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Convenient Synthesis of Benzotrithiepins and Benzotrithiocins from Dithiols and Thiiranes

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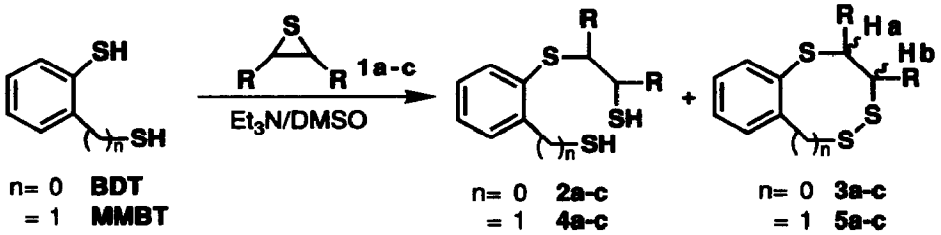
Abstract: 3,4-Dihydro-1,2,5-benzotrithiepin, 6*H*-2,3-dihydro-1,4,5-benzotrithiocin, and these derivatives were conveniently synthesized in good yields upon treating 1,2-benzenedithiol and 2-mercaptomethylbenzenethiol with various thiiranes in the presence of triethylamine in a polar solvent.

Recently, the characteristic chemical properties of cyclic polysulfides have attracted wide attention in the field of organosulfur chemistry.[1] We have also reported new methods for the synthesis of benzopentathiepin[2] and the related compound.[3] Furthermore, we have found many reactions for providing some heterocycles from such cyclic polysulfides.[4] For example, a direct formation of 1,2,5-benzotrithiepins **3**[5] and 1,4,5-benzotrithiocin **5**,[6] which are characterized by containing three different kinds of sulfur atoms as unsymmetrical monosulfide and disulfide moieties in the ring, has been achieved by treatment of benzopentathiepin and benzotetrathiepin, respectively, with alkenes in the presence of Lewis acid. To our knowledge, although many methods have been reported for the synthesis of trithiepans,[7] work on the formation of symmetrical trithiepins such as dibenzo[c,f][1,2,5]trithiepin has hitherto been limitted.[8] Especially, unsymmetrical 1,2,5-benzotrithiepin **3** and 1,4,5-benzotrithiocin **5** have never been synthesized except for our earlier examples.[5,6] In the course of our extensive studies on the organic chemistry of cyclic polysulfides,[9] our efforts were directed to the development of a convenient and more efficient method for synthesis of 3,4-dihydro-1,2,5-benzotrithiepin (**3a**), 6*H*-2,3-dihydro-1,4,5-benzotrithiocin (**5a**), and these derivatives (**3b,c** and **5b,c**). Now we have found a novel convenient synthetic method of **3a-c** and **5a-c** by treating the corresponding dithiols, 1,2-benzenedithiol (**BDT**) and 2-mercaptomethylbenzenethiol (**MMBT**), respectively, with thiiranes, **1a-c**, in the presence of triethylamine as a base in a polar solvent such as dimethyl sulfoxide (DMSO) (Scheme 1).



Scheme 1

Table 1. Reactions of Thiiranes 1 with Dithiols in the Presence of Triethylamine

Run[1)]	Dithiol	Thiirane R	Thiirane R	1	Solvent	React time/h	Yield of product/% 2 or 4		3 or 5	Condition
1	**BDT**	H	H	**1a**	DMSO	8	0	58	**3a**	air
2	**BDT**	H	H	**1a**	DMSO	8	50 **2a**	18	**3a**	Ar
3	**BDT**	Ph	Ph	*cis*-**1b**	DMSO	8	0	91	*trans*-**3b**	air
4	**BDT**	Ph	Ph	*trans*-**1b**	DMSO	3	0	37	*cis*-**3b**	air
5	**BDT**	Ph	Ph	*cis*-**1b**	DMF	8	0	58	*trans*-**3b**	air
6	**BDT**	Ph	Ph	*cis*-**1b**	Benzene	8	no reaction			air
7	**BDT**	Ph	Ph	*cis*-**1b**	CH_2Cl_2	8	no reaction			air
8	**BDT**	$-CH_2-(CH_2)_2-CH_2-$		**1c**	DMSO	6	0	60	**3c**	air
9	**MMBT**	H	H	**1a**	DMSO	8	0	80	**5a**	air
10	**MMBT**	Ph	Ph	*cis*-**1b**	DMSO	8	0	87	*trans*-**5b**	air
11	**MMBT**	Ph	Ph	*cis*-**1b**	DMSO	3	64 **4b**	19	*trans*-**5b**	Ar
12	**MMBT**	Ph	Ph	*trans*-**1b**	DMSO	3	0	17	*cis*-**5b**	air
13	**MMBT**	$-CH_2-(CH_2)_2-CH_2-$		**1c**	DMSO	8	0	81	**5c**	air

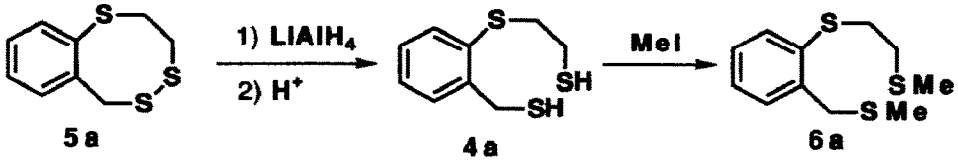
1) Dithiol, 0.3 mmol; **1**, 0.3 mmol; Et_3N, 0.075 mmol; React. temp, r t.

A typical procedure is as follows: To a solution of **BDT** (0.3 mmol) and triethylamine (0.075 mmol) in DMSO (3 ml) was added a solution of 1,2-diphenylthiirane (*cis*-**1b**) (0.3 mmol). After stirring for 8 h at room temperature, the solution was quenched with ether (10 ml) and poured into brine. The mixture obtained by extraction with ether (10 ml x 3) from the solution and then evaporation of the ether was chromatographed on silica gel using CCl_4 as an eluent to give *trans*-**3b**[10] in 91% yield.

BDT reacted readily with various thiiranes (**1**) in the presence of triethylamine as a base at room temperature in DMSO under air, to give the desired 1,2,5-benzotrithiepin **3a-c** in satisfactory yields as shown in Table 1 (Runs 1,3, 4, and 8-13). Interestingly, the treatment of **BDT** with **1a** under argon afforded an adduct, 2-mercaptoethyl 2-mercaptophenyl sulfide (**2a**), in 50% yield together with the desired **3a** of 18% (Run 2), to suggest apparently that the present reaction proceeds via oxidation of **2a**, which is formed intermediately, with oxygen in air. This fact was also confirmed by the same reactions under argon to give intermediate dithiol as shown in run 11. Moreover, in the present reaction, we found that the solvent used plays an important role. Thus, although some organic solvents such as DMSO, N,N-dimethylformamide (DMF), benzene, and dichloromethane were used as the solvent, favorable results were obtained upon using DMSO and DMF (Runs 1-5) while the use of benzene and dichloromethane did not give **3** at all (Runs 6 and 7). Furthermore, it should be emphasized that the use of DMSO or DMF as a solvent gives directly the desired trithiepin **3** without any oxidizing agent. Next, to study the stereochemistry of the present reaction, *cis*- and *trans*-1,2-diphenylthiiranes were employed under the same conditions. Here, *cis*-**1b** reacted readily with **BDT**, whereas *trans*-**1b** gave **3** in low yield because *trans*-**1b** decomposed to 1,2-diphenylethene and sulfur under this condition (Runs 4 and 12). The ^1H NMR study for two methine protons, Ha and Hb in Scheme 1, of the product **3** revealed that the *cis*-adduct was obtained from *trans*-**1b** while *trans*-adduct from

cis-**1b** (Runs 3 and 4). Thus, J_{Ha-Hb} for *trans*-**3b** is 10.7 Hz and 3.9 Hz for *cis*- **3b**. These facts imply undoubtedly that the reaction of dithiol with thiirane proceeds stereospecifically via "*trans*-substitution".

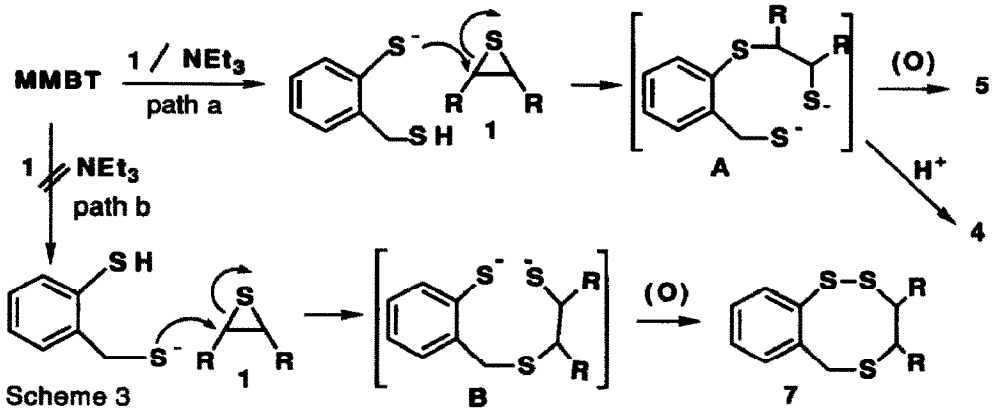
Similarly, reactions of **MMBT** with thiiranes **1a-c** were carried out under the same conditions and resulted in the formation of 2,3,6-benzotrithiocin **5a-c** via intermediate dithiol **4a-c** as shown in Scheme 1 and Table 1 (Runs 9-13). Based on the NMR study of the products, these reactions were also shown to proceed by *trans*-addition of dithiol to thiirane. Further confirmation of the products was performed as follows. Thus, the treatment of **5a**[11] with $LiAlH_4$ following methylation with CH_3I afforded only 2-methylthiomethylphenyl 2-methylthioethyl sulfide **6a**[12] via **4a** without any other product as shown in Scheme 2.



5a 4a 6a

Scheme 2

Based on the above mentioned results, the typical reaction pathway for the reaction using **MMBT** is illustrated as follows (Scheme 3). A nucleophilic "*trans*-substitution" of benzenethiolate to thiirane carbon occurs initially to give intermediate **A** (path a), which is protonated to 2-mercaptomethylphenyl 1,2-disubstituted-2-mercaptoethyl sulfide **4**. The intermediate **A** is readily oxidized with oxygen in air in a polar solvent to form **5**. Since we did not obtain any product, for example **7**, derived from intermediate **B**, path b is ruled out.



Scheme 3 A B 7

In conclusion, we have established a convenient method for the synthesis of 1,2,5-benzotrithiepin **3** and 1,4,5-benzotrithiocin **5** from the corresponding dithiols **BDT** and **MMBT** with thiiranes **1**. Further studies on the chemical behavior of **3** and **5** are now in progress in our laboratory. [13]

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10. *trans*-3,4-Dihydro-3,4-diphenyl-1,2,5-benzotrithiepin (*trans*-**3b**): Colorless needles; mp 178.0-179.0 °C (EtOH); Since some conformers are involved in this compound, ^{1}H NMR was measured at 50 °C (323 K) to simplify the spectra. ^{1}H NMR (400 MHz, $CDCl_3$, 323 K) δ = 4.57 (1H, d, J=10.7Hz, -CH<), 4.81 (1H, d, J = 10.7Hz, -CH<), 7.02-7.16 (10H, m, arom), 7.26-7.31 (2H, m, arom), 7.70-7.72 (1H, m, arom), and 7.82-7.84 (1H, m, arom); IR (KBr) 3058, 3026, 2943, 1488, 1419, 758, and 740 cm^{-1}; MS (70 eV) m/z 352 (M+). Anal. calcd for $C_{20}H_{16}S_3$: C, 68.14; H, 4.57%. Found: C, 68.41; H, 4.57%.
11. 6*H*-2,3-Dihydro-1,4,5-benzotrithiocin (**5a**): Colorless needles; mp 60.0 - 61.0 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.09 (4H, brs, $-CH_2CH_2-$), 4.29 (2H, s, $-CH_2-$), 7.21 (1H, dd, J= 7.5 and 1.5 Hz, arom), 7. 27 (1H, ddd, J = 7.5, 7.5, and 1.5 Hz, arom), 7.36 (1H, ddd, J = 7.5, 7.5, and 1.3 Hz, arom), and 7.69 (1H, dd, J = 7.5 and 1.3 Hz, arom); IR (KBr) 3055, 2920, 2887, 1466, 1433, 767, and 739 cm^{-1}; MS (70 eV) m/z 214 (M+). Anal. calcd for $C_9H_{10}S_3$: C, 50.43; H, 4.70%. Found: C, 50.32; H, 4.88%.
12. 2-(Methylthiomethyl)phenyl 2-(methylthio)ethyl sulfides (**6a**): Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.04 (3H, s, $-SCH_3$), 2.12 (3H, s, $-SCH_3$), 2.69-2.73 (2H, m, $-CH_2-$), 3.12-3.16 (2H, m, $-CH_2-$), 3.88 (2H, s, Ar-CH_2-SMe), 7.17 (1H, ddd, J=7.4, 7.4, and 1.6 Hz, arom), 7.23 (1H, ddd, J=7.4, 7.4, and 1.6 Hz, arom), 7.27 (1H, dd, J=7.4 and 1.6 Hz, arom), and 7.40 (1H, dd, J=7.4 and 1.6 Hz, arom); IR (neat) 3056, 2969, 2914, 2832, 1588, 1466, 1432, and 743 cm^{-1}; MS (70 eV) m/z 244 (M+). Anal. calcd for $C_{11}H_{16}S_3$: C, 54.05 ; H, 6.60%. Found: C, 53.93 ; H, 6.69%.
13. The results of the oxidation of **3** with various oxidizing agents and the alkylation should be reported in the near future.

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