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COPPER-MEDIATED N-ARYLATION IN THE SYNTHESIS OF ARYLADENINES

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Abstract - A series of N3 and N9 aryladenines was prepared by arylation of 8-bromoadenine under modified Chan-Lam-Evans coupling conditions followed by reductive debromination with hydrogen on palladium. Conditions of arylation were optimised to maximise the yield of N3-arylated products. The selectivity of the reaction varied with temperature the ligand used. The best results were obtained in DMF with phenanthroline as a ligand at 60°C.

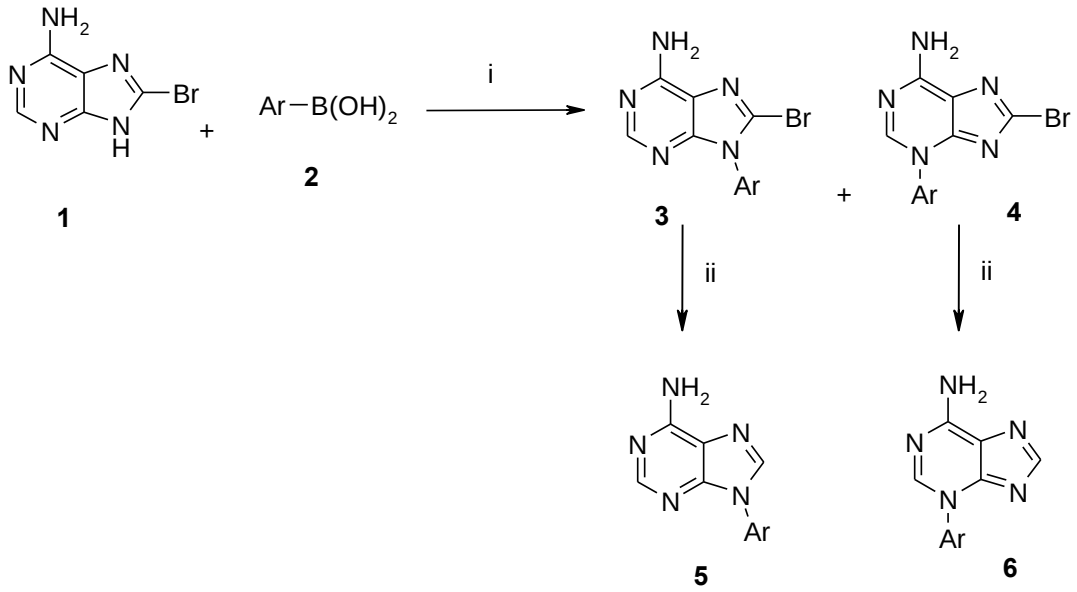
INTRODUCTION

Substituted purines attracted much interest as therapeutics, molecular tools and probes for investigating biological systems.[1] Due to their similarity with adenosine, many 9-substituted adenines interact with adenosine receptors showing important biological activity including antiviral and cytostatic effect.[2] On the other hand, little is known about biological activity of 3-substituted adenines. Arylation at purine ring nitrogens in the DNA may occur *in vivo* by the attack of arene oxides, reactive metabolic intermediates derived from aromatic hydrocarbons, followed by elimination of water.[3] Modifications at the N3-position of adenine in the DNA are of special interest, because they result in destabilisation of the N-gylcosidic bond. N3-Alkyl- and aryladenines are then cleaved off the DNA strand and can be therefore found in body fluids, mainly in urine.[4] Unlike in the double stranded DNA, the N3 position in adenine is not a prominent site of attack by alkylating or arylating reagents so that adenine itself cannot be used for preparation of 3-aryl-derivatives.[5] In our previous work on 3-alkyladenines we found that 8-bromoadenine (**1**) can be successfully used as a precursor to adenine giving satisfactory yields of N3-alkylated products. After alkylation it can be easily converted to adenine derivatives by Pd-catalysed debromination.[6] In this work we studied the selectivity of Chan-Lam-Evans arylation[7] of **1** with

arylboronic acids (**2a-f**) with the aim to prepare 3-aryladenines. Some of these, namely 3-phenyladenine, will be used in toxicological studies on the DNA adducts arising from exposure to benzene.

RESULTS AND DISCUSSION

N-Arylation of adenine and 8-bromoadenine. According to a previous report by Bakkestuen and Gundersen Cu(II)-mediated arylation of adenine by arylborobic acids in DCM was unsuccessful due to the lack of solubility.[8] This problem was solved using bis-Boc-protected adenine as a more soluble adenine precursor.[9] More recently, unprotected adenine was arylated efficiently at N9 position with arylboronic acids using Cu(II) and TMEDA in aqueous methanol.[10] Similarly, we found that the protection of adenine was not needed when phenanthroline was used as a ligand instead of triethylamine and DMF as a solvent. Under these conditions the arylation of adenine with phenylboronic acid (**2a**), yielded 69 % of 9-phenyladenine (**3a**).



Scheme 1: Preparation of 3- and 9-aryladenines from 8-bromoadenine. (i) $Cu(OAc)_2$, diamine ligand, DMF; (ii) H_2/Pd-C, MeOH

Similarly, 4-vinylphenylboronic acid at the same reaction conditions gave 60% of 9-(4-vinylphenyl)-adenine (**3b**). No aryladenines except 9-aryl isomers were formed by arylation of adenine. In the endeavour to obtain 3-aryladenines (**4a-f**) 8-bromoadenine was used as a precursor to adenine having a different charge distribution (Scheme 1). Reaction conditions for its arylation were first tested with **2a** as an arylating reagent. The reaction in DCM at room temperature gave poor yields (< 5%) because of poor solubility of **1** in this solvent. Somewhat better yields were obtained in methanol (10 - 21%). These were further improved when DMF was used as a solvent. Selectivity of the reaction was greatly influenced by

the ligand used and by reaction temperature (Table 1). Low reaction temperature and phenanthroline as the ligand led to an increase in the proportion of 3-phenyl-8-bromoadenine (**4a**). On the other hand,

Table 1: Selectivity of the arylation of 8-bromoadenine (**1**) with phenylboronic acid in DMF

Ligand	Temperature [°C]	Reaction time [h]	Yield (**3a + 4a**)	Selectivity **4a** : **3a**
Phenanthroline	40	72	55	3 : 1
Phenanthroline	60	24	72	2.5 : 1
Phenanthroline	90	24	73	1.5 : 1
Phenanthroline	100	24	76	1 : 1
2,2´-Bipyridyl	60	24	10	1 : 1
Pyridine	60	24	55	1.5 : 1
TMEDA	60	3	16	1 : 3

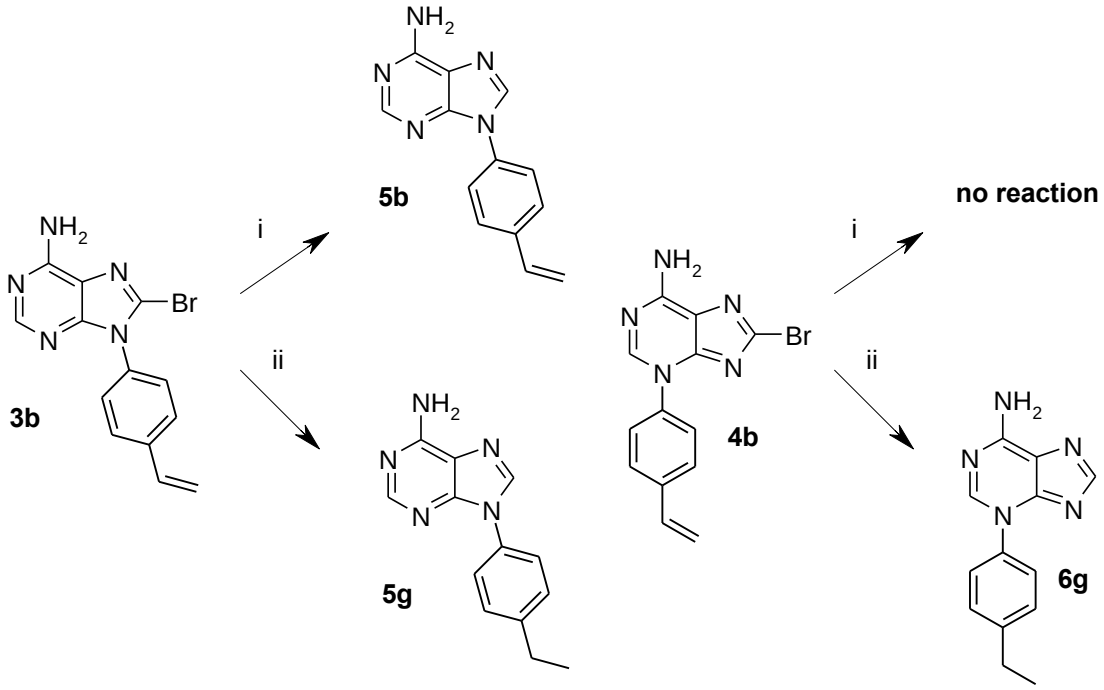
N,N,N',N'-Tetramethylethylenediamine (TMEDA) gave mainly 9-phenyl-8-bromoadenine (3**a**) while 2,2'-bipyridyl gave a 1:1 mixture of **3a** and **4a**. In the latter case, however, the yield of arylation was poor. Optimised reaction conditions were used for arylation of **1** with a series of six arylboronic acids (Table 2).

Table 2: Copper(II)-mediated arylation of 8-bromoadenine (**1**) with arylboronic acids **2a – f** at 90°C

Boronic acid **2** X-$C_6H_4B(OH)_2$	Products	Yield [%] N3 + N9 substituted	Selectivity N3 : N9 substituted
2a, X = H	**4a** + **3a**	73	1.5 : 1
2b, X = *p*-vinyl	**4b** + **3b**	63	2 : 1
2c, X = *o*-Me	**4c** + **5c**	31	1 : 1
2d, X = *m*-Me	**4d** + **5d**	62	3 : 1
2e, X = *p*-Me	**4e** + **5e**	56	1 : 1
2f, X = *p*-OMe	**4f** + **3f**	50	2 : 1

The reaction proceeded smoothly under aerobic conditions requiring at least one equivalent of copper(II) salt. In an argon atmosphere the yields were significantly lower. Final products were obtained by reductive debromination with hydrogen on palladium. However, in the case of three tolyl derivatives the N9 substituted adenines **5c-5e** were formed in the course of arylation so that 8-bromo-9-tolyladenines **3c – 3e** could not be isolated. In these cases a mixture of 8-bromo-3-tolyladenine (**3c-3e**) with 9-tolyladenine (**5c-5e**) was obtained. The mechanism of reductive debromination under the conditions of arylation is not known. Such a reaction can be explained by formation of an 8-purinylcuprate, which would give 8-H-purine derivative in the protic environment containing water from phenanthroline hydrate and acidic NH

from purine. Reductive debromination of all aryl-8-bromoadenines obtained was accomplished with hydrogen on palladium with 25 – 36 % yield. Resulting isomeric aryladenines were separated by column chromatography. For vinylphenyl derivatives **3b** and **4b**, however, this method led to a simultaneous hydrogenation of the vinyl group yielding corresponding *p*-ethylphenyl derivatives **5g** and **6g**, respectively.



Scheme 2: Debromination of *p*-vinylphenyl derivatives **3b** and **4b**. (i) 1. *t*-BuLi, toluene, 60°C, 2. EtOH; (ii) H_2/Pd-C, MeOH or Bu_3SnH, AIBN

Further attempts to selectively remove bromine from **3b** and **4b** failed either for a lack of reactivity or for a parallel reduction of the vinyl group. So, reduction with tributyltin hydride in the presence of AIBN[11] gave ethylphenyl-adenine derivatives **5g** and **6g**, respectively. On the other hand, **3b** reacted with *tert*-butyllithium in toluene at 60°C to give expected product **5b** whereas 3-aryl isomer **4b** did not react at the same reaction conditions at all. Starting material was recovered from the reaction mixture (Scheme 2). Similarly, a model reaction of 9-benzyl-8-bromoadenine (**7**) with *tert*-butyllithium gave 9-benzyladenine (**8**) in a 50% yield whereas 3-benzyl-8-bromoadenine (**9**) did not react at all.

Structure assignment of the isomeric products **3** - **6** was done on the basis of 1D and 2D NMR spectra (HMQC and HMBC). The most apparent distinctive feature of 3-aryladenines **3a-f** and **6a-f** as compared to corresponding 9-aryl derivatives was the presence of two exchangable NH signals in ^{1}H-NMR spectra as broad singlets at nearly 8.2 and 8.4 ppm (Figure 1).

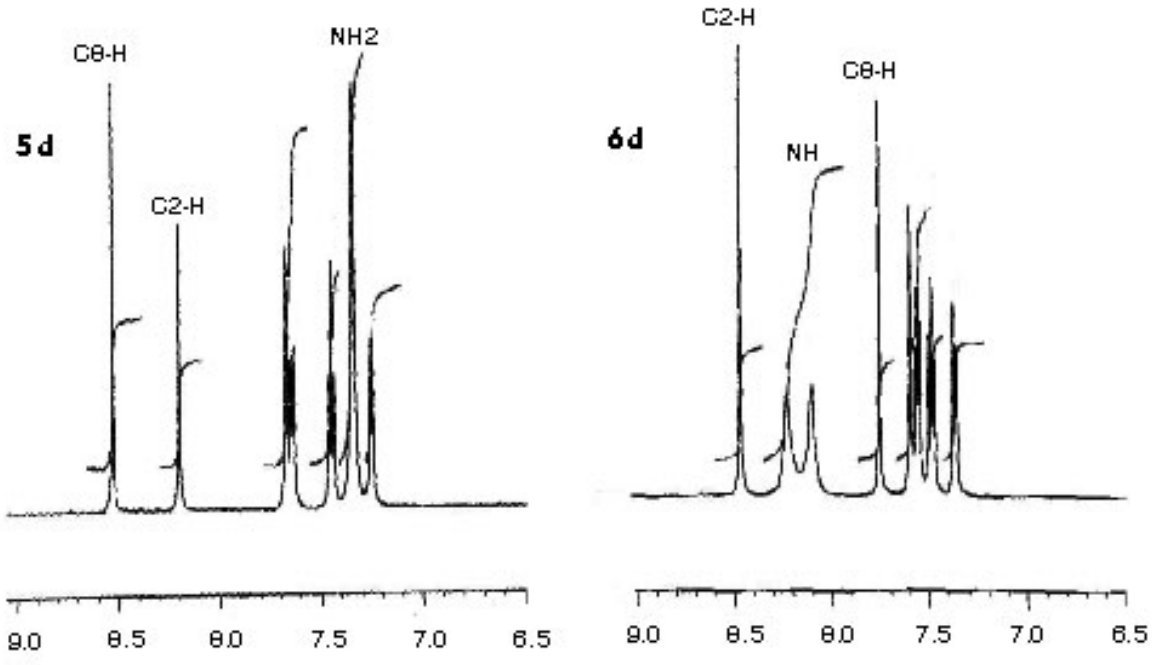


Figure 1: Typical ^{1}H-NMR apectra of N9- and N3-aryladenines (**5d** and **6d**, respectively)

These two signals indicate that at least in the DMSO solution 3-aryladenines are present in a tautomeric form with two different NH groups (Figure 2, structure A and B). However, according to previous quantum chemical calculations[10] the most stable isomer is the one with exocyclic NH_2 group (Figure 2, structure C).

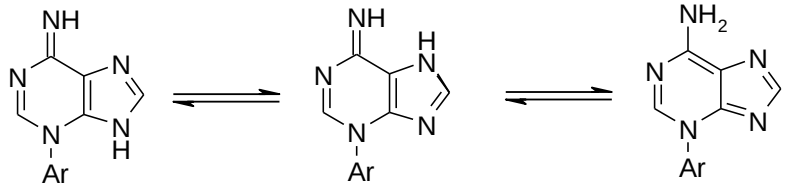


Figure 2: Tautomeric structures of aryladenines

Several diagnostic signals in one dimensional ^{1}H NMR and ^{13}C NMR spectra were found, which can be used to distinguish between N3 and N9 aryl adenines and bromoadenines. When comparing with corresponding chemical shift values in adenine, 3-aryladenines show a marked downfield shift for C2-*H* protons whereas C8-*H* protons are shifted upfield. In contrast, in 9-aryladenins both C2-*H* and C8-*H* signals are shifted downfield by nearly 0.08-0.11 (except for **5c**, which is shifted upfield by 0.1 ppm) and 0.13-0.49 ppm, respectively.

Analogously, 3-aryl-8-bromodenines showed a strong downfield shift by 0.14-0.34 ppm for C2-*H* while N9-substitution has little effect on C2-*H* (0.07-0.08 ppm upfield). Hence, an aryl substitution at neighbouring nitrogen has a deshielding effect on purine ring hydrogens in both adenine and 8-bromoadenine.

An aryl substitution at distant nitrogen, however, may have either little effect or, in the case of 3-aryladenine even a shielding effect. In ^{13}C NMR spectra C8 signals were strongly influenced by aryl substitution at N3 while C2 signals were not. On the other hand, N9 aryl substitution caused a significant downfield shift of C2 signals (about 8 ppm) and a somewhat weaker upfield shift (5-6 ppm) of C8 signals. Other signals remained almost unchanged. In 8-bromoadenines both N3 and N9 substitution caused a downfiled shift of the C8 signals whereas C2 signals were slightly shifted downfield by N9 aryl and upfiled by N3 aryl substitution. Diagnostic chemical shifts ($\Delta = \delta_i - \delta_a$) are listed in the Table 3.

Table 3: Selected diagnostic chemical shifts $\Delta = \delta_i - \delta_0$, where δ_0 is chemical shift of adenine/8-bromoadenine, δ_i are chemical shifts of aryladenines/arylbromoadenines in ppm

Compound	Compound type	Chemical shifts $\Delta = \delta_i - \delta_0$ in ppm				
		C2-*H*	C8-*H*	*C*2	*C*8	*C*4
3a	9-aryl	-0.01	-	2	5	-1
3b	9-aryl	-0.02	-	2	6	-1
3f	9-aryl	-0.01	-	1	19	0
4a	3-aryl	0.40	-	-7	18	-3
4b	3-aryl	0.41	-	-8	18	-3
4c	3-aryl	0.27	-	-7	19	-3
4d	3-aryl	0.35	-	-7	19	-2
4e	3-aryl	0.31	-	-7	18	-3
4f	3-aryl	-0.01	-	-7	19	-2
5a	9-aryl	0.08	0.44	10	-6	-1
5b	9-aryl	0.11	0.49	10	-6	0
5c	9-aryl	-0.01	0.13	9	-5	0
5d	9-aryl	0.08	0.40	9	-6	-1
5e	9-aryl	0.06	0.37	9	-6	-1
5f	9-aryl	0.07	0.35	10	-5	0
6a	3-aryl	0.38	-0.37	-1	8	4
6c	3-aryl	0.24	-0.37	0	6	0
6d	3-aryl	0.35	-0.37	-1	7	-1
6e	3-aryl	0.34	-0.37	-1	7	4
6f	3-aryl	0.32	-0.36	0	7	1

EXPERIMENTAL

Column chromatography was performed on silica gel 60 purchased from Fluka, particle size 0.063-0.200 mm. For thin-layer chromatography Merck Silica gel 60 F_{254} plates were used. Dimethylformamide (DMF) was dried by vacuum distillation from phosphorus pentoxide and stored over molecular sieves.

Other chemicals obtained from commercial sources were of analytical or synthetic grade and were used as received. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Avance DRX500 (500 MHz for ^{1}H) or with Varian Mercury 300 (300 MHz for ^{1}H) Fourier transform NMR spectrometer. In the HMBC experiments, the parameters were set to show cross-peaks for nuclei interacting with a $J_{H,C}$ coupling constant of 7 Hz. High resolution mass spectra were measured on an Autospec Ultra sector mass spectrometer (Micromass).

Arylation of adenine: A mixture of adenine (1 mmol), boronic acid **2a** or **2b** (1.5 mmol), phenanthroline (1.5 mmol), and copper(II) acetate (1.5 mmol) in DMF (5 mL) was heated in an oil bath to 90°C under aerobic conditions for 24 h. Progress of the reaction was monitored by TLC with a mixture of $CHCl_3$ and MeOH 10/1 as an eluent. DMF was distilled off in a vacuum, MeOH was added to the residue and the resulting suspension was filtred through a layer of Kieselguhr. After evaporation of the solvent in a vacuum column chromatography on silica gel was carried out using $CHCl_3$/MeOH 20/1 followed by $CHCl_3$/MeOH 10/1 for elution. Analytically pure compounds **5a** and **5b** were obtained by crystallization from toluene.

9-Phenyladenine (5a): white crystals, yield 69%, R_f = 0.48; mp 213-215°C; also obtained by debromination of **3a** (yield 40%); ^{1}H NMR (DMSO-d_6): δ = 7.45 – 7.87 (m, 5H, Ar-*H*); 8.20 (s, 1H, C2-*H*); 8.57 (s, 1H, C8-*H*); ^{13}C NMR (DMSO-d_6): 119.3 (*C*5); 123.2, 127.7 and 129.7 (Ar *C*H); 135.2 (Ar *C*); 139.9 (*C*8); 149.3 (*C*4); 153.8 (*C*2); 156.3 (*C*6). *Anal.* Calcd for $C_{11}H_9N_5 \times 1/3H_2O$: C, 60.8; H, 4.5; N, 32.1. Found: C, 60.5; H, 4.1; N, 32.2.

9-(4-Vinylphenyl)adenine (5b): white crystals, yield 60 %, R_f = 0.52; mp 234-236°C; also obtained by debromination of **3b** by *tert*-butyllithium (yield 31%); ^{1}H NMR (DMSO-d_6): δ = 5.35 (d, 1H, J = 11.2 Hz, =CH_2); 5.93 (d, 1H, J = 17.8 Hz, =CH_2); 6.82 (dd, 2H, J = 11.2 and 17.8 Hz, =C*H*); 7.40 (br s, 2H, N*H*); 7.69 (d, 2H, J = 8.5 Hz, Ar-*H*); 7.91 (d, 2H, J = 8.5 Hz, Ar-*H*); 8,23 (s, 1H, C2-*H*); 8.62 (s, 1H, C8-*H*); ^{13}C NMR (DMSO-d_6): 116.0 (=*C*H_2); 120.2 (*C*5); 123.7 and 128.0 (Ar *C*H); 135.4 (Ar *C*N); 136.5 (=*C*H); 137.0 (Ar *C*C); 140.3 (*C*8); 150.0 (*C*4); 154.0 (*C*2); 157.2 (*C*6). *Anal.* Calcd for $C_{13}H_{11}N_5$: C, 65.8; H, 4.7; N, 29.5. Found: C, 65.6; H, 4.6; N, 29.7.

General procedure for the arylation of 8-bromoadenine: A mixture of 8-bromoadenine (1 mmol), arylboronic acid (1.5 mmol), phenanthroline (1.5 mmol), and copper(II) acetate (1.5 mmol) in DMF (5 mL) was heated in an oil bath to 90°C under aerobic conditions for 24 h. Progress of the reaction was monitored by TLC with a mixture of $CHCl_3$ and MeOH 10/1 as an eluent. DMF was distilled off in a vacuum, MeOH was added to the residue and the resulting suspension was filtred through a layer of Kieselguhr. After evaporation of the solvent in a vacuum, column chromatography on silica gel was

carried out using $CHCl_3$/MeOH 20/1 followed by $CHCl_3$/MeOH 10/1 for elution. N3 and N9 arylated products were either incompletely separated or co-eluted in the same fractions, thus their ratio was determined from integral intensities of appropriate signals in ^{1}H NMR spectra. Pure samples of aryl-8-bromoadenines **3** and **4** were obtained by semi-preparative reversed phase HPLC on a 10 × 250 mm column Biospher PSI00 C18, particle size 10 μ using a MeOH – H_2O mixture as an eluent at a flow rate of 2.5 mL/min.

8-Bromo-3-phenyladenine (4a): white solid; mp > 250°C; ^{1}H NMR (DMSO-d_6): δ = 7.56 – 7.74 (m, 5H, Ar-*H*); 8.30 and 8.44 (br s, 2H, NH_2); 8.48 (s, 1H, C2-*H*); ^{13}C NMR (DMSO-d_6): δ = 121.1 (*C*5); 125.7, 129.2 and 129,4 (Ar *C*-H); 137.2 (Ar *C*); 139.4 (*C*8); 143.5 (*C*2); 149.6 (*C*4); 153.5 (*C*6); HMBC: Cross-peak of C2-*H* δ = 8.48 ppm with Ar *C*-N at 137.2 ppm. *Anal.* Calcd for $C_{11}H_8N_5Br \times 2/5\ H_2O$: C, 44.4; H, 3.0; N, 23.5. Found: C, 44.6; H, 2.6; N, 23.4.

8-Bromo-9-phenyladenine (3a): white solid; mp 242-243°C; ^{1}H NMR (DMSO-d_6): δ = 7.52 – 7.62 (m, 5H, Ar-*H*); 8.07 (s, 1H, C2-*H*); ^{13}C NMR (DMSO-d_6): 118.9 (*C*5); 126.4 (*C*8); 128.2, 129.4 and 129,5 (Ar *C*H); 133.8 (Ar *C*); 152.0 (*C*4); 153.3 (*C*2); 154.9 (*C*6). *Anal.* Calcd for $C_{11}H_8N_5Br$: C, 45.5; H, 2.8; N, 24.1. Found: C, 45.8; H, 2.4; N, 24.4.

8-Bromo-3-(4-vinylphenyl)adenine (4b): yellowish solid; mp > 250°C; ^{1}H NMR (DMSO-d_6): δ = 5.38 (d, 1H, J = 10.8 Hz, =CH_2); 5.96 (d, 1H, J = 17.8 Hz, =CH_2); 6.84 (dd, 1H, J = 10.8 and 17.8 Hz, =C*H*); 7.69 (s, 4H, Ar-*H*); 8.28 (br s, 1H, N*H*); 8.43 (br s, 1H, N*H*); 8.49 (s, 1H, C2-*H*). ^{13}C NMR (DMSO-d_6): 116.1 (=*C*H_2); 121.1 (*C*5); 125.8 and 127.0 (Ar *C*H); 135.5 (=*C*H); 136.4 (Ar *C*N); 138.0 (Ar *C*C); 139.4 (*C*8); 143.4 (*C*2); 149.5 (*C*4); 153.5 (*C*6); HMBC: Cross-peak of C2-*H* at δ = 8.49 ppm with Ar *C*-N at 136.4 ppm. *Anal.* Calcd for $C_{13}H_{10}N_5Br$: C, 49.4; H, 3.2; N, 22.2. Found: C, 49.3; H, 3.2; N, 22.1.

8-Bromo-9-(4-vinylphenyl)adenine (3b): yellowish solid; mp 214-216°C; ^{1}H NMR (DMSO-d_6): δ = 5.40 (d, 1H, J = 10.9 Hz, =C*H*); 5.97 (d, 1H, J = 17.6 Hz, =C*H*); 6.85 (dd, 1H, J = 10.9 and 17.6 Hz, =C*H*); 7.49 (d, 2H, J = 7.9 Hz, Ar-*H*); 7.67 (d, 2H, J = 8.2 Hz, Ar-*H*); 8.06 (s, 1H, C2-*H*). ^{13}C NMR (DMSO-d_6): 116.3 (=*C*H_2); 118.9 (*C*5); 126.5 (*C*8); 127.0 and 128.4 (Ar *C*H); 133.1 (Ar *C*N); 135.6 (=*C*H); 138.3 (Ar *C*C); 151.8 (*C*4); 153.4 (*C*2); 155.0 (*C*6). HRMS: Calcd for $C_{13}H_{10}N_5Br$: 315.0120. Found 315.0105.

8-Bromo-3-(2-tolyl)adenine (4c): yellowish solid; decomposition at 235°C; ^{1}H NMR (DMSO-d_6): δ = 2.05 (s, 3H, CH_3); 7.41 – 7.52 (m, 4H, Ar-*H*); 8.28 (br s, 1H, N*H*); 8.35 (s, 1H, C2-*H*); 8.45 (br s, 1H, N*H*). ^{13}C NMR (DMSO-d_6): 17.1 (*C*H_3); 121.0 (*C*5); 127.1, 127.7, 130.1 and 131.1 (Ar *C*-H); 134.8 (Ar *C*-C); 136.3 (Ar *C*-N); 139.6 (*C*8); 144.0 (*C*2); 150.0 (*C*4); 153.7 (*C*6); HMBC: Cross-peak of C2-*H* at δ = 8.35 ppm with Ar *C*-N at 136.3 ppm. HRMS: Calcd for $C_{12}H_{10}N_5Br$: 303.0120; Found 303.0122.

8-Bromo-3-(3-tolyl)adenine (4d): yellowish solid; mp 248-249°C; ^{1}H NMR (DMSO-d_6): δ = 2.43 (s, 3H,

C*H*$_3$); 7.39 – 7.56 (m, 4H, Ar-*H*); 8.30 (br s, 1H, N*H*); 8.43 (br s, 1H, N*H*); 8.46 (s, 1H, C2-*H*). ^{13}C NMR (DMSO-d_6): 21.7 (*C*H$_3$); 122.0 (*C*5); 123.7, 126.9, 130.1 and 130.7 (Ar *C*H); 138.0 (Ar *C*-N); 140.0 (Ar *C*C); 140.3 (*C*8); 144.3 (*C*2); 150.5 (*C*4); 154.4 (*C*6); HMBC: Cross-peak of C2-*H* at δ = 8.46 ppm with Ar *C*-N at 138.0 ppm. HRMS: Calcd for $C_{12}H_{10}N_5Br$: 303.0120; Found 303.0119.

8-Bromo-3-(4-tolyl)adenine (4e): yellowish solid; mp 244-245°C; ^{1}H NMR (DMSO-d_6): δ = 2.40 (s, 3H, C*H*$_3$); 7.40 (d, 2H, J = 8.3 Hz, Ar-*H*); 7.58 (d, 2H, J = 8.3 Hz, Ar-*H*); 8.24 (br s, 1H, N*H*); 8.38 (br s, 1H, N*H*); 8.39 (s, 1H, C2-*H*). ^{13}C NMR (DMSO-d_6): 20.7 (*C*H$_3$); 121.2 (*C*5); 125.5 and 129.8 (Ar *C*-H); 134.7 (Ar *C*-N); 138.9 (Ar *C*-C); 139.4 (*C*8); 143.5 (*C*2); 149.7 (*C*4); 153.5 (*C*6); HMBC: Cross-peak of C2-*H* at δ = 8.39 ppm with Ar *C*-N at 134.7 ppm. *Anal.* Calcd for $C_{12}H_{10}N_5Br$: C, 47.4; H, 3.3; N, 23.0. Found: C, 47.6; H, 3.5; N, 23.4.

8-Bromo-3-(4-methoxyphenyl)adenine (4f): yellowish solid; mp > 250°C; ^{1}H NMR (DMSO-d_6): δ = 3.85 (s, 3H, C*H*$_3$); 7.15 (d, 2H, J = 8.8 Hz, Ar-*H*); 7.65 (d, 2H, J = 8.8 Hz, Ar-*H*); 8.25 (br s, 1H, N*H*); 8.40 (br s, 1H, N*H*); 8.43 (s, 1H, C2-*H*). ^{13}C NMR (DMSO-d_6): 56.5 (*C*H$_3$); 122.0 (*C*5); 115.4 and 127.9 (Ar *C*-H); 130.9 (Ar *C*-N); 140.3 (*C*8); 144.4 (*C*2); 150.8 (*C*4); 154.4 (*C*6); 160.5 (Ar *C*-O); HMBC: Cross-peak of C2-*H* at δ = 8.43 ppm with Ar *C*-N at 130.9 ppm. HRMS: Calcd for $C_{12}H_{10}N_5OBr$: 319.0069. Found 319.0055.

8-Bromo-9-(4-methoxyphenyl)adenine (3f): yellowish solid; mp 248-249°C; ^{1}H NMR (DMSO-d_6): δ = 2.51 (s, 3H, OC*H*$_3$); 7.14 (d, 2H, J = 8.7 Hz, Ar-*H*); 7.65 (d, 2H, J = 8.7 Hz, Ar-*H*); 7.47 (br s, 2H, N*H*); 8.07 (s, 1H, C2-*H*). ^{13}C NMR (DMSO-d_6): δ = 56.4 (*C*H$_3$); 119.7 (*C*5); 127.3 (Ar *C*N); 115.4 and 130.3 (Ar *C*-H); 140.3 (*C*8); 152.8 (*C*4); 154.1 (*C*2); 155.8 (*C*6); 160.7 (Ar *C*-O). HRMS: Calcd for $C_{12}H_{10}N_5OBr$: 319.0069. Found: 319.0063.

General procedure for reductive debromination of aryl-8-bromoadenines:

Pure isomers or a mixture of **3** and **4** (0.66mmol) and palladium catalyst (10 % Pd-C; 35mg; 5% mol.) and ammonium formate (250mg) in absolute MeOH (25mL) was heated in an oil bath to 60°C under argon atmosphere for 6 h. The catalyst was then filtred off and washed with aqueous MeOH. The solvent was evaporated *in vacuo* to yield crude product mixture of **5** and **6,** which was separated by column chromatography on silica gel using a stepwise gradient of $CHCl_3$/MeOH 10/1 to 6/1 for elution. Products were purified by crystallization from aqueous EtOH or MeOH.

3-Phenyladenine (6a): Obtained by debromination of **4a** (yield 37 %) or a from a mixture of **3a** and **4a** as white crystals; decomposition at 201°C; ^{1}H NMR (DMSO-d_6): δ = 7.54 – 7.79 (m, 5H, Ar-*H*); 7.78 (s, 1H, C8-*H*); 8.16 and 8.34 (br s, 2H, N*H*$_2$); 8.50 (s, 1H, C2-*H*); ^{13}C NMR (DMSO-d_6): 120.1 (*C*5); 125.6, 129.0 and 129.3 (Ar *C*H); 137.8 (Ar *C*); 143.0 (*C*2); 149.6 (*C*4); 152.6 (*C*8); 154.9 (*C*6); HMBC: Cross-

peak of C2-*H* (δ = 8.50 ppm with Ar *C* at 137.8 ppm. *Anal.* Calcd for $C_{11}H_9N_5 \times 1.45\ H_2O$: C, 55.67; H, 5.02; N, 29.52. Found: C, 55.35; H, 4.66; N, 29.87.

3-(2-Tolyl)adenine (6c): Obtained by debromination of **4c** (yield 24 %) or a 1 : 1 mixture of **4c** and **5c** as yellowish crystals; R_f = 0.14; mp > 250°C; ^{1}H NMR (DMSO-d_6): δ = 2.04 (s, 3H, CH_3); 7.40 – 7.53 (m, 4H, Ar-*H*); 7.76 (s, 1H, C8-*H*); 8.17 (br s, 1H, N-*H*); 8.23 (br s, 1H, N-*H*); 8.36 (s, 1H, C2-*H*). ^{13}C NMR (DMSO-d_6): δ = 17.2 (*C*H_3); 119.3 (*C*5); 127.0, 127.7, 129.8 and 131.0 (Ar *C*-H); 134.9 (Ar *C*-C); 136.8 (Ar *C*-N); 143.8 (*C*2); 149.8 (*C*4); 152.3 (*C*8); 154.9 (*C*6); HMBC: Cross-peak of C2-*H* at δ = 8.36 ppm with Ar *C*-N at 136.8 ppm. *Anal.* Calcd for $C_{12}H_{11}N_5 \times 1/4\ H_2O$: C, 62.7; H, 5.1; N, 30.5. Found: C, 62.9; H, 4.9; N, 30.6.

9-(2-Tolyl)adenine (5c): Obtained by arylation of bromoadenine **1** with **2c** followed by separation on a silica gel column (yield 15 %) as white crystals from aqueous EtOH; R_f = 0.48; mp 197-199°C; ^{1}H NMR (DMSO-d_6): δ = 2.08 (s, 3H, CH_3); 7.35 (br s, 2H, N*H*); 7.39 – 7.46 (m, 4H, Ar-*H*); 8.11 (s, 1H, C2-*H*); 8.26 (s, 1H, C8-*H*); ^{13}C NMR (DMSO-d_6): 17.5 (*C*H_3); 118.4 (*C*5); 126.9, 127.9, 129.1 and 131.0 (Ar *C*H); 133.7 (Ar *C*N); 134.9 (Ar *C*C); 140.8 (*C*8); 150.1 (*C*4); 153.0 (*C*2); 156.3 (*C*6). *Anal.* Calcd. for $C_{12}H_{11}N_5 \times 1/4$ EtOH: C, 63.4; H, 5.3; N, 29.6. Found: C, 63.7; H, 5.0; N, 29.8.

3-(3-Tolyl)adenine (6d): Obtained by debromination of **4d** (yield 58 %) or a mixture of **4d** and **5d** as white crystals; R_f = 0.16; mp > 250°C; ^{1}H NMR (DMSO-d_6): δ = 2.41 (s, 3H, CH_3); 7.36 – 7.60 (m, 4H, Ar-*H*); 7.76 (s, 1H, C8-*H*); 8.10 (br s, 1H, N*H*); 8.23 (br s, 1H, N*H*); 8.47 (s, 1H, C2-*H*). ^{13}C NMR (DMSO-d_6): 20.86 (*C*H_3); 120.1 (*C*5); 122.6, 126.0, 129.1 and 129.5 (Ar *C*H); 137.7 (Ar *C*C); 139.0 (Ar *C*N); 142.8 (*C*2); 149.6 (*C*4); 152.6 (*C*8); 154.8 (*C*6); HMBC: Cross-peak of C2-*H* at δ = 8.47 ppm with Ar *C*-N at 139.0 ppm. *Anal.* Calcd for $C_{12}H_{11}N_5 \times 1/8\ H_2O$: C, 63.4; H, 5.0; N, 30.8. Found: C, 63.3; H, 4.9; N, 30.9.

9-(3-Tolyl)adenine (5d): Obtained by arylation of bromoadenine **1** with **2d** followed by separation on a silica gel column (yield 26 %) as white crystals; R_f = 0.51; mp 225-226°C; ^{1}H NMR (DMSO-d_6): δ = 2.39 (s, 3H, CH_3); 7.35 (br s, 2H, N*H*); 7.24 – 7.68 (m, 4H, Ar-*H*); 8.20 (s, 1H, C2-*H*); 8.53 (s, 1H, C8-*H*); ^{13}C NMR (DMSO-d_6): 20.9 (*C*H_3); 119.1 (*C*5); 120.1, 123.4, 128.1 and 129.3 (Ar *C*-H); 134.9 (Ar *C*N); 139.1 (Ar *C*C); 139.7 (*C*8); 149.0 (*C*4); 153.1 (*C*2); 156.2 (*C*6). *Anal.* Calcd for $C_{12}H_{11}N_5$: C, 64.0; H, 4.9; N, 31.1. Found: C, 63.8; H, 4.9; N, 31.1.

3-(4-Tolyl)adenine (6e): Obtained by debromination of **4e** (yield 47 %) or a mixture of **4e** and **5e** as white crystals; R_f = 0.16; mp > 250°C; ^{1}H NMR (DMSO-d_6): 2.42 (s, 3H, CH_3); 7.41 (d, 2H, J = 7.9 Hz, Ar-*H*); 7.65 (d, 2H, J = 7.9 Hz, Ar-*H*); 7.76 (s, 1H, C8-*H*); 8.10 (br s, 1H, N*H*); 8.17 (br s, 1H, N*H*); 8.46 (s, 1H, C2-*H*). ^{13}C NMR (DMSO-d_6): 20.66 (*C*H_3); 119.5 (*C*5); 125.4 and 129.7 (Ar *C*H); 135.3 (Ar *C*C); 138.6 (Ar *C*N); 142.9 (*C*2); 152.6 (*C*8); 154.2 (*C*4); 154.8 (*C*6); HMBC: Cross-peak of C2-*H* at δ = 8.46 ppm with Ar *C*-N at 135.3 ppm. *Anal.* Calcd for $C_{12}H_{11}N_5 \times 2\ 1/4\ H_2O$: C, 54.2; H, 5.9; N, 26.4.

Found: C, 54.3; H, 6.0; N, 26.3.

9-(4-Tolyl)adenine (5e): Obtained by arylation of bromoadenine **1** with **2e** followed by separation on a silica gel column (yield 22 %) as white crystals; R_f = 0.49; mp > 250°C; ^{1}H NMR (DMSO-d_6): δ = 2.37 (s, 3H, CH_3); 7.32 (br s, 2H, N*H*); 7.37 (d, 2H, J = 7.8 Hz, Ar-*H*); 7.71 (d, 2H, J = 7.8 Hz, Ar-*H*); 8.18 (s, 1H, C2-*H*); 8.50 (s, 1H, C8-*H*); ^{13}C NMR (DMSO-d_6): 20.8 (*C*H_3); 119.3 (*C*5); 123.2 and 130.2 (Ar *C*H); 132.7 (Ar *C*N); 137.4 (Ar *C*C); 140.0 (*C*8); 149.3 (*C*4); 153.4 (*C*2); 156.4 (*C*6). *Anal.* Calcd for $C_{12}H_{11}N_5$: C, 64.0; H, 4.9; N, 31.1. Found: C, 63.8; H, 5.1; N, 30.9.

3-(4-Methoxyphenyl)adenine (6f): Obtained by debromination of **4f** (yield 43 %) or a mixture of **3f** and **4f** as white crystals from aqueous EtOH; R_f = 0.14; mp > 250°C; ^{1}H NMR (DMSO-d_6): δ = 3.85 (s, 3H, CH_3); 7.14 (d, 2H, J = 8.7 Hz, Ar-*H*); 7.68 (d, 2H, J = 8.7 Hz, Ar-*H*); 7.77 (s, 1H, C8-*H*); 8.10 (br s, 1H, N*H*); 8.26 (br s, 1H, N*H*); 8.44 (s, 1H, C2-*H*). ^{13}C NMR (DMSO-d_6): 56.44 (*C*H_3); 115.3 (Ar *C*H); 120.9 (*C*5); 127.8 (Ar *C*H); 131.5 (Ar *C*N); 143.9 (*C*2); 150.7 (*C*4); 153.4 (*C*8); 155.6 (*C*6); 160.3 (Ar *C*-O); HMBC: Cross-peak of C2-*H* at δ = 8.44 ppm with Ar *C*-N at 131.5 ppm. *Anal.* Calcd for $C_{12}H_{11}N_5O$ × 1/3 EtOH: C, 59.3; H, 5.1; N, 27.3. Found: C, 58.9; H, 5.2; N, 27.3.

9-(4-Methoxyphenyl)adenine (5f): Obtained by debromination of **3f** (yield 52 %) or a mixture of **3f** and **4f** as white crystals from aqueous ethanol; R_f = 0.46; mp 233-234°C; ^{1}H NMR (DMSO-d_6): δ = 3.83 (s, 3H, CH_3); 7.13 (d, 2H, J = 8.7 Hz, Ar-*H*); 7.32 (br s, 2H, N*H*); 7.76 (d, 2H, J = 8.8 Hz, Ar-*H*); 8.19 (s, 1H, C2-*H*); 8.48 (s, 1H, C8-*H*); ^{13}C NMR (DMSO-d_6): δ = 56.4 (*C*H_3); 115.4 (Ar *C*H); 120.0 (*C*5); 125.5 (Ar *C*H); 128.9 (Ar *C*N); 140.6 (*C*8); 150.1 (*C*4); 153.9 (*C*2); 157.2 (*C*6); 159.3 (Ar *C*-O). *Anal.* Calcd. for $C_{12}H_{11}N_5O$ × 1/2 EtOH: C, 59.1; H, 5.3; N, 27.0. Found: C, 59.4; H, 5.2; N, 26.8.

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