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Aminohaloborane in Organic Synthesis. IX.¹⁾ Exclusive *ortho* Acylation Reaction of *N*-Monoaminoalkylanilines

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The exclusive *ortho* acylation reaction of aniline derivatives using boron trichloride made possible the one-step synthesis of 2-acyl-*N*-monoaminoalkylanilines (**1**) and the corresponding imines (**2**) from *N*-monoaminoalkylanilines, even in the case of compounds with a bulky substituent at the nitrogen atom. Conventional methods only give **1** via elaborate procedures.

Keywords—regioselective reaction; 2-acylaniline derivative; 2-acylaniline-imine derivative; boron trichloride

Continuing our studies on the exclusive *ortho* acylation reaction of anilines using boron trichloride and nitriles,²⁾ we tried to extend this methodology to the synthesis of 2-acyl-*N*-monoaminoalkylanilines **1** and the corresponding imines **2**, which are unknown in the literature, except for **1** ($R_1 = (\text{CH}_2)_{2-3}\text{N}(\text{Et})_2$, $R_2 = \text{Ph}$).³⁾ Our present study showed that when the group causing the steric hinderance included an aliphatic amine moiety, the reaction proceeded very well. This offered an interesting contrast to our original method, in which 2-benzoylanilines carrying bulky substituents on the nitrogen, such as compounds **4a** and **4b**, were obtained only in moderate yields, 40% and 30%, starting from **3a** and **3b** (Chart 1).

Chart 1

We found that *N*-(1-methyl-4-piperidiny)aniline (**5a**) gave the desired compound **1a** in almost quantitative yield when **5a** was treated with boron trichloride to give an intermediary anilindichloroborane **6**, followed by heating with benzonitrile and acidic work-up (method A). The corresponding 2-benzoylaniline-imine **2a** was also isolated in excellent yield after alkaline work-up (Chart 2).

To test whether the presence of the aliphatic amine moiety would facilitate the reaction, we tried the reaction of **3a** with benzonitrile in the presence of an equimolar amount of *N*-methylpiperidine, but observed no improvement in the yield of **4a**. Thus, the presence of the

Chart 2

aliphatic amine on the nitrogen atom of aniline activated the reaction in some way. When nitriles having a low boiling point (under 150 °C) or anilines bearing a substituent labile to Lewis acid were used, a solution of aminoalkylanilines, boron trichloride and nitriles in dichloroethane was refluxed (method B). Our method was successfully applied to anilines carrying various aminoalkyl groups on the nitrogen atom, such as **5**, **7**, **8**, **9**, **10**, and **11**; thus, various 2-acylanilines **1**, **12**, **13**, **14**, **15**, **16** and imines **2** could be synthesized in excellent to good yields (Table I). Anilines carrying a secondary amine substituent such as **5j** and **5k** could also undergo the reaction; when the dihydrochlorides of **5j** and **5k** were treated with two molar equivalents of boron trichloride according to method B, **2l** and **2m**, respectively, were obtained (Tables II and III).

Comp.	R ₁	R ₂
5, 1, 2		aryl, alkyl
7, 12		aryl, alkyl, α-haloalkyl
8, 13		aryl, alkyl, α-haloalkyl
9, 14	a: b: c:	aryl
10, 15	$-(CH_2)_2N(C_2H_5)_2$	aryl
11, 16	a, b: $-(CH_2)_2-NPh$ c: $-(CH_2)_3-NCH_3$	aryl, alkyl

Chart 3

The advantage of our new method is clear from a comparison of our process for obtaining **1a** with that using a conventional procedure involving Fischer's indole synthesis *via*

TABLE I. 2-Acyl-*N*-monoaminoalkylanilines

Compd.	X	R ₁	R ₂	mp °C (From)	Method (Time, h)	Yield (%)	¹ H-NMR ^{a)} (CDCl ₃ δ)	Formula		
								Analysis ^{b)} (%)	Calcd (Found)	C H N
1a	H		Ph	193–203 2·HBr (Acetone)	A (3)	99		C ₁₉ H ₂₂ N ₂ O·2HBr 50.02 5.30 6.14 (50.17 5.36 6.06)		
1b	H		2-Cl-Ph	128–129 (Et ₂ O-hexane)	A (3)	99		C ₁₉ H ₂₁ ClN ₂ O 69.39 6.44 8.52 (69.43 6.36 8.49)		
1c	H		2-F-Ph	98–100 (CH ₂ Cl ₂ -hexane)	A (3)	97		C ₁₉ H ₂₁ FN ₂ O 73.05 6.78 8.97 (73.02 6.79 9.08)		
1d	H		4-F-Ph	152–182 (dec.) 2HCl, 0.5H ₂ O (iso-PrOH-Et ₂ O)	A (15)	96		C ₁₉ H ₂₁ FNO ₂ ·2HCl· 0.5H ₂ O 57.87 6.13 7.10 (57.90 6.14 7.09)		
1e	H		<i>n</i> -Bu	178–198 (dec.) 2HBr (iso-PrOH-Et ₂ O)	B (20)	87	1.0 (3H, t, <i>J</i> = 7 Hz, CH ₂ CH ₃)	C ₁₇ H ₂₈ Br ₂ N ₂ O 46.80 6.47 6.42 (46.72 6.61 6.42)		
1f	4-Cl		Ph	Oil	A (3)	99			^{c)}	
1g	4-Cl		2-Cl-Ph	101–102 (Et ₂ O-hexane)	A (3)	92		C ₁₉ H ₂₀ Cl ₂ N ₂ O 62.81 5.55 7.71 (62.84 5.46 7.65)		
1h	4-Cl		CH ₃	226–227 (dec.) 2HCl (CH ₃ OH)	B (40)	93	2.6 (3H, s, COCH ₃)	C ₁₄ H ₁₉ ClN ₂ O·2HCl· 0.5CH ₃ OH 48.96 6.52 7.88 (48.97 6.25 8.38)		
1i	4-Cl		2-F-Ph	Oil	A (3)	99			^{c)}	

1j	4-Br		2-F-Ph	194-197 C ₂ H ₅ O ₄ (iso-PrOH-Et ₂ O)	A (3)	97	C ₁₉ H ₂₀ BrFN ₂ O·C ₂ H ₅ O ₄ 52.40 4.60 5.82 (52.11 4.61 5.90)
1k	4-OCH ₃		2-F-Ph	117-118 (Et ₂ O-hexane)	B (12)	56	C ₂₀ H ₂₃ FN ₂ O ₂ 70.15 6.77 8.18 (70.26 6.82 8.10)
1l	4-NO ₂		2-Cl-Ph	154-156 (CH ₂ Cl ₂ -Et ₂ O)	A ^d (70)	53	C ₁₉ H ₂₀ ClN ₃ O ₃ 16.04 5.32 11.24 (61.09 5.28 11.32)
1m	5-F		2-F-Ph	118-120 (CH ₂ Cl ₂ -Et ₂ O)	A (15)	67	C ₁₉ H ₂₀ F ₂ N ₂ O 69.07 6.10 8.48 (69.27 6.02 8.50)
1n	4-N(CH ₃) ₂		Ph	Oil	A (8)	88	2.6 (6H, s, N(CH ₃) ₂) e)
1o	4-F		2-F-Ph	Oil	A (3)	99	e)
1p	4,5-di-Cl		2-F-Ph	Oil	A (50)	86 ^e	e)
12a	H		Ph	205-210 HCl	A (16)	90	C ₂₅ H ₂₆ N ₂ O·HCl 73.78 6.69 6.89 (73.58 6.65 6.92)
12b	H		-CH ₂ Cl	(CH ₂ Cl ₂ -acetone) 167-168 HCl	B ^f (3)	83	C ₂₀ H ₂₃ N ₂ O·HCl 63.32 6.38 7.39 (63.40 6.41 7.37)
13a	H		Ph	223-232 HCl	A (3)	93	C ₂₆ H ₂₈ N ₂ O·HCl 74.18 6.94 6.66 (73.93 6.95 6.66)
13b	H		-CH ₂ Cl	(CH ₃ OH-acetone) 178-179 HCl	B ^f (3)	83	C ₂₁ H ₂₅ ClN ₂ O·HCl 64.12 6.66 7.12 (64.29 6.73 7.14)
13c	5-CH ₃		Ph	(CH ₂ Cl ₂ -acetone) 222-228 HCl	A (3)	81	C ₂₇ H ₃₀ N ₂ O·HCl 74.54 7.18 6.44 (74.10 7.25 6.41)
13d	4-Cl		Ph	(CH ₂ Cl ₂ -acetone) 203-208 HCl	A (3)	91	C ₂₆ H ₂₈ ClN ₂ O·HCl· 1/2CH ₃ COCH ₃ 67.78 6.53 5.86 (67.59 6.41 5.89)
14a	4-Cl		2-Cl-Ph	Oil	A (3)	93	e)

Compd.	X	R ₁	R ₂	mp °C (From)	Method (Time, h)	Yield (%)	¹ H-NMR ^{a)} (CDCl ₃ δ)	Formula		
								Analysis ^{b)} (%)	Calcd (Found)	
								C	H	N
14b	4-Cl		2-Cl-Ph	205—209 HCl (CH ₂ Cl ₂ -acetone)	A (15)	95		C ₁₈ H ₁₈ Cl ₂ N ₂ O·HCl		
15	H	-CH ₂ CH ₂ N(Et) ₂	Ph	51—53 (<i>n</i> -Hexane)	A (3)	88 ^{g)}	1.05 (6H, t, <i>J</i> = 7 Hz, -N(CH ₂ CH ₃) ₂) 2.4—2.8 (6H, q × 2, <i>J</i> = 7 Hz, <i>J</i> = 6 Hz, -NCH ₂ CH ₂ N(CH ₂ CH ₃) ₂) 3.3 (2H, q, <i>J</i> = 6 Hz, HNCH ₂ CH ₂ N(CH ₂ CH ₃) ₂)	C ₁₉ H ₂₄ N ₂ O		
16a	H	-CH ₂ CH ₂ N	Ph	205—209 HCl (Acetone)	^{h)} (2)	97		C ₂₃ H ₂₇ N ₂ O·1.5HCl		
16b	H	-CH ₂ CH ₂ N	CH ₃	94—95 (Et ₂ O- <i>n</i> -hexane)	B ⁱ⁾ (20)	94 ^{g)}	2.6 (3H, s, COCH ₃)	C ₂₀ H ₂₅ N ₃ O		
16c	H	-(CH ₂) ₃ N	Ph	Oil	A (15)	61 ^{g)}	2.1 (3H, s, NCH ₃)			^{c)}

IR spectra (CHCl_3 or film) of all compounds showed absorptions at *ca.* 3300–3200 cm^{-1} (NH) and at *ca.* 1630–1610 cm^{-1} (C=O). *a)* ^1H -NMR spectra (CDCl_3 , δ) of all compounds showed absorptions at *ca.* 1.5–3.8 (m, aliph. H), at *ca.* 6.4–7.8 (m, arom. H) and *ca.* 8.5–9.0 (d, $J=6\text{ Hz}$, NH). Besides these absorptions, **1** and **14** showed absorptions at *ca.* 2.3–2.4 δ (s, 3H , NCH_3). Values of other characteristic absorptions are also given in the table. *b)* Analytical values of halogens were within $\pm 0.4\%$ of the calculated values. *c)* Not analyzed. *d)* BCl_3 was added to a solution of *N*-(1-methyl-4-piperidinyl)-4-nitroaniline and PhCN in dichloroethane and the mixture was treated according to Method A.

f) The reaction mixture was worked up with dil. HCl according to the general method and the acidic layer was extracted with CH_2Cl_2 . Evaporation of the solvent gave the hydrochloride of **12b** or **13b**. *g*) The crude product was purified on SiO_2 using CH_2Cl_2 containing 1–5% CH_3OH or $\text{CH}_3\text{COOC}_2\text{H}_5$. *h*) A mixture of *N*-[2-(4-phenyl-1-piperazinyl)ethyl]aniline·3HCl (5 mmol), BCl_3 (5 × 1.2 mmol) and PhCN (5 × 20 mmol) in toluene was heated at 145 °C for 2 h. *i*) *N*-[2-(4-Phenyl-1-piperazinyl)ethyl]aniline·3HCl was used.

TABLE II. 2-Acyl-*N*-(4-piperidynyl)aniline-imines

Compd.	X	R ₁	R ₂	mp C (From)	Yield (%)	¹ H-NMR ^{a)} (CDCl ₃ δ)	Formula Analysis ^{b)} (%) Calcd (Found)		
							C	H	N
2a	H	CH ₃	Ph	117—118 (EtOH)	90		C ₁₉ H ₂₃ N ₃ 77.77 7.80 14.32 (78.00 7.91 14.26)		
2b	H	CH ₃	CH ₃	101—102 (Et ₂ O)	83	2.5 (3H, s, HN=CCH ₃)	C ₁₄ H ₂₁ N ₃ 72.68 9.15 18.17 (72.94 9.01 18.30)		
2c	4-Cl	CH ₃	Ph	115—117 (Et ₂ O)	98		C ₁₉ H ₂₂ ClN ₃ 69.60 6.77 12.82 (69.64 6.49 12.74)		
2d	4-Cl	CH ₃	CH ₃	125—127 (Et ₂ O)	55	2.5 (3H, s, HN=CCH ₃)	C ₁₄ H ₂₀ ClN ₃ 63.26 7.59 15.81 (63.26 7.44 15.54)		
2e	4-Cl	CH ₃	2-F-Ph	145—146 (Et ₂ O)	92		C ₁₉ H ₂₁ ClFN ₃ 65.98 6.12 12.15 (65.75 5.92 12.02)		
2f	4-F	CH ₃	Ph	130—131 (CH ₂ Cl ₂ -Et ₂ O)	87		C ₁₉ H ₂₂ FN ₃ 73.28 7.12 13.49 (73.36 7.21 13.40)		
2g	4-F	CH ₃	2-F-Ph	131—132 (CH ₂ Cl ₂ -Et ₂ O)	96		C ₁₉ H ₂₁ F ₂ N ₃ 69.28 6.43 12.76 (69.68 6.36 12.80)		
2h	4-CH ₃	CH ₃	2-Cl-Ph	111—113 (Et ₂ O)	90	2.1 (3H, s, CCH ₃)	C ₂₀ H ₂₄ ClN ₃ 70.28 7.08 12.29 (69.85 6.76 12.11)		
2i	4-OCH ₃	CH ₃	2-F-Ph	132—134 (Et ₂ O)	50	3.55 (3H, s, OCH ₃)	C ₂₀ H ₂₄ FN ₃ O 70.36 7.09 12.31 (70.27 6.98 12.29)		
2j	4-Br	CH ₃	Ph	110—112 (CH ₂ Cl ₂ -Et ₂ O)	92		C ₁₉ H ₂₂ BrN ₃ 61.29 5.96 11.29 (61.13 5.81 11.28)		
2k	4-Cl	CH ₃	2-Cl-Ph	157—159 (Et ₂ O-hexane)	97		C ₁₉ H ₂₁ Cl ₂ N ₃ 62.99 5.84 11.60 (62.96 5.84 11.59)		
2l	4-F	CH ₃	2-Cl-Ph	138—139 (C ₆ H ₆ -hexane)	97		C ₁₉ H ₂₁ ClFN ₃ 65.98 6.12 12.15 (66.23 6.19 12.19)		
2m	H	H	Ph	Oil	99 ^{d)}	1.2—3.8 (m, aliph. H) 6.3—7.6 (m, arom. H) 9.4 (2H, br s, -NH and =NH)			c)
2n	4-Cl	H	2-F-Ph	Oil	99 ^{d)}	1.2—3.8 (m, aliph. H) 6.6—7.5 (m, arom. H) 9.5 (1H, s, =NH) 9.8 (1H, d, J=7 Hz, -NH-<)			c)
2o	4-Cl	c)	2-F-Ph	Oil	99	1.5—4.0 (m, aliph. H) 3.63 (s, NCH ₂ Ph) 6.5—7.6 (m, arom. H) 9.50 (1H, s, =NH) 9.8 (1H, d, J=7 Hz, -NH-<)			c)

IR spectra (CHCl₃ or film) of all compounds showed absorptions at ca. 3300—3200 cm⁻¹ (NH) and 1610—1600 cm⁻¹ (=NH). ^{a)} ¹H-NMR spectra (CDCl₃, δ) of all compounds except 2l, 2m and 2n showed at ca. 1.5—3.8 (m, aliph. H) at ca. 2.3 (s, NCH₃), at ca. 6.5—7.5 (m, arom. H) at ca. 9.3—9.9 (1H, d, J=7 Hz, -NH-<) and at ca. 9.3—9.5 (1H, s, =NH). The values of other characteristic absorptions are given in the table. ^{b)} Analytical values of halogens were within ±0.4% of the calculated values. ^{c)} Not analyzed. ^{d)} A mixture of BCl₃ (12 × 2.2 mmol), *N*-(4-piperidynyl)-aniline · 2HCl (12 mmol) and PhCN (12 × 1.2 mmol) in dichloroethane (40 ml) was refluxed for 36 h. ^{e)}

TABLE III. *N*-Azacycloalkylanilines

Compd. ^{a)}	X	R	mp °C ^{b)} or bp °C	Yield ^{c)} (%)
5a ⁵⁾	H		82—83	78
5b ⁵⁾	4-Cl		91—92	78
5c ⁵⁾	4-F		92—93	79
5d ^{d)}	4-Br		85—87	58
5e ⁵⁾	4-CH ₃		125—127 (1 mm)	67
5f	4-OCH ₃		130—145 (1 mm)	82
5g	4-NO ₂		153—155	56
5h ⁵⁾	3,4-diCl		80—81	63
5i	4-N(CH ₃) ₂		139—141 (1 mm)	66
5j	H		226—240 ^{e)}	69
5k	4-Cl		279—280 ^{e)}	69
7	H		87—88	82
8a	H		96—98	81
8b	3-CH ₃		Oil	86
9a	4-Cl		Oil	49
9b	4-Cl		50—51	57
9c ^{f)}	4-Cl		178 (1 mm)	77

a) All compounds gave reasonable elemental analysis values (C, H, N). b) Recrystallized from Et₂O-*n*-hexane. c) Based on the *N*-substituted-3- or -4-oxo-piperidine or -pyrrolidine used. d) Prepared by using a Dean-Stark apparatus charged with SiO₂. e) Melting point °C (dec.) of dihydrochloride (EtOH). f) Prepared by heating 1-benzyl-3-chloropyrrolidine hydrochloride⁹⁾ (30 mmol) with *p*-chloroaniline (0.15 mol) at 160 °C for 2 h.

17 and **18** (37% yield over four steps). Another example is compound **19**, which was previously accessible only by an elaborate route including acylation, reduction, and back oxidation³⁾ (Chart 4).

The starting materials **5**, **7**, **8**, **9**, **10**, and **11** were synthesized in a conventional manner with some modification; **5**, **7**, and **8** were obtained by treatment of the anilines with the corresponding 1-alkyl-4-oxo-piperidine in the presence of molecular sieve⁴⁾ followed by NaBH₄ reduction.⁵⁾ However, *N*-(1-methyl-4-piperidiny)-4-nitroaniline (**5g**) was synthesized by heating of 4-fluoronitrobenzene with 4-amino-1-methylpiperidine. Compounds **5j** and **5k** were synthesized by treatment of anilines with 1-ethoxycarbonyl-4-oxo-piperidine followed by

Chart 4

NaBH_4 reduction and hydrolysis with 6 N HCl. Compound **9** was obtained by condensation of the anilines with 1-ethoxycarbonyl-3-mesyloxy-piperidine or -pyrrolidine followed by reduction with lithium aluminum hydride (Chart 5 and Table III). Compounds **10** and **11** were synthesized according to the known methods.⁶⁻⁸⁾

Chart 5

Thus, our method for synthesizing **1** and the corresponding imine **2** by using the exclusive *ortho* acylation reaction of *N*-monoaminoalkylanilines is a simple one, and may be suitable for obtaining intermediates for some pharmacologically interesting compounds.

Experimental

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. Infrared (IR) spectra were recorded in CHCl_3 solution with a Hitachi 260-10 IRS spectrophotometer. Wave numbers are expressed

in reciprocal centimeters. Nuclear magnetic resonance (NMR) spectra were taken in CDCl_3 solution on a Varian EM-390 or T-60 spectrophotometer. Chemical shifts are expressed as δ values (parts per million) from tetramethylsilane. Column chromatography was conducted using silica gel (E. Merck, 70–230 mesh ASTM) and aluminum oxide (E. Merck, Standardisiert). Silica gel GF and aluminum oxide F254 (E. Merck) were used for analytical thin-layer chromatography (TLC). In cases where products were isolated by solvent extraction, the procedure generally followed was to extract the aqueous layer with two to three portions of the indicated solvent, then to wash the organic layer with saturated $\text{NaCl-H}_2\text{O}$ or H_2O and dry it over Na_2SO_4 or MgSO_4 .

2-Acyl-*N*-monoaminoalkylaniline (1) and the Corresponding Imine (2) General Procedure—Method A: To a stirred solution of BCl_3 (25×1.2 mmol) in toluene (15 ml) was added a solution of a *N*-monoaminoalkylaniline **5** (25 mmol) in toluene (40 ml) under ice cooling. The resulting mixture was refluxed for 1 h and then the solvent was distilled off. To the resulting syrup, a nitrile (25×2 mmol) was added, and the mixture was heated at 150°C (bath temperature) for 3 to 20 h under stirring. The progress of the reaction was monitored by TLC (Al_2O_3 , CH_2Cl_2), which showed a yellow spot of 2-acylaniline. After cooling, ice and 1 *N* HCl (15 ml) were added and the mixture was warmed at 100°C for 20 min under stirring to hydrolyze the corresponding ketimine. If the hydrochloride of compound **1** crystallized, it was filtered off and recrystallized. Otherwise, the acid layer was washed with ether or CH_2Cl_2 and alkalinized with conc. NH_4OH or K_2CO_3 . The mixture was extracted with CH_2Cl_2 . In most cases the product showed a single spot on TLC and was used directly as the starting material for the next step. When some polar fractions had to be removed, filtration of a solution of the crude product in CH_2Cl_2 over Al_2O_3 was effective. To obtain the corresponding imine **2**, a solution of NaOH (20 g) in H_2O (40 ml) and CH_3OH (70 ml) was added to the cooled reaction mixture and the mixture was stirred at room temperature for 2 h. Extraction with CH_2Cl_2 and evaporation of the extract after drying gave almost pure **2**.

Method B: To a stirred solution of BCl_3 (20×1.2 mmol) in dichloroethane (12 ml) was added a solution of *N*-monoaminoalkylaniline **5** (20 mmol) in the same solvent (38 ml) under ice cooling. A nitrile was added and the mixture was refluxed for 20 h. Work-up as described in method A gave **1** (Tables I and II).

2-(4-Fluorobenzoyl)-*N*-isopropyl-5-methylaniline (4a)—According to the general method A and work-up described in the literature,²⁾ **4a** was obtained from *N*-isopropyl-3-methylaniline (prepared from 3-methylaniline and isopropyl iodide by refluxing for 45 min in the presence of NaHCO_3 , bp $106\text{--}109^\circ\text{C}$ (15 mmHg), 77%) and 4-fluorobenzonitrile after purification by chromatography (SiO_2 , benzene) in 40% yield. Oil, IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3300, 1620. $^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (6H, d, $J=7$ Hz), 2.3 (3H, s), 3.8 (1H, q, $J=7$ Hz), 6.2–7.7 (7H, m, including ABX pattern), 8.5 (1H, br s). 2-(4-Fluorobenzoyl)-*N*-isopropyl-3-methylaniline was also obtained as a more polar fraction in 3% yield. Oil, IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3400, 1660. $^1\text{H-NMR}$ (CDCl_3) δ : 1.1 (6H, d, $J=7$ Hz), 2.0 (3H, s), 3.6 (1H, q, $J=7$ Hz), 4.0 (1H, br s), 6.5–8.0 (7H, m).

2-Benzoyl-*N*-cyclohexyl-5-methylaniline (4b)—By using a procedure similar to that described for **4a**, **4b** was obtained from *N*-cyclohexyl-3-methylaniline (prepared from 3-methylaniline and cyclohexanone followed by reduction with NaBH_4 , bp 104°C (2 mmHg), 70%) and benzonitrile in 31% yield. Oil, IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3270, 1610. $^1\text{H-NMR}$ (CDCl_3) δ : 1.0–2.2 (10H, m), 2.3 (3H, s), 3.5 (1H, br s), 6.2–7.7 (8H, m, including ABX pattern), 8.8 (1H, d, $J=8$ Hz).

***N*-(1-Methyl-4-piperidiny)-*N*-nitrosoaniline (17a)**—To a stirred solution of *N*-(1-methyl-4-piperidiny)aniline (3.8 g, 20 mmol) in EtOH (15 ml) containing conc. HCl (42 ml, 20×2.5 mmol) was added a solution of NaNO_2 (1.52 g, 20×1.1 mmol) in H_2O dropwise at -10°C , and the solution was stirred at the same temperature for 1 h. After the addition of K_2CO_3 , the whole was extracted with CH_2Cl_2 . The extract was evaporated and the residue was crystallized from Et_2O and petroleum-ether, giving **17a** (4.25 g, 97%, mp $78\text{--}79^\circ\text{C}$). Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}$: C, 65.72; H, 7.81; N, 19.16. Found: C, 65.94; H, 7.79; N, 19.18. IR $\nu_{\text{max}}^{\text{CHCl}_3} \text{cm}^{-1}$: 1451 (N–NO).

***N*-Amino-*N*-(1-methyl-4-piperidiny)aniline (17b)**—To a stirred solution of **17a** (3.9 g, 17.8 mmol) in dried Et_2O (80 ml) was added LiAlH_4 (0.74 g, 17.8×1.1 mmol, recrystallized from dried Et_2O) at 5°C , and the mixture was stirred at room temperature. Further, LiAlH_4 (three 0.3 g portions) was added at 1 h intervals. After quenching of excess LiAlH_4 with wet Et_2O , the precipitate was filtered off and washed with Et_2O . The filtrate was concentrated and the residue was crystallized from Et_2O and *n*-hexane, giving **17b** (2.8 g, 77%, mp $64\text{--}65^\circ\text{C}$). Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{N}_3$: C, 70.20; H, 9.33; N, 20.47. Found: C, 70.23; H, 9.25; N, 20.40. IR $\nu_{\text{max}}^{\text{CHCl}_3} \text{cm}^{-1}$: 3368, 1599.

***N*-(1-Methyl-4-piperidiny)-3-phenylindole (18)**—A mixture of **17b** (2.48 g, 12.1 mmol) and phenylacetaldehyde (1.74 g, 12×1.2 mmol) was heated at 100°C for 1 h. After removal of the excess reagent, the resulting oily phenylhydrazone (3.7 g) was heated in 1.35 *N* HCl gas/EtOH (60 ml) at reflux for 1 h. After removal of the solvent, ice water and K_2CO_3 were added and the mixture was extracted with CH_2Cl_2 . Recrystallization of the product from $\text{Et}_2\text{O-n-hexane}$ gave **18** (2.73 g, 78%, mp $112\text{--}114^\circ\text{C}$). Anal. Calcd for C, 82.72; H, 7.64; N, 9.65. Found: C, 82.76;

H, 7.55; N, 9.21. $^1\text{H-NMR}$ (CDCl_3) δ : 4.2 (1H, m), $\text{N}-\text{CH}_2$ 7.0–8.0 (9H, m, arom. H).

2-Benzoyl-*N*-(1-methyl-4-piperidiny)aniline (1a) from Compound 18—Dry ozone was bubbled (100 l/h O_2 -stream) into a solution of **18** (290 mg) in AcOH (3 ml) at room temperature for 5 min. After the excess ozone had been expelled by flushing with dry N_2 , ice and dil. NH_4OH were added, and the mixture was extracted with Et_2O . The oily

extract, 2-benzoyl-*N*-(1-methyl-4-piperidinyl)-*N*-formylaniline, was dissolved in 6 *N* HCl (4 ml) and the solution was refluxed for 1.5 h. After cooling, ice and K₂CO₃ were added, and the mixture was extracted with CH₂Cl₂. The extract was purified on SiO₂ using CH₂Cl₂ and CH₂Cl₂ containing 1% CH₃OH, giving oily **1a** (185 mg, 63%).

(1-Alkyl-4-piperidinyl)aniline (5, 7, 8)—A solution of an aniline (30 × 1.2 mmol) and 1-alkyl-4-oxo-piperidine (30 mmol) in benzene (12 ml) was refluxed (20 h) or stirred at room temperature (50–70 h) in the presence of molecular sieve 4A (6 g). Et₂O was added, then the molecular sieve was filtered off and washed with Et₂O. The filtrate and washing were combined and concentrated, and the residue was dissolved in 95% EtOH (50 ml). To the stirred solution was added NaBH₄ (15 mmol) and the solution was stirred at room temperature for 5 h. After removal of EtOH, H₂O was added and the mixture was extracted with CH₂Cl₂. The extract was evaporated and the residue was crystallized from Et₂O–petroleum-ether or distilled under reduced pressure.

1-(Methyl-4-piperidinyl)-4-nitroaniline (5g)—A mixture of 4-amino-1-methylpiperidine (4.82 g, 32.3 mmol) and 4-fluoronitrobenzene (4.56 g, 32.3 mmol) was warmed at 100 °C for 7 h. After cooling, 1 *N* HCl (40 ml) was added and the mixture was washed with Et₂O. The acidic layer was alkalinized with conc. NH₄OH and extracted with CH₂Cl₂. Recrystallization of the extract from Et₂O–petroleum-ether gave **5g** (4.27 g, 56%, mp 153–155 °C).

4-Chloro-*N*-(4-piperidinyl)aniline (5k) and *N*-(4-Piperidinyl)aniline (5j)—A solution of 4-chloroaniline (7.65 g, 60 mmol) and 1-ethoxycarbonyl-4-oxo-piperidine (8.56 g, 50 mmol) in benzene (20 ml) was refluxed for 20 h in the presence of molecular sieve 4A (20 g) under stirring. Subsequent reduction and work-up (NaBH₄; 950 mg, 25 mmol, 95% EtOH; 75 ml) in the same manner as above gave 4-chloro-*N*-(1-ethoxycarbonyl-4-piperidinyl)aniline (mp 118–120 °C, 10.5 g, 74%). *Anal.* Calcd for C₁₄H₁₉ClN₂O₂: C, 59.46; H, 6.77; Cl, 12.53; N, 9.91. Found: C, 59.17; H, 6.63; Cl, 12.36; N, 9.93. 4-Chloro-*N*-(1-ethoxycarbonyl-4-piperidinyl)aniline (10 g) was refluxed for 16 h in 6 *N* HCl (50 ml). After removal of HCl, the residue was crystallized from 99% EtOH, giving **5k** · 2 HCl (mp 279–280 °C (dec.) 92%). *N*-(4-Piperidinyl)aniline (**5j**) was obtained in a similar manner.

4-Chloro-(1-methyl-3-piperidinyl)aniline (9a) and 4-Chloro-(1-methyl-3-pyrrolidinyl)aniline (9b)—1-Ethoxycarbonyl-3-mesyloxypiperidine, prepared by NaBH₄ reduction of 1-ethoxycarbonyl-3-oxo-piperidine followed by mesylation using MsCl and pyridine (8.7 g, 35 mmol, oil, IR $\nu_{\max}^{\text{film}}$ cm⁻¹: 1690 (NCOOEt), 1350, 1180 (OSO₂), ¹H-NMR (CDCl₃) δ : 3.05 (3H, s, SO₃CH₃)), was heated with 4-chloroaniline (13.3 g, 35 × 3 mmol) at 160 °C for 5 h. After cooling, ice water was added and the mixture was extracted with Et₂O. After removal of excess 4-chloroaniline from the extract at reduced pressure, purification of the residue on a Lobar column B (CHCl₃: EtOAc = 10:1) gave oily 4-chloro-(1-ethoxycarbonyl-3-piperidinyl)aniline (4.87 g, 49%). To a stirred suspension of LiAlH₄ (1.96 g, 17.2 × 3 mmol) in Et₂O (50 ml) was added dropwise a solution of 4-chloro-(1-ethoxycarbonyl-3-piperidinyl)aniline (4.87 g), and the mixture was refluxed for 30 min under stirring. After cooling, wet Et₂O was added and the precipitate was filtered off and washed with Et₂O. Concentration of the filtrate gave oily **9a** (3.91 g). ¹H-NMR (CDCl₃) δ : 1.2–4.0 (m, aliph. H), 2.3 (s, NCH₃), 6.4–7.3 (m, arom. H). Compound **9b** was obtained in a manner analogous to that described for **9a**.

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