REACTIONS OF 4-METHYLENE-2-PHENYL-2-OXAZOLIN-5-ONES WITH SULFUR YLIDES

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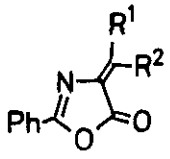
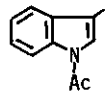
The reaction of 2-phenyl-4-phenylmethylene-2-oxazolin-5-one with dimethyloxosulfonium methylide proceeded via a nucleophilic attack of the methylide on the carbonyl carbon in the oxazolinone with concurrent ring opening to give 1:1 adduct, dimethyloxosulfonium (2-benzamido)cinnamoylmethylide. On the other hand, dimethylsulfonium phenacylide reacted with 4-phenylmethylene-, 4-(p-acetoxyphenyl)methylene-, 4-styrylmethylene-, 4-(2-furyl)methylene-, 4-[3-(1-acetylindolyl)]methylene-, or 4-dimethylmethylene-2-phenyl-2-oxazolin-5-one to give two stereoisomeric spirocyclopropanes and/or γ-pyrone derivatives respectively, whose yields were dependent on the reaction conditions.

Since it is known that 2-oxazolin-5-ones are useful intermediates for the synthesis of α-acylamino acids or α-amino acids, cyclopropanation of 4-methylene-2-oxazolin-5-ones would provide a useful route to biologically interesting cyclopropylogs of α-amino acids. For this purpose several workers[1-3] have investigated the cyclopropanation of 4-arylmethylene-2-oxazolin-5-ones with diazomethane, and conversion of spiro[cyclopropane-1,4'-oxazolinones] to cyclopropylogs of α-amino acids. On the other hand, it has recently been reported that 4-arylmethylene-2-pyrazolin-5-ones[4], 4-arylmethylene-2-isoxazolin-5-ones[5], and 3-arylmethyleneindolin-2-ones[6] reacted with carbonyl-stabilized sulfur ylides to afford the corresponding spirocyclopropane derivatives respectively. However, little attention has been paid to the reaction of 4-methylene-2-oxazolin-5-ones with sulfur ylides. We now wish to report our findings on the reaction of 4-methylene-2-phenyl-2-oxazolin-5-ones with sulfur ylides.

Six 4-methylene-2-phenyl-2-oxazolin-5-ones (1 — 6) employed here were prepared from hippuric acid and benzaldehyde, p-acetoxybenzaldehyde, trans-cinnamaldehyde, furfural, 1-acetylindole-3-carbaldehyde, or acetone according to the Erlenmeyer method[7]. It has been reported that the Erlenmeyer method usually gives the thermodynamically stable (Z)-4-arylmethylene-2-oxazolin-5-ones.[8] Since the melting points of 2-phenyl-4-phenylmethylene- (1) and 2-phenyl-4-styrylmethylene-2-oxazolin-5-

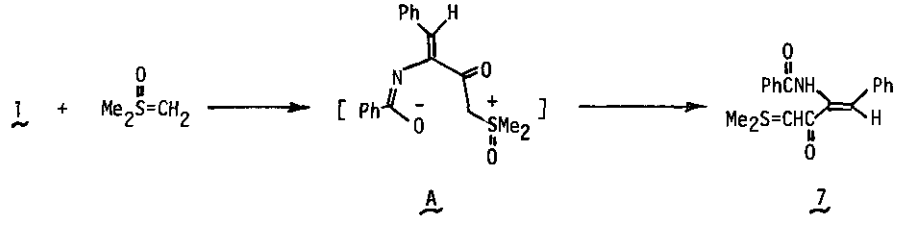
one (3) agreed with reported melting points of the corresponding (Z)-isomers, other 4-methylene-2-oxazolin-5-ones, 2, 4 and 5, were deduced to be (Z)-isomers respectively.[9]



1: R^1=Ph, R^2=H; 2: R^1=p-$AcOC_6H_4$, R^2=H
3: R^1=Ph-CH=CH, R^2=H; 4: R^1=2-furyl, R^2=H
5: R^1=  , R^2=H; 6: R^1=R^2=Me

1: mp 166-167°C (lit.[8] mp 166-167°C); IR (KBr) 1800 (C=O), 1655 cm^{-1} (C=N). 2: mp 180-181°C; IR (KBr) 1800, 1760 (C=O), 1660 cm^{-1} (C=N). 3: mp 152-153°C (lit.[8] mp 153°C); IR (KBr) 1790 (C=O), 1640 cm^{-1} (C=N). 4: mp 173-174°C (lit.[10] mp 171°C); IR (KBr) 1795 (C=O), 1660 cm^{-1} (C=N). 5: mp 204-205°C; IR (KBr) 1790 (C=O), 1640 cm^{-1} (C=N). 6: mp 98-99°C (lit.[10] mp 99-100°C); IR (KBr) 1790 (C=O), 1675 cm^{-1} (C=N).

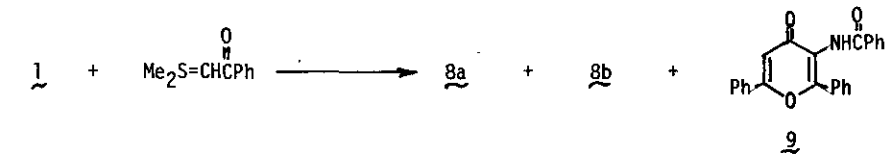
Although oxazolinone 1 did not react with dimethylsulfonium methylide, 1 reacted with dimethyloxosulfonium methylide, generated in situ from trimethyloxosulfonium chloride and sodium hydride, in DMSO at room temperature for 3 h to give 1:1 adduct, dimethyloxosulfonium (2-benzamido)cinnamoylmethylide 7, in 53% yield. Structural elucidation of 7 was accomplished on the basis of spectral data. 7: mp 157-158°C; IR (KBr) 3280, 1635, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (6H, s), 4.91 (1H, s, S=CH), 7.01 (1H, s, =CH), 7.1-8.0 (10H, m), 8.25 (1H, broad s, NH).



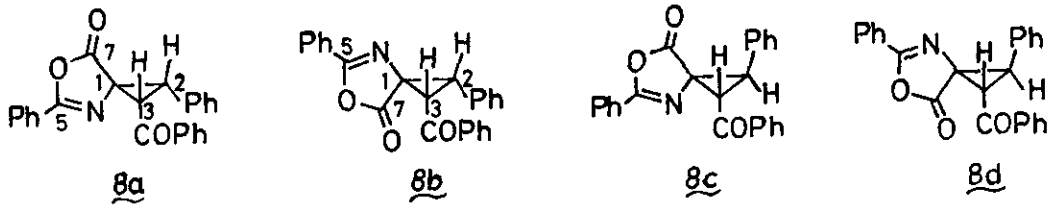
Scheme 1

The pathway for the formation of 7 is illustrated in Scheme 1. A nucleophilic attack of the ylide does not occur at the exo-methylene carbon, but instead takes place at the carbonyl carbon of 1 to yield zwitterion A with concurrent ring opening. Subsequent hydrogen transfer in A gives stable 7. Next, we have investigated the reaction of 1 with a carbonyl-stabilized sulfur ylide. When 1 was allowed to react with dimethylsulfonium phenacylide, generated in situ from dimethylphenacylsulfonium bromide and sodium hydride, in THF at 0°C, a mixture of two isomeric spirocyclopropanes was obtained. Theoretically four stereoisomers, 8a, 8b, 8c, and 8d, are possible for the structure of spirocyclopropane derived from 1 and phenacylide. On the basis of spectral data and chemical conversions described below, however, two spirocyclopropanes obtained were assigned 8a and 8b respectively. The same reaction at room temperature or under reflux afforded a small amount of γ-

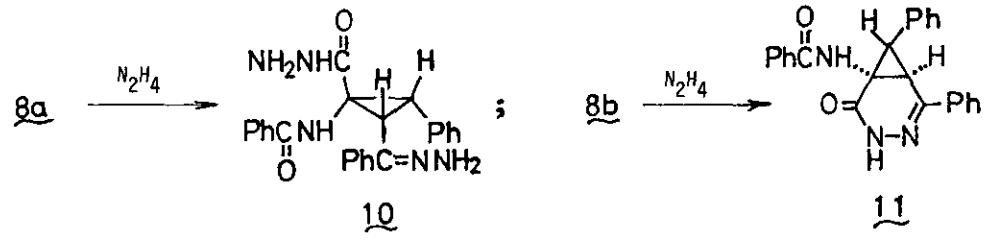
pyrone derivative 9 together with spirocyclopropanes 8a and 8b (Scheme 2).



	8a	8b	9
0°C, 5 h	78.5%	6%	—
r.t., 5 h	40.5%	38.5%	11%
reflux, 1 h	44%	27.5%	6.5%



8a 8b 8c 8d



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Scheme 2

8a: mp 192-193°C; IR (KBr) 1810, 1680 (C=O), 1645 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 4.24, 4.42 (each 1H, d, CH, J=9.0 Hz), 7.24-8.03 (15H, m); ^{13}C NMR ($CDCl_3$) δ 39.3 (d, 2-C), 39.7 (d, 3-C), 59.3 (s, 1-C), 163.0 (s, 5-C), 177.8 (s, 7-C), 190.3 (s, COPh); MS m/e 367 (M^+).

8b: mp 154-155°C; IR (KBr) 1810, 1685 (C=O), 1630 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 4.02, 4.16 (each 1H, d, CH, J=9.2 Hz), 7.24-8.02 (15H, m); ^{13}C NMR ($CDCl_3$) δ 39.0 (d, 2-C), 42.6 (d, 3-C), 58.2 (s, 1-C), 163.2 (s, 5-C), 172.8 (s, 7-C), 189.0 (s, COPh); MS m/e 367 (M^+).

9: mp 231-232.5°C; IR (KBr) 3300 (NH), 1695, 1670 (C=O), 1635 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ6.81 (1H, s, =CH), 7.3-7.9 (15H, m), 7.95 (1H, broad, NH, exchanged with D_2O); MS m/e 367 (M^+).

It is well known that cis-cyclopropanes exhibit greater coupling constants (7.9-9.3[11], 8-10 Hz[12]) than those (5.3-6.6[11], 4-7 Hz[12]) of trans ones. The coupling constants for 2-H and 3-H of the cyclopropane rings in 8a and 8b are 9.0 and 9.2 Hz respectively indicating that both 8a and 8b have cis-cyclopropane moieties. Thus, 8c and 8d having trans-cyclopropane structures can be readily excluded. Now both 2-H and 3-H of 8a appeared at lower fields than those of 8b. This fact would be explained by considering anisotropy of the carbonyl group in oxazolinone ring of 8a.

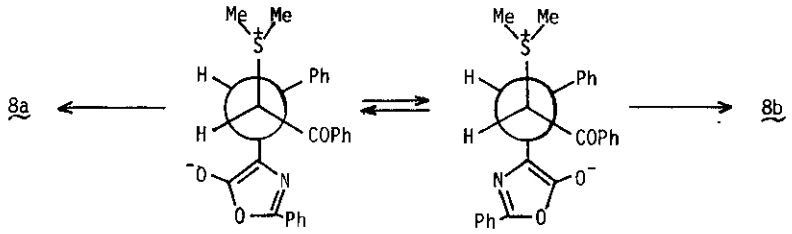
Additional evidences for structures 8a and 8b were obtained by the chemical conversions. The reaction of 8a with excess hydrazine hydrate in ethanol at room temperature for 24 h afforded 1-benzamido-2-benzoylhydrazono-3-phenylcyclopropanecarbohydrazide (10) in 46% yield, whereas 8b afforded

1-benzamido-5,7-diphenyl-3,4-diazabicyclo[4.1.0]hept-4-en-2-one (11) in 87% yield from the reaction under the same conditions.

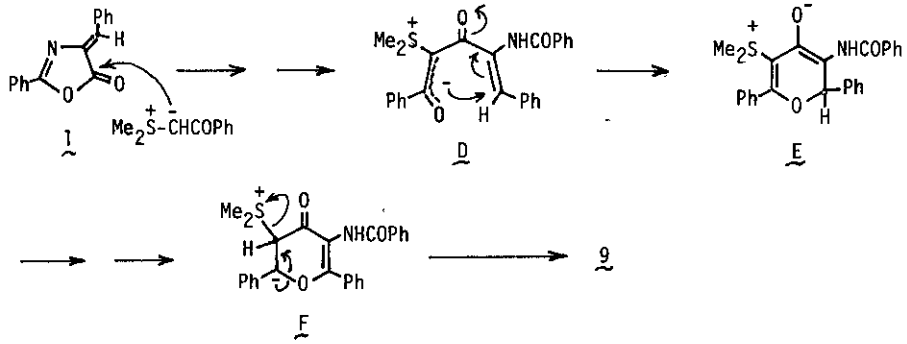
10: mp 196-198°C; IR (KBr) 3400-3300, 1680, 1665, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.34, 3.72 (each 1H, d, >CH, J=8.0 Hz), 3.73-3.84 (2H, broad, NH_2), 6.96-7.90 (17H, m, ArH + NH_2), 8.32 (1H, broad, NH), 8.92 (1H, s, NH); MS m/e 354 (M^+ - $CONHNH_2$).

11: mp 272-274°C; IR (KBr) 3260, 3220, 1670, 1650, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.87, 3.36 (each 1H, d, >CH, J=6.5 Hz), 6.42, 8.61 (each 1H, broad, NH), 7.28-7.84 (15H, m); MS m/e 381 (M^+).

As mentioned above, the reaction of 1 with phenacylide afforded two stereoisomeric cis-cyclopropanes 8a and 8b whose relative yields were dependent on the reaction conditions. It is known that cyclopropanation with a sulfur ylide proceeds via a 1,4-conjugate addition with the formation of a zwitterion, followed by a 1,3-elimination of dimethyl sulfide. The Newman projections clearly indicate that zwitterion B which gives 8a is more favorable than zwitterion C which is the precursor of 8b, because of a significant steric interaction between the enolate and phenyl group in C. On



the basis of the results shown in Scheme 2, it can be concluded that the favorable zwitterion B predominantly exists at a low temperature, whereas B and C are present comparably at a high temperature. The pathway for the formation of γ-pyrone derivative 9 is assumed as depicted in Scheme 3. At a higher temperature phenacylide partially attacks on the carbonyl carbon of 1 to yield zwitterion D

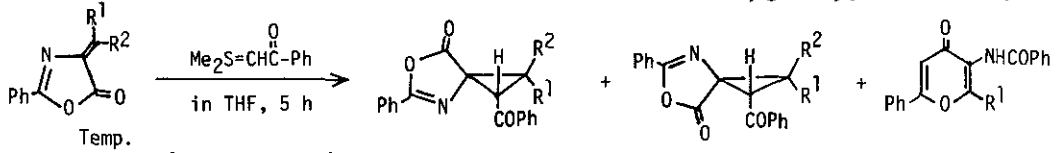


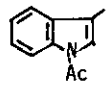
Scheme 3

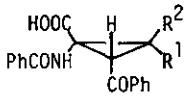
with concurrent ring opening, followed by hydrogen transfer. Subsequent ring closure of D yields E, which is then transformed into F with hydrogen transfer. Finally, elimination of dimethyl sulfide

in 7 *gives* γ*-pyrone derivative* 9.

The reaction of other 4-methyleneoxazolinones 2 — 6 with phenacylide was investigated, and the results are shown in Scheme 4. In analogy with the case of 1, two spirocyclopropanes and/or γ-pyrone derivative were obtained in most cases. Structural elucidation of all products was accomplished on the basis of spectral data. Since it was found that 12a and 13a were hydrolyzed to the corresponding α-benzoylamino acids 20 and 21 respectively during work-up with chromatography, figures in parentheses shown in Scheme 4 indicate the total yields of 12a and 20 or 13a and 21.



2	0°C	R^1=p-AcOC$_6$H$_4$, R^2=H	12a	17.5%(67.5%)	12b	—		—
	r.t.			36%(61.5%)		21.5%		—
3	0°C	R^1=Ph-CH=CH, R^2=H	13a	11%(58.5%)	13b	—	14	3.5%
	r.t.			22.5%(39.5%)		26.5%		3%
4	0°C	R^1=2-furyl, R^2=H	15a	52.5%	15b	4.5%	16	7.5%
5	0°C	R^1=  , R^2=H	17a	49%		—	18	10.5%
6	0°C	R^1=R^2=Me	19a	61%	19b	22.5%		—



20: R^1=p-AcOC$_6$H$_4$, R^2=H

21: R^1=Ph-CH=CH, R^2=H

Scheme 4

12a: mp 159-160°C; IR (KBr) 1810, 1760, 1690 (C=O), 1635 cm^{-1} (C=N); ^{1}H NMR (CDCl$_3$) δ 2.28 (3H, s, CH$_3$), 4.21, 4.39 (each 1H, d, >CH, J=8.0 Hz), 7.0-7.6, 7.8-8.0 (14H, m); MS m/e 425 (M$^+$).

12b: mp 176-177°C; IR (KBr) 1810, 1760, 1690 (C=O), 1635 cm^{-1} (C=N); ^{1}H NMR (CDCl$_3$) δ 2.28 (3H, s, CH$_3$), 3.98, 4.12 (each 1H, d, >CH, J=9.0 Hz), 7.0-7.6, 7.94-8.04 (14H, m); MS m/e 425 (M$^+$).

13a: mp 163-164°C; IR (KBr) 1810, 1680 (C=O), 1625 cm^{-1} (C=N); ^{1}H NMR (CDCl$_3$) δ 3.66 (1H, t, >CH, J=8.7, 8.8 Hz), 3.94 (1H, d, >CH, J=8.7 Hz), 6.26 (1H, q, =CH, J=8.8, 16.0 Hz), 6.82 (1H, d, =CH, J=16.0 Hz), 7.2-8.08 (15H, m); MS m/e 393 (M$^+$).

13b: mp 124-125°C; IR (KBr) 1805, 1680 (C=O), 1620 cm^{-1} (C=N); ^{1}H NMR (CDCl$_3$) δ 3.92 (2H, m, >CH), 6.42 (1H, m, =CH), 6.82 (1H, d, =CH, J=16.0 Hz), 7.2-8.1 (15H, m); MS m/e 393 (M$^+$).

14: mp > 300°C; IR (KBr) 3340 (NH), 1680, 1660 (C=O), 1620 cm^{-1} (C=C); MS m/e 393 (M$^+$).

15a: mp 163-165°C; IR (KBr) 1800, 1680 (C=O), 1630 cm^{-1} (C=N); ^{1}H NMR (CDCl$_3$) δ 4.22, 4.36 (each 1H, d, >CH, J=8.8 Hz), 6.38 (2H, m, furan ring-H), 7.2-7.64, 7.78-8.04 (11H, m, ArH + furan ring-H); MS m/e 357 (M$^+$).

15b: mp 140-141°C; IR (KBr) 1810, 1690 (C=O), 1635 cm^{-1} (C=N); ^{1}H NMR (CDCl$_3$) δ 4.02, 4.27 (each

1H, d, >CH, J=8.9 Hz), 6.38 (2H, m, furan ring-H), 7.28-7.64, 7.82-8.02 (11H, m ArH + furan ring-H); MS m/e 357 (M^+).

16: mp 214-217°C; IR (KBr) 3320 (NH), 1665 (C=O), 1630 cm^{-1} (C=O, C=C); ^1H NMR ($CDCl_3$) δ 6.72 (2H, m, furan ring-H), 7.3-8.1 (13H, m, ArH + furan ring-H + NH); MS m/e 357 (M^+).

17a: mp 191-192°C; IR (KBr) 1810, 1705, 1680 (C=O), 1630 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 2.62 (3H, s, CH_3), 4.15 (1H, d, >CH, J=8.5 Hz), 4.39 (1H, dd, >CH, J=8.5, 1.0 Hz), 7.1-7.6, 7.8-8.04, 8.3-8.42 (15H, m, ArH + =CH); MS m/e 448 (M^+).

18: mp 248-250°C; IR (KBr) 3250 (NH), 1710, 1690 (C=O), 1630 cm^{-1} (C=O, C=C); ^1H NMR ($CDCl_3$) δ 2.65 (3H, s, CH_3), 7.2-8.0, 8.2-8.4 (17H, m, ArH + =CH + NH); MS m/e 448 (M^+).

19a: mp 150-151°C; IR (KBr) 1800, 1685 (C=O), 1640 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 1.55, 1.69 (each 3H, s, CH_3), 3.41 (1H, s, >CH), 7.26-8.08 (10H, m); MS m/e 319 (M^+).

19b: mp 104-105°C; IR (KBr) 1795, 1685 (C=O), 1640 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 1.60, 1.65 (each 3H, s, CH_3), 3.36 (1H, s, >CH), 7.2-8.0 (10H, m); MS m/e 319 (M^+).

20: mp 163-164°C; IR (KBr) 3310 (NH), 3100-2400 (OH), 1750, 1715, 1680, 1645 cm^{-1} (C=O); MS m/e 443 (M^+).

21: mp 173-175°C; IR (KBr) 3330 (NH), 3100-2400 (OH), 1710, 1660, 1640 (C=O), 1620 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 3.34 (1H, dd, >CH, J=9.0, 8.0 Hz), 4.18 (1H, d, >CH, J=8.0 Hz), 6.22 (1H, dd, =CH, J=9.0, 16.0 Hz), 6.85 (1H, d, =CH, J=16.0 Hz), 7.0-8.1 (15H, m), 9.33 (1H, s, NH), 11.3 (1H, broad, OH); MS m/e 411 (M^+).

At 0°C the spirocyclopropane of a-type was formed as the major product respectively, reflecting the predominant formation of favorable zwitterion of β-type. Assigned structures 19a and 19b can be also supported by the NMR data indicating the protons of methine and one of methyls in 19a appear at lower fields than those in 19b.

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