Reactions of (*E*)-*O*-Arylbenzaldoximes with Secondary Amines in Acetonitrile. Effect of β-Aryl Substituents upon the Competition between E2 and S_NAr Reactions

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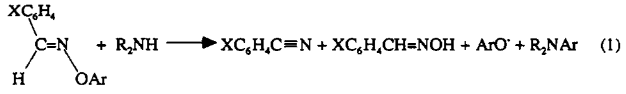
Reactions of (*E*)-*O*-arylbenzaldoximes in which the *O*-aryl group is 2,4-dinitrophenyl (**1a-d**) and picryl (**2a-d**) with secondary amines in acetonitrile have been studied kinetically. The reactions proceeded via competing E2 and S_NAr mechanisms. For eliminations from **1a-d** promoted by R_2NH in MeCN, the transition state was changed toward E1cb-like by a more electron-withdrawing β-aryl substituent and a stronger base. On the other hand, the transition states for eliminations from **2a-d** and for the S_NAr reactions of all substrates were relatively insensitive to the variation of either β-aryl substituent or base strength. The yield of S_NAr product increased with base concentration, electron-withdrawing ability of the *O*-aryl group, and base strength. When the electron-withdrawing ability of the β-aryl substituent is increased, the yield of S_NAr product from **1a-d** decreased, although no clear trend was observed for **2a-d**. From these results, factors that influence the competition between E2 and S_NAr reaction pathways are assessed.

Recently, we reported that the reactions of (*E*)-*O*-arylbenzaldoximes **1** and **2** with secondary amines in acetonitrile proceeded by competing E2 and S_NAr mechanism.[1] The second rate-determining step of the S_NAr reactions involved both uncatalyzed and base-catalyzed pathways. The yield of the S_NAr product increased with base concentration, electron-withdrawing ability of the *O*-aryl group, and base strength. However, the effect of β-aryl substituent upon the competition between these two reactions has not been investigated. An electron-withdrawing β-aryl substituent is expected to increase both the acidity of the C_β-H bond and the leaving ability of the oximate anion to enhance the rates of the both processes. Since the β-aryl substituent is closer to the C_β-H bond than to the O–Ar bond, the E2 reaction is expected to be more strongly influenced by the inductive effect of the substituent. On the other hand, the S_NAr reaction could be more sensitive to the resonance effect of the β-aryl substituent because the developing negative charge on the oxygen atom of the oximate leaving group may be stabilized by resonance, whereas that on the β-carbon cannot be because the C_β-H bond is orthogonal to the π-orbitals of β-aryl ring. To assess the relative importance of these two factors upon the competition between these two reactions we have investigated the reactions of (*E*)-*O*-arylbenzaldoximes with secondary amines in acetonitrile (eq 1).



$$XC_6H_4(H)C{=}N{-}OAr + R_2NH \longrightarrow XC_6H_4C{\equiv}N + XC_6H_4CH{=}NOH + ArO^- + R_2NAr \quad (1)$$

	Ar		X	R_2NH
1	2,4-dinitrophenyl	a	H	pyrrolidine
2	picryl	b	*p*-MeO	piperidine
		c	*m*-Br	tetrahydroisoquinoline
		d	*p*-NO_2	morpholine

Results

(*E*)-*O*-Arylbenzaldoximes **1a–d** and **2a–d** were synthesized,[1–4] and the rates of reactions with R_2NH in MeCN were determined as reported previously.[1] The observed rate constants were multiplied by the yields of the S_NAr and elimination products to determine the observed rate constants, $k_{obs}{}^S$ and $k_{obs}{}^E$, for the respective processes. The k^S and $k_2{}^E$ values were calculated by dividing the $k_{obs}{}^S$ and $k_{obs}{}^E$ values by base concentration. The rate constants are summarized in Tables SI-SX in the supplementary material.

Bronsted plots for eliminations from **1a–d** and **2a–d** promoted by R_2NH in MeCN gave straight lines with excellent correlation (plots not shown). For eliminations from **1a–d**, the value increases from 0.58 to 0.68 as the electron-withdrawing ability of the β-aryl substituent increases. However, no clear trend is observed for the reactions of **2a–d** (Table I). The β_{lg} values were calculated from the rate constants for piperidine-promoted eliminations from **1a–d** and **2a–d** and the pK_{lg} values of aryl oxides.[5] The $|\beta_{lg}|$ value decreases with increased electron-withdrawing ability of the β-aryl substituent (Table I).

The influence of the β-aryl substituent upon the elimination rates correlated satisfactorily with the Hammett equation with σ values (plots not shown). The Hammett ρ values are listed in Table II. For eliminations from **1a–d**, the values increase from 1.0 to 1.3 with stronger base, although no clear trend is observed for **2a–d**.

The influence of the leaving group upon the elimination reaction is summarized in Table III. The rate increased by 1.6×10^3 fold, Hammett ρ decreased from 1.2 to 0.57, and Bronsted β decreased from 0.61 to 0.54 as the leaving group was improved from 2,4-dinitrophenoxide to picrate.

For the S_NAr reactions of **2a-d** with R_2NH in MeCN, plots of k^S *vs* base concentration gave straight lines (plots not shown). On the other hand, the k^S values for **1a–d**

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[1] Cho, B. R.; Min, B. K.; Lee, C. W.; Je, J. T. *J. Org. Chem.* **1991,** *56,* 5513.

[2] Cho, B. R.; Lee, J. C.; Cho, N. S.; Kim, K. D. *J. Chem. Soc. Perkin Trans. 2* **1989,** 489.

[3] Cho, B. R.; Kim, K. D.; Lee, J. C.; Cho, N. S. *J. Am. Chem. Soc.* **1988,** *110,* 6145.

[4] Cho, B. R.; Jung, J.; Ahn, E. K. *J. Am. Chem. Soc.* **1992,** *114,* 3425.

[5] Coetzee, J. F. *Prog. Phys. Org. Chem.* **1965,** *4,* 45.

0022-3263/93/1958-6190$04.00/0

Table I. Effect of Aryl Substituent upon Bronsted β and β_{lg} Values for Eliminations from (*E*)-$XC_6H_4CH{=}NOAr$ Promoted by R_2NH in MeCN at 25.0 °C

	β value		
	Ar = 2,4-dinitrophenyl	Ar = picryl	$\lvert\beta_{lg}\rvert^a$
p-NO_2	0.68 ± 0.03	0.57 ± 0.06	0.56
m-Br	0.61 ± 0.04	0.60 ± 0.07	0.63
H	0.61 ± 0.05	0.54 ± 0.04	0.64
p-CH_3O	0.58 ± 0.05	0.56 ± 0.06	0.70

[a] The base was piperidine.

Table II. Effect of Base Strength upon Hammett ρ Values for Eliminations from (*E*)-$XC_6H_4CH{=}NOAr$ Promoted by R_2NH in MeCN at 25.0 °C

		ρ value	
	$pK_a{}^a$	Ar = 2,4-dinitrophenyl	Ar = picryl
pyrrolidine	19.6	1.3 ± 0.1	0.51 ± 0.06
piperidine	18.9	1.2 ± 0.1	0.57 ± 0.08
tetrahydroisoquinoline	17.1	1.0 ± 0.1	0.46 ± 0.06
morpholine	16.6	1.0 ± 0.1	0.46 ± 0.07

[a] Reference 5.

Table III. Transition-State Parameters for Eliminations from (*E*)-$XC_6H_4CH{=}NOAr$ Promoted by Piperidine in MeCN

	Ar = 2,4-dinitrophenyl	Ar = picryl
$pK_a{}^a$	16.0	11.0
rel rate	1	1.6×10^3
ρ	1.2 ± 0.1	0.57 ± 0.08
β	0.61 ± 0.05	0.54 ± 0.01

[a] Reference 5.

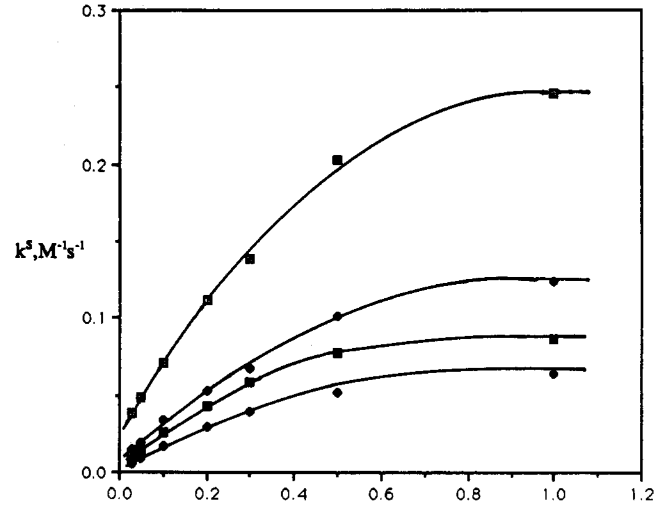

Figure 1. Plots of k_A *vs* base concentration for S_NAr Reactions of (*E*)-$XC_6H_4CH{=}NOC_6H_4$-2,4-$(NO_2)_2$ with piperidine in MeCN (X = *p*-NO_2 (⊡), *m*-Br (♦), H (■), *p*-CH_3O (◊)).

showed a curvelinear relationship with the base concentration (Figure 1). The result is attributed to both the change in rate-determining step and the solvent effect (vide infra). Therefore, the k^S values determined at [R_2NH] <0.20 M were used in the kinetic analysis.

Plots of log k^S *vs* pK_a values of the base gave straight lines (plots not shown). Since the k^S value is a function of base concentrations (Scheme I), the values at base concentrations of 1.00×10^{-1} and 1.00×10^{-3} M for **1a–d** and **2a–d**, respectively, were used in the plot. The Bronsted plots showed excellent correlation (plots not shown). The β values are very close to 1.0 for all of the reactions (Table IV).

The rates of the S_NAr reactions correlated satisfactorily with the Hammett equation utilizing σ values. The Hammett ρ values are in the range of 0.43–0.68 and show no clear trend with the change in either base or *O*-aryl substituent (Table V).

Yields of S_NAr and E2 products for the reactions of **1a-d** and **2a-d** with R_2NH in MeCN were determined at various base concentrations by comparing the absorption of the reaction products with those for authentic samples of the products. The yields of S_NAr product increased with base concentration, electron-withdrawing ability of O-aryl substituent, and base strength. For reactions of **1a–d**, the yield decreased with more electron-withdrawing β-aryl substituent, although no such trend is observed for **2a–d**. The results are summarized in Tables VI and VII.

Discussion

Mechanism and Transition State Structure for the Elimination Reactions. Earlier it was established that the reactions of **1a** and **2a** with secondary amines produce the elimination products via an E2 mechanism.[1] The transition-state parameters for R_2NH-promoted eliminations from **1** reveal that the effects of aryl substituents, base strength, and leaving group variations upon the nitrile-forming transition state are very similar to those observed for R_3N-promoted eliminations from the same substrate.[3] For eliminations from 1 promoted by R_2NH in MeCN, Bronsted β increases and $\lvert\beta_{lg}\rvert$ decreases with the enhancement of the electron-withdrawing ability of the β-aryl substituent (Table I). This indicates an increase in the C_β–H bond cleavage, a significant decrease in the N_α–OAr bond rupture, and a shift of the transition state toward the E1cb corner in the reaction coordinate diagram.[6]

Similarly, the Hammett ρ values increase slightly as the base strength becomes stronger (Table II), indicating a gradual increase in the transition-state carbanionic character with a stronger base. The result is consistent with a shift of the transition state toward the reactant and the E1cb corner in the reaction coordinate diagram.[6]

When the leaving group was changed from 2,4-dinitrophenoxide to picrate, the rate increased by 1.6×10^3-fold and both Hammett ρ and Bronsted β values decreased (Table III). The result can also be interpreted with the reaction coordinate diagram in terms of a shift of the transition state toward the reactant and the E1 corner.[6] Very recently we proposed that the More O'Ferrall–Jencks diagram may be successfully employed for reactions with reactivity difference of 3000-fold when the structures of the transition states are closely related.[7] The present result provides an additional example in support of our previous conclusion.

For R_2NH-promoted eliminations from **2**, both Hammett ρ and β values remained nearly the same with the variation of the β-aryl substituent and the base. The much lower sensitivity of the transition states for eliminations from **2** to the variations of reactant structures apparently results from the much higher reactivity.

Mechanism and Structure–Reactivity Relationship for the S_NAr Reactions. In previous work it has been established that the reactions of **1a** and **2a** with secondary amines in MeCN proceed by an addition–elimination

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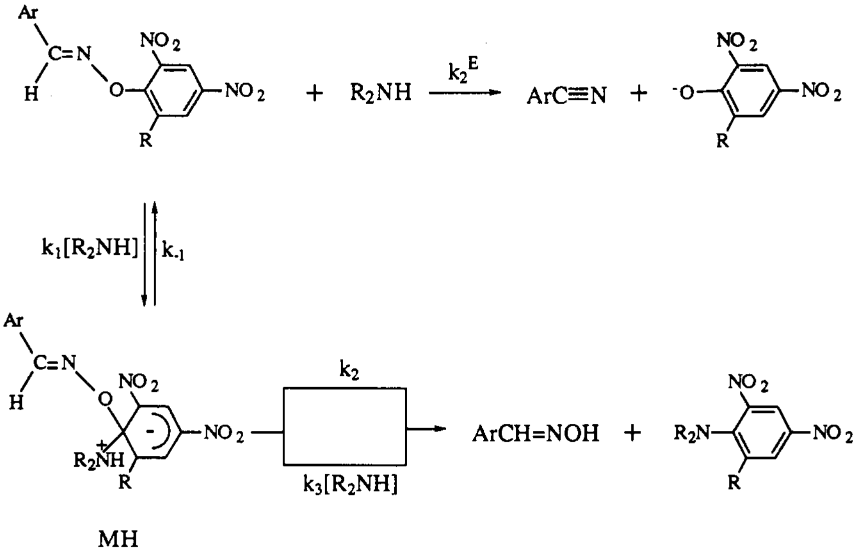
(6) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper & Row: New York, 1987; pp 199–205.

(7) Cho, B. R.; Jang, W. J.; Je, J. T.; Bartsch, R. A. *J. Org. Chem.* **1993**, *58*, 3901.

Scheme I



$$k_{obs} = (k_2^E + k^S)[R_2NH]$$

$$k^S = (k_1k_2 + k_1k_3[R_2NH])/(k_{-1} + k_2 + k_3[R_2NH])$$

Table IV. Bronsted β Values for S_NAr from (E)-$XC_6H_4CH{=}NOAr$ Promoted by R_2NH in MeCN

	β value	
	Ar = 2,4-dinitrophenyl[a]	Ar = picryl[b]
p-NO_2	0.92 ± 0.11	1.0 ± 0.13
m-Br	0.97 ± 0.12	0.98 ± 0.14
H	0.98 ± 0.11	1.1 ± 0.10
p-CH_3O	0.97 ± 0.12	1.0 ± 0.13

[a] Base concentration was 1.00×10^{-1} M. [b] Base concentration was 1.00×10^{-3} M.

Table V. Hammett ρ Values for S_NAr from (E)-$XC_6H_4CH{=}NOAr$ Promoted by R_2NH in MeCN

	ρ value	
	Ar = 2,4-dinitrophenyl[a]	Ar = picryl[b]
pyrrolidine	0.43 ± 0.03	0.53 ± 0.08
piperidine	0.51 ± 0.05	0.49 ± 0.09
tetrahydroisoquinoline	0.68 ± 0.10	0.59 ± 0.04
morpholine	0.53 ± 0.02	0.63 ± 0.15

[a] Base concentration was 1.00×10^{-1} M. [b] Base concentration was 1.00×10^{-3} M.

Table VI. Yields of S_NAr Product for Reactions of (E)-$XC_6H_4CH{=}NOC_6H_4$-2,4-$(NO_2)_2$ with R_2NH in MeCN

		% yield of S_NAr product when the base is			
$[R_2NH]$,M	X	pyrrolidine	piperidine	tetrahydroisoquinoline	morpholine
0.20	p-NO_2		62	36	33
	m-Br		66	48	57
	H		82	53	62
	p-CH_3O		92	62	77
0.10	p-NO_2	73	51	33	31
	m-Br	85	63	35	42
	H	89	77	51	48
	p-CH_3O	89	84	58	67
0.05	p-NO_2	69	43	31	23
	m-Br	82	51	32	28
	H	87	64	36	32
	p-CH_3O	88	73	43	48
0.03	p-NO_2	62	39	27	18
	m-Br	78	48	24	18
	H	83	53	24	23
	p-CH_3O	85	64	32	36

mechanism in which the second step is rate determining (Scheme I). For all reactions, the k^S values increased linearly with base concentration at $[R_2NH] < 0.20$ M. This result indicates that $k_{-1} \gg k_2 + k_3[R_2NH]$ and the k^S expression in Scheme I can be simplified to $k^S = (k_1k_2 + k_1k_3[R_2NH])/k_{-1}$. Therefore, all of the reactions surveyed in the present study must proceed by the same addition–elimination mechanism in this base concentration range.

On the other hand, the k^S values for the reactions of **1a–d** showed curvelinear relationship at higher base concentration (Figure 1). The result can be attributed to both the change in rate-determining step and the solvent effect. For reaction of **1a** with piperidine, the $k_1k_3/k_{-1} = 0.24$ M^{-2} s^{-1} and $k_1k_2/k_{-1} = 0.0019$ M^{-1} s^{-1} were obtained from the slope and the intercept of the linear portion of the plot at $[R_2NH] < 0.20$ M. If one assumes that the curvelinear plot is obtained because the first step becomes rate determining at [piperidine] = 1.0 M, then $k^S = 0.087$ M^{-1} s^{-1} determined at this base concentration should equal to k_1 (Figure 1). Utilizing $k_1 = 0.087$ M^{-1} s^{-1}, $[R_2NH] = 1.0$ M, $k_1k_3/k_{-1} = 0.24$ M^{-2} s^{-1}, and $k_1k_2/k_{-1} = 0.0019$ M^{-1} s^{-1}, $(k_2 + k_3[R_2NH])/k_{-1} = 2.8$ is calculated. This does not satisfy $k_2 + k_3[R_2NH] \gg k_{-1}$ required for the change in rate-determining step but indicates that both steps are partially involved in the rate-determining step.[8-11] Moreover, the reactivity of the amines in MeCN should decrease with increased amine concentration due to the hydrogen bonding ability of the amines.[5] Therefore, it seems reasonable to assume that the curvelinear relationship is observed due to both the change in rate-determining step and the solvent effect.

The slope of the plots of log k^S vs pK_a of the bases for the S_NAr reactions are summarized in Table IV. The β values are very close to 1.0 for reactions of both **1a–d** and **2a–d**, indicating that the nucleophile–carbon bonds are

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[8] Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: New York, 1968.

[9] Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147.

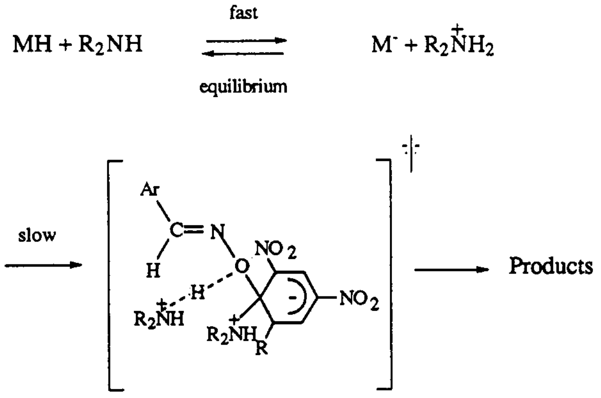
[10] Bacaloglu, R.; Bunton, C. A.; Orgeta, F. *J. Am. Chem. Soc.* **1988**, *110*, 3495.

[11] Jain, A. K.; Kumar, A.; Sarma, K. N. *J. Chem. Soc., Perkin Trans 2* **1989**, 153.

Table VII. Yields of S_NAr Product for Reactions of (*E*)-$XC_6H_4CH{=}NOPic$ with R_2NH in MeCN

		% yield of S_NAr product when the base is			
$10^2[R_2NH]$, M	X	pyrrolidine	piperidine	tetrahydroisoquinoline	morpholine
3.00	p-NO_2			83	96
	m-Br			88	98
	H			83	92
	p-CH_3O			87	99
0.50	p-NO_2			51	76
	m-Br			53	77
	H			50	66
	p-CH_3O			46	78
0.10	p-NO_2	100	51	19	40
	m-Br	87	49	19	49
	H	85	48	20	24
	p-CH_3O	85	39	13	34
0.05	p-NO_2	89	39		
	m-Br	82	41		
	H	73	44		
	p-CH_3O	59	36		

Scheme II



completely formed in these transition states.[12] Thus, the transition states for the S_NAr reactions are insensitive to the variation of the β-substituents.

For the S_NAr reactions of **1a–d**, the rate constants correlated with σ values in the Hammett plot. In addition, the ρ values are 0.43-0.68 and show no clear trend with the change in base (Table V). The result can be explained with a specific base-general acid catalysis for the k_3 process (Scheme II).[9] Since the oxygen atom of the oximate moiety is hydrogen bonded to $R_2NH_2^+$ in this transition state, little negative charge should be available for resonance stabilization by the β-aryl substituents. Moreover, the k_3 step is the dominant pathway of the rate-determining step as indicated by the large k_3/k_2 ratio.[13] Therefore, it is reasonable to expect that the Hammett plot should correlate with σ values and exhibit small ρ values. Similar values are obtained for **2a–d**, despite the 10^5-fold difference in reactivity.[1] Furthermore, the values are very similar to 0.43 and 0.68 obtained for the reactions of the **1a** and **2a** with MeONa in MeOH, even though the rate-determining step changes to the first step in this base–solvent system.[4] Thus, the effect of β-aryl substituent upon the S_NAr reactions appears relatively insensitive to the variation of the base, *O*-aryl substituent, and the base–solvent system.

Competition between E2 and S_NAr Reactions. The yields of S_NAr product for the reactions of **1a–d** and **2a–d** with R_2NH in MeCN are summarized in Tables VI and VII, respectively. The yield increased with base concentration, electron-withdrawing ability of *O*-aryl substituent, and the base strength. This result confirms our previous observation for the reactions of the unsubstituted compounds **1a** and **2a**, which has been interpreted with the rate equation, relative influence of the *O*-aryl substituent upon the E2 and S_NAr transition states, and the β values.[1]

For reactions of **1a–d**, the yield of S_NAr product decreased as the electron-withdrawing ability of the β-aryl substituent increased. The result can readily be explained with the different sensitivity of the E2 and S_NAr reactions to the variation of the substituents. The Hammett ρ values for the E2 and S_NAr processes are 1.0–1.3 and 0.43–0.68, respectively, indicating that the former is more sensitive to the variation of the β-aryl substituent. Therefore, the yield of S_NAr product should decrease with more electron-withdrawing β-aryl substituent. The greater sensitivity of the E2 reaction to the β-aryl substituent can be attributed to the relative distance between the substituent and the reaction site. Since the C_β-H bond is parallel to the β-aryl ring, the β-aryl substituent is expected to influence the E2 reaction primarily through inductive effect. In addition, the S_NAr reaction should also be influenced by the inductive effect of the substituent because the k_3 process is the predominant pathway of the rate-limiting step (vide supra). Therefore, the E2 reaction should be more sensitive to the electron-withdrawing ability of the substituent than the S_NAr reaction because the substituent is closer to the C_β-H bond than to the O–Ar bond.

In contrast, the yield of the S_NAr product for **2a–d** remained nearly the same regardless of the nature of the β-aryl substituent. The relative insensitivity of the yield to the electron-withdrawing ability of the substituent apparently results from the similar ρ values for the E2 and S_NAr processes. The Hammett ρ values for the E2 and S_NAr reactions for **2a–d** are in the range of 0.46–0.57 and 0.53–0.63, respectively (Tables II and V). Therefore, the yield for **2a–d** should remain nearly constant for all substituents.

Experimental Section

(E)-O-Arylbenzaldoximes were prepared by reactions of (E)-benzaldoximes with appropriate aryl halides.[1–4] The kinetic studies were carried out as previously reported.[1]

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Supplementary Material Available: Rate constants for E2 and S_NAr reactions of (*E*)-*O*-2,4-dinitrophenylbenzaldoxime (**1**) and (*E*)-*O*-picrylbenzaldoxime (**2**) with R_2NH in MeCN at 25.0 °C (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[12] Although k^S is a function of base concentration, the k^S value determined at given base concentration should reflect the relative rates of the S_NAr reactions. Therefore, the slope of log k^S vs pK_a of the base could be taken as the susceptibility of the S_NAr rate to the base strength.[1]

[13] For reactions of **1a–d** and **2a–d** with pyrrolidine, the calculated k_3/k_2 values are in the range of 1–4 × 10^2 and 1–4 × 10^3, respectively. Since the partitioning of the k_2 and k_3 processes is determined by $k_3[R_2NH]/k_2$ and $[R_2NH] = 1.00 \times 10^{-2}$ and 1.00×10^{-3} M, respectively, were used in the Hammett studies, the latter should be the dominant pathway.