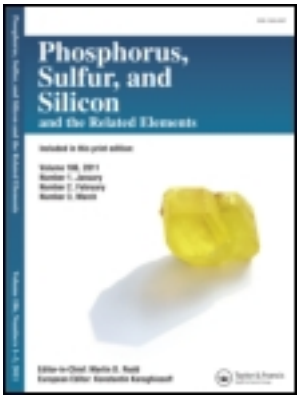

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The Synthesis of Sulfinylphthalimides and their Reactions with Some Nucleophiles in Dioxane

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THE SYNTHESIS OF SULFINYLPHTHALIMIDES AND THEIR REACTIONS WITH SOME NUCLEOPHILES IN DIOXANE

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Abstract *In this study, some N-(p-substituted-arylsulfinyl)phthalimides (**1a–1e**) were synthesized. The synthesized compounds were examined with respect to their substitution reactions with sodium ethoxide, sodium methoxide, methylamine, and t-butylamine in dioxane. The substituent effect was investigated at 30.0 ± 0.1 °C. The activation entropy was also studied, and negative $\Delta S^{\neq}$ values were obtained. Configuration inversions were observed in the substitution reactions. This result is in conformity with the S_N2 mechanism.*

[Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental resource*: *Characterization of -(p-Substituted-arylsulfinyl)phthalimides 1a–b.]*

Keywords Arylsulfinylphthalimides; substituent effect; activation entropy; solvent effect; S_N2

INTRODUCTION

In the literature, the first reported sulfenimide was N-(trichloromethylthio)phthalimide, which was prepared by Kittleson[1] by the reaction of trichloromethanesulfenylchloride with sodium phthalimide. Alkyl and arylthioimides act as efficient sulfur transfer agents.[2] Since the early 20th century, the chemistry of sulfinamides has been of continuing interest[3] because they are valuable precursors for the synthesis of chiral amines and their derivatives, aziridines, sulfoximines, and related species, benzothiozines, olefins, and ketones.[4] Sulfinylphthalimides react rapidly with nucleophiles, resulting in displacement of the phthalimide anion and formation of the corresponding sulfinyl derivative.[5] Harpp and Back attempted to synthesize N-(alkyl- and arylsulfinyl)phthalimides for possible use as sulfinyl transfer reagents and reported that thiophthalimides conveniently oxidized to the corresponding sulfinyl analogs in high yield by treatment with 1 equivelent of *m*-chloroperbenzoic acid.[6] Nucleophilic substitution at sulfur has been theoretically studied by Bachrach.[7] In a recent study, this reaction was explored for the particular case of sulfinyl chlorides.[8] Um et al. Reported, along with kinetic evidence for a stepwise mechanism, the first spectroscopic observation of an intermediate in the reaction of a sulfinate ester with NaOEt in anhydrous EtOH.[9] A study of the kinetics and mechanism

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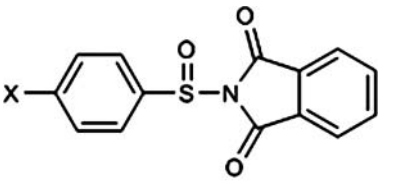
of the acid catalyzed hydrolysis of a series of N-(*p*-substitutedarylsulfinyl)phthalimides have been studied in concentrated aqueous mineral acids in our laboratory.[10] We now report a complementary study of the nucleophilic substitution reactions of a series of N-(*p*-substitutedarylsulfinyl)phthalimides **(1a–e)** in dioxane (Scheme 1).



1a X= CH_3
1b X= H
1c X=Cl
1d X= OCH_3
1e X= NO_2

Scheme 1

RESULTS AND DISCUSSION

In this study, N-(*p*-toluenesulfinyl)phthalimide (**1a**), N-(phenylsulfinyl)phthalimide (**1b**), N-(*p*-chlorophenylsulfinyl)phthalimide (**1c**), N-(*p*-methoxyphenylsulfinyl)phthalimide (**1d**), and N-(*p*-nitrophenylsulfinyl)phthalimide (**1e**) have been synthesized. The synthesized compounds were examined with respect to their substitution reactions with sodium ethoxide, sodium methoxide, methylamine, and *t*-butylamine in dioxane. In order to determine the mechanism, substituent effect, solvent effect, activation entropy, configuration change, and nucleophile effect were used as criteria.

The substituent effect was investigated at 30.0 ± 0.1 °C in dioxane. Positive *p* values were obtained for the substitution of N-(*p*-substitutedarylsulfinyl)phthalimides with sodium ethoxide, sodium methoxide, metylamine, and *t*-butylamine. Electron withdrawing substituent ($-Cl$, $-NO_2$) increases the reaction rate (Figure 1), while an electron donating substituent ($-CH_3$, $-OCH_3$) leads to a decrease. A positive *p* value indicates the S_N2 mechanism or addition-elimination mechanism. The *p* values for the reaction of N-(phenylsulfinyl)phthalimide in dioxane with sodium ethoxide, sodium methoxide, methylamine, and *t*-butylamine were 0.83, 0.72, 0.68, and 1.51, respectively. Similar behavior has been observed for the alkaline hydrolysis of sulfonimidic esters.[11] The kinetic results are demonstrated graphically in Figures 1–4.

The activation entropy was also studied, and negative $\Delta S^{\neq}$ values were obtained. The $\Delta S^{\neq}$ values for the reaction of N-(phenylsulfinyl)phthalimide in dioxane with sodium methoxide, sodium ethoxide, methylamine, and *t*-butylamine were −79.53, −90.97, −135.1, and −139.20 J/mol K, respectively. The negative $\Delta S^{\neq}$ values indicate that the reaction followed the S_N2 mechanism or addition-elimination mechanism. Similar behavior has been observed for the aminolysis of 1-tosyl-3-methyl imidazolium chloride.[12] Arrhenius parameters for the reaction of N-(phenylsulfinyl)phthalimide in dioxane with sodium ethoxide, sodium methoxide, methylamine, and *t*-butylamine are shown in Table 1.

Second order kinetics, showing dependence both on the nucleophile and on the substrate, are widely observed in nucleophilic substitutions.[13] It was also observed that the

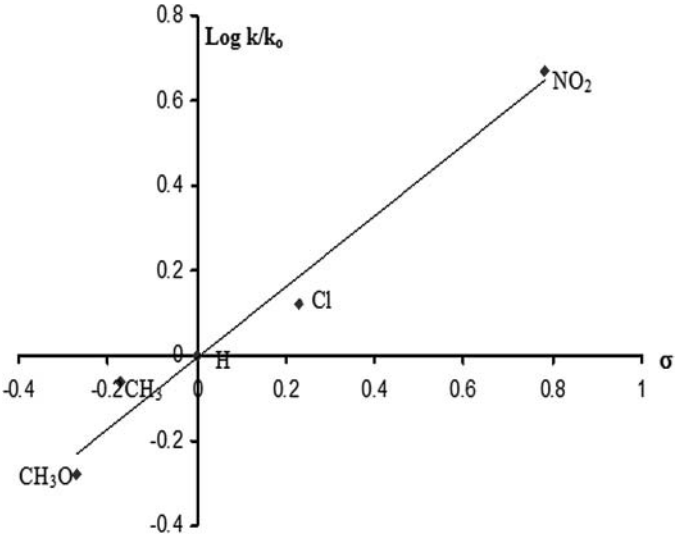


Figure 1 Hammett plots for the reaction of N-(p-substitutedarylsulfinyl)phthalimide in dioxane with sodium ethoxide.

reactions with sodium ethoxide and sodium methoxide nucleophiles took place much faster than those with methylamine and *t*-butylamine nucleophiles as shown in Table 2.

Configuration inversion was observed in the substitution reaction of N-(*p*-methoxyphenylsulfinyl)phthalimide with *t*-butylamine in dioxane. The rotation of the plane of polarized light changed from $+1.2^\circ$ to -1.3°. This result is in consisted with the S_N2 mechanism.

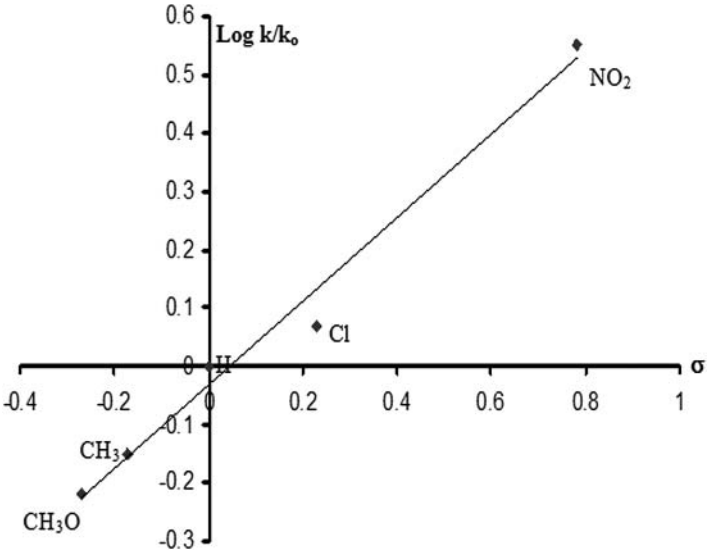


Figure 2 Hammett plots for the reaction of N-(p-substitutedarylsulfinyl)phthalimide in dioxane with sodium methoxide.

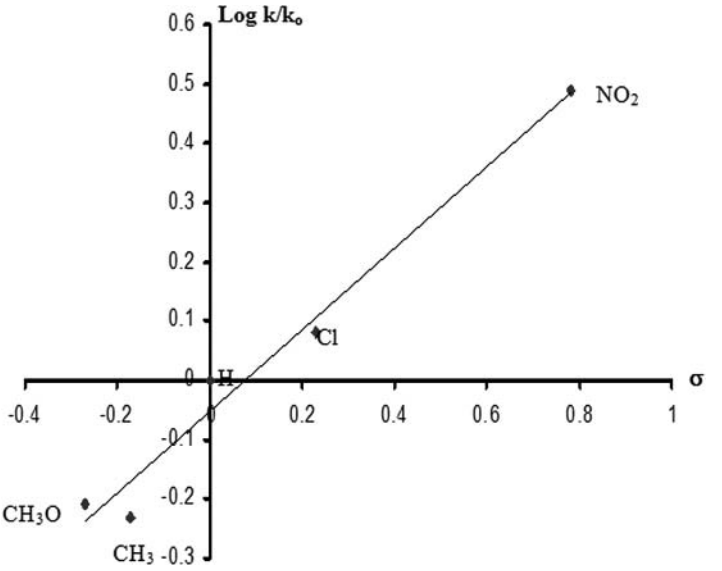


Figure 3 Hammett plots for the reaction of N-(p-substitutedarylsulfinyl)phthalimide in dioxane with methylamine.

In the light of the overall evidence, we propose that the substitution reactions of a series of N-(*p*-substitutedarylsulfinyl)phthalimides with sodium ethoxide, sodium methoxide, methylamine, and *t*-butylamine occur with S_N2 mechanism or addition-elimination mechanism, as shown in Schemes 2 and 3 respectively.

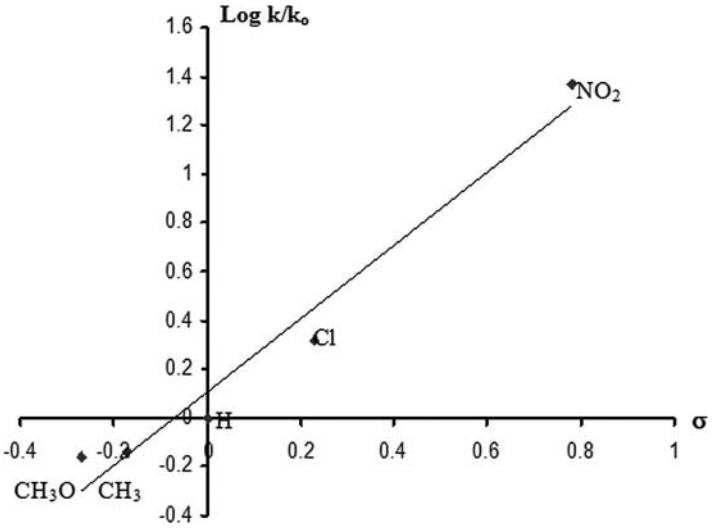
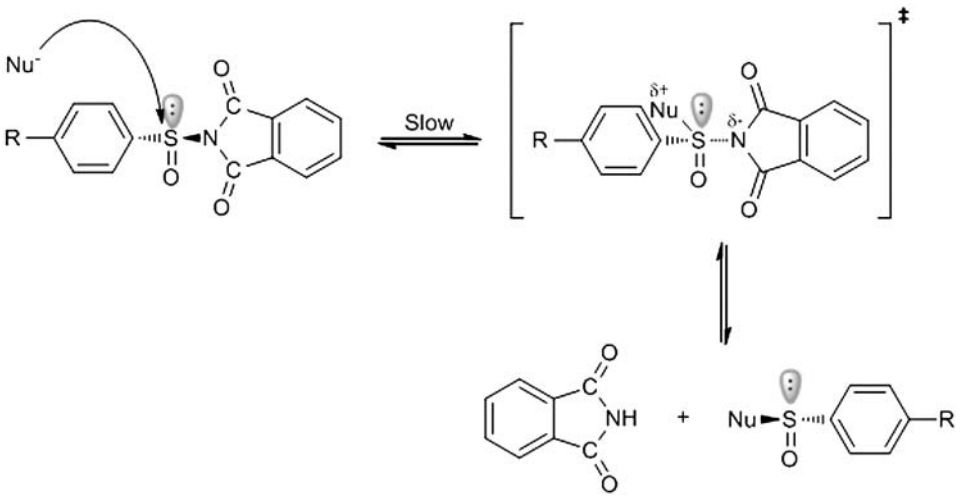


Figure 4 Hammett plots for the reaction of N-(p-substitutedarylsulfinyl)phthalimide in dioxane with *t*-butylamine.

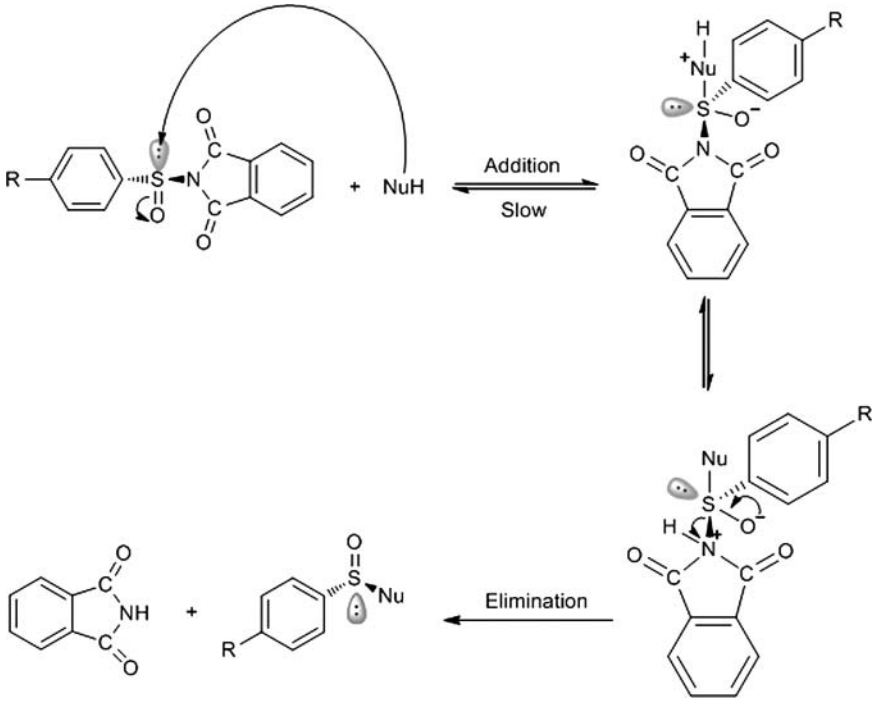


Scheme 2

EXPERIMENTAL

Materials and Methods

N-(*p*-Substituted-arylsulfinyl)phthalimides **1a–e** were prepared from the corresponding N-(*p*-substitutedarylthio)phthalimides with *m*-chloroperbenzoic acid in chloroform as



Scheme 3

Table 1 Activation parameters for the reaction of N-(phenylsulfinyl)phthalimide in dioxane with sodium ethoxide, sodium methoxide, methylamine, and *t*-butylamine

Nucleophile	$\Delta H^{\neq}$ (kJ/mol)	$\Delta S^{\neq}$ (J/molK)	R^2
Sodium methoxide	41.01	−79.53	0.996
Sodium ethoxide	37.62	−90.97	0.999
t-Butylamine	36.99	−139.2	0.991
Methylamine	37.29	−135.1	0.971

described by Harpp and Back.[5] N-(*p*-Substitutedarylthio)phthalimides were prepared from the corresponding *p*-substitutedthiophenol by reaction with phthalimide in hot acetonitrile and pyridine then a solution of bromine in acetonitrile, as described by Klose, Reese, and Song.[14] All melting points were determined using an electrothermal digital melting point apparatus.

1a m.p. 191 °C –192 °C (lit.[5] 191–194 °C); found C, 62.99; H, 4.11; N, 4.98; calc. for $C_{15}H_{11}NSO_3$ C, 63.14; H, 3.89; N, 4.91%;

1b m.p. 150–153.5 °C (lit.[5] 150 °C –153 °C); found C, 61.71; H, 3.37; N, 4.83; calc. for $C_{14}H_9NSO_3$ C, 61.98; H, 3.34; N, 5.16%;

1c m.p. 212 °C –213 °C; found C, 55.31; H, 2.60; N, 4.78; calc. For $C_{14}H_8NSO_3Cl$ C, 55.00; H, 2.64; N, 4.58%; IR $\upsilon = 3084$ cm^{-1} (C-H), 1609–1467 cm^{-1} (C=C), 1108 cm^{-1} (C-N), 1090 cm^{-1} (S-O), 711 cm^{-1} (Ar–Cl), 685 cm^{-1} (C-S); ^{1}H NMR ($CDCl_3$): $\delta =$ 8.13–8.09 (dd, 2H, $J = 1.62$ Hz), 8.02–7.98 (dd, 2H, $J = 2.24$ Hz), 7.78–7.71 (d, 2H, $J =$ 3.18 Hz), 7.68–7.63 (d, 2H, $J = 4.13$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 165.1$, 139.3, 138.6, 135.3, 131.5, 129.8, 126.7 124.7.

Table 2 Values of k_2 ($M^{-1}s^{-1}$) for the substitution of N-(*p*-substitutedarylsulfinyl)phthalimides with nucleophiles at 30.0 ± 0.1 °C in dioxane

Nucleophile	Substituent	k_2 ($M^{-1}s^{-1}$)
Sodium ethoxide	CH_3O	23.72
	CH_3	39.38
	H	45.21
	Cl	58.93
	NO_2	209.76
Sodium methoxide	CH_3O	25.57
	CH_3	30.06
	H	42.92
	Cl	50.65
	NO_2	151.92
t-Butylamine	CH_3O	0.110
	CH_3	0.114
	H	0.158
	Cl	0.331
	NO_2	3.750
Methylamine	CH_3O	0.130
	CH_3	0.124
	H	0.211
	Cl	0.257
	NO_2	0.635

1d m.p. 181 °C–184 °C; found C, 59.53; H, 3.59; N, 4.54; calc. for $C_{15}H_{11}NSO_4$ C, 59.79; H, 3.68; N, 4.65%; IR $\upsilon = 3084\ cm^{-1}$ (C-H), 1601–1466 cm^{-1} (C=C), 1197 cm^{-1} (C-N), 1062 cm^{-1} (S-O), 604 cm^{-1} (C-S); ^{1}H NMR ($CDCl_3$): $\delta = 7.91–7.86$ (dd, 2H, $J = 3.02$ Hz), 7.79–7.78 (d, 2H, $J = 3.73$ Hz), 7.76–7.71 (dd, 2H, $J = 2.38$ Hz), 6.86–6.82 (d, 2H, $J = 5.10$ Hz), 3.78 (3H, CH_3O); ^{13}C NMR ($CDCl_3$): $\delta = 167.8, 161.4, 136.7, 134.5, 132.0, 125.3, 123.9, 114.6, 55.4$.

1e m.p. 175 °C –178 °C; found C, 54.00; H, 2.49; N, 8.75; calc. for $C_{14}H_8N_2SO_5$ C, 54.16; H, 2.55; N, 8.86%; IR $\upsilon = 3052\ cm^{-1}$ (C-H), 1610–1542 cm^{-1} (C=C), 1494 cm^{-1} (C-NO_2), 1198 cm^{-1} (C-N), 1100 cm^{-1} (S-O), 552 cm^{-1} (C-S); ^{1}H NMR ($CDCl_3$): $\delta = 8.18–8.14$ (d, 2H, $J = 4.32$ Hz), 8.04–7.98 (dd, 2H, $J = 3.86$ Hz), 7.92–7.85 (dd, 2H, $J = 2.73$ Hz), 7.42–7.38 (d, 2H, $J = 3.14$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 167.0, 146.8, 144.6, 135.3, 131.6, 125.7, 124.5, 124.4$.

Kinetic Studies

The rates of substitution reactions of N-(*p*-substituted-arylsulfinyl)phthalimides were followed spectrophotometrically using a GBC Cintra 20 Model UV-VIS spectrophotometer with a thermostatted cell compartment (±0.05 °C). The values of k_1 were calculated from the standard equation using a least-squares procedure. All kinetic measurements were duplicated, and the average deviation from the mean was <3%. Second-order rate constants (k_2) were calculated from the slope of the plots of pseudo-first-order rate constants versus nucleophile concentrations (at least five different concentrations).

Product Analysis

Sodium methoxide (0.09 g, 1.67 mmol) was added to *p*-toluenesulfinylphthalimide (0.48 g, 1.67 mmol) in dioxane. The reaction mixture was stirred for seven days at room temperature. Dioxane was evaporated in vacuo. The reaction mixture was poured out anhydrous ether (20 mL). Insoluble material was then filtered. Ether was evaporated in vacuo. The resulting colorless oil was treated with chloroform. White solid was filtered. Chloroform was evaporated in vacuo. Methyl *p*-toluenesulfinate was obtained (0.22 g, 77%) as colorless oil. $n_D^{21} = 1.5420$, lit.[15] $n_D^{21} = 1.5416$; ^{1}H NMR ($CDCl_3$): $\delta = 7.55–7.51$ (d, 2H, $J = 8.14$ Hz), 7.30–7.26 (d, 2H, $J = 8.23$ Hz), 3.38 (3H,−OCH_3), 2.36 (3H, -CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 138.8, 134.2, 128.0, 124.6, 67.1, 21.3$.

Analysis of the products also was determined by comparing the UV spectrum obtained after completion of the kinetic experiment with the spectrum of the expected products at the same concentration and under the same conditions. Thus, for the reaction of N-(*p*-toluenesulfinyl)phthalimide with sodium methoxide, the UV spectrum recorded at the end of the reaction was identical with that of a 1:1 mixture of sodium phthalimide and methyl *p*-toluenesulfinate.

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