splitting patterns are abbreviated as follows: s, singlet; d, doublet; m, multiplet; dd, doublet of doublets; dm, doublet of multiplets. Shift experiments used Resolve-Al EuFOD [Aldrich Chemical Co., tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium]. Infrared spectra (IR) were taken on a Perkin-Elmer Model 237B grating spectrophotometer; only major band positions (cm⁻¹) are reported. Reactions were routinely followed by thin-layer chromatography (TLC) using Analtech PGBE silica gel GF plates (250 μm) with ethyl acetate–cyclohexane (3:2) as developing solvent; visualization was achieved by spraying with 10% aqueous sulfuric acid followed by heating at 150 °C. Preparative TLC used the same type solvent and plates but with 1000 μm thickness. Uncorrected melting points were determined between cover glasses on an aluminum block microscope hot stage. Solvents were reagent grade and, when necessary, were purified according to standard procedures.[11] Where the simple cis/trans designation of stereochemistry is ambiguous, compounds are named according to the IUPAC system,[12] in which the cis or trans relationship of each substituent is related to the reference substituent designated by *r*.

2,5-Dihydro-2,5-dimethoxyfuran. Our sample of commercially available 2,5-dihydro-2,5-dimethoxyfuran (Aldrich Chemical Co.) was a 70:30 mixture of cis and trans isomers as determined by integration of the 300-MHz NMR spectrum of cis H-2 + H-5 signals vs. the trans H-2 + H-5 signals. The separation of methoxy signals was not sufficient to allow integration: ¹H NMR δ 6.07 (s, 2 H, H-3 + H-4), 5.92 (s, ~0.6 H, H-2 + H-5 trans), 5.63 (s, ~1.4 H, H-2 + H-5 cis), 3.44–3.42 (2 s, 6 H, OCH₃). The assignment of cis and trans isomers is unambiguous, based on direct comparison with the spectrum of the pure trans isomer (vide infra).[8]

***r*-3,*cis*-4-Dihydroxy-*trans*-2,*trans*-5-dimethoxytetrahydrofuran[2,5] (3).** To commercial 2,5-dihydro-2,5-dimethoxyfuran (1.0 g, 7.7 mmol, 70:30 1-2) in tetrahydrofuran (THF, 10 mL) at −10 °C under nitrogen was added dropwise with vigorous stirring KMnO₄ (1.22 g, 7.7 mmol; 50% theoretical excess for glycol formation) in H₂O (45 mL) at such a rate that the temperature did not exceed 5 °C. The resulting reaction mixture with the MnO₂ sludge was stirred at room temperature for 12 h; the MnO₂ was removed by filtration and washed with THF (3 × 30 mL). Solvents and unreacted starting material were removed by vacuum distillation [ultimately to 50 °C (0.1 mm of pressure)] leaving an oil, which was dissolved in ethyl acetate, dried (MgSO₄), and reconcentrated to give 0.61 g of 3 (48% overall yield, 69% yield of the cis diol based on the 0.70 g of the cis 1 present in the original mixture). This oil crystallized on triturating with ether at −15 °C: mp 34.0–35.5 °C, (lit. mp 36 °C,[3b] 34–36 °C[2]); IR 3425, 1450 cm⁻¹; ¹H NMR, cf. Table I. Anal. Calcd for C₆H₁₂O₅: C, 43.90; H, 7.37. Found: C, 43.60; H, 7.50. The solvent was removed from the original volatile fraction to give a residue (0.3 g), which was shown by NMR to be 2 uncontaminated with 1.

Treatment of 10 g of 70:30 mixture of 1 and 2 with 8.1 g of KMnO₄ (the theoretical amount to react with both cis and trans isomers in the mixture) in THF–H₂O under the same conditions gave the crystalline diol 3, 6.9 g (78% based on the 7 g of 1 in the starting mixture), and a recovery of 1.7 g (57%) of unreacted trans isomer 2. However, oxidation in aqueous ethanol or methanol consumed both cis and trans isomers and gave an inseparable mixture of diols 3 and 4.

***dl*-*r*-3,*cis*-4-Dihydroxy-*cis*-2,*trans*-5-dimethoxytetrahydrofuran.[5,7] (4).** The trans isomer 2, recovered from the THF–H₂O oxidation, was oxidized with KMnO₄ in aqueous ethanol according to the literature[2,3a] to give 4, mp 63–64 °C (lit. mp 60–62 °C) in 70% yield.

Monoacetylation of 3. A solution of 0.5 g (3 mmol) of 3, 0.25 g (2.9 mmol) of acetic anhydride, and 0.4 g of pyridine in 10 mL of CHCl₃ was refluxed for 15 h. Volatiles were removed, and the residue was separated by preparative TLC to give three fractions: recovered starting material 3, R_f 0.32, 140 mg (28%); monoacetate 7, R_f 0.55, 300 mg (50%); diacetate 8, R_f 0.77, 80 mg (11%), mp 93–94 °C (lit.[2,5] 97–98 °C).

Benzoylation of 3. A mixture of 1.0 g (6 mmol) of 3, 3.44 g (24 mmol) of benzoyl chloride, and 4.0 g of pyridine in 30 mL CHCl₃ was refluxed for 14 h to give 2.0 g (88%) of white crystals of 9; recrystallization from ethanol gave 1.8 g; mp 86–87 °C; IR (Nujol mull) 1725, 1750 cm⁻¹ (aryl ester). Anal. Calcd for C₂₀H₂₀O₇: C, 69.51; H, 5.41. Found: C, 69.35; H, 5.38.

***dl*-*trans*-4-Bromo-*r*-3-hydroxy-*trans*-2,*cis*-5-dimethoxytetrahydrofuran (6).** At 0 °C a 0.4 M HOBr solution (25 mL, 10 mmol) was added to 2 (0.8 g, 6 mmol) and stirred for 12 h at 20 °C. The reaction mixture was neutralized (NaHCO₃), saturated with NaCl, and extracted with CHCl₃. The organic layer was dried (MgSO₄) and the solvent evaporated to leave a colorless syrup of 6, 1.3 g (93%). Anal. Calcd for C₆H₁₁BrO₄: C, 31.73; H, 4.88. Found: C, 31.40; H, 5.10.


Nucleophilic Substitution Reaction of Alkyl Halide by Anion on a Macroporous Polymer Resin

Kazuaki Sukata

Nihon Tokushu Kagaku Kogyo Co., Ltd. 1, Takijiri-aza-hashimoto, Izumi-cho, Iwaki, Fukushima 970-04, Japan

In recent years, it has been reported that nucleophilic substitutions of alkyl halides with anions are accelerated when the anionic species are impregnated on inorganic solid supports such as alumina and silica gel.[1,2] Subsequently, Quici and Regen have shown that alumina acts as a triphase catalyst.[3] Ando et al. have pointed out the importance of a trace of water in the system using alumina as a triphase catalyst[4] and have more recently shown that ultrasound accelerates the reaction.[5] On the other hand, many substitution reactions using reagents ionically bound to polymer supports such as basic anion-exchange resins have been well-known.[6] I wish to report that the substitution reaction is accelerated even by a simple impregnation of reagents on macroporous polymer resins such as Amberlite XAD-2, XAD-4, and XAD-7, which have no capability of ion-exchange and no function for phase-transfer catalysis.

$$\text{KX} + \text{RY} \xrightarrow{\text{XAD}} \text{RX} + \text{KY}$$
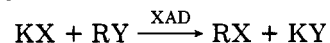
X: CN; AcO; I

R: PhCH₂; *n*-C₄H₉; *n*-C₈H₁₇

Y: Cl; Br; I

Results and Discussion

In a preliminary experiment, the reaction was performed with benzyl chloride and KCN impregnated onto several

---

(11) Fieser, L.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 759.

(12) IUPAC, *J. Org. Chem.* **1970**, *35*, 2849. Cis and trans are designated with respect to the primary reference substituent *r*.

(1) Regen, S. L.; Quici, S.; Liaw, S.-J. *J. Org. Chem.* **1979**, *44*, 2029.

(2) Bram, G.; Filleben-Khan, T.; Geraghty, N. *Synth. Commun.* **1980**, *10*, 279.

(3) Quici, S.; Regen, S. L. *J. Org. Chem.* **1979**, *44*, 3436.

(4) Ando, T.; Kawate, T.; Yamawaki, J.; Hanafusa, T.; *Chem. Lett.* **1982**, 935.

(5) Ando, T.; Kawate, T.; Ichihara, J.; Hanafusa, T. *Chem. Lett.* **1984**, 725.

(6) Hodge, P. In "Polymer-Supported Reactions in Organic Synthesis", Wiley: New York, 1980; Chapter 2, p 83.

Table I. Cyanation of PhCH₂Cl Using KCN–Support Reagent[a]

support	time, h	product, % yield		
		PhCH₂CN	PhCH₂OH	(PhCH₂)₂O
none[c]	6	0	0	0
none[d]	6	0	0	0
XAD-4	6	31	~0	~0
XAD-7	6	15	~0	~0
XAD-2	6	35	~0	~0
XAD-2[e]	6	42	~0	~0
XAD-2	24	55	~0	~0
XAD-2[e]	24	71	~0	~0
alumina	6	7	<1	54
activated C[f]	6	2	~0	~0

[a] All reactions were carried out with KCN (40 mmol)–support (8.0 g) and PhCH₂Cl (10 mmol) without any solvent at 65 °C. Unless otherwise noted, KCN–support reagent was dried under vacuum (0.1 mmHg) at 90 °C for 4 h. [b] Determined by GLC using *n*-pentadecane as an internal standard. [c] KCN (finely powdered) was used as obtained. [d] KCN (finely powdered) was dried under vacuum (0.1 mmHg) for 4 h at 90 °C. [e] KCN–XAD-2 reagent was dried at 90 °C and 20 mmHg for 4 h. [f] Granular activated charcoal was ground in a mortar.
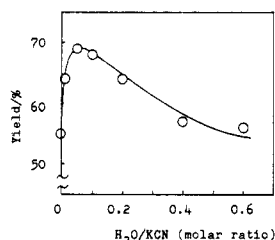

Figure 1. Plots of the yield of PhCH₂CN vs. the H₂O/KCN molar ratio. The reactions were carried out with KCN–XAD-2 reagent and PhCH₂Cl at 65 °C for 24 h.

supports without any solvent. Table I shows the results. When no support was used, no benzyl cyanide was obtained. Also, when activated charcoal was employed, almost no reaction took place. In the case of alumina, although the conversion of benzyl chloride was very fast, the main product was dibenzyl ether. This finding is quite in contrast to the result reported by Regen et al.,[1] in which the reaction in toluene as a solvent gave nitriles in very high yields. In contrast to alumina, KCN impregnated on Amberlite XAD-2, XAD-4, and XAD-7 (KCN–XAD-2, KCN–XAD-4, KCN–XAD-7 reagent) gave benzyl cyanide in moderate yields without any byproducts such as benzyl alcohol and dibenzyl ether. A mixture of powdered KCN and XAD resin, however, gave no product. In this system, the influence of a trace of water was observed: The reactivity of the KCN–XAD-2 reagent dried at 20 mmHg was higher than that dried at 0.1 mmHg.

The influence of water was investigated in detail by the reaction of benzyl chloride with the KCN–XAD-2 reagent. Figure 1 shows the relationship between the yield of benzyl cyanide and the molar ratio of the added water to KCN. The effect of amounts of water similar to that found in the presence of alumina as a triphase catalyst[4,5] was observed. The yield of benzyl cyanide showed a maximum value at the molar ratio H₂O/KCN = 0.05, which is extremely smaller than the molar ratio (0.7) for the reaction of KCN with benzyl bromide in the presence of alumina.[5] This is probably due to the difference in the degree of interaction between KCN and alumina and between KCN and XAD resin.

Table II shows the results of substitution reactions by other anions using XAD-2 resin. The reactions were carried out with an alkyl halide and KX–XAD-2 reagent which was dried at 90 °C and 20 mmHg for 4 h without

Table II. Substitution Reactions on XAD-2[a]

KX	alkyl halide	time, h	yield, %
KCN	PhCH₂Br	24	79
	PhCH₂Cl	24	71
	n-C₄H₉Br	48	30
	n-C₄H₉I	24	46
	n-C₈H₁₇Br	48	26
	n-C₈H₁₇I	24	30
KOAc	PhCH₂Br[b]	48	<1
	PhCH₂Br	24	86
	n-C₄H₉Br[b]	48	~0
	n-C₄H₉Br	24	50
	n-C₄H₉I	24	16
	n-C₈H₁₇Br	24	45
	n-C₈H₁₇I	24	15
KI	*n*-C₈H₁₇Br[b]	24	<1
	n-C₄H₉Br	24	85
	n-C₈H₁₇Br	24	52

[a] All reactions were carried out with KX (40 mmol)–XAD-2 (8.0 g) and alkyl halide (10 mmol) at 65 °C. KX–XAD-2 reagent was dried at 90 °C and 20 mmHg for 4 h. [b] No support was used.

any solvent. Almost no reaction took place when no support was used. The reaction with KX–XAD-2 reagent gave substitution products in moderate to good yields.

Regen et al.[1,3] have described that in the presence of alumina, the reactivity of alkyl bromide is superior to that of alkyl iodide toward nucleophilic substitution by chloride, cyanide, and acetate ions. In the presence of XAD-2 as a support, the reactivity of alkyl iodide was higher than that of alkyl bromide for the reaction with KCN; whereas, for the reaction with KOAc, alkyl iodide was inferior to alkyl bromide. From the HSAB principle,[7] it was predicted that the reactivity of alkyl iodide having a "soft" leaving group, I⁻, is higher than that of alkyl bromide bearing a "harder" leaving group, Br⁻, toward the substitution by "soft" CN⁻, whereas alkyl bromide is superior to alkyl iodide toward the substitution by a "hard" AcO⁻. The present results are consistent with this prediction. Anions impregnated on alumina seem to be much "harder" than those supported on XAD resin.

Experimental Section

Materials. Unless otherwise stated, reagents were obtained commercially and used without further purification. Alumina (Merck 90 neutral, 70–230 mesh, activity I, catalog no. 1077) was used as obtained. Amberlite XAD resins, which were purchased from Organo Co., were washed with methanol and dried under reduced pressure. Activated charcoal was pulverized in a mortar.

All impregnated reagents were prepared by the following standard procedures.

KCN–XAD Reagent (Dry). XAD resin (8.0 g) was mixed with KCN (40 mmol) in 90% aqueous methanol (50 mL), and the water and methanol were removed under reduced pressure at 50 °C. The impregnated reagent was further dried under vacuum (0.1 mmHg) at 90 °C for 4 h.

KCN–XAD Reagent (Wet). A mixture of KCN and XAD resin in 90% aqueous methanol was evaporated under reduced pressure at 50 °C. The impregnated reagent was further dried at 90 °C and 20 mmHg for 4 h. In these methods, no effort was made to physically separate nonimpregnated KX.

Typical Procedure for the Substitution Reaction by KX–XAD Reagents. In all reactions, alkyl halide was directly added to the flask in which the KX–XAD reagent was made and dried. All the products are known compounds and were identified by comparing GLC retention times with those of authentic samples.

Benzyl Cyanide. A mixture of benzyl chloride (1.26 g, 10 mmol) and KCN–XAD-2 reagent (dry) made from KCN (2.60 g, 40 mmol) and XAD-2 resin (8.0 g) was vigorously shaken for several minutes and then heated at 65 °C for 6 h. After the

(7) Ho, T.-L. *Chem. Rev.* **1975,** *75*, 1.

mixture was cooled, the solid material was eluted with benzene (50 mL). The yield was determined by GLC (Silicon OV 17, 3 m × 3 mm, 180 °C) using *n*-pentadecane as an internal standard.

n-Butyl Acetate. A mixture of *n*-butyl bromide (1.37 g, 10 mmol) and KOAc–XAD-2 reagent (wet) made from KOAc (3.93 g, 40 mmol) and XAD-2 resin (8.0 g) was vigorously shaken for several minutes and then heated at 65 °C for 24 h. After the same treatment as benzyl cyanide, the yield was determined by GLC (PEG-20M, 3 m × 3 mm, 80 °C) using toluene as an internal standard.

n-Octyl Iodide. A mixture of *n*-octyl bromide (1.93 g, 10 mmol) and KI–XAD-2 reagent (wet) made from KI (6.64 g, 40 mmol) and XAD-2 resin (8.0 g) was vigorously shaken for several minutes and then heated at 65 °C for 24 h. After the same treatment as *n*-butyl acetate, the yield was determined by GLC (silicon OV 17, 3 m × 3 mm, 180 °C) using *n*-pentadecane as an internal standard.

The Influence of Water in the Reaction of KCN and Benzyl Chloride (Molar Ratio, $H_2O/KCN = 0.2$). Water (0.14 g, 8 mmol) was added to the KCN–XAD-2 reagent (dry) made from KCN (2.60 g, 40 mmol) and XAD-2 resin (8.0 g). This mixture had been vigorously shaken for several minutes at 65 °C before benzyl chloride (1.26 g, 10 mmol) was added. The mixture was vigorously shaken for several minutes and heated at 65 °C for 24 h. The same treatment was made as benzyl cyanide described above.

Registry No. PhCH₂Cl, 100-44-7; *n*-C₄H₉Br, 109-65-9; *n*-C₈H₁₇Br, 111-83-1; PhCH₂Br, 100-39-0; *n*-C₄H₉I, 542-69-8; *n*-C₈H₁₇I, 629-27-6; PhCH₂CN, 140-29-4; *n*-C₄H₈OAc, 123-86-4; *n*-C₄H₉CN, 110-59-8; *n*-C₈H₁₇CN, 2243-27-8; PhCH₂OAc, 140-11-4; *n*-C₈H₁₇OAc, 112-14-1; KCN, 151-50-8; KOAc, 127-08-2; KI, 7681-11-0; H₂O, 7732-18-5; XAD-2, 9060-05-3; XAD-4, 37380-42-0; XAD-7, 37380-43-1.
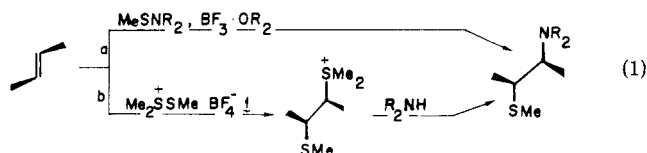

Boron Trifluoride Catalyzed Addition of Disulfides to Alkenes

Marjorie C. Caserio,* Cindy L. Fisher, and Jhong K. Kim

Department of Chemistry, University of California, Irvine, California 92717

Addition of sulfenyl compounds RSX to carbon–carbon multiple bonds is well documented for reagents such as sulfenyl halides and thiosulfonium salts in which the X atom or group is electron-attracting (X = Cl, ⁺SR₂).[1,2] Less polar reagents such as disulfides RSSR and sulfenamides RSNR₂ normally do not add to alkenes. However, we reported recently that addition of sulfenamides to alkenes can be achieved under the catalytic influence of boron trifluoride etherate (eq 1a) —thereby providing a

$$(1)$$

reasonable alternative to azasulfenylation of alkenes by addition of methylthiodimethylsulfonium salts 1 followed by displacement with amines (eq 1b).[3,4] We now report

that a similar BF₃-catalyzed addition of disulfides to alkenes is a very convenient way to prepare 1,2-dithioalkanes.

There are scattered reports in the literature relating to the electrophilic addition of dialkyl disulfides to alkene double bonds in the presence of iodine[5–7] or hydrogen fluoride.[8,9] The most explicit of these is a description of iodine-catalyzed addition of dimethyl disulfide for the determination of double bond position in linear alkenes.[5] There is, however, little information in the literature, as far as we know, that describes the yields, stereochemistry, and scope of catalyzed disulfide addition. The results that we now report hopefully will serve as useful information on the synthetic utility of disulfide addition under electrophilic conditions.

Results and Discussion

The reaction conditions are remarkably simple and, in most cases, involve addition of a catalytic amount of boron trifluoride etherate (BF₃·OMe₂ or BF₃·OEt₂) to a mixture of the disulfide and alkene in a solvent mixture of dichloromethane and nitromethane maintained at 0 °C to ambient temperature. Generally, the alkene was in excess of the disulfide. Methyl disulfide reacted with *cis*-2-butene to give a *single* adduct in high yield (>90%), which was identified as racemic *threo*-2,3-bis(methylthio)butane (2) (eq 2b). *trans*-2-Butene gave a single, but different, ad-

$$(2)$$

$$(3)$$
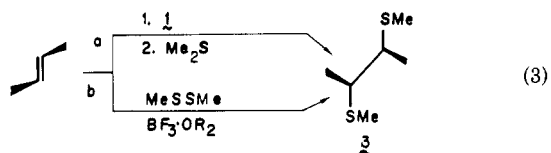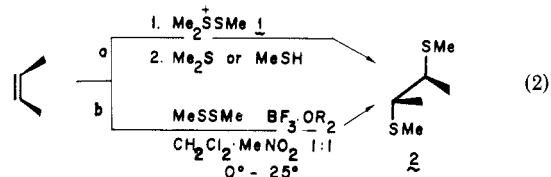
duct identified as *meso*-2,3-bis(methylthio)butane 3 in 96% yield (eq 3b). The products were identified by comparison with authentic samples and were, in fact, found to be indistinguishable from the adducts of a stepwise sequence of addition of 1 to *cis*- or *trans*-2-butene followed by reaction of the adduct thus formed with methyl sulfide or methanethiol (eq 2a or 3a).[3,11] These results illustrate that sulfenylation with dimethyl disulfide is a stereospecific reaction which leads to the product of *anti* addition.

The scope of the reaction can be seen from the results summarized in Table I. Dimethyl, diethyl, and diphenyl disulfides gave excellent yields of adducts in high stereospecificity with both *cis*- and *trans*-2-butene. Yields were moderate to low for diisopropyl disulfide, although ste-

(1) Schmid, G. H.; Garratt, D. G. In "The Chemistry of Functional Groups"; Patai, S., Ed.; Wiley: London, 1977; Supplement A, pp 828–858. Schmid, G. H. *Top. Sulfur Chem.* **1977**, *3*, 101.

(2) Helmkamp, G. K.; Olsen, B. A.; Pettit, D. J. *J. Org. Chem.* **1965**, *30*, 676. Helmkamp, G. K.; Olsen, B. A.; Koskinen, J. R. *Ibid.* **1965**, *30*, 1623.

(3) Caserio, M. C.; Kim, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 3231.

(4) Trost, B. M.; Shibata, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 3229.

(5) Francis, G. W.; Veland, K. *J. Chromatogr.* **1981**, *219*, 379.

(6) Schneider, H. J.; Bagnell, J. J.; Murdoch, G. C. *J. Org. Chem.* **1961**, *26*, 1987.

(7) Holmberg, B. *Ark. Kemi, Mineral. Geol.* **1939**, *13*, 1.

(8) Radical, electrochemical, and photochemical additions of disulfides to alkenes have also been reported. See also: Meyerson, S.; Fields, E. K. *Chem. Abstr.* **1981**, *94*, 174510.

(9) McCaulay, D. A.; Lien, A. P. U.S. Pat. 2519586; *Chem. Abstr.* **1950**, *44*, 10728.

(10) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826.

(11) Anderson, S. A.; Kim, J. K.; Caserio, M. C. *J. Org. Chem.* **1978**, *43*, 4822.