Chelation-Controlled, Palladium-Catalyzed Vinylic Substitution Reactions of Vinyl Ethers. 2-Arylethanal Equivalents from Aryl Halides

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The regioselectivity of palladium-catalyzed arylation reactions of a series of nitrogen-containing vinyl ethers is reported. The presence of a β-amino substituent gives a profound influence on regiochemistry. Thus, the arylation of [2-(dimethylamino)ethoxy]ethene (**1c**) with a variety of aryl iodides and bromides provides the β-arylation products [2-[2-(dimethylamino)ethoxy]ethenyl]arenes (**3**) with at least 95% selectivity and in good yields. The corresponding arylation of butoxyethene is a nonselective process giving a mixture of α- and β-substitution products. The palladium-catalyzed arylation of **1c** constitutes an entry to 2-arylethanals after cleavage of the enol ether. The directing effect of the amino group is discussed in terms of chelation with the intermediate arylpalladium halide.

Introduction

Palladium-catalyzed functionalization of aromatic halides and triflates has become common practice in preparative organic chemistry.[1] In particular, the introduction of groups containing three or more carbon atoms is facile via the Heck arylation[2] procedure. This method of carbon–carbon bond formation is compatible with a variety of functional groups and quite general with regard to the aromatic reagent. The Heck arylation is, however, not very useful for the attachment of two-carbon fragments. Although the cross-coupling methodology[3] using organometallics as ethylene equivalents has proven valuable for a number of systems, consideration of availability and operational simplicity leaves the direct vinylic substitution an attractive alternative to investigate. The utilization of acyclic heteroatom-carrying olefins in the latter reaction has been hampered, in particular by low regioselectivity.[4] Although some interesting exceptions have appeared,[5] modest yields have been reported by most authors.[6] The apparent applicability of a reliable procedure of the latter type in the synthesis of pharmaceutically important compounds,[7] e.g. arylethylamines or arylacetic acids,[8] has stimulated us to study model arylation reactions of simple enol ethers in some detail.[6] Useful regioselectivity can be achieved, but no generally applicable procedure has evolved so far.[5,9]

It has been demonstrated that the addition of organopalladium intermediates to olefins can be influenced by coordinating groups adjacent to the substrate double bond. In an early example, 2-vinylpyridine was reported to add "phenylpalladium chloride" with the opposite regiochemistry to that observed with styrene.[10]

Directing effects of similar nature are notoriously encountered in stoichiometric 1,2-addition reactions.[11] More recently, McCrindle and co-workers have communicated detailed studies on the chemistry of chelated palladium complexes of amino-functionalized enol ethers[12] and related ligands.[13] To our knowledge, no examples exist of the utilization of such chelating substrates in catalytic reactions.

We decided to investigate arylation reactions with enol ethers containing a coordinating substituent in an effort to achieve improved regiochemical control. Here, we report on our initial studies involving nitrogen-containing substrates derived from ethyl vinyl ether.

Chart I

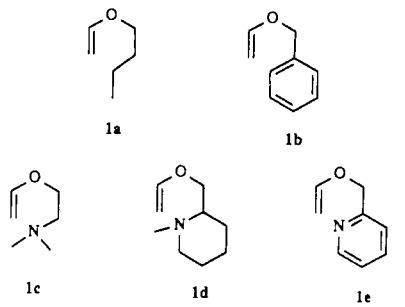

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Table I. Phenylation of Vinyl Ethers 1a–e with Iodobenzene or Bromobenzene

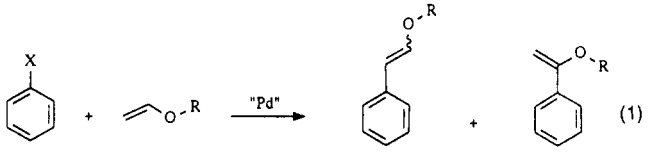
aryl halide	vinyl ether	procedure[a]	conditions	β-selectivity[b]	E/Z ratio[c]
PhI, **2a**	**1a**	A	100 °C, 16 h[d]	0.6	0.4
PhI, **2a**	**1b**	A	100 °C, 16 h[d]	0.7	0.6
PhI, **2a**	**1c**	A	100 °C, 16 h[d]	3.6	0.5
PhI, **2a**	**1d**	A	100 °C, 16 h[d]	7.1	0.3
PhI, **2a**	**1e**	A	100 °C, 16 h[d]	4.8	0.6
PhI, **2a**	**1b**	B	50 °C, 16 h[h]	2.5	2.5
PhI, **2a**	**1c**	B	50 °C, 16 h	50	0.7
PhI, **2a**	**1d**	B	80 °C, 24 h	26	1.0
PhI, **2a**	**1e**	B	80 °C, 48 h	1.0[e]	1.7[e]
PhI, **2a**	**1c**	B	80 °C, 16 h, PPh_3[f]	19	0.6
PhBr, **2b**	**1c**	B	80 °C, 16 h, PPh_3[f]	26[g]	0.9
PhBr, **2b**	**1c**	B	80 °C, 16 h, $P(o\text{-tol})_3$[d,f,h]	15[g]	1.7
PhBr, **2b**	**1c**	B	80 °C, 16 h, PPh_3[f,i]	12	0.7

[a] The reactions employed aryl halide (1 mmol), vinyl ether (1.2 mmol), and palladium acetate (0.03 mmol) in 5 mL of solvent. Procedure A: reaction in acetonitrile using triethylamine (1.5 mmol) as the base. Procedure B: reaction in dimethylformamide using K_2CO_3 (2 mmol)/Bu_4NCl (1 mmol) as the base. [b] Calculated as 3/4. Determined by GLC–MS. [c] (*E*)-3/(*Z*)-3 as determined by GLC–MS. [d] Starting material remained. [e] Extensive decomposition occurred. [f] 0.12 mmol of phosphine was present (Pd:P ratio 1:4). [g] Biphenyl was formed (ca. 35% based on bromobenzene). [h] $P(o\text{-tol})_3$ is tri(*o*-tolyl)phosphine. [i] This reaction employed 4 mmol of **1c** and 2 mL of solvent.

Results

We chose to initiate our studies with some stable and easily available β-amino functionalized vinyl ethers. The substrate structures are given in Chart I. The vinyl ethers **1b–e** were conveniently obtained via mercury(II)-catalyzed transetherification of ethyl vinyl ether,[14] although better methods are available for large-scale preparations.[15]

Arylation of **1a–e** with iodobenzene (**2a**) was performed under standard conditions to evaluate the influence of the amino function (eq 1). The results are summarized in



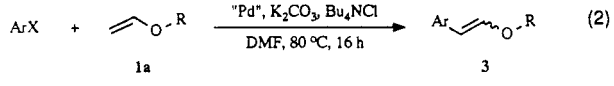
(1)

2a; X=I **2b**; X=Br — **1a-1e** — **3a-3e** — **4a-4e**

Table I. Under traditional Heck arylation conditions (CH_3CN, NEt_3, procedure A), a significant (5–10-fold) increase in β-selectivity was encountered starting from **1c–e** as compared to **1a** or **1b**, which both underwent essentially nonselective arylation.[4e] As expected, steric bulk from a phenyl group (**1b**) did not alter regiochemistry significantly. In this system, the piperidine-derived **1d** appeared to be superior to **1c** or **1e** with regard to β-selectivity. The reactivity, however, was found to be decreasing in the order **1c** > **1d** > **1e**, as estimated from GLC analysis of remaining **2a**. It was not surprising to find that much better regioselectivity could be obtained under phase-transfer conditions[16] (DMF, K_2CO_3, Bu_4NCl, procedure B), since these conditions allow the reactions to be run at lower temperature, and in the absence of competing trialkylamine. Here, the reactions were run until all of the starting **2a** had been consumed. Again, the same relative order of reactivity was observed among the chelating substrates. Complete conversion of **2a** was achieved in 16 h at 50 °C with **1c**. Useful regioselectivity was obtained with both **1c** and **1d**, both providing the β-arylated **3** with more than 95% selectivity, and in good yield. The phenylation of pyridine-derived **1e** was very sluggish under these conditions though, and decomposition of the products became a problem. The difference in regiochemistry from the arylation of **1b** in the two systems agrees with results obtained with **1a** reported elsewhere.[9a,4e] The *E*:*Z* ratio of **3** was not greatly influenced by the structure of starting **1**, but slightly higher using procedure B.

Since oxidative addition to aryl bromides normally requires the presence of a phosphine ligand,[2] we also assessed the effect of triarylphosphines for a possible extension of our procedure. The presence of 12 mol % of triphenylphosphine exerted a surprisingly minor influence on the product distribution from **2a** using **1c** as the substrate. Good regiocontrol prevailed also when the phenylation was performed with bromobenzene (**2b**), but large amounts of biphenyl were observed in the reaction mixture. By using 4 rather than 1.2 equiv of **1c**, however, the desired **3c** could be obtained in good yield also from this arylating agent.

We chose to use the most readily available vinyl ether **1c** to examine the generality of the procedure with respect to arylating agent. Reaction with several aryl halides was performed at 80 °C, at which temperature all of the starting halide was consumed on reaction overnight (eq 2).



(2)

1a — **3**

R= $-CH_2-CH_2-N(CH_3)_2$

The results obtained (Table II) indicated high efficiency and good regioselectivity with most aryl halides. The β-selectivities observed were in the range 12–77. Even 1,4-diiodobenzene allowed the isolation of a 76% yield of the desired dienol ether **3f**. Importantly, also 4-methoxy-1-iodobenzene gave a very good yield of β-arylation product. This regiocontrol is particularly impressive, since this halide has previously been shown to give 4-methoxyacetophenone as the only isolable product[4f,17] from the reaction with methyl vinyl ether. The 4-nitro halides **2f** and **2j** gave substantial amounts of biaryl, and thus inferior yields. Unfortunately, ortho-substituted derivatives studied so far gave no arylation products under the present

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(16) (a) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. (b) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.

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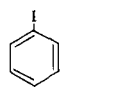
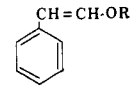
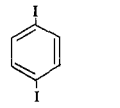
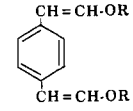
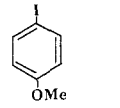
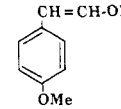
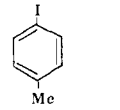
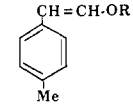
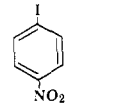
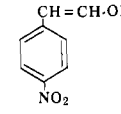
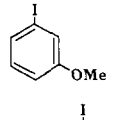
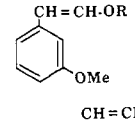
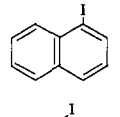
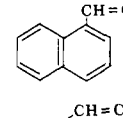
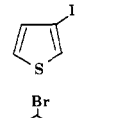
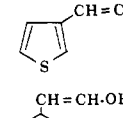
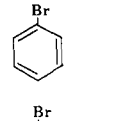
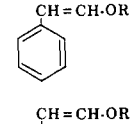
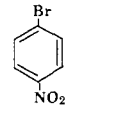
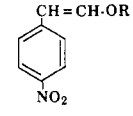
Table II. Arylation of 1c with Various Aryl Halides (eq 2)[a]

aryl halide	product[b]	yield,[c] %
 2a	 3a	80
 2c	 3f	76
 2d	 3g	83
 2e	 3h	85
 2f	 3i	45[d]
 2g	 3j	85[e]
 2h	 3k	76[e]
 2i	 3l	48
 2b	 3a	52[b]
 2j	 3i	58[d]

[a] The reactions utilized aryl halide (10 mmol), vinyl ether (**1c**, 12 mmol), K_2CO_3 (20 mmol), Bu_4NCl (10 mmol), and $Pd(OAc)_2$ (0.3 mmol, 3%), in 10 mL of DMF. The mixture was heated to 80 °C for 16 h. [b] *E*:*Z* mixture. See Experimental Section for details. R is $CH_2CH_2N(CH_3)_2$. [c] Yield of pure (>96% by GLC) isolated product, based on the aryl halide. [d] 4,4′-Dinitribiphenyl accounted for remaining material. [e] The reaction was performed on a 5-mmol scale. [f] The reaction was performed on a 1-mmol scale. Triphenylphosphine was added (Pd:P ratio 1:4).

conditions (2-iodophenol and 2-bromonitrobenzene). Equally disappointing results were encountered with 2-iodothiophene, which exclusively gave 2,2′-dithienyl. The reason for the reluctancy of these latter compounds to undergo the reaction is not apparent. Although only one aryl bromide has been applied thus far, the isolation of the desired **3a** in 52% yield (on a 1-mmol scale) from bromobenzene indicates that the use of such arylating agents is also possible.

In addition to the favorable regiochemistry achieved with **1c**, this olefin facilitated a very simple purification procedure. Thus, a mild acidic workup selectively hydrolyzed the minor α-arylated product (**4**) and removed any nonbasic side products. Pure **3** was obtained without chromatography or distillation.

We employed the nonacidic conditions reported by Kosarych and Cohen[18] for the cleavage of the parent **3a**

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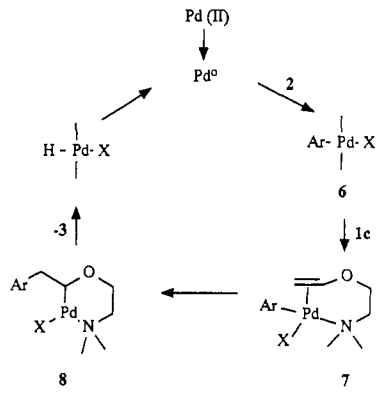
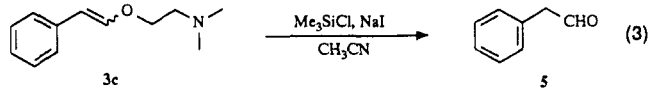
Scheme I



(eq 3). This procedure indeed allowed quantitative conversion of **3a** into 2-phenylethanal.



(3)

Discussion

Although we have made no detailed studies permitting the evaluation of the reaction mechanism for the arylation of substrates such as **1c–e**, it seems reasonable to suggest the catalytic cycle depicted in Scheme I. Initial reduction of the palladium(II) to the active zero-valent state is facile under the conditions.[19] The intermediacy of a chelated organopalladium species along the reaction coordinate is supported by some observations made in our exploratory studies (Table I). First, the regioselectivity observed with the substrates **1c–e** as compared to **1a** or **1b** is certainly not of a steric origin. Thus, the apparent electronic control[4e] of regiochemistry encountered with simple alkyl enol ethers appears to be efficiently suppressed by an adjacent amino substituent. Secondly, the rate of reaction was significantly lower for the three aminovinyl ethers, which might suggest an enhanced stability of intermediates such as **7** or **8**.[12b] Anchoring of the metal to the nitrogen atom in **7** may direct the collapse of the π-complex through either direct steric constraints, favoring the formation of **8**, or possibly by imposing a conformational change in the π-system, thus diminishing the polarization of the double bond. Investigation of arylation as well as vinylation reactions of analogous enol ethers, having a different relationship between the double bond and the coordinating heteroatom, should provide further insight into the mechanistic details of the process. These studies will be the subject of future reports.

In conclusion, the chelation-controlled arylation of **1c** appears to provide an alternative approach to arylethanals and related compounds. An extension to other precursors for the organopalladium reagent as well as new classes of chelating substrates promises to be worthwhile.

Experimental Section

Instrumentation. Mass spectra were obtained on a Finnigan 4021 gas chromatograph–mass spectrometer operating at 70 eV. ^1H NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts are given relative to internal tetramethylsilane in deuteriochloroform. Gas chromatographic analyses were performed on a Varian 3300 instrument, equipped with a 2.5 m × 2 mm glass column of 5% OV17 on Chromosorb W. A Varian 4270 integrator was used to determine peak areas. Elemental

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analyses were obtained from the Microanalytical Laboratory at the University of Lund. Arylation reactions were routinely performed in capped, heavy-walled Pyrex tubes, although ordinary flasks are useful for large-scale preparations.

Materials. Aryl halides were purchased from local suppliers and used as received. Amino alcohols were distilled prior to use. Palladium acetate was obtained from Johnson-Matthey Chemicals. All other reagents were commercially obtained and used without further purification. Solvents were stored over the appropriate molecular sieves. Pentane, used for workup, was distilled.

Preparation of Vinyl Ethers 1b–e. The synthesis of **1c** is representative:[14] Dry $Hg(OAc)_2$ (10 g) was dissolved in ethyl vinyl ether (50 mL) with stirring. To this solution was added a mixture of dimethylethanolamine (50 mL) in ethyl vinyl ether (50 mL), and the reaction mixture was refluxed for 16 h. After cooling, diethyl ether (100 mL) was added, and the obtained solution was washed with water (3 × 100 mL) and dried ($MgSO_4$). Distillation at aspirator pressure afforded **1c** as a colorless liquid[14b] (9.7 g, 17%): bp 120–22 °C (760 mmHg) (42 °C (40 mmHg)); ^1H NMR δ 6.40 (dd, 1 H, CH), 3.95 (m, 2 H, $CHCH_2$), 3.70 (t, 2 H, OCH_2), 2.51 (t, 2 H, CH_2N), 2.20 (s, 6 H, $N(CH_3)_2$). The other vinyl ethers were prepared similarly, in about 20% yield, but starting from 0.1 mol of the appropriate amino alcohol. Distillation produced vinyl ethers of satisfactory purity for use in the arylation experiments, but samples for elemental analysis were purified by column chromatography (aluminum oxide, pentane/ethyl acetate, 9/1).

[(Ethenyloxy)methyl]benzene (1b): colorless oil; bp 75–78 °C (12 mmHg); ^1H NMR δ 7.4–7.3 (m), 6.60 (dd, J = 7, 14 Hz), 4.80 (s), 4.35 (dd, J = 2, 14 Hz), 4.12 (dd, J = 2, 7 Hz). Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.50; H, 7.54.

1-Methyl-2-[(ethenyloxy)methyl]piperidine (1d): oil; bp 47–52 °C (1.2 mmHg); ^1H NMR δ 6.50 (dd, J = 7, 14 Hz), 4.10 (dd, J = 2, 14 Hz), 3.92 (dd, J = 2, 7 Hz), 3.65 (q), 2.80 (m), 2.22 (s), 2.04 (m), 1.7–1.4 (m). Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04. Found: C, 69.35; H, 11.05.

2-[(Ethenyloxy)methyl]pyridine (1e): oil; bp 86–90 °C (12 mmHg); ^1H NMR δ 8.53 (d), 7.69 (t), 7.41 (d), 7.18 (m), 6.60 (q), 4.88 (s), 4.30 (dd), 4.09 (dd). Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71. Found: C, 70.70; H, 6.91.

Exploratory Phenylation Reactions (Table I). Procedure A. To a heavy-walled Pyrex tube containing a solution of palladium acetate (0.007 g, 0.03 mmol) in 5 mL of acetonitrile were added iodobenzene (**2a**) (0.20 g, 1.0 mmol), triethylamine (0.15 g, 1.5 mmol), and the vinyl ether (**1a–e**, 1.2 mmol). The tube was closed with a Teflon-lined screw cap. The mixture was stirred at 100 °C for 16 h on an oil bath. After cooling, a sample was partitioned between 0.1 M NaOH and diethyl ether and analyzed by GLC–MS.

Procedure B. Palladium acetate (0.007 g, 0.03 mmol), K_2CO_3 (0.28 g, 2 mmol), Bu_4NCl (0.28 g, 1.0 mmol), and, if present, triarylphosphine ligand (0.12 mmol) were dissolved in 4 mL of dry DMF in a heavy-walled Pyrex tube. A mixture of iodobenzene (**2a**) or bromobenzene (**2b**) (1.0 mmol) and vinyl ether (**1a–e**, 1.2 mmol) in 1 mL of DMF was added, and the tube was capped. The reaction mixture was heated with stirring (see Table I for details) until the starting aryl halide had been consumed (GLC). The isomeric distribution was determined by GLC–MS from a small sample (~0.1 mL), which was taken up in diethyl ether and washed with 0.1 M NaOH. The remaining reaction mixture was diluted with 50 mL of diethyl ether and washed with water (4 × 25 mL). Drying ($MgSO_4$) and concentration gave a black, viscous oil, which was subjected to distillation in a Kugelrohr apparatus to afford the arylation product as a mixture of isomers (**3** and **4**). **3b** is a known compound.[20]

(*E*)/(*Z*)-1-Methyl-2-[[(2-phenylethenyl)oxy]methyl]piperidine (3d): oil; bp 125 °C (0.6 mmHg); MS m/e (relative intensity) 231 (2), 112 (5), 98 (100), 70 (13). Anal. (mixture of **3d** and **4d**). Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.70; H, 9.30.

(*E*)/(*Z*)-2-[[(2-Phenylethenyl)oxy]methyl]pyridine (3e): oil; bp 140 °C (0.6 mmHg); MS m/e (relative intensity) 211 (12), 182 (40), 92 (74), 91 (89), 65 (100). Anal. (mixture of **3e** and **4e**). Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20. Found: C, 79.55; H, 6.27.

Preparation of (*E*)/(*Z*)-[2-[2-(Dimethylamino)ethoxy]ethenyl]arenes (Table II). The synthesis of the parent **3c** is typical: Palladium acetate (0.07 g, 0.3 mmol), K_2CO_3 (2.8 g, 20 mmol) and Bu_4NCl (2.8 g, 10 mmol) were stirred in 15 mL of dry DMF in a thin-necked Pyrex tube for 5 min. To the yellow solution was added a mixture of iodobenzene (2.04 g, 10 mmol) and **1c** (1.38 g, 12 mmol) in 15 mL of dry DMF. The tube was capped and heated with stirring at 80 °C in an oil bath for 16 h. The reaction solution turned black within 1 h. After cooling, the solution was transferred to a separatory funnel containing 100 mL of pentane and washed twice with 50 mL of water, which was discarded. The organic layer was then extracted with 0.1 M HCl (4 × 50 mL). The aqueous extracts were combined, treated with 50 mL of pentane, and poured into a beaker containing 40 mL of 1 M NaOH and 100 mL of pentane. After the mixture was stirred for 10 min, the phases were separated and the aqueous layer was extracted with additional pentane (50 mL). After washing with brine and drying ($MgSO_4$), evaporation of the combined pentane solutions afforded the title compound (**3c**) as a pale yellow oil: 1.53 g (80%). *E*:*Z* = 34:66; GLC analysis indicated a purity of 97%: ^1H NMR δ 7.6–7.2 (m, aryl), 7.00 (d, J = 13 Hz, *E*), 6.21 (d, J = 7 Hz, *Z*), 5.85 (d, J = 13 Hz, *E*), 5.23 (d, J = 7 Hz, *Z*), 4.03 (t, CH_2O, *Z*), 3.93 (t, CH_2O, *E*), 2.68 (t, CH_2N, *Z*), 2.64 (t, CH_2N, *E*), 2.33 (s, CH_3N, *Z*), 2.31 (s, CH_3N, *E*); MS m/e (relative intensity) 191 (2), 91 (2), 72 (30), 58 (100). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96. Found: C, 75.35; H, 8.93.

1,4-Bis[2-[2-(dimethylamino)ethoxy]ethenyl]benzene (3f): *E*,*E*:*E*,*Z*:*Z*,*Z* = 12:26:62; yellow oil; ^1H NMR δ 7.5–7.1 (m), 7.00 (d, J = 13 Hz), 6.95 (d, J = 7 Hz), 5.80 (d, J = 13 Hz), 5.17 (dd, J = 7 Hz), 3.98 (dt), 3.88 (t), 2.63 (m), 2.29 (s), 2.28 (s); MS m/e (relative intensity) 304 (1), 86 (1), 72 (100), 58 (76). Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27. Found: C, 71.20; H, 9.05.

1-[2-[2-(Dimethylamino)ethoxy]ethenyl]-4-methoxybenzene (3g): *E*:*Z* = 33:67; yellow oil; ^1H NMR δ 7.5–6.8 (m), 6.91 (d, J = 13 Hz), 6.11 (d, J = 7 Hz), 5.81 (d, J = 13 Hz), 5.18 (d, J = 7 Hz), 3.99 (t), 3.88 (t), 3.78 (s), 3.77 (s), 2.65 (t), 2.62 (t), 2.31 (s), 2.30 (s); MS m/e (relative intensity) 221 (2), 121 (2), 72 (81), 58 (100). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65. Found: C, 70.30; H, 8.48.

1-[2-[2-(Dimethylamino)ethoxy]ethenyl]-4-methylbenzene (3h): *E*:*Z* = 35:65; pale yellow oil; ^1H NMR δ 7.5–7.1 (m), 7.00 (d, J = 13 Hz), 6.17 (d, J = 7 Hz), 5.84 (d, J = 13 Hz), 5.22 (d, J = 7 Hz), 4.02 (t), 3.92 (t), 2.67 (t), 2.64 (t), 2.33 (s), 2.32 (s); MS m/e (relative intensity) 205 (2), 105 (1), 72 (48), 58 (100). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33. Found: C, 75.75; H, 9.29.

1-[2-[2-(Dimethylamino)ethoxy]ethenyl]-4-nitrobenzene (3i): *E*:*Z* = 46:54; yellow oil; ^1H NMR δ 8.1–7.3 (m), 7.20 (d, J = 13 Hz), 6.40 (d, J = 7 Hz), 5.85 (d, J = 13 Hz), 5.28 (d, J = 7 Hz), 4.08 (t), 3.96 (t), 2.66 (t), 2.63 (t), 2.30 (s); MS m/e (relative intensity) 236 (1), 72 (8), 58 (100). Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83. Found: C, 60.87; H, 6.98.

1-[2-[2-(Dimethylamino)ethoxy]ethenyl]-3-methoxybenzene (3j): *E*:*Z* = 38:62; pale yellow oil; ^1H NMR δ 7.2–6.6 (m), 7.04 (d, J = 13 Hz), 6.20 (d, J = 7 Hz), 5.82 (d, J = 13 Hz), 5.21 (d, J = 7 Hz), 4.02 (t), 3.91 (t), 3.79 (s), 3.78 (s), 2.66 (t), 2.63 (t), 2.32 (s), 2.31 (s); MS m/e (relative intensity) 221 (2), 121 (1), 72 (37), 58 (100). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65. Found: C, 70.70; H, 8.57.

1-[2-[2-(Dimethylamino)ethoxy]ethenyl]naphthalene (3k): *E*:*Z* = 42:58; yellow oil; ^1H NMR δ 8.2–7.5 (m), 7.02 (d, J = 13 Hz), 6.57 (d, J = 13 Hz), 6.45 (d, J = 7 Hz), 5.95 (d, J = 7 Hz), 4.05 (m), 2.70 (m), 2.40 (s), 2.30 (s); MS m/e (relative intensity) 241 (2), 152 (2), 141 (2), 72 (64), 58 (100). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.72; H, 7.82.

3-[2-[2-(Dimethylamino)ethoxy]ethenyl]thiophene (3l): *E*:*Z* = 21:79; yellow oil; ^1H NMR δ 7.4–7.2 (m), 6.97 (d, J = 13 Hz), 6.16 (d, J = 7 Hz), 5.88 (d, J = 13 Hz), 5.37 (d, J = 7 Hz), 4.02 (t), 3.89 (t), 2.66 (t), 2.63 (t), 2.32 (s), 2.30 (s); MS m/e (relative intensity) 197 (1), 99 (3), 72 (42), 58 (100). Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66. Found: C, 60.90; H, 7.58.

Cleavage of 3a To Give 2-Phenylethanal (5).[18] A mixture of **3a** (0.80 g, 4.1 mmol) and sodium iodide (1.24 g, 8.3 mmol) was stirred in 85 mL of dry CH_3CN under argon. Trimethylsilyl chloride (1 mL, 8.3 mmol) was added through a syringe. After 1 h the yellow solution, containing a white precipitate, was poured

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into 100 mL of 0.5 M $Na_2S_2O_3$ and extracted with 100 mL of diethyl ether. After washing (2 × 50 mL of water) and drying, evaporation at aspirator pressure afforded 0.49 g (100%) of 2-phenylethanal, which was homogeneous according to GLC.

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Registry No. **1a**, 111-34-2; **1b**, 935-04-6; **1c**, 3622-76-2; **1d**, 129126-29-0; **1e**, 39565-48-5; **2a**, 591-50-4; **2b**, 108-86-1; **2c**, 624-38-4; **2d**, 696-62-8; **2e**, 624-31-7; **2f**, 636-98-6; **2g**, 766-85-8; **2h**, 90-14-2; **2i**, 10486-61-0; **2j**, 586-78-7; (*E*)-**3a**, 36586-17-1; (*Z*)-**3a**, 36586-16-0; (*E*)-**3b**, 69520-20-3; (*Z*)-**3b**, 78043-55-7; (*E*)-**3c**, 129126-30-3; (*Z*)-**3c**, 129126-31-4; (*E*)-**3d**, 129126-32-5; (*Z*)-**3d**, 129126-33-6; (*E*)-**3e**, 129126-34-7; (*Z*)-**3e**, 129126-35-8; (*E,E*)-**3f**, 129126-36-9; (*E,Z*)-**3f**, 129126-37-0; (*Z,Z*)-**3f**, 129126-38-1; (*E*)-**3g**, 129126-39-2; (*Z*)-**3g**, 129126-40-5; (*E*)-**3h**, 129126-41-6; (*Z*)-**3h**, 129126-42-7; (*E*)-**3i**, 129126-43-8; (*Z*)-**3i**, 129126-44-9; (*E*)-**3j**, 129126-45-0; (*Z*)-**3j**, 129126-46-1; (*E*)-**3k**, 129126-47-2; (*Z*)-**3k**, 129126-48-3; (*E*)-**3l**, 129126-49-4; (*Z*)-**3l**, 129126-50-7; **4a**, 56750-84-6; **4b**, 25109-98-2; **4c**, 129126-51-8; **4d**, 129126-52-9; **4e**, 129126-53-0; **5**, 122-78-1; palladium acetate, 3375-31-3.

Conformational Study of N-Substituted Adenines by Dynamic Proton NMR: Relatively High Barrier to Rotation about C^6–N^6 in N^3,N^6-Disubstituted Adenines

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Variable-temperature ^1H NMR experiments on six N^6-alkyladenines, additionally substituted at N^3, N^7, or N^9, were conducted in DMSO-d_6, $CDCl_3$, and D_2O. Two distinct conformations (syn and anti) were observed for N^3,N^6-disubstituted adenines in all solvents, resulting from hindered rotation about the C^6–N^6 bond. The free energy of activation ($\Delta G^\ddagger$) for conversion of the minor to the major conformer (39:61 ratio) of N^3-benzyl-N^6-isopropyladenine (**8**) was determined to be 15.8 kcal/mol (320 K, DMSO-d_6) by line-shape analysis (360 MHz). N^6,N^9-Disubstituted adenines displayed conformational nonequivalence (10:90 ratios) in $CDCl_3$, and only one species was seen in DMSO-d_6 (298 K). The analogous barrier to rotation was considerably lower for the N^6,N^9-disubstituted adenines, being 12.8 kcal/mol at 260 K for N^9-benzyl-N^6-isopropyladenine (**11**; $CDCl_3$, 360 MHz). The ratio of conformers for N^3-benzyl-N^6-methyladenine (**9**) was 24:76 (DMSO-d_6, 297 K), which shifted upon protonation to a 3:97 ratio.

Dynamic NMR (DNMR) spectroscopy has been a valuable tool in examining a variety of intramolecular rate processes.[1] For example, the barrier to rotation in *N*-methylaniline was found to be ca. 6–7 kcal/mol (free energy of activation, $\Delta G^\ddagger$).[2,3] In this case, it is unlikely that the aryl N–C atoms are planar, as the nitrogen in aniline itself is pyramidal.[4] Anilines bearing substituents that increase the extent of C–N double bond character, such as in *p*-nitroso-[5] or *p*-acetyl-*N*,*N*-dimethylaniline,[6] exist primarily in an in-plane conformation with a $\Delta G^\ddagger$ of ca. 8–10 kcal/mol. Likewise, *o*-nitro substituents induce planarity in neighboring amino groups due to hydrogen bonding and stabilization of C–N double bond isomers.[7] The aryl N–C atoms are in a planar arrangement in *o*-methyl-*N*-methylaniline because of unfavorable steric interactions between the two methyl groups.[8] A variety of other ortho-substituted and ortho,ortho-disubstituted anilines have relatively high barriers to rotation between the two out-of-plane conformations.[1,9]

Amino heterocycles typically display added stabilization of the in-plane conformers due to enhanced delocalization of the nitrogen lone pair into the π-deficient ring.[1] Fairly high barriers to rotation between two in-plane conformations have been observed. This behavior is analogous to the well-known hindered rotation of amidines and guanidines.[1d,10]

In the course of a medicinal chemistry project, we observed two sets of nonequivalent resonances in the 360-MHz ^1H NMR spectra (DMSO-d_6) of several disubstituted adenines. These resonances, which coalesced at 330 K, were attributed to two in-plane conformations resulting from restricted rotation about the C^6–N^6 bond, designated as syn and anti by virtue of the relative orientation of the N^6 substituent with N^1 (viz. A–D). Hindered rotation in

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