

SHORT COMMUNICATIONS

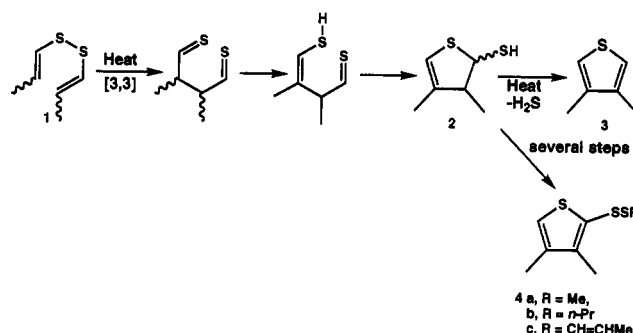
Allium Chemistry: Synthesis of Alk(en)yl 3,4-Dimethyl-2-thienyl Disulfides, Components of Distilled Oils and Extracts of *Allium* Species[†]

INTRODUCTION

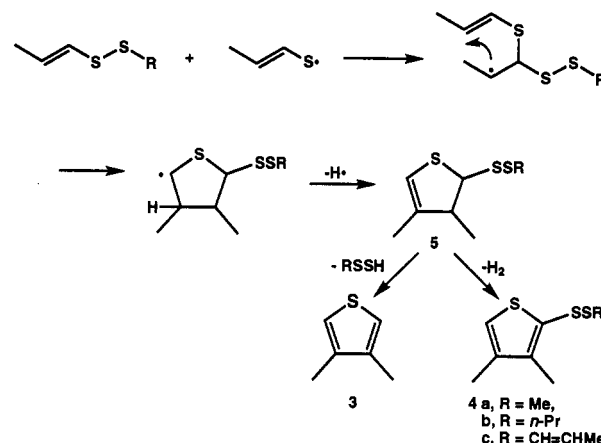
We recently reported the facile thermal conversion of bis(1-propenyl) disulfide (1) to *cis*- and *trans*-2-mercapto-3,4-dimethyl-2,3-dihydrothiophene (2) (Scheme I) and the latter to 3,4-dimethylthiophene (3). We suggested that in *Allium* distilled oils 3 originates, at least in part, from 2 by loss of hydrogen sulfide (Block and Zhao, 1990; Block, 1992). Ho and co-workers have reported the presence of 2 and 3, as well as methyl, *n*-propyl, and 1-propenyl 3,4-dimethyl-2-thienyl disulfides (4a-c, respectively) in distilled oils and extracts of Welsh onion (*Allium fistulosum* L. var. maichuon) and scallion (*A. fistulosum* L. var. caespitosum) (Kuo et al., 1990; Kuo and Ho, 1992a,b; Kuo, 1991), while Sinha and co-workers (Sinha et al., 1992) indicate that 3 and 4a are significant components of supercritical carbon dioxide (SC-CO₂) extracts of onion (*Allium cepa*). It has been suggested (Kuo et al., 1990; Boelens and Brandsma, 1972) that 3 and 4 are formed by a process involving radical addition of MeCH=CHS· to MeCH=CHSSR followed by ring closure and aromatization (Scheme II). We suggest that dihydrothiophenes, such as 5, are probable intermediates in the aromatization steps. Intermediate 5 might also result from reaction of 2 with RSX [R = Me, *n*-Pr, MeCH=CH-, X = SR' or S(O)R']. We describe here the first syntheses of 4a-c, applying aromatization procedures to 2 and its derivatives.

We initially examined the aromatization (dehydrogenation) of 2. A variety of procedures for elimination of hydrogen are known (March, 1992), including specific instances involving dihydrothiophenes (e.g., sulfur at 200 °C) (Block and Corey, 1969). However, the majority of

Scheme I



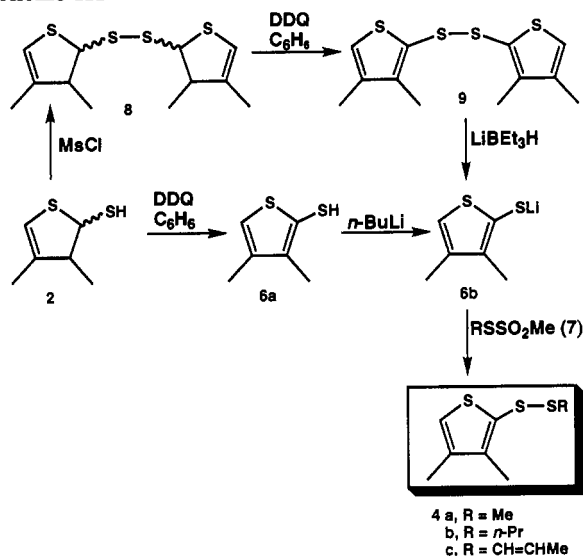
Scheme II



these methods were judged unsuitable for a compound such as 2, which possesses a reactive thiol group and exhibits instability toward heat and light. We found that 2 could be aromatized at room temperature by direct treatment of a crude solution in benzene with a slight excess of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), giving 3,4-dimethyl-2-thiophenethiol (6a) in fair yield. Thioalkylation of the corresponding lithium salt 6b with

[†] Presented at the Symposium on Sulfur Compounds in Foods, 206th National Meeting of the American Chemical Society, Division of Agricultural and Food Chemistry, Chicago, IL, Aug 25, 1993 (AGFD 86). At this meeting we were informed that independent syntheses of compounds 4a, 4b, and 6a from 2,5-dibromo-3-methylthiophene had just been completed (Bertram et al., 1993).

Scheme III



methanesulfonothioic acid *S*-methyl ester (MeSSO₂Me, 7a; Scheme III) affords 4a. A more satisfactory procedure involves conversion of 2 to bis(1,5-dihydro-3,4-dimethyl-2-thienyl) disulfide (8) using methanesulfonyl chloride, DDQ aromatization of 8 to bis(3,4-dimethyl-2-thienyl) disulfide (9), reductive cleavage of 9 with lithium triethylborohydride, and thioalkylation of the resultant lithium salt 6b with RSSO₂Me (R = Me, *n*-Pr, or MeCH=CH; 7a-c, respectively) giving 4a-c. Spectroscopic data for compounds 4a-c, 6a, and 8 (see Experimental Procedures) are in full accord with their proposed structures.

The mass spectra of synthetic 4a-c are identical with those reported for 4a-c found by GC-MS in distilled oils from Welsh onion and scallion (Kuo et al., 1990; Kuo and Ho, 1992a,b; Kuo, 1991), confirming the identity of the natural compounds. On the other hand, comparing "cryogenic" GC-MS (Block et al., 1992) data for SC-CO₂ extracts of onion (Calvey et al., 1993) with data obtained under identical conditions using synthetic 4a, we are unable to reproduce the claims of Sinha et al. (1992) for the presence of either 4a or major ("55%") amounts of an "isomer" of 4a in onion SC-CO₂ extracts. We suspect that in this latter work 4a and its isomer are artifacts whose formation is associated with the 280 °C GC injector temperature employed in analysis and that these compounds are not actually present in onion SC-CO₂ extracts (Block, 1993).

Pure synthetic samples of 4a-c in water were evaluated by "expert flavorists" who described odor and taste. Compound 4a had a nutty flavor with a 5-10 ppb detection threshold; 4b had a green, vegetative flavor at the 10-20 ppb detection threshold, with a cabbage flavor at higher levels; and 4c had a green, slightly sulfury and nutty flavor, with a 10-20 ppb detection threshold. In summary, 4a-c do not have characteristic fresh onion flavors but may contribute to the flavor of roasted onion or other *Allium* species.

EXPERIMENTAL PROCEDURES

Caution: Benzene is a cancer suspect agent and should be used only in a good hood; for larger scale work, alternative solvents of similar boiling points should be employed.

Bis(1,5-dihydro-3,4-dimethyl-2-thienyl) Disulfide (8). A solution of isomers of 1 (0.5 g, 3.42 mmol) in benzene (50 mL) was heated at 85 °C for 6 h and then concentrated in vacuo. The resultant yellow oil (2) was diluted with dry ether (20 mL), cooled to -60 °C, and treated with *n*-BuLi (2.5 M in hexanes, 1.4 mL,

3.5 mmol). The mixture was stirred at -50 to -30 °C for 30 min and treated with methanesulfonyl chloride (0.13 mL, 1.69 mmol). The mixture was warmed to -10 °C, water (5 mL) was added, stirring was continued for 15 min, the layers were separated, and the organic layer was dried (MgSO₄), filtered, and concentrated to yield a colorless oil which was purified by column chromatography (200-435-mesh silica gel, hexanes; TLC on 0.25 mm thick silica gel 60 F-254 showed *R*_f 0.8 with hexanes) to give the title compound (0.24 g, 50% yield) as a colorless oil which was a mixture of isomers according to its complex ¹H NMR spectrum.

Bis(3,4-dimethyl-2-thienyl) Disulfide (9). A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (313 mg, 1.38 mmol) in benzene (10 mL) was added to a solution of disulfide 8 (200 mg, 0.69 mmol) in benzene (10 mL) at room temperature. The mixture was stirred for 1 h at room temperature and at reflux for 2 h. After cooling, the mixture was diluted with ether (50 mL) and washed with saturated NaOH (20 mL). The alkaline wash was extracted with ether (20 mL). The combined organic layers were washed with water (2 × 20 mL), dried (MgSO₄), filtered, and concentrated, affording a yellow residue which was purified by flash column chromatography (as for 8 except using pentane; TLC *R*_f 0.39) to give the title compound as a yellow oil (50 mg, 26% yield): ¹H NMR (CDCl₃) δ 7.05 (br s, 1 H), 2.12 (d, *J* = 0.9 Hz, 3 H), 1.93 (s, 3H); ¹³C NMR (CDCl₃) δ 145.03, 138.03, 128.16, 15.56, 12.90; EI MS *m/z* 286 (M⁺, 44%), 143 (100%), 111 (10%), 99 (30%), 65 (14%), 45 (35%).

Methyl, *n*-Propyl, and 1-Propenyl 3,4-Dimethyl-2-thienyl Disulfides (4a-c, Respectively) from Disulfide 9. A solution of lithium triethylborohydride (1.0 M in THF, 3 equiv) was added under argon to a solution of disulfide 9 (1 equiv) in dry THF (3 mL) at -30 °C. The solution was warmed to room temperature, cooled to -20 °C, and treated all at once with a solution of RSSO₂Me (5 equiv) in THF (1 mL). The milky white reaction mixture was warmed to 10 °C during 2 h and then warmed to room temperature, treated with brine (3 mL), extracted with ether (20 mL), and again washed with brine. The aqueous washings were extracted with ether (10 mL), the combined organic layer was dried (MgSO₄), filtered, and concentrated, and the residue was purified by flash column chromatography.

Methyl 3,4-Dimethyl-2-thienyl Disulfide (4a). After addition of MeSO₂SMe and workup as above, chromatography (as for 8) using hexanes gave a yellow oil (89%): ¹H NMR (CDCl₃) δ 6.99 (br s, 1 H), 2.51 (s, 3 H), 2.24 (s, 3 H), 2.16 (d, *J* = 0.9 Hz, 3 H); ¹³C NMR (CDCl₃) δ 143.37, 138.34, 129.74, 124.57, 22.92, 15.59, 13.43; EI MS *m/z* 190 (M⁺, 82%), 143 (100%), 111 (16%), 99 (46%), 65 (14%), 45 (91%); HRMS calcd for C₇H₁₀S₃, 189.9945, found 189.9945.

***n*-Propyl 3,4-Dimethyl-2-thienyl Disulfide (4b).** After addition of MeSO₂SPr-*n* and workup as above, chromatography (as for 8) using hexanes (TLC *R*_f 0.45) gave a pale yellow oil (100%): ¹H NMR (CDCl₃) δ 6.96 (br s, 1 H), 2.77 (t, *J* = 7.2 Hz, 2 H), 2.23 (s, 3 H), 2.14 (s, 3 H), 1.75 (sextet, *J* = 7.2 Hz, 2 H), 0.98 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (CDCl₃) δ 143.13, 138.21, 130.42, 124.33, 40.62, 22.13, 15.58, 13.42, 13.16; EI MS *m/z* 218 (M⁺, 89%), 176 (14%), 143 (100%), 142 (21%), 112 (39%), 111 (42%), 99 (37%), 71 (14%), 65 (19%), 45 (57%); HRMS calcd for C₉H₁₄S₃, 218.0258, found 218.0258.

1-Propenyl 3,4-Dimethyl-2-thienyl Disulfide (4c). After addition of (*E,Z*)-MeSO₂SCH=CHMe (Block and Zhao, 1992) and workup as above, chromatography (as for 8) using hexanes (TLC *R*_f 0.40) gave a yellow oil (92%): ¹H NMR (CDCl₃) δ 6.89 (br s, 1 H), 6.34 (dq, *J* = 9.3, 1.5 Hz, 1 H), 5.77 (dq, *J* = 9.3, 6.9 Hz, 1 H), 2.25 (s, 3 H), 2.14 (d, *J* = 1.2 Hz, 3 H), 1.64 (dd, *J* = 66.9, 1.8 Hz, 3 H); ¹³C NMR (CDCl₃) δ 143.81, 138.19, 135.55, 128.32, 127.97, 125.09, 15.60, 14.34, 13.54; EI MS *m/z* 216 (M⁺, 46%), 152 (25%), 143 (100%), 111 (12%), 99 (34%), 45 (66%); HRMS calcd for C₉H₁₂S₃, 216.0101, found 216.0100.

3,4-Dimethyl-2-thiophenethiol (6a). A solution of isomers of 1 (0.1 g, 0.685 mmol) in benzene (50 mL) was heated at 85 °C for 3 h. After the solution cooled to room temperature, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 156 mg, 0.685 mmol) was added, and the solution was stirred for 36 h. The mixture was then filtered to remove the solid that was formed, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (as for 8 except using pentane; TLC *R*_f 0.39) to give the title compound (15 mg, 15%

yield) as a yellow oil: $^1\text{H NMR}$ (CDCl_3) δ 7.05 (br s, 1 H), 2.18 (s, 3 H), 1.92 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) δ 145.04, 138.05, 128.88, 126.16, 15.58, 12.91; EIMS m/z 144 (100%), 143 (25%), 129 (17%), 111 (86%), 99 (19%), 69 (23%), 67 (22%), 45 (60%).

Methyl 3,4-Dimethyl-2-thienyl Disulfide (4a) from Thiol 6a. A solution of *n*-butyllithium (2.5 M, 50 μL , 0.13 mmol) was added to **6a** (15 mg, 0.104 mmol) in dry THF (2 mL) at -78°C . A solution of MeSO_2SMe (40 mg, 0.317 mmol) in dry THF (1 mL) was added all at once. After warming to room temperature, the reaction was quenched with water and extracted with ether ($2 \times 10\text{ mL}$), the organic layer separated, dried, filtered, and concentrated, and the residue purified by flash chromatography (as for **8**, hexanes; TLC R_f 0.40), giving a pale yellow oil (11 mg) which, according to $^1\text{H NMR}$ analysis, was a mixture of **4a** and **9**.

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