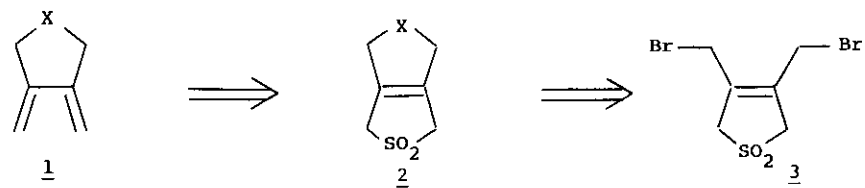
REACTIONS OF NUCLEOPHILES WITH 3,4-BIS(BROMOMETHYL)-2,5-DIHYDROTHIOPHENE-1,1-DIOXIDE

TA-SHUE CHOU* AND SU CHUN HUNG
INSTITUTE OF CHEMISTRY, ACADEMIA SINICA,
NANKANG, TAIPEI, TAIWAN, REPUBLIC OF CHINA

Abstract—*3,4-Bis(bromomethyl)-2,5-dihydrothiophene 1,1-dioxide was reacted with n-butylamine or sodium sulfide to give the sulfolene-fused pyrrolidine and hydrothiophene, respectively while its reaction with siloxide gave only the 1,4-elimination product. The difference in reactivity can be explained by the different nucleophilicity and basicity of these reactants.*

2,5-Dihydrothiophene 1,1-dioxides (3-sulfolenes) are known to undergo thermal extrusion of SO_2 at moderately elevated temperature,[1] therefore, compounds 2 can be envisioned as precursors for the heterocyclic ortho-quinodimethanes 1.[2] The disubstitution of 3,4-bis(bromomethyl)-3-sulfolenes 3[3] with a suitable nucleophile appears to be an attractive way for the preparation of 2 (Scheme I).

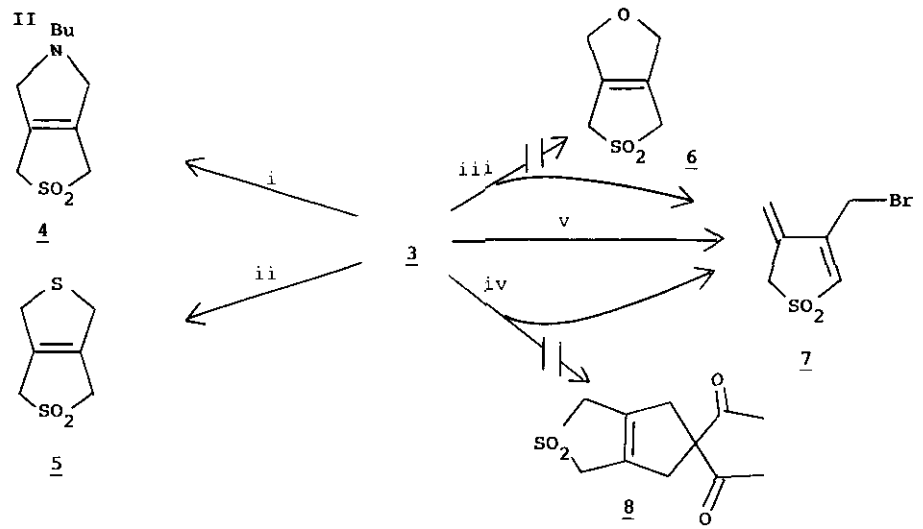
Scheme I



1 2 3

It was reported[4] that the reaction of 3 with a primary arylamine gave the cyclized product (2, X = NAr) while the reaction failed in an attempt to react 3 with sodium sulfide to form its sulfur analogue. An insoluble polymer was reported to be the only obtainable product. We treated 3 with n-$BuNH_2$ in dichloromethane with or without the presence of sodium carbonate and found that it indeed gave 4 in 65% yield and that the success could be extended to the preparation of the sulfur analogue despite the failure reported in literature.[4] The reaction of 3 with Na_2S-$9H_2O$ in 95% EtOH or with anhydrous Na_2S in absolute EtOH gave 5 in about 30% yield along with the formation of some gummy polymer. This reaction provides a very convenient way for the preparation of the stable precursor of the hydrothiophene ortho-quinodimethane (1, X = S)[5] (Scheme II).

Scheme II



i. N-$BuNH_2$, Na_2CO_3. ii. Na_2S. iii. $(Me_3Si)_2O$, Bu_4NF. iv. 2,4-pentanedione, K_2CO_3. v. K_2CO_3

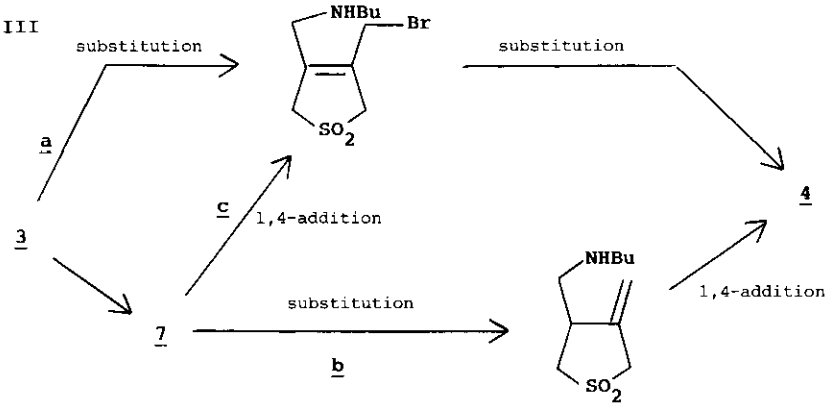
It is interesting that although 3 contains a reactive allylic bromide functionality, it is extraordinarily stable as compared with other allylic bromides. For example, 3 can be eluted through a silica gel column or HPLC column without any appreciable loss of material and remains unchanged in water for a few hours. A similar phenomenon has been observed in another allylic bromide, 4-bromo-2-sulfolene.[6] The highly electron-withdrawing sulfone functionality is believed to be responsible for the deactivation of the allylic bromides.

The attempt of using the above strategy in the preparation of the oxygen analogue 6 was unsuccessful. Treatment of 3 with H_2O/pyridine resulted in the formation of a complex mixture and treatment of 3 with $Me_3SiOSiMe_3$ in the presence of Bu_4NF gave only the 1,4-elimination product 7[7]. Reaction of 3 with solid K_2CO_3 in dichloromethane gave 7 almost quantitatively indicating the strong acidity of the α-proton and the extreme ease of the 1,4-elimination process. Reaction of 3 with 2,4-pentanedione using K_2CO_3 as base also resulted in 1,4-elimination without any detectable amount of the desired substitution product 8 (Scheme II).

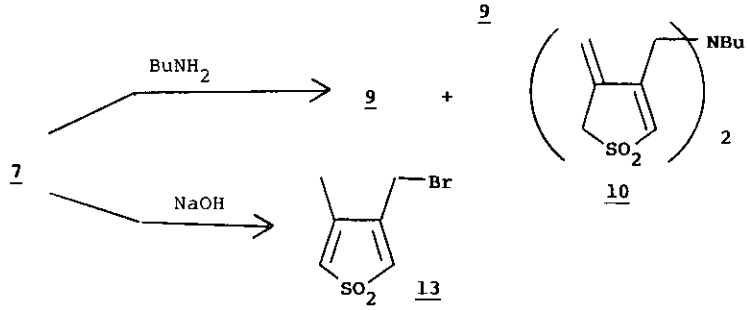
There are three possible pathways for the formation of 4 in the reaction of 3 with $BuNH_2$. One involves the direct nucleophilic disubstitution of the two bromides with the nitrogen atom (route a). The others involve first an amine base induced 1,4-elimination followed by either a substitution/1,4-addition sequence (route b)

or a 1,4-addition/substitution sequence (route c). The formation of 7 as a reaction intermediate (in route b or c) is not impossible since the 1,4-elimination of 3 is so easy. However, the reaction of 7 with 1.2 equivalent of $BuNH_2$ gave 9 and 10 without any detectable amount of 4.[8] In a similar reaction where $BuNH_2$ was used in large excess (10 equiv), 9 was the only product. No intramolecular cyclization reaction took place even after prolonged stirring of 9 in the presence K_2CO_3 (Scheme IV). The inability of 9 to cyclize is in agreement with the prediction that 5-endo-trigonal being a disfavored process.[9] The results rule out the possibility of route b. In addition, compound 11, prepared by the 1,4-elimination of 3-bromomethyl-3-sulfolene 12, was completely unreactive with $BuNH_2$ suggesting that route c is not involved either (eq 1). Therefore, route a is the most likely pathway for the formation of 4 where only nucleophilic substitution is involved. The formation of 5 must have taken place similarly by the direct disubstitution of the two bromides of 3 with the sulfide. It is interesting that the reaction of 7 with 1N NaOH resulted in no substitution reaction but only in double bond migration to 13 where the allylic bromide functionality remained unchanged (Scheme IV). The isomerization must have occurred by the deprotonation at the α-position followed by γ-protonation.

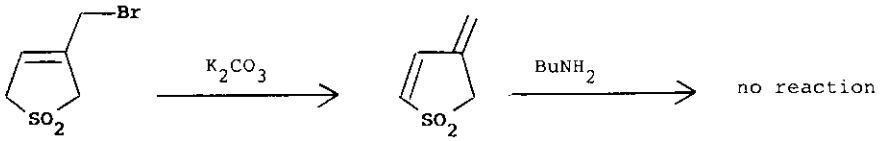
Scheme III



Scheme IV



eq 1



12 11

In summary, amines and sulfides are powerful nucleophiles so as to undertake nucleophilic substitution reactions on deactivated allylic bromides such as 3 and 7. However, siloxide and hydroxide are strong bases and medium nucleophiles so that they behave more as base toward these compounds containing acidic protons leading to different type of products.

EXPERIMENTAL

General Methods. ^1H NMR spectra were determined on a JEOL FX-100 or a Bruker AW-80 NMR spectrometer as solutions in $CDCl_3$. IR spectra were determined on a Perkin-Elmer 290 IR spectrophotometer. Mass spectra were recorded on a JEOL JMS-D-100 mass spectrometer. Elemental Analyses were performed at the Microanalysis Laboratory of the National Taiwan University, Taipei. All anhydrous solvents were freshly distilled before use.

5-Butyl-1,3,4,6-tetrahydrothieno[3,4-c]pyrrole 2,2-Dioxide (4). n-Butylamine (0.175 g, 2.4 mmol) was slowly added to a mixture of 3 (0.61 g, 2.0 mmol) and Na_2CO_3 (0.5 g) in CH_2Cl_2 (25 ml) and the resulting mixture was stirred at room temperature for 40 h. Brine (15 ml) was then added to the red reaction mixture and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 X 30 ml) and the combined organic layers were washed with brine and dried ($MgSO_4$). After removal of the solvent, the crude red oil was purified by column chromatography (aluminum oxide, $CHCl_3$) to give the pure 4 in 65% yield: IR (KBr) 2975, 2950, 1320, 1260, 1155, 1115 cm^{-1}; NMR δ 3.68 (s, 4H), 3.50 (s, 4H), 2.60 (t, 2H, J = 7 Hz), 1.35-1.50 (m, 4H), 0.88 (t, 3H, J = 7 Hz); MS m/z 215 (M^+), 172, 151 (base). Anal. Calcd for $C_{10}H_{18}NO_2S$: C, 55.8; H, 7.9; N, 6.5. Found: C, 55.4; H, 8.0; N, 6.2.

1,3,4,6-Tetrahydrothieno[3,4-c]thiophene 2,2-Dioxide (5).

Method A. Sodium sulfide nonahydrate (288 mg, 1.2 mmol) dissolved in H_2O (4 ml) was added to a mixture of 3 (304 mg, 1.0 mmol) in 95% EtOH (40 ml) and the resulting mixture was refluxed for 20 h. The solvent was removed under reduced pressure, then brine (10 ml) was added and the whole mixture was extracted with CH_2Cl_2 (3 X 30 ml). The combined organic layers were washed with brine and dried ($MgSO_4$). After removal of the solvent, the crude oil was purified by column chromatography (silica gel, CH_2Cl_2) to give the pure product 5 in 27% yield: IR (KBr) 1315, 1160, 1140, 1100 cm^{-1}; NMR δ 3.8 (s); MS m/z 176 (M^+), 111 (base), 97, 79. Anal. Calcd. for $C_6H_8O_2S_2$: C, 40.9; H, 4.6. Found: C,40.5; H, 4.45. The NMR spectrum of 5 was identical with that reported earlier.[5]

Method B. A mixture of anhydrous sodium sulfide (0.92 g, 11.8 mmol) and 3 (2.62 g, 8.6 mmol) in anhydrous EtOH (200 ml) was refluxed under nitrogen for 16 h whereupon the solvent was removed under reduced pressure. Brine (15 ml) was added and the mixture was extracted with CH_2Cl_2 (3 X 50 ml). The combined organic layer was then washed with brine and dried ($MgSO_4$). After removal of the solvent, the crude oil was purified by column chromatography to give pure 5 in 29% yield.

4-Bromomethyl-2-hydro-3-methylenethiophene 1,1-Dioxide (7).

Method A. A mixture of 3 (4.5 g, 15 mmol) and K_2CO_3 (18 g) in CH_2Cl_2 (300 ml) was stirred at room temperature under nitrogen for 5 days whereupon brine (30 ml) was added and layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 X 50 ml) and the combined organic layer was washed with brine, then dried ($MgSO_4$). Removal of the solvent gave the pure product 7 in 98% yield. Care must be taken to keep the temperature as low as possible during the concentration process; otherwise polymerization occurs very rapidly. However, compound 7 dissolved in CH_2Cl_2 in the presence of K_2CO_3 can be kept for at least two months. IR (KBr) 3020, 2960, 1730, 1595, 1400, 1300, 1220 cm^{-1}; NMR δ 6.68 (s, 1H), 5.66 (s, 1H), 5.50 (s, 1H), 4.20 (s, 2H), 4.08 (s, 2H); MS m/z 224, 222 (M^+), 195, 193, 175, 173, 160, 158, 143, 95, 77 (base). Anal. Calcd. for $C_6H_7BrO_2S$: C, 32.3; H, 3.2. Found: C, 32.3; H, 3.1.

Method B. To a mixture of 3 (304 mg, 1.0 mmol) and hexamethyldisiloxane (162 mg, 1 mmol) in anhydrous THF (40 ml) at -78°C under nitrogen was added tetrabutylammonium fluoride (2 mmol) dropwise. The cooling bath was removed and the reaction mixture was stirred at room temperature for 2 days. Brine (15 ml) was added to the dark brown solution and the layers separated. The aqueous layer was extracted with $CHCl_3$ (3 X 40 ml) and the combined organic layer was washed with

brine and dried ($MgSO_4$). After removal of solvent, the crude oil was purified by HPLC (LiChrosorb column, EtOAc) to give the pure product 7 in 70% yield.

4-(N-Butylaminomethyl)-2-hydro-3-methylenethiophene 1,1-Dioxide (9) and Bis(2-hydro-3-methylenethiophen-4-yl)-N-butylamine (10).

Method A. To a solution of $BuNH_2$ (2.2 ml, 22.4 mmol) in CH_2Cl_2 (20 ml) was added 3 (0.5 g, 2.24 mmol) in CH_2Cl_2 (10 ml) and the reaction mixture was stirred at room temperature for 16 h. Brine (10 ml) was added and the layers separated. The aqueous layer was extracted with $CHCl_3$ (3 X 20 ml) and the combined organic layer was washed with brine, then dried ($MgSO_4$). After removal of solvent, the crude oil was recrystallized with EtOAc/hexane (1:1) to give the pure product 9: IR (KBr) 3300, 2930, 1600, 1300, 1230 cm^{-1}; NMR δ 6.78 (s, 1H), 5.54 (s, 1H), 5.35 (s, 1H), 4.01 (s, 2H), 3.61 (s, 2H), 2.65 (t, 2H, J = 7 Hz), 1.30-1.50 (m, 5H), 0.93 (t, 3H, J = 7 Hz); MS m/z 215 (M^+), 172 (base), 151, 108, 107.

Method B. To a solution of $BuNH_2$ (2.7 mmol) in CH_2Cl_2 (10 ml) was added 3 (2.24 mmol) in CH_2Cl_2 and the reaction mixture was stirred at room temperature under nitrogen for 20 h. The mixture was worked up by the same way as described above to give a mixture of 9 (34%) and 10 (36%) which were separated by column chromatography (silica gel, EtOAc/hexane, 1:1). Compound 10: IR (neat) 3100, 2950, 1590, 1400, 1300, 1230, 1170, 1130, 1110 cm^{-1}; NMR δ 6.71 (s, 2H), 5.57 (s, 2H), 5.39 (s, 2H), 4.03 (s, 4H), 3.41 (s, 4H), 2.56 (t, 2H, J = 7 Hz), 1.20-1.80 (m, 4H), 0.93 (t, 3H, J = 7 Hz); MS m/z 357 (M^+), 314 (base), 293, 250, 118.

2-Hydro-3-methylenethiophene 1,1-Dioxide (11). A mixture of 3-bromomethyl-3-sulfolene (159 mg, 0.75 mmol) and K_2CO_3 (2 g) in CH_2Cl_2 (10 ml) was stirred at room temperature for 3 days. Brine (5 ml) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 X 20 ml) and the combined organic layer was washed with brine and dried ($MgSO_4$). Removal of the solvent gave pure product 11 in quantitative yield: IR (KBr) 3050, 2950, 1830, 1560, 1400, 1300, 1220, 1130 cm^{-1}; NMR δ 7.00 (d, 1H, J = 7 Hz), 6.74 (d, 1H, J = 7 Hz), 5.54 (s, 1H), 5.44 (s, 1H), 3.91 (s, 2H); MS m/z 130 (M^+), 101, 82 (base), 65, 51. Compound 11 polymerizes readily upon storing in neat form. However, it remains stable in CH_2Cl_2 solution in the presence of K_2CO_3.

3-Bromomethyl-4-methylthiophene 1,1-Dioxide (13). To a solution of 7 (180 mg, 0.8 mmol) in THF (20 ml) was added dropwise 1N NaOH (2 ml) and the reaction mixture

was stirred at room temperature for 24 h. THF was removed under reduced pressure and then brine (10 ml) was added. The aqueous layer was extracted with CH_2Cl_2 (3 X 15 ml) and the combined organic layer was washed with brine, then dried ($MgSO_4$). After removal of the solvent, the crude oil was purified by HPLC (LiChrosorb column, EtOAc/hexane, 1:1) to give the pure product 13 in 56% yield: IR (KBr) 3100, 2950, 1630, 1610, 1419, 1390, 1285, 1230, 1110 cm^{-1}; NMR δ 6.76 (s, 1H), 6.60 (s, 1H), 3.95 (s, 2H), 2.08 (s, 3H); MS m/z 224 (M^+), 222, 195, 193, 162, 160, 158, 143, 95 (base), 77. Anal. Calcd. for $C_6H_7BrO_2S$: C, 32.3; H, 3.1. Found: C, 32.3; H, 3.1.

ACKNOWLEDGMENT

We thank the National Science Council of Republic of China for financial support.

REFERENCES AND NOTES

1. (a) W.L. Mock, J. Am. Chem. Soc., 97, 3666 (1975). (b) S.D. McGregor and D.L. Lemal, J. Am. Chem. Soc., 88, 2858 (1966). (c) R.M. Kellogg and W.L. Prins, J. Org. Chem., 39, 2366 (1974).
2. (a) C. Kaneko and T. Naito, Heterocycles, 19, 2183 (1982). (b) W.S. Trahanovski and T.J. Cassady, J. Am. Chem. Soc., 106, 8197 (1984). (c) P. Magnus, T. Gallagher, P. Brown, and P. Pappalardo, Acct. Chem. Res., 17, 35 (1984).
3. G.B. Butler and R.M. Ottenbrite, Tetrahedron Lett., 4873 (1967).
4. (a) R.M. Ottenbrite and P.V. Alston, J. Org. Chem., 39, 1115 (1974). (b) R.M. Ottenbrite, Virginia J. Sci., 21, 196 (1970). (c) R.M. Ottenbrite, private communication.
5. Compound 5 has been prepared by other route, Y. Gaoni and S. Sadeh, J. Org. Chem., 45, 870 (1980).
6. W.J. Bailey and E.W. Cummins, J. Am. Chem. Soc., 76, 1932 (1954).
7. Similar 1,4-elimination reaction has been observed, however, the product has not been isolated or fully characterized, see reference 4(a).
8. Recently, compound similar to 9 was observed independently, R.M. Ottenbrite, private communication.
9. J.E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R.C. Thomas, J.Chem. Soc., Chem. Commun., 736 (1976).
10. R.C. Krug and T.F. Yen, J. Org. Chem., 21, 1082 (1956).

Received, 6th May, 1986