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 regiospecifically 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. The results of the X-ray structure analysis of 4 showed the delocalized structure of cyclopenta[b]thiapyran with peripheral 10π-electron system. 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.

\[ \text{CH(O\text{Me})}_2 \text{CH}_{\text{S Bu}^t} \text{CH} \rightarrow \text{X} \]

1: \( x = \text{OMe} \), 2: \( x = \text{S Bu}^t \)

\[ \text{CH(O\text{Me})}_2 \text{CH}_{\text{S Bu}^t} \text{CH} \rightarrow \text{X} \]

3: \( x = \text{OMe} \), 4: \( x = \text{S Bu}^t \)

\[ \text{CH(O\text{Me})}_2 \text{CH}_{\text{S Bu}^t} \text{CH} \rightarrow \text{X} \]

5: 6
We have prepared two isomeric t-butyl methyl derivatives (Scheme 1). The t-butyl substituted enynaldehyde dimethyl acetal (\(\text{I}^3\)) was treated with \(\text{n-BuLi}\) to give the lithio derivative (\(\text{II}\)). The reaction of \(\text{II}\) with methyl thiovinyl ketone (\(\text{II}^1\)) gave the hydroxy acetal (\(\text{III}\), yellow viscous oil, 93%). Treatment of \(\text{III}\) (6.46 mmol) with \(\text{CF}_3\text{COOH}\) (1 ml) - \(\text{CH(OMe)}_3\) (50 ml) at -15°C for 2 h gave the acetal-hemithioacetal (\(\text{IV}\), pale yellow viscous oil, 89%). Cyclization of \(\text{IV}\) (1.6 mmol) with \(\text{CF}_3\text{COOH}\) (2.5 ml) - \(\text{CH(OMe)}_3\) (10 ml) - \(\text{CH}_2\text{Cl}_2\) (50 ml) at -15°C for 20 min gave 4-t-butyl-5-methoxy-7-methylcyclpent[a]thiapyran (\(\text{V}\), relatively stable deep blue plates, mp 66.7 - 69.3°C, 27%; Mass (m/e): 234 (M\(^+\)), 219; \(\text{\textsuperscript{1}H NMR}\) (\(\text{CDCl}_3\)) \(\delta\) 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: \(\lambda_{\text{max}}^{\text{cyclohexane}}\) (e) 268.5 (14,200), 351.5 sh (3,600), 327.5 (10,400), 599 (620) nm). On the other hand, similar treatment of \(\text{V}\) (1.71 mmol) with \(\text{CF}_3\text{COOH}\) (1 ml) - \(\text{CH(OMe)}_3\) (25 ml) - \(\text{CH}_2\text{Cl}_2\) (25 ml) at -50°C yielded 0.5% of 4-t-butyl-5-t-butylthio-6-methylcyclpent[a]thiapyran (\(\text{VI}\) as deep red needles, mp 72.6 - 75.2°C; Mass (m/e): 276 (M\(^+\)), 219, 187; \(\text{\textsuperscript{1}H NMR}\) (\(\text{CDCl}_3\)) \(\delta\) 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 (\(\text{VII}\)). The reaction of the lithio derivative (\(\text{II}^1\)) derived from 3-methyl-2-penten-4-yn-1-al dimethyl acetal (\(\text{II}^6\)) with t-butyl thiovinyl ketone (\(\text{II}^1\)) afforded the isomeric hydroxy acetal (\(\text{IV}\), yellow viscous oil, 93%). The similar treatment of \(\text{IV}\) (8.55 mmol) with \(\text{CF}_3\text{COOH}\) (1.5 ml) - \(\text{CH(OMe)}_3\) (50 ml) at -15°C for 1.5 h gave a mixture of \(\text{IV}\) and \(\text{VII}\), which were separated by a column chromatography on alumina: \(\text{IV}\), yellow viscous oil, 83%; 6-t-butyl-5-t-butylthio-4-methylcyclpent[a]thiapyran (\(\text{VIII}\) stable red plates, mp 70.9 - 73.1°C, 1.5%; Mass (m/e): 276 (M\(^+\)), 219; \(\text{\textsuperscript{1}H NMR}\) (\(\text{CD}_2\text{Cl}_2\)) \(\delta\) 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); UV: \(\lambda_{\text{max}}^{\text{cyclohexane}}\) (e) 234 sh (10,600), 268.5 (12,500), 327.5 (10,400), 476.5 (701) nm). Cyclization of \(\text{IV}\) (1.58 mmol) with \(\text{CF}_3\text{COOH}\) (2.5 ml) - \(\text{CH(OMe)}_3\) (10 ml) - \(\text{CH}_2\text{Cl}_2\) (50 ml) at -15°C for 20 min gave 7-t-butyl-5-methoxy-4-methylcyclpent[a]thiapyran (\(\text{VIII}\), stable deep blue plates, mp 95.5 - 96.7°C, 49%; Mass (m/e): 234 (M\(^+\)), 219; \(\text{\textsuperscript{1}H NMR}\) (\(\text{CDCl}_3\)) \(\delta\) 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: \(\lambda_{\text{max}}^{\text{cyclohexane}}\) (e) 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 \(\text{VII}\). The cyclopenta[b]pyran (\(\text{X}\)) could be obtained as a main product (17%) on treatment of \(\text{IV}\) (1.55 mmol) with \(\text{CF}_3\text{COOH}\) (1 ml) - \(\text{CH(OMe)}_3\) (25 ml) - \(\text{CH}_2\text{Cl}_2\) (25 ml)
at -60 °C, and 0.3% of 18 was also obtained as a minor product.

In addition, reaction of 18 (3.82 mmol) with CF₃COOH (1 ml) - CH(OMe)₃ (5 ml) - CH₂Cl₂ (5 ml) in the presence of t-butyl mercaptan at -50 °C gave the acetal-thioacetal (24, yellow viscous oil, 48%). Cyclization of 25 (1.7 mmol) with CF₃COOH (4 ml) - CH(OMe)₃ (5 ml) - CH₂Cl₂ (50 ml) yielded 7-t-butyl-5-t-butylthio-4-methylcyclopenta[b]thiapyran (26, stable deep blue prisms, mp 105.2 - 107.6 °C), 66%; Mass (m/e): 292 (M⁺), 236, 235; ¹H NMR (acetone-d₆) δ 8.04 d (J=9.0, H₂), 7.40 s (H₆), 7.17 d (J=9.0, H₃), 3.18 s (CH₃), 1.47 s (t-Bu), 1.20 s (S-t-Bu); UV: λcyclohexane (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 $\text{I}_4$ and $\text{I}_6$, the use of larger amounts of $\text{CF}_3\text{COOH}$ and smaller amounts of $\text{CH(O Me)}_3$ leads to the formation of cyclopenta[b]thiapyrans ($\text{I}_6$, $\text{I}_7$, and $\text{I}_9$), whereas cyclopenta[b]pyrans ($\text{I}_3$ and $\text{I}_0$) are formed by using smaller amounts of $\text{CF}_3\text{COOH}$ and larger amounts of $\text{CH(O Me)}_3$.

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 ($\text{I}_8$) with 2-t-butylthiomethylene cyclohexanone ($\text{I}_7$) gave the hydroxy acetal ($\text{I}_{24}$, pale yellow oil, 95%). The hydroxy acetal ($\text{I}_{24}$) was converted into the acetal-hemithioacetal ($\text{I}_{25}$, pale yellow viscous oil, 82%) in the same manner as $\text{I}_{10}$. Cyclization of $\text{I}_{25}$ with $\text{CF}_3\text{COOH}$-$\text{CH(O Me)}_3$-$\text{CH}_2\text{Cl}_2$ gave only the cyclopenta[b]thiapyran derivative ($\text{I}_{26}$). The thiapyran ($\text{I}_{26}$) formed relatively stable deep blue plates which decomposed during thin-layer chromatography on alumina or silica gel ($\text{I}_{26}$, mp 102.3-103.4°C, 35%; Mass (m/e): 274 (M$^+$), 259; $^1$H NMR (CCl$_4$-acetone-d$_6$) δ 7.62 (J=9.5, H$_2$), 7.21 d (J=9.5, H$_3$), 3.88 s (OCH$_3$), 1.89 s (OCH$_3$), 1.54 s (t-Bu); UV: $\lambda_{\text{cyclohexane}}$ (ε) 239.5 (13,300), 283 (14,000), 356 sh (5.330), 361 (6,980), 387 (4,930), 609 (566) nm). Treatment of $\text{I}_{27}^8$ with $\text{n-BuLi}$ followed by reaction with $\text{I}_6$ led to the hydroxy acetal ($\text{I}_{28}$, yellow viscous oil, 98%), which was converted into the acetal-hemithioacetal ($\text{I}_{29}$, yellow viscous oil, 69%). Under the similar reaction conditions used for $\text{I}_{27}$, $\text{I}_{30}$ did not yield methoxy derivative, but small amounts of t-butylthio derivative ($\text{I}_{24}$, stable blue prisms, mp 114.8-115.9°C, 2%, Mass (m/e): 332 (M$^+$), 275; $^1$H 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: $\lambda_{\text{cyclohexane}}$ (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 ($\text{I}_{26}$) could be obtained as a main product from the acetal-hemithioacetal ($\text{I}_{31}$) derived from $\text{I}_{26}$.$^9$

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 ($\text{I}_3$) when alkyl groups are two methyl substituents (i.e., $\text{I}_0$), whereas cyclopenta[b]thiapyrans ($\text{I}_2$, $\text{I}_4$, $\text{I}_{26}$, and $\text{I}_{27}$) are formed when octadienyne-dials bear
two t-butyl groups or t-butyl group and cyclohexene ring (i.e., $^{1}$, $^{2}$, $^{3}$, $^{4}$, and $^{5}$). The methyl and t-butyl substituted octadiene-dials ($^{11}$ and $^{18}$) afford both cyclopenta[b]thiapyrans ($^{12}$ and $^{19}$) and cyclopenta[b]pyrans ($^{13}$ and $^{20}$).

Scheme 2

\[ \text{Scheme 2} \]
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 (1, 2, 3, and 4) and the formation of 3,5-dialkyl substituted cyclopenta[b]pyrans (5, 6, and 7). To explain the above-mentioned results, we assumed tentatively the formation of an intermediate (3) having cyclopenta-diene structure which is formed accompanying a rearrangement of t-butylthio group (Path B). Cyclization of (3) with sulfur or oxygen forms cyclopenta[b]thiapyran or

Path A

Path B
cyclopentalbpyran. Further experiments are in progress to elucidate the specific pathways of these interesting novel cyclization reactions.

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References and Notes
5) A satisfactory elemental analysis was obtained.
7) 2-t-Butylthiomethylene cyclohexanone (23) was prepared by the reaction of hydroxymethylene cyclohexanone with t-butylmercaptan in 56% yield. 23, colourless prisms, mp 58.4-60.3 °C. For hydroxymethylene cyclohexanone, see, C. Ainsworth, Org. Synth., Coll. Vol. IV, 1963, 536.
9) The hydroxy acetal (29) was converted into the acetal-thioacetal (31) with CF3COOH-t-BuSH-CH(OMe)3-CH2Cl2 at -60 to -50 °C for 50 min. 31, yellow viscous oil, 34%. Cyclization of 31 with CF3COOH-CH(OMe)3-CH2Cl2 at -15 °C for 1h gave the thiapyran (28) in 28% yield.

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