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A NOVEL SYNTHETIC APPROACH TO α-ALKYLIDENE-β-LACTAMS

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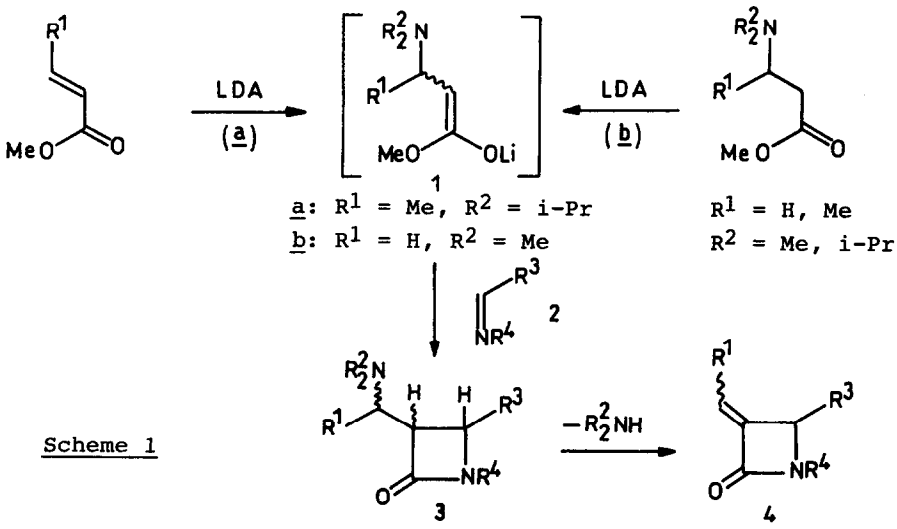
Summary: A simple strategy for the synthesis of various α-alkylidene-β-lactams **4** based upon the condensation between lithium enolates of 3-(*N*,*N*-dialkylamino)esters and imines followed by straightforward deamination of the resulting 3-aminoalkyl-β-lactams **3** is outlined. The synthesis of α-alkylidene-β-formyl-β-lactams is a particularly significant feature of this work.

The α-alkylidene-β-lactam unit is found as structural feature of several potent β-lactamase inhibitors such as the asparenomycins,[1] Ro15-1903,[2] and 6-[(Z)methoxymethylene]-penicillanic acid.[3] In addition, α-alkylidene-β-lactams are valuable synthetic intermediates which can serve not only for the introduction of the side chains common to the carbapenems[4] but also for the synthesis of other useful synthetic targets such as α-keto-β-lactams.[5,6] Typical procedures for the synthesis of α-alkylidene-β-lactams include the Pd-catalyzed carbonylation of 2-bromoallylamines,[7] the addition of chlorosulfonyl isocyanate to functionalized allenes,[4] and some olefination[3b,8] or elimination[5,9] methods on the appropriate β-lactams.

We describe here a convenient simple method for the synthesis of some α-ethylidene- and α-methylene-β-lactams **4** from imines **2** which involves the use of lithium β-(*N*,*N*-dialkylamino)ester enolates **1** as synthetic equivalents of the corresponding acrylate α-anions (Scheme 1).[10]



Scheme 1

The starting enolates 1 were obtained either by the conjugate addition of LDA to methyl crotonate[11] at -78°C (route a, R^2 = i-Pr) or by treatment of the related β-aminoester with LDA under standard conditions for the generation of enolates from simple esters[12] (route b) (Scheme 1). The intermediate enolate 1 (two equivalents) undergoes reaction with various simple and functionalized imines 2 to give the amino-β-lactams 3 in good to excellent yields generally (Table 1).[13,14] The reactions of enolate 1a with imines show *trans*-stereoselectivity exclusively giving mixtures of two diastereoisomers in different relative proportions depending on the method of generation of the enolate.[15] This contrasts with the reactions of enolate 1b which show a variable *cis*:*trans*-stereoselectivity, depending upon the nature of R^3 in the starting imine. The straightforward reaction of glyoxal diimine (2, R^3 = CH=NAr, R^4 = *p*-anisyl) with enolate 1a to give 3a is noteworthy as compared with the corresponding reaction of *N*-cinnamylidene p-methoxyaniline which failed to give the corresponding amino-β-lactam.

Table 1. Synthesis of 3-(α-Aminoalkyl)-β-lactams 3.[a]

Comp.[b]	R^1	R^2	R^3	R^4	Yield (%)[c]	*cis*:*trans* ratio[d]
3a	Me	i-Pr	CH=NAr	Ar	90	0:100[f]
3b	Me	i-Pr	2-furyl	Ar	60	0:100[f]
3c	Me	i-Pr	2-furyl	$SiMe_3$[e]/H	75	0:100[f]
3d	H	Me	CH=NAr	Ar	100	40: 60
3e	H	Me	2-furyl	Ar	77	50: 50
3f	H	Me	2-furyl	$SiMe_3$[e]/H	70	50: 50
3g	H	Me	Ph	Ar	63	94: 6
3h	H	Me	E-CH=CHPh	Ar	34	75: 25

a) All products 3 gave satisfactory analytical and spectral data (IR, ^{1}H and ^{13}C-NMR, and mass spectra).
b) In all cases Ar = *p*-$MeOC_6H_4$
c) Yield for pure, isolated product except 3d estimated from ^{1}H-NMR spectrum of the reaction mixture residue.
d) Determined by ^{1}H-NMR (300 MHz) integration. The stereochemical assignments are based on the values of *J* (H3-H4).
e) Upon hydrolysis replaced by a proton.
f) As a mixture of diastereoisomers in the ratio 70:30. Relative configuration remains undetermined.

Amino-β-lactams 3 may be considered to be masked α-alkylidene-β-lactams 4. Deprotection involves deamination which is accomplished in two different ways depending on the nature of R^2 (Scheme 1). For R^2 = i-Pr deamination was performed by heating under reflux in toluene with silica gel.[16] The dimethylamino group was better removed by

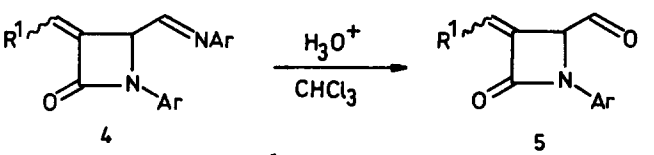
quaternization with methyl iodide followed by DBU-induced elimination.[10a] These results are summarized in Table 2. β-Lactams **4a** and **4b** were obtained as mixtures of E/Z isomers, whose stereochemistry has not yet been determined.

Table 2. Synthesis of α-Alkylidene-β-lactams 4.[a]

Comp.[b]	R^1	R^3	R^4	Method[c]	Yield (%)[d]
4a[e]	Me	CH=NAr	Ar	A	74
4b[e]	Me	2-furyl	Ar	A	98
4d	H	CH=NAr	Ar	B	40
4g	H	Ph	Ar	A,B	75,85
4h	H	*E*-CH=CHPh	Ar	A,B	37,80

a) All products **4** gave satisfactory analytical and spectral data (IR, ^{1}H and ^{13}C-NMR, and mass spectra).
b) In all cases Ar = *p*-$MeOC_6H_4$.
c) A: Silica gel/toluene/Δ. B: 1) ICH_3 excess/methanol/0°C; 2) DBU/acetone/room temperature.
d) Yield for pure, isolated product.
e) As mixture of E,Z-stereoisomers. Stereochemistry not determined.

Among different compounds **4** prepared, compounds **4a** and **4d** are of particular interest due to their potential β-formyl group, which can be easily obtained in nearly quantitative yield by simple hydrolysis of the corresponding 4-imino group (Scheme 2).[17] Thus, the synthesis of two α-alkylidene-β-formyl-β-lactams **5** is a particularly significant feature of this work.



4 **5**

R^1 = H, Me
Ar = 4-$MeOC_6H_4$

Scheme 2

Studies concerning the scope of the procedure presented as well as the use of compounds **5** as synthetic targets in β-lactam chemistry are now underway in our laboratory.

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