696-63-9; bis(2,4-dimethoxyphenyl) disulfide, 55990-92-6; CH_2I_2, 75-11-6; thiophenol, 108-98-5; $Br(CH_2)_2Br$, 106-93-4; dimethyl diazomalonate, 6773-29-1; ethyl diazoacetate, 623-73-4; triphenylmethylphosphonium bromide, 1779-49-3; di(n-propyl) disulfide, 629-19-6.

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Nucleophilic Cleavage of the Sulfur–Sulfur Bond by Phosphorus Nucleophiles. III. Kinetic Study of the Reduction of a Series of Ethyl Aryl Disulfides with Triphenylphosphine and Water[1]

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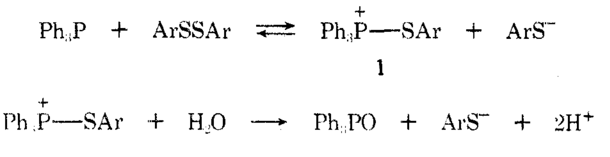
Received May 19, 1975

A stopped-flow kinetic study of the reaction of a series of ethyl substituted-phenyl disulfides (2) with triphenylphosphine (Ph_3P) in 50% dioxane–water at pH 13.3 is reported. This reaction results in reduction of the disulfide to yield the corresponding benzenethiol, ethanethiol, and triphenylphosphine oxide. Triphenylphosphine sulfide is not formed. In analogy with our previous study of the reaction of symmetrical aryl disulfides with Ph_3P a two-step mechanism is suggested. At pH 13.3 the first step is rate determining. A plot of log k_1 against σ yields a ρ value of 1.76 (standard deviation 0.07). The substituent effect data are interpreted to indicate that some negative charge is developed on both sulfur atoms in the transition state as bond making is somewhat advanced over bond breaking.

We recently reported[1] evidence to indicate that the reduction of symmetrical aryl disulfides with triphenylphosphine (Ph_3P) in aqueous dioxane involves at least two steps (Scheme I). The rate-determining step of this redox reaction was shown to be pH dependent. At both low and high pH, nucleophilic attack by Ph_3P on the S–S bond to form an intermediate thioalkoxyphosphonium cation (1) is rate limiting, while at intermediate pH the reversal of the first step becomes important and the reaction is kinetically more complex.[1] Based primarily on the large sensitivity of the first step of Scheme I to the electron-withdrawing nature of the disulfide substituents ($\beta = -1.02$, $\rho = 2.94$) it was tentatively suggested that nucleophilic attack by the phosphine occurs via a transition state in which negative charge is developed on both sulfur atoms, and that thus the sulfur undergoing attack is partially valence expanded as

Scheme I



$$Ph_3P + ArSSAr \rightleftharpoons \underset{1}{Ph_3\overset{+}{P}{-}SAr} + ArS^-$$

$$Ph_3\overset{+}{P}{-}SAr + H_2O \longrightarrow Ph_3PO + ArS^- + 2H^+$$

Table I
Cleavage of Ethyl-Substituted Phenyl Disulfides by Ph_3P[a]

Ethyl substituted-phenyl disulfide	pH	No. of runs	10^3 $[Ph_3P]_0$, M	$10^{-4}k$, l. mol^{-1} min^{-1}	pK_a substituted[b] benzenethiol
3, 4-NO_2	13.30, 13.60	6	0.80–1.6	6.54 ± 0.70	5.36
4, 3-NO_2	13.30	3	0.80–1.6	6.19 ± 0.65	6.08
5, 4-$COOCH_3$	13.30	3	0.80–1.6	1.44 ± 0.10	6.70
6, 3-Cl	13.30	3	0.80–1.6	1.08 ± 0.012	7.00
7, 4-Cl	13.30, 13.60	12	0.80–1.6	0.684 ± 0.068	7.40
8, 3-OCH_3	13.30	3	0.80–1.6	0.355 ± 0.034	
9, 4-OCH_3	13.30	3	1.0–3.0	0.0973 ± 0.010	8.45
10, 4-NH_2	13.30	3	2.0–4.0	0.0219 ± 0.0009	8.86

[a] In 50% dioxane-water, 30.0 ± 0.1°, ionic strength 0.10 (KCl), $[ArSSEt]_0 = 2\text{–}30 \times 10^{-5}$ M, $[Na_2EDTA] = 5.0 \times 10^{-4}$ M. [b] Experimentally determined under identical conditions (ref 1).

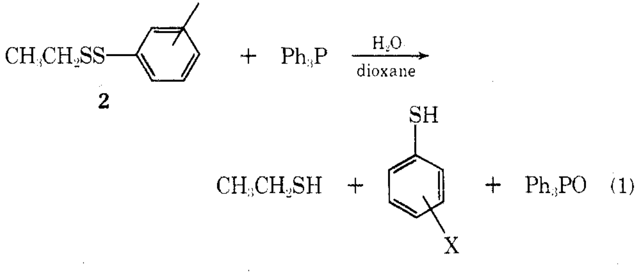
bond making is advanced over bond breaking. The timing of bond-making and bond-breaking steps in nucleophilic displacements at sulfenyl sulfur has been the object of intense investigation.[3] In order to pursue this question further, for the specific case of phosphine nucleophiles and disulfides, we report here an investigation of the reaction of Ph_3P with a series of ethyl aryl disulfides. It was hoped that a study of these unsymmetrical disulfides would provide substituent effect data about the leaving group sulfur, and that these data, when compared with the results of our previous study of symmetrical aryl disulfides, would allow us to draw some conclusions about the nature of the sulfur atom undergoing nucleophilic attack.[4]

Most previous studies of this reaction of unsymmetrical disulfides with nucleophiles are consistent with both kinetic and thermodynamic cleavage occurring in the direction to liberate the most stable mercaptide.[5,6] Although examples of kinetic cleavage in the opposite sense are known,[7] nucleophilic attack in these cases was likely dictated by steric effects. Thus, as a consequence of the small steric bulk of the ethyl substituent and the high pK_a of ethanethiol[8] it was anticipated that ethyl aryl disulfides would undergo kinetic attack by nucleophiles solely on the ethyl bearing sulfur.

Although several workers have studied the reduction of symmetrical aryl[1,9] and alkyl[10] disulfides with Ph_3P, the reaction of Ph_3P with unsymmetrical alkyl aryl disulfides has not been previously reported.

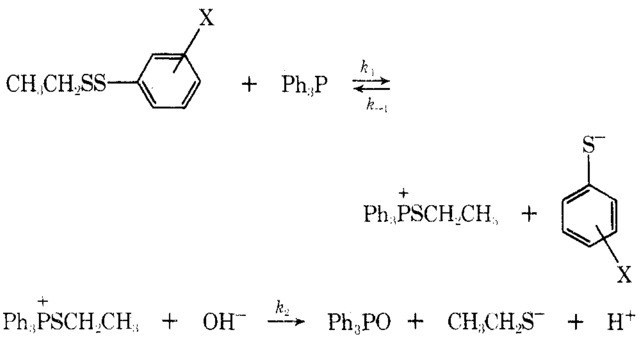
Results

The ethyl aryl disulfides (**2**) were conveniently prepared by the reaction[11] of N-(ethylthio)phthalimide[12] with the corresponding benzenethiol and were purified by a combination of preparative layer chromatography and distillation. Disulfides **2** are readily cleaved when treated at 30° with Ph_3P in aqueous dioxane (eq 1). Assay by uv indicated the formation of 1.0 ± 0.05 equiv of the corresponding benzenethiol (see Table II). Ethanethiol was also produced as evidenced by its characteristic odor and by gas chromatographic assay, but owing to its volatility no attempt was made to quantify its yield. For disulfides **4**, **7**, and **10** the yield of triphenylphosphine oxide (Ph_3PO) was determined by gas chromatography, under conditions (see Experimental Section) similar to those used in the kinetic studies, and varied from 70 to 100%. Significantly no (<1%) triphenylphosphine sulfide was detected.



The rate of cleavage of disulfides **3**–**10** by Ph_3P in 50% dioxane-water was measured at pH 13.3 (0.01 M NaOH), conditions which had previously been shown (for aryl disulfides) to involve nucleophilic attack by the phosphine in the rate-determining step.[1] Under these conditions the rate of formation of 1 equiv of the corresponding benzenethiol was clearly first order (r = 0.9995 or better) for 2–3 half-lives. The resulting second-order rate constants ($k_1 = k_{obsd}/[Ph_3P]$), determined at three or more Ph_3P concentrations, are summarized in Table I.[13] As a spot check, the second-order rate constants for disulfides **3** and **7** were shown to be unaffected by doubling the sodium hydroxide concentration. The observation of clean pseudo-first-order kinetics for 2–3 half-lives indicates that these unsymmetrical disulfides do not disproportionate, to any appreciable extent, under the conditions of the kinetic measurements, since the corresponding symmetrical aryl disulfides react with Ph_3P 10–20 times faster.[1] Moreover, the absence of upward curvature in the first-order plots during the second and third half-lives also indicates that although ethyl mercaptide is slightly more thiophilic[14] than Ph_3P it is not competitive under our pseudo-first-order conditions. The results described are consistent with the mechanism of Scheme II, in which the first step (k_1) is rate limiting.[15]

Scheme II



Discussion

A plot of log k_1 against the Hammett substituent constant σ is shown in Figure 1. The correlation for both meta and para substituents is excellent (the standard deviation

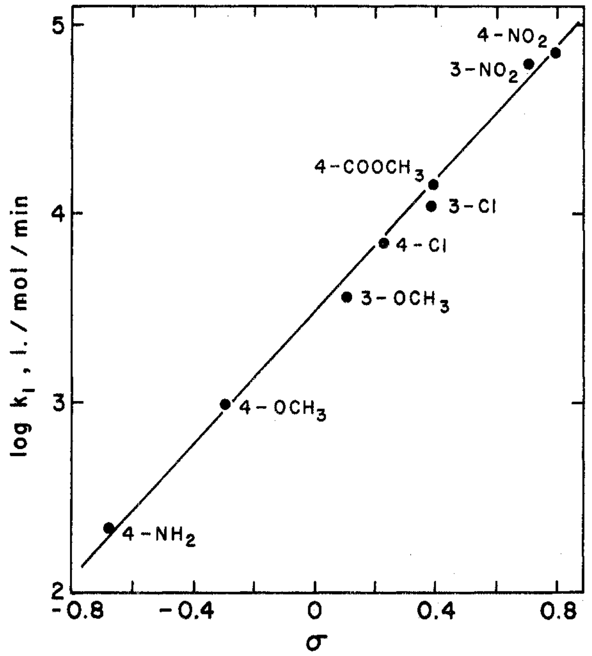
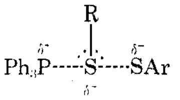


Figure 1. A plot of log k_1 vs. σ. The slope (ρ) is 1.76.

from the least-squares slope is 0.07) and yields a ρ value of 1.76.[16] Significant is the excellent correlation of strong π-electron conjugating para substituents (NH_2, OCH_3, NO_2), which is in marked contrast to the large deviations observed for those substituents in our previous study of symmetrical aryl disulfides. The nondeviation of π-conjugating para substituents is consistent with the assumption that attack by Ph_3P occurs solely at the ethyl bearing sulfur, since in our previous study the observed deviations were ascribed[5] to the effect of para substituents on the sulfur undergoing nucleophilic attack.[1]

The effect of aryl substituents on the Ph_3P cleavage of this series of ethyl aryl disulfides is only 60% as large as that observed under identical conditions for a similar series of symmetrical aryl disulfides.[1] To the extent that the reaction of eq 1 is a good model for the effect of substituents on the leaving group sulfur of a symmetrical aryl disulfide, a comparison of the ρ values for the two series would indicate that the large positive ρ value observed in the symmetrical series results from positive contributions from both the sulfur of the leaving group (ρ ~1.8) and the sulfur undergoing nucleophilic attack (ρ ~1.1). The substituent effect ascribed by this analysis to the sulfur undergoing nucleophilic attack appears to be somewhat larger than would be anticipated for a process in which bond formation and bond cleavage were equally advanced,[17] and thus would seem more consistent with a transition state such as **11** in which negative charge is developed on both sulfur atoms. Such a transition state would result if bond making were somewhat advanced over bond breaking.



$$\overset{\delta^-}{Ph_3P}\cdots\cdots\underset{\delta^-}{\overset{R}{S}}\cdots\cdots\overset{\delta^-}{S}Ar \qquad R = Ar, CH_3CH_2$$

11

Experimental Section

The purification of solvents, and the methods and instruments used for the stopped-flow and pH measurements, were described previously.[1] The wavelengths used for the kinetic measurements are summarized in Table II. "50% dioxane–water" refers to a dioxane–water solution made by diluting (0.5V) ml of dioxane to V ml with water in a volumetric flask.[1] Errors reported are ± one standard deviation from the mean for a series of measurements. All disulfide samples used for kinetic measurements were homogeneous by TLC (silica gel) and showed no trace of the corresponding symmetrical aryl disulfide, under TLC conditions which clearly resolved the two. Analytical gas–liquid chromatography (GC) utilized a Hewlett-Packard Model 700 with a flame ionization detector. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

Table II
Experimental Conditions for Kinetic Measurements

Ethyl substituted-phenyl disulfide	Wavelength followed, nm	ϵ_{EtSSAr} [a]	ϵ_{ArS^-} [a]
3, 4-NO_2	425	<10	16,300
4, 3-NO_2	428	<10	1,100
5, 4-$COOCH_3$	332	4,300	22,500
6, 3-Cl	330	35	290
7, 4-Cl	330	150	550
8, 3-OCH_3	352	140	48
9, 4-OCH_3	330	380	1,200
10, 4-NH_2	350	450	210

[a] Molar extinction coefficient. In 50% dioxane-water, 30°, pH 13.3 ionic strength 0.10 (KCl).

Preparation of Ethyl Substituted-Phenyl Disulfides. These materials were prepared in 40–80% yield by the reaction of N-(ethylthio)phthalimide[12] with the appropriate benzenethiol in refluxing benzene.[11a,b] Disulfides **3** and **4** were described previously.[11] The ethyl substituted-phenyl disulfides were stable to disproportionation and were easily purified by conventional chromatographic means.

They were also quite stable to disproportionation in solution. For example, 10^{-2} M solutions of disulfide **4** in dioxane and in 50% dioxane–water showed no traces of the corresponding symmetrical aryl disulfide (TLC assay) when stored in laboratory light on the bench top for 2 days. The TLC system was silica gel with 1:1 hexane–benzene as eluent: disulfide **4** R_f 0.5; 3-nitrophenyl disulfide R_f 0.3.

Ethyl-4-carbomethoxyphenyl Disulfide (5). The analytical (and kinetic) sample was purified by Kugelrohr distillation (oven temperature 118–124°, 0.03 Torr): ν_{max} (film) 1704, 1269, and 1099 cm^{-1}; ^1H NMR (CCl_4) τ 1.8–2.7 (A_2B_2 pattern, 4 H, ArH), 6.12 (s, 3 H, OCH_3), 7.26 (q, J = 7 Hz, 2 H, CH_2), and 8.70 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_{10}H_{12}O_2S_2$: C, 52.60; H, 5.30; S, 28.09. Found: C, 52.31; H, 5.27; S, 28.25.

Ethyl 3-Chlorophenyl Disulfide (6). The analytical (and kinetic) sample was prepared by preparative layer chromatography (silica gel–benzene) and Kugelrohr distillation (oven temperature 110–116°, 0.03 Torr): ν_{max} (film) 1558, 770, and 670 cm^{-1}; ^1H NMR (CCl_4) τ 2.1–3.2 (m, 4 H, ArH), 7.25 (q, J = 7 Hz, 2 H, CH_2), 8.69 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_8H_9ClS_2$: C, 46.93; H, 4.43; Cl, 17.32; S, 31.32. Found: C, 47.02; H, 4.86; Cl, 17.45; S, 31.16.

Ethyl 4-Chlorophenyl Disulfide (7). The analytical (and kinetic) sample was prepared by short-path distillation: bp 73–77° (0.15 Torr); ν_{max} (film) 1441 and 805 cm^{-1}; ^1H NMR (CCl_4) τ 2.4–2.9 (A_2B_2 pattern, 4 H, ArH), 7.36 (q, J = 7 Hz, 2 H, CH_2), 8.79 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_8H_9ClS_2$: C, 46.93; H, 4.43; Cl, 17.32; S, 31.32. Found: C, 47.14; H, 4.41; Cl, 17.23; S, 31.05.

Ethyl 3-Methoxyphenyl Disulfide (8). The analytical (and kinetic) sample was prepared by preparative layer chromatography (silica gel–benzene) and Kugelrohr distillation (oven temperature 110–116°, 0.03 Torr): ν_{max} (film) 1553, 846, 765, and 679 cm^{-1}; ^1H NMR (CCl_4) τ 2.7–3.6 (m, 4 H, ArH), 6.28 (s, 3 H, OCH_3), 7.33 (q, J = 7 Hz, 2 H, CH_2), 8.72 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_9H_{12}OS_2$: C, 53.96; H, 6.04; S, 32.01. Found: C, 54.02; H, 6.13; S, 32.26.

Ethyl 4-Methoxyphenyl Disulfide (9). The analytical (and kinetic) sample was prepared by Kugelrohr distillation (oven temperature 115–120°, 0.03 Torr); ν_{max} (film) 1225 and 822 cm^{-1}; ^1H NMR (CCl_4) τ 2.4–3.4 (A_2B_2 pattern, 4 H, ArH), 6.34 (s, 3 H, OCH_3), 7.36 (q, J = 7 Hz, 2 H, CH_2), 8.77 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_9H_{12}OS_2$: C, 53.96; H, 6.04. Found: 54.15; H, 6.23.

Table III
Yield of Triphenylphosphine Oxide by GC

Disulfide (mmol)	Ph_3PO formed, mmol (% theory)	Ph_3P recovered, mmol
4 (0.22)	0.15 (68)	0.34
7 (0.28)	0.21 (75)	0.32
10 (0.26)	0.26 (100)	0.22

Ethyl 4-Aminophenyl Disulfide (10). The analytical (and kinetic) sample was prepared by preparative layer chromatography (silica gel–10% ethyl acetate–90% benzene) and Kugelrohr distillation (oven temperature 114–120°, 0.03 Torr): ν_{max} (film) 3390, 3250, and 823 cm^{-1}; ^1H NMR (CCl_4) τ 2.5–3.7 (A_2B_2 pattern, 4 H, ArH), 6.40 (s, 2 H, NH_2), 7.32 (q, J = 7 Hz, 2 H, CH_2), 8.71 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_8H_{11}NS_2$: C, 51.85; H, 5.98; N, 7.56; S, 34.60. Found: C, 52.01, H, 5.98; N, 7.69; S, 34.24.

Products. Triphenylphosphine Oxide (Ph_3PO). A 0.02 M solution of sodium hydroxide in 50% aqueous dioxane, containing 5×10^{-4} M disodium ethylenediaminetetraacetic acid, was deoxygenated for 1 hr with oxygen-free nitrogen.[19] Triphenylphosphine (0.50 mmol) and disulfide **4**, **7**, or **10** (0.22–0.28 mmol) were added and the solution was stirred under a nitrogen atmosphere at 40° for 2–10 min. After cooling to room temperature 50 ml of ether was added, the aqueous layer was saturated with sodium chloride, and the organic layer was separated. The aqueous layer was washed with 50 ml of ether and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. A weighed amount of benzophenone was added as an internal standard and the product mixture was analyzed by GC.[21] Peak areas were corrected for detector response by standard methods. Triphenylphosphine sulfide could be detected at the 1% level. The results are summarized in Table III.

Acknowledgment. Financial support of this research by the National Institutes of Health (Grant GM-20674) is gratefully acknowledged.

Registry No.—**3**, 51351-84-9; **4**, 51351-85-0; **5**, 55975-71-8; **6**, 55975-72-9; **7**, 55975-73-0; **8**, 55975-74-1; **9**, 55975-41-2; **10**, 55975-42-3; triphenylphosphine oxide, 791-28-6; triphenylphosphine, 603-35-0.

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(2) (a) Alfred P. Sloan Foundation Fellow, 1975–1977; (b) U. C. President's Undergraduate Fellow, 1974–1975.

(3) The current status of this question is briefly summarized in ref 1. Other recent summaries include (a) J. L. Kice in "Sulfur in Organic and Inorganic Chemistry", Vol. 1, A. Senning, Ed., Marcel Dekker, New York, N.Y., 1971, Chapter 6; (b) E. Ciuffarin and A. Fava, *Prog. Phys. Org. Chem.*, **6**, 81 (1968); (c) L. Senatore, E. Ciuffarin, and A. Fava, *J. Am. Chem. Soc.*, **92**, 3035 (1970); (d) W. A. Pryor and K. Smith, *ibid.*, **92**, 2731 (1970).

(4) An alternate approach, in which one tries to isolate the substituent effect to the sulfur atom undergoing nucleophilic attack, was anticipated to be unsuccessful. Wright and coworkers[5] have previously shown that substituted-phenyl *p*-acetylphenyl disulfides and substituted-phenyl *p*-nitrophenyl disulfides undergo nucleophilic cleavage by cyanide to some extent by attack of cyanide on the *p*-acetylphenyl (or *p*-nitrophenyl) bearing sulfur. In our case, with Ph_3P as the nucleophile, corrections for the cleavage in this direction could not be made.

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(13) The uv change which accompanied the reduction of ethyl phenyl disulfide was so small that the reaction could not be conveniently studied.

(14) A. Fava and G. Pajaro, *J. Am. Chem. Soc.*, **78**, 5203 (1956); R. D. Ritter and J. H. Krueger, *ibid.*, **92**, 2316 (1970).

(15) Unpublished studies from our laboratory show that the hydrolysis of ethanethiolatotriphenylphosphonium hexachloroantimonate in 50% dioxane–water is specific base catalyzed and would be sufficiently fast at pH 13.3 that the first step (k_1) in Scheme II would be clearly rate limiting.

(16) Log k_1 also correlates well with the corresponding benzenethiol pK_a (determined under identical conditions)[1] and affords a Brønsted slope of $\beta = -0.71 \pm 0.07$.

(17) A model for such a process would be the S_N2 reaction of carbon compounds. Although substituent effects for the carbon undergoing nucleophilic attack are observed, these effects are small.[18] For example, introducing a meta NO_2 substituent results in rate accelerations (k_X/k_H) in the range of 0.8–3.5.[18] It is also typical for the S_N2 reactions of carbon compounds to be accelerated by both electron-withdrawing and electron-donating substituents.[18]

(18) Much of this data is summarized in the following references: A. Steitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962, pp 18–20; R. Fuch and D. M. Carelton, *J. Am. Chem. Soc.*, **85**, 104 (1963).

(19) Nitrogen was deoxygenated by bubbling sequentially through gas traps filled with chromous solution[20] and distilled H_2O.

(20) Cf. A. J. Gordon and R. A. Ford, "The Chemist's Companion", Wiley, New York, N.Y., 1972, p 438.

(21) A 8 ft × 0.12 in. column of 10% SP 2100 on 100/120 Supelcoport operated at 250° with a nitrogen carrier gas (45 ml/min) was used. This column cleanly separated Ph_3P, Ph_3PO, and Ph_3PS.

Aromatic Nucleophilic Substitution. V.[1] Confirmation of the Spiro Janovsky Complex in Base-Catalyzed Rearrangement of *N*-Acetyl-β-aminoethyl-2,4-dinitrophenyl Ether with Simultaneous Migration of Acetyl Group

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Received January 23, 1975

N-Acetyl-β-aminoethyl-2,4-dinitrophenyl ether readily undergoes a Smiles rearrangement in Me_2SO in the presence of tertiary-butanolic $KOC(CH_3)_3$ to give *N*-β-acetyloxyethyl- and *N*-β-hydroxyethyl-2,4-dinitroaniline. During the reaction, the spiro Janovsky complex is spectrometrically confirmed to exist.

Smiles rearrangements (eq 1) are typical intramolecular nucleophilic substitution reactions. The two carbon atoms joining X and Y may be part of an aliphatic or an aromatic system. It has been well established that aromatic nucleophilic substitution reactions proceed via Bunnett's intermediate.[2] Therefore, Smiles rearrangements can be assumed to be a good model for studying aromatic nucleophilic substitution mechanisms.