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Synthesis and reactions of benzopentathiepin having hydroxyl group

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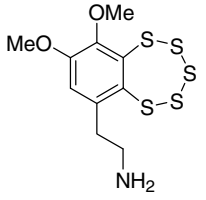
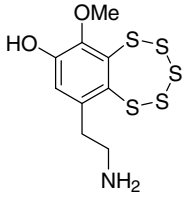
Abstract—The synthesis of benzopentathiepin having a hydroxyl group at the neighboring position of polysulfur ring was performed by demethylation of 6-ethyl-9-methoxybenzopentathiepin with hydrogenbromide. Benzotrithiole having hydroxyl group was not isolated at all. The hydroxyl group was also alkylated with alkyl iodide in the presence of weak base.

Cyclic benzopolychalcogenides such as benzopentathiepins,[1] benzotetrathiins,[2] and benzotrithioles[3] have been studied over three decades in respect of synthetic, structural, and biological interest.[4] We also developed several methods for the synthesis of the above compounds by sulfurization–cyclization of the corresponding 1,2-benzenedithiols or its synthetic equivalents.[5] Continuation of our findings of heterocyclic compounds containing chalcogen atoms has encouraged us to develop benzopolysulfides having a hydroxyl group as it is an active functionality for many organic reactions. Previously, we developed benzopentathiepins having pyridyl, pyrimidinyl and thienyl groups in the neighborhood of pentathiepin moiety.[6a] Pentathiepins fused to aromatics are marked for two broad applications: biological activity and application in material sciences.

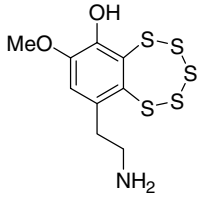
Ireland and co-workers isolated varacin (**1**) from marine ascidian and discovered that it exhibited significant antifungal and antitumor activity, and was as much as 100 times more potent than 5-fluorouracil toward the human colon cancer cell line HCT-116.[4a] A closely related benzopentathiepin, lissoclinotoxin A (**2**), also exhibited potent antimicrobial and antifungal activity.[4b,6b] The structures of bioactive natural products shown in Figure 1 are distinguishable by their hydroxyl and methoxy groups. Protection of phenolic group prior to pentathiepin ring synthesis and further regeneration of hydroxyl group without interference of pentathiepin ring are important steps for the synthesis of pentathiepins having hydroxyl groups, such as, isolissoclinotoxin



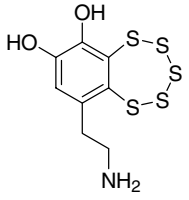
1; Varacin



2; Lissoclinotoxin A



3; Isolissoclinotoxin A



4; 3,4-Desmethylvaracin

Figure 1.

A (**3**) has already been synthesized by using weakly leaving MOM group by several steps.[4f] Therefore, some straightforward and high yielding methods for the synthesis of similar pentathiepins from their methoxy and phenolic derivatives are essential for the synthesis of important natural products such as **2** to **4**.[2,4,6b]

Poly and persulfurated aromatics have potential applications in electronic and photonic devices at molecular level or cathode active material in batteries.[7] Pentathiepin having hydroxyl group can be utilized as monomer for dendrimer, oligomer, and polymer synthesis to get new materials. Therefore, efficient methods for the synthesis of hydroxylbenzopentathiepin have paramount

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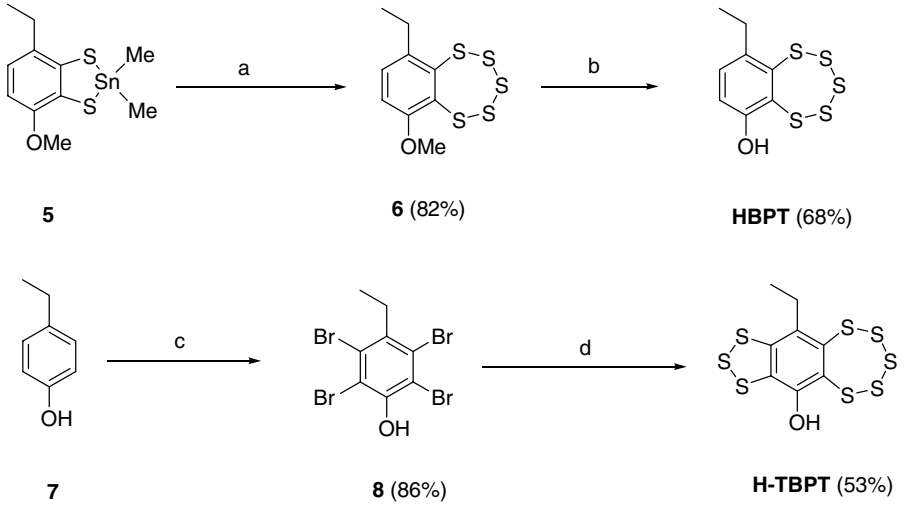
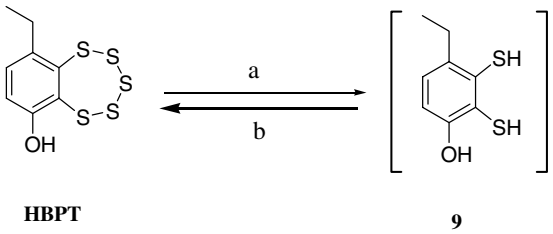


Scheme 1. Reagents and conditions: (a) S_2Cl_2, CH_2Cl_2, −78 °C, 12 h; (b) HBr, AcOH, reflux; (c) Br_2, Fe, CCl_4, rt, 18 h; (d) S_8/liquid NH_3, CH_2Cl_2, 120 °C, 24 h.

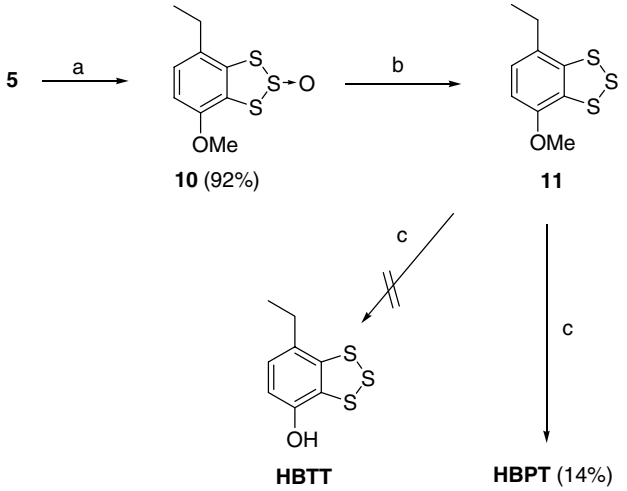
importance. The stability of benzopentathiepin ring regarding co-existence of polysulfide ring and hydroxyl group as neighbors and reactivity of hydroxyl group toward alkyl halides are also intriguing factors. Here, we report a new method for the synthesis benzopentathiepin having hydroxyl group at the neighboring position of pentathiepin ring including its reactivity toward various alkylting agents.

The synthesis was started from 4-ethyl-7-methoxy-2,2-dimethyl-1,3,2-benzodithiastannole (**5**) and respective route is illustrated in Scheme 1. Sulfurization of **5** in CH_2Cl_2 with S_2Cl_2 gave 6-ethyl-9-methoxybenzopentathiepin (**6**) in 82% yield.[8] Demethylation of **6** with HBr in AcOH under reflux afforded 6-ethyl-9-hydroxybenzopentathiepin (**HBPT**) in 68% yield, after chromatography. Mass spectra, IR and elemental analysis showed good agreement for the generation of both pentathiepin ring and hydroxyl group on benzene. So, pentathiepin having hydroxyl group is very stable under strong acidic condition. Introduction of a hydroxyl group on benzene having both trithiole and pentathiepin rings was carried out as follows. 4-Ethyl-1-hydroxybenzene (**7**) was brominated with Br_2 in CCl_4 at room temperature to give 4-ethyl-1-hydroxy-2,3,5,6-tetrabromobenzene[5c,d] (**8**) in 86% yield. A treatment of **8** with elemental sulfur in liquid NH_3 in titanium autoclave for 24 h afforded 6-ethyl-10-hydroxy[1,2,3]trithiolo[4,5-*h*]-benzopentathiepin (**H–TBPT**) in 53% yield.[5d]

Scheme 1 represents simple but fruitful methodologies for efficient production of **HBPT** and **H–TBPT**. These two products were unambiguously characterized by spectroscopic methods.[9,10] Generation of **HBPT** in high yield reveals that the methoxy group of **6** is easily demethylated by HBr but such demethylation does not interfere on the polysulfide ring. Reduction of **HBPT** with $NaBH_4$ in THF afforded 4-ethyl-1-hydroxy-2,3-benzenedithiol (**9**) and subsequent thiation of dithiol with S_8/NH_3 regenerated pentathiepin ring quantitatively (Scheme 2). Reversible reaction between dithiol and pentathiepin ring without interference of functional



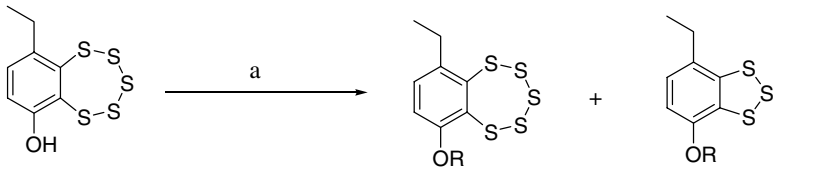
Scheme 2. Reagents and conditions: (a) $NaBH_4$, THF, H_3O^+; (b) S_8/NH_3, CH_2Cl_2, rt.



Scheme 3. Reagents and conditions: (a) $SOCl_2$, THF, 1 h, quant.; (b) NaI, $HClO_4$, THF, rt; (c) HBr/AcOH, reflux.

group emphasizes that **HBPT** has comparable stability as like as benzopentathiepin. Moreover, **HBPT** showed sufficient stability under strong acidic condition.

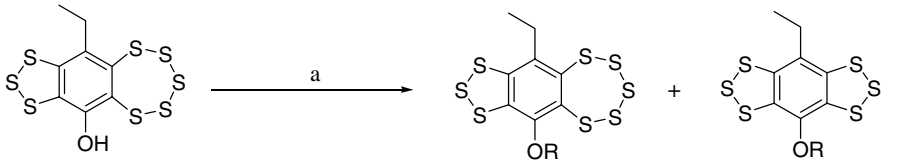
The attempt to get 4-ethyl-7-hydroxybenzotrithiole **(HBTT)** is described in Scheme 3. 4-Ethyl-7-methoxybenzotrithiole (**11**) was synthesized in 92% yield by an established procedures.[8,11] Demethylation of **11**



HBPT

6 (R = Me, 64%) **11** (R = Me, 11%)
12 (R = Et, 35%) **13** (R = Et, 28%)
14 (R = ^{i}Pr, 4%) **15** (R = ^{i}Pr, 6%)

Scheme 4. Reagents and conditions: (a) RI, K_2CO_3 (1.0 equiv), THF, reflux, rt.



H-TBPT

16 (R= CH_3, 84%) **17** (R = CH_3, Trace)
18 (R= $PhCH_2$, 78%) **19** (R= $PhCH_2$, Trace)

Scheme 5. Reagents and conditions: (a) RI, K_2CO_3 (2.0 equiv), THF, reflux, rt.

under the same reaction conditions did not give any **HBTT**, but surprisingly a small amount of **HBPT** was isolated. Since **HBTT** was not obtained experimentally, the ring opening occurred during the demethylation of **11**. It generated corresponding dithiolate dianion. An intermolecular sulfur rearrangement of dithiolate dianion gave stable **HBPT** in low yield (14%). Thus, the hydroxyl group stabilizes benzopentathiepin more rather than benzotrithiole.

Thermal stability of **6** was also checked by heating it in THF (neutral condition) under reflux for 24 h. The pentathiepin ring did not convert to trithiole, disulfide or others. Therefore, ethyl and methoxy groups of **6** also sterically do not effect on the stability of the pentathiepin ring.

Alkylation of **HBPT** was performed with alkyl iodides in the presence of 1 equiv of K_2CO_3 in THF and the results are summarized in Scheme 4. Generation of corresponding alkoxy benzopentathiepins reveals that the hydroxyl group is very active towards various electrophiles in the presence of a weak base. The presence of a base or electrophile generated some ring breaking side products. As the size of alkyl group increases, the comparative yields of alkoxybenzopentathiepins decreases and corresponding yields of alkoxybenzotrithioles increases. Thus, the ring contraction is not only for base or electrophile but also for steric hindrance arises by intramolecular interaction between the alkyl group and the polysulfide ring.

Finally, alkylation of **H–TBPT** was carried out in the presence of K_2CO_3 (Scheme 5). **H–TBPT** almost retained its ring system as the reaction mainly gave alkoxybenzopentathiepins together with a trace amount of ring contraction products **17** and **19**, which were identified by ^{1}H NMR. Such encouraging reactions of hydroxyl group significantly disclose that cyclic polysulfide of **H–TBPT** is more stable than that of **HBPT** and both compounds can be useful for condensation or other polymerization reactions.

In conclusion, two novel benzopentathiepin derivatives having hydroxyl group at the neighboring position of the pentathiepin ring were successfully synthesized by effective methods. The activity of the hydroxy group was examined by alkylation. Pentathiepins having hydroxyl group are promising starting materials for many reactions to get macromolecules containing polysulfide rings.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.109.

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9. *6-Ethyl-9-methoxybenzopentathiepin* (**6**):
Yellow crystals; mp 91.0–92.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, $J = 7.6$ Hz, 3H, CH_3), 2.82 (dq, $J = 7.6$, 13.9 Hz, 1H, CH_2), 2.93 (dq, $J = 7.6$, 13.9 Hz, 1H, CH_2), 3.87 (s, 3H, OCH_3), 6.91, (d, $J = 8.5$ Hz, 1H, ArH), 7.20 (d, $J = 8.5$ Hz, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.6, 29.1, 56.6, 114.2, 132.3, 132.5, 141.6, 145.2, 159.14; IR (KBr) 2960, 2924, 1576, 1543, 1460, 1263, 1236, 1222, 1177, 831, 785 cm^{-1}; MS (70 eV) *m*/*z* 294 (M^+); Anal. Calcd for $C_9H_{10}OS_5$: C, 36.70; H, 3.42. Found: C, 36.65; H, 3.42.
6-Ethyl-9-hydroxybenzopentathiepin (**HBPT**):
Pale yellow crystals; mp 70.0–70.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, $J = 7.5$ Hz, 3H, CH_3), 2.76 (dq, $J = 7.5$, 14.0 Hz, 1H, CH_2), 2.91 (dq, $J = 7.5$, 14.0 Hz, 1H, CH_2), 6.45 (s, 1H, OH), 6.97, (d, $J = 8.4$ Hz, 1H, ArH), 7.15 (d, $J = 8.4$ Hz, 1H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.68, 29.12, 118.66, 128.55, 133.55, 141.67, 143.46, 156.11; IR (KBr) 3422 cm^{-1} (OH); MS (70 eV) 280 *m*/*z* (M^+); Anal. Calcd for $C_8H_8OS_5$: C, 34.26; H, 2.87. Found: C, 34.10; H, 2.87.
4-Ethyl-1-hydroxy-2,3,5,6-tetrabromobenzene (**8**): Colorless crystals; mp 111.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, $J = 7.4$ Hz, 3H, CH_3), 3.19 (q, $J = 7.4$ Hz, 2H, CH_2), 6.10 (s, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.4, 34.1, 113.3, 126.1, 137.9, 149.4; IR (KBr) 3425 cm^{-1} (OH); MS (70 eV) *m*/*z* 422 (M^+−OH); Anal. Calcd for $C_8H_6Br_4O$: C, 21.95; H, 1.38. Found: C, 21.95; H, 1.45.
6-Ethyl-10-hydroxy[1,2,3]trithiolo[4,5-h]benzopentathiepin (**H–TBPT**): Red powder; mp 134.0–135.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, $J = 7.4$ Hz, 3H, CH_3), 2.89 (dq, $J = 7.4$, 14.8 Hz, 1H, CH_2), 2.99 (dq, $J = 7.4$, 14.8 Hz, 1H, CH_2),6.75 (s, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.8, 37.2, 122.0, 123.9, 131.1, 134.9, 138.5, 141.3; IR (KBr) 3421, 3401 cm^{-1} (OH); MS (70 eV) *m*/*z* 374 (M^+); Anal. Calcd for $C_8H_6OS_8$: C, 25.65; H, 1.61. Found: C, 25.61; H, 1.83.
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