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

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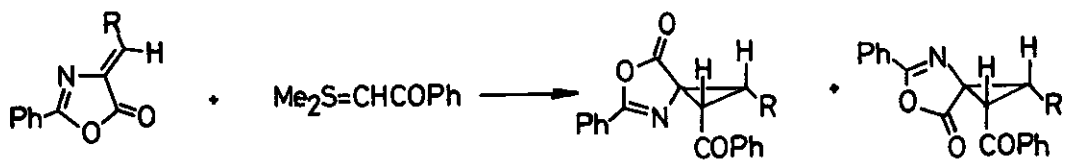
Abstract —— 4-Cycloalkylidene-2-phenyl-2-oxazolin-5-ones reacted with carbonyl-stabilized sulfur methylides to give the corresponding dispiro compounds, which on heating were converted into retro-ene reaction products. The reaction of 4-cinnamylidene-2-phenyl-2-oxazolin-5-one with sulfur allylides afforded 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 cyclopropylogs of α-amino acids[1]. This result is a great contrast to the formation of cis and trans

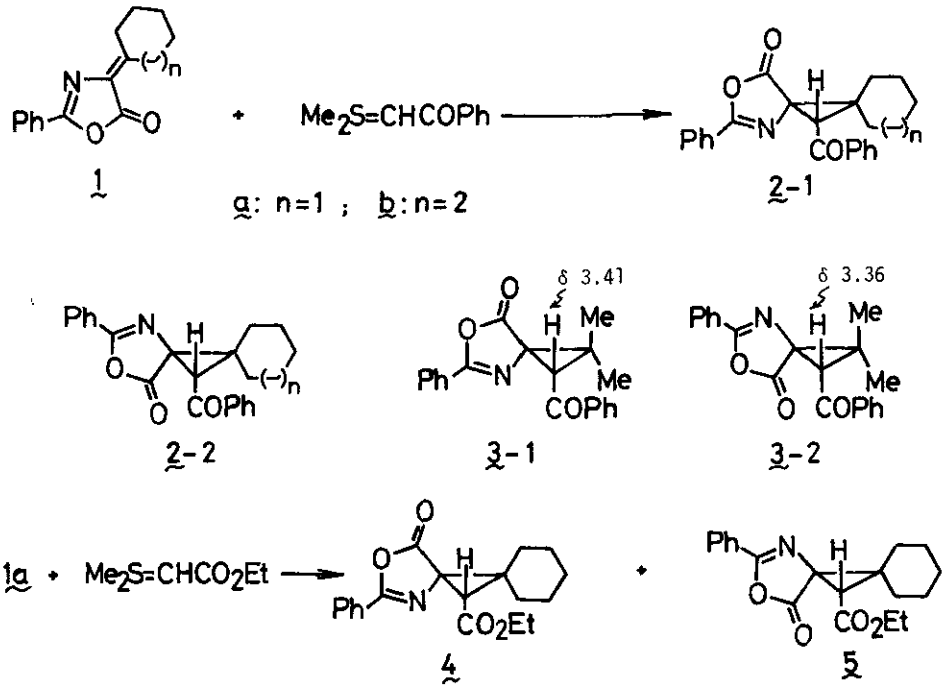


isomers, or a single cis isomer in the cyclopropanation of 3-arylmethyleneindolin-2-ones[2], or 4-arylmethylene-2-isoxazolin-5-ones[3] with the phenacylide, respectively.

As an extention 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-

2-phenyl-2-oxazolin-5-ones 1 with carbonyl-stabilized sulfur methylides. 4-Cyclohexylidene- (1a) or 4-cycloheptylidene-2-phenyl-2-oxazolin-5-one (1b)[4] 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[5]. 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 δ 3.42 and 3.47, respectively, which are comparable to the value of chemical shift of the methine proton of spirodimethylcyclopropane 3-1 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 3-1 arising from the preferred conformational intermediate were predominantly formed than stereoisomers such as 3-2[1].



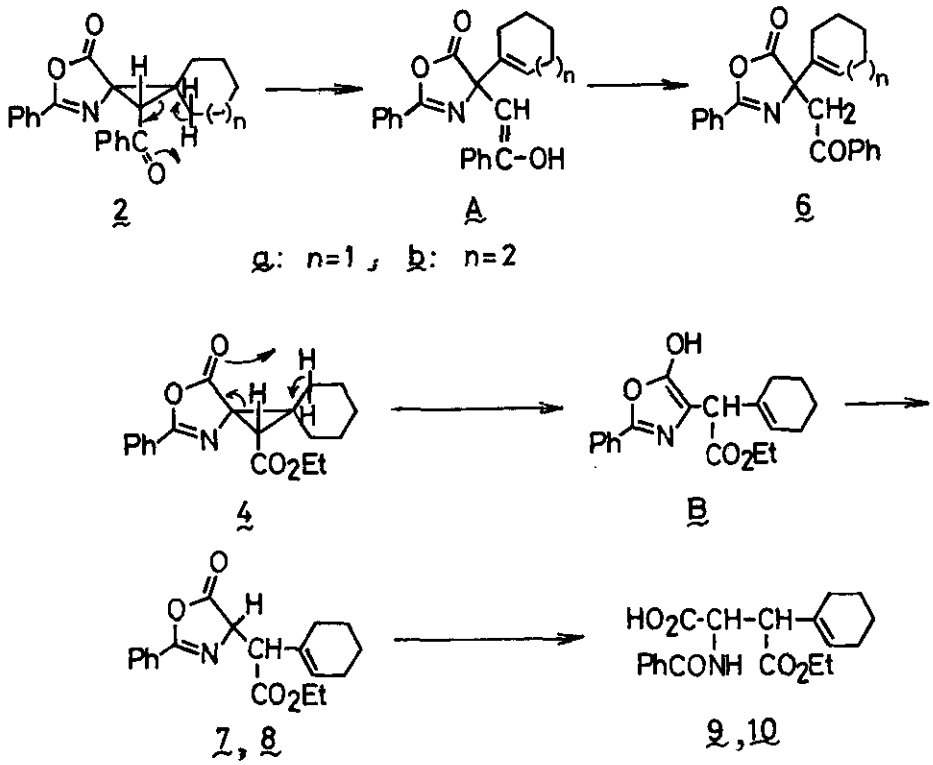
Scheme 1

On the other hand, the reaction of 1a 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 5.

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, 2a and 2b were converted into the expected retro-ene reaction products 6a and 6b in 73 and 26% yields, respectively. Structural elucidation of 6a and 6b, 4-(1-cyclohexenyl)- and 4-(1-cycloheptenyl)-4-phenacyl-2-phenyl-2-oxazolin-5-one, was accomplished on the basis of spectral data[7].

On the other hand, thermolysis of 4 in refluxing xylene for 5 h afforded a 94% yield of a mixture of two isomeric rearrangement products, 7 and 8, which was found to be ca 3:2 by the nmr spectroscopic estimation. Although isolation of each product was unsuccessful, 7 and 8 were assumed to be stereoisomeric 4-(1-cyclohexenyl-ethoxycarbonyl)methyl-2-phenyl-2-oxazolin-5-ones on the basis of spectral data[8] as well as chemical conversion. When a mixture of 7 and 8 (3:2) was treated with 1M NaOH aqueous solution in refluxing methanol for 7 h, two hydrolyzed products 9, mp 151-152°C, and 10, mp 141-142°C, were obtained in 34 and 21% yields, respectively[9]. However, the stereochemistry of 9 and 10 was not clear.



2 A 6

a: n=1, b: n=2

4 B

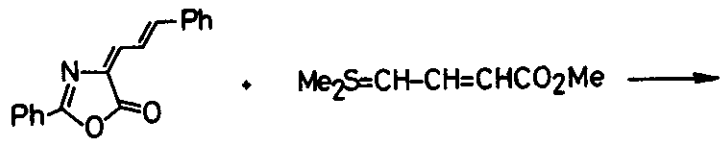
7, 8 9, 10

Scheme 2

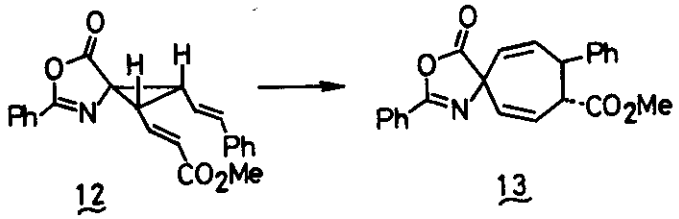
As shown in Scheme 2, in the thermolysis of 2 the benzoyl carbonyl group functions as a hydrogen

acceptor to give 6 via A, whereas in 4 the carbonyl group in the oxazolinone ring serves as a hydrogen acceptor to yield isomers 7 and 8 via 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)[1] 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

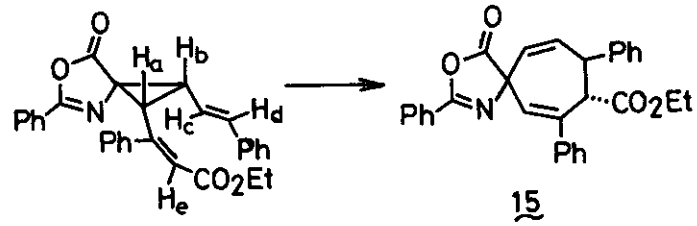


11 + $Me_2S{=}CH{-}CH{=}CHCO_2Me$ ⟶



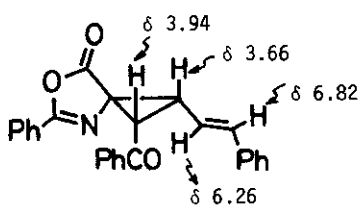
12 ⟶ 13

11 + $Me_2S(O){=}CH{-}C(Ph){=}CHCO_2Et$ ⟶



14 ⟶ 15

	14	15
for 3 h	4%	9%
for 42 h	—	32%



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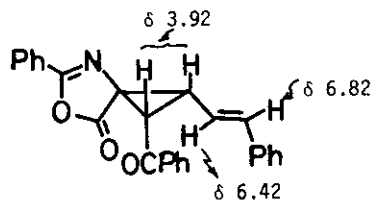

16-2

Scheme 3

crystalline compound 13 as the sole isolated product in 10% yield. On the basis of spectral data[11], 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[12] 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[13], 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 14 was strongly supported by comparison with ^{1}H nmr spectral data of 16-1 and 16-2 obtained from the reaction of 11 with phenacylide[1] (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.

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4. The compound 1a, mp 141-142°C (lit.[14] mp 137-138°C), was prepared from hippuric acid and cyclohexanone according to the Erlenmeyer method[15]. 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[16], since the yield of 1b according to the Erlenmeyer method was very poor. 1b: yield 62%; mp 88-89°C; ir (KBr) 1790, 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}; ^{1}H nmr ($CDCl_3$) δ 3.42 (1H, s, ≥C<u>H</u>); ^{13}C nmr ($CDCl_3$) 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}; ^{1}H nmr ($CDCl_3$) δ 3.47 (1H, s, ≥C<u>H</u>); MS m/e 373 (M^+).
6. 4: colorless oil; ir (neat) 1805, 1740, 1640, 1635 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.27 (3H, t), 2.68 (1H, s, ≥C<u>H</u>), 4.16 (2H, q). 5: ^{1}H nmr ($CDCl_3$) δ 1.27 (3H, t), 2.86 (1H, s, ≥C<u>H</u>), 4.20 (2H, q).
7. 6a: mp 166-171°C (dec); colorless needles; ir (KBr) 1820, 1680, 1640 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 4.63 (2H, m, C<u>H</u>$_2$COPh), 5.67 (1H, m, =C<u>H</u>); ^{13}C nmr ($CDCl_3$) δ 59.2 (t), 64.9 (s), 126.1 (t), 127.9, 162.6, 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}; ^{1}H nmr ($CDCl_3$) δ 4.78 (2H, m, C<u>H</u>$_2$COPh), 5.91 (1H, m, =C<u>H</u>); MS m/e 373 (M^+).
8. A mixture of 7 and 8: yellow oil; ^{1}H nmr ($CDCl_3$) δ 1.16 (t, ca 1.2H), 1.24 (t, ca 1.8H), 3.56

(1H, d, ≥C<u>H</u>, J=4.0 Hz), 5.15 (1H, dd, ≥C<u>H</u>, J=4.0, 9.0 Hz), 5.49 (1H, m, =C<u>H</u>), 7.60 (1H, d, N<u>H</u>, J=9.0 Hz), 8.29 (1H, broad, O<u>H</u>); MS m/e 345 (M^+). <u>10</u>: mp 141-142°C; colorless prisms; ir (KBr) 3375, 3200-2300, 1730, 1720, 1620 cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.26 (3H, t), 3.65 (1H, d, ≥C<u>H</u>, J=7.0 Hz), 5.09 (1H, dd, ≥C<u>H</u>, J=7.0, 10.0 Hz), 5.82 (1H, m, =C<u>H</u>), 6.69 (1H, d, N<u>H</u>, J=10.0 Hz), 7.30-7.80 (6H, m, Ar<u>H</u> + O<u>H</u>); MS m/e 345 (M^+).

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11. <u>13</u>: mp 161-162.5°C; colorless needles; ir (KBr) 1820, 1740, 1645 cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.71 (3H, s, OC<u>H</u>$_3$), 4.28 (1H, dddd, ≥C<u>H</u>, J=1.0, 1.3, 4.2, 5.5 Hz), 5.07 (1H, ddd, ≥C<u>H</u>, J=1.9, 4.2, 6.0 Hz), 5.76 (1H, ddd, =C<u>H</u>, J=1.3, 1.3, 11.8 Hz), 5.92 (1H, ddd, =C<u>H</u>, J=1.3, 1.9, 11.0 Hz), 6.02 (1H, dd, =C<u>H</u>, J=5.5, 11.8 Hz), 6.20 (1H, ddd, =C<u>H</u>, J=1.0, 6.0, 11.0 Hz); ^{13}C nmr ($CDCl_3$) δ 46.4 (s), 51.9 (d), 70.7, 160.5, 171.9, 179.6 (each s); MS m/e 373 (M^+).

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13. <u>14</u>: mp 148-149.5°C; yellow crystals; ir (KBr) 1810, 1710, 1620, 1610 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.96 (3H, t), 3.28 (1H, dd, H_b, J=10.0, 10.0 Hz), 3.68 (1H, dd, H_a, J=2.4, 10.0 Hz), 3.86 (2H, q), 5.62 (1H, dd, H_c, J=10.0, 16.2 Hz), 6.42 (1H, d, H_e, J=2.4 Hz), 6.44 (1H, d, H_d, J=16.2 Hz); MS m/e 463 (M^+). <u>15</u>: mp 155-156°C; pale yellow prisms; ir (KBr) 1815, 1710, 1635, 1620 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.06 (3H, t), 2.93 (1H, m, ≥C<u>H</u>), 3.72 (1H, dd, ≥C<u>H</u>, J=2.4, 12.0 Hz), 4.01 (2H, q), 6.32 (1H, d, =C<u>H</u>, J=2.4 Hz), 6.62 (2H, m, =C<u>H</u>); ^{13}C nmr ($CDCl_3$) 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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Received, 14th June, 1982