Studies on the Quaternization of Tertiary Amines (IV). Kinetics and Mechanism for the Reaction of Substituted Phenacyl Tosylates with Substituted Pyridines

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Substituent effects of substrate and nucleophile for the reaction of substituted phenacyl tosylates with pyridines were determined conductometrically in acetonitrile. Activation parameters for these reactions were also calculated. The substituent effects in nucleophile were increased with electron-donating power of pyridines and Brønsted linear relationship was shown. Rate constant was increased by both electron-donating and electron-attracting groups in the substrate. It seems that dissociative S_N2 (*"loose"* transition state) mechanism is operating in the case of electron-donating substituents while associative S_N2 (*"tight"* transition state) mechanism is operative in the case of electron-attracting substituents.

Introduction

While Menschutkin reaction of organic halides, like alkyl halides or benzyl halides, with tertiary amine in which quaternary ammonium salts were formed has been well known,[1-5] Menschutkin type reaction of organic compounds of which leaving group is not halide has not been studied very much.[6,7]

After a report of Slater and Twiss[8] that α-halo ketones easily undergo S_N2 displacement, numerous aspects of such reactions have been widely studied.[9-13] But Meschutkin type reaction of α-haloketone in which leaving group is sulfonate has not been well known.

In order to study substituent effects and reaction mechanism for the Menschutkin type reaction of organic compounds which contain ketone group, we investigated activation parameters and linear free energy relationships for the reactions of substituted phenacyl tosylates with pyridines in acetonitrile.

Experimental

Materials and Instruments. All materials used throughout were commercial products (Wako or Kasei Chemicals Co., Japan). Commercial grade pyridine was purified by distillation over potassium hydroxide serveral-times before use. Other liquid pyridines were used without further purification, but solid pyridines and substituted acetophenones were recrystallized to constant melting point. All purified pyridines were stored in brown ampoule or bottle filled with nitrogen gas. Acetonitrile was purified by distillation after standing with anhydrous potassium carbonates for three days at room temperature.

Conductance measurements were carried out with a W. W. D812 Weilheim Leitfähigkeitsmesser conductivity meter. Melting points were measured on a Büch 512 melting point apparatus. ^{1}H NMR were taken on a Varian 60-MHz spectrometer, using tetramethylsilane as an internal reference. Elemental analyses of reagents synthesized were performed at the Institute of Scientific and Industrial Research, Osaka University, Osaka, Japan.

Preparation of reagents

Over-all scheme of the experiments of this paper is shown in Figure 1.

Substituted Phenacyl Bromides. p-Methyl Phenacyl Bromide was prepared by Cowper and Davidson's method.[14] A solution of 18.58g. (0.14mole) of *p*-methyl acetophenone in 50cc. of pure anhydrous ether was placed in a dry three-necked flask fitted with a seperatory funnel, mechanical stirrer, and reflux condenser. The solution was cooled in an ice bath, 0.15g. of anydrous aluminum chloride was introduced, and 7.2cc. (0.14mole) of bromine was added gradually from the seperatory funnel, with stirring, at the rate of about 1cc per minute. After the bromine had been added, the ether and dissolved hydrogen bromide was removed at once under reduced pressure with a slight current of air. The products remained a solid mass and were recrystallized from methanol. mp 53-54°C (*lit.*, 53°C).

m-Nitro Phenacyl Bromide was prepared by following method. A solution of 24g (0.15mole) of *m*-nitro acetophenone in 150cc. of chloroform was placed in a dry three-necked flask, the solution was kept at room temperature, 0.15g. of anhydrous aluminum chloride was introduced, and 8.7cc (0.15mole) of bromine was added. After the bromine had been added, the ether and dissolved hydrogen bromide was removed at once under reduced pressure with a slight current of air. The products remained as a solid mass and were recrystallized from ethanol. mp 95°C (*lit.*[15], 96°C).

Silver Tosylate. To a solution of 9.5g (0.05mole) of *p*-toluene sulfonic acid·mono hydrate in 100cc. of acetonitrile in three-necked flask, 6.3g (0.027mole) of silver oxide was introduced, and then 200cc. of acetonitrile was added. The solution was

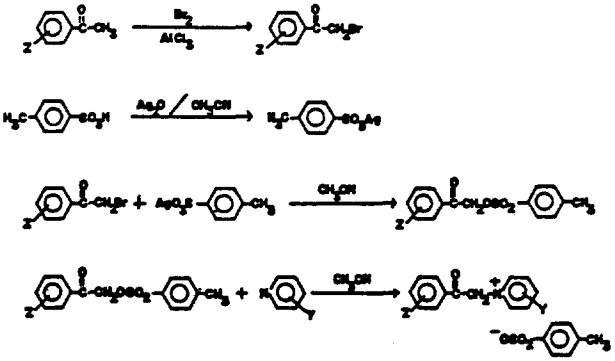

Figure 1. Over—all scheme of the experiments.

heated in a water bath at 50 °C for five hours. After filtering unreacted silver oxide and evaporating the filtrate under reduced pressure, silvery white crystals were obtained and recrystallized from absolute ethanol.

Substituted Phenacyl Tosylates. Under same procedures, seven substituted phenacyl tosylates were synthesized as following.

Phenacyl Tosylate; A solution of 15.5 g (0.055 mole) of silver tosylate in 500cc. of dry acetonitrile was placed in a dry three necked flask fitted with mechanical stirrer, reflux condenser, and thermometer, 10.0 g (0.05 mole) of phenacyl bromide was introduced. the solution was heated in a water bath at 50 °C for fifteen hours. After filtering silver bromide precipitated and evaporating the filtrate under reduced pressure, white solid was obtained. By extracting this solid using dry ether, and then evaporating the solution, white crystals were obtained and recrystallized from benzene-isopropyl alcohol. mp. 99 °C. yield, 6.8 g (47 %).

Anal. Calcd. for $C_{15}H_{14}O_4S$: C, 62.05: H, 4.87: S, 11.04, Found: C, 62.27: H, 4.96: S, 11.07. ^{1}H NMR ($CDCl_3$, δ2.5 (*s*, 3H, CH_3), 5.3 (*s*, 2H, CH_2), 7.3–7.9 (*m*, 9H, aromatic).

p-Methoxy Phenacyl Tosylate; white crystals. yield 0.72 g. (32 %), mp 119–120 °C.

Anal. Calcd. for $C_{16}H_{16}O_5S$: C, 59.99: H, 5.03, Found: C, 60.74: H, 5.04. ^{1}H NMR ($CDCl_3$), δ2.5 (*s*, 3H, CH_3), 3.9 (*s*, 3H, OCH_3), 5.3 (*s*, 2H, CH_2) 6.9–8.0 (*m*, 8H, aromatic). Mass spectrum, *m/e* 321 (M^+, 0.7 %), 135 (M^+-$CH_2O_3SC_6H_4CH_3$, 100 %).

p-Methyl Phenacyl Tosylate; white crystals. yield 1.2 g (36 %), mp 97 °C.

Anal. Calcd. for $C_{16}H_{16}O_4S$: C, 63.14: H, 5.30, Found: C, 63.61: H, 5.28. ^{1}H NMR ($CDCl_3$), δ2.5 (*s*, 6H, $2CH_3$), 5.3 (*s*, 2H, CH_2), 7.2–8.0 (*m*, 8H, aromatic). Mass spectrum, *m/e* 304.2 (M^+, 1.7 %), 119.1 (M^+-$CH_2O_3SC_6H_4CH_3$, 100 %).

p-Chloro Phenacyl Tosylate: white crystals. yield 1.4 g (43 %), mp 125–126 °C.

Anal. Calcd. for $C_{15}H_{13}O_4SCl$: C, 55.47: H, 4.03, Found: C, 55.91: H, 4.07. ^{1}H NMR ($CDCl_3$), δ2.5 (*s*, 3H, CH_3), 5.3 (*s*, 2H, CH_2), 7.3–8.0 (*m*, 8H, aromatic). Mass spectrum, *m/e* 324.1 (M^+, 1.5 %), 139 (M^+-$CH_2O_3SC_6H_4CH_3$, 100 %).

p-Bromo Phenacyl Tosylate; white crystals. yield 1.8 g (49 %), mp 130–131 °C.

Anal. Calcd. for $C_{15}H_{13}O_4SBr$: C, 48.79: H, 3.55, Found: C, 48.83: H, 3.35. ^{1}H NMR (DMSO-d_6), δ2.5 (*s*, 3H, CH_3), 5.6 (*s*, 2H, CH_2), 7.4–8.0 (*m*, 8H, aromatic). Mass spectrum, *m/e* 288.9 (M^+-Br, 2.8 %), 182.9 (M^+-$CH_2O_3SC_4CH_3$, 100 %).

p-Nitro Phenacyl Tosylate; white crystals. yield 1.7 g (51 %) mp 138–139 °C.

Anal. Calcd. for $C_{15}H_{13}O_6NS$: C, 53.73: H, 3.91: N, 4.18, Found: C, 54.04: H, 3.62: N, 4.29.

m-Nitro Phenacyl Tosylate; white crystals. yield 0.91 g (27 %), mp 112–113 °C.

Anal. Calcd. for $C_{15}H_{13}O_6NS$: C, 53.73: H, 3.91: N, 4.18, Found: C, 54.5: H, 4.0: N, 4.17. ^{1}H NMR (DMSO-d_6), δ2.5 (*s*, 3H, CH_3), 5.7 (*s*, 2H, CH_2), 7.4–8.4 (*m*, 8H, aromatic). Mass spectrum, *m/e* 335.1 (M^+, 2.2 %), 150($^+$ – $CH_2O_3SC_6H_4CH_3$, 100 %).

Phenacyl Phridinium Benzenesulfonate. A solution of 4.2 g (0.015 mole) of phenacyl benzenesulfonate in 50cc of dry acetonitrile was placed in a dry round-bottomed flask fitted with reflux condenser. 1.4 g (0.015 mole) of dry pyridine was introduced. The solution was refluxed in a water bath for five days. After evaporating the solution under reduced pressure, white crystals were obtained and washed with dry ether, and then recrystallized from isopropyl alcohol. mp. 127 °C.

Anal. Calcd. for $C_{19}H_{17}O_4NS$: C, 64.19: H, 4.82: N, 3.94, Found: C, 64.11: H, 5.02: N, 3.88.

Kinetic Measurements. The rates of reaction was measured by means of electric conductivity.[17] As the reaction proceeds, the electric conductance is increased because concentration of the salt formed in the reaction cell increasing as time goes on. The approximation is usually by the change in conductance in contrast with the linear function of the concentration.

A typical kinetic run is described as follows. The concentration of phenacyl tosylate was made just 0.005 mole/*l* in 15 m*l*. volumetric flask which was filled with nitrogen gas and acetonitrile. That of pyridine was made just 0.2 mole/*l* with above same. A kinetic run was initiated by placing 15 m*l* of pyridine solution in conductivity cell and adding 15 m*l*. of phenacyl tosylate solution to give a reaction mixture that was 0.1 mole/*l* in pyridine and 0.0025 mole/*l* in phenacyl tosylate.

All measurements were done with pyridines in large excess over phenacyl tosylate in acetonitrile. Reaction were generally run to about 3 to 4 half-lives. The temperature control was better than 0.05 °C at given temperature. Pseudo first-order rate constants were calculated from conventional plots of log (λ_∞-λ_t) against time using the least squares method.[18] The infinity reading was generally taken after 10 half-lives. Second-order rate constants were calculated from the slope of the observed first-order rate constants against pyridine concentration.

Activation energies were calculated from Arrhenius plot and activation entropies were obtained using the theory of absolute reaction rate,[19]

$$k=\frac{K_B\cdot T}{h}e\Delta S^*/R e-\Delta H^*/RT$$

TABLE 1: Activation Parameter and Kinetic Data for the Rx. of Phenacyl Tosylate with Pyridines in Acetonitrile

Substituent (*Y*)	$k_2 \times 10^5$(*l*/mole·sec) 35 °C	45 °C	55 °C	$\Delta H^{\neq}$ (kcal/mole)	$-\Delta S^{\neq}$ (e.u)	$\Delta G^{\neq}$ (kcal/mole)
(1) 4—NH_2	875	1560	3130	12.9	26.4	21.3
(2) 3—NH_2	122	267	542	14.3	25.5	22.4
(3) 4—CH_3	50	103	221	14.0	28.3	23.0
(4) 3—CH_3	37.1	75.0	156	13.8	29.6	23.2
(5) H	19.0	40.5	84.0	14.3	29.2	23.6
(6) 3—Cl		3.35	7.29	15.3	31.1	25.2
(7) 7—Br		3.33	6.83	14.3	34.3	25.2
(8) 4—CN		1.67	2.83	10.3	48.1	25.6

Results and Discussion

The Substituent Effects of Nucleophile. The second-order rate constants and activation parameters for the reaction of phenacyl tosylate with pyridines are summerized in Table 1.

From these results, electron-donating substituents in pyridine increase the rate, while electron-attracting substituents decrease its rate. It seems that the rates were controlled by activation entropy, because the value of the activation parameters show that the rates have a tendency to increase according to activation entropy increasing.

As expected, the rates of this reaction were much faster than those of the reaction of phenethyl tosylate with pyridines.[7] Steric effects may be responsible in part for the observed acceleration, since it is responsible that a carbonyl substituent provides less steric resistance to an incoming nucleophile than does a methylene group. It is also believed that a signficant stabilizing electronic interaction may be involved.[20] The p-type orbitals of the incoming and leaving groups would overlap with the π-orbitals of the carbonyl and phenyl groups.

The rates for the reaction of the phenacyl tosylate with substituted pyridines were well correlated by the σ constants giving a Hammett plot with a considerably large ρ value and the following equation was obtained from the Figure 2,

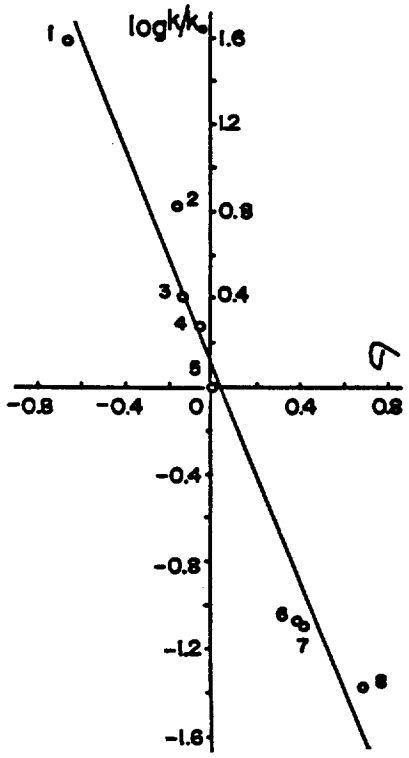

Figure 2. Hammett plot for the reaction of phenacyl tosylate with pyridines in CH_3CN at 45 °C.

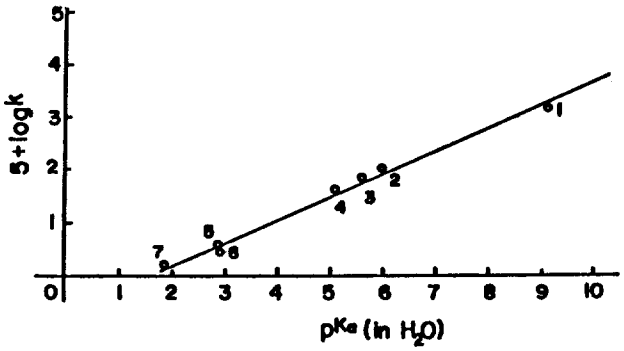

Figure 3. Correlation between log$k$ and pKa for the reaction of phenacyl tosylate with pyridines in CH_3CN at 45 °C.

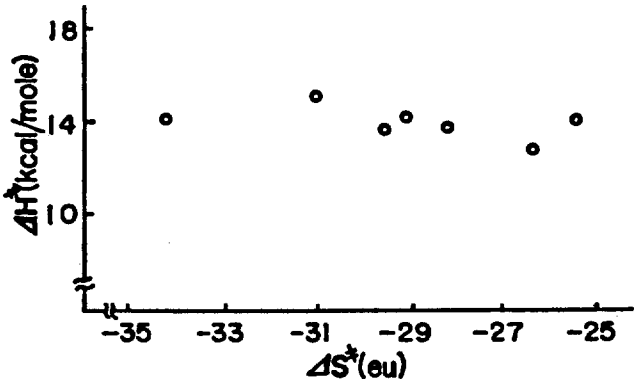

Figure 4. Correlation between activation enthalpie and entropies for the reaction of phenacyl tosylate with pyridines in CH_3CN at 45 °C.

$$\log k/k_0 = -2.48\ \sigma + 0.05 (r = 0.982) \text{ in } CH_3CN \text{ at } 45\,^{\circ}C.$$

It is believed that N atom, in the transition state of this reaction, has a fairly high δ + charge along with N···C bond formation.

It was generally accepted that BrØnsted linear relationship[21] was shown between reaction rates and basicities of nucleophiles in which attacking atom is the same in S_N2 reaction. In this study, a good linear relationship with very large β value was shown between log$k$ against pKa of pyridines (Figure 3),

$$\log k = 2.36\ \text{pKa} - 1.46 (r = 0.998) \text{ in } CH_3CN \text{ at } 45\,^{\circ}C.$$

From the β value, it can be inferred that N···C bond formation, in the transition state, is made considerable progress, and this is in agreement with the results of Hammett's ρ value.

Plotting activation enthalpies against activation entropies obtained in this reaction (no correlation, see Figure 4) can be compared with Forster and Laird's work[5] for the reaction of phenacyl bromide with pyridines, in which they have reported an isoenthalpic relationship.[22]

The substituent Effects of Substrate. The second-order rate constants and activation parameters for the reaction of substituted phenacyl tosylates with pyridine are summerized in Table 2.

Both electron-donating and electron-attracting substituents increase the rate. Hammett plots for this reaction show concave up. This results are consistent with the results of the reaction of substituted phenacyl bromides with quinoline,[23] and many othe reactions[24-26] have shown such curvature.

According to C.G. Swain, there is no grouping of ρ values into categories that could correspond to different kinds of

TABLE 2: Activation Parameter and Kinetic Data for the Rx. of Sbstituted Phenacyl Tosylates with Pyridine in Acetonitrile.

Substituent (Z)	$k_2 \times 10^4$(l/mole·sec) 35 °C	45 °C	55 °C	$\Delta H^{\ddagger}$ (kcal/mole)	$-\Delta S^{\ddagger}$ (e.u)	$\Delta G^{\ddagger}$ (kcal/mole)
(1) 4—CH_3O	2.29	4.88	11.30	15.5	25.0	23.5
(2) 4—CH_3	2.38	5.00	10.60	14.4	28.4	23.5
(3) H	1.90	4.05	8.40	14.3	29.2	23.6
(4) 4—Cl	4.06	9.29	15.00	12.8	32.3	23.1
(5) 4—Br	4.29	10.00	19.70	14.7	26.1	23.0
(6) 3—NO_2	3.78	8.10		14.2	28.1	23.2
(7) 4—NO_2	4.35	9.38	20.00	14.6	26.6	23.1

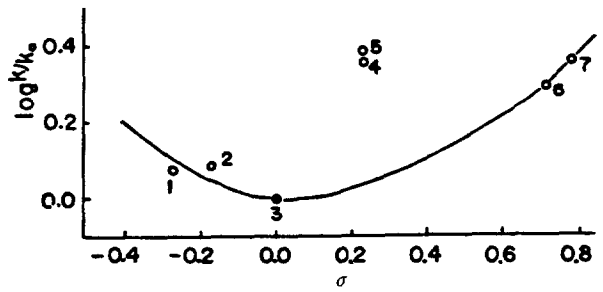

Figure 5. Hammett plot for the reaction of substituted phenacyl tosylates with pyridine in CH_3CN at 45 °C.

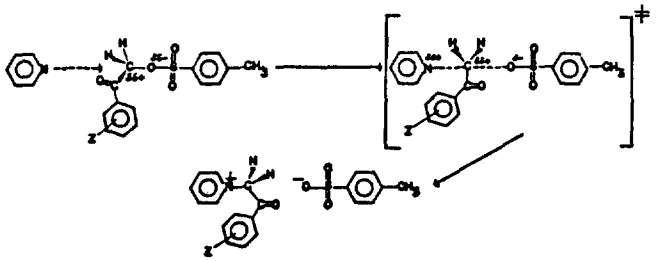

Figure 6. Schematic representation of the reaction profile.

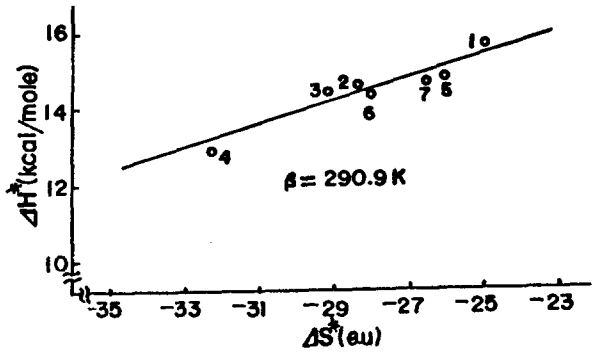

Figure 7. Isokinetic relationship for the reaction of substituted phenacyl tosylates with pyridine in CH_3CN at 45 °C.

mechanisms, and one might expect ρ to be a function of for the following reason. A strongly electron-donating substituent, *e.g.* *p*-methoxy, should not only stabilize a transition state having a high positive charge on substrate but, in so doing, it should also increase the capacity of the substrate (including substituent) for positive charge, and thereby favor more completion of bond breaking, relative to bond formation, at the transition state (more negative ρ than mean). A strongly electron-attracting substituent, *e.g.* *p*-nitro, should increase the capacity of the substrate for negative charge, and favor bond formation (more positive ρ than mean). This would predict a positive curvature (concave up) on a plot of log k/k_0. against σ.

It seems that the deviation of *p*-bromo and *p*-chloro groups from the curvature was also responsible for significant stabilizing electronic interaction in the transition state (Figure 6).

The plots of activation enthalphies against activation entropies obtained in this reaction are shown in Figure 7.

The isokinetic relationship was well correlated and isokinetic temperature was 290.9K. This results indicate that the reactions of substituted phenacyl tosylates with pyridine were controlled by activation entropy, as in common in S_N2 reaction.

In conclusion,from Hammett ρ and Brønsted β values, it is evident that the reaction of phenacyl tosylate with pyridines proceed through S_N2 mechanism in which N···C bond formation is considerably developped in the transition state. On the while, for the reaction of substituted phenacyl tosylate with pyridine, it seems that in the case of electron-donating substituents, the mechanism is dissociative S_N2 in which C···O bond breaking is more advanced ("loose" transition state), on the contrary, in the case of electron-attracting substituents, the mechanism is associative S_N2 in which N···C bond formation is more advanced ("tight" transition state).

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