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Synthesis of (purin-6-yl)acetates and 6-(2-hydroxyethyl)purines via cross-couplings of 6-chloropurines with the Reformatsky reagent

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Abstract—A novel approach to the synthesis of 6-(2-hydroxyethyl)purines was developed based on Pd-catalyzed cross-coupling reactions of 6-chloropurines with the Reformatsky reagent followed by reduction by $NaBH_4$ and treatment with MnO_2. This methodology was successfully applied to the syntheses of 6-(ethoxycarbonylmethyl)- and 6-(hydroxyethyl)purine bases and nucleosides.

Several types of purines bearing C-substituents at C-6 are biologically active. 6-Methylpurine and its ribonucleoside are highly cytotoxic[1] and its liberation by purine nucleoside phosphorylases from its non-toxic deoxyribonucleoside was proposed as a novel principle in the gene therapy of cancer.[2] 6-Aryl- and 6-hetarylpurine ribonucleosides exert[3] significant cytostatic effects and, moreover, some 6-hetarylpurine ribonucleosides exhibit[4] potent antiviral activity against HCV. Little was known about the biological activity of purines bearing functionalized C-substituents until recently when we reported the syntheses and cytostatic effects of 6-(hydroxymethyl)-,[5] 6-(fluoromethyl)-,[6] 6-(difluoromethyl)-[7] and 6-(trifluoromethyl)purine[8] ribonucleosides. Very recently, substituted 6-(2-aminovinyl)- and 6-(2-aminoethyl)purine derivatives were also found to exhibit cytostatic effects.[9]

Carbon substituents at C-6 of purines are efficiently introduced by cross-coupling reactions of 6-halopurines with various organometallics.[10] Functionalized C-substituents usually require suitable protection of the corresponding organometallics. So far, we have succeeded with the synthesis of 6-(hydroxymethyl)purines via coupling of acyloxymethylzinc iodides[5] and of purin-6-yl amino acids via coupling of protected amino acid organometallics.[11] For β-functionalized C-substituents the corresponding organometallics would not be stable due to β-elimination and, therefore, an alternative strategy based on conjugate additions of nucleophiles to 6-ethynyl- or 6-vinylpurines has been developed.[9,12] Here we report on an alternative strategy for the introduction of β-functionalized substituents via cross-coupling of halopurines with the Reformatsky reagent.

Purin-6-yl acetates were prepared previously in moderate yields by heterocyclization of pyrimidines,[13] by arylation of malonates[14] or ethyl acetoacetate[15] with 6-halo- or 6-tosyloxypurines followed by decarboxylation or cleavage of acetoacetate. The former method is laborious,[13] while the latter two approaches[14,15] were not reproducible reliably in our hands due to side reactions. Since these compounds are apparently useful intermediates for further functionalization, we have tried to develop a practical new approach for their syntheses based on Pd-catalyzed cross-coupling reactions of halopurines with the Reformatsky reagent under mild conditions.

Although the first Pd-catalyzed arylation of aryl halides was reported[16] in 1979, only the development of a new generation of sterically hindered phosphine ligands enabled application of this reaction to a wide range of aryl halides under mild conditions.[17] Therefore, our first study focused on optimization of the catalytic system. Reactions of $BrZnCH_2COOEt$ (**1**) with model 9-benzyl-6-chloropurine (**2a**) to give (purin-6-yl)acetate **3a** were performed using several types of phosphine ligands with varying ratios of Pd/ligand and amount of reagent

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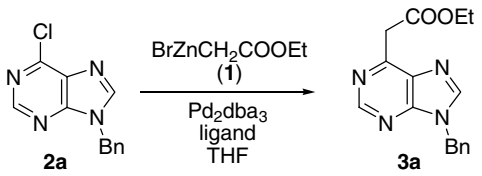


Scheme 1. Optimization of the cross-coupling of 6-chloropurine **2a** with the Reformatsky reagent **1**.

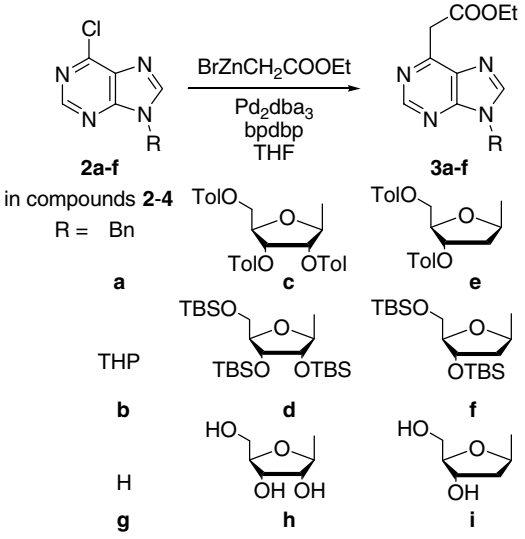
Table 1. Optimization of the cross-coupling of 6-chloropurine **2a** with the Reformatsky reagent **1**

Entry	Pd_2dba_3 (%)	Ligand	Ligand (%)	**1** (equiv)	Yield of **3a** (%)
1	1	P(*o*-tol)$_3$	4	2	0
2	1	P(*t*-Bu)$_3$·HBF_4	2	2	14
3	1	bpdbp[a]	4	2	31
4	2	bpdbp	8	2	48
5	2	bpdbp	8	4	91

[a] (2-Biphenyl)di-*tert*-butylphosphine.

(Scheme 1, Table 1). Reformatsky reagent **1** was generated from ethyl bromoacetate and zinc dust in analogy with the procedure published[18] for other organozincs using preactivation of zinc by trimethylsilyl chloride and 1,2-dibromoethane. While the use of P(*o*-tol)$_3$ ligand did not give any reaction, the use of P(*t*-Bu)$_3$·HBF_4 showed more promising reactivity and the best ligand proved to be (2-biphenyl)di-*tert*-butylphosphine (bpdbp) where the yield was significantly higher (Table 1, entries 1–3). Using the superior ratio 1:4 of Pd_2dba_3 and ligand and an increased amount of organozinc reagent **1** (4 equiv), an almost quantitative yield of **3a** was obtained (Table 1, entry 5).[19]

The optimized conditions were then applied to the syntheses of other derivatives. THP-Protected 6-chloropurine base **2b** and both toluoyl and silyl protected



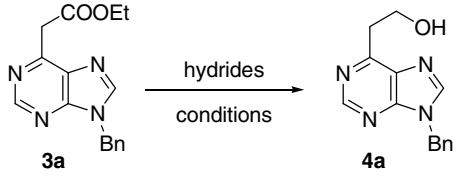
Scheme 2. Cross-coupling of the Reformatsky reagent with chloropurine derivatives **2a**–**f**.

Table 2. Cross-coupling of the Reformatsky reagent with chloropurine derivatives **2a**–**f**

Entry	Halopurine	Product	Yield (%)
1	**2a**	**3a**	91
2	**2b**	**3b**	76
3	**2c**	**3c**	75
4	**2d**	**3d**	97
5	**2e**	**3e**	67
6	**2f**	**3f**	96

ribo- and 2′-deoxyribonucleosides **2c**–**2f** reacted with organozinc **1** generally very well giving the corresponding purinylacetates **3b**–**3f** in good to excellent yields (Scheme 2, Table 2). The silyl protected nucleosides **3d** and **3f** were obtained in significantly better yields compared to toluoyl-protected **3c** and **3e** probably due to better stability under work-up conditions.

Having developed an efficient and practical methodology for the synthesis of (purin-6-yl)acetates, we next explored the possibility of reduction of the acetate ester group to a hydroxyethyl group, since 6-(hydroxyethyl)purines are interesting homologues of biologicaly active 6-(hydroxymethyl)purines.[5] Several types of complex metal hydrides or boranes, various solvents and conditions were investigated for the reduction of model acetate **3a** (Scheme 3, Table 3). Surprisingly, this reduction was very problematic and many of the reagents did not give any reaction or led to decomposition of the starting material (entries 1–3). Only the use of $NaBH_4$, DIBAH or $LiAlH_4/AlCl_3$ gave isolable quantities of desired product **4a**. In aprotic solvents suitable for acyl-protected nucleosides, no efficient reduction conditions were found.

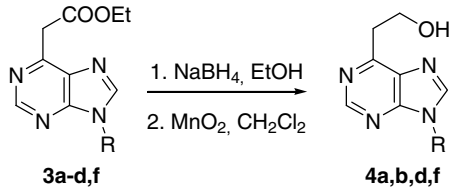


Scheme 3. Optimization of the reduction of **3a**.

Table 3. Optimization of the reduction of **3a**

Entry	Hydride (equiv)	Solvent	Temperature (°C)	Yield of **4a** (%)
1	Other hydrides[a]	THF	0–60	—
2	$NaBH_4$ (4)	DMF	40	decomp.
3	BH_3·Me_2S (6)	THF	Reflux	decomp.
4	$NaBH_4$ (3)	THF	Reflux	5[b]
5	DIBAH (1)	Toluene	0	15
6	$LiAlH_4/AlCl_3$ (3/1)	THF	0	26
7	DIBAH (3)	THF/tol	0	39
8	$NaBH_4$ (10)	Dioxane	60	40
9	$NaBH_4$ (10)	EtOH	50	54
10	$NaBH_4$ (10) followed by MnO_2	EtOH	rt	82

[a] $LiAlH_4$, $LiBEt_3H$, synhydride, L-Selectride or 9-BBN.
[b] The rest was unreacted compound.



Scheme 4. Preparative reductions of purines **3a**–**d**,**f**.

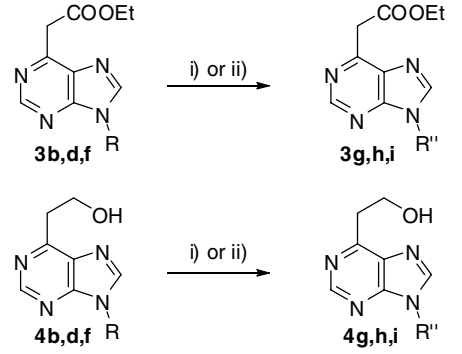
Table 4. Preparative reductions of purines **3a**–**d**,**f**[a]

Entry	Ester	Product	Yield (%)
1	**3a**	**4a**	82
2	**3b**	**4b**	65
3	**3c**	**4c**	0[b]
4	**3d**	**4d**	74
5	**3f**	**4f**	71

[a] Conditions: (1) $NaBH_4$ (10 equiv), EtOH, rt, 12 h; (2) MnO_2, CH_2Cl_2, rt, 1 h.
[b] Decomposition.

The best reducing agent was $NaBH_4$ in ethanol, which gave ca 50% preparative yield of **4a**. This product was accompanied by an unstable side product, which was partly identified (NMR) as a 1,6-dihydropurine formed by over-reduction. Therefore, the reaction mixture after reduction was treated with MnO_2 to re-oxidize the purine ring and this modification gave **4a** in a good yield of 82%. This procedure[20] was then applied to the reductions of protected bases and nucleosides **3b**–**d**,**f** (Scheme 4, Table 4). The toluoyl groups were not stable during the reduction in ethanol (entry 3) and therefore only the THP-protected purine **3b** and silylated nucleosides **3d**,**f** were successfully reduced to give the protected 6-(2-hydroxyethyl)purine base **4b** and nucleosides **4d**,**f** in good yields.

The THP-protecting group in 6-(ethoxycarbonylmethyl)purine **3b** and 6-(hydroxyethyl)purine **4b** was cleaved[21] using a catalytic amount of Dowex 50 (H^+ form) in ethanol at an elevated temperature for 3 h (Scheme 5) to give the corresponding free 9*H*-purine bases **3g** and **4g** (Table 5, entries 1 and 2). The silylated 6-(ethoxycarbonylmethyl)purine **3d** and **3f** and



Scheme 5. Deprotections of purines and nucleosides **3** and **4**. Reagents and conditions: for **b** (i) Dowex (H^+), EtOH, 70 °C, 3 h; for **d**,**f** (ii) $Et_3N{\cdot}3HF$, THF, rt, 18 h.

Table 5. Deprotection of purines and nucleosides **3** and **4**

Entry	Protected compd	Conditions[a]	Product	Yield (%)
1	**3b**	A	**3g**	93
2	**4b**	A	**4g**	75
3	**3d**	B	**3h**	96
4	**3f**	B	**3i**	65
5	**4d**	B	**4h**	92
6	**4f**	B	**4i**	69

[a] Method A: Dowex (H^+), EtOH, 70 °C, 3 h; B: $Et_3N{\cdot}3HF$, THF, rt, 18 h.

6-(hydroxyethyl)purine **4d** and **4f** nucleosides were deprotected[11b] with $Et_3N{\cdot}3HF$ (1.5 equiv for each silyl group) in THF. Free purine nucleosides **3h** and **3i** and **4h** and **4i** were obtained at room temperature after 18 h in good yields (Table 5, entries 3–6).

In conclusion, a novel efficient approach to (purin-6-yl)acetates was developed based on the Pd-catalyzed reactions of 6-chloropurines with the Reformatsky reagent. The acetates could be further reduced to a novel 6-(hydroxyethyl)purine derivatives. Ongoing applications of this methodology and follow-up functional group transformations in the syntheses of a large series of new interesting modified purine bases and nucleosides for biological activity screening and other biological applications will be published in due course.

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19. A solution of ethyl bromoacetate (417.5 mg, 278.33 μl, 2.5 mmol) in 3 ml of THF was added at rt to an argon-purged flask containing a suspension of zinc dust (327 mg, 5 mmol) preactivated with TMSCl (15 μl) in THF (2 ml). The suspension was stirred for 1 h, then the zinc was allowed to settle and 4 ml of the supernatant (4 ml) was transferred through a septum to a mixture of **2a** (122 mg, 0.5 mmol), Pd_2dba_3 (8 mg, 0.01 mmol) and bpdbp (12 mg, 0.04 mmol) in THF (1 ml) under Ar. The mixture was stirred for 12 h and then quenched with 1 M NH_4Cl (40 ml) and extracted with chloroform (3×30 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was chromatographed on a silica gel column (ethyl acetate/hexane) to give **3a** (91%). Yellowish crystals (CH_2Cl_2/heptane), mp 90–96 °C. MS (FAB): 297 (100, M+1). HRMS (FAB): for $C_{16}H_{17}N_4O_2$ ($M + H^+$) calculated 297.1351, found 297.1356. ^{1}H NMR (400 MHz, $CDCl_3$): 1.27 (t, 3 H, $J = 7.1$); 4.22 (q, 2H, $J = 7.1$); 4.26 (s, 2H); 5.45 (s, 2H); 7.29–7.41 (m, 5H); 8.04 (s, 1H); 8.97 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 14.11, 39.03, 47.37, 61.36, 127.92, 128.66, 129.16, 133.00, 134.93, 144.33, 151.32, 152.62, 154.55, 169.21. IR, ν_{max}: 2983, 1744, 1599, 1500, 1407, 1333, 1178 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.46; H. 5.37; N 18.50.
20. $NaBH_4$ (380 mg, 10 mmol) was added to a stirred solution of a purine **3a** (296 mg, 1 mmol) in EtOH (8 ml), the reaction was stirred at rt for 12 h and then quenched by MeOH (8 ml) and 1 M NH_4Cl (10 ml). The solvents were evaporated and the residue extracted with chloroform (3×30 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent evaporated. The residue was dissolved in CH_2Cl_2 (10 ml) and MnO_2 (174 mg, 2 mmol) was added. The mixture was sonicated at rt for 1 h, then filtered through Celite and the solvent evaporated. The residue was chromatographed on a silica gel column (chloroform/methanol) to give **4a** (82%). White crystals, mp 72–73 °C (CH_2Cl_2/heptane). MS (FAB): 255 (100, M+1), 91 (55). HRMS (FAB): for $C_{14}H_{15}N_4O$ ($M+H^+$) calculated 255.1246, found 255.1242. ^{1}H NMR (400 MHz, $CDCl_3$): 3.45 (t, 2H, $J = 5.4$,); 4.16 (bt, 2H, $J = 5.4$); 4.89 (bs, 1H); 5.45 (s, 2H); 7.28–7.40 (m, 5H); 8.04 (s, 1H); 8.90 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): 36.04, 47.25, 60.19, 127.81, 128.58, 129.08, 132.15, 134.85, 143.71, 150.70, 152.23, 161.14. IR, ν_{max}: 2931, 1596, 1500, 1407, 1331, 1196, 1063 cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 65.87; H, 5.47; N, 21.90.
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