N-Vinyl-2-Oxazolidinone: New Preparation Methods and First Uses as a Dienophile

Catherine Gaulon, Patricia Gizecki, Robert Dhal,* Gilles Dujardin*

UMR 6011 CNRS- Université du Maine, Laboratoire de Synthèse Organique (UCO2M)Faculté des Sciences, Avenue Olivier Messiaen, 72085 Le Mans Cedex 9, France
E-mail: dujardin@univ-lemans.fr

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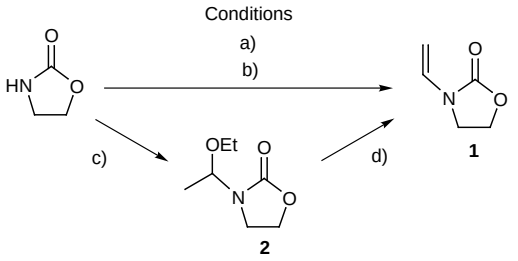
Abstract: *N*-Vinyloxazolidinone was conveniently prepared in 73% overall yield by an easy two-step procedure based on the dehydroalkoxylation of an intermediate hemiaminal using trimethylsilyl trifluoromethanesulfonate and triethylamine. The good dienophilicity of this enecarbamate was demonstrated in several [4+2] stereocontrolled processes involving activated 1-oxabutadienes under appropriate Lewis-acid catalyzed conditions. In addition, an unexpected amido-alkylation of the title compound is described under mild conditions.

Key-words: *N*-vinyl oxazolidinone, *N,O*-acetal, lanthanide, dienophile, heterocycloaddition

The development of new cycloreactants is a continuous challenge in the field of pericyclic reactions. Use of hetero-substituted dienes and dienophiles is of specific interest for the application of [4+2] homo- and heterocycloadditions towards natural and biologically active products synthesis.[1] Therefore, incorporating aza-substituted dienophiles in inverse-electron demand [4+2] cycloaddition processes can display large potentialities, especially for aminocyclitols and aza-sugar *de novo* access. Reports in this area mainly concerned the use of electron-rich enamines, but to our knowledge, none reported the use of weaker dienophiles such as enamides or enecarbamates.[2–5] We describe here the first examples of an inverse-electron demand heterocycloaddition using *N*-vinyl-2-oxazolidinone (**1**) as the dienophile. In addition, a new mercury-free preparation method of the title compound is reported.

Despite its usefulness as synthetic intermediate for several applications,[6] no efficient and generalizable preparation of *N*-vinyl-2-oxazolidinone (**1**) was known starting from 2-oxazolidinone. Typically, mercury(II) acetate-catalyzed exchange with butyl vinyl ether under pressure and heat was reported with low yields (*ca* 35%).[7] Under simple thermal conditions, we observed that conversion into **1** was greatly improved when using mercury(II) trifluoroacetate instead of mercury(II) acetate[8] (Scheme 1).

In order to proceed under mercury-free conditions, we intended to apply to 2-oxazolidinone the addition-elimination procedure previously established for *O*-vinylation of secondary alcohols.[9]



Scheme 1 Reagents and conditions : a) isobutyl vinyl ether, $Hg(OCOCH_3)_2$ 10 mol%, reflux, 24 h (Yield: 10%) . b) isobutyl vinyl ether, $Hg(OCOCF_3)_2$ 10 mol%, reflux, 24 h (Yield: 57%). c) $CH_3CH(OEt)_2$, CSA 5 mol%, 55 °C, 15 h. d) TMSOTf, NEt_3, 0 °C to r.t., CH_2Cl_2, 16 h (Yield: 73%, overall).

While 2-oxazolidinone addition to ethyl vinyl ether using trifluoroacetic acid led to some degradation, its reaction with acetaldehyde diethyl acetal using camphorsulfonic acid[10] as the catalyst produced quantitatively the desired *N,O*-acetal **2** (Scheme 1). We expected then that **2** could afford an efficient access to *N*-vinyl-2-oxazolidinone (**1**) via regiocontrolled elimination under Gassman-type conditions.[11] Indeed, a clean dehydroalkoxylation of the crude *N,O*-acetal **2** occurred using trimethylsilyl trifluoromethanesulfonate[12] and triethylamine, giving *N*-vinyl-2-oxazolidinone **1** in 73% overall yield (Scheme 1).[13] The regioselectivity of the elimination process appeared better than 99:1.

The dienophilicity of *N*-vinyl-2-oxazolidinone **1** was next examined with a representative electron-poor heterodiene, (*E*) methyl benzylidene pyruvate **3a** (Equation 1, Table 1) under various conditions. We observed that a 1:1 mixture of **1** and **3a** in refluxing cyclohexane followed a very clean cycloaddition process when catalytic amounts of organosoluble lanthanide salts such as $Eu(fod)_3$ or $Yb(fod)_3$ were added (entries 1 and 2).[14] The heteroadduct **4a** was thus obtained[15] with a high *cis* selectivity and was easily purified after simple removal of the solvent and chromatography. Without any Lewis acid, no reaction occurred, even after 24 h at 80 °C (entry 3).

Non-thermal conditions were also tested. The heteroadduct **4a** was rapidly obtained in high yield at –78 °C using 0.5 equiv of tin tetrachloride[16] (entry 4). Diminishing the ratio of Lewis acid led to weaker conversions even after prolongated reaction times and extensive degradation of the dienophile occurred in the medium (entries 5–7). As

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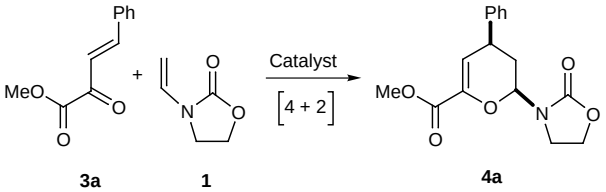
Table 1 Acid-Catalyzed Cycloaddition of **1** and **3a** into **4a**

Entry	Catalyst n (mol%).	Solvent	Conditions (Time, Temp.)	Yield[a] (%)	*Cis*/*Trans*[c]
1	$Eu(fod)_3$ (5)	Cyclohexane	18 h, reflux	88	97:3
2	$Yb(fod)_3$ (5)	Cyclohexane	15 h, reflux	88	98:2
3	none	Cyclohexane	24 h, reflux	0	–
4	$SnCl_4$ (50)	CH_2Cl_2	0.1 h, –78 °C	94	68:32
5	$SnCl_4$ (5)	CH_2Cl_2	2.5 h, –78 °C	10[b]	65:35
6	$SnCl_4$ (10)	CH_2Cl_2	2.5 h, –78 °C	44[b]	83:17
7	$SnCl_4$ (25)	CH_2Cl_2	0.2 h, –78 °C	76[b]	67:33
8	$TiCl_4$ (50)	CH_2Cl_2	0.1 h, –78 °C	60[b]	68:32

[a] Isolated yields after column chromatography.
[b] Conversion related to remaining diene.
[c] Ratio based on ^{1}H NMR (400 MHz) spectra of crude product.

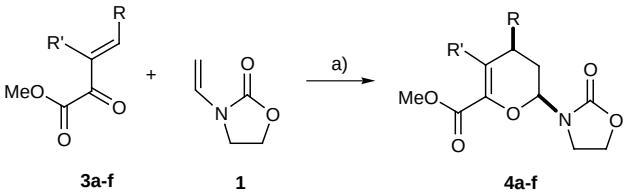
previously reported for others types of dienophiles, titanium tetrachloride revealed to be less efficient than tin tetrachloride for this cycloaddition process (entry 8 *vs* 4).[17]



Equation 1

In both cases, a weak *cis* selectivity was observed. It must be mentioned that non-chelating reagents like TMSOTf and $BF_3{\cdot}Et_2O$ completely failed to promote the reaction under the conditions successfully used with $SnCl_4$ and $TiCl_4$. This result may be due to a prior complexation of the catalyst with the carbamate moiety of the dienophile thus leading to degradation of the latter.

The efficiency of $Eu(fod)_3$ to catalyze and to stereocontrol the heterocycloaddition of *N*-vinyl-2-oxazolidinone **1** was next experienced with others activated 1-oxabutadienes **3** (Equation 2, Table 2). High yields and *cis*-selectivities were homogeneously obtained with aryl-substituted benzylidene pyruvates **3b**–**c**. A lower reactivity prevailed between *N*-vinyl-2-oxazolidinone **1** and 4-alkoxymethylidene pyruvates.[17] Extended reaction time (96 h) led to modest to good isolated yields (40–60%) of heteroadducts **4d**–**f** with partial recovery of starting materials. Interestingly, *cis/trans* ratios seemed severely dependent on the nature of heterodiene substituents.



Equation 2 Reagents and conditions : a) $Eu(fod)_3$ 5 mol%, cyclohexane, reflux.

The assignation of the 1,3-*cis* configuration to the major (or the only) isomer of adducts **4a-f** thus obtained was based on the common features displayed by ^{1}H NMR

Table 2 $Eu(fod)_3$-Catalyzed Heterocycloadditions of **1** with Heterodienes **3a**–**f**

Entry	Diene	R	R'	Adduct	Time (h).	Yield[a] (%)	*Cis* /*Trans*[b]
1	**3a**	Ph	H	**4a**	18	88	97:3
2	**3b**	*p*-MeO-C_6H_4	H	**4b**	15	80	98:2
3	**3c**	*p*-NO_2-C_6H_4	H	**4c**	38	86	98:2
4	**3d**	*t*-BuO	H	**4d**	96	60	90:10
5	**3e**	OBn	H	**4e**	96	40	65:35
6	**3f**	O-CH_2-CH_2-CH_2-		**4f**	96	41	>98:2

[a] Isolated yields after column chromatography.
[b] Ratio based on ^{1}H NMR (400 MHz) spectra of crude product.

spectra. This *cis* relationship between the oxazolidinyl moiety and the R group (Figure 1) was evidenced by the common axial character of hemiaminalic and allylic protons ($11.2 < J_{1/2ax} < 12.1$ Hz, $9.6 < J_{2ax/3} < 11.5$ Hz and $1.7 \text{ Hz} < J_{4/3} < 2.0$ Hz), consistent with a *cis*-pseudoequatorial arrangement of both substituents, favored by reverse anomeric effect.[18] Minor *trans* isomers, isolated in the case of **4a** and **4e**, exhibit again a pseudo equatorial position of the oxazolidinyl moiety, attested by the high value of $J_{1/2ax}$ (12.1 Hz and 11.3 Hz for **4a** *trans* and **4e** *trans* respectively). They are characterized by a pseudoaxial position of the phenyl group ($J_{2ax/3}$ = 6.6 Hz, $J_{4/3}$ = 5.3 Hz) and of the benzyl group ($J_{2ax/3}$ = 4.2 Hz, $J_{4/3}$ = 5.4 Hz) respectively.

With less reactive heterodienes such as **3g**, we observed the dimerisation of **1** (Scheme 2).

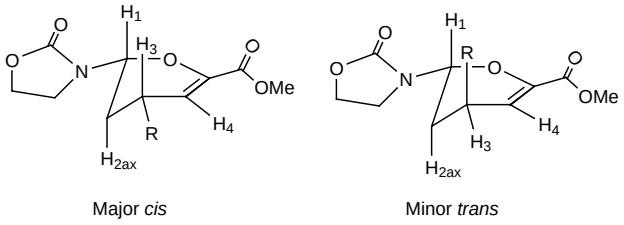
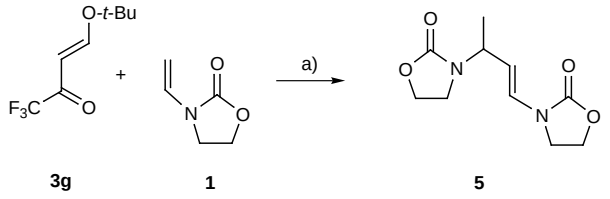


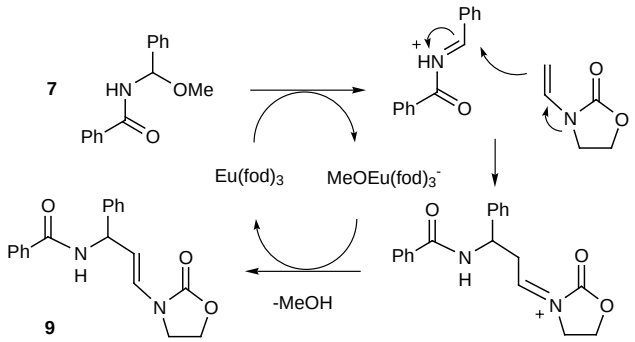
Figure 1 *Cis*/*trans* configuration of adducts **4a**–**e** based on ^{1}H NMR analysis.



Scheme 2 Reagents and conditions : a) Eu(fod)$_3$ 5 mol%, hydroquinone 10 mol%, cyclohexane–toluene, 1:1, reflux.

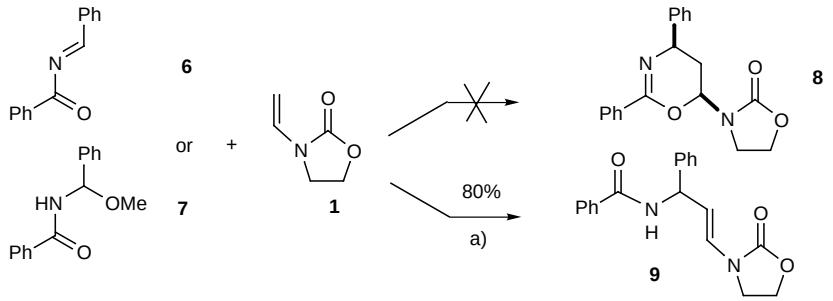
Recent results of our group demonstrated that acylimine **6** or its more available synthetic equivalent **7** can be efficient precursors of stable 6-alkoxy dihydrooxazines when opposed to vinyl ethers of some secondary alcohols under appropriate Lewis acid conditions.[19] Starting from *N*-vinyl-2-oxazolidinone **1**, all attempts to obtain the 6-oxazolidinyl dihydrooxazine **8** from **6** or **7** were unsuccessful.

With *N*,*O*-acetal **7**, an unexpected Eu(fod)$_3$-catalyzed reaction of **1** was observed in refluxing toluene (Scheme 3). The (*E*)-enecarbamate **9**[20] thus obtained in high yield after 60 h would result from the nucleophilic attack of **1** on an intermediate *N*-acyliminium, followed by β-elimination (Scheme 4). This assumption is consistent with the obtention of the dimer **5** (Scheme 2), that may proceed via the equilibrated formation of an *N*-acyliminium from the enamide.



Scheme 4

In summary, the present results indicate that *N*-vinyl-2-oxazolidinone **1** can act as a valuable dienophile in inverse electron demand heterocycloaddition. Considering 1) the good reactivity observed towards activated 1-oxabutadienes in chelating-Lewis acid conditions and 2) the specific synthetic potential of **4**-type adducts that may result in functional modifications of dihydropyranic and oxazolidinyl moieties at a further stage, such reactions could lead to fruitful applications in the field of *N*-glycosylated β-amino alcohols or α-amino acids. Asymmetric extension of this [4+2] methodology is currently under investigation by application of the mercury-free *N*-vinylation method to chiral 2-oxazolidinones.



Scheme 3 Eu(fod)$_3$-catalyzed amido-alkylation of **1**. Reagents and conditions : a) **7** (1.5 equiv), Eu(fod)$_3$ 5 mol%, toluene, reflux, 60 h.

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(13) *Preparation of N-vinyl-2-oxazolidinone* **1**: A mixture of oxazolidinone (2.05 g, 23.4 mmol), acetaldehyde diethyl acetal (33 mL, 0.23 mol) and D,L-camphorsulfonic acid (0.27 g, 1.17 mmol) was heated for 15 h at 55 °C. After cooling, aq. $NaHCO_3$ (15 mL) was added and the reaction mixture extracted with Et_2O (3 × 8 mL). The organic layer was washed with brine and dried over $MgSO_4$. Removal of solvent yielded crude *N*,*O*-acetal **2** (3.72 g, quantitative) used without further purification. To a cooled solution (0 °C) of crude *N*,*O*-acetal **2** (3.72 g, 23.4 mmol) in anhydrous CH_2Cl_2 under nitrogen (22 mL) were dropwise added distilled NEt_3 (4.9 mL, 37.7 mmol) and, trimethylsilyl triflate (5.5 mL, 30.4 mmol). After slow return to r.t. and stirring for 16 h, the mixture was filtered on basic alumina. Removal of solvent and purification by filtration (silica gel 4/1; ether) yielded **1** (1.95 g, 73%) as a pale yellow oil; R_f = 0.37 (Cyclohexane–AcOEt, 1:1); IR(film): 1753 (C=O), 1633 (C=C), 1248, 1080 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 3.72 (t, 2 H, $J_{4'\text{-}5'}$ = 8.2 Hz, H-4′), 4.30 (dd, 1 H, $J_{2B\text{-}1}$ = 15.8 Hz, J_{AB} = 1.0 Hz, H-2_B), 4.44 (dd, 1 H, $J_{2A\text{-}1}$ = 8.9 Hz, J_{AB} = 1.0 Hz, H-2_A), 4.47 (t, 2 H, $J_{5'\text{-}4'}$ = 8.2 Hz, H-5′), 6.89 (dd, 1 H, $J_{1\text{-}2B}$ = 15.8 Hz, $J_{1\text{-}2A}$ = 8.9 Hz, H-1); ^{13}C NMR(100 MHz, $CDCl_3$), δ 41.7 (C-4′), 62.0 (C-5′), 93.3 (C-2), 129.7 (C-1), 155.2 (C-2′)..

(14) *General preparation of hetero-adduct* **4a–f** *with Eu(fod)*$_3$: A solution of heterodiene **3** (0.5 mmol), *N*-vinyl-2-oxazolidinone **1** (0.5 mmol) and $Eu(fod)_3$ (0.025 mmol) in cyclohexane (5 mL) was refluxed under nitrogen for the time referred to Table 2. After removal of solvent the crude product was chromatographed (silica gel 40/1) using cyclohexane–AcOEt, 70:30 to 50:50. Compounds **4a–f** obtained with yields referred to Table 2 are new and analytical data of one representative example is included in ref. 15.

(15) *Analytical data of hetero-adduct* **4a** ***cis***: white crystal, mp 59–61 °C(ether); R_f = 0.23 (cyclohexane–AcOEt, 1:1); ^1H NMR (400 MHz, $CDCl_3$), δ 1.94 (dt, 1 H, J_{AB} = 12.8 Hz, $J_{2ax\text{-}3}$ = $J_{2ax\text{-}1}$ = 11.3 Hz, H-2_{ax}), 2.26 (ddt, 1 H, J_{AB} = 12.8 Hz, $J_{2eq\text{-}3}$ = 6.4 Hz, $J_{2eq\text{-}1}$ = $J_{2eq\text{-}4}$ = 2 Hz, H-2_{eq}), 3.57 (dt, 1 H, J_{AB} = $J_{4'B\text{-}5'B}$ = 8.9 Hz, $J_{4'B\text{-}5'A}$ = 6.2 Hz, H-4′$_B$), 3.81 (s, 3 H, OCH_3), 3.84 (m, 1 H, H-4′$_A$), 3.89 (ddd, 1 H, $J_{3\text{-}2ax}$ = 11.3 Hz, $J_{3\text{-}2eq}$ = 6.4 Hz, $J_{3\text{-}4}$ = 2.5 Hz, H-3), 4.38 (dt, 1 H, J_{AB} = $J_{5'B\text{-}4'B}$ = 8.9 Hz, $J_{5'B\text{-}4'A}$ = 6.9 Hz, H-5′$_B$), 4.46 (dt, 1 H, J_{AB} = $J_{5'A\text{-}4'A}$ = 8.9 Hz, $J_{5'A\text{-}4'B}$ = 6.2 Hz, H-5′$_A$), 5.76 (dd, 1 H, $J_{1\text{-}2ax}$ = 11.3 Hz, $J_{1\text{-}2eq}$ = 2 Hz, H-1), 6.17 (t, 1 H, $J_{4\text{-}3}$ = $J_{4\text{-}2eq}$ = 2 Hz, H-4), 7.22 (d, 2 H, *J* = 6.9 Hz, H_o), 7.29 (t, 1 H, *J* = 7.4 Hz, H_p), 7.35 (t, 2 H, *J* = 7.4 Hz, H_m); ^{13}C NMR (100 MHz, $CDCl_3$), δ 35.5 (C-2), 39.5 (C-3), 40.1 (C-4′), 52.7 (OCH_3), 62.9 (C-5′), 81.3 (C-1), 114.6 (C-4), 127.5 (C_o), 127.7 (C_p), 129.3 (C_m), 142.5 (C_n), 144.4 (C-5), 157.8 (C-2′), 163.0 (CO_2). IR(film): 1758 (C=O), 1643 (C=C), 1134, 1248, 1288 (C-O) cm^{-1}; SM $C_{16}H_{17}NO_5$ $[M]^{+\cdot}$ 303 (1.8%); HRMS (EI) calcd for $C_{16}H_{15}NO_4$ $[M\text{-}H_2O]^+$ 285.1001, found 285.1008.

(16) *Preparation of hetero-adduct* **4a** ***trans*** *with* $SnCl_4$: To a cooled solution (–78 °C) of heterodiene **3a** (95 mg, 0.5 mmol) and *N*-vinyl-2-oxazolidinone **1** (57 mg, 0.5 mmol) in anhydrous CH_2Cl_2 (5 mL) under nitrogen was added dropwise $SnCl_4$ 1 M in CH_2Cl_2 (0.25 mL, 0.25 mmol). After stirring (5 min) the mixture was quenched with sat. aq. $NaHCO_3$ (5 mL). After returning to r.t. and extraction with CH_2Cl_2 (2 × 5 mL), the resulting organic layer was dried ($MgSO_4$). Removal of solvent and purification by chromatography (silica gel 40/1; cyclohexane–AcOEt, 70:30 to 50:50) yielded **4a** (143 mg, 94%) as a mixture *cis*/*trans*, 68:32. **4a** ***trans*** was thus isolated as a white solid; R_f = 0.16 (cyclohexane–AcOEt, 1:1); ^1H NMR (400 MHz, $CDCl_3$), δ 2.03 (dq, 1 H, J_{AB} = 13.3 Hz, $J_{2eq\text{-}1}$ = $J_{2eq\text{-}3}$ = $J_{2eq\text{-}4}$ = 2 Hz, H-2_{eq}), 2.33 (ddd, 1 H, J_{AB} = 13.3 Hz, $J_{2ax\text{-}1}$ = 11.3 Hz, $J_{2ax\text{-}3}$ = 6.6 Hz, H-2_{ax}), 3.61 (dt, 1 H, J_{AB} = $J_{4'B\text{-}5'B}$ = 8.6 Hz, $J_{4'B\text{-}5'A}$ = 5.9 Hz, H-4′$_B$), 3.81 (m, 2 H, H-3 + H-4′$_A$), 3.83 (s, 3 H, OCH_3), 4.34 (q, 1 H, J_{AB} = $J_{5'B\text{-}4'B}$ = $J_{5'B\text{-}4'A}$ = 8.5 Hz, H-5′$_B$), 4.42 (dt, 1 H, J_{AB} = $J_{5'A\text{-}4'A}$ = 8.9 Hz, $J_{5'A\text{-}4'B}$ = 5.9 Hz, H-5′$_A$), 5.43 (dd, 1 H, $J_{1\text{-}2ax}$ = 11.3 Hz, $J_{1\text{-}2eq}$ = 2.2 Hz, H-1), 6.25 (dd, 1 H, $J_{4\text{-}3}$ = 5.3 Hz, $J_{4\text{-}2eq}$ = 1.5 Hz, H-4), 7.23 (d, 2 H, *J* = 6.9 Hz, H_o), 7.27 (t, 1 H, *J* = 5.9 Hz, H_p), 7.35 (t, 2 H, *J* = 7.4 Hz, H_m); ^{13}C NMR (100 MHz, $CDCl_3$), δ 33.8 (C-2), 37.1 (C-3), 40.5 (C-4′), 52.7 (OCH_3), 62.8 (C-5′), 77.7 (C-1), 111.9 (C-4), 127.6 (C_p), 128.4 C_o), 129.3 (C_m), 143.2 (C_n), 144.7 (C-5), 157.8 (C-2′), 163.1 (CO_2).

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(20) Selected data of **9**: ^{1}H NMR (400 MHz, $CDCl_3$), δ 6.87 (1 H, dd, *J* = 14.3 and 1.2 Hz), 5.13 (1 H, dd, *J* = 14.3 and 6.4 Hz).IR(film): 3309 (NH); 1747 (C=O), 1670 (C=C), 1637 (C=O) cm^{-1}.