in methanol (100 ml). Treatment with charcoal (0.5 g), filtration, and solvent removal from the filtrate produce a clear, colorless oil which crystallizes exothermically (*caution:* vigorous cooling must be employed to avoid detonation) to give 10.0 g (99%) of **6**: mp (crude) 67–68° (SEC); ir (KBr) 3300, 2150, 2100, 1315, 1270, 1070 $cm^{-1}$; nmr ($D_2O$) $\delta$ 3.98 (m, 2 H, CH), 4.13 (m, 4 H, $CH_2$).

***meso*-2,3-Diaminobutane-1,4-diol.** A solution of **6** (7.4 g; 0.043 mol) in methanol (200 ml) containing 5% Pd/C catalyst (1.0 g) is shaken overnight under hydrogen (125 psi). The catalyst is removed by filtration, and the filtrate is stripped of solvent to give 5.2 g (100%) of the diaminediol, mp 126–127°. A solution of this compound (1.2 g, 0.010 mol) in acetone (50 ml) treated with 40% HBr (5 ml), produces a crystalline precipitate, which was collected by suction filtration, washed with several portions of acetone and air dried to give 2.4 g (85%) of the dihydrobromide: mp 212–213° (SEC) (lit.[2] mp 214–215°). A similar solution of the diaminediol treated with concentrated HCl (3 ml) gives, upon identical workup, 1.8 g (93%) of the dihydrochloride: mp 240–242° (SEC) (lit.[2] mp 241.5–242.5°).

***meso*-2,3-Diazido-1,4-dimesyloxybutane (7).** A solution of **6** (11.2 g; 0.065 mol) in pyridine (100 ml) is stirred at 0° and treated dropwise with methanesulfonyl chloride (16.4 g, 0.143 mol) over a 0.5-hr period. Stirring is continued 4 hr, and the mixture is then poured into 1.3 l. of ice water. The crystalline product which separates is collected by suction filtration, washed with several portions of cold water, and air dried to give 20.2 g (95%) of **7**: mp (and remelt) 92.0–92.5° (SEC) (EtOH); ir (KBr) 2125, 1360, 1290, 1175, 930, 820 $cm^{-1}$; nmr (acetone-$d_6$) $\delta$ 3.27 (s, 6 H, $CH_3$), 4.24 (m, 2 H, CH), 4.63 (m, 4 H, $CH_2$).

*Anal.* Calcd for $C_6H_{12}N_6O_6S_2$: C, 21.90; H, 3.92; N, 25.53; S, 19.48. Found: C, 22.20; H, 3.72; N, 25.15; S. 19.85.

***cis*-3,4-Diazidoselenophane (8).** Sodium selenide (10.0 g; 0.080 mol) is added portionwise to a stirred, degassed solution of **7** (19.7 g, 0.60 mol) in dimethyl sulfoxide (300 ml) under a nitrogen blanket. The reaction exotherm causes the temperature to rise to 45–50°. After stirring overnight, the mixture is poured into ice water (1.5 l.) and extracted with ethyl ether (4 × 400 ml). The ether extracts are combined, washed with water (4 × 500 ml) and saturated sodium chloride solution (2 × 200 ml), and dried ($MgSO_4$). After filtration the yellow ethereal solution is stripped of solvent to produce a yellow-orange oil. The liquid is dissolved in methanol (50 ml) and eluted (MeOH) from a 1-in. diameter column packed with neutral alumina (100 g). The eluent is stripped of solvent to yield a mobile yellow liquid with a marked offensive odor. The liquid is redissolved in methanol (50 ml), serially treated with charcoal (1.5 g), and filtered until a clear, colorless solution is obtained. This solution is stripped of solvent to give 6.2 (48%) of **8** as a colorless, mobile liquid, homogeneous by tlc: ir (neat) 2110, 1335, 1265 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 3.00 (m, 4 H, $CH_2$), 412 (m, 2 H, CH).

***cis*-3,4-Diaminoselenophane (9).** A solution of **8** (6.2 g, 28.6 mol) in methanol (100 ml) containing Adams catalyst (0.5 g) is shaken overnight under hydrogen (125 psi). The catalyst is removed by filtration, and the filtrate is stripped of solvent to give 4.6 g (98%) of **9** as a colorless mobile liquid which readily absorbs carbon dioxide from the atmosphere. The diamine **9** is characterized as the dihydrochloride salt: mp 289–290° dec (SEC) (20% aqueous acetone); ir (KBr) 3100–2800, 1490 $cm^{-1}$; nmr ($D_2O$) $\delta$ 3.22 (m, 4 H, $CH_2$), 4.33 (m, 2 H, CH). Mass spectrum of the dihydrochloride gave a peak characteristic only of monoprotonated diamine **9** (70 eV), *m/e* 167 [(M + 1)$^+$].

***cis*-3,4-Ureyleneselenophane (10).** A solution of **9** (3.3 g, 0.020 mol) in benzene (50 ml) is treated with a 12.5% solution of phosgene (3.0 g, 0.030 mol) in benzene (24 ml) followed by pyridine (50 ml). After a 3-hr reflux, an additional 9 ml of phosgene solution (1.0 g; 0.010 mol) is added, and reflux is continued overnight. After removal of solvents under vacuum, water (200 ml) is added to the particulate residue, and the resulting slurry is vigorously stirred 0.5 hr. The solids are collected by suction filtration, washed with several portions of water, and air dried to give 2.0 g (53%) of **10**: mp 256–258° (SEC) (EtOH); 53%; ir (KBr) 3200, 1690, 1260 $cm^{-1}$; mass spectrum (70 eV) *m/e* 191 ($M^+$); nmr (DMSO-$d_6$) $\delta$ 3.2 (m, 4 H, $CH_2$), 4.64 (m, 2 H, CH).

**Acknowledgment.** Portions of this work were generously supported by the Joint Award Council of the Research Foundation of the State University of New York (JAC-40-259A, JAC-40-7123B).

**Registry No.**—**3**, 53431-90-6; **4**, 53431-91-7; **5**, 53431-92-8; **6**, 53431-93-9; **7**, 53431-94-0; **8**, 53431-95-1; **9**, 53431-96-2; **9** · 2HCl, 53431-97-3; **10**, 53431-98-4; methanesulfonyl chloride, 124-63-0; *meso*-2,3-diaminobutane-1,4-diol, 53431-99-5; sodium selenide, 1313-85-5.

## References and Notes

(1) Taken in part from the Ph.D. Thesis of R. L. Martin, State University of New York at Binghamton, 1974.
(2) P. F. Feit and O. T. Nielsen, *J. Med. Chem.*, **10**, 927 (1967).
(3) W. W. Simmon and M. Zanger, "The Sadtler Guide to NMR Spectra," Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1972, pp 105–106.
(4) R. Lett and A. Marguet, *Tetrahedron Lett.*, 2851, 2855 (1971).
(5) R. A. Raphael, *J. Chem. Soc.*, 401 (1952).
(6) N. A. Milas, S. Sussman, and H. S. Mason, *J. Amer. Chem. Soc.*, **61**, 1844 (1939).
(7) S. S. Brown and G. M. Timmis, *J. Chem. Soc.*, 3656 (1961).

---

## A Convenient and Stereoselective Dithiol Synthesis

E. L. Eliel,[1a] V. S. Rao,[1a] S. Smith,[1b,2] and R. O. Hutchins*[1b]

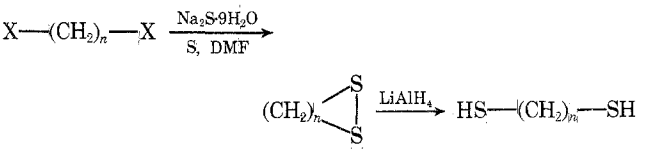
*W. R. Kenan, Jr., Laboratories of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514, and Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104*

*Received September 19, 1974*

Although several procedures are available for the preparation of dithiols,[3] our experience has been that the standard methods are often unreliable or give contaminated products, especially when tertiary or other hindered thiols are desired or where stereochemical control is required for the production of particular dithiol diastereomers. The need for relatively pure samples of such dithiols as precursors for various sulfur heterocycles[4] led us to investigate several approaches toward such systems. This Note describes a convenient dithiol synthesis which is particularly attractive for hindered systems and when a maximum of stereochemical control is essential.

The procedure involves initial conversion of a dihalide or disulfonate ester to a di- or polysulfide[5] by displacement with disulfide anion (prepared *in situ* from sodium sulfide and sulfur) and subsequent reduction to the dithiol with lithium aluminum hydride without prior isolation of intermediates. The pathway is illustrated in Scheme I and

**Scheme I**




or oligomers

Table I presents results for a variety of dithiols chosen to illustrate the versatility of the method with difficult to prepare compounds. For instance, entries 1 and 2 represent highly hindered systems, the former involving displacement of a bifunctional neopentyl system. Furthermore, minimal racemization of chiral centers occurs, thus allowing stereochemical control for the production of diastereomers (entries 3, 4, and 5). Finally, the secondary tertiary halide, 2-methyl-2,4-dibromopentane (entry 6), gave the otherwise difficult to obtain dithiol in respectable yield, presumably *via* initial displacement at the secondary carbon followed by internal substitution.

### Experimental Section

**Materials.** Dimethylformamide was reagent grade from a freshly opened bottle, used without further purification. The sulfonate

**Table I**
**Preparation of Dithiols by Nucleophilic Displacement with Disulfide followed by Lithium Aluminum Hydride Reduction**

| Entry | Compound | Time displ., hr (temp, °C) | Time red., hr | % yield dithiol[a] |
|---|---|---|---|---|
| 1 | 2,2-Dimethyl-1,3-propanediol dimesylate | 60 (100) | 3 | 61 |
| 2 | 2-*tert*-Butyl-1,3-propanediol ditosylate | 67 (80) | 3.25 | 70 |
| 3 | *meso*-2,4-Pentanediol ditosylate | 67 (80) | 2.5 | 71[b] |
| 4 | *dl*-2,4-Pentanediol ditosylate | 67 (80) | 2.5 | 71[c] |
| 5 | *meso*-2,5-Hexanediol ditosylate | 21.5 (80) | 1.25 | 56[d] |
| 6 | 2-Methyl-2,4-dibromopentane | 96[e] | 5 | 42[f] |
| 7 | 1,4-Dichlorobutane | 51.5 (80) | 12 | 60 |

[a] Yields are for isolated and purified products. [b] Composed of 92% meso and 8% *dl* isomers as determined by glpc. [c] Contains less than 0.5% meso isomer. [d] The reaction was carried out in two steps. The intermediate *cis*-3,6-dimethyl-1,2-dithiacyclohexane was isolated in 61% yield; subsequent reduction afforded the dithiol in 91% yield. The product showed a meso/*dl* ratio of *ca.* 98:2 (glpc). [e] Conducted at room temperature for 72 hr followed by 24 hr at 80°. [f] 92% pure (glpc).

esters were prepared by standard procedures[6a] from the diols and the appropriate sulfonyl chloride in pyridine. 2-Methyl-2,4-dibromopentane was prepared in 90% yield from the diol and phosphorus tribromide.[6b] Organic solutions were dried over anhydrous $MgSO_4$.

**Preparation of Dithiols. General Procedure.** An equal molar portion of the dihalide or sulfonate ester was added to equal molar portions of fresh, crushed sodium sulfide nonahydrate and sulfur in DMF (200–400 ml/0.10 mol of the substrate) and heated with stirring at the temperature and for the durations listed in Table I. The reaction mixture was then poured into water and cracked ice and extracted three times with hexane. The aqueous phase was acidified with concentrated HCl and extracted again with hexane. The combined organic solution was washed with water, dried, and concentrated on a rotary evaporator. The resulting yellow oil was added dropwise to a slurry of lithium aluminum hydride (usually 0.076 mol/0.1 mol of initial substrate) at such a rate that gentle reflux was maintained. After an appropriate period (Table I), the reaction mixtures were cautiously treated with water to destroy excess hydride, then excess 10% aqueous sulfuric acid was added and the product isolated from the ether phase and purified by distillation. Representative preparations are illustrated below.

***meso*-2,4-Pentanedithiol.** *meso*-2,4-Pentanediol ditosylate (105.6 g, 0.256 mol) was added to a mixture of $Na_2S \cdot 9H_2O$ (61.4 g, 0.256 mol) and sulfur (8.29 g, 0.256 mol) in 700 ml of dry DMF and the solution was stirred in a 1-l. flask equipped with a condenser and drying tube at 80–85° for 67 hr, and then poured into 1500 ml of water and *ca.* 500 g of cracked ice. The mixture was extracted three times with hexane, then the aqueous phase was acidified with concentrated HCl and extracted with hexane. The combined hexane solution was washed twice with water, dried, and concentrated on a rotary evaporator. The resulting yellow oil was added dropwise with stirring to a slurry of lithium aluminum hydride (7.37 g, 0.195 mol) in 250 ml of anhydrous ether at such a rate that gentle reflux ensued (*ca.* 0.5 hr). The solution was then stirred at ambient temperature for 2 hr, and then refluxed for 30 min and cooled to room temperature. Approximately 7.5 ml of water was added cautiously to the mixture followed by an excess amount of 10% aqueous sulfuric acid in order to dissolve the aluminum salts. Approximately 200 ml of ether was added and the layers separated. The aqueous layer was extracted three times with ether. The combined ether solutions were washed and dried. Concentration on a rotary evaporator afforded a pale yellow oil which was distilled to yield nearly colorless product, bp 83–85° (24 mm) (lit.[7] 74.5° (12 mm)). The yield was 24.8 g (71%). Analysis by glpc (10 ft 20% Carbowax 20M column) showed the product to contain *ca.* 8% of the *dl* isomer. In contrast, the *dl*-ditosylate under the same conditions yielded product containing less than 0.5% of *meso*-dithiol.

**2-Methyl-2,4-pentanedithiol.** To a solution of 12 g (0.05 mol) of $Na_2S \cdot 9H_2O$ and 1.2 g (0.05 mol) of sulfur in 100 ml of dry DMF was added dropwise 12.2 g (0.05 mol) of 2-methyl-2,4-dibromopentane at room temperature. The mixture was stirred for 3 days at room temperature and 1 day at 80–85° and then poured into a mixture of 300 ml of water and 200 g of ice. The mixture was extracted three times with hexane; the aqueous phase was acidified with concentrated HCl and again extracted twice with hexane. The combined hexane extract was washed twice with water and dried, and the solvent removed on a rotary evaporator. The resulting yellow oil was dissolved in 30 ml of dry ether and added dropwise with mechanical stirring to a slurry of 5 g (0.13 mol) of lithium aluminum hydride in 150 ml of dry ether at a rate to ensure gentle reflux. The solution was stirred at room temperature for 3 hr, refluxed for 2 hr, and cooled. The excess hydride was destroyed by cautious addition of water (15 ml) and then 10% aqueous sulfuric acid was added to dissolve the aluminum salts. An additional 100 ml of ether was added and the ether layer separated. The aqueous phase was extracted twice with 50-ml portions of ether and the combined ether extracts were washed twice with water and dried. Removal of the solvent gave a pale yellow oil, 6.6 g (*ca.* 89%), which was fractionally distilled to give a colorless oil (3.1 g, *ca.* 42%), bp 78–80° (20 mm), which was *ca.* 92% pure by glpc (25 ft 30% QF-1 on Chromosorb W). The ir and nmr spectra were identical with those of an authentic sample.[8] The contaminants were not identified, but did not appear to interfere with subsequent use of the product.

***cis*-3,6-Dimethyl-1,2-dithiacyclohexane.** The procedure was a slightly modified version of that described by Dodson and Nelson[5] in that $Na_2S \cdot 9H_2O$ was used instead of the anhydrous salt. The product was obtained in 61% yield, bp 78–80° (5 mm). Analysis by glpc (20% Carbowax 20M column) indicated a cis/trans ratio of *ca.* 96/4 and traces of two lower boiling components. The nmr spectrum corresponded to that reported.[9]

***meso*-2,5-Hexanedithiol.** A solution of *cis*-3,6-dimethyl-1,2-dithiacyclohexane (4.44 g, 30 mmol) in 10 ml of anhydrous ether was added dropwise to a stirred slurry of lithium aluminum hydride (864 mg, 22.8 mmol) in 20 ml of anhydrous ether over a 15-min period. The mixture was refluxed for 1.0 hr, and then worked up as previously described above. Distillation afforded 4.08 g (91%) of colorless product, bp 76–78° (5 mm) (lit.[10] bp 87–88° (12 mm), for the mixture of diastereomers). Analysis by glpc (10 ft 20% Carbowax 20M) indicated the meso/*dl* ratio to be *ca.* 98/2.

**Acknowledgment.** Part of this work was supported by National Science Foundation Grant GP-35699X.

**Registry No.**—2,2-Dimethyl-1,3-propanediol dimesylate, 53555-41-2; 2-*tert*-butyl-1,3-propanediol ditosylate, 24330-56-1; *meso*-2,4-pentanediol ditosylate, 24347-99-7; *dl*-2,4-pentanediol ditosylate, 24348-00-3; *meso*-2,5-hexanediol ditosylate, 53585-64-1; 2-methyl-2,4-dibromopentane, 28457-08-1; 1,4-dichlorobutane, 110-56-5; 2,2-dimethyl-1,3-propanedithiol, 53555-42-3; 2-*tert*-butyl-1,3-propanedithiol, 24330-57-2; *meso*-2,4-pentanedithiol, 5954-76-7; *dl*-2,4-pentanedithiol, 5953-46-8; *meso*-2,5-hexanedithiol, 53585-65-2; *dl*-2,5-hexanedithiol, 53585-66-3; 2-methyl-2,4-pentanedithiol, 52053-49-3; 1,4-butanedithiol, 1191-08-8; *cis*-3,6-dimethyl-1,2-dithiacyclohexane, 2506-33-4; *trans*-3,6-dimethyl-1,2-dithiacyclohexane, 2242-20-8.

## References and Notes

(1) (a) University of North Carolina; (b) Drexel University.
(2) Undergraduate research participant, 1973–1974.
(3) For a compilation and discussion of preparative methods for dithiols, see L. N. Owen in "Organic Sulfur Compounds," N. Kharasch, Ed., Pergamon Press, Elmsford, N.Y., 1961, pp 199–209.
(4) (a) For instance, substituted 1,3-dithiols are valuable for the preparation of various 1,3-dithianes (ref 4b,c) and 2-phospha-1,3-dithiacyclohexanes (ref 4d); (b) E. L. Eliel and R. O. Hutchins, *J. Amer. Chem. Soc.*, **91**, 2703 (1969); (c) E. L. Eliel, A. Abatjoglou, and A. A. Hartmann, *ibid.*, **94**, 4786 (1972); (d) R. O. Hutchins and B. E. Maryanoff, *ibid.*, **94**, 3266 (1972).

(5) With 1,3- or 1,4-dihalides or sulfonates the intermediates are the corresponding cyclic five- or six-membered ring disulfides, respectively. In fact, the method provides a convenient synthesis of such compounds; see, R. M. Dodson and V. C. Nelson, *J. Org. Chem.*, **33**, 3966 (1968). For other cases where cyclization cannot readily occur, oligodisulfides or oligotrisulfides presumably result.
(6) (a) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N.Y., 1967, pp 1179–1181; (b) J. D. Bartleson, R. E. Burk, and H. P. Lankelma, *J. Amer. Chem. Soc.*, **68**, 2513 (1946).
(7) C. G. Overberger and T. Kurtz, *J. Org. Chem.*, **31**, 288 (1966).
(8) E. L. Eliel, A. A. Hartmann, and A. G. Abatjoglou, *J. Amer. Chem. Soc.*, **96**, 1807 (1974).
(9) N. Isenberg and H. F. Herbrandson, *Tetrahedron*, **21**, 1067 (1965).
(10) C. Overberger, J. Ferraro, and F. Ortland, *J. Org. Chem.*, **26**, 3458 (1961).

## A New Conversion of 3,5-Disubstituted Isoxazoles to α,β-Unsaturated Ketones

Choji Kashima*

*Department of Chemistry, University of Tsukuba, Sakura-mura, Niihari-gun, Ibaraki, 300-31, Japan*

Yasuhiro Yamamoto and Yoshihiko Tsuda

*Department of Chemistry, Tokyo Kyoiku University, Otsuka, Tokyo, 102, Japan*

*Received May 21, 1974*

It is well known that 3,5-disubstituted isoxazoles are very stable compounds to acids, bases, hydrides, and oxidative reagents. Previously, we reported that 3,5-dimethylisoxazole, easily obtainable from 2,4-pentanedione and hydroxylamine, reacted regiospecifically at the methyl group in the 5 position with alkyl halides in the presence of an alkali amide in liquid ammonia.[1] Other electrophiles such as aldehydes, ketones, esters,[2] nitriles, and ketimines[3] react to give the corresponding alcohols, ketones, and amines. Recently, Büchi and his coworkers reported[4] that isoxazoles, prepared from α,β-unsaturated ketones, could be converted into α,β-unsaturated ketones (**11**) by reduction with sodium and *tert*-butyl alcohol in liquid ammonia.

In this paper, we describe how isoxazoles can be converted regiospecifically into α,β-unsaturated ketones (**6**), which are isomeric with **11**. As a typical example, 5-ethyl-3-methylisoxazole (**2b**), prepared from 3,5-dimethylisoxazole (**1**) and methyl iodide, was hydrogenated over a platinum catalyst to afford 2-amino-2-hexen-4-one (**3b**). The reduction of **3b** with sodium borohydride was attempted, but the expected reaction did not occur and the starting material was recovered. At this point the superdelocalizability for nucleophilic reagents ($Sr^N$) at C-4 of **3b** was calculated by the HMO method, to give the result shown in Table I.[5] The

**Table I**

| Compd | $Sr^N$ Values at C-4 | $Sr^N$ Values at C-2 |
|---|---|---|
| **3** | 1.9388 | 1.6494 |
| **4** | 2.0432 | 1.7400 |
| **7** | 2.0422 | 1.7423 |
| **9** | 2.0214 | 1.7259 |

corresponding $Sr^N$ value of the *N*-benzoyl derivative (**4b**) was also calculated and shown to be higher. Thus reduction of the carbonyl group of **4b** with sodium borohydride is expected to be easier and, indeed, on treatment with sodium borohydride, **4b** gave 2-benzamide-2-hexen-4-ol (**5b**). This

**Scheme I**