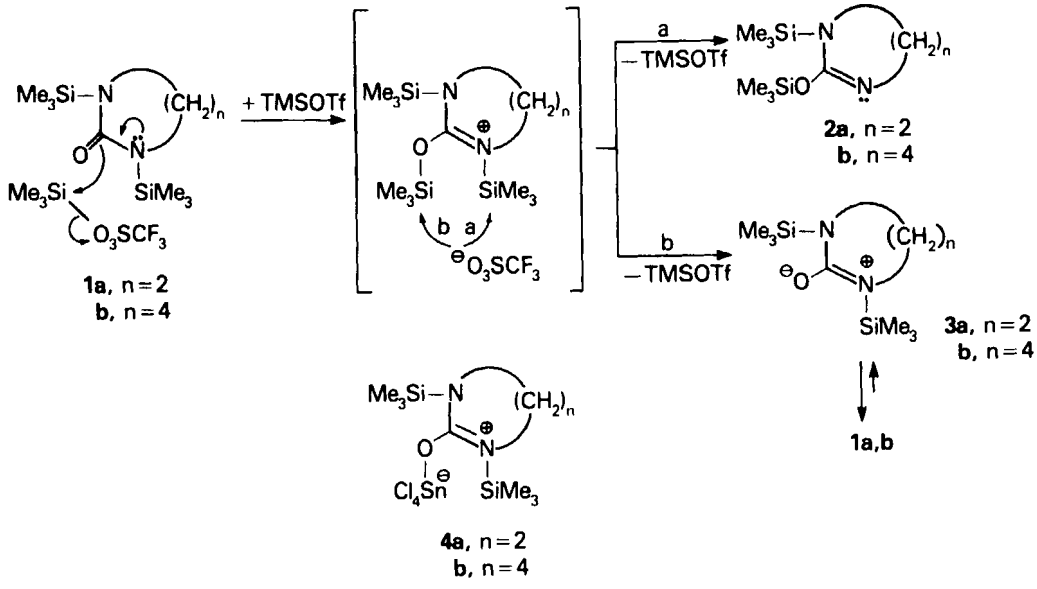
Abstract - Cyclic, saturated urea nucleosides, can be formed either by a direct N-glycosylation mechanism or by an intermolecular O- to N-transglycosylation process in the presence of a mild Lewis acid catalyst such as $(CH_3)_3SiSO_2CF_3$(TMSOTf). The mechanistic preference is controlled by the type of interaction between the persilylated ureas (1a,b) and TMSOTf which appears to be solvent dependent. Previously made tetramethyleneurea O-nucleoside (7b) rearranged very efficiently (86%) to the corresponding N-nucleoside 6b in the presence of TMSOTf.

Cyclic, saturated urea nucleosides, have been prepared in our laboratory by a mercury-catalyzed condensation reaction.[1] The success of the synthesis depended on the critical interaction between the N,N-bis(trimethylsilyl) urea and the mercuric oxide catalyst. This reaction was shown to proceed through the initial formation of an intermediate O-nucleoside which rearranged to the desired N-nucleoside by an intermolecular mechanism.[1] For this reason, the overall yield of the N-nucleoside was very much dependent on the efficiency of the intermolecular O → N interconversion. It was expedient, therefore, to search for other catalysts that would either lead to the N-nucleoside directly or increase the efficiency of the O → N interconversion.

 0732-8311/83/0201-0081$3.50/0

Results and Discussion

During the initial studies it was observed that $SnCl_4$ did not perform well as a catalyst for the glycosylation of cyclic, saturated ureas. It was rationalized that $SnCl_4$ possibly led to the formation of a strong and non-dissociable complex with the persilylated urea (1) that was incapable of reacting further (i.e., structure 4). The formation of σ-complexes between $SnCl_4$ and silylated uracils has been documented previously.[2] Based on the assumption that a weaker Lewis acid catalyst would produce a more dissociable complex, the reaction was studied with $(CH_3)_3SiSO_2CF_3$ (TMSOTf). Because TMSOTf is in addition a powerful silylating reagent it was expected to interact with 1 in the manner indicated to produce a N,O-bis(trimethylsilyl) urea (2) capable of forming the N-nucleoside directly as in a conventional Hilbert-Johnson reaction (path a).[2] An additional attractive feature of this catalyst was its well proven effectiveness in glycosylation reactions which allowed the use of crystalline 2,3,5-tri-O-benzoyl-1-O-acetyl-β-D-ribofuranose (5) as the starting sugar reagent instead of the unstable halogeno sugars.[2,3]



Before the experiment was conducted the interaction between this soluble catalyst and the persilylated ureas 1a and 1b was studied by ^{13}C-NMR spectroscopy. As described earlier, the ^{13}C-NMR spectrum of

persilylated ethyleneurea gave a simple pattern consistent with a N,N-bis(trimethylsilyl) urea structure (1a).[4] Similarly, as shown in FIGURE 1a, persilylated tetramethylene urea also gave a spectrum consistent with a symmetric N,N-bis(trimethylsilyl) urea structure (1b). Addition of 0.3 equivalents of TMSOTf changed the spectrum of 1b so that the lines corresponding to the carbon resonances of the ring methylene groups appeared broadened (FIGURE 1b). When 1.1 equivalents of TMSOTf were added, the lines sharpened again giving rise to a set of four peaks. This was consistent with the formation of a non-symmetrical species of the kind represented by structure 2b (FIGURE 1c). These changes were almost instantaneous and none of the new resonances coincided with those of untreated 1b. In addition, the carbonyl carbon resonance experienced an upfield shift of 7.54 ppm. All these data suggested that the spectrum corresponded to that of a single new species (2b) rather than that of a mixture of 1b and 2b.

If indeed the new species formed was the N,O-bis(trimethylsilylated) urea (2b) the possibility of generating the N-nucleoside by a direct displacement on the sugar was feasible. A systematic study of this reaction was undertaken, and it is summarized in TABLE 1.

Compound 1b and TMSOTf were reacted under almost the same conditions as those used for recording the NMR spectrum. Deuterated chloroform was replaced by dichloroethane and soon after the addition of one equivalent of TMSOTf to the persilylated urea, the 1-O-acetyl sugar 5 was added. Consistent with the initial expectations of a direct N-glycosylation, no O-nucleoside was observed at the initial stages of the reaction. However, the yield of the desired N-nucleoside was only 14% (TABLE 1, entry 1). The reaction was very sluggish and this allowed the sugar to gradually decompose in the presence of the Lewis acid catalyst. Use of excess catalyst was detrimental and produced an even lower yield of N-nucleoside. In theory, each time there is a 1b → 2b conversion a new molecule of catalyst is regenerated.

Under the same conditions, the reaction with 1a yielded no product with the exception of decomposed sugar by-products (TABLE 1, entry 2). However, when the temperature was raised to 60° for 1 hr, the N-nucleoside 6a formed and was the only observable product (TABLE 1, entry 3). As seen in the next entry a temperature increase in the reaction with 1b

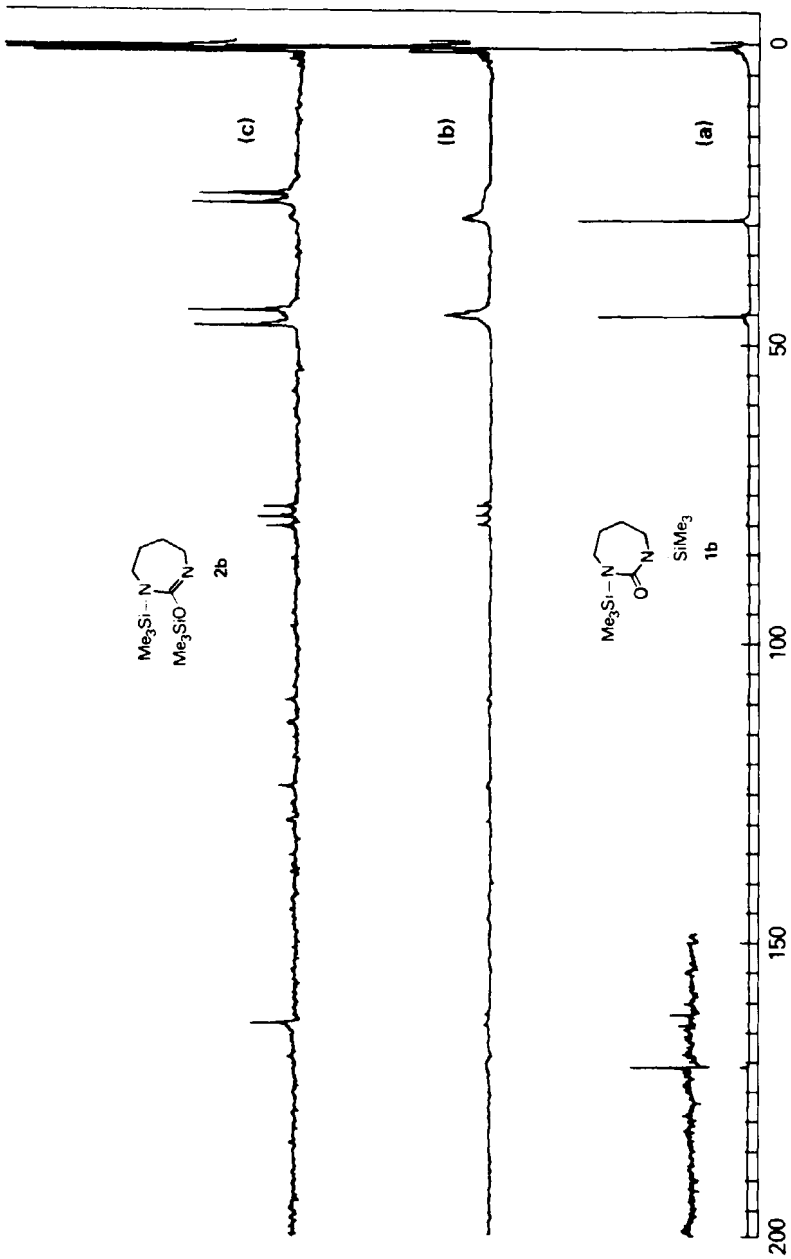
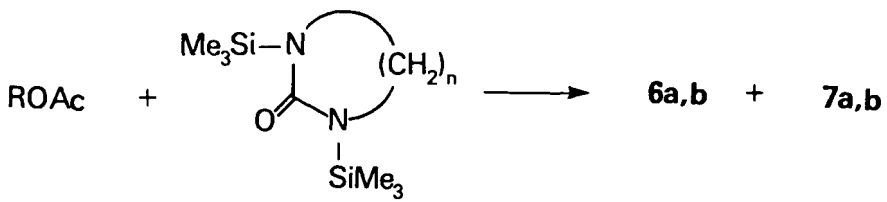


FIGURE 1. ^{13}C-NMR Spectra in $CDCl_3$ Demonstrating the Conversion of N,N-bis(trimethylsilyl) Urea 1b to the N,O-bis(trimethylsilyl) Urea 2b through the Action of TMSOTf. The Small Triplet Observed at 76.9 ppm in (b) and (c) is due to $CDCl_3$.

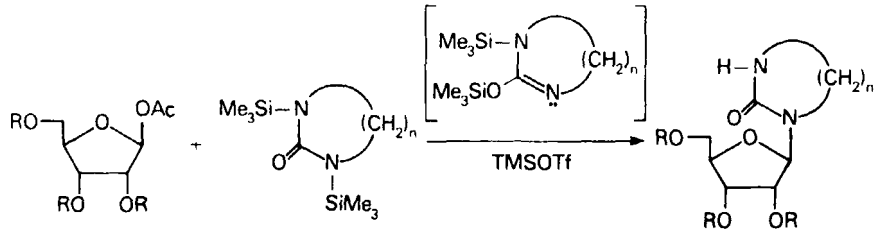
TABLE 1. Reaction Conditions for the Synthesis of O- and N-Nucleosides:



1a, n=2
b, n=4

Entry	R-OAc[a]/urea[b]	Solvent	Catalyst[c]	Urea	Time(h)	Temp(°C)	TLC (1h)[d]		Yield (%)[e]	
							O-nucl.	N-nucl.	O-nucl.	N-nucl.
1	1.05	$(CH_2Cl)_2$	TMSOTf	1b	18	25	-	major	traces	14
2	1.05	$(CH_2Cl)_2$	TMSOTf	1a	18	25	-	-	-	-
3	1.05	$(CH_2Cl)_2$	TMSOTf	1a	1	60	-	major	-	16
4	1.05	$(CH_2Cl)_2$	TMSOTf	1b	1	60	traces	major	traces	10
5	1.05	CH_3CN	TMSOTf	1b	18	25	-	-	-	-
6	1.05	benzene	TMSOTf	1b	18	25	major	traces	7	7
7	2.0	benzene	TMSOTf	1b	18	25	major	traces	3	5

[a] R = 2,3,5-tri-O-benzoyl-β-ribofuranosyl. [b] All cyclic ureas were persilylated. [c] The catalyst was added in equimolar amounts with respect to the urea. [d] Silca gel, methanol (4%) in methylene chloride. [e] In cases where mixtures were obtained, the yields were calculated by NMR (see ref. 1).



5 **1a**, n=2 **6a**, n=2 (16%)
b, n=4 **b**, n=4 (14%)

$$R = C\text{-}C_6H_5$$

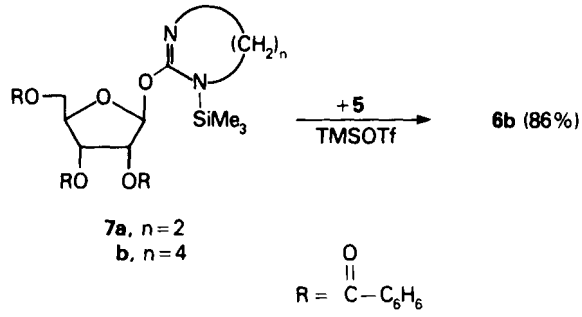
produced little change except for the reduction of the overall reaction time (TABLE 1, entry 4).

It was not surprising that 1a required a higher temperature to give the N-nucleoside 6a. Initially, from NMR experiments, it was found that addition of TMSOTf caused no change in the spectrum of 1a when observed at room temperature. If one studies the transformation of 1a to 2a and that of 1b to 2b with the aid of models, one sees that in the less flexible 1a there is greater crowding and steric repulsion between the N-trimethylsilyl group and the ring methylene hydrogens brought about by the change in hybridization of the nitrogen in the transition state from 1a to 2a. On the contrary, the more flexible seven-membered urea accommodates these changes with a minimum of steric repulsion that allows the reaction to occur at room temperature.

In order to improve the yields of the desired N-nucleoside, different solvents were studied. More polar solvents such as CH_3CN (TABLE 1, entry 5) induced decomposition with no observable product formation. When less polar solvents such as benzene were used, the reaction worked (TABLE 1, entries 6 and 7); however, in this instance the reaction was clearly proceeding via a O → N transglycosylation since only the O-nucleoside 7b was observed at the initial stages of the reaction. This reaction was also very inefficient and gave almost equal amounts of O- and N-nucleosides. It is possible that in this case the interaction between catalyst and persilylated urea occurred in a different manner (possibly through the formation of intermediates 3a,b).

In view of the fact that under these conditions, the sugar appeared to decompose faster than it reacted with either form of the silylated

ureas, it was decided to investigate the transformation of the O-nucleoside 7b, previously made in 51% yield by the mercuric oxide process, to the N-nucleoside 6b in the presence of TMSOTf. As demonstrated previously the major drawback of the mercury-catalyzed reaction was the relative inefficiency of $HgBr_2$ to induce the O → N rearrangement.[1] Up to the intermediate formation of the O-nucleoside, however, the reaction was fairly efficient when performed in the exclusive presence of yellow mercuric oxide.[1] Since $SnCl_4$ was incapable of inducing the O → N transglycosylation when performed on the silylated O-nucleoside,[1] the effectiveness of a milder Lewis acid catalyst was investigated. TMSOTf proved to be an excellent catalyst for the O → N transglycosylation which was accomplished very efficiently (86%) during the course of 3h at room temperature. This corresponded to an overall yield of 44% for the N-nucleoside 6b. The O-nucleoside was required to be persilylated and additional sugar 5 was necessary to initiate the intermolecular reaction.



In summary, it can be concluded that N-nucleosides of cyclic, saturated urea nucleosides can arise via two distinct mechanisms. If mercuric catalysts are used, the only observable path appears to be the O → N transglycosylation mechanism.[1] In the presence of milder Lewis acid catalysts, such as TMSOTf, the O → N transglycosylation mechanism still operates in benzene, while a direct N-glycosylation is almost exclusive albeit inefficient in either dichloroethane or methylenechloride. This latter mechanism is essentially the same as that of the modified Hilbert-Johnson glycosylation of aromatic ureas.[2] The low yields of the above direct displacement reaction may reflect a diminished nucleophilicity of

the nitrogen atom in 2a,b as compared to that of their aromatic counter parts. The milder Lewis acid catalyst TMSOTf proved very effective in converting previously synthesized O-nucleoside 7b to the desired N-nucleoside 6b. This reaction proceeded by an intermolecular transglycosylation mechanism similar to that previously described for the mercury catalysts.[1]

EXPERIMENTAL

General Methods: Proton NMR spectra were determined on Varian T-60 or HA-100D instruments. ^{13}C-NMR spectra were recorded on a Varian FT-80A spectrometer. Carbon NMR spectra were run at room temperature with all values referenced to ^{13}C of added dioxane, which was 66.67 ppm relative to Me_4Si. Columns for chromatography were packed with silica gel (Bio-Sil A, 200-400 mesh, Bio-Rad Laboratories) and eluted with mixtures of ethyl acetate-hexane. The methodology of Still et al.,[5] also known as flash chromatography, was used throughout. Thin-layer silica gel plates (250 μM) were purchased from Analtech,. Inc.

General Procedure for the Condensation Reaction of Persilylated Cyclic Ureas (1a,b) with 2,3,5-Tri-O-benzoyl-1-O-acetyl-β-D-ribofuranose (5) in the Presence of TMSOTf. To a suspension of the cyclic urea (3 mmol) stirred in dry acetonitrile (distilled over P_2O_5) at room temperature was added a six-fold excess (5 g, 19 mmol) of bis(trimethylsilyl)trifluoracetamide (BSTFA). The mixture was stirred for 2 hr at room temperature, and the excess of reagent and solvent were removed in vacuo to leave a clear oil. The oily persilylated urea was dissolved in 30 ml of the reaction solvent (see TABLE 1) and treated immediately with 0.6 ml (~3 mmol) of TMSOTf. After 2 minutes the corresponding amount of 5 (3.17 mmol or 6 mmol), as indicated in TABLE 1, was added and the mixture stirred at the indicated temperature and time (TABLE 1). TLC observations were made at several intervals during the first hour and at the end of the reaction. The reaction mixture was extracted with a saturated solution of $NaHCO_3$; the organic solvent was then washed with water and dried over anhydrous $MgSO_4$. The solution was reduced to ca. 5 ml and applied to a silica gel column. Elution of the column was performed with ethyl acetate-hexane (3:2). In this solvent system both O-

nucleosides and N-nucleosides elute as a single band which was easily separable from the rest of the faster-moving unreacted sugar derivatives. In those instances where mixtures were obtained (TABLE 1, entries 6 and 7) a TLC system consisting of a 4% methanol solution in methylene chloride allowed for easy separation of the two spots (TABLE 1). The relative yields were estimated from integration of the NMR signals corresponding to the anomeric protons of each isomer as reported previously.[1] When a single product was visualzed in the methanol-methylene chloride system, it was isolated as a solid foam. The NMR, and other physical properties of 6a, 6b and 7b agreed with those reported earlier.[1,4]

Conversion of the O-Nucleoside 7b to the Corresponding N-Nucleoside 6b in the Presence of TMSOTf. The O-nucleoside 7b[1] (0.3 g, 0.53 mmol) was silylated in CH_3CN (3 ml) with 1.5 ml of BSTFA for 1 hr at room temperature. The solvent and excess reagent were removed in vacuo and the remaining semisolid dissolved in 15 ml of 1,2-dichloroethane. The solution was cooled to 0°C and TMSOTf (0.2 ml) and 5 (0.25 g, 0.5 mmol) were added. The mixture was stirred at 0°C for 1 hr during which time very little O → N conversion was observed on TLC. After letting the temperature gradually rise to room temperature the O → N interconversion was faster and totally completed after 3 hr. After a similar workup, as previously described, and using flash chromatography (column length 150 mm, diameter 10mm), 0.260 g (86%) of pure N-nucleoside 6b was isolated.

Acknowledgment. I would like to thank Dr. L. V. Feyns, USP, for the ^{13}C-NMR data. Likewise, I would like to express my gratitude to Drs. John S. Driscoll and James A. Kelley of this laboratory for their many helpful discussions during the course of the work.

REFERENCES

1. Marquez, V.E.: Liu, P.S.; Linevsky, J.K. J. Org. Chem. 1982, 47, 1712.
2. Vorbruggen, H. In "Nucleoside Analogues. Chemistry, Biology and Medical Applications"; Walker, R.T., De Clercq, E., Eckstein, F., Eds.; Plenum Press: New York and London, 1979; pp. 35-69.

3. Vorbruggen, H.; Krolikiewicz, K.; Bennua, B., Chem. Ber. 1981, 114, 1234.
4. Liu, P.S.; Marquez, V.E.; Driscoll, J.S.; Fuller, R.W.; McCormack, J.J. J. Med. Chem. 1981, 24, 662.
5. Still, W.C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923.

Received January 6, 1983