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The Cycloaddition of Monoalkylketenes to 2-Oxoalkanoic Ester-Derived Imines: A Concise Stereoselective Approach to α,β-Disubstituted Aspartates and 3,4-Dialkylsubstituted β-Lactams.

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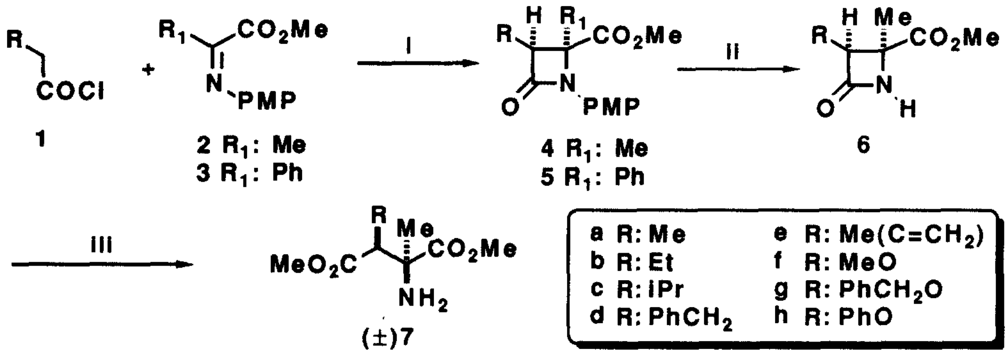
Abstract: α,β-Disubstituted aspartates were obtained with high stereoselectivities from 4-alkyl-4-alkoxycarbonyl β-lactams prepared via [2 +2] cycloaddition reaction of monoalkylketenes and 2-oxoalkanoic ester-derived imines. Preparation of cis-3,4-dialkyl β-lactams by decarboxylation of the above cycloadducts with the Chatgilialoglu's reagent is also described.

Since the pioneering work of Staudinger[1] in the early 1900's, numerous papers concerning the synthesis of β-lactams through [2 + 2] cycloaddition reaction of ketenes to aldehyde-derived imines have been reported. In particular, the development of this reaction to a practical level through dehydrohalogenation of substituted acetyl chlorides by means of tertiary organic bases, has provided one of the most expedient routes to 3,4-disubstituted β-lactams[2]. Hitherto, the main problems associated with the Staudinger reaction can be categorized according to the structural nature of both reaction components, the ketene and imine partners. First, the instability and the lack of reactivity of monoalkylketenes, generated by dehydrohalogenation of α-unactivated alkanoyl chlorides, with imines to produce 3-alkyl β-lactams in a single synthetic step[3]. Second, the imine-enamine tautomerism[4], that, for instance, should give low chemical yields of the expected β-lactams[5] or most notably the lack of optical purity in the case of chiral nonracemic imine compounds[6]. Third, the inaccessibility as well as the high instability of monomeric formaldehyde derived imines for the production of 4-unsubstituted β-lactams[7]. Finally, the control of the relative stereochemistry at the newly created stereogenic centers, although controlable[8], is not always predictable. Recent research from this laboratory aimed at understanding the main chemical and stereochemical control elements that govern the Staudinger reaction[9], has resulted in the development of this approach primarily through the use of monoalkylketenes and glyoxylic ester derived imines as a potential option to solve some of the aforementioned aspects. In this option, a wide variety of 3-alkyl-β-lactams, as building blocks of either carbapenem antibiotics or β-substituted aspartic acids, can be prepared in a highly stereochemically predictable manner[10]. Therefore, it seemed obvious to us that the use of 2-oxoalkanoic ester derived imines in such a cycloaddition process[11] should offer a straightforward solution to the existing problems of the Staudinger reaction. The alkoxycarbonyl group in the resulting cycloadducts could be removed under Barton's decarboxylative conditions or easily transformed into other functionalities thus providing a short and practical route to structurally different 3,4-dialkyl substituted β-lactams[12], whose conversion into azetidines, β-amino acids and amino alcohols can be easily envisaged[13]. This option should also possess a broader degree of generality than the usually employed lithium ester enolate-imine condensation, since this latter approach is subjected to the limitations imposed by the enolate reactivity which in certain situations does not produce the expected β-lactam compound[14]. Herein we report that a wide variety of 3,4-dialkyl-4-alkoxycarbonyl β-lactams can be directly obtained by reaction of alkanoyl chlorides and 2-oxoalkanoic ester-derived imines in the presence of triethylamine, leading to a new route to diverse α-substituted aspartic acid derivatives and 3,4-dialkyl substituted β-lactams[15]. In addition, this approach could also be employed for the development of potential elastase enzyme inhibitors which are of current widespread interest[16].

The reaction of propanoyl chloride **1a** with the representative imines **2** and **3** was first examined to determine the best reaction conditions in terms of chemical yield and stereoselectivity. Thus, we found that treatment of **1a** with the imine **2** in the presence of triethylamine and molecular sieves in refluxing benzene for 20h afforded the expected β-lactam **4a** in 85% isolated yield, together with small amounts of the corresponding *N*-p-methoxyphenylamide ($RCH_2CONHPMP$) and the enamide ($CH_2{=}C(CO_2Me)N(PMP)COCH_2R$) in 7% and 8% yield respectively. In the absence of molecular sieves the yield of the amide side products increased up to 40% and only 20% of the desired β-lactam was formed. Also the yield of the β-lactam **4a** decreased notably when the reaction was carried out at reflux in either methylene chloride or hexane overnight. The reaction of **1a** with the imine **3** under similar conditions was also examined, but in this case a three-fold excess of acid chloride and reflux in toluene was needed for a good yield (65%) of the expected 3-alkyl-4-phenyl-β-lactam **5a**.



Scheme 1 . Reagents and conditions: **i** NEt_3, C_6H_6 (or C_6H_5Me) molecular sieves 4A, reflux, 20h **ii** $(NH_4)_2Ce(NO_3)_6$ $MeCN\text{-}H_2O$, 0-5°C, 30min **iii** $ClSiMe_3$, MeOH, reflux. PMP group: $4\text{-}MeOC_6H_4$

Table I summarizes the results obtained from different acid chlorides and imines **2** and **3** and shows that remarkable stereoselectivity is observed, especially during the formation of 3-alkyl-β-lactams, as established by ^1H-NMR spectroscopy of the crude reaction products. Thus, for β-lactams of type **4** a singlet appeared at δ : 1.8 ppm corresponding to the 4-methyl group and, as depicted in the Scheme, the relative stereochemistry between the H and the Me groups at the C_3 and C_4 positions respectively was established by NOE experiments on β-lactams **4a**, **4c** and **4g**. Thus, by presaturation of the methyl groups at 1.8ppm a 10-12% increase of the C_3 (at 3.2 and 2.9 ppm respectively) protons was observed in azetidin-2-ones **4a** and **4c**. When both isomers of β-lactam **4g** were separated by column chromatography and subjected to the same test, the major isomer gave a 32 % NOE indicating a *cis* relationship between the C_3-H and the C_4-Me groups whilst the minor one gave 1% NOE. The stereochemical assignment for compounds **5** was established by observation of the chemical shift of the singlets corresponding to the C_3 protons. The singlet at higher field was assigned to the isomer with the C_3 proton *cis* to the phenyl group based upon the ring current effect[11].

Table 1. Cycloaddition of ketenes to 2-oxoalkanoic ester-derived imines[a].

Product	Yield, % [b]	cis:trans	m.p.; ºC [d]	^{1}H-NMR [e]	
				δ H-3	δ Me-4
4a	85 (33) 38, 40 [c]	100:0	80	3.24	1.81
4b	75 (58)	100:0	66-67	3.07	1.81
4c	82	100:0	76	2.89	1.83
4d	63	98:2	syrup	3.67	1.83
4e	25	100:0	80-81	3.13	1.85
4f	51	82/18	syrup	4.39	1.83
4g	58	82/18	syrup	4.56	1.76
5a	65	100:0	syrup	3.52	------
5c	72	100:0	126-128	3.12	------
5h	74	45:55	syrup	5.29	------

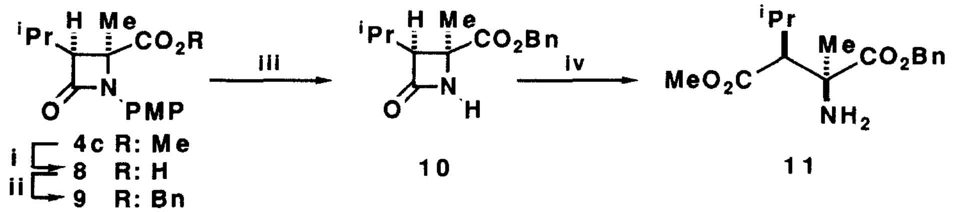
[a] Reactions conducted on 10 mmol scale in refluxing benzene (compounds **4**) or toluene (compounds **5**). (molar ratio RCH_2COCl: Imine: NEt_3 = 1.5: 1: 3 for compounds **4** and 3: 1: 3 for compounds **5**). [b] Yield of isolated pure product by column chromatography. The number in brackets refers to the isolated yield obtained when the reaction was carried out in the absence of molecular sieves. [c] Methylene chloride and acetonitrile used respectively as solvents. [d] Crystallized cis isomers from ethanol. [e] Measured at 300 MHz in $CDCl_3$ only cis isomers' data are given.

Table 2. β-Lactams **14** and **15**[a] and 3-Alkyl-4-methyl β-lactams **18** - **20**[b].

Compound	Yield, % [c]	cis: trans [d]	m.p.; ºC [e]	Compound	Yield, % [c]	cis: trans [d]	m.p.; ºC [e]
14a	42	100:0	138-140	**19a**	97	68:32	syrup
14c	35	100:0	syrup	**19c**	85	93:7	syrup
15a	42	100:0	syrup	**20a**	89	90:10	syrup
15c	37	100:0	60-62	**20b**	90	89: 11	47-49
14f	55	85:15	syrup	**20c**	96	92: 8	91-92
18a	88	84:16	syrup	**20f**	81	82:18	syrup

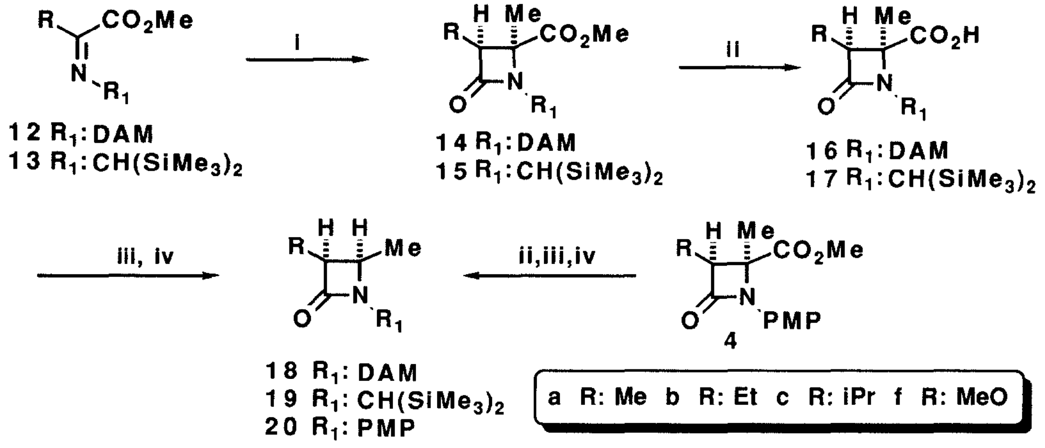
[a] Reactions conducted on 10 mmol scale in refluxing benzene. (molar ratio RCH_2COCl: Imine: NEt_3 = 1.5: 1: 3). [b] Reactions conducted on 2 mmol scale under nitrogen in refluxing benzene (molar ratio RCOOCl: $HSi(SiMe_3)_3$: AIBN = 1: 2: 0.2). [c] Yield of isolated pure product by column chromatography. [d] Isomer ratio determined by ^{1}H NMR. [e] Crystallized cis isomers from ethanol.

Conversion of the β-lactams, prepared as above, into α-substituted aspartates **7** was easily accomplished by *N*-dearylation[17] and further β-lactam ring opening of the resulting *N*-unsubstituted azetidin-2-ones **6** using trimethylchlorosilane in refluxing methanol. In each case tested the corresponding aspartates were obtained in good yields[18]. In order to differentiate the two carboxylic groups, we next examined the route from the benzyloxycarbonyl β-lactam **9** which was easily prepared in 90 % yield by treatment of the 4-carboxy β-lactam **8** with oxalyl chloride and then, with benzyl alcohol-triethylamine under *N,N*-dimethylaminopyridine catalysis. *N*-dearylation of **9** was followed by ring opening of the resulting β-lactam **10** to give **11** in 51 % overall yield, without detectable amounts of transesterification products.



Scheme 2 . Reagents and conditions: **i** LiI, pyr., reflux, 2h **ii** ClCOCOCl (2 equiv.), CH_2Cl_2, refl., then BnOH, NEt_3, DMAP cat., CH_2Cl_2, r.t., 20 h. **iii** $(NH_4)_2Ce(NO_3)_6$, MeCN,-H_2O, 0-5°C, 30min **iv** $ClSiMe_3$, MeOH, reflux. PMP group: 4-$MeOC_6H_4$

At this stage, the cycloaddition reaction was extended to the preparation of β-lactams **14** and **15** carrying *N*-alkyl substituents suitable for further removal under established conditions[19] and to study whether the presence of bulky groups at the nitrogen atom could have an influence on the stereoselectivity observed during the formation of 3-alkyl and 3-alkoxy β-lactams. However, as Table 2 shows, only moderated yields were obtained under the same reaction conditions as above. Increasing the amount of acyl chloride did not improve the yield and in each case the corresponding amide side product was also formed. Nonetheless, a single isomer was



Scheme 3 . Reagents and conditions: **i** RCH_2COCl, NEt_3, C_6H_6, 80°C, 20h **ii** LiI, pyr., reflux, 2h **iii** ClCOCOCl (2 eq.), CH_2Cl_2, 40°C, 1 h. **iv** $HSi(SiMe_3)_3$ (2 eq.), AIBN (0.2 eq.), C_6H_6, 80°C, 4h. PMP group: 4-$MeOC_6H_4$ DAM group: $(4\text{-}MeOC_6H_4)_2CH$.

produced for 3-alkyl β-lactams as determined by NOE experiments, but the 3-alkoxy β-lactams were obtained in similar stereoselectivities to above.

With these 4-alkoxycarbonyl β-lactams in hand we examined their transformation into 3,4-dialkyl β-lactams by simple decarboxylation of the corresponding acids **16** and **17**. It is also expected that *cis* isomers would be formed as major compounds, thus providing a complementary route to the existing methods leading to *trans* derivatives[12b]. Among different methods considered to achieve this goal, we focused on tris(trimethylsilyl)silane-promoted radical decarboxylation as a convenient option[20]. First, each compound **14** and **15** was transformed into the 4-carboxy β-lactam **16** and **17**, and these into the corresponding acyl chlorides. Treatment of each 4-chlorocarbonyl β-lactam with tris(trimethylsilyl)silane in benzene at reflux with AIBN as catalyst resulted in a radical decarbonylation affording the expected 4-methyl β-lactams **18** and **19** in excellent yield. The same sequence of reactions performed on β-lactams **4a**, **4b** and **4c** led to the corresponding 4-methyl derivatives **20a-c**. As Table 2 shows, in all cases a mixture of *cis* and *trans* isomers was produced in which the *cis* isomer predominated and could be easily separated by crystallization from ethanol.

In conclusion, the present work sets the basis for a solution to the remaining problems of the Staudinger reaction and offers a new approach to α-amino acids carrying a chiral quaternaty carbon center in a highly stereochemically predictable manner. Further studies on the use of either chiral, non racemic, α-alkoxy ketone-derived imines or chiral ketenes in such a cycloaddition process are being investigated in our laboratory and full details of this chemistry as well as its utility in the asymmetric synthesis of α,α-disubstituted amino acids and derivatives will be published in the near future.

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18 Representative data: Compound **4a**: M.p: 80ºC. ^{1}H NMR ($CDCl_3$) δ 7.30 (d, 2 H, J= 9.2 Hz, arom), 6.86 (d, 2 H, J= 9.1 Hz, arom.), 3.80 (s, 3 H, COOMe), 3.79 (s, 3 H, ArO-CH_3), 3.24 (q, 1 H, J= 7.5 Hz, CH-CO), 1.81 (s, 3 H, CH_3-C-N), 1.35 (d, 3 H, J= 7.5 Hz, CH_3-CO). ^{13}C NMR ($CDCl_3$) δ 171.5, 166.0, 156.2, 130.0, 119.3, 114.2, 64.7, 56.3, 55.4, 52.4, 20.2, 9.6. MS m/z: 263 (M^+). Compound **5c**: M.p: 126-128ºC. ^{1}H NMR ($CDCl_3$) δ 7.55-7.23 (m, 7H, arom), 6.79 (d, 2 H, J= 9.2Hz, arom), 3.79 (s, 3 H, $COOCH_3$), 3.76 (s, 3 H, $ArOCH_3$), 3.12 (d, 1 H, J= 10.3 Hz, CH), 2.34-2.24 (m, 1 H, J= 6.6 Hz, J= 10.3 Hz, C$\underline{H}CH_3$), 1.17 (d, 3 H, J= 6.6 Hz, CH_3), 1.07 (d, 3 H, J= 6.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 170.3, 165.8, 156.1, 137.0, 131.2, 128.6, 128.2, 127.0, 119.1, 114.2, 73.0, 55.5, 52.8, 27.1, 21.8, 20.7. MS m/z: 353 (M^+). Compound **7f**: Oil. ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 1 H, CH.), 3.76 (s, 3 H, $COOCH_3$), 3.71 (s, 3 H, $COOCH_3$), 3.32 (s, 3 H, OCH_3), 2.07 (s, 2H NH_2), 1.30 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 175.9, 170.5, 85.4, 61.7, 59 3, 53.1, 52.4, 23.1. MS m/z: 146 (M^+ - CO_2Me). Compound **11**: Oil. ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 5 H, arom.), 5.22 (d, 1 H, J= 12.2 Hz, $\underline{H}$CPh), 5.17 (d, 1 H, J= 12.2 Hz, $\underline{H}$CPh), 4.30 (s_b, 2H, NH_2), 3.71 (s, 3 H, $COOCH_3$), 2.86 (d, 1 H, J= 7.6 Hz, $CHCO_2Me$), 2.13 (m, 1 H, CH), 1.47 (s, 3H, CH_3), 0.89 (d, 3H, J=6.8 Hz, CH_3), 0.89 (d, 3H, J=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 170.0, 168.6, 125.2, 122.8, 61.5, 52.9, 45.6, 24.0, 22.6, 22.2, 15.6 MS m/z:158 (M^+ - CO_2CH_2Ph). Compound **20a**: Oil. ^{1}H NMR ($CDCl_3$) δ 7.32 (d, 2 H, J= 9.1 Hz, arom.), 6.87 (d, 2 H, J= 9.1 Hz, arom.), 4.22 (dq, 1 H, J= 5.8 Hz, J= 6.2 Hz, CH), 3.79 (s, 3 H, $ArOCH_3$), 3.40 (dq, 1 H, J= 5.8 Hz, J= 7.6 Hz, CH), 1.38 (d, 3H, J=6.4 Hz, CH_3), 1.27 (d, 3H, J=7.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ 168.0, 155.8, 131.0, 118.3, 114.3, 55.4, 50.5, 46.5, 13.6, 8.6. MS m/z: 205 (M^+).

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