Pergamon

Tetrahedron 58 (2002) 7431–7435

TETRAHEDRON

Covalent analogues of DNA base-pairs and triplets. Part 3: Synthesis of 1,4- and 1,3-bis(purin-6-yl)benzenes and 1-(1,3-dimethyluracil-5-yl)-3 or 4-(purin-9-yl)benzenes☆

Martina Havelková,[a] Dalimil Dvořák[a,*] and Michal Hocek[b,*]

[a]*Department of Organic Chemistry, Prague Institute of Chemical Technology, CZ-16628 Prague 6, Czech Republic*
[b]*Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, CZ-16610 Prague 6, Czech Republic*

Received 15 April 2002; revised 17 June 2002; accepted 11 July 2002

Abstract—The Stille cross-coupling reactions of 1,4- and 1,3-bis(trialkylstannyl)benzenes **2** or **3** with 9-benzyl-6-chloropurine (**1**) led either to mono-coupled 4- or 3-[(tributylstannyl)phenyl]benzenes **5a** and **5b** or to bis(9-benzylpurin-6-yl)benzenes (**4a** or **4b**) depending on the ratio of the starting compounds, nature of the stannane and conditions. Analogous reaction of **1** with benzene-1,4-diboronic acid gave selectively **4a** in good yield. The reaction of stannanes **5** with 1,3-dimethyl-5-iodouracil gave 1-(9-benzylpurin-6-yl)-4- or -3-(1,3-dimethyluracil-5-yl)benzenes (**10a** and **10b**) in low yields. Compounds **4** and **10** are novel types of covalently linked analogues of nucleobase-pairs.

1. Introduction

The effect of many clinically used antitumor agents is based on DNA cross-linking[1] or on intercalation[2] to DNA. Numerous models and analogues of Watson–Crick base-pairs consisting of annelated[3] or cross-linked[4] purine and pyrimidine heterocycles or even more simple aromatic rings[5,6] have been prepared. Such base-pairs/triplets analogues may interact with DNA (e.g. by intercalation); if incorporated into single stranded DNA, they are complementary to the abasic site of a damaged DNA strand; or alternatively, if incorporated to the duplex, they form permanent cross-links.

A number of diverse purine–purine conjugates containing linkage (9–9, 8–8, 9–8, 9–7, 9–6 and 6–6) of various lengths, including double- and triple-linked purinophanes, have been prepared[7] in order to study the π–π stacking of purine bases. The purine–purine dimers with a 6,6′-pyridine-2,6-bis(carboxamido) linker have been recently prepared[8] to study its H-bonding properties as potential artificial receptors. Methylene N^6,$N^{6'}$-linked-adenine–adenine dimers are formed by the reaction of carcinogenic formaldehyde with DNA, which was proved by independent synthesis[9] of the products. A variety of other N^6,$N^{6'}$-linked-adenine–adenine dimers, trimers and tetramers with the linkers of various lengths were prepared[10] and exhibited diverse types of biological activity (inhibition of adenosine kinase, ribosomal peptidyltransferase, etc.).

Very recently, we have prepared[11] various purine dimers linked through positions 6 and 6′ by acetylene, diacetylene, vinylene and ethylene linkers. Such carbon linkers connected to carbon atoms of the heterocycles were expected to be stable towards enzymatic degradation. Significant cytostatic activity has been found[11] in some bis(purin-6-yl)acetylenes and diacetylenes, while the partially and fully saturated derivatives were inactive. Also inactive were 1,3,4- and 1,3,5-tris(purin-6-yl)benzenes recently prepared[12] as analogues of Hoogsteen triplets. Taking into account the high cytostatic activity of 6-arylpurine ribonucleosides,[13] we have decided to prepare a new type of base-pair analogue consisting of purine dimers as well as purine–pyrimidine conjugates connected by *meta*- or *para*-phenylene linkers. Their synthesis is the subject of this paper.

2. Results and discussion

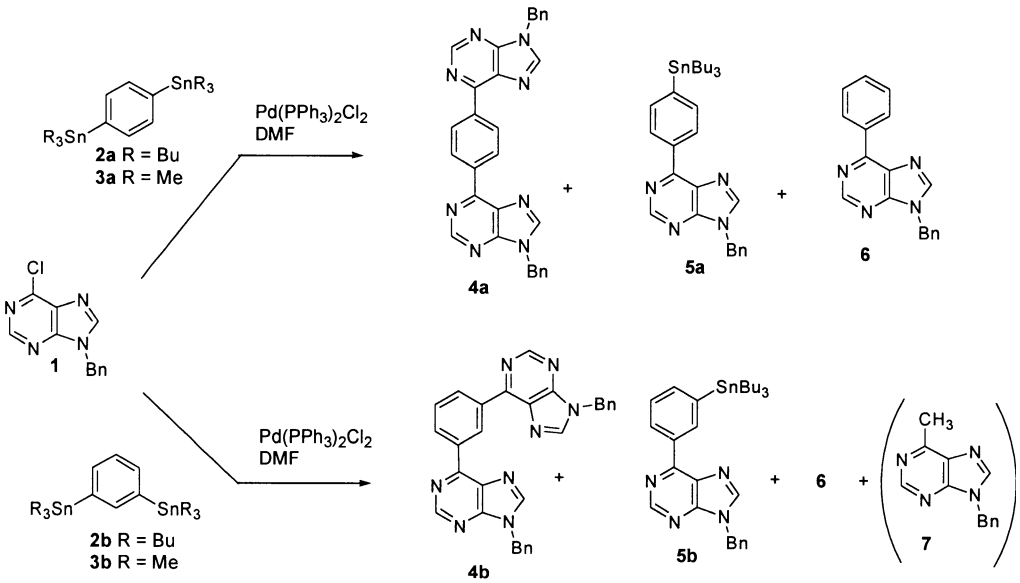
Cross-coupling reactions of 6-halopurines with aryl organometallics (arylmagnesium halides,[14] arylzinc halides,[15] arylstannanes[15] or arylboronic acids[13,16]) are very efficient methods for the preparation of 6-arylpurines. Therefore, the double cross-coupling reactions of phenylenebis(metallics) were the method of choice for the synthesis of the title compounds. Considering the lower stability of the corresponding phenylenebis(magnesium or zinc halides), we have chosen easily available 1,4- and 1,3-bis(trialkylstannyl)-benzenes as key starting compounds.

☆ For Part 2 see Ref. 11.

Keywords: purines; nucleobases; cross-coupling; stannanes.

* Corresponding authors. Tel.: +420-2-20183324; fax: +420-2-33331271; e-mail: dvorakd@vscht.cz; hocek@uochb.cas.cz

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00833-5



Scheme 1.

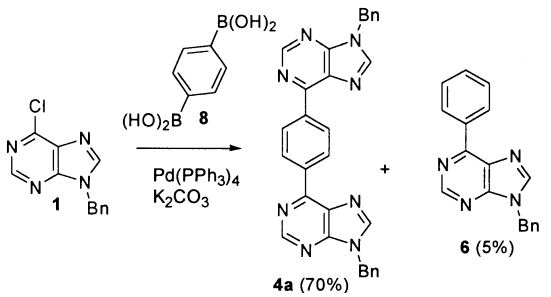
Thus, reactions of 9-benzyl-6-chloropurine (**1**) with 1,4- and 1,3-bis(tributylstannyl)benzenes (**2a** and **2b**) as well as with 1,4- and 1,3-bis(trimethylstannyl)benzenes (**3a** and **3b**) were studied (Scheme 1). In general, three types of products were obtained: the desired 1,4- or 1,3-bis(9-benzylpurin-6-yl)benzenes (**4a** or **4b**), 6-[4- or 3-(tributylstannyl)phenyl]-purine (**5a** or **5b**) as products of mono-coupling and 9-benzyl-6-phenylpurine (**6**) as the product of reductive destannylation of **5**. The ratio of the products strongly depended on the ratio of starting compounds, the nature of the stannane and the reaction conditions (Table 1). Several catalytic systems have been tested in the model reactions of **1** with **2a** and **2b** and, interestingly, only the reactions in presence of $Pd(PPh_3)_2Cl_2$ in DMF or NMP gave the double-coupling products **4**. Other catalysts, i.e. $Pd(PPh_3)_4$, $Pd_2(dba)_3/AsPPh_3$, $Pd_2(dba)_3/P(o\text{-tolyl})_3$, $Pd(dppf)Cl_2$, did not work at all or gave only low yields of mono-coupled products **5** and **6**. Reactions in NMP were somewhat faster than in DMF but due to easier and more efficient isolation of products, the latter solvent was used in preparative experiments. Addition of CuI accelerated the second coupling: no mono-coupled stannanes **5** were detected but the preparative yields of the bis(purinyl)benzenes **4** were only slightly improved (Table 1, entries 2 and 5) and the isolation of products was complicated by some iodine-containing by-products. Other additives (LiCl, $ZnCl_2$, $ZnBr_2$ or Cu_2O) were less effective or ineffective. While the reactions of bis(tributylstannyl)benzenes **2** gave mixtures of mono- and bis-coupled products **4** and **5**, the use of more reactive bis(trimethylstannyl)benzenes (**3a** and **3b**) gave the bis(purinyl)benzenes **4a** and **4b** in higher yields of 71 and 43%, respectively (Table 1, entries 7 and 8) accompanied by lower amounts of 6-phenylpurine **6** (no traces of the mono-stannanes **5** were detected). In the case of reaction of **1** with 1,3-bis(trimethylstannyl)benzene (**3b**), 9-benzyl-6-methylpurine (**7**, apparently product of methyl transfer from stannane) was isolated as major by-product. Its formation might be explained by a more sterically crowded transition state of the coupling in the case of the 1,3-disubstituted benzene. From these findings, two preparative methods could be formulated: (i) the reactions of bis(trimethylstannyl)benzenes **3** with 6-chloropurine **1** in a 1:2 ratio gives in reasonable yields and good selectivity the bis(purin-6-yl)benzenes **4a** or **4b** (Table 1, entries 7 and 8); (ii) the reactions of bis(tributylstannyl)benzenes **2** with 6-chloropurine **1** in a 2:1 ratio gives the [(tributylstannyl)-phenyl]purines **5a** or **5b** as major products in 65 and 69%, respectively (Table 1, entries 3 and 6).

Another possible approach to the title bis(purin-6-yl)benzenes could be the use of the Suzuki cross-coupling reaction of benzenediboronic acids with 6-halopurines. Due to the

Table 1. Reactions of purine **1** with stannanes **2** or **3**

Entry	Stannane	Ratio **2**(**3**)/**1**	Reaction time	Additive	Yields of products (%)		
					4	**5**	**6**
1	**2a**	1:2	19	–	33	23	25
2	**2a**	1:2	19	CuI	35	0	25
3	**2a**	2:1	16	–	31	65	Traces
4	**2b**	1:2	17	–	29	34	34
5	**2b**	1:2	17	CuI	44	0	34
6	**2b**	2:1	20	–	30	69	Traces
7	**3a**	1:2	9	–	71 (41)[a]	–	25
8	**3b**	1:2	15	–	43 (27)[a]	–[b]	20

[a] In parentheses isolated yield after crystallization.
[b] 9-Benzyl-6-methylpurine (**7**) was isolated as major byproduct in 35% yield.

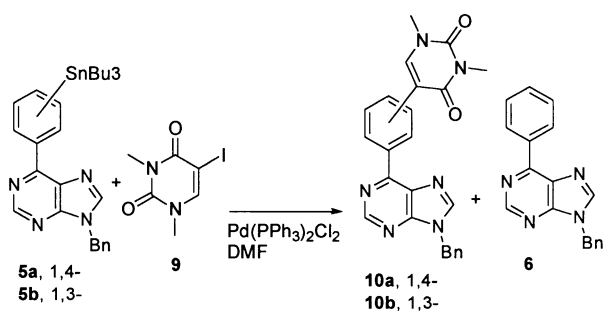


Scheme 2.

strong electron-withdrawing effect of the purine moiety and our previous finding[16a,b] that electron-poor arylboronic acids react with halopurines less efficiently (especially under anhydrous conditions), we expected that (if any) the mono-coupled products will be formed preferentially. However, the reaction of benzene-1,4-diboronic acid (**8**) with 6-chloropurine **1** in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in DME/H_2O proceeded very smoothly giving the 1,4-bis(9-benzylpurin-6-yl)benzene (**4a**) in a good yield of 70% (Scheme 2) accompanied by the 6-phenylpurine **6** as a minor by-product (5%). Interestingly, of the catalysts tested, $Pd(PPh_3)_4$ was the only one effective for this reaction, while, e.g. $Pd(PPh_3)_2Cl_2$ did not give any cross-coupling. When the reaction of chloropurine **1** with diboronic acid **8** in ratio 1:2 was attempted in order to isolate the mono-coupled product, an inseparable complex mixture of products has been obtained.

The formation of mono-coupled 4- or 3-[(tributylstannyl)-phenyl]benzenes **5a** and **5b** raised a possibility to synthesize another type of base-pair analogue: benzenes bearing two different nucleobases. Thus the stannanes **5a** and **5b** have been used for cross-coupling reactions with 1,3-dimethyl-5-iodouracil (**9**) in presence of $Pd(PPh_3)_2Cl_2$ in DMF (Scheme 3). The desired 1,4- and 1,3-hetero-disubstituted benzenes **10a** and **10b** were obtained in low yields of 20 and 19%, respectively. In both cases, the de-stannylated 6-phenylpurine **6** was the main product. No cross-coupling has been observed in the reaction of stannanes **5** with unprotected 5-iodouracil.

In conclusion, the methodology of Stille cross-coupling reactions of phenylenebis(stannanes) with 9-benzyl-6-chloropurine has been developed to prepare selectively either monocoupled 4- or 3-[(tributylstannyl)phenyl]benzenes **5a** and **5b** or bis(purin-6-yl)benzenes **4a** and **4b**. The disubstituted product **4a** could alternatively be prepared by analogous Suzuki–Miyaura coupling of benzene-1,4-



Scheme 3.

diboronic acid. The stannanes **5a** and **5b** could be used for another coupling with 1,3-dimethyl-5-iodouracil leading to the 1-(9-benzylpurin-6-yl)-4- or -3-(1,3-dimethyluracil-5-yl)benzenes (**10a** and **10b**) in low yields. Despite the low yields in the preparations of **10**, the homo- and hetero-disubstituted benzenes bearing two purine (compounds **4a** and **4b**) or one purine and one pyrimidine (compounds **10a** and **10b**) represent a novel type of covalently linked base-pair analogues. Preliminary cytostatic activity screening showed that, unlike the highly active bis(purin-6-yl)acetylenes and -diacetylenes, all the title phenylene linked base-pair models **4** and **10** were inactive. As the length of *para*-phenylene linker in compound **4a** is in between the acetylene and diacetylene, the absence of activity is little surprising and it might indicate that the acetylene- and diacetylene linkers in the original cytostatic compounds may form some covalent adducts with the target system (DNA or enzyme) that are excluded for the stable benzene derivatives. Application of the title novel methodology for the synthesis of analogous pairs of nucleosides is clearly an attractive new target and thus it will be the subject of our further investigations.

3. Experimental

Melting points were determined on a Kofler block and are uncorrected. NMR spectra were measured on a Varian Gemini 300 (^{1}H, 300.07 MHz; ^{13}C, 75.46 MHz), a Bruker AMX3 400 (^{1}H, 400.13 MHz and ^{13}C, 100.62 MHz) or a Bruker DRX 500 Avance (^{1}H, 500.13 MHz and ^{13}C, 125.77 MHz) spectrometer at 298 K. Unambiguous assignment of the NMR signals is based on $^{13}C\{^1H\}$, ^{13}C APT, COSY and ^{13}C HMBC spectra. IR spectra were recorded on Nicolet 750 FT-IR. Mass spectra were measured on ZAB-SEQ (VG Analytical) The solvents were dried and degassed by standard procedures, silica gel (ICN SiliTech, 32–63) was used for column chromatography. 9-Benzyl-6-chloropurine (**1**),[15d] 1,4-bis(trimethylstannyl)benzene (**3a**),[17] 1,3-bis(trimethylstannyl)benzene (**3b**)[17] and 1,3-dimethyl-5-iodouracil (**8**)[18] were prepared by the reported procedures. 1,4-Bis(tributylstannyl)benzene (**2a**), 1,3-bis(tributylstannyl)-benzene (**2b**) were prepared analogously to **3a** and **3b** and benzene-1,4-diboronic acid (**10**) was purchased from Lancaster. Known side-products **6** and **7** were identified based on comparison of their NMR and IR spectra with literature values.[15d]

3.1. Reactions of bis(trialkylstannyl)benzenes with 9-benzyl-6-chloropurine—general procedure

DMF (4 ml) was added to an argon purged flask containing 9-benzyl-6-chloropurine (**1**) (1–3 mmol), bis(trialkylstannyl)-benzene **2a**, **2b**, **3a** or **3b** (1–3 mmol), CuI (none or 0.2 mmol) and $Pd(PPh_3)_2Cl_2$ (134 mg, 0.19 mmol) and the mixture was stirred at 100°C for 9–20 h. After cooling to rt, the mixture was filtered through Celite and the Celite was washed with $CHCl_3$/MeOH (2:1). The collected fitrates were evaporated in vacuo and the residue was chromatographed on silica gel (100 g). At first the column was washed with light-petroleum and then the use of light-petroleum/diethyl ether/acetone (8:1:1) eluted stannanes **5**. Then the other products **4**, **6** and/or **7** were eluted with

$CHCl_3$/MeOH (99:1). For yields of products **4**–**6**, and/or **7** depending on the nature and ratio of starting compounds and reaction times see Table 1.

3.1.1. 1,4-Bis(9-benzylpurin-6-yl)benzene (4a). Colorless crystals, mp 295–297°C (DMF). ^{1}H NMR (500 MHz, 40°C, DMF-d_7) δ 5.87 (s, 4H, CH_2Ph), 7.52 (m, 2H, ArH), 7.57 (t, J=7.4 Hz, 4H, ArH), 7.68 (d, J=7.5 Hz, 4H, ArH), 9.07 (s, 2H, 8-PuH), 9.25 (s, 2H, 2-PuH), 9.35 (s, 4H, ArH). ^{13}C NMR (125 MHz, 40°C, DMF-d_7, APT) δ CH: 128.5, 128.6, 129.4, 130.3, 147.3, 152.8 (Ph, C8-Pu and C2-Pu); C, CH_2: 47.5 (CH_2Ph), 131.8, 137.5, 138.7, 153.0, 153.7. IR (KBr) ν 1573, 1516, 1446, 1327 cm^{-1}. Anal. Calcd for $C_{30}H_{22}N_8$ (494.5): C, 72.86; H, 4.48; N, 22.66; found: C, 72.50; H, 4.57; N, 22.43. HRMS (EI) calcd for $C_{30}H_{22}N_8$ $[M]^+$ 494.1967. Found: 494.1980.

3.1.2. 1,3-Bis(9-benzylpurin-6-yl)benzene (4b). Colorless crystals, mp 196–198°C ($CHCl_3$/EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (s, 4H, CH_2Ph), 7.31 (m, 10H, ArH), 7.76 (t, J=7.7 Hz, 1H, ArH), 8.12 (s, 2H, 8-Pu-H), 8.98 (d, J=7.5 Hz, 2H, ArH), 9.10 (s, 2H, 2-PuH), 10.14 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, APT) δ CH: 127.8, 128.6, 129.0, 129.1, 131.0, 132.3, 144.4 (C8-Pu), 152.7 (C2-Pu); C, CH_2: 47.2 (CH_2Ph), 131.0, 135.2, 136.2, 152.6, 154.7 (C4, C5, C6-Pu and C-Ph). IR (KBr) ν 1580, 1563, 1496, 1452, 1322, 1296, 1211, 1195 cm^{-1}. Anal. Calcd for $C_{30}H_{22}N_8$ (494.5): C, 72.86; H, 4.48; N, 22.66; found: C, 72.59; H, 4.50; N, 22.54. HRMS (EI) calcd for $C_{30}H_{22}N_8$ $[M]^+$ 494.1967. Found: 494.1963.

3.1.3. 9-Benzyl-6-[(4-tributylstannyl)phenyl]purine (5a). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J=7.3 Hz, 9H, CH_3), 1.098 (m, 6H, CH_2), 1.34 (m, 6H, CH_2), 1.56 (m, 6H, CH_2), 5.48 (s, 2H, CH_2Ph), 7.36 (m, 5H, CH_2Ph), 7.68 (d, J=8.0 Hz, J_{Sn-H}=36 Hz, 2H, ArH), 8.08 (s, 1H, 8-PuH), 8.68 (d, J=7.9 Hz, 2H, ArH), 9.05 (s, 1H, 2-PuH). ^{13}C NMR (125 MHz, $CDCl_3$, APT) δ CH, CH_3: 13.6 (CH_3), 127.8, 128.5, 128.7, 129.1, 136.8 (J_{Sn-C}= 30 Hz), 144.0 (C8-Pu), 152.6 (C2-Pu); C, CH_2: 9.6, 27.3, 29.1 ($CH_2CH_2CH_2CH_3$), 47.2 (CH_2Ph), 130.9, 135.1, 135.2, 146.8, 152.4, 155.5 (C4, C5, C6-Pu and C-Ph). IR ($CHCl_3$) ν 3018, 2959, 2928, 2872, 2854, 1581, 1542, 1446, 1384, 1327 cm^{-1}. FAB HRMS (m/z) calcd for $C_{30}H_{41}N_4$ ^{118}Sn 575.2347 $[M+H]^+$. Found: 575.2377.

3.1.4. 9-Benzyl-6-[(3-tributylstannyl)phenyl]purine (5b). Yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J=7.4 Hz, 9H, CH_3), 1.13 (m, 6H, CH_2), 1.35 (m, 6H, CH_2), 1.59 (m, 6H, CH_2), 5.47 (s, 2H, CH_2Ph), 7.35 (m, 5H, CH_2Ph), 7.52 (t, J=7.5 Hz, 1H, ArH), 7.62 (d, J=7.2 Hz, J_{Sn-H}=38 Hz, 1H, ArH), 8.07 (s, 1H, 8-PuH), 8.72 (d, J= 7.9 Hz, 1H, ArH), 8.88 (s, J_{Sn-H}=41 Hz, 1H, ArH), 9.06 (s, 1H, 2-PuH). ^{13}C NMR (125 MHz, $CDCl_3$, APT) δ CH, CH_3: 13.7 (CH_3), 127.8, 127.9, 128.5, 129.1, 129.7, 137.5 (J_{Sn-C}= 34 Hz), 139.0 (J_{Sn-C}=29 Hz), 139.2, 143.9 (C8-Pu), 152.6 (C2-Pu); C, CH_2: 9.7, 27.3, 29.1 ($CH_2CH_2CH_2CH_3$), 47.2 (CH_2Ph), 131.1, 134.9, 135.3, 142.5, 152.4, 155.6 (C4, C5, C6-Pu a C-Ph). IR ($CHCl_3$) ν 2995, 2959, 2928, 2872, 2854, 1578, 1558, 1498, 1456, 1325 cm^{-1}. Anal. Calcd for $C_{30}H_{40}N_4Sn \cdot 0.5H_2O$ (584.37): C, 61.66; H, 7.07; N, 9.59. Found: C, 61.54; H, 7.14; N, 9.20. FAB HRMS (m/z) calcd for $C_{30}H_{41}N_4^{118}Sn$ 575.2347 $[M+H]^+$. Found: 575.2341.

3.2. Reaction of 9-benzyl-6-chloropurine (1) with 1,4-phenylenediboronic acid

Mixture of benzene-1,4-diboronic acid (**8**, 100 mg, 0.603 mmol), 9-benzyl-6-chloropurine (**1**) (310 mg, 1.27 mmol), $Pd(PPh_3)_4$ (83 mg, 0.072 mmol), K_2CO_3 (473 mg, 3.42 mmol), DME (5 ml) and water (1.7 ml) was heated under argon to 80°C. After 1 h the reaction mixture was cooled and the separated product was filtered off, washed with DMF and MeOH and dried in vacuum. In this way 134 mg (45%) of pure **4a** was obtained. The filtrate was evaporated in vacuum and the chromatography on silica ($CHCl_3$/MeOH (95:5)) afforded another crop of **4a** (70 mg, 25%) and 9-benzyl-6-phenylpurine (**6**) (0.010 g, 6%).

3.2.1. 1-(9-Benzylpurin-6-yl)-4-(1,3-dimethyluracil-5-yl)benzene (10a). To the 9-benzyl-6-[(4-tributylstannyl)-phenyl]purine (**5a**) (114 mg, 0.19 mmol), 1,3-dimethyl-5-iodouracil (**8**) (92 mg, 0.35 mmol) and $Pd(PPh_3)_2Cl_2$ (36 mg, 0.05 mmol) DMF (4 ml) was added under argon and the mixture was heated to 100°C for 3.5 h. The mixture was then cooled, filtered through celite, the celite was washed with small amount of $CHCl_3$/MeOH (2:1) and the solvents were evaporated in vacuum. Chromatography of the residuum on silica gel (100 g, eluted with a gradient: light-petroleum→light-petroleum/ethyl acetate→ethyl acetate/MeOH 19:1) afforded **10a** (16 mg, 20%). 9-Benzyl-6-phenylpurine (**5**) (19 mg, 35%) was obtained as a side product. **10a**: Colorless crystals, mp 193–195°C ($CHCl_3$/toluene/heptane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 5.50 (s, 2H, CH_2Ph), 7.37 (m, 5H, ArH), 7.43 (s, 1H, C═CH–NCH_3), 7.74 (d, J=8.3 Hz, 2H, ArH), 8.13 (s, 1H, 8-PuH), 8.84 (d, J=8.3 Hz, 2H, ArH), 9.07 (s, 1H, 2-PuH). ^{13}C NMR (125 MHz, $CDCl_3$, APT) δ CH, CH_3: 28.4, 37.4, 127.8, 128.3, 128.6, 129.2, 129.8, 140.9, 144.2, 152.6; C, CH_2: 47.3, 113.7, 130.9, 135.0, 135.1, 135.5, 151.4, 152.5, 154.2, 162.1. IR ($CHCl_3$) ν 3012, 1705, 1657, 1582, 1452 cm^{-1}. Anal. Calcd for $C_{24}H_{20}N_6O_2$ (424.5): C, 67.91; H, 4.75; N, 19.80; found: C, 68.22; H, 4.90; N, 19.43. HRMS (EI) (m/z) calcd for $C_{24}H_{20}N_6O_2$ 424.1647. Found: 424.1631.

3.2.2. 1-(9-Benzylpurin-6-yl)-3-(1,3-dimethyluracil-5-yl)-benzene (10b). The same procedure as used for the preparation of **10a** starting from 9-benzyl-6-[(3-tributyl-stannyl)phenyl]purine (**5b**) (113 mg, 0.196 mmol), 1,3-dimethyl-5-iodouracil (**9**) (84 mg, 0.32 mmol) and $Pd(PPh_3)_2Cl_2$ (20 mg, 0.03 mmol) in DMF (4 ml) furnished after 1 h of heating and chromatography (the same conditions as for **10a**), 16 mg (19%) of desired **10b**. 9-Benzyl-6-phenylpurine (**6**) (13 mg, 23%) was obtained as a side product. **10b**: Colorless crystals, mp 212–214°C ($CHCl_3$/toluene/heptane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 5.51 (s, 2H, CH_2Ph), 7.36 (m, 5H, ArH), 7.50 (s, 1H, C═CH–NCH_3), 7.62 (t, J=7.7 Hz, 1H, ArH), 7.80 (d, J=7.7 Hz, ArH), 8.13 (s, 1H, 8-PuH), 8.83 (d, J=7.9 Hz, 1H, ArH), 8.87 (s, 1H, ArH), 9.08 (s, 1H, 2-PuH). ^{13}C NMR (100 MHz, $CDCl_3$, APT) δ CH, CH_3: 28.3, 37.1, 127.8, 128.6, 128.8, 129.0, 129.2, 129.4, 131.2, 140.7, 144.3, 152.6; C, CH_2: 47.3, 114.1, 131.0, 133.4, 135.2, 136.0, 151.5, 152.6, 154.4, 162.3. IR ($CHCl_3$) ν 3021, 1705, 1658, 1581, 1457, 1325 cm^{-1}. Anal. Calcd for $C_{24}H_{20}N_6O_2$ (424.5): C, 67.91; H, 4.75; N, 19.80;

found: C, 67.98; H, 4.65; N, 19.46. HRMS (EI) (*m/z*) calcd for $C_{24}H_{20}N_6O_2$ 424.1647. Found: 424.1632.

Acknowledgments

This work is a part of research projects Z4 055 905 and MSM 22231 00001. It was supported by the Grant Agency of the Czech Republic (Grant No. 203/00/0036).

References

1. Review: Rajski, S. R.; Williams, R. M. *Chem. Rev.* **1998**, *98*, 2723–2795.
2. Review: Baguley, B. C. *Anti-Cancer Drug. Des.* **1991**, *3*, 1–35.
3. Bhat, B.; Leonard, N. J.; Robinson, H.; Wang, A. H. J. *J. Am. Chem. Soc.* **1996**, *118*, 10744–10751, and references cited therein.
4. (a) Nagatsugi, F.; Uemura, K.; Nakashima, S.; Maeda, M.; Sasaki, S. *Tetrahedron Lett.* **1995**, *36*, 421–424. (b) Nagatsugi, F.; Uemura, K.; Nakashima, S.; Maeda, M.; Sasaki, S. *Tetrahedron* **1997**, *53*, 3035–3044. (c) Nagatsugi, F.; Kawasaki, T.; Usui, D.; Maeda, M.; Sasaki, S. *J. Am. Chem. Soc.* **1999**, *121*, 6753–6754. (d) Nagatsugi, F.; Usui, D.; Kawasaki, T.; Maeda, M.; Sasaki, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 343–345.
5. (a) Quiao, X.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 928–931. (b) Qiu, Y. L.; Li, H. Y.; Topalov, G.; Kishi, Y. *Tetrahedron Lett.* **2000**, *41*, 9425–9429. (c) Li, H. Y.; Qiu, Y. L.; Moyroud, E.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1471–1475. (d) Li, H. Y.; Qiu, Y. L.; Kishi, Y. *ChemBioChem* **2001**, *2*, 371–374.
6. (a) Ogawa, A. K.; Abou-Zied, O. K.; Tsui, V.; Jimenez, R.; Case, D. A.; Romesberg, F. E. *J. Am. Chem. Soc.* **2000**, *122*, 9917–9920. (b) Abou-Zied, O. K.; Jimenez, R.; Romesberg, F. E. *J. Am. Chem. Soc.* **2001**, *123*, 4613–4614.
7. (a) Leonard, N. J.; Ito, K. *J. Am. Chem. Soc.* **1973**, *95*, 4010–4016. (b) Akahori, K.; Hama, F.; Sakata, Y.; Misumi, S. *Tetrahedron Lett.* **1984**, *25*, 2379–2382. (c) Seyama, F.; Akahori, K.; Sakata, Y.; Misumi, S.; Aida, M.; Nagata, C. *J. Am. Chem. Soc.* **1988**, *110*, 2192–2201.
8. Crisp, G. T.; Jiang, Y. L. *Tetrahedron* **1999**, *55*, 549–560.
9. Chaw, Y. F. M.; Crane, L. E.; Lange, P.; Shapiro, R. *Biochemistry* **1980**, *19*, 5525–5531.
10. (a) Žemlička, J.; Owens, J. *J. Org. Chem.* **1977**, *42*, 517–523. (b) Bhuta, P.; Li, C.; Žemlička, J. *Biochem. Biophys. Res. Commun.* **1977**, *77*, 1237–1244. (c) Žemlička, J. *Biochemistry* **1980**, *19*, 163–168. (d) Murata, M.; Bhuta, P.; Owens, J.; Žemlička, J. *J. Med. Chem.* **1980**, *23*, 781–786. (e) Žemlička, J. *Tetrahedron Lett.* **1984**, *25*, 5619–5622. (f) Agathocleous, D. C.; Page, P. C. B.; Cosstick, R.; Galpin, I. J.; McLennan, A. G.; Prescott, M. *Tetrahedron* **1990**, *46*, 2047–2058.
11. Hocek, M.; Votruba, I. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1055–1058.
12. Hocek, M.; Stará, I. G.; Starý, I.; Dvořáková, H. *Tetrahedron Lett.* **2001**, *42*, 519–521.
13. (a) Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *J. Med. Chem.* **2000**, *43*, 1817–1825. (b) Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1683–1697. (c) Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *Collect. Czech. Chem. Commun.* **2001**, *66*, 483–499. (d) Hocek, M.; Holý, A.; Dvořáková, H. *Collect. Czech. Chem. Commun.* **2002**, *67*, 325–335.
14. (a) Bergstrom, D. E.; Reddy, P. A. *Tetrahedron Lett.* **1982**, *23*, 4191–4194. (b) Sugimura, H.; Takei, H. *Bull. Chem. Soc. Jpn* **1985**, *58*, 664–666. (c) Estep, K. G.; Josef, K. A.; Bacon, E. R.; Carabates, P. M.; Rumney, IV., S.; Pilling, G. M.; Krafte, D. S.; Volberg, W. A.; Dillon, K.; Dugrenier, N.; Briggs, G. M.; Canniff, P. C.; Gorczyca, W. P.; Stankus, G. P.; Ezrin, A. M. *J. Med. Chem.* **1995**, *38*, 2582–2595.
15. (a) Gundersen, L. L. *Tetrahedron Lett.* **1994**, *35*, 3155–3158. (b) Langli, G.; Gundersen, L. L.; Rise, F. *Tetrahedron* **1996**, *52*, 5625–5638. (c) Gundersen, L. L.; Langli, G.; Rise, F. *Tetrahedron Lett.* **1995**, *36*, 1945–1948. (d) Gundersen, L. L.; Bakkestuen, A. K.; Aasen, A. J.; Øveras, H.; Rise, F. *Tetrahedron* **1994**, *50*, 9743–9756. (e) Nolsoe, J. M. J.; Gundersen, L. L.; Rise, F. *Acta Chem. Scand.* **1999**, *53*, 366–372. (f) Hocek, M.; Masojídková, M.; Holý, A. *Collect. Czech. Chem. Commun.* **1997**, *62*, 136–146. (g) Česnek, M.; Hocek, M.; Holý, A. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1357–1373.
16. (a) Havelková, M.; Hocek, M.; Česnek, M.; Dvořák, D. *Synlett* **1999**, 1145–1147. (b) Havelková, M.; Dvořák, D.; Hocek, M. *Synthesis* **2001**, 1704–1710. (c) Lakshman, M. K.; Hilmer, J. H.; Martin, J. Q.; Keeler, J. C.; Dinh, Y. Q. V.; Ngassa, F. N.; Russon, L. M. *J. Am. Chem. Soc.* **2001**, *123*, 7779–7787.
17. Eisch, J. J.; Kotowicz, B. W. *Eur. J. Inorg. Chem.* **1998**, 761–769.
18. Das, B.; Kundu, N. G. *Synth. Commun.* **1988**, *18*, 855–867.