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Review

Thiohydantoin Nucleosides. Synthesis Approaches

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Summary. Several thiohydantoin *N*-nucleosides and their *S*-glycosides were prepared *via* different approaches which involved the direct glycosylation of the free thiohydantoin bases or their silylated derivatives with the corresponding sugar moieties in the presence of base or *Lewis* acid. Deprotection was carried out in acidic or basic medium. The site of *N*- and/or *S*-glycosylation was determined by NMR and UV measurements. In similar manner, hydantoin nucleosides were prepared.

Keywords. Biological activity; Glycosylation; Sugar derivatives; Pyrimidines; Hydantoin and thiohydantoin nucleosides.

Introduction

Hydantoin (**1**) was isolated first by *Bayer* [1] in the course of his classic research on uric acid (1861). The 2-thio analogue **2** was reported in 1890 [2]. The family of these compounds have been investigated intensively in connection with the structural activity of peptides, pencillin [3], 4-thiohydantoin (**3**) [4], 2,4-dithiohydantoin (**4**) [5], and their alkyl and aryl derivatives (Scheme 1). Reviews on the chemistry of hydantoins (2,4-imidazolidinediones) including thiohydantoins appeared successively in 1950 [6], 1957 [7], 1966 [8], and 1985 [9]. *Edward*'s review [8] dealt only with thiohydantoins, while *Ware*'s review [6] was particularly exhaustive.

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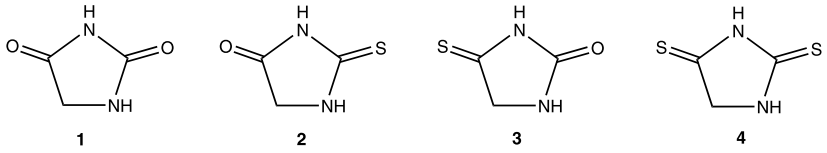
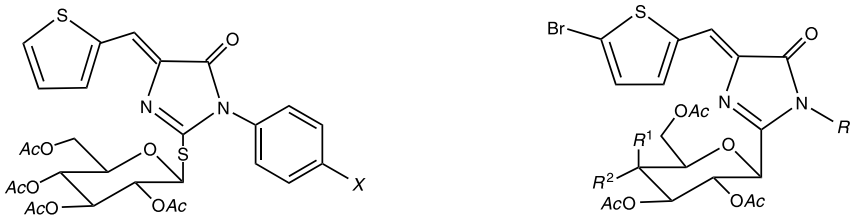


Scheme 1



5a: *X* = H
5b: *X* = Cl

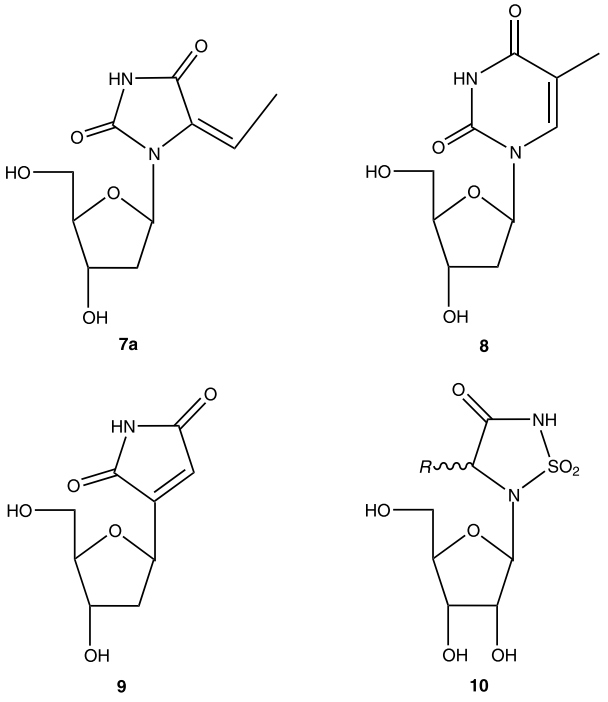
6a: *R* = *Ph*; R^1 = H; R^2 = *Ac*
6b: *R* = morpholinomethyl; R^1 = *Ac*; R^2 = H

Scheme 2

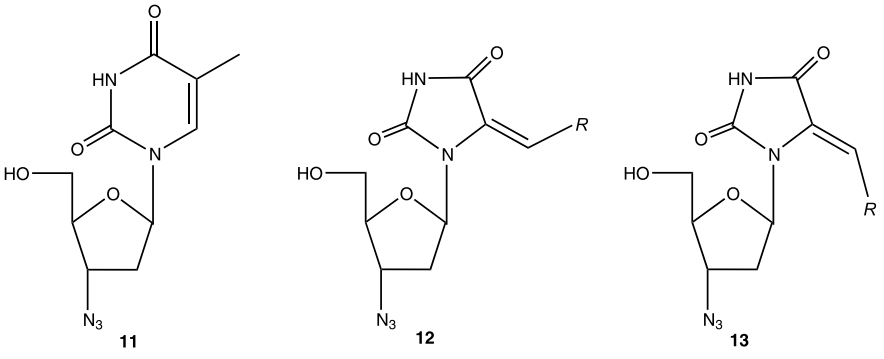
Several thiohydantoins exhibited a variety of biological activities including antiviral and antitumor activities. Examples of such compounds were 5-(2-thienylmethylene)-3-phenyl-2-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-2-thiohydantoin (**5a**) and the 3-(4-chlorophenyl) analogue **5b** [10], which showed remarkable activity against both HSV-1 and HSV-2. The thioglycosyl hydantoin **6a** proved to possess a broad spectrum antitumor activity against a wide range of different human cell lines of nine tumor subpanels causing both cytostatic and cytotoxic effects, with medium lethal concentrations (LC_{50}) at 15.1, 41.7, and 83.2 μM. On the other hand, the galactoside analogue **6b** showed potential selectivity against leukemia cell lines [11] (Scheme 2).

Attention had been focused on the synthesis of glycosylated hydantoin derivatives because of their resemblance with natural nucleosides, in particular (*E*)-l-(2-deoxy-β-*D*-*erythro*pentofuranosyl)-5-ethylidene-2,4-imidazolidinedione (**7a**) [12], a potent nucleoside derived from thymidine (**8**). It is derived by ring contraction of the nucleobase by a *de facto* rearrangement of carbonyl from C-5 to C-6. Thymidine itself was isolated a long time ago from thymonucleic acid [13–16] and consequently there has been strong interest in synthesizing modified thymine nucleosides as potential drugs. The possibility of finding interesting five-membered ring analogues of thymidine is best illustrated with showdomycin (**9**), which is a broad spectrum antibiotic first isolated from *Streptomyces showdoensis* [17]. This antibiotic has been found to exhibit activity against *Ehrlich ascites* tumor *in vivo* and against cultured HeLa cells [18, 19]. *Suhadolink et al.* [20] and *Kozikowski et al.* [21] have reported the antibacterial and antitumor activities of the similar class of the *C*-nucleosides family [20, 21] (Scheme 3). Recently, *Dewynter et al.* [22] described the preparation of a series of pseudo-nucleosides containing the sulfahydantoin 1,2,5-thiadiazolidine-3-one-1,1-dioxide (**10**) [23] as aglycone.

Azidothymidine (*AZT*, Zudividine®, **11**) [24] was the first drug at the market to treat HIV infection. However, it displays remarkable toxicity [25, 26]. Therefore,



Scheme 3



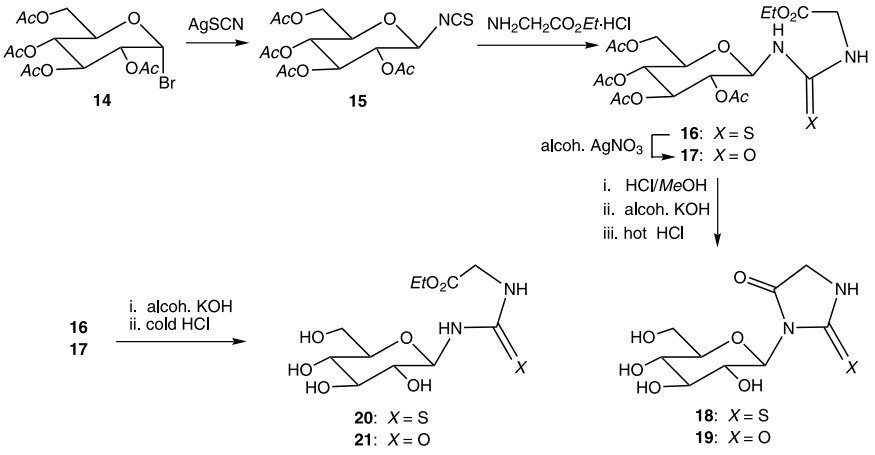
Scheme 4

there is still an urgent need for new antiviral agents with low toxicity to normal cells. Such compounds might be *AZT* analogues bearing 2,4-imidazolidindione as a nucleobase, *e.g.* (*E*)- and (*Z*)-1-(3-azido-2,3-dideoxy-β-D-*erthyro*pentofuranosyl)-5-(substituted ethylidene)-2,4-imidazolidinediones **12** and **13** [27].

2-Thiohydantoin Nucleosides

Nitrogen Glycosylation Reactions

N-3 Glycosylation involves the reaction of glycine ethyl ester hydrochloride nucleoside with pyranosyl sugars. The main synthetic route to 2-thiohydantoin

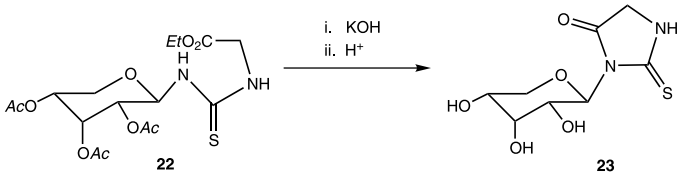


Scheme 5

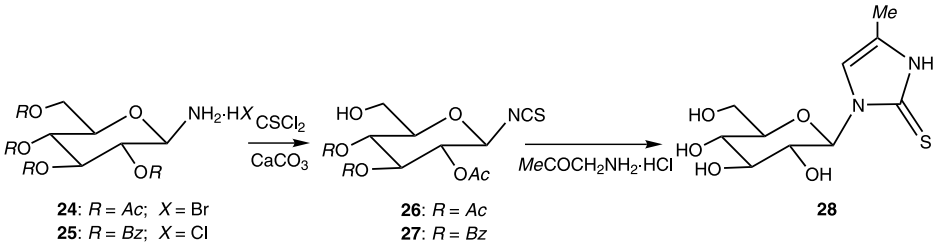
nucleosides started with the construction of the heterocycle residue from suitably C-1 functionalised sugar derivatives. Reaction of 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl isothiocyanate (**15**) [28, 29], obtained form the bromo analogue **14** and silver thiocyanate with glycine ethyl ester hydrochloride in the presence of pyridine, gave almost quantitatively ethyl (2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl) thiohydantoate (**16**). The oxygen analogue **17** was prepared from **16** by treatment with alcoholic silver nitrate. Deblocking of **16** with *Me*OH/HCl followed by saponification and acidification with hot HCl furnished **18**. Similarly, **19** was obtained from **17**. Meanwhile **20** and **21** were prepared from saponification of **16** and **17** followed by acidification with cold HCl.

Fernandez et al. [30] have applied the same approach for the cyclization of the thiourea residue in the presence of base to furnish the 2-thiohydantoins. Thus, treatment of *N*-ethoxycarbonylmethyl-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)thiourea (**16**) or the -β-*D*-ribopyranosyl analogue **22** with KOH, followed by acidification furnished 3-(β-*D*-glucopyranosyl)-2-thiohydantoin (**18**) or the ribo analogue **23** (Scheme 6).

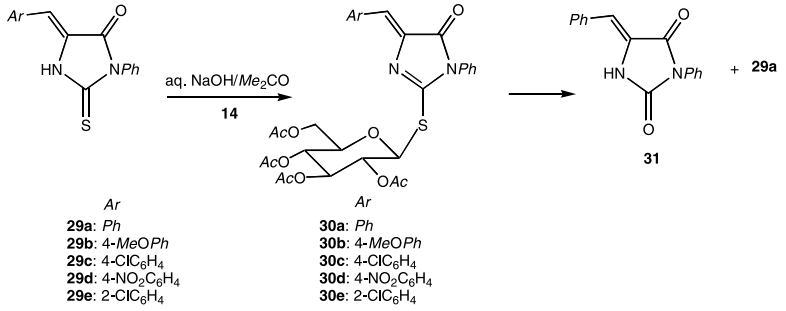
Reaction of the glucopyranosylamine hydrobromide **24** and hydrochloride analogue **25**, prepared from the corresponding 2,3,4-tri-*O*-acetyl-1-*N*-(2,2-diethoxycarbonylvinyl)-6-*O*-trityl-β-*D*-gluco-pyranosylamines [31] hydrobromide (hydrochloride) with thiophosgene in basic medium afforded the isothiocyanate derivatives **26** and **27** [32]. Treatment of **26** and **27** with amino acetone hydrochloride followed by deacylation gave the 2-thioimidazoline derivative **28** [33] (Scheme 7).



Scheme 6



Scheme 7



Scheme 8

Sulfur Glycosylation Reactions

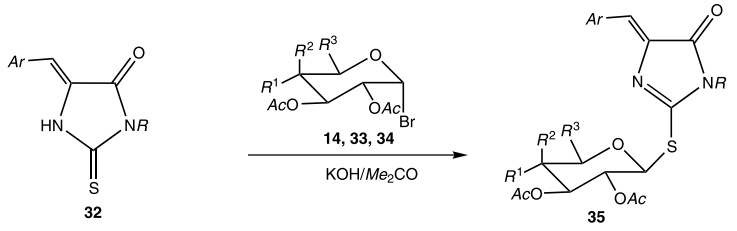
Thioglycosides of 2-Thiohydantoins Carrying Pyranosyl Sugars

The main synthesis route to thiohydantoin carrying glycosides was the direct condensation between the appropriate 2-thiohydantoin bases with the bromo peracylated sugars in the presence of aqueous base. Treatment of 5-arylidene-3-phenyl-2-thiohydantoins **29a**–**29e** with **14** in the presence of aqueous NaOH and acetone at 23°C provided the thioglycosides **30a**–**30e**, while hydrolysis of **30a** with conc. *Me*OH/HCl afforded the free bases **29a** and **31** [34] (Scheme 8).

Following the same approach, 3-substituted-2-thiohydantoins **32a**–**32d** were reacted with **14**, the *D*-galactopyranosyl- **33**, and *D*-xylopyranosyl-analogues **34** to furnish, probably *via* Walden inversion [35, 36], the corresponding 5-arylidene-3-substituted-2-β-*D*-glucopyranoside (**35a**–**35d**), β-*D*-galactopyranoside (**35e**–**35h**), and β-*D*-xylopyranoside (**35i**–**35m**) derivatives of 2-thiohydantoins [37] (Scheme 9).

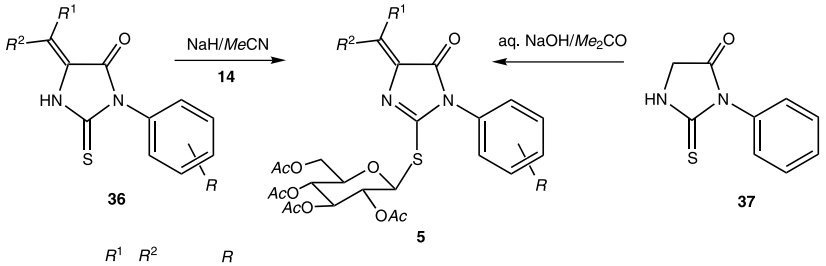
Numerous examples of thioglycosides carrying 2-thiohydantoins with various substituents have been synthesized in the presence of hydride ions. Thus, **5a**–**5g** were obtained from treatment of **36a**–**36g** with **14** in the presence of NaH. Alternatively, **5g** has been synthesized by treatment of 3-phenyl-2-thiohydantoin **37** with aqueous NaOH and acetone [10] (Scheme 10).

When 5-arylidene-3-substituted-2-thiohydantoins **38a**–**38d** were treated with 1.1 eq. of aqueous NaOH or K_2CO_3 in acetone followed by addition of **14**, the corresponding (*Z*)-2-thiohydantoin nucleosides **39a**–**39d** were obtained. Hydrolysis of **39a** or **39c** with conc. HCl in refluxing *Et*OH afforded (*Z*)-5-arylidene-3-



32, 14, 33-35	Ar	R	R^1	R^2	R^3
a:	*Ph*	*Me*	O*Ac*	H	CH_2O*Ac*
b:	4-*Me*OC_6H_4	*Me*	O*Ac*	H	CH_2O*Ac*
c:	4-ClC_6H_4	*Me*	O*Ac*	H	CH_2O*Ac*
d:	*Ph*	CH_2-morph.	O*Ac*	H	CH_2O*Ac*
e:	*Ph*	*Me*	H	O*Ac*	CH_2O*Ac*
f:	4-O*Me*C_6H_4	*Me*	H	O*Ac*	CH_2O*Ac*
g:	4-ClC_6H_4	*Me*	H	O*Ac*	CH_2O*Ac*
h:	*Ph*	CH_2-morph.	H	O*Ac*	CH_2O*Ac*
i:	*Ph*	*Me*	O*Ac*	H	H
j:	4-O*Me*C_6H_4	*Me*	O*Ac*	H	H
k:	4-ClC_6H_4	*Me*	O*Ac*	H	H
l:	*Ph*	CH_2-morph.	O*Ac*	H	H
m:	*Ph*	*Ph*	O*Ac*	H	H

Scheme 9

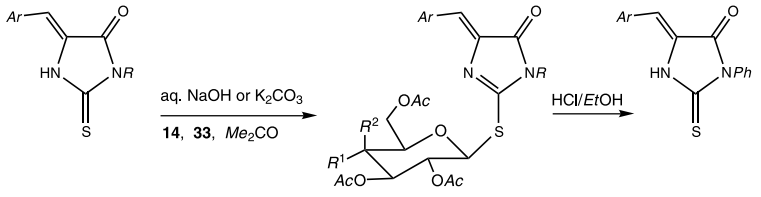


	R^1	R^2	R
5, 36a:	H	2-thienyl	H
5, 36b:	H	2-thienyl	4-Cl
5, 36c:	H	2-thienyl	4-O*Me*Ph
5, 36d:	H	2-thienyl	4-CO_2*Et*
5, 36e:	H	2-thienyl	3-*Me*
5, 36f:	H	3-indolyl	H
5, 36g:	*Me*	*Me*	H

Scheme 10

substituted-2,4-imdazolidindiones **40a** or **40b**. Following the same method, the galacto analogues **39e**–**39h** were synthesized by condensation of **38a**–**38d** with **33** [38] (Scheme 11).

2-Thiohydantoin derivatives **41a**–**41d** bearing a heterocyclic side chain at position 5 were reacted with **14** or the galacto analogue **33** in the presence of hydride ions and *Me*CN as the solvent to give 5-arylidene-3-substituted-2-thiohydantoin nucleosides **6a**, **6c**, and **6d**, as well as the galacto derivative of 2-thiohydantoin **6b** [39] (Scheme 12). More examples of the gluco and galacto derivatives of 2-thiohydantoins having differently substituted 5-(*Z*)-arylidene groups, such as 3-phenyl-, 3-methyl-, 2-thienyl-, 2- and 3-indolyl-, 2-pyridyl-, and furyl-groups, have been reported [40, 41]. These new derivatives of the thioglycosides **43** bearing 3-allyl-5-(*Z*)-arylidene groups were prepared by condensation of the corresponding 2-thiohydantoins **42a**–**42f** with **14** in presence of hydride ions in anhyd. *Me*CN. Compound **43a** was synthesized *via* an alternative route by condensation of the silyl

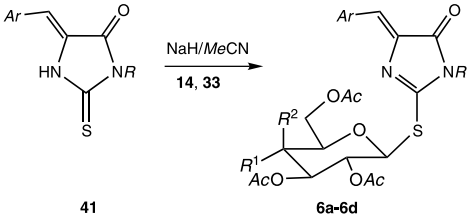


Ar	R
38a: 2-naphthyl	*Ph*
38b: 2-naphthyl	*Me*
38c: 2-hydroxy-1-naphthyl	*Ph*
38d: 2-hydroxy-1-naphthyl	*Me*

Ar	R	R^1	R^2
39a: 2-naphthyl	*Ph*	O*Ac*	H
39b: 2-naphthyl	*Me*	O*Ac*	H
39c: 2-hydroxy-1-naphthyl	*Ph*	O*Ac*	H
39d: 2-hydroxy-1-naphthyl	*Me*	O*Ac*	H
39e: 2-naphthyl	*Ph*	H	O*Ac*
39f: 2-naphthyl	*Me*	H	O*Ac*
39g: 2-hydroxy-1-naphthyl	*Ph*	H	O*Ac*
39h: 2-hydroxy-1-naphthyl	*Me*	H	O*Ac*

Ar
40a: 2-naphthyl
40b: 2-naphthyl

Scheme 11

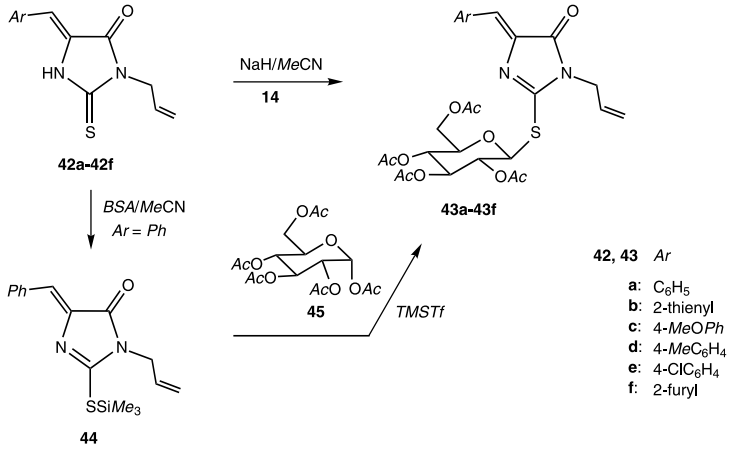


41 **6a-6d**

41, 6 Ar	R	R^1	R^2
a: 5-bromo-2-thienyl	CH_2-morph.	O*Ac*	H
b: 5-bromo-2-thienyl	*Ph*	H	O*Ac*
c: 5-bromo-2-thienyl	*Ph*	O*Ac*	H
d: 5-(2-COOH*Ph* S)-2-thienyl	*Ph*	H	O*Ac*

Scheme 12

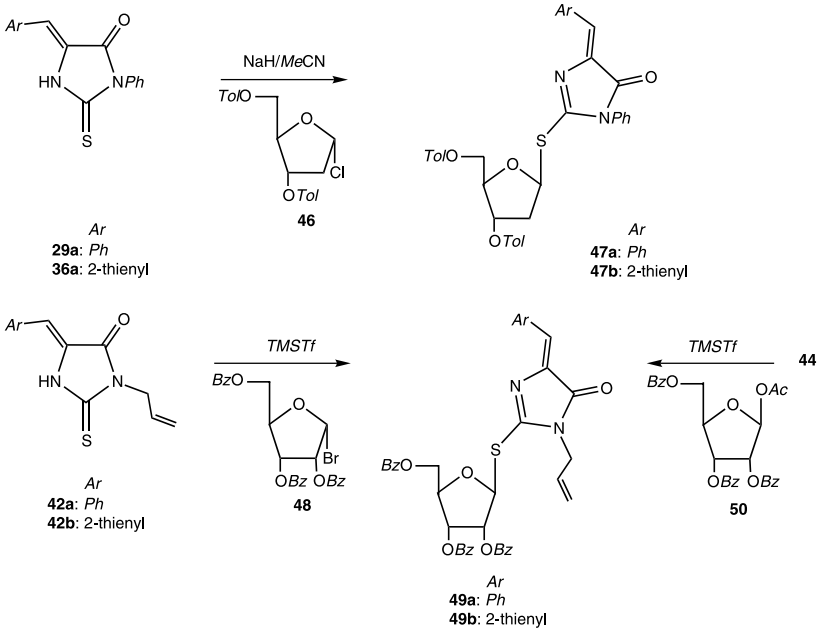
derivative **44**, which in turn was prepared from **42a** with bis-(trimethylsilyl)acetamide (*BSA*) in *Me*CN, and α-*D*-glucose pentaacetate (**45**) in presence of trimethylsilyl trifluoromethanesulfonate (*TMSTf*). The thioglycoside **43a** was isolated by



42a-42f **43a-43f** **44** **45**

42, 43 Ar
a: C_6H_5
b: 2-thienyl
c: 4-*MeO*Ph
d: 4-*Me*C_6H_4
e: 4-ClC_6H_4
f: 2-furyl

Scheme 13



Scheme 14

chromatography and no *N*-nucleoside was detected [41] (Scheme 13). In a similar manner, the galacto-analogues have been prepared [42].

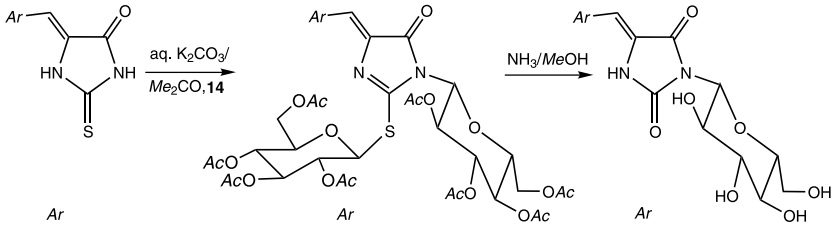
Thioglycosides of 2-Thiohydantoins Carrying Furanosyl Sugars

Pedersen et al. [10] have followed the previous synthetic routes to prepare the thioglycosides carrying furanosyl residues, such as 5-benzylidene-3-phenyl-2-(3,5-di-*O*-toluoyl-*erythro*-β-*D*-pentofuranosyl)-2-thiohydantoin (**47a**) and its 5-(2-thienyl)-analogue **47b**, by condensation of the corresponding bases **29a** and **36a** with **46** in the presence of NaH in anhyd. *Me*CN (Scheme 14). Similar treatment of **42a**, **42b** with **48** afforded the thioglycosides **49a**, **49b**. Alternatively, **49a** was synthesized in a good yield by condensation of the silylated base **44** with **50** in the presence of *TMSTf* and anhyd. *Me*CN [41] (Scheme 14).

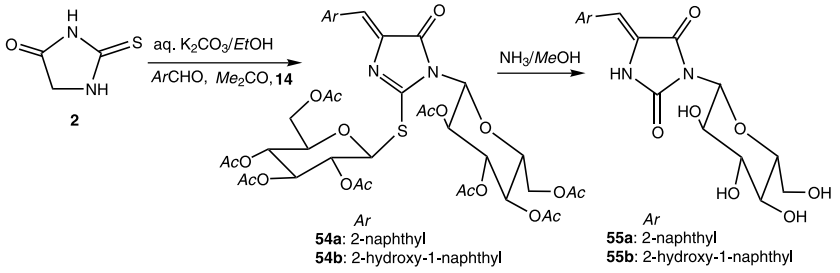
Nitrogen and Sulfur Glycosylation Reactions

Bis-glycosylation takes place on both *S*- and *N*-atoms of the unsubstituted hydantoins. The bis-glycosylated hydantoin was hydrolysed to the *N*-3 glycosylated analogue on treatment with $NH_3/MeOH$. Thus, reaction of 5-arylidene-2-thiohydantoins **51a** or **51b** with **14** in the presence of aqueous K_2CO_3 afforded **52a** or **52b**, which gave the 5-(*Z*)-arylidene-3-(β-*D*-glycopyranosyl)-hydantoins **53a** or **53b** on treatment with $NH_3/MeOH$ [40] (Scheme 15). Similarly, the *D*-galacto analogues have been prepared [38].

Various derivatives of bis-glycosilated derivatives of 2-thiohydantoins **2** have been synthesized by reaction of **2** with aromatic aldehydes in presence of ethanolic K_2CO_3 followed by addition of **14** in acetone to give **54a**, **54b**. Deprotection with



Scheme 15

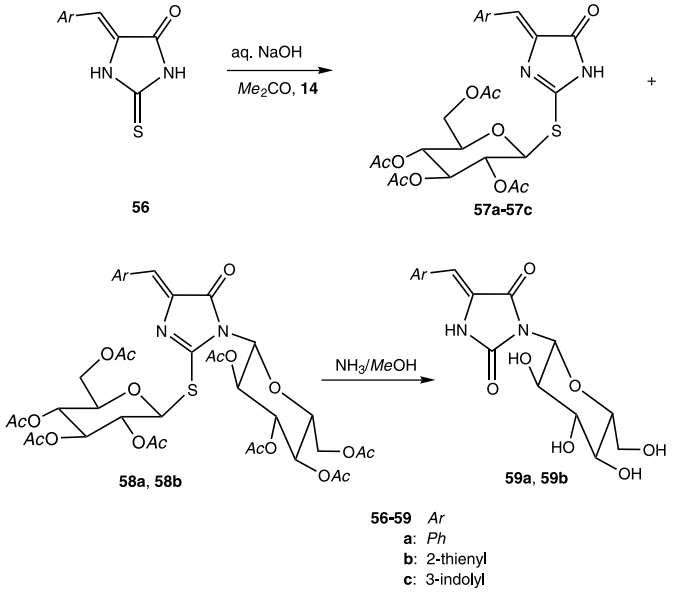


Scheme 16

$NH_3/MeOH$ afforded 5-(*Z*)-arylidene-3-(β-*D*-glycopyranosyl)hydantoins **55a**, **55b** [40] (Scheme 16).

When 5-arylidene-2-thiohydantoins **56a**–**56c** were treated with **14** in aqueous acetone, mono- and bis-glycosylation afforded **57a**–**57c** and **58a** or **58b**. Upon deprotection of the bis-products **58a** or **58b** with $NH_3/MeOH$, the thioglycosyl group was most likely replaced by an oxo group *via* a nucleophilic substitution reaction. Subsequent deacetylation afforded the *N*-3 glycosyl hydantoin derivatives **59a** or **59b** [10]. However, formation of the 2-oxo derivative directly from the moisture cannot be excluded. This type of cleavage explains why the deprotection of compounds **5** [10], **30a**–**30e** [34], **35a**–**35m** [37], **39a**–**39h** [38], **6a**–**6d** [39], **43a**–**43l** [41], **47a** or **47b** [10], and **49a** or **49b** [41] in saturated $NH_3/MeOH$ is unsuccessful. Recently, various derivatives of such nucleosides have been prepared [42–44].

The glycosylation of the hydantoins was confirmed by comparison with the previously reported ^1H NMR (*DMSO*-d_6) spectrum of 5-(phenylmethylene)-3-methylhydantoin, which has been characterized by the signal of N^1–H at $\delta = 10.72$ ppm whereas N^3–H of the 1-methylhydanoin analogue resonated at $\delta = 11.38$ ppm [45]. The ^1H NMR spectra of **59a** and **59b** showed an NH signal at $\delta = 10.9$ and 10.70 ppm corresponding to N^1–H, proving the N-3 glycosylation. The glycosylation at N-3 of **59a** was further confirmed by N*O*E experiments. Thus, on irradiation at 10.91 ppm, a large N*O*E enhancement was found for the *ortho* protons of the phenyl group whereas on irradiation of the *ortho* protons a small enhancement was detected for NH. These data proved the (*Z*)-configuration of the exocyclic double bond in **59a** [10] (Scheme 17).

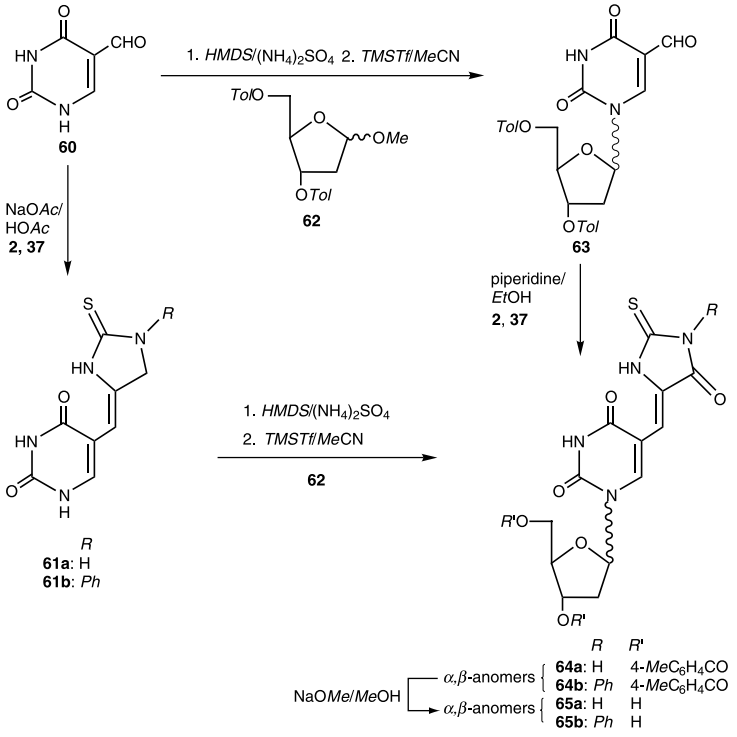


Scheme 17

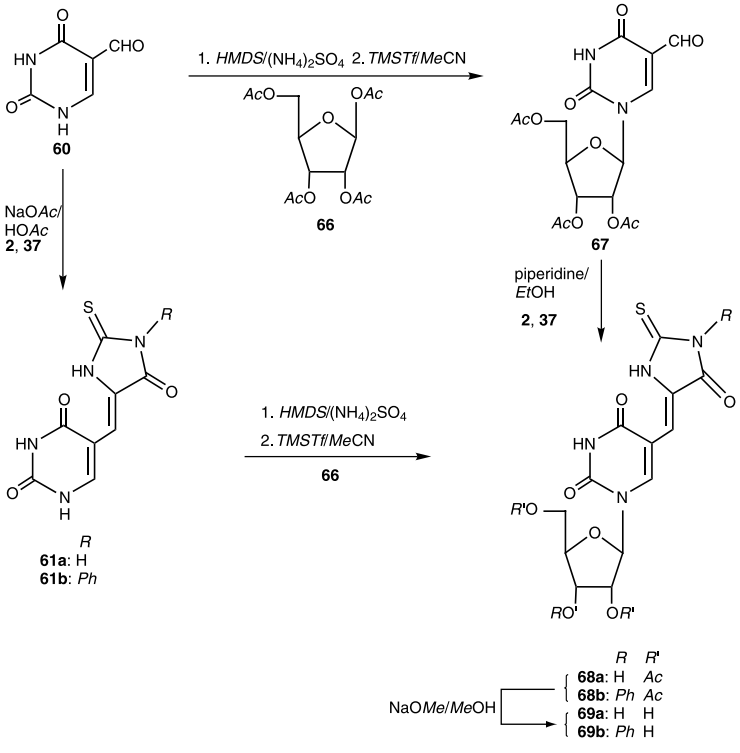
Glycosylation Reactions Involving 5-(Uracil-5-ylmethylene)-2-Thiohydantoin with Furanosyl Sugars

5-Formyluracil (**60**) prepared in two steps from uracil in 30% yield according to Refs. [46, 47] was condensed with **2** or 3-phenyl-2-thiohydantoin (**37**) by refluxing in a mixture of NaO*Ac* and HO*Ac* to give 5-(uracil-5-ylmethylene)-2-thiohydantoin (**61a**) and the 3-phenyl-analogue **61b**. Silylation of **61a** or **61b** with hexamethyldisilazane (*HMDS*) in presence of $(NH_4)_2SO_4$ as the catalyst [48] followed by addition of **62** [49, 50] in the presence of *TMSTf* [51] as a *Lewis* acid and anhyd. *Me*CN as the solvent afforded an anomeric mixture (α/β) of the corresponding 5-[1-(2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranosyl)uracil-5-ylmethylene]-2-thiohydantoins **64a**, **64b**. The glycosylation took place on the pyrimidine and not on the hydantoin ring. This was proven by synthesizing the same nucleosides by an alternative route. Thus, coupling of the silylated derivative of **60** with **62** afforded a mixture of **63** in 63% (α:β = 1:2). Condensation of **63** with **2** and **37** by using piperidine as the catalyst provided the α- and β-anomers of **64a** and **64b**. Deprotection with NaO*Me* in *Me*OH afforded the free nucleosides **65a** and **65b**, which were separated by chromatography [52] (Scheme 18).

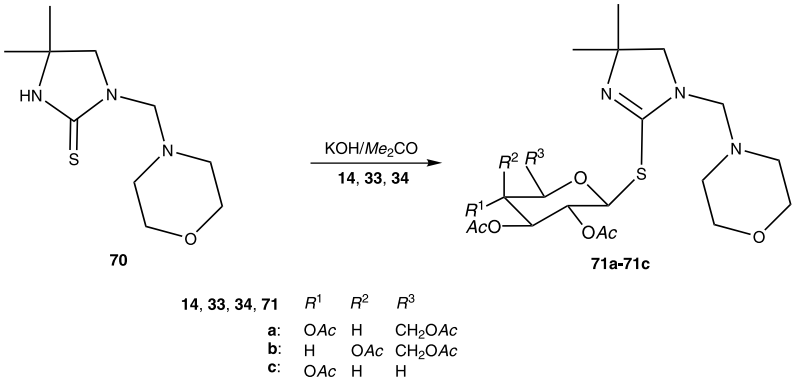
Similar treatment of the silylated 5-formyluracil **60** with **66** resulted in the formation of the uracil nucleoside **67** (72%). Coupling of **67** with **2** or **37** by using piperidine as the catalyst gave the corresponding α/β mixture of 5-(2,3,5-tri-*O*-acetyl-D-ribofuranosyluracil-5-ylmethylene)-2-thiohydantoin (**68a**) and the 3-phenyl analogue **68b**. Only one diastereoisomer of **68** with regard to the new double bond was observed, which most likely is of (*Z*)-configuration as compared to the products obtained from condensation of hydantoins with aldehydes [42]. However, confirmation was not possible because the (*E*)-stereoisomer was not available as a reference. Removal of the acetyl groups of **68a** and **68b** by NaO*Me* in *Me*OH



Scheme 18



Scheme 19



Scheme 20

furnished after chromatography the 5-(β-D-ribofuranosyluracil-5-ylmethylene)-2-thiohydantoins **69a** and **69b**. An alternative route for the synthesis of **68a** involved condensation of the silylated **61a** with the sugar moiety **66** in presence of *TMSTf*. The β-anomer was isolated by chromatography [53]. The N*O*E investigation of **68b** showed a strong enhancement for H-6 on the uracil ring on irradiation of H-2′. This indicated a preferential *anti*-rotamer conformation of the nucleobase around the glycosidic bond [53] (Scheme 19).

2,4-Dithiohydantoin Nucleosides

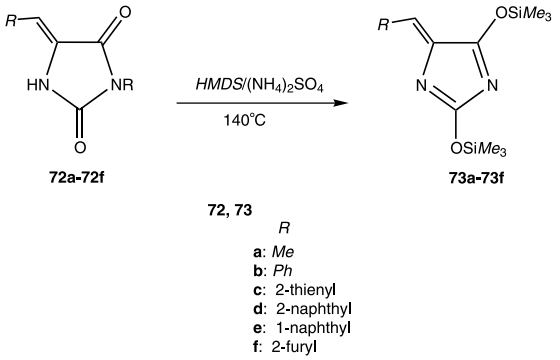
5,5-Dimethyl-3-morpholinomethyl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-hexopyranosyl)-2,4-dithiohydantoins (**71a** and **71b**) and the xylopyranosyl analogue **71c** were synthesized by the reaction of 5,5-dimethyl-3-morpholinomethyl-2,4-dithiohydantoin (**70**) with **14**, **33**, and **34** in presence of aqueous KOH and acetone at 23°C [37] (Scheme 20).

Hydantoin Nucleosides

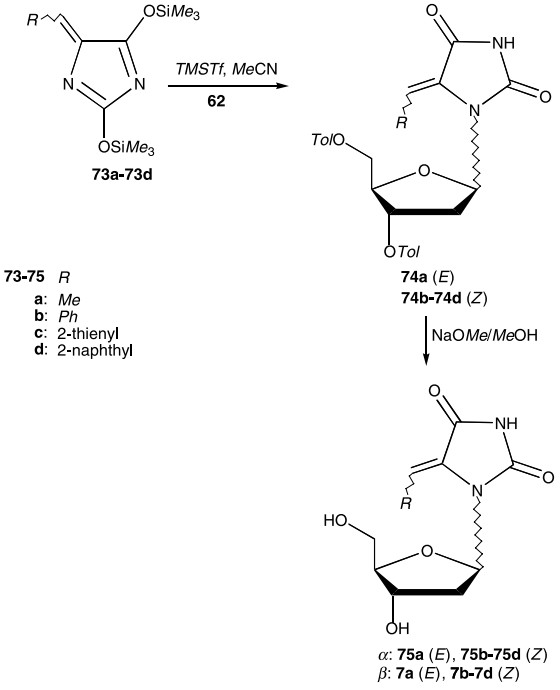
Nitrogen Glycosylation Reactions Involving Hydantoins with Furanosyl Sugars

N-1 Glycosylation Reactions

It has been reported that silylation of hydantoin bases occured on both amido groups to give the bis- silylated derivatives, such as the silylated 5-alkylidene-**73a** and 5-arylidene-2,4-imidazolidinediones **73b–73f** (Scheme 21). Various hydantoin nucleosides have been synthesized by coupling the silylated hydantoins with the sugar precursors in the presence of a *Lewis* acid. For example, 1-(2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-D-*erythro*-pentofuranosyl)-5-(substituted methylene)-2,4-imiazolidinediones **74a–74d** were obtained in 60–80% (*E*/*Z*), as reported by *Vorbrüggen et al.* [51, 54], by coupling of **73a–73d** with **62** in presence of *TMSTf*. No other nucleoside was detected in this reaction. Removal of the toluoyl group of **74a–74d** with NaO*Me* in *Me*OH at 23°C furnished the free nucleosides (*E*/*Z*)



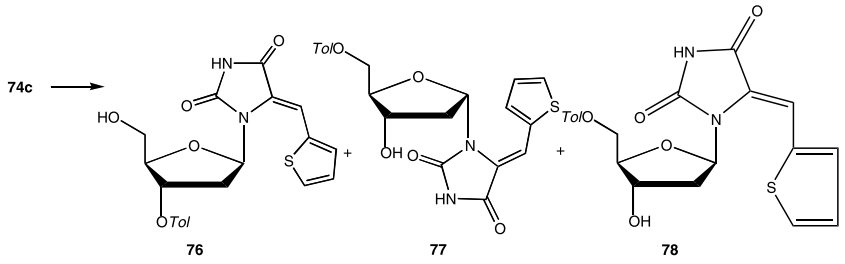
Scheme 21



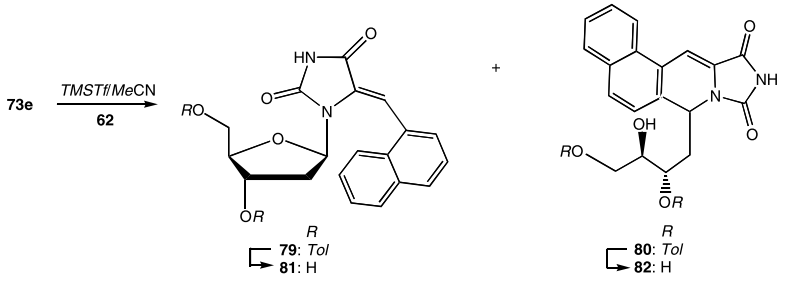
Scheme 22

7a–**7d** and **75a**–**75d** [12] (Scheme 22). Unexpectedly, treatment of **74c** with $NH_3/MeOH$ at 23°C showed incomplete reaction even after 3 days, and instead the three partially protected nucleosides **76**–**78** were isolated. Characteristic downfield shifts were observed for H-5′ in the ^1H NMR spectra of the α/β mixture **77** and **78** in comparison with those of H-5′ of the 5′-*O* deprotected **76** [12] (Scheme 23).

When the trimethylsilyl derivative **73e** was condensed with **62** in the presence of *TMSTf* at −10°C for 3 days, two products were isolated, namely (*Z*)-l-(2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-*D*-*erythro*-pentofuranosyl)-5-(1-naphthylmethylene)-2,4-imidazolidinedione (**79**) and 7-[2,4-bis-*O*-(4-methylbenzoyl)-l-deoxy-*D*-erythrit-l-yl]benz[*f*]imidazo[l,5-*b*]isoquinoline-9,11-(7*H*,10*H*)-dione (**80**). These were separated by chromatography in 20 and 50% yields. The free



Scheme 23

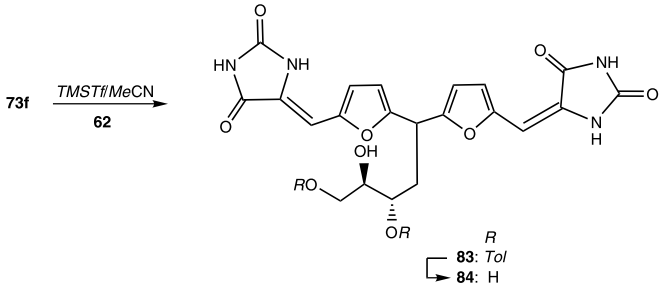


Scheme 24

nucleosides **81** and **82** were obtained by treatment with NaO*Me* in *Me*OH at 23°C [12] (Scheme 24).

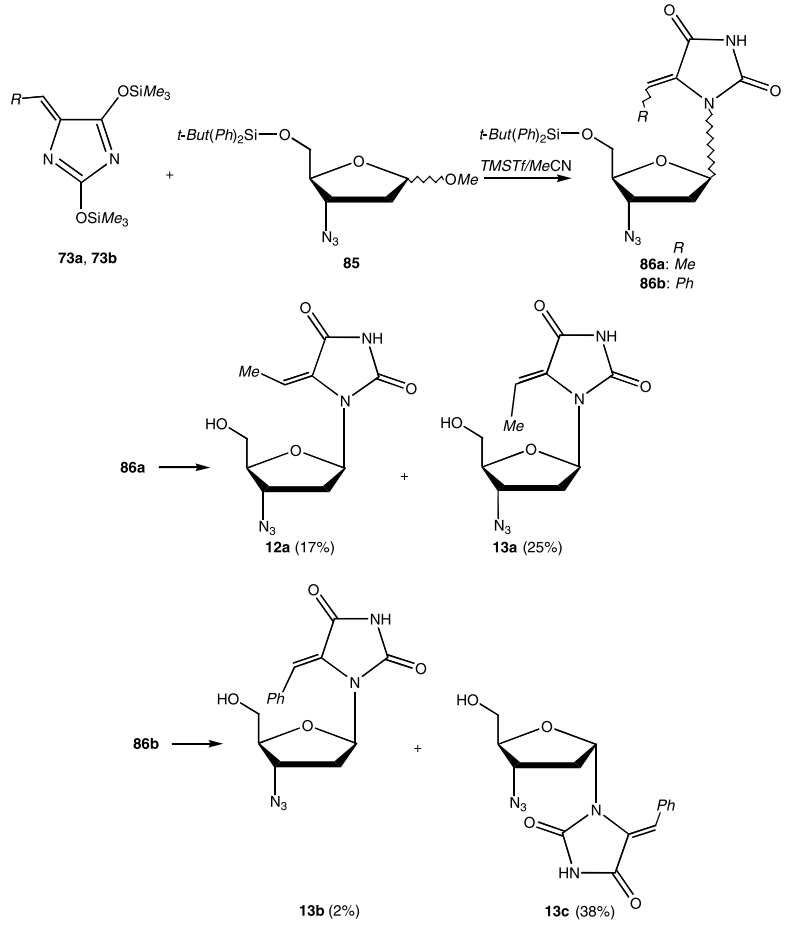
Additional hydantoins bearing different substituents were prepared such as the (2*S*,3*S*)-1,3-bis-*O*-(4-methylbenzoyl)-5,5-bis[5-[2,4-dioxo-5-imidazolidinylidene)-methyl]furan-2-yl]pentane-1,2,3-triol (**83**) (21%) from coupling of the trimethylsilyl derivative **73f** with **62** in presence of *TMSTf* at −10°C for 3 days. Removal of the protecting toluoyl groups from **83** with NaO*Me* in *Me*OH at 23°C furnished **84** [12] (Scheme 25).

Interesting examples of hydantoin nucleosides were synthesized by coupling the azido sugar derivative **85** [55] with the silylated bases **73a**, **73b** in presence of *TMSTf* to give the 1-(3-azido-5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-D-*erythro*-pentofuranosyl)-5-(alkylmethylene)-2,4-imidazolidinediones **86a**, **86b**. The nucleoside **86a** was isolated as a 4:1 (α:β) anomeric mixture (E/Z) in 46% yield, while **86b** was isolated as a 4:1 (α:β) mixture (50%). Deprotection of **86a** with tetrabu-

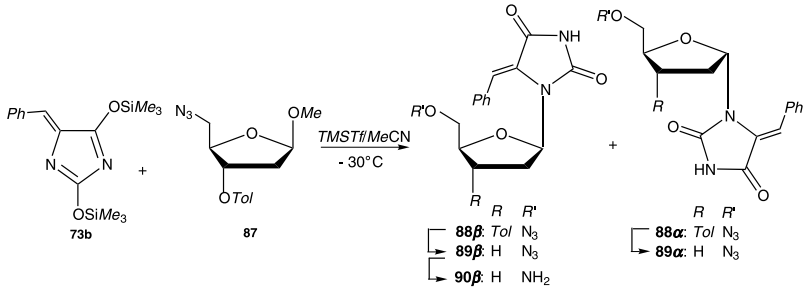


Scheme 25

tylammonium fluoride in *THF* at 23°C provided the (*E*)-l-(3-azido-2,3-dideoxy-β-*D*-*erythro*-pentofuranosyl)-5-ethylidene-2,4-imidazolidinedione (**12a**) (17%) and the (*Z*)-isomer **13a** (25%). In a similar manner, (*Z*)-l-(3-azido-2,3-dideoxy-β-*D*-*erythro*-pentofuranosyl)-5-(phenylmethylene)-2,4-imidazolidindione (**13b**) and the α-anomer **13c** were obtained from **86b** in 2% and 38% yields [27] (Scheme 26).



Scheme 26



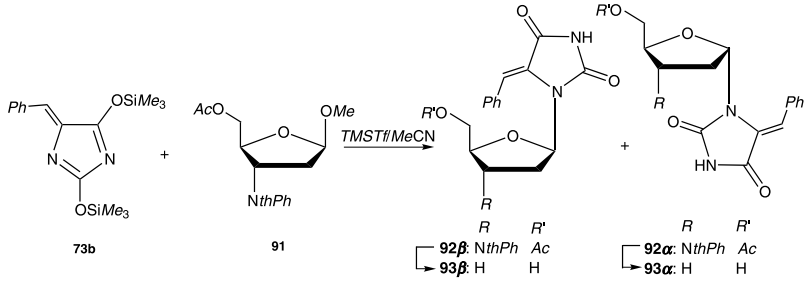
Scheme 27

Pedersen et al. [56] have described the synthesis of (*Z*)-2,4-imidazolidinedione nucleosides **88** (22%) as α:β (1:1) mixture by coupling of **87** with **73b** at -30°C in presence of *TMSTf*. Removal of the toluoyl group of **88** was employed by treatment with NaO*Me* in *Me*OH at 23°C to give (*Z*)-l-(5-azido-2,5-dideoxy-*D-erythro*-pentofuranosyl)-5-(phenylmethylene)-2,4-imidazolidinediones (**89**), which were separated by chromatography. Reduction of **89*β*** with tin(II) chloride in *Me*OH afforded the corresponding amino analogue **90*β*** in 10% yield (Scheme 27).

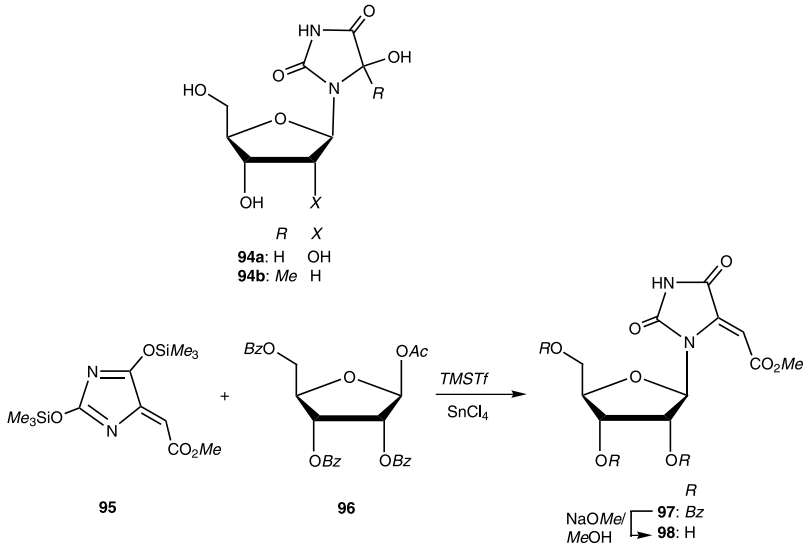
Similarly, condensation of **73b** with the sugar derivative **91** [57] in presence of *TMSTf* at -30°C yielded the α:β (4:5) mixture of (*Z*)-l-(5-*O*-acetyl-2,3-dideoxy-3-phthalimido-*D-erythro*-pentofuranosyl)-2,4-imidazolidinediones (**92**) (22%), which were isolated by chromatography. Removal of the phthaloyl group was performed of both α- and β-anomers with methylamine in abs. *Et*OH at 23°C to furnish the free nucleoside **93*β*** as well as **93*α*** (Scheme 28).

N-3 Glycosylation Reactions

Muramatsu et al. [58, 59] have reported the formation of 1-glycosylated 5-hydroxyhydantoins **94a** and **94b** by ozonolysis of cytidine, uridine, and thymidine as



Scheme 28



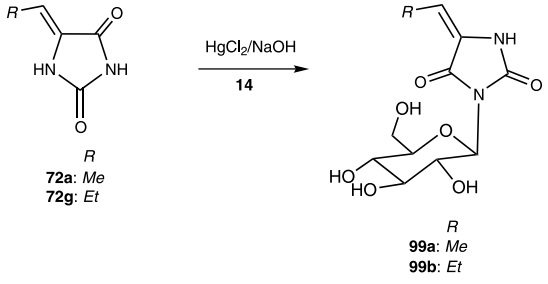
Scheme 29

examples of *N*-3-glycosyl hydantoin nucleosides. These were followed by syntheses of interesting nucleosides, such as 3-(2,3,5-tri-*O*-benzoyl-β-*D*-ribofuranosyl)-5-(carbomethylidene)hydantoin (**97**), which was obtained predominately by coupling of the silylated hydantoin **95** with **96** using $SnCl_4$ as *Lewis* acid and CH_2Cl_2 as the solvent. Debenzoylation of **97** with NaO*Me* in *Me*OH yielded the corresponding free nucleoside **98** [60] (Scheme 29).

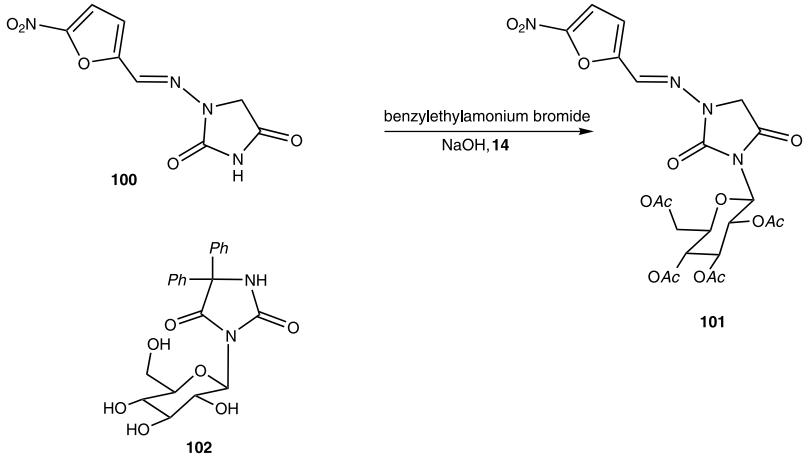
Nitrogen Glycosylation Reactions Involving Hydantoins with Pyranosyl Sugars

Mentzer et al. [61] have synthesized 5-alkylidene-3-(β-*D*-glucopyranosyl)hydantoins **99a** and **99b** by coupling 5-alkylidenehydantoins **72a** and **72g** with **14** in the presence of $HgCl_2$ and NaOH (Scheme 30).

Powell et al. [62, 63] have reported the synthesis of β-*D*-glucopyranosylnitrohydantoin **101** by dissolving **100** and benzylethylammonium bromide in aqueous NaOH followed by treatment with a solution of **14** in $CHCl_3$. Compound **101** was also prepared by an alternative method from **100** and **14** under phase transfer catalyst conditions [64]. More examples in the series of *N*-3 hydantoin nucleosides bearing pyranosyl sugars have been reported, such as the 3-(β-*D*-glucopyranosyl)-5,5-diphenylhydantoin (**102**) [64] (Scheme 31).



Scheme 30



Scheme 31

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