SYNTHESIS AND PROPERTIES OF DERIVATIVES OF CYCLOPENTA[b]PYRAN AND CYCLOPENTA[b]THIAPYRAN ISOELECTRONIC WITH AZULENE

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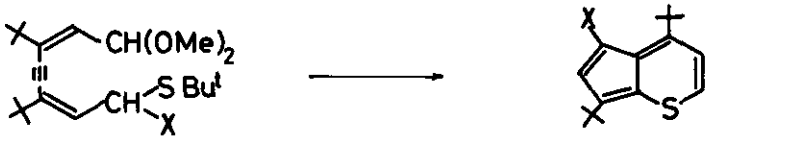
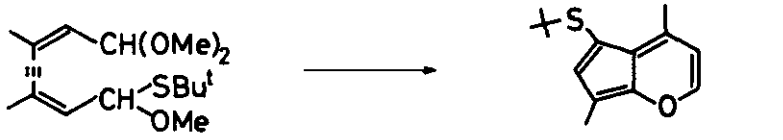
Abstract — Cyclopenta[b]pyran and cyclopenta[b]thiapyran derivatives isoelectronic with azulene have been synthesized by intramolecular cyclization of substituted octadienyne-dials. The cyclization reaction of octadienyne-dials proceeds regio-specifically and the formation of cyclopenta[b]pyrans and/or cyclopenta[b]thiapyrans depends on a subtle variety of the reaction conditions.

Recently we have reported the formation of cyclopenta[b]thiapyran derivatives (3 and 4) and cyclopenta[b]pyran (5) by acid-catalyzed intramolecular cyclization[1]. The results of the X-ray structure analysis of 4 showed the delocalized structure of cyclopenta[b]thiapyran with peripheral 10π-electron system[2].
In order to clarify the mechanism of this interesting cyclization reaction and to get further information on the properties of these azulene analogues, we have carried out the cyclization of octadienyne-dials bearing different substituent groups.



1: X=OMe, 2: X=SBu^t　　3: X=OMe, 4: X=SBu^t



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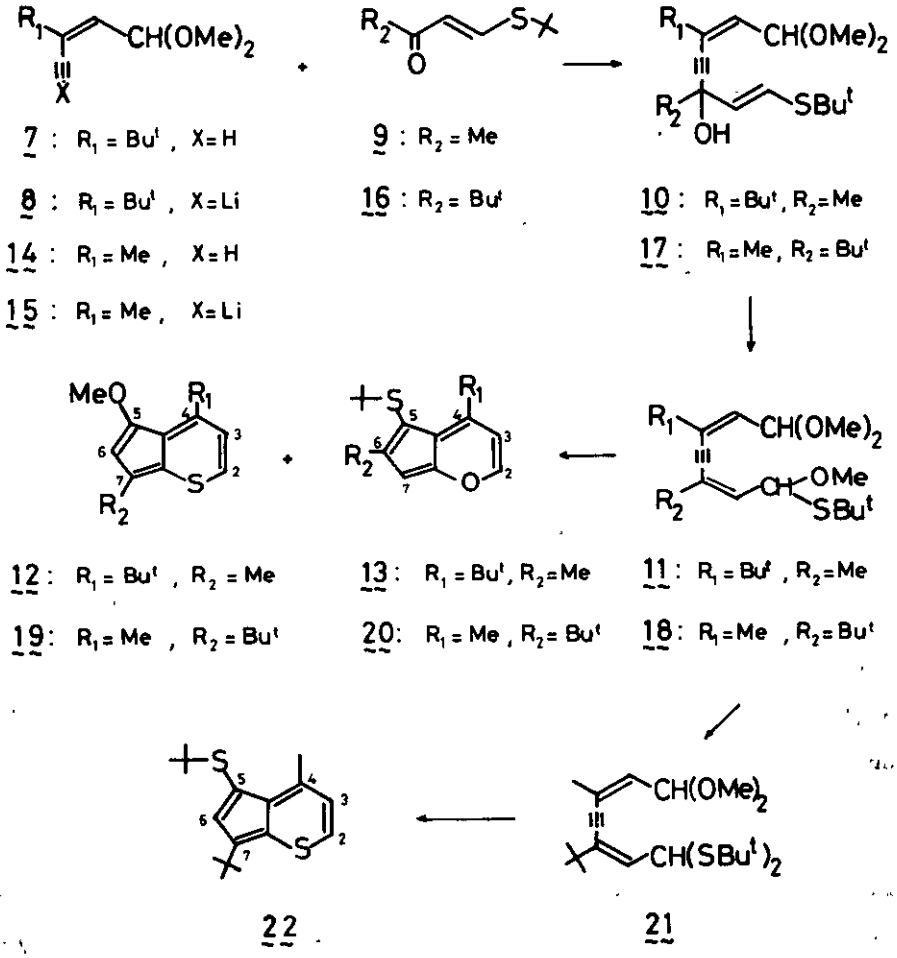
We have prepared two isomeric *t*-butyl methyl derivatives (Scheme 1). The *t*-butyl substituted enynaldehyde dimethyl acetal (7)[3] was treated with *n*-BuLi to give the lithio derivative (8). The reaction of 8 with methyl thiovinyl ketone (9)[4] gave the hydroxy acetal (10, yellow viscous oil, 93%). Treatment of 10 (6.46 mmol) with CF_3COOH (1 ml) - $CH(OMe)_3$ (50 ml) at -15°C for 2 h gave the acetal-hemithioacetal (11, pale yellow viscous oil, 89%). Cyclization of 11 (1.6 mmol) with CF_3COOH (2.5 ml) - $CH(OMe)_3$ (10 ml) - CH_2Cl_2 (50 ml) at -15°C for *20 min* gave 4-*t*-butyl-5-methoxy-7-methylcyclopenta[b]thiapyran (12, relatively stable deep blue plates, mp 66.7 ∿ 69.3°C[5], 27%; Mass(m/e): 234 (M^+), 219; ^1H NMR (CCl_4-acetone-d_6) δ 7.50 d (J=10.0, H_2), 7.07 d (J=10.0, H_3), 6.32 s (H_6), 3.86 s (OCH_3), 2.22 s (CH_3), 1.50 s (*t*-Bu); UV: $\lambda_{max}^{cyclohexane}$ (ε) 268.5 (14,200), 351.5 sh (3,600), 363 (4,200), 375.5 sh (2,950), 633 (624), 670 sh (589) nm). On the other hand, similar treatment of 11 (1.7 mmol) with CF_3COOH (1 ml) - $CH(OMe)_3$ (25 ml) - CH_2Cl_2 (25 ml) at -50 ∿ 0°C yielded 0.5% of 4-*t*-butyl-5-*t*-butylthio-6-methylcyclopenta-[b]pyran (13) as deep red needles, mp 72.6 ∿ 75.2°C; Mass(m/e): 276 (M^+), 219, 187; ^1H NMR (CD_2Cl_2) δ 7.66 d (J=5.5, H_2), 6.62 d (J=5.5, H_3), 6.18 s (H_7), 2.54 s (CH_3), 1.64 s (*t*-Bu), 1.12 (S-*t*-Bu), but none of the thiapyran (12).

The reaction of the lithio derivative (15) derived from 3-methyl-2-penten-4-yn-1-al dimethyl acetal (14)[6] with *t*-butyl thiovinyl ketone (16)[1] afforded the isomeric hydroxy acetal (17, yellow viscous oil, 93%). The similar treatment of 17 (8.55 mmol) with CF_3COOH (1.5 ml) - $CH(OMe)_3$ (50 ml) at -15°C for 1.5 h gave a mixture of 18 and 20, which were separated by a column chromatography on alumina: 18, yellow viscous oil, 83%; 6-*t*-butyl-5-*t*-butylthio-4-methylcyclopenta[b]pyran (20, stable red plates, mp 70.9 ∿ 73.1°C[5], 1.5%; Mass(m/e) 276 (M^+), 219; ^1H NMR (CD_2Cl_2) δ 7.59 d (J=5.0, H_2), 6.23 s (H_7), 6.20 d (J=5.0, H_3), 2.95 s (CH_3), 1.49 s (*t*-Bu), 1.20 s (S-*t*-Bu); UV: $\lambda_{max}^{cyclohexane}$ (ε) 234 sh (10,600), 268.5 (12,500), 327.5 (10,400), 476.5 (701) nm). Cyclization of 18 (1.58 mmol) with CF_3COOH (2.5 ml) - $CH(OMe)_3$ (10 ml) - CH_2Cl_2 (50 ml) at -15°C for 20 min gave 7-*t*-butyl-5-methoxy-4-methylcyclopenta[b]thiapyran (19, stable deep blue plates, mp 95.5 ∿ 96.7°C[5], 49%; Mass(m/e): 234 (M^+), 219; ^1H NMR (CCl_4-acetone-d_6) δ 7.32 d (J=9.0, H_2), 6.61 d (J=9.0, H_3), 6.23 s (H_6), 3.81 s (OCH_3), 2.64 s (CH_3), 1.38 s (S-*t*-Bu); UV: $\lambda_{max}^{cyclohexane}$ (ε) 225.5 sh (12,000), 270 sh (12,600), 283 (13,300), 346.5 sh (2,930), 353 (3,140), 367.5 sh (2.280), 599 (620) nm) along with a trace amount of 20. The cyclopenta[b]pyran (20) could be obtained as a main product (17%) on treatment of 18 (1.55 mmol) with CF_3COOH (1 ml) - $CH(OMe)_3$ (25 ml) - CH_2Cl_2 (25 ml)

at -60 ∿ 0°C, and 0.3% of 19 was also obtained as a minor product.

In addition, reaction of 17 (3.82 mmol) with CF_3COOH (1 ml) - $CH(OMe)_3$ (5 ml) - CH_2Cl_2 (5 ml) in the presence of *t*-butyl mercaptan at -50 ∿ -15°C gave the acetal-thioacetal (21, yellow viscous oil, 48%). Cyclization of 21 (1.7 mmol) with CF_3COOH (4 ml) - $CH(OMe)_3$ (5 ml) - CH_2Cl_2 (50 ml) yielded 7-*t*-butyl-5-*t*-butylthio-4-methylcyclopenta[b]thiapyran (22, stable deep blue prisms, mp 105.2 ∿ 107.6°C[5], 66%; Mass(m/e): 292 (M^+), 236, 235; ^1H NMR (acetone-d_6) δ 8.04 d (J=9.0, H_2), 7.40 s (H_6), 7.17 d (J=9.0, H_3), 3.18 s (CH_3), 1.47 s (*t*-Bu), 1.20 s (S-*t*-Bu); UV: $\lambda_{max}^{cyclohexane}$ (ε) 224.5 (17,400), 289.5 (18,900), 294.5 sh (16,800), 349 (4,240), 556.5 (1,210) nm).



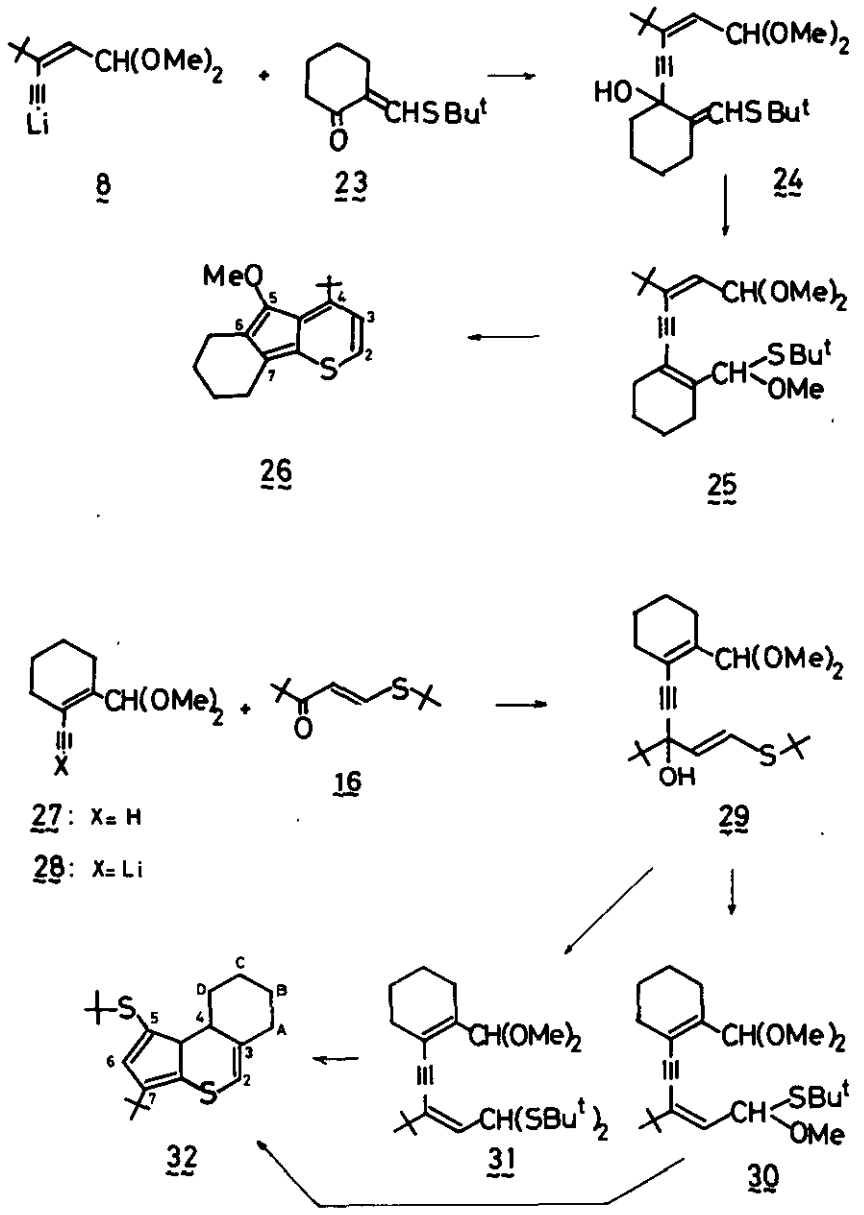
Scheme 1

From these results, the cyclization reaction of the octadienyne-dials bearing *t*-butyl and methyl groups was found to be regiospecific and the formation of cyclopenta[b]pyrans and/or cyclopenta[b]thiapyrans depends on a subtle variety of the reaction conditions. In the case of 11 and 18, the use of larger amounts of CF_3COOH and smaller amounts of $CH(OMe)_3$ leads to the formation of cyclopenta[b]-thiapyrans (12 and 19), whereas cyclopenta[b]pyrans (13 and 20) are formed by using smaller amounts of CF_3COOH and larger amounts of $CH(OMe)_3$.

In order to obtain further information regarding the mode of cyclization, the same reaction of octadienyne-dial derivatives containing cyclohexene ring was examined (Scheme 2). The reaction of the lithio derivative (8) with 2-*t*-butylthiomethylene cyclohexanone (23)[7] gave the hydroxy acetal (24, pale yellow oil, 95%). The hydroxy acetal (24) was converted into the acetal-hemithioacetal (25, pale yellow viscous oil, 82%) in the same manner as 10. Cyclization of 25 with CF_3COOH-$CH(OMe)_3$-CH_2Cl_2 gave only the cyclopenta[b]thiapyran derivative (26). The thiapyran (26) formed relatively stable deep blue plates which decomposed during thin-layer chromatography on alumina or silica gel (26, mp 102.3 ∿ 103.4°C, 35%; Mass (m/e): 274 (M^+), 259; ^1H NMR (CCl_4-acetone-d_6) δ 7.62 d (J=9.5, H_2), 7.21 d (J=9.5, H_3), 3.88 s (OCH_3), 2.97 ∿ 2.56 m (allylic CH_2), 1.89 ∿ 1.55 m (non-allylic CH_2), 1.54 s (*t*-Bu); UV: $\lambda_{max}^{cyclohexane}$ (ε) 239.5 (13,300), 283 (14,000), 356 sh (5.330), 361 (6,980), 387 (4,930), 609 (566) nm). Treatment of 27[8] with *n*-BuLi followed by reaction with 16 led to the hydroxy acetal (29, yellow viscous oil, 98%), which was converted into the acetal-hemithioacetal (30, yellow viscous oil, 69%). Under the similar reaction conditions used for 25, 30 did not yield methoxy derivative, but small amounts of *t*-butylthio derivative (32, stable blue prisms, mp 114.8 ∿ 115.9°C, 2%, Mass(m/e): 332 (M^+), 275; ^1H NMR (CCl_4-acetone-d_6) δ 2.44 br.s (H_2), 2.71 s (H_6), 5.95 ∿ 6.09 m (H_D), 7.06 ∿ 7.19 m (H_A), 8.08 ∿ 8.25 m (H_B, H_C), 8.54 s (*t*-Bu), 8.82 s (S-*t*-Bu); UV: $\lambda_{max}^{cyclohexane}$ (ε) 217 (19,900), 242.5 sh (13,200), 293.5 (17,300), 353 (4,930), 574.5 (1,240) nm) was obtained. The thiapyran derivative (32) could be obtained as a main product from the acetal-thioacetal (31) derived from 29[9].

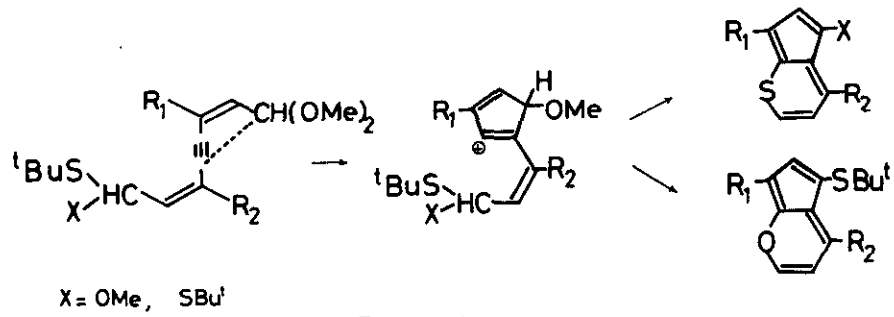
Thus, the formation of cyclopenta[b]thiapyrans and/or cyclopenta[b]pyrans in the acid-catalyzed intramolecular cyclization is influenced by the alkyl substituent groups of the octadienyne-dial derivatives. The cyclization leads to cyclopenta-[b]pyran (6) when alkyl groups are two methyl substituents (*i.e.*, 5), whereas cyclopenta[b]thiapyrans (3, 4, 26, and 32) are formed when octadienyne-dials bear

two *t*-butyl groups or *t*-butyl group and cyclohexene ring (*i.e.*, 1, 2, 25, 30, and 31). The methyl and *t*-butyl substituted octadienyne-dials (11 and 18) afford both cyclopenta[b]thiapyrans (12 and 19) and cyclopenta[b]pyrans (13 and 20).

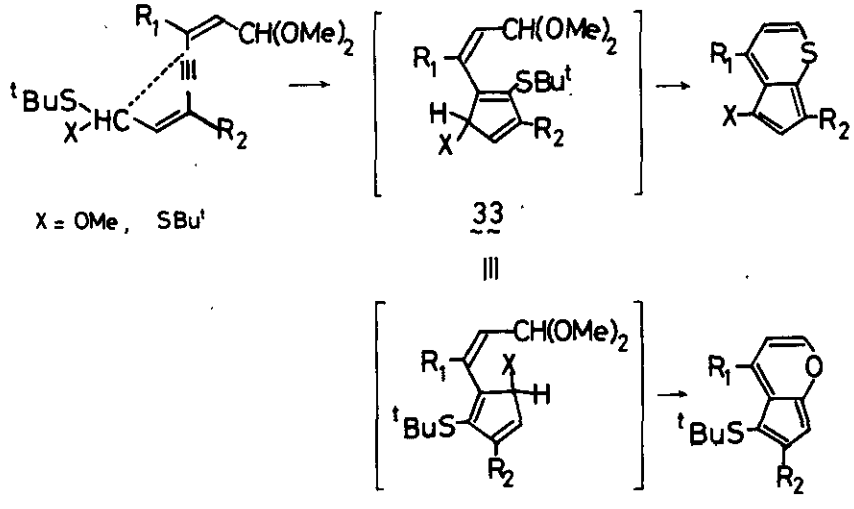


Scheme 2

The mechanism of these reactions is not yet completely investigated. A possible pathway is the formation of a five-membered ring with acetal group participation, followed by cyclization to cyclopenta[b]thiapyran and cyclopenta[b]pyran (Path A). However, this path cannot explain the orientation of alkyl groups of cyclopenta-[b]thiapyrans (12, 19, 22, 26, and 32) and the formation of 3,5-dialkyl substituted cyclopenta[b]pyrans (6, 13, and 20). To explain the above-mentioned results, we assumed tentatively the formation of an intermediate (33) having cyclopentadiene structure which is formed accompanying a rearrangement of *t*-butylthio group (Path B). Cyclization of 33 with sulfur or oxygen forms cyclopenta[b]thiapyran or



Path A



Path B

cyclopenta[b]pyran. Further experiments are in progress to elucidate the specific pathways of these interesting novel cyclization reactions.

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References and Notes

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6) For 3-methyl-2-penten-4-yn-1-al, see, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc., 1946, 937; I. Heilbron, E. R. H. Jones, and M. Julia, ibid., 1949, 1430.

7) 2-*t*-Butylthiomethylene cyclohexanone (23) was prepared by the reaction of hydroxymethylene cyclohexanone with *t*-butylmercaptan in 56% yield. 23, colorless prisms, mp 58.4 ∿ 60.3 °C. For hydroxymethylene cyclohexanone, see, C. Ainsworth, Org. Synth., Coll. Vol. IV, 1963, 536.

8) For 2-ethynyl-1-cyclohexenecarboxaldehyde, see, P. Schiess, H. L. Chia, and C. Suter, Tetrahedron Lett., 1968, 5747; G. M. Pilling and F. Sondheimer, J. Am. Chem. Soc., 1971, 93, 1970.

9) The hydroxy acetal (29) was converted into the acetal-thioacetal (31) with CF_3COOH-*t*-BuSH-$CH(OMe)_3$-CH_2Cl_2 at -60 ∿ -50°C for 50 min. 31, yellow viscous oil, 34%. Cyclization of 31 with CF_3COOH-$CH(OMe)_3$-CH_2Cl_2 at -15°C for 1h gave the thiapyran (32) in 28% yield.

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