

Amidines. V. Smiles Rearrangement of N^1 -(p -Nitrobenzenesulfonyl)- N^1,N^2 -diarylacetamidines

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N^1 -Tosyl- N^1,N^2 -diarylacetamidine (1) suffered nucleophilic attack of N -tosylamines and N -acylamines at the amidine central carbon to give N^1 -tosyl and N^1 -acyl derivatives of N^1,N^2 -disubstituted acetamidine in the presence of a basic catalyst.

Preparation of N^1 -(p -nitrobenzenesulfonyl)- N^1,N^2 -diarylacetamidines (8) was attempted to obtain better starting materials for the above amide exchange reaction. These compounds, however, proved to be unsuitable for the purpose because they readily underwent Smiles rearrangement to give N^1 -(p -nitrophenyl)- N^1,N^2 -diarylacetamidines (9) with loss of sulfur dioxide.

N^1 -(p -Nitrophenyl)- N^1 -(p -methylphenyl)- N^2 -(p -chlorophenyl)acetamidine (9d) was formed when an ethanol solution of N^1 -(p -nitrobenzenesulfonyl)- N^1 -(p -chlorophenyl)- N^2 -(p -methylphenyl)acetamidine (8d) was refluxed for 2.5 h in the absence of any catalyst.

Keywords N -tosylacetamidine; N -acylacetamidine; N^1 -(p -nitrobenzenesulfonyl)- N^1,N^2 -diarylacetamidine; Smiles rearrangement; trisubstituted acetamidine; amide exchange reaction; alcoholysis; kinetic study

N^1 -Tosyl- N^1,N^2 -diarylacetamidines (1) react with arylamines to afford unsymmetrical N^1,N^2 -diarylacetamidines (2) and N -tosylarylamines under basic conditions.¹⁾ In this work, amide exchange reactions of N -tosylamine and N -acylamine with 1 were examined. These reactions can be expected to give unsymmetrical N^1 -tosylacetamidines (1) and N^1 -acylacetamidines (3) (Chart 1), respectively. It was found that the amide exchange reaction is dependent on the electronic character of the substituents on the aromatic rings.

Reaction of N^1 -Tosyl- N^1,N^2 -diarylacetamidines with N -Tosylamines and N -Acylamines When a dimethylformamide (DMF) solution of equimolar amounts of N^1 -tosyl- N^1,N^2 -di(p -chlorophenyl)acetamidine (1a) and the sodium salt of N -tosyl- p -toluidine was heated, N^1 -tosyl- N^1 -(p -methylphenyl)- N^2 -(p -chlorophenyl)acetamidine (1b) and N -tosyl- p -chloroaniline were formed (Chart 2). The starting materials were recovered when equimolar amounts of N^1 -tosyl- N^1,N^2 -di(p -methylphenyl)acetamidine (1c) and the sodium salt of N -tosyl- p -chloroaniline were treated under the same conditions. The results were not unexpected because of the poorer electrophilicity of the amidine central carbon of 1c than that of 1a, and the poorer leaving ability of the N -tosyl- p -methylphenylamino group than that of the N -tosyl- p -chlorophenylamino group of the tetrahedral intermediate. When 1c was treated with an equimolar amount of the sodium salt of N -tosyl- p -anisidine under the same conditions, about half of the starting material was converted into N^1 -tosyl- N^1 -(p -methoxyphenyl)- N^2 -(p -methylphenyl)acetamidine (1d) (Chart 2). The results showed that the electrophilicity of the central carbon of 1c is too weak to allow easy nucleophilic attack of sulfonamide anion.

There are three substituents (X, Y and Z, Chart 2) affecting the electrophilic character of the amidine central carbon, and X and Z would affect the leaving ability of the N -benzenesulfonylamino group. Willi²⁾ reported that the dissociation constants of N -(substituted benzenesulfonyl)-arylamines are related to the electronic properties of substituents on the benzenesulfonyl group by the Hammett reaction constant, ρ , of 1.14 and to those of substituents on the arylamino group by ρ^- of 1.74.

Compounds 1 were alcoholized in ethanol-tetrahydrofuran (THF) solution to give N -tosylamines and ethyl N -arylacetimidates in good yield in the presence of sodium ethoxide.³⁾ Alcoholysis of 1a, N^1 -(p -chlorobenzenesulfonyl)- N^1,N^2 -di(p -chlorophenyl)acetamidine (4) and N^1 -(m -nitrobenzenesulfonyl)- N^1,N^2 -di(p -chlorophenyl)acetamidine (5a) was examined kinetically to elucidate the electronic effect of the substituent Z on the electrophilic character of the amidine central carbon of N^1 -(substituted benzenesulfonyl)- N^1,N^2 -diarylacetamidines (Chart 3).

The ultraviolet (UV) spectra of 1a, N -tosyl- p -chloroaniline and ethyl N -(p -chlorophenyl)acetimidate in 0.1 N sodium ethoxide in ethanol (containing 1% THF) solution at 40 °C are shown in Fig. 1. Absorption by imide is always less than that by 1a at all wavelengths examined. In such circumstances, evaluation of the proportion of each component may be subject to substantial error. The proportion of each component calculated by the least-squares method with three variables was, however, consistent with that calculated by the same method using two variables, which were the proportions of 1a and of the sum of N -tosyl- p -chloroaniline and imide, on the assumption that equimolar amounts of the latter two were formed

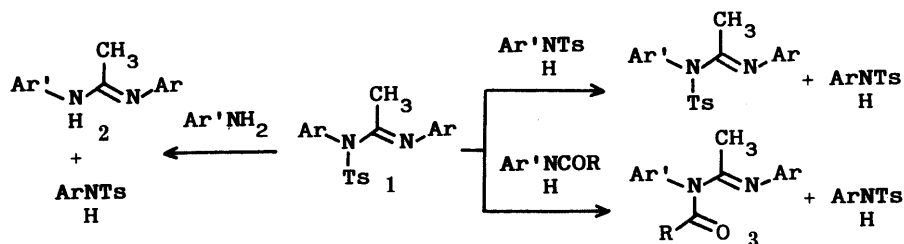
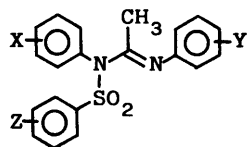
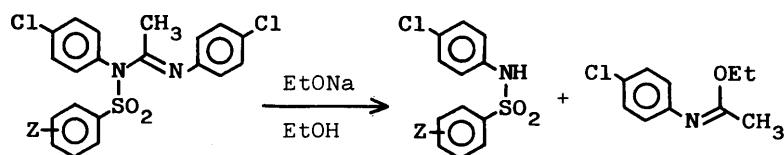
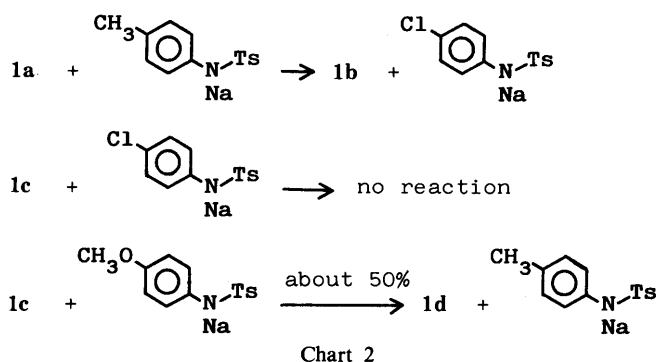


Chart 1

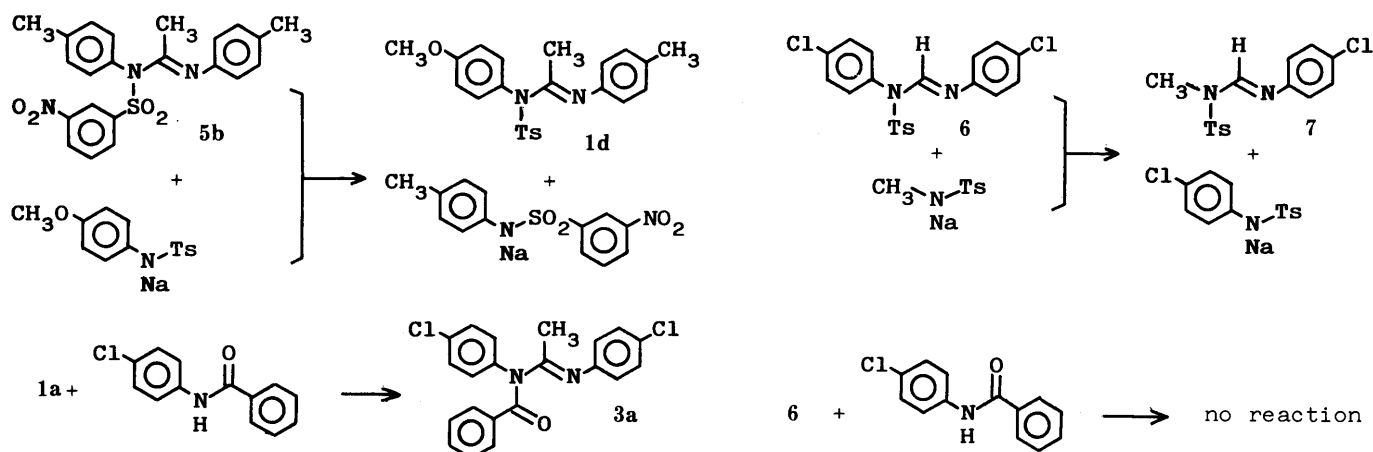
in the reaction solution. The rate constants (s^{-1} , at $40^\circ C$) obtained were as follows (standard deviations are shown in parentheses): **1a**, $1.28(0.040) \times 10^{-5}$; **4**, $5.32(0.144) \times 10^{-5}$; **5a**, $2.66(0.205) \times 10^{-4}$. The results showed that the electronic effect of the substituent Z has a greater influence upon the rate of alcoholysis of N^1 -(substituted benzene-



	X	Y	Z		X	Y	Z
1a	<i>p</i> -Cl	<i>p</i> -Cl	<i>p</i> -CH ₃	5a	<i>p</i> -Cl	<i>p</i> -Cl	<i>m</i> -NO ₂
1b	<i>p</i> -CH ₃	<i>p</i> -Cl	<i>p</i> -CH ₃	5b	<i>p</i> -CH ₃	<i>p</i> -CH ₃	<i>m</i> -NO ₂
1c	<i>p</i> -CH ₃	<i>p</i> -CH ₃	<i>p</i> -CH ₃	8a	<i>p</i> -CH ₃	<i>p</i> -CH ₃	<i>p</i> -NO ₂
1d	<i>p</i> -CH ₃ O	<i>p</i> -CH ₃	<i>p</i> -CH ₃	8b	<i>p</i> -Cl	<i>p</i> -Cl	<i>p</i> -NO ₂
4	<i>p</i> -Cl	<i>p</i> -Cl	<i>p</i> -Cl	8c	<i>p</i> -CH ₃	<i>p</i> -Cl	<i>p</i> -NO ₂
				8d	<i>p</i> -Cl	<i>p</i> -CH ₃	<i>p</i> -NO ₂



Z: 1a: *p*-CH₃; 4: *p*-Cl; 5a: *m*-NO₂



sulfonyl)- N^1,N^2 -diarylacetimides than the acidity of the corresponding sulfonamide. Introduction of electron-withdrawing Z would be expected to promote the amide exchange reaction on the amidine central carbon. Thus, compound **1d** was obtained in good yield when N^1 -(*m*-nitrobenzenesulfonyl)- N^1,N^2 -di(*p*-methylphenyl)acetamidine (**5b**) was heated with the sodium salt of *N*-tosyl-*p*-anisidine in dimethyl sulfoxide (DMSO) solution (Chart 3).

N^1 -Tosyl- N^1,N^2 -di(*p*-chlorophenyl)formamidine (**6**) did not react with *N*-tosyl-*p*-toluidine, showing that *N*-tosyl derivatives of diarylformamidines are less sensitive to the nucleophilic attack of amide anion than those of diarylacetimides. The only instance of this reaction of **6** was that of

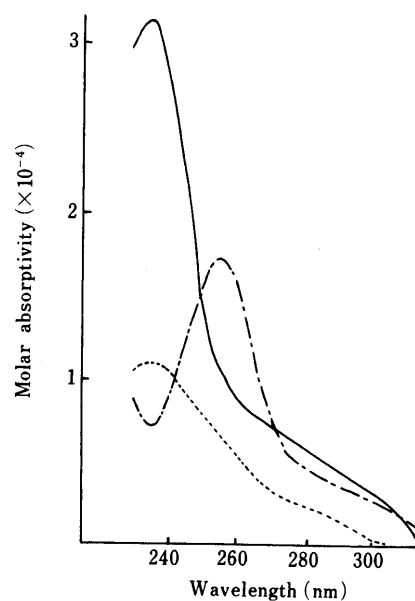


Fig. 1. UV Spectra of **1a** (—), *N*-Tosyl-*p*-chloroaniline (---) and Ethyl *N*-(*p*-Chlorophenyl)acetimidate (.....) in EtOH (Containing 1% THF) in the Presence of 0.1 N NaOEt at $40^\circ C$

6 and the sodium salt of *N*-tosylmethylamine, which gave *N*¹-tosyl-*N*¹-methyl-*N*²-(*p*-chlorophenyl)formamidine (**7**) in 62% yield (Chart 3).

N-Benzoyl-*p*-chloroaniline did not react with **6** at room temperature even in the presence of potassium *tert*-butoxide, while it reacted with **1a** to give *N*¹-benzoyl-*N*¹,*N*²-di(*p*-chlorophenyl)acetamidine (**3a**) under the same conditions (Chart 3). Reaction of *N*-benzoyl-*p*-toluidine and **1c** proceeded only to a small extent under the same conditions. The ¹H nuclear magnetic resonance (¹H-NMR) spectrum of the sodium hydroxide-insoluble part of the crude product showed that the mixture consisted of *N*¹-benzoyl-*N*¹,*N*²-di(*p*-methylphenyl)acetamidine (**3b**) and both starting materials. The reaction of *N*-benzoyl-*p*-toluidine and **5b** was also not completed on standing for 5 d in DMSO solution in the presence of 1.5 eq of potassium *tert*-butoxide.

Smiles Rearrangement of *N*¹-(*p*-Nitrobenzenesulfonyl)-*N*¹,*N*²-diarylacetamidines Preparation of *N*¹-(*p*-nitrobenzenesulfonyl)-*N*¹,*N*²-diarylacetamidines (**8**) was attempted to seek more electrophilic substrates which were expected to be more susceptible to the attack of amide anion. Compounds **8**, however, proved to be unsuitable for the purpose because of their predisposition to undergo Smiles rearrangement.

*N*¹-(*p*-Nitrobenzenesulfonyl)-*N*¹,*N*²-di(*p*-methylphenyl)acetamidine (**8a**) was obtained as crystals melting at 157 °C when *N*¹,*N*²-di(*p*-methylphenyl)acetamidine (**2a**) and *p*-nitrobenzenesulfonyl chloride were kept in dichloromethane solution for 1 d at room temperature in the presence of triethylamine, and petroleum benzin was added to a dichloromethane solution of the crude product. However, recrystallization of **8a** from ethanol gave crystals (**9a**) melting at 126 °C. The results of elemental analysis of **9a** were consistent with the values required for the molecular formula of C₂₂H₂₁N₃O₂. When a 50% aqueous ethanol solution of **9a** was refluxed for 12.5 h in the presence of hydrochloric acid, *N*-(*p*-nitrophenyl)-*p*-toluidine (44%) and small amounts of *N*-acetyl-*N*-(*p*-nitrophenyl)-*p*-toluidine and *p*-toluidine (56%) were obtained together with the starting material (9%). This determined the structure of **9a** to be *N*¹-(*p*-nitrophenyl)-*N*¹,*N*²-di(*p*-methylphenyl)acetamidine (Chart 4).

In a typical Smiles rearrangement, *o*-hydroxydiphenyl sulfone gives phenoxybenzenesulfonic acid. An instance of loss of sulfur dioxide during the reaction was reported by Backer and Moed,⁴⁾ i.e., *p*-nitrophenylguanidine was form-

ed on heating of *p*-nitrobenzenesulfonylguanidine in the presence of sodium hydroxide.

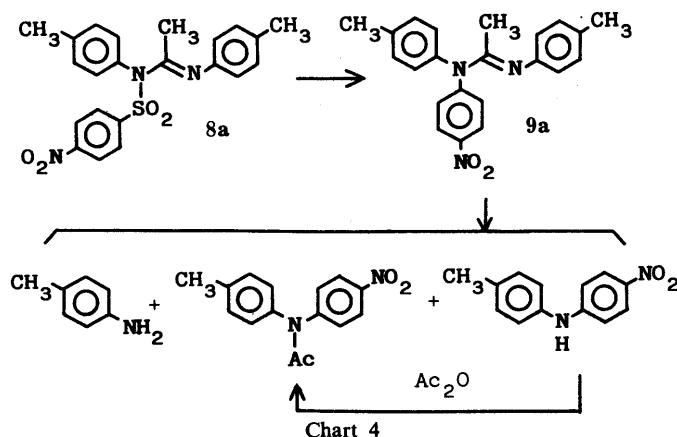
Smiles rearrangement of **8a** proceeded slowly in benzene solution. The reaction proceeded to the extent of 58% upon refluxing of a benzene solution of **8a** for 2.5 h, on the basis of ¹H-NMR evidence, while the reaction was completed in 2.5 h upon refluxing an ethanol solution of **8a**. The results imply that the reaction can be rationalized in terms of a mechanism according to which the dipolar character of the substrate is enhanced on going from the reactant to the transition state.

*N*¹-(*p*-Nitrophenyl)-*N*¹,*N*²-di(*p*-chlorophenyl)acetamidine (**9b**) was obtained from *N*¹-(*p*-nitrobenzenesulfonyl)-*N*¹,*N*²-di(*p*-chlorophenyl)acetamidine (**8b**) in a similar manner. The completion of the reaction required refluxing of an ethanol solution of **8b** for 23 h.

For the elucidation of the reaction mechanism, *N*¹-(*p*-nitrobenzenesulfonyl) derivatives of unsymmetrical acetamidines were prepared. *N*¹-(*p*-Nitrobenzenesulfonyl)-*N*¹-(*p*-methylphenyl)-*N*²-(*p*-chlorophenyl)acetamidine (**8c**, mp 191 °C) and *N*¹-(*p*-nitrobenzenesulfonyl)-*N*¹-(*p*-chlorophenyl)-*N*²-(*p*-methylphenyl)acetamidine (**8d**, mp 173 °C) were isolated by preparative thin layer chromatography (PTLC) of the crude product which was obtained from the reaction of *N*¹-(*p*-methylphenyl)-*N*²-(*p*-chlorophenyl)acetamidine (**2b**) and *p*-nitrobenzenesulfonyl chloride in pyridine solution. The structures of **8c** and **8d** were ascertained by ¹H-NMR analysis (Chart 5). In Chart 5, the chemical shift of each signal is given in δ (ppm). The assignment of each signal was confirmed by nuclear Overhauser effect (NOE) and internuclear double resonance (INDOR) techniques, and each proposed structure is consistent with the fact that the signals of *o*-positions of an *N*²-aryl group are observed at high applied magnetic field.¹⁾

Beckmann rearrangement⁵⁾ of *p*-chloroacetophenoxime tosylate in the presence of the sodium salt of *N*-(*p*-nitrobenzenesulfonyl)-*p*-toluidine gave **8c** in good yield. The reaction was carried out by refluxing THF solution of both substrates for 30 min. Compound **8d** was also prepared from *p*-methylacetophenoxime, tosyl chloride and the sodium salt of *N*-(*p*-nitrobenzenesulfonyl)-*p*-chloroaniline. Smiles rearrangement of **8c** and **8d** did not take place under these conditions (Chart 5). *N*¹-(*p*-Nitrophenyl)-*N*¹-(*p*-chlorophenyl)-*N*²-(*p*-methylphenyl)acetamidine (**9c**) was obtained when an ethanol solution of **8c** was refluxed for 17 h, showing that the *p*-nitrophenyl group migrated to the *N*² atom of **8c**. The structure of **9c** was confirmed by acid hydrolysis, which gave *N*-(*p*-nitrophenyl)-*p*-chloroaniline, *N*-acetyl-*N*-(*p*-nitrophenyl)-*p*-chloroaniline and *p*-toluidine (Chart 5). Minkin *et al.*⁶⁾ reported 1,3-*N,N*-sigmatropic rearrangement of *N*¹-(2,4-dinitrophenyl)-*N*¹,*N*²-diarylbenzamidines and *N*¹-picryl-*N*¹,*N*²-diarylbenzamidines in chlorobenzene solution. Compound **9c** showed no change under reflux for 2 h in chlorobenzene solution, showing that the further 1,3-*N,N*-migration of the *p*-nitrophenyl group did not take place under these conditions. Similarly, *N*¹-(*p*-nitrophenyl)-*N*¹-(*p*-methylphenyl)-*N*²-(*p*-chlorophenyl)acetamidine (**9d**) was obtained when an ethanol solution of **8d** was refluxed for 2.5 h. The structure of **9d** was also confirmed by acid hydrolysis (Chart 5).

The reaction was accelerated by electron-withdrawing substituents on the *N*¹-aryl group and electron-releasing



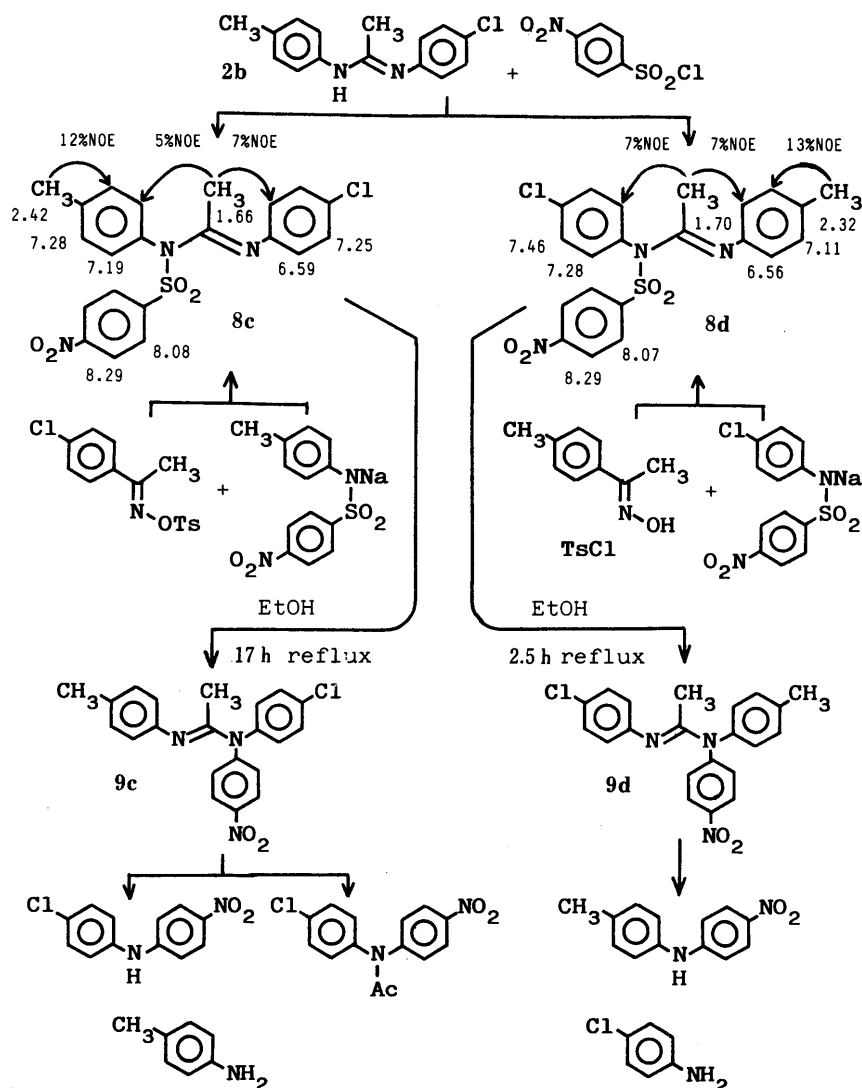


Chart 5

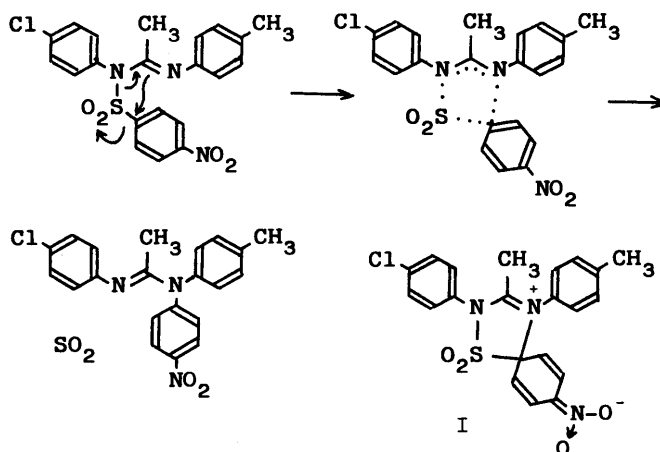


Chart 6

substituents on the *N*²-aryl group of 8. The reaction mechanism is probably similar to that of a typical Smiles rearrangement as shown in Chart 6. There is also the possibility that the reaction proceeds through a Meisenheimer type intermediate (I, Chart 6). The mechanism is consistent with the fact that the dipolar character of the substrate is enhanced on going from the reactant to the transition state.

Experimental

All melting points are uncorrected. ¹H-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: s (singlet), d (doublet), t (triplet), ddd (double double doublet). UV spectra were measured on a Hitachi spectrophotometer (model 139). *N*¹,*N*²-Di(*p*-chlorophenyl)acetamidine, *N*¹,*N*²-di(*p*-methylphenyl)acetamidine and *N*¹-tosyl-*N*²-di(*p*-methylphenyl)acetamidine were prepared according to a previous paper.⁷⁾ The samples of 1b,³⁾ 3a,⁷⁾ *N*-tosylarylamines, *N*-acylarylamines and arylamines described in this section were identical with the corresponding authentic samples on the basis of comparison of their infrared (IR) spectra or mixed melting point measurement.

Reaction of 1a and the Sodium Salt of *N*-Tosyl-*p*-toluidine A DMF solution (30 ml) of 1a (1.08 g, 2.5 mmol) and the sodium salt of *N*-tosyl-*p*-toluidine (0.71 g, 2.5 mmol) was heated at 100 °C for 15 h. The mixture was concentrated under reduced pressure. The ether-insoluble part of the residue was dissolved in CHCl₃, and the CHCl₃ layer was extracted successively with 2*N* NaOH and water. The ether solution was also extracted with H₂O, and *N*-tosyl-*p*-chloroaniline (0.33 g, 47%) was obtained from the combined NaOH and H₂O layer after recrystallization from petroleum benzine. The CHCl₃ layer was concentrated under reduced pressure, and the residue was recrystallized from EtOH to give 0.51 g (54%) of 1b.

Preparation of 4 *N*¹,*N*²-Di(*p*-chlorophenyl)acetamidine (2.79 g, 0.01 mol) and *p*-chlorobenzenesulfonyl chloride (2.11 g, 0.01 mol) were dissolved in 10 ml of anhydrous pyridine. The mixture was allowed to stand for 1 d at room temperature. The precipitate was collected, washed with H₂O, dried and recrystallized from AcOEt to give 2.80 g (62%) of 4. mp 200 °C. Anal. Calcd for C₂₀H₁₅Cl₃N₂O₂S: C, 52.94; H, 3.33; N, 6.17.

Found: C, 52.95; H, 3.47; N, 6.18. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.66 (3H, s, 2-position), 6.60 (2H, d, $J=9$ Hz, 2'- and 6''-positions), 7.25 (2H, d, $J=9$ Hz, 2'- and 6''-positions), 7.26 (2H, d, $J=9$ Hz, 3'- and 5''-positions), 7.44 (4H, d, $J=9$ Hz, 3'-, 5'- and 3'''-, 5'''-positions) and 7.83 (2H, d, $J=9$ Hz, 2'''- and 6'''-positions).

Preparation of 5b N^1,N^2 -Di(*p*-methylphenyl)acetamide (9.52 g, 0.04 mol), *m*-nitrobenzenesulfonyl chloride (13.29 g, 0.06 mol) and Et_3N (8.08 g, 0.08 mol) were dissolved in 60 ml of benzene. The mixture was allowed to stand for 1 d at room temperature. The mixture was washed successively with H_2O , 7% NaHCO_3 and H_2O , dried over Na_2SO_4 , and concentrated under reduced pressure. The viscous oil obtained was crystallized by successive addition of ether and petroleum benzin. The crystals were collected and recrystallized from EtOH to give 15.43 g (91%) of **5b**. mp 138 °C. *Anal.* Calcd for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_4\text{S}$: C, 62.40; H, 5.00; N, 9.92. Found: C, 62.10; H, 5.15; N, 9.64. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.68 (3H, s, 2-position), 2.30 and 2.43 (each 3H, s, aryl CH_3), 6.55 (2H, d, $J=8$ Hz, 2''- and 6''-positions), 7.08 (2H, d, $J=8$ Hz, 3''- and 5''-positions), 7.20 (2H, d, $J=9$ Hz, 3'- and 5'-positions), 7.27 (2H, d, $J=9$ Hz, 2'- and 6'-positions), 7.65 (1H, t, $J=8$ Hz, 5'''-position), 8.30 (1H, ddd, $J=1, 2, 8$ Hz, 6'''-position), 8.42 (1H, ddd, $J=1, 2, 8$ Hz, 4'''-position) and 8.76 (1H, t, $J=2$ Hz, 2'''-position).

Preparation of 5a N^1,N^2 -Di(*p*-chlorophenyl)acetamide (11.16 g, 0.04 mol) and *m*-nitrobenzenesulfonyl chloride (8.86 g, 0.06 mol) were dissolved in 12 ml of pyridine. The mixture was allowed to stand for 2 d at room temperature. The precipitate was collected, and washed successively with a small amount of pyridine and H_2O , and recrystallized from EtOH to give 7.81 g (42%) of **5a**. *m*-Nitrobenzenesulfonyl chloride (2.0 g) was added to the pyridine mother liquor, and the mixture was allowed to stand for 1 d. Work-up of the mixture gave additional **5a** (3.81 g, 20%). mp 174 °C. *Anal.* Calcd for $\text{C}_{20}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_4\text{S}$: C, 51.73; H, 3.26; N, 9.05. Found: C, 51.58; H, 3.43; N, 8.97. $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 1.70 (3H, s, 2-position), 6.57 (2H, d, $J=9$ Hz, 2'- and 6''-positions), 7.23 (4H, d, $J=9$ Hz, 3'-, 5'- and 3'''-, 5'''-positions), 7.43 (2H, d, $J=9$ Hz, 2'- and 6'-positions), 7.63 (1H, t, $J=8$ Hz, 5'''-position), 8.20 and 8.43 (each 1H, ddd, $J=1, 2, 8$ Hz, 4'''- and 6'''-positions) and 8.73 (1H, t, $J=2$ Hz, 2'''-position).

Reaction of 5b and the Sodium Salt of *N*-Tosyl-*p*-anisidine Compound **5b** (0.42 g, 1 mmol) and the sodium salt of *N*-tosyl-*p*-anisidine (0.90 g, 3 mmol) were dissolved in 5 ml of DMSO. The mixture was heated at 90 °C in an oil bath for 4 h. The mixture was concentrated under reduced pressure. The residue was dissolved in CHCl_3 and the solution was washed with 20 ml of 2N NaOH. The CHCl_3 layer was concentrated under reduced pressure, and the residue was washed with a small amount of ether, and recrystallized from EtOH to give 0.27 g (66%) of **1d**. mp 129 °C. *Anal.* Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$: C, 67.62; H, 5.92; N, 6.86. Found: C, 67.48; H, 5.93; N, 6.90. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 1.64 (3H, s, 2-position), 2.30 (3H, s, CH_3), 3.85 (3H, s, CH_3O), 6.55 (2H, d, $J=8$ Hz, 2''- and 6''-positions), 6.93 (2H, d, $J=9$ Hz, 3'- and 5'-positions), 7.07 (2H, d, $J=8$ Hz, 3''- and 5''-positions), 7.23 (2H, d, $J=9$ Hz, 2'- and 6'-positions), 7.24 (2H, d, $J=9$ Hz, 3'''- and 5'''-positions) and 7.82 (2H, d, $J=9$ Hz, 2'''- and 6'''-positions).

Reaction of 6 and *N*-Tosylmethylamine Compound **6** (0.42 g, 1 mmol) and the sodium salt of *N*-tosylmethylamine (0.41 g, 2 mmol) were dissolved in 10 ml of DMF. The mixture was heated at 90 °C for 2 h. The mixture was concentrated under reduced pressure. The residue was dissolved in CHCl_3 , and the solution was washed successively with two portions of 5 ml of 2N NaOH and H_2O , dried over MgSO_4 , and concentrated under reduced pressure. Recrystallization of the residue from petroleum benzin gave 0.20 g (62%) of **7**. mp 107 °C. *Anal.* Calcd for $\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}$: C, 55.81; H, 4.68; N, 8.68. Found: C, 56.08; H, 4.65; N, 8.76. $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 2.43 (3H, s, tosyl CH_3), 3.15 (3H, s, N-CH_3), 6.92 (2H, d, $J=9$ Hz, 2''- and 6''-positions), 7.25 (2H, d, $J=9$ Hz, 3''- and 5''-positions), 7.33 (2H, d, $J=9$ Hz, 3'''- and 5'''-positions), 7.70 (2H, d, $J=9$ Hz, 2'''- and 6'''-positions) and 8.42 (1H, s, 1-position).

Reaction of 1a and *N*-Benzoyl-*p*-chloroaniline A mixture of *tert*-BuOK (0.27 g, 2.4 mmol), *N*-benzoyl-*p*-chloroaniline (0.46 g, 2 mmol) and 25 ml of anhydrous THF was stirred for 15 min at room temperature under N_2 . A solution of **1a** (0.95 g, 2.2 mmol) in 30 ml of anhydrous THF was added to the mixture, and the whole was allowed to stand for 17 h at room temperature. The mixture was saturated with CO_2 , and concentrated under reduced pressure. Ether and H_2O were added to the residue, and the ether layer was extracted with 1N NaOH. The NaOH layer was treated as usual to give 0.44 g (78%) of *N*-tosyl-*p*-chloroaniline. The ether layer was dried over Na_2SO_4 , and concentrated under reduced pressure. Fractional recrystallization of the residue gave recovered *N*-benzoyl-*p*-

chloroaniline (0.07 g, 15%) as a first deposit and **3a** (0.45 g, 59%) as a second deposit.

Preparation of 8a N^1,N^2 -Di(*p*-methylphenyl)acetamide (2.38 g, 10 mmol) and Et_3N (1.50 g, 15 mmol) were dissolved in 10 ml of CH_2Cl_2 . A solution of *p*-nitrobenzenesulfonyl chloride (2.66 g, 12 mmol) in 10 ml of CH_2Cl_2 was added to the mixture under ice-cooling. The whole was allowed to stand for 1 d at room temperature, and then water was added. The CH_2Cl_2 layer was washed with 2N NaOH, dried over K_2CO_3 , and concentrated under reduced pressure at below 40 °C. Then CH_2Cl_2 (11 ml) was added to the residue, and the mixture was filtered. Petroleum benzin was added to the filtrate and the precipitate was collected to give 2.74 g (65%) of **8a**. mp 157 °C (dec.). *Anal.* Calcd for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_4\text{S}$: C, 62.40; H, 5.00; N, 9.92. Found: C, 62.54; H, 4.99; N, 10.02. $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 1.65 (3H, s, 2-position), 2.28 and 2.38 (each 3H, s, aryl CH_3), 6.53 (2H, d, $J=8$ Hz, 2''- and 6''-positions), 7.08 (2H, d, $J=8$ Hz, 3''- and 5''-positions), 7.22 (4H, s, 2'-, 6'- and 3'-, 5'-positions), 8.03 (2H, d, $J=9$ Hz, 2'''- and 6'''-positions) and 8.23 (2H, d, $J=9$ Hz, 3'''- and 5'''-positions).

Preparation of N^1 -(*p*-Nitrobenzenesulfonyl)- N^1,N^2 -di(*p*-chlorophenyl)-acetamide (8b) N^1,N^2 -Di(*p*-chlorophenyl)acetamide (2.79 g, 10 mmol) was dissolved in 10 ml of anhydrous pyridine. *p*-Nitrobenzenesulfonyl chloride (2.66 g, 12 mmol) was added in portions, and the mixture was allowed to stand for 2 d at room temperature. The precipitate was collected, washed with H_2O , and dissolved in CH_2Cl_2 . The solution was dried over Na_2SO_4 , and concentrated under reduced pressure to a point at which a crystalline mass began to deposit. The crystals were collected to give 4.08 g (88%) of **8b**. mp 193.5 °C (dec.). *Anal.* Calcd for $\text{C}_{20}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_7$: C, 51.73; H, 3.26; N, 9.05. Found: C, 51.88; H, 3.30; N, 9.11. $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 1.68 (3H, s, 2-position), 6.52 (2H, d, $J=8$ Hz, 2''- and 6''-positions), 7.20 (2H, d, $J=8$ Hz, 3''- and 5''-positions), 7.22 (2H, d, $J=9$ Hz, 2'- and 6'-positions), 7.42 (2H, d, $J=9$ Hz, 3'- and 5'-positions), 8.03 (2H, d, $J=9$ Hz, 2'''- and 6'''-positions) and 8.23 (2H, d, $J=9$ Hz, 3'''- and 5'''-positions).

Smiles Rearrangement of 8a and 8b A mixture of **8a** (0.85 g, 2 mmol) and 100 ml of anhydrous EtOH was refluxed for 2.5 h, and concentrated under reduced pressure. The residue was recrystallized from EtOH to give 0.47 g (66%) of **9a**. mp 126.5 °C. *Anal.* Calcd for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_5$: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.47; H, 5.96; N, 11.72. $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 1.83 (3H, s, 2-position), 2.25 and 2.33 (each 3H, s, aryl CH_3), 6.67 (2H, d, $J=8$ Hz, 2- and 6-positions of N^2 -aryl), 7.02 (2H, d, $J=8$ Hz, 3- and 5-positions of N^2 -aryl), 7.15 (4H, s, 2-, 6- and 3-, 5-positions of N^1 - $\text{CH}_3\text{C}_6\text{H}_4$), 7.32 (2H, d, $J=9$ Hz, 2- and 6-positions of N^1 - $\text{O}_2\text{NC}_6\text{H}_4$) and 8.02 (2H, d, $J=9$ Hz, 3- and 5-positions of N^1 - $\text{O}_2\text{NC}_6\text{H}_4$).

A mixture of **8b** (0.93 g, 2 mmol) and 100 ml of anhydrous EtOH was refluxed for 23 h, and concentrated under reduced pressure. The residue was recrystallized from EtOH to give 0.40 g (59%) of **9b**. mp 173 °C. *Anal.* Calcd for $\text{C}_{20}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_5$: C, 60.02; H, 3.78; N, 10.50. Found: C, 60.09; H, 3.79; N, 10.52. $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 1.88 (3H, s, 2-position), 6.55 (2H, d, $J=9$ Hz, 2- and 6-positions of N^2 -aryl), 7.22 (2H, d, $J=9$ Hz, 2- and 6-positions of N^1 - $\text{CH}_3\text{C}_6\text{H}_4$), 7.27 (2H, d, $J=9$ Hz, 3- and 5-positions of N^2 -aryl), 7.32 (2H, d, $J=9$ Hz, 2- and 6-positions of N^1 - $\text{O}_2\text{NC}_6\text{H}_4$), 7.40 (2H, d, $J=9$ Hz, 3- and 5-positions of N^1 - $\text{CH}_3\text{C}_6\text{H}_4$) and 8.17 (2H, d, $J=9$ Hz, 3- and 5-positions of N^1 - $\text{O}_2\text{NC}_6\text{H}_4$).

Acid Hydrolysis of 9a and N^1 -(*p*-Nitrophenyl)- N^1,N^2 -di(*p*-chlorophenyl)acetamide (9b) Compound **9a** (0.36 g, 1 mmol) was dissolved in 3 ml of EtOH, and 2 ml of 2N HCl was added to the solution. The mixture was refluxed for 12.5 h. The precipitate was collected to give crude *N*-(*p*-nitrophenyl)-*p*-toluidine. The mother liquor was concentrated under reduced pressure, and ether and 2N HCl were added to the residue. The HCl layer was treated as usual to give *p*-toluidine (0.06 g, 56%) and recovered **9a** (0.06 g, 9%). The ether layer was subjected to PTLC (silica gel with benzene: AcOEt = 50:1) to give crude *N*-acetyl-*N*-(*p*-nitrophenyl)-*p*-toluidine and *N*-(*p*-nitrophenyl)-*p*-toluidine. The former was recrystallized from petroleum benzin to give 0.01 g (4%) of pure sample. mp 126 °C. The combined *N*-(*p*-nitrophenyl)-*p*-toluidine was recrystallized from EtOH to give 0.10 g (44%) of pure sample. mp 139 °C (lit.⁸) mp 138 °C. An authentic sample of *N*-(*p*-nitrophenyl)-*p*-toluidine was prepared according to Fauss *et al.*⁹ and was identical with the sample obtained by hydrolysis of **9a** on the basis of mixed melting point measurement and comparison of their IR spectra. An authentic sample of *N*-acetyl-*N*-(*p*-nitrophenyl)-*p*-toluidine was prepared by the reaction of *N*-(*p*-nitrophenyl)-*p*-toluidine and Ac_2O in pyridine solution in the presence of 4-dimethylaminopyridine. It gave mp 116 °C (lit.¹⁰) mp 117 °C, and was identical with the sample obtained by hydrolysis of **9a** on the basis of mixed melting point measurement and comparison of their IR spectra.

Hydrolysis of **9b** (0.40 g, 1 mmol) was carried out in the same manner as that of **9a** to give 0.08 g (63%) of *p*-chloroaniline and 0.16 g (65%) of *N*-(*p*-nitrophenyl)-*p*-chloroaniline. mp 180 °C (lit.¹¹) mp 186–186.5 °C. An authentic sample of *N*-(*p*-nitrophenyl)-*p*-chloroaniline was prepared according to Fauss *et al.*,⁹ and was identical with the sample obtained by hydrolysis of **9b** on the basis of mixed melting point measurement and comparison of their IR spectra.

Preparation of 2b *N*¹-Tosyl-*N*¹,*N*²-di(*p*-methylphenyl)acetamidine (7.84 g, 0.02 mol) and *p*-chloroaniline (2.17 g, 0.017 mol) were dissolved in 120 ml of anhydrous THF. Then 20 ml of hexane solution (1.6 M) of *n*-BuLi was added under N₂. The mixture was kept for 30 min at room temperature, and saturated with CO₂. A small amount of H₂O was added to the mixture, and the whole was concentrated under reduced pressure. Ether was added to the residue, and the ether layer was extracted with 1 N NaOH. The NaOH layer was treated as usual to give 2.78 g (53%) of *N*-tosyl-*p*-toluidine. Forty milliliters of 1 N HCl was added to the ether layer with stirring under ice-cooling. The precipitate (the HCl salt of **2b**) was collected and treated as usual to give 2.18 g (50%) of **2b**. mp 103 °C. *Anal.* Calcd for C₁₅H₁₅ClN₂: C, 69.80; H, 5.89; N, 10.65. Found: C, 69.63; H, 5.84; N, 10.83. ¹H-NMR (CDCl₃, 60 MHz) δ: 1.93 (3H, s, 2-position), 2.30 (3H, s, aryl CH₃), 6.98 (2H, d, *J* = 9 Hz, 2'- and 6'-positions), 7.08 (4H, s, 2', 6'- and 3'-, 5'-positions) and 7.22 (2H, d, *J* = 9 Hz, 3'- and 5'-positions).

Reaction of 2b and *p*-Nitrobenzenesulfonyl Chloride Compound **2b** (1.52 g, 6 mmol) was dissolved in 1.5 ml of anhydrous pyridine, and *p*-nitrobenzenesulfonyl chloride (1.59 g, 7.2 mmol) was added to the solution. The whole was allowed to stand for 2 d at room temperature. Water was added to the mixture, and the resultant precipitate was collected, washed with a small amount of ether, and dissolved in CH₂Cl₂. The solution was washed with 10 ml of 1 N NaOH, dried over K₂CO₃, and concentrated under reduced pressure at below 40 °C. The residue (1.62 g) was proved to be a mixture of **8c** and **8d** (1 : 1) on the basis of ¹H-NMR evidence. A part of the sample (0.05 g) was subjected to PTLC (silica gel with benzene : AcOEt = 50 : 1) to give small amounts of **8c** and **8d**. **8c**, mp 191 °C (dec.). *Anal.* Calcd for C₂₁H₁₈ClN₃O₄: C, 56.82; H, 4.09; N, 9.47. Found: C, 56.95; H, 4.09; N, 9.47. ¹H-NMR (CDCl₃, 400 MHz) is shown in Chart 5. **8d**, mp 173 °C (dec.). *Anal.* Calcd for C₂₁H₁₈ClN₃O₄: C, 56.82; H, 4.09; N, 9.47. Found: C, 56.79; H, 4.12; N, 9.42. ¹H-NMR (CDCl₃, 400 MHz) is shown in Chart 5.

Preparation of 8c by Beckmann Rearrangement of *p*-Chloroacetophenoxime Tosylate in the Presence of the Sodium Salt of *N*-(*p*-Nitrobenzenesulfonyl)-*p*-toluidine A mixture of *p*-chloroacetophenoxime tosylate (1.62 g, 5 mmol), the sodium salt of *N*-(*p*-nitrobenzenesulfonyl)-*p*-toluidine (1.62 g, 5 mmol), a small amount of anhydrous K₂CO₃ and 20 ml of anhydrous dioxane was refluxed for 30 min. The mixture was filtered hot, and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂, and the solution was washed with 1 N NaOH, dried over K₂CO₃, and concentrated under reduced pressure at below 40 °C. The residue was dissolved in a small amount of CH₂Cl₂ and petroleum ether was added to the solution. The precipitate was collected to give 1.30 g (59%) of **8c**, which was identical with the sample obtained by the reaction of **2b** and *p*-nitrobenzenesulfonyl chloride on the basis of comparison of their IR spectra.

Preparation of 8d by Beckmann Rearrangement of *p*-Methylacetophenoxime Tosylate in the Presence of the Sodium Salt of *N*-(*p*-Nitrobenzenesulfonyl)-*p*-chloroaniline A solution of *p*-methylacetophenoxime (0.75 g, 5 mmol), tosyl chloride (0.95 g, 5 mmol), and Et₃N (0.61 g, 6 mmol) in 6 ml of anhydrous THF was allowed to stand in an ice-box for 1 d, and filtered. The filtrate was added to a mixture of the sodium salt of *N*-(*p*-nitrobenzenesulfonyl)-*p*-chloroaniline (1.67 g, 5 mmol) and 40 ml of anhydrous THF under stirring. The mixture was refluxed for 1 h, then filtered hot, and the filtrate was concentrated under reduced pressure. The residue was dissolved in CHCl₃, and the solution was washed with 1 N NaOH, dried over K₂CO₃, and concentrated under reduced pressure. The residue was dissolved in a small amount of CH₂Cl₂, and petroleum ether was added to the solution. The precipitate was collected to give 1.10 g (50%) of **8d**, which was identical with a sample obtained by the reaction of **2b** and *p*-nitrobenzenesulfonyl chloride on the basis of comparison of their IR spectra.

Smiles Rearrangement of 8d A solution of **8d** (0.89 g, 2 mmol) in 100 ml of EtOH was refluxed for 2.5 h. The mixture was concentrated under reduced pressure, and the residue was recrystallized from EtOH to give 0.69 g (91%) of **9d**. mp 133 °C. *Anal.* Calcd for C₂₁H₁₈ClN₃O₂: C, 66.40; H, 4.78; N, 11.06. Found: C, 66.22; H, 4.81; N, 10.94. ¹H-NMR (CDCl₃, 400 MHz) δ: 1.85 (3H, s, 2-position), 2.40 (3H, s, aryl CH₃), 6.74 (2H, d,

J = 9 Hz, 2- and 6-positions of N²-aryl), 7.13 (2H, d, *J* = 9 Hz, 2- and 6-positions of CH₃C₆H₄), 7.25 (2H, d, *J* = 9 Hz, 3- and 5-positions of N²-aryl), 7.26 (2H, d, *J* = 9 Hz, 3- and 5-positions of CH₃C₆H₄), 7.37 (2H, d, *J* = 9 Hz, 2- and 6-positions of O₂NC₆H₄) and 8.12 (2H, d, *J* = 9 Hz, 3- and 5-positions of O₂NC₆H₄). These assignments were confirmed by NOE and INDOR techniques. Hydrolysis of **9d** was achieved as follows: 2 ml of 2 N HCl was added to a solution of **9d** (0.38 g, 1 mmol) in 3 ml of EtOH, and the mixture was refluxed for 12.5 h. Work-up of the reaction mixture in the same manner as in the case of hydrolysis of **9a** gave 0.05 g (39%) of *p*-chloroaniline, a trace of **9d** and 0.05 g (22%) of *N*-(*p*-nitrophenyl)-*p*-toluidine, mp 139 °C, which was identical with an authentic sample on the basis of mixed melting point measurement and comparison of their IR spectra.

Smiles Rearrangement of 8c A solution of **8c** (0.89 g, 2 mmol) in 100 ml of anhydrous EtOH was refluxed for 17 h, and concentrated under reduced pressure. Recrystallization of the residue gave 0.57 g (75%) of **9c**. mp 173 °C. *Anal.* Calcd for C₂₁H₁₈ClN₃O₂: C, 66.40; H, 4.78; N, 11.06. Found: C, 66.52; H, 4.84; N, 11.06. ¹H-NMR (CDCl₃, 400 MHz) δ: 1.88 (3H, s, 2-position), 2.31 (3H, s, aryl CH₃), 6.69 (2H, d, *J* = 8 Hz, 2- and 6-positions of N²-aryl), 7.11 (2H, d, *J* = 8 Hz, 3- and 5-positions of N²-aryl), 7.19 (2H, d, *J* = 9 Hz, 2- and 6-positions of ClC₆H₄), 7.33 (2H, d, *J* = 9 Hz, 2- and 6-positions of O₂NC₆H₄), 7.42 (2H, d, *J* = 9 Hz, 3- and 5-positions of ClC₆H₄) and 8.14 (2H, d, *J* = 9 Hz, 3- and 5-positions of O₂NC₆H₄). These assignments were confirmed by NOE and INDOR techniques. Hydrolysis of **9c** (0.38 g, 1 mmol) was achieved in the same manner as that of **9a** to give 0.02 g (19%) of *p*-toluidine, a small amount of **9c**, 0.01 g (4%) of *N*-acetyl-*N*-(*p*-nitrophenyl)-*p*-chloroaniline, mp 116 °C, and 0.12 g (48%) of *N*-(*p*-nitrophenyl)-*p*-chloroaniline, mp 180 °C, which was identical with the sample obtained by hydrolysis of **9b** on the basis of mixed melting point measurement and comparison of their IR spectra. An authentic sample of *N*-acetyl-*N*-(*p*-nitrophenyl)-*p*-chloroaniline was prepared as follows: a solution of *N*-(*p*-nitrophenyl)-*p*-chloroaniline (1.24 g, 5 mmol), Ac₂O (1.02 g, 10 mmol) and 4-dimethylaminopyridine (0.56 g, 5 mmol) in 5 ml of pyridine was refluxed for 9 h. Ether was added, and the mixture was washed with 2 N HCl, dried over Na₂SO₄, and concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 0.34 g (24%) of *N*-acetyl-*N*-(*p*-nitrophenyl)-*p*-chloroaniline. mp 116 °C. *Anal.* Calcd for C₁₄H₁₁ClN₂O₃: C, 57.84; H, 3.81; N, 9.64. Found: C, 58.04; H, 3.84; N, 9.65. ¹H-NMR (CDCl₃, 60 MHz) δ: 2.10 (3H, s, CH₃), 7.18 (2H, d, *J* = 9 Hz, 2-, 6- or 3-, 5-positions of ClC₆H₄), 7.40 (2H, d, *J* = 9 Hz, 2- and 6-positions of O₂NC₆H₄), 7.47 (2H, d, *J* = 9 Hz, 2-, 6- or 3-, 5-positions of ClC₆H₄) and 8.17 (2H, d, *J* = 9 Hz, 3- and 5-positions of O₂NC₆H₄). The sample was identical with that obtained by hydrolysis of **9c** on the basis of mixed melting point measurement and comparison of their IR spectra.

Kinetic Runs A THF solution (1 ml) of the substrate (3 × 10⁻³ M) was added to EtOH containing 0.1 N NaOEt in a 100 ml volumetric flask which had been pre-incubated at 40 °C. The mixture was diluted to the mark with the same NaOEt solution. The kinetic runs were carried out at 40 °C. The proportions of the substrate, *N*-(substituted benzenesulfonyl)-*p*-chloroaniline and ethyl *N*-(*p*-chlorophenyl)acetimidate were calculated from the absorbancies of the reaction solution at 235, 240, 245, 250, 255 and 260 nm (for **1a**); 235, 240, 250, 255 and 260 nm (for **4**) and 235, 240, 255 and 260 nm (for **5a**).

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