Synthesis of 3-Aryl-3-pyridylallylamines Related to Zimelidine via Palladium-Catalyzed Amination

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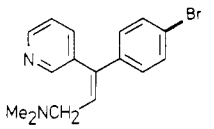
Reaction of aryl pyridyl ketones **1** with vinylmagnesium bromide followed by acetylation of the products **2** with acetic anhydride/Et_3N and with 4-(dimethylamino)pyridine (DMAP) as a catalyst gave acetates **3** in high yields. Treatment of acetates **3** with dimethylamine in the presence of a palladium catalyst produced a mixture of *E* and *Z* isomers of 3-aryl-3-pyridylallylamines **4**.

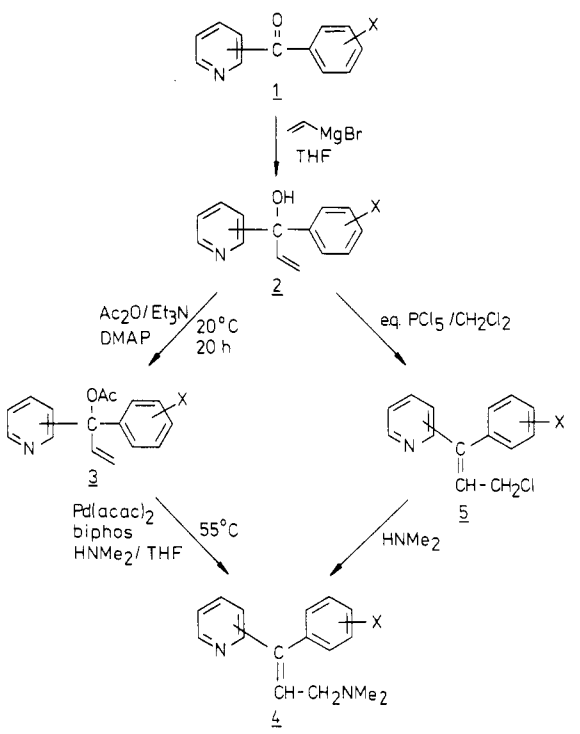
Zimelidine ((*Z*)-**4d**) is a new antidepressant agent which promises to offer clinical advantages over presently available drugs.[1] In contrast to tricyclic antidepressant drugs, it selectively inhibits the serotonin neuronal reuptake.[2]



Z - 4d

Several methods for the synthesis of **4d** and its analogues have been described,[3-6] and in one of these[5,6] the tertiary alcohol **2** is converted to the rearranged allylic chloride **5**, which on subsequent amination affords amines **4** (Scheme I). An attractive method for the synthesis of compounds **4** would be the direct allylic amination of the 1-aryl-1-pyridylpropene. Unfortunately no effective reactions for allylic amination have yet been described, and only procedures that give allylic amides from olefins are known.[7-9] In principle, amination of π-allylpalladium complexes constitutes an oxidative allylic amination,[10,11] since the π-allyl complexes can be generated from the olefin by using stoichometric amounts of palladium.[12] In the present paper we have studied the palladium-catalyzed amination[13] of allylic acetates **3** to produce **4**, a reaction that proceeds via π-allylpalladium complexes.

Scheme I



X =	H	4-F	4-Cl	4-Br	4-OMe	2-Br
3-pyridyl	a	b	c	d	e	f
4-pyridyl	g					
2-pyridyl	h					

Results and Discussion

The general route for the preparation of allylic amines **4** is outlined in Scheme I. Treatment of the ketone **1** with vinylmagnesium bromide gave the allylic alcohol **2** in about 85% yield. Acetylation of **2** with 4-(dimethylamino)-pyridine (DMAP)[14] as a catalyst proceeded smoothly at room temperature,[15] and in most cases almost a quantitative yield of **3** was obtained. Reaction of the acetate **3** with dimethylamine in the presence of palladium acetylacetonate ($Pd(acac)_2$) and bis(diphenylphosphino)ethane

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(15) Acetylation without DMAP (Ac_2O/pyridine) required more vigorous conditions (110 °C, 24 h), giving a considerable amount of allylic rearrangement product and a moderate yield.

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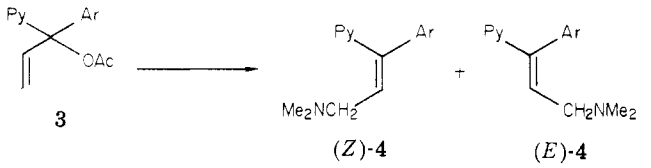
Table I. Palladium-Catalyzed Dimethylamination of Allylic Acetates 3[a]



compd	Ar	Py	phosphine	reaction time, h	% yield of 4[b]	Z/E[c] ratio
3a	C_6H_5	3-pyridyl	biphos	1	72	1.0:1
3b	p-FC_6H_4	3-pyridyl	biphos	2	44	1.1:1
3c	p-ClC_6H_4	3-pyridyl	biphos	1.7	79	1.2:1
3d	p-BrC_6H_4	3-pyridyl	biphos	2	87	1.2:1
	p-BrC_6H_4	3-pyridyl	PPh_3	4	75	1.2:1
	p-BrC_6H_4	3-pyridyl	PBu_3	48	80	1.2:1
	p-BrC_6H_4	3-pyridyl	PCy_3	100	<5	
	p-BrC_6H_4	3-pyridyl	$P(OPh)_3$	1.2	19[d]	1.1:1
3e	p-$MeOC_6H_4$	3-pyridyl	biphos	1	52	0.9:1
3f	o-BrC_6H_4	3-pyridyl	biphos	2	36	0.7:1[e]
3g	C_6H_5	4-pyridyl	biphos	2	57[d]	0.8:1
	C_6H_5	4-pyridyl	biphos	8	70	0.8:1
3h	C_6H_5	2-pyridyl	biphos	23	28[d]	1.7:1
	C_6H_5	2-pyridyl	PPh_3	48	24	0.9:1

[a] All reactions were performed in THF at 55 °C (see Experimental Section). [b] All yields refer to isolated pure products after chromatography on silica. [c] The Z/E ratios were determined by NMR (cf. Table III) and checked in some cases with HPLC. Further characterization of the Z isomers of **4a–f** [elemental analyses of the oxalates (C, H, N, ±0.4), mass spectra, UV spectra] has been done, and these data are included in Table IV. [d] The reaction was not complete in these cases. [e] Formally, the isomer having pyridyl and amine in a cis relation should be named the E isomer in this case, due to the ortho substitution. However, all compounds having the pyridyl and nitrogen in a cis relationship have been named the Z isomer.

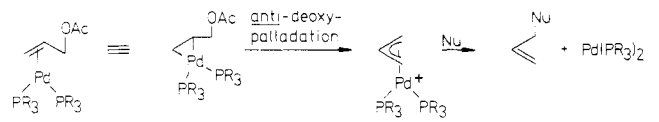
(biphos) produced a mixture of E and Z isomers of **4**. The amination was usually rapid at 55 °C, and in most cases the reaction was completed within 1 h. Results from amination of some different acetates **3** are shown in Table I. The acetate **3** was completely unreactive toward amine in the absence of the palladium catalyst. Thus treatment of the acetate **3d** with dimethylamine at 55 °C for 24 h gave no amine **4d**.

Attempts to use the alcohol **2** as the substrate in the palladium-catalyzed amination resulted only in recovery of starting material, and no allylic amine could be detected. It has been claimed[13a,b] that allylic alcohols function as substrates in the palladium-catalyzed amination. For example, it was reported that allyl alcohol (2-propen-1-ol) itself gave a quantitative yield of allylamine when reacted with diethylamine in the presence of $Pd(acac)_2$. We have not been able to repeat that particular experiment in our laboratory, and all attempts to aminate the allylic alcohols **2c** and **2d** were unsuccessful.

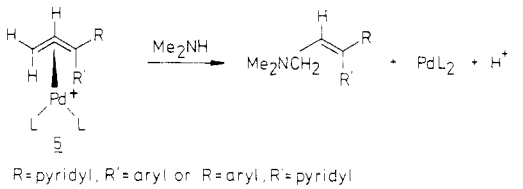
In most cases the Z and E isomers of **4** were formed in approximately equal amounts. Increased or decreased reaction time did not change the Z/E ratio significantly, and a control experiment showed that the product **4** is stable toward isomerization. Thus reaction of **3d** with dimethylamine under the usual reaction conditions in the presence of 1 equiv of pure (*Z*)-**4d** resulted in a Z/E ratio of 3.5:1 in the isolated amine **4d**.

The mechanism generally accepted for the palladium-catalyzed nucleophilic substitution involves formation of a palladium(0) phosphine complex from $Pd(acac)_2$ and the appropriate phosphine. Coordination of the double bond to palladium(0) followed by a trans-type elimination would give a π-allylpalladium intermediate, which is then attacked by the nucleophile (Scheme II).[12,16] Nucleophilic attack on preformed π-allylpalladium complexes generally occurs trans (inversion),[11a,17,18] although cis attack (retention) by coordinated acetate has recently been demonstrated.[18]

Scheme II



Since the Z/E ratio in the product amines **4** is not a result of isomerization (vide supra), the observed Z/E ratio most likely reflects the geometry in the intermediate π-allylpalladium complex **5**. The ratio (*Z*)-**4**/(*E*)-**4** of approximately 1:1 obtained in most cases thus suggests that there is no preference for either of the two substituents (pyridyl or aryl) over the other to adopt a syn or anti position in the π-allyl complex.



For an estimate of the importance of syn–anti isomerization in the intermediate π-allyl complex **5**, the terminal acetate **6** was used as the substrate in the palladium-catalyzed amination (eq 1). Amination of **6** with dimethylamine mainly gave (*Z*)-**4d** [(*Z*)-**4d**/(*E*)-**4d** ratio of

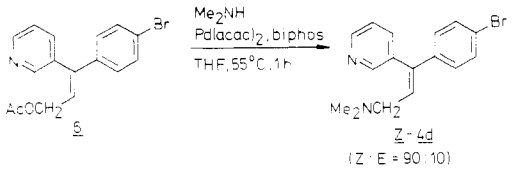


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Table II. 1-Aryl-1-pyridyl-2-propen-1-ol[a] (2)

compd	pyridyl	X	yield, %	mp, °C	recryst solvent	formula	anal.[b]
2a	3	H	91	90-92	Et_2O	$C_{14}H_{13}NO$	C, H, N, O
2b	3	4-F	85	80-81	Et_2O-C_5H_{12}	$C_{14}H_{12}FNO$	C, H, N, F
2c	3	4-Cl	88	82.5-84	PhMe	$C_{14}H_{12}ClNO$	C, H, Cl, N, O
2d	3	4-Br	85	76-77[c]	Et_2O	$C_{14}H_{12}BrNO$	C, H, Br, N, O
2e	3	4-OMe	88	76-78	Et_2O-C_5H_{12}	$C_{15}H_{15}NO_2$	C, H, N, O
2f	3	2-Br	86	111-112	i-Pr_2O	$C_{14}H_{12}BrNO$	C, H, Br, N, O
2g	4	H	31	135-137	Et_2O	$C_{14}H_{13}NO$	C, H, N, O
2h	2	H	91	oil		$C_{14}H_{13}NO$	C, H, N, O

[a] Prepared according to the general procedure (Experimental Section). [b] All compounds gave satisfactory elemental analyses (±0.4) for the elements indicated. [c] Lit.[5a] mp 68-70 °C.

9:1], showing that the olefin geometry is essentially retained in the substitution reaction. Thus syn–anti isomerization in **5** must be slow compared to nucleophilic attack. The retention of the olefin geometry in the amination of **6** is consistent with the retention observed in other palladium-catalyzed nucleophilic substitutions of allylic acetoxy groups in trisubstituted olefins.[16,19]

In order to evaluate the influence of the pyridine nitrogen on the rate and stereoselectivity of the amination reaction, the derivatives **3a,g,h** were synthesized and aminated. The reactivity of the substrates was found to be 3-pyridyl > 4-pyridyl ≫ 2-pyridyl, and the Z/E ratio for the allylic amines **4g,a,h** produced (biphos as ligand) were 0.8:1 (4-pyridyl), 1:1 (3-pyridyl), and 1.7:1 (2-pyridyl). The lower reactivity of 2- and 4-pyridyl compounds **3h** and **3g** is in agreement with a rate-determining formation of a π-allylpalladium intermediate, if one assumes that there is carbonium ion character in the substitution of acetate by palladium.[20] The much lower reactivity of **3h** compared to **3g** is unexpected[20] and suggests that coordination of the pyridine nitrogen to palladium takes place in the 2-pyridyl case. This would also explain the slight preference for the Z isomer of **4h**.

The effect of different phosphines as ligands was also investigated. Of the phosphines tried, biphos and triphenyl phosphine gave the best results. The reaction rate was found to be biphos ≈ PPh_3 > PBu_3 >>> PCy_3 (tricyclohexylphosphine). Thus the amination of compound **3d** at 55 °C was terminated within 1 h with biphos, whereas PBu_3 required 48 h to go to completion. PCy_3 gave essentially no product even after 100 h at 55 °C.

Conclusions

The acetylation–amination sequence presented here provides a mild procedure for the regiospecific transformation of alcohols **2** to allylic amines **4**. However, the stereoselectivity in the rearrangement–amination step is poor, but the reaction may be useful in those cases where both isomers are required. The Z forms of **4** may in many cases be obtained in considerable excess via chlorination of **2** by PCl_5 followed by amination (Scheme I).[5,6] However, the chlorination route is not straightforward for substrates such as **2e**, where the aromatic ring contains an electron-donating group. The palladium-catalyzed route (Scheme I), due to its mildness, seems to tolerate a wider scope of substitution and should be useful when the aromatic ring contains electron-donating substituents.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 421 spectrophotometer. NMR spectra were obtained with a Varian EM-360, a Varian T-60, or a Bruker WP 200 FT spectrometer. Mass spectra were obtained by using a LKB 9000 spectrometer. Melting points are uncorrected. Tetrahydrofuran (THF) was distilled over potassium/benzophenone under nitrogen. Triethylamine was distilled over potassium hydroxide. 4-(Dimethylamino)pyridine (DMAP) and 2-, 3-, and 4-benzoylpyridine were purchased from Fluka AG. Palladium acetylacetonate ($Pd(acac)_2$) was prepared according to White.[21] (*Z*)-3-(4-Bromophenyl)-3-(3-pyridyl)-2-propen-1-ol was prepared by acid rearrangement of **2d**.[22]

Preparation of Ketones 1. The ketones **1b–f** were prepared by Friedel–Crafts acylation of the appropriate aromatic compound by nicotinoyl chloride according to the procedure described by Wolffenstein and Hartwich.[23]

1b: yield 57%; mp 92–93 °C (lit.[24] mp 74.5 °C). Anal. Calcd for $C_{12}H_8FNO$: C, 71.64; H, 4.01; F, 9.44; N, 6.96. Found: C, 71.69; H, 4.11; F, 9.36; N, 6.93.

1c: yield 51%; mp 89–90 °C (lit.[25] mp 88–89 °C).

1d: yield 52%; mp 123–124.5 °C (lit.[26] mp 127–128 °C).

1e: yield 15%; mp 95–97 °C (lit.[23] mp 99 °C).

1f: the hydrochloride of this compound was isolated from the reaction mixture from the preparation of **1d**; mp (hydrochloride) 184–186 °C; NMR (D_2O + Me_2SO-d_6) δ 9.1 (br d, 1, 2-pyridyl) 9.0 (br dd, 1, 6-pyridyl) 8.8 (dt, 1, 4-pyridyl), 8.1 (ddd, 1, 5-pyridyl) 7.8 (m, 1, 6-phenyl), 7.7-7.4 (m, 3, aromatic); IR (KBr) 2230, 2050, 2000, 1950, 1678, 1602, 1288, 1250, 935, 746, 665 cm^{-1}. Anal. Calcd for $C_{12}H_8BrNO$·HCl: C, 48.27; H, 3.04; Cl, 11.87. Found: C, 48.35; H, 2.95; Cl, 12.00.

General Procedure for the Preparation of 1-Aryl-1-pyridyl-2-propen-1-ol (2). A solution of vinyl bromide (13.4 g, 125 mmol) in anhydrous THF (40 mL) was added to magnesium (3.2 g, 130 mmol) in THF (10 mL) under nitrogen at 60 °C. After reflux for 1 h the Grignard reagent was added under stirring to the appropriate aryl pyridyl ketone **1** (100 mmol) in THF (80 mL) at 10–20 °C. After the mixture was stirred at ambient temperature for 2 h, a solution of 6 g of ammonium chloride in 30 mL of water was added with ice cooling. The mixture was filtered, and the organic layer was collected and evaporated. The residue was dissolved in ether, treated with charcoal and dried ($MgSO_4$). Evaporation of the solvent gave an oil, which in certain cases solidified and was recrystallized. The results are shown in Table II.

Spectral Data for Alcohols 2. 1-Phenyl-1-(3-pyridyl)-2-propen-1-ol (2a): NMR ($CDCl_3$, 60 MHz) δ 8.5–8.2 (m, 2, 2- and 6-pyridyl), 7.8–7.0 (m, 7, aromatic), 6.42 (dd, 1, CH) 5.28, 5.23 (AB part of ABX, J_{AB} = 1.4, J_{AX} = 11, J_{BX} = 18 Hz, 2, C=CH_2); IR (KBr) 3140 (br), 1415, 995, 980, 925, 905, 810, 712, 702 cm^{-1}.

1-(4-Fluorophenyl)-1-(3-pyridyl)-2-propen-1-ol (2b): NMR ($CDCl_3$, 60 MHz) δ 8.40 (br d, 1, 2-pyridyl), 8.28 (br d, 1, 6-pyridyl), 7.70 (dt, 1, 4-pyridyl), 7.5–6.8 (m, 5 aromatic), 6.43 (dd, 1, CH), 5.30, 5.25 (AB part of ABX, J_{AB} = 1.4, J_{AX} = 11, J_{BX} = 18, 2, C=CH_2); IR (KBr) 3100 (br), 1505, 1228, 1060, 948, 852 cm^{-1}.

1-(4-Chlorophenyl)-1-(3-pyridyl)-2-propen-1-ol (2c): NMR ($CDCl_3$, 200 MHz) δ 8.49 (br d, 1, 2-pyridyl), 8.41 (br dd, 1,

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Table III. NMR Data for Amines 4[a]

	δ (t, 1, CH)	δ (d, 2, CH_2N)[e]	δ (s, 6, NMe_2)	G((Z)-allyl)/ G((E)-allyl)
(Z)-4a	6.32	2.98 (J = 7.3)	2.22	2.4
(E)-4a	6.26	3.03 (J = 7.0)	2.22	
(Z)-4b	6.24	2.98 (J = 6.2)	2.23	2.1
(E)-4b	6.24	3.01 (J = 6.2)	2.24	
(Z)-4c	6.30	2.97 (J = 7.0)	2.23	2.5
(E)-4c	6.27	3.00 (J = 7.0)	2.24	
(Z)-4d	6.29	2.98 (J = 6.7)	2.23	2.4
(E)-4d	6.26	3.01 (J = 6.7)	2.24	
(Z)-4e[b]	6.21	2.95 (J = 7.0)	2.23	1.7
(E)-4e[b]	6.18	3.05 (J = 7.0)	2.25	
(Z)-4f[c]	6.00	3.19 (J = 6.7)	2.28	2.1
(E)-4f[c]	6.42	2.92 (J = 6.7)	2.24	
(Z)-4g	6.29	2.98 (J = 7.0)	2.24	1.8
(E)-4g	6.43	3.03 (J = 6.7)	2.24	
(Z)-4h	6.28	3.08 (J = 6.7)	2.24	d
(E)-4h	6.95	3.02 (J = 6.7)	2.25	

[a] Shifts are given in parts per million relative to tetramethylsilane. The assignment of Z and E isomers 4a-g was made by using lanthanide shift reagents as recently described for this class of compounds.[27] The reagent $Eu(fod)_3$ coordinates preferentially to the pyridine nitrogen, resulting in a larger gradient for the Z isomer [G((Z)-allyl)] than for the E isomer [G((E)-allyl)]. [b] δ_{OMe} 3.85 (E) and 3.78 (Z). [c] See footnote e in Table I. [d] The assignment of (E)- and (Z)-4h was based on the shifts of the vinyl protons (δ 6.95 for the E isomer) and the observed $Eu(fod)_3$-induced line broadening (FT, 200 MHz) of the dimethyl and methylene groups of the Z isomer, indicating a chelating coordination to the nitrogen atoms in this case. [e] J values are given in hertz.

6-pyridyl), 7.68 (dt, 1, 4-pyridyl), 7.3–7.2 (m, 5, aromatic), 6.43 (dd, 1, CH), 5.37 (br d, J = 11.3 Hz, 1, one of C=CH_2), 5.30 (br d, J = 17.4 Hz, 1, one of C=CH_2); IR (KBr) 3110 (br), 1598, 1192, 1093, 1002, 985, 918, 828, 816 cm^{-1}.

1-(4-Bromophenyl)-1-(3-pyridyl)-2-propen-1-ol (2d): NMR ($CDCl_3$, 60 MHz) δ 8.45 (br d, 1, 2-pyridyl), 8.38 (br dd, 1, 6-pyridyl), 7.67 (dt, 1, 4-pyridyl), 7.5–7.2 (m, 5, aromatic), 6.41 (dd, 1, CH) 5.35, 5.29 (AB part of ABX, J_{AB} = 1, J_{AX} = 11, J_{BX} = 17 Hz, 2, C=CH_2); IR (KBr) 3110 (br), 1484, 1420, 1009, 930, 910, 825, 811 cm^{-1}.

1-(4-Methoxyphenyl)-1-(3-pyridyl)-2-propen-1-ol (2e): NMR ($CDCl_3$, 200 MHz) δ 8.57 (dd, 1, 2-pyridyl), 8.45 (dd, 1, 6-pyridyl), 7.71 (dt, 1, 4-pyridyl), 7.3–7.2 (m, 3, 5-pyridyl and AA' part of AA'BB' in phenyl), 6.86 (BB' part of AA'BB', 2, 3,5-phenyl), 6.46 (dd, 1, CH), 5.34 (dd, J = 17.0, 1.0 Hz, 1, one of C=CH_2), 5.31 (dd, J = 10.5, 1.0 Hz, 1, one in C=CH_2), 3.80 (s, 3, CH_3O), 3.0 (br s, 1, OH).

1-(2-Bromophenyl)-1-(3-pyridyl)-2-propen-1-ol (2f): NMR ($CDCl_3$, 60 MHz) 8.4–8.3 (m, 2, 2- and 6-pyridyl), 7.9–7.1 (m, 6, aromatic), 6.57 (dd, 1, CH), 5.33 (m, 2, C=CH_2); IR (KBr) 3080 (br), 1500, 1460, 1250, 1178, 770, 760 cm^{-1}.

1-Phenyl-1-(4-pyridyl)-2-propen-1-ol (2g): NMR ($CDCl_3$, 60 MHz) δ 8.5–8.3 (m, 2, 2- and 6-pyridyl), 7.4–7.2 (m, 7, aromatic), 6.45 (dd, 1, CH), 5.31, 5.26 (AB part of ABX, J_{AB} = 1, J_{AX} = 11, J_{BX} = 17 Hz, 2, C=CH_2); IR (KBr) 3130 (br), 1598, 1192, 1002, 920, 762, 700 cm^{-1}.

1-Phenyl-1-(2-pyridyl)-2-propen-1-ol (2h): NMR ($CDCl_3$, 60 MHz) δ 8.5–8.3 (m, 1, 6-pyridyl), 7.9–7.0 (m, 8, aromatic), 6.52 (dd, 1, CH), 6.0 (br, 1, OH), 5.31, 5.25 (AB part of ABX, 2, C=CH_2).

Acetylation of Alcohols 2. Acetate 3. A mixture of alcohol **2c** (0.69 g, 2.8 mmol), acetic anhydride (0.9 mL), and 4-(dimethylamino)pyridine (85 mg) was stirred in triethylamine (3.3 mL, distilled over KOH) at 20 °C for 20 h. Methanol was added, and after 10 min the mixture was concentrated in vacuo. Ether (25 mL) was added, and the ether phase was washed with saturated aqueous $NaHCO_3$ (3 × 15 mL) and dried ($MgSO_4$). Evaporation of the solvent gave 0.925 g (90%) of acetate **3c**, which was essentially pure and was used without any further purification: NMR ($CDCl_3$) δ 8.7–8.5 (m, 2, 2- and 6-pyridyl), 7.9–7.0 (m, 6, aromatic), 7.05 (dd (the low-field peak concealed), 1, CH) 5.48 (br d, J = 12 Hz, 1, one in C=CH_2), 4.88 (br d, J = 17 Hz, 1, one in C=CH_2), 2.14 (s, 3, CH_3); IR (KBr) 1742, 1238, 1220, 1012 cm^{-1}.

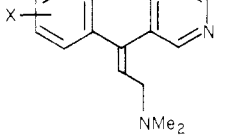
The following compounds were prepared by the same procedure (in some cases the crude acetate was filtered through a short column of silica (CH_2Cl_2)).

3a: yield 97%; NMR ($CDCl_3$) δ 8.7–8.4 (m, 2, 2- and 6-pyridyl), 7.6–7.1 (m, 7, aromatic), 7.02 (dd (the low-field peak concealed), 1, CH), 5.42 (br d, J = 11 Hz, 1, one in C=CH_2) 4.81 (br d, J = 17 Hz, 1, one in C=CH_2), 2.12 (s, 3, CH_3); IR (neat) 1742, 1240, 1225, 1018, 715, 700 cm^{-1}.

3b: yield 65%; NMR ($CDCl_3$) δ 8.7–8.6 (m, 2, 2- and 6-pyridyl) 7.7–7.1 (m, 6, aromatic), 7.01 (dd, 1, CH), 5.49 (br d, J = 10.5 Hz, 1, one in C=CH_2), 4.85 (br d, J = 17.3 Hz, 1, one in C=CH_2), 2.14 (s, 3, CH_3).

3d: yield 85%; NMR ($CDCl_3$) δ 8.70 (br dd, 2-pyridyl), 8.6 (br dd, 1, 6-pyridyl), 7.68 (dt, 1, 4-pyridyl), 7.47 (AA' part of AA'BB', 3, 5-phenyl), 7.35 (ddd, 1, 3-pyridyl), 7.23 (BB' part of AA'BB',

Table IV. (Z)-3-Aryl-3-(3-pyridyl)allylamines



compd	X	mp, °C[a]	solvent	mass spectra (70 eV),[e] m/e	UV spectra,[b] nm λmax (ε)	UV spectra,[b] nm λmin (ε)	formula	anal.[c]
4a	H	152–155	EtOH	238 (M, 100), 194 (82), 58 (100)	238 (13 500)	220 (10 600)	$C_{16}H_{18}N_2 \cdot 1.5\ C_2H_2O_4$	C, H, N, O
4b	4-F	151–155	EtOH	256 (M, 97), 212 (80), 58 (100)	239 (13 900)	223 (12 100)	$C_{16}H_{17}FN_2 \cdot C_2H_2O_4$	C, H, F, N
4c	4-Cl	164–168	EtOH	274/272 (M, 19/55), 193 (33), 58 (100)	246 (17 600)	224 (12 400)	$C_{16}H_{17}ClN_2 \cdot C_2H_2O_4$	C, H, Cl, N, O
4d	4-Br	196–199	EtOH	318/316 (M, 29/29), 193 (61), 58 (100)	250 (19 700)	225 (14 000)	$C_{16}H_{17}BrN_2 \cdot 2HCl \cdot H_2O$	C, H, Br, Cl, N, O
4e	4-MeO	175–177	EtOH(aq)	268 (M, 100), 224 (96), 58 (73)	255 (16 900)	231 (10 300)	$C_{17}H_{20}N_2O \cdot C_2H_2O_4$	C, H, N, O
4f[d]	2-Br	148–149	EtOH	318/316 (M, 7/8), 237 (100), 58 (94)	261 (5300)		$C_{16}H_{17}BrN_2 \cdot C_2H_2O_4$	C, H, Br, N, O

[a] Oxalates except for 4d (dihydrochloride). [b] In 0.1 M HCl. [c] Satisfactory elemental analyses were obtained (±0.4%) for the elements indicated. [d] Formally E isomer. [e] Relative intensities are given in parentheses.

2, 6-phenyl), 7.02 (dd, 1, CH), 5.49 (dd, J = 10.7, 0.7 Hz, 1, one of C=CH_2), 4.85 (dd, J = 17.3, 0.7 Hz, 1, one in C=CH_2) 2.15 (s, 3, CH_3); IR (neat) 1742, 1240, 1220, 1018, 1010 cm^{-1}.

3e: yield 80%; NMR ($CDCl_3$) δ 8.7–8.4 (m, 2, 2- and 6-pyridyl), 7.56 (dt, 1, 4-pyridyl), 7.4–6.7 (m, 6, aromatic and CH), 5.39 (dd, J = 11.0, 1.4 Hz), 1, one in C=CH_2), 4.78 (dd, J = 17.4, 1.4 Hz, 1, one in C=CH_2), 3.78 (s, 3, CH_3O), 2.10 (s, 3, CH_3).

3f: yield 80%; NMR ($CDCl_3$) δ 8.6–8.4 (m, 2, 2- and 6-pyridyl), 7.8–7.1 (m, 6, aromatic), 7.08 (dd (partly concealed), 1, CH), 5.43 (br d, J = 11.0 Hz, 1, one of C=CH_2), 4.72 (br d, J = 17.4 Hz, 1, one of C=CH_2), 2.16 (s, 3, CH_3).

3g: yield 86%; NMR ($CDCl_3$) δ 8.8–8.3 (m, 2, 2- and 6-pyridyl), 7.9–7.1 (m, 7, aromatic), 6.96 (dd (partly concealed), 1, CH), 5.39 (br d, J = 11.4 Hz, 1, one of C=CH_2), 4.80 (br d, J = 17.4 Hz, 1, one of C=CH_2), 2.11 (s, 3, CH_3); IR (neat) 1742, 1593, 1408, 1230, 1210, 700 cm^{-1}.

3h: yield 47% (after chromatography); NMR ($CDCl_3$) δ 8.6–8.4 (m, 1, 6-pyridyl), 7.7–6.8 (m, 8, aromatic), 6.49 (dd, 1, CH), 5.36 (dd, J = 11.0, 1.6 Hz, 1, one of C=CH_2), 4.90 (dd, J = 17.6, 1.6 Hz, 1, one of C=CH_2), 2.16 (s, 3, CH_3); IR(KBr) 1730, 1250, 1240, 762, 706 cm^{-1}.

(Z)-3-Acetoxy-1-(4-bromophenyl)-1-(3-pyridyl)propene (6) was prepared from (Z)-3-(4-bromophenyl)-3-(3-pyridyl)-2-propen-1-ol by using the same procedure: yield 80%; NMR ($CDCl_3$) 8.8–8.3 (br s, 2, 2- and 6-pyridyl), 7.6–7.1 (m, 6, aromatic), 6.29 (t, 1, CH), 4.60 (d, J = 7.3 Hz, 2, CH_2O), 2.08 (s, 3, CH_3).

Palladium-Catalyzed Amination of Acetates 3 to 4. Compound 4c. Palladium acetylacetonate (9.3 mg, 0.03 mmol), 1,2-bis(diphenylphosphino)ethane (17.5 mg, 0.04 mmol), and acetate **3c** (211 mg, 0.78 mmol) were dissolved in THF (2.2 mL) at room temperature under nitrogen. A solution of dimethylamine in THF (3.2 mL of a 2.5 M solution) was added, and the resulting mixture was warmed to 55 °C and allowed to react for 1 h and 40 min. Evaporation of the solvent and workup by preparative TLC (silica gel; EtOAc–hexane–Et_3N, 48:48:4) gave 158 mg (79%) of **4c** as a mixture of E and Z isomers (Z/E ratio of 1.2). Anal. Calcd for $C_{16}H_{17}ClN_2$: C, 70.45; H, 6.28; N, 10.27. Found: C, 70.07; H, 6.31; N, 9.94.

The same procedure was used for the amination of the other acetates **3**. Results are given in Table I.

NMR Data for Amines 4 ($CDCl_3$). The 2- and 6-pyridyl protons appear in the region δ 8.6–8.4 and the other aromatic protons in the region δ 7.6–6.9. The detailed spectra of the remaining protons are given in Table III and physical and spectral data in Table IV: mass spectrum of **4d**, m/z (relative intensity) 318 (M^+, 26), 317 (24), 316 (M^+, 27), 315 (21), 240 (21), 238 (25), 193 (99), 192 (44), 161 (37), 70 (67), 58 (100).

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Registry No. **1a**, 5424-19-1; **1b**, 52779-56-3; **1c**, 14548-44-8; **1d**, 14548-45-9; **1e**, 23826-71-3; **1f**, 77744-06-0; **1f**·HCl, 77744-07-1; **1g**, 14548-46-0; **1h**, 91-02-1; **2a**, 77744-08-2; **2b**, 77744-09-3; **2c**, 77744-10-6; **2d**, 70263-43-3; **2e**, 77744-11-7; **2f**, 77744-12-8; **2g**, 77744-13-9; **2h**, 77744-14-0; **3a**, 77744-15-1; **3b**, 77744-16-2; **3c**, 77744-17-3; **3d**, 77744-18-4; **3e**, 77744-19-5; **3f**, 77744-20-8; **3g**, 77744-21-9; **3h**, 77744-22-0; (E)-**4a**, 58325-71-6; (Z)-**4a**, 58574-55-3; (Z)-**4a** sesquioxalate, 77744-23-1; (E)-**4b**, 77744-24-2; (Z)-**4b**, 77744-25-3; (Z)-**4b** oxalate, 77744-26-4; (E)-**4c**, 77744-27-5; (Z)-**4c**, 77744-28-6; (Z)-**4c** oxalate, 77744-29-7; (E)-**4d**, 56775-89-4; (Z)-**4d**, 56775-88-3; (Z)-**4d**·2HCl, 60525-15-7; (E)-**4e**, 77744-30-0; (Z)-**4e**, 77744-31-1; (Z)-**4e** oxalate, 77744-32-2; (E)-**4f**, 77744-33-3; (Z)-**4f**, 77744-34-4; (Z)-**4f** oxalate, 77744-35-5; (E)-**4g**, 58325-72-7; (Z)-**4g**, 58574-58-6; (E)-**4h**, 35344-68-4; (Z)-**4h**, 35344-69-5; **6**, 77744-36-6; (Z)-3-(4-bromophenyl)-3-(3-pyridyl)-2-propen-1-ol, 77470-73-6; palladium acetylacetonate, 14024-61-4.

A General Synthesis of N-Substituted 2-Azaadamantanes and Their 4,8-Disubstituted Derivatives[1]

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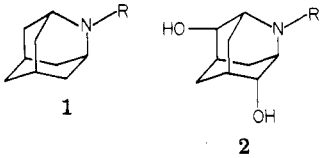
A general synthesis of N-substituted 2-azaadamantanes (1) is reported, along with the corresponding 4,8-dihydroxy derivatives (2). The synthesis offers the advantage of the use of inexpensive and readily available starting material. Dione **3**, obtained by decarboxylation of Meerwein's ester, is converted to diene **4** by Bamford–Stevens-type elimination of the corresponding ditosylhydrazone. Epoxidation of **4** affords diepoxide **12**, which reacts with primary amines to form the 2-azaadamantyl skeleton **2**. Removal of the hydroxyl groups to give **1** is accomplished by using $SOCl_2$ and then $LiAlH_4$.

There has been considerable interest in the chemistry and potential uses of the heteroadamantanes for a number of years.[2] While the 2-oxa- and 2-thiaadamantyl systems have been studied in some detail,[3] the corresponding 2-azaadamantyl system **1** is less familiar. One reason for this may be attendant greater synthetic difficulties for **1**. As part of another project, we had need for a number of N-substituted congeners of **1**, having stereochemically defined *anti,anti*-4,8-dihydroxy substituents, as in **2** (R = H, alkyl, aryl). Although syntheses of derivatives of **1** have



1 2

been reported,[4-9] the products either lack suitable func-

(1) An account of this work was presented at the 181st National Meeting of the American Chemical Society, Atlanta, GA, March 30, 1981.

(2) For reviews, see (a) Fort, R.C., Jr. "Adamantanes, the Chemistry of Diamond Molecules;" Dekker: New York, 1975; (b) Kafka, Z.; Galik, V. *Chem. Listy* **1978**, *72*, 509.

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