Russian Chemical Reviews **68** (6) 483 – 504 (1999) © 1999 Russian Academy of Sciences and Turpion Ltd

UDC 577.113.3 :: 547.854 : 547.3

C-Alkenylation of pyrimidine nucleosides and their analogues

A F Nasonov, G A Korshunova

Contents

I.	Introduction	483
II.	Alkenylation of organoelement nucleoside derivatives and their analogues	484
III.	Alkenylation of *C*-halogeno derivatives and triflates of nucleosides and their analogues	493
IV.	Alkenylation of non-substituted nucleosides and their analogues	501
V.	Conclusion	502

Abstract. Methods for C-alkenylation of heterocycle moieties of pyrimidine nucleosides and their analogues are generalised. The methods employing both organoelement nucleoside derivatives (organomercury, -tin, -boron and -lithium) and organoelement alkene derivatives (organomagnesium, -boron, -aluminium, -tin and -silicon) as well as palladium-catalysed oxidative coupling and photochemical reactions are considered. The reaction conditions (the role of solvents, catalysts and co-catalysts, temperature and time modes) are discussed. The advantages and the drawbacks of different approaches for introduction of alkenyl groups are discussed. Examples of practical applications of alkenylated nucleoside derivatives and their analogues are given. The bibliography includes 92 references.

I. Introduction

Derivatives of pyrimidine nucleosides with substituents at positions 5 and 6 have been the permanent focus of attention of investigators. The number of papers devoted to the synthesis and application of these compounds is rapidly increasing. This interest is largely associated with antiviral and antitumour properties of these nucleosides and the possibility of using them as probes for studying the interactions between biomolecules [1,2] or as fluorescent probes for DNA sequencing.

Very often these properties are exhibited by nucleosides containing a C–C bond with various substituents at positions 5 and 6 (alkyl, alkenyl, alkynyl, aryl, hydroxyalkyl, acyl, *etc.*). In this context, systematisation of methods used for the synthesis of such compounds is especially important. A review [3] on C-alkylation of nucleosides which is devoted to problems of synthesis of the majority of derivatives with the above substituents was published in 1990. A detailed study [4] describing the synthesis of alkynyl derivatives of nucleosides and their analogues has appeared more recently.

A F Nasonov Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119899 Moscow, Russian Federation.
Fax (7-095) 939 31 81. Tel. (7-095) 939 30 20.
E-mail: anat@peplab.genebee.msu.su
G A Korshunova A N Belozersky Research Institute of Physicochemical Biology, Leninskie Gory, 119899 Moscow, Russian Federation.
Fax (7-095) 939 31 81. Tel. (7-095) 939 54 12.
E-mail: korshunova@peplab.genebee.msu.su

Received 16 June 1998
Uspekhi Khimii **68** (6) 532 – 554 (1999); translated by R L Birnova

Alkenyl-substituted nucleosides seem to play the most crucial role among other nucleosides under consideration; these are extensively used in practically all the fields mentioned above. Thus 5-(*E*)-bromovinyluridine and its carbocyclic analogues, 5-(*E*)-(propen-1-yl)uridine and 5-(*E*)-(3,3,3-trifluoropropen-1-yl)uridine, are known as efficient antiviral agents. Many alkenyl derivatives, particularly those containing a porphyrin fragment,[5] manifest an antitumour activity. The extensively investigated reactions between certain alkenes and nucleosides are used to prepare probes to study biomolecules. These reactions allow both direct incorporation of a label into a biomolecule and its addition through an alkenyl linker. As an illustration, we can refer to biotin-containing probes,[6] photoactivated labels [7,8] and fluorescent probes [9] used in DNA sequencing. Evidently, alkenyl linkers can also be used for other purposes. An interesting example is the addition of carborane-containing fragments [10] used in anticancer boron neutron capture therapy (BNCT).

It can be mentioned that the synthesis of alkenyl derivatives of pyrimidine nucleosides and their analogues has a number of special features and often presents a more complicated task than the alkenylation of classical aromatic compounds, *e.g.,* benzene. Such complications can be associated with both the preparation of the starting activated nucleosides and the conducting of the alkenylation reaction. They result from the presence of several reactive functional groups in the nucleoside molecule and the complex behaviour of the quasi-aromatic system of pyrimidine nucleic bases. For example, alkenylation of mercury derivatives of nucleosides with non-activated alkenes in methanol yields predominantly α-methoxyalkyl derivatives, which are not typical of the analogous reactions for the benzene series.

One can say that generalised information on these reactions has not been adequately addressed in the literature, especially when one takes into consideration that all the presently known methods of C-alkenylation of pyrimidine nucleosides are extremely diverse. The reviews [11,12] describing the synthesis of alkenyl-substituted nucleosides point to the exclusive use of 5-mercurionucleoside derivatives. It is of note that the first of them [11] was published as long ago as in 1982, while the second one [12] is rather a summary of results obtained by the authors in the preceding period. Even since the publication of the review by Krečmerová,[3] several novel alkenyl nucleoside analogues and methods of their synthesis have appeared, which necessitates generalisation and critical evaluation of the vast body of experimental data concerning the methods of synthesis of pyrimidine nucleosides with C-alkenylated heterocycles.

All the currently known methods used for the synthesis of alkenylated pyrimidine nucleosides can be conventionally divided

into two groups. The most efficient (Group 1) methods consist in the direct formation of the C−C bond of a nucleoside with an alkenyl substituent. In contrast, Group 2 methods in which the pyrimidine ring is formed in the first step with subsequent glycosylation, have serious drawbacks. These include the necessity for preliminary preparation of reagents for cyclisation and the formation of a mixture of α- and β-anomers in the glycosylation step. The present review deals with the description of Group 1 methods, *viz*., direct alkenylation of the pyrimidine ring of nucleosides and their analogues at position 5 or 6.

From our standpoint, the methods of direct alkenylation should best be classified according to the structural features of nucleosides and alkenylating agents involved in the reaction. The choice of compounds to be introduced in the reaction is determined, among other factors, by the ease of their synthesis. In many respects, this factor is crucial for a synthesis-oriented chemist. Thus 5-chloromercury derivatives of nucleosides formed under mild conditions are widely employed in the coupling with alkenes; examples of 'reversed' coupling of nucleosides by this reaction are unknown. The readers who are interested in the mechanisms of the reactions discussed below can be referred to the monograph.[13] According to the structure of reagents (alkenylating reagents) and substrates (nucleosides), the methods used for alkenylation of pyrimidine nucleosides can be classified as follows:

1. *Alkenylation of nucleosides containing a C−E bond (E is the electropositive element, viz., Hg, B, Sn and Li)*. Coupling of organomercury nucleoside derivatives with alkenes and cross-coupling of organoboron and organotin nucleoside derivatives with alkenyl halides are catalysed by palladium compounds. Nucleoside organolithium derivatives and their analogues as nucleophiles substitute the fluorine atom in perfluoro- or fluorochloroalkenes.

2. *Alkenylation of nucleosides with a C−Hal or a C−OTf bond*. The methods referred to this group can be additionally divided into four subgroups:

a. Reactions of halogeno derivatives of nucleosides with alkenes in which carbon atoms at the double bond are not linked to heteroelements.

b. Reactions of halogeno derivatives of nucleosides with vinyl acetate.

c. Reactions of halogeno derivatives or triflates of nucleosides with organoelement derivatives of alkenes [Group III (B, Al) or Group IV elements (Si, Sn, Zr)].

d. Photochemical introduction of alkenyl groups into nucleosides.

The reactions related to the first three groups are catalysed by palladium compounds.

3. *Coupling of non-substituted nucleosides with alkenes*. These include addition of nucleosides to activated alkenes, cross-coupling with triflate derivatives of alkenes and addition to alkenyl organomagnesium compounds. The first two reactions are catalysed by palladium complexes.

II. Alkenylation of organoelement nucleoside derivatives and their analogues

1. Coupling of organomercury derivatives of pyrimidine nucleosides and their analogues with alkenes

Coupling of 5-mercury derivatives of pyrimidine nucleosides with alkenes was the first reaction [14] used in the synthesis of alkenylated nucleosides by direct formation of the C−C bond between the substituent being introduced and the heterocycle. It is also the first reaction which has a versatile preparative significance for C-alkylation of nucleosides in general, since the alkenyl group being introduced can be further (or directly, in the course of the reaction) subjected to easy modification. Reduction of vinyl groups with hydrogen over a platinum catalyst and decarboxylation of carboxyvinyl groups are typical examples of such modifications. The regio- and stereoselectivity of addition of certain substituents is an important feature of the alkenylation reaction. As a matter of fact, this coupling represents the Heck reaction,[15,16] although its application to nucleosides has a number of specific features (see below). Its mechanism[13,15,16] can be presented as a sequence of transmetallation reactions (Hg is replaced by Pd), insertion of an alkene and reductive elimination, and for the sake of simplicity can be represented as follows:

$$ArHgX \xrightarrow[-HgX_2]{PdX_2} ArPdX \xrightarrow{H_2C=CHY} \longrightarrow ArCH_2CHY \xrightarrow[-PdHX]{} ArCH=CHY;$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad | \qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad PdX$$

$$PdHX \longrightarrow Pd(0) + HX.$$

This reaction occurs easily for all types of nucleic acid components (nucleic bases, nucleosides and nucleotides). 5-Chloromercurio-, 5-acetoxymercurio- and 5-trifluoroacetoxymercurio-pyrimidine nucleosides are normally used.[17,18] Depending on the solubility of the starting compounds and reaction products, the reaction is carried out in methanol, dimethylformamide, acetonitrile or aqueous–organic media. Li_2PdCl_4, Na_2PdCl_4, K_2PdCl_4 and $Li_2Pd(OAc)_2Cl_2$ are most commonly used as catalysts (Table 1).

In the alkenylation of 5-mercurionucleoside derivatives, Pd(II) is irreversibly reduced to Pd(0); therefore, the catalyst has to be used in at least equimolar amounts. To avoid this, an agent which oxidises Pd(0) to Pd(II) (as a rule, $CuCl_2$) is added to the reaction mixture. This allows the use of palladium in catalytic quantities (~ 0.2 mol. %), but the yield of the target product is slightly lower (Table 1, entries 12, 27 and 30). The mechanism of such coupling has been described in the original study by Heck [15] as well as in the review [11] devoted to the behaviour of nucleosides and their analogues in this reaction. As can be seen from Table 1 (entries 1 and 5), significant differences from the classical Heck reaction are observed when the reaction is carried out in methanol: with ethylene and propylene devoid of M-effects, methoxyalkyl nucleoside derivatives are formed predominantly. Moreover, the reaction with propylene gives all types of alkenyl isomers , *viz*., *cis*-, *trans*- and isopropenyl isomers. These regularities are observed with all simple vinyl compounds of the type $H_2C=CHR$ (R = Me, OMe, OAc, Hal). In principle, the formation of α-methoxyalkyl derivatives in the reaction of nucleoside 5-mercury derivatives with ethylene and certain alkenes that react regioselectively (Table 1, entries 2–4, 8 and 9) is not important, since methoxy derivatives, as alkenes, are reduced with hydrogen over 10% Pd/C to the corresponding saturated derivatives in overall yields of about 60%–80%. The double bond C(5)=C(6) in the pyrimidine ring is unaffected by this process. Much better results are achieved in reactions with activated alkenes, particularly with styrene derivatives, esters, amides and nitriles of acrylic, metacrylic and crotonic acids. Here, the reaction usually proceeds regio- and stereoselectively (the β-carbon atom of the double bond is linked to the heterocycle, exclusively *E*-isomers are formed). The product yields vary from 10% to 80%, being, on the average, ~ 40%–60%.

A typical synthetic procedure consists in the following. An appropriate mercurionucleoside (mercury derivatives of nucleosides are insoluble in any known solvent, although a recent report [38] describes the synthesis of water-soluble mercury derivatives) is suspended in an excess of an alkene (1.2–11.0 moles per mole of nucleoside) or the substrate is stirred under the pressure of the corresponding gaseous alkene in the presence of 1 equiv. of a palladium catalyst or of 0.1–0.2 equiv. of a Pd catalyst and 2–4 equiv. of $CuCl_2$ at room temperature or with heating to 50–60 °C. After termination of the reaction, Pd is separated by filtration and mercury salts are precipitated by passing hydrogen sulfide through the reaction mixture or by reduction with sodium borohydride. The latter is used, in particular, for subsequent hydrogenation over Pd/C. In some cases, after removal of

Table 1. Alkenylation of 5-mercuriopyrimidine nucleosides.

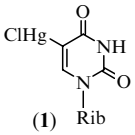
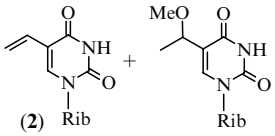
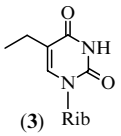
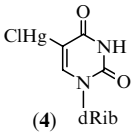
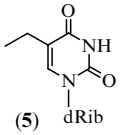
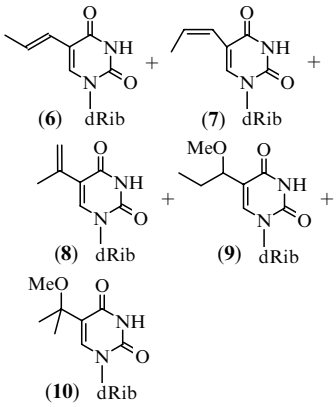
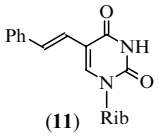
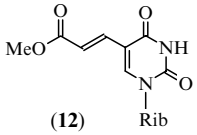
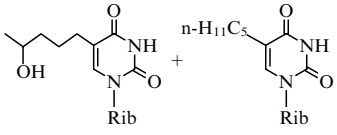
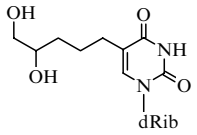
Entry	Substrate [a]	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
1	 (**1**)	$H_2C=CH_2$	1) 0.1 M Na_2PdCl_4, MeOH, 9 h; 2) H_2S	 (**2**)	6 (without isolation) + 39	19
2	**1**	$H_2C=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, 3 h; 2) $NaBH_4$, ice; 3) H_2, 10% Pd/C, MeOH, 16 h	 (**3**)	86	19
3	**1**	$H_2C=CH_2$	1) 0.1 M Li_2PdCl_4, $CuCl_2$, MeOH, 3 h; 2) H_2S; 3) H_2, 10% Pd/C, MeOH, 18 h	**3**	48	19
4	 (**4**)	$H_2C=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, 12 h; 2) $NaBH_4$, 0 °C; 3) H_2, 10% Pd/C, MeOH – H_2O, 24 h	 (**5**)	57	19
5	**4**	$MeCH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, 2 h; 2) H_2S	 (**6**) (**7**) (**8**) (**9**) (**10**)	11 [b] (**6**:**9**:**10** = 2.3 : 1.4 : 1.0; the yield of products **7** and **8** is low)	19
6	**1**	$PhCH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, Ar, 3 h; 2) $NaBH_4$ – EtOH	 (**11**)	39	19
7	**1**	$H_2C=CHCO_2Me$	1) 0.1 M Li_2PdCl_4, MeOH, Ar, 10 h; 2) H_2S	 (**12**)	48	19
8	**1**	$H_2C=CHCH_2$ – – CH(OH)Me	1) 0.1 M Li_2PdCl_4, MeOH, Ar, 2 h; 2) $NaBH_4$ – Pr^iOH; 3) H_2, MeOH, 14 h		55 + 12	19
9	**4**	$H_2C=CHCH_2$ – – $CH(OH)CH_2OBn$	1) 0.1 M Li_2PdCl_4, MeOH, 3 h; 2) $NaBH_4$ – MeOH; 3) H_2, 10% Pd/C, MeOH, 20 h		57	19

Table 1 (continued).

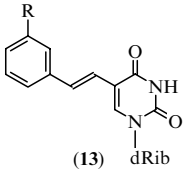
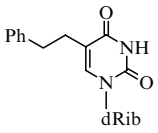
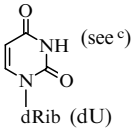
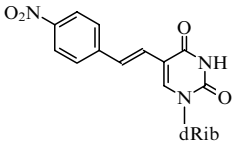
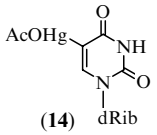
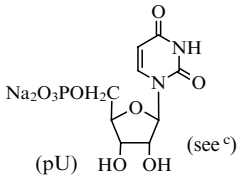
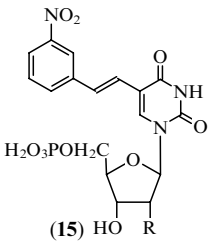
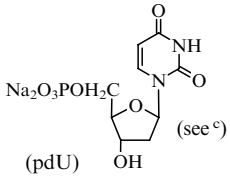
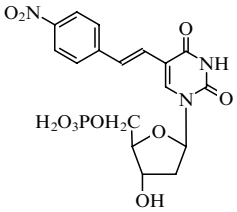
Entry	Substrate [a]	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
10	**4**	$PhCH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, 12 h; 2) H_2S	 (**13**)		
				13, R = H	57	18
11	**4**	*m*-$O_2NC_6H_4CH=CH_2$	the same but t = 18 h	**13**, R = NO_2	50	18
12	**4**	*m*-$O_2NC_6H_4CH=CH_2$	the same but with the addition of $CuCl_2$	**13**, R = NO_2	47	18
13	**4**	$PhCH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, 18 h; 2) $NaBH_4$–MeOH; 3) H_2, 10% Pd/C, MeOH, 20 h		58	18
14	 (see [c])	$PhCH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, 12 h; 2) H_2S	**13**, R = H	45	18
15	dU (see [c])	*m*-$O_2NC_6H_4CH=CH_2$	the same	**13**, R = NO_2	62	18
16	dU (see [d])	*m*-$O_2NC_6H_4CH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, −30 °C, 18 h; 2) H_2S	**13**, R = NO_2	52	18
17	dU (see [c])	*p*-$O_2NC_6H_4CH=CH_2$	the same but at 60 °C		11	18
18	 (**14**)	*m*-$O_2NC_6H_4CH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, THF, 6 h; 2) H_2S	**13**, R = NO_2	80	18
19	**14**	*m*-$H_2NC_6H_4CH=CH_2$	the same but under reflux, 9 h	**13**, R = NH_2	30	18
20	 (pU) (see [c])	*m*-$O_2NC_6H_4CH=CH_2$	1) 0.14 M Li_2PdCl_4, MeOH–H_2O, 50 °C, 0.5 h; 2) H_2S	 (**15**)		
				15, R = OH	82	18
21	 (pdU) (see [c])	*m*-$O_2NC_6H_4CH=CH_2$	the same	**15**, R = H	66	18
22	pdU	*p*-$O_2NC_6H_4CH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH–Et_2O–H_2O, 60 °C, 6 h; 2) H_2S		59	18

Table 1 (continued).

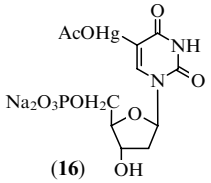
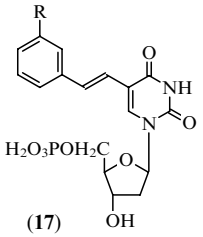
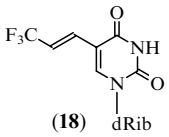
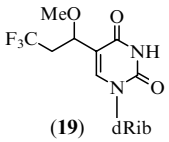
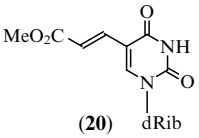
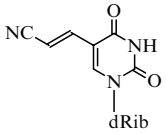
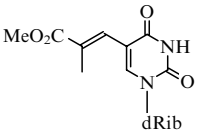
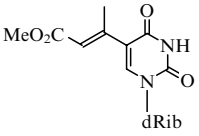
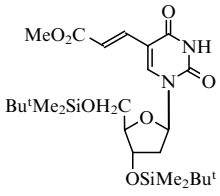
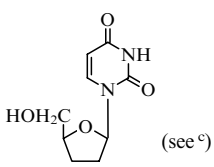
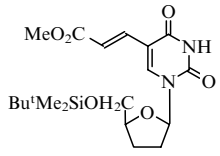
Entry	Substrate [a]	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
23	 (**16**)	$PhCH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH – THF – H_2O, 50 °C, 5 h; 2) H_2S	 (**17**)		
				17, R = H	50	18
24	**16**	*m*-$N_3C_6H_4CH=CH_2$	1) 0.274 M Li_2PdCl_4, MeOH – H_2O, 50 °C, 2.5 h 2) H_2S	**17**, R = N_3	25	18
25	**4**	$F_3CCH=CH_2$	1) Li_2PdCl_4, MeOH, 20 °C, 3.5 h; 2) H_2S	 (**18**) +  (**19**)	17 + 36	20
26	**4**	$F_3CCH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, 20 °C, 6.5 h; 2) H_2S	**18** + **19**	26 + 59	21
27	**4**	$H_2C=CHCO_2Me$	1) 0.1 M Li_2PdCl_4, $CuCl_2$, MeOH, 20 °C, 3 h; 2) H_2S	 (**20**)	60	22
28	**4**	$H_2C=CHCN$	1) 0.1 M Li_2PdCl_4, MeOH, 20 °C, 12 h; 2) H_2S		16	22
29	**4**	$H_2C=C(Me)CO_2Me$	1) 0.1 M Li_2PdCl_4, MeOH, 20 °C, 16 h; 2) H_2S		63	22
30	**4**	$MeCH=CHCO_2Me$	1) 0.1 M Li_2PdCl_4, $CuCl_2$, MeOH, 20 °C, 96 h; 2) H_2S		21	22
31	dU (see [c])	$H_2C=CHCO_2Me$	1) 0.1 M Li_2PdCl_4, Et_3N, MeOH, 20 °C, 12 – 16 h; 2) H_2S 3) Bu^tMe_2SiCl, imidazole, DMF, 20 °C, 18 h		76	23
32	 (see [c])	$H_2C=CHCO_2Me$	the same		65	23

Table 1 (continued).

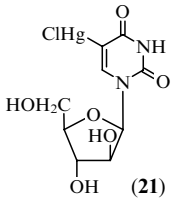
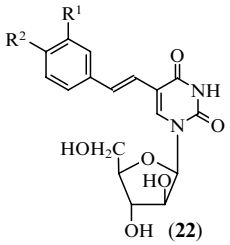
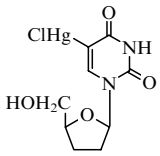
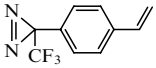
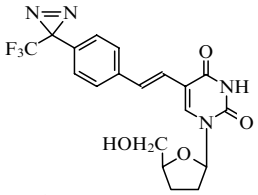
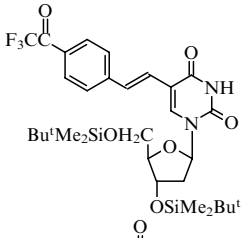
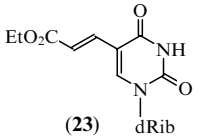
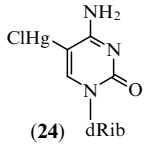
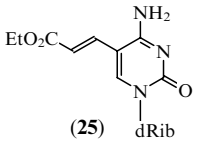
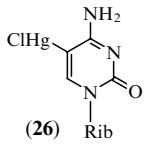
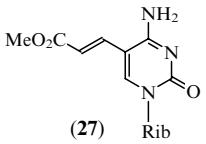
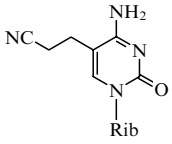
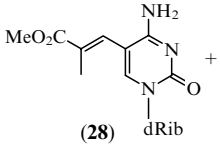
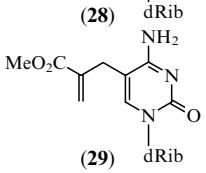
Entry	Substrate [a]	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
33	 (**21**)	$PhCH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, 24 h; 2) H_2S	 (**22**)		
				22, $R^1 = R^2 = H$	49	24
34	**21**	p-$O_2NC_6H_4CH=CH_2$	the same	**22**, $R^1 = H$, $R^2 = NO_2$	19	24
35	**21**	m-$O_2NC_6H_4CH=CH_2$	"	**22**, $R^1 = NO_2$, $R^2 = H$	22	24
36			0.1 M Li_2PdCl_4, MeOH, 20 °C, 5 h		10	8
37	**4**	p-$CF_3COC_6H_4CH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, 20 °C, 2 h; 2) Bu^tMe_2SiCl, imidazole, DMF, 20 °C, 4 h		21	25
38	**4**	$H_2C=CHCO_2Et$	Li_2PdCl_4	 (**23**)	–	26
39	 (**24**)	$H_2C=CHCO_2Et$	the same	 (**25**)	–	26
40	 (**26**)	$H_2C=CHCO_2Me$	1) 0.1 M Li_2PdCl_4, MeOH, 20 °C, 8 h; 2) H_2S	 (**27**)	42	27
41	**26**	$H_2C=CHCN$	1) 0.1 M Li_2PdCl_4, DMF, 20 °C, 6 days; 2) $NaBH_4 - H_2O$		32	27
42	**24**	$H_2C=C(Me)CO_2Me$	the same	 (**28**) +  (**29**)	12 [b] (**28** : **29** = 1 : 2)	27

Table 1 (continued).

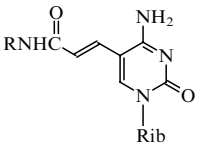
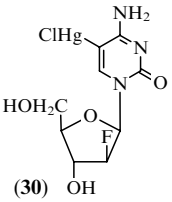
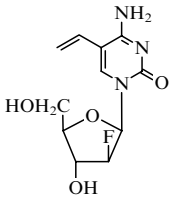
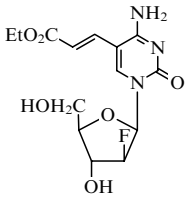
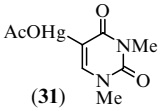
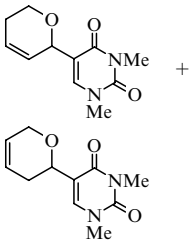
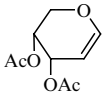
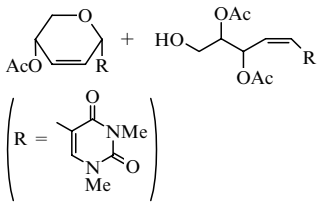
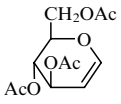
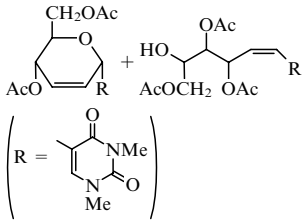
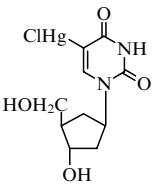
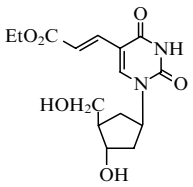
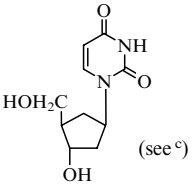
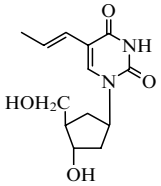
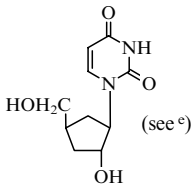
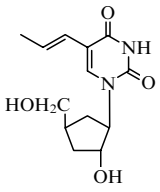
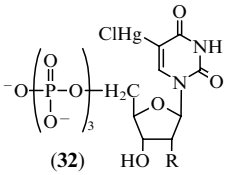
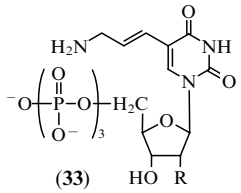
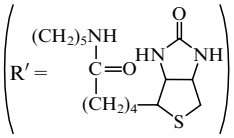
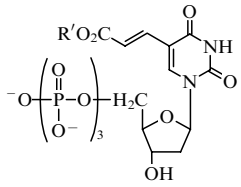
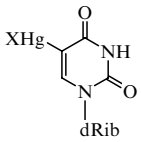
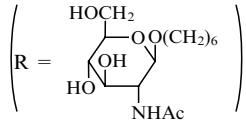
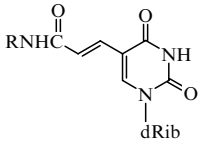
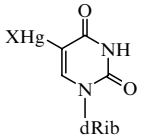
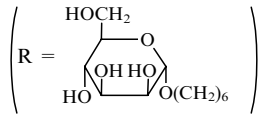
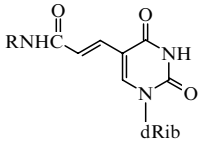
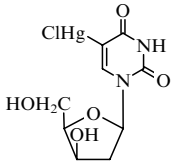
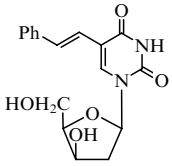
Entry	Substrate [a]	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
43	**26**	$H_2C=CHCONHR$ ($R = (CH_2)_5CO_2Me$)	1) 0.1 M Li_2PdCl_4, MeOH, 24 h; 2) H_2S		34	28
44	 (**30**)	$H_2C=CH_2$	1) 0.095 M Li_2PdCl_4, DMF, 20 °C, 7 h; 2) H_2S, MeOH, 0 °C		57	29
45	**30**	$H_2C=CHCO_2Et$	1) 0.105 M Li_2PdCl_4, MeOH, 20 °C, 7 h; 2) H_2S		23	29
46	 (**31**)		1) $Pd(OAc)_2$, LiCl, MeCN, 25 °C, 12 h; 2) H_2S		66 + 24	30, 31
47	**31**		the same		20 + 32	31
48	**31**		"		20 + 73	31
49		$H_2C=CHCO_2Et$	1) 0.1 M Li_2PdCl_4, MeOH, N_2, 20 h; 2) H_2S		57	32
50	 (see [c])	$ClCH_2CH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, 3 h; 2) H_2S; 3) EtOH, $RhCl(PPh_3)_3$, N_2, 16–36 h		19	33

Table 1 (continued).

Entry	Substrate [a]	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
51	 (see [e])	$ClCH_2CH=CH_2$	1) 0.1 M Li_2PdCl_4, MeOH, 3 h; 2) H_2S; 3) EtOH, $RhCl(PPh_3)_3$, N_2, 16–36 h		–	33
52	 (**32**)	$H_3\overset{+}{N}CH_2CH=CH_2$	0.125 M K_2PdCl_4, 0.1 M AcONa–H_2O (pH 5), 20 °C, 18–24 h	 (**33**)		
	32, R = H			**33**, R = H	20	33–35
53	**32**, R = OH	$H_3\overset{+}{N}CH_2CH=CH_2$	the same	**33**, R = OH	–	33, 34
54	**32**, R = H	$H_2C=CHCO_2R'$ 	0.02 M Li_2PdCl_4, MeOH–H_2O, 20 °C, 17 h		55	6
55		$H_2C=CHCONHR$ 	Pd catalysis		–	36
56		$H_2C=CHCONHR$ 	the same		–	36
57		$H_2C=CHPh$	1) 0.1 M Li_2PdCl_4, MeOH, 24 h; 2) H_2S		14	37

[a] Abbreviations used: Rib, D-β-ribofuranosyl; dRib, 2′-deoxy-β-D-ribofuranosyl; dU, 2′-deoxyuridine; pU, uridine 5′-phosphate; pdU, 2′-deoxyuridine 5′-phosphate. [b] Overall yield. [c] The organomercury derivative was synthesised *in situ* by treatment with $Hg(OAc)_2$ in H_2O (50–60 °C). [d] The same under the action of $Hg(OCOCF_3)_2$ in THF. [e] The same under the action of $Hg(OAc)_2$, then NaCl.

palladium the mixture is concentrated and immediately subjected to column chromatography on silica gel.

The use of DMF as a solvent permits one to obtain nucleosides, *e.g.,* 5-vinylcytidine and its analogues with a modified carbohydrate residue (yields ~ 60%) that cannot be obtained when the reaction is performed in methanol (Table 1, entry 44). Unfortunately, under these conditions the reaction of uridine with ethylene gives exclusively a polymeric product.[29]

The outcome of the alkenylation reaction depends on the nature of the alkene used. Acrolein does not apparently react with 5-mercury derivatives of nucleosides. Under the action of acrylonitrile, the corresponding C-alkenylated nucleosides are formed in low yields (Table 1, entries 28 and 41); the adduct with cytidine is reduced upon standard treatment of the reaction mixture with sodium borohydride to give the corresponding saturated derivative (32%), while hydrogen sulfide does not destroy the palladium complex formed in the reaction. High yields of alkenylation products are obtained in the case of various acrylic acid esters and amides (Table 1, entries 7, 27, 28, 31, 32, 40 and 43). Styrene derivatives containing an electron-withdrawing group in the *para*-position react less readily than their *meta*-substituted analogues (Table 1, entries 34 and 35). Aminostyrenes react less readily than nitrostyrenes (Table 1, entries 18 and 19). It is not always clear which particular factors, *i.e.,* electronic effects or solubility, influence the yields of reaction products when *para*- and *meta*-isomers of styrene derivatives are used as alkenylating reagents. Thus the yields of the reaction products of a 5-mercury derivative of 2′-deoxyuridine 5′-phosphate (pdU) with *p*- and *m*-nitrostyr-

enes in $H_2O-MeOH-Et_2O$ are comparable (59% and 66%, respectively) (Table 1, entries 21 and 22).

Reactions of nucleotides with alkenes in aqueous-organic media give rise to several valuable compounds. Thus the reaction of 5-acetoxymercurio-2′-deoxyuridine 5′-phosphate with 3-azidostyrene gave a photoactivated uridine derivative which inhibits thymidylate synthase (Table 1, entry 24). Coupling of 5-chloromercuriouridine 5′-triphosphate with allylamine (Table 1, entries 52 and 53) results in the formation of a linker useful for labelling studies.

Organomercury derivatives of nucleic bases can also react with alkenes. For example, two 5-substituted 1,3-dimethyluracils are formed from 5-acetoxymercurio-1,3-dimethyluracil and 3,4-dihydro-2*H*-pyran (Table 1, entry 46). An attempt has been made to use this reaction in the synthesis of C-nucleosides;[31] however, in this case cyclic derivatives are predominantly formed.

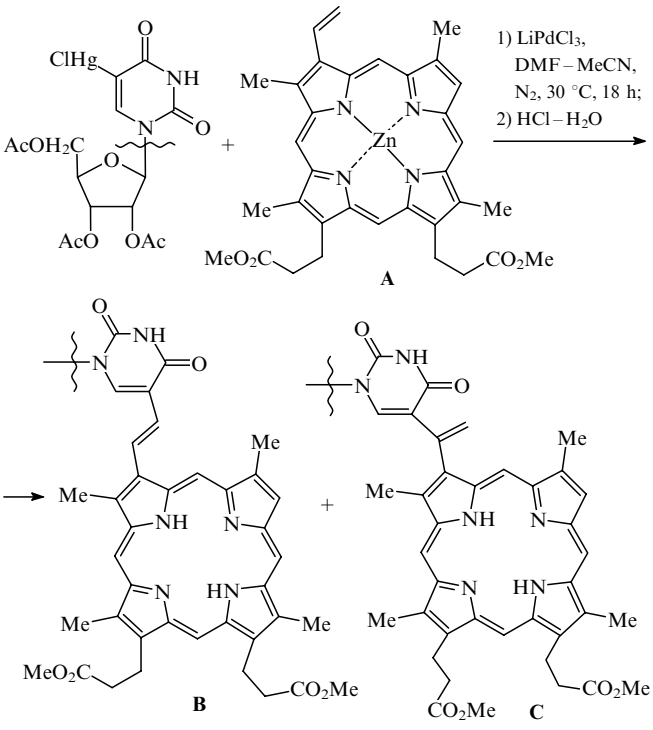
In addition to the above-mentioned compounds, allyl chlorides were introduced into the reaction with 5-mercurionucleosides and their derivatives (Table 1, entries 50 and 51).[33,39] The allylation of mercury derivatives of aromatic compounds in the presence of a Pd catalyst was described for the first time by Heck.[40] Strictly speaking, this reaction is irrelevant to the material described in this Section, but 5-allylated nucleosides obtained by this method are easily isomerised into the corresponding 5-(alk-1-enyl)pyrimidine nucleosides to give exclusively *trans*-isomers in the presence of rhodium complexes.

It should be remembered that direct coupling of non-activated alkenes with mercury derivatives of nucleosides normally gives complex mixtures of products.

This method (*i.e.,* coupling with alkenes) was used to obtain a series of substituted nucleosides that were further used as antiviral agents. An example is 5-(*E*)-bromovinyluridine and its carbocyclic analogues, 5-(*E*)-(prop-1-enyl)uridine [19] and 5-(*E*)-(3,3,3-trifluoroprop-1-enyl)uridine.[21]

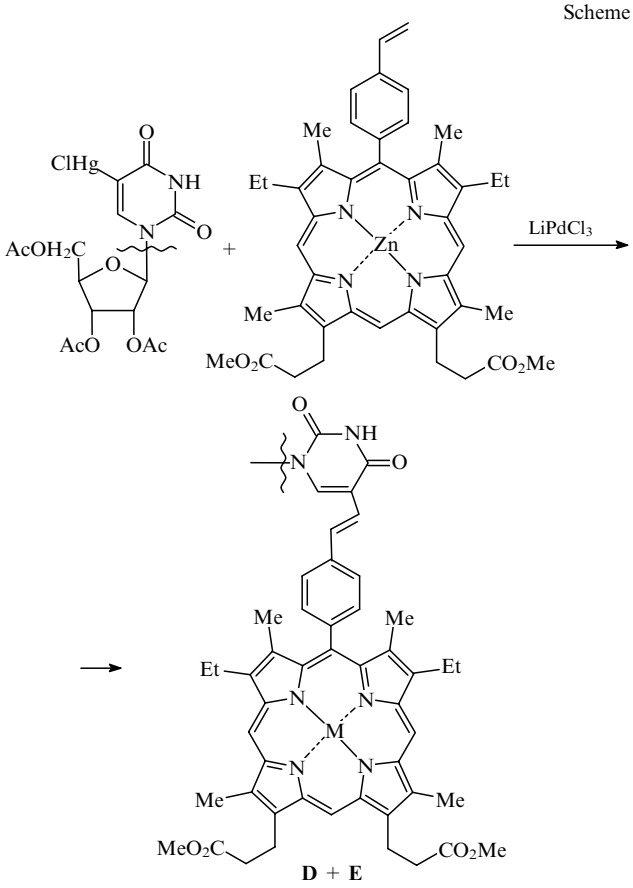
Of definite interest are the attempts to use nucleoside derivatives containing a porphyrin fragment as antitumour agents.[33,39] A covalent binding of vinylporphyrins at position 5 of uridine has been carried out recently.[5] Thus porphyrin **A** (Scheme 1) was introduced into the reaction with an excess (3.3 equiv.) of acetylated 5-chloromercuriouridine in the presence of 1 equiv. (with respect to uridine) of a Pd catalyst. This reaction gave a mixture of *trans*- (**B**, 16.5%) and *gem*-isomers (**C**, 19.6%) irrespective of the fact that the vinyl group of porphyrin was conjugated with an aromatic system.

Scheme 1



However, in the presence of a styryl group in the porphyrin fragment, this coupling occurs regio- and stereoselectively. It is noteworthy that this reaction is accompanied by partial substitution of Pd for Zn in the porphyrin fragment of the reaction product (Scheme 2).[5]

Scheme 2

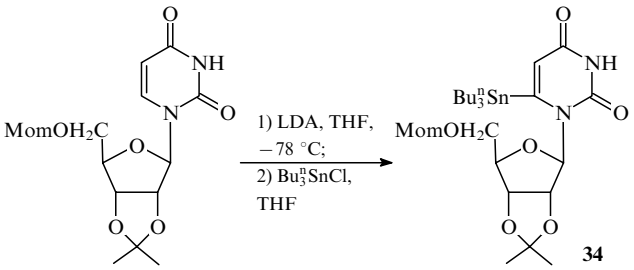


M = Zn (**D**, 29%), Pd (**E**, 44%).

Yet another rapidly developing field of the application of alkenylated nucleosides is their use for probing biological molecules in structural and functional studies. To this end, labels are introduced into nucleosides that are directly linked to the pyrimidine ring (Table 1, entries 36 and 37) or separated from it by a linker (Table 1, entry 54). Aminoallyl, aminoalkylacrylamide and acrylate groups at position 5 are the linkers of choice.

2. Cross-coupling of organotin pyrimidine derivatives of nucleosides with alkenyl halides

One of approaches to the synthesis of 6-alkenylated pyrimidine derivatives of nucleosides is based on the reaction of 6-tributylstannyl derivatives of nucleosides **34** with alkenyl halides (the Stille reaction).[41] An alternative approach consists in the reaction of 6-iodo-substituted pyrimidine nucleosides and their analogues with organoelement derivatives of alkenes (see below). Organotin derivatives of pyrimidine nucleosides are prepared from the corresponding lithium derivatives (6-iodopyrimidine nucleosides and their analogues are synthesised in a similar way) according to the following scheme:



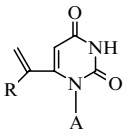
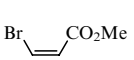
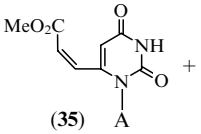
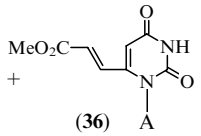
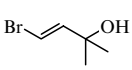
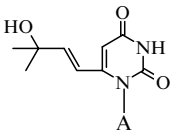
Mom = $MeOCH_2$.

It should be noted that despite the data [42] on the synthesis of the 5-trimethylstannyl derivative of a pyrimidine nucleoside and its arylation, we are not aware of its application for the incorporation of alkenyl groups. The mechanism of this conversion,[13] similar to the mechanisms of other cross-coupling reactions of organometallic compounds with alkyl halides in the presence of transition metal complexes, represents a sequence of reactions of oxidative addition of a transition metal with a low oxidation number [most often, Pd(0) or Ni(0); complexes of low-valent metals can be formed *in situ*] to aryl or vinyl halides with subsequent transmetallation (substitution of R′ for the halogen atom) and reductive elimination.

$$M(0) \xrightarrow{RX} RM(II)X \xrightarrow[-M'X]{R'M'} RM(II)R' \longrightarrow R-R' + M(0).$$

Alkenylation of 6-tributylstannylnucleosides has made it possible to obtain the corresponding alkenyl derivatives the yields of which vary from moderate to high (Table 2).[43] Depending on the reagent's structure, one can synthesise *cis*-, *trans*- and *gem*-isomers. As can be seen from the reaction scheme, transition metal complexes are required exclusively in catalytic amounts in

Table 2. Alkenylation of the organotin nucleoside derivative **34**.[43]

Entry	Reagent	*t* /min	Product	Yield (%)
1	$H_2C=CHBr$			
		100	R = H	80
2	$H_2C=CBrCO_2Et$	75	R = CO_2Et	56
3		10	 (**35**) +  (**36**)	81 [a] (**35** : **36** = 3 : 1)
4		60		70

Note: The reaction was carried out in DMF at 80 °C in the presence of 0.1 equiv. of $Pd(PPh_3)_4$ as a catalyst and with 0.2 equiv. of CuI;

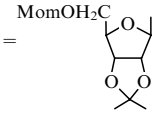
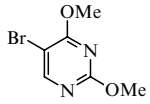
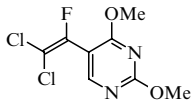
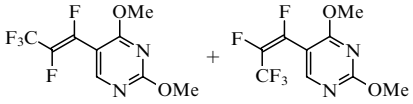
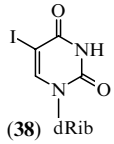
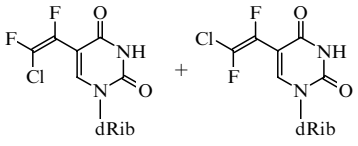
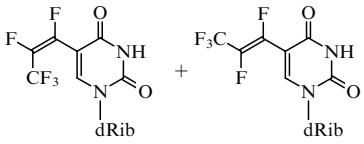
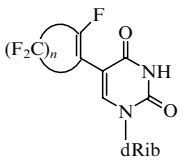
A = . [a] Overall yield.

Table 3. Alkenylation of organolithium derivatives of nucleosides and their analogues.[46]

Entry	Substrate [a]	Reagent	Solvent	*t* /h	Product	Yield (%)
1	 (**37**)	$Cl_2C=CF_2$	Et_2O	1.5		55
2	**37**	$CF_3CF=CF_2$	Et_2O	1.0		42 [b]
3	 (**38**) dRib (see [c])	$ClFC=CF_2$	n-C_6H_{14}	1.0		6 [b]
4	**38** (see [c])	$CF_3CF=CF_2$	n-C_6H_{14}	1.0		24 [b]
5	**38** (see [c])	$CF_3CF=CF_2$	n-C_6H_{14}	1.0		
						n = 3: 7; n = 4: 9

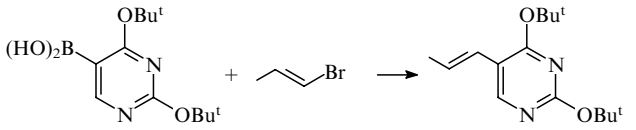
[a] The corresponding organolithium derivatives are prepared by treatment of the substrate with Bu^nLi. [b] Overall yield. [c] Prior to coupling, the hydroxy groups of the substrate were protected by the action of $(Me_3Si)_2NH-Me_3SiCl-Py$.

this case. It should be noted that in some syntheses the presence of copper(I) iodide permits one to increase the product yields more than twofold. Presumably, the role of CuI is connected with the formation of an organocopper intermediate in the transmetallation of Pd for Sn.

3. Cross-coupling of organoboron derivatives of nucleoside analogues with alkenyl halides

Only one example of such a coupling is known (Scheme 3). Transmetallation of organoboron compounds was extensively studied by Suzuki[44] who was the first to establish that this reaction requires the presence of a base. Organoboron compounds are prepared from the corresponding organolithium derivatives. In the above example, the target product is formed in 72% yield (Scheme 3).[45]

Scheme 3



Reagents and conditions: $Pd(PPh_3)_4$, 1 M $NaHCO_3$, $MeO(CH_2)_2OMe$, N_2, 4 h.

It should be remembered that this type of product cannot be obtained by coupling of organomercury derivatives with alkenes.

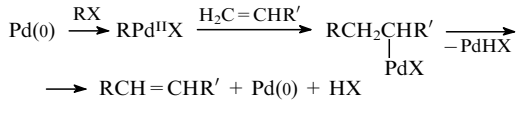
4. Reactions of organolithium derivatives of pyrimidine nucleosides and their analogues with fluoroalkenes

Alkenyl derivatives of pyrimidine bases and nucleosides can also be obtained by nucleophilic substitution of polyfluoroalkenes with the corresponding organolithium derivatives. The reaction of 5-bromo-2,4-dimethoxypyrimidine (**37**) and 5-iodo-3′,5′-di-*O*-trimethylsilyl-2′-deoxyuridine with butyllithium was carried out in an atmosphere of nitrogen at −70 °C. After addition of an excess (5 equiv.) of the fluorinated alkene, the reaction mixture was kept at a temperature of solid carbon dioxide for 4 days (Table 3). The product yields were small, as a rule, but higher with nucleic bases (42% – 55%) than with nucleosides (6% – 24%). In addition, the reaction is not stereoselective (*Z*- and *E*-isomers are formed). Perfluorocycloalkenes could be added at position 5 of deoxyuridine, but the yields of the products were as low as a few per cent.[46]

III. Alkenylation of *C*-halogeno derivatives and triflates of nucleosides and their analogues

1. The Heck-type coupling of iodonucleosides with alkenes

Yet another example of the Heck-type coupling[47] is the reaction of iodonucleosides and their analogues with alkenes in the presence of palladium compounds, which has found wide use in nucleoside chemistry. Its application in organic synthesis has been described in several reviews.[48,49] This reaction was discovered independently by Heck[47] and a group of Japanese investigators.[50] Its mechanism consists in oxidative addition of vinyl or aryl halides to Pd(0) with subsequent insertion of an alkene at the aryl(vinyl) – palladium bond and elimination of PdHX with regeneration of Pd(0).



The reaction of alkenes with both nucleosides and nucleic bases has been described. Depending on the position of the iodine in the pyrimidine ring, one can obtain 5- and 6-substituted derivatives. Most often, activated alkenes of the acrylic ester type are introduced into the reaction; arylvinyl ketones and terminal aliphatic alkenes are also used. Of special interest is the synthesis of 5- and 6-vinyl derivatives of pyrimidine nucleosides from the corresponding iodonucleosides and 1-arylpropynols in the presence of CuI as the co-catalyst and the synthesis of 5-vinyl derivatives of nucleosides and nucleic bases from the corresponding iodo derivatives and vinyl acetate.

The coupling is carried out in dioxane, DMF, acetonitrile or aqueous-organic mixtures. $Pd(OAc)_2$ in the presence of Et_3N and PPh_3 or $Pd(PPh_3)_2Cl_2/Et_3N$ are used as catalysts. In the latter case, small amounts of CuI are added. In contrast with the reaction of mercurionucleosides with alkenes, this type of the Heck reaction requires catalytic (but not equimolar) amounts of palladium (most often, as small as 0.05 – 0.15 equiv.). Depending on the reaction conditions and the nature of nucleosides and reagents used, the yields of the products vary from 8% to 90%. In general, the yields are higher than those in analogous reactions of mercurionucleosides with alkenes. The literature data concerning the synthesis of alkenylated nucleosides by the Heck reaction are summarised in Table 4.

These examples demonstrate that pretreatment of the catalyst significantly increases the yield of the product (Table 4, entries 1 and 2). When contemplating the influence of reaction conditions, one cannot but note the recently established increase in the product yield in the coupling of 5-iodo-2,4-dimethoxypyrimidine with methyl acrylate in water (Table 4, entry 29) rather than in organic solvents (the heterogenous Heck reaction[64]). It is interesting to note that under these conditions the coupling occurs at room temperature, while the classical Heck reaction requires heating to 70 – 90 °C, which slightly restricts its application. An increase in temperature to 50 °C in the heterogenous reaction results in deiodination of the original pyrimidine and decreases the yield from 90% to 79%. It should be noted that deiodination of nucleosides and their analogues is also the main side reaction in other types of the Heck coupling reaction.[65] Presumably, milder conditions of the heterogenous reaction favour the inhibition of side reactions and increase the yields of the target products.

High yields of the target compounds in this particular reaction are achieved with alkyl acrylates and arylvinyl ketones as alkenylating reagents. In contrast, the use of terminal alkenes with alkyl substituents results in low yields (Table 4, entries 5 – 7). Low yields are also characteristic of coupling of vinyl acetate with uridine (the yield of 5-vinyluridine is 37%) and cytidine (8%), although vinyl acetate reacts readily with derivatives of nucleic bases under different conditions in ~ 60% yields (Table 4, entries 27 and 28). Alkynylation of the corresponding 6-iodo-substituted uracils with 1-arylpropynols occurs through intermediate formation of allenic alcohols, which are further isomerised into aroylalkenyl derivatives of nucleic bases (Table 4, entries 20 – 26).[60] Obviously, a mixture of *cis*- and *trans*-isomers is formed in this case, although this aspect has not been specially discussed.[60]

The first alkynylation of aryl iodides was described simultaneously by Heck[66] and Cassar.[67] The Sonogashira reaction[68] (addition of CuI) in the Robins and Barr[69] modification (Et_3N as the base) is used in the synthesis of the corresponding nucleosides. A detailed description of this reaction is given in the review.[4]

Of note is a recently published paper[70] devoted to the synthesis of a porphyrin derivative of deoxyuridine (reaction of acrylamidoporphyrin with 5-iodo-2′-deoxyuridine, 5-IdU) (Scheme 4) used to investigate the reactions of porphyrins with the DNA double helix.

Coupling of a 5-iodo-substituted nucleoside or its analogue with methyl or ethyl acrylates followed by decarboxylation – bromination of the resulting product with *N*-bromosuccinimide is used in the synthesis of antiviral analogues of nucleosides containing the *E*-bromovinyl group at position 5 of the pyrimidine ring more often (due to higher yields) than other alkenylation reactions.

Table 4. Heck alkenylation of iodo derivatives of nucleosides and their analogues.

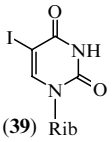
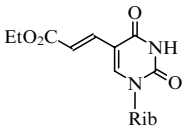
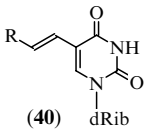
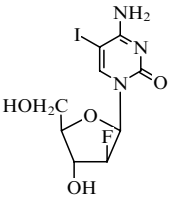
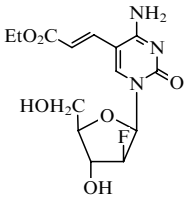
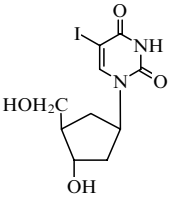
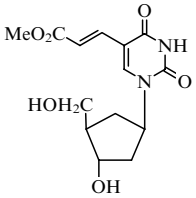
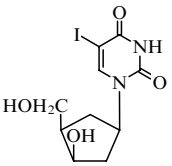
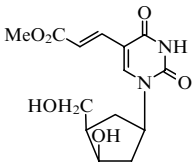
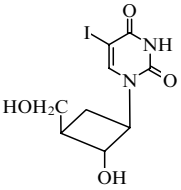
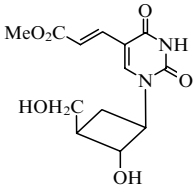
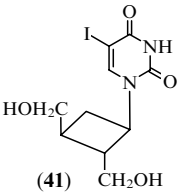
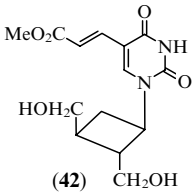
Entry	Substrate	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
1	 (**39**)	$H_2C=CHCO_2Me$	$Pd(OAc)_2$, PPh_3, Et_3N, Δ, 12 h	**12**	53	19
2	**39**	$H_2C=CHCO_2Me$	$Pd(OAc)_2$, PPh_3, Et_3N–dioxane (1 : 8), 70 °C, 1 h	**12**	86 [a]	51
3	**39**	$H_2C=CHCO_2Et$	$Pd(PPh_3)_2Cl_2$, Et_3N, MeCN, 80 °C, 24 h		79	52
4	**38**	$H_2C=CHCO_2Me$	$Pd(OAc)_2$, PPh_3, Et_3N–dioxane, Δ, 40 min	**20**	70 [a]	53
5	**38**	$Pr^nCH=CH_2$	$Pd(OAc)_2$, Et_3N, 100 °C, 12 h	 (**40**) dRib		
				40, R = Pr^n	25	22
6	**38**	$Bu^nCH=CH_2$	the same but t = 2 h	**40**, R = Bu^n	15	22
7	**38**	$Bu^tCH=CH_2$	the same but t = 48 h	**40**, R = Bu^t	16	22
8		$H_2C=CHCO_2Et$	$Pd(OAc)_2$, PPh_3, Et_3N, DMF, Ar, 85 °C, 24 h		37	29
9		$H_2C=CHCO_2Me$	$Pd(OAc)_2$, PPh_3, Et_3N, dioxane, 85 °C, 3 h		80 [a]	54
10		$H_2C=CHCO_2Me$	the same		64	55
11	 (racemate)	$H_2C=CHCO_2Me$	$Pd(OAc)_2$, PPh_3, Et_3N, dioxane, Ar, 70 °C, 2.5 h	 (racemate)	66 [a]	56
12	 (**41**) **41** (racemate)	$H_2C=CHCO_2Me$	the same but t = 4 h	 (**42**) **42** (racemate)	75 [a]	56

Table 4 (continued).

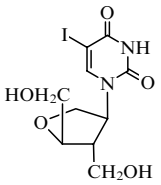
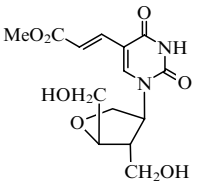
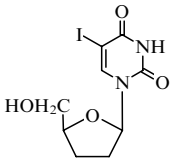
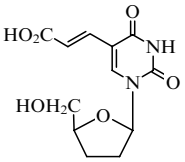
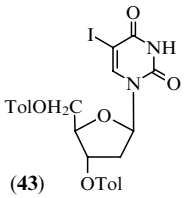
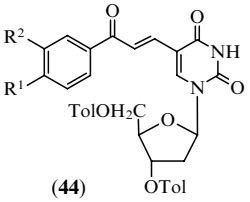
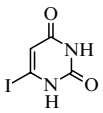
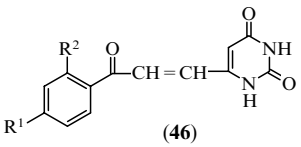
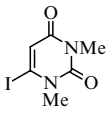
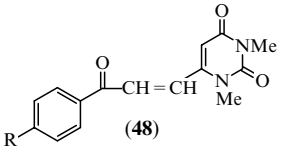
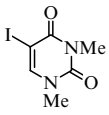
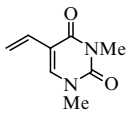
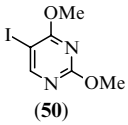
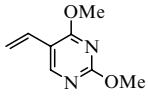
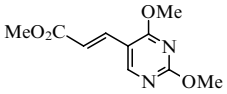
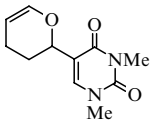
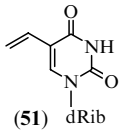
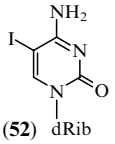
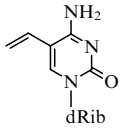
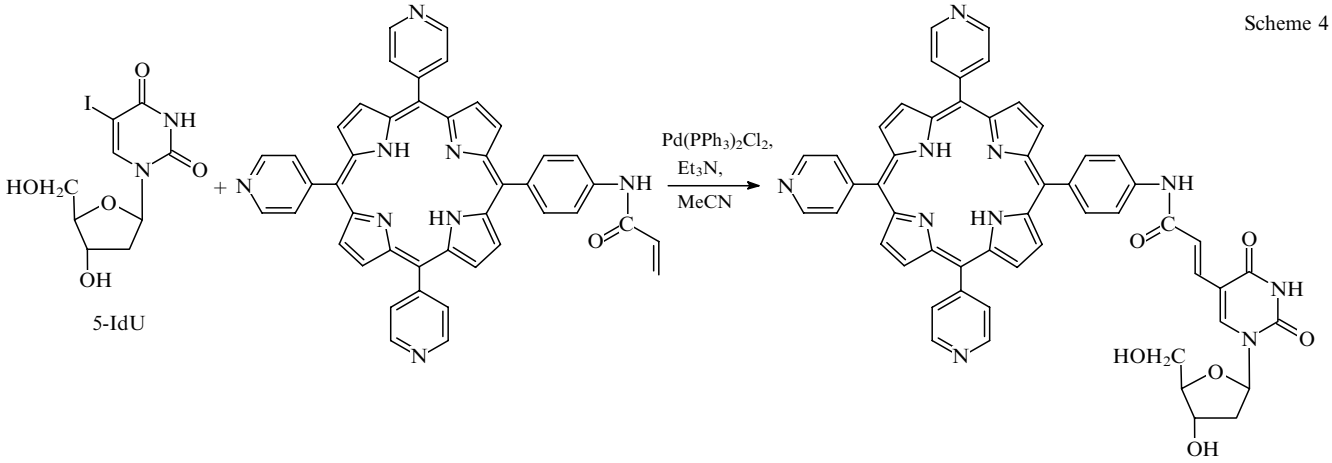
Entry	Substrate	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
13	**41** (homochiral)	$H_2C=CHCO_2Me$	$Pd(OAc)_2$, PPh_3, Et_3N, dioxane, Ar, 70 °C, 4 h	**42** (homochiral)	69 [a]	56
14		$H_2C=CHCO_2Me$	$Pd(OAc)_2$, PPh_3, Et_3N, DMF, Ar, 75 °C, 10 h		56 [a]	57
15		$H_2C=CHCO_2H$	$Pd(OAc)_2$, PPh_3, Et_3N, dioxane, 1 N NaOH, 95 °C, 3 h		49	58
16	 (**43**)	$PhC(O)CH=CH_2$	$Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, N_2, 80 °C, 24 h	 (**44**)		
				44, $R^1 = R^2 = H$	62	59
17	**43**	*p*-$MeC_6H_4C(O)CH=CH_2$	the same	**44**, R^1 = Me, R^2 = H	78	59
18	**43**	*p*-$MeOC_6H_4C(O)CH=CH_2$	"	**44**, R^1 = OMe, R^2 = H	62	59
19	**43**	*m*-$MeC_6H_4C(O)CH=CH_2$	"	**44**, R^1 = H, R^2 = Me	62	59
20	 (**45**)	$PhCH(OH)C\equiv CH$	$Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, N_2, 55 °C, 6 h	 (**46**)		
				46, $R^1 = R^2 = H$	39	60
21	**45**	*p*-$MeC_6H_4CH(OH)C\equiv CH$	the same	**46**, R^1 = Me, R^2 = H	60	60
22	**45**	*p*-$MeOC_6H_4CH(OH)C\equiv CH$	"	**46**, R^1 = OMe, R^2 = H	57	60
23	**45**	*o*-$MeOC_6H_4CH(OH)C\equiv CH$	"	**46**, R^1 = H, R^2 = OMe	35	60
24	 (**47**)	$PhCH(OH)C\equiv CH$	"	 (**48**)		
				48, R = H	76	60
25	**47**	*p*-$MeC_6H_4CH(OH)C\equiv CH$	"	**48**, R = Me	80	60
26	**47**	*p*-$MeOC_6H_4CH(OH)C\equiv CH$	"	**48**, R = OMe	58	60
27	 (**49**)	$H_2C=CHOAc$	$Pd(PPh_3)_2(OAc)_2$, Et_3N, 100 °C, 5 h		60	61
28	 (**50**)	$H_2C=CHOAc$	the same		58	61

Table 4 (continued).

Entry	Substrate	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
29	**50**	$H_2C=CHCO_2Me$	$Pd(OAc)_2$, PPh_3, K_2CO_3, Bu_4NHSO_4, H_2O, 20 °C, 90 h		90	62
30	**49**		$Pd(PPh_3)_2(OAc)_2$, Et_3N, 100 °C, 5 h		64	30
31	**38**	$H_2C=CHOAc$	$Pd(OAc)_2$, PPh_3, Et_3N, DMF, 70 °C, 5.5 h	 (**51**)	37 [a]	63
32	 (**52**)	$H_2C=CHOAc$	$Pd(OAc)_2$, PPh_3, Et_3N, DMF, 90 °C, 2 h		8 [a]	63

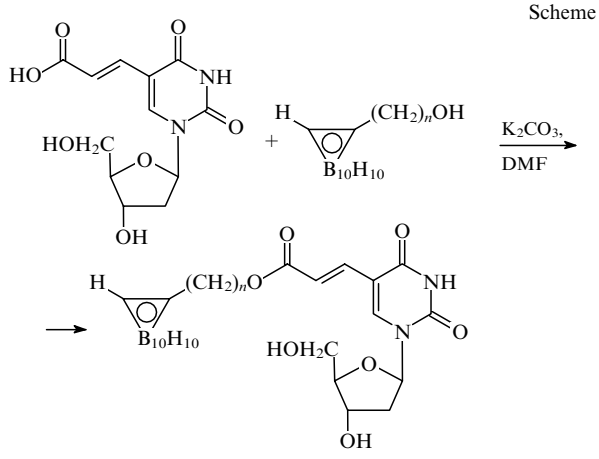
[a] The catalyst was prepared beforehand by heating $Pd(OAc)_2$, PPh_3 and Et_3N in dioxane or DMF up to the appearance of deep red colouring (10–20 min) at 70–75 °C.

Scheme 4



The addition of carborane-containing fragments [10] to 5-alkenyl nucleosides (Scheme 5) is an illustrative example of the application of alkenyl fragments as linkers; this reaction is used in cancer boron neutron capture therapy (for a review, see Ref. 71).

Scheme 5



2. Cross-coupling of nucleoside halogeno derivatives and triflates with organoelement derivatives of alkenes

Recently, coupling of 5-halogeno derivatives and 5-triflates of nucleosides with organoelement derivatives of alkenes has acquired growing popularity for the synthesis of the corresponding 5-alkenyl derivatives of nucleosides.[72–84] As mentioned above, in this case alkene derivatives with Group III (boron and aluminium) and Group IV elements (silicon, tin, zirconium) of the Periodic system are used as the starting compounds. The literature data on alkenylation of 5-halogeno derivatives and 5-triflates of nucleosides are summarised in Table 5. The mechanisms of the corresponding reactions are considered in Section II.2 exemplified in the cross-coupling of organotin nucleoside derivatives with alkenyl halides.

An essential advantage of this method is the possibility of performing the reaction with non-activated alkenes to obtain the corresponding 5-alkenyl-substituted nucleosides (particularly, 5-vinyl-substituted ones) (Table 5, entries 3, 13, 18, 26, 29–31, 33 and 35) in good yields.

It should be remembered that of all 5-mercurionucleosides only the 5-mercuriocytidine derivative reacts with ethylene in DMF under conditions of the Heck reaction (Table 1, entry 44); 5-vinyluridine undergoes polymerisation under these condi-

Table 5. Alkenylation of halogeno derivatives and triflates of nucleosides and their analogues with organoelement derivatives of alkenes.

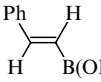
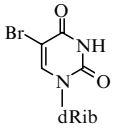
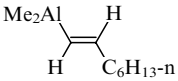
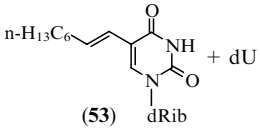
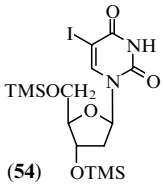
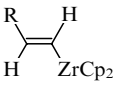
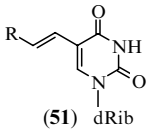
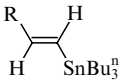
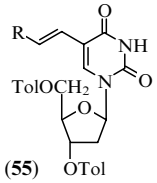
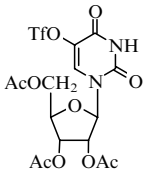
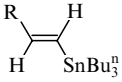
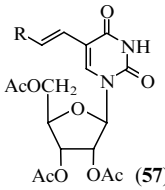
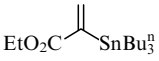
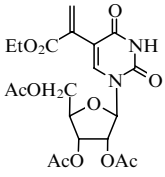
Entry	Substrate	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
1	**38**		Pd(*m*-$Ph_2PC_6H_4SO_3M)_3$ (M = Na, K), H_2O–MeOH, N_2, 80 °C, 3 h	**13**, R = H	47	72
2			1) HMDS–$(NH_4)_2SO_4$; 2) $PdCl_2$, PPh_3, THF, Ar, 24 h; 3) NH_4Cl–H_2O–MeOH, 2.5–24 h	 (**53**)	27 [a]	73
3	 (**54**)		1) $Pd(PhCN)_2Cl_2$, 20 °C, 15 h; 2) H_2O–MeOH	 (**51**)		
		R = H		**51**, R = H	83	74, 75
4	**54**	$R = Bu^n$	the same	**51**, $R = Bu^n$	95	74
5	**54**	$R = C_8H_{17}$-n	"	**51**, $R = C_8H_{17}$-n	96	74
6	**54**	R = Ph	"	**51**, R = Ph	85	74
7	**54**	R = *p*-$MeOC_6H_4$	"	**51**, R = *p*-$MeOC_6H_4$	39	74
8	**54**	$R = HC{\equiv}C(CH_2)_2$	"	**51**, $R = HC{\equiv}C(CH_2)_2$	80	74
9	**54**	$R = MeCHCl(CH_2)_2$	"	**51**, $R = MeCHCl(CH_2)_2$	89	74
10	**54**	$R = MeCHCN(CH_2)_2$	"	**51**, $R = MeCHCN(CH_2)_2$	76	74
11	**54**	R = EtO	"	**51**, R = EtO	49	74
12	**54**	$R = H_2C{=}CMe$	"	**51**, $R = H_2C{=}CMe$	30	74
13	**43**		$Pd(PPh_3)_2Cl_2$, MeCN, N_2	 (**55**)		
		R = H	20 °C, 6 h	**55**, R = H	86	76
14	**43**	$R = SiMe_3$	60 °C, 16 h	**55**, $R = SiMe_3$	82	76
15	**43**	R = Ph	50 °C, 16 h	**55**, R = Ph	81	76
16	**43**	$R = CO_2Et$	50 °C, 20 h	**55**, $R = CO_2Et$	57	76
17	**43**	$R = CH_2OTHP$	60 °C, 16 h	**55**, $R = CH_2OTHP$	82	76
18	 (**56**)		$Pd(PPh_3)_4$, LiCl, dioxane, N_2, Δ	 (**57**)		
		R = H	4 h	**57**, R = H	87	77, 78
19	**56**	$R = SiMe_3$	4 h	**57**, $R = SiMe_3$	73	77, 78
20	**56**	R = Ph	8 h	**57**, R = Ph	75	77, 78
21	**56**	$R = Pr^iMe_2CSiMe_2OCH_2$	5 h	**57**, $R = Pr^iMe_2CSiMe_2OCH_2$	92	77, 78
22	**56**	$R = CO_2Et$	1 h	**57**, $R = CO_2Et$	92	77, 78
23	**56**		$Pd(PPh_3)_4$, LiCl, dioxane, N_2, Δ 15 h		46	77, 78

Table 5 (continued).

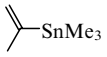
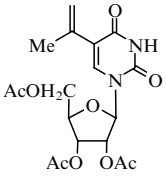
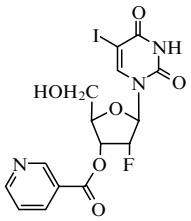
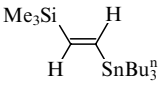
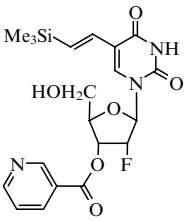
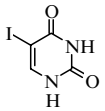
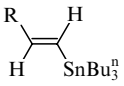
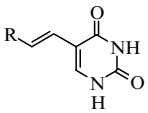
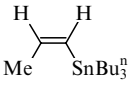
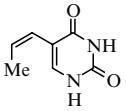
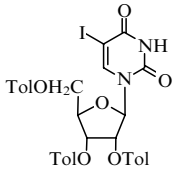
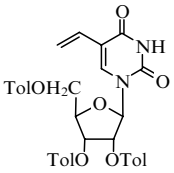
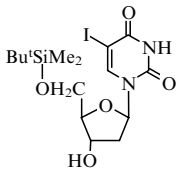
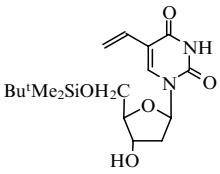
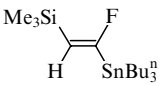
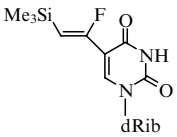
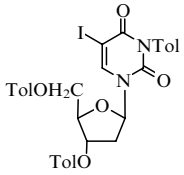
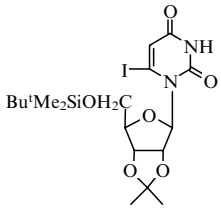
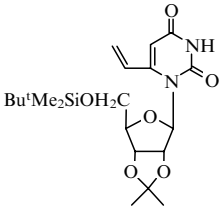
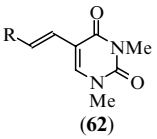
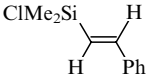
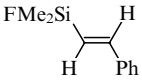
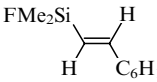
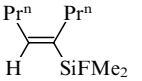
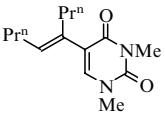
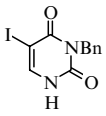
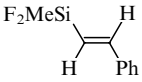
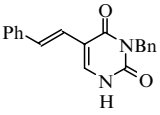
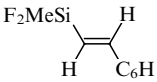
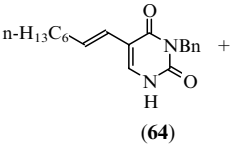
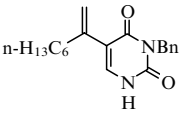
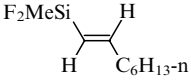
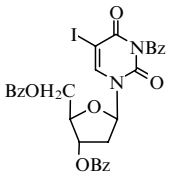
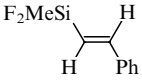
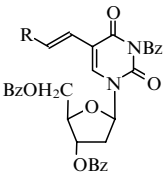
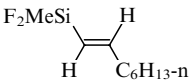
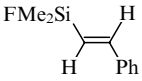
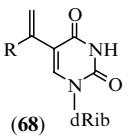
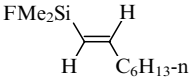
Entry	Substrate	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
24	**56**		the same but t = 5 h		86	77, 78
25			$Pd(PPh_3)_2Cl_2$, THF, Ar, 50 °C, 16 h		50	79
26	 (**58**)		$Pd_2(dba)_3$, TFurP, NMP, 20 °C, 16 h	 (**59**)		
		R = H		**59**, R = H	89	80
27	**58**	R = Ph	the same	**59**, R = Ph	92	80
28	**58**		$Pd_2(dba)_3$, TFurP, NMP, 16 h at 20 °C and 5 h at 50 °C		70	80
29	 (**60**)	$H_2C=CHSnBu^n_3$	$Pd_2(dba)_3$, TFurP, NMP, 20 °C, 72 h	 (**61**)	76	80
30	**60**	$H_2C=CHSnBu^n_3$	$Pd_2(dba)_3$, TFurP, THF, 50 °C, 40 h	**61**	98	80
31		$H_2C=CHSnBu^n_3$	$Pd_2(dba)_3$, TFurP, NMP, 20 °C, 72 h		91	80
32	**38**		$Pd(PPh_3)_4$, DMF, Ar, 100 °C, 4 h		28	81
33		$(H_2C=CH)_4Sn$	1) $Pd(PPh_3)_4$, HMPA, N_2, 60 °C, 18 h; 2) MeONa – MeOH	**51**	80	82
34		$H_2C=CHSnBu^n_3$	$Pd(PPh_3)_4$, DMF, Ar, 90 °C, 1.5 h		95	83

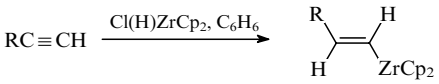
Table 5 (continued).

Entry	Substrate	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
35	**49**	$H_2C=CHSiMe_2Cl$	$[(\eta^3\text{-}C_3H_5)PdCl]_2$, Bu_4NF, THF, Ar, 60 °C, 14 h	 (**62**)		
				62, R = H	82	84
36	**49**		the same	**62**, R = Ph	70	84
37	**49**		"	**62**, R = Ph	69	84
38	**49**		"	**62**, R = C_6H_{13}-n	70	84
39	**49**		"		63	84
40	 (**63**)		"		58	84
41	**63**		"	 (**64**) +  (**65**)	53 [a] (**64** : **65** = 2 : 1)	84
42	**58**		"	the reaction does not occur	–	84
43	 (**66**)		"	 (**67**)		
				67, R = Ph	64	84
44	**66**		"	**67**, R = C_6H_{13}-n	60	84
45	**38**		"	**13** +  (R = Ph) (**68**)	79 [a] (**13** : **68** = 5 : 1)	84
46	**38**		"	**53** + **68** (R = C_6H_{13}-n)	74 [a] (**53** : **68** = 2 : 1)	84

Note. The following abbreviations are used: TFurP, tris(2-furyl)phosphine; NMP, *N*-methylpyrrolidone; HMPA, hexamethylphosphorotriamide (hexametapol); THP, tetrahydropyranyl; dba, dibenzylideneacetone. [a] Overall yield.

tions.[29] In the reaction of vinyl acetate with 5-iodouridine, the yield of the target product is as low as 37% (Table 4, entry 31), while the yield of vinylcytidine is even lower (8%) (Table 4, entry 32).[63]

As can be seen from the results presented in Table 5, there are only a few examples of nucleoside alkenylation with organoboron and organoaluminium compounds and the yields of reaction products are low. Thus styrylboronic acid reacts with 5-iodo-deoxyuridine in the presence of $Pd(m\text{-}Ph_2PC_6H_4SO_3M)_3$ (M = K, Na) even in aqueous-organic media, the yield of the target product is 47% (Table 5, entry 1).[72] The possibility of carrying out the reaction in the presence of water is important, particularly for modification of oligonucleotides. In the coupling of organoaluminium alkene derivatives with nucleosides, the product yields are significantly lower (Table 5, entry 2).[73] However, the use of organozirconium alkene derivatives and $Pd(PhCN)_2Cl_2$ as a catalyst makes it possible to obtain a broad spectrum of 5-alkenylnucleoside derivatives, including vinyl (Table 5, entry 3), alkylvinyl (Table 5, entries 4 and 5), containing a second multiple bond in the chain introduced (Table 5, entries 8 and 12), styryl (Table 5, entries 6 and 7) and other derivatives. It is of note that the reaction (*e.g.*, with 5-iodo-2′-deoxy-3′,5′-di-*O*-trimethylsilyluridine in THF) occurs even at room temperature.[74, 75] The zirconium-containing alkenyl reagent is synthesised from the corresponding alkyne and the Schwartz reagent.



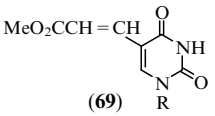
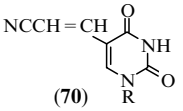
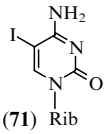
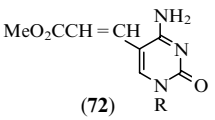
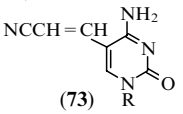
Organotin compounds are most often used for C-alkenylation of nucleosides. Alkenyltributyltin is normally employed for this purpose; alkenyltrimethyltin (Table 5, entry 24) and tetraalkenyltin (Table 5, entry 33) are used less often. The amounts of the alkenylating reagent vary from 1 to 5 equiv. 5-Iodo-substituted nucleosides and nucleoside 5-triflates (as a rule, with protected hydroxy groups) serve as substrates. The reactions are conducted in acetonitrile, dioxane, THF, *N*-methylpyrrolidone, hexametapol and DMF. $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, $Pd(PPh_3)_4$ in the presence of LiCl and $Pd_2(dba)_3$ in the presence of TFurP serve as catalysts. The yields of the target compounds obtained by this method vary from 28% to 98%. Depending on the reagent's structure, one can obtain *trans*-, *cis*- (Table 5, entry 28) and *gem*-products (Table 5, entries 23 and 24).

The reaction of alkenylfluoro- and alkenylchlorosilanes with 5-iodouracil and 5-iodo-2′-deoxyuridine derivatives, which gives target products in high yields, has been studied recently.[84] To obvious merits of organosilicon reagents one can relate their low toxicity, moisture resistance and low cost. This reaction was carried out in the presence of 0.025 equiv. of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and 2 equiv. of Bu^n_4NF. This method allows the modification of the pyrimidine ring with alkenyl radicals of various structure, *e.g.,* vinyl (Table 5, entry 35), styryl (Table 5, entries 36, 37, 40, 43 and 45), alkylvinyl (Table 5, entries 38, 41, 44 and 46), *etc*. As a rule, protected substrates are used; non-protected halogeno derivatives of nucleosides react with organosilicon compounds less readily. Thus 5-iodouracil does not react with alkenylfluoro- and alkenylchlorosilanes and 5-iododeoxyuridine forms a mixture of *trans*- and *gem*-isomers.

3. Photochemical alkenylation of nucleosides

The advantages of the photochemical reaction of activated alkenes with 5-iodopyrimidine nucleosides are technologically simple and versatile procedures used for the synthesis and isolation. However, the yields of the target products are small, varying from low (12%) to moderate (41%) (the literature data on photochemical coupling of nucleosides with alkenes are presented in Table 6). In addition, alkenes are linked non-stereoselectively to give a mixture of *cis*- and *trans*-isomers. Therefore, it is reasonable to use this reaction exclusively for the synthesis of the corresponding alkyl derivatives by hydrogenation of the alkenyl-

Table 6. Photochemical alkenylation of nucleosides.

Entry	Substrate	Reagent	Product (a mixture of *E*- and *Z*-isomers)	Yield (%)	Ref.
1	**39**	$H_2C=CHCO_2Me$	 (**69**)		
			69, R = Rib	38	85
2	**38**	$H_2C=CHCO_2Me$	**69**, R = dRib	41	85
3	**39**	$H_2C=CHCN$	 (**70**)		
			70, R = Rib	12	85
4	**38**	$H_2C=CHCN$	**70**, R = dRib	14	85
5	 (**71**)	$H_2C=CHCO_2Me$	 (**72**)		
			72, R = Rib	22	86
6	**52**	$H_2C=CHCO_2Me$	**72**, R = dRib	24	86
7	**71**	$H_2C=CHCN$	 (**73**)		
			73, R = Rib	18	86
8	**52**	$H_2C=CHCN$	**73**, R = dRib	20	86

Note: The reaction was carried out in three steps: (1) HMDS, Py, Ar, 18 h; (2) alkene, MeCN, *hv* = 254 nm, 24 h; (3) H_2O.

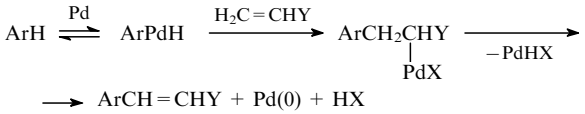
ated product over Pd/C. Alkenyl fragments are added to the trimethylsilylated 5-iodonucleoside upon irradiation of the reaction mixture with light of the wavelength of 254 nm in deoxygenated and dry acetonitrile for 24 h.

IV. Alkenylation of non-substituted nucleosides and their analogues

Pyrimidine nucleosides and their analogues that are not substituted at positions 5 and 6 of the heterocycle can also enter into the alkenylation reaction. Three versions of this reaction are known, *viz*., oxidative coupling of alkenes (predominantly, activated ones), cross-coupling with vinyl triflates (both reactions are carried out in the presence of Pd compounds) and nucleophilic addition of alkenylmagnesium derivatives at position 6 of the pyrimidine ring.

1. Oxidative coupling of activated alkenes

Oxidative coupling of alkenes (the Fujiwara reaction [87]) is carried out in the presence of 1 equiv. of $Pd(OAc)_2$ on boiling in acetonitrile or at room temperature (Table 7). The mechanism of this reaction seems to consist in the formation of an arylpalladium hydride intermediate followed by insertion of the alkene at the Ar–Pd bond and reductive elimination of PdHX to give Pd(0).[88]



Reactions of 1,3-dimethyluracil with activated alkenes (methyl acrylate, acrylamide, methyl vinyl ketone and styrene) give uracil derivatives substituted at position 5 in good yields; all these reactions result in *trans*-isomers. In the case of non-activated alkenes, *gem*-isomers are formed as admixtures. It is of note that acrolein diethyl acetal also enters into the reaction, which permits one to introduce an alkenyl substituent with a terminal aldehyde group into the pyrimidine base (Table 7, entry 13). It should be remembered that this reaction cannot be realised with mercurionucleosides. The products of coupling nucleosides with acrolein diethyl acetal could not be obtained thus far. In general, nucleosides add alkenes less readily in this reaction (Table 7, entries 6, 7 and 14). Only in the case of 2′,3′-*O*-isopropylidene-protected nucleosides could the methyl acrylate group be introduced at

Table 7. Alkenylation of non-substituted nucleosides with activated alkenes.

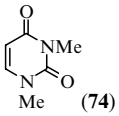
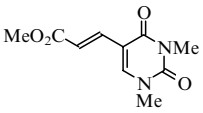
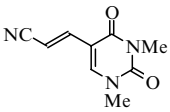
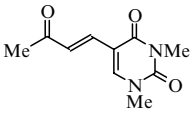
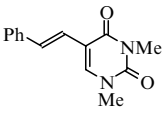
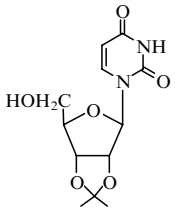
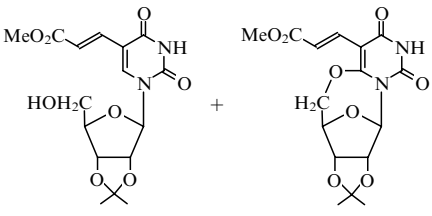
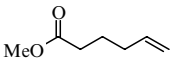
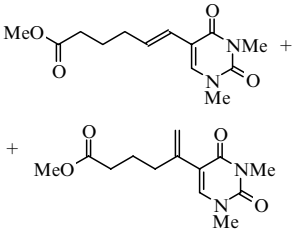
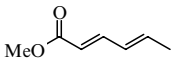
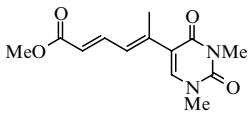
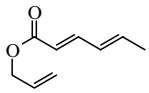
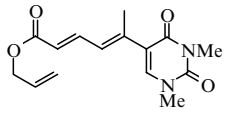
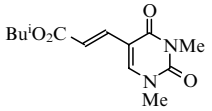
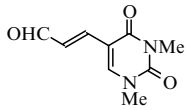
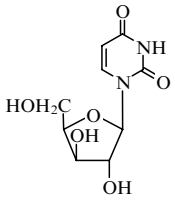
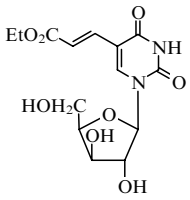
Entry	Substrate	Reagent	*t* /h	Product	Yield (%)	Ref.
1	 (**74**)	$H_2C=CHCO_2Me$	24		92	89
2	**74**	$H_2C=CHCN$	16		73	89
3	**74**	$H_2C=CHCOMe$	16		74	89
4	**74**	$H_2C=CHPh$	13		86	89
5	dU	$H_2C=CHCO_2Me$	32	**20**	56	89
6	dU	$H_2C=CHPh$	62	**13**, R = H	35	89
7	Urd	$H_2C=CHCO_2Me$	72	**12**	47	89
8		$H_2C=CHCO_2Me$	53 [a]		74 + 23	89
9	**74**		24		36 + 10	90

Table 7 (continued).

Entry	Substrate	Reagent	*t* /h	Product	Yield (%)	Ref.
10	**74**		24		25	90
11	**74**		24		23	90
12	**74**	$H_2C=CHCO_2Bu^i$	24		–	90
13	**74**	$H_2C=CHCH(OEt)_2$	24 [a]		80	90
14		$H_2C=CHCO_2Et$	24		40	90

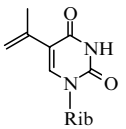
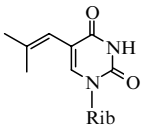
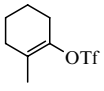
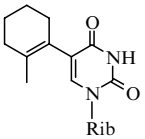
Note: The reaction was carried out in the presence of 1.2 equiv. of $Pd(OAc)_2$ in boiling acetonitrile. Urd is uridine (1-β-D-ribofuranosyluracil). [a] The reaction was carried out at room temperature.

position 5 of the pyrimidine ring (Table 7, entry 8); the target product was obtained in good yield (74%).

2. Oxidative coupling with vinyl triflates

Vinyl triflates react with non-substituted nucleosides in the presence of a catalyst [$(Pd(PPh_3)_4$ ($\sim$0.05 equiv.)] and an excess of LiCl in THF to give the corresponding alkenyl derivatives in moderate yields (Table 8). This reaction, as the coupling with organoelement alkene derivatives, permits one to introduce non-activated alkenyl substituents into position 5 of the pyrimidine ring. Depending on the structure of the vinyl triflate reagent, one can obtain various regio- and stereoisomers.

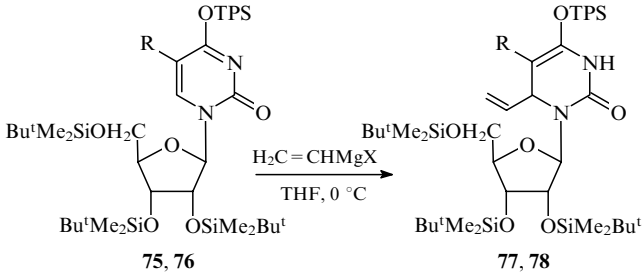
Table 8. Alkenylation of non-substituted nucleosides with vinyl triflates.[91]

Entry	Reagent	Product	Yield (%)
1	$H_2C=C(Me)OTf$		54
2	$Me_2C=CHOTf$		43
3			45.7

Note: Reaction conditions: LiCl, $Pd(PPh_3)_4$, THF, N_2, 48 h; Urd, uridine (1-β-D-ribofuranosyluracil) as a substrate.

3. Addition of alkenylmagnesium derivatives

Vinylmagnesium bromide and chloride are added at position 6 of the pyrimidine ring of the protected nucleosides; this reaction gives 6-alkenyldihydropyrimidine derivatives of nucleosides in good yields. Thus reaction of protected uridine **75** with vinylmagnesium chloride [83, 92] and reaction of the 5-bromo derivative **76** with vinylmagnesium bromide (Ar, 1 h) give their 6-vinyldihydro derivatives **77** and **78** (yields 61% and 96%, respectively).



75, **76** **77**, **78**

R = H (**75**, **77**), Br (**76**, **78**).

The attempts [83] to oxidise reaction products to pyrimidine derivatives of nucleosides were unsuccessful.

V. Conclusion

Numerous methods for C-alkenylation of nucleosides and their analogues are currently known, which differ in complexity, reaction conditions and the possibility of obtaining substituted nucleosides with a predetermined structure. In our opinion, the most promising approaches involve reactions of organoelement alkene derivatives, in particular, organotin (in non-aqueous

solvents) and organoboron derivatives (in H_2O or aqueous-organic media). Organosilicon derivatives of alkenes seem to be promising reagents that might replace toxic organotin compounds in future, although their cross-coupling is insufficiently developed yet. Mercury derivatives of nucleosides used to introduce alkenyl substituents will hardly lose their significance by virtue of their availability, which can be attributed to the ease of their preparation and the presence of a large body of experimental material that helps selecting the conditions for a specific synthesis. However, in more distant future this method will most likely be replaced by analogous procedures, *e.g.,* the Heck-type coupling of iodonucleosides with alkenes, which affords higher yields of the target products and precludes the use of toxic substrates. The methods of oxidative coupling of nucleosides with activated alkenes and alkenyl triflates also attract attention owing to their experimental simplicity. At the same time, literature data concerning these methods are scarce, which makes difficult their application in the synthesis of novel compounds and long-range prognoses. And finally, the use of photochemical alkenylation of nucleosides for preparative purposes will, most probably, hardly have any practical significance.

References

1. S A Fleming *Tetrahedron* **51** 12479 (1995)
2. G Ya Sheflyan, E A Kubareva, E S Gromova *Usp. Khim.* **65** 765 (1996) [*Russ. Chem. Rev.* **65** 709 (1996)]
3. M Krečmerová *Chem. Listy* **84** 1282 (1990)
4. V A Korshun, E V Manasova, Yu A Berlin *Bioorg. Khim.* **23** 324 (1997) [a]
5. X Jiang, R K Pandey, K M Smith *J. Chem. Soc., Perkin Trans. 1* 1607 (1996)
6. P S Nelson, C Bahl, I Gibbons *Nucleosides Nucleotides* **5** 233 (1986)
7. B Bartholomew, G A Kassavetis, B R Braun, E P Geiduschek *EMBO J.* **9** 2197 (1990)
8. T Yamaguchi, M Saneyoshi *Nucleosides Nucleotides* **15** 607 (1996)
9. J A Brumbaugh, L R Middendorf, D L Grone, J L Ruth *Proc. Natl. Acad. Sci. USA* **85** 5610 (1988)
10. F-G Rong, A H Soloway *Nucleosides Nucleotides* **13** 2021 (1994)
11. D E Bergstrom *Nucleosides Nucleotides* **1** 1 (1982)
12. D E Bergstrom, X Lin, G Wang, D Rotstein, P Beal, K Norrix, J Ruth *Synlett* 179 (1992)
13. J P Collman, L S Hegedas, J Norton, R G Finke *Principles and Applications of Organotransition Metal Chemistry* (Mill Valley, CA: University Science Books, 1987)
14. D E Bergstrom, J L Ruth *J. Am. Chem. Soc.* **98** 1587 (1976)
15. R F Heck *J. Am. Chem. Soc.* **90** 5518 (1968)
16. R F Heck *Palladium Reagents in Organic Syntheses* (New York: Academic Press, 1985)
17. D E Bergstrom, J L Ruth *J. Carbohydr. Nucleosides Nucleotides* **4** 257 (1977)
18. C F Bigge, P Kalaritis, J R Deck, M P Mertes *J. Am. Chem. Soc.* **102** 2033 (1980)
19. D E Bergstrom, M K Ogawa *J. Am. Chem. Soc.* **100** 8106 (1978)
20. Y Wataya, A Matsuda, D V Santi, D E Bergstrom, J L Ruth *J. Med. Chem.* **22** 339 (1979)
21. D E Bergstrom, J L Ruth, P A Reddy, E De Clercq *J. Med. Chem.* **27** 279 (1984)
22. J Goodchild, R A Porter, R H Raper, I S Sim, R M Upton, J Viney, H J Wadsworh *J. Med. Chem.* **26** 1252 (1983)
23. Y-M Cho, F Johnson *Tetrahedron Lett.* **35** 1149 (1994)
24. S Izuta, M Saneyoshi *Chem. Pharm. Bull.* **35** 4829 (1987)
25. T Yamaguchi, K Suyama, K Narita, S Kohgo, A Tomikawa, M Saneyoshi *Nucl. Acids Res.* **25** 2352 (1997)
26. A S Jones, G Verhelst, R T Walker *Tetrahedron Lett.* 4415 (1979)
27. D E Bergstrom, H Inoe, P A Reddy *J. Org. Chem.* **47** 2174 (1982)
28. G W Ashley, P A Bartlett *J. Biol. Chem.* **259** 13615 (1984)
29. M E Perlman, K A Watanabe, R F Schinazi, J J Fox *J. Med. Chem.* **28** 741 (1985)
30. I Arai, G D Daves Jr *J. Org. Chem.* **43** 4110 (1978)
31. I Arai, G D Daves Jr *J. Am. Chem. Soc.* **100** 287 (1978)
32. R C Cookson, P J Dudfield, R F Newton, P Ravenscroft, D I C Scopes *Eur. J. Med. Chem.* **20** 375 (1985)
33. J Goodchild, H J Wadsworh, I S Sim *Nucleosides Nucleotides* **5** 571 (1986)
34. P R Langer, A A Waldrop, D C Ward *Proc. Natl. Acad. Sci. USA* **78** 6633 (1981)
35. M Shimkus, J Levy, T Herman *Proc. Natl. Acad. Sci. USA* **82** 2593 (1985)
36. S Pochet, S R Sarfati, J Igolen *Nucleosides Nucleotides* **8** 1073 (1989)
37. T Yamaguchi, M Saneyoshi *Nucleosides Nucleotides* **11** 373 (1992)
38. US Appl. 95-382 892; *Chem. Abstr.* **125** 248 329 (1996)
39. D E Bergstrom, J L Ruth, P Warwick *J. Org. Chem.* **46** 1432 (1981)
40. R F Heck *J. Am. Chem. Soc.* **90** 5531 (1968)
41. J K Stille *Angew. Chem., Int. Ed. Engl.* **25** 502 (1986)
42. P Wigerinck, L Kerremans, P Claes, R Snoeck, P Maudhal, E De Clercq, P Herdewijn *J. Med. Chem.* **36** 538 (1993)
43. G Palmisano, M Santagostino *Tetrahedron* **49** 2533 (1993)
44. N Miyaura, A Suzuki *Chem. Lett.* 879 (1981)
45. D Peters, A-B Hörnfeldt, S Gronowitz *J. Heterocycl. Chem.* **27** 2165 (1990)
46. P L Coe, M R Harnden, A S Jones, S A Noble, R T Walker *J. Med. Chem.* **25** 1329 (1982)
47. R F Heck, J P Nolley Jr *J. Org. Chem.* **37** 2320 (1972)
48. A de Meijere, F E Meyer *Angew. Chem., Int. Ed. Engl.* **33** 2379 (1994)
49. W Carbi, I Candiani *Acc. Chem. Res.* **28** 2 (1995)
50. T Mizoroki, K Mori, A Ozaki *Bull. Soc. Chem. Jpn.* **44** 581 (1971)
51. E De Clercq, C Desgranges, P Herdewijn, I S Sim, A S Jones, M J McLean, R T Walker *J. Med. Chem.* **29** 213 (1986)
52. R Kumar, L Xu, E E Knaus, L I Wiebe, D R Tovell, D L Tyrrell, T-M Allen *J. Med. Chem.* **33** 717 (1990)
53. M Ashwell, A S Jones, A Kumar, J R Sayers, R T Walker, T Sakuma, E De Clercq *Tetrahedron* **43** 4601 (1987)
54. P Herdewijn, E De Clercq, J Balzarini, H Vanderhaeghe *J. Med. Chem.* **28** 550 (1985)
55. L J J Hronowski, W A Szarek *J. Chem. Soc., Chem. Commun.* 1547 (1990)
56. W A Slusarchyk, G S Bisacchi, A K Field, D R Hockstein, G A Jacobs, B McGeever-Rubin, J A Tino, A V Tuomari, G A Yamanaka, M G Young, R Zahler *J. Med. Chem.* **35** 1799 (1992)
57. J A Tino, J M Clark, A K Field, G A Jacobs, K A Lis, T L Michalik, B McGeever-Rubin, W A Slusarchyk, S H Spergel, J E Sundeen, A V Tuomari, E R Weaver, M G Young, R Zahler *J. Med. Chem.* **36** 1221 (1993)
58. T-S Lin, M S Chen, Y-S Gao, I Ghazzouli, W H Prusoff *J. Med. Chem.* **30** 440 (1987)
59. N G Kundu, J S Mahatny, C P Spears, G Andrei, R Snoeck, J Balzarini, E De Clercq *Bioorg. Med. Chem. Lett.* **5** 1627 (1995)
60. N G Kundu, P Das *J. Chem. Soc., Chem. Commun.* 99 (1995)
61. I Arai, G D Daves Jr *J. Heterocycl. Chem.* **15** 351 (1978)
62. I Basnak, S Takatori, R T Walker *Tetrahedron Lett.* **38** 4869 (1997)
63. S G Rahim, M J H Duggan, R T Walker, A S Jones, R L Dyer, J Balzarini, E De Clercq *Nucl. Acids Res.* **10** 5285 (1982)
64. A Lubineau, J Augé, Y Queneau *Synthesis* 741 (1994)
65. R F Whale, P L Coe, R T Walker *Nucleosides Nucleotides* **11** 1425 (1992)
66. H A Dieck, R F Heck *J. Organomet. Chem.* **93** 259 (1975)
67. L Cassar *J. Organomet. Chem.* **93** 253 (1975)
68. K Sonogashira, Y Tohda, N Hagihara *Tetrahedron Lett.* 4467 (1975)
69. M J Robins, P J Barr *Tetrahedron Lett.* **22** 421 (1981)
70. H Li, L Czuchajowski, W R Trumble *J. Heterocycl. Chem.* **34** 999 (1997)
71. N M Goudgaon, G F El-Kattan, R F Schinazi *Nucleosides Nucleotides* **13** 849 (1994)
72. A L Casalnuovo, J C Calabrese *J. Am. Chem. Soc.* **112** 4324 (1990)
73. K Hirota, Y Kitade, Y Kanbe, Y Isobe, Y Maki *Synthesis* 213 (1993)
74. P Vincent, J-P Beacourt, L Pichat *Tetrahedron Lett.* **23** 63 (1982)
75. P Vincent, J-P Beacourt, L Pichat, J Balzarini, E De Clercq *Nucleosides Nucleotides* **4** 447 (1985)
76. G T Crisp *Synth. Commun.* **19** 2117 (1989)
77. G T Crisp, B L Flynn *Tetrahedron Lett.* **31** 1347 (1990)
78. B L Flynn, V Macolino, G T Crisp *Nucleosides Nucleotides* **10** 763 (1991)

79. K W Morin, L I Wiebe, E E Knaus *Carbohydr. Res.* **49** 109 (1993)
80. V Farina, S I Hauck *Synlett* 157 (1991)
81. D P Matthews, R S Gross, J R McCarthy *Tetrahedron Lett.* **35** 1027 (1994)
82. P Herdewijn, L Kerremans, P Wigerinck, F Vandendriessche, A Van Aerschot *Tetrahedron Lett.* **32** 4397 (1991)
83. S Manfredini, P G Baraldi, R Bazzanini, M Marangoni, D Simoni, J Balzarini, E De Clercq *J. Med. Chem.* **38** 199 (1995)
84. H Matsuhashi, Y Hatanaka, M Kuroboshi, T Hiyama *Heterocycles* **42** 375 (1996)
85. M E Hassan *Recl. Trav. Chim. Pays-Bas* **105** 30 (1986)
86. M E Hassan *Bull. Soc. Chim. Belg.* **100** 627 (1991)
87. I Moritani, Y Fujiwara *Synthesis* 524 (1973)
88. A E Shilov, G B Shul'pin *Aktivatsiya i Kataliticheskie Reaktsii Uglevodorodov* (Activation and Catalytic Reactions of Hydrocarbons) (Moscow: Nauka, 1995) p. 277
89. K Hirota, Y Isobe, Y Kitade, Y Maki *Synthesis* 495 (1987)
90. G A Tolstikov, A G Mustafin, R R Gataullin, L V Spirikhin, V S Sultanova, I B Abdrakhmanov *Izv. Akad. Nauk, Ser. Khim.* 1616 (1992) [b]
91. M E Hassan *Can. J. Chem.* 198 (1990)
92. N Bischofberger *Tetrahedron Lett.* **30** 1621 (1989)

[a] — *Russ. J. Bioorg. Chem. (Engl. Transl.)*
[b] — *Russ. Chem. Bull. (Engl. Transl.)*