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Unusual Regiochemistry of Cycloaddition of Ketenes to (*R*)-2-*tert*-Butyldihydrooxazole Derivatives. A Simple Route towards Enantiomerically Pure Functionalised α-Aminocyclobutanones.

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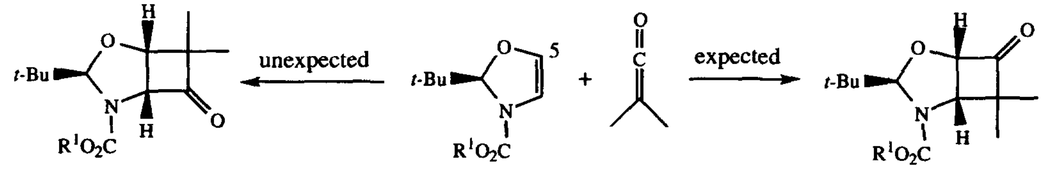
Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

Abstract: Ketenes have been found to cycloadd with (*R*)-2-*tert*-Butyldihydrooxazole 1 and 2 to yield predominantly regioisomers 4 resulting from steric control rather than electronic control. The cycloadditions provide a practical route to enantiomerically pure protected 2-amino-3-hydroxycyclobutanones. © 1997 Elsevier Science Ltd.

In connection with studies of new inhibitors of bacterial D,D-peptidases,[1] we required a flexible route towards enantiomerically pure 2-aminocyclobutanones which could be functionalised at C-3 and C-4. (*R*)-2-*tert*-butyldihydrooxazole **1** which can be readily prepared[2] from (*S*)-serine appeared to us as an attractive olefinic building block which should react with ketenes from the less-hindered face of the olefin to generate enantiomerically pure cyclobutanones (Scheme 1).



4

1, R^1 = Me

2, R^1 = *t*-Bu

3

Scheme 1

However Seebach *et al* have shown[3] that electrophilic additions to **1** always occur at C-5 as a result of the lower energy of an acyliminium ion relative to that of an oxonium ion.[4] Thus it was anticipated that the reaction of **1** with ketenes would produce regioisomer **3** rather than **4**. Extra steps would then be needed to generate a carbonyl group α to the nitrogen. This paper reports the unexpected observation that ketenes reacted with **1** and **2** to yield predominantly adducts **4**.

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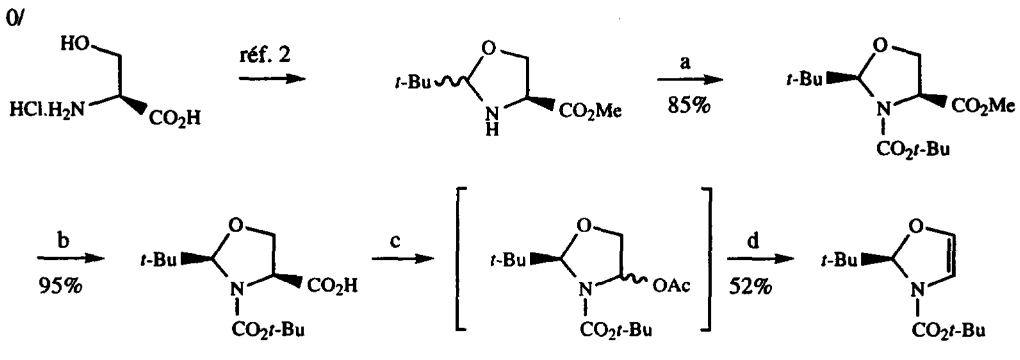
Compounds **1** (R^1 = Me) and **2** (R^1 = *t*-Bu) were prepared according to the route published by Seebach *et al* [2] except for the oxidative decarboxylation step. A thermal oxidative decarboxylation with lead tetraacetate was preferred to the electrochemical method. Compound **2** is new. It was obtained in 34% overall yield from (*S*)-serine methyl ester hydrochloride (Scheme 2).

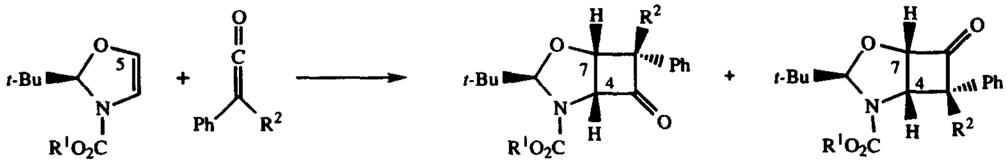


(*R*)-**2**

Reaction conditions : a : Boc_2O, Et_3N, THF, 12 h, RT; b : KOH, MeOH, 12 h, RT; c : $Pb(OAc)_4$, benzene, Δ, 8 h; d : NH_4Br, $Cl(CH_2)_2Cl$, Δ, 12h

Scheme 2

The results of the cycloaddition of **1** and **2** with diphenyl[5] and phenylchloro[6] ketenes are described in Scheme 3 and Table 1. When R^1 = Me, the isomer composition was determined by NMR of the crude mixture. When R^1 = *t*-Bu, it was determined after flash-chromatography of the reaction mixture. Structures of **4b**, **4c**, **3c** and **3d** were confirmed by X-ray diffraction analyses.[7]



		4	**3**
a : R^1 = Me, R^2 = Ph	80%	5.1	1
b : R^1 = *t*-bu, R^2 = Ph	37%	4	1
c : R^1 = Me, R^2 = Cl	87%	10	1
d : R^1 = *t*-bu, R^2 = Cl	60%	5.9	1

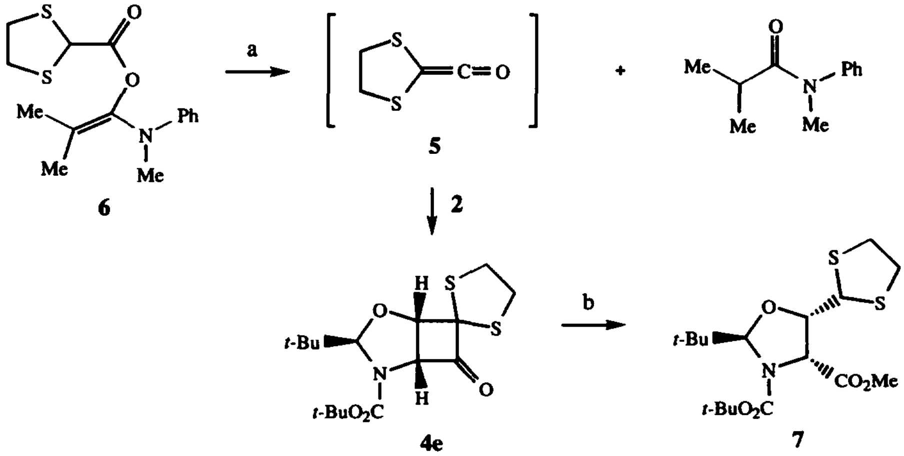
Scheme 3

Table 1 : Cycloaddition Conditions and Characterisation of Adducts

entry	Conditions	Adduct 4			Adduct 3		
		$\delta_{C}{}^{7}$	$\delta_{C}{}^{4}$	δ_{CH_3}	$\delta_{C}{}^{7}$	$\delta_{C}{}^{7}$	δ_{CH_3}
a	diphenylketene (3 eq.)[a] toluene, Δ, 2 hrs	79	73	3.73	91	62	3.15
b	diphenylketene (3 eq.)[a] toluene, Δ, 2 hrs	79	73	1.49	91	62	1.10
c	phenylchloroketene (2 eq.)[b] cyclohexane, 60°C, 2 hrs	82	74	3.75	92	66	3.06
d	phenylchloroketene (2 eq.)[b] cyclohexane, 60°C, 2 hrs	82	74	1.49	91	66	1.10
e	toluene, Δ, 7 hrs, Scheme 4	81	74	1.48			

a) Prepared according to ref. 5. b) Generated from phenylacetyl chloride and triethylamine.

Ketene **5**, a synthetic equivalent of the unknown dimer of CO, was generated by thermolysis of **6** in the presence of **2** (Scheme 4).[8] The reaction gave only one regioisomer **4e**. Its structure was established by comparison of its ^{1}H and ^{13}C NMR spectra with those of compound **4c-d**. Further support came from the transformation of **4e** into crystalline **7** which was submitted to X-ray diffraction analysis.[9]



Conditions a: toluene Δ, 7 hrs, 40% yield; b : NaOH, H_2O-acetone, RT then CH_2N_2 in ether

Scheme 4

These unusual results indicate that the electronic preference for the formation of **3** was outweighed by steric interactions between the ketene endo-substituent and the nitrogen substituent.[10] Also they provide a direct and practical route towards enantiomerically pure protected 2-amino-3-hydroxycyclobutanones **4** which are potential sources of biologically interesting compounds.

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