DAEHAN HWAHAK HWOEJEE
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3차 아민의 4차화 반응에 관한 연구 (제 5 보). 페나실 아렌술포네이트류에 의한 피리딘의 4차화반응

李 五 錫
안동대학 화학과
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Studies on the Quaternization of Tertiary Amine (V). The Quaternization of Pyridine with Phenacyl Arenesulfonates

Oh Seuk Lee
Department of Chemistry, Andong National University, Andong 660, Korea
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요 약. 페나실 치환 벤젠술포네이트류와 피리딘의 반응속도를 아세토니트릴과 메탄올 용매속에서 각각 35, 45, 그리고 55°C에서 전기전도도법으로 측정하였다. 이탈기 내의 치환기 효과는 치환기의 전자끌기 능력이 클수록 반응이 빨라지므로써 이탈기의 이탈 능력이 반응속도에 직접 영향을 미쳤다. 또한 양성자성 용매인 메탄올과 비양성자성 용매인 아세토니트릴에서의 반응을 비교한 결과 수소결합을 통한 특성 용매화가 작용되고 있음을 알수 있었다. 그러므로 이 반응에서 피리딘이 기질의 카르보닐기에 속도 결정 단계로 첨가되는 메카니즘을 배제시킬수 있었다.

ABSTRACT. The effect of substituent inleaving group on the rates of reactions of phenacyl substituted-benzenesulfonates with pyridine was determined conductometrically in acetonitrile and in methanol at 35, 45, and 55°C, respectively. The reaction rate became faster in proportion to electron-attracting ability of substituent, which indicates that the substituent in leaving group can directly control reaction rate. It was shown that the specific to the carbonyl carbon as the rate-determining step.

INTRODUCTION

Although the nucleophilic substitution reactions of α-halogenocarbonyl compounds, e.g., phenacyl halides, have attracted considerable attention over several decades[1~15], many aspects of the reaction mechanism remain poorly understood and contradictory opinions abound. This is due to two reaction sites in α-halogenocarbonyl compounds for a nucleophile to attack in the rate-determining step leading to the corresponding transition states, respectively.

According to Hughes[14] the inductive effect of the carbonyl group enhances the normal polarity of the carbon-halogen bond by increasing electron deficiency at the α-carbon. The more polar the carbon-halogen bond the faster will be the attack of nucleophiles in bimolecular displacement, consequently a direct displacement of the halogen from the α-carbon atom can be envisaged. On the other hand, Baker[15] suggested that the initial as well as rate-determining step is the addition of the nucleophile to the carbonyl carbon from which the addend is then transferred to the α-position, with displacement of halogen, in a fast step. This involves the

formation of an intermediate in which the nucleophile is covalently bonded to the carbonyl carbon. Other modes of interaction[5~6] of the nucleophile with carbonyl group have also been proposed.

In the previous paper[16] we reported our results on the kinetics of the reactions of substituted phenacyl tosylates with substituted pyridines. As an extension, the reactions between phenacyl substituted-benzenesulfonates and pyridine have now been investigated to elucidate the transition states. The rate studies have also been done by changing the solvent from acetonitrile to methanol for the evaluation of medium effect.

EXPERIMENTAL

Materials and Instruments

Reagent grade of *p*-bromobenzenesulfonyl chloride and other materials were purchased from Aldrich and Wako. The pyridine was purified and stored in a bottle filled with nitrogen. Acetonitrile was purified by distillation after standing with anhydrous potassium carbonates for three days at room temperature. Analytical grade methanol was used without further purification.

Conductance measurements were carried out with a Metrohm 660 conductometer. Melting points were measured on a Büch 512 melting point apparatus. ^{1}H NMR spectra were recorded using a Varian 60-MHz spectrometer with tetramethylsilane as an internal reference. Mass spectra were determined with Hewlett Packard 5985 mass spectrometer and elemental analyses were performed on Perkin Elmer Model 240 CHN analyzer.

Preparation of reagents

Over-all scheme of the experiments is shown in *Fig.* 1.

Substituted Benzenesulfonyl Chloride

p-Methoxybenzenesulfonyl chloride was prepared by chlorosulfonation of anisole with chlorosulfonic acid by Morgan's method[17] and recrystallized from petroleum ether. m.p. 40°C (lit., [17] 40~42°C)

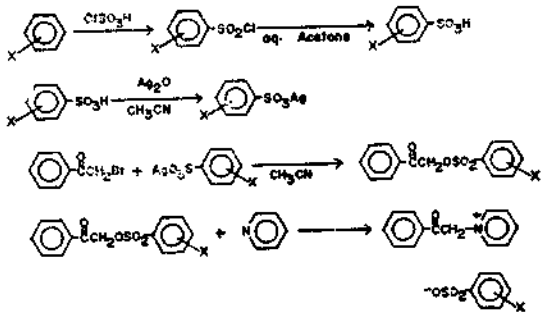

Fig. 1. Over-all scheme of the experiments.

m-Nitrobenzenesulfonyl chloride was prepared by chlorosulfonation of sodium *m*-nitrobenzenesulfonate and recrystallized from ligroin. m.p. 61°C (lit., [18] 62°C)

Substituted Benzenesulfonic Acid

Under same procedures, three substituted benzenesulfonic acids were synthesized as following.

p-Methoxybenzenesulfonic acid; A solution of 25g. (0.12mole) of *p*-methoxybenzenesulfonyl chloride in aqueous acetone (100m*l* acetone with 30m*l* water) was refluxed for two hours, and then was evaporated under reduced pressure. hygroscopic crystal.

m-Nitrobenzenesulfonic acid; Prepared by hydrolysis of *m*-nitrobenzenesulfonyl chloride. needle shape hygroscopic crystal.

p-Bromobenzenesulfonic acid; Prepared by hydrolysis of *p*-bromobenzenesulfonyl chloride and recrystallized from ethanol. m.p. 102°C (lit[18]., 102~103°C)

Substituted Silver Benzenesulfonate

According to Emmons' method[19], seven substituted silver benzenesulfonates were synthesized from corresponding substituted benzenesulfonic acid.

Siver benzenesulfonate; white crystal.

Silver p-methoxybenzenesulfonate; silverly white crystal.

Silver p-methylbenzenesulfonate; silverly white crystal.

Silver p-chlorobenzenesulfonate; silverly white crystal.

Silver p-bromobenzenesulfonate; white crystal.

Silver p-nitrobenzenesulfonate; pale yellow crystal.

Silver m-nitrobenzenesulfonate; pale yellow crystal.

Phenacyl Arenesulfonates

Using same procedures, seven phenacyl arenesulfonates were prepared as follows.

Phenacyl benzenesulfonate; A solution of 14.6g. (0.055mole) of silver benzenesulfonate in 500m*l* of dry acetonitrile was placed in a dry three necked flask fitted with mechanical stirrer, reflux condenser, and thermometer. Phenacyl bromide (10.0g., 0.05mole) was introduced and then 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. m.p. 82°C, yield 7.5g. (54%).

Anal. Calcd. for $C_{14}H_{12}O_4S$: C, 60.86: H, 4.38: S, 11.60, Found: C, 60.83: H, 4.39: S, 11.63. ^{1}H NMR ($CDCl_3$), δ 5.3 (*s*, 2H, CH_2), 7.3~8.1 (*m*, 10H, aromatic). Mass spectrum, m/e 276.2 (M^+, 0.1%), 141 (M^+-$C_6H_5COCH_2O$, 0.2%), 105(M^+-$CH_2OSO_2C_6H_5$, 100%).

Phenacyl p-methoxybenzenesulfonate; white crystals, yield 6.4g (42%), mp 128°C. Anal. Calcd. for $C_{15}H_{14}O_5S$: C, 58.81: H, 4.61, Found: C, 58.72: H, 4.35. ^{1}HNMR($CDCl_3$+DMSO-d_6), δ 3.9(*s*, 3H, OCH_3), 5.3(*s*, 2H, CH_2), 6.9~8.0(*m*, 9H, aromatic). Mass spectrum, m/e 306.2 ($M^{\cdot+}$, 14.1%), 107.1($M^{\cdot+}$-$C_6H_5COCH_2OSO_2$, 14%) 105($M^{\cdot+}$-$CH_2OSO_2C_6H_5$, 100%).

Phenacyl p-methylbenzenesulfonate; white crystals, yield 6.8g (47%), mp 99°C. Anal. Calcd. for $C_{15}H_{14}O_4S$: C, 62.05: H, 4.86: S, 11.04, Found: C, 62.27: H, 4.96: S, 11.07. ^{1}H NMR($CDDl_3$), δ 2.5(*s*, 3H, CH_3), 5.3(*s*, 2H, CH_2), 7.3~7.9 (*m*, 9H, aromatic). Mass spectrum, m/e 290.2 ($M^{\cdot+}$, 0.2%), 155.2 ($M^{\cdot+}$-$C_6H_5COCH_2O$, 0.2%), 105($M^{\cdot+}$-$CH_2OSO_2C_6H_5$, 100%).

Phenacyl p-chlorobenzenesulfonate; white crystals, yield 8.3g (53%), mp 94°C. Anal. Calcd. for $C_{14}H_{11}O_4SCl$: C, 54.11: H, 3.57, Found: C, 54.76: H, 3.51. ^{1}H NMR($CDCl_3$), δ 5.4(*s*, 2H, CH_2), 7.4~8.0(*m*, 9H, aromatic). Mass spectrum, m/e 310.8($M^{\cdot+}$, 0.1%), 111 ($M^{\cdot+}$-$C_6H_5COCH_2OSO_2$, 19.2%), 105($M^{\cdot+}$-$CH_2OSO_2C_6H_5$, 100%)

Phenacyl p-bromobenzenesulfonate; white crystals, yield 9.2g(52%), mp 104°C. Anal. Calcd. for $C_{14}H_{11}O_4SBr$: C, 47.34: H, 3.12, Found: C, 47.71: H, 3.34. ^{1}H NMR($CDCl_3$+DMSO-d_6), δ 5.4(*s*, 2H, CH_2), 7.4~7.9 (*m*, 9H, aromatic). Mass spectrum, m/e 356.3(M+2, 0.5%), 354.3($M^{\cdot+}$, 0.5%), 157(M+2-$C_6H_5COCH_2OSO_2$, 24%) 155($M^{\cdot+}$-$C_6H_5COCH_2OSO_2$, 23.5%), 105($M^{\cdot+}$-$CH_2OSO_2C_6H_5$, 100%).

Phenacyl p-nitrobenzenesulfonate; white crystals, yield 8.4g (52%), mp 136~138°C. Anal. Calcd. for $C_{14}H_{11}O_6NS$: C, 52.33: H, 3.45: N, 4.36, Found: C, 52.43: H, 3.41: N, 4.47. ^{1}H NMR ($CDCl_3$+DMSO-d_6), δ 5.6 (*s*, 2H, CH_2), 7.5~8.4(*m*, 9H, aromatic). Mass spectrum, m/e 186.1($M^{\cdot+}$-$C_6H_5COCH_2O$, 6.9%), 122.1($M^{\cdot+}$-$C_6H_5COCH_2OSO_2$, 12%), 105($M^{\cdot+}$-$CH_2OSO_2C_6H_4NO_2$, 100%).

Phenacy m-nitrobenzenesulfonate; white crys-

tals, yield 7.2g (45%), mp 90°C. Anal. Calcd. for $C_{14}H_{11}O_6NS$: C, 52.33: H, 3.45: N, 4.36, Found: C, 52.88: H, 3.55: N, 4.55. ^1H NMR ($CDCl_3$), δ 5.5(*s*, 2H, CH_2), 7.4~8.5(*m*, 9H, aromatic). Mass spectrum, m/e 186.1 ($M^{\cdot+}$-$C_6H_5COCH_2O$, 6.8%), 122.2($M^{\cdot+}$-$C_6H_5COCH_2OSO_2$, 13%), 105($M^{\cdot+}$-$CH_2OSO_2C_6H_4NO_2$, 100%).

Kinetic Measurements.

The rates of reaction were measured by means of electric conductivity[20]. As the reaction proceeds, the electric conductance of reaction mixture is increased because concentration of the salt formed in the reaction cell increases for reaction time. The linearity of conductance for concentration of the salt, which was not exactly linear, was approximated.

A typical kinetic run was described in the previous paper[16]. All measurements were done with pyridine in large excess over phenacyl arenesulfonates. Reaction were generally run for about 3 to 4 half-lives of substrate. The temperature deviation was within 0.05°C at the given temperatures. Pseudo first-order rate constants were calculated from the plots of log ($\lambda_\infty - \lambda_t$) against time using the least square method[21]. The infinity reading was generally taken after 10 half-lives of substrate. 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 absolute rate theory:[22]

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

RESULTS AND DISCUSSION

The rate constants and activation parameters for the reaction of phenacyl substituted-benzenesulfonates with pyridine in acetonitrile are summarized in *Table* 1.

The reaction rate becomes faster in proportion to the electron-attracting power of substituent. It may show that the interactions between the partial negative charge of sulfonate oxyen and electron-attracting group on benzene ring enhance the rate.

The rates for the reaction of phenacyl substituted-benzenesulfonates with pyridine in acetonitrile were well correlated with σ constants giving a Hammett ρ value of 1.36 and the following equation was obtained from *Fig.* 2.

$\log k/k_0 = 1.36\sigma + 0.04 (r = 0.986)$ at 45°C.

This may be compared with the nucleophilic substitution or solvolysis reactions of various esters of substituted benzenesulfonic acid. The rates of those reactions[23~27] also have good correlations with σ, and the ρ values are in the range of 1~2.

Table 1. Rates and activation parameters for the reaction of phenacyl arenesulfonates with pyridine in acetonitrile

Substituent (X)	$k_2 \times 10^4$(1/mole·sec) 35°C	45°C	55°C	ΔH^* (kcal/mole)	$-\Delta S^*$ (eu)	ΔG^* (kcal/mole)
(1) 4-NO_2	37.2	76.8	115	13.5	25.9	21.7
(2) 3-NO_2	35.9	71.0	109	12.6	28.8	21.8
(3) 4-Cl	12.6	25.8	59.0	14.9	23.7	22.4
(4) 4-Br	8.53	18.2	37.6	14.3	26.3	22.6
(5) H	3.25	7.39	16.3	15.6	24.1	23.2
(6) 4-CH_3	1.90	4.05	8.40	14.3	29.2	23.6
(7) 4-CH_3O	1.39	3.18	6.70	15.2	27.0	23.7

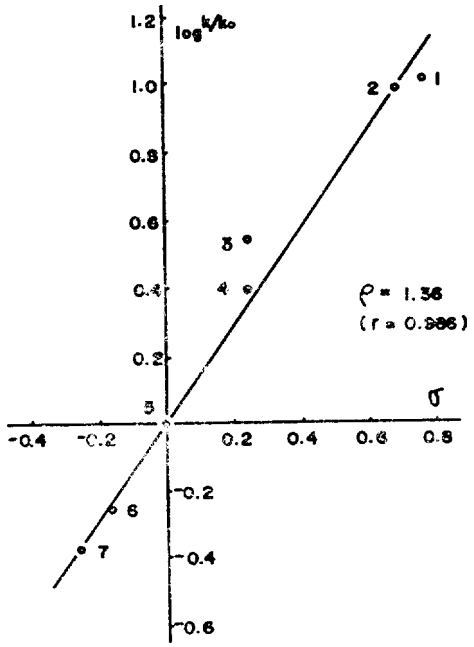

Fig. 2. Hammett plot for the reaction of phenacyl substituted-benzenesulfonates with pyridine in CH_3CN at 45°C.

The plot of enthalpies of activation against entropies of activation shows no relationship as shown in *Fig.* 3.

The rate constants and activation parameters for the reaction of phenacyl substituted-benzenesulfonates with pyridine in methanol are summarized in *Table* 2.

If we make a comparison between the rate constants of the reactions of phenacyl substituted-benzenesulfonates with pyridine in acetonitrile and those in methanol, the reaction rates are considerably reduced in methanol; $k_{CH_3OH}/k_{CH_3CN}=0.66$. We may assume that the polar solvent effect on the rates is nearly equal in the two solvents, because the dielectric constant of methanol is 32.63 and that of acetonitrile is 36.02 at 25°C. The strong solvation of nucleophile may be the result of hydrogen-bonding with methanol and accordingly retards the rates.

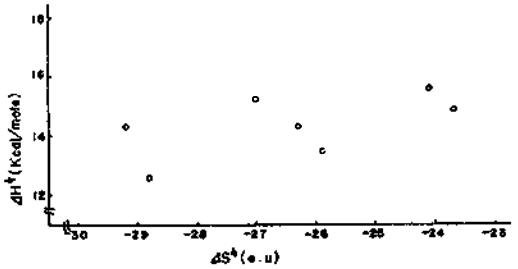

Fig. 3. Correlation between enthalpies of activation and entropies of activation for the reaction of phenacyl substituted-benzenesulfonates with pyridine in CH_3CN.

The ρ value is 1.14 for the reactions in methanol (*Fig.* 4) which is smaller than that for the reactions in acetonitrile, 1.36 (*Fig.* 2).

This is because the partial negative charge of sulfonate oxygen developed in transition state can be dispersed in methanol by hydrogen-bonding with solvent molecules, while in acetonitrile such interaction is negligible and the partial negative charge of sulfonate oxygen can

Table 2. Rates and activation parameters for the reaction of phenacyl arenesulfonates with pyridine in methanol

Substituent (X)	$k_2\times10^4$(1/mole·sec) 35°C	45°C	55°C	$\Delta H^{\neq}$ (kcal/mole)	$-\Delta S^{\neq}$ (eu)	$\Delta G^{\neq}$ (kcal/mole)
(1) 4-NO_2	15.3	38.5	83.3	16.4	18.2	22.2
(2) 3-NO_2	15.4	39.9	83.5	16.4	18.1	22.1
(3) 4-Br	4.65	11.5	24.6	16.1	21.4	22.9
(4) 4-Cl	4.62	11.2	23.9	15.9	22.2	22.9
(5) H	2.36	5.60	11.8	15.5	24.9	23.4
(6) 4-CH_3	1.55	3.74	7.98	15.9	24.5	23.6
(7) 4-CH_3O	1.08	2.64	5.92	16.4	23.3	23.9

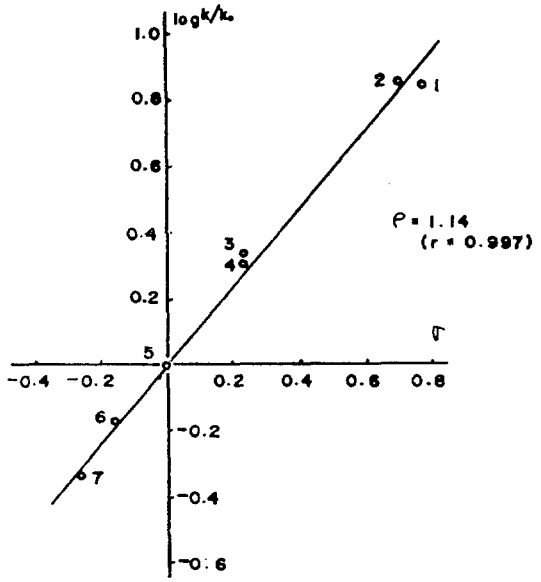

Fig. 4. Hammett plot for the reaction of phenacyl substituted-benzenesulfonates with pyridine in CH_3OH at 45°C.

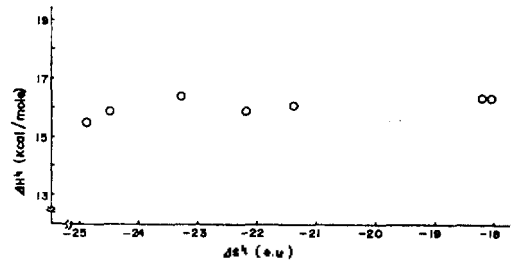

Fig. 5. Correlation between enthalpies of activation and entropies of activation for the reaction of phenacyl substituted-benzenesulfonates with pyridine in CH_3OH.

interact effectively with substituent of benzene ring.

The plot of enthalpies of activation against entropies of activation shows isoenthalpic relationship[28] and the rates are thus controlled by entropy of activation (*Fig.* 5), but shows no such relation for the reactions in acetonitrile (*Fig.* 3).

This is caused by the reduction of the freedom of solvent molecule in methanol due to the interaction of hydrogen-bonding between the partial negative charge on the sulfonate oxygen and the hydroxyl group of methanol. And the extent of the interaction of hydrogen-bonding is larger when electron-donating group is substituted in benzene ring depending on the increased isolation of charge compared with the case where electron-attracting group is substituted and thereby entropy loss becomes larger. In acetonitrile, however, such interactions could be negligible. Other reactions of the esters of arenesulfonic acids in protic solvents, which proceed by either S_N2 or S_N1 reaction, were shown to be controlled by entropy of activation[25~29].

In conclusion, for substituent effect of leaving group the reaction rates become faster in proportion to the electron-attracting power of substituent indicating the influence of the leaving ability on reaction rate. As for solvent effects, it was shown that the specific solvation via hydrogen-bonding is operative in methanol. We can therefore exclude the rate-determining addition of pyridine to the carbonyl carbon in the transition state, in addition to the Hammett ρ values of phenacyl moiety[16] showing not very fully developed charge on the carbon atom of the reaction site in the transition state.

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