Nucleophilic Substitution Reactions of 1-Phenylethyl Benzenesulfonates with Anilines in Methanol–Acetonitrile[1]

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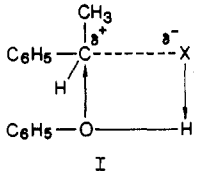
Nucleophilic substitution reactions of 1-phenylethyl benzenesulfonates with anilines have been investigated in methanol–acetonitrile mixtures at 25 °C. Magnitudes of the Hammett coefficients ρ_X, ρ_Y, and ρ_Z indicate that a stronger nucleophile leads to a greater degree of bond cleavage whereas a stronger nucleofuge leads to tighter bond formation in the transition state. Magnitudes of cross interaction constants between substituents in the nucleophile and in the leaving group are unusually large, which is rationalized by an intermolecular S_Ni mechanism with retention of product configuration involving a four-center transition state. Cross interaction constants also indicate that bond formation has progressed somewhat but bond breaking is extensive in the transition state so that its structure resembles that expected for an S_N1 mechanism. The ratio of solvatochromic parameters a/s is relatively small, indicating that electrophilic assistance by methanol is less than that for normal S_N1 or S_N2 reactions.

Nucleophilic substitution reactions of 1-phenylethyl derivatives display a variety of mechanisms. Tidwell et al.[2] reported that solvolyses of 1-phenylethyl tosylates proceed by an ion-pair mechanism involving nucleophilic attack on the ion pair. Jencks et al.[3] concluded that reactions of 1-phenylethyl derivatives with azide ion in an ionizing solvent proceed through a concerted S_N2 displacement mechanism with an open "exploded" transition state (TS) that closely resembles a carbocation. Extensive studies on phenolyses of 1-phenylethyl systems, however, led Okamoto et al.[4] to propose an intermolecular S_Ni mechanism involving a four-center TS (I) with net retention of configuration in the phenolysis products. We have reported the use of cross interaction constants, ρ_{ij}, (eq 1)



I

$$\log (k_{ij}/k_{HH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \quad (1)$$

for investigating the mechanisms of reactions in solution. We have shown that the intensity of interactions between substituents i and j, indicated by the magnitudes of cross interaction constants, $|\rho_{ij}|$, varies inversely with the distance between the two substituents[5a] and is enhanced strongly by the formation of a bypass bridge structure that provides an additional interaction route in the TS.[5c]

We here present the results of kinetic studies on nucleophilic substitution reactions of substituted 1-phenylethyl benzenesulfonates with anilines in methanol–acetonitrile mixtures (eq 2). We have found an unusual enhancement of cross interaction between substituents X in the nucleophile and Z in the leaving group, indicating that reaction 2 is a retentive displacement proceeding by an intermolecular S_Ni mechanism.

$$2XC_6H_4NH_2 + YC_6H_4CH(CH_3)OSO_2C_6H_4Z \xrightarrow{\text{MeOH–MeCN}} YC_6H_4CH(CH_3)NHC_6H_4X + XC_6H_4NH_3^+ + {}^-OSO_2C_6H_4Z \quad (2)$$

X = *p*-CH_3, H, *p*-Cl, *m*-NO_2

Y = *p*-OCH_3, *p*-CH_3, H, *p*-Cl

Z = *p*-CH_3, H, *p*-Cl, *p*-NO_2

Table I. Pseudo-First-Order Rate Constants ($k_1 \times 10^4$ s^{-1}) and Activation Parameters for the Methanolysis of 1-Phenylethyl *p*-Nitrobenzenesulfonates in MeOH–MeCN

% (v/v) MeOH	temp, °C				act. parameters	
	25.0	35.0	45.0	55.0	$\Delta H^{\ddagger a}$	$-\Delta S^{\ddagger b}$
100	2.89	4.50	7.82	13.4	10.0	51.9
90	2.59	4.21	7.70	12.8	10.2	51.3
80	2.23	3.78	6.80	11.7	10.8	49.2
70	1.76	3.10	5.80	10.6	11.4	47.7
50	0.658	1.46	3.24	6.50	13.9	42.8

[a] kcal mol^{-1}. [b] eu.

Results and Discussion

Rate constants and activation parameters for the methanolysis of 1-phenylethyl *p*-nitrobenzenesulfonates in methanol–acetonitrile mixtures are summarized in Table I. The rate is seen to increase with the methanol content of the solvent mixtures. Second-order rate constants k_2 for the reaction of 1-phenylethyl benzenesulfonates with anilines, (2), were obtained from slopes of the plots of pseudo-first-order rate constants, k_1^{obsd}, versus aniline concentration (eq 3, Table II). Tables I and II reveal that

$$k_1^{obsd} = k_1 + k_2[\text{aniline}] \quad (3)$$

the methanolysis rates k_1 are negligible compared to k_2 in most cases and hence that methanolysis should not interfere with determinations of k_2. However, for the reactions of 1-phenylethyl derivatives with *m*-nitroaniline, ratios of k_2/k_1 are $\simeq$20, so that Guggenheim plots for the determination of k_1^{obsd} begin to deviate from an initial

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Table II. Second-Order Rate Constants ($k_2 \times 10^2$ L·mol^{-1}·s^{-1}) for the Reaction of Y-1-Phenylethyl Z-Benzenesulfonates with X-Anilines in MeOH–MeCN at 25 °C

% (v/v) MeOH	X in $XC_6H_4NH_2$	Y = *p*-OCH_3			Y = *p*-CH_3			Y = H			Y = *p*-Cl		
		Z = *p*-CH_3	Z = H	Z = *p*-Cl	Z = *p*-CH_3	Z = H	Z = *p*-Cl	Z = *p*-CH_3	Z = H	Z = *p*-Cl	Z = *p*-CH_3	Z = H	Z = *p*-Cl
100	*p*-CH_3	15.8	20.2	32.9	14.6	18.7	30.9	12.5	16.9	27.8	10.8	14.4	24.2
	H	6.27	10.2	15.6	5.85	9.15	14.4	5.02	7.94	12.5	4.01	6.31	10.3
	p-Cl	2.50	3.66	4.23	2.21	3.24	3.84	1.84	2.73	3.27	1.45	2.17	2.64
	m-NO_2	0.253	0.278	0.383	0.223	0.248	0.345	0.183	0.203	0.288	0.137	0.156	0.227
80	*p*-CH_3	14.4	19.3	32.0	13.0	16.6	30.1	11.4	15.1	27.1	9.68	13.7	23.5
	H	6.04	8.42	13.2	5.43	7.73	12.1	4.60	6.62	10.5	3.71	5.79	8.66
	p-Cl	2.28	3.31	4.11	2.05	2.99	3.70	1.69	2.50	3.11	1.31	1.94	2.44
	m-NO_2	0.211	0.260	0.293	0.187	0.229	0.260	0.151	0.186	0.213	0.112	0.141	0.163
50	*p*-CH_3	10.1	14.0	21.7	9.34	13.1	20.3	8.16	11.8	18.1	6.86	9.99	15.5
	H	4.38	6.67	10.4	3.95	6.11	9.49	3.32	5.20	8.12	2.66	4.13	6.53
	p-Cl	1.51	2.21	2.73	1.35	1.97	2.44	1.11	1.63	2.02	0.864	1.27	1.57
	m-NO_2	0.137	0.155	0.191	0.120	0.135	0.168	0.0955	0.109	0.136	0.0657	0.0761	0.0950

% (v/v) MeOH	X in $XC_6H_4NH_2$	Y = H			Y = *p*-Cl		
		Z = *p*-NO_2	Z = *p*-Cl	Z = *p*-NO_2	Z = *p*-NO_2	Z = *p*-Cl	Z = *p*-NO_2
100	*p*-CH_3	120	42.8	10.7	1.45	2.17	2.64	8.92
	H	42.8	12.5	3.27	0.599	0.288	0.203	0.487
	p-Cl	10.7	3.27	2.73	0.203	0.183	0.345	0.702	0.248	0.771	0.156	0.227	0.487
	m-NO_2	0.599	0.288	0.203	0.248	0.345	0.702	0.248	0.771	0.156	0.227	0.487
80	*p*-CH_3	112	27.1	15.1	9.68	13.7	23.5	100
	H	34.6	10.5	6.62	3.71	5.79	8.66	30.3
	p-Cl	9.00	3.11	2.50	1.31	1.94	2.44	7.34
	m-NO_2	0.503	0.213	0.186	0.112	0.141	0.163	0.387
50	*p*-CH_3	93.1	18.1	11.8	6.86	9.99	15.5	83.1
	H	31.0	8.12	5.20	2.66	4.13	6.53	26.1
	p-Cl	7.72	2.02	1.63	0.864	1.27	1.57	6.99
	m-NO_2	0.359	0.136	0.109	0.0657	0.0761	0.0950	0.246

straight line. Apparently the benzenesulfonic acid produced in the reaction caused reversion of the product 1-phenylethyl methyl ether back to the reactants. It is known that acids can cleave 1-phenylethyl ethers readily at room temperature.[4,6] We therefore used k_1^{obsd} values for these reactions obtained from the slopes of the initial straight line parts of the plots. The plots of eq 3 then gave good linearities with correlation coefficients ≥0.990, and the intercepts k_1 agreed with the values determined independently by methanolysis.

Effect of Substituents. Table II indicates that the rate increases with a strong nucleophile (X = *p*-CH_3) and with a good leaving group (Z = *p*-NO_2). A small rate decrease is also found with a more electron-withdrawing substituent in the substrate (Y = *p*-Cl). Variations of Hammett ρ_X and Brønsted β_N parameters (obtained by varying X in the nucleophile) with substituents Y in the substrate and Z in the leaving group are summarized in Table III. The ρ_X values are relatively large and negative, indicating considerable charge transfer from the nucleophile to the substrate, and hence considerable bond formation, in the TS. The magnitudes of ρ_X and β_N increase with a better leaving group (Z = *p*-NO_2) and with a more electron-withdrawing substituent in the substrate (Y = *p*-Cl).

The ρ_Z and β_{lg} values (obtained by varying substituent Z in the leaving group) are shown in Table IV. The magnitudes of ρ_Z and β_{lg} increase with a more electron-donating substituent in the nucleophile (X = *p*-CH_3) and with a more electron-withdrawing substituent in the substrate (Y = *p*-Cl). Thus a stronger nucleophile leads to a greater degree of bond breaking, and a stronger nucleofuge (Z = *p*-NO_2) leads to tighter bond formation. An electron-withdrawing group (Y = *p*-Cl) in the substrate seems to enhance both bond formation and bond cleavage. This type of push–pull behavior between the nucleophile and nucleofuge in the TS is general in the dissociative S_N2 mechanism[7,8] and is also in agreement with the predictions of the MO theoretical model for assessing effects of substituents on the TS in S_N2-type reactions.[8]

The interaction between the nucleophile and leaving group in the TS is evidence for a concerted S_N2 displacement mechanism for reaction 2. However, steric hindrance by the methyl group of the 1-phenylethyl system should decrease the amount of bond formation and increase the cationic character of the TS compared with that in substitution reactions of benzyl derivatives.

Although a better correlation is obtained with σ^+ in the Hammett plots for the solvolysis of substituted 1-phenylethyl chlorides,[3] we found plots with normal σ values for substituents Y in the substrate more satisfactory. Examples of ρ values determined with σ_Y and σ_Y^+ are compared in Table V; correlations are deteriorated in the plots with σ^+ (ρ_Y^+). The better correlation obtained with σ and the relatively small values of ρ_Y indicate that the positive charge development at the α carbon is not sufficient to warrant $\rho_Y^+\sigma_Y^+$ plots. The magnitude of ρ_Y, determined with σ_Y (Table VI), is greater with a weaker nucleophile (X = *m*-NO_2) and nucleofuge (Z = *p*-CH_3). Since the magnitude of ρ_Y (<0) is a measure of positive charge development at the reaction center in the TS, a greater $|\rho_Y|$ value for a less nucleophilic entering group

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Table III. Hammett ρ_X[a] (β_N[b]) Values for the Reaction of Y-1-Phenylethyl Z-Benzenesulfonates with X-Anilines in MeOH–MeCN at 25 °C

	Y = *p*-OCH_3				Y = *p*-CH_3				Y = H				Y = *p*-Cl			
% (v/v) MeOH	Z = *p*-CH_3	Z = H	Z = *p*-Cl	Z = *p*-NO_2	Z = *p*-CH_3	Z = H	Z = *p*-Cl	Z = *p*-NO_2	Z = *p*-CH_3	Z = H	Z = *p*-Cl	Z = *p*-NO_2	Z = *p*-CH_3	Z = H	Z = *p*-Cl	Z = *p*-NO_2
100	−2.02	−2.13	−2.22	−2.56	−2.04	−2.15	−2.24	−2.58	−2.07	−2.19	−2.27	−2.61	−2.13	−2.24	−2.32	−2.67
	(0.68)	(0.72)	(0.75)	(0.86)	(0.69)	(0.72)	(0.75)	(0.87)	(0.69)	(0.74)	(0.76)	(0.88)	(0.71)	(0.75)	(0.78)	(0.89)
80	−2.07	−2.12	−2.32	−2.59	−2.08	−2.17	−2.34	−2.59	−2.12	−2.23	−2.39	−2.65	−2.18	−2.26	−2.45	−2.72
	(0.70)	(0.71)	(0.78)	(0.87)	(0.70)	(0.73)	(0.79)	(0.87)	(0.71)	(0.75)	(0.80)	(0.89)	(0.73)	(0.76)	(0.82)	(0.91)
50	−2.12	−2.24	−2.37	−2.66	−2.14	−2.27	−2.40	−2.69	−2.19	−2.32	−2.44	−2.74	−2.28	−2.41	−2.54	−2.86
	(0.71)	(0.75)	(0.79)	(0.89)	(0.72)	(0.76)	(0.80)	(0.90)	(0.73)	(0.78)	(0.82)	(0.92)	(0.77)	(0.81)	(0.85)	(0.96)

[a] Correlation coefficients, $r > 0.998$. Hammett substituent constants, σ_X, used for these determinations were taken from: Gilliom, R. D. *Introduction to Physical Organic Chemistry*; Addision-Wesley: Reading, MA, 1970; p 147. [b] The pK_a values of anilines were taken from: Streitwieser, A., Jr.; Heathcock, C. H. *Organic Chemistry*, 2nd ed.; Macmillan: New York, 1976; p 737.

Table IV. Hammett ρ_Z[a] (β_{lg}[b]) Values for the Reaction of Y-1-Phenylethyl Z-Benzenesulfonates with X-Anilines in MeOH–MeCN at 25 °C

% (v/v) MeOH	X in $XC_6H_4NH_2$	Y = *p*-OCH_3	Y = *p*-CH_3	Y = H	Y = *p*-Cl
100	*p*-CH_3	1.02 (−0.34)	1.03 (−0.34)	1.05 (−0.35)	1.08 (−0.36)
	H	0.95 (−0.32)	0.95 (−0.32)	0.97 (−0.32)	1.00 (−0.33)
	p-Cl	0.74 (−0.25)	0.74 (−0.25)	0.79 (−0.26)	0.81 (−0.27)
	m-NO_2	0.53 (−0.18)	0.54 (−0.18)	0.56 (−0.19)	0.60 (−0.20)
80	*p*-CH_3	1.02 (−0.34)	1.04 (−0.35)	1.07 (−0.36)	1.08 (−0.36)
	H	0.90 (−0.30)	0.90 (−0.30)	0.92 (−0.31)	0.95 (−0.32)
	p-Cl	0.72 (−0.24)	0.74 (−0.25)	0.75 (−0.25)	0.77 (−0.26)
	m-NO_2	0.52 (−0.17)	0.54 (−0.18)	0.55 (−0.18)	0.56 (−0.19)
50	*p*-CH_3	1.11 (−0.37)	1.11 (−0.37)	1.12 (−0.37)	1.15 (−0.38)
	H	0.97 (−0.33)	0.99 (−0.33)	1.01 (−0.34)	1.04 (−0.35)
	p-Cl	0.86 (−0.29)	0.86 (−0.29)	0.88 (−0.29)	0.95 (−0.32)
	m-NO_2	0.60 (−0.20)	0.61 (−0.21)	0.62 (−0.21)	0.62 (−0.21)

[a] Correlation coefficients, $r > 0.990$. The σ_Z values were taken from the same source as those for σ_X in Table III. [b] The $pK_{lg}^{CH_3}$ values for methyl transfer from substituted arenesulfonates to benzenesulfonates in sulfolane were used in the β_{lg} determination: Hoffmann, R. V.; Sharkweiler, J. M. *J. Am. Chem. Soc.* **1986**, *108*, 5536.

Table V. Comparison of ρ Values Obtained with σ_Y (ρ_Y) and σ_Y^+ (ρ_Y^+)[a]

	Z = *p*-CH_3	Z = H	Z = *p*-Cl	Z = *p*-NO_2
ρ_Y	−0.39 (0.998)	−0.41 (0.999)	−0.36 (1.000)	−0.30 (1.000)
ρ_Y^+	−0.17 (0.962)	−0.18 (0.978)	−0.15 (0.973)	−0.13 (0.976)

[a] In methanol, with X = H at 25.0 °C. Values in parentheses are correlation coefficients. The σ_Y and σ_Y^+ values are taken from the same source as those for σ_X in Table III.

reflects less charge transfer from the nucleophile to the reaction center, resulting in less neutralization of positive charge. However, a smaller $|\rho_Y|$ value for a stronger nucleofugic group (*p*-NO_2) reflects more bond formation than bond cleavage with an increase in nucleofugic strength of the leaving group. This must mean that the change in the degree of bond breaking with nucleofugic strength is less than that in bond formation, since bond breaking is much more advanced in the TS as indicated by the negative values of ρ_Y.

Although we can use the magnitudes of ρ_X and ρ_Z as measures of bond formation and bond cleavage, respectively, this is only feasible within a series of reactions, since the efficiency of charge transmission may differ in different reaction series.[4b] On the other hand, cross interaction constants[4] are not affected by variable charge transmission and therefore provide a better measure of the TS structure. The magnitudes of cross interaction constants ρ_{XY} (Table VII) are relatively small. For S_N2 reactions involving aniline nucleophiles the $|\rho_{XY}|$ values range from 0.60 to 1.20,[9]

Table VI. Hammett ρ_Y Values[a] for the Reaction of Y-1-Phenylethyl Z-Benzenesulfonates with X-Anilines in MeOH–MeCN at 25 °C

% (v/v) MeOH	X in $XC_6H_4NH_2$	Z = *p*-CH_3	Z = H	Z = *p*-Cl	Z = *p*-NO_2
100	*p*-CH_3	−0.33	−0.29	−0.27	−0.20
	H	−0.39	−0.41	−0.36	−0.30
	p-Cl	−0.47	−0.45	−0.41	−0.32
	m-NO_2	−0.53	−0.50	−0.45	−0.40
80	*p*-CH_3	−0.34	−0.28	−0.27	−0.22
	H	−0.42	−0.33	−0.37	−0.30
	p-Cl	−0.48	−0.46	−0.45	−0.39
	m-NO_2	−0.55	−0.53	−0.51	−0.48
50	*p*-CH_3	−0.34	−0.29	−0.29	−0.25
	H	−0.43	−0.42	−0.40	−0.32
	p-Cl	−0.49	−0.48	−0.48	−0.33
	m-NO_2	−0.64	−0.62	−0.60	−0.61

[a] Correlation coefficients, $r > 0.993$. The σ_Y values are taken from the same source as those for σ_X in Table III.

and hence the $|\rho_{XY}|$ of 0.21–0.25 in methanol (Table VII) is less than half the values for the S_N2 reactions, indicating much less bond formation in the TS of reaction 2. The magnitude of ρ_{XY}, and hence the degree of bond formation in the TS, is greater with a stronger nucleofugic group (Z = *p*-NO_2), which agrees with our conclusion based on the magnitudes of ρ_X and ρ_Z. Moreover, we find that values of $|\rho_{YZ}|$ are even smaller, indicating a grossly dissociative nature of the TS for this reaction. The magnitudes of ρ_{YZ} are comparable to those for the dissociative S_N2 reactions of benzyl benzenesulfonates with anilines in methanol (ρ_{YZ} = 0.11 for X = H).[5a,10] The value of $|\rho_{YZ}|$ decreases, and

(9) Substituted (X) anilines reacting with various substrate (with Y) gave the following ρ_{XY} values: $YC_6H_4CH_2SO_2Cl \xrightarrow{MeOH,\ 35\ °C}$, ρ_{XY} = −0.69 (Kang, H. K. Ph.D. Thesis, Inha University); $YC_6H_4SO_2Cl \xrightarrow{MeOH,\ 35\ °C}$, ρ_{XY} = −0.70 (Lee, I.; Koo, I. S. *Tetrahedron* **1983**, *39*, 1803); $YC_6H_4CH_2Cl \xrightarrow{MeOH,\ 50\ °C}$, ρ_{XY} = −0.77 (Ballistreri, F. P.; Maccarone, E.; Mamo, A. *J. Org. Chem.* **1976**, *41*, 3364) $YC_6H_4CH_2OSO_2C_6H_4 \xrightarrow{MeOH,\ 35\ °C}$, ρ_{XY} = −0.62 (ref 5a); $YC_6H_4CH_2SO_2F \xrightarrow{MeOH,\ 45\ °C}$, ρ_{XY} = −1.24 (ref 5b).

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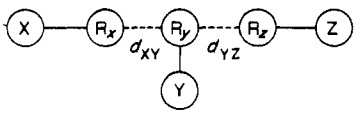
Table VII. ρ_i, ρ_j, and ρ_{ij} Values for the Reaction of Y-1-Phenylethyl Z-Benzenesulfonates with X-Anilines in MeOH–MeCN at 25.0 °C

% (v/v) MeOH	Z	ρ_X	ρ_Y	ρ_{XY}	CC[a]	% (v/v) MeOH	X	ρ_Y	ρ_Z	ρ_{YZ}	CC[a]	% (v/v) MeOH	Y	ρ_X	ρ_Z	ρ_{XZ}	CC[a]
100	*p*-CH_3	−2.07	−0.39	−0.22	0.999	100	*p*-CH_3	−0.30	1.04	0.10	0.997	100	*p*-OCH_3	−2.11	0.91	−0.55	0.999
	H	−2.20	−0.37	−0.21	0.999		H	−0.39	0.97	0.11	0.999		*p*-CH_3	−2.13	0.91	−0.55	0.999
	p-Cl	−2.27	−0.34	−0.23	1.000		*p*-Cl	−0.45	0.78	0.13	0.991		H	−2.17	0.95	−0.56	0.999
	p-NO_2	−2.61	−0.25	−0.25	1.000		*m*-NO_2	−0.50	0.56	0.14	0.997		*p*-Cl	−2.22	0.98	−0.56	0.999
80	*p*-CH_3	−2.12	−0.41	−0.23	1.000	80	*p*-CH_3	−0.30	1.06	0.11	0.998	80	*p*-OCH_3	−2.16	0.90	−0.56	0.999
	H	−2.18	−0.34	−0.26	0.999		H	−0.37	0.92	0.10	1.000		*p*-CH_3	−2.17	0.91	−0.56	0.999
	p-Cl	−2.39	−0.35	−0.26	1.000		*p*-Cl	−0.47	0.75	0.10	0.995		H	−2.21	0.93	−0.58	0.999
	p-NO_2	−2.65	−0.29	−0.28	1.000		*m*-NO_2	−0.53	0.55	0.10	0.991		*p*-Cl	−2.28	0.95	−0.58	0.999
50	*p*-CH_3	−2.18	−0.41	−0.24	1.000	50	*p*-CH_3	−0.31	1.13	0.10	0.995	50	*p*-OCH_3	−2.23	1.00	−0.56	0.999
	H	−2.32	−0.38	−0.28	0.999		H	−0.42	1.01	0.12	0.999		*p*-CH_3	−2.26	1.00	−0.56	0.999
	p-Cl	−2.44	−0.38	−0.27	0.999		*p*-Cl	−0.48	0.90	0.15	0.990		H	−2.30	1.02	−0.56	0.999
	p-NO_2	−2.74	−0.30	−0.31	1.000		*m*-NO_2	−0.56	0.61	0.15	0.999		*p*-Cl	−2.36	1.05	−0.60	0.999

[a] Multiple correlation coefficients.

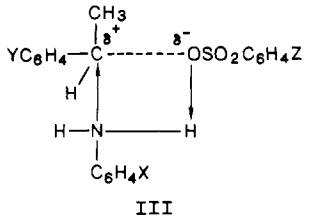
hence bond cleavage increases, with a stronger nucleophile (*p*-CH_3), which is also consistent with our conclusion based on the magnitudes of ρ_X and ρ_Z.

The TS involved in an S_N-type reaction can be schematically represented as II. It consists of three fragments:



II

a nucleophile with substituent X and reaction center R_X, a substrate with Y and R_Y, and a leaving group with Z and R_Z. Since the polar and resonance effects of the substituents are transmitted through reaction centers R_X, R_Y, and R_Z, the magnitude of cross interaction will be inversely proportional to the distances between reaction centers,[5a] $|\rho_{XY}| \propto 1/d_{XY}$, $|\rho_{YZ}| \propto 1/d_{YZ}$, and $|\rho_{XZ}| \propto 1/(d_{XY} + d_{YZ})$. The lengths of carbon chains connecting substituents to the reaction centers may be considered to remain constant in the activation process for all practical purposes. Thus in the nucleophilic substitution reactions (S_N1 and S_N2), we should expect the $|\rho_{XZ}|$ value to be the smallest among the three cross interaction constants $|\rho_{XY}|$, $|\rho_{YZ}|$, and $|\rho_{XZ}|$, since $(d_{XY} + d_{YZ})$ is greater than either d_{XY} or d_{YZ}. The $|\rho_{XZ}|$ values for the reactions of benzyl benzenesulfonates with anilines were in fact found to be the smallest ($\simeq$0.10).[5a,10] In contrast, the $|\rho_{XZ}|$ for reaction 2 (Table VII) is the greatest of the three. This unusual enhancement of the cross interaction between X and Z can only be rationalized by a four-center TS (III), i.e., by an intermolecular S_Ni mechanism.[4] The two substituents X and Z in III can interact by two routes; the additional interaction route is provided by a bypass hydrogen-bond bridge, so that the approach of the nucleophile aniline is restricted to the front side, leading to retention of configuration in the amine product. Since the two TS structures I and III are essentially the same, the mechanism proposed by Okamoto et al.[4] for the phenolysis of 1-phenylethyl derivatives supports the same mechanism for reaction 2.



III

One way of confirming the four-center TS is to compare the $|\rho_{XZ}|$ values for a reaction with a nucleophile having no hydrogen atoms for bridge formation, e.g., *N*,*N*-dimethylanilines (DMA), with the $|\rho_{XZ}|$ values in Table VII. Kinetic studies with DMAs conducted under the same conditions used in reaction 2 gave markedly smaller values of $|\rho_{XZ}|$, 0.23–0.25,[11] about half that for anilines. The impossibility of hydrogen-bond bridge formation should be the main cause of the smaller $|\rho_{XZ}|$. However, the rather large $|\rho_{XZ}|$ value for the DMA reaction compared to that for dissociative S_N2 reactions ($|\rho_{XZ}| \simeq 1.0$)[5a] may indicate a direct electrostatic interaction between R_X and R_Z in reactions with DMA and with anilines. Another possible origin of the relatively large $|\rho_{XZ}|$ values for the DMA reaction is a greater degree of bond formation, DMA being a better nucleophile. The $|\rho_{XY}|$ values of 0.35–0.39 with DMAs indicate some increase in bond formation compared with the reaction with anilines, for which $|\rho_{XY}|$ values are 0.21–0.25.

Effect of Solvent. The increase in rate with increase in the methanol content of the solvent (Tables I and II) is consistent with electrophilic assistance and bond cleavage by methanol, although the effect is relatively small. The magnitudes of ρ_X, ρ_Z, ρ_{XY}, and ρ_{YZ} indicate that bond formation as well as bond breaking increases with the acetonitrile content of solvent. However, the increase in the magnitude of ρ_{XZ} with acetonitrile content indicates that the increase in bond formation is somewhat greater than that in bond breaking, as discussed under substituent effects. Although the rate decreases, both bond formation and cleavage increase in the TS with acetonitrile content. This implies that the TS becomes less stable, and hence the activation barrier becomes higher, with an increase in acetonitrile content, but the TS shifts to a later position on the reaction coordinate in accord with the Hammond postulate.[12]

The ratio of a/s derived from Taft's solvatochromic equation (eq 4) is a measure of the contribution of hydrogen bond donor acidity (α) relative to that of the polarity polarizability (π^*) of solvent in the TS. For aniline nucleophiles the hydrogen bond acceptor basicity contribution of solvent ($b\beta$) was found to be negligible.[13] The value of a/s in normal S_N2 reactions is 0.5–0.7[13,14] and is greater in S_N1 reactions.[13] We determined 64 values of a/s for reaction 2 using three solvent mixtures and found an average value of 0.28, which is remarkably lower than those

$$\log k = a\alpha + s\pi^* + b\beta + \text{constant} \quad (4)$$

(11) Lee, I.; Kim, H. Y.; Lee, H. W., submitted for publication.
(12) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.
(13) Kamlet, M. J.; Abboud, J. L.; Taft, R. W. *Prog. Phys. Org. Chem.* **1981**, *13*, 485.
(14) Kang, H. K. Ph.D. Thesis, Inha University, 1987, p 48.

for other S_N reactions. It appears therefore that the hydrogen bond donor acidity of the solvent in assisting electrophilic bond cleavage of the leaving group in reaction 2 contributes much less than in other S_N reactions. This is consistent with the intermolecular S_Ni mechanism for reaction 2, since the TS with the four-center structure III is most likely to show less response to hydrogen-bonding assistance in the bond cleavage of the leaving group. Thus solvent effects also support an intermolecular S_Ni mechanism in reaction 2.

Experimental Section

Materials. Anilines were purified as described previously.[10a] G.R. grade solvents MeOH and MeCN were used without further purification. Substituted acetophenones (Tokyo Kasei Chemicals) were redistilled and recrystallized.

Preparation of Substituted 1-Phenylethyl Benzenesulfonates. The method of Tipson[15] was used. To the acetophenone was added $LiAlH_4$ (10%), and the mixture was refluxed with stirring at room temperature for ~12 h. The resulting 1-phenylethyl alcohols were distilled under reduced pressure, treated with NaH for ~1 h, and then reacted with the benzenesulfonyl halide for ~12 h at 0 °C. The mixture was filtered and the ether evaporated. Liquid esters were distilled. Solid esters were recrystallized from ether and dried in a vacuum oven. Purity was confirmed by a single spot in TLC (silica gel plate, eluent 40% dichloromethane–cyclohexane).

1-(*p*-Methoxyphenyl)ethyl tosylate: mp 50–51 °C; R_f (TLC) 0.41; IR (KBr) 1625, 1525, 1470, 1370, 1165 cm^{-1}; ^1H NMR δ 2.2 (s, 3 H, CH_3), 2.4 (s, 3 H, CH_3), 3.9 (s, 3 H, OCH_3), 5.0 (q, J = 6.0 Hz, 1 H), 7.05–7.21 (d, J = 8.3 Hz, 4 H), 7.19–7.37 (d, J = 8.0 Hz, 4 H). Anal. Calcd for $C_{16}H_{18}O_4S$: C, 61.55; H, 5.91. Found: C, 61.23; H, 5.86.

1-(*p*-Methylphenyl)ethyl tosylate: mp 37–39 °C; R_f (TLC) 0.57; IR (KBr) 1605, 1507, 1380, 1357, 1155, 825 cm^{-1}; ^1H NMR δ 2.14 (d, J = 6.0 Hz, 3 H, CH_3), 2.20 and 2.24 (s, 3 H, CH_3), 4.72 (s, 1 H), 6.90–7.12 (d, J = 8.0 Hz, 4 H, ar), 6.95–7.28 (d, J = 8.3 Hz, 4 H, ar). Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25. Found: C, 66.21; H, 6.01.

1-(*p*-Chlorophenyl)ethyl tosylate: mp 56–57 °C; R_f (TLC) 0.41; IR (KBr) 1625, 1527, 1470, 1365, 1095, 915 cm^{-1}; ^1H NMR δ 2.17 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 4.80 (q, J = 6.0 Hz, 1 H), 7.01–7.18 (d, J = 8.5 Hz, 4 H, ar), 7.2–7.29 (s, 4 H, ar). Anal. Calcd for $C_{15}H_{15}O_3SCl$: C, 57.97; H, 4.86. Found: C, 57.11; H, 4.91.

1-Phenylethyl tosylate: mp 32–33 °C; R_f (TLC) 0.59; IR (KBr) 1615, 1507, 1455, 1325, 1155, 856 cm^{-1}; ^1H NMR δ 2.08 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 4.66 (q, J = 6.5 Hz, 1 H), 6.90–7.11 (s, 5 H, ar), 7.12–7.25 (d, J = 7.5 Hz, 4 H, ar). Anal. Calcd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84. Found: C, 64.78; H, 5.93.

1-(*p*-Methoxyphenyl)ethyl benzenesulfonate: mp 84 °C; R_f (TLC) 0.39; IR (neat) 1610, 1555, 1450, 1340, 1275, 1160 cm^{-1}; ^1H NMR δ 1.74 (s, 3 H, CH_3), 3.67 (s, 3 H, OCH_3), 4.52 (s, 1 H), 6.73–7.01 (d, J = 8.0 Hz, 4 H, ar), 6.97–7.29 (s, 5 H, ar).

1-(*p*-Methylphenyl)ethyl benzenesulfonate: mp 83–84 °C; R_f (TLC) 0.47; IR (neat) 1607, 1547, 1430, 1335, 1160, 855 cm^{-1}; ^1H NMR δ 1.72 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 4.47 (s, 1 H), 6.80–7.01 (d, J = 8.0 Hz, 4 H, ar), 7.03–7.22 (s, 5 H, ar).

1-Phenylethyl benzenesulfonate: mp 56–57 °C; R_f (TLC) 0.48; IR (neat) 1627, 1557, 1455, 1345, 1170, 870 cm^{-1}; ^1H NMR δ 1.74 (s, 3 H, CH_3), 4.53 (s, 1 H), 6.72–6.97 (s, 5 H, ar), 6.90–7.21 (s, 5 H, ar).

1-(*p*-Chlorophenyl)ethyl benzenesulfonate: mp 64 °C; R_f (TLC) 0.36; IR (neat) 1620, 1570, 1365, 1175, 1097, 865 cm^{-1}; ^1H NMR δ 2.11 (s, 3 H, CH_3), 4.72 (s, 1 H), 6.92–7.11 (s, 4 H, ar), 7.07–7.24 (s, 5 H, ar).

1-(*p*-Methoxyphenyl)ethyl *p*-chlorobenzenesulfonate: mp 57–59 °C; R_f (TLC) 0.36; IR (Nujol) 1635, 1535, 1465, 1365, 1165, 1100, 920 cm^{-1}; ^1H NMR δ 2.25 (s, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 4.85 (s, 1 H), 7.11–7.28 (s, 4 H, ar), 7.29–7.42 (s, 4 H, ar). Anal. Calcd for $C_{15}H_{15}O_4SCl$: C, 55.13; H, 4.63. Found: C, 54.51; H, 4.61.

1-(*p*-Methylphenyl)ethyl *p*-chlorobenzenesulfonate: mp 44–46 °C; R_f (TLC) 0.44; IR (Nujol) 1617, 1511, 1385, 1347, 1154, 1095, 850 cm^{-1}; ^1H NMR δ 2.24 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 4.82 (s, 1 H), 7.11–7.32 (d, J = 8.5 Hz, 4 H, ar), 7.29–7.52 (s, 4 H, ar). Anal. Calcd for $C_{15}H_{15}O_3SCl$: C, 57.97; H, 4.86. Found: C, 58.01; H, 4.81.

1-Phenylethyl *p*-chlorobenzenesulfonate: mp 38–39 °C; R_f (TLC) 0.46; IR (Nujol) 1630, 1535, 1461, 1349, 1161, 1097, 917 cm^{-1}; ^1H NMR δ 2.17 (s, 3 H, CH_3), 4.69 (q, J = 6.0 Hz, 1 H), 7.07–7.29 (s, 5 H, ar), 7.30–7.54 (s, 4 H, ar). Anal. Calcd for $C_{14}H_{13}O_3SCl$: C, 56.66; H, 4.42. Found: C, 56.61; H, 4.43.

1-(*p*-Chlorophenyl)ethyl *p*-chlorobenzenesulfonate: mp 62–64 °C; R_f (TLC) 0.33; IR (Nujol) 1643, 1537, 1480, 1371, 1169, 1090, 927 cm^{-1}; ^1H NMR δ 2.31 (s, 3 H, CH_3), 4.91 (s, 1 H), 7.24–7.46 (s, 4 H, ar), 7.49–7.63 (s, 4 H, ar). Anal. Calcd for $C_{14}H_{12}O_3SCl_2$: C, 50.77; H, 3.65. Found: C, 50.71; H, 3.73.

1-(*p*-Methoxyphenyl)ethyl *p*-nitrobenzenesulfonate: mp 78–80 °C; R_f (TLC) 0.32; IR (KBr) 1645, 1560, 1547, 1410, 1360, 1347, 945 cm^{-1}; ^1H NMR δ 2.33 (s, 3 H, CH_3), 4.37 (s, 3 H, OCH_3), 5.01 (s, 1 H), 7.52–7.76 (s, 4 H, ar), 7.74–8.01 (s, 4 H, ar). Anal. Calcd for $C_{15}H_{15}O_6NS$: C, 53.41; H, 4.48; N, 4.15. Found: C, 52.89; H, 4.52; N, 4.02.

1-(*p*-Methylphenyl)ethyl *p*-nitrobenzenesulfonate: mp 74–76 °C; R_f (TLC) 0.37; IR (KBr) 1550, 1469, 1345, 1344, 1160 cm^{-1}; ^1H NMR δ 2.31 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 4.97 (q, J = 6.5 Hz, 1 H), 7.48–7.71 (d, J = 9 Hz, 4 H, ar), 7.70–7.95 (s, 4 H, ar). Anal. Calcd for $C_{15}H_{15}O_5NS$: C, 56.06; H, 4.71; N, 4.35. Found: C, 56.01; H, 4.73; N, 4.29.

1-Phenylethyl *p*-nitrobenzenesulfonate: mp 68–70 °C; R_f (TLC) 0.38; IR (KBr) 1644, 1555, 1545, 1405, 1350, 1346, 946 cm^{-1}; ^1H NMR δ 2.33 (s, 3 H, CH_3), 5.00 (s, 1 H), 7.51–7.75 (s, 5 H, ar), 7.73–8.01 (s, 4 H, ar). Anal. Calcd for $C_{14}H_{13}O_5NS$: C, 54.72; H, 4.26; N, 4.56. Found: C, 54.14; H, 4.17; N, 4.17.

1-(*p*-Chlorophenyl)ethyl *p*-nitrobenzenesulfonate: mp 85–86 °C; R_f (TLC) 0.28; IR (KBr) 1645, 1560, 1550, 1365, 1351, 1215, 950 cm^{-1}; ^1H NMR δ 2.45 (s, 3 H, CH_3), 5.11 (s, 1 H), 7.55–7.80 (s, 4 H, ar), 7.79–8.11 (s, 4 H, ar). Anal. Calcd for $C_{14}H_{12}O_5NSCl$: C, 49.20; H, 3.54; N, 4.10. Found: C, 49.14; H, 3.56; N, 4.07.

Rate Constants. Rates were measured conductometrically at 25.0 °C. Pseudo-first-order rate constants k_1^{obsd} were determined by the method of Guggenheim with a large excess of the aniline. Second-order rate constants k_2 were obtained from the slope of a plot of k_1^{obsd} vs [aniline] (eq 3), where k_1 is the rate constant for methanolysis. Four or more different concentrations of the aniline were used in the plot of eq 3. Duplicate kinetic runs showed that rates were reproducible within ±3%.

Reactions of sulfonates with anilines were followed by IR using the disappearance of the aniline peak at 1600–1650 cm^{-1}, the appearance of the NH peak at 3200–3500 cm^{-1}, and the increase in the C–N peak at 1250 cm^{-1}.

The product anilide and the byproduct methyl ether were separated from the reaction mixture by TLC, using R_f values that had been determined independently. IR spectra were taken with a Nicolet MX-1 FT-IR on a KBr tablet. Typical spectral data are as follows.

1-(*p*-Methoxyphenyl)ethyl benzanilide: R_f 0.59; IR (KBr) 3400, 3050, 1630, 1250, 1180, 850, 650 cm^{-1}; ^1H NMR δ 2.5 (s, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 4.25 (q, J = 6.0 Hz, 1 H), 6.80–7.10 (d, J = 8.0 Hz, 4 H, ar), 7.20–7.50 (q, J = 7.5 Hz, 5 H, ar). Anal. Calcd for $C_{15}H_{17}ON$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.11; H, 7.56; N, 6.24.

1-(*p*-Methoxyphenyl)ethyl methyl ether: R_f 0.35; IR (neat) 2940, 2840, 1610, 1515, 1450, 1375, 1290, 1250, 1180, 1105, 1040, 840 cm^{-1}; ^1H NMR δ 1.30 (d, J = 6.0 Hz, 3 H, CH_3), 3.05 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 4.05 (q, J = 6.0 Hz, 1 H), 6.50–6.90 (q, J = 8.0 Hz, 4 H, ar). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.20; H, 8.57.

Acknowledgment. We thank the Ministry of Education and the Korea Science and Engineering Foundation for support of this work.

Registry No. *p*-$H_3CC_6H_4NH_2$, 106-49-0; $C_6H_5NH_2$, 62-53-3; *p*-$ClC_6H_4NH_2$, 106-47-8; *m*-$O_2NC_6H_4NH_2$, 99-09-2; *p*-$H_3COC_6H_4CH(CH_3)OSO_2C_6H_4$-*p*-$CH_3$, 114200-06-5; *p*-

(15) (a) Tipson, R. S. *J. Org. Chem.* **1944**, *9*, 235. (b) Perin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: Oxford, 1980.

$H_3COC_6H_4CH(CH_3)OSO_2C_6H_5$, 114200-07-6; *p*-$H_3COC_6H_4CH(CH_3)OSO_2C_6H_4$-*p*-Cl, 114200-08-7; *p*-$H_3COC_6H_4CH(CH_3)OSO_2C_6H_4$-*p*-$NO_2$, 114200-09-8; *p*-$H_3CC_6H_4CH(CH_3)OSO_iC_6H_4$-*p*-$CH_3$, 82925-34-6; *p*-$H_3CC_6H_4CH(CH_3)OSO_2C_6H_5$, 114200-10-1; *p*-$H_3CC_6H_4CH(CH_3)OSO_2C_6H_4$-*p*-Cl, 114200-11-2; *p*-$H_3CC_6H_4CH(CH_3)OSO_2C_6H_4$-*p*-$NO_2$, 114200-12-3; $C_6H_5CH(CH_3)OSO_2C_6H_4$-*p*-$CH_3$, 6749-54-8; $C_6H_5CH(CH_3)OSO_2C_6H_5$, 113694-01-2; $C_6H_5CH(CH_3)OSO_2C_6H_4$-*p*-Cl, 114200-13-4; $C_6H_5CH(CH_3)OSO_2C_6H_4$-*p*-$NO_2$, 114200-14-5; *p*-$ClC_6H_4CH(CH_3)OSO_2C_6H_4$-*p*-$CH_3$, 114200-15-6; *p*-$ClC_6H_4CH(CH_3)OSO_2C_6H_5$, 114200-16-7; *p*-$ClC_6H_4CH(CH_3)OSO_2C_6H_4$-*p*-Cl, 114200-17-8; *p*-$ClC_6H_4CH(CH_3)OSO_2C_6H_4$-*p*-$NO_2$, 114200-18-9; *p*-Methoxyacetophenone, 100-06-1; *p*-methylacetophenone, 122-00-9; *p*-chloroacetophenone, 99-91-2; acetophenone, 98-86-2; 1-(*p*-methoxyphenyl)ethyl benzanilide, 114200-19-0; 1-(*p*-methoxyphenyl)ethyl methyl ether, 77525-91-8.

A Novel Carbon–Carbon Bond Formation Reaction at the C_4 Position of an Azetidin-2-one by Means of Radical Cyclization[1]

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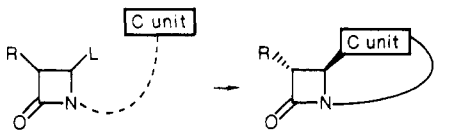
A novel synthesis of carbacepham and carbacephem ring systems through 1,6-bond coupling by a radical cyclization reaction is described.

Recently much attention has been focused on the exploration of a synthetic strategy for nonclassical β-lactam antibiotics, such as thienamycin[2] and PS-5,[3] originating from their attractive physiological activities.[4] Among the number of synthetic routes[5] the carbon–carbon bond formation reaction at the C_4 position of an azetidinone has become of increasing interest[6] (Scheme I). We have already reported a new carbon–carbon bond formation reaction at the C_4 position of an azetidinone by employing an enolate anion[7] and carbene species[6] as nucleophiles, and the application of this reaction led to a short synthesis of PS-5 antibiotics.[8] As an extension of our work on the synthesis of nonclassical β-lactam antibiotics, we have explored the radical cyclization reaction[9] of 4-(phenylthio)azetidin-2-one.

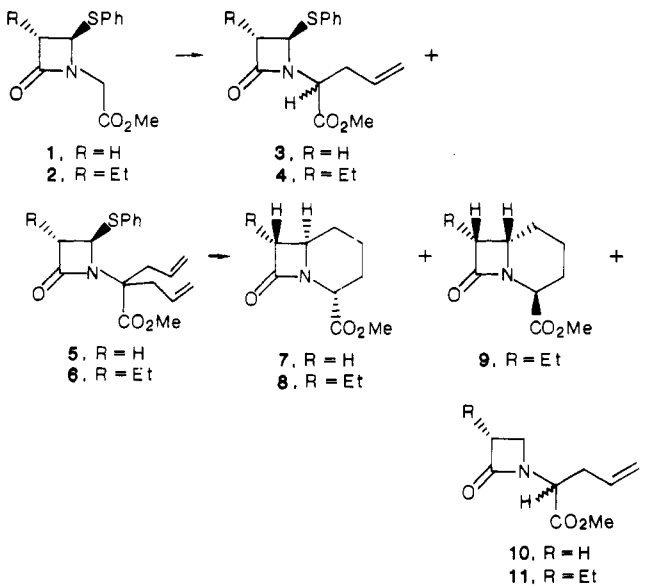
Results and Discussion

Alkylation of *N*-[(methoxycarbonyl)methyl]-4-(phenylthio)azetidin-2-one (1) with allyl bromide in the presence of lithium hexamethyldisilazide in dry tetrahydrofuran at −78 °C gave the allyl derivative **3** as an inseparable mixture of diastereomers in a ratio of 2:3, in 77% yield, together with the diallyl compound **5**. Radical cyclization of the mixture **3** was carried out by treatment with tri-*n*-butyltin hydride in the presence of a catalytic amount of α,α′-azobis(isobutyronitrile) (AIBN) for 18 h, yielding the carbacepham derivative **7** in 43% yield (66% yield based on consumed starting material), together with a small amount of the desulfurized compound **10**. Formation of a carbapenam ring system, which might be an another possible cyclization product, could not be observed under these conditions. This observation was rationalized by assuming that a larger energy would be required for the formation of the 1-azabicyclo[3.2.0]heptan-7-one ring system having a large strain energy than the 1-azabicyclo[4.2.0]octan-7-one ring system. Therefore, the formation of a carbacepham would be the predominant reaction, although a similar reaction[10] with the pyrrolidinone de-

Scheme I



Scheme II



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