Preparation of Functionalized Unsymmetrical Disulfides by a Base-induced Crossed Reaction of Symmetrical Disulfides

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Highly functionalized, unsymmetrical disulfides (presumed metabolites of a bioactive sulfide) were synthesized by a base-induced, crossed reaction of two different symmetrical disulfides. The reaction was also applied to the preparation of a vitamin B_1 derivative, Prosultiamine.

We report here a practical synthesis of highly functionalized, unsymmetrical disulfides by a base-induced, crossed reaction of two different symmetrical disulfides.

The alkaline decomposition of a disulfide (R^1SSR^1) generates a thiolate (R^1S^-) (the other product X depends on the structure of the disulfide) (eq. 1).[1] It is well documented that the thiolate (R^1S^-) can cleave the disulfide bond of another disulfide (R^2SSR^2) to yield R^1SSR^2 with extrusion of R^2S^- (eq. 2).[2] In turn, the resulting R^2S^- may cleave the disulfide bond of R^1SSR^1 to give R^1SSR^2 with regeneration of R^1S^- (eq. 3). If these three reactions operate successively and successfully, the whole results are the formation of two molecules of R^1SSR^2 from R^1SSR^1 and R^2SSR^2 (eq. 4). Generally speaking, however, these sequences are not promising as a synthesis of unsymmetrical disulfides because they are composed of three equibrium reactions, thereby providing a mixture of three disulfides which will make the isolation of the desired R^1SSR^2 laborious.

$$R^1\text{–S–S–}R^1 + OH^- \rightleftharpoons R^1\text{–}S^- + X \quad (1)$$

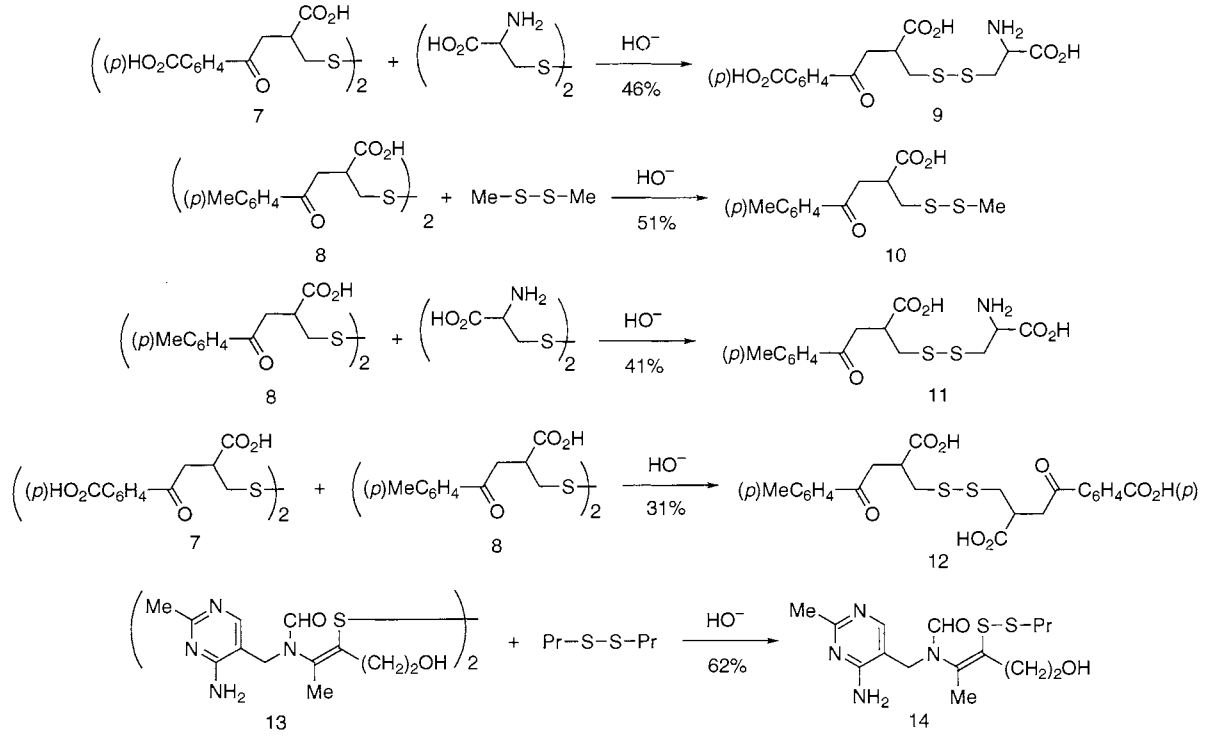
$$R^1\text{–}S^- + R^2\text{–S–S–}R^2 \rightleftharpoons R^1\text{–S–S–}R^2 + R^2\text{–}S^- \quad (2)$$

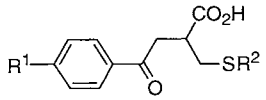
$$R^2\text{–}S^- + R^1\text{–S–S–}R^1 \rightleftharpoons R^1\text{–S–S–}R^2 + R^1\text{–}S^- \quad (3)$$

$$R^1\text{–S–S–}R^1 + R^2\text{–S–S–}R^2 \overset{OH^-}{\rightleftharpoons} 2\,R^1\text{–S–S–}R^2 \quad (4)$$

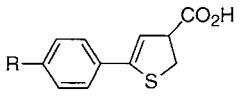
In our study on a bioactive sulfide KE-298 (**1**), we needed the authentic samples of unsymmetrical disulfides (**9**)-(**12**) which were presumed to be metabolites of **1**. Conventional synthetic methods for unsymmetrical disulfides, i.e., reactions of R^1SX (X = Cl, SO_2R, SO_3^-, NR_2, SCO_2R, NO) with thiols (R^2SH),[3] are difficult to apply to the synthesis of **9**-**12** since the thiols **3** and **4** are not isolable because they readily cyclize to form the dihydrothiophenes **5** and **6**, respectively, under neutral to acidic conditions. Meanwhile, the disulfides **7** and **8** are readily obtainable from **2** and **1**, respectively, by alkaline hydrolysis followed by iodine oxidation in situ. We therefore attempted reactions of **7** and **8** with other symmetrical disulfides under alkaline conditions with expectation of obtaining **9**-**12**. Here we show that the expected reaction works truely in a practical way.

In all of the cases, L-cystine and dimethyl and dipropyl disulfides, which are commercially available and inexpensive, were used in threefold excess. The desired unsymmetrical





1: R^1 = Me, R^2 = Ac
2: R^1 = CO_2H, R^2 = Ac
3: R^1 = CO_2H, R^2 = H
4: R^1 = Me, R^2 = H



5: R = CO_2H
6: R = Me

disulfides were easily isolated by making use of acidity or solubility difference. Thus a mixture of **7** (1 mmol), L-cystine (3 mmol), and NaOH (10.2 mmol) in water (5 ml) was stirred for 2 h at 30 °C. The mixture was acidified by 1M HCl (9.2 mmol) after dilution with water (25 ml) and THF (25 ml), and the resulting unreacted L-cystine was removed by filtration. Further acidification of the filtrate by 1M HCl (1.0 mmol) and removal of THF under reduced pressure resulted in the separation of a mixture of **9** and **7**. The mixture was washed with hot THF (50 ml) to remove **7** and then recrystallized from MeOH to give **9** in 46% yield.[4,5] Preparation of **11** and **12** was also carried out in water.[4,5] Meanwhile, preparation of **10** was carried out in MeOH containing water. Thus a mixture of **8** (5 mmol), dimethyl disulfide (15 mmol), NaOH (11 mmol), and water (5 ml) in MeOH (48 ml) was stirred for 6 h at 30 °C. The resulting mixture was acidified by 1M HCl (14 mmol) and then evaporated to dryness under reduced pressure. The residue was extracted with boiling hexane (300 ml) and the extract, after evaporation of the hexane, was recrystallized from Et_2O/hexane to give **10** in 51% yield.[4,5]

Further, the reaction was applied to the preparation of a vitamin B_1 derivative, Prosultiamine **14**, which is currently of clinical use. Thus a mixture of the disulfide **13** (10 mmol), dipropyl disulfide (30 mmol), NaOH (2 mmol),[6] and water (1 ml) in MeOH (56 ml) was stirred for 6 h at 30 °C. The mixture was acidified by 1M HCl (2.2 mmol) and then evaporated. The residue was washed with hexane (20 ml) to remove the unreacted dipropyl disulfide. The residue was treated with AcOEt (100 ml) and the insoluble disulfide **13** was removed by filtration. The filtrate was concentrated to result in the separation of **14** in 62% yield.

The new method developed above is rather unexpected but practical enough because of simple reaction and workup procedures. Further application of the present disulfide synthesis and mechanism of the reaction are under investigation in our laboratories.

References and Notes

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2 A. Fava, A. Iliceto, and E. Camera, *J. Am. Chem. Soc.*, **79**, 833 (1957).

3 P. C. B. Page, R. D. Wilkes, and D. Reynolds, "Comprehensive Organic Functional Group Transformations," ed by A. R. Katrizky, O. Meth-Cohn, and C. W. Rees, Pergamon, Oxford (1995), Vol. 2, Chapter 2.03.

4 Disulfides **9**-**12** gave satisfactory elemental analyses (C, H, N, S).

5 **9:** mp 185-187 °C (dec); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.70-3.75 (m, 8H), 8.06 (s, 4H), 10.20 (br s, 3H, disappeared on addition of D_2O); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 38.7 (CH_2), 39.4 (CH_2), 39.6 (CH_2), 39.8 (CH), 40.2 (CH_2), 40.5 (CH), 40.5 (CH_2), 41.0 (CH_2), 52.8 (CH), 52.9 (CH), 127.98 (CH), 128.04 (CH), 129.6 (CH), 135.2 (C), 135.3 (C), 139.2 (C), 139.4 (C), 166.8 (C), 169.1 (C), 169.4 (C), 174.5 (C), 174.6 (C), 197.8 (C), 198.0 (C); IR (KBr) 3006, 1684, 1640, 1504, 1408, 1294 cm^{-1}; SIMS (POS, GLY) *m/z* 388 $[M+H]^+$. **10**: mp 84-85 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.39 (s, 3H), 2.42 (s, 3H), 2.88-3.60 (m, 5H), 7.35 (d, 2H, J = 8.1 Hz), 7.89 (d, 2 H, J = 8.1 Hz), 12.53 (s, 1H, disappeared on addition of D_2O); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.1 (CH_3), 22.3 (CH_3), 38.6 (CH_2), 38.9 (CH_2), 39.9 (CH), 128.0 (CH), 129.3 (CH), 133.9 (C), 143.7 (C), 174.4 (C), 197.3 (C); IR (KBr) 2910, 1704, 1676, 1608 cm^{-1}; SIMS (POS, 3-NBA) *m/z* 285$[M+H]^+$. **11:** mp 167-168 °C (dec.); ^{1}H NMR (DMSO-d_6, 500 MHz) δ2.38 (s, 3H), 2.75-3.80 (m, 8H), 7.33 (d, 2 H, J = 7.9 Hz), 7.87 (d, 2H, J = 7.9 Hz), 9.44 (br s, 2H, disappeared on addition of D_2O); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 21.2 (CH_3), 38.3 (CH_2), 39.0 (CH_2), 39.3 (CH_2), 39.7 (CH), 40.3 (CH_2), 40.6 (CH), 40.6 (CH_2), 41.1 (CH_2), 52.9 (CH), 53.0 (CH), 128.0 (CH), 128.0 (CH), 129.3 (CH), 133.9 (C), 134.0 (C), 143.6 (C), 143.6 (C), 169.1 (C), 169.4 (C), 174.6 (C), 174.8 (C), 197.4 (C), 197.6 (C). IR (KBr) 3266, 2970, 1688, 1608, 1500, 1406, 1342, 1186 cm^{-1}; SIMS (POS, 3-NBA) *m/z* 358 $[M+H]^+$. **12:** mp 98-102 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.37 (s, 3H), 2.90-3.60 (m, 10H), 7.28-7.36 (m, 2H), 7.80-7.90 (m, 2H), 8.05 (s, 2H), 8.07 (s, 2H), 12.83 (br s, 3H, disappeared on addition of D_2O); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 21.6 (CH_3), 39.0 (CH_2), 39.4 (CH_2), 39.9 (CH_2), 40.3 (CH), 128.4 (CH), 128.5 (CH), 129.7 (CH), 130.0 (CH), 134.2 (C), 134.3 (C), 135.0 (C), 139.75 (C), 139.78 (C), 144.1 (C), 167.0 (C), 174.7 (C), 174.8 (C), 197.67 (C), 197.72 (C), 198.1 (C), 198.2 (C); IR (KBr) 2912, 1705, 1690, 1606 cm^{-1}; SIMS (POS, GLY) *m/z* 505 $[M+H]^+$.

6 A catalytic amount of NaOH effects the conversion to **14** in this case. However, in other cases, the use of NaOH in excess is required because the starting disulfides possess carboxyl group(s).