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Mechanisms of Alkoxide Substitution Reactions at the Carbon–Nitrogen Double Bond. Stereoelectronic Control during Nucleophilic Substitution[1]

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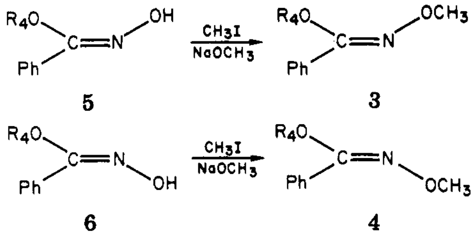
The stereochemistry and mechanisms of the alkoxide substitution reactions of *O*-methylbenzohydroximoyl chlorides (1 and 2) and alkyl *O*-methylbenzohydroximates (3 and 4) have been investigated. The reactions of the (*Z*)-hydroximoyl chlorides 1 with alkoxides in 10% methanol–90% Me_2SO proceed with ≥95% retention of configuration to give the (*Z*)-hydroximates 3. The alkoxide reactions of the (*E*)-hydroximoyl chlorides 2 are usually less stereospecific and give ≥77% of the substitution product (4), corresponding to retention of configuration. The reactions of the hydroximoyl chlorides **1a** and **2a** with methoxide ion follow second-order kinetics and have approximately the same rate constants. The reaction of the hydroximoyl bromide **1h** with methoxide is only 2.2 times faster than that of the chloride **1a**. The methoxide substitution rates of five (*Z*)-hydroximoyl chlorides (**1a**, **1d–g**) give a Hammett correlation with σ with a ρ value of 1.90. These observations are consistent with a mechanism in which a hydroximoyl chloride (1) undergoes rate-determining nucleophilic attack by methoxide to form a tetrahedral intermediate which rapidly loses chloride ion to give the hydroximate 3. The (*Z*)-hydroximate **3e** undergoes a methoxide substitution reaction to give **4e** but at a considerably slower rate than the (*Z*)-hydroximoyl chloride **1a** ($k(\mathbf{1a})/k(\mathbf{3e}) = 53$). The second-order rate constant for the reaction of the (*Z*)-hydroximate **3e** with methoxide is about 300 times greater than the rate constant for the reaction of the (*E*)-hydroximate **4e** with methoxide. The reaction of methoxide with the (*E*)-hydroximate **4e** initially produces mainly the *Z* product **3a**, but the product distribution changes with time, and eventually the *E* isomer **4a** predominates. The change in product distribution during the course of this reaction is due to a methoxide-catalyzed isomerization of **3a** to **4a**. The stereochemistry and relative rates of the reactions of 1–4 with methoxide ion are interpreted in terms of Deslongchamp's theory of stereoelectronic control. It is suggested that stereoelectronically controlled loss of chloride ion from the tetrahedral intermediate 12 (from the reaction of **1a** with methoxide ion) is faster than either loss of methoxide ion to give starting material or stereomutation. In the tetrahedral intermediate 13 (from **2a**), stereomutation to 12 and 14 and stereoelectronically controlled loss of chloride ion from 12 and 14 are faster processes than loss of methoxide ion from 13. The tetrahedral intermediate 15 (from **3e**) undergoes stereoelectronically controlled loss of methoxide or ethoxide ion faster than it undergoes stereomutation. In the case of the intermediate 17 (from **4e**), stereoelectronically controlled loss of methoxide ion to give starting material is faster than stereomutation.

In 1973 we communicated the first examples of stereospecific nucleophilic substitution at the carbon-nitrogen double bond.[3] The reaction of methoxide ion with the *Z* and *E* isomers of *O*-methylbenzohydroximoyl chlorides (Chart I, 1 and 2) were reported to give predominately methyl *O*-methylbenzohydroximates (3 and 4) with inverted configurations. Although the configurations of the hydroximates were established by independent synthesis[4] (Scheme I), the configurations of the hydroximoyl chlorides were assigned on the basis of a dipole moment study. Shortly after publication of a paper on the synthesis and configurational assignments for the hydroximoyl chlorides,[5] it became evident from our work on the solvolysis reactions of these compounds[6] that the configurational assignments based on dipole moments were probably incorrect. An X-ray crystallographic analysis[7] of **1d** confirmed our suspicions, and the previous assignment of configurations[3,5] for these compounds must be reversed. Since the configurations of the hydroximoyl chlorides are now known with certainty, we now make a full report on our investigations into the bimolecular substitution reactions of these compounds.

Scheme I[a]



[a] 5a and 6a, $R_4 = CH_3$; 5b and 6b, $R_4 = C_2H_5$; 3a and 4a, $R_4 = CH_3$; 3e and 4e, $R_4 = C_2H_5$.

Table I. Product Distributions in the Reactions of (*Z*)- and (*E*)-*O*-Alkylbenzohydroximoyl Chlorides (1 and 2) with Alkoxides[a]

hydroximoyl chloride	alkoxide	substitution product distribution % *Z*	substitution product distribution % *E*
1a	CH_3O	98 (3a)	2 (4a)
2a	CH_3O	23 (3a)	77 (4a)
1b	CH_3O	98 (3b)	2 (4b)
2b	CH_3O	5 (3b)	95 (4b)
1c	CH_3O	98 (3c)	2 (4c)
2c	CH_3O	9 (3c)	91 (4c)
1d	CH_3O	98 (3d)	2 (4d)
2d	CH_3O	16 (3d)	84 (4d)
1a	C_2H_5O	95 (3e)	5 (4e)
2a	C_2H_5O	14 (3e)	86 (4e)

[a] All reactions were carried out in 10% methanol–90% Me_2SO (v/v) at 44.6 °C.

Results

The reaction of the (*Z*)-hydroximoyl chloride **1a** with methoxide ion in 10% methanol–90% dimethyl sulfoxide

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[1] Part of this work was reported at the 3rd IUPAC Conference on Physical Organic Chemistry, LaGrande Motte, France, Sept 10, 1976; Abstracts, p 59.

[2] Taken in part from the Ph.D. Dissertation of E.A.N. (Texas Woman's University, May 1975) and the M.A. Thesis of C.W. (Sam Houston State University, May 1971).

[3] Johnson, J. E.; Nalley, E. A.; Weidig, C. *J. Am. Chem. Soc.* **1973**, *95*, 2051.

[4] Johnson, J. E.; Springfield, J. R.; Hwang, J. S.; Hayes, L. J.; Cunningham, W. C.; McClaugherty, D. L. *J. Org. Chem.* **1971**, *36*, 284.

[5] Johnson, J. E.; Nalley, E. A.; Kunz, Y. K.; Springfield, J. R. *J. Org. Chem.* **1976**, *41*, 252.

[6] Johnson, J. E.; Cornell, S. C. *J. Org. Chem.* **1980**, *45*, 4144.

[7] Bertolasi, V.; Sacerdoti, M.; Tassi, D. *Cryst. Struct. Commun.* **1977**, *6*, 335.

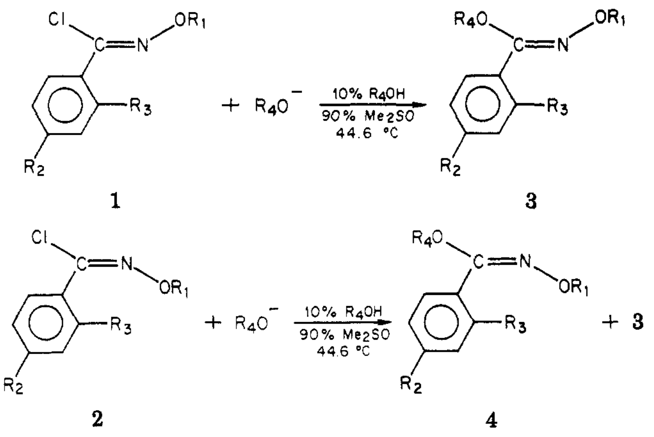
0022-3263/81/1946-3623$01.25/0

Table II. Second-Order Rate Constants[a] for Methoxide Substitution Reactions of *O*-Methylbenzohydroximoyl Halides 1 and 2 and Alkyl *O*-Methylbenzohydroximates 3 and 4

compd	temp, °C	10^2[compd], M	$10^2[MeO^-]$, M	10^2k, M^{-1} s^{-1}	dev, %[b]
1a	44.6	2.00	2.05	1.27	3.1
1a	44.6	2.00	2.84	1.24	0.8
1a	44.6	2.00	4.08	1.29	1.6
1a	44.6	2.00	5.87	1.23	1.8
1a	44.6	2.00	7.55	1.22	2.5
1a	44.6	2.00	10.4	1.24	2.4
1a	44.6	4.03	2.84	1.19	5.9
1a	44.6	6.01	2.84	1.25	0
1a	44.6	8.17	2.84	1.23	1.6
1a	44.6	10.0	2.84	1.13	5.3
1a	24.6	2.00	4.10	0.169	0.6
1a	29.6	2.00	4.10	0.273	0.4
1a	34.6	2.00	4.10	0.487	1.4
1a	44.6	2.00	4.10	1.30	1.5
1a	49.5	2.00	4.10	1.93	2.1
2a	44.6	8.04	2.84	1.42	4.9
1d	20.6	2.00	4.10	6.76	6.6
1d	23.0	2.00	4.10	9.80	1.1
1d	25.6	2.00	4.10	9.93	5.7
1d	29.6	2.00	4.10	14.9	0
1d	44.6			45.4[c]	
1e	44.6	2.01	7.90	0.780	0.6
1f	44.6	2.02	2.92	5.53	1.3
1g	44.6	2.00	8.03	0.520	1.2
1h	44.6	2.01-8.03	2.84	2.74	4.3
3e	44.6	1.11-1.37	27.4	0.0232	4.3
4e	44.6	1.56-1.65	40.0	0.0000783	1.4
3a	44.6	1.57-1.96	40.0	0.00159[d]	2.4

[a] All reactions were carried out in 10% methanol-90% Me_2SO (v/v). [b] Deviation from average of two results. [c] Calculated by extrapolation of a plot of ln (k/T) vs. $1/T$. [d] Second-order rate constant for isomerization of 3a to 4a.

Scheme II



(Me_2SO) gives almost exclusively the (*Z*)-hydroximate **3a** (Scheme II, Table I). The (*E*)-hydroximoyl chloride (**2a**) reaction is considerably less stereospecific, giving 77% of the (*E*)-hydroximate **4a** and 23% of the *Z* isomer **3a** The lower specificity in the reaction of **2a** is not due to an isomerization of **2a** to **1a**. The (*E*)-hydroximoyl chloride (**2a**) reaction was analyzed at various stages of completion, and it was found that no isomerization to the (*Z*)-hydroximoyl chloride occurs,[9] and the hydroximate product distribution (**3a** and **4a**) remains essentially constant throughout the course of the reaction. Although a *p*-nitro substituent has little effect (**1d** and **2d**) on the *E–Z* product distribution, the introduction of an *o*-methyl group increases the specificity of the (*E*)-hydroximoyl chloride reaction. The (*E*)-chloride **2b** gives 95% of the (*E*)-hydroximate and only 5% of the *Z* isomer. Similarly, the (*E*)-*O*-isopropylhydroximoyl chloride **2c** also gives almost complete retention of configuration. In all of the derivatives studied in this and earlier work,[4,8] the (*Z*)-hydroximoyl chlorides gave ≥95% retention of configuration when reacted with alkoxides.

Table III. Activation Parameters for the Reaction of (*Z*)-*O*-Methylbenzohydroximoyl Chlorides with Methoxide

compd	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
1a	18	−10
1d	14	−17

To ensure that rearrangement of the alkoxy groups is not occurring during the substitution process, the substitution reactions of **1a** and **2a** were carried out with ethoxide ion (Table I). The substitution products **3e** and **4e** were independently synthesized from the *Z* and *E* isomers of ethyl benzohydroximate (**5b** and **6b** in Scheme I) whose configurations have been established.[4,10]

An investigation into the rate of the (*Z*)-hydroximoyl chloride **1a**–sodium methoxide reaction showed it to be first-order in both hydroximoyl chloride and methoxide ion [Table II, k(av) = 1.24×10^{-2} M^{-1} s^{-1}]. The second-order rate constant for the (*E*)-hydroximoyl chloride **2a**–sodium methoxide reaction is only slightly greater than that for the *Z* isomer. In comparison, the uncatalyzed hydrolysis of the (*Z*)-chloride **1a**, which involves unimolecular dissociation to a nitrilium ion, was found to be 470 times faster than hydrolysis of the *E* isomer **2a**.[6] In order to determine the effect of the leaving group on this reaction, the reaction rate of the (*Z*)-hydroximoyl bromide **1h** with methoxide ion was measured. The reaction of **1h** is only 2.2 times faster than the chloride **1a** which is a con-

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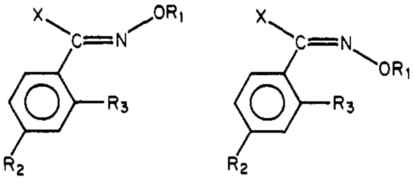
(8) The reactions of (*Z*)-hydroximoyl chlorides with alkoxides reported in ref 4 were carried out in 100% alcohol solutions.

(9) Our earlier report[3] that **2a** partially isomerizes to **1a** during the reaction of **2a** with methoxide ion is incorrect.

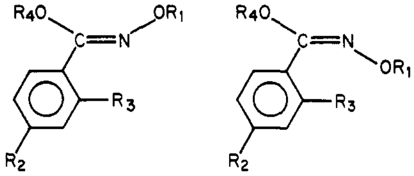
(10) Exner, O.; Jehlicka, V.; Reiser, A. *Collect. Czech. Chem. Commun.* 1959, *24*, 3207.

Chart I



1 2

1a and 2a, $R_1 = CH_3$; $R_2 = R_3 = H$; X = Cl
1b and 2b, $R_1 = R_3 = CH_3$; $R_2 = H$; X = Cl
1c and 2c, $R_1 = i\text{-}C_3H_7$; $R_2 = R_3 = H$; X = Cl
1d and 2d, $R_1 = CH_3$; $R_2 = NO_2$; $R_3 = H$; X = Cl
1e, $R_1 = R_2 = CH_3$; $R_3 = H$; X = Cl
1f, $R_1 = CH_3$; $R_3 = H$; R_2 = X = Cl
1g, $R_1 = CH_3$; $R_2 = OCH_3$; $R_3 = H$; X = Cl
1h, $R_1 = CH_3$; $R_2 = R_3 = H$; X = Br



3 4

3a and 4a, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
3b and 4b, $R_1 = R_3 = R_4 = CH_3$; $R_2 = H$
3c and 4c, $R_1 = i\text{-}C_3H_7$; $R_2 = R_3 = H$; $R_4 = CH_3$
3d and 4d, $R_1 = R_4 = CH_3$; $R_2 = NO_2$; $R_3 = H$
3e and 4e, $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = C_2H_5$

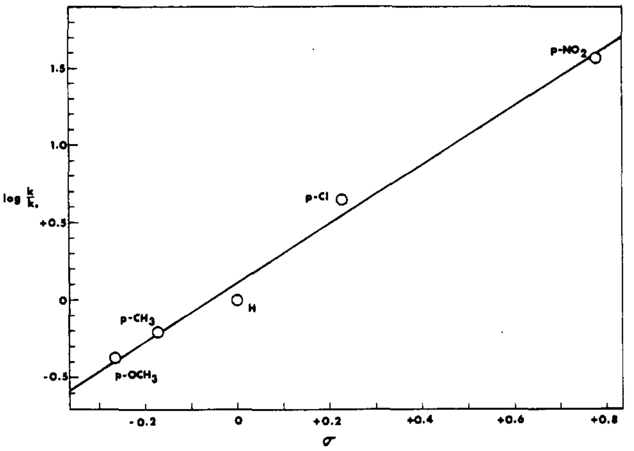


Figure 1. Hammett plot (σ) for methoxide substitution in (Z)-O-methylbenzohydroximoyl chlorides (1) in 10% methanol–90% Me_2SO at 44.6 °C.

siderably smaller difference than the 42-fold increase observed by us[6] in the uncatalyzed hydrolysis of **1a** and **1h**.

The activation parameters for the reaction of hydroximoyl chlorides **1a** and **1b** (Table III) with methoxide are similar to the values reported for the bimolecular reactions of vinyl halides with alkoxides.[11] Both the enthalpy and the entropy of activation for **1a** are significantly lower than for the corresponding unimolecular reaction[6] ($\Delta H^{\ddagger} = 39$ kcal/mol; $\Delta S^{\ddagger} = 8$ eu).

The effect of substituents on the (Z)-hydroximoyl chloride reaction was investigated by measuring the rates of methoxide ion substitution for four para-substituted derivatives (**1d–g**). A reasonably good Hammett correlation was obtained with σ with a ρ value of 1.90 ± 0.35 (Figure 1). In comparison, the ρ value obtained for the unimolecular reaction[6] of **1** was −2.40 with σ^+.

Scheme III

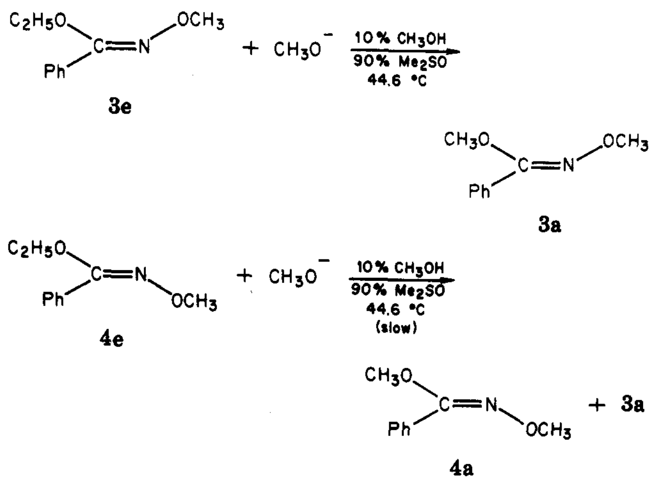


Table IV. Product Distribution of 3a and 4a during the Reaction of Ethyl (E)-O-Methylbenzohydroximate (4e) with Sodium Methoxide[a]

reaction time, h	product distribution[b] % Z (3a)	 % E (4a)
14.3	91.3	8.7
31.0	74.9	25.1
55.0	61.0	39.0
102	41.7	58.3
121	26.0	74.0

[a] Reactions carried out in 10% methanol–90% Me_2SO with [4e] = 1.57 or 19.6 M and $[CH_3O^-]$ = 0.40 M; temperature = 44.6 °C. [b] Average of two results.

When the (Z)- or (E)-hydroximates **3a** and **4a** were subjected to the substitution reaction conditions (sodium methoxide in 10% methanol–90% Me_2SO at 44.6 °C), they did not undergo any detectable rearrangement during the time required for the methoxide substitution reactions of **1a** or **2a** to take place. This observation does not exclude the possibility that methoxide ion is reacting with **1a** and/or **2a** with retention of configuration and thus not causing a change in the substitution product distribution. In fact, we have found that the (Z)-hydroximate **3a** will undergo a substitution reaction when ethoxide ion is used as the nucleophile. When **3a** was reacted for 24 h with ethoxide ion in 10% ethanol–90% Me_2SO at 44.6 °C, the (Z)-hydroximate **3e** was produced. Surprisingly, the corresponding reaction of **4a** with ethoxide ion did not give an appreciable amount of product in 24 h. In order to compare the rates of the hydroximate substitution reactions with the rates of the hydroximoyl chloride reactions, we reacted the hydroximates **3e** and **4e** with methoxide ion in 10% methanol–90% Me_2SO. The hydroximate **3e** gave **3a** (Scheme III) with a rate constant of 2.3×10^{-4} M^{-1} s^{-1}, while the E isomer (**4e**) reacted much more slowly ($k = 7.83 \times 10^{-7}$ M^{-1} s^{-1}) and gave a mixture of the (Z)- and (E)-hydroximates **3a** and **4a**. During the slow reaction of **4e** with methoxide ion, it was observed that the product distribution (**3a** and **4a**) was not constant (Table IV). Initially the Z isomer (**3a**) was formed almost exclusively, but this gradually changed so that eventually the E isomer (**4a**) was the major product of the reaction. It has been determined that this change in product distribution is due to a slow methoxide-catalyzed isomerization of the (Z)-hydroximate **3a** to the E isomer. The rate constant for the isomerization was found to be about 20 times greater than the rate constant for the methoxide substitution reaction of **4e**. The isomerization of **3a** to **4a** was followed until the

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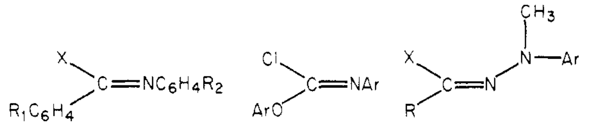
[11] Rappoport, Z. *Adv. Phys. Org. Chem.* **1969**, *7*, 1.

Chart II



7a, X = Cl
b, X = CN

8

9a, X = Cl
b, X = Br
c, X = OCH$_3$

distribution of the isomers was 98% *E* (**4a**) to 2% *Z* (**3a**), demonstrating that the (*E*)-hydroximate is at least 2.5 kcal/mol more stable than the *Z* isomer. Since the isomerization of **3a** to **4a** is slow, it is clear that all of the substitution reactions observed in this work are kinetically controlled processes (except, of course, the reaction of **4e** with methoxide, where the kinetically controlled product isomerizes during the reaction).

Discussion

Relatively few studies on the mechanism of bimolecular substitution at the carbon–nitrogen double bond have appeared in the literature. The most extensive work on bimolecular substitution has been carried out by Ta-Shma and Rappoport[12,13] on the reactions of diarylimidoyl chlorides (**7a**, Chart II) with secondary amines in benzene[13] or acetonitrile.[12] In benzene solution with an imidoyl chloride substituted by an electron-donating group (**7a**, R_1 or R_2 = *p*-OCH_3, etc.) they suggested that the reaction involves an ion pair, where the ion pair returns to starting material faster than it reacts with the amine [S_N2(IP)]. In the case of an electron-attracting substituent (**7a**, R_1 or R_2 = *p*-NO_2, etc.) they proposed that the reaction proceeds by a nucleophilic addition–elimination pathway. A third-order, amine-catalyzed process was superimposed on the bimolecular routes. In the more polar solvent, acetonitrile, the reactions of imidoyl chlorides with secondary amines proceed through nitrilium ions (either as ion pairs or free ions) except with strongly nucleophilic amines and strong electron–withdrawing substituents, in which case the reactions proceed by a nucleophilic addition–elimination pathway. Ta-Shma and Rappoport[14] have also investigated the bimolecular substitution reactions of *N*-arylbenzimidoyl cyanides (**7b**) with amines (in acetonitrile) and alkoxides (in alcohol). The change to a poorer leaving group caused the substitution reactions to proceed only by the addition–elimination pathway, regardless of the electronic nature of the substituents in **7b**. The stereochemistry of the imidoyl chloride and cyanide reactions could not be determined because the geometric isomers of these compounds and their substitution products are not known. A study of substituent effects[15] on the basic hydrolysis of aryl *N*-arylchloroimidates (8) indicated that these compounds react by an addition–elimination mechanism.

Besides our original paper, only one report has appeared on the stereochemistry of bimolecular substitution at the carbon–nitrogen double bond. Hegarty et al.[16] found that the (*Z*)-hydrazonyl halides **9a** and **9b** react with methoxide ion to give only the (*Z*)-hydrozonate **9c**. This result is in agreement with our observation that the (*Z*)-hydroximoyl chlorides **1** give nearly exclusive formation of the (*Z*)-hydroximates **3**. Unfortunately, it was not possible to investigate the stereochemistry of methoxide substitution reactions with (*E*)-hydrazonyl halides due to the configurational instability of the *E* isomers.

All of our observations, including second-order kinetics, the element effect, and substituent effects are consistent with a mechanism in which a hydroximoyl chloride **1** undergoes rate-determining nucleophilic attack by methoxide to form a tetrahedral intermediate which rapidly loses chloride ion to give the hydroximate **3**. The element effect has been used in vinylic systems to distinguish between addition–elimination and S_N1 mechanisms. The k_{Br}/k_{Cl} ratio is usually in the range of 1–2 for addition–elimination[11,13,17] while ratios in the range of 20–80 have been reported for the S_N1 mechanism.[13,18] In the more closely related hydrazonyl halides **9**, an element effect (k_{Br}/k_{Cl}) of 0.2 has been reported[16] for the bimolecular reaction with methoxide ion. This element effect, however, must be evaluated with caution since it was determined from a comparison of two hydrazonyl halides with different substituents [**9a**: R = C_6H_5, Ar = $C_6H_3(NO_2)_2$; **9b**: R = *t*-C_4H_9, Ar = $C_6H_3(NO_2)_2$]. The hydrolysis of hydroximoyl halides[6] **1**, as well as the hydrolysis of imidoyl halides[12] and hydrazonyl halides[19] which react via the S_N1 mechanism, give k_{Br}/k_{Cl} ratios in the range of 30–440. Thus, a k_{Br}/k_{Cl} ratio of 2.1 for the reactions of **1** with methoxide ion provides strong evidence that the reactions are proceeding by an addition–elimination mechanism.

The effect of para substituents on this reaction supports this conclusion. A ρ value of 1.90 with σ is similar to the value reported by Hegarty et al.[15] for the basic hydrolysis of aryl *N*-arylchloroimidates **8** [ρ(Ar) = 1.41 and $\rho(Ar^1)$ = 2.39] which have been proposed to react by nucleophilic attack by hydroxide to give a tetrahedral intermediate. In comparison, the hydrolysis of hydroximoyl chlorides[6] **1** and related systems,[15,21–23] which react through nitrilium ion intermediates, give negative ρ values.

Although a rapid predissociation of **1** followed by rate-determining attack by methoxide ion S_N2(IP) would explain the second-order kinetics, such a mechanism is not consistent with the observed positive ρ value, the element effect, or for that matter retention of configuration during the reaction. Furthermore, we have found that the hydroximoyl chlorides **1** react very slowly under solvolysis conditions which would not be expected of compounds that react by an S_N2(IP) mechanism.[23]

The stereochemistry of the methoxide-substitution reactions of hydroximoyl chlorides and hydroximates can be rationalized in terms of Deslongchamps' theory of stereoelectronic control.[24] According to Deslongchamps' theory, cleavage of a tetrahedral intermediate with stereoelectronic control occurs when two heteroatoms each

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[12] Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1976**, *98*, 8460.

[13] Ta-Sham, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1977**, *99*, 1845.

[14] Ta-Shma, R.; Rappoport, Z. *J. Chem. Soc., Perkin Trans. 2* **1977**, 659.

[15] Hegarty, A. F.; Cronin, J. D.; Scott, F. L. *J. Chem. Soc., Perkin Trans. 2* **1975**, 429.

[16] (a) Hegarty, A. F.; McCormack, M. T.; Hathaway, B. J.; Hulett, L. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1136. (b) McCormack, M. T.; Hegarty, A. F. *Tetrahedron Lett.* **1976**, 395.

[17] (a) Rappoport, Z.; Topol, A. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1823. (b) *Ibid.* **1975**, 863.

[18] Stang, P. J.; Rappoport, Z.; Hanack, M.; Subramanian, L. R. "Vinyl Cations"; Academic Press: New York, 1979; p 328.

[19] Scott, F. L.; Cronin, D. A.; O'Halloran, J. K. *J. Chem. Soc. C* **1971**, 2769.

[20] Cronin, J.; Hegarty, A. F.; Casbell, P. A.; Scott, F. L. *J. Chem. Soc., Perkin Trans 2* **1973**, 1708.

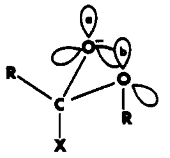
[21] Hegarty, A. F.; O'Driscoll, J.; O'Halloran, J. K.; Scott, F. L. *J. Chem. Soc., Perkin Trans. 2*, **1972**, 1887.

[22] Donovan, J.; Cronin, J.; Scott, F. L.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1050.

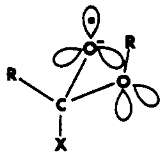
[23] It should also be pointed out that the hydroximoyl chlorides 1 and 2 are inert to alcoholic silver nitrate solution[3] which is inconsistent with an S_N2(IP) process.

[24] (a) Deslongchamps, P. *Heterocycles* **1977**, *7*, 1271; (b) *Pure Appl. Chem.*, **1975**, *43*, 351; (c) *Tetrahedron* **1975**, *31*, 2463.

have one nonbonded electron pair antiperiplanar to the leaving group. For example, the theory predicts that the tetrahedral intermediate **10** with two nonbonded pairs (a and b) antiperiplanar to the leaving group X should undergo rapid cleavage in comparison to the tetrahedral intermediate **11** which has only one nonbonded pair (a) antiperiplanar to the leaving group. In addition to the primary postulate, the theory proposes that (a) the conformation of the reactant is transferred to the tetrahedral intermediate, (b) the tetrahedral intermediate undergoes stereoelectronically controlled bond cleavage before any conformational change can occur, and (c) when a tetrahedral intermediate cannot undergo stereoelectronically controlled bond cleavage, the cleavage is slower than the rate of conformational changes.



10

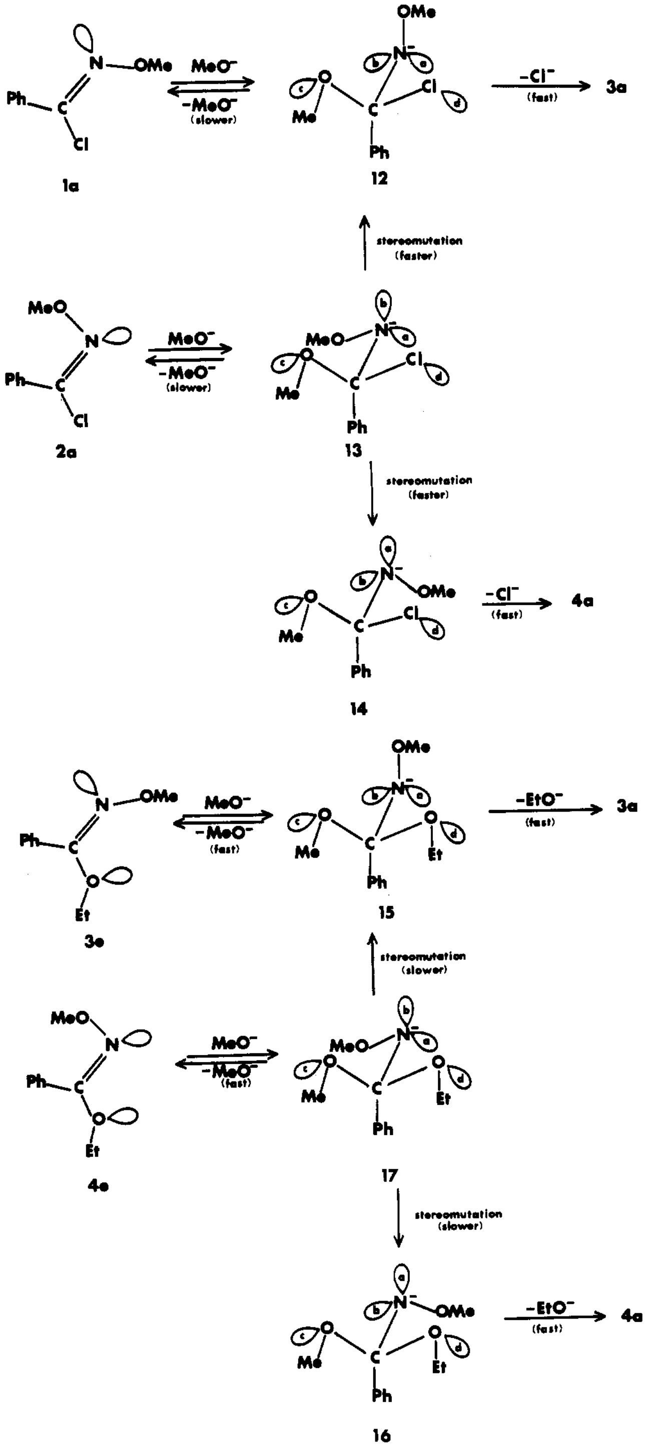


11

In Scheme IV the tetrahedral intermediates from reaction of methoxide ion with **1a**, **2a**, **3e**, and **4e** are shown with the antiperiplanar electron pairs on directly bonded heteroatoms. The structures have been simplified by omitting the nonbonded electron pairs on the two oxygen atoms that are not antiperiplanar to a leaving group.[25] The tetrahedral intermediate **12** from the (*Z*)-hydroximoyl chloride **1a** should undergo C–Cl bond cleavage with stereoelectronic control (nonbonded electron pairs b and c antiperiplanar to the chlorine) to give the (*Z*)-hydroximate **3a**. Although there is stereoelectronic control in the reverse direction (electron pairs a and d antiperiplanar to the MeO group), one would not expect this process to compete favorably with the forward reaction since chloride ion is a much better leaving group than methoxide. The tetrahedral intermediate **13**, from the (*E*)-hydroximoyl chloride, cannot undergo stereoelectronically controlled C–Cl bond cleavage, and thus one would predict that the rate of C–Cl cleavage should be slower than the rate of stereomutation (rotation and nitrogen inversion) to give conformations which lead to the formation of a mixture of hydroximates with the *E* isomer predominating. Similarly, the tetrahedral intermediate **15**, from the (*Z*)-hydroximate **3e**, should undergo C–OEt bond cleavage with stereoelectronic control (electron pairs b and c). In this case, however, the stereoelectronically controlled reverse reaction (electron pairs a and b) should compete with the forward reaction since ethoxide and methoxide should have about the same leaving group abilities. This explanation would account for at least part of the difference in methoxide substitution rates between **1a** and **3e**. The tetrahedral intermediate **17** formed in the reaction of the (*E*)-hydroximate **4e** with methoxide cannot undergo stereoelectronically controlled elimination of ethoxide ion to form product. Thus, the stereoelectronically controlled elimination of methoxide ion (electron pairs a and d) to give starting material is essentially the only process that occurs, and the overall rate of product formation is much slower than that of the *Z* isomer.

The preceding explanations, however, do not answer an important question concerning these reactions. Why does the tetrahedral intermediate **17** almost always return to starting material, while the tetrahedral intermediate **13** almost always proceeds to product? In other words, why should the tetrahedral intermediate **13** undergo rapid stereomutation and product formation while the intermediate **17** prefers to revert to starting material? To answer this question, we suggest that the stereoelectronically controlled reverse reaction in **13** (**13** → **2a**) is not as fast as stereomutation because of poor overlap of a relatively large 3p orbital on chlorine with the smaller developing 2p orbital on carbon. Thus, the activation energy for the reverse reaction of **13** (**13** → **2a**) is not lowered enough by the stereoelectronic effect to make it competitive with stereomutation. In the reverse reaction of the tetrahedral intermediate **17** (**17** → **4e**), where there is

Scheme IV



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[25] The hydroximates **3e** and **4e** are shown in Scheme IV in the s-trans conformation. The s-cis conformations of **3e** and **4e** would also give a tetrahedral intermediate with an electron pair antiperiplanar to the OMe group.

better overlap of similar-sized orbitals (second principle quantum number sp^3 hybrid orbital with the developing 2p orbital on carbon), the stereoelectronic effect lowers the activation energy of the reaction to the extent that it is a faster process than stereomutation.

To summarize, we suggest that stereoelectronically controlled loss of chloride ion from the tetrahedral intermediate **12** is faster than either loss of methoxide ion or stereomutation. In the tetrahedral intermediate **13**, stereomutation to **12** and **14** and stereoelectronically controlled loss of chloride ion from **12** and **14** are faster processes than loss of methoxide ion from **13**. In this mechanistic scheme the hydroximoyl chlorides **1a** and **2a** react at similar rates because the rates of nucleophilic attack by methoxide ion on these isomers are similar. Furthermore, the tetrahedral intermediate **15** formed from the (*Z*)-hydroximate **3e** loses either methoxide ion or ethoxide ion faster than it undergoes stereomutation. The tetrahedral intermediate **17** from the (*E*)-hydroximate loses methoxide ion to produce starting material faster than it undergoes stereomutation.

The preceding discussion of the methoxide substitution reactions of the hydroximates **3e** and **4e** assumed rate-determining nucleophilic attack followed by rapid stereoelectronically controlled elimination from the tetrahedral intermediate. Ta-Shma and Rappoport[14] have attributed the lower reactivity of imidoyl cyanides **7b** with amines when compared with that of imidoyl halides **7a** to a change in the rate-determining step with a change in leaving groups. They suggested that nucleophilic attack is rate determining with good leaving groups (halide), whereas the elimination step is rate determining with the poorer leaving group (cyanide). A similar conclusion was drawn by Rappoport[26-28] to rationalize a decrease in the nucleophilic substitution rate of activated vinyl cyanides as compared to the corresponding chlorides.

The kinetic scheme of Ta-shma and Rappoport offers an alternate explanation of our results. In this interpretation, the hydroximoyl chlorides **1a** and **2a** undergo rate-determining nucleophilic attack and rapid loss of chloride ion. With the hydroximates **3e** and **4e**, however, the rate-determining step is loss of the poorer leaving group ethoxide ion. Since the elimination of ethoxide ion is rate determining, stereomutation would occur, and both isomers would react through a common intermediate. This would account for the fact that both **3e** and **4e** give the same kinetic product **4a**. This interpretation of our results, however, requires that the ca. 300-fold difference in rates between the (*Z*)- and (*E*)-hydroximates be due solely to a slower rate of nucleophilic attack by methoxide ion on the *E* isomer as compared to that for the *Z* isomer; i.e., stereoelectronic control in the tetrahedral intermediates does not play a role in determining the relative rates of the methoxide substitution reactions of **3e** and **4e**. The lower rate of nucleophilic attack on the (*E*)-hydroximate **4e** could be due to the effect of a noncoplanar phenyl group which would increase the steric factor for nucleophilic attack as well as alter the electron density at the hydroximoyl carbon atom. The greater degree of π overlap in the (*Z*)-hydroximate apparently is responsible for the higher molar absorptivity in the ultraviolet spectrum of the *Z* isomer **3e** as compared to the *E* isomer **4e** [**3e**, λ_{max} 259 nm (ϵ 11 200); **4e**, λ_{max} = 260 nm (ϵ 5010); in cyclohexane]. The difficulty with this argument is that the ultraviolet spectra of the isomeric hydroximoyl chlorides **1a** and **2a** also indicate a greater degree of twisting of the phenyl group in the *E* isomer as compared to the *Z* isomer [**1a**, λ_{max} 257 nm (ϵ 12 000); **2a**, λ_{max} 256 nm (ϵ 7590); in cyclohexane[5]]. Thus, one would expect approximately the same steric and electronic factors to be operating in the hydroximoyl chlorides due to an increased twisting of the phenyl in the *E* isomers. This effect seems to be small since the hydroximoyl chlorides react at approximately the same rate with methoxide ion. Since $k(Z)/k(E)$ for the hydroximates **3e** and **4e** is equal to ca. 300, it seems likely that nucleophilic attack by methoxide ion is rate determining and that the difference in reaction rates between the two isomers is due to stereoelectronic effects, i.e., the reversibility of the *E*-hydroximate reaction. Furthermore, the lower reactivity of the (*Z*)-hydroximate **3e** as compared to the (*Z*)-chloride **1a** [$k(\mathbf{1a})/k(\mathbf{3e})$ = 53] is probably due to the reversibility of the (*Z*)-hydroximate reaction combined with a lower rate of nucleophilic attack of methoxide ion on the hydroximate.

Although some of the details of the mechanisms suggested herein require substantiation, it is clear that stereoelectronic control plays an important, if not dominant, role in the rates and stereochemistry of bimolecular substitution at the carbon-nitrogen double bond.

Experimental Section

General Methods. All inorganic chemicals were reagent grade. The dimethyl sulfoxide (Aldrich) and methanol (Baker) were spectrophotometric grade and were stored over 4A molecular sieves under a dry nitrogen atmosphere. All solvent transfers were carried out by using syringe techniques with the aid of dry nitrogen pressure. Periodic checks of solvent dryness were made by using the Karl-Fischer technique. These checks showed the water content of the solvents to be less than 0.025%. The water used in this study was distilled in glass and had a pH of 6.5. The hydroximoyl halides (**1a-h** and **2a-d**) and hydroximates (**3a-c** and **4a-c**) were prepared according to published procedures.[4,5] ^{1}H NMR spectra were obtained on either a Varian A-60A or a Varian EM-390 NMR spectrometer. The gas-liquid chromatography (GLC, analytical and preparative) was carried out with a column (30 ft × 0.375 in.) consisting of 20% silicone gum rubber (SE-30) on 45-60-mesh Chromosorb W. The high-pressure liquid chromatography (HPLC) was performed on a Model ALC-202 Waters Associates high-pressure liquid chromatograph fitted with an ultraviolet absorption detector. The analyses were carried out on a Waters Corasil analytical column with 3% chloroform (Mallinchrodt analytical reagent grade) in hexane (Aldrich, spectrophotometric grade) as the mobile phase. Normalization factors for the GLC and HPLC peak areas were determined by injecting samples containing known amounts of reactants and products. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Elemental microanalyses were performed at Atlantic Microlab.

General Procedure for Substitution Product Analysis. An 0.8 M sodium methoxide solution (5.0 mL) was added to the hydroximoyl chloride (or hydroximate; 4.0 mmol) dissolved in dimethyl sulfoxide (90 mL) and methanol (5 mL), and the reaction flask was suspended in a constant-temperature bath at 44.6 °C. The reaction was quenched by pouring it into ice-water (100 mL). Sodium chloride was added to the aqueous solution until it was saturated, and the solution was extracted with ether (4 × 10 mL). The ether extracts were dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was usually analyzed by GLC or HPLC. The GLC and HPLC retention times of the hydroximate products were compared to the retention times of the authentic samples. In the case of the methoxide substitution reactions of **1d** and **2d**, the hydroximate product distributions (**3d** and **4d**) were determined by ^{1}H NMR spectroscopy. The hydroximates **3d** and **4d** have not been reported previously. The hydroximate **3d** (mp 74-75 °C) was obtained by the reaction of **1d** with sodium methoxide. A sample of **4d** (mp 52-54 °C) was

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(26) (a) Rappoport, Z. *J. Chem. Soc.* **1963**, 4498. (b) Rappoport, Z.; Greenzaid, P.; Horowitz, A. *J. Chem. Soc.* **1964**, 1334.

(27) (a) Rappoport, Z.; Ta-Shma, R. *J. Chem. Soc. B* **1971**, 871. (b) *Ibid.* **1971**, 1461.

(28) Rappoport, Z.; Peled, P. *J. Chem. Soc., Perkin Trans. 2* **1973**, 616.

isolated from a mixture of **3d** and **4d** (prepared by isomerization of **3d** in benzene–hydrogen chloride solution[5]) by column chromatography (silica gel, 10% benzene–90% hexane eluant). Both **3d** and **4d** were recrystallized from methanol–water before elemental analysis. For **3d**: NMR ($CDCl_3$) δ 3.98 (s, $COCH_3$), 4.12 (s, $NOCH_3$), 7.99 (d, J = 9 Hz, 2 H, aromatic H), 8.31 (d, J = 9 Hz, 2 H, aromatic H).

Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.54; H, 4.87; N, 13.21.

For **4d**: NMR ($CDCl_3$) δ 3.90 and 3.92 (2 s, $COCH_3$ and $NOCH_3$), 8.04 (d, J = 9 Hz, 2 H, aromatic H), 8.31 (d, J = 9 Hz, 2 H, aromatic H).

Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.45, H, 4.81; N, 13.33.

Kinetic Methods. (A) Reactions of Hydroximoyl Chlorides with Sodium Methoxide. The sodium methoxide solutions were prepared by adding clean sodium to a flask of dry methanol. The necks of the flask were fitted with rubber septum caps so that the hydrogen gas could be vented through a hypodermic needle during the reaction. The stock solutions of sodium methoxide were approximately 1.5 M and were stored in closed containers under dry nitrogen. The stock solutions were diluted with methanol and the resulting solutions were titrated with standardized sulfuric acid. The hydroximoyl chloride was weighed into a 50-mL volumetric flask, 38 mL of Me_2SO was added, and the flask was thermostated in a constant-temperature bath (±0.01 °C). The standardized sodium methoxide solution was thermostated in a separate container. After allowing 15-min for thermal equilibration, 5 mL of the sodium methoxide solution was added with a pipet to the 50-mL volumetric flask. When the last drop of solution drained from the pipet, the timer was started. The reaction mixture was quickly diluted to the mark with previously thermostated Me_2SO and then shaken to ensure complete mixing of the solutions. Aliquots (5 mL) were taken with a pipet from the volumetric flask and quenched by addition to water (100 mL). It was discovered during the course of this work that the titration method used for following the rates of these reactions was very sensitive to the pH of the water used to quench the reaction. Consequently, only water with a pH near 6.5 was used for the quenching. The time was recorded for each aliquot when the last drop of solution drained from the pipet. Three or four drops of indicator (methyl red–bromocresol green) were added to the solution. The solution was then titrated with standardized sulfuric acid (usually 0.01–0.015 N) to a pH of 5.1 by using a Leeds and Northrup expanded-scale pH meter, with the indicator serving as an approximate method of determining the end point (blue to red wine). The solution was magnetically stirred during the titration. Titration of known amounts of sodium methoxide, obtained by weighing anhydrous sodium methoxide, proved that equivalents were being titrated at the end point. To ensure that the reaction was stopped by addition to water, we took two aliquots simultaneously on one run for each compound studied. One aliquot was titrated immediately after quenching with water, and the second was titrated 30 min later. In every case the titers were found to be the same. Reaction rates were usually measured to 90% completion of the reaction. The second-order rate constants and the Hammett ρ value were calculated by a least-squares evaluation of the data.

(B) Reactions of Hydroximates 3e and 4e with Sodium Methoxide and the Methoxide-Catalyzed Isomerization of 3a to 4a. The procedure for measuring the rates of these reactions was the same as described in part A except that after the reaction was quenched with water, the aqueous solution was saturated with sodium chloride and extracted with ether (4 × 10 mL). The ether extracts were dried over anhydrous magnesium sulfate and evaporated in vacuo, and the residue was analyzed by GLC.

Independent Syntheses of the Alkyl *O*-Methylbenzohydroximates 3a, 4a, 3e, and 4e. The general procedure for the independent synthesis of an alkyl *O*-alkylbenzohydroximate has been described previously.[4] The hydroximates **3e** and **4e** were prepared by methylation (methyl iodide–sodium methoxide in methanol) of the *Z* and *E* isomers of ethyl benzohydroximate (**5b** and **6b**, respectively). The hydroximates **5b** and **6b** were prepared according to published procedures,[4] and the hydroximates **3e** and **4e** were purified by preparative GLC. For **3e**: NMR ($CDCl_3$) δ 1.27 (t, J = 8 Hz, CH_2CH_3), 3.86 (s, OCH_3), 4.33 (q, J = 8 Hz, OCH_2), 7.2–7.5 (m, 3 H, aromatic H), 7.7–8.0 (m, 2 H, aromatic H); UV (cyclohexane) 259 nm (ϵ 11 200).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.07; H, 7.35; N, 7.77.

For **4e**: NMR ($CDCl_3$) δ 1.31 (t, J = 8 Hz, CH_2CH_3) 3.78 (s, OCH_3), 4.20 (q, J = 8 Hz, OCH_2), 7.2–7.5 (m, 3 H, aromatic H), 7.7–8.0 (m, 2 H, aromatic H); UV (cyclohexane) 260 nm (ϵ 5010).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.09; H, 7.35; N, 7.80.

The hydroximates **3a** and **4a** were prepared by methylation (methyl iodide–sodium methoxide in methanol) of methyl (*Z*)-benzohydroximate [**5a**: mp 40–42 °C (lit.[29,30] mp 44 °C); NMR ($CDCl_3$) δ 3.98 (s, OCH_3), 7.2–7.8 (2 m, 3 H and 2 H, aromatic H)] and methyl (*E*)-benzohydroximate [**6a**: mp 50–52 °C (lit.[29,30] mp 52–53 °C); NMR ($CDCl_3$) δ 3.83 (s, OCH_3), 7.3–8.0 (2 m, 3 H and 2 H, aromatic H)]. The spectral properties of **3a** and **4a** have been reported previously.[5]

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Registry No. 1a, 41071-35-6; **1b**, 57139-37-4; **1c**, 57139-39-6; **1d**, 41071-37-8; **1e**, 57139-33-0; **1f**, 57139-34-1; **1g**, 57139-36-3; **1h**, 57139-40-9; **2a**, 41071-34-5; **2b**, 57139-30-7; **2c**, 57139-32-9; **2d**, 41071-36-7; **3a**, 41071-39-0; **3b**, 57139-45-4; **3c**, 57139-46-5; **3d**, 41071-41-4; **3e**, 78109-12-3; **4a**, 41071-40-3; **4b**, 57139-42-1; **4c**, 57139-43-2; **4d**, 41071-42-5; **4e**, 78109-13-4; **5a**, 68525-46-2; **5b**, 7340-49-0; **6a**, 68525-45-1; **6b**, 7340-17-2.

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(29) Blaser, R.; Imfeld, P.; Schindler, O. *Helv. Chim. Acta* **1969**, *52*, 569.

(30) Werner, A.; Subak, J. *Ber.* **1896**, *29*, 1153.