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Microwave-assisted $Pd(OH)_2$-catalyzed direct C–H arylation of free-(NH_2) adenines with aryl halides

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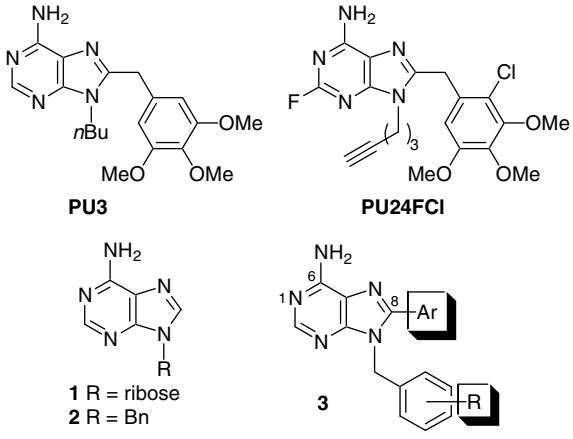
ABSTRACT

A direct C–H arylation of free-(NH_2) adenines using $Pd(OH)_2/C$ (Pearlman's catalyst) and stoichiometric amount of copper iodide under ligandless microwave activation is described. This new protocol proved to be highly effective to synthesize a variety of 8-aryladenine derivatives **3** without prior protection of the amino substituent. The arylation reaction takes place rapidly within few minutes and allows the coupling to proceed regioselectively at the 8-position with a wide range of aryl halides including aryl iodides, bromides and the less reactive aryl chlorides.

Substituted purines are important structural elements of therapeutic drug molecules, and have been demonstrated to provide high-affinity ligands for a variety of proteins.[1] Many molecules bearing this heterocycle nucleus are well known to display a wide variety of interesting biological properties. Some of them are reported as cyclin-dependent kinase inhibitors,[2] adenosine receptor antagonists,[3] modulators of multidrug resistance,[4] antiviral[5] and antineoplastic agents.[6] Recent works demonstrated that C8-substituted purine derivatives having a C6 free-amino group, such as PU3, PU24FCl as well as their 8-arylsulfanyl analogues,[7] have emerged as hsp90 inhibitors, an exciting new target in cancer drug discovery.[8]

In an ongoing medicinal chemistry programme towards hsp90,[9] we required a rapid and versatile access to 8-aryladenines of type **3**, which includes two centres for introduction of diversity into adenine molecule. The literature reports a short number of synthetic routes to these compounds. They are usually prepared by the Pd-catalyzed C–C cross-coupling of organometallic reagents[10] with *N*-protected 8-bromoadenines. While these reactions are suitable methods, they require the preparation of either or both reagents using multi-step reaction sequences therefore time-consuming and economically inefficient. (see Scheme 1)

Over the past decade, direct C–H arylation of heteroarenes[11] has been intensively studied as an attractive and a simple alternative to traditional cross-coupling methods for creating hetero-



Scheme 1.

aryl–aryl bonds. Hocek[12] and Fairlamb[13] described the direct aryl functionalization of free-(NH_2) adenine nucleosides **1** to give in moderate to good yields C8-arylated adenine nucleoside derivatives together with a small amount of N-arylation products.[12a] In both studies, optimal conditions were found to require $Pd(OAc)_2$ as a catalyst in association with CuI, Cs_2CO_3 or piperidine as a base and heating in DMF. Although progress has been made for this reaction, it requires prolonged reaction times (5–13 h) that can seriously affect the yield of the C–H arylation and the use of a large excess of CuI (3 equiv) as additive. Additionally, in most cases, only

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aryl iodide reagents are used. To our knowledge, cheaper and generally more available aryl chlorides have never been employed.[14] Therefore, alternative routes and more reliable procedures for this transformation are welcome. The remaining challenge is to develop a simple catalytic system for such transformation without compromising reagent safety, simplicity, and practicality. Herein we report our general approach to provide a variety of 8-aryladenine derivatives **3** from various aryl halides including aryl iodides, bromides as well as the less reactive aryl chlorides. We found that the use of $Pd(OH)_2/C$ (Pearlman's catalyst) under ligandless microwave irradiations proves to be an efficient catalyst system allowing the reaction to take place rapidly (from hours to just few minutes), even when using a stoichiometric amount of copper salt.

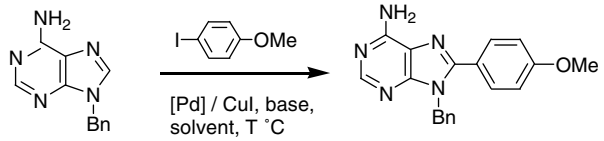
To optimize experimental conditions for the preparation of target compounds **3**, the coupling of unprotected adenine **2** with 4-iodoanisole was selected as a model reaction. The results are summarized in Table 1.

Initially the reaction was investigated according to Hocek procedure: $Pd(OAc)_2$ (5 mol %), CuI (3 equiv), piperidine (5 equiv) in DMF.[12a] After heating at 120 °C for 20 h, the expected coupling product **3a** was formed in 55% yield (entry 1). Increasing the temperature to 150 °C for 5 h gave a slightly better result (entry 2). Switching to Fairlamb conditions[13] (Cs_2CO_3 as a base instead of piperidine, 120 °C, 13 h) gave the target 8-aryladenine **3a**, but in a lower yield (45%, entry 3), even when the reaction was carried out at 160 °C (25%, entry 4). The palladium source was then explored. Thus, when running the reaction in DMF at 160 °C with $Pd_2(dba)_3$ instead of $Pd(OAc)_2$, contrary to Fairlamb conditions,[13] high rate was observed, and direct C–H arylation reaction of **2** provided **3a** in 56% yield within 4 h (entry 5). Of the palladium sources screened, the highest yield was achieved by using $Pd(OH)_2/C$, clearly indicating that in the present reaction, Pearlman's catalyst[15] proved to be superior to all other choices. Under these conditions, the target 8-aryladenine **3a** was formed in good yield (72%, entry 6).

Having determined optimal conditions for the formation of **3a** using classical heating, we attempted to use microwave activation[16] in order to enhance the reaction rate and possibly to reduce the reaction time as well as to increase the yield and the substrate scope.[17] Microwave-assisted organic synthesis has emerged during the past two decades as another valuable technology for synthetic organic and medicinal chemists.[18] We were pleased to find that direct arylation of **2** under microwave irradiation using similar conditions as those of entry 6 provided **3a** in a 76% isolated yield after only 30 min (entry 7). Under these conditions, replacement of DMF by DMA produced **3a** with a comparable yield (entry 8), whereas the use of 1,4-dioxane did not promote any coupling reaction (entry 9). Among several polar solvents tested, NMP is the unrivaled solvent choice for this direct C–H arylation, as **3a** was formed in excellent yield within 30 min (85%, entry 10). Interestingly, a similar result was obtained using a stoichiometric amount (1 equiv) of the CuI additive (84%, not shown in Table). Finally, The best conditions were found to require: 4-iodoanisole (1.5 equiv), $Pd(OH)_2/C$ (5 mol %), CuI (1 equiv), Cs_2CO_3 (2.0 equiv) in NMP at 160 °C for 15 min; and **3a** was formed in 90% yield (entry 11). It should be noted that attempting to carry out the reaction using traditional oil bath heating (160 °C, 15 min, sealed tube), resulted in partial conversion (ca. 20%, entry 12). This result clearly demonstrated the benefit to use microwave irradiations.

Prompted by these results, we subsequently investigated the substrate scope for the C–H arylation of **2**. Results summarized in Table 2 show that the optimized conditions described above proved to be general for the selective C-8 arylation with a large series of functionalized aryl halides.[19] The reaction worked well with *para* electron-rich aryl iodides, bromides as well as the less reactive aryl chlorides (entries 1–5), even those containing base sensitive

Table 1
Optimization coupling reaction of **2** with 4-iodoanisole under various conditions[a]

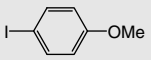
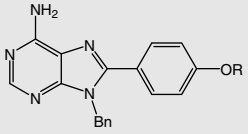
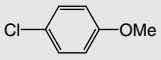
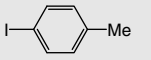
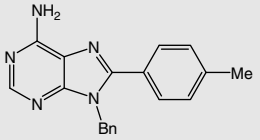
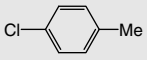
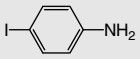
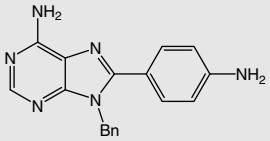
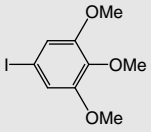
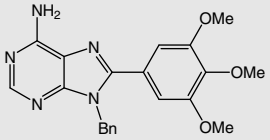
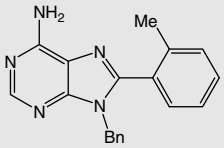
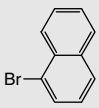
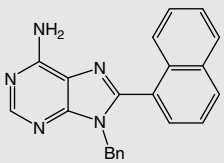
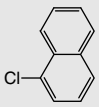
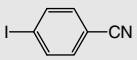
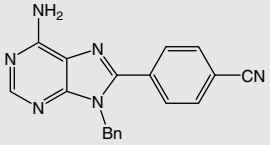
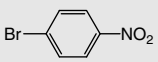
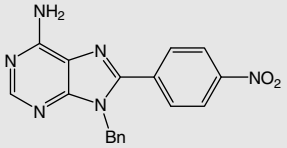
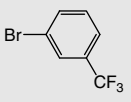
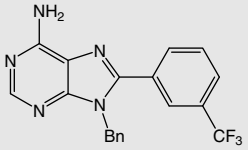


2 **3a**

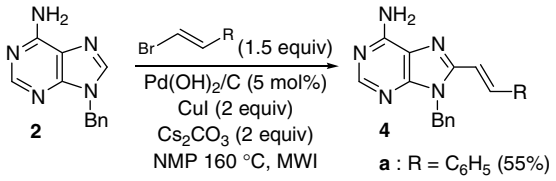
Entry	[Pd][b]	Base	Solvent	T[j] (°C)	Time (h)	Yield[c] (%)
1	$Pd(OAc)_2$	Piperidine[d]	DMF	120 (Δ)	20	55
2	$Pd(OAc)_2$	Piperidine[d]	DMF	150 (Δ)	5	61
3	$Pd(OAc)_2$	Cs_2CO_3[e]	DMF	120 (Δ)	13	45
4	$Pd(OAc)_2$	Cs_2CO_3	DMF	160 (Δ)	16	25
5	$Pd_2(dba)_3$	Cs_2CO_3	DMF	160 (Δ)	4	56
6	$Pd(OH)_2/C$	Cs_2CO_3	DMF	160 (Δ)	4	72
7	$Pd(OH)_2/C$	Cs_2CO_3	DMF	160 (MWI)	0.5	76
8	$Pd(OH)_2/C$	Cs_2CO_3	DMA	160 (MWI)	0.5	71
9	$Pd(OH)_2/C$	Cs_2CO_3	1,4-Dioxane	160 (MWI)	0.5	0
10	$Pd(OH)_2/C$	Cs_2CO_3	NMP	160 (MWI)	0.5	85[f]
11	$Pd(OH)_2/C$	Cs_2CO_3	NMP	160 (MWI)[g]	0.25	90[h]
12	$Pd(OH)_2/C$	Cs_2CO_3	NMP	160 (Δ)	0.25	nd[i]

[a] Unless otherwise stated, all reactions were heated in solvent using **2** (1.0 equiv), 4-iodoanisole (2.0 equiv), [Pd] (5 mol %), CuI (3 equiv) and base (2.5 equiv).
[b] No reaction occurred without palladium catalyst or copper salt.
[c] Isolated yields.
[d] 5 equiv of piperidine were used, Hocek conditions, see Ref. 12a.
[e] 2.5 equiv of Cs_2CO_3 were used, Fairlamb conditions, see Ref. 13.
[f] A 84% yield of **3a** was obtained, when using CuI (1 equiv). Partial conversion (ca. 20%) was observed in the presence of a catalytic amount (20 mol %).
[g] A 74% yield of **3a** was obtained when running the reaction at 130 °C for 5 h.
[h] Best conditions were found to be: **2** (1.0 equiv), 4-iodoanisole (1.5 equiv), $Pd(OH)_2/C$ (5 mol %), CuI (1 equiv) and Cs_2CO_3 (2.0 equiv), MWI, 160 °C, 15 min. For a general procedure: see, Ref. 19.
[i] Yield not determined; 20% of conversion was observed.
[j] Δ: standard heating, MWI: microwave irradiation.

Table 2
Synthesis of C-8 aryladenine derivatives **3** from **2**[19]

Entry	Aryl halide	Time (h)	Product **3**			Yield[a] (%)
1		0.25		R = Me	**3a**	90
2		2		R = Me R = H	**3a** **3b**	60 22
3		0.25			**3c**	78
4		1				70[b]
5		1			**3d**	81
6		0.50			**3e**	55[c]
7		0.25			**3f**	42
8		0.25			**3g**	95
9		1				85
10		0.25			**3h**	68[d]
11		0.25			**3i**	43
12		0.25			**3j**	82

[a] Isolated yield.
[b] No reaction occurred under Hocek or Fairlamb conditions, see: Refs. 12a and 13.
[c] 2 equiv of 3,4,5-trimethoxyiodobenzene were used.
[d] A 7% of benzamide compound was isolated as a side product.



Scheme 2.

groups without their prior protection (entry 5). Substrate 3,4,5-trimethoxyiodobenzene reacted reasonably well giving **3e** in acceptable yield (entry 6). On switching the substituents to the ortho position, the coupled product **3f** was formed in a lower yield (42%, entry 7), indicating that steric hindrance appears to play an important role. However, the use of 1-halonaphthalene (bromo or chloro derivative), as the arene coupling partner, gave the expected arylation product **3g** in excellent yields (entries 8 and 9). Electron-deficient aryl iodides, bromides also reacted with adenine **2** to provide **3h-j** in moderate to good yields with substitution being tolerated at each of the *meta* and *para* positions (entries 10–12).

Although the reactivity of aryl chlorides was moderate in comparison with their corresponding iodo and bromo derivatives, as it requires longer reaction times (1–2 h instead of 15 min), the yields of C−H arylation were equally effective with either iodo, bromo and chloro reagents (compare entries 1, 3, 8 and 2, 4, 9, respectively). The lower yield observed with 4-chloroanisole (entry 2) is due to the formation of side product **3b** (22%) resulting from deprotection of the methoxy substituent under the reaction conditions employed (160 °C, 2 h). Because of the excellent results observed using aryl chlorides as coupling partners, we attempted to compare the efficiency of our new catalytic system with those of the literature. Thus, when running the reaction of **2** with 4-tolyl chloride under Hocek or Fairlamb conditions, no reaction occurred and only starting material was recovered. These results clearly indicated that our conditions are a highly effective protocol and general for the C–H arylation of adenine substrates.

Having successfully generated 8-aryladenines **3** from aryl halides, we have tried to extend the C−H arylation reaction of free-(NH_2) adenine **2** to vinyl halides. These reagents would lead to compounds **4** which are vinylogous of our target structures **3**. A preliminary experiment, depicted below, showed that β-(*E*)-bromostyrene reacted with **2**, under our optimized conditions, to give stereoselectively the coupling product **4a**, as a unique *E*-isomer. It should be mentioned that it was necessary to add more copper iodide (2 equiv) to obtain a satisfactory yield (55%, Scheme 2).

In conclusion, we have developed an efficient and regioselective arylation of free-(NH_2) adenines based on the use of Pearlman's catalyst under ligandless microwave activation. The reaction took place rapidly within few minutes even using a stoichiometric amount of copper salt. Accordingly, a variety of aryl iodides, bromides as well as chlorides have been successfully employed, to provide rapid access to C-8 substituted adenines in good to excellent yields. This new protocol appears to be general, and applications of our new catalytic system to other substituted heterocycles are under investigation. The synthesis of a library of new adenine derivatives **3** as well as **4** as potential hsp90 inhibitors will be reported in due course.

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19. *General procedure for Pd-catalyzed couplings of N-bezyladenine* **2** *with various arylhalides*: A flame-dried resealable 2–5 mL Pyrex reaction vessel was charged with the solid reactant(s): $Pd(OH)_2/C$ (20% on carbon) (5.0 mol %),

CuI (1.0 mmol), *N*-benzyladenine **2** (1.0 mmol), aryl halide (1.5 mmol) and Cs_2CO_3 (2.0 mmol). The reaction vessel was capped with a rubber septum, evacuated and backfilled with argon; this evacuation/backfill sequence was repeated one additional time. The liquid reactant(s) and NMP (6 mL per mmol) were added through the septum. The septum was replaced with a Teflon screwcap. The reaction vessel was sealed, then placed in the Emrys Optimizer and exposed to microwave irradiation according to the following specifications: temperature: 160 °C; time: (see Tables); fixed hold time: on; sample absorption: high; pre-stirring: 60 s. The resulting suspension was cooled to room temperature and filtered through a pad of Celite eluting with CH_2Cl_2/MeOH (7:3), and the inorganic salts were removed. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

Compound **3a**: Yield: 90%; TLC: R_f 0.33 (CH_2Cl_2/MeOH 95:5); mp = 104–106 °C; IR (neat): 3157, 1661, 1606, 1530, 1458, 1332, 1298, 1266, 1179, 1031, 834, 727, 694; ^{1}H NMR ($CDCl_3$, 300 MHz): 3.78 (s, 3H), 5.39 (s, 2H), 5.85 (s, 2H, N*H*), 6.88 (d, 2H, *J* = 8.5 Hz), 7.01 (m, 2H), 7.21 (m, 3H), 7.45 (d, 2H, *J* = 8.5 Hz), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 47.0, 55.4, 114.3 (2C), 119.2, 121.8, 126.6 (2C), 127.8, 128.9 (2C), 130.6 (2C), 136.5, 151.8, 152.0, 152.8, 155.0, 161.1; *m/z* MS (ES+) 332.0 $(M+H)^+$.

Compound **3d**: Yield: 81%; TLC: R_f 0.19 (CH_2Cl_2/MeOH 95:5); mp = 170–172 °C; IR (neat): 3127, 1654, 1606, 1451, 1331, 1300, 1184, 835, 729, 695; ^{1}H NMR ($CDCl_3$, 300 MHz): 5.46 (s, 2H), 5.58 (s, 2H), 6.60 (d, 2H, *J* = 8.4 Hz), 7.01 (d, 2H, *J* = 7,30 Hz), 7.25 (m, 5H), 7.36 (d, 2H, *J* = 8.4 Hz), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 46.1, 113.3 (2C), 118.4, 116.4, 126.2 (2C), 127.3, 128.0 (2C), 128.6 (2C), 137.3, 150.3, 151.0, 151.3, 152.0, 155.3; *m/z* MS (ES+) 317.0 $(M+H)^+$.

Compound **3g**: Yield: 95%; TLC: R_f 0.32 (CH_2Cl_2/MeOH 95:5); mp = 184–186 °C; IR (neat): 3337, 3164, 1610, 1606, 1572, 1496, 1454, 1450, 1432, 1322, 1315, 800, 775, 722, 695; ^{1}H NMR ($CDCl_3$, 300 MHz): 5.13 (s, 2H), 6.11 (s, 2H, N*H*), 6.71 (m, 2H), 7.00 (m, 3H), 7.40 (m, 5H), 7.84 (d, 1H, *J* = 8.2 Hz), 7.92 (d, 1H, *J* = 8.2 Hz), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 46.9, 119.2, 124.9 (2C), 126.6, 126.9, 127.4 (3C), 127.7, 128.4 (2C), 128.5, 128.8, 130.8, 131.9, 133.5, 136.0, 150.3, 151.2, 153.1, 155.3; *m/z* MS (ES+) 352.0 $(M+H)^+$.

Compound **3h**: Yield: 68%; TLC: R_f 0.31 (CH_2Cl_2/MeOH 95:5); mp = 215–217 °C; IR (neat): 3373, 3168, 2228, 1648, 1593, 1580, 1527, 1490, 1461, 1408, 1310, 1302, 1277, 1110, 1065, 1019, 849, 720, 714, 694; ^{1}H NMR ($CDCl_3$, 300 MHz): 5.43 (s, 2H), 6.00 (bs, 2H, N*H*), 6.96–6.99 (m, 2H), 7.19–7.24 (m, 3H), 7.66 (s, 4H), 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 47.1, 113.9, 118.0, 126.4 (2C), 128.2, 129.1 (2C), 129.6 (2C), 132.5 (2C), 134.0, 135.9, 149.4, 152.2, 153.6, 155.5; *m/z* MS (ES+) 327.0 $(M+H)^+$.