The first direct C–H arylation of purine nucleosides†

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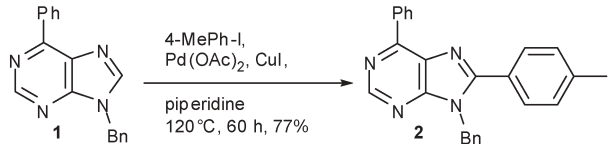
Pd-catalyzed direct C–H arylation of unprotected purine nucleosides with aryl iodides at position 8 was developed to allow a straightforward single-step introduction of diverse aryl groups.

8-Arylpurine nucleosides are metabolites[1] of DNA damage by arylhydrazines and they find a wide range of applications in self-assembly[2] and as optical probes[3] for oligonucleotide hybridization. They are usually prepared by cross-coupling reactions[4] of arylstannanes or arylboronic acids with protected 8-bromopurine nucleosides in organic solvents. Recently, aqueous-phase Suzuki–Miyaura reactions of unprotected 8-bromopurine nucleosides with boronic acids have been developed,[5] allowing a straightforward synthesis of the 8-arylpurine nucleosides. However, there is still a need for new alternative efficient methodologies for the synthesis of these important compounds, especially for aryl groups where the corresponding organometallic reagent is not readily accessible or sufficiently stable or reactive.

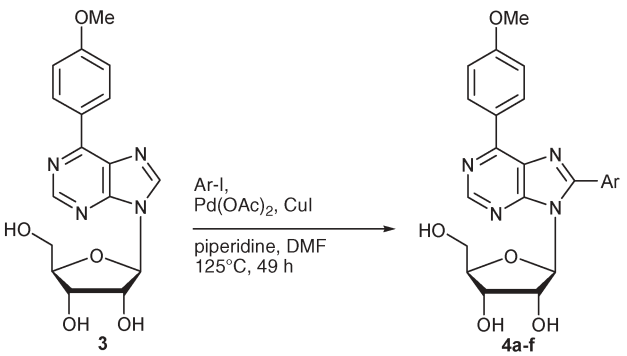
Direct C–H arylation is one of the most efficient and useful methods of C–H activation[6] and, as an alternative to classical cross-coupling reactions, it was applied to many carbo- and heterocycles.[7] Recently, we have developed[8] a new efficient Pd-catalyzed direct C–H arylation of 9-benzylpurines at position 8 with aryl iodides in the presence of CuI and Cs_2CO_3 in DMF and used[8] it in combination with cross-couplings for regioselective consecutive synthesis of 6,8-di- and 2,6,8-trisubstituted purines. Here we report on the extension of this methodology to arylation of unprotected purine nucleosides.

Our previously reported protocol[8] for direct C–H arylation of purines used rather harsh conditions (160 °C) and long reaction times (60 h) to achieve efficient conversions. Such conditions are not compatible with rather labile nucleosides and therefore, for such applications, the procedure must be further optimized to lower the temperature. Based on the assumption that the long-term heating of DMF generates some dimethylamine which may influence the rate of the reaction, we have used piperidine (4 equiv.) as a higher-boiling secondary amine in the model reaction of 9-benzyl-6-phenylpurine (**1**) with 4-tolyl iodide (Scheme 1). Indeed, we have found that it accelerates the reaction and even at 120 °C the 8-arylpurine product **2** was formed in a good yield of 77% after 60 h.



Scheme 1 Model C–H arylation of 9-benzyl-6-phenylpurine.

Under such conditions purine nucleosides should be reasonably stable and therefore we have used the reaction for model C–H arylation of an unprotected 6-(4-methoxyphenyl)purine ribonucleoside (**3**, Scheme 2, Table 1). In the first experiment (entry 1), nucleoside **3** reacted with 4-tolyl iodide (2 equiv.) in the presence of $Pd(OAc)_2$ (5 mol%), CuI (3 equiv.) and piperidine (5 equiv.) in DMF at 125 °C for 20 h. The desired 8-tolylpurine nucleoside **4a** was isolated in 39% yield along with unreacted starting compound (*ca.* 30%) and some unidentified by-products of decomposition. When the same reaction was performed for 49 h, the isolated yield of **4a** was improved to 50% (entry 2). Further prolongation of reaction time led to a higher degree of decomposition and did not bring any improvement in the yield of **4a**. Therefore, further experiments with other aryl halides were performed under the above-mentioned conditions for 49 h. 4-Tolyl bromide was



Scheme 2 C–H arylation of 6-(4-methoxyphenyl)purine ribonucleoside.

Table 1 C–H arylations of nucleoside **3**

Entry	Ar–X	Product	Yield (%)
1	4-Tol–I	**4a**	39[a]
2	4-Tol–I	**4a**	50
3	4-Tol–Br	**4a**	30
4	Ph–I	**4b**	43
5	3-Tol–I	**4c**	47
6	4-MeOPh–I	**4d**	45
7	2-Tol–I	**4e**	27
8	1-pyrenyl–Br	**4f**	30

[a] Reaction time 20 h.

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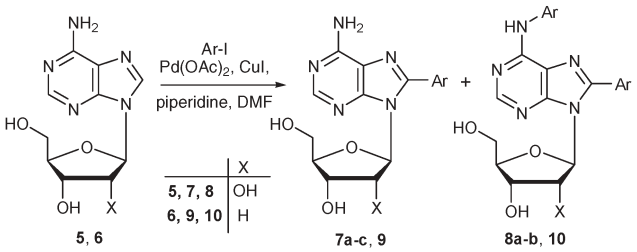

Scheme 3 C–H arylation of adenosines.

Table 2 C–H arylation of adenosines **5** and **6**

Entry	5,6	Time/temperature	Ar–X	Products (Yields)
1	**5**	22 h/100 °C	4-Tol–I	**7a** (50%) **8a** (12%)
2	**5**	20 h/125 °C	4-Tol–I	**7a** (56%) **8a** (18%)
3	**5**	60 h/150 °C	4-Tol–I	decomposition
4	**5**	5 h/150 °C	4-Tol–I	**7a** (68%) **8a** (15%)
5	**5**	5 h/150 °C	3-Tol–I	**7b** (55%) **8b** (12%)
6	**5**	5 h/150 °C	1-pyrenyl–Br	**7c** (62%) —
7	**6**	5 h/150 °C	4-Tol–I	decomposition
8	**6**	5 h/125 °C	4-Tol–I	**9** (31%) **10** (8%)

somewhat less reactive, giving **4a** in 30% yield. Iodobenzene, 3-tolyl iodide and 4-methoxyphenyl iodide reacted reasonably well, giving the corresponding nucleosides **4b–4d** in acceptable yields of 43–47%. The more sterically hindered 2-tolyl iodide gave nucleoside **4e** in a lower 27% yield. 1-Bromopyrene was also less reactive but still gave the 8-pyrenylpurine nucleoside **4f** in 30% yield.

Having this straightforward methodology in hand, we further explored the possibility of direct arylation of natural adenine nucleosides **5** and **6**. The first experiments were performed with the more stable adenosine **5** (Scheme 3, Table 2). Its reaction with 4-tolyl iodide under analogous conditions at 100 °C for 22 h gave 8-tolyladenosine (**7a**) in a good yield of 50%. A side-product of this reaction was the N^6,8-diarylated nucleoside **8a** (12%) as the product of subsequent Cu-catalyzed *N*-arylation. TLC analysis showed the presence of a significant amount of starting compound which was not isolated due to its immobility on the chromatography column. When the reaction was performed at 125 °C, the conversion was somewhat higher to give 56% of the desired **7a** and 18% of diarylated nucleoside **8a**. The same reaction at 150 °C for 60 h gave complete decomposition of the nucleosides. However, when the reaction was performed at 150 °C for just 5 h, **7a** was isolated in 68% yield. This optimized procedure was then used for arylation of **5** with other aryl halides. Its reaction with 3-tolyl iodide gave the desired 8-aryladenosine **7b** in 55% yield accompanied by 12% of the diarylated **8b**. Reaction of **5** with 1-bromopyrene gave the 8-(pyren-1-yl)adenosine **7c** in a good yield of 62% (no diarylated by-product was observed in this case). Finally, labile 2′-deoxyadenosine **6** was tested as a substrate for the C–H arylation. Here, we had to use a lower temperature (125 °C) for a shorter time (5 h) to prevent decomposition (entries 7,8). Under such conditions, 8-tolyl-2′-deoxyadenosine (**9**) was isolated in an acceptable 31% yield along with diarylated compound **10** (8%).

In conclusion, the use of piperidine as a base in direct C–H arylation of purines makes it possible to decrease the reaction temperature and apply this reaction for arylation of nucleosides. Unprotected purine nucleosides can be easily arylated by diverse aryl iodides or bromides at position 8 in *ca.* 30–70% yields using this methodology. In arylation of adenosines N^6,8-diarylated minor side-products are also formed in *ca.* 10% yields. Though the yields of the desired 8-arylated nucleosides are rather moderate and lower than in most cross-coupling reactions of 8-bromopurine nucleosides with arylstannanes or -boronic acids, this methodology is applicable directly to purine nucleosides without the need to halogenate them and makes use of easily available aryl iodides rather than the more expensive arylboronic acids or toxic arylstannanes and thus saves 1–2 steps of the synthesis. Also it can be an attractive alternative in cases where the corresponding organometallic reagent is inaccessible or unstable. It is the first example of successful direct C–H arylation of purine nucleosides and work on further applications of this methodology in the synthesis of modified nucleosides or oligonucleotides is under way.

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Notes and references

1 (*a*) K. Kohda, H. Tsunomoto, T. Kasamatsu, F. Sawamura, I. Teashima and S. Shibutani, *Chem. Res. Toxicol.*, 1997, **10**, 1351–1358; (*b*) P. M. Ganett, J. H. Powell, R. Rao, X. Shi, T. Lawson, C. Kolar and B. Toth, *Chem. Res. Toxicol.*, 1999, **12**, 297–304; (*c*) Q. Dai, D. Xu, K. Lim and R. G. Harvey, *J. Org. Chem.*, 2007, **72**, 4856–4863.

2 (*a*) J. L. Sessler and J. Jayawickramarajah, *Chem. Commun.*, 2005, 1939–1949; (*b*) J. L. Sessler, C. M. Lawrence and J. Jayawickramarajah, *Chem. Soc. Rev.*, 2007, **36**, 314–325; (*c*) J. L. Sessler, J. Jayawickramarajah, C. L. Sherman and J. S. Brodbeldt, *J. Am. Chem. Soc.*, 2004, **126**, 11460–11461; (*d*) J. L. Sessler, M. Sathiosatham, C. T. Brown, T. A. Rhosdes and G. Wiederrecht, *J. Am. Chem. Soc.*, 2001, **123**, 3655–3660; (*e*) V. Gubala, J. E. Betancourt and J. M. Rivera, *Org. Lett.*, 2004, **6**, 4735–4738.

3 (*a*) E. Mayer, L. Valis, R. Huber, N. Amann and H.-A. Wagenknecht, *Synthesis*, 2003, 2335–2340; (*b*) L. Valis and H.-A. Wagenknecht, *Synlett*, 2005, 2281–2284; (*c*) L. Valis, E. Mayer-Enthart and H.-A. Wagenknecht, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3184–3187.

4 For reviews on cross-coupling reactions of purines see: (*a*) M. Hocek, *Eur. J. Org. Chem.*, 2003, 245–254; (*b*) L. A. Agrofoglio, I. Gillaizeau and Y. Saito, *Chem. Rev.*, 2003, **103**, 1875–1916.

5 (*a*) E. C. Western, J. R. Daft, E. M. Johnson, P. M. Gannett and K. H. Shaughnessy, *J. Org. Chem.*, 2003, **68**, 6767–6774; (*b*) E. C. Western and K. H. Shaughnessy, *J. Org. Chem.*, 2005, **70**, 6378–6388; (*c*) P. Čapek and M. Hocek, *Synlett*, 2005, 3005–3007; (*d*) P. Čapek, R. Pohl and M. Hocek, *Org. Biomol. Chem.*, 2006, **4**, 2278–2284; (*e*) M. Vrábel, R. Pohl, B. Klepetářová, I. Votruba and M. Hocek, *Org. Biomol. Chem.*, 2007, **5**, 2849–2857.

6 Reviews: (*a*) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, **417**, 507–514; (*b*) K. Godula and D. Sames, *Science*, 2006, **312**, 67–72.

7 (*a*) F. Bellina, S. Cauteruccio, L. Mannina, R. Rossi and S. Viel, *J. Org. Chem.*, 2005, **70**, 3997–4005; (*b*) F. Bellina, S. Cauteruccio, L. Mannina, R. Rossi and S. Viel, *Eur. J. Org. Chem.*, 2005, 693–703; (*c*) F. Bellina, S. Cauteruccio and R. Rossi, *Eur. J. Org. Chem.*, 2006, 1379–1382; (*d*) F. Bellina, C. Calandri, S. Cauteruccio and R. Rossi, *Tetrahedron*, 2007, **63**, 1970–1980; (*e*) Review: I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173–1193.

8 I. Čerňa, R. Pohl, B. Klepetářová and M. Hocek, *Org. Lett.*, 2006, **8**, 5389–5392.

