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Synthesis, Reaction, and Structure of Chiral *N*-Methyl-2-oxazolidinones from 3-Ethoxy-6-(*N*-methyl-*N*-*tert*-butoxycarbonyl)amino-2,4-hexadienoates

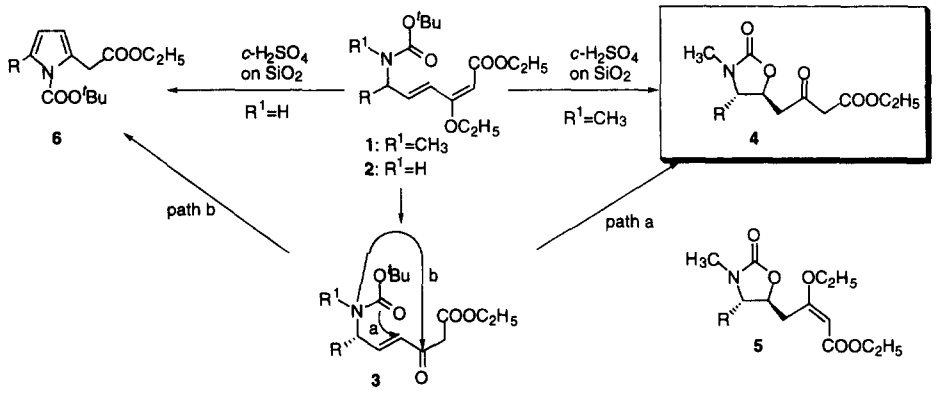
Tomikazu Kawano, Kenji Negoro, and Ikuo Ueda*

The Institute of Scientific and Industrial Research, Osaka University, Mihogaoka, Ibaraki, Osaka 567, Japan

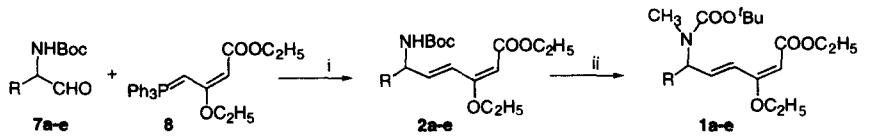
Abstract: *N*-methyl-2-oxazolidinones (**4**) are obtained stereo- and regio-selectively when 3-ethoxy-6-(*N*-methyl-*N*-*tert*-butoxycarbonyl)amino-2,4-hexadienoates (**1**) are treated with concentrated sulfuric acid (1.0 equiv.) supported on silicagel in dichloromethane at 0 °C. **4** were shown to be intermediates for the construction of *N*-methylpyrrole ring. The structure and properties of **4** and related compounds are also described. © 1997 Elsevier Science Ltd.

Chiral 2-oxazolidinones are routinely employed in organic synthesis as chiral auxiliaries for asymmetric C-C bond formation.[1] The traditional method for the preparation of 2-oxazolidinones has been the transformation of amino alcohols to cyclic carbamates using various condensation reagents.[2] Recently, we have reported the ring-construction of dihydropyridones[3], dihydropyrans[3], furylacetates[4] and cyclopent-2-en-1-ones[5] by the use of 3-ethoxy-2,4-hexadienoates bearing a functional group on the 6-position as synthetic synthons. In the course of our studies on the scope and limitations of this ring-construction, we have found that *N*-methyl-2-oxazolidinones (**4**) are obtained stereo- and regio-selectively when 3-ethoxy-6-(*N*-methyl-*N*-*tert*-butoxycarbonyl)amino-2,4-hexadienoates (**1**) are treated with concentrated sulfuric acid (*c*-H_2SO_4; 1.0 equiv.) supported on silicagel[6] at 0 °C in dichloromethane (path a). On the other hand, 6-(*N*-*tert*-butoxycarbonyl)amino-3-ethoxy-2,4-hexadienoates (**2**) are shown to afford pyrrole derivatives (**6**) under similar conditions (path b). Both reactions proceed through 6-(*N*-*tert*-butoxycarbonyl)amino-3-oxo-4-hexenoates (**3**) (Scheme 1). We report here synthesis, reaction, and structure of **4** and related compounds.

Scheme 1.



Scheme 2.



a: R=(*S*)-$C_6H_5CH_2$, **b**: R=(*R*)-$C_6H_5CH_2$, **c**: R=(*S*)-*iso*-Pro, **d**: R=(*R*)-*iso*-Pro, **e**: R=H

Reagents and conditions: i) THF, r.t., 24 h. ii) NaH, DMF, 0 °C, and then CH_3I, 0 °C, 2 h.

Scheme 2 shows the synthesis of key intermediates (**1**). α-(*N*-*tert*-Butoxycarbonyl)aminoacetaldehyde

(**7a**) prepared from commercially available (*L*)-phenylalanine according to the described procedure in the literature[7] was reacted with (2-ethoxy-3-ethoxycarbonylallylidene)triphenylphosphorane (**8**)[8] to give 6-(*N*-*tert*-butoxycarbonyl)amino-3-ethoxy-2,4-hexadienoate (**2a**) in 99% yield. Reaction of **2a** with methyl iodide in the presence of sodium hydride gave (**1a**) in a quantitative yield. The same treatment applied to **7b-e** afforded **1b-e** in good yields, respectively.

One of our attempts was to convert **1** to *N*-methylpyrrole derivatives. The reaction of **1b** with acids was first examined. Treatment of **1b** under the chosen acidic conditions of 3*N* HCl in THF, 47% HBr in THF and *c*-H_2SO_4 supported on silicagel did not afford the desired *N*-methylpyrroles. Unprecedentedly, **1b** reacted with *c*-H_2SO_4 (0.2 equiv.) supported on silicagel at room temperature for 20 h in dichloromethane to afford 2-oxazolidinone (**5b**)[9] in 8% yield along with 6-amino-3-oxo-hexenoate (**3b**) in a (3:1) equilibrium mixture of keto form and enol form in 47% yield.

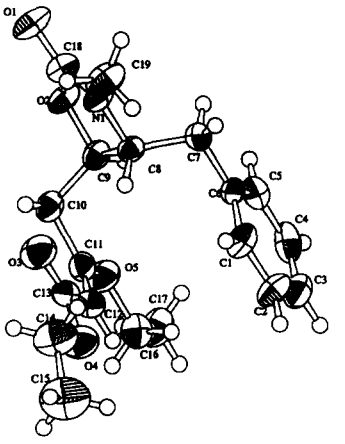
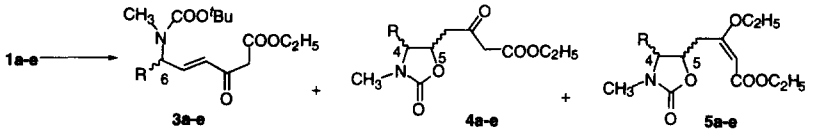


Figure 1. The ORTEP structure of **5b**

The structure of **5b** was determined on the basis of IR and NMR spectral data and elementary analyses. Finally, the structure was confirmed by an X-ray crystal analysis of **5b** (a colorless prismatic crystal). Two substituents at the 4- and 5-positions were shown to have a trans relationship. The configuration of the 4-position was assigned to be (*R*) which is referred to that of the starting material, *D*-phenylalanine. Thus, the configuration of the 5-position also was determined as (*R*). The ORTEP structure is shown in Figure 1.[10]

Table 1. Reaction of **1** with concentrated sulfuric acid supported on silicagel



a: R=(*S*)-$C_6H_5CH_2$, **b**: R=(*R*)-$C_6H_5CH_2$, **c**: R=(*S*)-*iso*-Pro,**d**: R=(*R*)-*iso*-Pro, **e**: R=H

Entry	Starting material		Conditions[2] *c*-H_2SO_4 (equiv.)	Temperature (°C)	Time (h)	Product (%)[3] 3-Oxo-4-hexenoate	2-Oxazolidinone	
1	**1b**	R	0.2	r.t.	20	(6R) **3b** (47)	(4R,5R) **4b** (n.d.)	(4R,5R) **5b** (8)
2	**1b**	R	0.2	0	3	(6R) **3b** (52)	(4R,5R) **4b** (18)	(4R,5R) **5b** (19)
3	**1b**	R	1.0	0	0.25	(6R) **3b** (15)	(4R,5R) **4b** (50)	(4R,5R) **5b** (12)
4	**1b**	R	1.0	0	0.5	(6R) **3b** (2)	(4R,5R) **4b** (77)	(4R,5R) **5b** (12)
5	**1b**	R	1.0	0	1.0	(6R) **3b** (n.d.)[4]	(4R,5R) **4b** (78)	(4R,5R) **5b** (11)
6	**1c**	R	1.0	0	2.0	(6R) **3c** (n.d.)	(4R,5R) **4c** (78)	(4R,5R) **5c** (9)
7	**1b**	R	1.0	0	3.0	(6R) **3b** (n.d.)	(4R,5R) **4b** (79)	(4R,5R) **5b** (4)
8	**1b**	R	1.0	0	12	(6R) **3b** (n.d.)	(4R,5R) **4b** (77)	(4R,5R) **5b** (n.d.)
9	**1b**	R	2.0	0	1	(6R) **3b** (n.d.)	(4R,5R) **4b** (67)	(4R,5R) **5b** (n.d.)
10	**1a**	S	1.0	0	3.0	(6S) **3a** (n.d.)	(4S,5S) **4a** (85)	(4S,5S) **5a** (8)
11	**1c**	S	1.0	0	3.0	(6S) **3c** (n.d.)	(4S,5S) **4c** (88)	(4S,5S) **5c** (2)
12	**1d**	R	1.0	0	3.0	(6R) **3d** (n.d.)	(4R,5R) **4d** (72)	(4R,5R) **5d** (11)
13[1]	**1e**	-	1.0	0	0.33	**3e** (n.d.)	**4e** (22)	**5e** (17)

1) *N*-Methyl-2-pyrrolylacetate was obtained in 13% yield. 2) A solution of **1** (1 mmol) in CH_2Cl_2 (5 ml) was stirred in the presence of *c*-H_2SO_4 supported on silicagel. 3) Isolated yield. 4) n.d.; not detected.

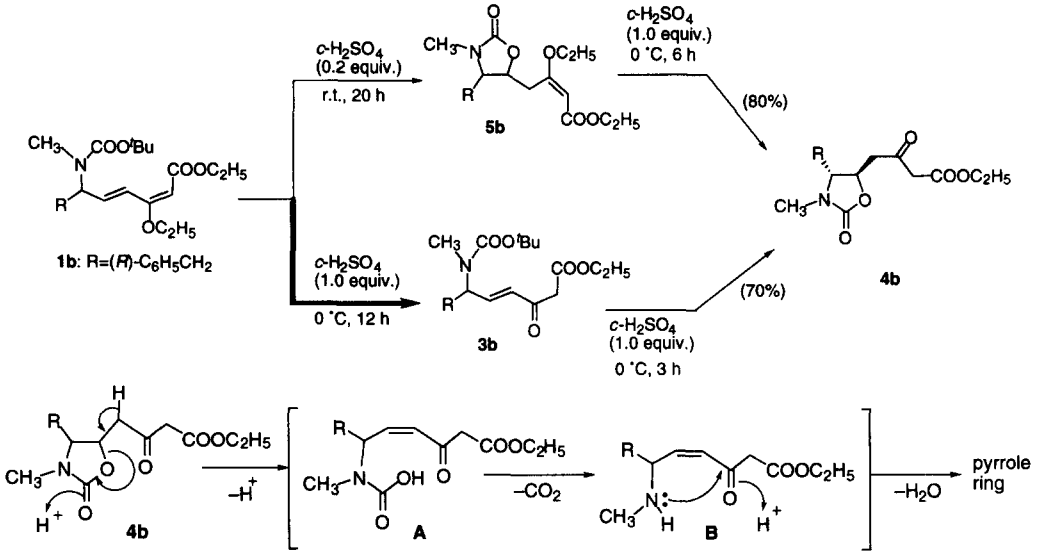
Then, the cyclization reaction of **1** with *c*-H_2SO_4 supported on silicagel in dichloromethane was examined

in detail (Table 1). Reaction of **1b** with *c*-H_2SO_4 (0.2 equiv.) at room temperature for 20 h or at 0 °C for 3 h proceeded concertedly to afford **3b** and **5b**, the former of which was in higher yield than the latter, indicating that the hydrolysis of enolether group occurred more rapidly than the cyclization reaction (entries 1 and 2). Three-hour treatment of **1a-d** with *c*-H_2SO_4 (1.0 equiv.) at 0 °C afforded corresponding 2-oxazolidinones (**4a-d** and **5a-d**) in good to excellent yields. (entries 7, 10, 11, 12). Under the conditions of either a high acid concentration (entry 9) or a longer reaction time (entry 8), **1b** afforded only **4b** in good yields. When **1e** was reacted with *c*-H_2SO_4 (1.0 equiv.) at 0 °C for 20 min, 2-oxazolidinones (**4e** and **5e**) were obtained in 22% and 17% yields along with ethyl *N*-methyl-2-pyrrolylacetate in 13% yield (entry 13). Thus, the reactions described here were shown to proceed depending on three factors of acid concentration, temperature and time.

Additionally, **5b** was converted to **4b** in 80% yield on treatment with *c*-H_2SO_4 (1.0 equiv.) at 0 °C for 6 h in dichloromethane, which was in a (6:1) equilibrium mixture of keto form and enol form, while three-hour treatment of **3b** under the same conditions afforded **4b** in 70% yield. Being allowed to stand at room temperature, **4b** was gradually converted to *N*-methyl-5-benzyl-2-pyrrolylacetate.[11]

The outline of the construction of the 2-oxazolidinone and *N*-methylpyrrole rings is illustrated in Scheme 4 for **1b** as a typical example. Reaction of **1b** with *c*-H_2SO_4 at low acid concentration affords **3b** and **5b** which are converted to **4b** under the specified conditions. A main pathway to **4b** from **1b** will be the one through **3b**. On the other hand, the formation of pyrrole ring from **4b** can be explained by intramolecular cyclization of γ-amino-α,β-unsaturated carbonyl compound (**B**) which is formed via an intermediate (**A**).

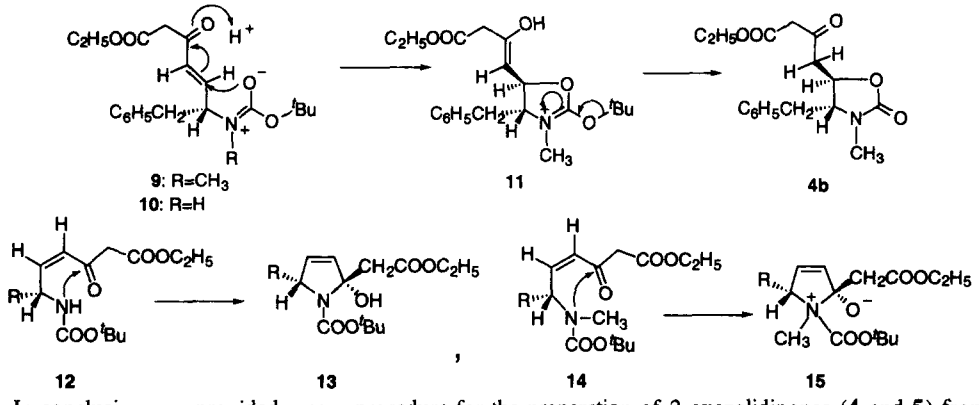
Scheme 4.



This cyclization described here is highly promoted by a structural feature of the 3-ethoxy-2,4-hexadienoate function and the presence of an *N*-methyl substituent (Scheme 5). The reaction can be understood best in terms of a Michael-type addition of carbonyl group at an end of the α,β-unsaturated carbonyl function, being accelerated by acid. From data of Agami et al.[12], the effect of the methyl group for the construction of the 2-oxazolidinone ring will be estimated as follows: *N*-methylated substrate **9** and **10** at the ground state will afford similar relative conformations corresponding to the one depicted in Scheme 5. The *N*-methylated substrate **9** may cyclize easily with a compression of the internal C-N=C angle due to the *N*-methyl group in agreement with the Thorpe-Ingold effect[13] to give **4b** stereo- and regio-selectively via an intermediate **11**. On the other hand, the precursors (**12** and **14**) for the pyrrole ring construction with similar relative conformations undergo intramolecular cyclization to give respective intermediates **13** and **15**, the latter of which will be an unstable intermediate, compared to the former. Owing to the easier production of **13** over **15**, it can be hypothesized that

the cyclization of **9** to a 2-oxazolidinone ring is favored over that to the pyrrole ring.[13] Therefore, the conformational effect for the formation of 2-oxazolidinones would be responsible for the reactivity enhancement promoted by the *N*-methyl substituent.

Scheme 5.



In conclusion, we provided a new procedure for the preparation of 2-oxazolidinones (**4** and **5**) from **1**. And it is apparent that the acid concentration and methyl group on the nitrogen will play an important role in this cyclization. Although we have not studied the scope of this method yet, it appears to have potential for application to the synthesis of a wide variety of 2-oxazolidinones and *N*-substituted pyrroles because of the ready availability of many amino acids and simple allylidenephosphoranes.

Acknowledgments

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9. All new compounds in this paper gave satisfactory IR, NMR, Mass spectra and elementary analyses. Selected physical data are as follows. **5a**: Colorless prisms, mp 89.5-92.5 °C (ether-hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (m, 3 H), 7.10 (d, *J*= 6.8 Hz, 2 H), 4.89 (s, 1 H), 4.46 (ddd, *J*= 4.1, 6.3, 7.0 Hz, 1 H), 4.12 (q, *J*= 7.2 Hz, 2 H), 3.69 (ddd, *J*= 4.1, 4.9, 8.3 Hz, 1 H), 3.62 (ddd, *J*= 7.0, 9.5, 14 Hz, 1 H), 3.47 (ddd, *J*= 7.0, 9.5, 14 Hz, 1 H), 3.10-2.95(m, 3H), 2.87 (s, 3H), 2.70 (dd, *J*=8.3, 14 Hz, 1 H), 1.27 (t, *J*=7.2 Hz, 3 H), 1.23 (t, *J*=7.0 Hz, 3 H) ppm; IR (KBr): 3000, 2950, 1755, 1710, 1635 cm^{-1}. MS (FAB) m/z 348 [(M+H)$^+$]. *Anal:* Found: C, 65.63; H, 7.13; N, 4.04%. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03%. $[\alpha]_D$: -29.1° (c 7.80, $CHCl_3$). As **4** are converted gradually to an *N*-methylpyrrole ring at room temperature, storage of the compounds should be done with care, keeping the temperature below -30°C.
10. The crystal data for **5b**: Crystal dimensions = 0.35x0.43x0.35 mm, Orthorhombic, Space group $P2_12_12_1$(no. 19), a=12.065 (4)Å, b=19.715(3)Å, c=7.772(5)Å, V=1848(1)Å^3; Z = 4; F(000)=744; D_{calc} 1.248 g/cm^3; The final R and R_w were 0.058 and 0.060 for 1378 observed reflections (I>3.00 (σ) I). The structure was solved by direct method (SAPI91) and refined by full-matrix least-squares techniques. Diffraction data were obtained using Rigaku AFC5R diffractometer at -75 °C.
11. Further studies on the formation of pyrrole ring are in progress.
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