

REDUCTIVE DIMERIZATION OF 2- AND 6-IODOPURINES: SIDE REACTION IN Pd-CATALYZED CROSS-COUPLING OF IODOPURINES

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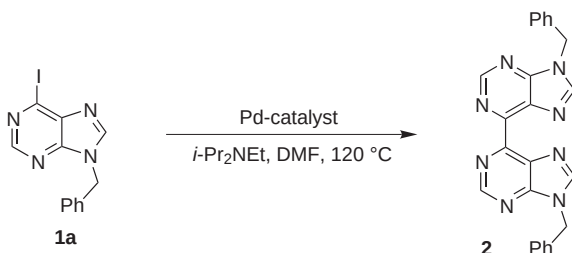
In the presence of a Pd catalyst and a base, 6- and 2-iodopurine derivatives undergo reductive C–C dimerization with the formation of the corresponding 6,6'- or 2,2'-dimers. The best results of the dimerization were obtained in the presence of *i*-Pr₂NEt as a base in DMF. Phosphine-free catalysts as well as catalysts containing phosphines can be used. In the presence of catalytic systems containing PPh₃ the dimerization does not proceed. This dimerization may become an important side reaction in the Stille or the Suzuki–Miyaura reactions of iodopurines.

Keywords: Reductive dimerization; Purines; Pd catalysis; Cross-coupling reactions; Biaryls; Nucleosides.

Various 2- and/or 6-substituted purines display interesting biological activities¹. Generally the biological activity screening and other applications of novel substituted purines are limited by methodologies available for their preparation. Palladium-catalyzed cross-coupling reactions², e.g., the Suzuki–Miyaura³, Stille⁴ and Sonogashira⁵ reactions of halopurines (or potentially arenesulfonylpurines⁶) are frequently utilized for the synthesis of novel substituted purines. In the course of our ongoing efforts to synthesize new substituted purines we observed the formation of 6,6'-purine dimers in attempts to accomplish the Heck reaction with 6-iodopurines as substrates. Such purine C–C dimers are virtually unknown, only 8,8'-dimers of nucleosides have been described as products of oxidative damage of DNA^{7a}. Formation of small amount of 8,8'-purine dimer was also observed in the course of Pd-mediated direct C–H arylation of purines in the presence of CuI^{7b}. Recently the synthesis of 6,8'-purine dimers, 6,8':6',8''-purine trimers, 6,8':6',8'':6'',8''-purine tetramers and a Pd complex of the corresponding cyclic tetramer based on the Negishi cross-coupling reaction has been published⁸. Since the formation of these previously unknown symmetrical

C–C bispurines may become a problem in Pd-catalyzed synthesis of purine derivatives, we decided to explore this side reaction more thoroughly.

At first we investigated the influence of the Pd catalyst and its ligand on the dimerization of 9-benzyl-6-iodopurine (**1a**), leading to the formation of the corresponding 6,6'-dimer **2** (Scheme 1, Table I).



SCHEME 1

In the presence of phosphine-free catalysts almost quantitative dimerization was observed with 9-benzyl-6-iodopurine (**1a**) (entries 1, 2), while with 9-benzyl-6-chloropurine only partial decomposition, but not dimerization occurred (entry 3). In contrast, using catalysts containing triphenylphosphine led only to decomposition of the starting **1a** and the dimer **2** was not formed (entries 4–6). Surprisingly, the reaction in the presence of other phosphine ligands resulted in the formation of **2**, mostly in high yield, and with quantitative conversion of **1a** (entries 7–15). The influence of bidentate ligands was also studied. With 1:1 Pd/ligand ratio, no dimerization was observed with DPPF, while DPPP gave low and (±)-BINAP almost quantitative yield of dimer **2** (entries 16, 18 and 20). When the ratio Pd/ligand 1:2 was used, the dimerization did not occur in any case (entries 17, 19 and 21), probably as a result of saturation of coordination sites.

Based on the above experiments we chose Pd(OAc)₂ as a source of palladium to establish the influence of a base, solvent and the temperature on the course of the reaction. The results are summarized in Table II. Dimerization of **1a** proceeds in DMF at 120 °C in the presence of tertiary amines, giving better yield with *i*-Pr₂NEt (entry 1) than with Et₃N (entry 2). In the presence of K₂CO₃ or without a base the reaction does not occur (entries 3 and 4). Lowering the temperature to 100 °C led to a decrease in the yield of **2**, and at 80 °C the dimerization did not proceed at all (entries 5 and 6). As far as the solvents are concerned, DMA gave similar results as DMF (entry 7). In other tested solvents the dimerization does not take place (entries 8–11), probably due to low polarity (toluene) and/or low boiling point (acetonitrile, 1,2-dichloroethane, THF) of the solvent.

TABLE I
Influence of the Pd catalyst and ligand on the yield of dimer **2** (Scheme 1)^a

Entry	Catalyst ^b	Yield of 2 , % ^c	Unreacted 1a , % ^c
1	Pd ₂ (dba) ₃ ·CHCl ₃	97	0
2	Pd(OAc) ₂	94 (46) ^d	0
3	Pd(OAc) ₂ ^e	0	69
4	Pd(PPh ₃) ₄	0	0
5	Pd(PPh ₃) ₂ Cl ₂	0	0
6	Pd(OAc) ₂ + 2 PPh ₃	0	23
7	Pd(OAc) ₂ + 2 TFP	89	0
8	Pd(OAc) ₂ + 4 TFP	77	0
9	Pd(OAc) ₂ + 2 (o-tolyl) ₃ P	54	0
10	Pd(OAc) ₂ + 2 AsPh ₃	57	0
11	Pd(OAc) ₂ + 2 BiPheCy ₂ P	87	0
12	Pd(OAc) ₂ + 2 Cy ₃ P	32	0
13	Pd(OAc) ₂ + 2 <i>t</i> -Bu ₃ P	96	0
14	Pd(OAc) ₂ + 2 (PhO) ₃ P	66	0
15	Pd(OAc) ₂ + 2 (MeO) ₃ P	86	0
16	Pd(OAc) ₂ + DPPF	0	96
17	Pd(OAc) ₂ + 2 DPPF	0	86
18	Pd(OAc) ₂ + DPPP	33	30
19	Pd(OAc) ₂ + 2 DPPP	0	66
20	Pd(OAc) ₂ + (±)-BINAP	97	0
21	Pd(OAc) ₂ + 2 (±)-BINAP	0	64

^a Reaction conditions: 9-benzyl-6-iodopurine, Pd catalyst corresponding to 5 mole % of Pd/substrate, *i*-Pr₂NEt (2 equiv.), DMF, 120 °C, 16 h. ^b Abbreviations: dba, 1,5-diphenyl-1,4-pentadien-3-one ligand; TFP, tri(2-furyl)phosphine; BiPheCy₂P, (2-biphenyl)dicyclohexylphosphine; Cy₃P, tricyclohexylphosphine; DPPF, 1,1'-bis(diphenylphosphino)ferrocene; DPPP, 1,3-bis(diphenylphosphino)propane; BINAP, 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene. ^c NMR yield (1,3,5-trinitrobenzene as internal standard). ^d Isolated yield. ^e 9-Benzyl-6-chloropurine (**1b**).

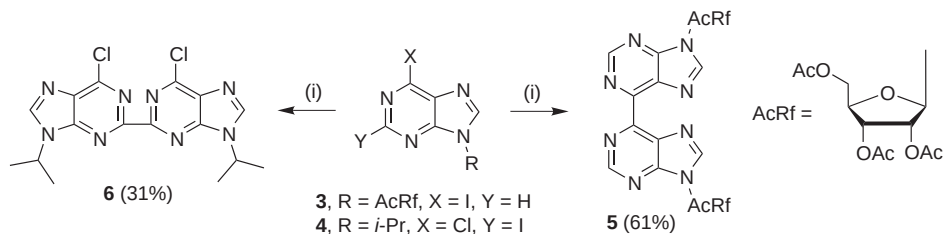
TABLE II
Influence of the base, solvent and temperature on the yield of dimer **2**^a

Entry	Solvent	Temperature, °C	Base	Yield of 2 , % ^b	Unreacted 1a , % ^b
1	DMF	120	<i>i</i> -Pr ₂ NEt	94	0
2	DMF	120	Et ₃ N	61	0
3	DMF	120	K ₂ CO ₃	0	0
4	DMF	120	none	0	0
5	DMF	100	<i>i</i> -Pr ₂ NEt	75	traces
6	DMF	80	<i>i</i> -Pr ₂ NEt	0	76
7	DMA	120	<i>i</i> -Pr ₂ NEt	95	0
8	Toluene	100	<i>i</i> -Pr ₂ NEt	0	62
9	MeCN	80	<i>i</i> -Pr ₂ NEt	0	77
10	(CH ₂ Cl) ₂	80	<i>i</i> -Pr ₂ NEt	0	89
11	THF	60	<i>i</i> -Pr ₂ NEt	0	96

^a Reaction conditions: 9-benzyl-6-iodopurine (**1a**), Pd(OAc)₂ (5 mole %), base (2 equiv.), 16 h.

^b NMR yield (1,3,5-trinitrobenzene as internal standard).

The optimized reaction conditions (Pd(OAc)₂, DMF, *i*-Pr₂NEt, 120 °C) were used to examine the reductive dimerization of acetylated 6-iodoribonucleoside **3** and 6-chloro-2-iodo-9-isopropylpurine (**4**), respectively (Scheme 2). While the 6,6'-dimeric nucleoside **5** was obtained in 61% yield, the yield of the purine 2,2'-dimer **6** was only 31%.

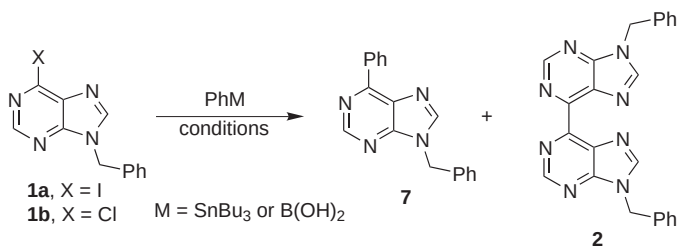


Reagents and conditions: (i) Pd(OAc)₂ (5 mole %), *i*-PrNEt (2 equiv.), DMF, 120 °C, 16 h

SCHEME 2

Reductive dimerization of aryl halides in the course of the palladium-catalyzed cross-coupling reactions has been documented many times. From the mechanistic point of view, formation of Pd^{IV} intermediate by repeated oxidative addition, disproportionation of the originally formed Pd^{II} intermediate to diarylpalladium and Pd^{II} halide, and Heck-type reaction of primarily formed arylpalladium halide with aryl halide followed by β -elimination of halogen have been considered⁹. However, to the best of our knowledge, no detailed mechanistic study has been made so far. In the course of the reductive coupling of the above halopurines, the palladium was necessarily oxidized to Pd^{II} . Since the reaction is catalytic with respect to palladium, the reduction of Pd^{II} to Pd^0 occurred, the most likely reducing agent being the amine used as a base. This explains that the reaction proceeds with $i\text{-Pr}_2\text{NEt}$ or Et_3N but not with K_2CO_3 .

As we have already mentioned, formation of the purine 6,6'-dimer **2** has been observed in Pd-catalyzed reactions of 9-benzyl-6-iodopurine (**1a**). Since cross-coupling reactions are commonly used for the preparation of purine derivatives, the formation of purine 6,6'-dimers under the conditions of the Stille and Suzuki–Miyaura coupling of **1a** was addressed. For this purpose, conditions described in the literature and also combinations of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ as a usual source of $\text{Pd}(0)$ with several phosphines were used (Scheme 3, Tables III and IV).



SCHEME 3

The Stille reaction has been commonly used for the preparation of 6-substituted purines⁴. Under the conditions reported by Gundersen^{4a,4b}, only the formation of the expected cross-coupling product **7** was observed in the reaction of **1a** or **1b** with tributyl(phenyl)stannane (Table III, entries 1, 2). Interestingly, in the case of iodo derivative **1a** only low conversion of the starting compound was observed. When $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ as phosphine-free catalyst was used for the coupling of **1a**, a significant amount of dimer **2** was formed together with the expected product of the cross-coupling reaction, compound **7**. The yield of **2** is practically independent of the cata-

lyst loading, while the yield of **7** decreases with decreasing amount of the catalyst (Table III, entries 3–5). Also, when tri(2-furyl)phosphine (entries 6 and 7) was used as ligand, formation of ca. 20% of the dimer **2** was observed regardless of the Pd/ligand ratio used. (±)-BINAP in the 1:1 Pd/ligand ratio gave a similar result (entry 8), while excess of (±)-BINAP suppressed the reaction (entry 9).

The Suzuki–Miyaura reaction, widely used in the synthesis of purine derivatives³ gave similar results to the Stille coupling. Under two previously described conditions (toluene or DME/H₂O mixture)^{3a}, only formation of the cross-coupling product **7** was observed in the presence of Pd(PPh₃)₄ with both chloro and iodo derivatives (Table IV, entries 1–4). Similarly to Stille coupling, the chloro derivative **1b** afforded a much higher yield of **7** compared with the iodo derivative **1a**. Again, when no triphenylphosphine was used for the reaction of iodo derivative **1a**, formation of dimer **2** was observed. Compared with the reaction in toluene, the amount of **2** was significantly higher if the reaction was run in DMF (Table III, entries 5–7). Surprisingly, 9-benzyl-6-chloropurine **1b** remained practically unchanged under these conditions (entry 8). With the TFP/Pd ratio 1:1, dimer **2** be-

TABLE III
Reductive dimerization as a side reaction in the Stille coupling (Scheme 3, M = SnBu₃)^a

Entry	X	Catalytic system ^b	Yield of 2 , % ^c	Yield of 7 , % ^c
1	Cl (1b)	Pd(PPh ₃) ₂ Cl ₂ ^e	0	69
2	I (1a)	Pd(PPh ₃) ₂ Cl ₂ ^f	0	19 (65) ^d
3	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃	16	76
4	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃	14	65 (21) ^d
5	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃	15	53 (30) ^d
6	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃ + 2 TFP	22	48
7	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃ ^f + 4 TFP	19	54
8	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃ + 2 (±)-BINAP	23	36
9	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃ + 4 (±)-BINAP	0	traces (90) ^d

^a Reaction conditions: 9-benzyl-6-iodopurine (**1a**) or 9-benzyl-6-chloropurine (**1b**), Pd catalyst (5 mole %), PhSnBu₃ (1.5 equiv.), DMF, 110 °C, 16 h. ^b For abbreviations see Table I, note ^b. ^c NMR yield (1,3,5-trinitrobenzene as internal standard). ^d Unreacted starting compound. ^e 2.5 mole % of the catalyst. ^f 1.25 mole % of the catalyst.

came the main product (entry 9). Excess of TFP suppresses formation of both the dimer **2** and also the coupling product **7** (entries 10 and 11). The effect of ($\pm$)-BINAP as a representative of bidentate ligands is similar (entries 12 and 13).

In the above cross-coupling reactions tertiary amines as reducing agents do not participate. In these reactions, DMF, which is known to decompose at high temperatures forming CO and dimethylamine, may serve as reducing agent. When DMF is not present, the dimerization also proceeds, but to a much lower extent. In this case stannane or boronic acid used in the reaction play probably the role of the reducing agents.

TABLE IV
Reductive dimerization as a side reaction in the Suzuki–Miyaura coupling (Scheme 3, M = B(OH)₂)^a

Entry	X	Catalytic system ^b	Solvent	Yield of 2 , % ^c	Yield of 7 , % ^c
1	Cl (1b)	Pd(PPh ₃) ₄	toluene	0	95 ^d
2	Cl (1b)	Pd(PPh ₃) ₄	DME/H ₂ O	0	95 ^d
3	I (1a)	Pd(PPh ₃) ₄	toluene	0	40
4	I (1a)	Pd(PPh ₃) ₄	DME/H ₂ O	0	32 (64) ^e
5	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃	toluene	6	16 (45) ^e
6	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃	DMF	55	43
7	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃ ^f	DMF	26	30 (35) ^e
8	Cl (1b)	Pd ₂ (dba) ₃ ·CHCl ₃	DMF	0	(96) ^e
9	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃ + 2 TFP	DMF	45	18
10	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃ ^f + 4 TFP	DMF	8	13 (69) ^e
11	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃ ^g + 8 TFP	DMF	4	7 (50) ^e
12	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃ + 2 ($\pm$)-BINAP	DMF	26	54 (10) ^e
13	I (1a)	Pd ₂ (dba) ₃ ·CHCl ₃ + 4 ($\pm$)-BINAP	DMF	0	0 (38) ^e

^a Reaction conditions^{9a}: 9-benzyl-6-iodopurine (**1a**) or 9-benzyl-6-chloropurine (**1b**), PhB(OH)₂ (1.2 equiv.), Pd catalyst (5 mole %), 2 M aq. K₂CO₃ (1.25 equiv.), DME, 80 °C, 16 h. With other solvents, dry K₂CO₃ (1.25 equiv.) at 100 °C was used. ^b For abbreviations see Table I, note ^b. ^c NMR yield (1,3,5-trinitrobenzene as internal standard). ^d Ref.^{3a}. ^e Unreacted starting compound. ^f 2.5 mole % of the catalyst. ^g 1.25 mole % of the catalyst.

It is worth noting, that in both reactions 9-benzyl-6-chloropurine always gives higher yields of the cross-coupled product than 6-iodo derivative regardless of whether the dimer is formed or not. 9-Benzyl-6-iodopurine tends to decompose under the conditions of Pd-catalyzed reactions. Thus, 9-benzyl-6-chloropurine is a much better substrate for cross-coupling reactions.

In conclusion, iodopurines are prone to form symmetrical C–C dimers in the presence of Pd catalysts, especially when tertiary amines are used. Their tendency to dimerize is significant in polar solvents like DMF at temperatures above 100 °C. The nature of the used ligand is also important. Dimers are not formed when the catalyst contains triphenylphosphine ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{OAc})_2 + \text{PPh}_3$, etc.), while in the presence of other phosphines or under ligand-free conditions the dimerization proceeds. Bidentate ligands except of BINAP suppress dimerization, especially when two equivalents to the palladium are used. The formation of 6,6'-purine dimers may become an important side reaction in the Suzuki–Miyaura and Stille reactions of 6-iodopurines. To avoid dimerization, the following suggestions can be summarized: chloro derivatives are more suitable for cross-coupling reactions than the corresponding iodo derivatives. The yield of the cross-coupled product is always higher compared with 6-iodo derivative and the dimer is not formed. If possible, the reaction should be catalyzed with PPh_3 -containing catalysts below 100 °C. Polar solvents like DMF or DMA should be avoided.

The described symmetrical 6,6'- and 2,2'-purine dimers are new compounds, which can be obtained by the above Pd-catalyzed dimerization. The reaction proceeds with high yields, however, the product isolation is laborious and is accompanied by high losses due to highly polar nature of these compounds. Therefore, we developed a different, more convenient approach to these compounds (based on Cu(I) mediated dimerization of iodopurines). This will be the subject of separate publication.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. NMR spectra (δ , ppm; J , Hz) were measured on a Varian Gemini 300 (^1H , 300.07 MHz; ^{13}C , 75.46 MHz) spectrometer at 298 K. Unambiguous assignment of NMR signals is based on $^{13}\text{C}\{^1\text{H}\}$, ^{13}C APT, COSY, ^1H - ^{13}C HMQC and ^1H - ^{13}C HMBC spectra. IR spectra (cm^{-1}) were recorded on a Nicolet 750 FT-IR. Mass spectra were measured on an Autospec Ultima (Micromass) spectrometer. The solvents were dried and degassed by standard procedures. Silica gel (ICN SiliTech, 32-63) was used for column chromatography. 9-Benzyl-6-iodopurine^{4a} (**1**), 6-iodo-

9-(*O*-triacetyl- β -D-ribofuranosyl)purine¹⁰ and 6-chloro-2-iodo-9-isopropylpurine¹¹ (**4**) were prepared by the reported procedures.

General Procedure for Palladium-Catalyzed Reductive Dimerization of Iodopurines

To a mixture of iodopurine (0.25 mmol) and Pd(OAc)₂ (3 mg, 0.0125 mmol) under argon, DMF (3 ml) was added followed by *i*-Pr₂NEt (0.09 ml, 0.5 mmol). The resulting mixture was heated to 120 °C and stirred for 16 h. DMF was then removed in vacuum, the resulting solid was dissolved in acetone and supported on silica (2 g). Flash chromatography in ethyl acetate:methanol 9:1 afforded the corresponding dimer.

9,9'-Dibenzyl-9*H*,9*H*'-6,6'-bipurine (**2**). Yield 46%. ¹H NMR (CDCl₃, 300 MHz): 5.54 (s, 4 H, CH₂Ph); 7.36 (br s, 10 H, ArH); 8.23 (s, 2 H, H-8); 9.31 (s, 2 H, H-2). ¹³C NMR (CDCl₃, 75 MHz): 47.5, 127.8, 128.6, 129.1, 132.2, 134.7, 146.2, 151.8, 152.7, 153.1. IR (CHCl₃): 2992, 1578, 1568, 1498, 1457, 1438, 1397, 1329, 1254, 1201, 1174. HR-MS (EI): calculated for C₂₄H₁₈N₈ 418.1654, found 418.1643.

9,9'-Bis(*O*-triacetyl- β -D-ribofuranosyl)-9*H*,9*H*'-6,6'-bipurine (**5**). Yield 61%. ¹H NMR (CDCl₃, 300 MHz): 2.09 (s, 6 H, COCH₃); 2.14 (s, 6 H, COCH₃); 2.17 (s, 6 H, COCH₃); 4.44 (m, 4 H, OCH₂); 4.51 (m, 2 H, CH₂CHO); 5.68 (m, 2 H, CHOAc); 6.01 (t, *J* = 5.77, 2 H, CHOAc); 6.37 (d, *J* = 5.77, 2 H, CH); 8.45 (s, 2 H, H-8); 9.30 (s, 2 H, H-2). ¹³C NMR (CDCl₃, 75 MHz): 20.3, 20.5, 20.7, 63.0, 70.7, 73.0, 80.6, 86.1, 133.0, 144.7, 152.0, 152.8, 152.9, 169.2, 169.5, 170.2. IR (CHCl₃): 2869, 1752, 1673, 1581, 1491, 1437, 1388, 1330, 1266, 1226. HR-MS (EI): calculated for C₃₂H₃₄N₈O₁₄ 754.2194, found 754.2168.

6,6'-Dichloro-9,9'-diisopropyl-9*H*,9*H*'-2,2'-bipurine (**6**). Yield 31%. ¹H NMR (CDCl₃, 300 MHz): 1.71 (d, *J* = 6.78, 12 H, CH(CH₃)₂); 5.24 (m, 2 H, CH(CH₃)₂); 8.33 (s, 2 H, H-8). ¹³C NMR (CDCl₃, 75 MHz): 23.0, 47.8, 131.7, 144.2, 151.4, 152.1, 155.9. IR (CHCl₃): 2992, 1729, 1591, 1554, 1489, 1462, 1395, 1376, 1363, 1325. HR-MS (EI): calculated for C₁₆H₁₆Cl₂N₈ 390.0875, found 390.0877.

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