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SYNTHESIS OF PROTECTED (PURIN-6-YL)GLYCINES *VIA* Pd-CATALYZED α-ARYLATION OF ETHYL *N*-(DIPHENYL-METHYLIDENE)GLYCINATE WITH 6-IODOPURINES

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Abstract – A synthesis of protected (purin-6-yl)glycines, potential building blocks of stable covalent peptide-nucleic acids conjugates, was achieved *via* Pd-catalyzed α-arylation of ethyl *N*-(diphenylmethylidene)glycinate with 6-iodopurine.

INTRODUCTION

Purines bearing a carbon substituent in the position 6 are a subject of extensive investigation and were found to display diverse biological activities (e.g. cytostatic[1], antibacterial or antimycobacterial[2]). They are easily available by cross-coupling reactions[3] of 6-halopurines with various organometallic reagents. However, a synthesis of purine derivatives bearing highly substituted C-substituents in the position 6 is so far underdeveloped, though these compounds are quite attractive as potential receptor ligands and building blocks for the synthesis of conjugates of nucleosides or nucleic acids with other types of biorelevant compounds. A prominent new type of these compounds would be (purin-6-yl)glycines that contain structural patterns of antiviral 6-(aminomethyl)purines,[4] possess two easily derivatisible functional groups and apparently could serve as building blocks for the synthesis of purine-peptide conjugates linked *via* stable (hardly enzymatically degradable) C-C bond. In this Note, we report on our preliminary results in the straightforward synthesis of the title compounds *via* Pd-catalyzed α-arylation of a protected glycine with 6-iodopurines.

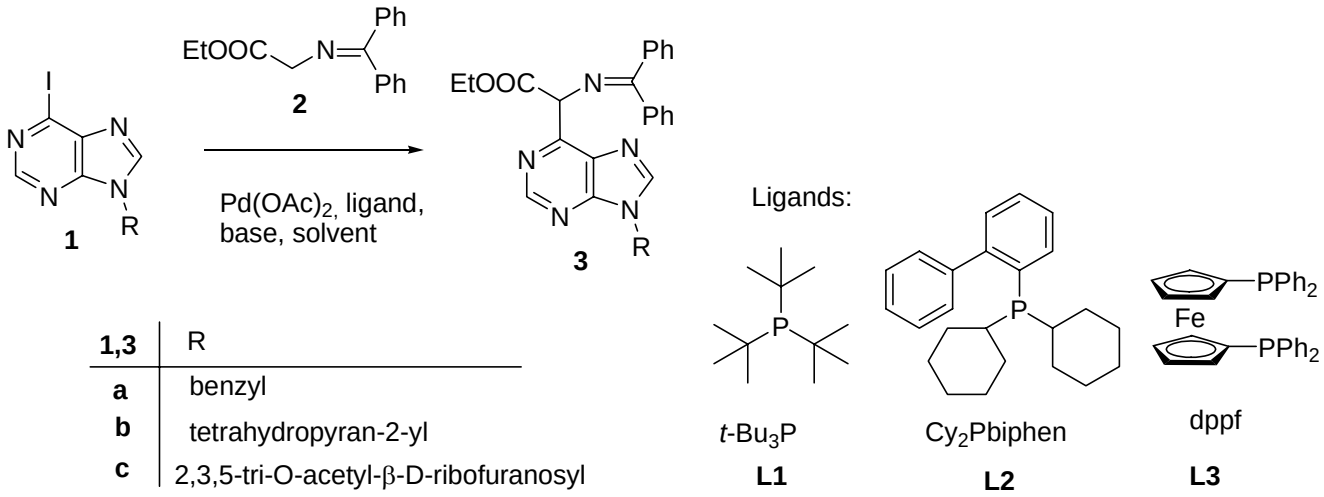
In the past, arylglycines were not very easily available and usually they were prepared by Strecker synthesis[5] or Freidel-Crafts reaction.[6] Only recently, the Hartwig's and Buchwald's developments in arylation of salts of C-acids[7] enabled an efficient direct arylation of protected glycines.[8] This method was

based on Pd-catalyzed cross-coupling of an enolate derived from $Ph_2C{=}NCH_2COOEt$ with aryl halides (usually iodobenzene). Extremely air sensitive *t*-Bu_3P or carbene ligands were used for the generation of the palladium catalytic system and K_3PO_4 was used as a base.

RESULTS AND DISCUSSION

This methodology has been used for analogous reaction of 9-benzyl-6-iodopurine (**1a**) with protected glycine (**2**) (Scheme 1 and Table I). At first, the literature conditions using *t*-Bu_3P (**L1**) in toluene were applied and the desired 9-benzyl-6-[ethoxycarbonyl-(diphenylmethylidene)aminomethyl]purine (**3a**) was obtained in 32% yield. In the next experiments, the air-sensitive *t*-Bu_3P was replaced by commercially available and more stable Cy_2Pbiphen (**L2**) or dppf (**L3**) in toluene or dioxane. While the reaction in presence of (**L2**) in toluene gave lower yield of 16%, the reactions in dioxane afforded **3a** in the yields of 37 and 32%, respectively.

Therefore, the conditions, bases and solvents were optimized. The use of bases other than K_3PO_4 (K_2CO_3, NaH, Et_3N) did not lead to any reaction or gave very low yields. Out of the solvents tried, the use of DMF turned out to be superior to afford the product (**3a**) in an acceptable yield of 55%. This optimized procedure was applied in the analogous reactions of 9-(tetrahydropyran-2-yl) protected 6-iodopurine derivative (**1b**) and acyl-protected nucleoside (**1c**) to give the corresponding purinylglycines (**3b**) and (**3c**) in 63 and 31%, respectively. On the other hand the reaction of 9-benzyl-6-chloropurine (**1d**) under analogous conditions did not proceed indicating that only more reactive 6-iodopurines are suitable substrates for this reaction.



1,3	R
a	benzyl
b	tetrahydropyran-2-yl
c	2,3,5-tri-O-acetyl-β-D-ribofuranosyl

Scheme 1 α-Arylations of **2** with 6-Iodopurines.

Table I α-Arylations of **2** with 6-Halopurines

Entry	Starting compound	Ligand	Base	Solvent	Time (h)	Product	Yield (%)
1	**1a**	**L1**	K_3PO_4	toluene	10	**3a**	32
2	**1a**	**L2**	K_3PO_4	toluene	28	**3a**	16
3	**1a**	**L2**	K_3PO_4	dioxane	14	**3a**	37
4	**1a**	**L3**	K_3PO_4	dioxane	14	**3a**	32
5	**1a**	**L2**	NaH	toluene	28	**3a**	7
6	**1a**	**L2**	Et_3N	toluene	10	**3a**	0
7	**1a**	**L2**	K_3PO_4	DMF	8	**3a**	55
8	**1b**	**L2**	K_3PO_4	DMF	8	**3b**	63
9	**1c**	**L2**	K_3PO_4	DMF	8	**3c**	31
10	**1d**[a]	**L2**	K_3PO_4	DMF	8	**3a**	0

[a] 9-Benzyl-6-chloropurine (**1d**).

In conclusion, a straightforward synthesis of protected (purin-6-yl)glycines can be easily achieved in acceptable yields using Pd-catalyzed arylations of ethyl *N*-(diphenylmethylidene)glycinate with 6-iodopurines. Air-sensitive *t*-Bu_3P can be efficiently replaced by commercially available 2-(dicyclohexylphosphino)biphenyl. Efforts on deprotection of the title compounds (**3a-3c**) making use of hydrogenolysis or acidic cleavage of the imine and/or basic hydrolysis of the ester failed giving complex mixtures of products (including products of decarboxylation and deamination side-reactions) out of which the target amino acids could not have been successfully isolated.

EXPERIMENTAL

General Procedure. Solvent (10 mL) was added through a septum to an argon purged flask containing a 6-iodopurine (**1**, 1 mmol), ethyl [(diphenylmethylidene)amino]acetate (**2**, 374 mg, 1.28 mmol), base (2 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol) and phosphine ligand (0.2 mmol for a monodentate ligand or 0.1 mmol for a bidentate ligand). The mixture was stirred at 100 °C. The solvents were evaporated and the residue was chromatographed on a silica gel column (100 g, ethyl acetate-hexanes 1:2 to 5:1) to give the products (**3**). For details see Table 1.

9-Benzyl-6-[ethoxycarbonyl-(diphenylmethylidene)aminomethyl]purine **(3a)**: Colourless crystals mp 189-192 °C (CH_2Cl_2/heptane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.17 (t, 3 H, J = 7.1, CH_3CH$_2$); 4.20 (d, 2 H, J = 7.1, CH$_3$CH_2); 5.40 (d, 1 H, J_{gem}= 15.1, CH$_2$Ph-a); 5.45 (d, 1 H, J_{gem}= 15.1, CH$_2$Ph-b); 6.01 (s, 1 H, COC*H*N); 7.26-7.44 (m, 13 H, H-arom.); 7.71 (d, 2 H, J = 7.5, H-arom.); 8.00 (s, 1 H, H-8); 9.01 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 14.05 (CH$_3$); 47.29 (*C*H$_2$Ph); 61.54 (*C*H$_2$CH$_3$); 67.62 (CO*C*HN); 127.90, 127.95, 128.55, 128.58, 128.81, 129.11, 129.25, 130.51 (CH-arom.); 132.22, 135.08, 136.10, 139.42 (C-5 and C-*i*-arom.); 144.34 (CH-8); 151.94 (C-4); 152.69 (CH-2); 157.33 (C-6); 169.27 (C=O);

172.75 (C=N). FAB MS, *m/z* (rel.%): 476 (6) [M+H], 91 (100). Exact MS (FAB HR MS) found: 476.2068; calcd for $C_{29}H_{26}N_5O_2$ [M+H]: 476.2087. Anal. Calcd for $C_{29}H_{25}N_5O_2$: C, 73.25; H, 5.30; N, 14.73. Found: C, 73.44; H, 5.40; N, 14.51.

6-[Ethoxycarbonyl-(diphenylmethylidene)aminomethyl]-9-(tetrahydropyran-2-yl)purine **(3b)** (mixture of diastereoisomers): Yellow amorphous solid. IR ($CHCl_3$): 1743, 1653, 1623, 1597, 1495, 1447, 1333. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (t, 3 H, *J* = 7.1, C*H*$_3$CH$_2$); 1.64-2.15 (m, 6 H, CH$_2$-THP); 3.79 (brt, 1 H, *J* = 10.8, CH$_2$-Oa); 4.16-4.22 (m, 3 H, C*H*$_2$CH$_3$ and CH$_2$-Ob); 5.80 (d, 1 H, *J* = 9.8, OCHN); 5.98 and 6.00 (2 x s, 2 x 1/2 H, NCHCO); 7.26-7.72 (m, 10 H, H-arom.); 8.25 (s, 1 H, H-8); 8.98 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 14.04 (*C*H$_3$CH$_2$); 22.75, 24.83 and 31.74 (CH$_2$-THP); 61.59 (*C*H$_2$CH$_3$); 67.66 (CO*C*HN); 68.81 (CH$_2$-O); 81.95 (N*C*HO); 127.90, 128.24, 128.58, 128.85, 129.26 and 130.53 (CH-arom.); 132.32, 136.04 and 139.37 (C-5 and C-*i*-arom.); 142.35 (CH-8); 151.09 (C-4); 152.50 (CH-2); 157.31 (C-6); 169.23 (C=O); 172.79 (C=N). FAB MS, *m/z* (rel.%): 470 (32) [M+H], 386 (100), 312 (65), 165 (68), 85 (40). Exact MS (FAB HR MS) found: 470.2178; calcd for $C_{27}H_{28}N_5O_3$ [M+H]: 470.2192. Anal. Calcd for $C_{27}H_{27}N_5O_3$: C, 69.07; H, 5.80; N, 14.92. Found: C, 69.34; H, 5.54; N, 14.60.

6-[Ethoxycarbonyl-(diphenylmethylidene)aminomethyl]-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine **(3c)** (mixture of diastereoisomers): Yellow amorphous solid. IR ($CHCl_3$): 1749, 1654, 1617, 1595, 1497, 1408, 1370, 1333, 1238. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.18 (t, 3 H, *J* = 7.1, C*H*$_3$CH$_2$); 2.09, 2.11, 2.15 (3 x s, 3 x 3 H, C*H*$_3$CO); 4.22 (d, 2 H, *J* = 7.1, CH$_3$C*H*$_2$); 4.37-4.48 (m, 3 H, H-4' and H-5'); 5.69 (brm, 1 H, H-3'); 5.96-6.00 (m, 2 H, H-2' and COC*H*N); 6.25 (d, 1 H, *J* = 5.2, H-1'); 7.26-7.71 (m, 10 H, H-arom.); 8.17 (s, 1 H, H-8); 8.99 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 14.05 (*C*H$_3$CH$_2$); 20.36, 20.49 and 20.72 (*C*H$_3$CO); 61.68 (*C*H$_2$CH$_3$); 63.00 and 63.05 (CH$_2$-5'); 67.74 and 67.81 (CO*C*HN); 70.59 and 70.62 (CH-3'); 72.96 and 73.03 (CH-2'); 80.40 (CH-4'); 86.25 and 86.30 (CH-1'); 127.86, 127.94, 128.60, 128.89, 129.24 and 130.60 (CH-arom.); 132.94, 135.98, 139.30 (C-5 and C-*i*-arom.); 142.88 (CH-8); 151.41 (C-4); 152.76 (CH-2); 157.85 (C-6); 169.10, 169.30, 169.53 and 170.28 (C=O); 173.00 (C=N). FAB MS, *m/z* (rel.%): 644 (20) [M+H], 386 (32), 312 (35), 139 (100). Anal. Calcd for $C_{33}H_{33}N_5O_9$: C, 61.58; H, 5.17; N, 10.88. Found: C, 61.47; H, 5.40; N, 10.50.

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