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Modifications at the C(5) position of pyrimidine nucleosides

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This review summarizes the state of knowledge on the chemical methods of C(5)-modifications of uridine and cytidine derivatives and may serve as a useful tool for synthetic chemists to choose an appropriate reaction protocol. The synthesis of 5-substituted uracil derivatives is gaining an increasing interest because of their possible applications in medicine and pharmacy. Modifications at the C(5) position of pyrimidine nucleosides can enhance their biostability, bioavailability or(and) biological activity. Among the C(5)-modified nucleosides, 5-halopyrimidines exhibit anticancer, antiviral, radio- and photosensitizing properties. Besides 5-halo-substituted derivatives, there are other examples of nucleosides with confirmed biological activity containing a C – C bond at the C(5) position in the pyrimidine ring. In recent decades, scientists have achieved great progress in the field of cross-coupling reactions. Among them, nickel-catalyzed processes provide a broad spectrum of synthetic methods that are based on less toxic and cheaper starting materials. This review summarizes the synthetic approaches based on the coupling or halogenation reactions, which enable 5-substituted pyrimidine nucleosides to be obtained. Moreover, the importance of the systems considered for medicine and pharmacy is briefly discussed.
The bibliography includes 197 references.

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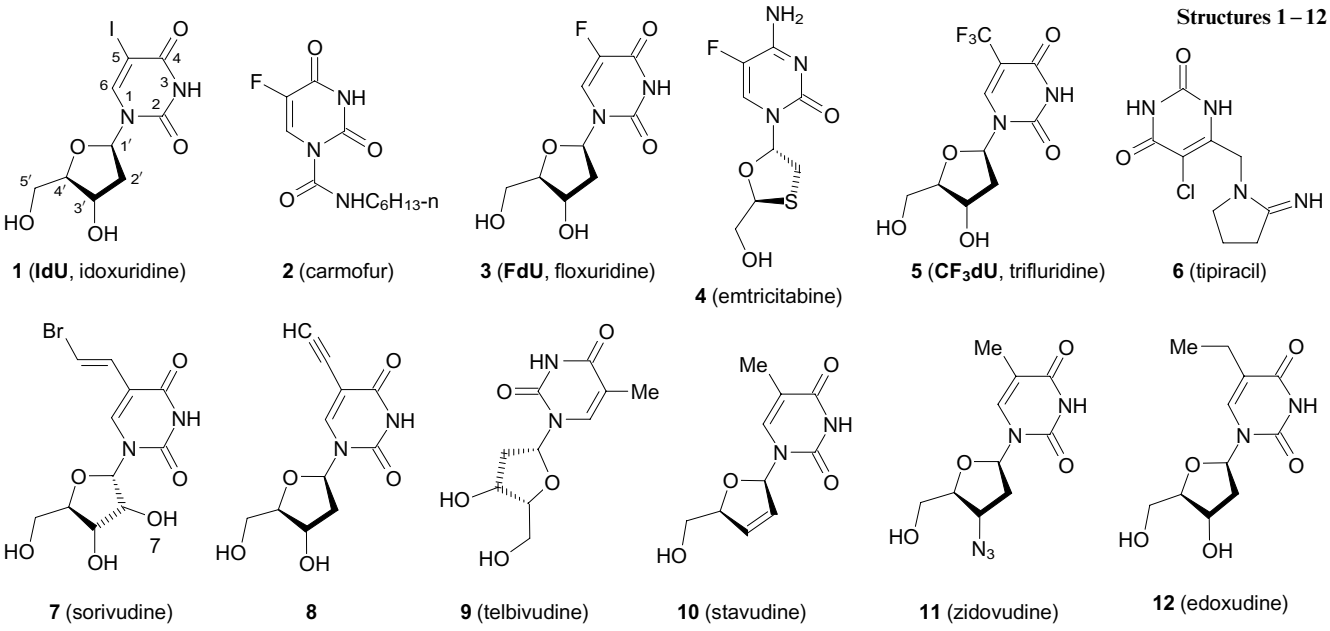
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1. Introduction

The synthesis of 5-substituted uracil derivatives is gaining increasing interest because of their biological activities.[1 – 3] Chemical modification at the C(5) position of pyrimidine nucleosides can enhance their biostability and bioavailability or change their effect on an organism.[4, 5] Among the C(5)-modified nucleosides, 5-halopyrimidines exhibit anticancer, antiviral, radio- and photosensitizing properties. Research carried out with these compounds, revealed an important information regarding their cellular biochemistry and affinity towards transporter proteins; moreover, enzyme – substrate specific interactions have been elucidated with their help.[6, 7]

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Structures 1 – 12



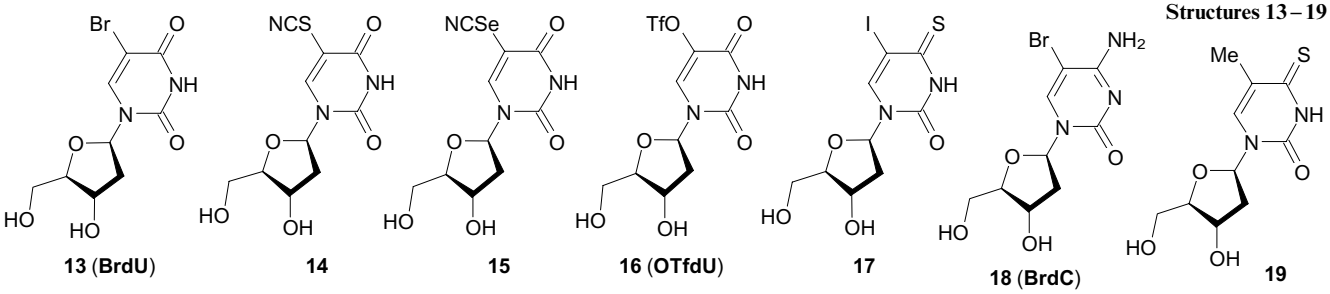
There are several drugs based on 5-halo-modified pyrimidine nucleosides available on the market, *e.g.*, 5-iodo-2′-deoxyuridine **1** (**IdU**, idoxuridine — INN; Stoxil™ and Herplex Liquifilm™) used against feline herpes virus (FHV-1)[8] or 1-hexylcarbamoyl-5-fluorouracil (**2**, carmofur — INN; Mifurol™) employed against resected colorectal cancer.[9] 5-Fluorouracil-based compounds are popular antimetabolites, among which 5-fluoro-2′-deoxyuridine **3** (**FdU**, floxuridine — INN, FUDR™) is a well-known anticancer drug used in colorectal, kidney and stomach cancer therapy.[10] 5-Fluorocytidine derivative **4** (emtricitabine — INN; Emtriva™) is used in the treatment of human immunodeficiency virus (HIV).[11] In addition, 5-chlorouridine derivatives are also known to possess anti-HIV activity,[12] while 5-halopyrimidine nucleosides are active against the varicella-zoster virus (VZV).[13]

Besides 5-halo-substituted derivatives, there are some other examples of nucleosides with confirmed biological activity containing a C—C bond at the C(5) position in the pyrimidine ring. One of them, 5-trifluoromethyl-2′-deoxyuridine **5** (**CF_3dU**, trifluridine — INN; Viroptic™) is used against herpes simplex virus (HSV-1 and HSV-2)[14,15] and, in combination with tipiracil **6** (Lonsurf™), against metastatic colorectal cancer.[16] Another example is the nucleoside **7**, which consists of 5-bromovinyluracil moiety connected to D-arabinose (sorivudine — INN; Usevir™ and Brovavir™).[17] This substance is a potent anti-HSV-1, -VZV and -Epstein—Barr virus (EBV) drug. Some other examples of 5-substituted nucleosides with confirmed biological activities are: 5-ethynyl-2′-deoxyuridine **8** used against herpes simplex-1 strain LYONS and KOS,[18] the L-isomer of thymidine **9** (telbivudine — INN; Tyzeka™) — anti-HBV,[19] 2′,3′-didehydro-3′-deoxythymidine **10** (stavudine — INN; Zerit™) — anti-HIV,[20] 3′-azido-3′-deoxythymidine **11** (zidovudine — INN; Retrovir™) — anti-HIV[21] and 5-ethyl-2′-deoxyuridine **12** (edoxudine — INN; Aedurid™ and Virostat™) — anti-HSV agents.[22]

Other interesting features of 5-substituted nucleosides are their radio- and photosensitizing properties associated with an ability to undergo dissociative electron attachment (DEA)[23] and photo-induced electron transfer (PET), respectively.[24] These phenomena occur in deoxyribonucleic acid (DNA) labelled with uracil nucleosides possessing a substantial electron affinity and relatively weak C(5)—X bond or the consecutive bond within the X substituent.[25,26] It should be noted that hydrated electrons (e_{aq}^-), the second most abundant product of water (the main constituent of every cell) radiolysis,[27] attach to high electron affinity sites in DNA (to radiosensitizing nucleosides in the labelled DNA) and trigger a low-barrier or barrierless DEA if the bonds mentioned above are sufficiently weak, which makes hydrated electron transfer an irreversible process.[28,29] DEA itself, in turn, produces reactive radicals, which undergo secondary hydrogen transfer reactions leading to strand breaks or cross-links.[30,31] Although e_{aq}^- easily attaches to native DNA, a competitive protonation of the anions formed on pyrimidines (sites of the highest electron affinity in the native DNA) prevents the formation of strand breaks.[32] The protonation is not an issue for the labelled

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Structures 13 – 19



13 (**BrdU**) **14** **15** **16** (**OTfdU**) **17** **18** (**BrdC**) **19**

Tf is triflate

DNA due to the swift dissociation triggered by DEA. The most thoroughly studied compound in this class of nucleosides is 5-bromo-2′-deoxyuridine **13** (**BrdU**),[33,34] which easily incorporates into DNA during replication or repair of the latter.[35] As a result, **BrdU**-labelled cells are 3 – 4 times more sensitive to ionizing radiation than those from the control.[36–39] Other examples of such compounds are: 5-thiocyanato- **14**, 5-selenocyanato- **15**, 5-trifluoromethanesulfonyl- **16** (**OTfdU**) and 5-iodo-4-thio-2′-deoxyuridine **17**.[40–42]

As far as PET is concerned, the maximum yield of photoinduced damage (SSB) occurs for DNA sequences such as 5′-GAA**BrdU**, in which the photosensitizer (**BrdU 13**) is separated from guanine by two adenine moieties.[43,44] Such configuration assures the most efficient electron transfer between the photoexcited **BrdU 13** (the photooxidant) and guanine of the lowest ionization potential among the native nucleobases.[45] The ground state anion of **BrdU 13** formed due to such long-range ET undergoes dissociation similar to that observed for DEA triggered by the above e^-_{aq} attachment to the labelled DNA.[46] A similar PET process was observed for the oligonucleotide labelled with 5-bromo-2′-deoxycytidine (**BrdC**) **18**.[47] On the other hand, the photoinduced formation of intra-strand thiethane is probably responsible for the cytotoxicity of 4-thiothymidine **19** incorporated into cellular DNA.[1,48]

In the current review, we gathered methods of chemical modification of pyrimidine nucleosides at the C(5) position. Taking into account the above-mentioned facts, it is clear that many biologically active pyrimidine nucleosides contain a C – C bond or halogen atom. Therefore, it is essential to possess a wide range of distinct methods for their synthesis. In recent decades, a great progress in the field of cross-coupling reactions has been made.[49] Among them, nickel-catalyzed processes provide a broad spectrum of synthetic applications that are based on less toxic and cheaper starting materials.[49] Many of the coupling reactions proceed in aqueous solutions, which make them environmentally friendly.[50,51] It is worth noting that in the synthesis of 5-substituted pyrimidine nucleosides, more than coupling or halogenation reactions should be considered. Indeed, various synthetic methods for the introduction of a wide range of other substituents at the C(5) position are described in the recent literature. During the chemical synthesis of such compounds, chemists often have to decide whether to protect hydroxyl groups present in the sugar unit. In many cases, it is inevitable. On the one hand, the overall synthetic procedure is extended by additional protection and deprotection steps, while, on the other hand, protected intermediates become more hydrophobic, which usually facilitates the purification step. This review, in an accessible way, summarizes the state of knowledge about the chemical methods of C(5) modifications of uridine and cytidine derivatives. As far as we know, previous review papers concerning this topic appeared as early as in 1972[52] and 1988.[53]

The following abbreviations are used in the current review:

ACN — acetonitrile,
BAIB — [bis(acetoxy)iodo]benzene,
BOC — *tert*-butoxycarbonyl,
bpy — 2,2′-bipyridine,
BrC — 5-bromocytidine,
BrdC — 5-bromo-2′-deoxycytidine,
BrdU — 5-bromo-2′-deoxyuridine,
BrU — 5-bromouridine,
Bz — benzoyl,
CAN — ceric ammonium nitrate,
CF_3dU — 5-trifluoromethyl-2′-deoxyuridine,
ClC — 5-chlorocytidine,
CldC — 5-chloro-2′-deoxycytidine,
CldU — 5-chloro-2′-deoxyuridine,
ClU — 5-chlorouridine,
m-CPBA — *m*-chloroperoxybenzoic acid,
dba — dibenzylideneacetone,
DEA — dissociative electron attachment,
DIPEA — diisopropylethylamine,
DMA — *N*,*N*-dimethylacetamide,
DMDO — dimethyldioxirane,
DMP — Dess – Martin periodinane,
DMTr — 4,4′-dimethoxytrityl,
DNA — deoxyribonucleic acid,
DTT — dithiothreitol,
e^-_{aq} — hydrated electron,
EBV — Epstein – Barr virus,
EDC — 1,2-dichloroethane,
EDTA — ethylenediaminetetraacetic acid,
fac-Ir(ppy)$_3$ — *fac*-tris(2-phenylpyridine)iridium,
FdU — 5-fluoro-2′-deoxyuridine,
FHV — Feline Herpes Virus,
FU — 5-fluorouridine,
HIV — Human Immunodeficiency Virus,
HMDS — 1,1,1,3,3,3-hexamethyldisilazane,
HMPA — hexamethylphosphoramide,
HSV — Herpes Simplex Virus,
IC — 5-iodocytidine,
IdC — 5-iodo-2′-deoxycytidine,
IdU — 5-iodo-2′-deoxyuridine,
IU — 5-iodouridine,
LDA — lithium diisopropylamide,
MedU — 5-methyl-2′-deoxyuridine,
MMTr — 4-methoxytrityl,
[MoeMIm][Ms] — 1-methoxyethyl-3-methylimidazolium methanesulfonate,

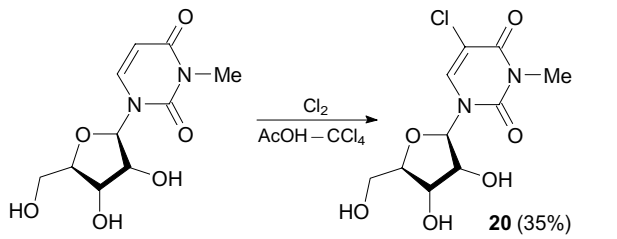
[MoeMIm][TFA] — 1-methoxyethyl-3-methylimidazolium trifluoroacetate,
MW — microwave irradiation,
NADPH — nicotinamide adenine dinucleotide,
NBS — *N*-bromosuccinimide,
NCS — *N*-chlorosuccinimide,
NH_2dC — 5-amino-2′-deoxycytidine,
NH_2dU — 5-amino-2′-deoxyuridine,
NH_2U — 5-aminouridine,
NIS — *N*-iodosuccinimide,
NMO — *N*-methylmorpholine,
NO_2dC — 5-nitro-2′-deoxycytidine,
NO_2dU — 5-nitro-2′-deoxyuridine,
NO_2U — 5-nitrouridine,
OHdC — 5-hydroxy-2′-deoxycytidine,
OHdU — 5-hydroxy-2′-deoxyuridine,
OHU — 5-hydroxyuridine,
OTfdU — 5-trifluoromethanesulfonyl-2′-deoxyuridine,
OTfU — 5-trifluoromethanesulfonyluridine,
PET — photo-induced electron transfer,
PTABS — 1,3,5-triaza-7-phosphaadamantane butane sulfonate,
PTAPS — 1,3,5-triaza-7-phosphaadamantane propane sulfonate,
Py — pyridine,
SHdU — 5-mercapto-2′-deoxyuridine,
SMBI — sodium monobromoisocyanurate,
SSB — maximum yield of photoinduced damage,
TBAF — tetrabutylammonium fluoride,
TBDMS — *tert*-butyldimethylsilyl,
TEMPO — 2,2,6,6-tetramethyl-1-piperidinyloxyl,
TFA — trifluoroacetic acid,
Th — thienyl,
TMCS — trimethylchlorosilane,
TMEDA — *N*,*N*,*N*′,*N*′-tetramethylethylenediamine,
VZV — Varicella-Zoster Virus.

2. Halogenation

2.1. Chlorination

The synthesis of 5-chlorouridine derivative was first reported by Visser *et al.*,[54] who obtained 5-chloro-3-methyluridine **20** by the reaction between 3-methyluridine and chlorine in acetic acid (Scheme 1).

Scheme 1



Fukuhara and Visser[55] obtained 5-chlorocytidine **21** (**ClC**) by a three-step protocol (Table 1, entry 1). At first, cytidine was transformed into its triacetate analogue, which was submitted to the radical reaction with chlorine. After a deprotection step with ammonia in methanol, the product was crystallized from ethanol. The overall yield of the process was 41%.[55] Three years later, the same synthetic protocol was used by Frisch and Visser[56] for the initial synthesis of 5-chloro-2′-deoxycytidine **22** (**CldC**) (see Table 1, entry 1) in higher (62%) yield.

Another valuable method to introduce the chlorine substituent at the C(5) position of cytidine with use of *N*-chlorosuccinimide (NCS) in an inert solvent was first reported in 1969 (**ClC 21**, Table 1, entry 2). However, the authors of this patent did not provide a detailed synthetic procedure and the yield of the product.[57]

Kikugawa *et al.*[58] modified the above procedure by carrying out the reaction of cytidine with NCS in a glacial acetic acid at 105 °C. After crystallization from ethanol, **ClC** (**21**) and 5-chlorouridine (**23**, **ClU**) were obtained in 61% yields in both cases.

A different approach to chlorination at the C(5) position was described by Ryu and MacCoss.[59] The reaction proceeded with a treatment of cytidine, 2′-deoxycytidine or uridine with *m*-chloroperoxybenzoic acid (*m*-CPBA) in the presence of HCl in *N*,*N*-dimethylacetamide (DMA) at room temperature to afford compounds **21** – **23** respectively (see Table 1, entry 3). Compared to previously given examples, this chlorination protocol has a few advantages: reactions are carried out under mild conditions, the yields are higher and the reaction times are relatively short (3 h).

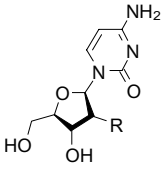
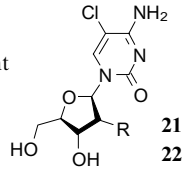
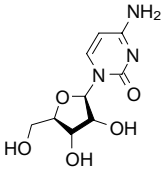
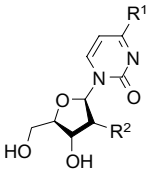
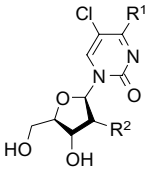
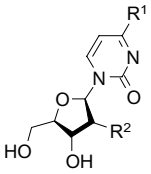
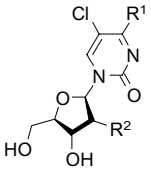
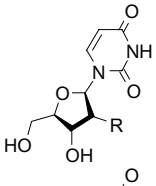
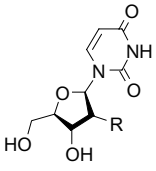
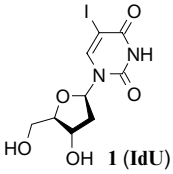
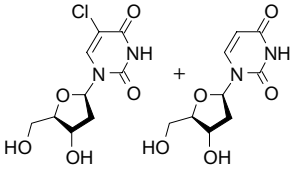
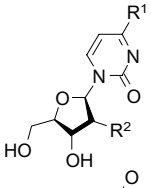
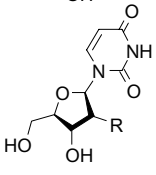
In 1989, compounds **21**, **23** and their 2′-deoxy analogues [**22** and **24** (**CldU**)] were obtained *via* the oxidative chlorination of appropriate nucleosides with a clorine cation, generated *in situ* in the reaction of benzoyl (BzCl) or acetyl chloride (AcCl) with DMF to produce the chloride anion, which was oxidized with *m*-CPBA solution in DMF at the next step (see Table 1, entry 4).[60] The reactions were carried out at room temperature without the protection of hydroxyl groups within the sugar moiety, giving products in moderate (44% – 54%) yields.

Ceric ammonium nitrate (CAN) is a very useful oxidizing agent in laboratory practice. For instance, it oxidizes secondary alcohols to ketones,[61] benzylic alcohols to aldehydes,[61] and sulfides to sulfoxides.[62] CAN has also received much attention in the carbon – halogen bond formation reaction.[63] A reaction of non-protected nucleosides with lithium chloride, mediated by CAN, afforded the corresponding 5-chloro derivatives **23** and **24** in high yields (Table 1, entry 5).[64] Chlorination was performed in acetonitrile (ACN) – AcOH solution at 80 °C for 6 h. The addition of AcOH significantly improved the kinetics of the reaction and shortened it by up to four times. This protocol works well with acetyl-protected nucleosides as well.

A mild and highly efficient chlorination method was proposed by Kumar *et al.*,[65] who used NCS as the chloride anion source. When treated with NCS at room temperature, acetylated or non-acetylated uridines generated chloronium cations that subsequently reacted with NaN_3 to give 5-chloro-6-azido-5,6-dihydro-intermediates. These derivatives were then converted to their 5-chloro analogues **ClU** (**23** and **ClduU** (**24**) by mild heating to 45 °C in 45% and 84% yields, respectively (see Table 1, entry 6).

A crucial observation was reported in 1999. It was found that a DNA fragment with **IdU** (**1**) in its structure can undergo a halogen exchange at the sp^2-carbon of **1** mediated by photoirradiation (see Table 1, entry 7). Researchers managed to replace the iodine atom in **IdU** (**1**) with chlorine and bromine, but they failed with the fluorine one.[66] The reaction goes through a plausible $S_{RN}1$ mechanism, which comprises the creation of an excited state of 5-iodo-2′-deoxyuridine; at the second step, this reacts with a chloride

Table 1. Chlorination methods for uridine and cytidine.

Entry	Substrate	Step	Reagent	Reaction conditions				Product	Yield (%)	Ref.
				catalyst	solvent	T/°C	t/h(min)			
1		1 2 3	AcOH Cl_2, UV –	– – NH_3	Py CCl_4 MeOH	0 rt rt	Overnight 72 h	 **21** (**ClC**): R = OH; **22** (**CldC**): R = H **21**, **22**	41, 62	55, 56
2		1	NCS	–	AcOH	–	–	**21** (**ClC**)	n/a, 61	57, 58
3		1	HCl	*m*-CPBA	DMA or DMF	rt	3 h	 **21**, **22**: $R^1 = NH_2$; **23**: $R^1 = R^2 = OH$ **21 – 23** (**ClU**)	56 – 90	59
4		1	BzCl	*m*-CPBA	DMF	rt	30 min	 **21 – 23**, **24**: R^1 = OH, R^2 = H **21 – 24** (**CldU**)	44 – 54	60
5		1	LiCl	CAN	ACN, AcOH	80	6 h	**23**: R = OH, **24**: R = H	88, 94	64
6		1	NCS	NaN_3	1,2-dimethoxyethane	45	8 – 12 h	**23**: R = OH, **24**: R = H	45, 84	65
7	 **1** (**IdU**)	1	*hv*, NaCl	irradiation at 302 nm	H_2O	0	10 min	 **24** (**CldU**)	19	66
8		1	NCS	–	[MoeMIm][Ms]	50	20 min	**21 – 24**	84 – 92	69
9		1	LiCl	CAN	[MoeMIm][Ms]	50	5 h	**23**, **24**	30, 32	70

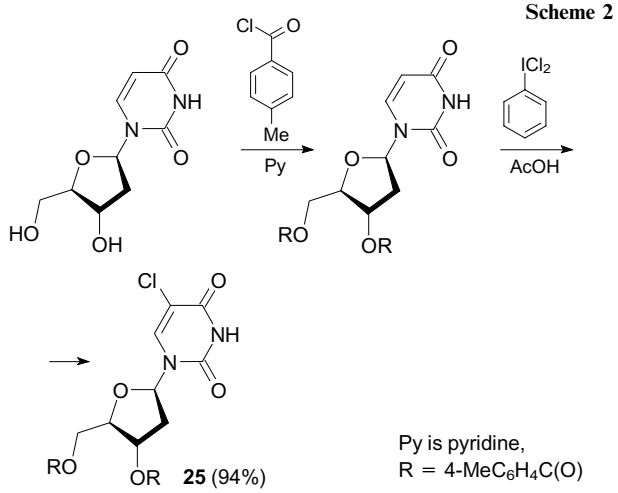
NCS is *N*-chlorosuccinimide, CAN is ceric ammonium nitrate, [MoeMIm][Ms] is 1-methoxyethyl-3-methylimidazolium methanesulfonate, DMA is *N*,*N*-dimethylacetamide, *m*-CPBA is *meta*-chloroperoxybenzoic acid, n/a is not available.

anion to form a corresponding radical anion.[67,68] The reaction can terminate to give 2′-deoxyuridine or **CldU** (**24**), which means that it is not chemoselective. **CldU** (**24**) and 2′-deoxyuridine were obtained in the yields of 19% and 30%, respectively, in a 4 M NaCl solution irradiated with a transilluminator (302 nm) for 10 min, reaching the consumption of **IdU** (**1**) at the 49% level. In this case, a halogen-elimination dominates over a halogen-exchange reaction.

In 2009, Kumar's research group[69] published two articles describing very efficient and environmentally friendly novel chlorination methods for uridine, cytidine and their 2′-deoxy analogues using ionic liquids as solvents. However, in fact, they have modified already existing protocols. In the first example, C(5)-chlorination was achieved through the treatment of an appropriate nucleoside with NCS in an ionic liquid, thus omitting the use of the catalyst, *i.e.* AcOH (see Table 1, entry 8). The reactions proceeded in very good yields in all cases (84% – 92%). The highest yields were achieved in the case of uridine and cytidine at 50 °C using 1-methoxyethyl-3-methylimidazolium methanesulfonate ([MoeMIm][Ms]) ionic liquid. The second work published in the same year related to the CAN-mediated method.[70] A solution of ACN – AcOH, previously used as a solvent mixture, was replaced by the ionic liquid (see Table 1, entry 9). Although the yields for products **23** and **24** were relatively low (30% and 58%), the authors managed to obtain **CldU** (**24**), which was not accessible through the already reported CAN-based method. The highest yields were achieved again with the use of the [MoeMIm][Ms] ionic liquid.

An interesting method for utilizing iodobenzene dichloride as a chloride anion source was introduced in 1982 by Robins *et al.*[71] With this method, 3′,5′-di-*O*-4-methylbenzoyl-5-chloro-2′-deoxyuridine **25** was obtained (Scheme 2). A major benefit of this method was the very short reaction time (15 min) while keeping the yield at an excellent level.

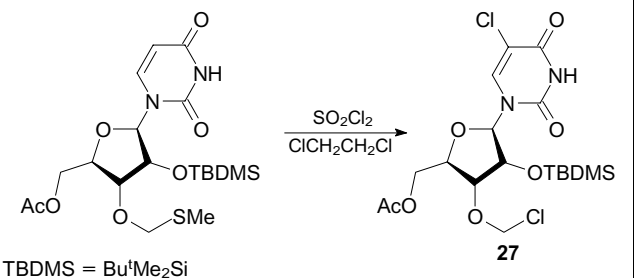
Scheme 2



A plausible mechanism for this reaction could be based on the report of Liu *et al.*[72] Although their two assumptions related to the reaction of iodobenzene dichloride with alkenes in the presence of DMF, it is possible to adapt these schemes to the described case. Thus, two alternative pathways can be suggested. The first mechanism comprises a nucleophilic attack of an acetic acid molecule on iodobenzene dichloride, followed by deprotonation. The key intermediate (confirmed with ^{1}H NMR spectrum and LC-MS analysis data) obtained in this way reacts in the next step with 3′,5′-di-*O*-*p*-toluoyl-2′-deoxyuridine to afford eventually the 5-chloro-6-acetoxy-5,6-dihydro analogue of 2′-deoxyuridine **26** (Scheme 3). The second hypothetic mechanism premises a reaction between 3′,5′-di-*O*-4-methylbenzoyl-2′-deoxyuridine and iodobenzene dichloride to form a chloronium cation, which, at the next step, reacts as an electrophile with an acetic acid molecule. After deprotonation, compound **26** is formed (see Scheme 3). According to the authors' opinion, compound **26** can undergo an extra elimination step to form the desired product **25**, which is possible due to the increased acidity of the H(5) proton.

In 2000, trying to obtain the 3′-*O*-chloromethyl derivative of uridine from its 3′-*O*-methylthiomethyluridine analogue, Zavgorodny *et al.*[73] noticed that an additional chlorination side reaction at the C(5) position in pyrimidine base occurred giving compound **27** in an unstated yield (Scheme 4). In this case, it was undesirable and unexpected, but examples of using SO_2Cl_2 as a chlorinating agent for uridine derivatives have been known in chemical literature.[74 – 76] The authors mentioned that when 2′-*O*-methylthiomethyluridine analogue was treated with SO_2Cl_2, no chlorination was observed at the C(5) position in the pyrimidine moiety under the same reaction conditions.

Scheme 4



2.2. Bromination

The first example of uridine bromination at the C(5) position was reported by Levene and La Forge,[77] who treated uridine with bromine water to afford 5-bromouridine **28** (**BrU**) in an unstated yield (Table 2, entry 1).

The same synthetic protocol similar to that described for chlorination[55,56] (see Table 1, entry 1) was used to synthe-

Scheme 3

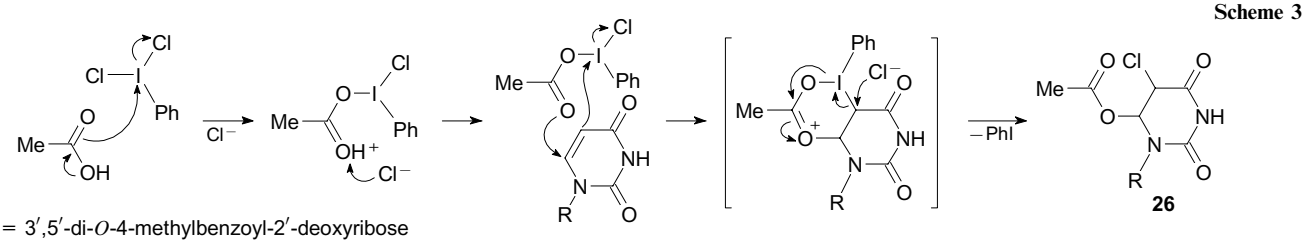
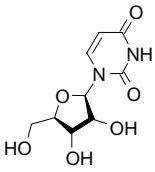
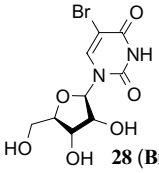
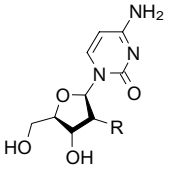
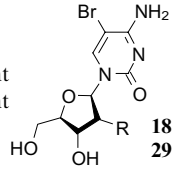
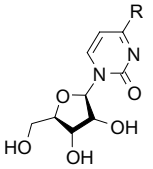
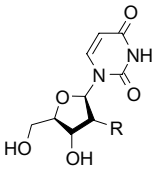
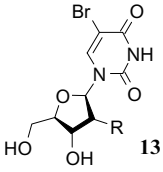
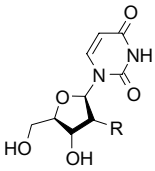
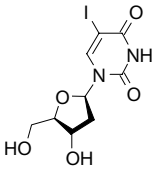
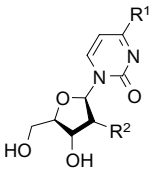
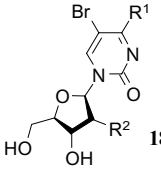
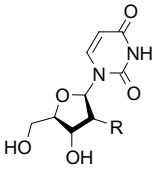


Table 2. Bromination methods for uridine and cytidine.

Entry	Substrate	Step	Reagent	Reaction conditions				Product	Yield (%)	Ref.
				catalyst	solvent	T/°C	t/h(min)			
1		1 2	Br_2 –	– –	H_2O –	– Δ	– –	 **28** (**BrU**)	n/a	77
2		1 2 3	AcOH Br_2/UV –	– – NH_3	Py CCl_4 MeOH	0 rt rt	Overnight Overnight 72 h	 **18** (**BrdC**): R = H, **29** (**BrC**): R = OH **18**, **29**	70, 62	55, 56
3		1	NBS	–	DMF	rt	16 h	**28**, **29**	62, 83	78
4		1	LiBr	CAN	ACN	80	0.5 h	 **13** (**BrdU**): R = H **13**, **28**	81, 82	66
5		1	NBS	NaN_3	1,2-dimethoxyethane	25	24 h	**13**, **28**	95, 90	65
6	 **1** (**IdU**)	1	*hv*/NaBr	irradiation at 302 nm	H_2O	0	10 min	**13**	48	66
7		1	NBS	–	[MoeMIm][TFA]	5	25 min	 **18** (**BrdC**): $R^1 = NH_2$, $R^2 = H$ **13**, **18**, **28**, **29**	85 – 98	69
8		1	LiBr	CAN	[MoeMIm][Ms]	50	30 min	**13**, **28**	86, 80	70

size 5-bromocytidine **29** (**BrC**) and its 2′-deoxy derivative **18** (**BrdC**), in 70% and 62% yields, respectively, with the only difference that bromine was used instead of chlorine (see Table 2, entry 2).

In 1969, Srivastava and Nagpal[78] brominated uridine and cytidine by treating them with *N*-bromosuccinimide (NBS) in DMF. As a result, compounds **28** and **29** were obtained in good yields (see Table 2, entry 3). The similar bromination reaction can be performed in a moderate yield with NBS in ACN.[79]

Utilizing a very similar synthetic procedure to that mediated by CAN (see Table 1, entry 5), it is possible to

obtain 5-bromonucleosides **13** and **28** in excellent yields (see Table 2, entry 4).[64] In this case, the reaction times were shorter than for the 5-chloronucleosides (1.5 h in both cases) and the addition of AcOH was not required.

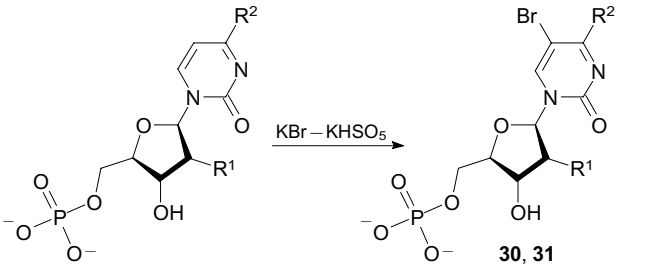
Bromination can be performed with NBS – NaN_3 in 1,2-dimethoxyethane as it was described by Kumar *et al.*[65] In this case, to obtain **BrdU** (**13**) and **BrU** (**28**) (see Table 2, entry 5), longer reaction times were required compared to chlorination, using the same procedure (see Table 1, entry 6) but compounds **13** and **28** were synthesized in 95% and 90% yields, respectively.

Kawai *et al.*[66] obtained **BrdU** (**13**) *via* the same synthetic protocol as for **CldU** (**24**) (see Table 1, entry 7). Substrate **IdU** (**1**), photoirradiated with a transilluminator (302 nm) in an aqueous 4 M NaBr solution, was consumed to a greater extent (87%), giving **BrdU** (**13**) as the major reaction product (48% yield) as well as 2′-deoxyuridine (39% yield) (see Table 2, entry 6). In this case, a halogen-exchange reaction dominated over the halogen-elimination process.

As described in section 2.1, ionic liquids are great media to perform halogenation reactions. Using ionic liquids, it was possible to obtain 5-bromo derivatives of nucleosides and 2′-deoxynucleosides in very good to excellent yields (80% – 98%) (see Table 2, entries 7 and 8). All ionic liquids used in these methods were successfully recovered and reused in further reactions.[69, 70]

A different approach to the bromination reaction was proposed by Ross and Burrows[80] in 1997. They reported the use of KBr – $KHSO_5$ system as an effective and convenient way to introduce a bromine atom into the C(5) position of a pyrimidine base. A presumed halogenating agent is Br_2, formed *in situ* from $Br^- - HSO_5^-$. The successful bromination of uridine 5′-monophosphate **30** and 2′-deoxycytidine 5′-monophosphate **31** was described (Scheme 5).[80]

Scheme 5

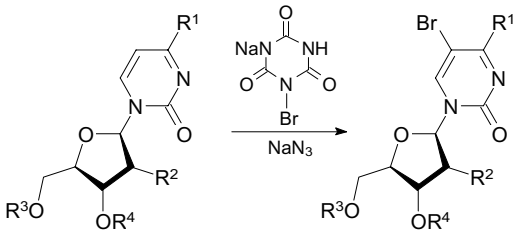


30, **31**

30: $R^1 = R^2 = OH$,
31: $R^1 = H$, $R^2 = NH_2$

Sodium monobromoisocyanurate (SMBI) is a commercially available reagent similar to NBS. It is an urea trimer and is expected to be environmentally friendly. In 2013, Maity and Stromberg[81] published a simple application of SMBI, assisted by NaN_3, as a brominating system for pyrimidine nucleosides. The authors also investigated the reaction in the absence of NaN_3, but in this case they isolated the desired products in very low yields. The N_3^- anion acts as a good leaving group at the C(6) position in the *in situ* formed 5-bromo-6-azido-5,6-dihydro intermediates, similar to the reaction illustrated in Table 1, entry 6. The researchers managed to obtain a series of 5-bromo derivatives **13**, **18**, **28**, **29**, **32**, **33** in moderate to excellent yields (59% – 93%) (Scheme 6). This method is applicable

Scheme 6



13, **18**, **28**, **29**, **32**, **33**

$R^2 = R^3 = R^4 = H$: $R^1 = OH$ (**13**, **BrdU**), NH_2 (**18**, **BrdC**);
$R^3 = R^4 = H$, $R^2 = OH$: $R^1 = OH$ (**28**, **BrU**), NH_2 (**29**, **BrC**);
$R^3 = R^4 = H$, $R^2 = OMe$: $R^1 = OH$ (**32**), NH_2 (**33**)

both to protected and unprotected pyrimidine and purine nucleosides. Its unique advantage is the possibility to brominate the 4,4′-dimethoxytrityl- (DMTr) or 4-methoxytrityl- (MMTr) protected nucleosides, which is not possible with other synthetic protocols due to the lability of DMTr and MMTr protecting groups under acidic conditions. According to the authors, this is the first example of a bromination reaction of such type.

2.3. Iodination

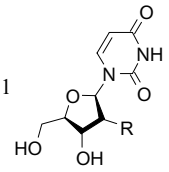
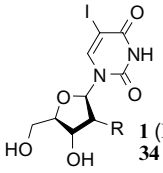
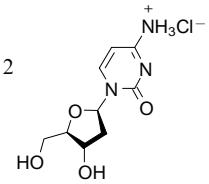
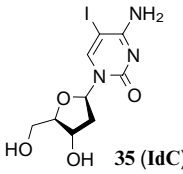
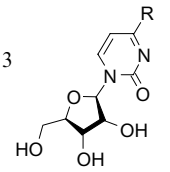
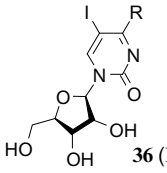
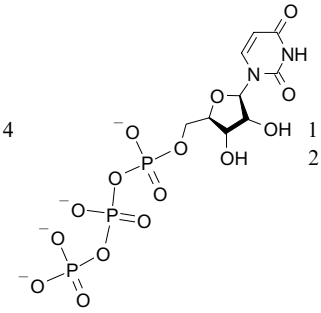
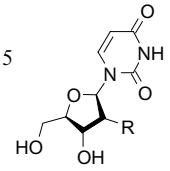
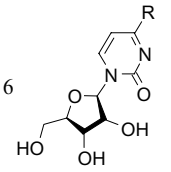
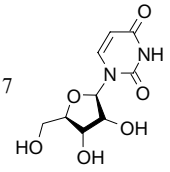
The pioneering reports of successful iodination of pyrimidine nucleosides were published by Prusoff *et al.*,[7, 82] who synthesized 5-iodouridine **34** (**IU**) and **1** (**IdU**) in 66% and 56% yields, respectively, by refluxing (2′-deoxy)uridine with KI or I_2 for 2 h in an aqueous HNO_3 solution (Table 3, entry 1).

The first convenient synthetic procedure for obtaining 5-iodo-2′-deoxycytidine **35** (**IdC**) was described in 1961.[83] At that time, all known iodination systems suitable for uridines led to the cleavage of the *N*-glycosidic bond in cytidines. A breakthrough method was proposed by Chang and Welch.[84] Unlike citric acid, iodic acid, chosen as an oxidizing agent, did not affect the *N*-glycosidic bond in the substrate. A mixture of 2′-deoxycytidine hydrochloride, iodic acid, iodine and CCl_4 was stirred in an aqueous AcOH solution (see Table 3, entry 2) for 1.5 h. After a brief workup, the residue was diluted with water and pH was adjusted to 10. Raw product was crystallized from water to obtain **35** (**IdC**) in an overall yield of 68%. The same procedure, starting from cytidine hemisulfate, was performed to obtain 5-iodocytidine **36** (**IC**).

IU (**34**) and **IC** (**36**) were synthesized in a similar manner, *via* the treatment of uridine and cytidine with an iodine monochloride solution in CCl_4 in *N*-ethylacetamide, respectively (see Table 3, Entry 3).[85] Furthermore, the same group of researchers afforded **IU** (**34**) in an alternative way, starting from uridine 5′-triphosphate in the form of tetraethylammonium salt, which underwent reaction with NIS in DMSO in the presence of *n*-butyl disulfide. The isolated product, 5-iodouridine 5′-triphosphate, was degraded by 60% HF acid (1 h, 0 °C) to provide **IU** (**34**) in an unstated yield (see Table 3, entry 4).[85]

An original but inefficient attempt to introduce the iodine atom into the C(5) position was proposed by Dale *et al.*[86] In the first step, uridine or its 2′-deoxy analogue were mercurated with mercuric acetate in an aqueous sodium acetate solution. Mercuric derivatives thus obtained were subsequently iodinated with I_2 in ethanol, affording

Table 3. Iodination methods for uridine and cytidine.

Entry	Substrate	Step	Reagent	Reaction conditions				Product	Yield (%)	Ref.
				catalyst	solvent	T/°C	t/h(min)			
1		1	KI or I_2	HNO_3	H_2O/ $CHCl_3$	reflux	2 h	 **1** (**IdU**): R = H; **34** (**IU**): R = OH **1**, **34**	66, 56	7, 82
2		1	I_2	HIO_3	CCl_4/ AcOH/ H_2O	40	95 min	 **35** (**IdC**)	68	83
		2	–	NaOH	H_2O	–	–			
3		1	ICl	–	CCl_4/ *N*-ethyl-acetamide	rt	1h	 **36** (**IC**): R = NH_2 **34**, **36**	n/a, 85	85
4		1	NIS	*n*-BuSS*n*-Bu	DMSO	rt	3 h	**34**	n/a	85
		2		HF	–	0	1 h			
5		1	$(AcO)_2Hg$	–	H_2O	50	3 h	**1**, **34**	3, 3	86
		2	I_2	–	EtOH	20	1 h			
6		1	NIS	MW	DMF	–	3 min	**34**, **36**	65, 72	87
7		1	I_2	$AgNO_3$	MeOH	40	3 h	**1**, **34**	100, 100	89 – 91

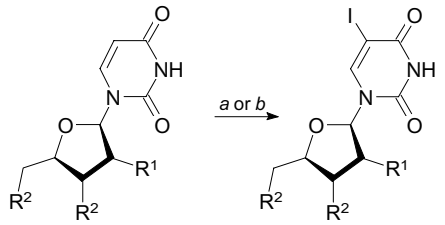
the desired products **1** and **34** in poor yields (see Table 3, entry 5).

A very useful modification of the halogenation technique shown in Table 1, entry 2 and Table 2, entry 3, was reported in 2003.[85] Earlier, NIS was found to be unreactive towards uridines or cytidines unlike NCS or NBS. However, under microwave irradiation (200 W), the reaction proceeds giving corresponding products **34** and **36** in fair yields (65% and 72%, respectively, see Table 3, entry 6).[87] The protection of 3′- and 5′-hydroxyl groups was not necessary.

Recently, a well-known mild reaction protocol using I_2-AgNO_3 was adapted to iodinate uridines.[88] Products **1** (**IdU**) and **34** (**IU**) were obtained in quantitative yields (3 h, 40 °C) and used subsequently as starting materials in coupling reactions (see Table 3, entry 7).[89 – 91]

In 1988, Asakura and Robins [92] pioneered the use of CAN as a catalyst in the iodination reaction. Protected uridines were treated with iodine in the presence of CAN in ACN or DMF. The desired raw products were crystallized from ethanol to obtain compounds **37** – **39** in excellent yields (Scheme 7, conditions *a*). Later, the same authors [64] broadened a series of iodinating agents by introducing NaI and LiI without worsening the yields of the desired products (sections 2.1, 2.2). Here, LiI turned out to be as effective as I_2 within the same reaction time (1 h), whereas reactions with NaI were far more prolonged (up to 8 h).

Scheme 7



37 – **39** (91 – 97%),
1, **40** – **42** (71 – 98%)

(*a*) I_2 – CAN, ACN or DMF; R^2 = OAc: R^1 = OAc (**37**), H (**38**);
$R^1 = R^2$ = OBz (**39**); CAN = $(NH_4)_2Ce(NO_3)_6$; ACN = MeCN;
(*b*) $I_2 - Ag_2SO_4$, MeOH; R^2 = OH: R^1 = H (**1**, **IdU**), OH (**40**, **IU**);
$R^1 = R^2$ = OAc (**41**), Bz (**42**)

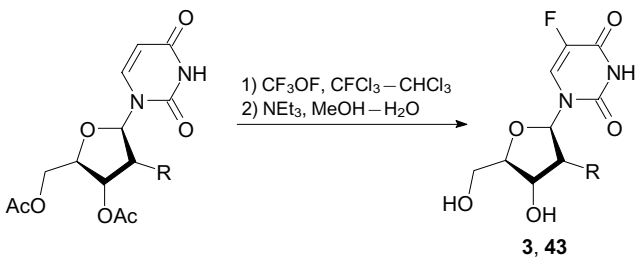
Both protected and unprotected uridines can be iodinated with I_2 in the presence of silver sulfate in MeOH.[93] This facile and very time-effecient protocol enables 5-iodo derivatives **1** and **40** – **42** to be obtained in very good to excellent yields in usually less than 12 min (see Scheme 7, conditions *b*).

5-Iodination of different pyrimidine nucleosides can also be performed in the same manner as that presented in Table 1, entries 8 and 9; and Table 2, entries 7 and 8 with the use of NIS or LiI – CAN system in ionic liquids.[69, 70]

2.4. Fluorination

Robins and Naik [94] presented the novel, direct fluorination method for the synthesis of 5-fluoro nucleosides using trifluoromethyl hypofluorite as a fluorinating agent. Acetylated 2′-deoxyuridine or uridine were treated with CF_3OF in $CHCl_3 - CFCl_3$ solution at −78 °C. In the second step, upon the addition of triethylamine solution in aqueous methanol, a molecule of CF_3OH is eliminated and hydroxyl groups are simultaneously deprotected, affording final products **3** (**FdU**) and 5-fluorouridine **43** (**FU**) (Scheme 8).

Scheme 8



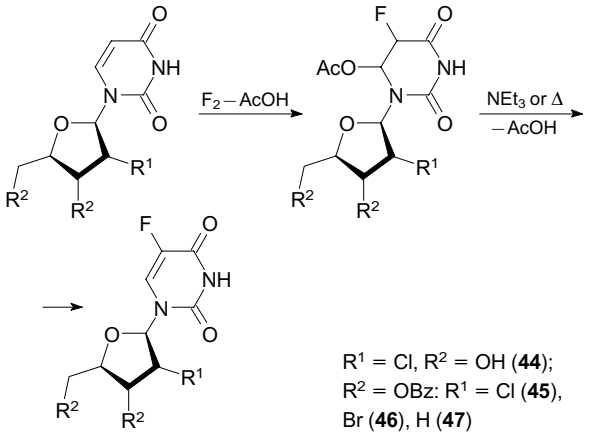
3, **43**

R = H (**3**, **FdU**, 80%), OH (**43**, **FU**, 55%)

This methodology has also been successfully adapted to fluorinate cytidines.[95]

Both protected and unprotected uridines can be transformed into their 5-fluoro-analogues by treatment with a solution of elemental fluorine in AcOH followed by heating or refluxing in NEt_3 (Scheme 9).[96] The reaction intermediate is 5,6-dihydroderivative generated *in situ*, which further transforms to a final product under the action of NEt_3. Corresponding 5-fluoro derivatives **44** – **47** were isolated in moderate to very good yields.

Scheme 9

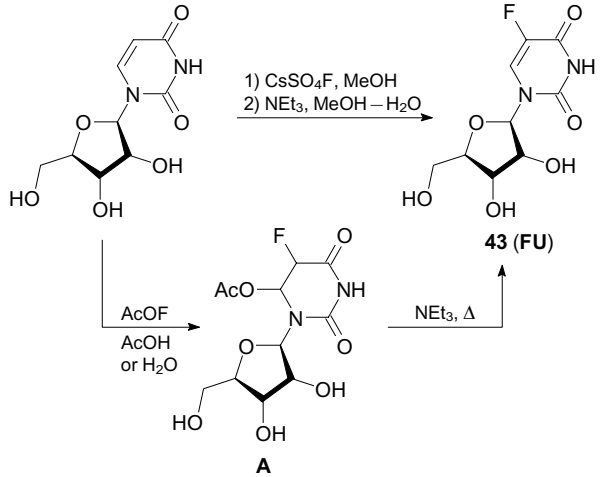


R^1 = Cl, R^2 = OH (**44**);
R^2 = OBz: R^1 = Cl (**45**),
Br (**46**), H (**47**)

44 – **47** (48 – 82%)

The further development of fluorination techniques led to the discovery of cesium fluoroxysulfate — a convenient and stable reagent for introducing the fluorine atom into the molecule at room temperature. $CsSO_4F$ was successfully used as a 5-fluorinating agent for uridine, corresponding to the above-mentioned CF_3OF (both compounds are from the same hypofluorite family). The $CsSO_4F$-mediated method allowed **FU** (**43**) to be obtained in a 79% yield (Scheme 10).[97]

Scheme 10



43 (**FU**)

A

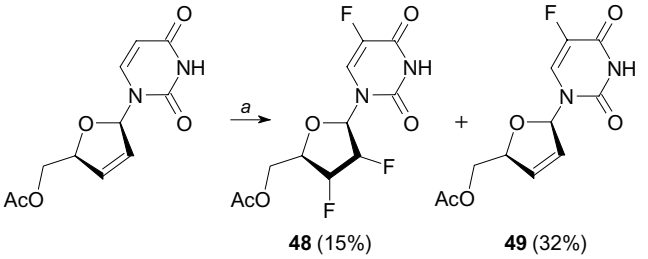
Another variation of the reaction of pyrimidine nucleosides with hypofluorites was proposed by Visser *et al.*[98] This scientific team used acetyl hypofluorite to generate the 5,6-dihydro-intermediates of the type **A**, which are known to be stable and isolable by column chromatography. The

obtained 5-fluoro-6-acetoxy-5,6-dihydrouridine **A** was then treated with NEt_3 to afford eventually compound **43** in an unstated yield (see Scheme 10). Moreover, the authors submitted a very interesting and detailed discussion of stereochemistry of such 5,6-dihydro-intermediates that are furnished during this kind of reactions.

In 1994, Coe *et al.*[99] proposed the direct fluorination reaction of 5′-*O*-acetyl-2′,3′-didehydro-2′,3′-dideoxyuridine in the presence of F_2 and EtOH as the proton donor (Scheme 11). Earlier, such reaction was shown to proceed through the electrophilic *syn*-addition to the 5,6-double bond of the pyrimidine nucleoside.[100] In this case, the formed 5,6-dihydro-intermediates could not be isolated, contrary to fluorination of uridines with F_2-AcOH system,[96] where such entities could be isolated in good yields. Moreover, the authors claimed that this was the first example of the stereospecific *cis*-addition of fluorine to the 2′,3′-double bond within the sugar moiety (compound **48**) and the first example of the reaction with elemental fluorine, where the *N*-glycosidic bond was cleaved to a negligible extent.[99]

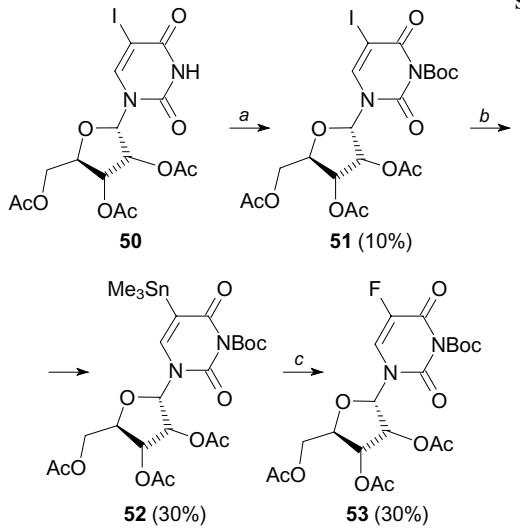
Selectfluor is a specific fluorinating agent and a trademark of Air Products and Chemicals. It is a derivative of 1,4-diazabicyclo[2.2.2]octane and was first described by Banks *et al.*[101] As a fluorine donor, it was utilized in fluorodestannylation of 3-*N*-Boc-5-trimethylstannyl-2′,3′,5′-tri-*O*-acetyl arabinosyl uridine **52**, prepared from its analogue — 5-iodosubstituted arabinosyl uridine **50**.[102] In the first step, compound **50** was Boc-protected, then a stannyl moiety was introduced at the C(5) position of **51** in the presence of a palladium catalyst. Finally, **52** was treated with Selectfluor to provide 5-fluoro-analogue **53** (Scheme 12).

Scheme 11

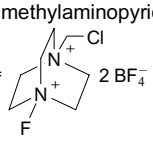


(*a*) F_2-N_2, $CHCl_3$, EtOH, $CFCl_3$, −78 °C

Scheme 12



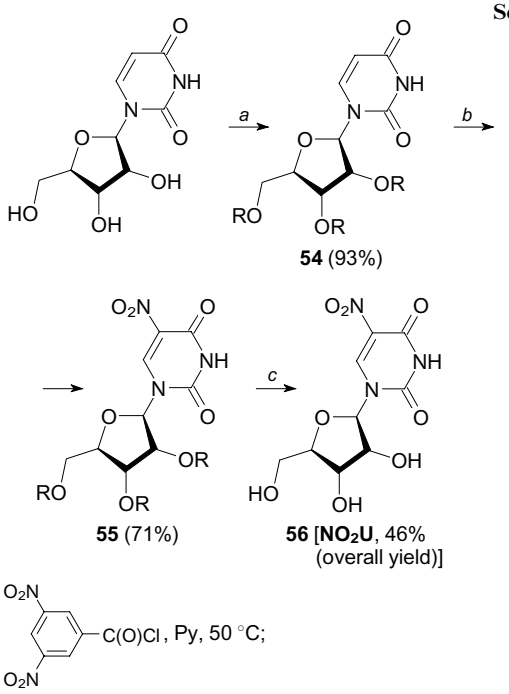
(*a*) $(Boc)_2O$, DMAP, THF, rt; (*b*) Sn_2Me_6, $(PPh_3)_2PdCl_2$, 1,4-dioxane, 80 °C; (*c*) Selectfluor, ACN, 50 °C; Boc is *tert*-butoxycarbonyl, DMAP is 4-dimethylaminopyridine;

Selectfluor = 

3. Nitration

From the beginning, scientists indicated the difficulties associated with introducing a nitro moiety into the structure of a pyrimidine nucleoside. They faced the cleavage of the *N*-glycosidic bond as well as an oxidation of 4′-hydroxymethyl group to carboxyl moiety. The very first nitration reaction of uridine was performed by Leven and La Forge,[77] in which the product had an intact *N*-glycosidic bond but the 4′-hydroxymethyl group was oxidized furnishing 5-nitro-4′-carboxyuridine. In order to avoid these synthetic issues, Wempen *et al.*[103] protected the 2′-, 3′- and 5′-hydroxyl groups with a 3,5-dinitrobenzoyl chloride. The protected derivative **54** was then nitrated with the fuming HNO_3 in the presence of H_2SO_4 affording 5-nitro analogue **55**, which was eventually deprotected by treatment with sodium ethoxide to give 5-nitrouridine **56** (**NO_2U**) (Scheme 13).

Scheme 13



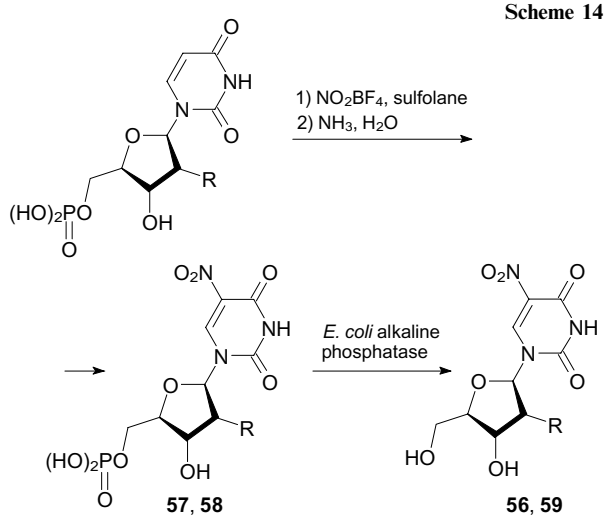
(*a*) Py, 50 °C;

(*b*) conc. H_2SO_4 – fuming HNO_3 (1 : 1 v/v), rt → 50 °C;
(*c*) 1) EtONa – EtOH, Δ; 2) conc. H_2SO_4;
R = 3,5-dinitrobenzoyl, Py is pyridine

Another nitration method concerns the use of nitronium tetrafluoroborate. However, attempts to nitrate uridine and 2′-deoxyuridine with this mild reagent in the solution of sulfolane were unsuccessful. Even with sugar hydroxyl groups protected with acetyl or isopropylidene groups, the

major product proved to be 5-nitrouracil in all cases.[104] Similar nitrating conditions, applied to 2′-deoxyuridine or uridine 5′-monophosphate, followed by conversion to their ammonium salts, led to the corresponding 5-nitro derivatives **57**, **58** in low to moderate yields (the authors did not indicate precise yields, but gave a range of 28% – 42%). In the next step, compounds **57**, **58** were enzymatically dephosphorylated using *Escherichia coli* alkaline phosphatase, giving 5-nitro-2′-deoxyuridine **59** (**NO_2dU**) in 58% yield and **NO_2U** (**56**) in an unstated yield (Scheme 14).[104]

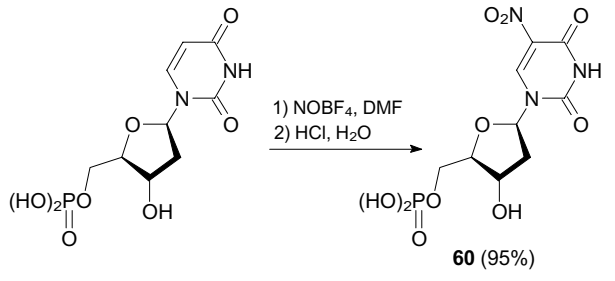
Scheme 14



R = H [**57**, **59** (**NO_2dU**)], OH [**56** (**NO_2U**), **58**]

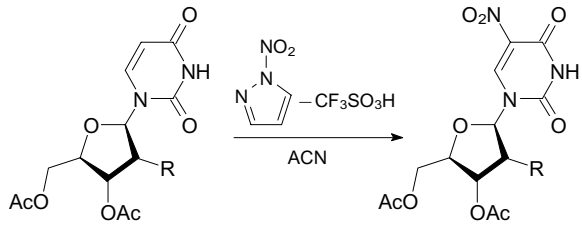
Two nitration methods described above caused an extensive cleavage of the *N*-glycosidic bond, which was a significant drawback. Even with protected 2′-, 3′- and 5′-hydroxyl groups products were obtained in rather low to moderate yields. A nitrosating reagent — nitrosonium tetrafluoroborate — was investigated against its capability of indirect introducing of a nitro group into the C(5) position of nucleosides.[105] It was shown that a short-term (5 min) treatment of 2′-deoxyuridine 5′-monophosphate, in its acid form, with an excess of $NOBF_4$ in anhydrous DMF gave 5-nitro-2′-deoxyuridine 5′-monophosphate **60** in an excellent yield after acidification with HCl (Scheme 15). Moreover, the authors did not exclude the possibility of a 3′-*O*-nitration product to arise, but it was completely eliminated by using short reaction times.

Scheme 15



1-Nitropyrazole in the presence of Lewis or Brønsted acid is an efficient nitration agent for aromatic compounds.[106] While investigating the mechanism of the reaction and the influence of an acid catalyst, it turned out that triflic acid (CF_3SO_3H) can also be effectively used in this procedure. According to the authors, a true nitrating agent seems to be *N*-protonated *N*-nitropyrazole transferring the nitro group to *e.g.*, nucleosides. Giziewicz *et al.*[107] managed to nitrate acetyl-protected uridine and 2′-deoxyuridine with 1-nitropyrazole – CF_3SO_3H system, affording compounds **61** and **62** (Scheme 16). However, despite the excellent yields, this reaction is much more time-consuming than other methods. Disregarding the protection and deprotection steps, the nitration process lasted for 72 h.

Scheme 16



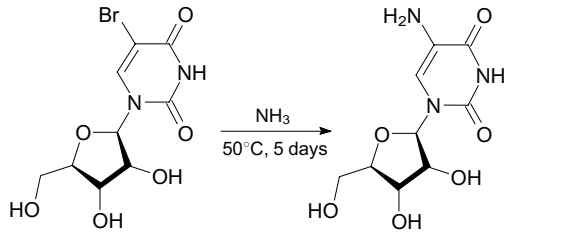
R = H (**61**, 78%), OAc (**62**, 97%)

No examples of the direct nitration of cytidines have been reported so far. Such compounds can be obtained, *i.e.* through the S_N2 reaction of 4-mesyl-5-nitrouridines with ammonia in water[108] or by glycosylation of silylated 5-nitrocytosines with protected 1-chloropentofuranose.[109]

4. Amination

The first example of synthesis of 5-aminouridine (**NH_2U**) **63** was reported by Roberts and Visser.[110] Compound **BrU** (**28**) was treated with liquid ammonia in a bomb tube. After the reaction was completed, NH_3 was evaporated and the raw product was crystallized from 2-propanol – H_2O mixture to furnish **NH_2U** (**63**) (Scheme 17).

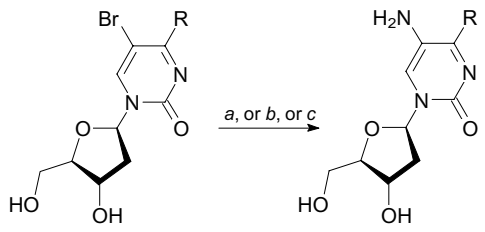
Scheme 17



The synthesis of 5-amino-2′-deoxyuridine (**NH_2dU**) **64** was published for the first time by Beltz and Visser,[111] who treated **BrdU** (**13**) with liquid ammonia in anhydrous alcohol. They obtained a raw product **64**, which was crystallized from anhydrous alcohol to provide **NH_2dU** (**64**) in a very poor yield (Scheme 18, conditions *a*).[95]

Later, this reaction was modified by using 3 – 4-fold excess of liquid ammonia (8 mL for 1 g of a substrate) in the absence of solvent. It resulted in shortening of the reaction time from 7 days to 24 h, and the yields of **NH_2dU** (**64**) were significantly improved (up to 74% after column chromatography) (see Scheme 18, conditions *b*).[112] It is worth noting that the later purification method is more

Scheme 18



13, **18** **64** (**NH_2dU**), **65** (**NH_2dC**)

(*a*) NH_3 (liq) – alcohol, 55 °C, 7 days (8%);
(*b*) NH_3 (liq) (excess), 24 h (74%);
(*c*) $NH_3 - H_2O$, 55 °C, 4 days (6%);
R = OH (**13**, **64**), NH_2 (**18**, **65**)

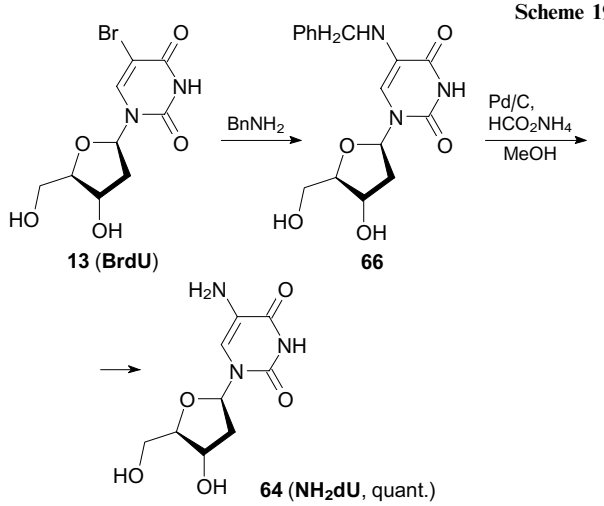
suitable than the former one (crystallization, see [111]) as providing much higher yield of compound **64**. Nevertheless, such an improved yield along with a shortened reaction time under almost identical conditions of the process may seem surprising.

It was also possible to obtain **NH_2dU** (**64**) by treating **BrdU** (**13**) with an aqueous ammonia solution in a screw cap vial for 4 days at 55 °C though in a very poor yield (see Scheme 18, conditions *c*).[113] Furthermore, without giving any details, the authors mentioned that the same synthetic procedure performed with **IdU** (**1**) gave **NH_2dU** (**64**) as well. However, this method can not be recommended as a synthetic one, since this reaction was only investigated in order to explain problems which the authors faced during the deprotection reactions of the oligonucleotides obtained by the phosphotriester method. Lowering the reaction temperature to 37 °C was found to prevent 5-halouridines from an undesirable substitution with amino moiety.

In 1992, 5-amino-2′-deoxycytidine (**65**, **NH_2dC**) was successfully obtained by Barawkar *et al.*[114] using the similar protocol as described by Beltz and Visser.[111] Compound **65** was isolated by flash column chromatography in 38% yield as a pale-yellow solid (see Scheme 18).[114]

A great alternative for the reactions presented in Scheme 18 is a benzylamination – reduction approach. When heated with benzylamine, **BrdU** (**13**) gives 5-benzylamino-2′-deoxyuridine **66**. Subsequent hydrogenolysis of **66** in the presence of Pd/C catalyst and ammonium formate, affords **NH_2dU** (**64**) quantitatively (Scheme 19).[115] The advantages of this procedure over the nucleophilic substitution of a halogen atom with ammonia are as follows: a) yields are improved from poor/moderate to quantitative; b) there is no need to use liquid ammonia; and c) long-lasting processes are shortened to 5 – 6 h overall.

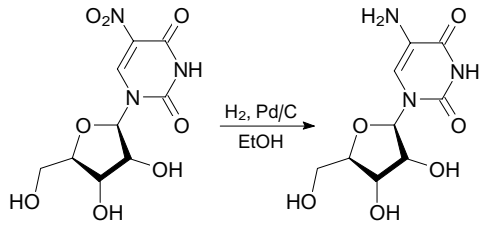
Scheme 19



13 (**BrdU**) **66** **64** (**NH_2dU**, quant.)

A distinct methodology for synthesizing 5-amino-substituted nucleosides is the reduction of 5-nitro derivatives. One of the first examples of such reaction comprised hydrogenation of **NO_2U** (**56**) on the Pd/C catalyst in ethanol followed by crystallization of the raw product from 2-propanol/H_2O mixture to obtain **NH_2U** (**63**) (Scheme 20).[103]

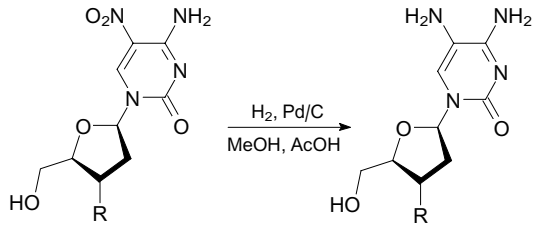
Scheme 20



56 (**NO_2U**) **63** (**NH_2U**, 22%)

Not only 5-nitrouridines can be converted to 5-amino-analogues by using $H_2 - Pd/C$ system, but 5-nitrocytidines are also susceptible to this reaction. Compounds **NH_2dC 65** and **69** were synthesized in 95% and 85% yields by treating 5-nitro-2′-deoxycytidine (**NO_2dC**) **67** or 5-nitro-2′,3′-dideoxycytidine **68** with $H_2 - Pd/C$ in methanol (in the case of **NO_2dC 67**, AcOH was also added) (Scheme 21).[109]

Scheme 21

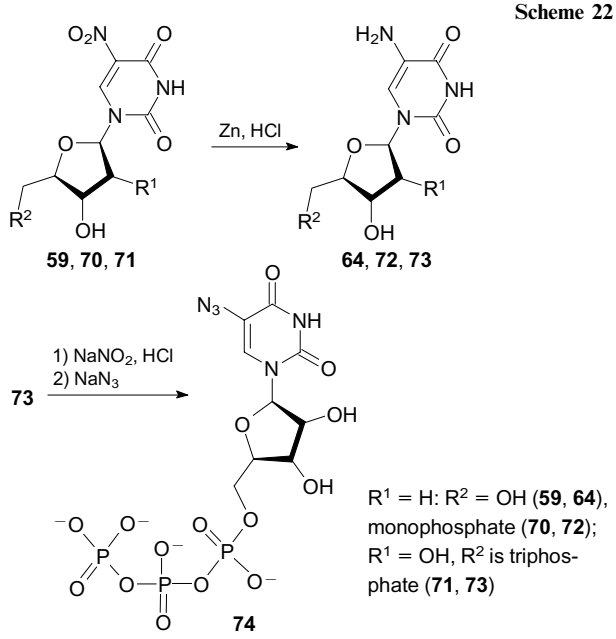


67 (**NO_2dC**), **68** **65** (**NH_2dC**, 95%), **69** (85%)

R = OH (**65**, **67**), H (**68**, **69**)

The third type of reduction of a nitro group at the C(5) position in nucleosides is a widely used Zn – HCl method. The reduction of 5-nitrocytidines according to this protocol is problematic due to the instant protonation of the amino group present in the pyrimidine base of cytidine. Therefore, the only known examples relate to the use of 5-nitrouridines. On the other hand, the first noteworthy thing is that the Zn – HCl method can be adapted to both uridine nucleosides and nucleotides. Treating **NO_2dU** (**59**),[115] 5-nitro-2′-deoxyuridine 5′-monophosphate (**70**)[105] or 5-nitrouridine 5′-triphosphate (**71**)[116] with granulated zinc in HCl gave corresponding 5-amino-analogues **64**, **72** and **73** in 60% – 70% (overall yield for conversion of 5-nitrouridine 5′-monophosphate to compound **72**, calculated on the basis of known extinction coefficient) and 37% (overall yield for conversion of uridine 5′-triphosphate to 5-azidouridine 5′-triphosphate **74**), respectively (Scheme 22). Compound **73** was additionally transformed into its 5-azido

Scheme 22



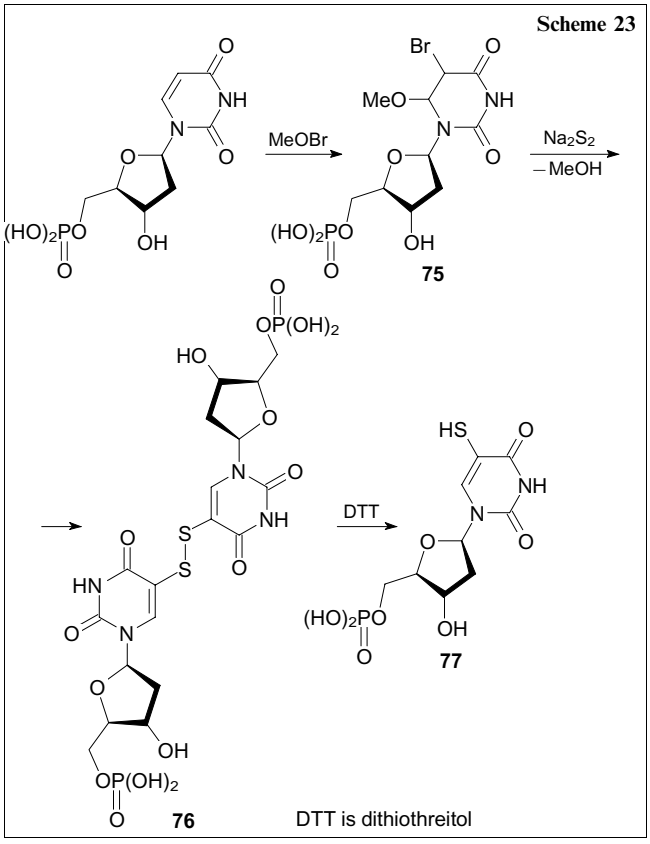
derivative **74** *via* the *in situ* formed diazonium salt followed by the addition of NaN_3.[116]

5. Sulfanylation, selenylation and telluration

5.1. Sulfanylation

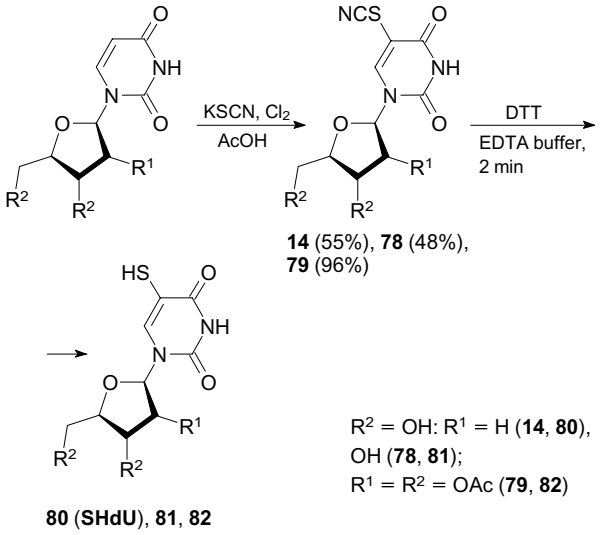
The pioneering attempts for obtaining 5-mercapto analogues of nucleosides included chemical or enzymatical glycosylation of an appropriate base with a modified sugar moiety.[117,118] The earliest example of the direct sulfanylation at the C(5) position in pyrimidine nucleosides was reported in 1970.[119] 2′-Deoxyuridine 5′-monophosphate treated with methyl hypobromite gave 5,6-dihydro-intermediate **75**, which was isolated and crystallized from MeOH – Et_2O mixture. Upon reaction with sodium disulfide, compound **75** was transformed to disulfide **76**. Further treatment with dithiothreitol (DTT) resulted in a fast reduction to 5-mercapto-2′-deoxyuridine 5′-monophosphate **77** in an overall yield of 68% (Scheme 23).

Scheme 23



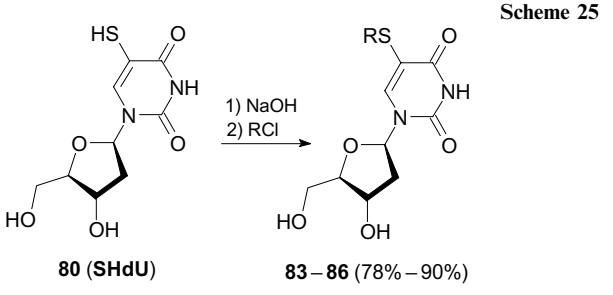
In 1972, Nagamachi *et al.*[120] proposed the synthesis of 5-thiocyanato analogues **14**, **78** and **79** with their possibile subsequent reduction to 5-mercapto derivatives **80** – **82**. In the first step, uridine derivatives were added to a mixture of glacial acetic acid and potassium thiocyanate, saturated with an appropriate amount of chlorine gas. Thiocyanogen chloride, generated *in situ*, is an appropriate thiocyanating agent. After 1 h, the reactions were quenched by the addition of cyclohexene; the raw 5-thiocyanato analogues **14**, **78** and **79** were crystallized from ethanol to furnish pure products in 48% – 96% yields (Scheme 24). The highest yield (96%) was reached for 2′,3′,5′-tri-*O*-acetyl-protected uridine **79**. The subsequent reduction of 5-thiocyanatouridines was performed with DTT in EDTA buffer to furnish 5-mercapto derivatives **80** – **82** in unstated yields (see Scheme 24).

Scheme 24



Among sulfur derivatives of pyrimidine nucleosides, particular attention was paid to their 5-(alkylsulfanyl) analogues. The existence of several reaction centres prone to alkylation in nucleosides, makes this process difficult to

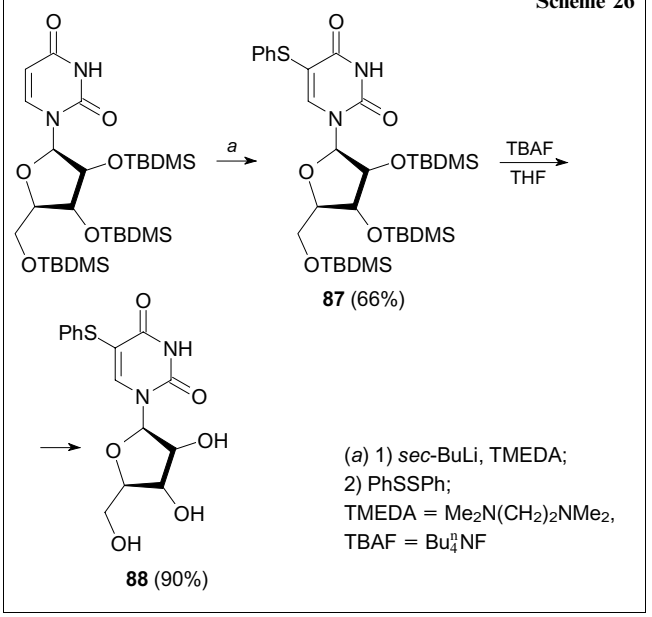
Scheme 25



perform. Taking into account the fact that the thiol proton is more acidic than protons of the 2′-deoxyribosyl moiety, it is possible to quantitatively generate the 2′-deoxyuridynyl sulfide anion with sodium hydroxide without protecting 3′- and 5′-hydroxyl groups. Such anions enter an alkylation reaction with different alkyl halides to provide compounds **83** – **86** in high yields (Scheme 25).[121]

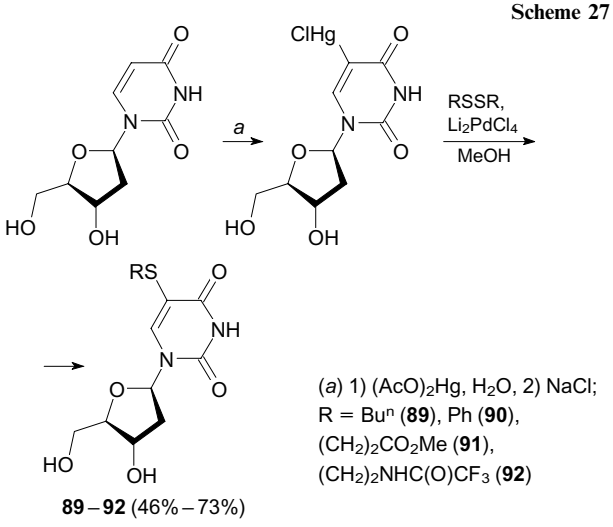
It is also possible to furnish 5-substituted uridine derivatives using a lithiation reaction. Lithiation at the C(5) or C(6) positions is strongly affected by the chemical constitution of a nucleoside. For example, the reaction between 2′,3′-*O*-isopropylidene-5′-*O*-methoxymethyluridine and lithium diisopropylamide (LDA) gives mostly C(6) lithiated product, whereas 2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)uridine provides no lithiation products under these conditions.[122] The reason for that is twofold: a) too low basicity of LDA to deprotonate the H(5), and b) inaccessibility of the C(6) position due to steric hindrances caused by the bulky 2′-*O*-*tert*-butyldimethylsilyl (2′-*O*-TBDMS) protecting group. Lithiation at the C(5) position of 2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)uridine with *sec*-BuLi, which is much stronger base than LDA, in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) followed by subsequent reaction with PhSSPh led to the 2′,3′,5′-protected 5-phenylthiouridine **87** (Scheme 26). It is worth noting that researchers managed to reach C(5)-lithiation levels up to 86% when using *sec*-BuLi – TMEDA system. The removal of the protecting groups could be finally performed by treating compound **87** with tetrabutylammonium fluoride (TBAF) in THF to obtain 5-phenylthiouridine **88**.

Scheme 26



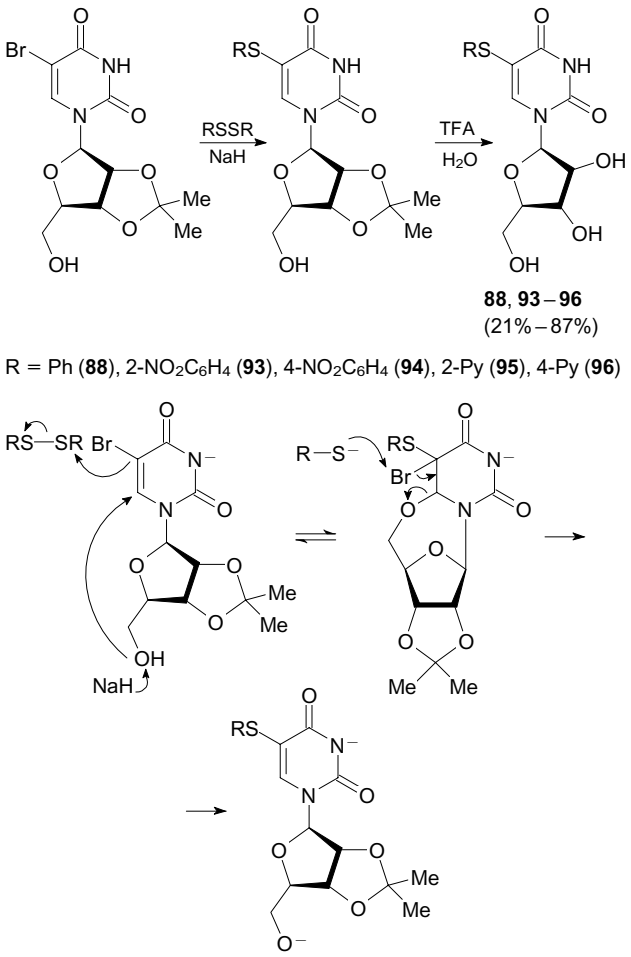
Another way to introduce an alkyl- or arylsulfanyl substituent into the nucleoside structure is the reaction of 5-mercurated analogues with disulfide in the presence of lithium palladium chloride. 5-Mercurinucleosides are easily available *via* the reaction of a corresponding nucleoside with mercury acetate in water.[123] In 1989, Bergstrom *et al.*[124] used this methodology to synthesize derivatives of 2′-deoxyuridine **89** – **92**. Treating 5-chloromercuri-2′-deoxyuridine with dialkyl or diphenyl disulfides in the presence of 1 equiv. of Li_2PdCl_4 in methanol overnight led to the corresponding analogues **89** – **92** in moderate yields (Scheme 27). It should be mentioned that in the case of more polar disulfides, *e.g.*, 3,3′-dithiodipropionic acid or 2,2′-dithiodiethanol, 2 equiv. of Li_2PdCl_4 were needed to initiate the reaction.

Scheme 27



To synthesize 5-(arylsulfanyl) derivatives of uridine, one can start from 2′,3′-*O*-isopropylidene-5-bromouridine. Its reactions with disulfides in the presence of sodium hydride in dry DMF provided a series of 5-(arylsulfanyl) derivatives

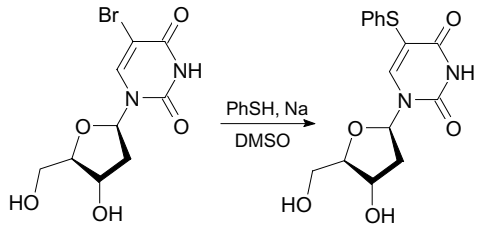
Scheme 28



88 and **93** – **96** (Scheme 28).[125] Diaryl disulfides bearing strong electron-withdrawing substituents in the aryl rings (*e.g.*, NO_2 group) reacted much more rapidly than their diphenyl or di-2-pyridinyl analogues (1 h *vs.* 48 and 72 h respectively). The authors devoted a great deal of effort trying to explain the possible mechanism of this reaction. They evaluated the effect of 1-*N* substituent on the process and came to the conclusion that the influence of the 5′-OH group in 2′-deoxyribose or the 2′-OH group in β-D-arabinofuranose is crucial. After deprotonation, these moieties are involved in the nucleophilic attack to form O^6,5′- or O^6,2′-cyclo-5,6-dihydro-carbanion intermediates, which are then stabilized by reaction with electrophiles. Subsequent debromination and β-elimination give the final product. Interestingly, even non-brominated 2′,3′-*O*-isopropylideneuridine or 1-β-D-arabinofuranosyluracil could undergo this type of reaction (the only mechanistic difference is attributed to the deprotonation reaction instead of debromination). The proposed mechanism for the above reaction is illustrated in Scheme 28.

In 2006, Zeng *et al.*[126] used thiophenol in the presence of sodium in DMSO to obtain 5-phenylthio-2′-deoxyuridine **90** starting from **BrdU** (**13**) (Scheme 29). This reaction is very interesting from the mechanistic point of view. Sodium reacts with PhSH and DMSO at the same time, giving sodium thiophenolate and methylsulfinylmethylide (dimsyl) sodium, respectively. Taking into account the work of Nampalli *et al.*[127] it is expected that with 1 : 3 ratio of PhSH : DMSO, the major product would be 5-dimsyl-2′-deoxyuridine but when the ratio is changed to 3 : 2, 5-phenylthio-2′-deoxyuridine **90** predominates. The function of DMSO is twofold: a) it supports the solubility of **BrdU** (**13**) and b) solvates sodium cations, rendering the thiophenolate anions more reactive.

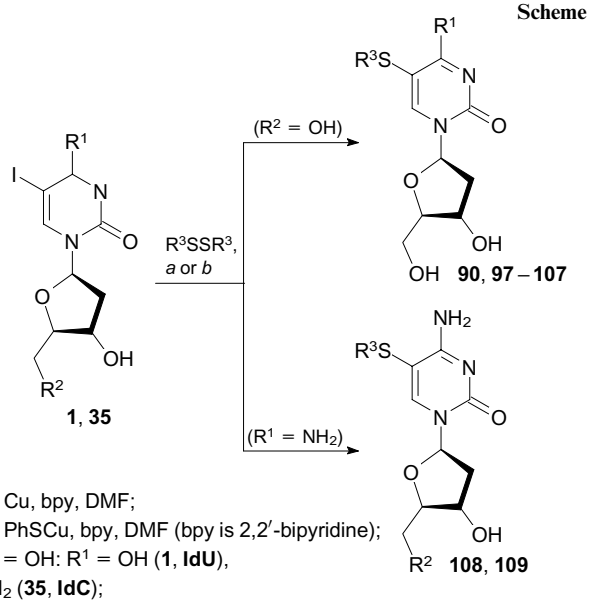
Scheme 29



13 (BrdU) **90**

One of the latest approaches towards modifying the pyrimidine base in nucleosides with an alkyl(aryl)sulfanyl moiety is Cu-promoted sulfanylation.[128] Unprotected **IdU** (**1**) and **IdC** (**35**) treated with dialkyl or diaryl disulfides – Cu^- or copper(I) thiophenolate, in the presence of 2,2′-bipyridine (bpy) in DMF, furnished the corresponding derivatives **90**, **97** – **107** in poor to moderate yields (Scheme 30). It is worth admitting that when using copper(I) thiophenolate the researchers did not observe particular improvement in the reaction yields in case of obtaining compound **102**, thus they decided not to imply it to 5-iodo-2′-deoxyuridine. The same methods were adapted for the modification of 5-iodo-2′-deoxycytidine 5′-triphosphate in 7% and 24% yields, respectively (compounds **108** – **109**, see Scheme 30). The yields for **108** – **109** were poor but, according to the authors, it was the first attempt to modify 2′-deoxycytidine 5′-triphosphate in this way (see Scheme 30).

Scheme 30

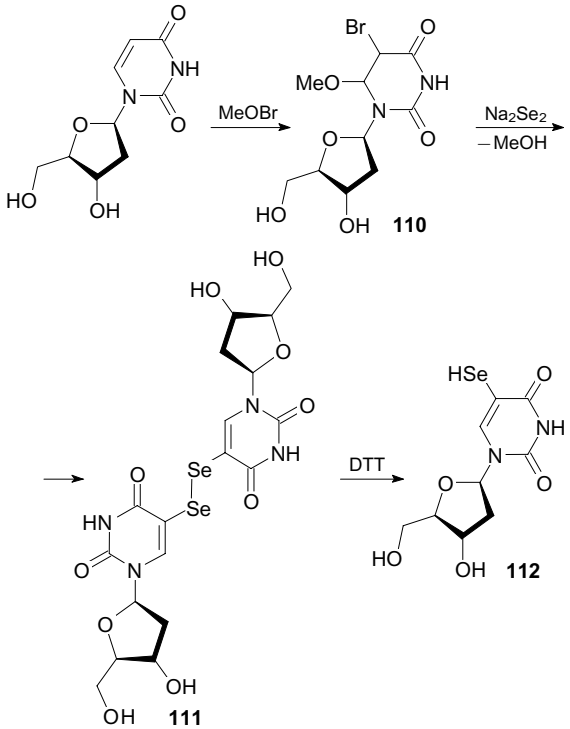


(*a*) Cu, bpy, DMF;
(*b*) PhSCu, bpy, DMF (bpy is 2,2′-bipyridine);
R^2 = OH: R^1 = OH (**1**, **IdU**),
NH_2 (**35**, **IdC**);
R^1 = R^2 = OH: R^3 = Ph (**90**), $C_6H_4(NO_2)_2$-2,4 (**97**), $C_6H_4NO_2$-4 (**98**), C_6H_4OMe-4 (**99**), 2-Th (**100**), Me (**101**); Th is thienyl;
R^1 = NH_2, R^2 = OH: R^3 = Ph (**102**), $C_6H_4(NO_2)$-2,4 (**103**), $C_6H_4NO_4$-4 (**104**), C_6H_4OMe-4 (**105**), 2-Th (**106**), Me (**107**);
R^1 = NH_2; R^2 = triphosphate; R^3 = Ph (**108**), 2-Th (**109**)

5.2. Selenylation

5-Selenium-substituted uridine derivatives were first reported by the same research group which pioneered in sulfanylation of uridines in 1970.[119] Similarly, 2′-deoxyuridine was treated with methyl hypobromite to provide 5,6-dihydro-intermediate **110**, which was converted to **111** by reaction with sodium diselenide. Subsequent reduction with DTT resulted in 5-hydroseleno-2′-deoxyuridine **112** (Scheme 31).[129] However, the authors did not isolate it,

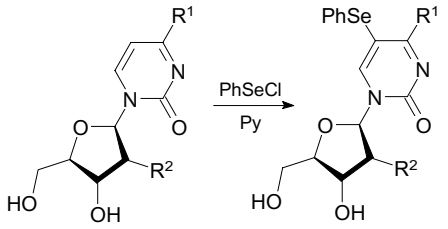
Scheme 31



showing that such hydroseleno derivatives were slowly decomposing under acidic conditions, which made a purifying process more difficult. The formation of compound **112** was confirmed by IR and ^{1}H NMR spectroscopy data and by comparison with similar spectra collected for the corresponding thio analogue **77** (see Scheme 23).

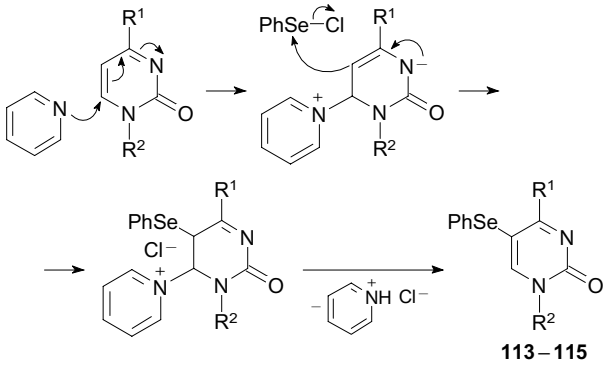
Schinazi *et al.*[130] proposed the direct synthesis of 5-phenylselenenyl analogues of uridine and cytidine by treating nucleoside substrates with phenylselenenyl chloride in pyridine. The products **113** – **115** are formed in 24 h in moderate yields (Scheme 32). Although a mechanism of this process is unknown, an article by Zima and Liotta[131] concerning a discussion over the reaction of unsaturated ketones with phenylselenenyl chloride in pyridine can shed some light on its mechanistic aspects. A plausible mechanism comprises: a) the Michael addition of pyridine to the 5,6-double bond, b) a nucleophilic attack of 6-piridyl intermediate on the selenium atom in phenylselenenyl chloride and c) the elimination of pyridinium hydrochloride (see Scheme 32).

Scheme 32



113 – **115** (38% – 49%)

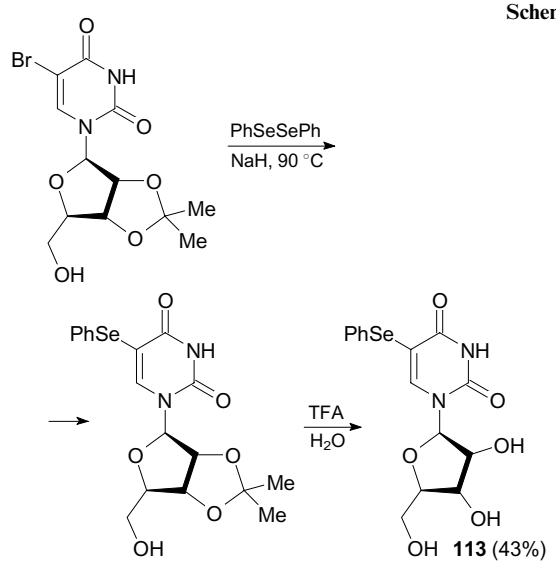
$R^1 = R^2 = OH$ (**113**); $R^1 = OH$, $R^2 = H$ (**114**); $R^1 = NH_2$, $R^2 = OH$ (**115**)



113 – **115**

$R^1 = OH$ or NH_2, R^2 is 2′-deoxyribose or ribose

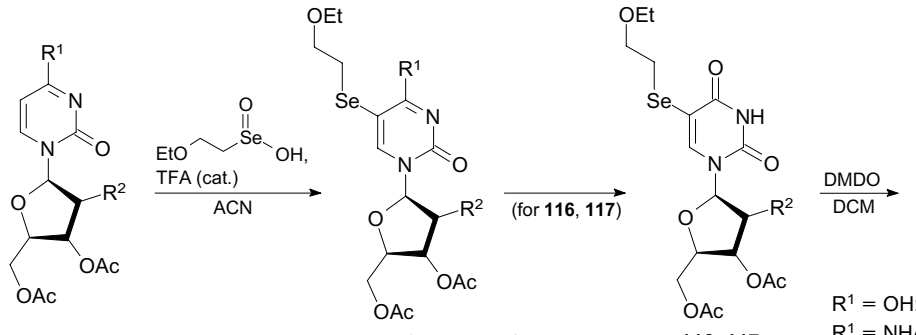
Scheme 33



113 (43%)

It is also possible to introduce the phenylselenenyl moiety into the C(5) position of pyrimidine nucleosides *via* an approach presented earlier in this paper.[125] In this case, 2′,3′-*O*-isopropylidene-5-bromouridine treated with diphenyl diselenide in the presence of NaH gave, after deprotection, the desired 5-phenylselenouridine **113** (Scheme 33).

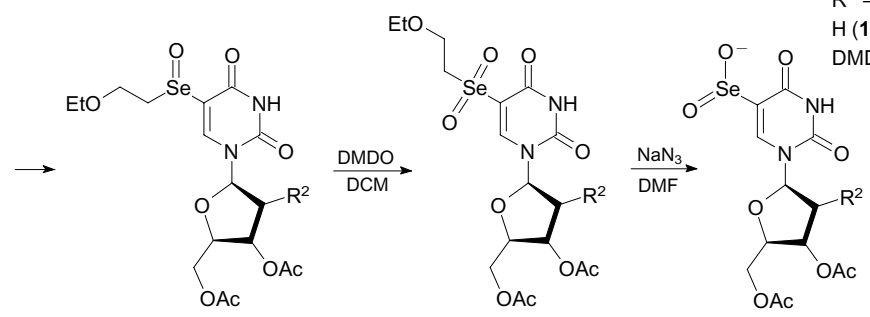
Scheme 34



116 – **118** (46% – 61%)

116, **117**

R^1 = OH: R^2 = OAc (**116**), H (**117**);
R^1 = NHAc, R^2 = OAc (**118**);
R^2 = OAc (**119**, **121**, **123**),
H (**120**, **122**, **124**);
DMDO is dimethyldioxirane

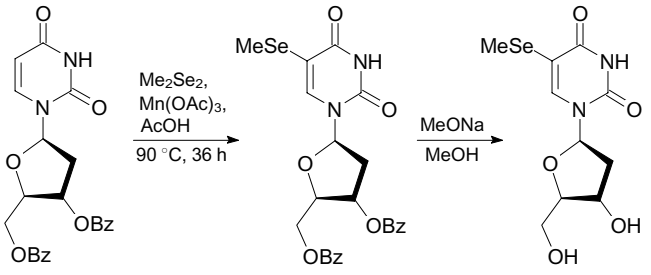


119, **120** **121**, **122** **123**, **124**

A very interesting work was published by Abdo *et al.*[132] Based on their experience with alkaneseleninic acids as effective electrophiles towards phenols or indols,[133, 134] they managed to adapt this procedure to nucleosides. Reactions between 2-ethoxyethaneseleninic acid and appropriate acetyl-protected nucleosides in the presence of catalytic amounts of TFA gave the corresponding products **116** – **118** in moderate yields (Scheme 34). In a modified reaction procedure the reaction solvent was replaced with water and non-protected substrates were used to afford final products in similar to slightly better yields (38% – 71%) compared to the results achieved in ACN. Furthermore, compounds **116** and **117** were oxidized with dimethyldioxirane (DMDO) to corresponding selenoxides **119**, **120** and selenones **121**, **122**. Additionally, selenones were transformed into seleninic acids **123**, **124** *via* nucleophilic dealkylation with the use of NaN_3 in DMF (see Scheme 34).[132]

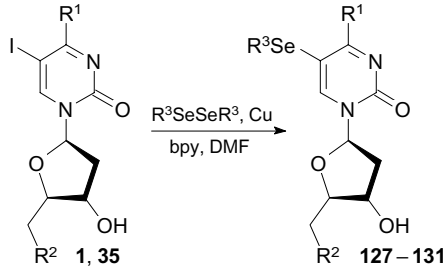
In 2009, Hassan *et al.*[135] reported the synthesis of 5-alkylselenyl nucleosides. For this purpose, several Lewis acids were screened to find the best agent, which could interact with dimethyl diselenide to initiate the alkyl selenylation process. Manganese(III) acetate was shown to be the most efficient. Treating 3′,5′-di-*O*-benzoyl-2′-deoxyuridine with MeSeSeMe in the presence of $Mn(OAc)_3$ in AcOH afforded the 5-methylselenyl analogue **125** (Scheme 35). To furnish the non-protected 5-methylselenoderivative **126**, the quantitative removal of the protecting groups with MeONa in MeOH was performed.

Scheme 35



It is also possible to modify the C(5) position of nucleosides and nucleotides using methodology similar to that described in section 5.1.[128] Treating **1** (**IdU**) or **35** (**IdC**) with diphenyl or dimethyl diselenide in the presence of Cu and bpy in DMF gave the corresponding 5-substituted analogues **127** – **130**. The same reaction applied to 5-iodo-2′-deoxycytidine 5′-triphosphate afforded its 5-selenylated derivative **131** in 34% yield (Scheme 36).

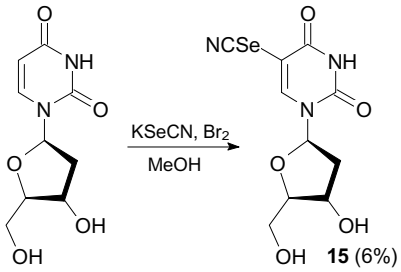
Scheme 36



R^2 = OH: R^1 = OH (**1**), NH_2 (**35**); R^2 is triphosphate, $R^1 = NH_2$;
$R^1 = R^2$ = OH: R^3 = Ph (**127**), Me (**128**);
$R^1 = NH_2$, R^2 = OH: R^3 = Ph (**129**), Me (**130**);
$R^1 = NH_2$, R^2 is triphosphate, R^3 = Ph (**131**)

In 2018, Rak's research team managed to synthesize 5-selenocyanato-2′-deoxyuridine **15**.[40] They adapted a selenocyanation method published by Agenäs.[136] The reaction between 2′-deoxyuridine and a cyanogen $(SeCN)_2$ obtained *in situ* from KSeCN and Br_2 in MeOH gave the 5-selenocyanato derivative **15** in as low as 6% yield (Scheme 37). Such a low yield was probably due to the very weak solubility of 2′-deoxyuridine in MeOH and consequently, its low conversion.[40]

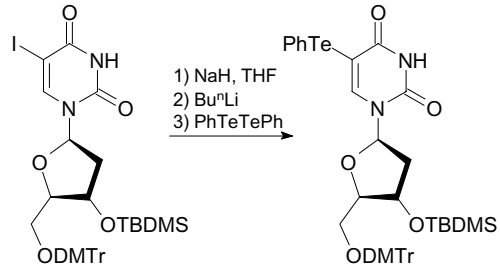
Scheme 37



5.3. Telluration

The only report concerning 5-telluro nucleoside derivatives was published in 2011 by Sheng *et al.*,[137] who synthesized 3′-*O*-TBDMS-5′-ODMTr-5-phenyltelluro-2′-deoxyuridine **132** by treating the corresponding 5-iodo-2′-deoxyuridine with NaH, Bu^nLi and finally with PhTeTePh (Scheme 38). It is noteworthy that during purification step authors faced the problem of separating the desired product from its 6-PhTe isomer. Subsequently, the isolated **132** was converted to its 3′-phosphoramidite derivative and then coupled to a previously designed DNA sequence in an overall yield of about 71%.

Scheme 38



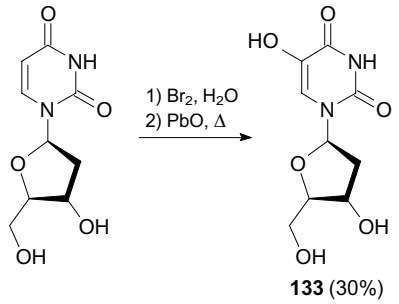
Tr is trityl

6. Hydroxylation

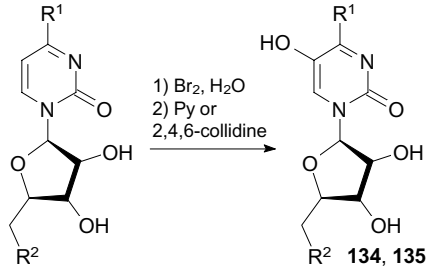
5-Hydroxy-2′-deoxyuridine (**OHdU**) **133** was first synthesized by Beltz and Visser [138] by treatment of 2′-deoxyuridine with bromine water, followed by the addition of lead(II) oxide. Heating at reflux for 30 min followed by chilling to 0 °C resulted in the precipitation of lead(II) bromide (Scheme 39). However, since this method requires handling toxic lead(II) compounds, it can not be recommended.

In 1968, it was discovered that treating uridine 5′-diphosphate with bromine water and pyridine afforded the corresponding 5-hydroxyuridine 5′-diphosphate analogue **134** (Scheme 40).[139]

Scheme 39



Scheme 40

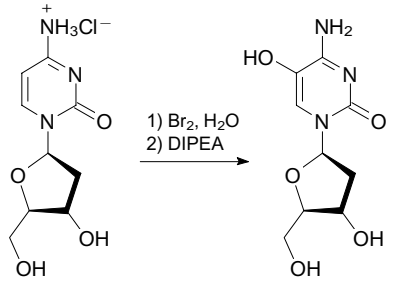


R^2 is diphosphate: R^1 = OH (**134**), NH_2 (**135**, 34%)

Five years later, Eaton and Hutchinson[140] synthesized the corresponding cytidine analogue **135** by the reaction of cytidine 5′-diphosphate with bromine water and 2,4,6-collidine (see Scheme 40). Moreover, they proposed a possible mechanism for the formation of 5-hydroxy derivatives. It comprises the addition of hypobromous acid, formed *in situ* in the bromine water, to the 5,6-double bond in the pyrimidine ring. The bromine atom at the C(5) position in such bromohydrin intermediate can be substituted with a hydroxyl group; then, this 5,6-dihydroxy derivative eliminates water to give 5-hydroxynucleoside. Interestingly, when pyridine was used instead of 2,4,6-collidine, a deamination reaction occurred and 5-hydroxyuridine 5′-diphosphate was the major product.

In 1998, 5-hydroxy-2′-deoxycytidine **136** (**OHdC**) was synthesized using the same synthetic protocol as for compound **135**. The starting material was 2′-deoxycytidine hydrochloride and instead of 2,4,6-collidine, *N*,*N*-diisopropylethylamine (DIPEA) was used (Scheme 41).[141]

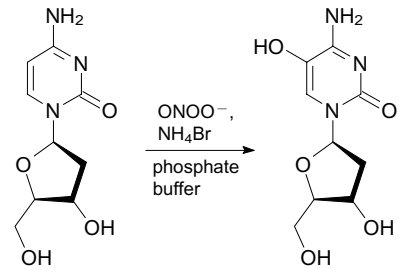
Scheme 41



DIPEA = $EtNPr^i_2$

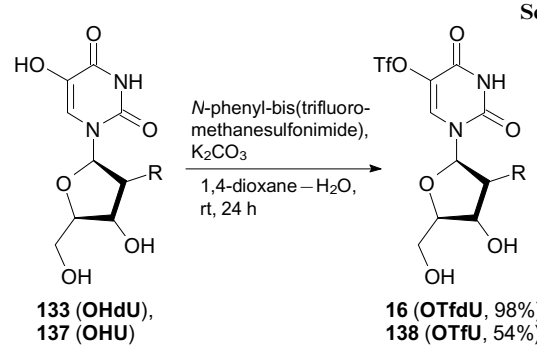
In 2008, the synthesis of peroxynitrite $ONOO^-$ from $^{\bullet}NO$ and $^{\bullet}O_2^-$ in cells was investigated.[142] The latter two species are formed *via* enzymatic action of the nitric oxide synthase and NADPH oxidase or xanthine oxidoreductase, respectively. Peroxynitrite itself is very reactive and in the presence of NH_4Br it presumably forms hypobromous acid, which can add to the 5,6-double bond of nucleoside, as described earlier in this section, eventually giving 5-hydroxynucleoside after a basic treatment. In the laboratory, peroxynitrite can be generated from $NaNO_2$ treated with the acidified H_2O_2 solution.[143] 2′-Deoxycytidine added to the $ONOO^-$ solution in phosphate buffer in the presence of NH_4Br afforded **136** (**OHdC**) (Scheme 42).

Scheme 42



Compound **133** (**OHdU**) or 5-hydroxyuridine **137** (**OHU**) can be easily converted into their 5-trifluoromethanesulfonyl analogues without needing to protect the hydroxyl groups in the sugar unit. Crisp and Flynn[144, 145] performed reactions of compounds **133** and **137** with *N*-phenylbis(trifluoromethanesulfonimide) in 1,4-dioxane – water mixture in the presence of potassium carbonate. The procedures were carried out under mild conditions yielding triflates **16** (**OTfdU**) and 5-trifluoromethanesulfonyluridine **138** (**OTfU**) in 98% and 54% yields, respectively (Scheme 43).

Scheme 43



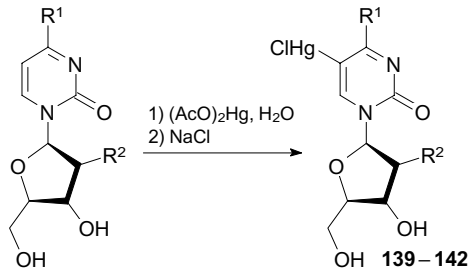
R = H (**16**, **133**), OH (**137**, **138**)

7. Metal derivatives

One of the most explored 5-metal nucleosides are 5-mercuri analogues. In 1975, Dale *et al.*[123] synthesized 5-mercuriuridine and cytidine and their 2′-deoxy derivatives. The reaction between appropriate nucleoside and mercury(II) acetate, followed by the addition of a sodium chloride aqueous solution gave 5-chloromercuri nucleosides **139** – **142** (Scheme 44). These compounds, reacting with alkenes in the presence of Li_2PdCl_4 in MeOH, provide an approach to a vast group of C(5)-alkylated nucleosides. Some examples of such reactions are presented below (Scheme 45).[146 – 150]

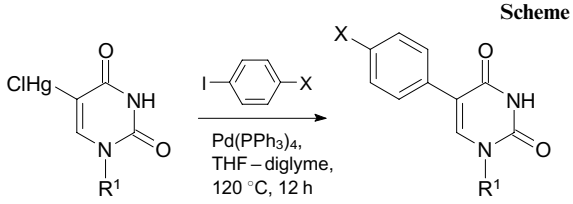
Several amendments were made to this process in which allylic chlorides, alcohols and acetates were used instead of

Scheme 44



R^1 = OH: R^2 = H (**139**), OH (**140**); R^1 = NH_2: R^2 = H (**141**), OH (**142**)

Scheme 47



R^1 is acetyl-protected 2′-deoxyribose; X = OMe, CF_3, CN, NH_2

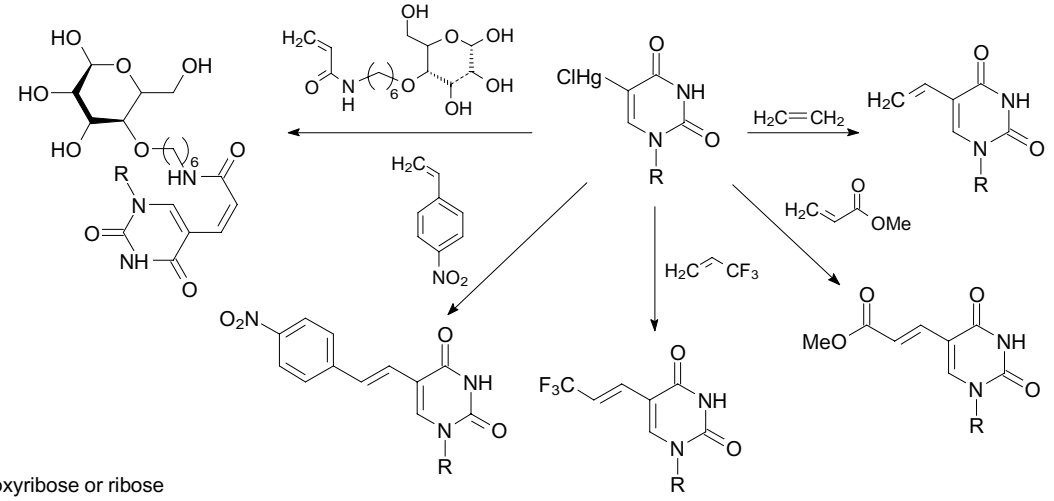
alkenes. Bergstrom *et al.*[151] synthesized a wide series of 5-alkyl-substituted pyrimidine nucleosides (Scheme 46). It is worth noticing that some of the reactions presented in this publication gave non-intuitive products. The authors, based on Heck's reports,[152] described Li_2PdCl_4 as a catalyst and the reason for this allylic rearrangement. Generally, good to very good yields of reactions were obtained for alkenes with lower electron density. On the other hand, yields were much poorer for alkenes with electron-donating groups.

Starting from acetyl-protected 5-mercuri derivatives, it is also possible to obtain C(5)-arylated uridines. In this case, an appropriate 5-mercuri derivative was treated with *para*-substituted iodobenzene in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] in THF – diglyme mixture for 12 h at 120 °C to provide 3′,5′-di-*O*-acetyl-5-arylated-2′-deoxyuridines in 40% – 70% yields (Scheme 47).[153, 154] The reaction also proceeded with non-protected 5-mercuri nucleosides as starting materials, but with poorer yields due to their much lower solubility in THF.

Moreover, as shown in Table 3, entry 5, and in Scheme 27,[86, 124] starting from 5-mercuri derivatives, one can afford the corresponding 5-iodo and 5-(alkylsulfanyl) nucleosides.

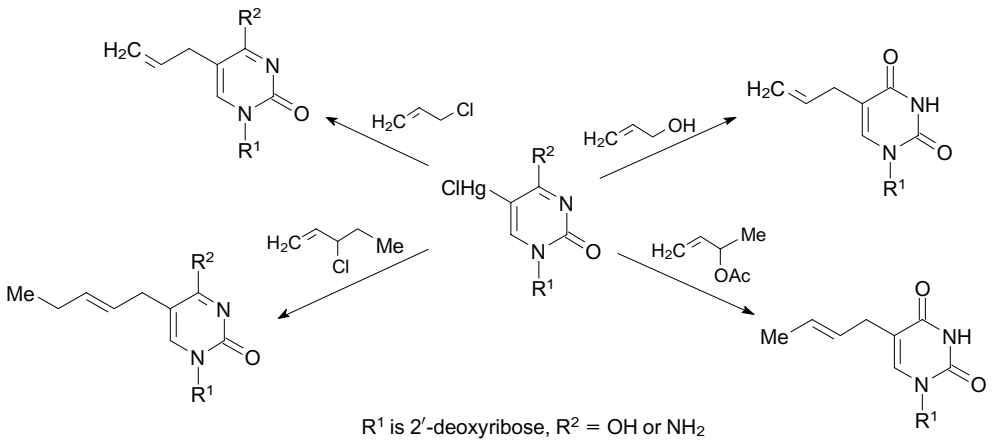
In 1985, Schinazi and Prusoff[155] obtained 5-boro- and 5-trimethylsilyl derivatives of 2′-deoxyuridine. Treating **13** (**BrdU**) with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and trimethylchlorosilane (TMCS) in pyridine furnished 3′,5′-di-(*O*-trimethylsilyl)-5-bromo-2′-deoxyuridine **143**. Subsequent treatment with Bu^nLi at −50 °C led to the *in situ* lithiated compound **144**, which was mixed with tri-*n*-butyl

Scheme 45



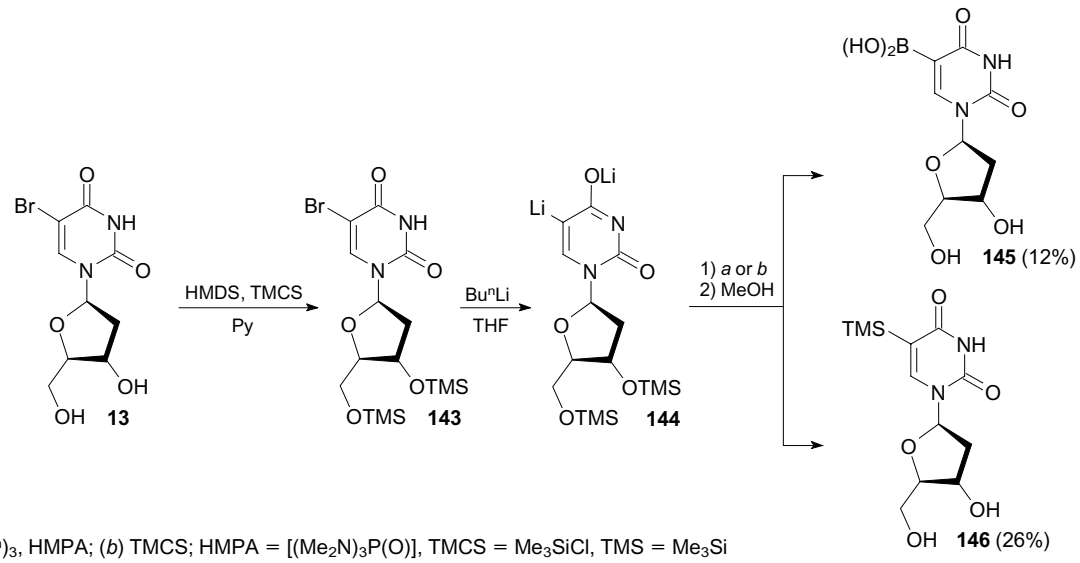
R is 2′-deoxyribose or ribose

Scheme 46



R^1 is 2′-deoxyribose, R^2 = OH or NH_2

Scheme 48



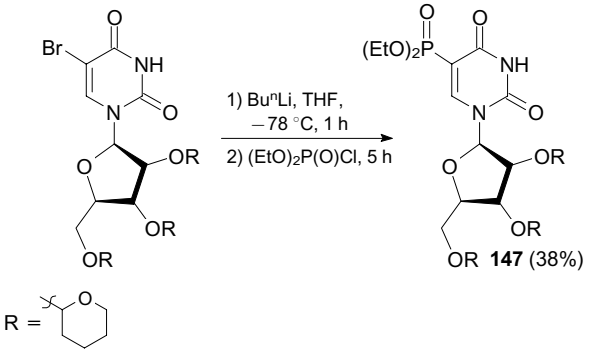
(*a*) $B(OBu^n)_3$, HMPA; (*b*) TMCS; HMPA = $[(Me_2N)_3P(O)]$, TMCS = Me_3SiCl, TMS = Me_3Si

borate in the next step in the presence of hexamethylphosphoramide or TMCS, followed by hydrolysis of the resulting 3′,5′-trimethylsilyl ethers to afford compounds **145** and **146**, respectively (Scheme 48).

8. Phosphonylation

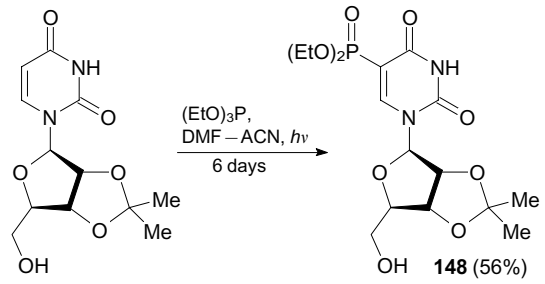
The first report on 5-phosphono nucleoside comes from 1986. 2′,3′,5′-Tri-*O*-(tetrahydro-2-pyranyl)-5-bromouridine was first lithiated and then phosphorylated with diethyl chlorophosphate to afford the desired product **147** (Scheme 49).[156] Hydroxyl groups in the starting compound were protected with tetrahydropyranyl ethers, which are one of the earliest entities applied for protecting alcohols. Their stability against basic conditions, combined with easy removal, make them attractive in organic synthesis.

Scheme 49



The same research group[157] proposed a diverse phosphonylation reaction. Irradiating 2′,3′-*O*-isopropylideneuridine with a low-pressure mercury lamp generated an excited state of this compound, which reacted with triethyl phosphite in DMF – ACN mixture to provide a radical intermediate, disproportionating to ethyl radical and 2′,3′-*O*-isopropylideneuridine-5-phosphonate **148** (Scheme 50). The overall reaction time was 6 days, which makes it difficult to handle.

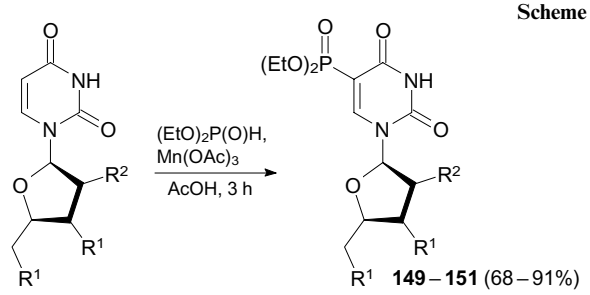
Scheme 50



A highly efficient method for 5-phosphonylation of nucleosides was published by Kim *et al.*[158] in 2013. It assumes the use of dialkyl H-phosphonate in the presence of manganese(III) acetate. In this oxidative cross-coupling reaction, a phosphonyl radical, generated *in situ*, acts as an electrophile. Three derivatives of uridine **149** – **151** were synthesized in very good to excellent yields by heating the substrates with diethyl H-phosphonate in the presence of $Mn(OAc)_3$ in AcOH for 3 h (Scheme 51). During the reaction, it is important to keep the temperature below 50 °C, because of the possible formation of *N*-glycosidic bond cleavage byproducts.

Taking into account three above-described phosphonylation methods, the mild protocol proposed by Kim *et al.*[158] gives a simple, effective and fast access to 5-phosphono nucleosides and also to some uracil and purine derivatives.

Scheme 51



$R^1 = R^2 = H$ (**149**), OH (**150**); $R^1 = OH$, $R^2 = H$ (**151**)

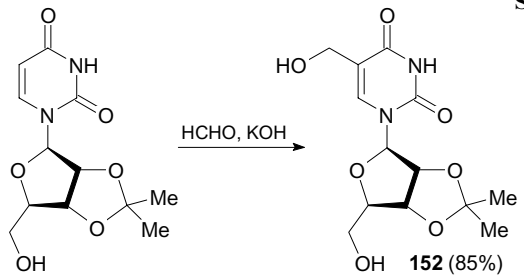
9. The C – C bond formation

One of the most chemically explored areas in the modification of nucleosides at the C(5) position is the C – C bond formation. In sections 9.1 – 9.4, we listed the most popular and synthetically useful methodologies for obtaining hydroxymethylated, formylated and carboxylated derivatives as well as the products of heterocoupling reactions.

9.1. Hydroxymethylated derivatives

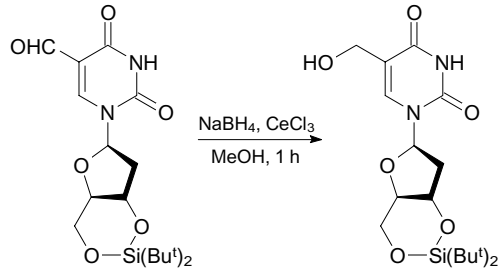
In 1966, Scheit[159] described the synthesis of 5-hydroxymethyl derivative of 2′,3′-*O*-isopropylideneuridine. Treating 2′,3′-protected uridine with paraformaldehyde in 0.5 M KOH aqueous solution afforded compound **152** (Scheme 52). Later, this synthetic procedure was modified by using NEt_3 instead of KOH aqueous solution.[160, 161]

Scheme 52



A different approach towards introducing the hydroxymethyl moiety into the nucleoside comprises the reduction of its formyl precursor. An exemplary method is based on treating the 5-formyl-2′-deoxyuridine derivative with sodium borohydride in the presence of cerium(III) chloride in MeOH. The reaction was completed in 1 h to give the final product **153** in good yield (Scheme 53).[161]

Scheme 53

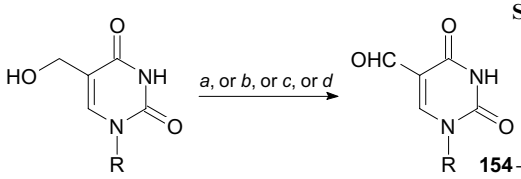


9.2. Formylated analogues

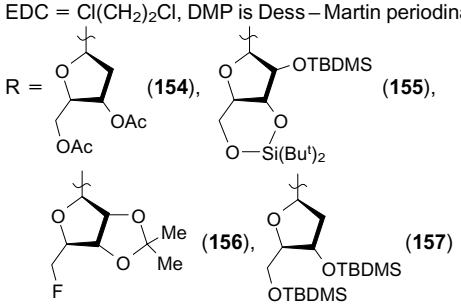
5-Hydroxymethyl moiety can be oxidized in various ways to a 5-formyl substituent. The most popular synthetic protocols are shown in Scheme 54.[162 – 165] The highest yields were reached in the case of oxidation with pyridinium chlorochromate (see Scheme 54, conditions *a*) and Dess – Martin periodinane (DMP) (see Scheme 54, conditions *b*), in 72% and 77% yields, respectively. Oxidation reactions with MnO_2 (see Scheme 54, conditions *c*) and RuO_2 (see Scheme 54, conditions *d*) were performed in moderate yields of 34% and 45%, respectively.

In 1994, Crouch and Eaton[166] described the synthesis of 5-formyl derivative **158** through a facile modification of Stille coupling conditions.[167] An 8-hour reaction between 5-iodo derivative and CO in the presence of Pd^0 catalyst and

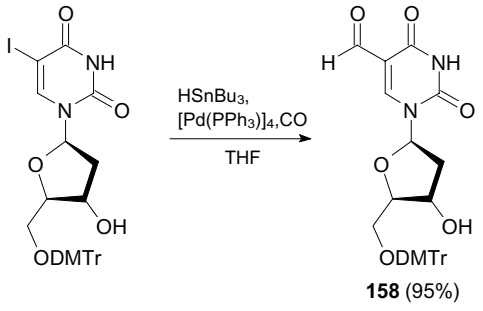
Scheme 54



(*a*) CrO_3, Py·HCl, Al_2O_3, EDC (**154**, 72%); (*b*) DMP, DCM (**155**, 77%); (*c*) MnO_2, PhMe (**156**, 34%); (*d*) RuO_2, 1,4-dioxane (**157**, 45%); EDC = $Cl(CH_2)_2Cl$, DMP is Dess – Martin periodinane;



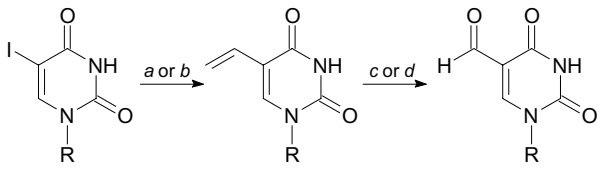
Scheme 55



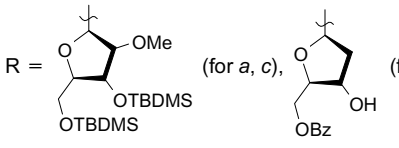
tributyltin hydride led to 5′-ODMTr-5-formyl-2′-deoxyuridine **158** (Scheme 55).[166]

Other two-step procedures, presented below, can be alternatives for the above-mentioned reaction, which requires the use of CO (see Scheme 55). In the first step of the presented methods, 5-vinyl nucleoside analogues **159** or **161** were obtained (Scheme 56, conditions *a* or *b*) and then subjected to dihydroxylation with OsO_4 in the presence of a base. Vicinal diols thus obtained were then cleaved by $NaIO_4$ to give compounds **160** or **162** in overall 35% and 77% yields, respectively (see Scheme 56, conditions *c*

Scheme 56



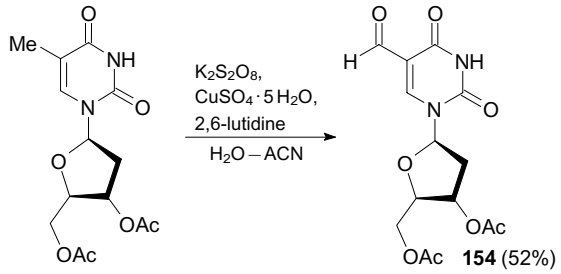
(*a*) $MeCO_2CH{=}CH_2$, $Pd(OAc)_2$, PPh_3, THF;
(*b*) $Bu^n_3SnCH{=}CH_2$, $Pd(PPh_3)_2Cl_2$, THF;
(*c*) 1) OsO_4, NMO; 2) $NaIO_4$;
(*d*) 1) OsO_4, 2,6-lutidine; 2) $NaIO_4$; NMO is *N*-methylmorpholine;



or *d*).[168, 169] Despite the fact that these two reactions exclude the use of CO, they are tedious and time-consuming and the yields of the products are lower.

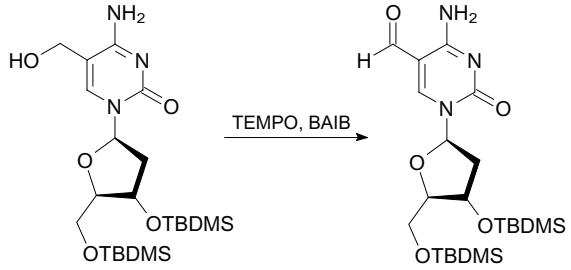
In 1993, Matsuda *et al.*[170] described the direct synthesis of 5-formyl derivative **154** by heating 3′,5′-di-*O*-acetyl-protected thymidine with potassium peroxysulfate in the presence of $CuSO_4$ and 2,6-lutidine (Scheme 57).

Scheme 57



A very efficient method for obtaining 5-formyl derivative of 2′-deoxycytidine was reported by Sun *et al.*[171] This research team modified an oxidation procedure of the corresponding 5-hydroxymethyl analogues by using stoichiometric amounts of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) and [bis(acetoxy)iodo]benzene (BAIB). The treatment of 5-hydroxymethyl substituted 2′-deoxycytidine gave its 5-formyl derivative **163** rather rapidly and in high yield (Scheme 58). The mechanism of this oxidation reaction is unknown, but there are two very interesting articles that discuss this topic in more detail.[172, 173]

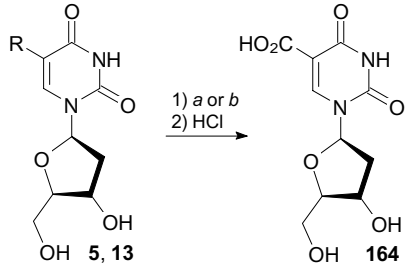
Scheme 58



9.3. Carboxylic acid derivatives

The synthesis of 5-carboxy-2′-deoxyuridine was first reported in 1967. Compound **BrdU** (**13**) subjected to the reaction with Bu^nLi, followed by the addition of solid CO_2 and acidification with HCl, gave the desired product **164** (Scheme 59).[174]

Scheme 59

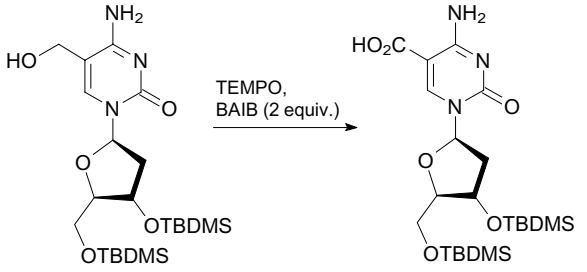


(*a*) Bu^nLi, THF, −65 °C, CO_2 (for **13**, 27% yield); (*b*) NaOH, H_2O (for **5**, 99% yield); R = Br (**13**), CF_3 (**5**)

More convenient and effective method for introducing the carboxyl moiety into the nucleoside structure is the alkaline hydrolysis of 5-trifluorothymidine. The plausible mechanism comprises the formation of difluorohydroxy and hypothetical monofluorocarbonyl intermediates.[175] Treating **CF_3dU** (**5**) with aqueous NaOH solution afforded product **164** in much higher yield (90%) (see Scheme 59, conditions *b*).[176]

It is also possible to get 5-carboxyl moiety by oxidizing the 5-hydroxymethyl substituent with TEMPO – BAIB system. As it was shown in Scheme 58, using stoichiometric amounts of this system, one can get an aldehyde. With 2 equiv., a hydroxymethyl derivative is oxidized to carboxylic acid. Thus, the reaction between 5-hydroxymethyl-2′-deoxycytidine and TEMPO – BAIB gave the corresponding 5-carboxyl analogue **165** (Scheme 60).[171]

Scheme 60



9.4. Heterocoupling reactions

Table 4 presents different heterocoupling approaches. In case of nucleosides, the C – C coupling reactions are mainly catalyzed by Pd^0, but copper, iridium and ruthenium catalysts can also be used. Some of such reactions are photo-catalyzed as well. Previously, in section 7 we showed examples of the C – C bond formation with the use of 5-halogenomercuri compounds in the presence of Li_2PdCl_4 (see Schemes 45 – 47).

In 2016, Bhilare *et al.*[177] described two phosphatriazene ligands (PTABS and PTAPS) that along with $Pd(OAc)_2$ form very efficient catalysts for Suzuki – Miyaura, Sonogashira and Heck couplings. The enhanced solubility of these complexes in water provides the possibility to recycle them more easily and to avoid a preparative column chromatography purification step. Non-protected 5-iodo nucleosides **1**, **35** treated with PTABS, $Pd(OAc)_2$ and subsequently with 2-benzofuranylboronic acid, phenylacetylene or 4-bromostyrene, in the presence of NEt_3, gave compounds **166** – **168** in high yields (Table 4, entries 1 – 3).

Compound **IdU** (**1**) reacts with 2-(trimethylstannyl)pyridine in the presence of $PdCl_2(PPh_3)_2$ in 1,4-dioxane to afford 5-(pyridin-2-yl)-2′-deoxyuridine **169** (see Table 4, entry 4).[178]

C-Alkylation reactions can be also performed under irradiation. Entries 5 – 7 show three different methodologies covering this topic. Al-Razzak *et al.*[179] described the photochemical aromatic substitution regarding to the synthesis of uridine derivatives. A solution of 5-trimethylsilyl-2′-deoxyuridine obtained from 5-iodo-2′-deoxyuridine and HMDS, was reacted with 2,3,5-trimethyl-1,4-dimethoxybenzene under irradiation at 310 nm to give the desired product **170** (see Table 4, entry 5).[179]

Fac-tris(2-phenylpyridine)iridium [*Fac*-Ir(ppy)$_3$], a very efficient photoredox catalyst, was successfully used in the

Table 4. Heterocoupling reactions of uridine and its derivatives.

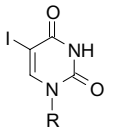
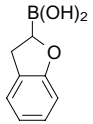
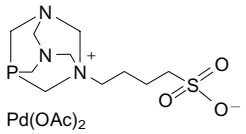
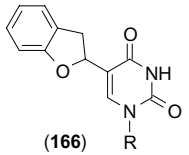
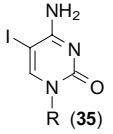
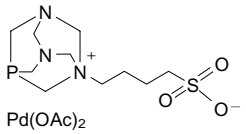
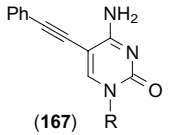
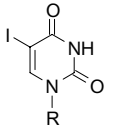
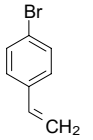
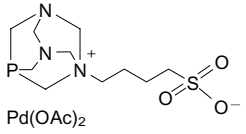
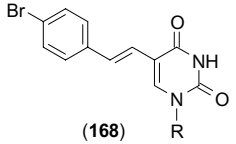
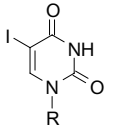
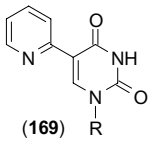
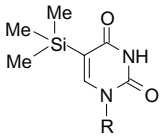
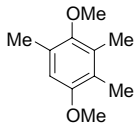
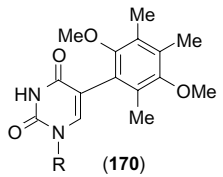
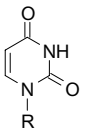
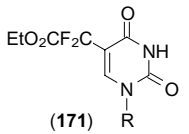
Entry	Substrate	Reagent	Reaction conditions				Product	Yield (%)	Ref.
			catalyst	solvent	T/°C	t/h			
1	 (**1**, **IdU**)			H_2O	80	3	 (**166**)	88	86
2	 (**35**)	PhC≡CH		H_2O, ACN	80	0.75	 (**167**)	75	177
3	 (**1**, **IdU**)			H_2O, ACN	80	18	 (**168**)	88	177
4	 (**1**, **IdU**)		$PdCl_2(PPh_3)_2$	1,4-dioxane	90	1	 (**169**)	83	178
5			irradiation at 310 nm	ACN	40	48	 (**170**)	15	179
6		$BrCF_2CO_2Et$	*fac*-Ir(ppy)$_3$, irradiation at 460 nm	DMSO	rt	24	 (**171**)	84	180

Table 4 (continued).

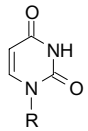
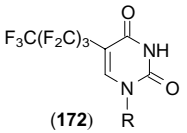
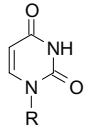
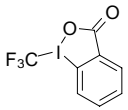
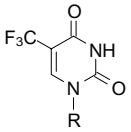
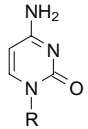
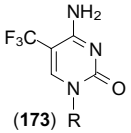
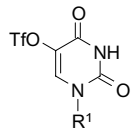
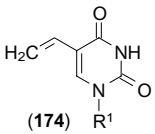
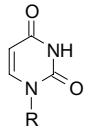
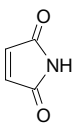
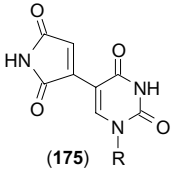
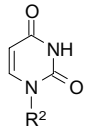
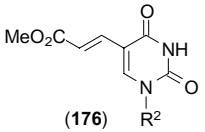
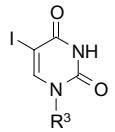
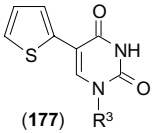
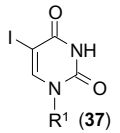
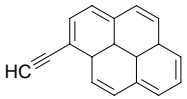
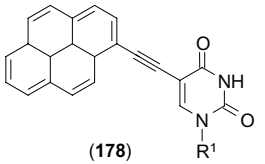
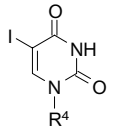
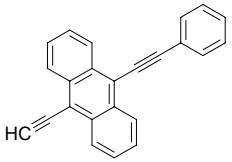
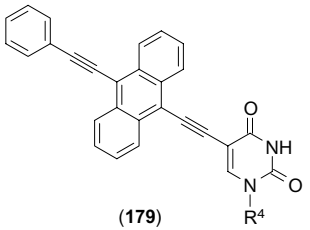
Entry	Substrate	Reagent	Reaction conditions				Product	Yield (%)	Ref.
			catalyst	solvent	T/°C	t/h			
7		$I(CF_2)_3CF_3$	$Ru(bpy)_3Cl_2$, irradiation at 460 nm	DMSO	rt	24	 (**172**)	44	181
8			CuI	DMF	40	23	 (**5**, **CF_3dU**)	73	182
9		CF_3SO_2Na	Bu^tO_2H	H_2O	rt	3	 (**173**)	73	183
10			$Pd(PPh_3)_4$, LiCl	1,4-dioxane	reflux	4	 (**174**)	87	145
11			$Pd(OAc)_2$	ACN	reflux	17	 (**175**)	10	184
12			$Pd(OAc)_2$, $PhCO_3Bu^t$	ACN	rt	53	 (**176**)	74	185
13	 (**34**, **IU**)		$Pd_2(dba)_3$, TBAF	DMF	100	1	 (**177**)	98	186

Table 4 (continued).

Entry	Substrate	Reagent	Reaction conditions				Product	Yield (%)	Ref.
			catalyst	solvent	T /°C	t /h			
14	 (**37**)		$Pd(PPh_3)_4$, CuI, NEt_3	DMF	50	2	 (**178**)	83	187
15			$Pd(PPh_3)_4$, CuI, NEt_3	DMF	50	2	 (**179**)	n/a	188, 189

R is 2′-deoxyribose, R^1 is 3′,5′-di-*O*-acetyl-2′-deoxyribose, R^2 is 2′,3′-isopropylideneribose, R^3 is ribose, R^4 is 3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-2′-deoxyribose.

visible-light-induced coupling difluoroalkylation. He *et al.*[180] synthesized compound **171**, starting from 2′-deoxyuridine and ethyl bromodifluoroacetate (see Table 4, entry 6).[180]

The same research group[181] studied 5-perfluoroalkylation of uridines. Using the same protocol as for **171** they obtained compound **172** in a very poor yield. To resolve this problem, they used perfluoroalkyl iodide as a substrate instead of bromide, and $Ru(bpy)_3Cl_2$ as a catalyst. It turned out that DMSO was the most efficient solvent (comparing to DMF or ACN); cesium carbonate was chosen as a base. These modified conditions resulted in the formation of 5-perfluorinated analogue **172** in moderate yield (see Table 4, entry 7).

The next two examples relate to a 5-trifluoromethylation of nucleosides. The presence of CF_3 group is very crucial from the pharmaceutical and agrochemical points of view. This moiety is found in *e.g.*, Viroptic drug (**5**, Fig. 2). There are two possible ways to synthesize 5-trifluoromethylated nucleosides. The first, method comprises the reaction of a nucleoside with Togni's reagent in the presence of copper(I) iodide. Togni's reagent is a simple trifluoromethylating agent and it is one of the first examples of stable hypervalent iodine derivatives.[190] It was successfully used in 5-trifluoromethylation of 2′-deoxyuridine to produce **CF_3dU** (**5**) (see Table 4, entry 8).[182]

The second way to introduce CF_3 group into a nucleoside is the reaction with sodium trifluoromethanesulfinate in the presence of *tert*-butyl hydroperoxide as a radical source. 2′-Deoxycytidine treated with the aforementioned system yielded 5-trifluoromethyl-2′-deoxycytidine **173** in a very good yield (see Table 4, entry 9).[183]

Acetyl-protected 5-triflate derivatives can enter various coupling reactions with terminal alkynes or organostannanes.[144, 145] The example of organostannane palladium-catalyzed coupling to nucleoside triflate is shown in Table 4, entry 10. Thus, 3′,5′-di-*O*-acetyl-5-trifluoromethanesulfonyl-2′-deoxyuridine was reacted with ethenyltributylstannane in the presence of $Pd(PPh_3)_4$ and LiCl in 1,4-dioxane, affording 3′,5′-di-*O*-acetyl-5-ethenyl-2′-deoxyuridine **174** in an 87% yield after isolation by preparative column chromatography. The authors indicated that the organostannanes, with both electron-donating and electron-withdrawing substituents, coupled to triflates with similar efficacy.

Itahara[184] reported a possibility of introducing a maleimide moiety at the C(5) position of uracils and uridines. The reaction between 2′-deoxyuridine and maleimide in the presence of $Pd(OAc)_2$ gave the product **175** in as low as 10% yield (Table 4, entry 11). It is worth noticing that in the case of uracil derivatives the yields of the final products were higher (up to 56%) when using re-oxidants such as AgOAc, $Na_2S_2O_8$ and $Cu(OAc)_2$.

2′,3′-Isopropylideneuridine reacted with methyl acrylate in the presence of $Pd(OAc)_2$ and *tert*-butyl perbenzoate to afford product **176** in high yield (see Table 4, entry 12).[185] The reaction was carried out at room temperature which is convenient; nevertheless, the time taken was longer compared to other examples from Table 4.

A very simple and efficient protocol for the synthesis of 5-aryluridines was introduced by Wnuk and coworkers.[186] 5-Iodonucleosides were coupled with furan or thiophene in the presence of tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] and TBAF in DMF at 100 °C for 1 – 2 h. Not only the yields of the products were good to excellent (45% – 98%), but this method also kept the *N*-glycosidic bond stable in case of 2′-deoxyuridine substrates. The reaction worked well with both protected and unprotected nucleosides and avoided the use of toxic compounds. In an example shown in Table 4, entry 13, **IU** (**34**) was treated with thiophene in the presence of $Pd_2(dba)_3$ and TBAF in DMF to give 5-(thiophen-2-yl)uridine **177** in nearly quantitative yield.

Pyrene analogues are known to possess the ability to intercalate into duplex DNA and, along with their extended lifetime of the excited state, such derivatives can serve for DNA structural studies. Korshun *et al.*[187] described the introduction of the 1-ethynylpyrenyl moiety into the 2′-deoxyuridine structure. Starting from 3′,5′-di-*O*-acetyl-5-iodo-2′-deoxyuridine **37** and keeping the coupling conditions adapted from previous works,[191, 192] they managed to obtain compound **178** in high yield (see Table 4, entry 14), which was later quantitatively deprotected, phosphitylated and used as a substrate in further oligonucleotide synthesis.

A series of 5-alkynyl-2′-deoxyuridines having various bulky substituents was synthesized and tested against HSV-1. Among them, compound **179** exhibited significant antiviral activity. In order to obtain it, 3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-5-iodo-2′-deoxyuridine was reacted with 9-ethynyl-10-(phenylethynyl)anthracene in the presence of $Pd(PPh_3)_4$, CuI and NEt_3. The reaction proceeded under standard Sonogashira coupling conditions, giving derivative **179** (see Table 4, entry 15).[188]

10. Conclusion

In this review, we have collected the most popular methods for chemical modifications at the C(5) position of pyrimidine nucleosides. Problems that organic chemists have to deal with while performing the synthesis include: a) protection and deprotection of hydroxyl groups within a sugar unit, b) low reaction yields, c) stereochemistry and stereoselectivity aspects, d) the use of heavy metal-based reagents, and e) the use of toxic solvents. These aspects are especially important when synthesizing biologically active compounds on preparative scales.

One of the latest trends organic chemists can benefit from is mechanochemistry. This involves the application of a mechanical force, *e.g.*, shearing, grinding or stretching, to the substrates in order to trigger the formation or cleavage of chemical bonds. Reactions are usually performed in a mixer ball mill or mortar grinder. This branch of chemistry is of great value due to the possibility of reducing or completely eliminating the use of solvents, enhancing the conversion of substrates or even obtaining products that were unavailable with previously used methods. Furthermore, in many cases, reaction times are shorter and side reactions can be limited. There are only a few examples of mechanochemical processes in terms of nucleoside chemistry.[193] Among them, the protection and deprotection of hydroxyl groups in sugar units,[194 – 196] and the Boc-protection of amine or carboxylic acid functions present in the nucleoside[196, 197] seem to be the most vital in case of organic synthesis. These reactions can be a great alternative to their classic solvent-based versions and are in perfect agreement with the principles of 'green' chemistry. Although mechanochemistry is rapidly developing in the field of organic chemistry, much further effort needs to be put into exploring this valuable area of science.

Taking into account the fact that C(5)-modified pyrimidine nucleosides are vital for medicine and pharmacy, searching for and developing rapid and efficient ways to synthesize them are highly demanded. 5-Halogenonucleosides and their analogues with the C−C bond at the C(5) position exhibit anticancer, antiviral, radio- and photosensitizing properties. Moreover, some of them are active against such viruses as HSV-1, HSV-2, VZV or EBV. 5-Substituted uridines and cytidines, due to their structural similarity to native nucleosides, can be incorporated into DNA at the cellular level, which makes them good candidates for efficient chemotherapeutic agents. Moreover, radiotherapy, used in *ca.* 50% of cancer patients, as well as photodynamic therapy could benefit directly from the C(5)-modified pyrimidine (radio)photosensitizers. To summarize, from the medical point of view, exploration of the therapeutic potential of C(5)-modified nucleosides should certainly continue. Finally, we should not forget that the synthesis always precedes the successive studies. Keeping this fact in mind, this review paper is a great tool for synthetic chemists to search for an appropriate reaction, which is often not easy as each of them has its own merits.

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