SYNTHESIS OF SOME OXAZOLIN-5-ONE-4-SPIRO-1'-CYCLOPROPANES HAVING FUNCTIONAL GROUPS AND THEIR THERMAL REARRANGEMENTS

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Abstract — 4-Cycloalkylidene-2-phenyl-2-oxazolin-5-ones reacted with carbonyl-stabilized sulfur methylides to give the corresponding dispiro compounds, which on heating were converted into retro-ene reaction products. The reaction of 4-cinnamylidene-2-phenyl-2-oxazolin-5-one with sulfur allylides afforded the Cope rearrangement products, accompanied by a spiro-cis-divinylcyclopropane in a certain case.

Recently, we have reported the cyclopropanation of 4-methylene-2-phenyl-2-oxazolin-5-ones with dimethylsulfonium phenacylide leading to the formation of two stereoisomeric oxazolin-5-one-4-spiro-1'-cis disubstituted cyclopropanes which are precursors for biologically interesting cyclopropyllogs of α-amino acids. This result is a great contrast to the formation of cis and trans isomers, or a single cis isomer in the cyclopropanation of 3-arylmethyleneindolin-2-ones, or 4-arylmethylene-2-isoxazolin-5-ones with the phenacylide, respectively.

As an extension of the above reaction, we planned to investigate the synthesis of analogous spirocyclopropanes bearing appropriate functional groups favoring a thermal rearrangement of the cyclopropane skeleton, because rearranged products are also possible to be transformed into novel α-amino acid derivatives. In this communication we wish to report the synthesis of some such spirocyclopropanes and their thermal rearrangements.

Oxazolin-5-one-4,1'-spirocyclopropane-2',1''-spirocycloalkanes (dispiro compounds). First, we have investigated the synthesis of the above dispiro compounds by the reaction of 4-cycloalkylidene-

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2-phenyl-2-oxazolin-5-ones \( \text{I} \) with carbonyl-stabilized sulfur methylides. 4-Cyclohexylidene- (Ia) or 4-cycloheptylidene-2-phenyl-2-oxazolin-5-one (Ib) reacted with dimethylsulfonium phenacylide, generated in situ from dimethylphenacylsulfonium bromide and sodium hydride, in dry THF at 0°C for 5 h to give the corresponding dispiro compound 2a or 2b as the single product in 84 or 35% yield, respectively. Two stereoisomers, 2-1 and 2-2, are possible for the structure of dispiro compound 2. On the basis of the mode of formation as well as the \( ^1 \)H nmr spectra, however, we assumed that the dispiro compound 2 has the structure 2-1 rather than 2-2. The methine protons of 2a and 2b appeared at \( \delta \) 3.42 and 3.47, respectively, which are comparable to the value of chemical shift of the methine proton of spirodimethylcyclopropane 2-1 but not that of stereoisomer 3-2 \(^1 \) (Scheme 1).

The previous results also disclosed that in the cyclopropanation of oxazolinones at low temperature spirocyclopropanes such as 2-1 arising from the preferred conformational intermediate were predominantly formed than stereoisomers such as 2-2 \(^1 \).

On the other hand, the reaction of Ia with ethyl (dimethylsulfuranylidene)acetate under similar conditions afforded a mixture of two stereoisomeric dispiro compounds, whose ratio was estimated to be ca 3:1 by the nmr spectroscopy, in 97% yield. However, isolation of the minor product was unsuccessful. Although the assignment of stereochemistry of two isomers was very difficult on the basis of their spectral data \(^6 \), it was assumed that the major product is 4 arising from the
preferred conformational intermediate and the minor one is $\mathbf{b}$.

Since the above dispiro compounds have a cyclopropane moiety in which a carbonyl group (hydrogen acceptor) and ring methylene group (hydrogen donor) are cis, they are expected to undergo a retro-ene reaction. On heating in refluxing toluene for 3 h, $\mathbf{a}$ and $\mathbf{b}$ were converted into the expected retro-ene reaction products $\mathbf{6a}$ and $\mathbf{6b}$ in 73 and 26% yields, respectively. Structural elucidation of $\mathbf{6a}$ and $\mathbf{6b}$, 4-(1-cyclohexenyl)- and 4-(1-cycloheptenyl)-4-phenacyl-2-phenyl-2-oxazolin-5-one, was accomplished on the basis of spectral data.

On the other hand, thermolysis of $\mathbf{4}$ in refluxing xylene for 5 h afforded a 94% yield of a mixture of two isomeric rearrangement products, $\mathbf{J}$ and $\mathbf{K}$, which was found to be ca 3:2 by the nmr spectroscopic estimation. Although isolation of each product was unsuccessful, $\mathbf{J}$ and $\mathbf{K}$ were assumed to be stereoisomeric 4-(1-cyclohexenyl-ethoxycarbonyl)methyl-2-phenyl-2-oxazolin-5-ones on the basis of spectral data as well as chemical conversion. When a mixture of $\mathbf{J}$ and $\mathbf{K}$ (3:2) was treated with 1M NaOH aqueous solution in refluxing methanol for 7 h, two hydrolyzed products $\mathbf{2}$, mp 151-152°C, and $\mathbf{10}$, mp 141-142°C, were obtained in 34 and 21% yields, respectively. However, the stereochemistry of $\mathbf{2}$ and $\mathbf{10}$ was not clear.

As shown in Scheme 2, in the thermolysis of $\mathbf{2}$ the benzoyl carbonyl group functions as a hydrogen
acceptor to give \( \text{I} \) via \( \text{A} \), whereas in \( \text{A} \) the carbonyl group in the oxazolinone ring serves as a hydrogen acceptor to yield isomers \( \text{J} \) and \( \text{K} \) via \( \text{B} \).

Oxazolin-5-one-4-spiro-1'-2',3'-cis-divinylcyclopropanes (spiro-cis-divinylcyclopropanes). Next, we have investigated the synthesis of spiro-cis-divinylcyclopropanes which are able to undergo the Cope rearrangement. The reaction of 4-cinnamylidene-2-phenyl-2-oxazolin-5-one (11) with dimethylsulfonium 3-methoxycarbonylallylide \( ^{10} \), generated in situ from 3-methoxycarbonylallyldimethylsulfonium bromide and sodium hydride, in dry THF at room temperature for 3 h afforded a

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{O} \quad \text{O} \\
\text{Ph} & \quad \text{Me}_2\text{S} = \text{CH} = \text{CH} = \text{CHCO}_2\text{Me} \quad \rightarrow \\
\text{Ph} & \quad \text{H} \quad \text{H} \quad \text{O} \\
\text{Ph} & \quad \text{O} \quad \text{Ph} \\
\end{align*}
\]

\( \text{11} \)

Next, we have investigated the synthesis of spiro-cis-divinylcyclopropanes which are able to undergo the Cope rearrangement. The reaction of 4-cinnamylidene-2-phenyl-2-oxazolin-5-one (11) with dimethylsulfonium 3-methoxycarbonylallylide \( ^{10} \), generated in situ from 3-methoxycarbonylallyldimethylsulfonium bromide and sodium hydride, in dry THF at room temperature for 3 h afforded a

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{O} \quad \text{O} \\
\text{Ph} & \quad \text{Me}_2\text{S} = \text{CH} = \text{CH} = \text{CHCO}_2\text{Me} \quad \rightarrow \\
\text{Ph} & \quad \text{Ph} \quad \text{H} \quad \text{H} \quad \text{O} \\
\text{Ph} & \quad \text{O} \quad \text{Ph} \\
\end{align*}
\]

\( \text{12} \)

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{O} \quad \text{O} \\
\text{Ph} & \quad \text{Me}_2\text{S} = \text{CH} = \text{CH} = \text{CHCO}_2\text{Et} \quad \rightarrow \\
\text{Ph} & \quad \text{Ph} \quad \text{H} \quad \text{H} \quad \text{O} \\
\text{Ph} & \quad \text{O} \quad \text{Ph} \\
\end{align*}
\]

\( \text{13} \)

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{O} \quad \text{O} \\
\text{Ph} & \quad \text{Me}_2\text{S} = \text{CH} = \text{CH} = \text{CHCO}_2\text{Et} \quad \rightarrow \\
\text{Ph} & \quad \text{Ph} \quad \text{H} \quad \text{H} \quad \text{O} \\
\text{Ph} & \quad \text{O} \quad \text{Ph} \\
\end{align*}
\]

\( \text{14} \)

for 3 h \( 4\% \)

for 42 h \( 9\% \)

for 3 h \( 4\% \)

for 42 h \( 32\% \)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \quad \text{N} \quad \text{O} \\
\text{Ph} & \quad \text{Ph} \quad \text{Ph} \quad \text{H} \quad \text{H} \\
\text{Ph} & \quad \text{O} \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\( \text{16-1} \)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \quad \text{N} \quad \text{O} \\
\text{Ph} & \quad \text{Ph} \quad \text{Ph} \quad \text{H} \quad \text{H} \\
\text{Ph} & \quad \text{O} \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\( \text{16-2} \)

Scheme 3
crystalline compound 13 as the sole isolated product in 10% yield. On the basis of spectral data, the compound 13 was deduced as cyclohepta-1,4-diene-3-spiro-4'-oxazolinone arising from the Cope rearrangement of an initially formed spiro-cis-divinylcyclopropane 12.

On the other hand, 11 reacted with dimethyloxosulfonium-3-ethoxycarbonyl-2-phenylallylide in dry THF at room temperature for 3 h to give two products 14 and 15, whereas 15 was only obtained from the reaction for 42 h. On the basis of spectral data, 14 was assigned as the spiro-cis-divinylcyclopropane and 15 as its Cope rearrangement product. In fact, on heating in refluxing benzene for 4 h 14 was transformed into 15 in 50% yield. The assigned structure 15 was strongly supported by comparison with 'H nmr spectral data of 16-1 and 16-2 obtained from the reaction of 11 with phenacylide (Scheme 3). The configurations of spiro carbons in the Cope rearrangement products 13 and 15 are not clear, although the phenyl and ester groups at 6- and 7-positions are assumed to be trans taking account a concerted Cope rearrangements of 12 and 14, respectively.

REFERENCES AND NOTES

4. The compound 1b, mp 141-142°C (lit. mp 137-138°C), was prepared from hippuric acid and cyclohexanone according to the Erlenmeyer method. The compound 1b was prepared from the reaction of the enamine, derived from cycloheptanone and morpholine, with 2-phenyl-2-oxazolin-5-one by the modified Lawson's method, since the yield of 1b according to the Erlenmeyer method was very poor. 1b: yield 62%; mp 88-89°C; ir (KBr) 1790, 1680, 1640 cm⁻¹; MS m/e 255 (M⁺).

All new compounds in this paper gave satisfactory elemental analyses.

5. 2a: mp 134-135°C; colorless prisms; ir (KBr) 1800, 1690, 1635 cm⁻¹; 'H nmr (CDCl3) δ 3.42 (1H, s, CH); 13C nmr (CDCl3) δ 46.4 (s), 46.9 (d), 59.3, 161.0, 175.4 (each s); MS m/e 359 (M⁺). 2b: mp 106-107°C; colorless prisms; ir (KBr) 1790, 1690, 1640 cm⁻¹; 'H nmr (CDCl3) δ 3.47 (1H, s, CH); MS m/e 373 (M⁺).

6. 4: colorless oil; ir (neat) 1805, 1740, 1640, 1635 cm⁻¹; 'H nmr (CDCl3) δ 1.27 (3H, t), 2.68 (1H, s, CH), 4.16 (2H, q). 5: 1H nmr (CDCl3) δ 1.27 (3H, t), 2.86 (1H, s, CH), 4.20 (2H, q). 7. 6a: mp 166-171°C (dec); colorless needles; ir (KBr) 1820, 1680, 1640 cm⁻¹; 'H nmr (CDCl3) δ 4.63 (2H, m, CH₂COPh), 5.61 (1H, m, CH); 13C nmr (CDCl3) δ 59.2 (t), 64.9 (s), 126.1 (t), 127.9, 162.5, 176.9, 196.3 (each s); MS m/e 359 (M⁺). 6b: mp 163-165°C; colorless prisms; ir (KBr) 1830, 1675, 1650 cm⁻¹; 'H nmr (CDCl3) δ 4.78 (2H, m, CH₂COPh), 5.91 (1H, m, =CH); MS m/e 373 (M⁺).

8. A mixture of 2 and 8: yellow oil; 'H nmr (CDCl3) δ 1.16 (t, ca. 1.2H), 1.24 (t, ca. 1.8H), 3.56
(1H, d, =CH, J=4.0 Hz), 5.15 (1H, dd, =CH, J=4.0, 9.0 Hz), 5.49 (1H, m, =CH), 7.60 (1H, d, NH, J=9.0 Hz), 8.29 (1H, broad, OH); MS m/e 345 (M⁺). 10: mp 141-142°C; colorless prisms; ir (KBr) 3375, 3200-2300, 1730, 1720, 1620 cm⁻¹; ¹H nmr (DMSO-d₆) δ 1.26 (3H, t), 3.65 (1H, d, XH, J=5.7.0 Hz), 5.09 (1H, dd, SC!, J=7.0, 10.0 Hz), 5.82 (1H, m, =CH), 6.69 (1H, d, NH, J=10.0 Hz), 7.30-7.80 (6H, m, Ar!); MS m/e 345 (M⁺).


11. 13: mp 161-162.5°C; colorless needles; ir (KBr) 1820, 1740, 1645 cm⁻¹; ¹H nmr (CDCl₃) δ 3.71 (3H, s, OCH₃), 4.28 (1H, dddd, =CH, J=1.0, 1.3, 4.2, 5.5 Hz), 5.07 (1H, ddd, =CH, J=1.9, 4.2, 6.0 Hz), 5.76 (1H, ddd, =CH, J=1.3, 1.3, 11.8 Hz), 5.92 (1H, ddd, =CH, J=1.3, 1.9, 11.0 Hz), 6.02 (1H, dd, =CH, J=5.5, 11.8 Hz), 6.20 (1H, ddd, =CH, J=1.0, 6.0, 11.0 Hz); ¹³C nmr (CDCl₃) δ 46.4 (s), 51.9 (d), 70.7, 160.5, 171.9, 179.6 (each s); MS m/e 373 (M⁺).


13. 14: mp 148-149.5°C; yellow crystals; ir (KBr) 1810, 1710, 1620, 1610 cm⁻¹; ¹H nmr (CDCl₃) δ 0.96 (3H, t), 3.28 (1H, dd, Hb, J=10.0, 10.0 Hz), 3.68 (1H, dd, Hb, J=1.0, 10.0 Hz), 3.86 (2H, q), 5.62 (1H, dd, Hc, J=10.0, 16.2 Hz), 6.42 (1H, d, He, J=2.4 Hz), 6.44 (1H, d, Hd, J=16.2 Hz); MS m/e 463 (M⁺). 15: mp 155-156°C; pale yellow prisms; ir (KBr) 1815, 1710, 1635, 1620 cm⁻¹; ¹H nmr (CDCl₃) δ 1.06 (3H, t), 2.93 (1H, m, =CH), 3.72 (1H, dd, =CH, J=2.4, 12.0 Hz), 4.01 (2H, q), 6.32 (1H, d, =CH, J=2.4 Hz), 6.62 (2H, m, =CH); ¹³C nmr (CDCl₃) δ 40.3, 42.6 (each d), 59.5, 162.1, 165.6, 175.2 (each s); MS m/e 463 (M⁺).


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