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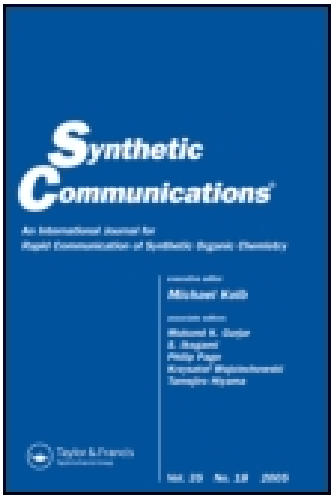

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DIRECT ARYLATION OF ADENINE BY FLUORO- AND CHLORONITROBENZENES: EFFECT OF MICROWAVES

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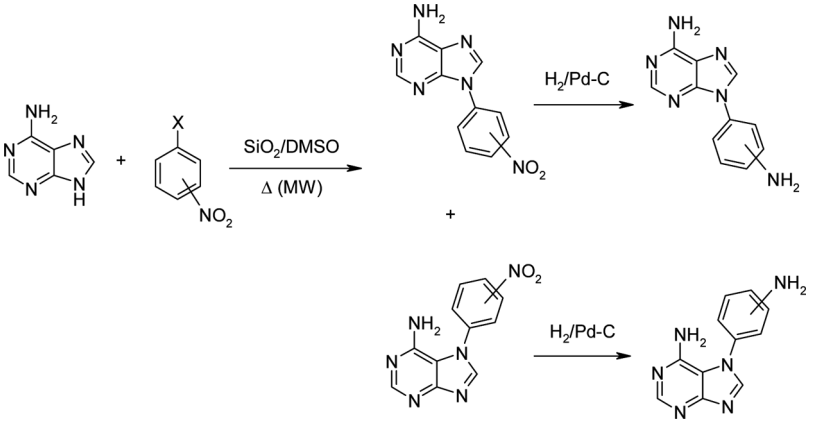
GRAPHICAL ABSTRACT



Abstract *Direct arylation of adenine with fluoro- and chloronitrobenzenes leads to mixtures of* N9 *and* N7 *substituted adenines. After separation by column chromatography, the individual isomers can be efficiently hydrogenated on Pd to give the corresponding aminophenyladenines. A significant enhancement of the reaction rate by microwave irradiation was observed. This two-step procedure was found to be a feasible route to otherwise hardly available 7-aminophenyladenines. Correlation between calculated shielding constants and experimental values of chemical shifts in* ^{13}C *and* ^{15}N *NMR was used for assignment of the site of substitution.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Chemoselectivity; microwave chemistry; *N*-arylation; purines

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INTRODUCTION

Substituted purines continue to attract attention as biologically active compounds, molecular tools, and probes for investigating biological systems.[1–4] Because of their similarity to adenosine, many 9-substituted adenines interact with adenosine receptors, showing important biological activity including antiviral and cytostatic effects.[5–7] Although 7-substituted adenines are not so readily available, some of them were also shown to have significant activity against viruses.[8] Position 9 of adenine appears to be the most reactive one in the reactions with various electrophiles, although these reactions are generally not completely regioselective so that mixtures of isomers are formed.[9–14] In connection with our research on DNA adducts we studied previously copper-mediated *N*-arylation of adenine by arylboronic acids, which gave mixtures of 9- and 3-arylated adenines and was found to be a feasible route to the latter ones.[15] Direct arylation of adenine (**1**) with several halo-nitrobenzenes was studied by Zare et al.[16,17] Reactions gave moderate to good yields of 9-substituted adenines if accomplished in dimethylsulfoxide (DMSO) at 150 °C in the presence of Cs_2CO_3 of K_2CO_3 and silica gel as a solid support, but rather long reaction times were needed.[16] The same reaction was performed also in ionic liquids in the presence of ZnO[17] as well as in dimethylformamide (DMF) in the presence of KF/Al_2O_3.[18] In these latter cases a significant rate-enhancing effect of microwaves was reported. However, 9-substituted adenines were always the only isomers identified.

Many reactions can be accelerated by microwave irradiation, some of them in a spectacular way. It is, however, not clear whether the effect of microwave in these reactions is purely thermal (i.e., caused by a very efficient heating in the whole volume) or if some nonthermal microwave-specific effects exist.[19,20] Arylation reactions performed in heterogeneous systems containing polar solvents are likely to be enhanced by both thermal and nonthermal effects of microwaves. In fact, nonthermal effects cannot be easily separated from the thermal ones, because both of them may arise from similar interactions between microwave fields and the material.[19] In many cases where acceleration of a reaction was shown, reaction temperature and time profile were not measured with sufficient accuracy. Very often, what is referred to as reaction temperature is not actually measured directly in the reaction mixture but is the temperature of the heating medium, mainly oil bath. This was also the case of hitherto reported arylations of adenine.[16–18] Therefore, we decided to perform a comparative study of adenine arylation by fluoro- and chloronitrobenzenes with the aim to characterize expected minor product(s) of the reaction and to assess the effect of microwaves on the reaction rate and regioselectivity under the conditions of controlled reaction temperature and, if possible, to distinguish between purely thermal and microwave-specific effects.

RESULTS AND DISCUSSION

Reaction of adenine (**1**) with 2- and 4-fluoronitrobenzene (**2a** and **2b**) under the conditions described by Khalafi-Nezhad et al.[16] proceeded quickly so that it was complete within minutes. Under these conditions, differences between classical and microwave-assisted reactions were within the range of experimental uncertainty and possible effect of microwaves was not measurable (Table 1). In both cases

Table 1. Arylation of adenine (**1**) by halonitrobenzenes (**2**) at 150 °C with and without MW irradiation; analytical yields (mean ± SE; n = 3) as determined by HPLC-UV

Halo-nitrobenzene	Reaction time (min)	MW	Yield of aryladenine (%)			Product ratio
			3	**4**	**3 + 4**	**3/4**
2-Fluoro-**2a**	5	No	40.7 ± 2.6	37.5 ± 3.0	78.2	52/48
2-Fluoro-**2a**	5	Yes	42.0 ± 2.3	41.8 ± 3.4	83.8	50/50
2-Fluoro-**2a**	25	No	41.2 ± 3.6	29.6 ± 2.2	70.8	58/42
2-Fluoro-**2a**	25	Yes	42.6 ± 1.2	24.9 ± 1.1	67.5	63/37
4-Fluoro-**2b**	5	No	65.4 ± 2.9	29.0 ± 2.0	94.4	70/30
4-Fluoro-**2b**	5	Yes	67.5 ± 2.0	30.2 ± 0.6	97.7	69/31
4-Fluoro-**2b**	25	No	65.3 ± 3.0	17.6 ± 0.8	82.9	79/21
4-Fluoro-**2b**	25	Yes	58.5 ± 3.0	16.9 ± 1.2	75.4	78/22
2-Chloro-**2c**	25	No	13.9 ± 2.6	2.2 ± 0.6	16.1	86/14
2-Chloro-**2c**	25	Yes	20.4 ± 1.8	3.8 ± 0.3	24.2	84/16
2-Chloro-**2c**	50	No	28.3 ± 4.4	4.5 ± 0.7	32.8	86/14
2-Chloro-**2c**	50	Yes	44.0 ± 3.1	6.4 ± 0.5	50.4	87/13
4-Chloro-**2d**	25	No	38.2 ± 4.4	3.5 ± 0.3	41.7	92/8
4-Chloro-**2d**	25	Yes	50.9 ± 2.1	4.8 ± 0.5	55.7	91/9
4-Chloro-**2d**	50	No	61.2 ± 3.8	5.3 ± 0.5	66.5	92/8
4-Chloro-**2d**	50	Yes	71.5 ± 3.5	6.3 ± 0.3	77.8	92/8

corresponding 9-nitrophenyladenine (**3**) was the main product slightly predominating over a new isomer, which was isolated and identified by NMR and mass spectrometry as 7-(2-nitrophenyl)- and 7-(4-nitrophenyl)adenine (**4a** and **4b**) for reactions with **2a** and **2b**, respectively. The site of substitution was confirmed by correlation of calculated shielding constants with experimental chemical shift values for ^{13}C and ^{15}N nuclei (vide infra).

Arylations with fluoroarenes bearing strongly electron-withdrawing substituents generally proceed much faster than those with chloro- and bromoarenes.[21,22] Therefore, the effect of microwaves on the reactions of **1** with 2- and 4-chloronitrobenzenes (**2c** and **2d**) should become more apparent compared to that obtained with fluoronitrobenzenes **2a** and **2b**. To obtain identical or closely similar temperature profiles irrespective of whether the reaction was heated in an oil bath or in a microwave oven, we first measured the temperature profile after immersion of the reaction flask into the oil bath, which was preheated to 150 °C. After 5 min, a steady-state temperature of 142 °C in the reaction mixture was achieved. Then, the same temperature profile was programmed in the microwave oven (Fig. 1).

Reactions were performed in triplicates, and the yields were determined analytically by high-performance liquid chromatography (HPLC) with a photodiode array (PDA) detection. Peaks were identified by a preliminary or simultaneous analysis using electrospray ionization–mass spectrometry (ESI-MS) detection in series with PDA and confirmed by comparison with authentic samples of **3a, 3b, 4a**, and **4b**. A typical chromatogram is shown in the Fig. 2. Isolated products were used as analytical standards for calibration of the ultraviolet (UV) responses. As shown in Table 1, the yields of both 9- and 7-arylated products were significantly greater in the microwave-assisted experiments. Prolongation of the reaction time over 50 min did not lead to any significant increase in product yields. The greatest total yields **3 + 4** were obtained with fluoronitrobenzenes **2a** and **2b** after 5 min of heating. *Ortho*

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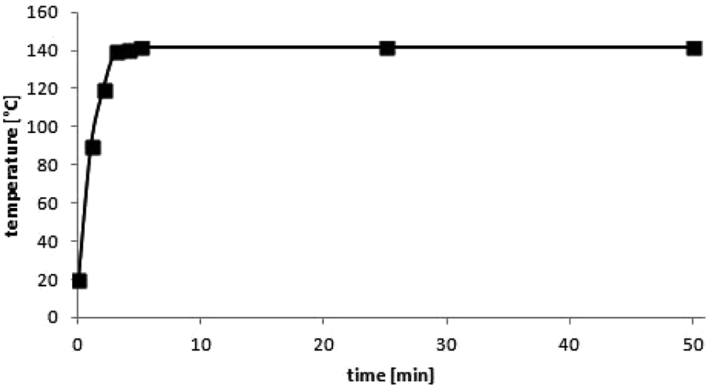

Figure 1. Temperature profile determined after immersing the reaction flask into the oil bath preheated to 150 °C and programmed in the microwave reactor.

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isomer **2a** was somewhat less reactive and gave approximately 1:1 mixture of **3a** and **4a**. Prolonged heating (25 min) led to a significant decrease in the yield of *N*7-isomer **4a** while the yield of *N*9-isomer remained almost unchanged. Compared to **2a** *para* isomer **2b** gave a significantly greater yield of *N*9-isomer **3b** but not of **4b** so that the product ratio **3**:**4** increased to 3:1 (Table 1).

These trends can be explained by formation of diarylated adenines, which were detected as minor products by HPLC-MS at m/z 272 (Fig. 2). The yield of *N*7-isomers, unlike that of the *N*9-isomers, decreased with reaction time, indicating their greater reactivity in the subsequent arylation.

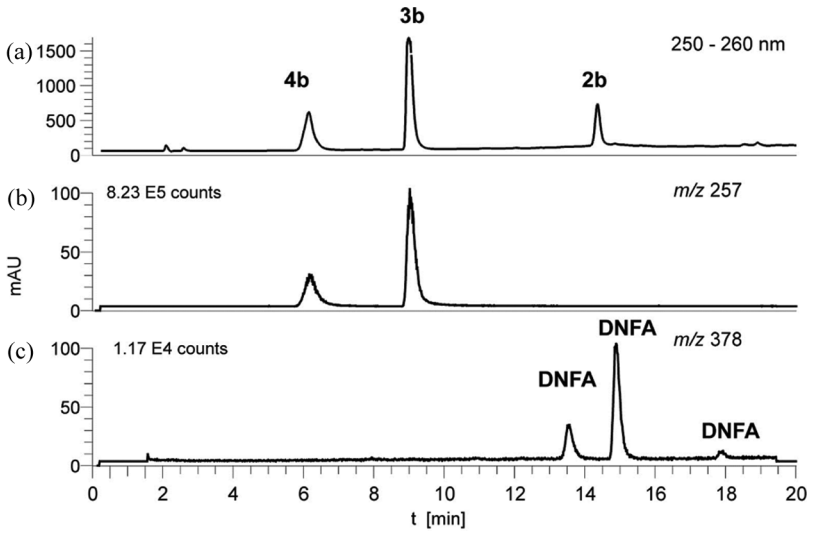

Figure 2. Typical chromatogram of the reaction mixture from the reaction of adenine (**1**) with 4-fluornitrobenzene (**2b**). (a) UV trace taken in the range of 250–260 nm; (b) MS trace, SIM at m/z 257 for detecting the **3** and **4** isomers; (c) MS trace, SIM at m/z 378 for detecting dinitrophenyladenines (DNFA). The intensity ranges for traces b and c (in ion counts) differ by nearly two orders of magnitude.

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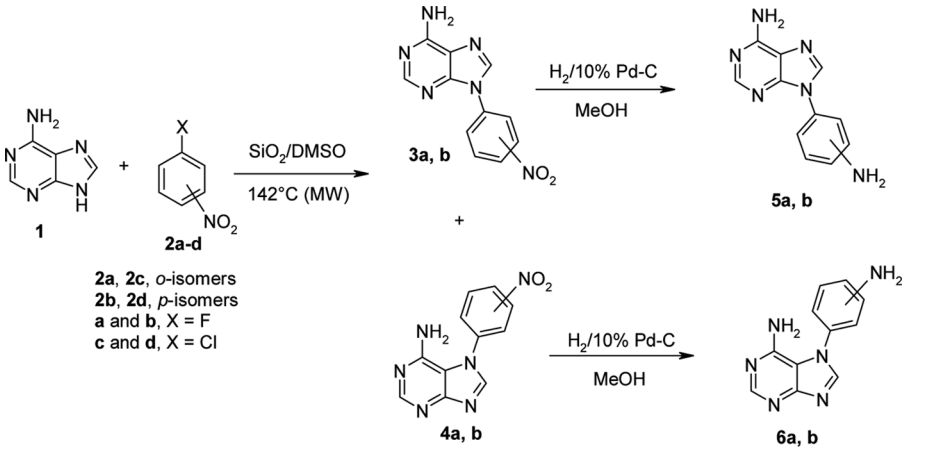
Compared to fluoronitrobenzenes, chloronitrobenzenes **2c** and **2d** gave much lower total yields and showed a different regioselectivity. Corresponding *N*9-isomers **3a** and **3b**, respectively, were the predominant products. Microwave irradiation had a modest but significant effect, increasing the total yield, whereas it had no effect upon product ratio.

Direct arylation by fluoronitroarenes appears to be a suitable synthetic route toward 7-aryladenines, which are otherwise hardly available. It has been reported that adenine reacts with electrophiles predominantly at positions *N*9, minor sites of attack being *N*3 and *N*1 positions.[7–14] The attack at *N*1 results in Dewar rearrangement, affording products of substitution at the exocyclic amino group N^6.[23] The method described here leads to a mixture of *N*7 and *N*9 isomers, which can be efficiently separated by column chromatography on silica gel and further used for preparation of corresponding aminoaryladenines. The latter compounds were obtained smoothly in good yields by palladium-catalyzed hydrogenation of nitrophenyladenines **3a, 3b, 4a**, and **4b** (Scheme 1). Formation of the *N*7 isomers was unexpected as this position has shown minor or no reactivity in hitherto known reactions of adenine with various electrophiles.[7–14]

Observed significant acceleration of the reaction by microwave irradiation cannot be attributed to purely nonthermal microwave-specific effects because in heterogeneous mixtures temperature inhomogeneity may easily occur. It is likely that polar water molecules at the surface of silica gel are selectively heated by microwaves.[19,20] Therefore, even if temperatures measured macroscopically in the reaction mixtures are equal, in the case of microwave irradiation the temperature at the actual site of reaction, which is most likely the interface between silica gel and DMSO, can be higher.

For structural assignment, a complete set of ^{1}H, ^{13}C, and ^{15}N NMR chemical shifts of the studied isomers were determined experimentally in solution by combination of ^{1}H, ^{13}C-APT, ^{1}H-^{13}C HMQC (heteronuclear multiple quantum correlation), ^{1}H-^{13}C HMBC (heteronuclear multiple bond correlation), and ^{1}H-^{15}N HMBC. ^{15}N chemical shifts were extracted from ^{1}H-^{15}N HMBC experiments. These



Scheme 1. Arylation of adenine with halonitrobenzenes followed by nitro group reduction.

experiments allowed us to exclude substitution at *N*1, *N*3 as well as at the exocyclic N^6 position. However, they did not allow us to distinguish between *N*7 and *N*9 substituted isomers because aryl substituents lack a hydrogen at *ipso* position, which would otherwise make possible the assignment by heterocorrelated ^{1}H-^{13}C 2D NMR experiments (HMBC). Preliminary assignment of positional isomers was therefore based on the assumption that *N*9-substituted products should predominate. To prove or disprove this assumption, correlation between calculated shielding constant and experimental ^{13}C and ^{15}N NMR chemical shifts was performed for nitroaryladenines **3a, 3b, 4a**, and **4b**.

Conformational analysis found two pairs of minima on the potential energy hypersurface pertaining to two pairs of enanatiomeric rotamers for 2-nitrophenyladenines **3a** and **4a**, and only one pair of minima pertaining to the most populated pair of enantiomers for 4-nitrophenyladenines **3b** and **4b** (Figs. 3 and 4).

Dihedral angles C_4-N_9-C_{ipso}-C_{ortho} of the most populated conformers of **3a** were 55° and 135° and that of **3b** was −31°. Similarly, dihedral angles C_5-N_7-C_{ipso}-C_{ortho} were −126° and 72° for **4a** and 42° for **4b**. The shielding constants (^{13}C and ^{15}N) were then calculated for the most populated conformers using Becke-6-Lee-Parr (B3LYP) hybrid functional implemented in Gaussian03 package[24] with or without solvent effects (DMSO). Correlation between calculated shielding constants and experimental values of ^{13}C and ^{15}N chemical shifts in simulated solvent (DMSO) are shown on Figs. 5 and 6 for 2-nitrophenyl- and 4-nitrophenyladenines, respectively. Very good

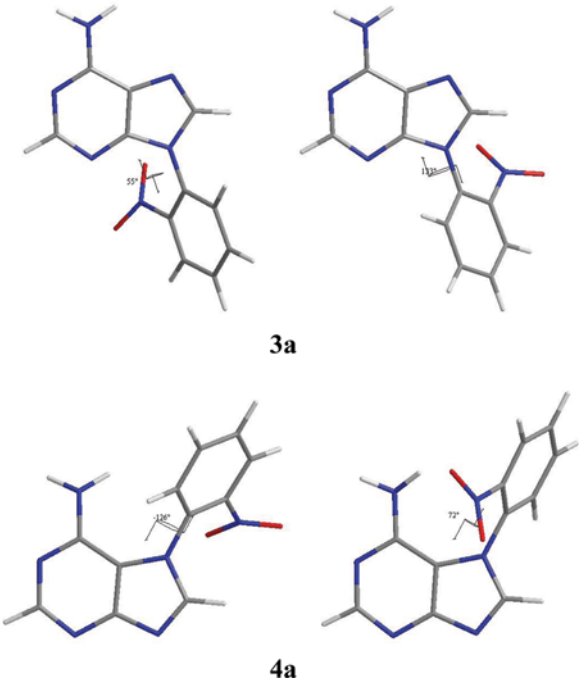


Figure 3. The optimized structures of 9-(2-nitrophenyl)adenine (**3a**) and 7-(2-nitrophenyl)adenine (**4a**). Two enantiomeric pairs of conformers at local minima of energy were found for each regioisomer. (Figure is provided in color online.)

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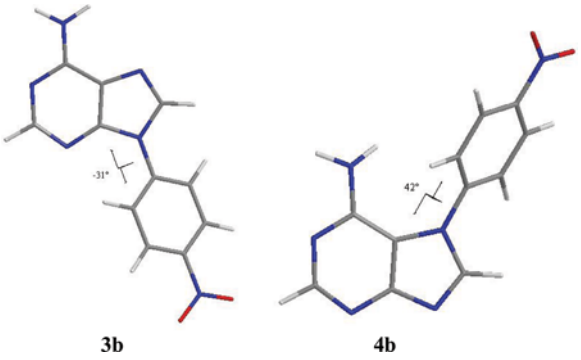

Figure 4. The optimized structure of 9-(4-nitrophenyl)adenine (**3b**) and 7-(4-nitrophenyl)adenine (**4b**). For each regioisomer, only one enantiomeric pair of conformers at local energy minimum was found. (Figure is provided in color online.)

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correlation was obtained in all cases ($R^2 > 0.989$). These results confirmed our preliminary structural assignment of all positional isomers.

In conclusion, direct arylation of adenine with fluoro- and chloronitroarenes followed by nitro group reduction is a feasible synthetic route to both 7- and 9-aminoaryladenines. A significant rate-enhancing effect of microwave irradiation was observed in controlled experiments at the same reaction temperature. This effect can be attributed to thermal inhomogeneity of the reaction mixtures rather than to a purely nonthermal effect of microwaves.

EXPERIMENTAL

Adenine (purity > 99.5%) and DMSO, extra dry on molecular sieves, were purchased from Acros Organics (Belgium). Silica gel 60, particle size 63–200 μm, was from Fluka. All other chemicals were of analytical or synthetic grade and were used as received. Microwave activation experiments were performed in a Synthewave 402 reactor from Prolabo (France) working at 2.47 GHz with a maximum output of 300 W containing a cylindrical quartz reactor rotating around a static glass paddle. The reactor was operated in programmed temperature mode, the temperature of the reaction mixture being measured by an infrared sensor. Merck silica-gel 60 F_{254} plates were used for thin-layer chromatography (TLC) analyses. HPLC analyses were performed on a Janeiro LC system (Thermo Fisher Scientific), consisting of two Rheos 2200 pumps, CTC PAL autosampler, a photodiode-array detector PDA, and an LXQ linear trap mass spectrometer with electrospray ionization (ESI). Capillary temperature was set to 300 °C; capillary voltage was 4.2 kV. Nitrogen was used as drying gas; helium was used as collision gas. Samples were injected on a BDS Hypersil C18 column 15 × 2.1 mm, 5 μm particle size. The mobile phase consisted of acetonitril and aqueous formic acid. Formic acid concentration was kept constant at 0.15%, and acetonitrile concentration increased linearly starting from 8.5% to 58% within 15 min and further to 73.5% in an additional 5 min. The flow rate was 200 μL/min. NMR spectra were measured on a Bruker 600 Avance (600 MHz for ^{1}H) or a Varian Mercury 300 (300 MHz for ^{1}H) spectrometer.

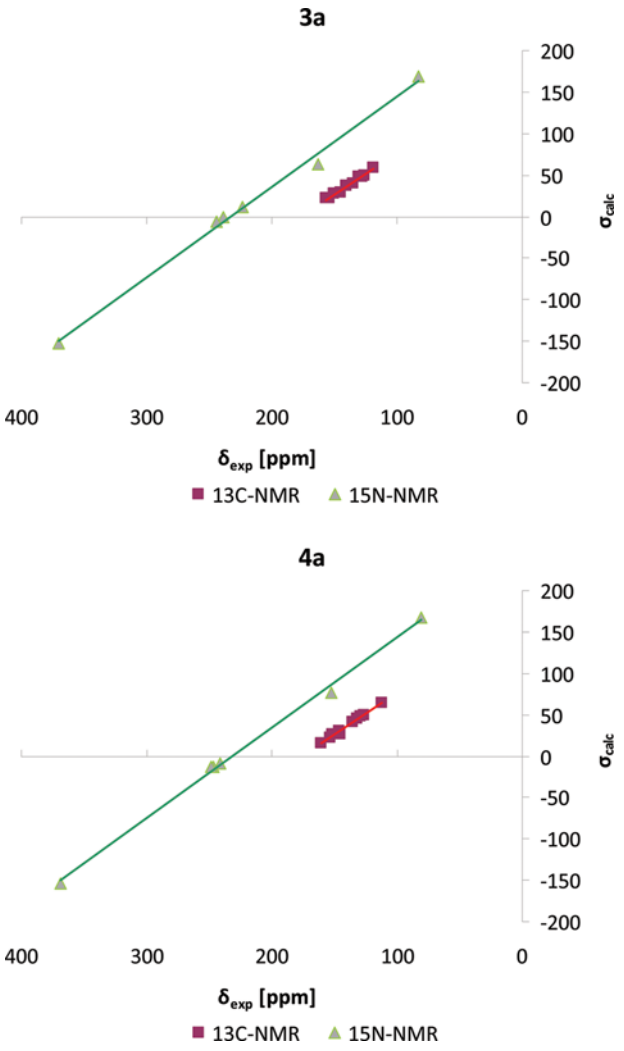

Figure 5. Correlation between calculated isotropic part of shielding tensor σ_{calc} and experimental chemical shift δ_{exp} of **3a** and **4a**. (Figure is provided in color online.)

High-resolution mass spectra were measured on an LTQ Orbitrap Velos instrument (Thermo Fisher Scientific) using electrospray ionization.

Arylation of Adenine, General Procedure 1: Conventional Heating

A mixture of adenine (1.351 g, 10 mmol), halonitrobenzene **2** (2.60 g, 16.5 mmol), dry potassium carbonate (1.382 g, 10 mmol), and silica gel (3.5 g) in 10 mL DMSO was placed into a 25-mL, three-necked flask equipped with magnetic stirrer and a thermometer. The flask was immersed into an oil bath, which was preheated to 150 °C, and the reaction temperature was registered in 1-min intervals

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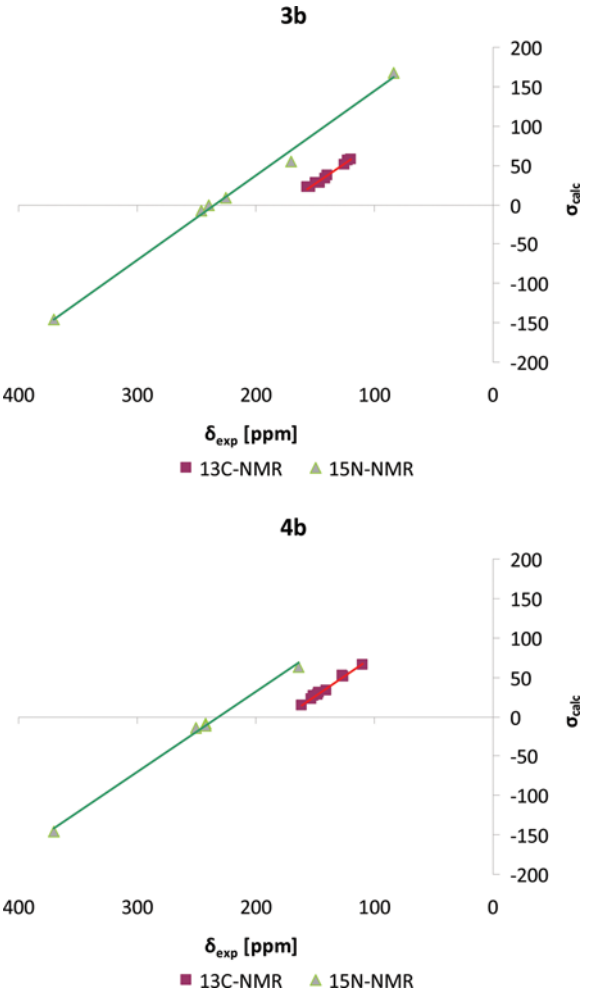

Figure 6. Correlation of calculated isotropic part of shielding tensor σ_{calc} and experimental chemical shift δ_{exp} of **3b** and **4b**. (Figure is provided in color online.)

until it reached steady state. Samples (100 µL) were taken after 25 and 50 min, diluted 4000 times with aqueous methanol (1:1), and analyzed by HPLC-UV-ESI-MS.

Arylation of Adenine, General Procedure 2: Microwave Irradiation

A mixture of adenine (1.351 g, 10 mmol), chloronitrobenzene **2c** or **2d** (2.60 g, 16.5 mmol), dry potassium carbonate (1.382 g, 10 mmol), and silica gel (3.5 g) in 10 mL DMSO was placed into a cylindrical quartz vessel, which was then placed into the microwave reactor. Reaction temperature was programmed to simulate the temperature profile obtained during conventional heating experiments. Because it was not possible to take samples without interrupting the irradiation, separate

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experiments were used for each time point. Hence the reaction was stopped after 10, 25, or 50 min, and diluted samples of the reaction mixture were then analyzed by HPLC-UV-ESI-MS.

9-(2-Nitrophenyl)adenine (3a)[17]. Compound **3a** was obtained as the main product by reaction of **1** with **2a** (general procedure 1).

7-(2-Nitrophenyl)adenine (4a). Compound **4a** was obtained as a by-product of **3a**. The yield was 303 mg (12%). $R_f = 0.30$ (10:1 chloroform–methanol). ^{1}H NMR (DMSO-d_6): $\delta = 6.29$ (br s, 2H, NH_2), 7.81 (d, $J = 8$ Hz, 1H, 6′-H), 7.88 (t, $J = 8$ Hz, 1H, 4′-H), 7.97 (t, $J = 8$ Hz, 1H, 5′-H), 8.31 (s, 1H, 2-H), 8.35 (d, $J = 8$ Hz, 1H, 3′-H), 8.50 (s, 1H, 8-H) ppm.

7-(4-Nitrophenyl)adenine (4b). Compound **4b** was obtained as a by-product of **3b**. The yield was 203 mg (8%). $R_f = 0.25$ (8:1 chloroform–methanol). ^{1}H NMR (DMSO-d_6): $\delta = 6.52$ (br s, 2H, NH_2), 7.82 (d, $J = 8.4$ Hz, 2H, 2′-H), 8.35 (s, 1H, 2-H), 8.46 (d, $J = 8.4$ Hz, 2H, 3′-H), 8.66 (s, 1H, 8-H) ppm. ^{13}C NMR (DMSO-d^6): $\delta = 110.3$ (C5), 125.7 (C3′), 126.6 (C2′), 140.9 (C1′), 146.6 (C8), 147.3 (C4′), 151.8 (C6), 153.6 (C2), 161.2 (C4) ppm.

9-(4-Nitrophenyl)adenine (3b)[26]. Compound **3b** was obtained as the main product by reaction of **1** with **2b** (general procedure 1).

Preparation of Aminophenyladenines: General Procedure 3

The catalyst, 10% palladium on charcoal (31 mg, 15 mol % Pd), was activated by heating for 1 h to 90 °C in the stream of argon. The reaction flask was than cooled to ambient temperature; nitrophenyladenine **3a, 4a, 3b**, or **4b** (50 mg, 1.95 mmol) solution in 20 mL of absolute methanol was added, and the reaction mixture was evacuated and filled with argon repeatedly to remove oxygen. A gentle stream of hydrogen was introduced, and the reaction mixture was heated to 30 °C for 20 h. The catalyst was filtered off and washed carefully with methanol. The washes were added to the filtrate, and methanol was then evaporated in a vacuum to yield pure products.

9-(2-Aminophenyl)adenine (5a). White powder, mp 243–244 °C, obtained from **3a**, yield 39 mg, 89%. ^{1}H NMR (DMSO-d_6): $\delta = 5.08$ (br s, 2H, ArNH_2), 6.68 (t, $J = 7.5$ Hz, 1H, 5′-H), 6.91 (d, $J = 8.1$ Hz, 1H, 3′-H), 7.10 (d, $J = 7.8$ Hz, 1H, 6′-H), 7.20 (t, $J = 7.7$ Hz, 1H, 4′-H), 7.32 (br s, 2H, NH_2), 8.12 (s, 1H, 2-H), 8.15 (s, 1H, 8-H) ppm. ^{13}C NMR: $\delta = 116.7$ (C5′), 116.8 (C3′), 119.2 (C5), 120.2 (C1′), 128.7 (C6′), 130.1 (C4′), 141.6 (C8), 145.0 (C2′), 150.6 (C4), 153.2 (C2), 156.7 (C6) ppm. HRMS (ESI): calcd. for $C_{11}H_{10}N_7$ 227.1040; found 227.1040.

7-(2-Aminophenyl)adenine (6a). White powder, mp > 260 °C, obtained from **4a**, yield 36 mg, 82%. ^{1}H NMR (DMSO-d_6): $\delta = 5.40$ (br s, 2H, Ar-NH_2), 5.88 (br s, 2H, NH_2), 6.70 (t, $J = 7.5$ Hz, 1H, 5′-H), 6.94 (d, $J = 8.2$ Hz, 1H, 3′-H), 7.14 (d, $J = 7.8$ Hz, 1H, 6′-H), 7.27 (t, $J = 7.7$ Hz, 1H, 4′-H), 8.27 (s, 1H, 2-H), 8.29 (s, 1H, 8-H) ppm. ^{13}C NMR $\delta = 112.5$ (C5), 116.6 (C3′), 116.9 (C5′), 120.3 (C1′), 129.3 (C6′), 131.3 (C4′), 145.6 (C2′), 146.4 (C8), 151.9 (C6), 152.9 (C2), 160.0 (C4) ppm. HRMS (ESI): calcd. for $C_{11}H_{10}N_7$ 227.1040; found 227.1040

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9-(4-Aminophenyl)adenine (5b). White powder, mp > 260 °C, obtained from **3b**, yield 35 mg, 80%. ^{1}H NMR (DMSO-d$_6$): δ = 6.73 (d, J = 8.7 Hz, 2H, 3′-H), 7.40 (d, J = 8.7 Hz, 2H, 2′-H), 7.41 (br s, 2H, NH_2), 8.19 (s, 1H, 2-H), 8.37 (s, 1H, 8-H) ppm. ^{13}C NMR (DMSO-d$_6$): δ = 114.4 (C3′), 119.5 (C5), 124.0 (C1′), 125.1 (C2′), 140.7 (C8), 148.8 (C4′), 149.7 (C4), 152.8 (C2), 156.3 (C6) ppm. HRMS (ESI): calcd. for $C_{11}H_{10}N_7$ 227.1040; found 227.1041.

7-(4-Aminophenyl)adenine (6b). White powder, mp > 260 °C, obtained from **4b**, yield 40 mg, 91%. ^{1}H NMR (DMSO-d$_6$): δ = 5.59 (br s, 2H, Ar-NH_2), 5.93 (br s, 2H, NH_2), 6.72 (d, J = 8.6 Hz, 2H, 3′-H), 7.21 (d, J = 8.6 Hz, 2H, 2′-H), 8.27 (s, 1H, 2-H), 8.32 (s, 1H, 8-H) ppm. ^{13}C NMR (DMSO-d$_6$): δ = 111.7 (C5), 114.3 (C3′), 123.6 (C1′), 127.5 (C2′), 146.2 (C8), 150.4 (C4′), 151.7 (C6), 152.9 (C2), 159.7 (C4) ppm. HRMS (ESI): calcd. for $C_{11}H_{10}N_7$ 227.1040; found 227.1040

SUPPORTING INFORMATION

Full experimental detail, ^{1}H and ^{13}C NMR spectra, and HPLC traces can be found via the Supplementary Content section of this article's Web page.

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