Amidines. VII. Hydrolysis and Alcoholysis of Carboxamides under Mild Conditions

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Hydrolysis and alcoholysis of carboxamides derived from primary aliphatic amines were achieved under mild conditions. Amide exchange reaction between carboxamides and N^1-acyl-N^1,N^2-di(*p*-nitrophenyl)formamidines (1) gave N^1-acyl-N^1-alkyl-N^2-(*p*-nitrophenyl)formamidines (2) which were readily hydrolyzed or alcoholyzed to give N^1-alkyl-N^2-(*p*-nitrophenyl)formamidines (4) and carboxylic acid or its ester. Compounds 4 were hydrolyzed to give aliphatic amine and *N*-formyl-*p*-nitroaniline in the presence of acetic acid or hydrochloric acid at room temperature. For the alcoholysis of *N*-acyl derivatives of amino alcohols, protection of the hydroxyl substituent by an acyl group was essential because the reaction of 1 and *N*-acyl derivatives of amino alcohols was quite complex. Alcoholysis of *N*-ethyl-*N*,*N*′-ethylenebis(*p*-chlorobenzamide) (8a) by this method gave *N*-(2-aminoethyl)-*N*-ethyl-*p*-chlorobenzamide (8b). Thus, the selective alcoholysis of diacyl derivative of diamines, which contain primary and secondary amino groups, was achieved.

Keywords hydrolysis; alcoholysis; amide exchange reaction; N^1-acyl-N^1,N^2-di(*p*-nitrophenyl)formamidine; N^1-acyl-N^1-alkyl-N^2-(*p*-nitrophenyl)formamidine; N^1-alkyl-N^2-(*p*-nitrophenyl)formamidine; carboxamide

In the preceding paper[1] we reported a new method for hydrolysis and alcoholysis of *N*-acylarylamines under mild conditions. The reaction of N^1-tosyl-N^1-(*p*-nitrophenyl)-N^2-(*m*-nitrophenyl)acetamidine and *N*-acylarylamine gave N^1-acyl-N^1-aryl-N^2-(*m*-nitrophenyl)acetamidine by amide exchange reaction in the presence of a basic catalyst, and subsequent alkaline hydrolysis or alcoholysis of the N^1-acylamidines gave N^1-aryl-N^2-(*m*-nitrophenyl)acetamidines and carboxylic acid or its ester at room temperature. N^1-Aryl-N^2-(*m*-nitrophenyl)acetamidines were hydrolyzed to give arylamine and *N*-acetyl-*m*-nitroaniline on heating its aqueous tetrahydrofuran (THF) solution in the presence of acetic acid.[1] This method would, however, hardly be applicable to the hydrolysis of carboxamides derived from aliphatic amines because N^1-alkyl-N^2-arylacetamidines undergo acid hydrolysis with great difficulty. For example, the hydrolysis of N^1-methyl-N^2-(2,4-dinitrophenyl)acetamidine proceeds to the extent of about 50% after 3 d while the period of half-decay for the hydrolysis of N^1-phenyl-N^2-(2,4-dinitrophenyl)acetamidine is 5.7 h in 20% aqueous dioxane solution in the presence of 0.01 N hydrochloric acid at 25 °C.[2]

To hydrolyze carboxamides derived from aliphatic amines by this method, N^1-alkyl-N^2-arylformamidine must be prepared first from carboxamide and formamidine derivatives by means of the amide exchange reaction. Amide exchange reaction between carboxamides and N^1-tosyl-N^1,N^2-diarylformamidines, however, hardly takes place even in the presence of a basic catalyst.[3] Therefore, use of N^1-acyl-N^1,N^2-di(*p*-nitrophenyl)formamidine (**1**) was tested for hydrolysis and alcoholysis of carboxamides by this method (Chart 1).

As a preliminary experiment, formation of N^1-(*p*-chlorobenzoyl)-N^1-(*p*-methylbenzyl)-N^2-(*p*-nitrophenyl)-formamidine (**2a**)[1] by the reaction of equimolar amounts of N^1-(*p*-chlorobenzoyl)-N^1,N^2-di(*p*-nitrophenyl)formamidine (**1a**)[4] and *N*-(*p*-chlorobenzoyl)-*p*-methylbenzylamine (**3a**) was followed in terms of the ^{1}H nuclear magnetic resonance (^{1}H-NMR) spectrum (dimethylsulfoxide-d_6 (DMSO-d_6)) of the products using the signals at δ 8.80 (1-position of **1a**), 4.45 (methylene group of **3a**) and 5.18 (methylene group of **2a**). Compounds **1a** and **3a** were allowed to react in THF solution at room temperature under four different conditions by adding either 1) an equimolar amount of *n*-butyllithium, or 2) 0.8 molar eq. amount of *n*-butyllithium, or 3) an equimolar amount of *n*-butyllithium and 0.2 molar eq. amount of diisopropylamine, or 4) 1.5 molar eq. amount of *n*-butyllithium and an equimolar amount of diisopropylamine. The results under each condition were as follows. 1) The substrate **1a** disappeared within 2 h while **3a** remained almost unchanged. The signal of **2a** was hardly detectable and instead a singlet signal at δ 8.87 appeared gradually. 2) The substrate **1a** almost disappeared within 1 h, and about half of **3a** was converted

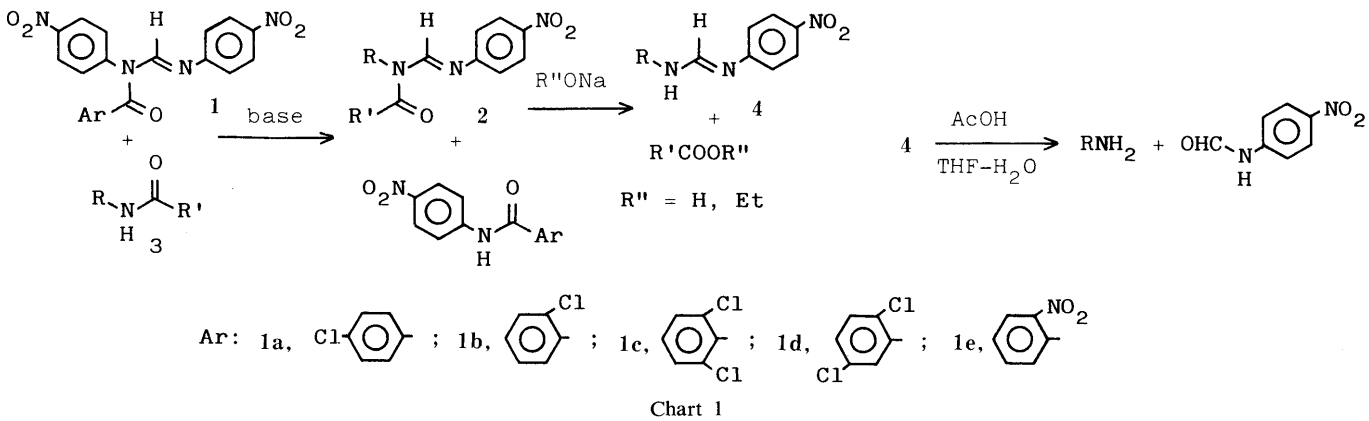


Chart 1

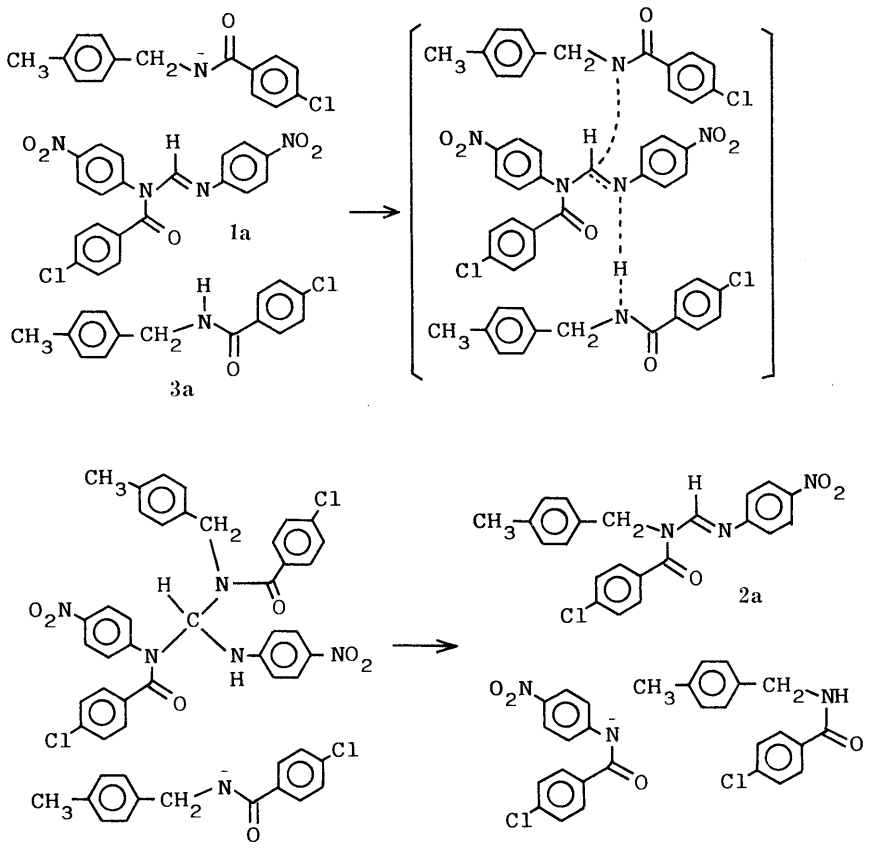


Chart 2

into **2a**. A small singlet signal was observed at δ 8.87 in this case as well. 3) The results under this condition were similar to those under condition 2. 4) The substrates **1a** and **3a** disappeared entirely within 30 min, and the spectrum indicated that the products consist of equimolar amounts of **2a** and *N*-(*p*-chlorobenzoyl)-*p*-nitroaniline. No signal was detected at δ 8.87. These results imply that a proton donor, free carboxamide or diisopropylamine, which would assist the attack of carboxamide anion on the amidine central carbon as a general acid, is essential for the amide exchange reaction between N^1-acylamidine and carboxamide (Chart 2).

Compound **2a** and a product (**5**) melting at 217 °C were obtained when a THF solution of equimolar amounts of **1a** and **3a** was allowed to stand overnight after addition of 0.5 molar eq. amount of *n*-butyllithium. The results of elemental analysis of **5** were consistent with the values required for the molecular formula $C_{20}H_{14}N_6O_6$, and the ^{1}H-NMR spectrum (DMSO-d_6) showed a singlet signal at δ 8.87. Compound **5** was hydrolyzed to give *N*-formyl-*p*-nitroaniline and *p*-nitroaniline when an aqueous THF solution of **5** was allowed to stand overnight at room temperature in the presence of acetic acid. The structure of **5** was determined to be *N*,*N*-bis(*p*-nitrophenylimino-methyl)-*p*-nitroaniline on the basis of the results of acid hydrolysis and the ^{1}H-NMR spectrum (see Experimental). The mechanism of the formation of **5** in the reaction of **1a** and **3a** is probably as follows: compound **1a** was first hydrolyzed to give N^1,N^2-di(*p*-nitrophenyl)formamidine (**4a**) and *p*-chlorobenzoic acid under alkaline conditions, because the reaction medium would contain a trace of water. The conjugate base of **4a** then attacked the amidine central

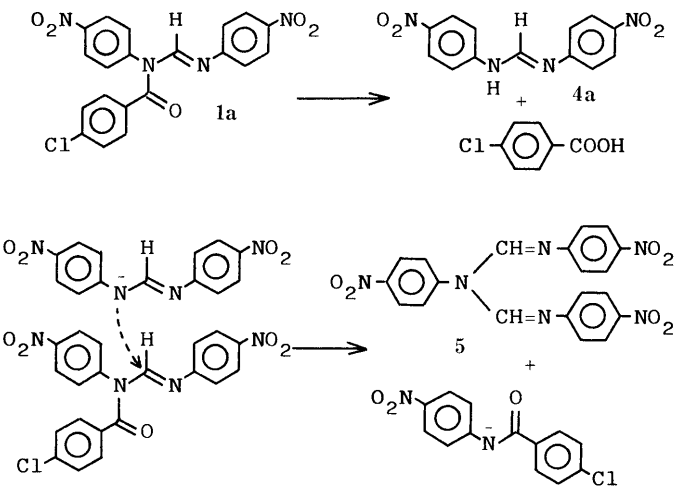


Chart 3

carbon of **1a** to give **5** and *N*-(*p*-chlorobenzoyl)-*p*-nitroaniline (Chart 3). The reaction of **4a** and **1a** in THF solution in the presence of lithium diisopropylamide (LDA) gave **5** and *N*-(*p*-chlorobenzoyl)-*p*-nitroaniline. When a mixture of a THF solution of **5** and aqueous sodium hydroxide solution was stirred at room temperature, **4a** and *p*-nitroaniline were obtained, providing further evidence for the structure of **5**. Alkaline hydrolysis of **5** should afford **4a** and *N*-formyl-*p*-nitroaniline as an intermediate, and the latter is probably further hydrolyzed to give *p*-nitroaniline and formic acid under the experimental conditions.

Reaction of **1a** and **3a** under condition 4 gave **2a** in 87% yield. N^1-(*p*-Chlorobenzoyl)-N^1-(α-phenethyl)-N^2-(*p*-

nitrophenyl)formamidine (**2b**), N^1-(*p*-chlorobenzoyl)-N^1-(*p*-methylphenyl)-N^2-(*p*-nitrophenyl)formamidine (**2c**) and N^1-(*p*-chlorobenzoyl)-N^1-(*p*-methoxyphenyl)-N^2-(*p*-nitrophenyl)formamidine (**2d**) were prepared from the corresponding carboxamides under similar conditions in rather unsatisfactory yields.[5]

N^1-(*o*-Chlorobenzoyl)-N^1,N^2-di(*p*-nitrophenyl)formamidine (**1b**) was prepared to suppress hydrolysis of the amide carbonyl group due to steric hindrance by the chlorine subtituent.[6] Reaction of **1b** and *N*-(*p*-chlorobenzoyl)-α-phenethylamine (**3b**) was followed by ^{1}H-NMR spectroscopy (chloroform-*d*) of the products using the signals at δ 8.84 (1-position of **1b**), 1.58 (methyl group of **3b**), 1.98 (methyl group of **2b**), 5.28 (methine group of **3b**) and 6.25 (methine group of **2b**). Compounds **1b** and **3b** were allowed to react under similar conditions to those used in preliminary experiment 4 on the reaction of **1a** and **3a**. The amide exchange reaction between **1b** and **3b**, however, proceeded to the extent of only about 50% within 1 h while the substrate **1b** completely disappeared in the same period of time. Incompleteness of the reaction is not due to the occurrence of the reverse process, because when **2b** and *N*-(*o*-chlorobenzoyl)-*p*-nitroaniline were allowed to react under the same conditions as used in the amide exchange reaction, these compounds were recovered quantitatively. To promote the amide exchange reaction between **1b** and **3b**, the reaction was tested in the presence of various additives. The results were as follows: 3 molar eq amount of 12-crown-4, 50%; 3 molar eq amount of dimethylformamide, 66%; 3 molar eq amount of 1,4-diazabicyclo[2.2.2]octane (DABCO), 75%; 3 molar eq amount of hexamethylphosphoric triamide (HMPA), 83%; 8 molar eq amount of HMPA, 50%. The yield of **2b** was 60% in the reaction of **3b** and 1.3 molar eq amount of **1b** in the presence of 3 molar eq amount of HMPA.

Alkaline hydrolysis of N^1-acyl-N^1,N^2-diarylformamidine takes place exclusively at the amide carbonyl group to give amidine and carboxylic acid except for **1a**, where hydroxide ion also attacks the amidine central carbon to a small extent in addition to the amide carbonyl carbon.[4] N^1-(*p*-Methylbenzyl)-N^2-(*p*-nitrophenyl)formamidine (**4b**) (52%), *p*-chlorobenzoic acid (64%), **3a** (23%) and *p*-nitroaniline (14%) were obtained when a mixture of THF solution of **2a** and aqueous sodium hydroxide solution was stirred for 3 h at room temperature. The results showed that hydrolysis at the amidine central carbon takes place in addition to the amide carbonyl group to give **3a** and *N*-formyl-*p*-nitroaniline, and the latter was further hydrolyzed to give *p*-nitroaniline and formic acid. When an ethanol–THF solution of **2a** was kept for 4 h at room temperature in the presence of sodium ethoxide, **4b** (78%), ethyl *p*-chlorobenzoate (60%), **3a** (6%) and *p*-nitroaniline (14%) were obtained, showing that the alcoholysis reaction takes place at the amidine central carbon to a lesser extent as compared with alkaline hydrolysis of **2a** (Chart 4). The alcoholysis of **2a** should afford ethyl *N*-(*p*-nitrophenyl)formimidate as an intermediate, and the imidate was probably hydrolyzed to give *p*-nitroaniline during the isolation of products.

Acid hydrolysis of unsymmetrical N^1,N^2-disubstituted formamidine affords the more basic amine and the *N*-formyl derivative of the less basic amine.[2] Compound **4b** was readily hydrolyzed to give *p*-methylbenzylamine (83%, as the hydrochloride) and *N*-formyl-*p*-nitroaniline (88%) when an aqueous THF solution of **4b** was allowed to stand overnight at room temperature in the presence of acetic acid. Thus, the hydrolysis and alcoholysis of **3a** were performed under the mild conditions (Chart 1).

The one-pot hydrolysis and alcoholysis of various carboxamides (Chart 1, Ar = *o*-chlorophenyl) were achieved *via* N^1-acyl-N^1-alkyl-N^2-(*p*-nitrophenyl)formamidine (**2**) and N^1-alkyl-N^2-(*p*-nitrophenyl)formamidines (**4**). The results are shown in Table I. In general, prolonged heating is required for the hydrolysis of carboxamides under strongly acidic or alkaline conditions. Under these conditions, the process may be accompanied with various side reactions. For example, heating under reflux of *N*-(*p*-chlorobenzoyl)furfurylamine in 6 M hydrochloric acid–ethanol solution, generated polymerized products. The reaction proceeded very slowly in 2 M hydrochloric acid–ethanol solution generating *p*-chlorobenzoic acid as a sole product, while furfurylamine could not be detected.

The reaction of *p*-chlorobenzoic acid and (+)-α-phenethylamine (97% ee) with 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) gave (−)-**3b**, $[\alpha]_D^{27}$ −25.6° (c = 0.46, ethanol). One-pot alcoholysis of (−)-**3b** gave ethyl *p*-chlorobenzoate (74%) and (+)-α-phenethylamine (64%, 99% ee). The chirality of the amine moiety was retained

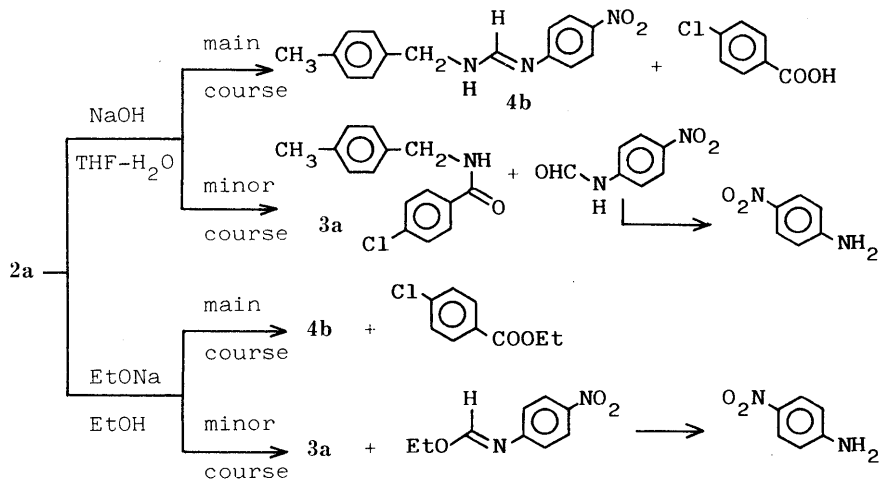
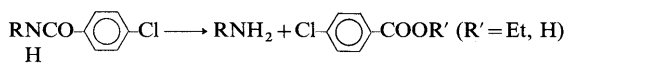
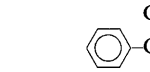
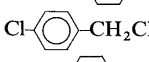
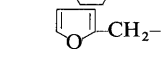
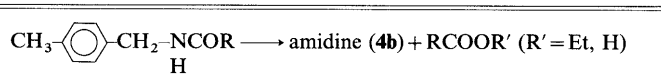


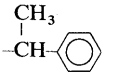
Chart 4

TABLE I. One-Pot Alcoholysis and Hydrolysis of Carboxamides[a]



R	1b (mol)	LDA (mol)	Alcoholysis Yield (%) Amine	Alcoholysis Yield (%) Ester	Hydrolysis Yield (%) Amine	Hydrolysis Yield (%) Acid
	1.3	1.5	56	63	50	61
	1.2	1.2	63	71	56	68
	1.3	1.5	55	65	52	64
	1.5	1.5	45	46		
n-Bu-	1.2	1.2	89[b]	80	77[b]	78



R	1b (mol)	LDA (mol)	Alcoholysis Yield (%) Amidine	Alcoholysis Yield (%) Ester	Hydrolysis Yield (%) Amidine	Hydrolysis Yield (%) Acid
	1.2	1.2	66	69	66	68
	1.2	1.2	72	68		
	1.2	1.2	58	48	50	47

a) Compound **1b** was used as the substrate for the amide exchange reaction. Each amide exchange reaction was carried out in the presence of an excess of 0.2 molar eq amount of diisopropylamine. *b*) Yield as the amidine.

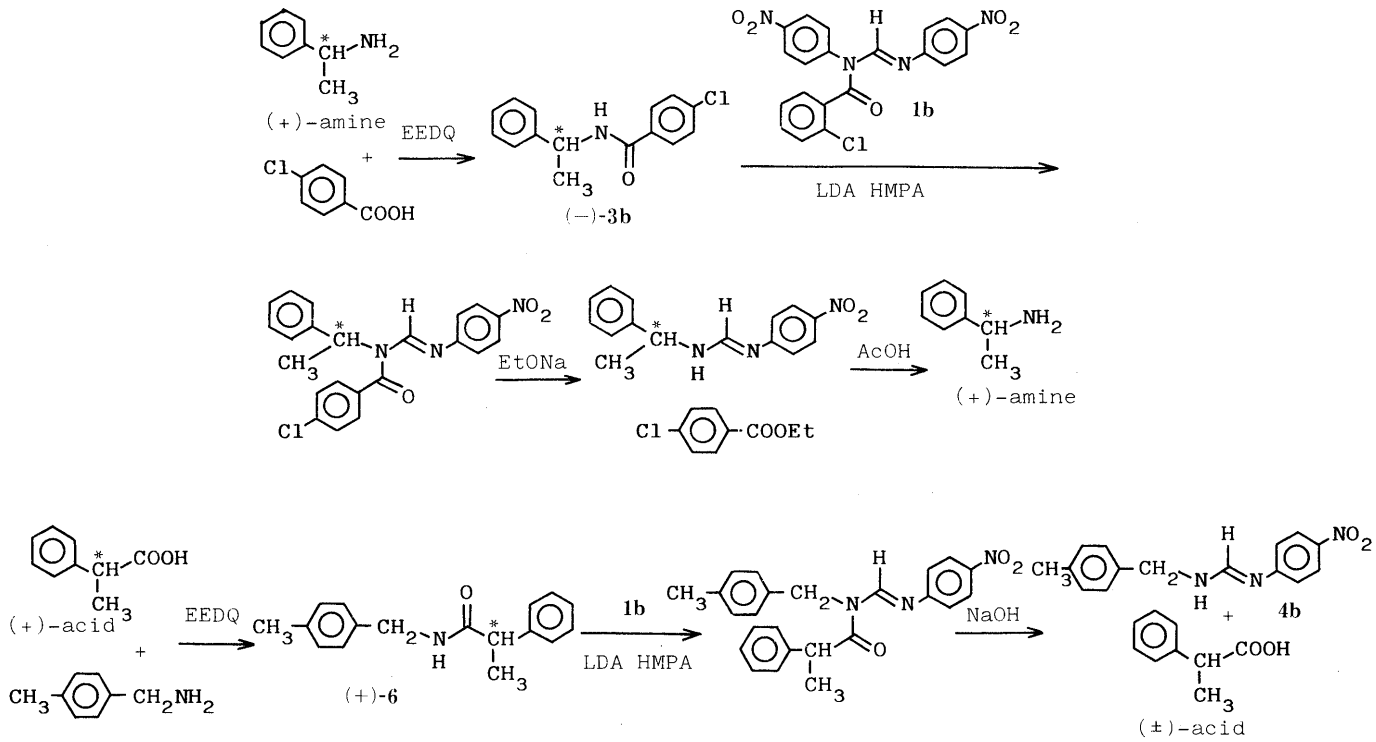


Chart 5

throughout the alcoholysis process. On the other hand, hydrolysis of carboxamides derived from optically active carboxylic acids, having an asymmetric center at the α-position, by this method gave racemized products. The reaction of *p*-methylbenzylamine and (+)-α-phenylpropionic acid, $[\alpha]_D^{28}$ +78.1° (c=0.79, ethanol), with EEDQ gave (+)-*N*-(α-phenylpropionyl)-*p*-methylbenzylamine [(+)-**6**], $[\alpha]_D^{27}$ +17.8° (c=0.58, ethanol). One-pot hydrolysis of the latter by this method gave α-phenylpropionic acid (47%), $[\alpha]_D^{28}$ +7.6° (c=0.52, ethanol) (Chart 5).

The reaction of **1b** and carboxamide carrying a hydroxyl group was quite complex. When **1b** and 4-(*p*-chlorobenzoylamino)-1-butanol (**7a**) were allowed to react in THF solution in the presence of LDA and HMPA, thin layer chromatography (TLC) of the products showed many spots, and a small amount of 4-(*p*-chlorobenzoylamino)-1-butyl *p*-chlorobenzoate was isolated from the products, implying that the hydroxyl group of **7a** participates in the reaction. One-pot alcoholysis of 4-(*p*-chlorobenzoylamino)-1-butyl acetate (**7b**) gave 57% of 4-amino-1-butanol and 72% of ethyl *p*-chlorobenzoate (Chart 6). Protection of the hydroxyl group is essential for the alcoholysis of *N*-acyl derivatives of amino alcohols by this method.

This hydrolysis and alcoholysis are characteristic of carboxamides derived from primary amines. The preparation of monoacyl derivatives in which an acyl group is attached to the secondary amino group would be possible by this alcoholysis of diacyl derivatives of diamines with primary and secondary amino groups.

One-pot alcoholysis of *N*-ethyl-*N*,*N*′-ethylenebis(*p*-chlorobenzamide) (**8a**) gave *N*-(2-aminoethyl)-*N*-ethyl-*p*-chlorobenzamide (**8b**), which was isolated as the perchlorate,

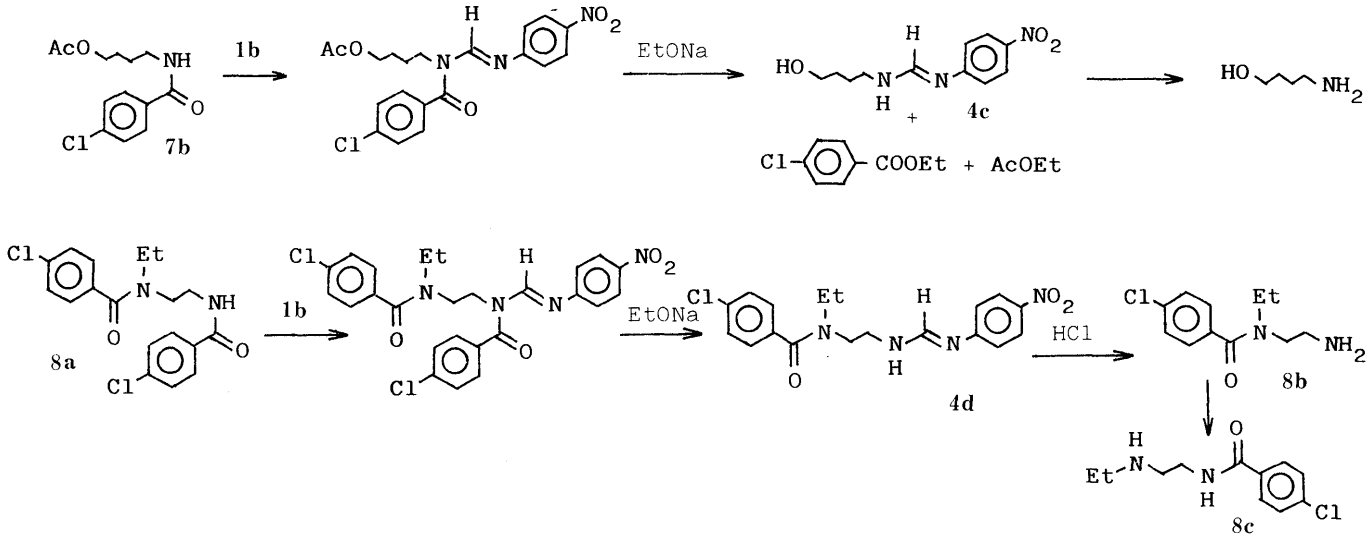


Chart 6

when the hydrolysis of the intermediate, N^1-{2-[*N*-(*p*-chlorobenzoyl)-*N*-ethyl]aminoethyl}-N^2-(*p*-nitrophenyl)-formamidine (**4d**), was conducted in aqueous THF solution in the presence of hydrochloric acid. When the perchlorate of **8b** was treated with an ethanol solution of sodium ethoxide, *N*-[2-(ethylamino)ethyl]-*p*-chlorobenzamide (**8c**) was obtained probably due to 1,4-*N*,*N*-acyl migration in **8b**. Stiring[7] reported that 1,4-*N*,*N*-acyl migration readily takes place in the *N*-acylethylenediamine system. When the hydrolysis of the intermediate **4d** was conducted in the presence of acetic acid in a one-pot alcoholysis of **8a**, **8c** was directly obtained. Probably 1,4-*N*,*N*-acyl migration took place during the hydrolysis process (Chart 6).

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were recorded on JEOL PMX-60 and JEOL GX-400 NMR spectrometers with tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), double triplet (dt), multiplet (m) and broad (br). Optical rotations were measured with a JASCO DIP-4 polarimeter.

Compounds **2a**,[1] **2d**,[1] **3a**,[1] **4b**,[8] amines, *N*-acylamines, esters, carboxylic acids and amidines described in this section were identical with the corresponding authentic samples on the basis of the mixed melting point measurement or the comparison of their infrared (IR) spectra. Compounds **1a**,[4] **1e**,[8] **3a**,[1] and **4b**[8] were prepared according to the cited references.

Preparation of Carboxamides The following carboxamides were prepared from the corresponding amines and acyl chlorides by the usual method. *dl*-*N*-(*p*-Chlorobenzoyl)-α-phenethylamine (**3b**), mp 149 °C (benzene). *Anal.* Calcd for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43; N, 5.39. Found: C, 69.01; H, 5.47; N, 5.45. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.55 (3H, d, J=7 Hz, CH_3), 5.23 (1H, quintet, J=7 Hz, CH) which was converted into a quartet signal on the addition of D_2O, 6.57 (1H, br d, J=7 Hz, NH) which disappeared on the addition of D_2O, 7.30 (2H, d, J=8 Hz, 3- and 5-positions of aroyl), 7.32 (5H, s, phenyl) and 7.67 (2H, d, J=8 Hz, 2- and 6-positions of aroyl). *N*-(*p*-Chlorobenzoyl)-2-(*p*-chlorophenyl)ethylamine, mp 148 °C (benzene). *Anal.* Calcd for $C_{15}H_{13}Cl_2NO$: C, 61.24; H, 4.45; N, 4.76. Found: C, 61.11; H, 4.48; N, 4.76. ^{1}H-NMR (CD_3OD, 60 MHz) δ: 2.90 (2H, t, J=8 Hz, $-C\underline{H}_2CH_2N-$), 3.63 (2H, t, J=8 Hz, $-CH_2C\underline{H}_2N-$), 7.27 (4H, s, ClC_6H_4-), 7.45 (2H, d, J=9 Hz, 3- and 5-positions of aroyl) and 7.78 (2H, d, J=9 Hz, 2- and 6-positions of aroyl). *N*-(*p*-Chlorobenzoyl)cyclohexylamine, mp 184 °C (benzene). *Anal.* Calcd for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.78; N, 5.89. Found: C, 65.38; H, 6.82; N, 5.84. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.0—2.17 (10H, m, $-CH_2-$), 3.93 (1H, m, –CH–), 6.07 (1H, br s, NH), 7.30 (2H, d, J=9 Hz, 3- and 5-positions of aroyl) and 7.63 (2H, d, J=9 Hz, 2- and 6-positions of aroyl). *N*-(*p*-Chlorobenzoyl)furfurylamine, mp 123 °C (benzene). *Anal.* Calcd for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94. Found: C, 60.97; H, 4.31; N, 5.94. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 4.62 (2H, d, J=5 Hz, CH_2), 6.30 (1H, dd, J=3.5, 0.5 Hz, 3-position of furyl), 6.34 (1H, dd, J=3.5, 2 Hz, 4-position of furyl), 6.52 (1H, br t, J=5 Hz, NH), 7.38 (1H, dd, J=2, 0.5 Hz, 5-position of furyl), 7.39 (2H, d, J=9 Hz, 3- and 5-positions of aroyl) and 7.73 (2H, d, J=9 Hz, 2- and 6-positions of aroyl). *N*-(*p*-Chlorobenzoyl)-*n*-butylamine, mp 81 °C (petroleum benzin). *Anal.* Calcd for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.67; N, 6.62. Found: C, 62.23; H, 6.74; N, 6.59. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 0.83—1.83 (7H, m, $C\underline{H}_3C\underline{H}_2C\underline{H}_2CH_2-$), 3.47 (2H, q, J=6.5 Hz, $CH_3CH_2CH_2C\underline{H}_2-$), 6.23 (1H, br s, NH), 7.38 (2H, d, J=9 Hz, 3- and 5-positions of aroyl) and 7.70 (2H, d, J=9 Hz, 2- and 6-positions of aroyl). 4-(*p*-Chlorobenzoylamino)-1-butanol (**7a**) was prepared from equimolar amounts of 4-amino-1-butanol and *p*-chlorobenzoyl chloride under ice-cooling in the presence of Et_3N. mp 109 °C ($CHCl_3$). *Anal.* Calcd for $C_{11}H_{14}ClNO_2$: C, 58.03; H, 6.20; N, 6.15. Found: C, 57.90; H, 6.25; N, 6.18. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.68 (2H, m, 2- or 3-position), 1.73 (2H, m, 2- or 3-position), 3.48 (2H, q, J=6 Hz, 4-position), 3.72 (2H, t, J=6 Hz, 1-position), 6.71 (1H, br s, NH), 7.38 (2H, d, J=9 Hz, 3- and 5-positions of aroyl) and 7.71 (2H, d, J=9 Hz, 2- and 6-positions of aroyl). 4-(*p*-Chlorobenzoylamino)-1-butyl acetate (**7b**) was prepared by acetylation of **7a** using acetic anhydride. mp 75 °C (petroleum benzin). *Anal.* Calcd for $C_{13}H_{16}ClNO_3$: C, 57.89; H, 5.98; N, 5.19. Found: C, 57.87; H, 6.07; N, 5.19. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.67 (4H, m, 2- and 3-positions), 2.03 (3H, s, CH_3), 3.47 (2H, q, J=6 Hz, 4-position), 4.12 (2H, t, J=6 Hz, 1-position), 6.72 (1H, br s, NH), 7.37 (2H, d, J=8 Hz, 3- and 5-positions of aroyl) and 7.75 (2H, d, J=8 Hz, 2- and 6-positions of aroyl). 4-(*p*-Chlorobenzoylamino)-1-butyl *p*-chlorobenzoate was prepared by the reaction of **7a** and *p*-chlorobenzoyl chloride. mp 151 °C (benzene). *Anal.* Calcd for $C_{18}H_{17}Cl_2NO_3$: C, 59.03; H, 4.68; N, 3.82. Found: C, 58.81; H, 4.66; N, 4.07. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.78 (2H, m, 3-position), 1.86 (2H, m, 2-position), 3.53 (2H, q, J=6 Hz, 4-position), 4.37 (2H, t, J=6 Hz, 1-position), 6.30 (1H, br s, NH), 7.39 (2H, d, J=9 Hz, 3- and 5-positions of $-NCOC_6H_4Cl$), 7.41 (2H, d, J=9 Hz, 3- and 5-positions of $-OCOC_6H_4Cl$), 7.71 (2H, d, J=9 Hz, 2- and 6-positions of $-NCOC_6H_4Cl$) and 7.97 (2H, d, J=9 Hz, 2- and 6-positions of $-OCOC_6H_4Cl$). *N*-Ethyl-*N*,*N*′-ethylenebis(*p*-chlorobenzamide) (**8a**), mp 168 °C (EtOH). *Anal.* Calcd for $C_{18}H_{18}Cl_2N_2O_2$: C, 59.19; H, 4.97; N, 7.67. Found: C, 59.15; H, 4.97; N, 7.70. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.18 (3H, br t, J=7 Hz, $C\underline{H}_3CH_2$), 3.33 (2H, br q, J=7 Hz, $CH_3C\underline{H}_2$), 3.74 and 3.81 (each 2H, m, $C\underline{H}_2C\underline{H}_2$), 7.27 and 7.36 (each 2H, d, J=8 Hz, N-aroyl), 7.38 (2H, d, J=8 Hz, 3- and 5-positions of N′-aroyl), 7.78 (2H, d, J=8 Hz, 2- and 6-positions of N′-aroyl) and 7.82 (1H, br s, NH). *N*-(*p*-Methylbenzyl)cyclohexanecarboxamide was prepared in 61% yield by the reaction of *p*-methylbenzylamine and cyclohexanecarboxylic acid in THF solution in the presence of EEDQ. mp 138 °C (petroleum benzin). *Anal.* Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.57; H, 9.19; N, 6.13. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.0—2.0 (10H, m, cyclohexyl), 2.33 (3H, s, CH_3), 4.42 (2H, d, J=6 Hz, $C\underline{H}_2C_6H_4CH_3$), 5.67 (1H, br s, NH) and 7.13 (4H, s, $C_6\underline{H}_4CH_3$). *dl*-*N*-(α-Phenylpropionyl)-*p*-methylbenzylamine (**6**) was prepared in 77% yield by the reaction of *p*-

methylbenzylamine and *dl*-α-phenylpropionic acid in benzene solution in the presence of EEDQ. mp 78 °C (petroleum benzin). *Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.31; H, 7.59; N, 5.44. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.52 (3H, d, J=7 Hz, $COCHC\underline{H}_3$), 2.28 (3H, s, CH_3), 3.57 (1H, q, J=7 Hz, CH), 4.23 (2H, d, J=6 Hz, CH_2), 5.67 (1H, br s, NH), 7.02 (4H, s, $CH_3C_6\underline{H}_4CH_2$) and 7.25 (5H, s, phenyl). (−)-*N*-(*p*-Chlorobenzoyl)-α-phenethylamine [(−)-**3b**] was prepared from *p*-chlorobenzoic acid and (+)-α-phenethylamine, $[\alpha]_D^{25}$ +29.1° (c=0.41, EtOH) lit.,[9] $[\alpha]_D^{15}$ +30.4° (c=14.72, EtOH), in 89% yield on refluxing of their THF soluton in the presence of EEDQ for 6 h. mp 153.5°C (benzene). *Anal.* Calcd for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43; N, 5.39. Found: C, 69.40; H, 5.42; N, 5.48. (+)-**6** was prepared in 80% yield by the reaction of *p*-methylbenzylamine and (+)-α-phenylpropionic acid, $[\alpha]_D^{28}$ +78.1° (c=0.79, EtOH) lit.,[10] $[\alpha]_D^{25}$ +79.0° (c=1.67, EtOH), in benzene solution in the presence of EEDQ. mp 100 °C (petroleum benzin). *Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.36; H, 7.62; N, 5.71.

N^1-(*o*-Chlorobenzoyl)-N^1,N^2-di(*p*-nitrophenyl)formamidine (1b) A mixture of **4a** (28.62 g, 0.1 mol), *o*-chlorobenzoyl chloride (21.00 g, 0.12 mol), Et_3N (13.16 g, 0.13 mol) and 180 ml of anhydrous benzene was refluxed for 1 h. The mixture was allowed to stand overnight. The precipitate was collected, washed successively with 7% $NaHCO_3$ and H_2O, and recrystallized from benzene to give 36.17 g (85%) of **1b**. mp 175 °C. *Anal.* Calcd for $C_{20}H_{13}ClN_4O_5$: C, 56.55; H, 3.08; N, 13.19. Found: C, 56.60; H, 3.11; N, 13.10. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.06 (2H, d, J=9 Hz, 2″- and 6″-positions), 7.29—7.44 (4H, m, 3‴-, 4‴-, 5‴- and 6‴-positions), 7.54 (2H, d, J=9 Hz, 2′- and 6′-positions), 8.17 (2H, d, J=9 Hz, 3″- and 5″-positions), 8.27 (2H, d, J=9 Hz, 3′- and 5′-positions) and 8.84 (1H, s, 1-position).

N^1-(2,6-Dichlorobenzoyl)-N^1,N^2-di(*p*-nitrophenyl)formamidine (1c) 2,6-Dichlorobenzoyl chloride (6.28 g, 30 mmol) was added to a stirred mixture of **4a** (7.16 g, 25 mmol), 4-dimethylaminopyridine (DMAP) (0.28 g, 2.5 mmol), Et_3N (3.54 g, 35 mmol) and 20 ml of anhydrous THF under ice-cooling. The mixture was stirred for 1 h under ice-cooling. Anhydrous ether (70 ml) was added to the clear reaction solution, and the precipitate was collected, then washed successively with H_2O, 7% $NaHCO_3$ and H_2O. Chloroform was added to the precipitate and the mixture was filtered. The $CHCl_3$ layer was dried over K_2CO_3, and concentrated under reduced pressure. The residue was recrystallized from benzene to give 6.25 g (54%) of **1c**. mp 177.5 °C. *Anal.* Calcd for $C_{20}H_{12}Cl_2N_4O_5$: C, 52.31; H, 2.63; N, 12.20. Found: C, 52.35; H, 2.63; N, 12.30. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.15 (d, J=9 Hz, 2″- and 6″-positions), 7.20 (3H, m, 3‴-, 4‴- and 5‴-positions), 7.66 (d, J=9 Hz, 2′- and 6′-positions), 8.18 (d, J=9 Hz, 3′- and 5′-positions), 8.21 (d, J=9 Hz, 3″- and 5″-positions) and 9.21 (s, 1-position). Other small signals due to a conformational isomer were observed at δ 6.91 (d, J=9 Hz, 2″- and 6″-positions), 7.49 (m, 3‴-, 4‴- and 5‴-positions), 7.63 (d, J=9 Hz, 2′- and 6′-positions), 7.99 (s, 1-position), 8.13 (d, J=9 Hz, 3″- and 5″-positions) and 8.44 (d, J=9 Hz, 3′ and 5′-positions). The relative integrated intensities of the signals showed that the ratio of the two conformers was 3:1.

N^1-(2,5-Dichlorobenzoyl)-N^1,N^2-di(*p*-nitrophenyl)formamidine (1d) A mixture of **4a** (5.72 g, 20 mmol), 2,5-dichlorobenzoyl chloride (4.61 g, 22 mmol), Et_3N (3.03 g, 30 mmol) and 40 ml of anhydrous benzene was refluxed for 1 h. The precipitate was collected, and washed successively with H_2O, 7% $NaHCO_3$ and H_2O. Recrystallization of the precipitate from benzene gave 8.04 g (88%) of **1d**. mp 202 °C. *Anal.* Calcd for $C_{20}H_{12}Cl_2N_4O_5$: C, 52.31; H, 2.63; N, 12.20. Found: C, 52.38; H, 2.69; N, 12.33. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 7.03 (2H, d, J=9 Hz, 2″- and 6″-positions), 7.25—7.42 (3H, m, 3‴-, 4‴- and 6‴-positions), 7.50 (2H, d, J=9 Hz, 2′- and 6′-positions), 8.15 (2H, d, J=9 Hz, 3″- and 5″-positions), 8.27 (2H, d, J=9 Hz, 3′- and 5′-positions) and 8.72 (1H, s, 1-position).

Formation of 5 in the Reaction of 1a and 3a Compound **3a** (1.04 g, 4 mmol) was dissolved in 30 ml of THF and 1.3 ml of hexane solution of *n*-BuLi (1.6 M) was added under N_2 with ice-cooling. The solution was added to a solution of **1a** (1.70 g, 4 mmol) in 30 ml of THF under N_2 with ice-cooling. The mixture was allowed to stand overnight at room temperature, then saturated with CO_2, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, and extracted with 7% $NaHCO_3$. Work-up of the $NaHCO_3$ layer gave 0.13 g of *p*-chlorobenzoic acid. The $CHCl_3$ layer was dried over K_2CO_3, and concentrated. A small amount of $CHCl_3$ was added to the residue, and the precipitate [1.18 g, a mixture of *N*-(*p*-chlorobenzoyl)-*p*-nitroaniline and **3a**] was filtered off. The filtrate was concentrated, and the precipitate was collected to give a small amount of crude **5**. Recrystallization from AcOEt gave 0.06 g (4%) of pure **5**. mp 217 °C. *Anal.* Calcd for $C_{20}H_{14}N_6O_6$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.47; H, 3.31; N, 19.01. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.30 (4H, d, J=9 Hz, 2- and 6-positions of $=N-C_6H_4$), 7.84 (2H, d, J=9 Hz, 2- and 6-positions of $-N-C_6H_4$), 8.24 (4H, d, J=9 Hz, 3- and 5-positions of $=N-C_6H_4$), 8.40 (2H, d, J=9 Hz 3- and 5-positions of $-N-C_6H_4$) and 8.87 (2H, s, $-CH=$). The $CHCl_3$ mother liquor was concentrated to dryness, and the residue was washed with ether to give 0.30 g (18%) of **2a**.

Preparation of 5 by the Reaction of 1a and 4a A solution of LDA (12 mmol) in anhydrous THF–hexane was added to a solution of **1a** (4.25 g, 10 mmol) and **4a** (1.43 g, 5 mmol) in 80 ml of anhydrous THF under N_2 with ice-cooling. The mixture was kept for 20 min at room temperature, then saturated with CO_2 and concentrated under reduced pressure, and 200 ml of $CHCl_3$ and 100 ml of 7% $NaHCO_3$ were added to the residue. The insoluble part was collected to give 2.77 g of crude **4a**. The aqueous layer was treated as usual to give 0.07 g (9%) of *p*-chlorobenzoic acid. The $CHCl_3$ layer was concentrated under reduced pressure, and 20 ml of $CHCl_3$ was added to the residue. The insoluble part was collected to give 0.99 g (72%) of *N*-(*p*-chlorobenzoyl)-*p*-nitroaniline. The $CHCl_3$ layer was concentrated under reduced pressure, and ether was added to the residue. The insoluble part was collected to give 0.90 g (42%) of crude **5**. Recrystallization from AcOEt gave 0.44 g (20%) of pure **5**.

Acid Hydrolysis of 5 A mixture of **5** (0.0874 g, 0.2 mmol), 7 ml of THF, 2.5 ml of H_2O and 0.5 g of AcOH was allowed to stand overnight at room temperature, then 15 ml of 7% $NaHCO_3$ was added, and the whole was concentrated under reduced pressure to remove THF. The precipitate was collected, and 5 ml of ether was added to it. The insoluble part was collected to give crude *N*-formyl-*p*-nitroaniline. Recrystallization from AcOEt gave 0.0333 g (50%) of pure sample. The ether layer was treated as usual to give 0.0246 g (89%) of *p*-nitroaniline.

Alkaline Hydrolysis of 5 A mixture of a solution of **5** (0.0870 g, 0.2 mmol) in 7 ml of THF and 2 ml of 1 N NaOH was stirred for 90 min at room temperature, then saturated with CO_2, and concentrated under reduced pressure to remove THF. The precipitate was collected, and 10 ml of ether was added to it. The insoluble part was collected to give 0.0448 g (78%) of **4a**. The ether layer was treated as usual to give 0.0201 g (73%) of *p*-nitroaniline.

Preparation of 2a from 1a and 3a A hexane solution of *n*-BuLi (1.56 M, 7.7 ml) was added to a mixture of **3a** (2.08 g, 8 mmol), diisopropylamine (0.81 g, 8 mmol) and 40 ml of anhydrous THF under ice-cooling and N_2. The whole was added to a solution of **1a** (4.08 g, 9.6 mmol) in 50 ml of anhydrous THF under ice-cooling. The mixture was kept for 45 min at room temperature, and saturated with CO_2, and concentrated under reduced pressure, and $CHCl_3$ and 7% $NaHCO_3$ were added to the residue. The $CHCl_3$ layer was dried over K_2CO_3, and concentrated under reduced pressure. A small amount of $CHCl_3$ was added to the residue, and the insoluble part was collected to give 1.55 g (70%) of *N*-(*p*-chlorobenzoyl)-*p*-nitroaniline. The $CHCl_3$ layer was concentrated under reduced pressure. A small amount of $CHCl_3$ was added to the residue, and 0.25 g (7%) of **5** was obtained from the insoluble part. The mother liquor was concentrated under reduced pressure, and ether was added to the residue. The precipitate was collected, and recrystallized from petroleum benzin to give 2.82 g (87%) of **2a**.

Preparation of 2b from 1a and 3b A hexane solution of *n*-BuLi (1.84 M, 9.8 ml) was added to a mixture of **3b** (3.89 g, 15 mmol), diisopropylamine (2.12 g, 21 mmol) and 10 ml of anhydrous THF under N_2 with ice-cooling. The whole was added to a mixture of **1a** (9.55 g, 22.5 mmol) and 44 ml of anhydrous THF. The mixture was allowed to stand overnight at room temperature, then saturated with CO_2, and concentrated under reduced pressure, and $CHCl_3$ and 7% $NaHCO_3$ were added to the residue. The $CHCl_3$ layer was dried over K_2CO_3, and concentrated under reduced pressure. A small amount of $CHCl_3$ was added to the residue and the mixture was filtered. The filtrate was concentrated under reduced pressure, and ether was added to the residue. The precipitate was collected, and recrystallized from petroleum benzin to give 2.36 g (39%) of **2b**. mp 127 °C. *Anal.* Calcd for $C_{22}H_{18}ClN_3O_3$: C, 64.48; H, 4.45; N, 10.30. Found: C, 64.57; H, 4.40; N, 10.45. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.98 (3H, d, J=7 Hz, CH_3), 6.26 (1H, q, J=7 Hz, CH), 6.91 (2H, d, J=9 Hz, 2″- and 6″-positions), 7.27 (1H, t, J=7 Hz, *p*-position of phenyl), 7.36 (2H, t, J=7 Hz, *m*-position of phenyl), 7.44 (2H, d, J=9 Hz, 2‴- and 6‴-positions or 3‴- and 5‴-positions), 7.49 (2H, d, J=9 Hz, 2‴- and 6‴-positions or 3‴- and 5‴-positions), 7.51 (2H, d, J=7 Hz, *o*-position of phenyl), 8.13 (2H, d, J=9 Hz, 3″- and 5″-positions) and 8.17 (1H, s, 1-position).

Preparation of 2c from 1a and *N*-(*p*-Chlorobenzoyl)-*p*-toluidine A hexane solution of *n*-BuLi (1.56 M, 4.81 ml) was added to a mixture of *N*-(*p*-chlorobenzoyl)-*p*-toluidine (1.23 g, 5 mmol), diisopropylamine (0.51 g, 5 mmol) and 50 ml of anhydrous THF under ice-cooling and N_2. The

whole was added to a solution of **1a** (2.55 g, 6 mmol) in 50 ml of anhydrous THF under ice-cooling. The mixture was kept for 1 h at room temperature, then saturated with CO_2, and concentrated under reduced pressure, and $CHCl_3$ and 7% $NaHCO_3$ were added to the residue. The $CHCl_3$ layer was dried over K_2CO_3, and concentrated under reduced pressure. A small amount of $CHCl_3$ was added to the residue and the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was recrystallized from benzene to give 0.61 g (31%) of **2c**. mp 158 °C. *Anal.* Calcd for $C_{21}H_{16}ClN_3O_3$: C, 64.05; H, 4.10; N, 10.67. Found: C, 64.16; H, 4.07; N, 10.76. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.35 (3H, s, CH_3), 7.08 (2H, d, J=9 Hz, 2′- and 6′-positions), 7.10 (2H, d, J=9 Hz, 2″- and 6″-positions), 7.18 (2H, d, J=9 Hz, 3′- and 5′-positions), 7.25 (2H, d, J=9 Hz, 3‴- and 5‴-positions), 7.39 (2H, d, J=9 Hz, 2‴- and 6‴-positions), 8.19 (2H, d, J=9 Hz, 3″- and 5″-positions) and 9.01 (1H, s, 1-position).

Preparation of 2d from 1a and *N*-(*p*-Chlorobenzoyl)-*p*-anisidine A hexane solution of *n*-BuLi (1.84 M, 9.8 ml) was added to a mixture of *N*-(*p*-chlorobenzoyl)-*p*-anisidine (3.92 g, 15 mmol), diisopropylamine (2.12 g, 21 mmol) and 18 ml of anhydrous THF under N_2 with ice-cooling. The whole was added to a solution of **1a** (7.00 g, 17 mmol) in 40 ml of anhydrous THF. The mixture was kept for 1 h at room temperature, then saturated with CO_2, and concentrated under reduced pressure, and $CHCl_3$ and 7% $NaHCO_3$ were added to the residue. The $CHCl_3$ layer was dried over K_2CO_3, and concentrated under reduced pressure. A small amount of $CHCl_3$ was added to the residue, and the mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from benzene to give 1.91 g (34%) of **2d**.

Preparation of 2b from 1b and 3b in the Presence of HMPA A hexane solution of LDA [prepared from a hexane solution of *n*-BuLi (2.1 M, 7.14 ml) and diisopropylamine (1.72 g, 17 mmol)] was added to a solution of **3b** (2.60 g, 10 mmol) in 5 ml of anhydrous THF under N_2 with ice-cooling. The mixture was added to a solution of **1b** (5.52 g, 13 mmol) and HMPA (5.38 g, 30 mmol) in 7 ml of THF under ice-cooling. The whole was kept for 1 h at room temperature, saturated with CO_2, and concentrated under reduced pressure. Water was added to the residue, and was discarded by decantation to remove HMPA. The residue was dissolved in AcOEt. The AcOEt solution was washed with 7% $NaHCO_3$, dried over K_2CO_3, and concentrated under reduced pressure. A small amount of $CHCl_3$ was added to the residue and the mixture was filtered. The filtrate was concentrated under reduced pressure, and ether was added to the residue. The precipitate was collected and recrystallized from petroleum benzin to give 2.46 g (60%) of **2b**.

Alkaline Hydrolysis of 2a A mixture of a solution of **2a** (0.41 g, 1 mmol) in 3.5 ml of THF, 0.5 ml of H_2O and 1 ml of 1 N NaOH was stirred for 3 h at room temperature, then saturated with CO_2, and concentrated under reduced pressure to remove THF, and ether and 7% $NaHCO_3$ were added to the residue. The aqueous layer was treated as usual to give 0.10 g (64%) of *p*-chlorobenzoic acid. Then 2 ml of 1 N HCl was added to the ether layer under ice-cooling, and the mixture was stirred. The precipitate (the hydrochloride of **4b**) was collected, and treated as usual to give 0.14 g (52%) of **4b**. The ether layer was dried over K_2CO_3, and concentrated under reduced pressure. A small amount of ether was added to the residue, and the insoluble part was collected to give 0.06 g (23%) of **3a**. The ether layer was treated as usual to give 0.02 g (14%) of *p*-nitroaniline.

Alcoholysis of 2a Anhydrous EtOH (2 ml) was added to a solution of **2a** (0.41 g, 1 mmol) in 1 ml of anhydrous THF, and 0.2 ml of 1 N NaOEt was added to the mixture. The whole was kept for 4 h at room temperature, then saturated with CO_2, and concentrated under reduced pressure, and ether and 7% $NaHCO_3$ were added to the residue. Then 2 ml of 1 N HCl was added to the ether layer, and the precipitate (the hydrochloride of **4b**) was collected, and treated as usual to give 0.21 g (78%) of **4b**. The ether layer was dried over K_2CO_3, and concentrated under reduced pressure. A small amount of ether was added to the residue, and the insoluble part was collected, and treated as usual to give 0.015 g, (6%) of **3a**. The ether layer was concentrated under reduced pressure, petroleum benzin was added to the residue, and the insoluble part was collected to give 0.02 g (14%) of *p*-nitroaniline. The petroleum benzin layer was concentrated under reduced pressure, and the residue was distilled under reduced pressure to give 0.11 g (60%) of ethyl *p*-chlorobenzoate.

Acid Hydrolysis of 4b Water (20 ml) and AcOH (6.00 g) were added to a solution of **4b** (1.08 g, 4 mmol) in 24 ml of THF. The whole was allowed to stand overnight at room temperature, and added to a solution of Na_2CO_3 (15 g) in 100 ml of H_2O. The THF layer was separated, and the aqueous layer was extracted with ether. The ether layer was combined with the THF solution, and the whole was concentrated under reduced pressure. Ether was added to the residue, and the precipitate was collected, and treated as usual to give 0.58 g (88%) of *N*-formyl-*p*-nitroaniline. The aqueous layer was combined with the ether solution, and the whole was made acidic by the addition of HCl, then concentrated under reduced pressure to dryness. The residue was extracted with EtOH, and the EtOH solution was concentrated under reduced pressure to give 0.52 g (83%) of the hydrochloride of *p*-methylbenzylamine.

General Procedure for One-Pot Alcoholysis and Hydrolysis of Carboxamides A hexane solution of LDA [prepared from hexane solution of *n*-BuLi (1.76 M, 6.82 ml) and diisopropylamine (1.42 g, 14 mmol)] was added to a solution of a carboxamide (10 mmol) and HMPA (2.69 g, 15 mmol) in 5 ml of anhydrous THF under N_2 with ice-cooling. The mixture was added to a solution of **1b** (12—15 mmol, see Table I) and HMPA (2.69 g, 15 mmol) in 7 ml of anhydrous THF under N_2 with ice-cooling. The mixture was kept for 1 h at room temperature, then saturated with CO_2, and concentrated under reduced pressure. Water was added to the residue, and was discarded by decantation to remove HMPA. The residue was dissolved in AcOEt. The AcOEt layer was washed with 7% $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure, and $CHCl_3$ was added to the residue. The precipitate was collected to give *N*-(*o*-chlorobenzoyl)-*p*-nitroaniline. The $CHCl_3$ solution was concentrated under reduced pressure to give the crude N^1-acyl-N^1-alkyl-N^2-(*p*-nitrophenyl)formamidine (**2**). Alcoholysis of the crude **2** was achieved in the same manner as described in the section of alcoholysis of **2a** (reaction time was 1 h) to give the corresponding crude N^1-alkyl-N^2-(*p*-nitrophenyl)formamidine (**4**) and ester. Alkaline hydrolysis of the crude **2** was achieved in the same manner as described for the alkaline hydrolysis of **2a** to give crude **4** and carboxylic acid. For the alkaline hydrolysis of N^1-(α-phenylpropionyl)-N^1-(*p*-methylbenzyl)-N^2-(*p*-nitrophenyl)formamidine, 6 h stirring of the reaction mixture was required. Acid hydrolysis of the crude **4** was achieved in the same manner as described for the acid hydrolysis of **4b**.

One-pot alcoholysis of (−)-**3b** and hydrolysis of (+)-**6** were achieved in the same manner as described above. The results are described in the main text. Optical purities were measured by high performance liquid chromatography (HPLC) using a Crownpak CR column with $HClO_4$ (pH 1.5) +15% (v/v) MeOH.

One-Pot Alcoholysis of *N*-(*p*-Chlorobenzoyl)arylamine The reactions were carried out in the same manner as described in the preceding section in the absence of HMPA. The results (Ar, yield of arylamine, yield of ethyl *p*-chlorobenzoate) were as follows: *p*-methoxyphenyl, 33%, 47%; *p*-methylphenyl, 42%, 48%; phenyl, 40%, 51%; *p*-chlorophenyl, 34%, 49%.

One-Pot Alcoholysis of 7b A hexane solution of LDA [prepared from a hexane solution of *n*-BuLi (1.78 M, 6.74 ml) and diisopropylamine (1.42 g, 14 mmol)] was added to a solution of **7b** (2.58 g, 10 mmol) and HMPA (2.69 g, 15 mmol) in 5 ml of anhydrous THF under N_2 with ice-cooling. The whole was added to a solution of **1b** (5.10 g, 12 mmol) and HMPA (2.69 g, 15 mmol) in 7 ml of anhydrous THF under N_2 with ice-cooling. The mixture was kept for 1 h at room temperature, then saturated with CO_2, and concentrated under reduced pressure. Water was added to the residue, and was discarded by decantation to remove HMPA. The residue was dissolved in AcOEt, and the AcOEt solution was washed with 7% $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure, and $CHCl_3$ was added to the residue. The insoluble part was collected to give 2.62 g (81%) of *N*-(*o*-chlorobenzoyl)-*p*-nitroaniline. The $CHCl_3$ layer was concentrated under reduced pressure to give an oil; its ^{1}H-NMR spectrum ($CDCl_3$) showed a singlet signal due to the acetyl group at δ 2.00, implying that the acetoxy group remained intact thoughout the amide exchange process. The oil was dissolved in 10 ml of anhydrous THF, and 20 ml of anhydrous EtOH and 2 ml of 1 N NaOEt were added to the solution. The whole was kept for 3 h at room temperature, then saturated with CO_2, and concentrated under reduced pressure, and ether was added to the residue. The ether solution was washed with 7% $NaHCO_3$, and extracted with 1 N HCl. The ether layer was treated as usual to give 1.33 g (72%) of ethyl *p*-chlorobenzoate. The aqueous layer was treated as usual to give 1.35 g of crude N^1-(4-hydroxybutyl)-N^2-(*p*-nitrophenyl)formamidine (**4c**). A solution of crude **4c**, AcOH (15 g) and H_2O (50 ml) in 60 ml of THF was allowed to stand overnight at room temperature. The mixture was concentrated under reduced pressure at below 40 °C, and 1 N HCl was added to the residue. The precipitate was collected to give 1.01 g (61%) of *N*-formyl-*p*-nitroaniline. The aqueous layer was washed with ether and cocentrated under reduced pressure to dryness. Ether and 10 ml of 1 N NaOEt were added to the residue, and the mixture was stirred and filtered. The filtrate was concentrated under reduced pressure, and the residue was

distilled under reduced pressure to give 0.51 g (57%) of 4-amino-1-butanol.

In a separate experiment, pure **4c** was obtained by recrystallization of the crude **4c** from benzene–petroleum benzin. mp 99 °C. *Anal.* Calcd for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.99; H, 6.39; N, 17.42. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.69 (2H, m, 2′- or 3′-position), 1.78 (2H, m, 2′- or 3′-position), 3.53 (2H, br t, 1′-position), 3.75 (2H, t, J=6 Hz, 4′-position), 5.32 (1H, br s, NH), 7.02 (2H, d, J=9 Hz, 2″- and 6″-positions), 7.72 (1H, s, 1-position) and 8.15 (2H, d, J=9 Hz, 3″- and 5″-positions).

One-Pot Alcoholysis of 8a The amide exchange reaction between **8a** (3.65 g, 10 mmol) and **1b** (5.52 g, 13 mmol), and subsequent alcoholysis of the N^1-acylamidine were achieved in the same manner as described in the preceding section to give 3.01 g of crude N^1-{2-[*N*-ethyl-*N*-(*p*-chlorobenzoyl)amino]ethyl}-N^2-(*p*-nitrophenyl)formamidine (**4d**) and 1.21 g (66%) of ethyl *p*-chlorobenzoate. The crude **4d** was dissolved in 20 ml of THF, and 20 ml of 2 N HCl was added to the solution. The whole was allowed to stand overnight at room temperature, and concentrated under reduced pressure to remove THF. The remaining liquid was extracted four times with ether. The ether layer was treated as usual to give 0.98 g (71%) of *p*-nitroaniline. The aqueous layer was concentrated under reduced pressure to dryness at below 40 °C to give 1.21 g (53%) of the hydrochloride of **8b** as an oil. Then 10 ml of 1 N $HClO_4$ was added to the oil, and the precipitate was collected, and recrystallized from MeOH–$CHCl_3$ to give 1.02 g (30%) of the perchlorate of **8b**. mp 172 °C. *Anal.* Calcd for $C_{11}H_{16}Cl_2N_2O_5 \cdot 1/2H_2O$: C, 39.30; H, 5.10; N, 8.33. Found: C, 39.73; H, 4.86; N, 8.50. ^{1}H-NMR (DMSO-d_6, 70 °C, 400 MHz) δ: 1.07 (3H, t, J=7 Hz, CH_3CH_2), 3.05 (2H, br t, J=6.5 Hz, $CH_2CH_2NH_3$), 3.27 (2H, br q, J=7 Hz, CH_3CH_2), 3.59 (2H, br t, J=6.5 Hz, –N–CH_2CH_2), 7.46 (2H, d, J=8 Hz, 2- and 6-positions of aroyl), 7.50 (2H, d, J=8 Hz, 3- and 5-positions of aroyl) and 7.68 (3H, br s, NH_3).

In a separate experiment, pure **4d** was obtained by recrystallization of crude **4d** from benzene. mp 125 °C. *Anal.* Calcd for $C_{18}H_{19}ClN_4O_3$: C, 57.68; H, 5.11; N, 14.95. Found: C, 57.96; H, 5.12; N, 14.87. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.20 (3H, br t, J=6.5 Hz, CH_3CH_2), 3.36 (2H, br q, J=6.5 Hz, CH_3CH_2), 3.74 and 3.80 (each 2H, br s, CH_2CH_2), 6.68 (1H, br s, NH), 6.98 (2H, br d, J=8 Hz, 2″- and 6″-positions), 7.36 (2H, d, J=8 Hz, 2- and 6-positions or 3- and 5-positions of aroyl), 7.40 (2H, d, J=8 Hz, 2- and 6-positions or 3- and 5-positions of aroyl), 7.73 (1H, br s, 1-position) and 8.13 (2H, d, J=8 Hz, 3″- and 5″-positions).

1,4-*N*,*N*-Acyl Migration in 8b The perchlorate of **8b** (0.16 g, 0.5 mmol) was dissolved in 2 ml of anhydrous EtOH, and 2.5 ml of 1 N NaOEt was added to the solution. The whole was kept for 2 h at room temperature, then concentrated under reduced pressure. Ether was added to the residue and the mixture was filtered. The filtrate was concentrated under reduced pressure, and HCl–EtOH was added to the residue. The mixture was concentrated under reduced pressure, and the residue was recrystallized from benzene–EtOH to give 0.10 g (76%) of the hydrochloride of **8c**. mp 204 °C. *Anal.* Calcd for $C_{11}H_{16}Cl_2N_2O$: C, 50.20; H, 6.13; N, 10.64. Found: C, 50.07; H, 6.15; N, 10.69. Perchlorate of **8c**. mp 170 °C (MeOH). *Anal.* Calcd for $C_{11}H_{16}Cl_2N_2O_5$: C, 40.39; H, 4.93; N, 8.56. Found: C, 40.11; H, 5.03; N, 8.44. ^{1}H-NMR (DMSO-d_6, 70 °C, 400 MHz) δ: 1.21 (3H, t, J=7.5 Hz, CH_3CH_2), 3.03 (2H, br q, J=7.5 Hz, CH_3CH_2), 3.12 (2H, br t, J=5.5 Hz, CH_2CH_2NHCO), 3.56 (2H, dt, J=5, 5.5 Hz, CH_2CH_2NHCO), 7.55 (2H, d, J=9 Hz, 3- and 5-positions of aroyl), 7.87 (2H, d, J=9 Hz, 2- and 6-positions of aroyl), 8.26 (2H, br s, NH_2) and 8.53 (1H, br t, J=5 Hz, NHCO).

Acid Hydrolysis of Crude 4d in the Presence of AcOH The crude **4d**, which was obtained from 3.65 g (10 mmol) of **8a**, was dissolved in 60 ml of THF, and 50 ml of H_2O and 15 g of AcOH were added to the solution. The whole was allowed to stand overnight at room temperature, then concentrated under reduced pressure. Water was added to the residue, and the whole was concentrated under reduced pressure to remove AcOH. This procedure was repeated 4 times. Then 20 ml of 1 N HCl was added to the residue, and the precipitate was collected to give 1.28 g (77%) of *N*-formyl-*p*-nitroaniline. The aqueous layer was washed with ether, and concentrated under reduced pressure to dryness, and the residue was recrystallized from benzene–EtOH to give 1.26 g (48%) of the hydrochloride of **8c**.

References and Notes

1) M. Ono, K. Aoki, and S. Tamura, *Chem. Pharm. Bull.*, **38**, 1379 (1990).
2) M. Ono, R. Todoriki, I. Araya, and S. Tamura, *Chem. Pharm. Bull.*, **38**, 1373 (1990).
3) The starting materials were recovered unchanged when a dimethylformamide solution of N^1-tosyl-N^1,N^2-di(*p*-chlorophenyl)formamidine and the potassium salt of *N*-benzoyl-*p*-toluidine was heated at 90 °C for 2 h.
4) M. Ono and S. Tamura, *Chem. Pharm. Bull.*, **38**, 590 (1990).
5) Compound **1a** is rather unstable in THF solution in the presence of base. N^1-Acyl-N^1-aryl-N^2-(*p*-nitrophenyl)formamidines are also unstable under the same conditions while N^1-acyl-N^1-alkyl-N^2-(*p*-nitrophenyl)formamidines (**2**) remain unchanged for at least 1 d under the same conditions. Relatively low yields of N^1-acyl-N^1-aryl-N^2-(*p*-nitrophenyl)formamidines in the amide exchange reaction between *N*-acylarylamines and **1a** are probably due to the instability of the products under the experimental conditions.
6) Besides compound **1b**, N^1-(2,6-dichlorobenzoyl)-N^1,N^2-di(*p*-nitrophenyl)formamidine (**1c**), N^1-(2,5-dichlorobenzoyl)-N^1,N^2-di(*p*-nitrophenyl)formamidine (**1d**) and N^1-(*o*-nitrobenzoyl)-N^1,N^2-di(*p*-nitrophenyl)formamidine (**1e**) were tested as substrates for the amide exchange reaction. Compound **1e** could not be used owing to insufficient solubility in THF. Use of **1c** or **1d** in the amide exchange reaction gave no improvement in the yields of the products.
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