On the Syntheses of 8-Heteroaryl-substituted 9-(β-D-Ribofuranosyl)-2,6-diaminopurines through Pd-Catalyzed Coupling in the Presence of Cupric Oxide

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Convenient methods for the preparation of 9-(β-D-ribofuranosyl) derivatives of 8-(2- and 3-thienyl)-2,6-diaminopurine and of 8-(2- and 3-furyl)-2,6-diaminopurine, which are potential antiviral agents has been worked out. The key step was a Pd(0)-catalyzed Stille coupling between 2- and 3-tributylstannylthiophene and 2- and 3-tributylstannylfuran and trimethylsilyl protected 9-(β-D-ribofuranosyl)-2,6-diamino-8-bromopurine. The use of *N,N*-dimethylformamide as solvent at 110° and dichloro(diphenylphosphinepropane)palladium(II) [$PdCl_2$(dppp)] with cupric oxide as co-reagent was essential in order to obtain a fast reaction and high yields.

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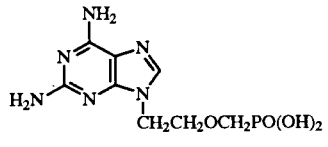
Introduction.

Nucleosides with a modified purine moiety are of interest in connection with their possible biological activity within the context of antiviral therapeutic agents. Modifications in the 8-position is of particular interest, because it influences strongly the syn/anti conformation of the nucleosides [2]. In several publications the alkylation at the C-8 position through palladium-catalysed couplings of 8-halo derivatives with tetralkyltin derivatives has been described [3-6], but to our knowledge no arylations have been carried out. In a recent paper a very convenient one-pot method consisting in *in situ* protection of the 8-bromo derivative with trimethyl silyl groups, followed by Pd(0)-catalyzed coupling with tetraalkyltin derivatives has been described [7]. Deprotection was achieved by treatment with potassium carbonate in methanol.

In connection with our interest in heteroaryl substituted nucleosides with potential antiviral properties, we have synthesized and studied 2-heteroaryl substituted adenosines and an 8-heteroaryl substituted guanosines [8]. They were prepared in high yields through Pd(0)-catalyzed couplings of 2-iodo- and 8-bromo derivatives with heteroaryl tin derivatives. Furthermore we have prepared and studied 5-heteroaryl substituted deoxyuridines and deoxycytidines [9-11] as well as arabinouracil- and cytosin derivatives [12].

During recent years great attention has been focused on several derivatives of 2,6-diaminopurines such as the acyclic [9-(2-phosphonylmethoxyethyl)-2,6-diaminopurine (PMEDAP) (**1**) [13], 9-(2'-3'-dideoxy-β-D-ribofuranosyl)-2,6-diaminopurine (ddDAPR) (**2**) [14], and the two carbocyclic analogues, (±)-*cis*-[4'-(2,6-diamino-9*H*-purin-9-yl)-2-cyclopentenyl]carbinol (C-D4DAP) (**3**) [15] and (±)-*cis*-[3'-(2,6-diamino-9*H*-purin-9-yl)cyclopentyl]-carbinol (C-DAP) (**4**) [15] have been proven to be potent inhibitors of HIV replication. It has also been found that



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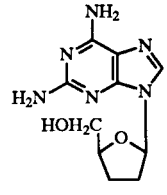

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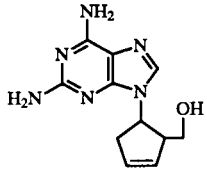

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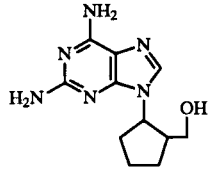

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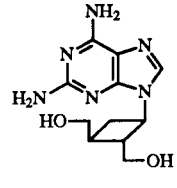

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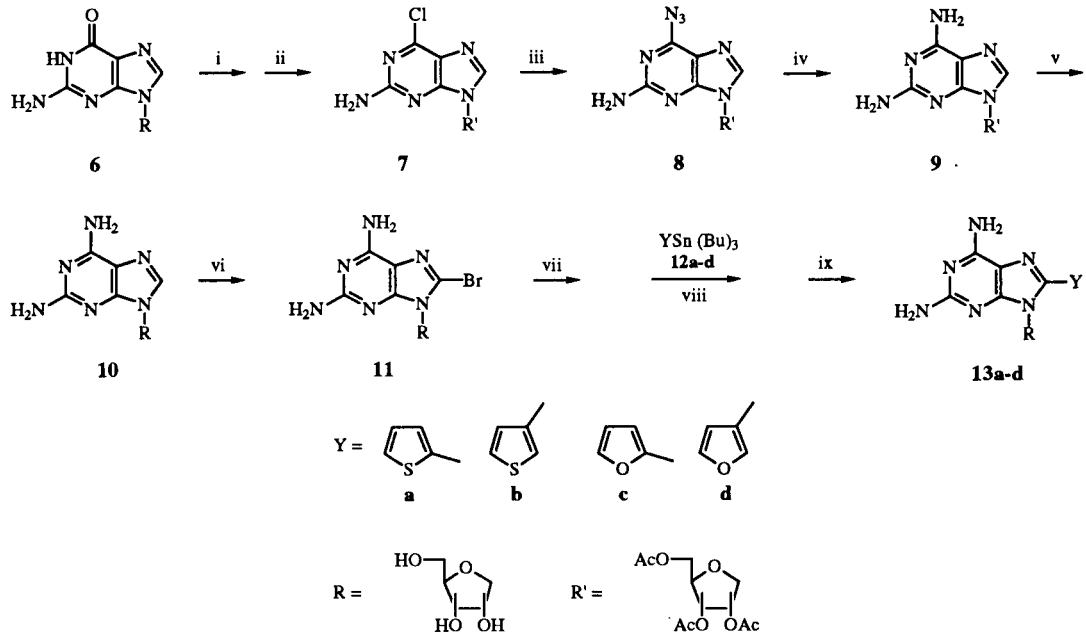
the 2-amino derivative of (±)-9-[2',3'-bis(hydroxymethyl)-1'-cyclobutyl]adenine (cyclobut A) (**5**), exert an antiviral activity against HIV (**5**) [16].

In the present paper the preparation of the 9-(β-D-ribofuranosyl) derivatives of 8-(2- and 3- thienyl)-2,6-diaminopurine and of 8-(2- and 3-furyl)-2,6-diaminopurine will be described.

Chemistry.

Starting from guanosine (**6**), 9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-2-amino-6-chloropurine (**7**) was prepared, which then through reaction with sodium azide in the presence of catalytic amounts of triethyl amine in acetonitrile was converted to the corresponding azide (**8**). 9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-diaminopurine (**9**) was then obtained by catalytic hydrogenation over palladium on carbon [17]. Deacetylation with methanolic ammonia gave the desired 9-(β-D-ribofuranosyl)-2,6-diaminopurine (**10**).

Bromination of **10** with saturated bromine-water in sodium acetate buffer, which has successfully been used for the bromination of adenosine and its 5'-phosphate [18]



i, Ac_2O, pyridine, DMF, Δ; ii, $POCl_3$, Me_2NPh, Et_4NCl, MeCN, Δ; iii, NaN_3, MeCN; iv, H_2/Pd-carbon; v, NH_3/MeOH; vi, NBS/H_2O; vii, HMDS, pyridine, $(NH_4)_2SO_4$, Δ; viii, see Table 1; ix, K_2CO_3, MeOH.

could not be used, as cleavage of the glycosidic bond occured giving a complex reaction product. Studies on the bromination of guanosine and guanine indicated that the 2,6-diaminopurine ring can also be destroyed under these reaction conditions [19]. An improved method for the synthesis of 8-bromo-2'-deoxyguanosine consisting in bromination with *N*-bromosuccinimide in water has recently been published [20]. We found that if aqueous *N*-bromosuccinimide is used at room temperature and the reaction time restricted to five minutes, 9-(β-D-ribofuranosyl)-2,6-diamino-8-bromopurine (**11**) could be obtained in a yield of 71% and only minor cleavage of the glycosidic bond occured. If the reaction with *N*-bromosuccinimide was carried out in an organic solvent, such as methylene chloride, at room temperature for 12 hours or at reflux the bromo derivative was formed slowly and in low yield and was contaminated with several byproducts. Compound **11** has also been prepared from 8-bromoguanosine [21]. Our method, however, avoids the use of high-pressure equipment. In addition compound **7** was available from a previous project [8].

We first attempted the one-pot procedure used for the preparation of 8-alkyl-substituted derivatives [7]. However, in our couplings with the heteroaryl stannanes only very low yields were obtained, probably depending upon the fact that the long reaction times neccessary caused self coupling of the tributylstannyl aryl compounds, debromination of the 2,6-diaminopurine riboside and cleavage of the glycosidic bond.

Recently, we have found a dramatic increase in yields and rates of the Stille coupling by using cupric oxide in stoichiometric amounts as co-reagent [22]. Cupric oxide was also found to be more effective with low yielding sluggish Stille reactions, than the previously used silver(I) oxide [23,24]. This methodology has also been succesfully applied in the synthesis of the twelve isomeric thieno(b)naphthyridines [25] and benzo[*c*]naphthyridines [26].

Carrying out the Pd-catalyzed coupling of **11**, using five equivalents of 2- and 3-tributylstannylthiophene and 2- and 3-tributylstannylfuran [10] using $PdCl_2(PPh_3)_2$ as catalyst in refluxing tetrahydrofuran, gave after 20-40 hours, the 8-heteroaryl derivatives **13a-d** in only 30-40% yield after deprotection of the trimethylsilyl groups with potassium carbonate in methanol at room temperature [7]. To improve the result we tried to promote the coupling reaction through the addition of cupric oxide as co-reagent [22]. When $PdCl_2$(dppb) was used as catalyst and cupric oxide as co-reagent in refluxing tetrahydrofuran the reaction did not proceed. Finally, changing the solvent to *N,N*-dimethylformamide and raising the temperature to 110°, as used by Gronowitz *et al.* [26] lead in the presence of cupric oxide to a fast reaction giving after two to three hours compounds **13a-d** in more than 80% yield after deprotection. The reaction time could be reduced further when $PdCl_2$(dppp) and cupric oxide as co-reagent was used. Under these reaction conditions only two equivalents of the tin reagent was needed. The yield was also improved to more than 80% (*cf.* Table 1).

Table 1

Reaction Conditions for Optimizing the Coupling Reaction Between the Heteroarylstannyl Compounds **12a-d** and Trimethylsilyl Protected 2,6-Diamino-8-bromopurine Ribofuranoside

Compound	Amount equivalent	Catalyst/ co-reagent	Solvent	Temp°	Reaction time (h)	Yield (%)
12a	5	$PdCl_2(PPh_3)_2$	THF	66	20	31
12b	"	"	"	66	40	40
12c	"	"	"	66	20	43
12d	"	"	"	66	20	39
12a	"	$PdCl_2$(dppb) CuO	"	66	3.0	---
12a	"	"	DMF	110	2.0	84
12b	"	"	"	100	3.5	28
12b	"	"	"	110	3.0	82
12c	"	"	"	110	3.0	81
12d	"	"	THF	66	3.0	---
12d	"	"	DMF	110	3.0	84
12a	2	$PdCl_2$(dppp) CuO	"	110	3/4	83
12c	"	"	"	110	1.0	85

The results of the antiviral tests for compounds **13a-d** as well as the acetyl protected ones are given elsewhere [8].

EXPERIMENTAL

Melting points are uncorrected. The ^1H nmr spectra were recorded on a Varian XL-300 spectrometer. The mass spectra were recorded on a JEOL-JMX-SX 102 spectrometer. Column chromatography was carried out using Merck silica gel 60. Elemental microanalyses were performed at Dornis and Kolbe, Mikroanalytisches Laboratorium, Mülheim a. d. Ruhr, Germany. Tetrahydrofuran (THF) was dried by refluxing and distillation over sodium wire. Pyridine was distilled and stored over 4 Å molecular sieves. All other solvents were distilled prior to use.

9-(β-D-Ribofuranosyl)-2,6-diamino-8-bromopurine (**11**).

A suspension of 277 mg (0.98 mmole) of 9-(β-D-ribofuranosyl)-2,6-diaminopurine (**10**) and 261.6 mg (1.47 mmoles) of *N*-bromosuccinimide in 2.3 ml of water was stirred at room temperature for five minutes. The solvent was removed *in vacuo* and the crude product was chromatographed using dichloromethane/methanol (9:1) as eluent to give 250 mg (71%) of the title compound, mp 231° dec; ^1H nmr (deuteriated dimethyl sulfoxide): δ 6.99 (s, 6-NH_2), 5.76 (s, 2-NH_2), 5.70 (d, 1H, H1', J = 7.0 Hz), 5.02 (dd, 1H, H2', J = 7.0 Hz), 4.12 (dd, 1H, H3'), 3.91 (dd, 1H, H4'), 3.70-3.47 (m, 2H, 5'-CH_2); ms: Calcd. for $C_{10}H_{13}O_4N_6Br$: hrms MW, 360.0182. Found: (M+1) 361.0263. Known compound [21].

General Procedure for Preparation of 9-(β-D-Ribofuranosyl)-8-(heteroaryl)-2,6-diaminopurine.

A suspension of 50.0 mg (0.138 mmole) of **11**, 5.0 ml of hexamethyldisilazan, 0.50 ml of anhydrous pyridine, in the presence of a catalytical amount of ammonium sulphate was refluxed under nitrogen for 4 hours. The volatiles were removed *in vacuo* to give the trimethylsilyl-protected nucleoside, which was used in the next step without further purification. The protected nucleoside was dissolved, the appropriate tributylstannyl arene **12a-d** and the catalyst/co-reagent was added. The reaction mixture was heated under nitrogen and when no starting material remained (checked by thin-layer chromatography), the solvent was removed *in vacuo*.

The trimethylsilyl groups were removed by treatment with potassium carbonate in methanol for 5 hours. The solvent was removed *in vacuo* and the residue chromatographed using a gradient of dichloromethane/methanol (99:1-9:1) as eluent. For the amount of the tributylstannyl arenes, catalyst, solvents, the reaction time used, and yields see Table 1.

9-(β-D-Ribofuranosyl)-8-(2"-thienyl)-2,6-diaminopurine (**13a**).

This compound had mp 120-122°; ^1H nmr (deuteriated dimethyl sulfoxide): δ 7.76 (dd, 1H, H5", J = 5.1, 1.1 Hz), 7.51 (dd, 1H, H3", J = 3.7, 1.1 Hz), 7.23 (dd, 1H, H4", J = 5.1, 3.7 Hz), 7.00 (s, 6-NH_2), 5.89 (d, 1H, H1', J = 7.1), 5.71 (s, 2-NH_2), 5.14 (m, 1H, H2', J = 7.1 Hz), 4.13 (m, 1H, H3'), 3.94 (dd, 1H, H4'), 3.70-3.55 (m, 2H, 5'-CH_2).

Anal. Calcd. for $C_{14}H_{16}O_4N_6S$: C, 46.15; H, 4.43; MW, 364.0954. Found: C, 46.10; H, 4.29; (M+1) 365.1032.

9-(β-D-Ribofuranosyl)-8-(3"-thienyl)-2,6-diaminopurine (**13b**).

This compound had mp 244° dec; ^1H nmr (deuteriated dimethyl sulfoxide): δ 7.91 (dd, 1H, H2", J = 3.0, 1.2 Hz), 7.74 (dd, 1H, H5", J = 5.0, 3.0 Hz), 7.45 (dd, 1H, H4", J = 5.0, 1.2 Hz), 6.96 (s, 6-NH_2), 5.79 (d, 1H, H1', J = 7.3), 5.64 (s, 2-NH_2), 5.07 (m, 1H, H2', J = 7.3 Hz), 4.11 (m, 1H, H3'), 3.92 (dd, 1H, H4'), 3.69-3.55 (m, 2H, 5'-CH_2).

Anal. Calcd. for $C_{14}H_{16}O_4N_6S$: C, 46.15; H, 4.43; N, 23.06; MW, 364.0954. Found: C, 45.95; H, 4.28; N, 22.88; (M+1) 365.1023.

9-(β-D-Ribofuranosyl)-8-(2"-furyl)-2,6-diaminopurine (**13c**).

This compound had mp 236° dec; ^1H nmr (deuteriated dimethyl sulfoxide): δ 7.92 (dd, 1H, H5", J = 1.8, 0.8 Hz), 7.04 (s, 6-NH_2), 6.96 (dd, 1H, H3", J = 3.5, 0.8 Hz), 6.71 (dd, 1H, H4", J = 3.5, 1.8 Hz), 5.97 (d, 1H, H1', J = 7.0), 5.72 (s, 2-NH_2), 5.06 (m, 1H, H2', J = 7.0 Hz), 4.14 (m, 1H, H3'), 3.95 (dd, 1H, H4'), 3.70-3.50 (m, 2H, 5'-CH_2).

Anal. Calcd. for $C_{14}H_{16}O_5N_6$: C, 48.28; H, 4.63; N, 24.13; MW, 348.12. Found: C, 48.16; H, 4.61; N, 23.96; MW, 348.

9-(β-D-Ribofuranosyl)-8-(3"-furyl)-2,6-diaminopurine (**13d**).

This compound had mp 188-191°; ^1H nmr (deuteriated dimethyl sulfoxide): δ 8.12 (dd, 1H, H2", J = 1.5, 0.8 Hz), 7.86 (t, 1H, H5", J = 1.8, 1.5 Hz), 6.95 (s, 6-NH_2), 6.86 (dd, 1H, H4", J = 1.8, 0.8 Hz), 5.76 (d, 1H, H1', J = 7.3), 5.63 (s, 2-NH_2), 5.02 (m, 1H, H2', J = 7.3 Hz), 4.12 (m, 1H, H3'), 3.94 (dd, 1H, H4'), 3.70-3.55 (m, 2H, 5'-CH_2).

Anal. Calcd. for $C_{14}H_{16}O_5N_6$: C, 48.28; H, 4.63; N, 24.13; MW, 348.12. Found: C, 47.97; H, 4.46; N, 23.61; MW, 348.

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