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# SYNTHESIS AND THERMAL STABILITY OF SOME 1-BENZOTHIEPINS

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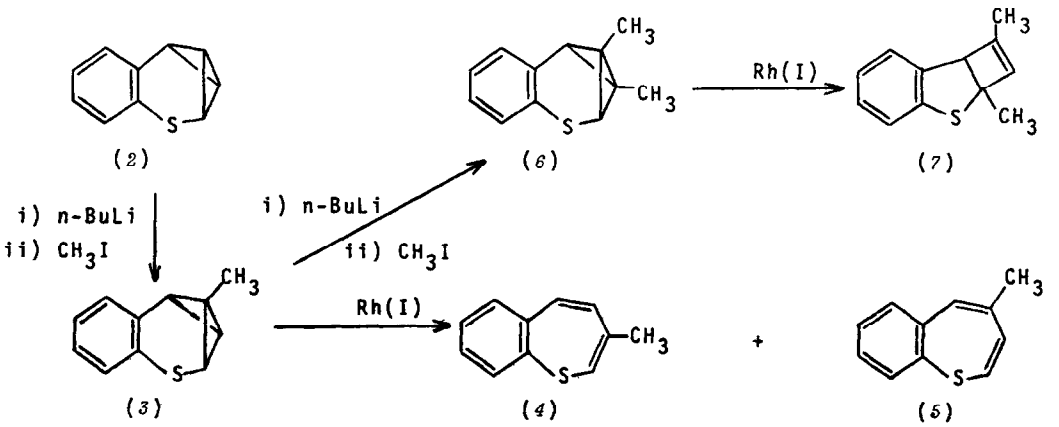
We have recently developed a novel approach to the synthesis of thermally labile 1-benzothiepin (*1*)[1] based on the rhodium complex promoted isomerization of 4,5-benzo-3-thiatricyclo[4.1.0.$0^{2,7}$]heptene (*2*).[2] This achievement, as well as the ease of introducing suitable substituent into the bridgehead position of the bicyclo[1.1.0]butane skeleton,[3] led immediately to attempt to apply this method to the synthesis of some 1-benzothiepin derivatives.

Treatment of *2* with *n*-BuLi in THF at -60°C [4] followed by quenching of the anion with methyl iodide gave 1-methyl-4,5-benzo-3-thiatricyclo[4.1.0.$0^{2,7}$]-heptene (*3*) in quantitative yield. Isomerization with $[Rh(CO)_2Cl]_2$ in chloroform at 0°C for 10 min afforded a mixture of 3-methyl- (*4*) and 4-methyl-1-benzothiepin (*5*) in a combined yield of 98% [ratio 1 : 1.3]. The separation of these isomers was rather tedious and proceeded by low temperature column chromatography on deactivated alumina containing 2.5% of water at -20°C (elution with pet. ether, bp <50°C).



For the synthesis of 3,4-dimethyl-1-benzothiepin, 1,7-dimethyl-4,5-benzo-3-thiatricyclo[4.1.0.0$^{2,7}$]heptene (*6*) was prepared by treatment of *3* with *n*-BuLi in THF and subsequently quenched with methyl iodide. However, when treated with $[Rh(CO)_2Cl]_2$ in chloroform, dimethyl derivative (*6*) unexpectedly exhibited a rearrangement to 1,6-dimethyl-3,4-benzo-2-thiabicyclo[3.2.0]hepta-3,6-diene (*7*), colorless liquid, $\lambda_{max}$(cyclohexane) 218 nm (log ε, 4.23), 255(s, 3.91), 258(3.92), 297(3.32), 305(3.27); NMR δ ($CCl_4$) 1.67(m, 6H, $CH_3$), 3.95(m, 1H, H-5, $J_{5,7}$=0.5 Hz), 5.84(dq, 1H, H-7, $J_{7,CH_3}$=1.7, $J_{7,5}$=0.5 Hz) and 6.88-7.14(m, 4H, arom.), exclusively. No dimethyl-1-benzothiepin could be detected in a reaction mixture.

Synthesis of the "peri" methyl substituted 1-benzothiepins, (*10*) and (*13*), was conveniently accomplished starting from 4-methylthiochrom-3-ene (*8*)[5] in good yields according to the following Scheme. Upon reaction with *n*-BuLi-$CH_2Cl_2$ complex in THF-ether-hexane (4:1:1) at -110°C,[2] the lithiated *8* underwent formation chiefly to 6-methyl-4,5-benzo-3-thiatricyclo[4.1.0.0$^{2,7}$]heptene (*9*) [25%] along with 5-methylbenzothiepin (*10*) [7%] and 5-methyl-3,4-benzo-2-thiabicyclo[3.2.0]-hepta-3,6-diene (*11*) [5%]. The structure of *11* follows from its spectral data [colorless liquid, $\lambda_{max}$(cyclohexane) 217(4.26), 221(s, 4.12), 239(3.78), 255(s, 3.85), 258(3.89), 263(s, 3.86), 296(3.27), 304(3.22); NMR δ ($CCl_4$) 1.62(s, 3H, $CH_3$), 4.18(dd, 1H, J=0.7, 0.4 Hz, H-1), 5.91(dd, 1H, J=2.8, 0.7 Hz, H-7), 6.14 (dd, 1H, J=2.8, 0.4 Hz, H-6), 6.91-7.13 (m, 4H, arom.)] and its ready formation from *10* by photoisomerization. Alternatively, the thiepin (*10*) was readily available as a sole product from $[Rh(CO)_2Cl]_2$ promoted isomerization of *9*. Following the same procedure, *9* was methylated with *n*-BuLi/$CH_3I$ at -60°C gave the dimethyl derivative (*12*) in almost quantitative yield. When *12* was treated with

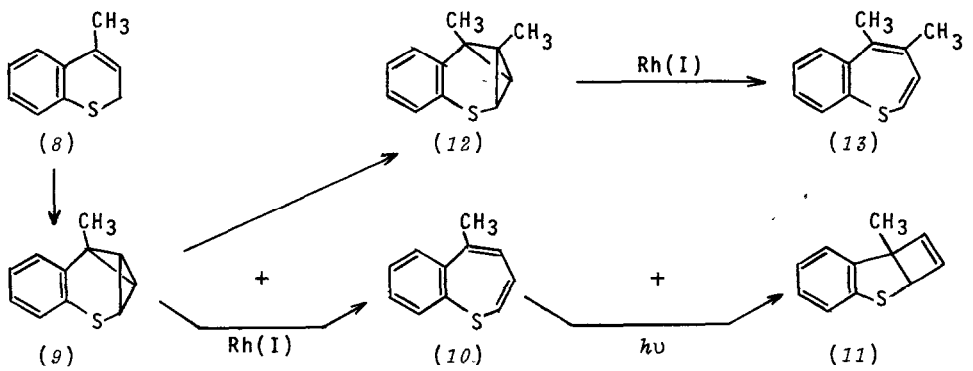


Table-1. Spectral Data of 4,5-Benzo-3-thiatricyclo[4.1.0.$0^{2,7}$]heptenes.

| | Appearance | UV $\lambda_{max}$ | NMR δ ppm (60 MHz, TMS) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | mp(°C) | nm(log ε) | $CH_3$ | $OCH_3$ | CHO | H-1,7 | H-2 | H-6 | arom. |
| 1-$CH_3$ (*3*) | colorless liquid | 224(4.16) 231(4.10) 274(3.86) | 1.70(s) | | | 1.65(t) J=2.5 | 3.44(dd) J=4.0 J=2.5 | 2.90(dd) J=4.0 J=2.5 | 6.65-7.07 (m, 4H) |
| 1,7-$(CH_3)_2$ (*6*) | colorless needless 31-32° | 226(4.09) 231(4.04) 277(3.87) | 1.52(s) | | | | 3.11(d) J=4.0 | 2.56(d) J=4.0 | 6.7-7.0 (m, 4H) |
| 6-$CH_3$ (*9*) | colorless prisms 16-17.5° | 222(4.12) 229(4.05) 272(3.91) | 1.41(s) | | | 1.69(d) J=2.9 | 3.55(t) J=2.9 | | 6.66-7.32 (m, 4H) |
| 1,6-$(CH_3)_2$ (*12*) | colorless liquid | 225(4.10) 231(4.04) 274(3.90) | 1.47(s) 1.62(s) | | | 1.54(d) J=2.8 | 3.42(d) J=2.8 | | 6.70-7.04 (m, 3H) 7.11-7.39 (m, 1H) |
| 1-$CO_2CH_3$ | pale yellow liquid | 224(4.31) 256(3.73) 276(3.91) | | 3.74(s) | | 2.58(t) J=3.3 | 4.25(dd) J=3.3 J=4.2 | 3.85(dd) J=3.3 J=4.2 | 6.79-7.35 (m, 4H) |
| 1-CHO | pale yellow liquid | 223(4.24) 259(3.81) 280(s, 3.52) | | | 9.73(s) | 2.73(t) J=3.3 | 4.35(dd) J=3.3 J=4.2 | 3.99(dd) J=3.3 J=4.2 | 6.83-7.34 (m, 4H) |

Table-2. Spectral Data of 1-Benzothiepins.

| | Appearance | UV $\lambda_{max}$ | NMR δ ppm (60 MHz, TMS) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | nm(log ε) | $CH_3$ | $OCH_3$ | CHO | H-2 | H-3 | H-4 | H-5 | arom. |
| 5-$CH_3$ (*10*) | pale yellow liquid | 217(4.20) 220(4.20) 257(4.08) 325(2.62) | 2.33 (b.s) | | | 5.75-6.05 (m) | 6.11-6.43 (m) | | | 7.17-7.35 (m,4H) |
| 4-$CH_3$ (*5*) | pale yellow liquid | 220(4.30) 226(4.26) 258(4.14) 336(2.61) | 2.05(d) J=1.3 | | | 5.89(d) J=8.7 | 6.21(d) J=8.7 | | 6.86 (b.s) | 7.01-7.33 (m,4H) |
| 3-$CH_3$ (*4*) | pale yellow liquid | 220(4.20) 226(4.16) 259(4.11) 342(2.41) | 1.91(d) J=1.2 | | | 5.61 (b.s) | | 6.31(d) J=11.8 | 6.92(d) J=11.8 | 7.02-7.34 (m,4H) |
| 4,5-$(CH_3)_2$ (*13*) | pale yellow liquid | 222(4.26) 229(4.21) 257(4.07) 330(s,2.66) | 1.98 (b.s) 2.28 | | | 6.03(d) J=8.7 | 6.19(dq) J=8.7 J=1.9 | | | 7.15 7.32 (m,4H) |
| 4-$CO_2CH_3$ | | | | 3.88(s) | | 6.15(d) J=9.2 | 7.03(d) J=9.2 | | 8.36 (b.s) | 7.2-7.6 (m,4H) |
| 4-CHO | | | | | 9.66(s) | 6.16(d) J=9.2 | 6.90(d) J=9.2 | | 7.81 (b.s) | 7.1-7.5 (m,4H) |

$[Rh(CO)_2Cl]_2$ in $CHCl_3$, isomerization occured with exclusive formation of *13*.

The synthesis of 4-methoxycarbonyl- and 4-formyl-1-benzothiepins was achieved by the procedure involving conversion of 1-lithiated compound of *2* to the corresponding thiatricycloheptenes by treatment with methyl chloroformate and ethyl formate, respectively and isomerization of these compounds with $[Rh(CO)_2Cl]_2$ in chloroform. Owing to the rapid rate of sulfur extrusion, these thiepins were obtained only in impure forms contaminated by the corresponding naphthalenes. The structures of the bicyclobutane derivatives and the thiepins described in this paper were unambiguously confirmed from their spectroscopic data summarized in Table-1 and 2, respectively.

The 1-benzothiepins obtained are thermally unstable and can be converted in $CCl_4$ to give the corresponding naphthalenes. The course of the reaction was monitored by $^1$H-NMR spectroscopy and the half-lives measured at 47°C are listed in Table-3. Inspection of the data of Table-3 indicates that, in contrast to the recent observation by Reinhoudt and Kowenhoven,[6] the thiepin system is stabilized by electron-donating methyl group (except for *13*) and destabilized by electron-withdrawing formyl group.[7]

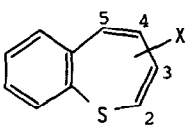



Table-3. Half-lives of 1-Benzothiepins at 47°C

| | 3-methyl X=3-$CH_3$ (*4*) | 5-methyl X=5-$CH_3$ (*10*) | 4-methyl X=4-$CH_3$ (*5*) | parent X=H (*1*) | 4-formyl X=4-CHO | 4,5-dimethyl X=4,5-$(CH_3)_2$ (*13*) |
|---|---|---|---|---|---|---|
| $t_{1/2}$ : | 100 min | 67 min | 62 min | 58 min | 49 min | 37 min |

REFERENCES AND FOOTNOTES

1) I. Murata, T. Tatsuoka, and Y. Sugihara, *Angew. Chem.*, 86, 161(1974); *Angew. Chem. internat. Ed.*, 13, 142(1974).

2) I. Murata, T. Tatsuoka, and Y. Sugihara, *Tetrahedron Lett.*, 4261(1973).

3) G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, 85, 2022(1963); L. A. Paquette and G. Zon, *ibid.*, 96, 203(1974).

4) When the lithiation was performed at somewhat higher temperature such as 0°C, rearrangement occurred with formation of 6-methyl-3,4-benzo-2-thiabicyclo[3.2.0]hepta-3,6-diene after quenching with methyl iodide.

5) F. Krollpfeiffer, H. Schultze, E. Schlumbohm, and E. Sommermeyer, *Ber.*, 58, 1654(1925); B. D. Tilak and V. M. Vaidya, *Tetrahedron Lett.*, 487(1963).

6) D. N. Reinhoudt and C. G. Kouwenhoven, *Chem. Comman.*, 1232, 1233(1972).

7) Satisfactory elemental analyses for all new compounds were obtained.