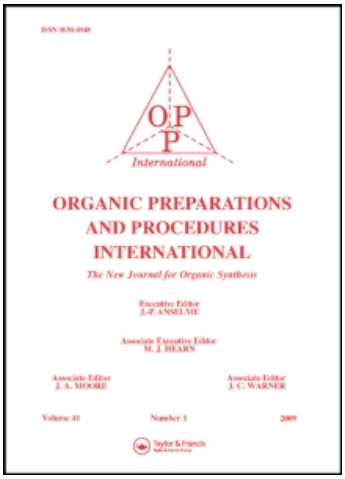

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SYNTHESIS OF 9-SUBSTITUTED GUANINES. A REVIEW

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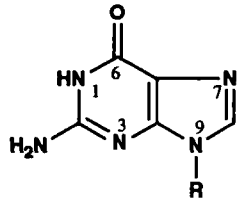
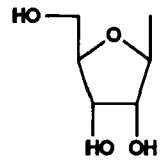
INTRODUCTION

Since the appearance of the antiviral carboacyclic nucleoside penciclovir **1d**[1] in 1972 and the acyclic nucleoside acyclovir **1b**[2-4] in 1977, much attention has been devoted to the synthesis of nucleosides, especially the acyclic guanosine analogues. Until then, efforts to synthesize 9-substituted guanines had been concentrated on the synthesis of guanosine **1a**.



1a-f



a) Guanosine

R = –$CH_2OCH_2CH_2OH$

b) Acyclovir

R = –$CH_2OCH(CH_2OH)_2$

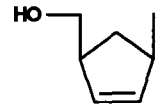
c) Ganciclovir (DHPG)

R = –$CH_2CH_2CH(CH_2OH)_2$

d) Penciclovir

R = –$CH_2CH_2CHOHCH_2OH$

e) Bucyclovir



f) Carbovir

The synthesis of 9-substituted guanines has not been reviewed previously. Hrebabecsky *et al.*[5] in 1974 provide references to the most frequently used methods in the synthesis of 9-glycosylguanines. In 1989, Robins *et al.*[6] and Kjellberg *et al.*[7] give surveys of methods starting from purine derivatives and alkylating agents. Yamazaki and Okutsu[8] in 1978 reviewed cyclization reactions of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA-riboside) and derivatives, which lead to guanosine **1a**. McCoss *et al.*[9] in 1986 surveyed the synthesis of guanine acyclonucleosides and acyclonucleotides. Chu and Cutler[10] in 1986 reviewed the syntheses of acyclovir analogues, and Remy and Secrist[11] in 1985 give a bibliography of acyclic nucleosides except for acyclovir, in which references to syntheses are given. Some general information about the synthesis of nucleosides have been given by Zorbach,[12] Watanabe *et al.*,[13] Vorbrüggen *et al.*[14], and De las Heras *et al.*[15] Finally, of the several monographs on nucleic acid chemistry appeared, two must be mentioned.[16,17] Kjellberg *et*

al.[18] have made some characterization of 7- and 9-substituted purine analogues by ^{1}H- and ^{13}C-NMR. The present review covers the period from 1970 to 1991, and only the syntheses of 9-substituted guanines without other substituents in the guanine ring will be discussed.

I. 9-*C*-SUBSTITUTED GUANINES

One of the main goals in developing new syntheses of 9-substituted guanines has been to suppress the formation of the 7-isomers, which can be very difficult to separate from the 9-isomers without use of column chromatography. In this review, the type of syntheses of 9-substituted guanines with a C-substituent are divided into three main categories:

A. Synthesis from purines

B. Synthesis from pyrimidines

C. Synthesis from imidazoles

A. SYNTHESIS FROM PURINES

Attempts to alkylate guanine directly have given poor results. The main problems are the low solubility of guanine and the several possible sites for substitution on the guanine molecule (N1-, N2-, N3-, O6-, N7- and N9-). Therefore, the preparative methods always start from protected guanines or other purines.

Since a considerable number of the methods uses the trimethylsilyl group as a type of protective group, we have found it appropriate to divide the methods into those based on non-silylated purines and those based on silylated purines (different modifications of the silyl-Hilbert-Johnson method). It is common for nearly all the syntheses starting from a purine, that the pure product has to be isolated by use of chromatography. Most attention in this section has been directed towards the alkylation step in the synthesis since the conversion to the corresponding 9-substituted guanine most often follows standard procedures.

1. From Non-Silylated Purines

Kjellberg *et al.*[7] have made some important studies on the alkylation of derivatives of guanine, where the synthesis of some 7- and 9-substituted guanines were investigated. The influence of the base, the alkylating agent, and of the type of derivatization of the purine moiety on the relative formation of the 7- and 9-isomers were studied.

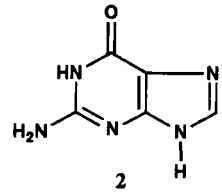
It seems that with guanine derivatives in the "keto-form" 7-alkylation is preferred whereas with guanine derivatives in the "enol-form" the 9-position is preferentially alkylated[7]. However high-temperature alkylation of N2,N(7,9)-diacetylguanine gives preferentially the 9-isomer (see *iii)*.

a) From C6-Oxopurines

i) From Guanine

Direct alkylation on guanine **2** has not been succesful. The different procedures have all led to low yields and non-regiospecific alkylation.

Thus alkylation at pH 12-13 gave N1-, N2-, N3-, O6-, N7-and N9-substitution.[19] Alkylation under phase-transfer conditions in THF (Bu_4NOH) gave N9/N7-ratio of (1:2)[20]. Kjellberg *et al.*[7] have unsuccessfully attempted to alkylate guanine in aq. NaOH-CH_2Cl_2 with tetraalkylammonium halogenide as phase transfer catalyst.

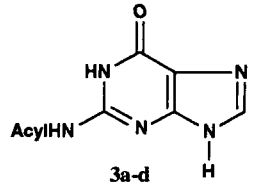


2

Alkylation of guanine **2** in DMF in the presence of NaH has been described using an epoxide derivative[21] and a tosylate derivative (in the presence of NaI).[22] In both cases the yields were low.

ii) From N2-Acylated Guanines

Iwamura *et al.*[23] condensed **3a** with some fully acetylated sugars by fusion and obtained mixtures of 7- and 9-isomers. The fusion was carried out with catalyst (p-TsOH, $ZnCl_2$, bis(p-nitrophenyl)phosphate) and without catalyst.



3a-d

a) acetyl b) palmitoyl
c) octanoyl d) nonanoyl

Furokawa *et al.*[24] condensed **3a-c** with tetraacetylated ribose under various Friedel-Crafts conditions. The highest yield was obtained with $AlCl_3$ in C_6H_5Cl. This Furokawa technique has been investigated further by Lee *et al.*[25] By condensing **3b** with triacetylated 2-azido-2-deoxyribose, Hobbs *et al.*[26] obtained a 2:3 mixture of 7- and 9-(2-azido-2-deoxy-β-D-ribofuranosyl)guanine. Kjellberg *et al.*[7] have studied the reaction of **3b** with 4-bromobutyl acetate in DMF under basic conditions (NaH, KH, K_2CO_3) at room temperature and found an N9/N7 ratio (1:1) in all three cases.

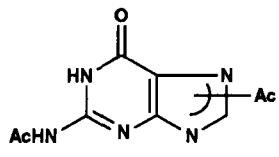
Alkylation of **3a** in DMF under basic conditions (NaH, Et_3N) has been carried out.[27-30] The yields were low and large amounts of the 7-isomer were formed. N7-N9 mixtures were also obtained by direct condensation of **3a** with α-bromosugars and alkylbromide compounds[31,32] in dimethylacetamide (DMA).

Condensation of **3b** with the BCl_3-complex of methyl-D-ribo-furanoside in $CHCl_3$ gave 15% guanosine.[33] 9-Substituted **3a-d** can be deacylated, e. g. by treatment with sodium methoxide in methanol.[24,25] Some investigations about the migration of substituents on the guanine molecule **3a** have been made.[13,23,31,32]

By transglycosylation of peracylated cytidine to **3a** in xylene-DMA with $HgBr_2$ as catalyst Miyaki *et al.*[34] obtained a (1:1) mixture of the 9- and 7-glycosylguanine.

iii) From Bisacetylated Guanine

The alkylation of **4** has only been carried out with β-*O*-activated alkylating agents (most often with an -OAc as leaving group). Condensation by fusion of **4** with fully acylated sugars or other β-*O*-activated alkylating agents with -OAc as leaving group, resulted in mixtures with a large content of the 7-isomer, whether catalysts like I_2,[35] *p*-TsOH,[36] and $EtSO_3H$[36-39] were used or not.[40]



4

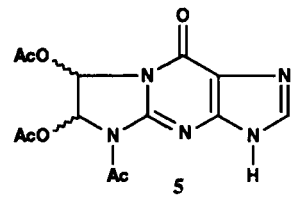
Matsumoto *et al.*[41] evaluated the effect of temperature and catalysts such as p-TsOH, sulfanilic acid, nitrobenzene sulfonic acid, $ZnCl_2$, and $FeSO_4$ on the acyclovir **1b** synthesis from **4** and 2-oxa-1,4-butanediol diacetate in DMSO. The yields were rather high, but a considerable amount of the 7-isomer was formed. Rather high yields of crude acyclovir (**1b**) were obtained at Wellcome[42] from **4** and 2-oxa-1,4-butanediol diacetate with p-TsOH as catalyst in toluene. No information was given about the amount of 7-isomer formed, but, according to Madre *et al.*[36] up to 25% of the 7-isomer was formed using similar reaction conditions.

Similar condensation of **4** has been carried out with β-*O*-activated or β-*S*-activated reagents with OAc as leaving group (p-TsOH/DMSO),[43,44] (bis(4-nitrophenyl)phosphatesulfolane).[45,46] Finally β-*O*-activated -$SOCH_3$ has been used as leaving group (DMF or DMSO, no catalyst).[47,48] Some investigations about the migration of the substituent in the condensation reaction with **4** have been done by McGee *et al.*[47] 9-Substituted **4** can be deacetylated e. g., by treatment with aq. methylamine.[42]

iv) From Other *C*6-Oxopurines

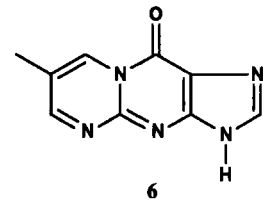
Kjellberg *et al.*[7,49] have studied the alkylation of **5** with 4-bromobutyl acetate in DMF (THF and CH_2Cl_2 resulted in low yields) at room temperature under basic conditions (NaH, KH, EtOTl, N,N'-dimethylpiperazine) and found a 0.06 - 0.5 N9/N7 ratio.

By alkylating **5** with 2-oxa-1,4-butanediol diacetate in toluene at reflux temperature Deufel *et al.*[50] obtained a 44% yield of the 9-substituted **5**, which was deacetylated with aq. methylamine to give acyclovir **1b**. No information was given about the N9/N7 ratio.



5

Kjellberg *et al.*[7,51] also studied the reaction of **6** with 4-bromobutyl acetate in DMF at room temperature under basic conditions (NaH, K_2CO_3) and found a (1:1) N9/N7 ratio. The product was hydrolyzed with 0.1 N aq. NaOH to give 9-(4-hydroxybutyl)-guanine.



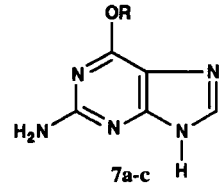
6

b) From O6-Substituted Purines

i) From *O*-Substituted Guanines

Substitution of **7** has been carried out with both non-activated and β-*O*-activated leaving groups.

Kjellberg *et al.*[7,52] studied the alkylation of **7a-c** with 4-bromobutyl acetate (among others) in DMF at room temperature under basic conditions (LiH, NaH, KH, K_2CO_3, Na_2CO_3, EtOTl). The highest N9/N7 ratio was obtained with LiH (6-10 with a 65-95% conversion). Kim *et al.*[53] obtained a (2:1) N9/N7 ratio (65% conversion) for a similar alkylation of **7b**.



7a-c

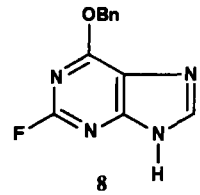
a) R = benzyl
b) R = 2-methoxyethyl
c) R = 1-butyl

The alkylation of **7a** and **7b** in DMF with LiH or NaH as base has been carried out with non-activated leaving groups[9,53-57] and with β-*O*-activated leaving groups (chloromethyl ethers).[49,53,58-61] It seems[7] that the highest N9/N7 ratio is obtained, when the alkylating agent has a β-*O*-activated leaving group.

Zahler *et al.* have alkylated **7a** with non-activated (OTs) carbocyclic alkylating agents in DMF using K_2CO_3/18-crown-6[62,63] and in sulfolane with an epoxy carbocyclic alkylating agent by use of NaH/18-crown-6.[64] The O-protecting group has been removed under many different conditions, depending also on the type of side chain.

ii) From 2-Fluoro-6-benzyloxypurine

8 has been condensed with acylated sugars under fusion conditions[65,66] with dichloroacetic acid as a catalyst. The yields of alkylated product were low.



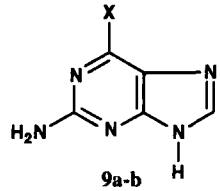
8

8 was obtained from O-benzylguanine **7a**. The 9-substituted **8** was converted to the guanine derivative by treatment with alcoholic ammonia followed by hydrogenation over palladium.[65,66]

c) From C6-Halopurines

i) From 2-Amino-6-halopurines

Although **9a** is rather difficult to obtain,[36,67] it has nevertheless been widely used as starting material for the synthesis of 9-substituted guanines.



9a-b
a) X = Cl
b) X = I

Kjellberg *et al.*[7] studied the N9/N7 ratio for the alkylation of **9a** with various non-activated alkyl halides in DMF under basic conditions (LiH, NaH, K_2CO_3). The N9/N7 ratios obtained were between 4 - 8, but the yields were low.

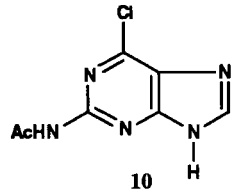
Other chemists have, however, obtained rather good yields starting from **9a** or **9b**. A large variety of leaving groups and side chain precursors have been used - activated as well as non-activated. High yields and high N9/N7 ratios have been obtained from **9a** using K_2CO_3 as the base and DMF[3,68-74] or DMSO[75-79] as the solvent. Thus, Harnden *et al.*[72] obtained a 70% yield after column chromatography by alkylation of **9a** with 5-(2-bromoethyl)-2,2-dimethyl-1,3-dioxan in DMF with K_2CO_3 at room temperature, with the 7-isomer barely detectable.

Other procedures for the condensation of **9a** with alkylating agents are: NaH/DMF[53,80-82]; **9a**, Na-salt/DMA;[83] NaH/CH_3CN;[84] TBAF/THF;[75,76] DBU/CH_3CN (Michael addition);[85] $Pd(Pph_3)_4$ or Pph_3/DEAD/THF.[86]

9b has been alkylated in high yield in DMF with K_2CO_3.[87,88] The 9-substituted **9a** and **9b** can be transformed into the corresponding guanine derivative, e.g. by hydrolysis with aq. hydrochloric acid.[68]

Ogilvie *et al.*[89] hydrolyzed a mixture (3:2) of N7- and N9-substituted **9a** with aq. NaOH in methanol and obtained pure 9-substituted guanine in 70% yield.

ii) From 2-Acetamino-6-chloropurine



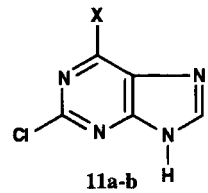
10

One of the old methods for the preparation of guanosine analogues is the condensation of the Hg-salt derivative of **10** and a halogenated sugar in benzene[90] or xylene[91-93] followed by transforming the resulting 9-substituted **10** to the corresponding guanine derivative, e. g. with 2-mercaptoethanol and sodium methoxide followed by hydrolysis. The yields were rather low.

10 has been condensed directly[94] under fusion conditions with a 4-thiofuranose derivative with p-TsOH as a catalyst.

iii) From 2,6-Dihalopurines

Alkylation of **11a** and **11b** has been carried out with β-*O*-activated alkylating agents.



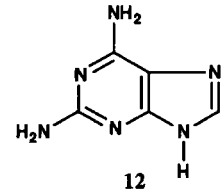
11a-b
a) X = Cl
b) X = I

Robins *et al.*[65] condensed **11a** with acylated sugars under fusion conditions in low yields. Hosono *et al.*[95] made some kinetic studies on this type of reaction and proved them to be of the second order. Montgomery *et al.*[96] examined various approaches to achieve the maximum amount of the 9-β-isomer of an arabinofuranosylguanine using **11a** with a protected glycosyl bromide in boiling 1,2-dichloroethane in the presence of 4A molecular sieves.

Schaeffer *et al.*[3] have used **11a** as starting material for acyclovir **1b** by alkylation with (2-benzoyloxyethoxy)methyl chloride in DMF with triethylamine as base or by fusion with 2-oxa-1,4-butanediol diacetate and p-TsOH as catalyst. The Na-salt of **11b** (from NaH) has been alkylated with (2-trimethylsilyloxyethoxy)methyl iodide at - 63°[97] in a 75% yield of the 9-isomer and 10% of the 7-isomer.

9-Substituted **11a** and **11b** can be converted to the corresponding guanine,[3] *e. g.* in 3 steps by: 1) ammonolysis of the 6-chloro group, 2) diazotation and hydrolysis of the generated 6-amino group, 3) ammonolysis of the 2-chloro group.

d) From 2,6-Diaminopurine



12

12 has been used as starting material in a synthesis of carbovir **1f**[56]. The Na-salt of **12** (from NaH) in DMF with 15-crown-5 was alkylated with a carbocyclic epoxide to give the 9-substituted **12** in a highly selective reaction. The product was - after protection of the 2-amino group - converted to the guanine analogue *via* diazotation of the 6-amino group and deprotection.

2. *via* Silylated Purines

The reaction of persilylated guanine derivatives with peracylated sugars or with acetoxy- or chloromethyl ether derivatives - often in the presence of a Friedel-Crafts catalyst like e.g. $SnCl_4$ or trimethylsilyl triflate ($CF_3SO_3SiMe_3$) (TMSTF) - has become a widely used synthetic method for the

preparation of 9-substituted guanines. The persilylated guanine derivatives are obtained by e. g. heating the corresponding guanine with an excess of hexamethyldisilazane (HMDS) in the presence of ammonium sulfate as catalyst, or with an excess of bis(trimethylsilyl)acetamide (BSA), whereby all reactive hydroxy, amino and mercapto groups are silylated. As the persilylated guanine derivatives are highly moisture sensitive they are never isolated, but alkylated *in situ* - after evaporating the excess of silylating agents.

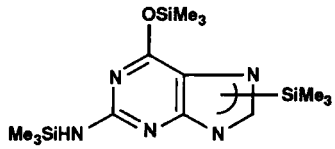
The above method is a so called modified *silyl*-Hilbert-Johnson nucleoside reaction, which has been described by Vorbrüggen *et al.*[14,98,99] using N2-acetylguanine as starting material. Further information about this method can be found in articles from Robins *et al.*[6] and Dudycz *et al.*[100]

The trimethylsilyl groups are easily removed from the product by alcoholysis or by basic or acid hydrolysis. The resulting reaction mixture often has to be worked up by column chromatography.

a) via Silylated C6-Oxopurines

i) via Silylated Guanine

The tris(trimethyl)silylated guanine **13** has mainly been used in the synthesis of acyclic guanosine analogues by condensing **13** - in the absence of Friedel-Crafts catalyst - with acetoxy- or chloromethyl ether derivatives.



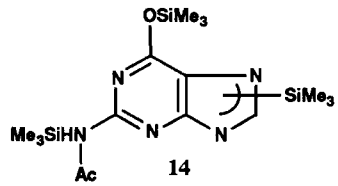
13

The condensation of **13** with a peracylated sugar (in the presence of an acid catalyst) to give a 9-glycosyl-guanine was initially described by Yamazaki *et al.*[101] Fair to good yields and high N9-regiospecificity have been achieved by Imbach *et al.*[102,103] by condensing **13** with an acetoxymethyl ether[102] or with peracetylated sugars under phase transfer conditions (KI and dibenzo-18-crown-6 in acetonitrile-benzene or toluene). High N9-regiospecificity (N9/N7 = 10:1) has been reported by Kim *et al.*[104,105] by condensing 2-oxa-1,4-butanediol diacetate with **13** in acetonitrile with CsI as catalyst. Phase transfer conditions have also been used by Ogilvie *et al.*[67] condensing **13** with a chloromethyl ether in acetonitrile with tetrabutylammonium iodide (Bu_4NI) as catalyst to give a high yield of a (7:3) N9/N7 ratio. The N9-isomer was isolated in 41% yield by fractionated crystallization. Similar condensations - but in THF - have been carried out by an Iranian group[106] using Bu_4NF as catalyst.

Kelley *et al.*[107] obtained up to 90% crude yield by condensing **13** with chloromethyl ethers in refluxing toluene in the presence of Et_3N. No information about the N9/N7 ratio was given, but Lin *et al.*[108] obtained a (4:1) to a (3:2) N9/N7 ratio under similar reaction conditions (see also refs. 3 and 109). By refluxing **13** with cyclohexyl iodide in toluene in the presence of Et_3N, Kjellberg *et al.*[7] obtained 20% of N7,N9-*bis*cyclohexylguanine (zwitterion). Ashton *et al.*[39,61] carried out this type of condensation with some chloromethyl ethers at elevated temperature in xylene without using Et_3N. The resulting N9-isomers - with a rather low N7-isomer content - were isolated by crystallization (no chromatography) in fairly good yields. Madre *et al.*[36] obtained a N9/N7-mixture by condensing a bromomethyl ether with **13** in 1,2-dichloroethane.

ii) via Silylated N2-Acetylated Guanine

The condensation reactions with the tris(trimethyl)silylated N2-acetylated guanine **14** are the most thoroughly investigated silyl-Hilbert-Johnson reactions in the guanine area.



14

The first example we have found of this condensation was carried out by Novák *et al.*[110] in the synthesis of 3'-deoxyguanosine. Very useful information pertaining this reaction can be obtained from Vorbrüggen *et al.*[14,98,99], Ogilvie *et al.*[67], Dudycz *et al.*[100], Garner *et al.*[111], and Robins *et al.*[6]. The condensation with **14** has always been carried out with β-*O*-activated reagents with Cl-, Br-, AcO- or MeS- as leaving groups. The most commonly used catalysts are TMSTF, $SnCl_4$ and $Hg(OAc)_2$. Acetonitrile, 1,2-dichloroethane and in one case THF have been used as solvent.

The use of trimethylsilyl perfluoroalkanesulfonates as Friedel-Crafts catalysts by Vorbrüggen *et al.*[98,99] has simplified the *silyl-* Hilbert-Johnson reaction by combining the several steps of the reaction (silylation of the guanine derivative, silylation of the catalyst and the nucleoside synthesis itself) into a simple one-step / one-pot reaction[100]. The method has mainly been used in the synthesis of 9-glycosylguanines. Thus Vorbrüggen *et al.*[99] obtained a 66% yield of guanosine **1a** from **14** and peracylated ribofuranose in 1,2-dichloroethane with TMSTF as catalyst. The method has been checked by Robinson *et al.*[6] who condensed **14** with different peracylated sugars under "the general Vorbrüggen conditions" (TMSTF/1,2-dichloroethane at 80° overnight) and obtained a (2-5:1) N9/N7 ratio. By using $SnCl_4$ as catalyst (instead of TMSTF) in 1,2-dichloroethane at ambient temperature Robinson *et al.*[6] obtained a (1:13-18) N9/N7 ratio. The N7-isomer could be isolated in 70-76% yield.

Dudycz *et al.*[100] combined BSA as a silylating reagent and TMSTF as a catalyst in a condensation of **14** with peracetylated ribofuranose in refluxing acetonitrile. HPLC analysis of the reaction mixture indicated that the 7-isomer was formed first, i.e. as the kinetic product, but that it was converted into the thermodynamically more stable 9-isomer, probably *via* the N7,N9-disubstituted **14**. After 8 hrs of reflux a 70% yield of the 9-isomer was obtained and 5% of the 7-isomer.

Garner *et al.*[111] studied the reaction of **14** with 2-*O*-acetylated and 2-*O*-benzoylated glycosides and concluded that kinetically controlled conditions ($SnCl_4/CH_3CN$, room temperature) selectively gave the N7-isomer, whereas 2-*O*-benzoylated glycosides selectively gave the N9-isomers under thermodynamically controlled conditions (TMSTF/1,2-dichloroethane, reflux).

TMSTF as catalyst in CH_3CN or 1,2-dichloroethane has also been used by others[112-114] in the synthesis of 9-glycosylguanines. Hrebabecky *et al.*[5] investigated the reaction of **14** with some acylated furanosyl bromides in acetonitrile in the presence of $Hg(OAc)_2$, and obtained up to 88% of 9-glycosylguanine with 100% regiospecificity. The work of Hrebabecky *et al.* was based on a method developed by Novák *et al.*[110] who - under similar reaction conditions - obtained a 34% yield of 3'-deoxyguanosine in a 100% regiospecific synthesis. The above reaction conditions using 1,2-dichloroethane as solvent have been used by Bobek[115] in the condensation of **14** with acylated glycosyl chlorides. The yields were low and the N9/N7 ratio about (1:2). Attempts to use the above

methods to prepare acyclic guanosine analogues have until now resulted in low yields and/or a low N9/N7 ratio.[67,116,117] Ogilvie *et al.*[67] condensed **14** with a chloromethyl ether in both acetonitrile and 1,2-dichloroethane with tetrabutylammonium iodide as catalyst. In both cases a (1:1) mixture of N9- and N7-isomer was obtained. The same authors[118] also condensed **14** with a thiomethyl methyl ether in THF with iodine as catalyst giving a (3:2) N9/N7 ratio.

A transglycosylation reaction of 3'-azido-3'-deoxy-5'-*O*-acetylthymidine with silylated N2-palmitoylguanine in acetonitrile with TMSTF as catalyst afforded a complex mixture of glycosylguanine isomers.[119]

iii) via Silylated 2-Bromohypoxanthine

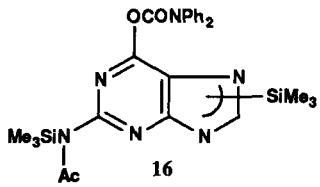
Condensation of **15** with tetra-*O*-acetylribofuranose using Vorbrüggen reaction conditions (Ref. 99) (TMSTF / acetonitrile, reflux) afforded a (2:3) mixture of the 9- and 7-substituted **15**[120]. The products were converted to the guanine derivatives by ammonolysis in aq. ammonia at 150°. Vaghefi *et al.*[121] obtained a (2:1) N9/N7-mixture using similar reaction conditions with 1-*O*-acetyl-2,3-di-*O*-benzoyl-5-deoxy-5-(diethoxyphosphinyl)-β-D-ribofuranose as alkylating agent.

15

b) via Silylated O-Substituted Purines

i) via Silylated N2-Acetylated 6-*O*-diphenylcarbamoylguanine

By condensation of **16** with peracylated glycosyl derivatives or α-halo ethers with TMSTF as catalyst in anhydrous toluene Robins *et al.*[6,122] obtained the corresponding 9-substituted guanine compounds in high yields with no 7-isomers detected. Similar reaction conditions have been used by Armstrong *et al.*[123] in a synthesis of an analogue to AZT.



16

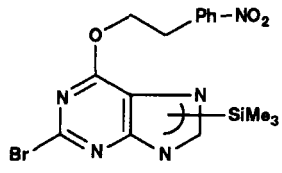
Subjection of 2-acetamido-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-diphenylcarbamoyloxypurine to their standard condensation conditions with TMSTF in anhydrous toluene at 80° resulted - after 2 hours - in a complete rearrangement to the corresponding 9-glycosyl isomer[6].

A variation of the above condensation method has been carried out by Kim *et al.*[81,124] in a synthesis of 9-substituted acyclic guanosine analogues from **16** using $Hg(CN)_2$ as catalyst in benzene.

The products were deprotected by ammonolysis in aq. MeOH[6].

ii) via Silylated 2-Bromo-6-(4-nitrophenylethoxy)purine

By condensation of **17** with peracylated ribofuranose derivatives in acetonitrile with TMSTF as catalyst, Raju *et al.*[125] obtained regioselectively 9-substituted products (N9/N7 ratios 20:1) in high yields.



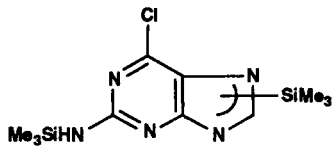
17

The same type of condensation - without catalyst - carried out with a bromomethyl ether - also resulted in a high yield of the 9-isomer (N9/N7 ratio 99:1). The products were transformed into the corresponding guanines by treating with 1) MeCN/DBU, 2) NH_3/MeOH (120°).

c) via Silylated 6-Chloropurines

i) via Silylated 2-Amino-6-chloropurine

Condensation of **18** with β-*O*-activated Cl- or Br-alkylating agents has been carried out in benzene (or toluene) - with $Hg(CN)_2$ as catalyst - in high yields and with high regiospecificity.



18

The method was originally described by Lee *et al.*[126] and has been further developed by Robins *et al.*[127] and Ogilvie *et al.*[67] Other authors have used this method.[60,81,128-130]

Variations of the method have been described: fusion[131], TMSCl-$SnCl_4$ / CH_3CN[132] and molecular sieves / $ClCH_2CH_2Cl$.[133]

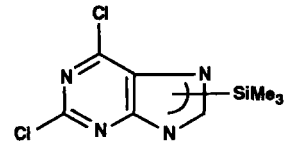
The 9-substituted **18** was converted to the guanine derivative, e.g. by hydrolysis with aq. NaOH in methanol[60] or by use of adenosine deaminase after a mild deprotection.[127]

ii) via Silylated 2-Acetamino-6-chloropurine

The N2-acetylated **18** was condensed in high yields with O-protected chloro- and bromofuranosyl derivatives in benzene or acetonitrile using $Hg(CN)_2$ as catalyst.[92,126] Changing the catalyst to TMSCl (excess from the silylation) resulted in low yields of product.[126]

iii) via Silylated 2,6-Dichloropurine

Condensation of **19** with (2-acetoxyethoxy)methyl bromide in benzene with $Hg(CN)_2$ as catalyst was carried out in high yield and with high N9-regiospecificity by Robins *et al.*[127]



19

Condensation of **19** with a pernitrobenzoylated sugar in acetonitrile in the presence of TMSTF has been described by Nord *et al.*[134]

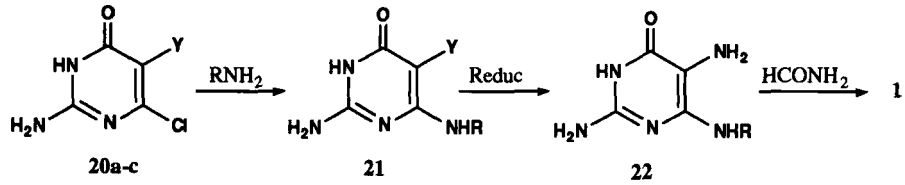
The 9-substituted **19** was converted to the corresponding guanine in two steps, e.g. by ammonolysis giving the diaminopurine, followed by treatment with adenosine deaminase.[127]

B. SYNTHESIS FROM PYRIMIDINES

Syntheses of 9-subtituted guanines from pyrimidine derivatives have mostly been described for guanines with an alkyl or an aralkyl substituent in the 9-position. The substituent is introduced in the pyrimidine ring by a nucleophilic reaction with the corresponding amino compound. Some of the advantages of using these routes are, that the 7-isomer is not formed and that column chromatography often can be avoided.

1. From N4-Substituted 6-Hydroxy-2,4,5-triaminopyrimidines

In 1959 Robins *et al.*[135] have synthesized a series of N9-alkyl, arylmethyl, and aryl substituted guanines by refluxing **22** in formamide. Other examples of this reaction are described.[136-138] **22** can be obtained from **20a**[137], **20b**[1], or **20c**[135-137] by substitution with RNH_2 followed by a reduction of the Y group.

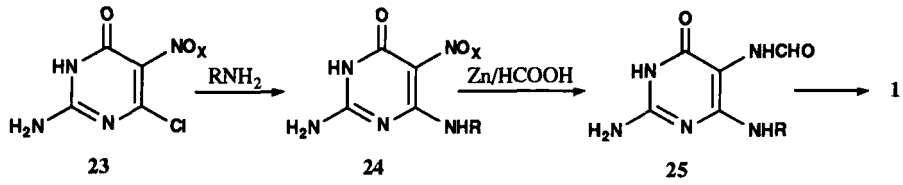


20a-c **21** **22**

a) Y = NO; b) Y = NO_2; c) Y = N=N-Ph

2. From N4-Substituted 2,4-Diamino-5-(formylamino)-6-hydroxypyrimidines

A similar series of 9-substituted guanines were produced in 1962 by Robins *et al.*[139] by refluxing **25** with formic acid / formamide. This method has also been used by other authors.[73,140] Other variations of the ring closure have been carried out by heating the title compound in formic acid,[141,142] DMF/K_2CO_3[138] or DMF/Na_2CO_3.[143] For example, **25** was prepared as shown below.

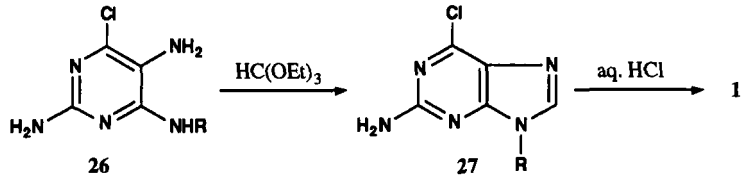


23 **24** **25**

X = 1 or 2

3. From N4-Substituted 6-Chloro-2,4,5-triaminopyrimidines

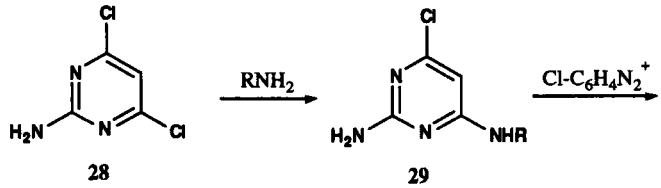
One of the most widely used methods for the preparation of 9-substituted guanines, especially carbocyclic, was developed in 1973 by Shealy *et al.*:[144] **26** is ring closed with $HC(OEt)_3$ in DMF[79,144-151] or DMA[152-155] with conc. hydrochloric acid as catalyst followed by acidic hydrolysis of the Cl-group. The ring closure reaction has also been carried out without solvent,[156,157] except for an excess of $HC(OEt)_3$. In one case[158] $(EtO)_2CHOAc$ - without conc. hydrochloric acid - has been used as reagent and solvent instead of $HC(OEt)_3$. The method is mild and the yields are usually high and only the 9-isomer is formed.



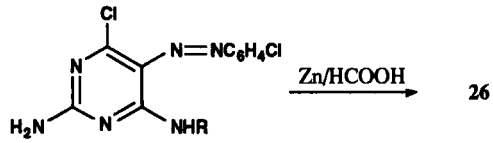
26 **27**

Two main methods, A[79,144-151,156-158] and B[152-154,159] have been used to prepare **26**:

Method A:



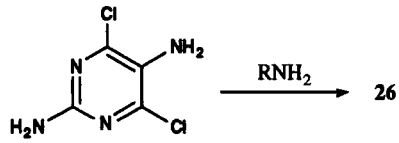
28 **29**



26

30

Method B:

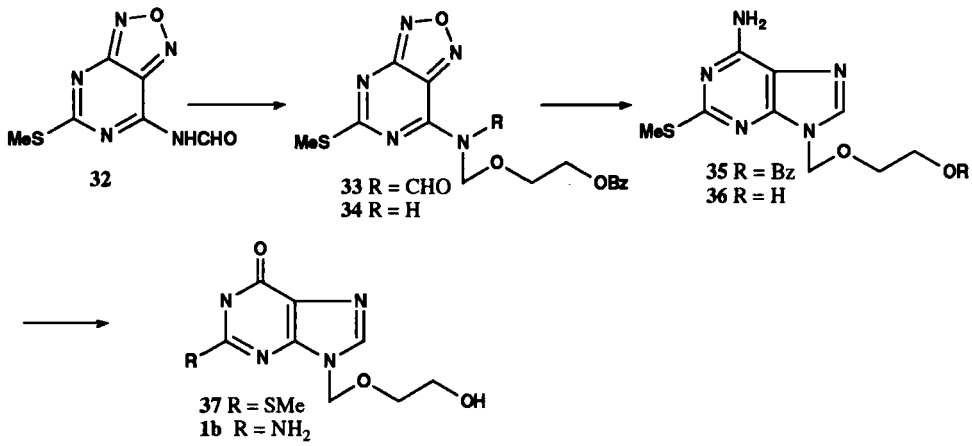


26

31

4. From Furazanopyrimidines

Kelly *et al.*[160] have described an eight step synthesis of acyclovir **1b** and analogues from 7-formamidofurazanopyrimidine **32**:



32

33 R = CHO
34 R = H

35 R = Bz
36 R = H

37 R = SMe
1b R = NH_2

Alkylation of **32** with 2-(benzoyloxy)ethoxymethyl chloride in DMF in the presence of Et_3N gave **33** and **34**. The mixture was reformylated with acetic formic anhydride to give **33**. Deformyla-

tion of **33** afforded **34**. Reductive cleavage of the furazan ring with zinc dust in acetic acid followed by cyclization and hydrolysis gave **36**. The 6-amino group of **36** was transformed with $NaNO_2$ in AcOH to give **37**. Subsequent amination with ammonia in ethanol gave **1b**.

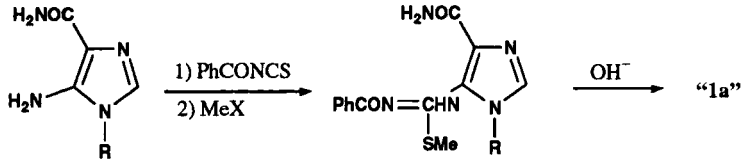
C. SYNTHESIS FROM IMIDAZOLES

Until recently only the cyclization *via* the commercially available AICA-riboside (5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide) or derivatives to guanosine **1a** had been described. The pioneers in this area - Yamazaki *et al.* - have developed two types of ring closure to guanosine (The Yamazaki Ring Closure A[161] and B[162-164]). They have also written a review article on the subject[8] covering the literature up to 1978. Therefore the Yamazaki methods will only be discussed briefly.

The Gea group has developed a general method[165] for the synthesis of 9-substituted guanines from 1-substituted AICA-compounds.

1. *via* Thiocarbamoylamino Imidazoles

The Yamazaki ring closure A[161] is shown in the scheme below:

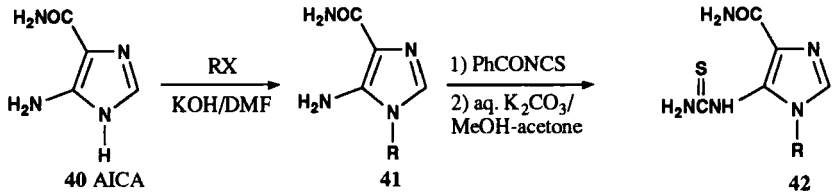


38 **39**

R = Ribosyl or isopropyleneribosyl

In an earlier work Yamazaki *et al.*[166] converted **39** to the guanidine derivative with ammonia before the ring closure. Variations of the above method have been described.[161,167-168] A ring closure, where R is a carbocyclic ring has also been carried out.[169,170]

The Gea ring closure[165]: The Gea group has recently developed a general method for the preparation of 9-substituted guanines:



40 AICA **41** **42**

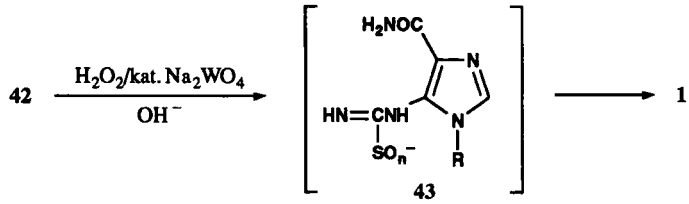
R = e. g. alkyl, benzyl, $CH_2OCH_2CH_2OR^1$, ribosyl

Heavy metal salt / OH^- → **1**

AICA **40** was 1-alkylated in DMF with KOH powder as the base. Treatment of the product **41** with benzoyl isothiocyanate in acetone, followed by hydrolysis afforded the thiourea compound **42** in

high yield. The key step, ring closure of the thiourea compound, was carried out in the presence of 1 equivalent of heavy metal ion (preferable Cu^{++}) in excess aq. NaOH. The yields were high (61-96%) and only the 9-isomer was formed.

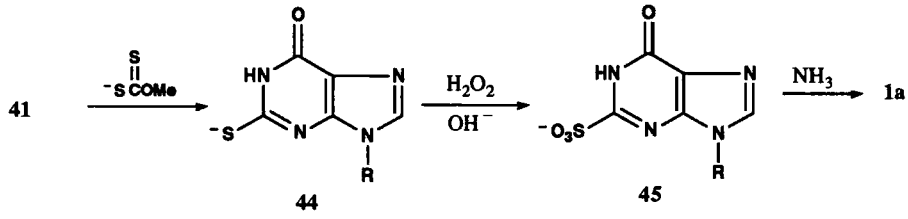
The ring closure of **42** could also be performed by oxidation with hydrogen peroxide in aq. NaOH,[165] but in this case the yields were lower (34-55%).



n = 2 or 3

2. *via* 2-Mercaptopurines

The Yamazaki ring closure B[162-164] is shown in the scheme below:



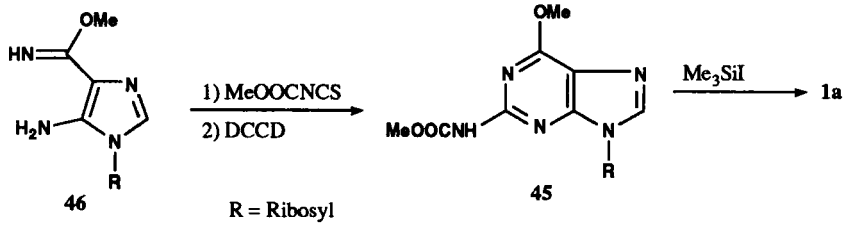
R = Ribosyl or isopropyleneribosyl

In one example,[162] **44** was S-methylated and oxidized with N-chlorosuccinimide to the methylsulphonate derivative, which was converted to guanosine **1a** with ammonia. Gosselin *et al.*[132,171] have synthesized α-guanosine by using the above ring closure B.

3. Other Ring Closure Methods

Townsend *et al.*[172,173] have developed two different ring closure methods (methods 1 and 2) for the preparation of guanosine **1a**:

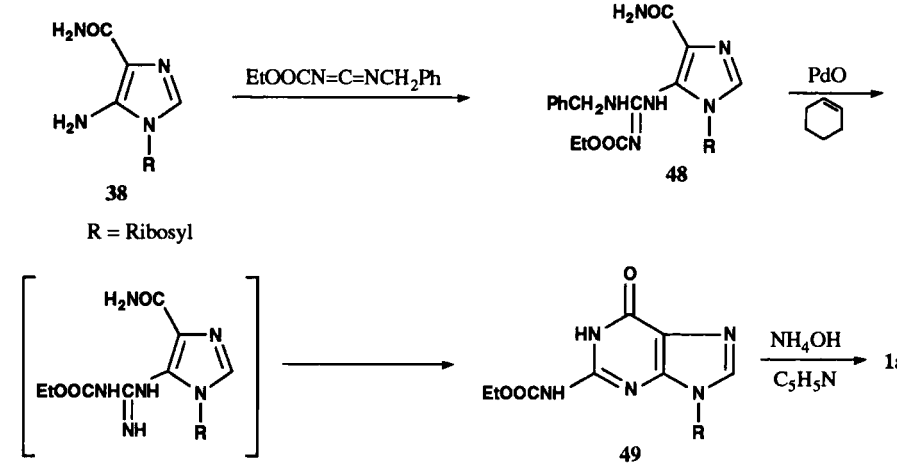
Method 1:[172]



R = Ribosyl

Methyl 5-amino-1-β-D-ribofuranosylimidazole-4-carboximidate **46** was treated with methoxycarbonyl isothiocyanate followed by DCC to give the purine ring **47** which was deprotected with iodotrimethylsilane to afford guanosine **1a**.

Method 2:[173]

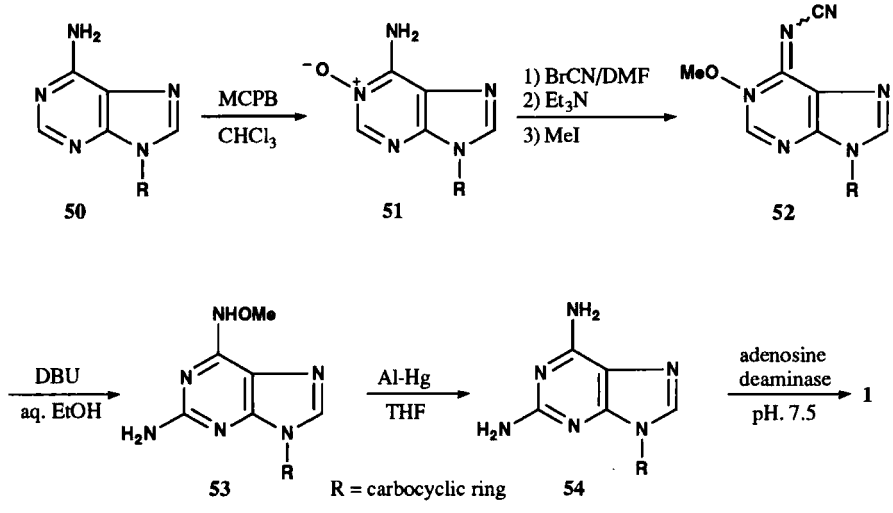


AICA-riboside **38** was treated with 1-(ethoxycarbonyl)-3-benzylcarbodiimide. By debenzylation of the resulting benzyl guanidine **48** with cyclohexene-PdO in refluxing EtOH ring closure took place and the N2-ethoxycarbonylguanosine **49** could be obtained. Deprotection with aq. ammonia in pyridine afforded guanosine.

D. OTHER METHODS

1. Interconversion of Adenines to Guanines

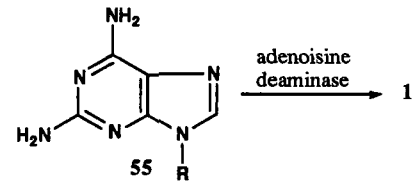
The Glaxo chemists have developed a general method (with several variations) for the interconversion of 9-substituted adenine to 9-substituted guanine[174,175]. One variant[175] is given in the scheme below:



The yields are high for each step. The above method is a modification of an adenosine-guanosine interconversion developed and described by Ueda *et al.*[176,177]

2. Enzymatic Transformations

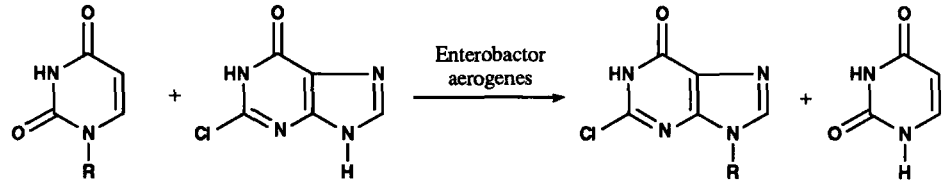
Enzymatic transformation of 9-substituted 2,6-diaminopurines **55** to 9-substituted guanines with adenosine deaminase has been carried out with R as glycosyl,[96] methyl(hydroxyethyl) ether (to acyclovir)[3,127] and as carbocyclic group.[175,178]



55

In a similar way 2',3'-dideoxyguanosine was obtained from the corresponding 2-amino-6-chloropurine by use of adenosine deaminase.[179]

Morisawa *et al.*[180] have described an enzymatic trans-arabinosylation between 2-chlorohypoxanthine **57** and 1-β-D-arabinofuranosyluracil **56** to 9-β-D-arabinofuranosyl-2-chlorohypoxanthine **58**, which was chemically converted to 9-β-D-arabino-furanosylguanine.



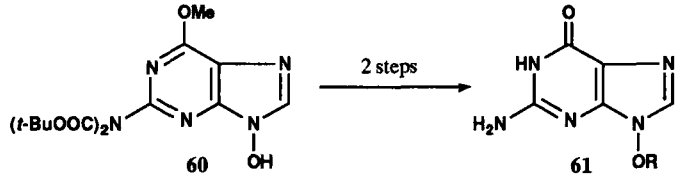
56 **57** **58** **59**

II. 9-*O*-SUBSTITUTED GUANINES

Until very recently 9-alkoxyguanines have been shown little attention. But Beecham's discovery of the antiviral effect of some 9-(mono- and dihydroxy-alkoxy)guanines has resulted in a seris of articles on the subject.

A. SYNTHESIS FROM 9-HYDROXYGUANINES

Harnden and Wyatt[181] have described a synthesis of 9-alkoxyguanine from a protected 9-hydroxyguanine:



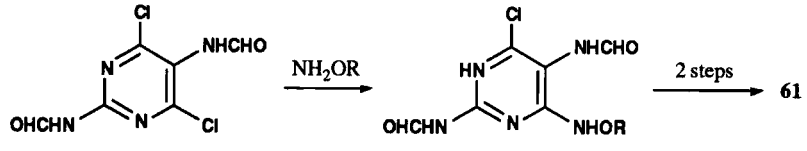
60 **61**

2-Amino-9-hydroxy-6-methoxypurine and the 2-(bis-t-butoxy-carbonyl)derivative **60** (obtained from 4,6-dichloro-2,5-diformamidinopyrimidine *via* the corresponding 2-amino-9-benzyloxy-6-methoxypurine) underwent O-alkylation under base catalyzed conditions (e.g., K_2CO_3/DMF) with an alkyl halide. **60** could also be coupled with an alcohol in THF in the presence of Pph_3 and

DEAD to give the protected 9-alkoxy derivative in 89% yield. Deprotection by reflux in 5M hydrochloric acid in ethanol gave the corresponding 9-alkoxyguanine **61**.

B. SYNTHESIS FROM PYRIMIDINES

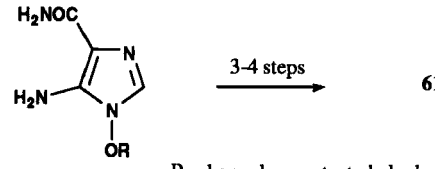
Harnden and Wyatt[182-184] have also developed a synthesis from 4,6-dichloro-2,5-diformamidinopyrimidine **62**, which was reacted with an alkoxyamine to give **63**. Cyclization of **63** by heating with diethoxymethyl acetate afforded the 9-alkoxy-6-chloropurine, which was converted to the corresponding guanine **61** by reflux with 80% formic acid.



62 **63** R = alkene or protected alcohol

C. SYNTHESIS FROM IMIDAZOLES

The Yamazaki ring closure A (see Sec. I.C.1.) has been employed in the synthesis of 9-alkoxyguanines:[182,185]

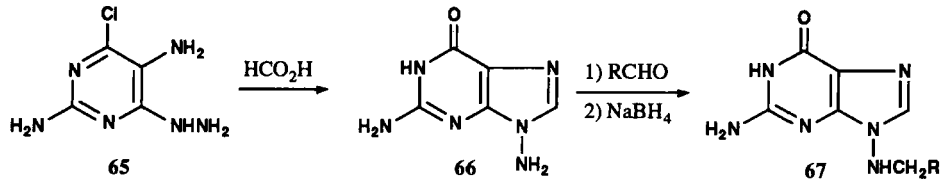


64 R = benzyl or protected alcohol

64 could be obtained from ethyl N-benzyloxy formimidate and 2-amino-2-cyanoacetamide[185] or from alkoxyamine and ethyl N-[(carbamoylcyano)methyl]formimidate.[182]

III. 9-*N*-SUBSTITUTED GUANINES

Only one article has been found concerning preparation of guanine with a 9-amino substituent: Harnden *et al.*[186] The synthesis was carried out by ring closure of the five-membered ring:



65 R = protected alcohol **66** **67**

Treatment of the above hydrazinopyrimidine **65** with refluxing formic acid afforded 9-aminoguanine **66** in 30-40% yield. N-alkylation was carried out by condensing with an aldehyde followed by reduction of the formed imino group with $NaBH_4$ to afford **67**.

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