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Direct C–H Arylation of Purines: Development of Methodology and Its Use in Regioselective Synthesis of 2,6,8-Trisubstituted Purines

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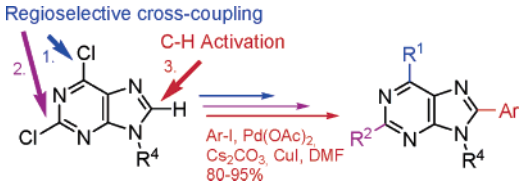
ABSTRACT



Direct C–H arylation of purines to position 8 by diverse aryl iodides was achieved with Pd catalysis in the presence of CuI and Cs_2CO_3. The methodology is general and efficient and was applied in the consecutive regioselective synthesis of 2,6,8-trisubstituted purines bearing three different C-substituents in combination with two cross-coupling reactions.

2,6,9-Tri- and 2,6,8,9-tetrasubstituted purines display a wide range of biological activities, i.e., inhibition of kinases,[1] tubulin polymerization,[2] antagonist effects to receptors,[3] etc. Combinatorial libraries of these compounds were prepared[4] on the solid-phase with regioselective nucleophilic substitutions of dihalopurines. However, regioselective introduction of C-substituents by cross-coupling reactions[5] is more problematic. While 2,6- and 6,8-dihalopurines give regioselective cross-couplings with most types of organometallics,[6] reactions of 2,6,8-trichloropurine proceed unselectively giving mixtures of products.[7] Therefore, we decided to combine the regioselective cross-couplings of 2,6-dihalopurines with direct C−H arylation in position 8 to develop a general selective approach to 2,6,8-trisubstituted purines bearing three different C-substituents.

C−H activation reactions have received prominent attention[8] in recent years as an alternative to cross-coupling reactions with use of organometallics. Direct C−H arylation of arenes and heterocycles has been achieved by using, e.g., Rh,[9] Ru,[10] or Pd[11,12] catalysis with different bases and many types of aryl halides. To the best of our knowledge, the only

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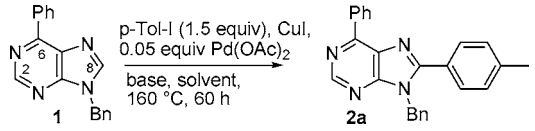
reported example of a direct C−H functionalization of purine moiety is a Rh-catalyzed alkylation by 3,3-dimethylbut-1-ene.[13] Here we report on the development of novel methodology of arylation of purines to position 8 by direct C−H arylation.

After some initial unsuccessful attempts on reactions of **1** with *p*-Tol-I under Rh and Co catalyses using diverse bases, we have focused on Pd catalysis with Cs salts as bases in the presence of CuI and PPh_3 in analogy to the systems recently applied to imidazoles.[12] Optimization of solvents (Table 1, entries 1 and 2) showed that DMF is the most

Table 1. Optimization of Direct Coupling of **1** with 4-MePh-I



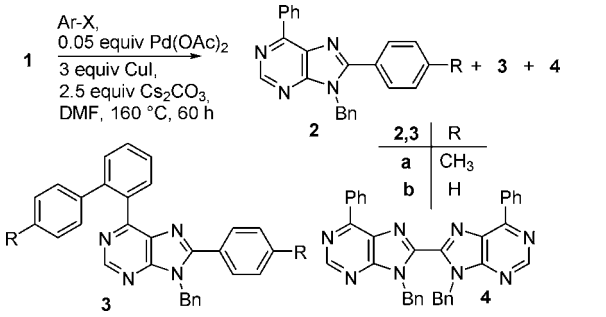
entry	base (equiv)	CuI (equiv)	solvent	ligand (mol %)	yield (%)
1	Cs_2CO_3 (1.5)	0.2	other[a]	PPh_3 (20)	traces
2	Cs_2CO_3 (1.5)	0.2	DMF	PPh_3 (20)	39
3	Cs_2CO_3 (1.5)	0.2	DMF	none	48
4	CsF (1.5)	0.2	DMF	none	12
5	Cs_2CO_3 (2.5)	2	DMF	none	87
6	Cs_2CO_3 (2.5)	3	DMF	none	95[b]
7	None	3	DMF	none	36

[a] Dioxane, acetonitrile, or toluene. [b] 2 equiv of 4-MePhI was used.

suitable, giving product **2a** in 39% yield after 60 h. Surprisingly, the same reaction without phosphine ligand gave an even better yield of 48% (entry 3) and therefore other experiments were performed ligandless. The use of CsF as base led to a decrease of the yield (entry 4). Increasing the amounts of CuI (2 equiv) and Cs_2CO_3 (2.5 equiv) afforded **2a** in a good yield of 87% (entry 5). Further increase of the amounts of Tol-I (2 equiv) and CuI (3 equiv) led to nearly quantitative yield of the product **2a** (entry 6) but still the reaction was quite slow and required 60 h at 160 °C to reach full conversion (analogous experiment at 120 °C gave just 50% conversion). The reaction in the absence of base[14] (entry 7) proceeded with a very low conversion of 36%. Thus the optimized conditions (entry 6) with CuI (3 equiv) and Cs_2CO_3 (2.5 equiv) at 160 °C were used[15] in further experiments.

When performing larger scale reactions in larger vials, we have observed formation of some byproducts in isolable amounts. To rationalize their formation, a set of reactions of **1** with Tol-I and Ph-I (2 or 10 equiv) in argon-purged small vials or in bigger vials set up in air was performed (Table 2). Reactions with 2 equiv of Ar-I in small (nearly

Table 2. Influence of Conditions to Formation of Byproducts



entry	reaction vessel[a]	ArI (equiv)	yield (%) 2	3	4
1	A	*p*-Tol-I (2)	95	traces	traces
2	B	*p*-Tol-I (2)	87	6	4[b]
3	B	*p*-Tol-I (10)	30	47	0
4	A	Ph-I (2)	92	traces	traces
5	B	Ph-I (2)	88	6	3[b]
6	B	Ph-I (10)	31	54	0
7	C	*p*-Tol-I (2)	10	5	11[b]

[a] A: 0.5 mmol, argon purged sealed 3 mL vial. B: 1 mmol, septum sealed 20 mL vial set up in air. C: 1 mmol, 20 mL vial opened to air. [b] Yields of **4** were recalculated on 0.5 mmol of **1**.

full) argon-purged sealed vials gave cleanly 8-arylpurines **2a**,**b** in excellent yields (entries 1 and 4). On the other hand, reactions performed in larger vials (1/4 full) set up in air and sealed by septum without purging with argon gave two types of byproducts in 2−6% yields (apparently caused by traces of oxygen). The first type of byproduct was identified as the product of double arylation to position 8 and to the ortho position of the phenyl group in position 6 (compounds **3a**,**b**). The second byproduct was 8,8′-bispurine **4**, so far unprecedented in the literature.[16] Its structure was determined by X-ray diffraction (Figure 1). Reactions with 10 equiv of

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(14) Analogy to conditions successfully used for arylation of imidazoles and benzimidazoles in ref 12c.

(15) General procedure: DMF (6 mL) was added through a septum to an argon purged vial containing **1** (286 mg, 1 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol %), CuI (571 mg, 3 mmol), aryl halide (2 mmol), and Cs_2CO_3 (815 mg, 2.5 mmol). The reaction mixture was heated to 160 °C for 60 h. The solvent was evaporated and products were isolated by flash column chromatography (gradient elution hexanes → ethyl acetate/hexanes 1:1). Analytical samples were crystalized from a mixture of $CHCl_3$/heptane.

(16) The only two known related examples of C−H homocoupling of heterocycles: (a) a Cu-mediated dimerization of benzothiazole: Chodowska-Palicka, J.; Nilsson, M. *Synthesis* **1974**, 128−129. (b) Recently described Pd-catalyzed dimerization of bromothiophenes in the presence of AgF: Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10930−10933.

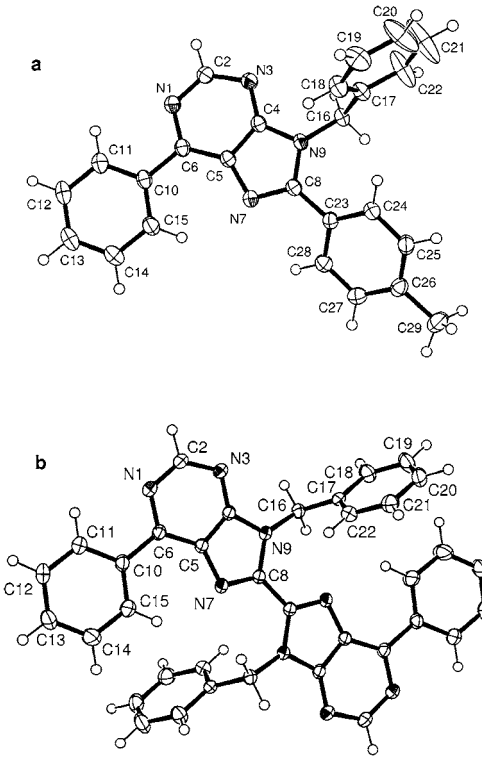


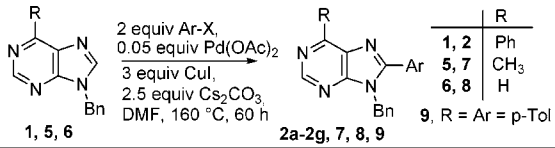
Figure 1. Crystals structures of **2a** (a, CCDC 617551) and **4** (b, CCDC 617550). Thermal ellipsoids at the 50% probability level.

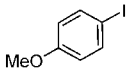
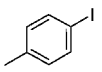
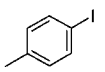
Ar-I set up in air gave rise to diarylated products **3a** or **3b** in ca. 50% yields. To further examine the influence of an excess of oxygen, an experiment fully opened to air was also performed (entry 7). The conversion was quite low (ca 26%) but the ratio of **2a** and dimer **4** was ca. 1:1 showing the crucial importance of oxygen for the side reaction. The mechanism of this reaction will be a subject of further studies but we suppose that it may consist of oxidative dimerization of 8-organocopper purine intermediates.

The optimized procedure was then used for introduction of diverse aryl groups to position 8 of several purines (Table 3). Arylation with substituted iodobenzenes proceeded very smoothly to give desired products **2a**−**e** in high yields around 90%. For comparison, *p*-Tol-Br underwent the reaction with significantly lower yield of 62% (entry 2). Reactions with iodopyridines proceeded with lower conversions to give products **2f**,**g** in 42% and 48%, respectively. Also 9-benzyl-6-methylpurine (**5**) underwent C−H activation selectively in position 8 to give product **7** in 82% yield (entry 9). Then we have tried a reaction of 6-unsubstituted 9-benzylpurine **6** to check whether the C−H in position 8 will still be preferentially substituted in competition with C−H in position 6. This reaction gave quite selectively the 8-arylpurine **8** in 86% accompanied by only a very minor amount (4%) of 6,8-diarylated product **9** confirming that C−H in position 8 is the most easily substituted.

Finally, the optimized experimental conditions for direct C−H arylation of purines in position 8 were applied to a sequential three-step synthesis of 2,6,8-trisubstituted purines

Table 3. Arylation of Purines to Position 8 by Optimized Procedure

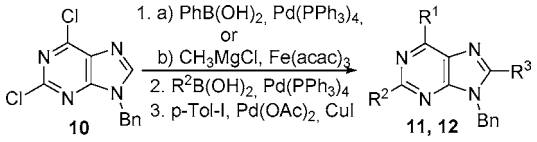


entry	purine	R	Ar-X	yield (%)
1	**1**	Ph		**2a** (95%)
2	**1**	Ph		**2a** (62%)
3	**1**	Ph		**2b** (92%)
4	**1**	Ph		**2c** (90%)
5	**1**	Ph		**2d** (85%)
6	**1**	Ph		**2e** (89%)
7	**1**	Ph		**2f** (42%)
8	**1**	Ph		**2g** (48%)
9	**5**	CH_3		**7** (82%)
10	**6**	H		**8** (86%)[a]

[a] Accompanied by 4% 9-benzyl-6,8-bis(*p*-tolyl)purine (**9**).

(Table 4). 9-Benzyl-2,6-dichloropurine (**10**) was reacted successively in one pot with two different arylboronic acids[6c]

Table 4. Consecutive Synthesis of 2,6,8-Trisubstituted Purines



entry	R^1	R^2	R^3	product	yield (%)
1	Ph	4-MeOPh	*p*-Tol	**11**	65[a]
2	Me	Ph	*p*-Tol	**12**	56[b]

[a] The first two steps were done in one pot, then the mixture was filtered and evaporated and the crude residue was directly used for the third step. [b] After the first step, the intermediate was isolated and used for the second step and then the reaction mixture was just filtered and evaporated and the crude residue was used for the last step.

and then, without isolation, the reaction mixture was just filtered, evaporated, and directly used for C−H arylation with *p*-tolyl iodide. The first aryl group was introduced to position 6, the second to position 2, and the third one to position 8 to give the desired product **11** in good total yield (65% over three steps). Analogously, **10** was methylated selectively to position 6 by Fe-catalyzed reaction with MeMgCl,[6d] followed by the Suzuki cross-coupling with phenylboronic acid in position 2 and C−H arylation with *p*-tolyl iodide in position 8 to give **12** in 56% yield.

In conclusion, a general Pd-catalyzed arylation of purines with aryl iodides by C−H activation in position 8 was developed by using Cs_2CO_3 and CuI as additives. Though the reaction conditions are rather harsh, the method can be efficiently applied in the synthesis of diverse 8-arylpurines and, in combination with regioselective cross-coupling reactions[6] of 2,6-dichloropurines, of 2,6,8-trisubstituted purines bearing three different C-substituents, analogues of important biologically active compounds.

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Supporting Information Available: Experimental procedures, analytical and spectral data, crystallographic data for **2a** and **4**, HMBC analysis of **3a**, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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