Cross Interaction Constants As a Measure of the Transition State Structure (Part 2). Nucleophilic Substitution Reactions of Phenacyl Bromides with Aniline in Methanol-Acetonitrile Mixtures

Ikchoon Lee* and In Chul Kim

Department of Chemistry, Inha University, Inchon 402-751. Received January 13, 1988

Kinetics and mechanism of the nucleophilic substitution reactions of phenacyl bromides with anilines in methanol-acetonitrile mixtures at 45.00C are reported. The reaction is found to proceed via S_N2 process, but the magnitudes of cross interaction constants, ρ_{XY}, between substituents X in the nucleophile and Y in substrate were unusually small, even after allowing for the fall off due to non-conjugative intervening –CO group in the reactant. As in the other phenacyl derivatives, the resonance shunt phenomenon was invoked to explain the remarkable diminuation of the $|\rho_{XY}|$ values.
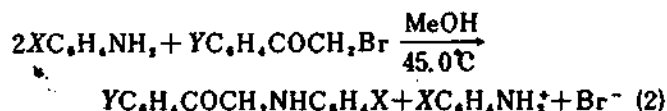
Introduction

The phenacyl derivatives have attracted considerable interest of organic[1] and theoretical chemists[2] due to the controversies surrounding the role played by the α-CO group in the rate enhancement. Recently it has been shown that the α-CO group participates in the enolate form, (I), giving extra stabilization of the transition state (TS).[2,3/4] This valence-

$$\overset{+}{N}\cdot \quad \overset{\displaystyle C}{\underset{\displaystyle \underset{R}{|}}{\underset{\displaystyle C——O^-}{\|}}} \quad \cdot L$$

(I)
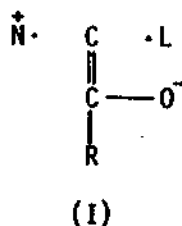
bond form of the carbanion configuration, (I), however dose not lead to an interaction between substituents X in the nucleophile (N) and Y in the substrate (R), but represents a structure in which the electronic changes on the reaction center carbon due to the charge transmission in the transition state leak to the α-CO group causing no cross interaction between the two substituents.[3/4] A remarkable consequence of this effect was found to be reflected in the unusually small cross interaction constants $|\rho_{XY}|$ in eq(1).[3]

$$\log (k_{XY}/k_{HH}) = \rho_X \sigma_X + \rho_Y \sigma_Y + \rho_{XY} \sigma_X \sigma_Y \qquad (1)$$

In this work we report the results of our kinetic investigations of the nucleophilic substitution reactions of phenacyl bromides with anilines in methanol-acetonitrile mixtures, (2).

$$2XC_6H_4NH_2 + YC_6H_4COCH_2Br \xrightarrow[\text{45.0°C}]{\text{MeOH}}$$

$$YC_6H_4COCH_2NHC_6H_4X + XC_6H_4NH_3^+ + Br^- \qquad (2)$$

X = *p*-OCH$_3$, *p*-CH$_3$, H, Cl ;

Y = H, *p*-Cl, *p*-NO$_2$

With the use of various selectivity parameters, we have discussed this "leak" or "shunt" phenomenon in the resonance[3/4] involved in the TS of the nucleophilic substitution reactions of phenacyl derivatives.

Results and Discussion

The second order rate constants, k_2 are summarized in Table 1. Reference to this Table shows that the rate is

Table 1. Second Order Rate Constants, k_2, ($\times 10^3 M^{-1} sec^{-1}$) for Reactions, $2XC_6H_4NH_2 + YC_6H_4COCH_2Br \longrightarrow YC_6H_4COCH_2\text{-}NHC_6H_4X + XC_6H_4NH_3^+ + Br^-$ in MeOH-MeCN Mixtures at 45.0°C

MeOH%v/v	X/Y	H	*p*-Cl	*p*-NO$_2$
	p-OCH$_3$	8.07	11.2	41.8
	p-CH$_3$	5.20	7.24	30.6
100	H	2.51(0.616)^a	3.78(0.923)	15.5(3.80)
	p-Cl	0.989	1.45	6.28
	p-OCH$_3$	5.46	7.39	30.1
	p-CH$_3$	3.61	4.99	21.3
80	H	1.77(0.427)	2.46(0.614)	11.1(2.51)
	p-Cl	0.658	0.926	4.34
	p-OCH$_3$	3.41	4.65	19.3
	p-CH$_3$	2.21	3.06	13.3
50	H	1.08(0.292)	1.51(0.399)	6.99(1.62)
	p-Cl	0.411	0.579	2.73

^{a}Values in parenthesis are those for phenacyl benzenesulfonates at the same reaction conditions.

Table 2. The Hammett ρ_X and Bronsted β_N ( ) values

MeOH%v/v	Y = H	*p*-Cl	*p*-NO$_2$
100	−1.82(0.66)	−1.76(0.64)	−1.67(0.60)
	[−1.99(0.72)]	−1.95(0.70)	−1.81(0.60)]^b
80	−1.84(0.66)	−1.81(0.65)	−1.69(0.61)
50	−1.84(0.66)	−1.81(0.66)	−1.70(0.61)

^{a}Correlation coefficients; r>0.998. ^{b} Values for phenacyl benzenesulfonates.

greater with a more electron donating substituent (EDS) in the nucleophile and with a more electron withdrawing substituent (EWS) in the substrate, suggesting the importance of the bond formation process in the transition state (TS). These reactivity trends are the same as those found for the reactions of phenacyl benzenesulfonates with anilines,[3/4] but the rates are faster by ca. 4 times than those of the benzenesulfonate series. the faster rate for bromide series should be due to the greater leaving ability of bromide compared to benzenesulfonate. This is supported by a small increase in the rate with the methanol content of the solvent, since methanol will assist bond breaking by weak hydrogen bon-

Table 3. The Hammett ρ_Y values[a]

MeOH% v/v X =	P-OCH₃	p-CH₃	H	p-Cl
100	0.56(0.57)[b]	0.60(0.60)	0.61(0.61)	0.63(0.63)
80	0.58	0.61	0.63	0.65
50	0.59	0.61	0.64	0.65

[a]Correlation coefficients; r>0.998. [b]Values in parenthesis are those for phenacyl benzenesulfonates.

Table 4. The Hammett coefficients and the cross interaction constants obtained by multiple regression using eq(1)

MeOH%v/v	ρ_X	ρ_Y	ρ_{XY}	corre. coeff.
100	−1.81	0.61	0.114	0.999
	(−1.97)[a]	(0.61)	(0.11)	(0.999)
80	−1.84	0.62	0.117	0.999
50	−1.83	0.63	0.107	0.999

[a]Values in parenthesis those for phenacyl benzenesulfonates.

ding to the anionic leaving group (LG).[4] The effects of substituents and the medium on the rate thus suggest that bond formation occures concertedly with bond breaking so that the reaction proceeds by the S_N2 mechanism.

The Hammett coefficients ρ_X obtained by the linear plots of log k_2 vs σ_X^5 (for substituents X in the nucleophile) are given in Table 2 together with the Bronsted β_N values.[6] The magnitudes of both ρ_X and β_N are relatively large indicating substantial charge transfer from the nucleophile in the TS, but are somewhat smaller than those for the benzenesulfonate series for which the rates were lower; between the two family of reactions, therefore, the reactivity-selectivity principle (RSP) holds.[7] The magnitudes of both ρ_X and β_N decrease, albeit small, with a more EWS in the substrate and with an increase in the methanol content of the medium; these selectivity trends are also in accord with the RSP.[7]

The simple Hammett coefficients, ρ_Y, for substituent (Y) variations in the substrate are presented in Table 3. The magnitudes of ρ_Y are similar to those of benzenesulfonate series, but here again $|\rho_Y|$ decreases with a more EDS in the nucleophile and with an increase in the MeOH content conforming to the RSP.[7]

The cross interaction constants, ρ_{XY}, determined by multiple regression analysis of the rate data in Table 1 using eq (1) are summarized in Table 4. The ρ_X and ρ_Y values obtained by the multiple regressin agree well with those obtained by the simple linear Hammett plots in Table 2 and 3 (values for X = Y = H).

In contrast to other S_N2 reaction series, the sign of ρ_{XY} for the phenacyl bromide series is positive indicating that a more EWS in the substrate, dσ_Y>0, leads to a less negative ρ_X and dρ_X >0, as can be seen in Table 2.

$$\rho_{xy} = \frac{\partial \rho_x}{\partial \sigma_y} > 0$$

The magnitude of ρ_{XY},~0.11, is similar to those for the reactions of phenacyl benzenesulfonates with anilines at 45.0 °C[3g] suggesting that a similar degree of bond formation is involved for the two series, although the LGs are different.

The unusually small $|\rho_{XY}|$ value is, however, characteristic of the phenacyl derivatives.[3g] $|\rho_{XY}|$ value is,

however, characteristic of the phenacyl derivatives.[3g] One reason for this could be a non-conjugative intervening group, α-CO, in between the reaction center, β-carbon, and the ring, which is known to reduce the $|\rho_{XY}|$ value, by approximately a factor of two.[8] However even after allowing for this decrease due to an intervening group, $|\rho_{XY}|$ is still considerably smaller than expected.

We have therefore invoked resonance "shunt" phenomenon[3/8] to account for this remarkable fall off of the magnitude of the selectivity parameter, $|\rho_{XY}|$; as the enolate structure, (I), shows, the charge transmitted from the nucleophile to the β-carbon leaks to the α-carbonyl group in the resonance so that the electron supply to the substituent Y in the substrate ring decreases deminishing the interaction between the substituents X and Y, and hence $|\rho_{XY}|$. A slight increase in the magnitudes of ρ_X, ρ_Y and ρ_{XY} with a decrease in the MeOH content appears to indicate a small increase in bond formation. However the variations are rather small to warrant a definite trend.

Experimental

References

1. (a) S. Winstein, E, Grunwald, and H. W. Jones, *J. Am. Chem. Soc.*, **73**, 2700 (1951); (b) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford, Univ. Press, Oxford, 1974, p. 73.; (c) J. W. Thorpe and J. Warkentin, *Can. J. Chem.*, **51**, 927 (1973); (d) W. Forster, and R. M. Lair, *J. Chem. Soc. Perkin* **2**, 135 (1982); (e) T. I. Yousef, and E. S. Lewis, *J. Am. Chem. Soc.*, **109**, 6137 (1987); (f) C. Srinivasan, A. Shunmugasunderam, and N. Arumugam, *J. Chem. Soc. Perkin* **2**, 17 (1985).

2. D. J. McLennan, and A. Pross, *J. Chem. Soc., Perkin* **2**, 981 (1984).

3. (a) I. Lee, and S. C. Sohn, *J. Chem. Soc. Chem. Commun.*, 1055(1986); (b) I. Lee, and H. K. Kang, *Tetrahedon Lett.*, **28**, 1183 (1987); (c) I. Lee, H. Y. Kim, and H. K. Kang, *J. Chem. Soc. Chem. Commun.*, 1217 (1987); (d) I. Lee, H. K. Kang, and H. W. Lee, *J. Am. Chem. Soc.*, **109**, 7472 (1987); (e) I. Lee, *Bull. Korean Chem. Soc.*, **8**, 426 (1987); (f) I. Lee, C. S. Shim, S. Y. Chung, and H. W. Lee, *ibid.*, **8**, 350 (1987); (g) I. Lee, C. S. Shim, S. Y. Chung, and H. W. Lee, *J. Chem. Soc. Perkin* **2**, In press; (h) I. Lee, H. Y. Kang, and H. W. Lee, *J. Org. Ch‑ n.*, In press.

4. I. Lee, S. C. Sohn, C. H. Kang, and Y. J. Oh, *J. Chem. Soc. Perkin* **2**, 1631 (1986).

5. The σ values were obtained from: R. A. Y. Jones, "Physical and mechanistic Organic Chemistry," Cam-

A Formal Synthesis of Sirenin

Bull. Korean Chem. Soc., Vol. 9, No. 3, 1988 135

bridge Univ. Press, Cambridge, 1976, p. 55.

6. The pK_a values in these determinations were obtained from: A. Streitweiser, Jr., C. H. Heathcock, "Organic Chemistry," 2nd ed., Macmillan, New York, 1976, p. 737.

7. (a) A. Pross, *Adv. Phys. Org. Chem.*, **14**, 69 (1977); (b) C.D. Johnson, *Chem. Rev.*, **75**, 755 (1978); (c) D. J. McLennan, *tetrahedron*, **34**, 2331 (1978); (d) C. D. Rit-

chie, *Acc. Chem. Res.*, **5**, 348 (1972); (e) E. Buncel, and H. Wilson, *J. Chem. Educ.*, **64**, 475 (1987)

8. R. D. Gilliom, "Introduction to Physical Organic Chemistry," Addison-Wesley, Reading, 1970, p. 148.

9. R. C. Weast, "CRC Handbook of Chemistry and Physics," 67th ed., CRC Press, Florida, 1986, Sect. C.

A Formal Synthesis of Sirenin

Jong-Gab Jun*

Department of Chemistry, Hallym University, 1 Okchon-Dong, Chunchon 200

Bradford P. Mundy

Department of Chemistry, Montana State University, Bozeman, MT 59717, U.S.A.

Received January 19, 1988

Cleavage of *exo*-7-substituted-6,8-dioxabicyclo[3.2.1]octanes with acetyl iodide results in the predominance of the *trans* alkene product. This bicyclic ketal fragmentation methodology is utilized to a formal synthesis of sirenin.

Introduction

Bicyclic ketals of the 6,8-dioxabicyclo[3.2.1]octane show unique feature in organic chemistry. Many insect pheromones, such as frontalin,[1] brevicomin,[2] and multistriatin,[3] have this kind of bicyclic ketal skeleton. Cleavage of these bicyclic ketals with acetyl iodide gives δ,ε-unsaturated ketones, that is also related to natural products such as the Douglas fir tussock moth pheromone[4] and solenopsin A.[5] It has been observed that the cleavage of exo-7-substituted bicyclic ketals results in formation of the *trans* alkene product.[6] (Scheme 1)
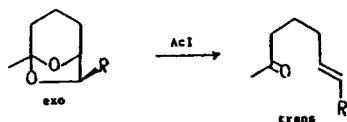
Scheme 1

Sirenin(1) is a sperm attractant produced by the female gametes of the water mold *Allomyces*.[7] 6,10-Dimethyl-5,9-nonadienoic acid(2) has been known to be a useful intermediate in the synthesis of sirenin by Grieco(Scheme 2).[8] We would like to report a facile preparation of 2 as a formal synthesis of sirenin to demonstrate the utility of the bicyclic ketal fragmentation methodology.
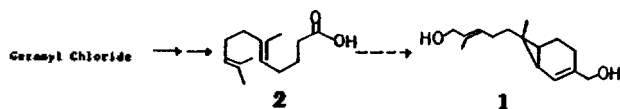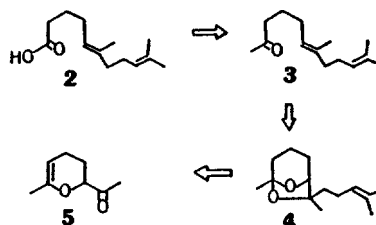

Scheme 2

Results and Discussion

The intermediate 2 has a δ,ε-unsaturated ketone with a

trans double bond, making this a prime target molecule for the application of the bicyclic ketal fragmentation protocol. The carboxylic acid moiety of 2 might be available from the methyl ketone of 7,11-dimethyldodeca-6,10-diene-2-one(3) by the reaction of haloform and also, 3 is the fragmentation product from 5,7-dimethyl-7-(4-methyl-3-pentene)-6,8-dioxabicyclo[3.2.1]octane(4). It is apparant that the compounds are intermediates by the retrosynthetic analysis shown in Scheme 3.

Scheme 3

To prepare the ketal 4, 2-acetyl-6-methyl-3,4-dihydro-2H-pyran(5) was added to a solution of 4-methyl-3-pentenyl-magnesium bromide in dry ether and the resulting alcohol was cyclized by adding 5% aqueous HCl solution. The *exo* and *endo* isomers of 4 were obtained in the ratio of 84:16 in 72% yield. The major *exo* isomer is the correct starting material for making the *trans* isomer of 3 by fragmentation. Cleavage with acetyl iodide gave the expected fragmentation product 3 in 20% yield. This was treated with a $KI-I_2$ reagent to give a positive yellow precipitate(CHI_3) which has a melting point of 119-121 °C. Due to low yield of the iodoform oxidation, we could not obtain a preparatively useful amount of 2. Thus, the product was converted to the methyl ester 6 and characterized only by high resolution mass spectrometer. (Sheme 4)